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Effects of olprinone on hepatosplanchnic circulation and mitochondrial oxidation in a porcine model of endotoxemia

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Abstract
Purpose. This study was performed in order to assess the effects of olprinone, a phosphodiesterase III inhibitor, on hepatic oxygen delivery (DO_2H), oxygen consumption (VO_2H), and mitochondrial oxidation in the liver of a porcine endotoxemia model.
Methods. Fourteen pigs received continuous infusion of endotoxin via the portal vein for 240 min. From t = 150 to t = 240 min, animals were randomly divided into two groups to receive saline (control [CONT]; $n = 7$), or olprinone (OLP; $n = 7$) via the central vein.
Results. In the OLP group, prior to olprinone treatment at 150 min, endotoxin induced significant decreases in the cardiac index (CI; from 120 ± 31 to 65 ± 13 ml·kg^{-1}·min^{-1}; $P < 0.01$) and DO_2H (from 3.58 ± 0.81 to 1.55 ± 0.49 ml·kg^{-1}·min^{-1}; $P < 0.01$), while VO_2H was maintained. After administration of olprinone (from t = 150 to t = 240 min), CI was unchanged, while DO_2H increased from 1.55 ± 0.49 to 1.93 ± 0.38 ml·kg^{-1}·min^{-1} ($P < 0.01$) and VO_2H increased from 0.42 ± 0.28 to 0.69 ± 0.38 ml·kg^{-1}·min^{-1} ($P < 0.01$). At t = 240 min, the oxidation level of cytochrome aa3 was significantly higher in the OLP group than in the CONT group (OLP, 66.2 ± 19.3% vs CONT, 26.4 ± 17.3%; $P < 0.01$).
Conclusion. Our data for this porcine endotoxemia model suggest that olprinone may have beneficial therapeutic effects in restoring not only systemic and hepatic circulation but also mitochondrial oxidation in the liver.

Key words Olprinone · Endotoxemia · Hepatic blood flow · Hepatic oxygen delivery · Cytochrome aa3

Introduction

Endotoxin is an important causative factor in peripheral vascular failure, resulting in hemodynamic depression that includes a reduction in hepatic blood flow followed by liver dysfunction and multiple organ failure [1]. Olprinone, a phosphodiesterase III inhibitor that exhibits positive inotropic and vasodilator actions [2], has been reported to significantly increase hepatosplanchnic perfusion in patients undergoing cardiac surgery [3], and to halt the disturbances seen in hepatic circulation in a porcine endotoxemia model [4]. However, an alternative hypothesis to account for the persistent high lactate levels found in sepsis, despite sufficient cardiac output (CO) and oxygen delivery, is based on the pathologic redistribution of blood flow, resulting in hidden hypoxic microcirculatory units being located next to well-perfused or even over-perfused normoxic units [5]. Furthermore, recent findings have highlighted the possibility that alterations in cellular oxygen metabolism, termed "cytopathic hypoxia," may be critical in the organ dysfunction observed during sepsis [6]. Therefore, if shunted microvascular units or cytopathic hypoxia were present in sepsis, increases in hepatosplanchnic perfusion and hepatic oxygen delivery induced by some agents would not guarantee adequate intracellular oxygenation and cellular energy metabolism in the tissue.

Near-infrared spectroscopy (NIRS) is a highly promising technique that allows direct and noninvasive measurement of tissue oxygenation by examining absorption differences in hemoglobin and cytochrome aa3 [7,8]. Because hemoglobin oxygenation is an indicator of extracellular oxygenation, NIRS cannot assess intracellular oxygenation correctly if shunted flow exists. On the other hand, cytochrome aa3 interacts directly with molecular O_2 and is responsible for 90% of cellular oxygen consumption through oxidative phosphorylation in mitochondria. Thus, the redox state of cytochrome aa3 may be a key indicator of intracellular oxygenation, even when shunted microvascular units are present.

To date, only inconclusive data about the effects of olprinone on the hepatic macro- and microcirculation

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during sepsis or endotoxemia are available. Hence, the aim of this study was to determine, in a porcine endotoxemia model, the effects of olprinone, not only on hepatic oxygen delivery and hepatic oxygen consumption but also on mitochondrial oxidation in the liver.

