in vivo *27*: 485-494 (2013)

Rat Hepatic and Splanchnic Vascular Responses to Anaphylactic Shock, Compared with Hemorrhagic or Vasodilator-induced Shock

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Abstract. *Background: Hemodynamics during anaphylactic shock remain unclear. We determined hepatic and splanchnic responses to anaphylactic hypotension, compared with hemorrhage or sodium nitroprusside (SNP)-induced hypotension, in anesthetized rats. Materials and Methods: Portal pressure, systemic arterial pressure (SAP), central venous pressure, portal and hepatic arterial blood flow were measured. Splanchnic (Rspl), portal venous (Rpv), and hepatic arterial (Rha) resistances were determined. Results: In rats with anaphylaxis induced by an intravenous injection of the ovalbumin antigen (n=6), hemorrhage (n=6), and SNP (2 mg/kg, n=6), SAP decreased similarly. During anaphylaxis, Rha and Rspl decreased only at 30 s after the antigen injection. Notably, Rpv increased markedly. During hemorrhage, Rspl and Rha increased and decreased, respectively, with Rpv not changing. After SNP, Rha and Rspl decreased with Rpv not changing. Conclusion: Hepatic and splanchnic vascular responses differ according to the type of shock. Anaphylactic hypotension is characterized by markedly increased portal venous resistance. Splanchnic and hepatic artery dilatation occurs only at the beginning of hypotension in anesthetized rats.*

Anaphylactic shock is a sudden, life-threatening allergic reaction associated with hypotension (1), initiated by exposure to a specific antigen in a sensitized organism. Circulatory manifestations include a rapid, precipitous and sustained decrease in systemic arterial blood pressure (SAP) with a concomitant decrease in cardiac output, which is primarily caused by reduced venous return to the heart (2). Arterial vasodilatation is considered to account for anaphylaxis-induced decrease in systemic arterial pressure (1, 2). However, total peripheral resistance (TPR), an indicator of arteriolar vasoconstrictive tone, is not necessarily reported to decrease (3-6), but rather increase (7-9) in patients with anaphylactic hypotension. In animal models of anaphylaxis, there are few reports that TPR decreased during anaphylactic hypotension. Indeed, TPR was reported to increase in monkeys (10) and dogs (11, 12) but also no changes have been reported in dogs (13), sheep (14) and rats (15), although an initial decrease (11%) followed by an 3.2-fold increase was observed in pigs (16). However, in these previous studies, blood flows were not measured continuously with microspheres or thermodilution methods. These intermittent measurements of blood flow might have missed rapid and transient alterations which occurred. Thus a continuous blood flow measurement is required to capture vividly and precisely quick changes during anaphylactic shock, especially at the early stage, when blood pressure falls rapidly.

Venous resistance is increased specifically in anaphylaxis in dogs (13) and rats (15), which may contribute to a decrease in venous return to the heart, resulting in a decrease in cardiac output and SAP. The considerable increase in portal venous resistance, as evidenced by acute portal hypertension in these two animal models (17-19), apparently accounts for the anaphylaxis-related increase in venous resistance. However the response of the hepatic artery within the liver is not known in the presence of acute portal hypertension in models of anaphylaxis.

Consequently in order to determine precisely not only the arterial resistance of the hepatic artery and the splanchnic vascular bed, but also the venous resistance of the portal

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Key Words: Anaphylaxis, circulatory shock, hemorrhage, sodium nitroprusside, hepatic circulation, splanchnic circulation, rat model.

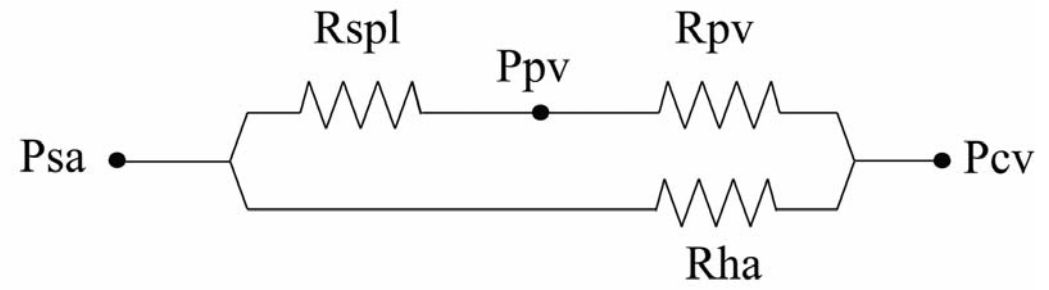

Figure 1. *Schematic representation of distribution of vascular resistances in rat splanchnic and hepatic circulation. Rspl, Splanchnic vascular resistance; Rpv, portal venous resistance; Rha, hepatic arterial resistance; SAP, systemic arterial pressure; PVP, portal venous pressure; CVP, central venous pressure.*

circulation, we continuously measured the blood flow of the hepatic artery and the portal vein with Doppler ultrasonic blood flow probes along with the pressure of the portal vein, aorta, and caval vein. In addition, in order to depict the characteristics of anaphylactic hypotension clearly, we compared these hemodynamic variables with those of hemorrhagic and vasodilator (sodium nitroprusside; SNP)-induced hypotension, in which the blood pressure was reduced to a similar extent to anaphylactic hypotension.

