

VENOUS RESISTANCE INCREASES DURING RAT ANAPHYLACTIC SHOCK

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ABSTRACT—Anaphylactic shock is a sudden, life-threatening allergic reaction associated with severe hypotension. The increased venous resistance accounts for the anaphylactic hypotension in anesthetized dogs. However, the change in peripheral vascular resistances during anaphylactic hypotension in other animals such as rats is not known. We measured the mean circulatory filling pressure using the mechanical occlusion method of inflation of the right atrial balloon along with systemic arterial pressure (P_{sa}), central venous pressure, and portal venous pressure. Cardiac output was also measured with the thermodilution method. From these hemodynamic variables, we calculated the total peripheral and venous (R_v) resistances during anaphylactic hypotension in anesthetized rats. These hemodynamic variables were compared with those in the hemorrhagic shock. After an intravenous injection of 0.6 mg antigen ovalbumin in sensitized rats, P_{sa} decreased from 119 ± 4 to 43 ± 2 mmHg, cardiac output decreased from 84.5 ± 5.7 to 37.8 ± 2.1 mL min⁻¹, central venous pressure decreased from 0.9 ± 0.1 to 0.1 ± 0.1 mmHg, and mean circulatory filling pressure also decreased from 6.0 ± 0.2 to 5.2 ± 0.3 mmHg. Thus, the R_v increased from 0.06 ± 0.05 to 0.15 ± 0.02 mmHg mL⁻¹ min⁻¹, but total peripheral resistance did not significantly change. Portal venous pressure also increased from 5.6 ± 0.5 to 21.5 ± 0.9 mmHg. Hematocrit markedly increased from the baseline values of $43\% \pm 1\%$ to $55\% \pm 1\%$ at 15 min after antigen. During hemorrhagic shock, P_{sa} decreased in the manner similar to anaphylactic shock; however, R_v did not significantly change, and portal venous pressure decreased. In conclusion, in rat anaphylactic shock, a substantial increase in R_v presumably due to hepatic venoconstriction may decrease venous return, resulting in systemic hypotension.

KEYWORDS—Anaphylactic shock, hemorrhagic shock, mean circulatory filling pressure, circulatory vascular resistance, portal venous pressure

INTRODUCTION

Anaphylactic shock is a sudden, life-threatening allergic reaction associated with severe hypotension (1) and 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 with a concomitant decrease in cardiac output (CO), which is primarily caused by alterations in the systemic circulation that influence blood flow to the heart because left ventricular function is relatively well preserved during anaphylactic shock (2). Wagner et al. (3) reported that the venous resistance (R_v) increased, although the total peripheral resistance did not change, during anaphylactic shock of anesthetized dogs instrumented for measurement of mean circulatory filling pressure (P_{mcf}). However, the responses of peripheral vascular resistances to anaphylactic shock in other animals such as rats are not known. We recently demonstrated that marked hepatic venoconstriction is observed in rat anaphylactic hypotension, and that the elimination of the splanchnic and hepatic vascular beds attenuates the anaphylactic hypotension in this species (4). Based on these findings, we have proposed that hepatic venoconstriction plays a

substantial role in the pathogenesis of rat anaphylactic shock. It is obvious that hepatic vasculature is included in the systemic venous system. Thus, we hypothesized that the R_v , rather than the arteriolar resistance, increases substantially in rat anaphylactic hypotension. In this study, to determine the total peripheral resistance (R_t) and R_v during rat anaphylactic shock, we measured the P_{mcf} and CO along with the systemic arterial pressure (P_{sa}) and central venous pressure (P_{cv}) in anesthetized and sensitized rat. Actually, P_{mcf} is the pressure measured in the vasculature immediately after cardiac arrest, after pressures in all parts of the circulation are made to equilibrate, and represents the effective driving force for venous return to the heart (5). Furthermore, we compared these hemodynamic variables with that of hemorrhagic shock.

MATERIALS AND METHODS

Animals

Twenty-eight male Sprague-Dawley (SD) rats (Japan SLC, Shizuoka, Japan) weighing 336 ± 4 g were maintained at 23°C and under pathogen-free conditions on a 12-h dark–12-h 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 equal volumes of complete Freund adjuvant (0.5 mL) with 1 mg ovalbumin (grade V, Sigma) dissolved in physiological saline (0.5 mL) (4). Nonsensitized rats were injected with complete Freund adjuvant and ovalbumin-free saline. Rats were used for the following experiments 2 weeks after injection.

Surgical preparation of animals

Rats were anesthetized with pentobarbital sodium (70 mg·kg⁻¹, i.p.) and placed supinely on a thermostatically controlled heating pad (ATC-101B; Unique Medical, Japan) that maintained body temperature at 36°C to 37°C throughout the experiment. The adequacy of anesthesia was monitored by the stability of

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TABLE 1. Baselines of hemodynamic variables in rats of the intact control, anaphylactic shock, and hemorrhagic shock groups

Groups	Intact control	Anaphylactic shock	Hemorrhagic shock
No. rats	6	6	6
Body weight (g)	327 ± 2	328 ± 7	326 ± 2
HR (beats per minute)	435 ± 7	427 ± 13	418 ± 12
P _{sa} (mmHg)	114 ± 2	119 ± 5	113 ± 3
P _{cv} (mmHg)	0.9 ± 0.1	1.0 ± 0.1	0.9 ± 0.1
P _{pv} (mmHg)	5.9 ± 0.2	5.7 ± 0.4	6.2 ± 0.3
FAP (mmHg)	21.8 ± 0.5	22.9 ± 1.2	20.5 ± 0.7
VPP (mmHg)	5.6 ± 0.2	5.7 ± 0.2	6.0 ± 0.3
PVPP (mmHg)	5.7 ± 0.2	5.9 ± 0.3	6.1 ± 0.4
P _{mcf} (mmHg)	5.8 ± 0.2	6.0 ± 0.2	6.3 ± 0.3
CO (mL·min ⁻¹)	80.4 ± 1.5	84.5 ± 5.7	81.4 ± 0.5
R _t (mmHg·mL ⁻¹ ·min ⁻¹)	1.53 ± 0.05	1.47 ± 0.13	1.38 ± 0.04
R _v (mmHg·mL ⁻¹ ·min ⁻¹)	0.07 ± 0.01	0.06 ± 0.01	0.07 ± 0.01

Values are given as mean ± SE.

