

Hepatic pre-sinusoidal vessels contract in anaphylactic hypotension in rabbits

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Abstract

Aim: The purpose of this study was to determine whether anaphylactic hypotension in rabbits is accompanied by hepatic venoconstriction, and the effects of anaphylaxis on hepatic segmental vascular resistances and liver weight in isolated perfused rabbit livers.

Methods: The rabbits were sensitized by subcutaneous injection of antigen of 2.5 mg ovalbumin with complete Freund's adjuvant three times at 1 week interval. One week after sensitization, anaphylaxis was induced by an injection of 2.5 mg ovalbumin into the jugular vein of pentobarbital anaesthetized rabbits or the perfusate of rabbit livers perfused via the portal vein at a constant flow. Using the double occlusion technique to estimate the hepatic sinusoidal pressure, pre- (R_{pre}) and post-sinusoidal (R_{post}) resistances were calculated for the isolated perfused livers.

Results: An antigen injection into the sensitized rabbits caused not only a decrease in systemic arterial pressure from 79 ± 2 to 40 ± 4 mmHg, but also an increase in portal venous pressure (P_{pv}) from 9.5 ± 2.2 to 24.1 ± 3.9 cmH₂O. Portal hypertension persisted for 8 min after the antigen injection. An injection of antigen into the perfusate caused a marked increase in P_{pv} from 5.4 ± 0.1 to 28.6 ± 2.4 cmH₂O at 6 min, but only a slight increase in double occlusion pressure from 2.2 ± 0.2 to 3.8 ± 0.2 cmH₂O, resulting in a selective increase in R_{pret} rather than R_{post} . Concomitant with the hepatic pre-sinusoidal constriction, liver weight loss occurred.

Conclusion: Anaphylactic hypotension in rabbits is accompanied by hepatic venoconstriction which is characterized by pre-sinusoidal contraction.

Keywords anaphylaxis, hepatic circulation, isolated perfused rabbit liver, portal hypertension.

The incidence of anaphylaxis is estimated between 1 in 10 000 and 1 in 20 000 anaesthesia, and any drug administered in the perioperative period can potentially produce life-threatening anaphylactic shock (Mertes & Laxenaire 2004). Anaphylactic hypotension is primarily caused by alterations in the systemic circulation that decrease blood flow to the heart (Brown 1995). Peripheral circulatory collapse is ascribed to hypovolemia, which results from a decrease in effective circulating blood volume. The latter could be due to

vasodilation with the peripheral pooling and increased vascular permeability with a shift of intravascular fluid to the extravascular space (Brown 1995). However, the exact hemodynamic mechanism for the peripheral pooling during anaphylactic shock is not well known. We have been putting an emphasis on the existence of antigen-induced hepatic venoconstriction and portal hypertension during anaphylactic shock.

Indeed, in canine experimental models of anaphylactic shock, antigen-induced selective constriction of

post-sinusoidal hepatic veins (Yamaguchi *et al.* 1994) play an important role in the pathogenesis of circulatory collapse (Wagner *et al.* 1986); anaphylaxis-induced hepatic venous constriction induces pooling of blood in liver itself, as well as in upstream splanchnic organs, both of which reduce venous return with resultant decrease in stroke volume and systemic arterial pressure. In addition, in rats, antigen-induced hepatic venoconstriction is also involved in anaphylactic hypotension (Shibamoto *et al.* 1999, 2005b). On the basis of these previous findings, we have proposed that antigen-induced hepatic venoconstriction plays an important role in pathogenesis of anaphylactic shock, and possibly serves as a common shock-inducing cause among mammals. However, in rabbits, the role of the liver is not known in anaphylactic hypotension, although right heart overload due to anaphylactic pulmonary hypertension is recognized as a factor causative of hypotension in this species (Cohen *et al.* 1951, Halonen *et al.* 1980). Thus, the first purpose of the present study was to determine whether anaphylactic hypotension is accompanied by hepatic venoconstriction in anaesthetized rabbits. To resolve this question, systemic arterial pressure and portal venous pressure were observed in sensitized rabbits after the antigen was intravenously administered.

