

ANAPHYLACTIC HEPATIC VENOCONSTRICTION IS ATTENUATED BY NITRIC OXIDE RELEASED VIA SHEAR STRESS-DEPENDENT AND -INDEPENDENT MECHANISMS IN GUINEA PIG

Toshishige Shibamoto,* Zonghai Ruan,* Sen Cui,* Yasutaka Kurata,* Tomonobu Koizumi† and Keishi Kubo†

*Department of Physiology, Kanazawa Medical University, Uchinada and †First Department of Medicine, Shinshu University School of Medicine, Matsumoto, Japan

SUMMARY

1. The role of shear stress in nitric oxide (NO)-mediated attenuation of anaphylactic venoconstriction was studied using an isolated ovalbumin-sensitized guinea pig liver.

2. Guinea pigs were actively sensitized by a subcutaneous injection of 1 mg ovalbumin. Two weeks after sensitization, the livers were perfused with diluted blood under constant flow or constant perfusion pressure. The constant flow could result in increased shear stress during constriction, while the constant perfusion pressure could prevent changes in shear stress. Using the double occlusion technique to estimate the hepatic sinusoidal pressure, pre- and postsinusoidal constriction was evaluated. Hepatic anaphylaxis was induced by an injection of ovalbumin (4 µg) into the perfusate, the volume of which was 40 mL.

3. Under either constant flow or pressure, anaphylaxis caused venoconstriction of predominantly presinusoids over postsinusoids, although anaphylactic venoconstriction under constant pressure was significantly greater than that under constant flow. When shear stress was held constant by maintaining constant perfusion pressure, a NO synthase inhibitor, *N*^ω-nitro-L-arginine methyl ester (L-NAME, 100 µmol/L), potentiated similarly both pre- and postsinusoidal constriction induced by anaphylaxis. This suggests that hepatic anaphylaxis shear stress-independently generates NO, resulting in dilatation of both pre- and postsinusoidal vessels in a similar magnitude. In contrast, when shear stress was allowed to rise under constant flow, anaphylactic presinusoidal constriction was preferentially potentiated by L-NAME.

4. Hepatic anaphylaxis can increase NO production in a shear stress-independent manner and dilates similarly both pre- and postsinusoids, while NO produced in a shear stress-dependent manner attenuates predominantly venoconstriction of the presinusoids where shear stress is preferentially increased.

Key words: anaphylaxis, double occlusion pressure, hepatic circulation, nitric oxide, shear stress.

INTRODUCTION

Nitric oxide (NO) is produced by the activation of the NO synthase 3 present in endothelial cells either by hormonal or physical stimuli such as shear stress and then regulates the vascular system.^{1,2} The modulation of peripheral resistance by NO has been shown to be a result of relaxation of the vascular smooth muscle. We have recently shown that hepatic anaphylactic venoconstriction is characterized by predominant presinusoidal constriction over postsinusoidal constriction and that NO attenuates preferentially constriction of these constricted extensively presinusoidal vessels, where increased shear stress could have augmented markedly contracted presinusoidal vessels in isolated guinea pig liver perfused at a constant flow.³ We assume that increased shear stress at the presinusoids with strong constriction may account for the vulnerability of the presinusoids to NO; anaphylaxis causes NO release from endothelium of the same presinusoidal vessel, leading to relaxation of the adjacent presinusoidal vascular smooth muscle cells in a paracrine manner. However, it is expected that anaphylactic reaction per se can release NO from endothelial cells via the shear stress-independent mechanism through humoral substances; most mediators of anaphylaxis, such as histamine,^{4,5} leukotrienes,⁶ thromboxane (Tx) A₂⁵ and platelet-activating factor (PAF),⁷ stimulate NO release from the vascular endothelium.

However, it is not known whether NO could be substantially released via a shear stress-independent mechanism in the liver vasculature exposed to anaphylaxis and could modulate anaphylactic hepatic venoconstriction. If so, it remains unknown which segment of the hepatic vessels is affected by NO released shear stress-independently.