Materials and Methods

Animals. Eighteen male Sprague-Dawley rats (Japan SLC, Shizuoka, Japan) weighing a mean±SE of 463±13 g were maintained at 23˚C and under pathogen-free conditions on a 12:12-hour dark/light cycle and allowed food and water *ad libitum*. The experiments conducted in the present study were approved by the Animal Research Committee of Kanazawa Medical University.

Sensitization. Rats were actively sensitized by the subcutaneous injection of an emulsion made by mixing complete Freund's adjuvant (0.5 ml) with 1 mg ovalbumin (grade V, Sigma, St. Louis, MO, USA) dissolved in saline (0.5 ml) (18). Non-sensitized rats were injected with the adjuvant and ovalbumin-free saline. Two weeks after injection, rats were used for the following experiment.

Surgical preparation of animals. Rats were anesthetized with pentobarbital sodium (50 mg/kg, *i.p.*) and placed on a thermostatically controlled heating pad (ATC-101B; Unique Medical, Osaka, Japan) that maintained body temperature at 36-37˚C. The adequacy of anesthesia was monitored by the stability of blood pressure and respiration during a pinch of the hindpaw. Supplemental doses of anesthetic (10% of the initial dose) were given *i.p.* as necessary. The trachea was intubated to facilitate spontaneous breathing. The right carotid artery and the right jugular vein were catheterized with a polyethylene tube (ID 0.4 mm, OD 0.6 mm) for measurement of SAP and central venous pressure (CVP), respectively. The right femoral artery of rats in the hemorrhage group was also catheterized (ID 0.3 mm, OD 0.5 mm) for withdrawing blood, as described below. Following a midline incision of the abdominal wall, a polyethylene catheter (ID 0.3 mm, OD 0.5 mm) was advanced into the portal vein *via* the caecal vein for continuous measurement of the portal venous pressure (PVP). The pulsed Doppler flow probes (MC2PSB and MC0.5PSB, Transonic Systems, Ithaca, NY, USA) were placed on the hepatic artery and portal vein for continuous measurement of the hepatic arterial (Qha) and portal venous (Qpv) blood flow.

Protocol of the experiment. The sensitized rats were assigned to the anaphylaxis group (n=6). The non-sensitized rats were randomly divided into the hemorrhage group (n=6) and the SNP group (n=6). The SAP, CVP and PVP were continuously measured with pressure transducers (TP-400T, Nihon-Kohden, Tokyo, Japan), and the reference level was set at the level of that of the right atrium. Heart rate (HR) and respiratory rate were measured by analyzing the data of SAP and CVP, respectively (PowerLab system, Model:ML870, AD Instruments, Castle Hill, Australia).

Hemodynamic parameters were recorded for at least 20 min after surgery. After the baseline measurements, the ovalbumin antigen (0.6 mg, *i.v.*) and SNP (2 mg/kg, *s.c.*) were administered to the anaphylaxis and SNP group, respectively. In the hemorrhage group, bleeding started through the right femoral artery catheter with a syringe pre-rinsed with heparin at an appropriate speed to reduce SAP in a manner similar to the anaphylaxis group. The proper volume of blood was re-perfused if necessary. These hemodynamic variables were digitally displayed and recorded at 40 Hz by PowerLab.

The splanchnic and hepatic circulation can be represented by the resistance circuit composed of the splanchnic vascular (Rspl), hepatic arterial (Rha) and portal venous (Rpv) resistances, as shown in Figure 1 and the following equations:

$$Rspl=(SAP-PVP)/Qpv \quad (Eq1)$$
$$Rpv=(PVP-CVP)/Qpv \quad (Eq2)$$
$$Rha=(SAP-CVP)/Qha \quad (Eq3)$$

Statistics. All results are expressed as the mean±SE. Statistical analyses were performed with repeated measurement analysis of variance, and a *p*-value less than 0.05 was considered significant. When a significant difference was obtained, *post hoc* analysis was performed with Fisher's post-test method. Comparison of individual data among the three groups was performed by analysis of variance followed by the Fisher's post-test method.

Table I. *Baseline values of the measured variables in the anaphylaxis, hemorrhage, and sodium nitroprusside (SNP) groups.*

Group (number of rats)	Systemic arterial pressure (mmHg)	Portal venous pressure (mmHg)	Central Venous pressure (mmHg)	Portal venous blood flow (ml/min)	Hepatic arterial blood flow (ml/min)	Splanchnic vascular resistance (mmHg min/ml)	Portal venous resistance (mmHg min/ml)	Hepatic arterial resistance (mmHg min/ml)	Heart rate (beats/ min)	Respiratory rate (n/min)
Anaphylaxis (n=6)	114±4	7.6±0.6	0.8±0.2	33.8±2.8	3.7±0.6	3.2±0.3	0.21±0.03	33.6±6.8	407±5	80±4
Hemorrhage (n=6)	119±3	7.2±0.5	0.8±0.3	32.6±2.4	3.7±0.4	3.5±0.3	0.20±0.02	34.2±5.5	414±7	80±3
SNP (n=6)	116±3	7.6±0.5	0.8±0.2	32.1±1.6	3.5±0.2	3.4±0.2	0.21±0.01	33.3±1.1	422±7	88±4

Values are means±SE.

