Original Article

Vasodilating prostaglandin E₁ does not reproduce interleukin-1 β -induced oxygen metabolism abnormalities in rabbits

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Background: We have reported that administration of recombinant human interleukin (IL)-1 β induced circulatory shock in rabbits by causing overproduction of vasodilating prostaglandin(s) and simultaneously impaired oxygen metabolism by causing an abnormal dependence of oxygen consumption (VO₂) on oxygen delivery (DO₂). The present study was carried out to compare the effect of administration of exogenous PGE₁ with that of IL-1 β on oxygen metabolism.

Methods: Sixteen rabbits were assigned to one of three groups and given a single injection of 10 μ g/kg IL-1 β (IL-1 β group, $n = 5$), continuous infusion of 1 μ g/kg/min PGE₁ (PGE₁ group, $n = 6$), or saline (control group, $n = 5$). All rabbits were subjected to stepwise cardiac tamponade to decrease DO₂ by inflating a balloon placed into the pericardial sac. The VO₂/DO₂ relation was analyzed by the dual-line method.

Results: Both IL-1 β and PGE₁ decreased the baseline value of mean arterial pressure by approximately 25% without inducing significant alteration of the cardiac index. With respect to the VO₂/DO₂ relation, the slope of the supply-independent line was significantly increased in the IL-1 β group ($y = 0.13x + 6.4$), but not in the PGE₁ group ($y = 0.01x + 10.0$) compared to that in the control group ($y = 0.05x + 8.7$).

Conclusion: These results indicate that simple vasodilation and hypotension induced by administration of PGE₁ are insufficient to account for the abnormal oxygen metabolism induced by IL-1 β .

Key words: Oxygen consumption, oxygen delivery, sepsis, shock, vascular resistance

INTRODUCTION

SEPSIS IN HUMANS is characterized by abnormal vasomotor regulation and impaired oxygen metabolism.^{1,2} Neurohumoral mediators released during sepsis alter vasomotor tone and peripheral vascular resistance, produce systemic hypotension, and contribute to the development of organ failure.^{3,4} Interleukin (IL)-1 β has been implicated as a key cytokine in sepsis.⁵ We previously reported that administration of IL-1 β to rabbits impaired oxygen metabolism by producing an abnormal dependence of oxygen delivery

(DO₂) on oxygen consumption (VO₂) in the supply-independent range of DO₂.⁶ As DO₂ decreases from the resting value, VO₂ is independent of DO₂ under normal physiologic conditions until a critical value of DO₂ (DO₂crit) is reached, below which VO₂ becomes DO₂-dependent.⁷ Unlike human sepsis, in which the underlying mechanism of hypotension and vascular hyporeactivity to typical vasopressors remains to be elucidated, the mediator of IL-1 β -induced shock in rabbits has been identified as vasodilating prostaglandin(s); treatment with ibuprofen, a cyclooxygenase inhibitor, reversed this shock by restoring systemic vascular resistance and simultaneously normalized the VO₂/DO₂ relation in the supply-independent range of DO₂.^{8,9} We speculated that the abnormal VO₂/DO₂ relation in the IL-1 β -induced rabbit shock model as well as in human septic shock is attributable to systemic vasodilation and hypotension resulting in a regional imbalance between perfusion and the demand for blood flow in tissue and organs. In contrast, there is significant evidence that the vasodilating prostaglandins

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have a therapeutic value both in animal models and in critically ill patients.^{10–12} The present study was designed to analyze the effect of prostaglandin E₁ (PGE₁) on the VO₂/DO₂ relation when PGE₁ was given at a dosage causing consistent systemic vasodilation and hypotension with the IL-1 β -induced circulatory shock.