Macedo and Lauth recently showed that if vasoconstriction is induced in a situation where blood flow is allowed to decline and perfusion pressure is not elevated, shear stress does not increase.⁸ In contrast, if flow is held steady, shear stress increases at the site of the constriction and leads to NO release.⁸ Thus, to achieve the above-mentioned objectives, hepatic anaphylaxis was examined with isolated guinea pig livers, that were perfused under constant flow or constant pressure to obtain situations with or without shear

Correspondence: Dr Toshishige Shibamoto, Department of Physiology, Kanazawa Medical University, Uchinada 920-0293, Japan.
Email: shibamo@kanazawa-med.ac.jp

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stress, respectively, in the presence of a NO synthase inhibitor, *N*^ω-nitro-L-arginine methyl ester (L-NAME) or D-NAME, an inactive enantiomer of L-NAME. The hepatic vasoconstrictive site was determined by measuring the sinusoidal pressure using the vascular occlusion methods.^{9,10}

METHODS

Twenty-four male Hartley guinea pigs weighing 346 ± 17 g (SD) were used in the current study. The present experiments were approved by the Animal Research Committee of Kanazawa Medical University. Guinea pigs were actively sensitized by a subcutaneous injection of an emulsion made by mixing equal volumes of complete Freund's adjuvant (0.5 mL) with 1 mg ovalbumin (grade V; Sigma, St. Louis, MO, USA) dissolved in physiological saline (0.5 mL). Two weeks after sensitization, the perfusion experiment was performed.

Isolated liver preparation

The animals were anaesthetized with pentobarbital sodium (35 mg/kg, i.p.) and mechanically ventilated with room air. The basic methods for isolated perfused liver was described elsewhere.^{3,9,10} In brief, a polyethylene tube was placed in the right carotid artery. After laparotomy, the cystic duct and the hepatic artery were ligated and the bile duct was cannulated with a small polyethylene tube. At 5 min after intra-arterial heparinization (500 U/kg), 8–9 mL of blood was withdrawn through the carotid arterial catheter. The intra-abdominal inferior vena cava (IVC) above the renal veins was ligated and the portal vein was cannulated with a stainless cannula (2.1 mm internal diameter, 3.0 mm outer diameter) for portal perfusion. After thoracotomy, for the outflow line, the supradiaphragmatic IVC was cannulated with the same size stainless cannula, then portal perfusion was begun with the heparinized autologous blood that was diluted with 5% bovine albumin (Sigma) in Krebs' solution ((in mmol) NaCl 118; KCl 5.9; MgSO₄ 1.2; CaCl₂ 2.5; NaH₂PO₄ 1.2; NaHCO₃ 25.5; glucose 5.6) at haematocrit of 8%. The liver was rapidly excised, suspended from an isometric transducer (TB-652T, Nihon-Kohden, Tokyo, Japan) and weighed continuously throughout the experimental period.

The liver was perfused recirculatingly at a constant flow rate or a constant pressure via the portal vein. For the constant flow perfusion, the circulating blood was pumped using a variable speed pump (Master-flex; Cole Parmer, Chicago, IL, USA) from the outflow reservoir through a heat exchanger (37°C) and a windkessel chamber to trap air bubbles as well as to buffer pressure fluctuations generated by the pump.³ The flow rate and the height of the outflow reservoir could be adjusted at any desired levels of portal venous pressure (Ppv) and hepatic venous pressure (Phv). For the constant pressure perfusion, the blood was pumped from the outflow reservoir through a heat exchanger (37°C) into the inflow reservoir, from which the blood flows gravimetrically into the portal cannula. An overflow tube was connected to the inflow and outflow reservoirs to maintain a constant portal perfusion pressure. The height of each reservoir could be adjusted independently to maintain Ppv and Phv at any desired level.¹⁰

In livers perfused either under constant flow or under constant pressure, the recirculating blood volume was 40 mL. The perfused blood in the outflow reservoir was oxygenated by bubbling with 95% O₂ and 5% CO₂. Portal venous pressure and Phv were measured using pressure transducers (TP-400T, Nihon-Kohden) attached by a sidearm to the appropriate cannulas with the reference points at the hepatic hilus. To occlude inflow and outflow perfusion lines simultaneously for measurement of the double occlusion pressure (Pdo), two solenoid valves were placed in a position that each sidearm cannula was between the corresponding solenoid valve and the liver. Portal blood flow rate (Q) was measured with an electromagnetic flow meter (MFV 1200, Nihon-Kohden) and the flow probe was positioned in the inflow line. Bile was collected drop by drop in a small tube suspended from the force transducer (SB-1T, Nihon-Kohden). One bile drop yielded 0.027 g and the time between drops was measured for determination of the bile flow rate.³ The hepatic vascular pressures, blood flow rate, liver weight

and bile weight were monitored continuously and displayed through a thermal physiograph (RMP-6008, Nihon-Kohden). Outputs were also digitized 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 Pdo.