Materials and methods

The experimental protocol employed in this study conformed to the guidelines issued for the care and use of laboratory animals at Kagoshima University Research Laboratories, and it was approved by the local ethics committee of Kagoshima University. Fourteen male specific pathogen-free (SPF) pigs, weighing 23.0 to 30.0 kg (mean, 26.1 kg) were fasted overnight, but had free access to water. The animals were premedicated with intramuscular 25 mg·kg^{-1} ketamine hydrochloride and 0.5 mg atropine sulfate. After induction with intravenous sodium pentobarbital (20 mg·kg^{-1}), anesthesia was maintained with 1.0% isoflurane. Muscle relaxation was achieved using intravenous pancuronium (0.1 mg·kg^{-1}, followed by continuous infusion at 0.1 mg·kg^{-1}·h^{-1}). The animals were mechanically ventilated (fraction of inspired oxygen, 50%) via an MD-705XL Anesthesia Machine (Senkouika, Tokyo, Japan), with tidal volume being adjusted so as to keep arterial carbon dioxide tension within a range of 35 to 40 mmHg.

Electrocardiogram was continuously monitored throughout the experiment. The right femoral artery was cannulated for arterial blood sampling and for measurement of arterial blood pressure. A double-lumen catheter was inserted into the left femoral vein for injection of inotropics. A Swan-Gantz thermodilution catheter (Opticathe 5.5 Fr; Abbott Critical Care Systems, Mountain View, CA, USA) was inserted through the right femoral vein, and positioned in the pulmonary artery under pressure guidance. The Swan-Gantz catheter was connected to a CO computer. Cardiac output (CO) was determined using the thermodilution technique, with repeated 5-ml injections of iced physiological saline in water. Through midline laparotomy, ultrasound transit-time flow probes (Transonic Systems, Ithaca, NY, USA) were placed around the hepatic artery (HA) and portal vein (PV) for continuous measurement of hepatic arterial blood flow (HAF) and portal venous flow (PVF). A 5.5-Fr catheter was passed from the right external jugular vein to the hepatic vein (HV). A 7-Fr double-lumen catheter (3-cm tip distance) was positioned within the PV via a branch of the superior mesenteric vein for the infusion of endotoxin (via the distal lumen) and for blood sampling (via the proximal lumen). The incision was then closed, and the catheters, flow probes, and NIRS light guides were secured by means of purse-string sutures.

After a 60-min stabilization period, consecutive measurements of systemic hemodynamics, blood gases, and hepatic blood flow were made, to evaluate both the progression of the induced shock and the effects of olprinone during endotoxemia. The time points for data collection were as follows: t = 0 (start of endotoxin infusion, initial baseline); t = 150 min (start of olprinone infusion, second baseline); and t = 180, 210, and 240 min. Blood samples were submitted to blood gas analysis (ABL 2; Radiometer, Copenhagen, Denmark). Arterial oxygen saturation (Sa_{O_2}), mixed venous oxygen saturation (Sv_{O_2}), hepatic venous oxygen saturation (Shv_{O_2}), portal venous oxygen saturation (S_{PVO_2}), and hemoglobin concentration (Hb) were measured at each time point by blood gas analysis, following calibration for pig blood. The cardiac index (CI), systemic oxygen delivery (DO_2), hepatic oxygen delivery (DO_2H), systemic oxygen consumption (VO_2), and hepatic oxygen consumption (VO_2H) were calculated as follows:

$$\mathrm{CI}\left(\mathrm{ml\cdot kg^{-1}\cdot min^{-1}}\right) = \mathrm{CO}/\mathrm{weight}$$

$$\mathrm{DO_2}\left(\mathrm{ml\cdot kg^{-1}\cdot min^{-1}}\right) = \left(1.39 \times \mathrm{Sa_{O_2}} \times \mathrm{Hb} + 0.0031 \times \mathrm{Pa_{O_2}}\right) \times \mathrm{CI} \times 10$$

$$\mathrm{DO_2H}\left(\mathrm{ml\cdot kg^{-1}\cdot min^{-1}}\right) = \left[\left(1.39 \times \mathrm{Hb} \times \mathrm{Sa_{O_2}} + 0.0031 \times \mathrm{Pa_{O_2}}\right) \times 10 \times \mathrm{HAF} + \left(1.39 \times \mathrm{Hb} \times \mathrm{Spv_{O_2}} + 0.0031 \times \mathrm{P_{PVO_2}}\right) \times 10 \times \mathrm{PVF}\right] / \mathrm{weight}$$