METHODS

Animals and surgery

THIS STUDY WAS approved by the Animal Care Committee of Osaka University (Osaka, Japan). Sixteen New Zealand White rabbits weighing 2.2–2.6 kg were anesthetized with pentobarbital sodium (25 mg/kg i.v. bolus, followed by constant infusion of 10 mg/kg/h). Normal saline was infused i.v. at a constant rate of 6 mL/kg/h throughout the experiment as a maintenance fluid and anesthetic carrier. Tracheotomy was carried out, and an endotracheal tube was inserted and secured with ligature. A catheter was inserted into the right carotid artery to measure arterial pressure and to sample arterial blood. A Swan-Ganz catheter (model TS094H-3F; Edwards Corp., Irvine, CA, USA) was advanced into the pulmonary artery through the right jugular vein to sample mixed venous blood and to determine cardiac output (Qt). To sample portal venous blood, a catheter was inserted by direct puncture into the portal vein by upper transverse laparotomy and was secured with cyanoacrylate glue. A small pericardiotomy was carried out in preparation for later placement of a balloon catheter. The abdomen was then closed with silk sutures, leaving a small window for approach to the pericardiotomized heart. After surgery, the rabbits were paralyzed with pancuronium bromide (0.2 mg i.v. bolus) and were ventilated mechanically with a Harvard Apparatus non-rebreathing ventilator (Holliston, MA, USA) at a tidal volume of 20 mL (FIO₂ = 50%) at frequencies adjusted to set the baseline arterial PCO₂ at approximately 40 mmHg. The ventilatory frequencies were not changed thereafter. The expiration outlet of the ventilator was connected to a thermal mass flow meter (model 3920E; Kofloc Inc., Tokyo, Japan) to monitor minute ventilation volume (VE). Supplementary doses of pancuronium bromide (0.1 mg) were given periodically during the experiment to prevent alterations in resting VO₂. Animals were maintained at a constant body temperature of 39.0–39.5°C on a heated operating table.

Measurements and calculations

We measured arterial, mixed venous, and portal venous blood gases with a blood gas analyzer (ABL510; Radiometer, Copenhagen, Denmark). Blood hemoglobin-bound oxygen content was measured with a CO-oximeter (IL482; Instru-

mentation Laboratories, Lexington, MA, USA) set for rabbit hemoglobin. Arterial O₂ content was calculated as sum of the product of the temperature-corrected O₂ tension and O₂ solubility in plasma and the hemoglobin-bound oxygen content. Heart rate and mean arterial pressure (MAP) were monitored and recorded simultaneously (models VC640G, RTA1200, AP641G, and AT601G; Nihon Kohden, Tokyo, Japan). Cardiac output was determined by the thermodilution technique (Explorer cardiac output computer; Baxter Healthcare, Deerfield, IL) with three 1-mL injections of room temperature normal saline. Cardiac output was converted to the cardiac index (CI) by dividing Qt by body weight (mL/min/kg). Room temperature was maintained at 24 $\pm$ 0.5°C. Exhaled gases were collected for 3 min in a gas-sampling chamber made of a high-compliance plastic bag (Tedlar; Masuda, Osaka, Japan), and the expired fractions of O₂ (FEO₂) and CO₂ (FECO₂) were measured with a medical gas analyzer (MG360; Minato Medical Science Co., Ltd., Osaka, Japan) immediately after sampling. Oxygen delivery was calculated as the product of arterial O₂ content and CI. Oxygen consumption was calculated as VO₂ (mL/min/kg) = (VE/weight) $\times$ {[(1 – FEO₂ – FECO₂) / (1 – FIO₂)] $\times$ FIO₂ – FEO₂}. The oxygen extraction ratio (O₂ER) was calculated by dividing VO₂ by DO₂.

Experimental protocol

After surgery, the animals were stabilized for 45 min, and a baseline dataset was obtained. The animals were then assigned randomly to either a PGE₁ group ($n = 6$), an IL-1 β group ($n = 5$), or a control group ($n = 5$). After the baseline measurements, the IL-1 β group received a bolus i.v. injection of 10 μ g/kg recombinant human IL-1 β (lot no. AD08; Genzyme/Techne, Cambridge, MA, USA) dissolved in normal saline at a concentration of 10 μ g/mL over 3 min. The PGE₁ group and the control group received an identical amount of saline without IL-1 β . In the PGE₁ group, continuous i.v. infusion of PGE₁ (Prostandin; Ono Pharmaceutical Co. Ltd, Osaka, Japan) dissolved in anesthetic carrier (10 μ g in 60 mL, in each syringe) was initiated simultaneously at 1 μ g/kg/min and was maintained throughout the study. Our preliminary study showed that the hypotensive effect of IL-1 β peaked approximately 15 min after the bolus injection and lasted approximately 2 h and that the continuous infusion of PGE₁ at 1 μ g/kg/min reproduced the hypotensive effect of IL-1 β . The first experimental data were obtained 30 min after the administration of PGE₁, IL-1 β , or saline. A balloon for cardiac tamponade was then inserted through the pericardial window. Cardiac tamponade was induced by inflating the balloon and adjusting the MAP to approximately 90% of that of the first experimental value. The