Experimental protocols

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. Then, the livers perfused either under constant flow or under constant pressure were further divided into the following two groups of the D-NAME and L-NAME groups, in which L-NAME (100 μmol/L; Sigma) and D-NAME (100 μmol/L; Sigma) was administered into the reservoir, respectively. Thus, any livers studied were pretreated with either L-NAME or D-NAME. Ovalbumin 4 μg was injected into the reservoir at 10 min after injection of L-NAME or D-NAME. This dose of 4 μg ovalbumin was smaller than that of our previous study (0.1 mg ovalbumin).³ The reason for adopting this smaller dose was that ovalbumin more than 4 μg caused strong anaphylactic venoconstriction, resulting in cessation of perfusion flow under constant pressure.

The hepatic sinusoidal pressure was measured by the double occlusion method.^{9,10} Both the inflow and outflow lines were simultaneously and instantaneously occluded for 10 s using the solenoid valves, after which Ppv and Phv rapidly equilibrated to a similar or identical pressure, which was Pdo. Actually, Pdo values were obtained from the digitized data of Ppv and Phv using an original program (LIVER software, Biomedical Science, Kanazawa, Japan). In each group, Pdo was measured at the baseline, just prior to an injection of antigen and 4 and 6 min after antigen and then at a 10 min interval for 60 min. However, all comparisons were made during the peak of the constrictor response.

The total portal-hepatic venous resistance (Rt), presinusoidal resistance (Rpre) and postsinusoidal resistance (Rpost) were calculated as follows:

$$R_t = (P_{pv} - P_{hv})/Q \quad [1]$$

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

$$R_{post} = (P_{do} - P_{hv})/Q \quad [3]$$

Statistics

All results are expressed as the means $\pm$ SD. Analysis of variance followed by Bonferroni's test was used to test for significant differences. Differences were considered as statistically significant at *P*-values less than 0.05.

RESULTS

The effect of L-NAME on basal hepatic circulation

After injection of L-NAME into the blood of constant flow-perfused liver, Ppv increased significantly from 7.4 ± 0.2 to 8.3 ± 0.5 cm H₂O. In constant pressure-perfused livers, L-NAME injection caused a decrease in blood flow from 45 ± 6 to 39 ± 7 mL/min per 10 g liver. However, D-NAME injection did not cause any changes in haemodynamic variables in either constant flow- or constant pressure-perfused liver. These findings indicate that endogenous NO dilates the hepatic vessels in basal states of isolated guinea pig livers perfused at a constant flow or constant pressure and that L-NAME (100 μmol/L) inhibits NO synthase in the present isolated blood-perfused guinea pig livers.

Constant flow perfusion study

Figure 1a shows a representative example of the response to an injection of 4 μg ovalbumin of a D-NAME-pretreated liver perfused at a constant flow. Within 1 min after an injection of

ovalbumin, venoconstriction occurred as evidenced by an increase in Ppv. Portal venous pressure reached peak levels of 14.8 ± 1.7 cm H₂O from the baseline of 7.3 ± 0.4 cm H₂O, as shown in Table 1. The Ppv-to-Phv gradient, the determinant of Rt, increased 2.1 times the baseline, indicating that Rt increased by the same degree, as shown in Fig. 2. The double occlusion manoeuvre performed at 4 min after antigen administration revealed the sinusoidal pressure of Pdo higher than that of the baseline. The Pdo-to-Phv gradient increased from the baseline of 2.9 ± 0.3 to 4.4 ± 0.6 cm H₂O, indicating an increase in Rpost. However, the increase in the Ppv-to-Pdo gradient (3.9 ± 0.4 vs 9.8 ± 1.3 , baseline vs peak) was greater than that in the Pdo-to-Phv gradient, indicating a greater increase in Rpre than Rpost. The liver weight did not show any significant changes after antigen. Concomitant with venoconstriction, bile flow slightly decreased to 74% of the baseline.

