Prostaglandin E₁ Increases Oxygen Extraction Capabilities in Experimental Sepsis

HAIBO ZHANG, MALIK BENLABED, HERBERT SPAPEN, DUC NAM NGUYEN, AND JEAN-LOUIS VINCENT

Department of Intensive Care, Erasme University Hospital, Free University of Brussels, B-1070 Brussels, Belgium

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By its microvascular and anti-inflammatory actions, prostaglandin E₁ (PGE₁) has been suggested both in animal models and in humans to have a therapeutic value in sepsis. To investigate whether PGE₁ could improve the oxygen extraction capabilities in severe sepsis, our study focused on the relationship between oxygen uptake ($\dot{V}O_2$) and oxygen delivery ($\dot{D}O_2$) during an acute reduction in blood flow induced by cardiac tamponade in endotoxic dogs. Thirty anesthetized, ventilated dogs were divided into three groups. A first group ($N = 10$) served as a control receiving 20 ml/kg/hr of saline intravenously. A second group ($N = 10$) received PGE₁ at 100 ng/kg/min along with the same saline infusion. A third group ($N = 10$) received the same dose of PGE₁ with only 1 ml/kg/hr of saline. Thirty minutes after the initiation of this therapy, *Escherichia coli* endotoxin (2 mg/kg) was injected in each dog. In each group, the administration of PGE₁, fluids, or both was continued throughout the study. Tamponade was then induced by repeated bolus injections of warm saline into the pericardial space. Steady-state measurements of $\dot{V}O_2$ (derived from the expired gases) and $\dot{D}O_2$ (the product of cardiac index and oxygen content) were obtained sequentially after each saline injection. The administration of PGE₁ + fluids resulted in significant increases in stroke volume, cardiac index, and $\dot{D}O_2$ and reductions in systemic and pulmonary vascular resistance. Stroke volume and cardiac index were lower in the PGE₁ alone than in the PGE₁ + fluids group. The $\dot{V}O_2$ levels at critical $\dot{D}O_2$ ($\dot{D}O_{2crit}$) were identical. However, $\dot{D}O_{2crit}$, which was 12.2 ± 2.8 ml/kg/min in the control group, was significantly decreased to 9.8 ± 2.0 ml/kg/min in the PGE₁ + fluids and to 9.3 ± 2.7 ml/kg/min in the PGE₁ alone group (both $P < 0.05$). Critical oxygen extraction ratio (O_2ER_{crit}) which was $47 \pm 14\%$ in the control group, was increased to $63 \pm 16\%$ in the PGE₁ + fluids group and to $61 \pm 17\%$ in the PGE₁ alone group (both $P < 0.05$). To investigate whether PGE₁ also improves oxygen extraction capabilities in the absence of endotoxin, a second series of experiments was performed in 14 dogs, receiving saline alone (Control, $N = 7$) or plus PGE₁ at 100 ng/kg/min (PGE₁, $N = 7$). $\dot{D}O_{2crit}$ was 10.7 ± 2.9 ml/kg/min in the PGE₁ group vs $10.1 \pm$

1.8 ml/kg/min in the control group (NS). O_2ER_{crit} tended to be higher in the PGE₁ group than that in the control group ($68 \pm 13\%$ vs $60 \pm 15\%$, $P = 0.054$). In conclusion, PGE₁ could almost entirely restore tissue oxygen extraction capabilities after endotoxin challenge on this dog model in which cardiac index was acutely reduced. The effects on oxygen extraction were present with or without concurrent saline administration, but the combination of PGE₁ with fluids improved global hemodynamics. Under control conditions, the influence of PGE₁ on the tissue oxygen extraction capabilities was not significant. © 1994 Academic Press, Inc.

INTRODUCTION

Severe sepsis is characterized by an increase in the cellular oxygen requirements, which must be met by an increase in oxygen delivery ($\dot{D}O_2$). Alteration in oxygen extraction may limit the ability of the tissues to maintain their oxygen uptake ($\dot{V}O_2$) when cardiac index and $\dot{D}O_2$ become inappropriate. The pathophysiological mechanisms involved in the alteration of the oxygen extraction have been related to a very complex cellular-humoral reaction, which eventually results in the release of toxic metabolites, including various proteases, arachidonic acid derivatives, and oxygen radicals. This process results in microembolic phenomena in the microcirculation, decreased sensitivity of the adrenergic receptors, alterations in the regulation of peripheral blood flow, impairment in the endothelial cell function, and alterations in microvascular permeability. The disruption of cellular function can also contribute to the abnormal oxygen utilization [1-3]. Once peripheral perfusion has been restored, a major therapeutic goal in sepsis is to maintain cardiac index and $\dot{D}O_2$ at sufficient levels. Attempts to increase oxygen extraction capabilities, although certainly appealing, have not been very successful.