animals were stabilized for 7 min in the new condition; the mixed expired gases were collected for the next 3 min and analyzed. A second set of experimental data was collected, and the balloon was deflated completely over 5 min to restore the hemodynamic status. The next dataset was collected when MAP was approximately 90% of that of the second experimental value. The stepwise cardiac tamponade series was continued in 15-min cycles until the animals could no longer maintain stable blood pressure. After the experiment was completed, the animals were killed by anesthetic overdose. The position of the Swan-Ganz catheter was confirmed by autopsy and was found to be proper in all cases.

Statistical analysis

All values are expressed as mean $\pm$ SD. Student's paired *t*-test was used to assess within-group differences. The critical value of DO_2 was determined for each animal from a plot of VO_2 against DO_2 by means of the dual-line method of Samsel and Schumacker;¹³ $\text{O}_2\text{ER}_{\text{crit}}$ was O_2ER at $\text{DO}_{2\text{crit}}$. After determination of individual critical point values, each dataset was divided into two subsets with respect to individual $\text{DO}_{2\text{crit}}$ values. Data in each experimental group were pooled. Simple linear regression was carried out for each data pool, and the differences in the slopes and the elevations between the experimental groups and the control group were compared for the supply-independent and supply-dependent lines by analysis of covariance.¹⁴ Data for PO_2 and the veno-arterial PCO_2 gradient, obtained from mixed venous or portal venous blood samples, were grouped into bins five DO_2 units wide and averaged. Mean differences in PO_2 and veno-arterial PCO_2 gradient were tested for significance by ANOVA followed by the Newman–Keuls test. A *P*-value less than 0.05 was considered statistically significant.

RESULTS

Effects of PGE_1 and $\text{IL-1}\beta$ on hemodynamics and oxygen metabolism

DURING THE FIRST 30 min, treatment with $\text{IL-1}\beta$ decreased MAP by approximately 23% without inducing significant alterations in heart rate or CI (Table 1). The $\text{IL-1}\beta$ group developed metabolic acidosis with a significant increase in plasma lactate concentration (Table 2). Continuous infusion of PGE_1 reproduced the $\text{IL-1}\beta$ -induced hemodynamic changes well, as indicated by a decrease in MAP by approximately 24%. However, this hemodynamic change was not associated with significant alterations in acid–base balance or plasma lactate concentration. The DO_2 , VO_2 , and O_2ER values were not affected by $\text{IL-1}\beta$ or PGE_1

Table 1. Hemodynamic parameters in rabbits treated with a single injection of $10 \mu\text{g/kg}$ interleukin- 1β ($\text{IL-1}\beta$ group; $n = 5$), continuous infusion of $1 \mu\text{g/kg/min}$ prostaglandin E_1 (PGE_1 group; $n = 6$), or saline (control group; $n = 5$)

Group		MAP (mmHg)	HR (b.p.m.)	CI (mL/kg/min)	Hb (g/dL)	pH	PaCO_2 (mmHg)	PaO_2 (mmHg)	BE (mEq/L)
PGE_1	Baseline	89 ± 7	290 ± 9	163 ± 22	12.1 ± 1.0	7.390 ± 0.05	42 ± 5	208 ± 18	0.2 ± 2.8
	1st exp.	$68 \pm 9^*$	277 ± 22	162 ± 12	12.3 ± 1.6	7.320 ± 0.03	47 ± 4	194 ± 30	-2.5 ± 1.7
$\text{IL-1}\beta$	Baseline	87 ± 3	278 ± 20	139 ± 18	13.3 ± 1.0	7.410 ± 0.04	36 ± 4	226 ± 30	-1.8 ± 2.9
	1st exp.	$67 \pm 9^*$	284 ± 17	148 ± 23	13.2 ± 1.4	7.329 ± 0.07	36 ± 5	222 ± 26	$-6.8 \pm 3.7^*$
Control	Baseline	82 ± 4	274 ± 16	161 ± 16	12.5 ± 1.0	7.437 ± 0.04	37 ± 3	231 ± 17	0.8 ± 1.2
	1st exp.	81 ± 5	271 ± 20	154 ± 23	12.6 ± 1.3	7.410 ± 0.03	38 ± 3	225 ± 25	-0.4 ± 0.4

*Statistically significant difference from the baseline value ($P < 0.05$). 1st exp, first experimental data; BE, base excess; CI, cardiac index; Hb, hemoglobin concentration; HR, heart rate; MAP, mean arterial pressure; PaCO_2 , arterial PCO_2 ; PaO_2 , arterial PO_2 .