$$\mathrm{VO_2}\left(\mathrm{ml\cdot kg^{-1}\cdot min^{-1}}\right) = \mathrm{DO_2} - \left(1.39 \times \mathrm{Sv_{O_2}} \times \mathrm{Hb} + 0.0031 \times \mathrm{Pv_{O_2}}\right) \times \mathrm{CI} \times 10$$

$$\mathrm{VO_2H}\left(\mathrm{ml\cdot kg^{-1}\cdot min^{-1}}\right) = \text{hepatic } \mathrm{DO_2} - \left[\left(1.39 \times \mathrm{Shv_{O_2}} \times \mathrm{Hb} + 0.0031 \times \mathrm{Phv_{O_2}}\right) \times 10 \times \left(\mathrm{HAF} + \mathrm{PVF}\right)\right] / \mathrm{weight}$$

where Pa_{O_2}, P_{VO_2}, P_{PVO_2}, and Phv_{O_2} are arterial oxygen pressure, mixed venous oxygen pressure, portal venous oxygen pressure, and hepatic venous oxygen pressure, respectively. Plasma lactate values were analyzed by blood gas analysis (ABL 2; Radiometer). Body temperature was kept constant throughout the study using an electrical heating blanket.

Experimental design

After a 60-min stabilization period, 14 animals received continuous infusion (1.7 μg·kg^{-1}·h^{-1}) of endotoxin (li-

popolysaccharide [LPS], Serotype O111: B4; Sigma, St. Louis, MO, USA) via the PV for 240 min. During the latter part of this infusion (from t = 150 to t = 240 min), animals were randomly divided into two groups to receive continuous saline (0.09 ml·kg^{-1}·h^{-1}; control [CONT] group; n = 7) or olprinone (0.3 μg·kg^{-1}·min^{-1}; OLP group; n = 7) via the central vein. In all groups, fluid replacement was achieved by continuous infusion of Ringer solution at 20 ml·kg^{-1}·h^{-1} throughout the experiment.

Mitochondrial oxidation and hemoglobin oxygenation

After the placing of a set of light guides on the liver surface at 2-cm intervals, regional hepatic mitochondrial oxidation (redox state of cytochrome aa3) and hemoglobin oxygenation were continuously monitored by NIRS (model OM110; Shimadzu, Kyoto, Japan) [9,10]. NIRS signals were analyzed by determining the maximal signal change, while the full scale for cytochrome aa3 (arbitrarily designated 100%) was obtained from the signal difference between maximal cytochrome aa3 oxidation (100%; resulting from aerobic conditions [10 min of respiration with 100% O_2 before administration of endotoxin]) and minimum cytochrome aa3 oxidation (0%; obtained under anaerobic conditions [20 min of respiration with 100% N_2 at the end of the experiment]). On the other hand, the hemoglobin oxygenation was taken as oxy-Hb minus deoxy-Hb, which was expressed as a percentage of the "full-scale" value obtained during the experiment.

Statistical analysis

Values for all results are expressed as means ± SD. The effects of endotoxin were evaluated after 150 min by paired t-test in each group. Due to group differences in the first (t = 0 min) and second (t = 150 min) baseline values in some parameters, the unpaired t-test was applied for changes in the parameters to evaluate dissimilarities in the effects of endotoxin in the groups. From 150 min (as a second baseline) to 240 min, the effects of olprinone during endotoxemia were evaluated by repeated measure one-way analysis of variance (ANOVA) followed by Fisher's protected least significant difference (PLSD) for multiple comparisons, in which each value was compared with the second baseline value. Differences between the two groups were evaluated by applying ANOVA for repeated measurements. If this procedure revealed significant differences, statistical comparisons between the groups at each measurement point were performed by unpaired t-test. A P value of less than 0.05 was considered significant.

Results

Systemic and hepatic circulation and oxygen transport

In the OLP group, prior to the start of olprinone treatment, endotoxin caused significant decreases in the CI, from 120 ± 31 to 65 ± 13 ml·kg^{-1}·min^{-1} ($P < 0.01$), and DO_2H, from 3.58 ± 0.81 to 1.55 ± 0.49 ml·kg^{-1}·min^{-1} ($P < 0.01$), while VO_2 and VO_2H were maintained (Figs. 1, 2; Table 1). After administration of olprinone during endotoxin infusion (from t = 150 to t = 240 min), CI and VO_2 remained unchanged, while DO_2H increased from 1.55 ± 0.49 to 1.93 ± 0.38 ml·kg^{-1}·min^{-1} ($P < 0.01$) and VO_2H increased from 0.42 ± 0.28 to 0.69 ± 0.38 ml·kg^{-1}·min^{-1} ($P < 0.01$). In contrast, from t = 150 to t = 240 min, CI, DO_2, and DO_2H decreased further in the CONT group, and at t = 240 min, the values of these parameters were significantly lower than those in the OLP group.