PVPP indicates portal venous plateau pressure.

blood pressure and respiration under control conditions and during a pinch of the hindpaw. Supplemental doses of anesthetic (10% of the initial dose) were given intraperitoneally as necessary. The trachea was intubated to facilitate spontaneous breathing. The right carotid artery was catheterized with a polyethylene tube (inside diameter [ID], 0.4 mm; outside diameter [OD], 0.6 mm) for measurement of P_{sa}. A temperature probe (OD, 0.3 mm) was placed in the ascending aorta through the same carotid artery to monitor blood temperature. To measure P_{cv} and P_{mcf}, a modified Swan-Ganz catheter was inserted through the right jugular vein, and the catheter tip was placed into the right atrium. It was secured at a correct location where rapid inflation with 0.35 mL air caused a smooth decline in P_{sa} to a final value of 20 to 25 mmHg and a simultaneous rise in P_{cv} to a plateau value of 5 to 7 mmHg. This Swan-Ganz catheter was modified by insertion of a thin polyethylene tube (ID, 0.3 mm; OD, 0.5 mm) with a small dead space (0.02 mL) through the inner canal of the catheter. This equipped thin tube was used for injections of cold saline (0.15 mL) into the right atrium to measure CO and for an intravenous injection of the antigen. To measure portal venous pressure (P_{pv}), another polyethylene catheter (ID, 0.3 mm; OD, 0.5 mm) was advanced into the portal vein via the caecal vein, with the tip of the catheter just protruding into the main portal vein. The right femoral artery of rats in the hemorrhagic shock group was also catheterized (ID, 0.3 mm; OD, 0.5 mm) for withdrawing blood, as described below.

Measurement of CO

Cardiac output was measured using the thermodilution method (modified for rats), as described previously (6). Briefly, a bolus of 0.15 mL ice-cold 0.9% saline (0°C) was injected into the right atrium through the thin tube of the Swan-Ganz catheter, as mentioned above. The variation of blood temperature in the ascending aorta was recorded via the temperature probe. Cardiac output was calculated using the following formula:

$$CO = k_{\text{spec}} \times (T_{\text{rat}} - T_{\text{inject}}) \times (V_{\text{inject}} - V_{\text{dead}}) / \int -\Delta T(t) \cdot dt \quad (1)$$

where T_{rat} represents the rat blood temperature, T_{inject} is the injectate temperature (0°C), V_{inject} is the injectate volume (0.15 mL), V_{dead} is the dead space volume of the venous catheter (0.02 mL), $\int -\Delta T(t) \cdot dt$ is the integral of temperature variation, which can be obtained from the computer. k_{spec} is the density factor defined as the product of specific heat and specific gravity of saline divided by the same product for blood ($k_{\text{spec}} = 1.102$ for 0.9% saline) (7).

The measurements of CO were performed in reduplicate, and then the mean value of CO was calculated for each observed point.

Measurement of $m P_{\text{mcf}}$ and calculation of peripheral vascular resistances

The P_{mcf} was measured by the method reported previously (5, 8, 9). Briefly, the right atrial balloon was rapidly inflated with 0.35 mL air for 7 s. This caused an immediate decline in P_{sa} and a simultaneous rise in P_{cv}, and the venous pressure plateaued approximately 5 s after balloon inflation. This method does not allow

full equalization of pressure throughout the circulation due to “trapping” of blood on the low-compliance arterial side. To correct for this, P_{mcf} was calculated from the following formula:

$$P_{\text{mcf}} = VPP + K (FAP - VPP) \quad (2)$$

where VPP is the venous plateau pressure, and FAP is the final arterial pressure during atrial balloon inflation. K is the ratio of the arterial-to-venous compliance. According to the previous report (8), a K value of 1/60 was used in this study. This has been shown to produce values of P_{mcf} nearly identical to those obtained through complete equalization of FAP and VPP by pumping blood from the arterial to the venous side of the circulation (8).

The R_t and R_v were calculated using the following equations:

$$R_t = (P_{\text{sa}} - P_{\text{cv}}) / CO \quad (3)$$

$$R_v = (P_{\text{mcf}} - P_{\text{cv}}) / CO \quad (4)$$

In addition, the portal venous plateau pressure during right atrial balloon inflation was also measured.

Preparation of hemorrhagic shock

Hemorrhagic shock was induced by withdrawing blood through the right femoral artery catheter with a heparin prerinse syringe at an appropriate speed to reduce P_{sa} in a manner similar to the anaphylactic shock. The proper volume of blood was reperfused if necessary.

Protocol of the experiment

The sensitized rats were assigned to the anaphylactic shock group ($n = 6$). The nonsensitized rats were randomly divided into the intact control group ($n = 6$) and the hemorrhagic shock group ($n = 6$). The P_{sa}, P_{cv}, and P_{pv} were continuously measured with pressure transducers (TP-400T; Nihon-Kohden, Tokyo, Japan), and the reference level was set at the level of right atrium. Heart rate (HR) was measured by triggering the R wave of electrocardiogram. The blood temperature was measured continuously with the Vigilance system (Model VGS; Baxter, Deerfield, Ill) via the temperature probe placed in the ascending aorta.

Hemodynamic parameters were observed for at least 20 min after surgery until a stable state was obtained. After the baseline measurements, ovalbumin antigen (0.6 mg, i.v.) was injected in the anaphylactic shock and intact control groups, or bleeding started in the hemorrhagic shock group. Cardiac output and P_{mcf} were measured at the baseline and at 3, 15, and 60 min after injection of antigen or start of bleeding. These hemodynamic variables were continuously displayed on a thermal physiograph (RMP-6008; Nihon-Kohden). Outputs were also digitally recorded at 20 Hz with PowerLab (ADInstruments, Colorado Springs, Colo).

Additional experiments were performed to determine the changes in hematocrit after antigen in the anesthetized sensitized ($n = 5$) and nonsensitized ($n = 5$) rats in which P_{sa}, P_{cv}, and P_{pv} were measured similarly, as described above. Hematocrit was measured at baseline and at 15, 30, 45, and 60 min after antigen injection.

Statistics

All results are expressed as the mean ± SE. Statistical analyses were performed with repeated-measure ANOVA, and a P value less than 0.05 was considered significant. When a significant difference was obtained, post hoc analysis was performed with the Bonferroni posttest correction method. Comparison of individual points among three groups was made by ANOVA, followed by the Bonferroni posttest correction method. In the hematocrit experiment, comparisons between the sensitized and nonsensitized rats were performed by Student t test.