Results

Baseline values of hemodynamic variables. Table I shows the baseline values of variables, which showed no significant difference among the groups. The mean values for all three groups were as follows; SAP, 116±2 mmHg; PVP, 7.5±0.3 mmHg; CVP, 0.8±0.2 mmHg; Qha, 3.6±0.2 ml/min; Qpv, 32.8±1.2 ml/min; Rspl, 3.37±0.2 mmHg/ml/min; Rha, 33.7±1.9 mmHg/ml/min; Rpv, 0.21±0.01 mmHg/ml/min. The ratio of Qha to Qpv (Qha/Qpv) was 0.11±0.01.

Hemodynamic response to anaphylaxis. Figure 2A shows a representative example of anaphylactic hypotension. The time course changes in SAP, CVP, PVP, Qha and Qpv of all three groups are summarized in Figures 3 and 4. As shown in Figure 2A, the earliest changes of an increase in PVP occurred at 0.22±0.02 min after antigen administration. Thereafter, Qha and Qpv transiently increased at 30 s, although statistical significance was recorded for Qha but not Qpv. In accordance with the transient increase in Qha and Qpv, SAP began to decrease rapidly (Figure 2A). After that, Qha and Qpv decreased to 1.1±0.2 and 7.2±1.1 ml/min, respectively, at 10 min (Figure 4). PVP reached a peak of 21.5±1.3 mmHg at 2 min, while SAP decreased to 60±4 mmHg at 1.45±0.04 min, followed by a gradual recovery to 68±8 mmHg at the end of experiment (Figure 3).

Figure 5 shows the summarized time course data for Rspl, Rha and Rpv. At 30 s after antigen administration, Rha and Rspl significantly decreased in accordance with the increase in Qha and Qpv. Thereafter, Rspl did not change significantly until 50 min after antigen administration, and then it significantly increased. Rpv increased considerably in parallel with the increase in PVP, reaching 10.5-fold the baseline level 2 min after antigen administration and then returned towards the baseline level.

Figure 6 shows the heart rate and respiratory rate. The heart rate did not change significantly until 50 min after antigen injection, and thereafter increased significantly. Respiratory rate was transiently lower between 2 and 5 min after antigen administration

Hemodynamic response to hemorrhage. Figure 2B shows a representative recording of the response of a rat suffering from hemorrhage in which blood was withdrawn so that the SAP decreased in the same manner as in the anaphylaxis group. Actually SAP decreased to 53±6 mmHg at 2 min after start of hemorrhage (Figure 3). As compared with the anaphylaxis group, the decrease in Qpv was similar, but that in Qha was significantly smaller, as shown in Figure 4. In contrast to the anaphylaxis group, PVP decreased significantly. The maximal volume of blood shed was 5.8±0.2 ml, and the blood loss was reinfused throughout the experimental period.

As shown in Figure 5, the response of Rha, Rpv and Rspl in the hemorrhage group was definitely different from that in the anaphylaxis group. Rspl increased significantly 1 min after the start of bleeding, with a peak level of 1.9-fold baseline at 4 min, and remained elevated throughout the experimental period. Rha decreased significantly to 56% of the baseline and returned to baseline at the end of the experiment. Rpv was significantly increased but only slightly and transiently. The heart rate significantly decreased by 93 beats/min 10 min after bleeding and remained at low levels (Figure 6). Respiratory rate did not show significant change (Figure 6).

Hemodynamic response to the vasodilator SNP. Figure 2C shows a representative recording of the response of a rat injected with SNP. SAP and PVP decreased similarly to the hemorrhage group (as shown in Figure 2C and 3). Qha and Qpv decreased, but the decrease in Qpv was much smaller than that of the other two groups (Figure 4). Rspl and Rha decreased significantly and returned to baseline at the end of the experiment (Figure 5). Rpv did not change significantly throughout the experimental period (Figure 5). The heart and respiratory rates did not change significantly after SNP injection (Figure 6).

Discussion

In this study, the blood flow to the liver *via* the portal vein and the hepatic artery was continuously measured, which permitted determination of Rspl, Rha, and Rpv during anaphylaxis