Prostaglandin E₁ (PGE₁) has several properties that could be beneficial for the treatment of severe sepsis. First, it is a potent vasodilator of the pulmonary [4, 5]

and the systemic circulation that could increase capillary blood flow [6]. Second, like prostacyclin, it also has important anti-inflammatory effects by blocking macrophage activation [7] and by inhibiting the neutrophil release of oxygen radicals and lysosomal enzymes [8–10]. Third, it can influence coagulation by inhibiting platelet aggregation [11] and by inducing fibrinolysis [12]. As a result, PGE₁ has been shown to reduce the vascular permeability changes induced by vasoactive mediators [13–15] and to have pronounced cytoprotective effects in various experimental models [16, 17].

A number of studies have suggested some protective effects of PGE₁ on the pulmonary circulation and the cardiovascular function in animal models [18–23] and in humans with adult respiratory distress syndrome (ARDS) [24–28]. Some of these studies [24, 25, 28] suggested that PGE₁ like prostacyclin [29] might exert beneficial effects by increasing oxygen availability to the tissues in patients with ARDS and sepsis.

There are very little data, however, concerning the influence of PGE₁ on tissue oxygen extraction in severe sepsis. We hypothesized that PGE₁ could improve the cellular oxygen availability of the tissues by increasing their oxygen extraction capabilities. We therefore evaluated the effects of PGE₁ on the relationship between VO₂ and DO₂ during endotoxin-induced hyperdynamic sepsis in the dog. To study the maximal extraction capabilities of the animals, we progressively reduced blood flow by inducing tamponade. As we observed that PGE₁ increased the extraction capabilities under these conditions, we also studied the effects of PGE₁ on this tamponade model in the absence of endotoxin. A same dose of PGE₁ infusion had no significant influence on the extraction capabilities in these control experiments.

MATERIALS AND METHODS

Surgical Preparation

Forty-four mongrel dogs weighing 20–32 kg were anesthetized with pentobarbital sodium (30 mg/kg) and pancuronium (0.1 mg/kg). After endotracheal intubation, the dogs were ventilated with room air (Servo ventilator 900B; Siemens-Elcoma, Sweden) at a rate of 12 breaths/min and a tidal volume adjusted to obtain an end-tidal carbon dioxide tension (P_aCO₂) between 32 and 38 mm Hg. Anesthesia was maintained by a constant infusion of 4 mg/kg/hr pentobarbital and pancuronium bromide at 0.075 mg/kg/hr (Infusomat II, B. Braun, Melsungen AG, Germany). Exhaled gases were directed through a mixing chamber for sampling. The gas analyzers (P. K. Morgan LTD., Chatham, Kent, England) for expired oxygen fractions (F_EO₂) and carbon dioxide (47210A Capnometer, Hewlett-Packard, Waltham, MA) were calibrated before the experiment. Expired minute volume (V_E) was measured with a spirometer (Haloscale Wright Respirometer, Edrington, London, UK) over a 2-min pe-

riod. Electrocardiogram was continuously monitored. A catheter for arterial pressure monitoring and blood sampling was transcutaneously inserted in the left femoral artery. Another catheter was inserted into the right femoral vein for fluid infusion. The right forepaw vein was catheterized for the PGE₁ infusion (Perfusor Akkuport, ED-EDL, Melsungen AG, Germany). After cutdown of the right jugular vein, a balloon-tipped pulmonary artery catheter (Swan-Ganz catheter Model 93A-131-7F, Baxter, Irvine, CA) was positioned in the pulmonary artery under guidance of pressure waves (monitor Sirecust 302A, Siemens, Erlangen, Germany). The left chest was entered through the fifth intercostal space and the pericardium was cannulated with a 16-gauge polyethylene catheter (Intracath, Deseret Medical Inc., Sandy, UT) with multiple side holes. This was secured with 00 silk purse-string sutures and sealed with medical glue. The chest was closed in three layers before a chest tube (Argyle, Trocar catheter A75, 28Ch-40cm, Tullamore, Ireland) was placed through the seventh intercostal space. Temperature was maintained at initial levels using a heating blanket or warming lamps.

Experimental Protocol

After the surgical preparation, the dog was returned to a supine position and permitted to stabilize for 30 min before the first baseline measurements (Baseline 1). The study consisted of two experimental series:

First series: Endotoxin experiments. Thirty dogs were randomly divided into three groups: Group 1 (10 dogs) received 20 ml/kg/h of normal saline; Group 2 (10 dogs) received the same saline infusion and 100 ng/kg/min of PGE₁ (Prostin, prepared in a saline solution of 10 µg/ml); Group 3 (10 dogs) received the same dose of PGE₁ with only 1 ml/kg/h of saline infusion. Thirty minutes later, a second set of baseline (Baseline 2) was determined, before a bolus of *Escherichia coli* endotoxin (055B5, Difco Laboratories, Detroit, MI) diluted in 0.9% saline (10 mg/ml) was injected. A third set of baseline measurements (Baseline 3) was obtained 30 min later, before tamponade was induced.

Second series: No endotoxin. Fourteen dogs were randomly divided into two groups (7 dogs for each group), the same protocols as those for Group 1 and Group 2 of the first series were applied, but no endotoxin was administered.