RESULTS

The baseline values of hemodynamic variables

Table 1 shows the baseline values of hemodynamic variables in all 3 groups in which CO and P_{mcf} were measured. There was no significant difference in any variable among three groups.

Hemodynamic variables during the anaphylactic shock

Figure 1A shows a representative example of the response to an intravenous injection of the ovalbumin antigen (0.6 mg) in a sensitized rat of the anaphylactic shock group. The time-course changes in P_{sa}, P_{cv}, and P_{pv} of the control, anaphylactic, and hemorrhagic shock groups are summarized in Figure 2; those of CO, P_{mcf}, and HR are summarized in Figure 3. After an antigen injection in the sensitized rats, P_{sa} rapidly decreased from the baseline of 119 ± 4 to 60 ± 5 mmHg at 1 min and then continued to decrease to the bottom of 43 ± 2 mmHg at 8 min, followed by a gradual recovery to 86 ± 3

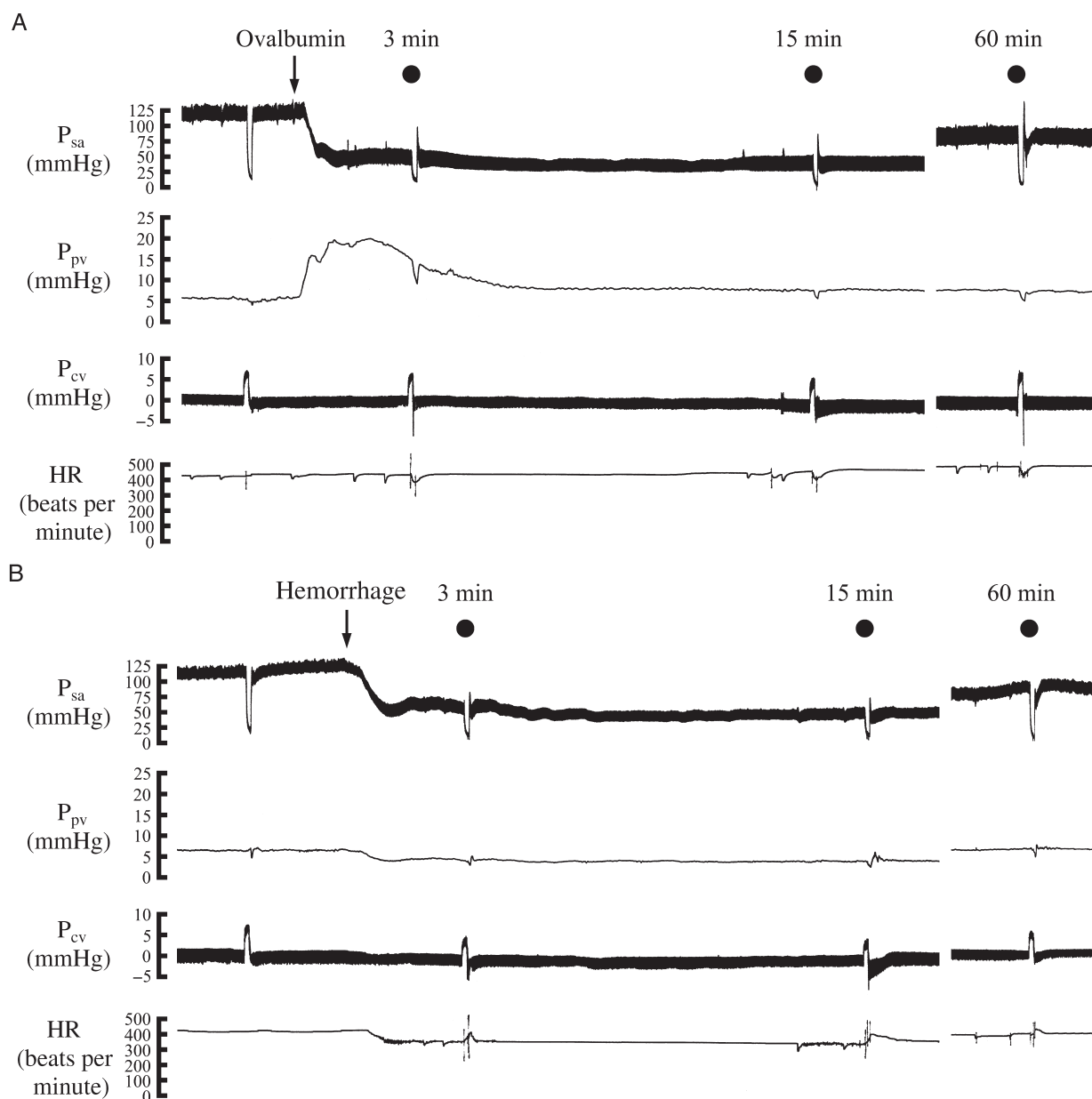


FIG. 1. Representative recordings of the hemodynamic responses of a sensitized rat to an intravenous injection of the ovalbumin antigen (0.6 mg) (A) and a rat suffering from hemorrhagic shock (B).

mmHg at the end of experiment (60 min), as shown in Figure 2. Systemic hypotension was accompanied by decreases in CO, P_{mcf} , and P_{cv} . Cardiac output significantly decreased from the baseline of 84.5 ± 5.7 to the bottom of 37.8 ± 2.1 mL min^{-1} at 15 min and then gradually recovered, but did not completely return to the baseline level at 60 min. Mean circulatory filling pressure slightly decreased from the baseline of 6.0 ± 0.2 to the bottom of 5.2 ± 0.3 mmHg at 15 min (Fig. 3), and P_{cv} also decreased from the baseline of 0.9 ± 0.1 to the bottom of 0.1 ± 0.1 mmHg at 10 min after antigen. Both P_{mcf} and P_{cv} recovered to the baseline level at the end of experiment. Simultaneously, P_{pv} increased to the peak of 21.5 ± 0.9 mmHg at 2 min after antigen from the baseline of 5.6 ± 0.5 mmHg and then recovered to 8.9 ± 0.5 mmHg at 10 min (Fig. 2). Heart rate did not change significantly after antigen injection.

Figure 4 shows the time-course data of R_t and R_v in the three groups studied. After antigen administration, R_t in the sensitized rats tended to decrease, but not significantly. However, R_v significantly increased, reaching 0.11 ± 0.01 (183% of the baseline) and 0.15 ± 0.02 (250% of the baseline) mmHg $\cdot \text{mL}^{-1} \text{min}^{-1}$ at 3 and 15 min, respectively, from the baseline of 0.06 ± 0.01 mmHg $\cdot \text{mL}^{-1} \text{min}^{-1}$, and then returned to 0.10 ± 0.01 mmHg $\cdot \text{mL}^{-1} \text{min}^{-1}$ at the end of the experiment.