The L-NAME pretreatment augmented the antigen-induced increase in Ppv by 7.2 cm H₂O, as compared with the D-NAME group (Table 1). Thus, the peak Rt levels in the L-NAME group was greater by 1.7-fold than that in the D-NAME group. However, L-NAME did not affect postantigen Pdo, as compared with the D-NAME groups. This indicates that L-NAME augmented peak Rpre (0.36 ± 0.12 vs 0.21 ± 0.04 cmH₂O/mL/min per 10 g liver weight; L-NAME vs D-NAME group), but not Rpost (0.09 ± 0.02 vs 0.09 ± 0.02 cmH₂O/mL/min per 10 g liver; L-NAME vs D-NAME group). This is reflected by significant greater values of postantigen Rpre/Rt ratio in the L-NAME group than the D-NAME group, as shown in Fig. 2.

Constant pressure perfusion study

Figure 1b shows a representative example of the response to 4 μ g ovalbumin of the D-NAME-pretreated liver perfused under constant pressure. Under constant pressure perfusion, venoconstriction was detected by a decrease in portal blood flow. Actually, the blood flow decreased from the baseline of 47 ± 6 to the nadir, 18 ± 4 mL/min per 10 g liver weight at 4 min after antigen injection. Although the height of the inflow reservoir was held constant, Ppv increased only slightly in response to antigen. The Phv was decreased as a result of a decrease in blood flow. Thus, the anaphylactic venoconstriction caused an increase in Rt by 3.5-fold at the baseline level after antigen administration, as shown in Fig. 3. The Pdo at 4 min was slightly decreased from the baseline value. Accordingly, the increase in Ppv-to-Pdo gradient was greater than that in the Pdo-to-Phv gradient, indicating a greater increase in Rpre than Rpost, the findings consistent with the result obtained from the constant flow-perfused livers, as described above. Concomitants with a decrease in blood flow, the liver weight decreased by 1.9 ± 0.8 g/10 g. The bile flow was also decreased to 62% of baseline after antigen administration.

Under constant pressure perfusion, L-NAME also augmented anaphylactic venoconstriction, as evidenced by a greater decrease in blood flow in the L-NAME group than that in the D-NAME group (Table 1). The peak Rt levels in the L-NAME group were greater by 1.9-fold than that in the D-NAME, as shown in Fig. 3. However, there are no significant differences in peak levels of Ppv, Pdo, or Phv after antigen between the L-NAME and D-NAME groups.