In each animal of the two series, cardiac tamponade was progressively induced by repeated bolus injections of normal saline heated to 37°C into the pericardial space. The amount of saline injected was 20 ml for the first two injections, followed by 15 ml for the next two injections, and 10 ml thereafter until VO₂ started to fall from baseline. Then the amount of saline was reduced to 5 ml until the mean arterial pressure fell by 70% and the experiment was then ended. A steady state characterized

TABLE 1
Selected Parameters during Experimental Cardiac Tamponade Following Endotoxin Administration

	IPP (mm Hg)									
	Baseline 1	Baseline 2	Baseline 3	0	2	4	6	8	10	12
Heart rate (beats/min)										
Fluids (N = 10)	177 ± 13	189 ± 14	174 ± 24	173 ± 26	174 ± 27	171 ± 26	170 ± 24	166 ± 42	164 ± 39* (N = 8)	154 ± 32* (N = 6)
P + F (N = 10)	172 ± 11	177 ± 11	178 ± 19	177 ± 14	178 ± 16	169 ± 19	175 ± 23	172 ± 26	174 ± 22†	157 ± 30*†
PGE ₁ (N = 10)	171 ± 22	182 ± 23	209 ± 22*	207 ± 23*	184 ± 26	182 ± 20	176 ± 25	170 ± 27	151 ± 29* (N = 8)	120 ± 49* (N = 2)
PAOP (mm Hg)										
Fluids (N = 10)	3.4 ± 1.0	4.8 ± 1.2	3.7 ± 0.9	4.4 ± 1.1	5.8 ± 1.5	8.7 ± 1.4*	9.8 ± 1.7*	10.6 ± 1.5*	14.7 ± 1.6* (N = 8)	15.6 ± 1.8* (N = 6)
P + F (N = 10)	3.7 ± 0.9	3.4 ± 0.9	3.4 ± 1.2	4.1 ± 0.7	5.7 ± 1.6	7.6 ± 1.4*	9.4 ± 1.2*	9.5 ± 1.4*	12.8 ± 2.0*	14.5 ± 2.8*
PGE ₁ (N = 10)	3.4 ± 1.7	3.6 ± 1.5	3.6 ± 1.7	3.8 ± 1.1	6.0 ± 1.7	6.5 ± 1.4*	7.7 ± 1.4*	7.9 ± 1.5*	11.2 ± 1.6* (N = 8)	14.0 ± 3.1* (N = 2)
RAP (mm Hg)										
Fluids (N = 10)	3.1 ± 1.1	5.0 ± 0.8*	2.6 ± 1.4	3.6 ± 1.7	4.7 ± 0.9*	6.7 ± 1.1*	9.1 ± 1.5*	11.5 ± 1.6*	14.1 ± 1.6* (N = 8)	14.4 ± 2.6* (N = 6)
P + F (N = 10)	3.4 ± 1.0	3.5 ± 1.1	3.5 ± 1.2	4.3 ± 1.3	6.0 ± 1.3*	8.6 ± 1.0*	9.6 ± 1.2*	12.0 ± 0.8*	14.8 ± 1.2*	15.9 ± 1.3*
PGE ₁ (N = 10)	2.9 ± 1.2	3.0 ± 1.3	2.7 ± 1.1	3.1 ± 1.4	4.9 ± 1.5*	6.0 ± 1.3*	7.8 ± 1.8*	9.5 ± 2.0*	11.6 ± 3.1* (N = 8)	13.0 ± 2.1* (N = 2)
Stroke volume (ml)										
Fluids (N = 10)	13.5 ± 2.6	16.0 ± 3.6	18.6 ± 4.0*†	18.6 ± 3.7*†	17.8 ± 3.3*†	15.9 ± 3.7	13.6 ± 4.3	11.6 ± 2.9*	6.9 ± 2.3* (N = 8)	4.4 ± 3.6* (N = 6)