Hemodynamic variables during hemorrhagic shock

Figure 1B shows a representative recording of the response of a rat suffering from hemorrhagic shock in which blood was withdrawn so that P_{sa} was decreased in the same manner as the anaphylactic hypotension. As compared with the anaphylactic shock group, P_{cv} and CO also similarly

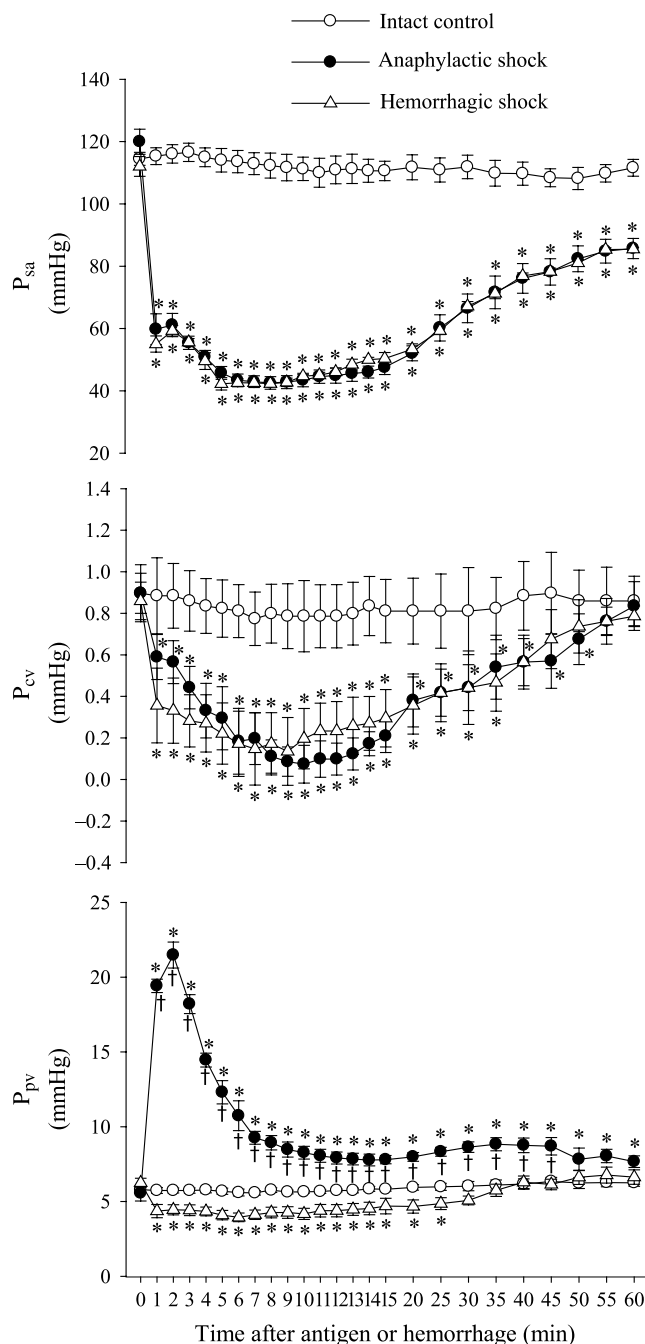


FIG. 2. Time-course changes in P_{sa} , P_{pv} , and P_{cv} of the intact control, anaphylactic shock, and hemorrhagic shock groups. Values are given as mean $\pm$ SE; $n = 6$. * $P < 0.05$ vs. baseline. †Significant different between the hemorrhagic shock group and the anaphylactic shock group.

decreased, as shown in Figures 2 and 3. However, the hemorrhagic shock group decreased more profoundly than the anaphylactic shock group: it decreased from the baseline of 6.3 ± 0.3 to 4.3 ± 0.4 and 4.0 ± 0.2 mmHg at 3 and 15 min, respectively. In contrast to the anaphylactic shock group, both P_{pv} and HR decreased: P_{pv} significantly decreased from the baseline of 6.3 ± 0.3 to 4.0 ± 0.3 mmHg at 6 min and then gradually recovered to the baseline level. Heart rate significantly decreased from the baseline of 418 ± 12 to 353 ± 9 and 338 ± 14 beats per minute at 3 and 15 min, respectively.

As shown in Figure 4, similar to the anaphylactic shock group, R_t did not significantly change in the hemorrhagic shock group. However, there was a significant difference in R_v after systemic hypotension between the two groups. In contrast to the anaphylactic shock group, R_v did not significantly increase in the hemorrhagic shock group.

Figure 5 shows venous return curves for the anaphylactic hypotension, hemorrhagic hypotension, and control groups. During anaphylactic hypotension, the slope of the venous return curves substantially decreased after antigen, whereas the decrease in P_{mcf} was small but significant. The slope of the venous return curves inversely correlated with the R_v . This