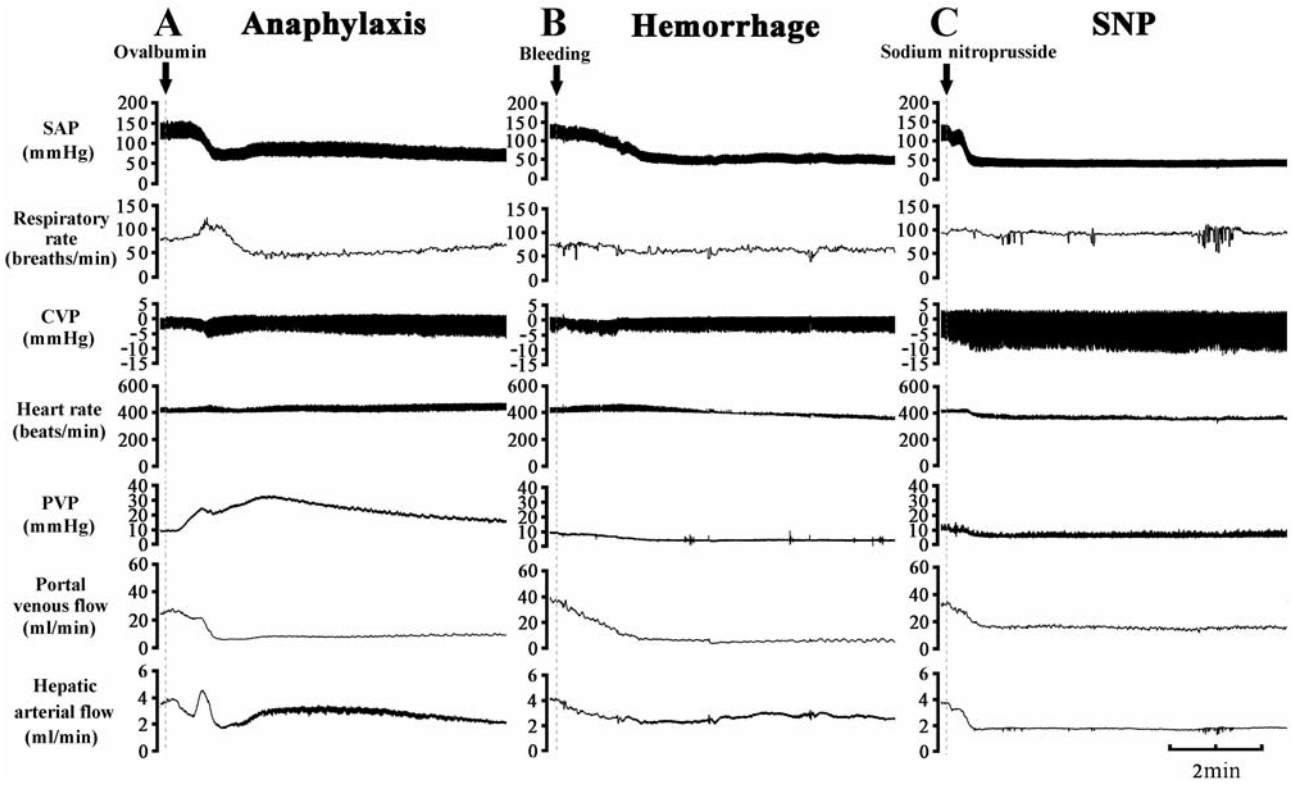

Figure 2. *Representative recordings of the hemodynamic responses in the anaphylaxis (A), hemorrhage (B), and SNP (C) groups.*

hypotension, as well as hemorrhagic hypotension and SNP-induced hypotension in anesthetized rats. The main finding was that the vascular resistance responses to anaphylactic hypotension were characterized by a considerable increase in Rpv, initial transient decreases in Rha and Rspl, and absence of a significant increase in Rspl in the early stage. In contrast, during hemorrhagic hypotension, Rspl and Rpv increased markedly and slightly, respectively, and Rha significantly decreased, while during SNP-induced hypotension, Rspl and Rha, both of which are mainly arterial resistances, decreased without a significant change in Rpv. To our knowledge, this study is the first to continuously record the changes in the vascular resistance of the liver and splanchnic vascular beds in rats during anaphylactic, hemorrhagic and vasodilator-induced hypotension, and demonstrated that they were quite different among these three hypotension models.

In the anaphylaxis group, immediately after antigen administration, Rha and Rspl decreased transiently, along with increases in Qha and Qpv. To our knowledge, this is the first study to demonstrate that vasodilation of the hepatic artery and splanchnic vascular beds definitely occurred transiently only in the early phase of anaphylaxis. Although arterial vasodilation is believed to be the primary mechanism for anaphylactic hypotension, this finding strongly suggests that vasodilatation of the hepatic artery and splanchnic vascular beds occurs only at the initial phase and is not sustained during systemic anaphylaxis in anesthetized rats. This is consistent with the initial and transient decrease in TPR during anaphylactic shock in rats (20). It should also be noted that the transient increase in Qha and Qpv coincided with the start of the fall in SAP. This suggests that vasodilatation of these arteries seem to trigger the fall of SAP.

In contrast to anaphylactic hypotension, Rha decreased significantly in response to hemorrhage (Figure 5). This finding is consistent with that of previous studies (21, 22) in which the hepatic arterial blood flow, as measured with the microsphere method, was relatively preserved during hemorrhage. One of the reasons for the preservation of the hepatic arterial blood flow in hemorrhagic rats may be related to the hepatic arterial buffer reflex: hepatic arterial vasodilatation occurs in the presence of decreased portal venous blood flow due to strong splanchnic vasoconstriction (23-25). In this respect, in the anaphylaxis group, the hepatic arterial buffer response might not have operated effectively, in that Rha did not change when Qpv decreased in a manner similar to the hemorrhage group. Further study is required of the changes in the hepatic arterial buffer reflex during systemic anaphylaxis.

