Prostaglandin E₁ Increases Oxygen Extraction Capabilities in Experimental Sepsis

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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 (VO₂) and oxygen delivery (DO₂) during an acute reduction in blood flow induced by cardiac tamponade in endotoxemic 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 VO₂ (derived from the expired gases) and DO₂ (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 DO₂ 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 VO₂ levels at critical DO₂ (DO₂crit) were identical. However, DO₂crit, 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 group and to 9.3 ± 2.7 ml/kg/min in the PGE₁ alone group (both P < 0.05). Critical oxygen extraction ratio (O₂ERcrit) which was 47 ± 14% in the control group, was increased to 65 ± 16% in the PGE₁ + fluids group and to 61 ± 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). DO₂crit was 10.7 ± 2.9 ml/kg/min in the PGE₁ group vs 10.1 ± 1.8 ml/kg/min in the control group (NS). O₂ERcrit tended to be higher in the PGE₁ group than that in the control group (88 ± 13% vs 60 ± 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.

INTRODUCTION

Severe sepsis is characterized by an increase in the cellular oxygen requirements, which must be met by an increase in oxygen delivery (DO₂). Alteration in oxygen extraction may limit the ability of the tissues to maintain their oxygen uptake (VO₂) when cardiac index and DO₂ become inappropiate. 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 DO₂ 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, PGE₂ 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 PGE₂ 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 PGE₂, 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 PGE₂ on tissue oxygen extraction in severe sepsis. We hypothesized that PGE₂ could improve the cellular oxygen availability of the tissues by increasing their oxygen extraction capabilities. We therefore evaluated the effects of PGE₂ 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 PGE₂ increased the extraction capabilities under these conditions, we also studied the effects of PGE₂ on this tamponade model in the absence of endotoxin. A same dose of PGE₂ infusion had no significant influence on the extraction capabilities in these control experiments.

MATERIALS AND METHODS

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 PGE₂ (Prostin, prepared in a saline solution of 10 μg/ml); Group 3 (10 dogs) received the same dose of PGE₂ 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 Endotoxic Administration

<table>
<thead>
<tr>
<th></th>
<th>Baseline 1</th>
<th>Baseline 2</th>
<th>Baseline 3</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart rate</strong></td>
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<tr>
<td>(beats/min)</td>
<td>177±13</td>
<td>169±14</td>
<td>174±24</td>
<td>173±25</td>
<td>174±27</td>
<td>171±26</td>
<td>170±24</td>
<td>160±42</td>
<td>164±39* (N=9)</td>
</tr>
<tr>
<td><strong>PAOP (mm Hg)</strong></td>
<td>172±11</td>
<td>177±11</td>
<td>178±19</td>
<td>177±14</td>
<td>178±16</td>
<td>169±10</td>
<td>175±23</td>
<td>172±28</td>
<td>174±27*</td>
</tr>
<tr>
<td><strong>PGE</strong> (N=10)</td>
<td>171±22</td>
<td>162±23</td>
<td>169±21</td>
<td>207±25*</td>
<td>207±25*</td>
<td>184±36</td>
<td>182±20</td>
<td>178±55</td>
<td>170±27</td>
</tr>
<tr>
<td><strong>RAP (mm Hg)</strong></td>
<td>172±11</td>
<td>177±11</td>
<td>178±19</td>
<td>177±14</td>
<td>178±16</td>
<td>169±10</td>
<td>175±23</td>
<td>172±28</td>
<td>174±27*</td>
</tr>
<tr>
<td><strong>Fluids (N=10)</strong></td>
<td>3.4±1.0</td>
<td>4.8±1.2</td>
<td>3.7±0.9</td>
<td>4.4±1.1</td>
<td>5.8±1.5</td>
<td>8.7±1.4*</td>
<td>9.8±1.7*</td>
<td>10.6±1.5*</td>
<td>14.7±1.6* (N=6)</td>
</tr>
<tr>
<td><strong>P + F (N=10)</strong></td>
<td>3.7±0.9</td>
<td>3.8±0.8</td>
<td>3.4±1.6</td>
<td>4.1±0.7</td>
<td>5.7±1.6</td>
<td>7.8±1.4*</td>
<td>9.4±1.2*</td>
<td>9.5±1.4*</td>
<td>12.8±2.0*</td>
</tr>
<tr>
<td><strong>PGE (N=10)</strong></td>
<td>3.4±0.7</td>
<td>3.6±1.6</td>
<td>3.6±1.7</td>
<td>3.8±1.1</td>
<td>6.0±1.7</td>
<td>6.3±1.4*</td>
<td>7.7±1.4*</td>
<td>7.9±1.5*</td>
<td>11.2±1.6* (N=6)</td>
</tr>
<tr>
<td><strong>Stroke volume (mL)</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fluids (N=10)</strong></td>
<td>3.1±1.1</td>
<td>5.0±0.8*</td>
<td>3.6±1.4</td>
<td>3.6±1.7</td>
<td>4.7±0.9*</td>
<td>6.7±1.1*</td>
<td>9.1±1.5*</td>
<td>11.5±1.0*</td>
<td>14.1±1.2* (N=8)</td>
</tr>
<tr>
<td><strong>P + F (N=10)</strong></td>
<td>3.4±1.0</td>
<td>3.5±1.3</td>
<td>3.5±1.2</td>
<td>4.3±1.3</td>
<td>5.0±1.3*</td>
<td>8.4±1.0*</td>
<td>9.6±1.2*</td>
<td>12.0±0.9*</td>
<td>14.8±1.2*</td>
</tr>
<tr>
<td><strong>PGE (N=10)</strong></td>
<td>2.9±1.2</td>
<td>3.0±1.3</td>
<td>2.7±1.1</td>
<td>3.1±1.4</td>
<td>4.9±1.5*</td>
<td>6.0±1.3*</td>
<td>7.8±1.8*</td>
<td>9.5±2.0*</td>
<td>11.6±3.1* (N=9)</td>
</tr>
</tbody>
</table>