Lactate concentration and mitochondrial and hemoglobin oxygenation in the liver

When endotoxin was continuously infused via the portal vein from t = 0 to t = 150 min, hepatic hemoglobin oxygenation and the redox state of cytochrome aa3 in the liver showed marked and progressive reductions in both groups (Fig. 3). After the administration of olprinone (from t = 150 to t = 240 min) in the OLP group, hepatic hemoglobin oxygenation increased gradually, while the oxidation level of cytochrome aa3 exhibited a further reduction until t = 180 min, after which it began to increase markedly. At t = 240 min, the oxidation level of cytochrome aa3 was significantly higher in the OLP group than in the CONT group (OLP; 66.2 ± 19.3% vs CONT; 26.4 ± 17.3%; $P < 0.01$).

Endotoxin caused significant increases in lactate values before t = 150 min in both groups (Fig. 4). After the administration of olprinone during endotoxin infusion, lactate concentration in the OLP group was unchanged (from t = 150 to t = 240 min). However, lactate concentration in the CONT group increased significantly, and at t = 240 min, it was significantly higher than that in the OLP group (OLP; 3.8 ± 0.6 mmol·l^{-1} vs CONT; 8.1 ± 3.5 mmol·l^{-1}; $P < 0.05$; Fig. 4).

Discussion

It is widely accepted that low systemic vascular resistance and increased cardiac output (CO) are observed during septic shock (hyperdynamic state) [11]. However, in the present study, fluid replacement was moderate (20 ml·kg^{-1}·h^{-1}) and this resulted in a hypodynamic model during continuous infusion of endotoxin via