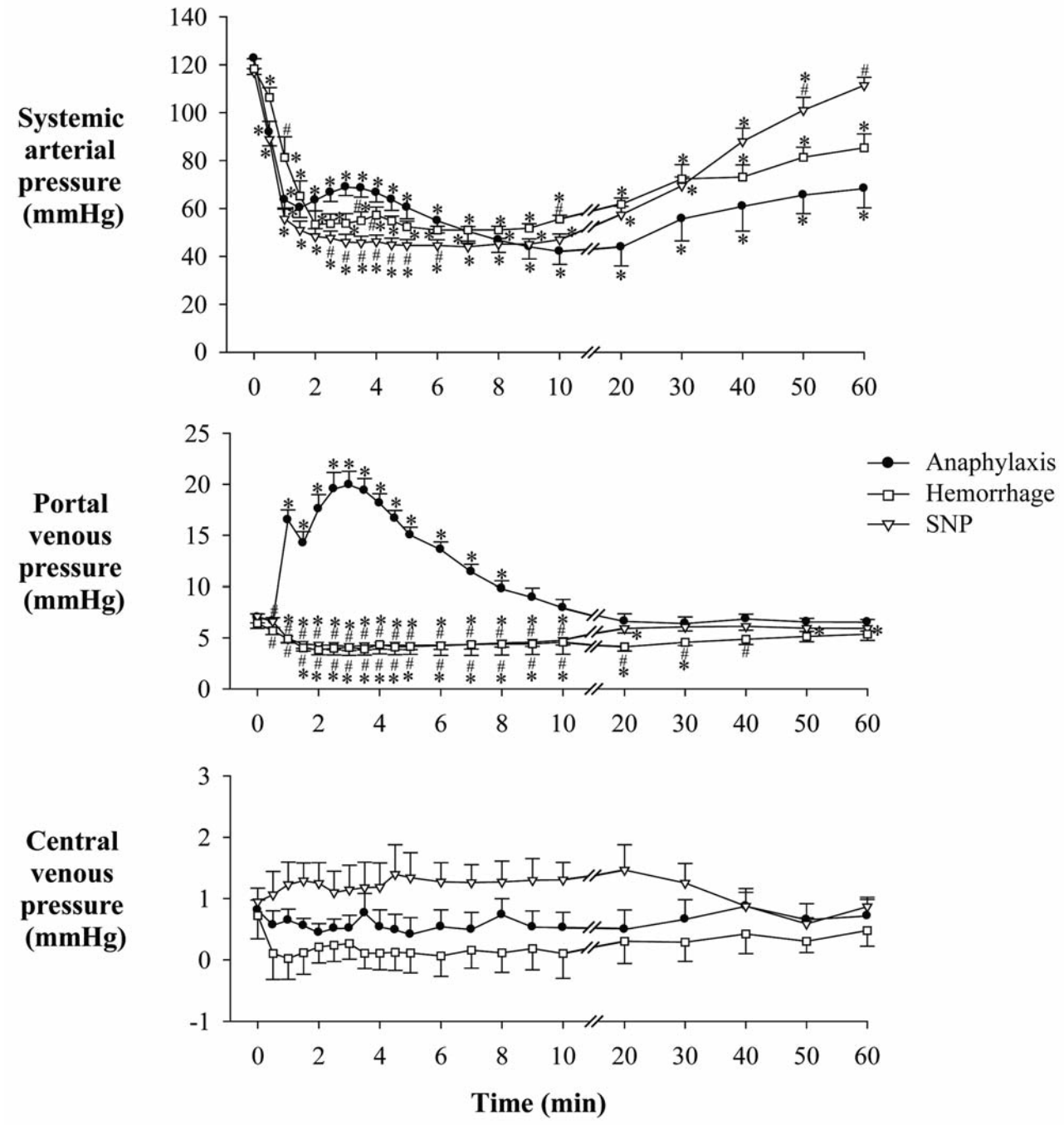

Figure 3. *Time course data of systemic arterial pressure, portal venous pressure and central venous pressure in the anaphylaxis, hemorrhage, and sodium nitroprusside (SNP) groups. Values are given as means±SE; n=6. *p<0.05 vs. baseline, #significantly different at p<0.05 from the anaphylaxis group.*

Rspl significantly increased in the hemorrhage group, but not in the anaphylaxis group. Enhanced vasoconstriction of the splanchnic vascular beds during hemorrhagic hypotension is a compensatory response for redistribution of blood flow to the brain and heart (23, 25. 26). No significant increase in Rspl, except the late stage in the anaphylaxis group, may suggest the absence of this compensatory response. The reasons for the difference in the Rspl response between the anaphylaxis and hemorrhage groups are currently not known. In the face of systemic hypotension, the