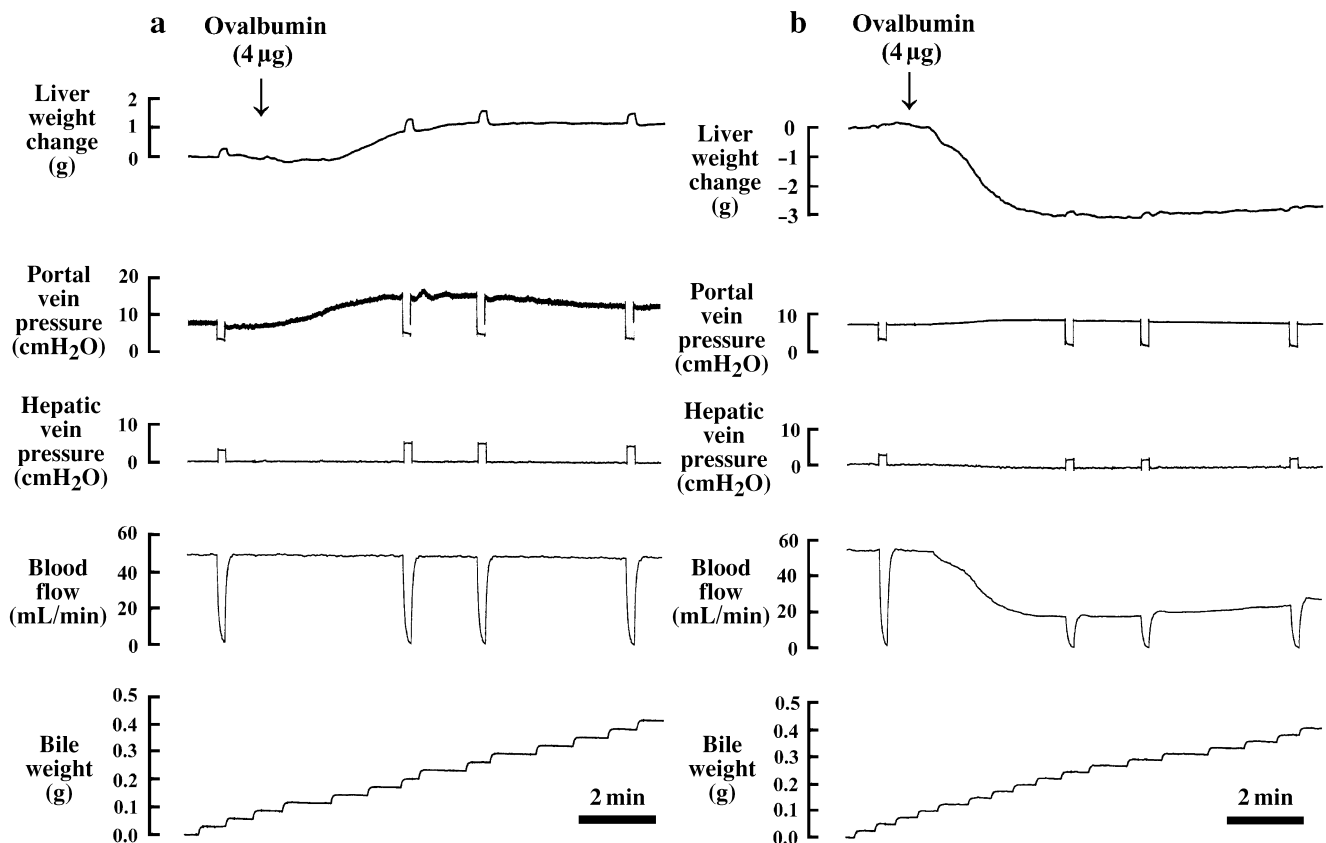


Fig. 1 Representative recordings of the response to the antigen, ovalbumin 4 μ g under a constant flow perfusion (a) and a constant pressure perfusion (b).

Table 1 Baseline and peak values of haemodynamic variables after an injection of antigen in isolated guinea pig livers

Groups	Number of animals	Constant flow				Constant pressure			
		D-NAME (n = 6)		L-NAME (n = 6)		D-NAME (n = 6)		L-NAME (n = 6)	
		Baseline	Peak	Baseline	Peak	Baseline	Peak	Baseline	Peak
Ppv	(cmH ₂ O)	7.3 ± 0.4	14.8 ± 1.7*	8.3 ± 0.5	22.0 ± 6.2**	7.6 ± 0.1	8.9 ± 0.2*	8.2 ± 0.4	9.5 ± 0.4*
Phv	(cmH ₂ O)	0.5 ± 0.2	0.5 ± 0.2	0.4 ± 0.2	0.4 ± 0.2	0.3 ± 0.2	-0.4 ± 0.3*	0.4 ± 0.2	-0.5 ± 0.2*
Pdo	(cmH ₂ O)	3.4 ± 0.2	4.9 ± 0.6*	3.5 ± 0.2	5.0 ± 0.8*	3.2 ± 0.2	2.4 ± 0.1*	3.4 ± 0.3	2.3 ± 0.5*
Blood flow	(ml/min/10 g)	49 ± 5	49 ± 5	47 ± 6	47 ± 6	47 ± 6	18 ± 4*	39 ± 7	11 ± 3**
Bile flow	(g/min)	0.038 ± 0.011	0.028 ± 0.010*	0.037 ± 0.008	0.021 ± 0.008*	0.034 ± 0.006	0.021 ± 0.005*	0.027 ± 0.006	0.013 ± 0.003**

Values are means ± SD. Ppv, portal vein pressure; Phv, hepatic venous pressure; Pdo, double occlusion pressure. **P* < 0.05 versus baseline. ***P* < 0.05 versus the corresponding D-NAME group.

Accordingly, the peak levels in both Rpre and Rpost were significantly and similarly greater in the L-NAME than that in the D-NAME group (1.9- and 1.8-fold). This is reflected by no significant differences in postantigen Rpre/Rt ratio between these two groups. This indicates that L-NAME augmented similarly in magnitude the antigen-induced increase in Rpre and Rpost.