P + F (N = 10)	14.2 ± 2.7	18.2 ± 4.1*	18.9 ± 3.7*†	23.2 ± 7.6*††	23.6 ± 9.0*††	19.7 ± 3.8*†	17.8 ± 8.7*†	15.4 ± 4.5†	10.6 ± 4.8*†	8.4 ± 4.9*†
PGE ₁ (N = 10)	15.5 ± 5.2	18.9 ± 4.8	12.2 ± 5.4*	13.9 ± 5.6	11.1 ± 5.4*	10.2 ± 5.5*	7.9 ± 4.2*	6.2 ± 2.1*	5.0 ± 3.8* (N = 8)	3.2 ± 2.4* (N = 2)
P_iO₂ (mm Hg)										
Fluids (N = 10)	69.9 ± 7.6	70.2 ± 6.5	63.7 ± 13.2	64.7 ± 13.1	62.7 ± 13.1	62.4 ± 12.1	62.7 ± 13.1	62.3 ± 12.4	61.7 ± 12.7 (N = 8)	58.5 ± 14.5 (N = 6)
P + F (N = 10)	73.5 ± 10.0	71.9 ± 7.6	70.7 ± 8.6	62.8 ± 2.6*	60.9 ± 5.6*	59.1 ± 5.9*	58.3 ± 7.5*	58.0 ± 4.3*	56.3 ± 7.7*	55.2 ± 7.6*
PGE ₁ (N = 10)	73.9 ± 7.3	73.9 ± 8.2	67.6 ± 11.2*	63.6 ± 11.3*	61.5 ± 10.2*	61.5 ± 9.0*	60.3 ± 7.5*	59.7 ± 8.5*	55.7 ± 8.5* (N = 8)	56.3 ± 7.8* (N = 2)
P_aO₂ (mm Hg)										
Fluids (N = 10)	41.5 ± 6.8	42.6 ± 5.7	41.4 ± 4.4	41.6 ± 5.8	40.7 ± 5.4	38.7 ± 5.0	35.1 ± 6.7*	31.8 ± 9.7*	29.4 ± 9.6* (N = 8)	28.7 ± 9.6* (N = 6)
P + F (N = 10)	41.4 ± 4.8	42.6 ± 5.9	42.6 ± 3.7	43.1 ± 4.3	42.8 ± 4.5	47.5 ± 7.3†	41.1 ± 6.3†	39.3 ± 4.3†	34.1 ± 5.4*	32.3 ± 7.4*†
PGE ₁ (N = 10)	39.1 ± 4.2	40.1 ± 4.2	36.0 ± 5.0*	38.4 ± 4.7	38.2 ± 4.6	35.4 ± 5.1*	31.2 ± 7.1*	28.8 ± 6.6*	25.2 ± 6.6* (N = 8)	21.3 ± 5.8* (N = 2)
Hemoglobin (g/dl)										
Fluids (N = 10)	16.8 ± 2.3	16.5 ± 2.2	16.6 ± 2.7	16.2 ± 2.7	15.9 ± 3.3	15.2 ± 3.1	15.5 ± 3.7	15.3 ± 3.4	17.5 ± 1.9 (N = 8)	18.0 ± 1.4 (N = 6)
P + F (N = 10)	16.2 ± 2.4	16.2 ± 2.3	16.2 ± 1.9	16.1 ± 2.0	15.3 ± 1.8	16.6 ± 2.0	15.8 ± 2.2	16.0 ± 2.3	15.3 ± 2.4	15.7 ± 2.5
PGE ₁ (N = 10)	14.6 ± 1.8	14.6 ± 1.8	15.3 ± 1.7	14.7 ± 1.7	15.7 ± 1.6	15.7 ± 1.9	15.9 ± 2.1	15.7 ± 2.2	15.6 ± 2.9 (N = 8)	14.0 ± 2.7 (N = 2)
Lactate (mmol/liter)										
Fluids (N = 10)	2.2 ± 0.5	1.8 ± 0.5*	2.8 ± 1.5	2.8 ± 1.2	3.2 ± 1.0*	3.8 ± 0.9*	4.7 ± 1.3*	6.5 ± 3.1*	7.4 ± 2.6* (N = 8)	5.8 ± 2.3* (N = 6)
P + F (N = 10)	2.0 ± 0.8	2.0 ± 0.5	2.4 ± 0.7	2.6 ± 0.8	2.7 ± 0.8	3.0 ± 0.9†	2.6 ± 0.9†	2.8 ± 1.2††	3.4 ± 1.2*††	4.3 ± 1.5*†
PGE ₁ (N = 10)	2.2 ± 0.7	1.9 ± 0.7*	2.7 ± 1.0	2.6 ± 1.1	3.4 ± 0.9*	3.2 ± 0.9*	3.8 ± 1.3*	4.3 ± 1.8*	5.6 ± 2.1* (N = 8)	4.8 ± 1.9* (N = 2)