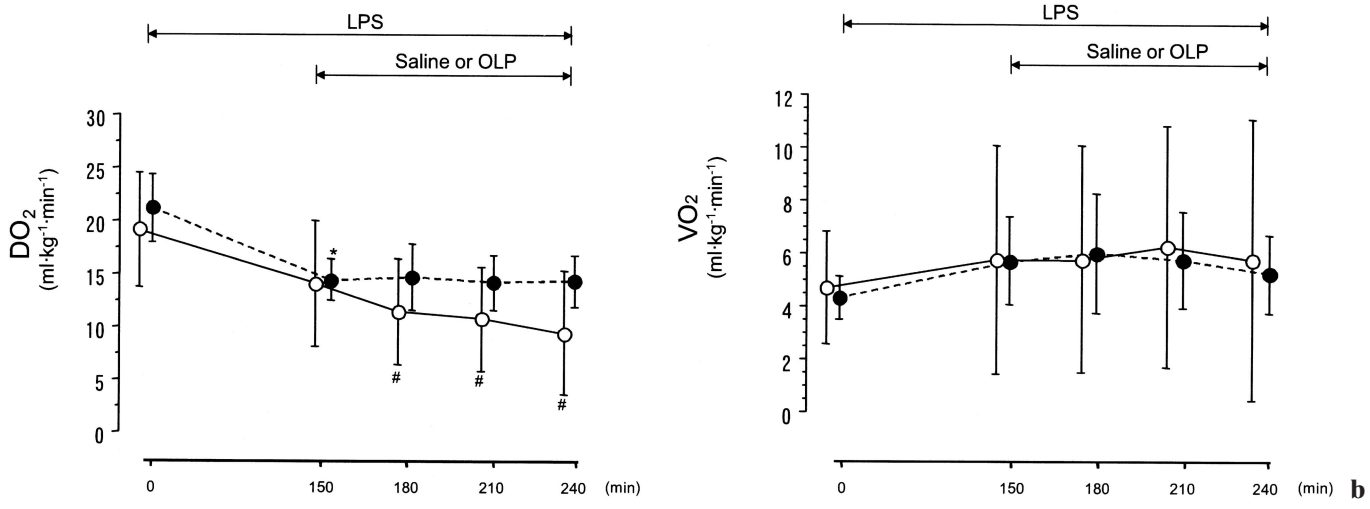

Fig. 1. Effects of olprinone (*OLP*) on **a** systemic oxygen delivery (DO_2) and **b** systemic oxygen consumption (VO_2) in porcine endotoxemia. Control (CONT) group (*open circles*) and OLP group (*closed circles*), intraportal endotoxin (lipopolysaccharide; *LPS*) infusion at a rate of 1.7 μg·kg^{-1}·h^{-1} for 240 min. CONT group (*open circles*), endotoxin infusion as above with saline 0.09 ml·kg^{-1}·h^{-1} from 150 to 240 min. OLP group (*closed circles*), endotoxin infusion as above with olprinone at 0.3 μg·kg^{-1}·min^{-1} from 150 to 240 min. Data values are expressed as means ± SD. * $P < 0.05$ vs initial baseline value (t = 0) in the same group; # $P < 0.05$ vs second baseline value (t = 150) in the same group

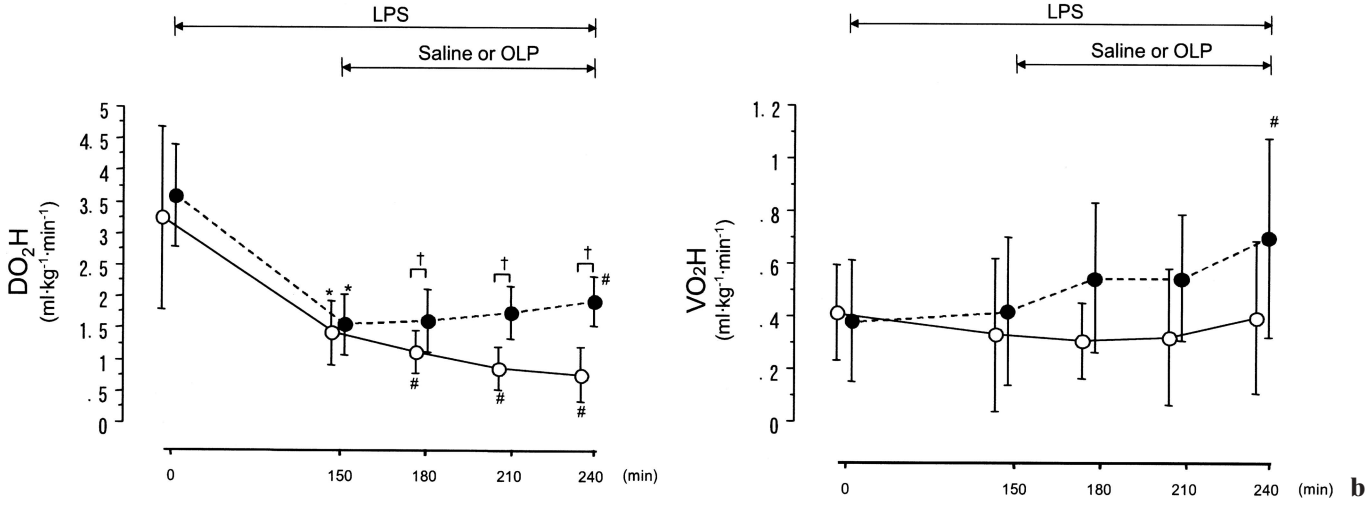

Fig. 2. Effects of olprinone on **a** hepatic oxygen delivery (DO_2H) and **b** hepatic oxygen consumption (VO_2H) in porcine endotoxemia. CONT group (*open circles*) and OLP group (*closed circles*), intraportal endotoxin infusion at a rate of 1.7 μg·kg^{-1}·h^{-1} for 240 min. CONT group (*open circles*), endotoxin infusion as above with saline 0.09 ml·kg^{-1}·h^{-1} from 150 to 240 min. OLP group (*closed circles*), endotoxin infusion as above with olprinone at 0.3 μg·kg^{-1}·min^{-1} from 150 to 240 min. Data values are expressed as means ± SD. * $P < 0.05$ vs initial baseline value (t = 0) in the same group; # $P < 0.05$ vs second baseline value (t = 150) in the same group; † $P < 0.05$ vs value obtained at the same time in the CONT group

the portal vein. A recent investigation suggested that myocardial dysfunction could actually occur early (<30 min) in septic shock [12]. Furthermore, Mutschler et al. [13] have reported that endotoxin caused a rapid cyclooxygenase (COX)-mediated inflammatory response in the myocardium (within 1 h) and that this early inflammation may have been a mediator of myocardial dysfunction in porcine endotoxemia. In the present study, this hypodynamic model was therefore adopted in order to avoid: (a) massive fluid challenge in septic shock, which may contribute to overpermeability pulmonary edema, causing severe respiratory failure [14]; and (b) aggressive fluid replacement, such as is used clinically, which may mask the pathophysiological