Species difference has been found in the hepatic vascular segments that preferentially contract during anaphylaxis: selective post-sinusoidal constriction occurs in sensitized canine livers (Yamaguchi *et al.* 1994), while predominant pre-sinusoidal but significant and substantial post-sinusoidal constriction occurs in guinea pig livers (Ruan *et al.* 2004a). Finally in rats, almost selective pre-sinusoidal constriction was observed (Shibamoto *et al.* 2005b). On the other hand, it is not known whether anaphylactic reaction in rabbits causes constriction of post-sinusoidal hepatic veins, resulting in hepatic congestion. To clarify the anaphylaxis-induced changes in hepatic vascular resistance distribution in rabbits, we herein established anaphylactic models of isolated portally perfused rabbit livers, in which the sinusoidal pressure was measured by the double occlusion method (Yamaguchi *et al.* 1994). Thus, the second purpose of the present study was to determine the effects of anaphylaxis on hepatic vascular resistance distribution and liver weight in isolated perfused rabbit livers.

Methods

Animals

Twenty-six male New Zealand white rabbits (Japan SLC, Shizuoka, Japan) weighing 2.8 ± 0.1 kg were used in this study. Rabbits were maintained at 22 °C

and under pathogen-free conditions on a 12 : 12-h 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

Rabbits were actively sensitized by the subcutaneous injection of an emulsion made by mixing equal volumes of complete Freund's adjuvant (0.5 mL) with 2.5 mg ovalbumin (grade V; Sigma, St Louis, MO, USA) dissolved in physiological saline (0.5 mL) three times at 1 week interval. Non-sensitized rabbits were injected with complete Freund's adjuvant and ovalbumin-free saline. One week after the third injection, the rabbits were used for the following *in vivo* or isolated perfused liver experiments.

In vivo experiment

One week after sensitization, sensitized ($n = 6$) and non-sensitized ($n = 5$) rabbits were anaesthetized with pentobarbital sodium (50 mg kg^{-1} , i.v.) and placed on a thermostatically controlled heating pad (ATC-101B; Unique Medical, Tokyo, Japan). The adequacy of anaesthesia was monitored by the stability of blood pressure and respiration under control conditions and during a pinch of the hindpaw. Supplemental doses of anaesthetic (10% of initial dose) were given if necessary. The right femoral artery and vein were catheterized to measure systemic arterial pressure (P_{sa}), and to inject antigen respectively. The right external jugular vein was catheterized, and the catheter tip was positioned at the confluence of the superior vena cava and the right atrium for measurement of the central venous pressure (P_{cv}). Heart rate (HR) was measured by triggering the R wave of electrocardiogram. Following an abdominal midline incision, the gastroduodenal vein was catheterized, and the catheter tip was positioned in the main portal vein for continuous measurement of the portal venous pressure (P_{pv}). After closure of the abdomen, the baseline measurements were started.

The P_{sa} , P_{cv} and P_{pv} were continuously measured with pressure transducers (TP-400T; Nihon-Kohden, Tokyo, Japan), and these pressures and HR were continuously displayed on a thermal physiograph (RMP-6008; Nihon-Kohden). Outputs were also digitally recorded at 20 Hz (PowerLab, ADInstruments). Haemodynamic parameters were observed for at least 20 min after surgery until a stable state was obtained. After the baseline measurements, 2.5 mg of the ovalbumin antigen was administered via the femoral vein catheter and the changes in variables were observed for 60 min.

Isolated liver experiment

One week after sensitization, the rabbits were anaesthetized with pentobarbital sodium (50 mg kg⁻¹, i.v.) and mechanically ventilated with room air. The basic method for isolated perfused rabbit liver was previously described (Shibamoto *et al.* 1999). Catheters were placed in the right carotid artery. After laparotomy, loose ligatures were placed around the hepatic artery, portal vein, inferior vena cava and common bile duct. At 5 min after heparinization (500 U kg⁻¹ i.v.), the rabbit was rapidly bled through the carotid arterial catheter. The aforementioned vessels and bile duct were ligated, and thoracotomy was performed. Then, the liver was rapidly excised and weighed. The portal vein and vena cava were cannulated with stainless cannulas (5 mm ID), whereas the hepatic artery was ligated to simplify analysis of the intrahepatic vascular circuit. The common bile duct was also cannulated with polyethylene tubing. Perfusion was begun within 5 min after excision of the liver.