Table 2. Oxygen metabolism parameters in rabbits treated with a single injection of 10 µg/kg interleukin-1β (IL-1β group; n = 5), continuous infusion of 1 µg/kg/min prostaglandin E₁ (PGE₁ group; n = 6), or saline (control group; n = 5)

Group	DO ₂ (mL/kg/min)	VO ₂ (mL/kg/min)	O ₂ ER (%)	Lac (mg/dL)	PvO ₂ (mmHg)	v-aDCO ₂ (mmHg)	PpO ₂ (mmHg)	p-aDCO ₂ (mmHg)
PGE ₁	Baseline	26.5 ± 4.6	40 ± 9	20 ± 4	54 ± 2	9 ± 4	58 ± 8	7 ± 4
	1st exp.	26.3 ± 4.1	39 ± 7	20 ± 4	52 ± 5	9 ± 3	62 ± 5	8 ± 5
IL-1β	Baseline	24.5 ± 1.7	40 ± 3	17 ± 4	53 ± 5	9 ± 2	60 ± 5	8 ± 3
	1st exp.	25.5 ± 1.6	38 ± 4	38 ± 4*	56 ± 8	10 ± 2	67 ± 13*	9 ± 4
Control	Baseline	27.1 ± 2.7	39 ± 7	15 ± 2	49 ± 4	9 ± 3	59 ± 7	8 ± 2
	1st exp.	26.1 ± 5.4	40 ± 9	15 ± 4	48 ± 4	10 ± 3	58 ± 10	7 ± 2

*Statistically significant difference from the baseline value ($P < 0.05$). 1st exp, first experimental data; DO₂, oxygen delivery; Lac, plasma lactate concentration; O₂ER, oxygen extraction ratio; p-aDCO₂, portal-arterial difference in PCO₂; PpO₂, portal venous PO₂; v-aDCO₂, mixed venous PO₂; PvO₂, mixed venous PO₂; v-aDCO₂, venous-arterial difference in PCO₂; VO₂, oxygen consumption.

administration. Neither IL-1β nor PGE₁ administration affected mixed venous PO₂ values or mixed veno-arterial differences in PCO₂. Portal venous PO₂ was increased significantly in response to IL-1β. The portal veno-arterial difference in PCO₂ was not affected by IL-1β or PGE₁ administration. The slopes of the MAP/CI regression line in the IL-1β and PGE₁ groups were significantly less than those in the control group (IL-1β, $y = 0.35x + 19.4$; PGE₁, $y = 0.34x + 16.2$; control, $y = 0.43x + 16.2$, $P < 0.05$).

VO₂/DO₂ relation and venous PO₂/DO₂ relation during stepwise cardiac tamponade

Plots of VO₂ against DO₂ for each rabbit are shown in Figure 1. The value of DO₂crit in the IL-1β group (11.0 ± 1.9 mL/min/kg) tended to be less than that in the PGE₁ group (13.0 ± 2.0 mL/min/kg) or the control group (12.9 ± 0.5 mL/min/kg), but these differences were not statistically significant because of large variance. There were no significant differences in the O₂ERcrit values between the three groups (PGE₁, $77 \pm 15\%$; IL-1β, $72 \pm 9\%$; control, $73 \pm 7\%$). Plots of the pooled data are shown in Figure 2. The slope of the supply-independent line of the IL-1β group ($y = 0.13x + 6.4$) differed significantly from that of the PGE₁ group ($y = 0.01x + 10.0$) or that of the control group ($y = 0.05x + 8.7$) ($P < 0.05$). The slopes of the supply-dependent line did not differ significantly between groups (IL-1β, $y = 0.56x + 1.4$; PGE₁, $y = 0.55x + 1.7$; control, $y = 0.64x + 1.2$). Relations between DO₂ and mixed venous PO₂ and portal venous PO₂ are shown in Figure 3. For DO₂ values between 10 and 20 mL/min/kg, mixed venous PO₂ was significantly greater in the IL-1β group than in the PGE₁ group or in the control group ($P < 0.05$). Portal venous PO₂ in the IL-1β group was significantly greater than that in the PGE₁ group or that in the control group for DO₂ values between 15 and 25 mL/min/kg ($P < 0.05$). A plot of the veno-arterial PCO₂ gradient against DO₂ in the systemic and splanchnic circulations is shown in Figure 4. There were no statistically significant differences in mean veno-arterial PCO₂ gradient values between the groups at any DO₂ range tested.