Table 1. Systemic and hepatic hemodynamics during endotoxemia

		Endotoxin					
		Initial baseline	Second baseline	Interventional period			Group × time (*P* value)
Parameter	Group	0 min	150 min	180 min	210 min	240 min	
MAP (mmHg)	CONT	104.1 ± 24.3	75.5 ± 27.6*	75.1 ± 31.0	69.3 ± 32.4	63.7 ± 31.4	NS
	OLP	103.8 ± 12.2	92.1 ± 22.7	89.0 ± 21.8	87.6 ± 21.7	91.8 ± 21.1	
MPAP (mmHg)	CONT	22.3 ± 6.7	29.9 ± 4.5*	29.7 ± 5.8	31.0 ± 7.1	30.9 ± 7.1	NS
	OLP	23.2 ± 4.7	30.6 ± 8.9*	31.2 ± 9.3	31.1 ± 10.6	31.0 ± 9.1	
CI ($ml \cdot kg^{-1} \cdot min^{-1}$)	CONT	109 ± 22	72 ± 28*	61 ± 27**	56 ± 26**	52 ± 33**	0.0041
	OLP	120 ± 31	65 ± 13*	69 ± 14	67 ± 14	68 ± 16	
SVR ($mmHg \cdot l^{-1} \cdot kg^{-1} \cdot min^{-1}$)	CONT	1.46 ± 0.55	1.53 ± 0.40*	1.84 ± 0.60	1.81 ± 0.71	1.84 ± 0.74	NS
	OLP	1.28 ± 0.43	2.09 ± 0.95*	1.92 ± 0.85	1.92 ± 0.83	2.02 ± 0.79	
HAF ($ml \cdot kg^{-1} \cdot min^{-1}$)	CONT	4.3 ± 1.7	3.7 ± 1.8	2.8 ± 1.5**	2.4 ± 1.5**	2.2 ± 1.8**	0.012
	OLP	3.9 ± 1.4	2.9 ± 0.8	2.7 ± 0.8	2.6 ± 0.6	2.7 ± 1.2	
PVF ($ml \cdot kg^{-1} \cdot min^{-1}$)	CONT	17.6 ± 7.4	6.4 ± 1.3*	6.6 ± 1.4	5.6 ± 1.6	4.9 ± 2.1**	<0.0001
	OLP	20.3 ± 6.6	7.2 ± 1.2*	8.6 ± 1.7*****	9.4 ± 1.9*****	10.3 ± 2.1*****	

* $P < 0.05$ vs initial baseline value (t = 0) in the same group; ** $P < 0.05$ vs second baseline value (t = 150) in the same group; *** $P < 0.05$ vs value obtained at the same time in the CONT group
Data values are expressed as means ± SD
MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; CI, cardiac index; SVR, systemic vascular resistance; HAF, hepatic arterial flow; PVF, portal venous flow

changes caused by endotoxin, such as myocardial depression.

Sepsis is characterized by the excessive production of inflammatory mediators and by the excessive activation of inflammatory cells, thus resulting in metabolic anarchy, including increased lactate concentration and metabolic acidosis, even during a hyperdynamic state with high CO. This condition may be associated with two hypothetical events: (a) the shunting of oxygen from the microcirculation, caused by a redistribution of regional blood flow in the microcirculation, as encountered in many organs in sepsis [5]; and (b) cytopathic hypoxia, defined as an acquired derangement in cellular energy metabolism by dysfunctional mitochondria, resulting in impaired adenosine triphosphate biosynthesis [6]. Therefore, in endotoxemia or sepsis, increases in CO, total hepatic blood flow, and hepatic oxygen delivery do not always guarantee adequate intracellular oxygenation and cellular energy metabolism in the tissue. We were not able to evaluate the affect of cytopathic hypoxia in the tissue, because we lacked data on the function and activation of pyruvate dehydrogenase, mitochondrial enzymes, nuclear enzyme poly-(ADP-ribosyl)-polymerase, and/or the uncoupled state of mitochondria. However, we measured the changes in mitochondrial oxidation, which are indicative of intracellular oxygenation, and lactate values, which are indicative of the progression of anaerobic metabolism. In this study, olprinone limited not only the progressive reduction of mitochondrial oxidation but also the marked increase in lactate concentration in endotoxemia. These data suggest that, among its beneficial therapeutic effects, olprinone may restore both reduced mitochondrial oxidation and cytopathic hypoxia (at least in this porcine model of endotoxemia).