The cannulated liver was suspended from an isometric transducer (TB-652T; Nihon-Kohden) and perfused via the portal vein at a constant flow rate with 200 mL of the heparinized autologous blood diluted with 5% bovine albumin (Sigma-Aldrich, St Louis, MO, USA) in Krebs solution (118 mM NaCl, 5.9 mM KCl, 1.2 mM MgSO₄, 2.5 mM CaCl₂, 1.2 mM NaH₂PO₄, 25.5 mM NaHCO₃, and 5.6 mM glucose) at Hct of 8% in a recirculating fashion. The blood was maintained at 37 °C by using a water bath, and the blood in the reservoir was continuously bubbled with 95% O₂–5% CO₂, which could provide perfusate oxygen tension of approx. 290 mmHg (Shibamoto *et al.* 1999, 2005a). A bubble trap was placed in the inflow line. P_{pv} and hepatic venous (P_{hv}) pressures were measured through the corresponding sidearm cannula by using pressure transducers (TP-400T; Nihon-Kohden) referenced to the level of the portal vein at the hepatic hilus. The portal blood flow rate (Q_{pv}) was measured with an electromagnetic flowmeter (MFV 1200; Nihon-Kohden), and the flow probe was positioned in the inflow line. To occlude the portal and hepatic venous lines simultaneously for measurement of the double occlusion pressure (P_{do}), solenoid valves were placed around the perfusion tubes upstream from the P_{pv} sidearm cannula and downstream from the P_{hv} sidearm cannula. Bile was continuously collected in a small tube suspended from the force transducer (45196A; NEC-Sanei, Tokyo, Japan). The weight of the tube was continuously measured, and the bile flow rate was expressed as grams per minute per 10 g liver weight. The P_{pv} , P_{hv} , Q_{pv} , liver weight and bile weight were monitored continuously and displayed through a thermal physiograph (RMP-6008; Nihon-Kohden). Outputs were also digit-

ized by the analogue–digital converter at a sampling rate of 100 Hz. These digitized values were displayed and recorded using a personal computer for later determination of P_{do} .

Hepatic haemodynamic parameters were observed for at least 20 min after the start of perfusion until an isogravimetric state (no weight gain or loss) was obtained by adjusting Q_{pv} and the height of the reservoir at a P_{hv} of 0–1 cmH₂O, and at a Q_{pv} of 27 ± 1 mL min⁻¹ (10 g liver weight)⁻¹. After the baseline measurements, the perfused livers excised from the sensitized rabbits (anaphylaxis group, $n = 9$) and non-sensitized rabbits (control group, $n = 6$) were challenged with ovalbumin 2.5 mg injected into the reservoir.

The hepatic sinusoidal pressure was measured by the double occlusion method (Yamaguchi *et al.* 1994), using the custom-made software (LIVER SOFTWARE, Biomedical Science, Kanazawa, Japan). Both the inflow and outflow lines were simultaneously and instantaneously occluded for 15 s with the solenoid valves, after which P_{pv} and P_{hv} rapidly equilibrated to a similar or identical pressure, which was P_{do} . The principle of the double occlusion method to estimate the sinusoidal pressure is derived from the concept of the mean circulating filling pressure of the systemic circulation (Rothe 1993). In each experimental group, P_{do} was measured at baseline and at 2, 4 and 6 min, and then at 10 min intervals up to 60 min after antigen.

The total portal-hepatic venous (R_t), pre-sinusoidal (R_{pre}) and post-sinusoidal (R_{post}) resistances were calculated as follows:

$$R_t = (P_{pv} - P_{hv})/Q_{pv} \quad (1)$$

$$R_{pre} = (P_{pv} - P_{do})/Q_{pv} \quad (2)$$

$$R_{post} = (P_{do} - P_{hv})/Q_{pv} \quad (3)$$

Statistics

All results are expressed as the means $\pm$ SE. Statistical analyses were performed with repeated measures analysis of variance, and a P -value <0.05 was considered significant. When a significant difference was obtained, *post hoc* analysis was performed with the Bonferroni post-test correction method.