Note. Values shown as mean ± SD. Fluids, Fluid infusion alone; P + F, PGE₁ plus fluids, PGE₁, PGE₁ infusion alone. Baseline 1, after stabilization; Baseline 2, after PGE₁, fluids, or both; Baseline 3, after endotoxin administration. IPP, intrapericardial pressure; PAOP, pulmonary artery occlusion pressure; RAP, right atrial pressure.

* P < 0.05 vs Baseline 1.

† P < 0.05 vs. Fluids.

†† P < 0.05 vs. PGE₁.

by stable heart rate, arterial pressure, $F_{E}O_2$, and $P_{a}CO_2$ was obtained between two successive pericardial saline injections. Then measurements were performed, including heart rate, systemic arterial pressure, pulmonary ar-

terial pressure, pulmonary arterial occlusion pressure, right atrial pressure, intrapericardial pressure, cardiac index, $F_{E}O_2$, $P_{a}CO_2$, V_E , arterial and mixed venous blood gases, and arterial blood lactate concentration.

TABLE 2
Values at Critical O₂ Delivery in Endotoxic Shock Series

	DO ₂ (ml/kg/min)	VO ₂ (ml/kg/min)	O ₂ ER (%)	Cardiac index (liters/min/kg)	Lactate (mmol/liter)
Fluids (N = 10)	12.2 ± 2.8	5.5 ± 1.2	46.6 ± 13.7	0.07 ± 0.02	4.9 ± 1.4
PGE ₁ + fluids (N = 10)	9.8 ± 2.0*	6.0 ± 1.2	63.2 ± 16.2*	0.05 ± 0.01*	3.5 ± 1.4*
PGE ₁ (N = 10)	9.3 ± 2.7*	5.3 ± 0.7	61.0 ± 16.6*	0.04 ± 0.01*	4.0 ± 1.5

Note. Values displayed as means ± SD.

* P < 0.05 vs fluids.

Pressures were measured with transducers at the mid-chest level, calibrated before each measurement, and recorded on a multichannel recorder (2600S recorder, Gould, Cleveland, OH). Cardiac output was determined by the thermodilution technique (Cardiac output computer, COM-2, Baxter, Irvine, CA) using three to five injections of 5 ml of cold 5% dextrose in ice water. Each injection was started at end-inspiration. After each cardiac output determination, arterial and mixed venous blood samples were simultaneously withdrawn for immediate measurement of arterial and mixed venous blood gases and hemoglobin oxygen saturations and hemoglobin and lactate concentrations [blood gas analyzer ABL2, Radiometer, Copenhagen, Denmark; Co-oximeter 282 (calibrated for canine blood), Instrumentation Laboratories, Lexington, MA; and lactate analyzer 640, Kontron Instruments, Basel, Switzerland]. $\dot{V}O_2$ was determined from the formula

$$\dot{V}O_2 \text{ (ml/kg/min)} = V_E \text{ (ml/kg)} \times \{[(1 - F_{E}O_2 - F_{E}CO_2)/(1 - 0.21)] \times 0.21 - F_{E}O_2\},$$

where $F_{E}CO_2$ represents the expired carbon dioxide fraction. $\dot{V}O_2$ was calculated as the product of cardiac index and arterial oxygen content. Oxygen extraction ratio (O_2ER) was derived from the ratio of $\dot{V}O_2/\dot{V}O_{2i}$.

Statistical Methods

A dual-line regression method [30] was used to determine the critical $\dot{V}O_2$ ($\dot{V}O_{2crit}$) in each animal from a plot of $\dot{V}O_2/\dot{V}O_{2i}$. The critical O_2ER ($O_{2ERcrit}$) was calculated by the ratio of $\dot{V}O_2/\dot{V}O_{2i}$ at $\dot{V}O_{2crit}$. An ANOVA for repeated measurements was used to make the statistical analysis. When the F value was statistically significant, inter- and intragroup comparisons for repeated data were made by Dunnett's multiple comparison test. A Student t test was used to compare the values at $\dot{V}O_{2crit}$. The slopes of $\dot{V}O_2/\dot{V}O_{2i}$ were tested by covariance analysis. All data are expressed as means $\pm$ SD. Statistical significance was accepted at $P < 0.05$.

RESULTS

Endotoxin Experiments (Tables 1 and 2 and Figs. 1-4)

Before endotoxin. In the first group of animals, saline infusion was associated with an increase in mean arterial pressure, in cardiac filling pressures, and in cardiac index. In the group given PGE₁ + fluids, cardiac filling pressures were maintained and pulmonary artery pressure and systemic and pulmonary vascular resistances tended to decrease. Cardiac index and stroke volume increased to a larger extent than in the first group. $\dot{V}O_2$ also increased but $\dot{V}O_2$ remained stable. In the group receiving PGE₁ alone, these changes were less significant, but cardiac index increased.

After endotoxin. In all animals, endotoxin produced a significant decrease in mean arterial pressure. In the

FIG. 1. Relationship between mean arterial pressure (MAP), cardiac index (CI), systemic vascular resistance (SVR), and intrapericardial pressure (IPP) in the three groups of endotoxin-challenged animals. B1, measurements after stabilization; B2, 30 min after fluids, PGE₁ + fluids, or PGE₁ alone administration; B3, 30 min after endotoxin administration. * $P < 0.05$ vs fluids; † $P < 0.05$ vs PGE₁.

dogs treated only with fluids, stroke volume, cardiac index, and $\dot{V}O_2$ increased, but $\dot{V}O_2$ did not change; therefore, O_2ER tended to decrease. In the group given PGE₁ + fluids, the changes were similar, except that $\dot{V}O_2$ also increased. In the animals given only PGE₁, there was a

profound reduction in mean arterial pressure. Despite a significant increase in heart rate, cardiac index declined, indicating a marked reduction in stroke volume. A decrease in arterial oxygen tension (P_aO_2) contributed to a fall in DO_2 , but VO_2 remained constant due to a significant increase in O_2ER .