The phosphodiesterase III inhibitor olprinone is reported to be a potential immunomodulator, with its proposed effects including attenuation of the production of the pro-inflammatory cytokine interleukin (IL)-6 and induction of the production of the anti-inflammatory cytokine IL-10 [15]. Furthermore, olprinone has been reported to relax the small mesenteric artery of the rabbit via a direct endothelium-independent action on smooth muscle [2]. Possible explanations for the effects of olprinone according to these hypotheses may thus include vascular changes (systemic and regional) causing improved oxygen delivery, and metabolic reactions causing increased oxygen consumption, or a combination of these. In this study, continuous infusion of endotoxin caused a significant reduction in both systemic and hepatic oxygen delivery. Although olprinone antagonized the decrease in both systemic and hepatic oxygen delivery disturbed by the continuous infusion of endotoxin, the effects of olprinone on the hepatosplanchnic circulation seem to

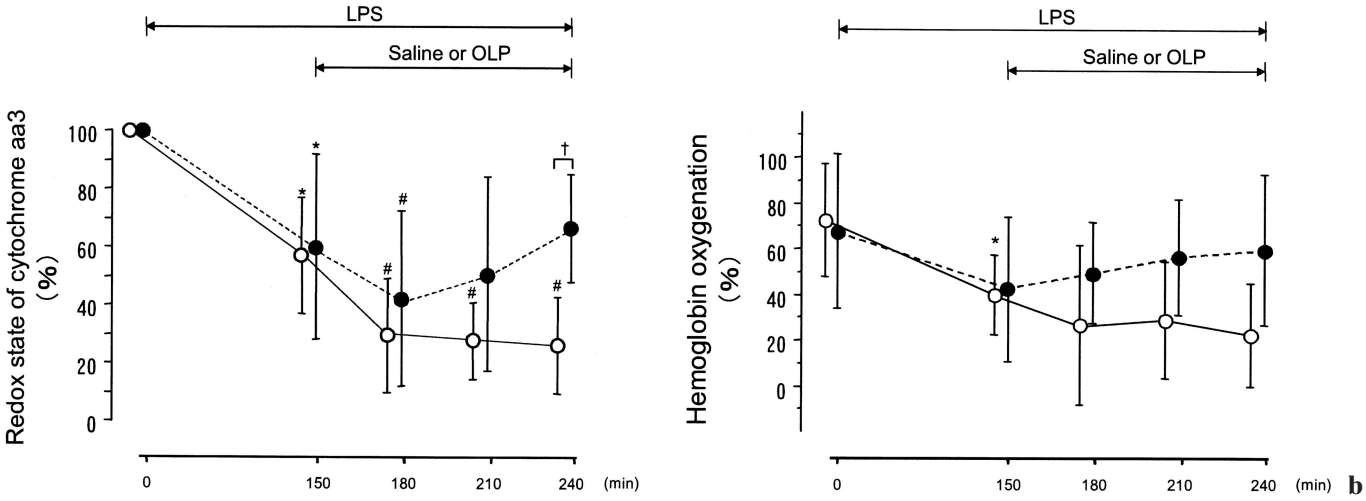

Fig. 3. Effects of olprinone on **a** redox state of cytochrome aa3 and **b** hemoglobin oxygenation in the liver in porcine endotoxemia. CONT group (*open circles*) and OLP group (*closed circles*), intraportal endotoxin infusion at a rate of 1.7 μg·kg^{-1}·h^{-1} for 240 min. CONT group (*open circles*), endotoxin infusion as above with saline 0.09 ml·kg^{-1}·h^{-1} from 150 to 240 min. OLP group (*closed circles*), endotoxin infusion as above with olprinone at 0.3 μg·kg^{-1}·min^{-1} from 150 to 240 min. Data values are expressed as means ± SD. * $P < 0.05$ vs initial baseline value (t = 0) in the same group; $^{\#}P < 0.05$ vs second baseline value (t = 150) in the same group; $^{\dagger}P < 0.05$ vs value obtained at the same time in the CONT group