Results

The response of the anaesthetized rabbits to antigen

Figure 1 shows a representative example of the response to an intravenous injection of the ovalbumin antigen in an anaesthetized rabbit sensitized with ovalbumin. Figure 2 shows the summary data of time course changes in P_{pv} , P_{sa} and P_{cv} . After an injection of antigen, P_{pv} initially increased and then P_{sa} and P_{cv}

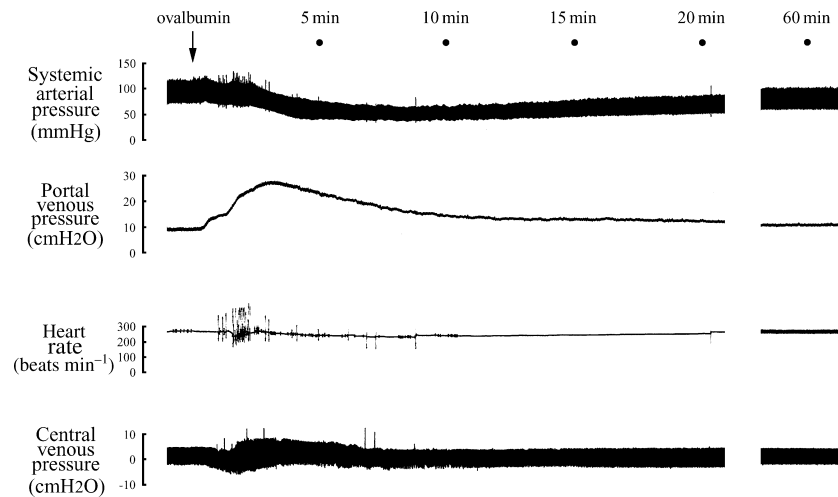


Figure 1 A representative recording of the response to ovalbumin antigen (2.5 mg) in an anesthetized sensitized rabbit.

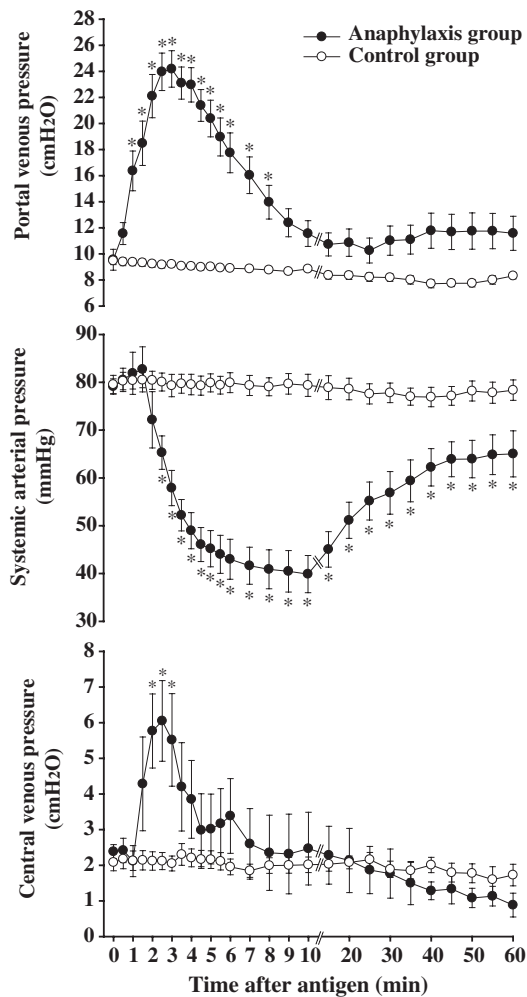


Figure 2 The summary of changes in the systemic arterial pressure, portal venous pressure and central venous pressure after antigen injection. Means $\pm$ SE; * P < 0.05 vs. baseline; closed circles, the anaphylaxis group (n = 6); open circles, the control group (n = 5).