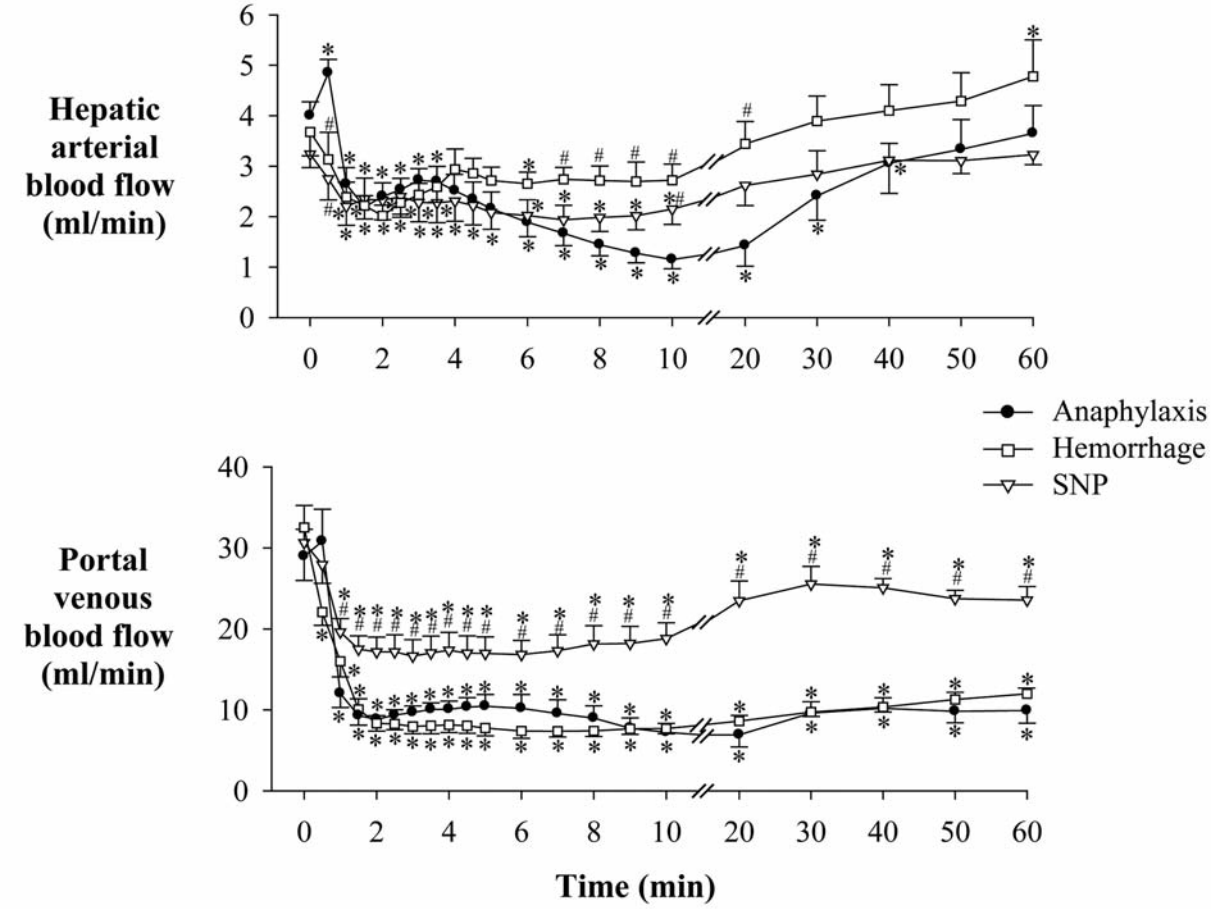

Figure 4. *Time course data of hepatic arterial blood flow and portal venous blood flow in the anaphylaxis, hemorrhage, and sodium nitroprusside (SNP) groups. Values are given as means±SE; n=6. *p<0.05 vs. baseline, #significantly different at p<0.05 from the anaphylaxis group.*

arterial baroreceptor reflex should activate the sympathetic nervous system, resulting in splanchnic vasoconstriction. This is the case of the hemorrhage group. In contrast, in the anaphylaxis group, arterial vasodilatation of the splanchnic vascular beds, which could be caused by chemical mediators released in the anaphylactic reactions, might counteract baroreceptor reflex-mediated vasoconstriction. Another possible explanation may be related to the anaphylaxis-induced inhibitory sympathetic response (27), resulting in impairment of compensatory vasoconstriction.

The considerable increase in Rpv after antigen administration is characteristic of rat anaphylactic hypotension. This increased Rpv may be ascribed to anaphylaxis-released vasoactive mediators such as leukotrienes and cyclooxygenase metabolites (28), which constrict portal veins in isolated perfused rat livers. In the SNP group, Rpv was not significantly changed, while both Rspl and Rha significantly decreased. The absence of decrease in Rpv in response to SNP was unexpected, since SNP has both arterial and venous vasodilatory effects, although its relaxant effects on the KCl- and norepinephrine-induced contractions of the portal vein are less potent than its effect on contraction of the mesenteric artery (29). One possible explanation is that the basal tone of the portal veins was so low, as compared with that of the artery, that the vasodilatory action of SNP on the portal veins, even if present, could not be detected *in vivo* in the rats. In the hemorrhage group, Rpv significantly increased at 3.5-10 min after bleeding, during which Ppv and Qpv markedly decreased. This increased Rpv may be explained by the sympathoexcitation, as described above, or derecruitment of liver capillary blood flow due to decreased Qpv.