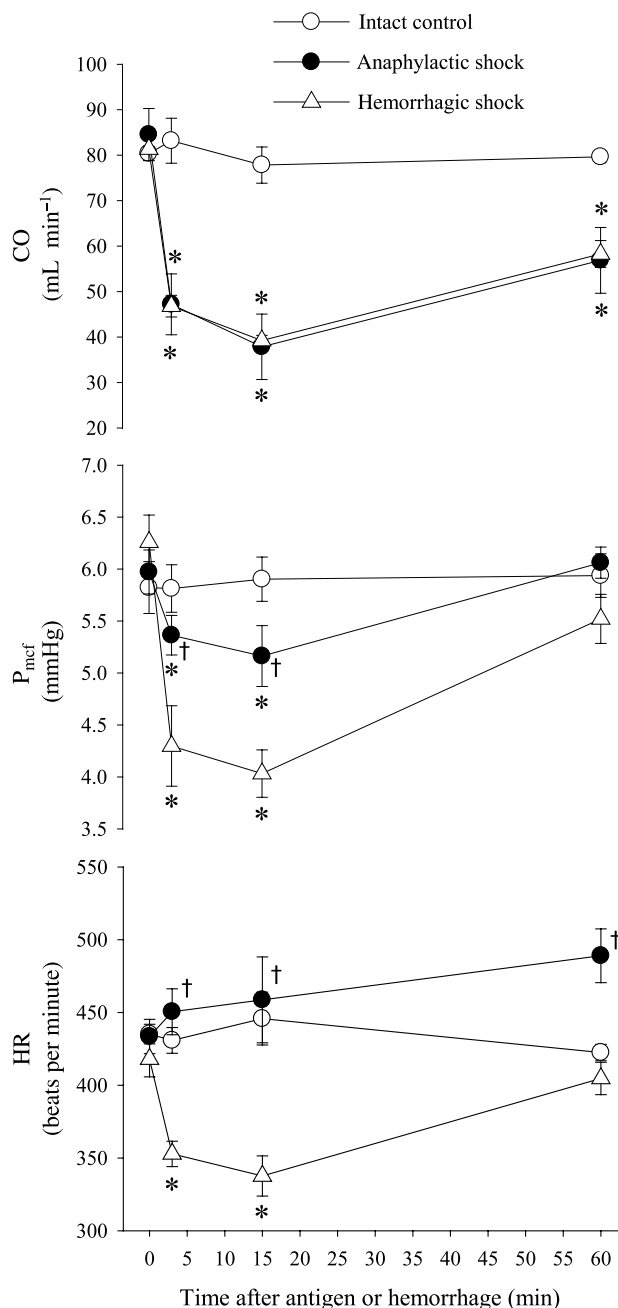


FIG. 3. Summary data of P_{mcf} , CO, and HR in the three groups. Values are given as mean $\pm$ SE; $n = 6$. * $P < 0.05$ vs. baseline. †Significant different between the hemorrhagic and the anaphylactic shock groups.

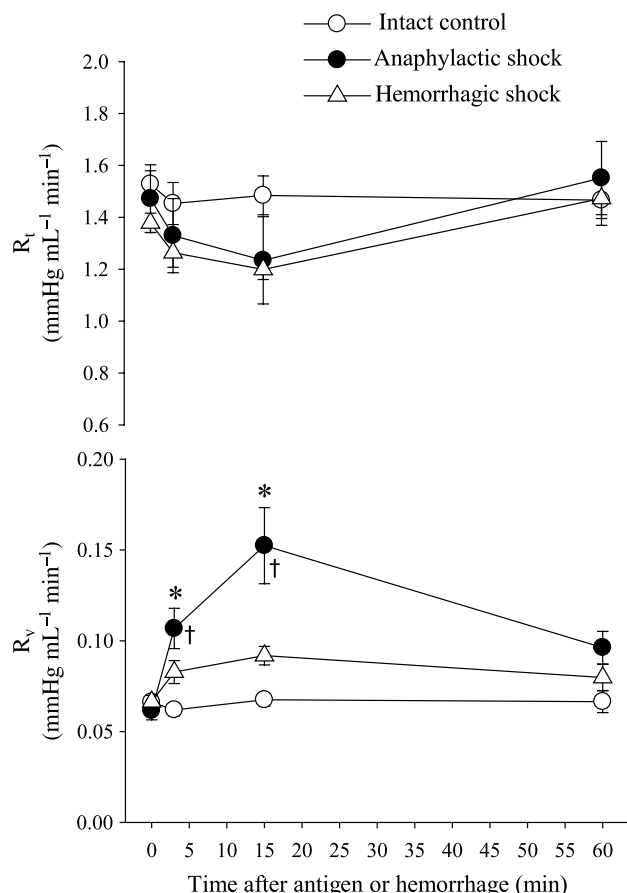


FIG. 4. Time-course data of R_t and R_v in the intact control, anaphylactic shock, and hemorrhagic shock groups. Values are given as mean $\pm$ SE; $n = 6$. * $P < 0.05$ vs. baseline. †Significant different between the hemorrhagic and the anaphylactic shock groups.

finding is consistent with an antigen-induced increase in R_v . In contrast to anaphylaxis, hemorrhagic hypotension produced a shift to the left of the venous return curves along the P_{cv} axis. A considerable decrease in P_{mcf} without a change in the slope of the relationship (R_v) indicates that hemorrhage decrease is an effective distending pressure of the venous system without changes in R_v . In the control group, an antigen injection had no effect on the venous return curves.

Hematocrit during hemorrhagic shock

Figure 6 shows the hematocrit values along with P_{pv} , P_{cv} , and P_{sa} in the sensitized and nonsensitized animals. The

hemodynamic response to antigen was similar to that as shown above, indicating that rat anaphylactic shock model was reproducible. The hematocrit increased markedly from a baseline value of $43\% \pm 1\%$ to $55\% \pm 1\%$ at 15 min after antigen in the sensitized rats. Then, hematocrit slightly decreased but remained at high levels at the end of the experiment. In the nonsensitized rats, an injection of antigen did not change hematocrit.

DISCUSSION

In this study, the antigen-induced decrease in P_{sa} was accompanied by the increases in R_v and P_{pv} and the decreases in P_{mcf} and CO during anaphylactic hypotension. The increased R_v (the resistance to venous return) and the decreased P_{mcf} (the driving pressure for venous return) can reduce the venous return, resulting in a decrease in CO. The markedly increased P_{pv} induced by anaphylactic hepatic venoconstriction obviously contributes to the increase in resistance to venous return and, therefore, to the anaphylactic hypotension (4). In contrast to the anaphylactic hypotension, there was a profound decrease in P_{mcf} and absence of increases in R_v and P_{pv} in the acute hemorrhagic shock, although similar time-course changes were observed in P_{sa} , P_{cv} , and CO. These results indicated that there are different cardiovascular regulatory mechanisms between these two circulatory shocks, and that the increase in R_v due to hepatic venoconstriction is the hemodynamic characteristics of rat anaphylactic hypotension.

Wagner et al. (3) reported that antigen caused a 58% decrease in arterial pressure, a 53% decrease in CO, a 47% increase in resistance to venous return, and a decrease in P_{mcf} from 7.0 ± 0.6 to 4.4 ± 0.4 mmHg, but no change in R_t in anesthetized dogs with anaphylactic hypotension. These findings are similar to those of the present study on rats with anaphylactic hypotension. However, there was no report on changes in the R_v in human anaphylactic shock. Moreover, the limited reports on changes in R_t of human anaphylactic shock were discordant or even contradictory (10, 11). This may be ascribed to the different severity of anaphylactic shock and the different primary disease because these reports often came from the patients being monitored in an intensive care unit for other severe diseases.