Cardiac tamponade. The stepwise increase in intrapericardial pressure resulted in progressive reductions in arterial pressure, cardiac index, stroke volume, DO_2 , and mixed venous oxygen tension (P_vO_2) in all animals. Pulmonary vascular resistance was lower in the dogs receiving PGE_1 + fluids than in those receiving fluids alone. Stroke volume and cardiac index were higher in the PGE_1 + fluids-treated group than in the other groups throughout the study. In contrast, in the animals given PGE_1 alone, mean systemic arterial pressure, stroke volume, and cardiac index were lower and vascular resistances were higher than those in the other groups. Before intrapericardial pressure reached 12 mm Hg, death occurred in 4 of the 10 dogs treated with fluids, 8 of the 10 dogs treated with PGE_1 , but none of the 10 dogs treated with PGE_1 + fluids.

FIG. 2. Relationship between mean pulmonary arterial pressure (MPAP), pulmonary vascular resistance (PVR), and intrapericardial pressure (IPP) in the three groups of endotoxin-challenged animals (see legend to Fig. 1 for details).

FIG. 3. Relationship between oxygen delivery (DO_2), oxygen uptake (VO_2), oxygen extraction ratio (O_2ER), and intrapericardial pressure (IPP) in the three groups of endotoxin-challenged animals (see legend to Fig. 1 for details).

Cardiac tamponade resulted in a progressive reduction in DO_2 . At any level of intrapericardial pressure, VO_2 remained higher in the PGE_1 + fluids-treated group than in the other groups. When intrapericardial pressure reached 12 mm Hg, VO_2 had fallen by 51 and 60% from baseline in the animals treated either with fluids or with PGE_1 alone, respectively (both $P < 0.01$) but only by 10% in those treated with PGE_1 and fluids ($P = NS$).

FIG. 4. Illustrative example of the relationship between oxygen uptake (VO_2) and oxygen delivery (DO_2) in one dog treated with fluids (triangles) and one dog treated with PGE_1 + fluids (open circles) after endotoxin challenge.

Blood lactate was lower in the PGE_1 + fluids-treated group than in the control group when intrapericardial pressure reached above 4 mm Hg.

At $\text{DO}_{2\text{crit}}$. $\text{DO}_{2\text{crit}}$ was 12.2 ± 2.8 ml/kg/min in the animals treated only with fluids vs 9.8 ± 2.0 ml/kg/min in those treated with PGE_1 + fluids and 9.3 ± 2.7 ml/kg/min in the animals treated with PGE_1 alone (both $P < 0.05$). VO_2 at $\text{DO}_{2\text{crit}}$ was slightly higher in the PGE_1 + fluids-treated dogs, but this difference did not reach statistical significance. $\text{O}_2\text{ER}_{\text{crit}}$ was $47 \pm 14\%$ in the group treated with only fluids vs $63 \pm 16\%$ with PGE_1 + fluids and $61 \pm 17\%$ with PGE_1 alone (both $P < 0.05$). Moreover, the slope of the VO_2/DO_2 -dependent line, which was 0.44 ± 0.15 in the animals treated only with fluids, 0.64 ± 0.15 in those treated with PGE_1 + fluids ($P < 0.01$), and 0.57 ± 0.24 in the PGE_1 alone-treated animals ($P = \text{NS}$). Blood lactate at $\text{DO}_{2\text{crit}}$ was lower in the PGE_1 + fluids-treated than in the control group.

Figure 4 represents the relation between VO_2 and DO_2 in a representative experiment.

No Endotoxin (Table 3 and Figs. 5 and 6)

The PGE_1 -treated animals had significant increase in cardiac index and DO_2 and reductions in systemic vascular resistance and blood lactate levels. DO_2 was higher and the O_2ER lower in the PGE_1 -treated group than in the control group only in the initial stages of cardiac tamponade. VO_2 had an identical course in the two groups. In the later stages of the study, pulmonary vascular resistance was lower in the PGE_1 group than in the control group.

$\text{DO}_{2\text{crit}}$ was similar in the two groups (10.7 ± 2.9 ml/kg/min in the PGE_1 and 10.1 ± 1.8 ml/kg/min in the control group, respectively, $P = \text{NS}$); VO_2 at $\text{DO}_{2\text{crit}}$ in the PGE_1 group tended to be higher than in the control

group (7.2 ± 1.3 vs 6.4 ± 1.3 ml/kg/min, $P = \text{NS}$). $\text{O}_2\text{ER}_{\text{crit}}$ was $68 \pm 13\%$ in the PGE_1 group vs $60 \pm 15\%$ in the control group ($P = 0.054$). There was no significant difference in the slopes of the VO_2/DO_2 -dependent lines (0.69 ± 0.29 vs 0.51 ± 0.33 , $P = \text{NS}$).

DISCUSSION

The present study tested the hypothesis that PGE_1 may improve systemic oxygen extraction capabilities in sepsis. The circulatory profile of the present model combining a bolus injection of endotoxin and generous fluid resuscitation reproduced the early hyperdynamic phase of clinical sepsis, characterized by an increase in stroke volume and cardiac index and a decrease in systemic vascular resistance. As it was shown in our earlier experience [31], this hyperdynamic profile could be achieved by the generous administration of a saline solution.