The present finding that the heart rate significantly decreased during hemorrhagic shock may be unexpected because the baroreceptor reflex could have elicited sympathoexcitation and tachycardia in response to hemorrhage-induced decrease in SAP. However, the response of heart rate to hemorrhage depends on the volume

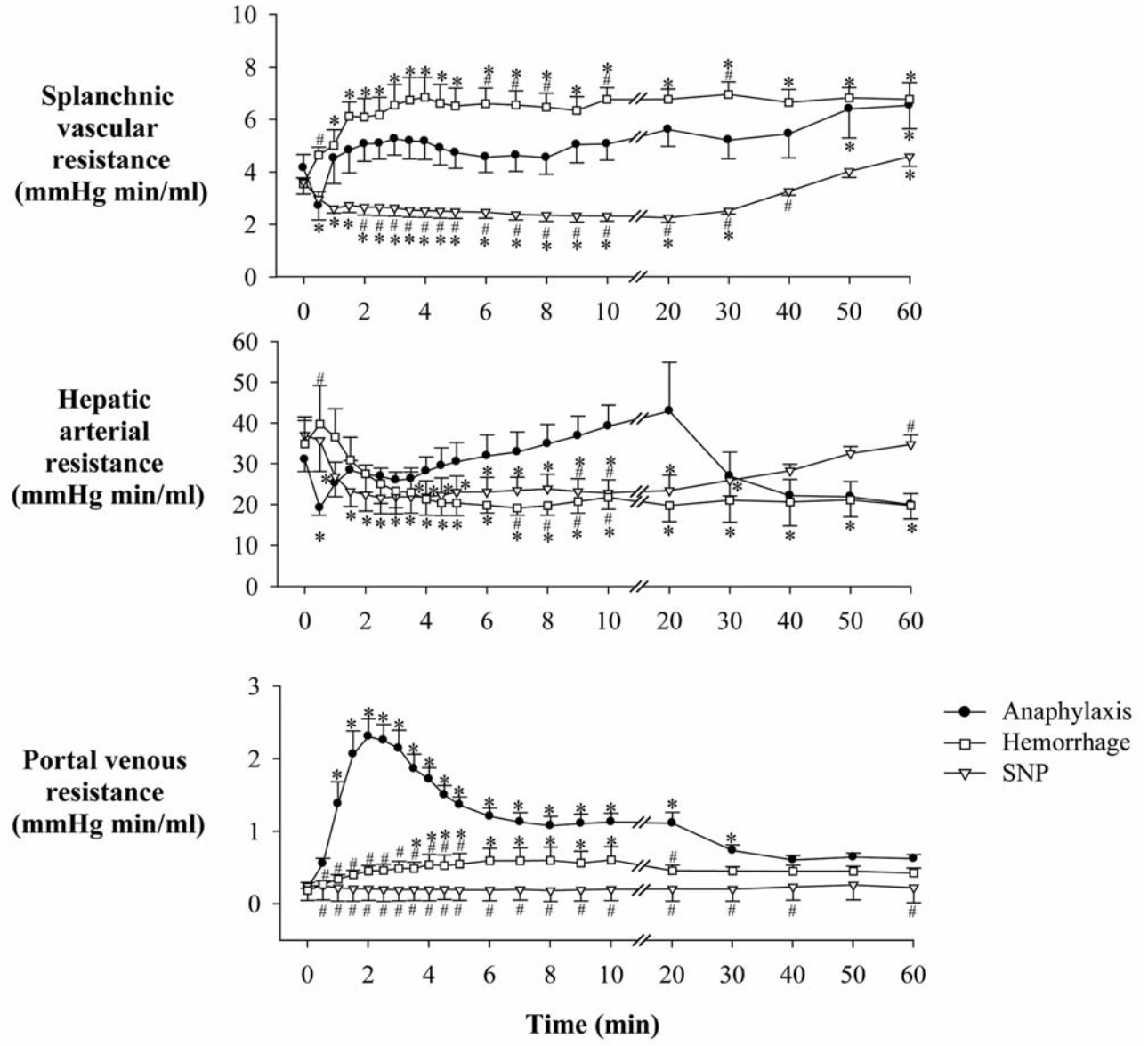

Figure 5. *Time course data of splanchnic vascular resistance, hepatic arterial resistance and portal venous resistance in the anaphylaxis, hemorrhage, and sodium nitroprusside (SNP) groups. Values are given as means±SE; n=6. *p<0.05 vs. baseline, #significantly different at p<0.05 from the anaphylaxis group.*

and speed of blood loss in anesthetized rats. The slow bleeding speed of 0.3-0.5 ml/min or decreasing SAP to about 40 mmHg over 10-20 min causes a biphasic cardiovascular response, an initial transient sympathoexcitation with tachycardia, followed by hypotension and bradycardia (30-32). In the present study, the bleeding was very quick, leading to a decrease in SAP to 53±6 mmHg from the baseline of 118±4 mmHg over 2 min, in order to reduce SAP to the same magnitude as that in the anaphylaxis group. This difference in the protocol might account for the absence of tachycardia in the present study. The mechanism for bradycardia in anesthetized rats with acute hemorrhage may be related to the activation of cardiac (ventricular) vagal C-fiber activity: the heart has to contract around an almost empty ventricular chamber, which causes mechanical squeezing of the myocardium, resulting in activation of ventricular vagal C-fibers, followed by activation of cardiac vagal efferents and finally bradycardia (33-35).