**Note.** Values shown as mean ± SD. Fluids, Fluid infusion alone; P + F, PGE, plus fluids, PGE, PGE, infusion alone. Baseline 1, after stabilization; Baseline 2, after PGE, fluids, or both; Baseline 3, after endotoxic administration. IPP, intrapercardial 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. PGE.

by stable heart rate, arterial pressure, \( F_O_2 \), and \( P_CO_2 \) was obtained between two successive pericardial saline injections. Then measurements were performed, including heart rate, systemic arterial pressure, pulmonary arterial pressure, pulmonary arterial occlusion pressure, right atrial pressure, intrapercardial pressure, cardiac index, \( F_O_2 \), \( P_CO_2 \), \( V_E \), arterial and mixed venous blood gases, and arterial blood lactate concentration.

### TABLE 2

Values at Critical \( O_2 \) Delivery in Endotoxic Shock Series

<table>
<thead>
<tr>
<th></th>
<th>( DO_2 ) (ml/kg/min)</th>
<th>( VO_2 ) (ml/kg/min)</th>
<th>( O_2ER ) (%)</th>
<th>Cardiac index (liters/min/kg)</th>
<th>Lactate (mmol/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fluids (N=10)</strong></td>
<td>12.2±2.8</td>
<td>5.5±1.2</td>
<td>46.6±13.7</td>
<td>0.07±0.02</td>
<td>4.9±1.4</td>
</tr>
<tr>
<td><strong>PGE + fluids (N=10)</strong></td>
<td>9.8±2.0*</td>
<td>6.0±1.2</td>
<td>63.2±16.2*</td>
<td>0.05±0.01*</td>
<td>3.5±1.4*</td>
</tr>
<tr>
<td><strong>PGE (N=10)</strong></td>
<td>9.3±2.7*</td>
<td>5.3±0.7</td>
<td>61.0±16.6*</td>
<td>0.04±0.01*</td>
<td>4.0±1.5</td>
</tr>
</tbody>
</table>

**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). VO₂ was determined from the formula

\[ \text{VO}_2 \text{ (ml/kg/min)} = V_E \text{ (ml/kg)} \times \left[ 1 - \frac{F_E O_2 - F_E CO_2}{1 - 0.21} \right] \times 0.21 - F_E O_2 , \]

where \( F_E CO_2 \) represents the expired carbon dioxide fraction. \( DO_2 \) was calculated as the product of cardiac index and arterial oxygen content. Oxygen extraction ratio (O₂ER) was derived from the ratio of \( VO_2/DO_2 \).