In anaphylactic shock, the increased R_v can result from the constriction of the systemic veins that might be induced by the released mediators. However, the exact vascular sites

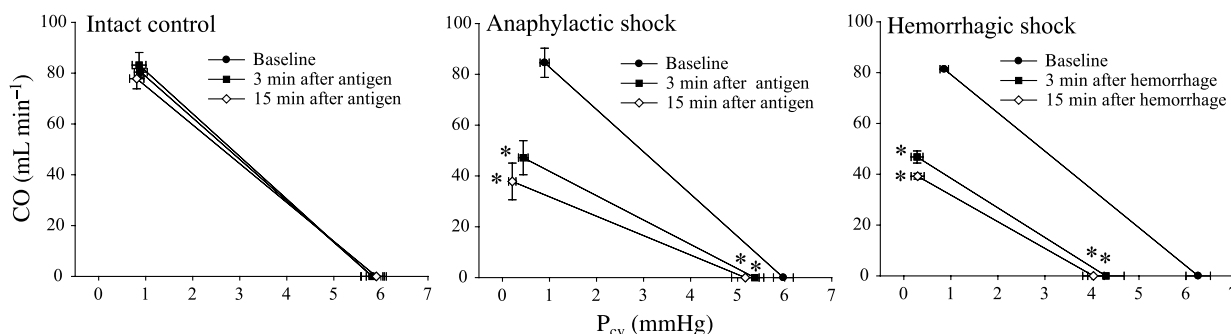


FIG. 5. Venous return curves in the intact control, anaphylactic shock and hemorrhagic shock groups. Solid circles, the baseline values; solid squares, the values at 3 min after antigen or bleeding; open diamonds, the values at 15 min after antigen or bleeding. Values are given as mean $\pm$ SE; $n = 6$. * $P < 0.05$ vs. baseline.

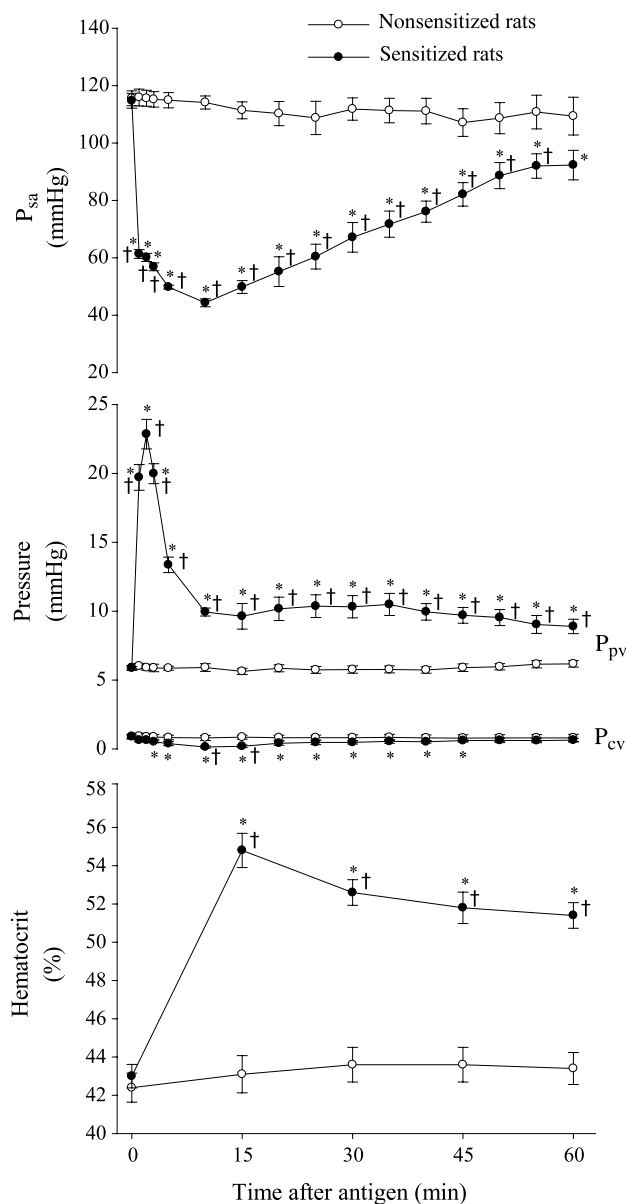


FIG. 6. Time-course changes in P_{sa} , P_{pv} , P_{cv} and hematocrit in the sensitized and nonsensitized rats. Values are given as mean $\pm$ SE; $n = 5$. * $P < 0.05$ vs. baseline. †Significantly different from the nonsensitized group.

responsible for the increased R_v associated with anaphylactic hypotension in the present study are not known. We think that constriction of the hepatic vasculature, as evidenced by an increase in P_{pv} , contributed to the increased R_v . Our previous studies of isolated perfused rat livers demonstrated that hepatic vascular constriction was induced by anaphylaxis (4). The hepatic vasculature is obviously included in the venous system, and the hepatic vascular resistance contributes to the R_v . We also recently demonstrated that the elimination of the splanchnic vascular beds, by the occlusions of the celiac and mesenteric arteries combined with total hepatectomy, attenuated rat anaphylactic hypotension (4). This study indicated that the hepatic venoconstriction plays a crucial role in the pathogenesis of circulatory collapse observed during rat anaphylaxis. The observed increased resistance to venous return, which is partly due to a large increase in hepatic R_v , may account for the rat anaphylactic hypotension.

In the present study, hematocrit increased considerably but transiently only at the early phase of anaphylactic hypotension, and it returned toward the baseline level 30 min after antigen. This increased hematocrit apparently indicated the plasma loss from the circulation. We think that the plasma extravasation might occur, at least in part, in the splanchnic vascular beds in the following process: The antigen-induced portal hypertension, as observed in the present study, may increase not only intravascular volume (blood pooling) of the upstream splanchnic vascular beds but also their capillary pressure, which can increase transcapillary fluid filtration. In addition, an anaphylaxis-induced increase in vascular permeability (12, 13) certainly augmented this filtration. Taken together, exaggerated fluid filtration from the splanchnic vasculature into the interstitium might result in hemoconcentration, although the permeability of other vascular beds might be increased (13, 14), and then it can also contribute to hemoconcentration.