To study the oxygen extraction capabilities of the whole body, we induced cardiac tamponade to acutely reduce blood flow. We recently observed that on this model, endotoxin administration increased $\text{DO}_{2\text{crit}}$ by more than 20%, i.e., from 9.5 to 12.1 ml/kg/min [32]. In the present study, PGE_1 administration resulted in significant improvement in oxygen extraction capabilities, as indicated by a marked reduction in $\text{DO}_{2\text{crit}}$ from 12.2 to less than 10 ml/kg/min, an increase in $\text{O}_2\text{ER}_{\text{crit}}$, and a greater slope for the dependent portion of the VO_2/DO_2 relationship. Actually, PGE_1 appeared to entirely restore the oxygen extraction capabilities [32, 33].

The increase in tissue oxygen extraction capabilities after PGE_1 administration may be related to the effects of the arteriolar and venular vasodilating effects of PGE_1 [34], which could reduce the diffusion distance for oxygen transfer from the capillaries to the cells [35, 36]. If this were true, the associated fluid administration would be crucial. We therefore also studied the effects of PGE_1 on oxygen extraction capabilities without volume expansion. As expected, the animals treated with PGE_1 + fluids had a greater cardiac index and DO_2 than those treated only by PGE_1 without volume administration. However, the improvement in oxygen extraction was unaltered.

PGE_1 can increase oxygen extraction capabilities after endotoxin by several mechanisms. By its microvascular action, PGE_1 may improve the microvascular blood supply and thereby increase the surface available for oxygen exchange. In support to this concept, Bulkley and co-workers [37–39] described that renin-angiotensin-mediated selective mesenteric vasoconstriction accounts for more than 40% of the overall increase in systemic vascular resistance during cardiac tamponade in pigs. The same investigators reported that prostacyclin and PGE_1 increased blood flow to mesenteric and renal vasculatures by their vasodilating effect. PGE_1 can also decrease adherence of neutrophils to the endothelial

TABLE 3

Selected Hemodynamic Parameters and Lactate during Cardiac Tamponade in the Absence of Endotoxin

	IPP (mm Hg)								
	Baseline 1	Baseline 2	0	2	4	6	8	10	12
Heart rate (beats/min)									
Control (N = 7)	157 ± 10	148 ± 15	153 ± 18	159 ± 27	162 ± 11	169 ± 21	165 ± 16	166 ± 14 (N = 4)	164 ± 12 (N = 2)
PGE ₁ (N = 7)	167 ± 15	171 ± 16	166 ± 24	165 ± 24	158 ± 39	162 ± 39	157 ± 29	145 ± 22*† (N = 5)	138 ± 10*† (N = 3)
MAP (mm Hg)									
Control (N = 7)	96 ± 21	98 ± 9	103 ± 16	96 ± 19	89 ± 17	77 ± 21*	71 ± 22*	58 ± 28* (N = 4)	45 ± 26* (N = 2)
PGE ₁ (N = 7)	108 ± 13	103 ± 15	106 ± 14	100 ± 11	91 ± 23	78 ± 24*	59 ± 21*	39 ± 17*† (N = 5)	36 ± 16* (N = 3)
MPAP (mm Hg)									
Control (N = 7)	12 ± 3	13 ± 2	14 ± 3	14 ± 2	15 ± 2	16 ± 2	17 ± 3*	18 ± 3* (N = 4)	18 ± 3* (N = 2)
PGE ₁ (N = 7)	14 ± 2	13 ± 2	13 ± 2	13 ± 1	14 ± 3	14 ± 3	15 ± 2	16 ± 3 (N = 5)	16 ± 2 (N = 3)
Cardiac index (liters/min/kg)									
Control (N = 7)	0.19 ± 0.04	0.19 ± 0.04	0.16 ± 0.05	0.12 ± 0.03*	0.11 ± 0.03*	0.09 ± 0.02*	0.08 ± 0.03*	0.07 ± 0.04* (N = 4)	0.04 ± 0.03* (N = 2)
PGE ₁ (N = 7)	0.20 ± 0.07	0.25 ± 0.06†	0.21 ± 0.05	0.18 ± 0.06†	0.14 ± 0.06*	0.10 ± 0.05*	0.08 ± 0.03*	0.05 ± 0.02* (N = 5)	0.01 ± 0.01* (N = 3)
Lactate (mmol/liter)									
Control (N = 7)	2.1 ± 1.5	2.0 ± 1.3	1.9 ± 0.7	2.3 ± 0.6	2.8 ± 0.8	3.4 ± 0.8*	3.8 ± 1.4*	5.5 ± 3.3* (N = 4)	5.8 ± 3.3* (N = 2)
PGE ₁ (N = 7)	2.0 ± 0.8	1.5 ± 0.6*	1.7 ± 0.7	1.7 ± 0.5	2.2 ± 0.7	2.8 ± 0.8†	3.3 ± 1.3*	4.5 ± 2.2*† (N = 5)	5.4 ± 2.1* (N = 3)

Note. Values shown as means ± SD. Baseline 1, after stabilization; Baseline 2, after PGE₁ administration. IPP, intrapericardial pressure; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure.