**Statistical Methods**

A dual-line regression method [30] was used to determine the critical \( DO_2 (DO_{2\text{crit}}) \) in each animal from a plot of \( VO_2/DO_2 \). The critical \( O_2 \)ER \( (O_2 \text{ER}_{\text{crit}}) \) was calculated by the ratio of \( VO_2/DO_2 \) at \( DO_{2\text{crit}} \). 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 \( DO_{2\text{crit}} \). The slopes of \( VO_2/DO_2 \) were tested by covariance analysis. All data are expressed as means ± 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. \( DO_2 \) also increased but \( VO_2 \) 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 dogs treated only with fluids, stroke volume, cardiac index, and \( DO_2 \) increased, but \( VO_2 \) did not change; therefore, \( O_2 \)ER tended to decrease. In the group given PGE₁ + fluids, the changes were similar, except that \( VO_2 \) 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 \( O_2 \)ER.

**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.

![Graph](image)

**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).

![Graph](image)

**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 \( (P = NS) \).
Blood lactate was lower in the PGE₁ + fluids-treated group than in the control group when intrapericardial pressure reached above 4 mm Hg.

At DO₂crit, DO₂work 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 PGE₁ + fluids and 9.3 ± 2.7 ml/kg/min in the animals treated with PGE₁ alone (both P < 0.05). VO₂ at DO₂crit was slightly higher in the PGE₁ + fluids-treated dogs, but this difference did not reach statistical significance. O₂ERcrit was 47 ± 14% in the group treated with only fluids vs 63 ± 16% with PGE₁ + fluids and 61 ± 17% with PGE₁ alone (both P < 0.05). Moreover, the slope of the VO₂/DO₂-dependent line, which was 0.44 ± 0.15 in the animals treated only with fluids, 0.64 ± 0.15 in those treated with PGE₁ + fluids (P < 0.01), and 0.57 ± 0.24 in the PGE₁ alone-treated animals (P = NS). Blood lactate at DO₂crit was lower in the PGE₁ + fluids-treated than in the control group.

Figure 4 represents the relation between VO₂ and DO₂ in a representative experiment.

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

The PGE₁-treated animals had significant increase in cardiac index and DO₂, and reductions in systemic vascular resistance and blood lactate levels. DO₂ was higher and the O₂ER lower in the PGE₁-treated group than in the control group only in the initial stages of cardiac tamponade. VO₂ had an identical course in the two groups. In the later stages of the study, pulmonary vascular resistance was lower in the PGE₁ group than in the control group.

DO₂crit was similar in the two groups (10.7 ± 2.9 ml/kg/min in the PGE₁, and 10.1 ± 1.8 ml/kg/min in the control group, respectively, P = NS); VO₂ at DO₂crit in the PGE₁ group tended to be higher than in the control group (7.2 ± 1.3 vs 6.4 ± 1.3 ml/kg/min, P = NS). O₂ERcrit was 68 ± 13% in the PGE₁ group vs 60 ± 15% in the control group (P = 0.054). There was no significant difference in the slopes of the VO₂/DO₂-dependent lines (0.69 ± 0.29 vs 0.51 ± 0.33, P = NS).

DISCUSSION

The present study tested the hypothesis that PGE₁ 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 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 DO₂crit by more than 20%, i.e., from 9.5 to 12.1 ml/kg/min [32]. In the present study, PGE₁ administration resulted in significant improvement in oxygen extraction capabilities, as indicated by a marked reduction in DO₂crit, from 12.2 to less than 10 ml/kg/min, an increase in O₂ERcrit, and a greater slope for the dependent portion of the VO₂/DO₂ relationship. Actually, PGE₁ appeared to entirely restore the oxygen extraction capabilities [32, 33].

The increase in tissue oxygen extraction capabilities after PGE₁ administration may be related to the effects of the arteriolar and venular vasodilating effects of PGE₁ [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 PGE₁ on oxygen extraction capabilities without volume expansion. As expected, the animals treated with PGE₁ + fluids had a greater cardiac index and DO₂ than those treated only by PGE₁ without volume administration. However, the improvement in oxygen extraction was unaltered.