As compared with the anaphylactic shock, the similar decrease in P_{sa} , P_{cv} , and CO was accompanied by more marked decrease in P_{mcf} in the hemorrhagic shock. Another substantial difference in hemodynamics between these two types of circulatory shock of rats was that the R_v did not significantly change in the hemorrhagic shock while markedly increased in the anaphylactic shock (Figs. 4 and 5). The absence of R_v increase in the hemorrhagic hypotension is consistent with the decrease in P_{pv} , which was passively caused by the circulatory blood volume reduction. In contrast, the increase in P_{pv} during anaphylactic shock was actively caused by chemical mediator-induced hepatic venoconstriction. The hepatic vascular response is substantially involved in the pathogenesis of systemic hypotension during anaphylactic shock (4), but not during hemorrhagic shock, in rats.

The present study showed that HR significantly decreased during hemorrhagic shock. This finding seems unexpected because the baroreceptor reflex could have elicited sympathoexcitation and tachycardia when P_{sa} decreased in response to hemorrhage. Actually, the response of HR to hemorrhage may depend on the volume and speed of blood loss. A progressive blood loss usually produces a biphasic cardiovascular response, an initial transiently compensatory phase of sympathoexcitation with tachycardia, followed by a decompensatory phase with hypotension and bradycardia (15–18). In the present study, the bleeding was very quick, leading to a decrease in P_{sa} to 42 ± 2 mmHg from the baseline of 113 ± 3 mmHg within 5 min, to reduce P_{sa} to the same magnitude as the anaphylactic shock. Although the bleeding speed of the other studies reported was much slow, usually 0.3 to 0.5 mL min^{-1} or decreasing P_{sa} to approximately 40 mmHg during 10 to 20 min (15–17). This difference in the protocol might account for the absence of tachycardia in the present study and also for the different results on R_t , which did not change in the hemorrhagic rats of the present study but increased in other studies (19–20). With respect to the mechanism for bradycardia during hemorrhagic shock, the investigations (21–24) demonstrated that the mechanical squeezing of “vigorous contraction of the heart around an empty chamber” when cardiac filling became critically low might stimulate the

increase of cardiac (ventricular) vagal C-fiber activity, resulting in activation of cardiac vagal efferents and bradycardia. In addition, central opioid and serotonin pathways seem to be involved in the second-phase sympathoinhibitory response of hemorrhagic shock (25–27) and peripheral and spinal cord opioid receptors (28, 29).

The present study has some limitations. First, the estimation of CO using the thermodilution method might be influenced by many factors. For example, indicator amount, temperature, and intrinsic CO affect thermodilution CO accuracy and reproducibility. Renner et al. (30) found that at low CO levels, reduced indicator impairs accuracy, which is perhaps related to indicator loss, whereas at high CO rates, reduced indicator impairs reproducibility, which is probably related to low signal-to-noise ratio. In addition, the undetected heat exchange during the passage through the pulmonary vasculature may induce overestimation of CO (31), but it has been reported that the heat exchange in the lungs is negligible (32–34). Second, P_{mcf} was measured by right atrial balloon inflation in the present study. The potential disadvantage is that the heart continues to beat, so some blood is displaced to the periphery from the pulmonary bed and beating heart during right atrial balloon inflation, which might cause the error in P_{mcf} measurement. However, Samar and Coleman (35) and Yamamoto et al. (8) reported no significant difference between P_{mcf} measured for beating heart and that during cardiac arrest. In addition, there can be some interference from the catheter and balloon in the atrium, but Yamamoto et al. (8) demonstrated no significant changes in P_{sa} , P_{cv} , HR, or CO after placing the balloon in anesthetized rats. Third, anesthetic agents have substantial effects on the results of the present study. The first effect of the pentobarbital anesthesia is related to the HR response to the antigen: HR at baseline (approximately 400 beats per minute) was high as compared with the unanesthetized rats (approximately 350 beats per minute) (36). One of the reasons for high HR in anesthetized rat can be ascribed to the vagolytic property of pentobarbital sodium (37) used in the present study: pentobarbital decreased cardioinhibitory parasympathetic activity that dominates the control of HR (37). In the present study, when P_{sa} decreased after the antigen, HR did not significantly increase. Although the absence of tachycardia in the initial phase of the anaphylactic hypotension of the pentobarbital-anesthetized SD rat was consistent with the other study (38), this finding contrasts with the tachycardia response to the antigen of the unanesthetized SD rats sensitized with ovalbumin in the same manner as our study (unpublished observation). Furthermore, as compared with the anesthetized anaphylactic rat, the sensitized unanesthetized rat recovered quickly from the anaphylactic hypotension (unpublished data) presumably due to the absence of anesthesia-related sympathoinhibition. Finally, the ligation of one carotid artery means that one baroreflex region was unloaded. However, all of our experiments were performed under the same background conditions so that a valid comparison can be made between the groups.

In summary, as compared with the hemorrhagic shock to exhibit the similar time-course changes in P_{sa} and CO, the increase in R_v was much greater in the anaphylactic shock,

which may be ascribed to the conspicuous increase in P_{pv} induced by anaphylactic hepatic vasoconstriction. The antigen-induced increase in R_v , along with the decrease in P_{mcf} , decreases the venous return, resulting in anaphylactic hypotension of anesthetized rats.