decreased and increased, respectively. Actually, approx. 1 min after an antigen injection, P_{sa} decreased from the baseline of 79 ± 2 mmHg to the nadir of 40 ± 4 mmHg at 10 min, followed by a gradual recovery to 65 ± 5 mmHg at 60 min. In contrast, after the shorter latent period following the antigen, P_{pv} began to increase gradually from the baseline of 9.5 ± 2.2 cmH₂O to the peak of 24.1 ± 3.9 cmH₂O at 3 min after antigen, and then decreased to 12 ± 1 cmH₂O at 10 min. After that, P_{pv} remained at this level, which was not significantly different from the baseline. The post-antigen period of up to 10 min during which P_{pv} remained elevated above the baseline (Fig. 2) was designated as the portal hypertension phase in the present study. It should be noted that P_{sa} persistently decreased during the portal hypertension phase (Fig. 2). After antigen, P_{cv} initially increased from the baseline of 2.4 ± 0.2 to 6.1 ± 1.1 cmH₂O at 2.5 min, and thereafter gradually decreased along with a decrease in P_{sa} . Heart rate did not increase but decreased in the presence of a fall in P_{sa} : heart rate significantly decreased from 278 ± 12 to 243 ± 15 beats min⁻¹ at 8 min after antigen in the anaphylaxis group. Neither of P_{sa} , P_{pv} nor P_{cv} was significantly changed by the antigen in the control animals during the experimental periods (Fig. 2).

The response of the blood-perfused livers to antigen

The excised liver weight measured just before perfusion experiment in the control and anaphylaxis group was 88 ± 4 and 90 ± 3 g respectively. An antigen injection caused hepatic venoconstriction, which was characterized by predominant pre-sinusoidal constriction and liver weight loss, as shown in Figs 3 and 4. Within 1 min after antigen, venoconstriction was evident by an

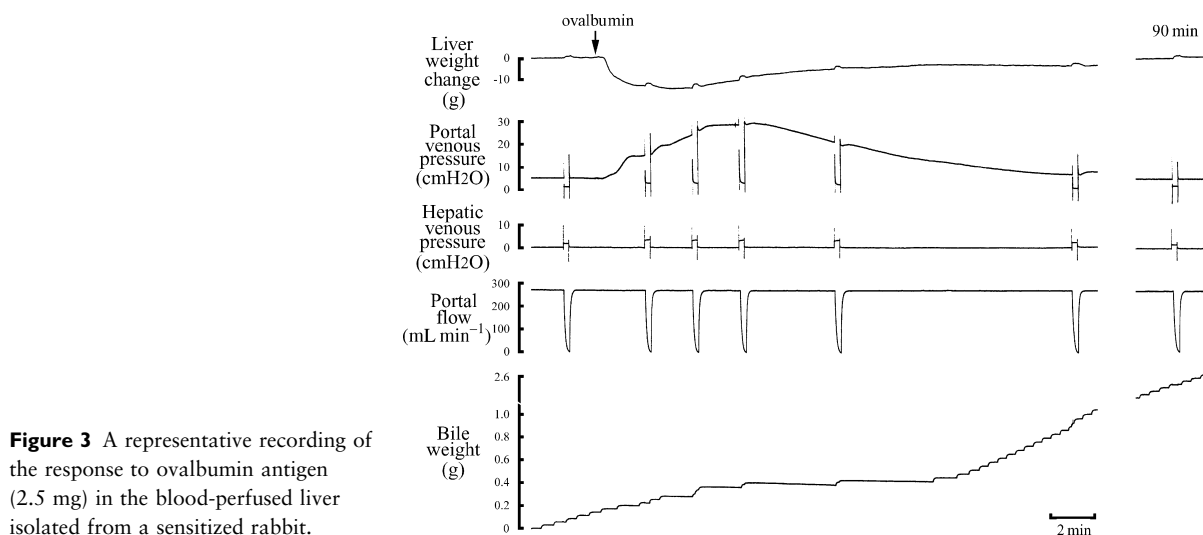


Figure 3 A representative recording of the response to ovalbumin antigen (2.5 mg) in the blood-perfused liver isolated from a sensitized rabbit.