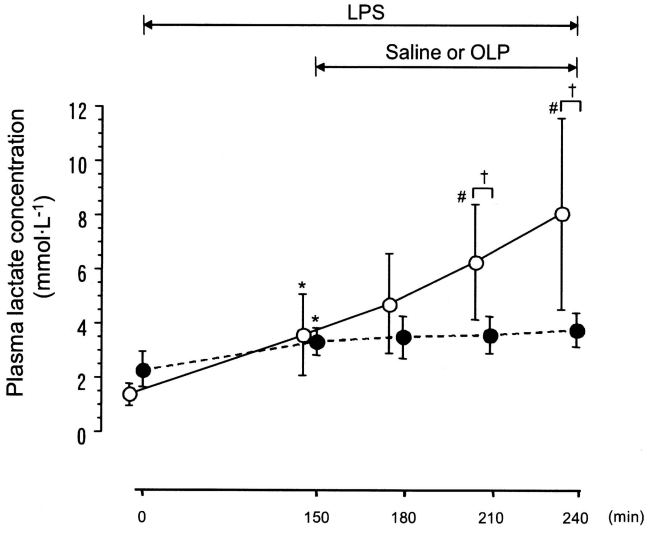

Fig. 4. Effects of olprinone on plasma lactate concentration in porcine endotoxemia. CONT group (*open circles*) and OLP group (*closed circles*), intraportal endotoxin infusion at a rate of 1.7 μg·kg^{-1}·h^{-1} for 240 min. CONT group (*open circles*), endotoxin infusion as above with saline 0.09 ml·kg^{-1}·h^{-1} from 150 to 240 min. OLP group (*closed circles*), endotoxin infusion as above with olprinone at 0.3 μg·kg^{-1}·min^{-1} from 150 to 240 min. Data values are expressed as means ± SD. * $P < 0.05$ vs initial baseline value (t = 0) in the same group; $^{\#}P < 0.05$ vs second baseline value (t = 150) in the same group; $^{\dagger}P < 0.05$ vs value obtained at the same time in the CONT group

differ from its effects on the systemic circulation. We found that hepatic oxygen consumption (but not systemic oxygen consumption) and hepatic oxygen delivery (but not systemic oxygen delivery) increased significantly after the administration of olprinone in endotoxemia. These data indicate that olprinone may be independent of the changes induced in systemic hemodynamics and that it has a more selective effect on the hepatosplanchnic circulation in endotoxemia. Interestingly, the administration of olprinone initially caused (from t = 150 to 180 min) increases in hepatic oxygen delivery and hepatic hemoglobin oxygenation, while mitochondrial oxidation was further reduced during these periods. These data indicate that intracellular oxygenation was impaired, even though extracellular oxygenation was improved at the initiation of olprinone administration. A possible explanation for this phenomenon is that olprinone may cause relaxation of large and non-nutrient veins in the initial period (from t = 150 to 180 min), leading to the causation of vascular steal by selective vasodilatation. Thirty minutes after the initiation of olprinone administration, relaxation may start to be evoked in nutrient veins, leading to improvements not only in hepatic hemoglobin oxygenation but also in mitochondrial oxidation. However, to explain this phenomenon more correctly, we need to evaluate in detail the relationship between micro- and macrovascular flow patterns, and changes in intra- and extracellular oxygenation in the liver during the administration of olprinone in endotoxemia.

In the present study, we characterized the effects of olprinone on systemic and hepatic oxygen delivery, and on the redox state of cytochrome aa3 in the liver during endotoxin challenge. Our results suggest that, in endotoxemia, olprinone may help to normalize not only the systemic and hepatic circulations but may also

help to normalize oxygen metabolism and intracellular oxygenation in the liver. However, whether olprinone improves systemic and hepatic oxygenation in a dose-dependent fashion has not been studied. Therefore, more work is clearly needed to investigate the mechanisms underlying the olprinone-induced improvements in hepatic oxygenation, using various concentrations of this agent. In addition, the question as to whether olprinone may be clinically effective in the prevention or treatment of acute liver dysfunction in endotoxemia awaits detailed evaluation.

In conclusion, we investigated the effects of olprinone on systemic and hepatic oxygen delivery, and on the redox state of cytochrome aa3 in the porcine liver during endotoxemia. Our data demonstrated that this drug improved both systemic and hepatic oxygen delivery when the delivery was disturbed by the continuous infusion of endotoxin. Furthermore, olprinone limited both the reduction of cytochrome aa3 and the increase in arterial lactate values seen in endotoxemia. Our data for this porcine endotoxemia model suggest that olprinone may have beneficial therapeutic effects in restoring not only the systemic and hepatic circulations but also mitochondrial oxidation in the liver.

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