REFERENCES

1. Brown AFT: Anaphylactic shock: mechanism and treatment. *J Accid Emerg Med* 12:89–100, 1995.
2. Brown SG: Cardiovascular aspects of anaphylaxis: implications for treatment and diagnosis. *Curr Opin Allergy Clin Immunol* 5:359–364, 2005.
3. Wagner EM, Mitzner WA, Bleecker ER: Peripheral circulatory alterations in canine anaphylactic shock. *Am J Physiol Heart Circ Physiol* 251:H934–H940, 1986.
4. Shibamoto T, Cui S, Ruan Z, Liu W, Takano H, Kurata Y: Hepatic venoconstriction is involved in anaphylactic hypotension in rats. *Am J Physiol Heart Circ Physiol* 289:H1436–H1441, 2005.
5. Rothe CF: Mean circulatory filling pressure: its meaning and measurement. *J Appl Physiol* 74:499–509, 1993.
6. Cabrales P, Acero C, Intaglietta M, Tsai AG: Measurement of the cardiac output in small animals by thermodilution. *Microvasc Res* 66:77–82, 2003.
7. Loer SA, Wietasch JK, Scheeren TW: Does bronchial thermodilution allow estimation of cardiac output? *Intensive Care Med* 25:211–215, 1999.
8. Yamamoto J, Trippodo NC, Ishise S, Frohlich ED: Total vascular pressure-volume relationship in the conscious rat. *Am J Physiol* 238:H823–H828, 1980.
9. Pang CCY: Measurement of body venous tone. *J Pharmacol Methods* 44:341–361, 2000.
10. Tani H, Horibe M, Tanaka H, Arai K, Tsuchiya T: Clinical observation of hemodynamic changes during anaphylactic reaction. *Masui* 40:1856–1862, 1991.
11. Liu PY, Lee CH, Lin LJ, Chen JH: Refractory anaphylactic shock associated with ketoconazole treatment. *Ann Pharmacother* 39:547–550, 2005.
12. Withers GD, Kubes P, Ibbotson G, Scott RB: Anaphylaxis-induced mesenteric vascular permeability, granulocyte adhesion, and platelet aggregates in rat. *Am J Physiol* 275:H274–H284, 1998.
13. Leng W, Chang K, Williamson JR, Jakschik BA: Increased regional vascular albumin permeation in the rat during anaphylaxis. *J Immunol* 142:1982–1985, 1989.
14. Jancar S, Sirois MG, Carrier J, Braquet P, Sirois P: PAF induces rat plasma extravasation and releases eicosanoids during anaphylaxis. *Inflammation* 15:347–354, 1991.
15. Miller JH, Grattan DR, Averill RL: Effect of alcohol, neurohypophysectomy, and vasopressin antagonists on hemorrhage-induced bradycardia in the rat. *Proc Soc Exp Biol Med* 202:320–330, 1993.
16. Evans RG, Hayes IP, Ludbrook J: Does the haemodynamic response to acute central hypovolaemia depend on the rate of fall of cardiac output? *Clin Exp Pharmacol Physiol* 19:657–661, 1992.
17. Scrogin KE: 5-HT_{1A} receptor agonist 8-OH-DPAT acts in the hindbrain to reverse the sympatholytic response to severe hemorrhage. *Am J Physiol* 284:R782–R791, 2003.
18. Little RA: 1988 Fitts lecture: heart rate changes after hemorrhage and injury—a reappraisal. *J Trauma* 29:903–906, 1989.
19. Jochem J, Zwirska-Korcza K, Gwozdz B, Walichiewicz P, Josko J: Cardiac and regional haemodynamic effects of endothelin-1 in rats subjected to critical haemorrhagic hypotension. *J Physiol Pharmacol* 54:383–396, 2003.
20. Sharma AC, Singh G, Gulati A: Decompensation characterized by decreased perfusion of the heart and brain during hemorrhagic shock: role of endothelin-1. *J Trauma* 53:531–536, 2002.
21. Ditting T, Hilgers KF, Scrogin KE, Stetter A, Linz P, Veelken R: Mechanosensitive cardiac C-fiber response to changes in left ventricular filling, coronary perfusion pressure, hemorrhage, and volume expansion in rats. *Am J Physiol Heart Circ Physiol* 288:H541–H552, 2005.
22. Skoog P, Mansson J, Thoren P: Changes in renal sympathetic outflow during hypotensive hemorrhage in rats. *Acta Physiol Scand* 125:655–660, 1985.
23. Oberg B, Thoren P: Increased activity in left ventricular receptors during hemorrhage or occlusion of caval veins in the cat. A possible cause of the vaso-vagal reaction. *Acta Physiol Scand* 85:164–173, 1972.
24. Thoren P: Role of cardiac vagal C-fibers in cardiovascular control. *Rev Physiol Biochem Pharmacol* 86:1–94, 1979.
25. Dean C, Bago M: Renal sympathoinhibition mediated by 5-HT_{1A} receptors in the RVLM during severe hemorrhage in rats. *Am J Physiol Regul Integr Comp Physiol* 282:R122–R130, 2002.
26. Pelaez NM, Schreihöfer AM, Guyenet PG: Decompensated hemorrhage activates serotonergic neurons in the subependymal parapyramidal region of the rat medulla. *Am J Physiol Regul Integr Comp Physiol* 283:R688–R697, 2002.

27. Jochem J, Josko J, Gwozdz B: Endogenous opioid peptides system in haemorrhagic shock—central cardiovascular regulation. *Med Sci Monit* 7:545–549, 2001.
28. Ang KK, McRitchie RJ, Minson JB, Llewellyn-Smith IJ, Pilowsky PM, Chalmers JP, Arnold LF: Activation of spinal opioid receptors contributes to hypotension after hemorrhage in conscious rats. *Am J Physiol Heart Circ Physiol* 276:H1552–H1558, 1999.
29. Burke SL, Dorward PK: Influence of endogenous opiates and cardiac afferents on renal nerve activity during haemorrhage in conscious rabbits. *J Physiol* 402:9–27, 1988.
30. Renner LE, Morton MJ, Sakuma GY: Indicator amount, temperature, and intrinsic cardiac output affect thermodilution cardiac output accuracy and reproducibility. *Crit Care Med* 21:586–597, 1993.
31. Hayes BE, Will JA, Zarnstorff WC, Bisgard GE: Limitations of thermodilution cardiac output measurements in the rat. *Am J Physiol* 246:H754–H760, 1984.
32. Arfors KE, Malmberg P, Pavsek K: Conservation of thermal indicator in lung circulation. *Cardiovasc Res* 5:530–534, 1971.
33. Bock J, Deufelhard P, Hoeft A, Korb H, Wolpers HG, Steinmann J, Hellige G: Thermal recovery after passage of the pulmonary circulation assessed by deconvolution. *J Appl Physiol* 64:1210–1216, 1988.
34. Loer SA, Wietasch JK, Scheeren TW: Does bronchial thermodilution allow estimation of cardiac output? *Intensive Care Med* 25:211–215, 1999.
35. Samar RE, Coleman TG: Measurement of mean circulatory filling pressure and vascular capacitance in the rat. *Am J Physiol* 234:H94–H100, 1978.
36. Smith TL, Coleman TG, Stanek KA, Murphy WR: Hemodynamic monitoring for 24 h in unanesthetized rats. *Am J Physiol* 253:H1335–H1341, 1987.
37. Murthy VS, Zagar ME, Vollmer RR, Schmidt DH: Pentobarbital-induced changes in vagal tone and reflex vagal activity in rabbits. *Eur J Pharmacol* 84:41–50, 1982.
38. Potas JR, Briscoe H, Horiuchi J, Killinger S, Dampney RA: Renal sympathetic and cardiac changes associated with anaphylactic hypotension. *Auton Neurosci* 112:25–30, 2004.