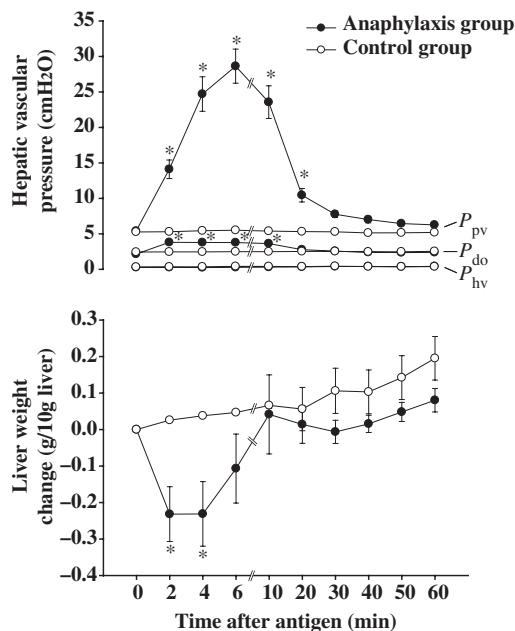


Figure 4 The summary of changes in hepatic vascular pressures and liver weight changes after antigen injection in isolated perfused rabbit livers. Means $\pm$ SE; * $P < 0.05$ vs. baseline and the control group; P_{pv} , portal venous pressure; P_{do} , double occlusion pressure; P_{hv} , hepatic venous pressure; closed circles, the anaphylaxis group ($n = 9$); open circles, the control group ($n = 6$).

increased P_{pv} . P_{pv} gradually increased to the peak value of 28.6 ± 2.4 cmH₂O from the baseline of 5.4 ± 0.1 cmH₂O at 6 min after antigen (Fig. 4). The double occlusion maneuver performed at 6 min after antigen revealed a P_{do} of 3.8 ± 0.2 cmH₂O that was significantly higher than that of the baseline of 2.2 ± 0.2 cmH₂O. Therefore, the P_{pv} -to- P_{do} gradient (in conjunction with the flow), the indicator of R_{pre} (eqn 2), increased markedly from the baseline of

3.3 ± 0.1 to 24.8 ± 2.1 cmH₂O, while the P_{do} -to- P_{hv} gradient, the indicator of R_{post} (eqn 3), increased only slightly, but significantly, from the baseline of 1.9 ± 0.1 to 3.5 ± 0.2 cmH₂O (Fig. 4). Thus, R_{pre} increased by 680% the baseline from 0.12 ± 0.01 to 0.94 ± 0.10 cmH₂O mL min⁻¹ (10 g liver weight), while R_{post} increased by only 85% from 0.07 ± 0.01 to 0.13 ± 0.01 cmH₂O mL min⁻¹ (10 g liver weight) (Fig. 5). This indicates that the antigen almost selectively increased R_{pre} rather than R_{post} , as reflected by a significant increase in R_{pre}/R_t ratio from the baseline of 0.64 ± 0.03 to 0.87 ± 0.01 . P_{pv} , and thus R_t , returned close to the baseline at 20 min after antigen. Concomitant with venoconstriction, the liver weight showed a decrease, reaching the nadir, -0.2 ± 0.1 g (10 g liver weight)⁻¹, at 2 min. Then, the liver weight returned to nearly the baseline at 10 min after antigen. The bile flow decreased to 20% of the baseline level of 3.7 ± 0.5 g min⁻¹ (10 g liver weight)⁻¹ during the maximal venoconstriction, as shown in Fig. 3. In the control rabbit liver, any haemodynamic variables did not change significantly after antigen (Figs 4 and 5).

Discussion

In this study, we examined whether hepatic venoconstriction occurs during rabbit anaphylactic hypotension. There are two major findings of the present study. The first finding (derived from the anaesthetized rabbit experiments) is that P_{pv} markedly increased during anaphylactic hypotension induced by an intravenous injection of the ovalbumin antigen in anaesthetized rabbits. Another finding (derived from the isolated perfused rabbit liver experiments) is that hepatic anaphylactic venoconstriction is characterized by almost selective pre-sinusoidal constriction and liver weight loss.