PGE₁ can increase oxygen extraction capabilities after endotoxin by several mechanisms. By its microvascular action, PGE₁ 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 PGE₁ increased blood flow to mesenteric and renal vasculatures by their vasodilating effect. PGE₁ can also decrease adherence of neutrophils to the endothelial
## TABLE 3

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

<table>
<thead>
<tr>
<th>IPP (mm Hg)</th>
<th>Baseline 1</th>
<th>Baseline 2</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
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</tr>
<tr>
<td>Control (N = 7)</td>
<td>157 ± 19</td>
<td>148 ± 15</td>
<td>153 ± 18</td>
<td>159 ± 27</td>
<td>162 ± 11</td>
<td>169 ± 21</td>
<td>165 ± 16</td>
<td>166 ± 14 (N = 4)</td>
<td>164 ± 12 (N = 2)</td>
</tr>
<tr>
<td>PGE&lt;sub&gt;1&lt;/sub&gt; (N = 7)</td>
<td>187 ± 15</td>
<td>171 ± 18</td>
<td>166 ± 24</td>
<td>165 ± 24</td>
<td>158 ± 39</td>
<td>152 ± 39</td>
<td>157 ± 29</td>
<td>146 ± 24*N (N = 5)</td>
<td>138 ± 10*N (N = 3)</td>
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<td>MAP (mm Hg)</td>
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<tr>
<td>Control (N = 7)</td>
<td>96 ± 21</td>
<td>98 ± 9</td>
<td>100 ± 16</td>
<td>96 ± 19</td>
<td>89 ± 17</td>
<td>77 ± 21*N</td>
<td>71 ± 22*N</td>
<td>58 ± 28*N (N = 4)</td>
<td>42 ± 26*N (N = 2)</td>
</tr>
<tr>
<td>PGE&lt;sub&gt;1&lt;/sub&gt; (N = 7)</td>
<td>108 ± 13</td>
<td>103 ± 15</td>
<td>106 ± 14</td>
<td>100 ± 11</td>
<td>91 ± 23</td>
<td>78 ± 24*N</td>
<td>59 ± 21*N</td>
<td>39 ± 17*N (N = 6)</td>
<td>36 ± 16*N (N = 3)</td>
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<tr>
<td>MPAP (mm Hg)</td>
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<td></td>
</tr>
<tr>
<td>Control (N = 7)</td>
<td>12 ± 2</td>
<td>13 ± 2</td>
<td>14 ± 2</td>
<td>14 ± 2</td>
<td>15 ± 2</td>
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<td>17 ± 2*N</td>
<td>18 ± 3*N (N = 4)</td>
<td>18 ± 3*N (N = 2)</td>
</tr>
<tr>
<td>PGE&lt;sub&gt;1&lt;/sub&gt; (N = 7)</td>
<td>14 ± 2</td>
<td>13 ± 2</td>
<td>12 ± 2</td>
<td>12 ± 2</td>
<td>14 ± 2</td>
<td>14 ± 2</td>
<td>15 ± 2</td>
<td>16 ± 6 (N = 6)</td>
<td>16 ± 2 (N = 3)</td>
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<tr>
<td>Cardiac index</td>
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<td></td>
<td></td>
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<tr>
<td>(liter/min/kg)</td>
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<tr>
<td>Control (N = 7)</td>
<td>0.19 ± 0.04</td>
<td>0.19 ± 0.04</td>
<td>0.16 ± 0.05</td>
<td>0.12 ± 0.05*N</td>
<td>0.11 ± 0.03</td>
<td>0.09 ± 0.02*N</td>
<td>0.08 ± 0.03*N</td>
<td>0.07 ± 0.04*N (N = 4)</td>
<td>0.04 ± 0.03*N (N = 2)</td>
</tr>
<tr>
<td>PGE&lt;sub&gt;1&lt;/sub&gt; (N = 7)</td>
<td>0.20 ± 0.07</td>
<td>0.25 ± 0.06*</td>
<td>0.21 ± 0.05</td>
<td>0.18 ± 0.06*</td>
<td>0.14 ± 0.05</td>
<td>0.10 ± 0.03*</td>
<td>0.08 ± 0.03*N</td>
<td>0.05 ± 0.02*N (N = 5)</td>
<td>0.01 ± 0.01*N (N = 3)</td>
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<tr>
<td>Lactate (mmol/liter)</td>
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<tr>
<td>Control (N = 7)</td>
<td>2.1 ± 1.5</td>
<td>2.0 ± 1.3</td>
<td>1.9 ± 0.7</td>
<td>2.2 ± 0.6</td>
<td>2.8 ± 0.3</td>
<td>3.4 ± 0.8</td>
<td>3.8 ± 1.4</td>
<td>5.6 ± 3.5 (N = 4)</td>
<td>3.8 ± 2.2*N (N = 3)</td>
</tr>
<tr>
<td>PGE&lt;sub&gt;1&lt;/sub&gt; (N = 7)</td>
<td>2.0 ± 0.8</td>
<td>1.6 ± 0.6*</td>
<td>1.7 ± 0.7</td>
<td>1.7 ± 0.5</td>
<td>2.2 ± 0.7</td>
<td>2.8 ± 0.8</td>
<td>3.3 ± 1.2</td>
<td>4.5 ± 2.2*N (N = 5)</td>
<td>5.4 ± 2.1*N (N = 5)</td>
</tr>
</tbody>
</table>