DISCUSSION

The present study shows that NO synthesis inhibition augmented anaphylactic venoconstriction in isolated guinea pig livers perfused either under constant pressure or constant flow. These findings indicate that hepatic anaphylaxis can release NO not only via the shear stress-dependent mechanism (under constant flow perfusion) but also via the shear stress-independent mechanism (under constant pressure perfusion). Furthermore, NO released in the shear stress-independent manner dilates both pre- and post-sinusoidal vessels similarly. In contrast, NO released in the shear stress-dependent manner attenuates predominantly venoconstriction of the presinusoids where shear stress is preferentially increased.

Hepatic venoconstriction that occurs under constant pressure perfusion does not necessarily accompany NO release. Actually, in the *in vivo* cat experiment, L-NAME, an inhibitor of NO synthesis, did not augment noradrenaline-induced hepatic venoconstriction under constant pressure, but it did under constant flow.¹¹ The same findings were also observed in perfused rat livers.¹² Thus, the finding of the present study that L-NAME potentiates anaphylactic

Constant flow

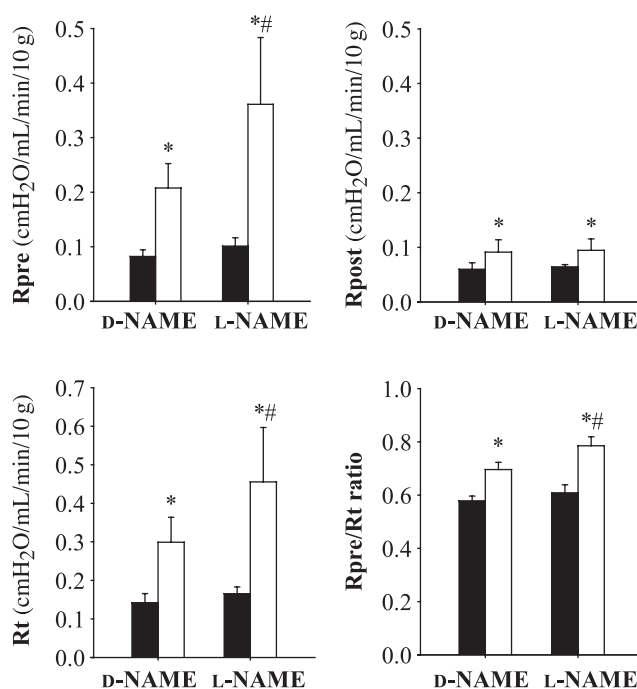


Fig. 2 The baseline (closed columns) and peak levels (open columns) of the pre (Rpre) and postsinusoidal (Rpost) resistances, the total hepatic vascular resistance (Rt) and the Rpre-to-Rt ratio under constant flow perfusion after an injection of the antigen in the D-NAME and L-NAME groups. Values are given as mean ± SD. *n* = 7. **P* < 0.05 versus the baseline. ***P* < 0.05 versus the D-NAME group.

hepatic venoconstriction under constant pressure perfusion is interesting and contrasts with the more physiological venoconstriction induced by noradrenaline, a mediator released tonically from the sympathetic nerve endings.

The methodological basis of the present study to explore the roles of shear stress in the perfused livers was derived from the assumption proposed by Macedo and Lauth.⁸ In isolated perfused vessels, the relationship between the wall shear stress (τ) and blood flow (Q), internal radius (r) and blood viscosity (η) is given as follows: $\tau = (m + 2) \eta Q / (\pi r^3)$.¹³

The value of m depends on the flow condition; with laminar flow, $m = 2$ and with turbulent flow $m > 2$. The value of m in our preparation was assumed to remain constant during the experiments. Under constant flow when Q remains constant, anaphylactic venoconstriction causes a decrease in r , thereby an increase in shear stress. If turbulence did increase at the constricted site, shear stress would further increase. When anaphylactic vasoconstriction was induced under constant pressure perfusion, flow was reduced such that the ratio of flow to the radius of the vessels was maintained constant, as defined by this cubic relationship. Therefore, the wall shear stress should be maintained constant throughout this experiment, if perfusion pressure is held constant.⁸

The mechanism why NO was released during hepatic anaphylaxis in a shear stress-independent fashion, i.e. under constant pressure perfusion, may be ascribed to humoral substances released by anaphylactic reaction per se. We assume that the chemical mediators such as PAF, TxA_2 , histamine, leukotriene and serotonin

might act on the corresponding receptor of the endothelium, resulting in the subsequent activation of endothelial nitric oxide synthase and production of NO. Actually it is reported that most mediators of anaphylaxis, such as histamine,^{4,5} leukotrienes,⁶ TxA_2 ⁵ and PAF,⁷ all stimulate NO release from the vascular endothelium.