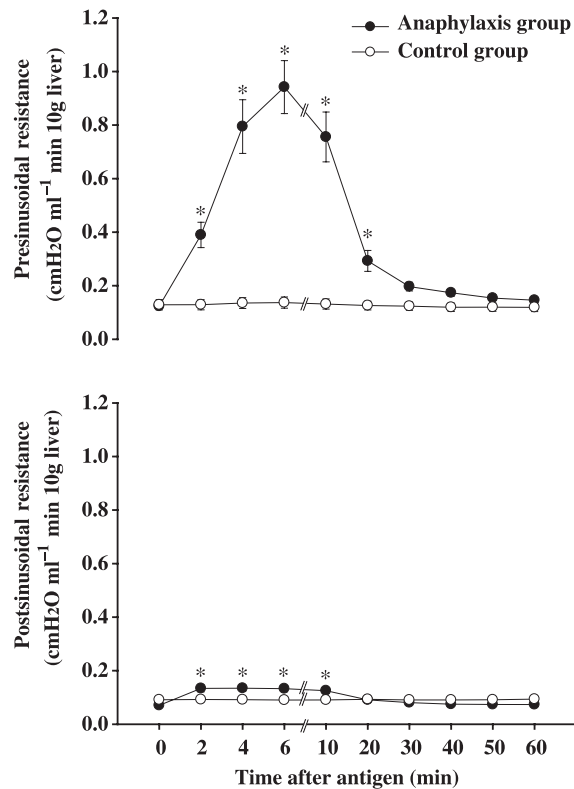


Figure 5 The summary of changes in pre- and post-sinusoidal resistances after antigen injection in isolated perfused rabbit livers. Means $\pm$ SE; * $P < 0.05$ vs. baseline and the control group; closed circles, the anaphylaxis group ($n = 9$); open circles, the control group ($n = 6$).

To the best of our knowledge, this is the first study to demonstrate that anaphylactic hypotension in rabbits is accompanied by substantial hepatic venoconstriction. Indeed, anaphylactic hepatic venoconstriction has been reported in rats (Hines & Fisher 1992, Shibamoto *et al.* 2005b), guinea pigs (Ruan *et al.* 2004a) and dogs (Weil 1917, Yamaguchi *et al.* 1994). With respect to the physiological significance of hepatic venoconstriction in anaphylactic hypotension, we speculate the following pathophysiological process: anaphylactic hepatic venoconstriction results in portal hypertension which then causes congestion of the upstream splanchnic organs, blood pooling, with resultant decrease in venous return and effective circulating blood volume, and finally augmentation of anaphylactic hypotension.

In the present study, P_{cv} increased significantly but slightly by 3.7 cmH₂O, which may be primarily caused by increased right ventricular load probably due to anaphylaxis-induced pulmonary vascular resistance (Cohen *et al.* 1951, Halonen *et al.* 1980). Unlikely, this increase in P_{cv} substantially contributed to the increase in P_{pv} , because this increase in P_{cv} was very small and short-lasting, when compared with that in P_{pv} . We think that the increase in P_{pv} was primarily caused by

hepatic venoconstriction, as demonstrated in the isolated perfused rabbit livers.

Concerning species difference in the hepatic vascular segments that preferentially contract during anaphylaxis: post-sinusoids selectively contract in canine livers (Yamaguchi *et al.* 1994), while predominant pre-sinusoidal but substantial post-sinusoidal constriction occurs in guinea pig livers (Ruan *et al.* 2004a), and finally almost selective pre-sinusoidal constriction occurs in rat livers (Shibamoto *et al.* 2005b). In the present study, by measuring the sinusoidal pressure with the double occlusion method (Yamaguchi *et al.* 1994) in perfused sensitized rabbit livers, we here clearly showed that anaphylactic hepatic venoconstriction in rabbits was characterized by a marked pre-sinusoidal contraction and only a slight post-sinusoidal contraction (Figs 3 and 4), which was different from that in dogs or guinea pigs, but similar to that in rats.