* $P < 0.05$ vs Baseline 1.

† $P < 0.05$ between control and PGE₁.

membrane and subsequent neutrophil-mediated tissue injury [8, 13, 14] associated with a reduced release of oxygen free radicals [9, 10]. PGE₁ can also block coagulation by its anti-platelet [11] and fibrinolytic actions [12].

To differentiate specific effects of PGE₁ during endotoxin-induced alterations from an unspecific effect of this vasodilating substance, we studied the effects of the administration of PGE₁ with fluids in the absence of endotoxin. Since the first part of the study had shown the importance of adequate volume loading during the PGE₁ administration, we did not study a PGE₁ alone group in this second series of control experiments. In the absence of endotoxin, the effects of PGE₁ on oxygen extraction capabilities were not significant, suggesting that PGE₁ specifically counteracts the peripheral effects of endotoxin. These latter results differ from those recently reported by Groeneveld and co-workers [23] showing that PGE₁ significantly decreased DO_{2crit} by increasing O_2ER_{crit} when incremental positive end-expiratory pressure was applied in pigs. These differences may be due to differences in animal models and also in doses of PGE₁, since Groeneveld *et al.* [23] used a very high dose of 200 ng/kg/min of PGE₁. Intriguingly, these authors reported a baseline O_2ER of 41% and an O_2ER_{crit} of 48%, whereas we, like others, observed a baseline O_2ER below 25% and an O_2ER_{crit} between 60 and 70% in the control and between 45 and 50% in the endotoxic conditions [30, 32, 33, 40]. Although normal O_2ER values have been less well established for pigs than for dogs, these differences raise the possibility that oxygen extraction capabilities were altered in the study by Groeneveld *et al.* [23].

The present protocol allowed us to study only one dose of PGE₁. We chose a dose of 100 ng/kg/min since it is considered the maximal dose without a detrimental effect on the systemic arterial pressure [20]. At this dose, PGE₁ increased stroke volume and cardiac index and reduced systemic and pulmonary vascular resistance. These cardiovascular effects of PGE₁ have been reported in other experimental [18–21] and clinical [6, 24, 25, 41] studies. In the PGE₁-treated animals we also observed a slight reduction in P_aO_2 , which can be explained by an inhibition of the hypoxic pulmonary vasoconstriction related to the pulmonary vasodilating properties of PGE₁ [42]. An additional finding was that dogs treated with PGE₁ + fluids showed greater tolerance to higher intrapericardial pressure than the other animals. The lower lactate level at DO_{2crit} in the animals treated by PGE₁ + fluids than in the other groups also suggests an improvement in cellular oxygen availability. In the earlier experimental and clinical studies, several groups of investigators reported that PGE₁ increased cardiac index, DO_2 , or VO_2 , and suggested a beneficial effect of PGE₁ on systemic tissue perfusion [19, 24, 25, 28, 41]. As in the other studies, the present investigation explored only the global effects of PGE₁ on the relation between VO_2 and DO_2 , and the effects of PGE₁ might not be equally distributed to all organs. However, Raper *et al.* [43] recently reported that PGE₁ could increase systemic blood flow proportionately to all organs, except the kidney.

The clinical application of these observations may be limited by several factors. First, although no detrimental systemic hypotension was observed with PGE₁, vasodi-

lators should be administered cautiously during sepsis when vasodilation is already prominent. Second, PGE₁, like other prostaglandins, might reduce the immunological response to infection [44]. Third, the reduction in P_aO_2 induced by PGE₁ might not be well tolerated in the presence of severe respiratory failure. Several clinical studies [24–26] reported that an infusion of PGE₁ in patients with ARDS could be beneficial, but a large multicenter study [41] failed to show an increased survival in PGE₁-treated patients. However, this study included 100 patients with ARDS due to a variety of disease states and was not specifically focused on sepsis. In addition, the dose of 30 ng/kg/min administered in that study was lower than the one used in the present study. The present results are encouraging, because they demonstrate that a therapeutic intervention may significantly increase oxygen extraction in severe sepsis. Although sepsis is characterized by a fall in vascular tone, vasoconstrictive catecholamines have not been shown conclusively to increase oxygen extraction capabilities [40, 45, 46]. The present study demonstrates that a vasodilating prostaglandin can exert beneficial circulatory effects in endotoxic shock.

FIG. 5. Relationship between systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), and intrapericardial pressure (IPP) in the control experiments. B1, measurements after stabilization; B2, 30 min after either fluids or PGE₁ + fluids administration. * $P < 0.05$ vs PGE₁.

FIG. 6. Relationship between oxygen delivery (DO_2), oxygen uptake (VO_2), oxygen extraction ratio (O_2ER), and intrapericardial pressure (IPP) in the control experiments (see legend to Fig. 5 for details).

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