Note. Values shown as means ± SD. Baseline 1, after stabilization; Baseline 2, after PGE<sub>1</sub> 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 PGE<sub>1</sub>.

membrane and subsequent neutrophil-mediated tissue injury [8, 13, 14] associated with a reduced release of oxygen free radicals [9, 10]. PGE<sub>1</sub> can also block coagulation by its anti-platelet [11] and fibrinolytic actions [12].

To differentiate specific effects of PGE<sub>1</sub> during endotoxin-induced alterations from an unspecified effect of this vasodilating substance, we studied the effects of the administration of PGE<sub>1</sub> with fluids in the absence of endotoxin. Since the first part of the study had shown the importance of adequate volume loading during the PGE<sub>1</sub> administration, we did not study a PGE<sub>1</sub> alone group in this second series of control experiments. In the absence of endotoxin, the effects of PGE<sub>1</sub> on oxygen extraction capabilities were not significant, suggesting that PGE<sub>1</sub> specifically counteracts the peripheral effects of endotoxin. These latter results differ from those recently reported by Groeneveld and co-workers [23] showing that PGE<sub>1</sub> significantly decreased DO<sub>2crit</sub> by increasing O2ERcrit 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 PGE<sub>1</sub>, since Groeneveld et al. [23] used a very high dose of 200 ng/kg/min of PGE<sub>1</sub>. Intriguingly, these authors reported a baseline O2ER of 41% and an O2ERcrit of 48%, whereas we, like others, observed a baseline O2ER below 25% and an O2ERcrit between 60 and 70% in the control and between 45 and 50% in the endotoxic conditions [30, 32, 33, 40]. Although normal O2ER 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 PGE<sub>1</sub>. 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, PGE<sub>1</sub> increased stroke volume and cardiac index and reduced systemic and pulmonary vascular resistance. These cardiovascular effects of PGE<sub>1</sub> have been reported in other experimental [18–21] and clinical [6, 24, 25, 41] studies. In the PGE<sub>1</sub>-treated animals we also observed a slight reduction in P<sub>50</sub>O<sub>2</sub>, which can be explained by an inhibition of the hypoxic pulmonary vasoconstriction related to the pulmonary vasodilating properties of PGE<sub>1</sub> [42]. An additional finding was that dogs treated with PGE<sub>1</sub> + fluids showed greater tolerance to higher intrapericardial pressure than the other animals. The lower lactate level at DO<sub>2crit</sub> in the animals treated by PGE<sub>1</sub> + 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 PGE<sub>1</sub> increased cardiac index, DO<sub>2</sub>, or VO<sub>2</sub>, and suggested a beneficial effect of PGE<sub>1</sub> on systemic tissue perfusion [19, 24, 25, 28, 41]. As in the other studies, the present investigation explored only the global effects of PGE<sub>1</sub> on the relation between VO<sub>2</sub> and DO<sub>2</sub>, and the effects of PGE<sub>1</sub> might not be equally distributed to all organs. However, Raper et al. [43] recently reported that PGE<sub>1</sub> 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 PGE<sub>1</sub>, vasodi-
lators should be administered cautiously during sepsis when vasodilation is already prominent. Second, PGE\(_1\), like other prostaglandins, might reduce the immunological response to infection [44]. Third, the reduction in \(P_a\)\(O_2\) induced by PGE\(_1\) might not be well tolerated in the presence of severe respiratory failure. Several clinical studies [24–26] reported that an infusion of PGE\(_1\) in patients with ARDS could be beneficial, but a large multicenter study [41] failed to show an increased survival in PGE\(_1\)-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.

![Graphs and figures](image)

**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 PGE\(_1\) + fluids administration. *P* < 0.05 vs PGE\(_1\).

**FIG. 6.** Relationship between oxygen delivery (DO\(_2\)), oxygen uptake (VO\(_2\)), oxygen extraction ratio (O\(_2\)ER), and intrapericardial pressure (IPP) in the control experiments (see legend to Fig. 5 for details).

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