DISCUSSION

RESULTS OF THE present study confirmed the IL-1β-induced abnormalities in hemodynamics and oxygen metabolism reported previously.^{6,8,9,15} Analysis of the MAP/CI regression lines during cardiac tamponade showed that the vascular tone was decreased throughout the experimental period. Exogenous administration of IL-1β induced abnormal dependence of VO₂ on DO₂ as indicated by the

Fig. 1. Relation between oxygen delivery (DO_2) and oxygen consumption (VO_2) in rabbits treated with a single injection of $10 \mu\text{g/kg}$ interleukin- 1β (IL- 1β group, $n = 5$), continuous infusion of $1 \mu\text{g/kg/min}$ prostaglandin E_1 (PGE_1 group, $n = 6$), or saline (control group, $n = 5$). The critical value of DO_2 ($\text{DO}_{2\text{crit}}$) below which VO_2 becomes DO_2 -dependent, as determined by the dual-line method, is shown in each plot.

early dissociation of the supply-independent lines between the IL- 1β group and the control group. Mixed-venous and portal venous blood samples showed greater mean venous PO_2 in the IL- 1β group than in the control group in the supply-independent range of DO_2 . Mean values of the veno-arterial PCO_2 difference in the IL- 1β group were similar to those in the control group in this range, suggesting that the increases in mixed-venous and portal venous PO_2 were not due to an increase in oxygen supply or a decrease in metabolic rate in the tissue. A possible explanation may be that as Q_t declines during IL- 1β -induced shock, ineffective blood supply to tissues occurs through a mechanism such as peripheral arterio-venous shunting. The dual-line method does not appear to detect the actual value of $\text{DO}_{2\text{crit}}$, at which hypoxic tissue appears, but instead indicates a point at which the entire cells become hypoxic during IL- 1β -induced shock.

Continuous infusion of PGE_1 reproduced IL- 1β -induced alterations in hemodynamics well but failed to induce circulatory shock. The animals showed no manifestation of tissue hypoxia such as metabolic acidosis or lactatemia. Analysis of the VO_2/DO_2 relation during the infusion of PGE_1 showed that systemic oxygen uptake was independent of DO_2 in the supply-independent range because the slope of the supply-independent line in the PGE_1 group was flat, similar to that in the control group. Prostaglandin E_1 did not induce abnormal oxygen metabolism in splanchnic circulation according to portal venous blood samples. We have reported the effect of ibuprofen, a cyclooxygenase inhibitor, on IL- 1β -induced abnormalities in hemodynamics and oxygen metabolism.⁹ Rabbits developed circulatory shock as indicated by a significant decrease in MAP with lactatemia at 15 min after injection of IL- 1β , and sustained hypotension for approximately 2 h. Post-treatment with 10 mg/kg i.v. ibuprofen at

15 min completely restored MAP to baseline level and abolished the development of lactatemia by 30 min. Ibuprofen also significantly attenuated the IL-1 β -induced increase in the slope of the supply-independent line and restored both mixed and portal venous PO₂ values to control levels, indicating that IL-1 β -induced shock and abnormal dependence of VO₂ on DO₂ in rabbits are mediated predominantly by

Fig. 2. Relation between oxygen delivery (DO₂) and oxygen consumption (VO₂) during stagnant hypoxia in rabbits. All data from animals treated with a single injection of 10 μ g/kg interleukin-1 β (IL-1 β group, $n = 5$), continuous infusion of 1 μ g/kg/min prostaglandin E₁ (PGE₁ group, $n = 6$), or saline (control group, $n = 5$) are shown. The six lines that define supply-dependent and supply-independent lines were calculated from the pooled data. + and dashed lines, PGE₁ group; ○ and solid lines, IL-1 β group; ● and semi-dashed lines, control group.

vasodilating prostaglandins. However, in the present study, continuous infusion of vasodilating PGE₁ failed to mimic IL-1 β -induced abnormalities in oxygen metabolism. What, then, is responsible for the difference between the IL-1 β -induced shock and the PGE₁-induced hypotension?