The mechanism for such a species-dependent response is not clear. Canine post-sinusoidal hepatic veins anatomically contain smooth muscle sphincters in hepatic initial sublobular veins (Ekataksin & Kaneda 1999), which may cause selective post-sinusoidal contraction. Maass-Moreno & Rothe (1992) also reported that major pressure gradients must lie upstream from the large (>2 mm) hepatic veins in dogs. Indeed, these post-sinusoidal veins vigorously contract in response to various mediators of anaphylactic reaction, such as histamine (Urayama *et al.* 1996), thromboxane A₂ (Urayama *et al.* 1996), and platelet-activating factor (PAF) (Wang *et al.* 1997). In guinea pig livers, the anaphylactic pre-sinusoidal constriction may be caused mainly by PAF, while the post-sinusoidal constriction is caused by cysteinyl-leukotrienes (Shibamoto *et al.* 2005a). Actually, PAF predominantly contracts pre-sinusoidal vessels in guinea pig livers (Ruan *et al.* 2004b). However, the studies on effects of anaphylaxis-related vasoactive substances are limited on the segmental vascular resistances of rabbit livers. We have previously reported that histamine selectively contracts pre-sinusoids of isolated rabbit livers perfused with blood-free perfusate (Shibamoto *et al.* 1999). This finding is consistent with the present finding of predominant pre-sinusoidal constriction of the antigen challenged liver. However, the vasoconstrictive sites of the anaphylaxis-related chemical mediators other than histamine, were currently unknown. Further study is required to identify the chemical mediators responsible for the anaphylactic hepatic venoconstriction in rabbits and their vasoconstrictive sites.

In contrast to the liver weight gain response to the antigen of dogs (Yamaguchi *et al.* 1994) and guinea pigs (Ruan *et al.* 2004a), a liver weight loss was induced by marked anaphylactic pre-sinusoidal constriction in isolated perfused rabbit livers. With the constant perfusion

of the liver, the mechanism of the weight loss is unknown. This liver weight loss may be due to hepatic vascular blood loss. Likely the blood volume of the sinusoids, which were situated downstream to the selectively constricted pre-sinusoids, might be reduced. On the other hand, we believe that this possible reduction of intrahepatic blood volume as reflected by liver weight loss in isolated anaphylactic livers occurs similarly in anaesthetized animals. The hepatic vascular blood loss could serve as autotransfusion which might counteract the decrease in circulating blood volume and systemic hypotension in rats. Although the anaphylactic liver itself might have expelled the intrahepatic reserve blood to the systemic circulation and then contributed to supplementation of circulating blood volume, anaphylactic hypotension had occurred. This suggests that the blood mobilized from the liver is not enough to compensate fully the blood pressure fall induced by systemic anaphylaxis. Actually, in the present study, the maximum liver weight loss, which may serve as autotransfusion, was $-0.2 \text{ g (10 g liver)}^{-1}$. With an active increase in the tension developed by the smooth muscle in the hepatic vessel walls, up to 50% of the hepatic blood volume can be mobilized (Greenway & Lutt 1989). Since the liver blood volume is $350 \text{ mL kg liver}^{-1}$, a 50% of liver blood volume is thus equivalent to a $1.75 \text{ mL (10 g liver)}^{-1}$ (Rothe & Maass-Moreno 1998). The liver volume loss of $0.2 \text{ mL (10 g liver)}^{-1}$ estimated from the liver weight loss in the present study is only 11% of the maximal mobilized blood volume. We suppose that this small volume of autotransfusion might not effectively contribute to compensation of anaphylaxis-induced circulating blood volume loss.

Conclusion

We determined the response of rabbit hepatic circulation to the antigen in anaesthetized rabbits and in isolated perfused rabbit livers. An intravenous injection of antigen (2.5 mg ovalbumin) caused not only a profound decrease in P_{sa} but also an increase in P_{pv} . In addition, in isolated perfused sensitized rabbit livers, hepatic anaphylaxis caused almost selective pre-sinusoidal constriction, and liver weight loss. On the basis of these findings, we conclude that anaphylactic hypotension in rabbit is accompanied by almost selective pre-sinusoidal contraction of the liver, which could induce splanchnic congestion and subsequent decrease in venous return and then contribute to hypotension.

Conflict of interest

The authors declare that there is no conflict of interest.

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