One of the most interesting findings of the present study is that the amplitude of the L-NAME-induced potentiation of anaphylactic venoconstriction is similar for presinusoids and postsinusoids. This may suggest that NO was generated from both pre- and postsinusoids. The exact mechanism for this NO release at pre- and postsinusoids is not known. Hepatic interstitial mast cells might release the above-mentioned mediators, which then diffuse along all of the hepatic vessels and bind endothelial receptors, causing endothelial release of NO, which then relaxes the adjacent smooth muscle cells, with resultant relaxation of pre- and postsinusoidal vessels. However, the morphological study revealed that livers from normal guinea pigs contained substantial numbers of alcian blue positive mast cells distributed mainly in the connective tissue of portal tracts.¹⁴ However, although local and systemic anaphylaxis has been presumed to be caused predominantly, if not exclusively, through the activation of mast cells, other cell types, such as macrophages and lymphocytes, also release certain inflammatory mediators upon stimulation with specific antigens.¹⁵⁻¹⁷ In the livers, there are a large number of intravascular resident macrophages, called Kupffer cells. The mediators released intravascularly from these Kupffer cells might have diffused and reacted with endothelium of the pre- and post sinusoids. Further studies are required in this respect.

Under constant flow perfusion, the anaphylactic venoconstriction of the presinusoids was exclusively augmented by a NO synthase inhibitor of L-NAME. This result is consistent with our previous results³ in that L-NAME pretreatment augmented the anaphylaxis-induced increase in Rpre by 120%, while it did increase in Rpost only by 20% in constant flow perfused guinea pig livers challenged with the higher dose of antigen (0.1 mg). These findings suggest that NO might be released during anaphylaxis selectively in presinusoidal vessels of constant flow perfused livers. The mechanism for this selective vulnerability of presinusoids to NO may be considered as follows; as shown in the constant flow D-NAME group, anaphylaxis constricted predominantly presinusoidal vessels, where elevated shear stress increased NO release from the same presinusoidal endothelium, leading to relaxation of the adjacent presinusoidal vascular smooth muscle cells in a paracrine manner.

N^ω-Nitro-L-arginine methyl ester augmented anaphylactic venoconstriction in guinea pig livers perfused either at the constant flow (shear stress elevated) or at the constant pressure (shear stress not elevated). Nitric oxide released in a shear stress-independent manner attenuates hepatic venoconstriction of both pre- and postsinusoids similarly, while NO produced in a shear stress-dependent manner attenuates predominantly venoconstriction of the presinusoids where shear stress is preferentially increased.

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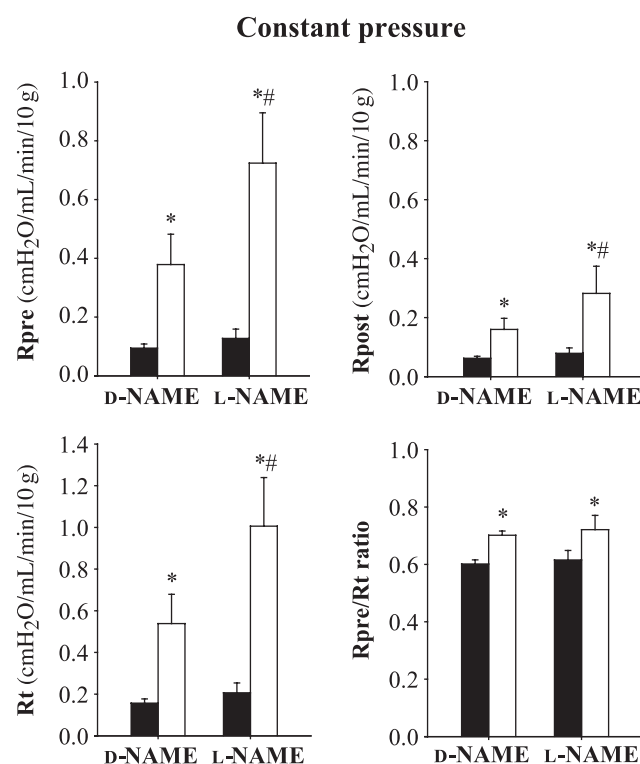


Fig. 3 The baseline (closed columns) and peak levels (open columns) of the pre (Rpre) and postsinusoidal (Rpost) resistances, the total hepatic vascular resistance (Rt) and the Rpre-to-Rt ratio under constant pressure perfusion after an injection of the antigen in the D-NAME and L-NAME groups. Values are given as mean $\pm$ SD. $n = 7$. * $P < 0.05$ versus the baseline. ** $P < 0.05$ versus the D-NAME group.