There is a published report pertaining to the effect of PGE₁ on the VO₂/DO₂ relation. Groeneveld *et al.* analyzed the effect of PGE₁ on the VO₂/DO₂ relation during an incremental increase in positive end-expiratory pressure from 0 to 20 cmH₂O in intact pigs.¹⁶ Compared to the control group, the experimental group, with continuous i.v. infusion of 0.2 μ g/kg/min PGE₁, showed a significantly greater O₂ERcrit at a significantly lesser DO₂crit. Their study was designed to include intact animals with or without continuous infusion of PGE₁ and was very similar to ours. However, they restricted the data to five or six points, resulting in wide variation in individual VO₂/DO₂ data plots. Their results require careful interpretation because of the limited accuracy of the critical point values, but nonetheless indicated that PGE₁-induced vasodilation has no detrimental effect on oxygen uptake in intact pigs.

Given the information, the IL-1 β -induced abnormal dependence of VO₂ on DO₂ appears not to be attributable to such generalized vasodilation as that induced by exogenous administration of PGE₁. Even though the net hypotensive effect of PGE₁ was equal to that in IL-1 β -induced shock, the level of the pathologic induction of vasodilating mediators in response to IL-1 β may vary from tissue to tissue. Hypotension induced by PGE₁ likely differed from the IL-1 β -induced pathologic process involving the gut, as judged by the obser-

Fig. 3. Relation between oxygen delivery (DO₂) and venous PO₂ during stagnant hypoxia in rabbits. Left, DO₂ versus mixed venous PO₂. Right, DO₂ versus portal PO₂. +, group that received a continuous infusion of 1 μ g/kg/min prostaglandin E₁ (PGE₁; $n = 6$); ○, group that received a single injection of 10 μ g/kg interleukin-1 β (IL-1 β ; $n = 5$); ●, group that received a continuous infusion of saline (control; $n = 5$). Symbols with error bars indicate the mean $\pm$ SD in each of five bins that are five DO₂ units wide. *Statistically significant difference ($P < 0.05$) from the corresponding control value.

Fig. 4. Relation between oxygen delivery (DO_2) and veno-arterial PCO_2 gradient during stagnant hypoxia in rabbits treated with a single injection of $10 \mu\text{g/kg}$ interleukin- 1β (IL- 1β group, $n = 5$; $\circ$), continuous infusion of $1 \mu\text{g/kg/min}$ prostaglandin E_1 (PGE_1 group, $n = 6$; $\pm$), or saline (control group, $n = 5$; $\bullet$). Left, DO_2 versus the venoarterial PCO_2 gradient in mixed venous blood. Right, DO_2 versus the venoarterial PCO_2 gradient in portal blood. Symbols with error bars indicate the mean $\pm$ SD in each of five bins that are five DO_2 units wide.

vation of portal venous PO_2 . There is evidence that heterogeneity of blood flow to tissues result in defects in oxygen extraction. Humer and colleagues showed that endotoxin increases the heterogeneity of gut capillary transit times, used to estimate the DO_2 /oxygen demand distribution, reflecting decreased oxygen extraction in pigs.¹⁷ Heterogeneity of blood flow to the splanchnic circulation may explain the pathophysiology of IL- 1β -induced abnormal dependence of VO_2 on DO_2 , although there was insufficient evidence to verify this in the current study.

In summary, the IL- 1β -induced shock in rabbits was characterized by an abnormal dependence of VO_2 on DO_2 in the supply-independent range of DO_2 and by an increase in portal venous PO_2 in the absence of alteration in the veno-arterial PCO_2 differences during stagnant hypoxia. Continuous infusion of PGE_1 at the dosage that induced equivalent hypotension to that in IL- 1β -induced shock failed to reproduce an abnormal dependence of VO_2 on DO_2 or an increase in portal venous PO_2 . These results indicate that simple vasodilation and hypotension induced by exogenous administration of PGE_1 are not sufficient to account for abnormal oxygen metabolism in the IL- 1β -induced sepsis model.

CONFLICT OF INTEREST

NONE.

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