The respiratory rate significantly decreased in the anaphylaxis group, but not in the hemorrhage or SNP groups. The reduction of respiratory rate or apnea in anaphylactic

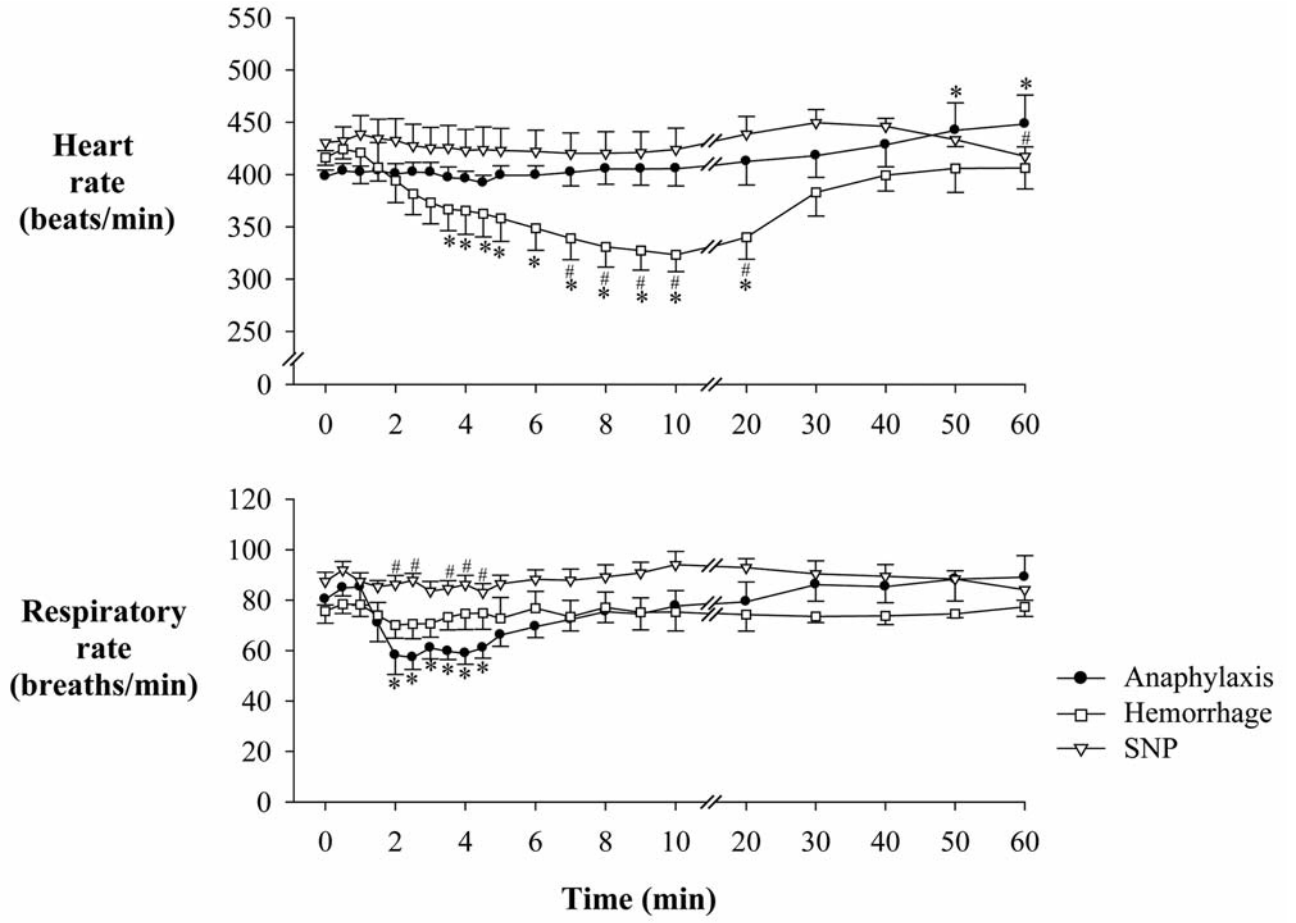

Figure 6. *Time course data of heart rate and respiratory rate in the anaphylaxis, hemorrhage, and sodium nitroprusside (SNP) groups. Values are given as means±SE; n=6. *p<0.05 vs. baseline, #significantly different at p<0.05 from the anaphylaxis group.*

shock models was also reported in dogs (36), calves (37), horses (38) and rabbits (39). As far as we are aware of, the present study for the first time demonstrated that rats also show a decrease in respiratory rate during anaphylactic hypotension. The mechanism for the anaphylaxis-induced inhibition of the respiratory rate seems to be dependent on the reflex *via* the vagal nerve (37).

In summary, the hepatic and splanchnic vascular resistance responses differ depending on the cause of hypotension in anesthetized rats. Anaphylactic hypotension in rats is characterized by markedly increased portal venous resistance and absence of significant vasoconstriction of splanchnic vascular beds in the early stage. Hepatic arterial dilatation and splanchnic vasodilation occur transiently only at the beginning of anaphylactic hypotension, and seems to trigger the fall of the SAP.

Conflicts of Interest

The Authors have no conflict of interest to declare.

Acknowledgements

This study was supported by a Grant-in-Aid for Scientific Research (23592268, 25462839) from the Ministry of Education, Culture, Sports, Sciences and Technology of Japan, and Grants from Kanazawa Medical University (SR2012-04).

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Received May 1, 2013
Revised June 8, 2013
Accepted June 10, 2013