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REFERENCES

1. Moncada S, Higgs A. The L-arginine-nitric oxide pathway. *N. Engl. J. Med.* 1993; **329**: 2002–12.
2. Rees DD, Palmer RMJ, Moncada S. Role of endothelium-derived nitric oxide in regulation of blood pressure. *Proc. Natl. Acad. Sci. USA* 1989; **86**: 3375–8.
3. Ruan Z, Shibamoto T, Shimo T, Tsuchida H, Koizumi T, Nishio M. NO, but not CO, attenuates anaphylaxis-induced postsinusoidal contraction and congestion in guinea pig liver. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 2004; **286**: R94–100.
4. Lamparter B, Gross SS, Levi R. Nitric oxide and the cardiovascular actions of histamine. *Agents Actions* 1992; (Special conference issue): C187–90.
5. Lantoin F, Iouzaen L, Devynck MA, Millanvove-Van Brussel E, David-Dufilho M. Nitric oxide production in human endothelial cells stimulated by histamine requires Ca^{2+} influx. *Biochem. J.* 1998; **330**: 695–9.
6. Sakuma I, Gross S, Levi R. Peptidoleukotrienes induce an endothelium-dependent relaxation of guinea pig main pulmonary artery and thoracic aorta. *Prostaglandins* 1987; **34**: 685–96.
7. Kamata K, Mori T, Shigenobu K, Kasuya Y. Endothelium-dependent vasodilator effects of platelet activating factor on rat resistance vessels. *Br. J. Pharmacol.* 1989; **98**: 1360–4.
8. Macedo MP, Lauth WW. Shear-induced modulation by nitric oxide of sympathetic nerves in mesenteric artery. *Can. J. Physiol. Pharmacol.* 1996; **74**: 692–700.
9. Shibamoto T, Wang HG, Miyahara T, Tanaka S, Haniu H, Koyama S. Presinusoidal vessels predominantly contract in response to norepinephrine, histamine, and KCl in rabbit liver. *J. Appl. Physiol.* 1999; **87**: 1404–12.
10. Yamaguchi Y, Shibamoto T, Hayashi T, Saeki Y, Tanaka S. Hepatic vascular response to anaphylaxis in isolated canine liver. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 1994; **267**: R268–74.
11. Macedo MP, Lauth WW. Shear-induced modulation of vasoconstriction in the hepatic artery and vein by nitric oxide. *Am. J. Physiol. Gastrointest. Liver Physiol.* 1998; **274**: G253–60.
12. Pastor CM, Hadengue A. Shear stress modulates the vascular tone in perfused livers isolated from normal rats. *Hepatology* 2000; **32**: 786–91.
13. Kamiya A, Togawa T. Adaptive regulation of wall shear stress to flow change in the canine carotid artery. *Am. J. Physiol. Heart Circ. Physiol.* 1980; **239**: H14–21.
14. Hagmann W, Hacker HJ, Buchholz U. Resident mast cells are the main initiators of anaphylactic leukotriene production in the liver. *Hepatology* 1992; **16**: 1477–84.
15. Conrad DH, Campbell KA, Bartlett WC, Squire CM, Dierks SE. Structure and function of the low affinity IgE receptor. *Adv. Exp. Med. Biol.* 1994; **347**: 17–30.
16. Dessaint JP, Capron A. IgE and inflammatory cells: The cellular networks in allergy. *Int. Arch. Allergy Appl. Immunol.* 1989; **90** (Suppl. 1): 28–31.
17. Kikutani H, Yokota A, Uchibayashi N *et al.* Structure and function of Fc epsilon receptor II (Fc epsilon RII/CD23): A point of contact between the effector phase of allergy and B cell differentiation. *Ciba Found. Symp.* 1989; **147**: 23–31.