Prostacyclin but not Phentolamine Increases Oxygen Consumption and Skin Microvascular Blood Flow in Patients with Sepsis and Respiratory Failure*

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Inadequate tissue oxygenation may occur in critically ill patients with sepsis despite an apparently adequate O₂ transport (\(\dot{V}O_2\)), and this may contribute to the development of an O₂ debt and to multiple organ failure. It has been shown that increasing \(\dot{V}O_2\) by infusing a vasodilator may reveal this O₂ debt in septic patients. To investigate whether the site of action of vasodilators may be of importance in unmasking such an O₂ debt, we administered prostacyclin, a prostaglandin with a preferential effect on the microcirculation, and phentolamine, an arteriolar vasodilator, in 11 patients studied during the first 48 hours after the onset of sepsis, and compared their effect on whole body oxygen consumption (\(\dot{V}O_2\)) and skin microvascular blood flow. The results demonstrated that increasing \(\dot{V}O_2\) by prostacyclin but not by phentolamine significantly increases \(\dot{V}O_2\) in critically ill patients with sepsis. The site of action of vasodilators may therefore play an important role in their ability to unmask an O₂ debt. (Chest 1990; 98:1467-72)

\[\dot{V}O_2 = \text{oxygen consumption; } \dot{V}O_2 = \text{oxygen transport; LDF = laser Doppler flowmetry; MAF = mean systemic arterial pressure; MAP = mean pulmonary arterial blood pressure; CVP = central venous pressure; PCWP = pulmonary capillary wedge pressure; SVR = systemic vascular resistance}\]

Sepsis associated with the development of multiple organ failure is a major cause of mortality in critically ill patients.1 A number of mechanisms have been proposed for the pathogenesis of cell damage and organ dysfunction in sepsis, including an inappropriate release of mediators involved in the inflammatory response2-8 and a maldistribution of blood flow in the microcirculation due to the loss of autoregulation of the tissue perfusion,6 microembolization,7 and endothelial cell injury.8 This maldistribution of blood flow at the microcirculatory level produces a defective tissue oxygenation due to an impaired perfusion of nutritive capillaries, as suggested by lower partial oxygen pressure in muscle tissue and O₂ extraction found in critically ill patients with sepsis than without sepsis.9 This may lead to the development of a supply-dependent oxygen consumption and an O₂ debt despite an apparently adequate total body oxygen transport.10-13

Such disturbances in the microcirculation observed in septic patients could be revealed by laser Doppler flowmetry, a new noninvasive method which gives an accurate measurement of the microcirculatory flow when compared to \(^{133}\)Xe washout technique11 or direct measurement of capillary flow velocity by dynamic capillaroscopy.12 It has the advantage to provide a continuous assessment of skin microvascular blood flow, one of the accessible microcirculatory beds in man, by a noninvasive method.14-16

When prostacyclin was used to increase \(\dot{V}O_2\) and to detect such an O₂ debt in critically ill patients with respiratory failure, a significant increase in \(\dot{V}O_2\) was found in those patients who ultimately died.17 In contrast, similar results have not been observed with phentolamine.18 Our hypothesis is that prostacyclin could act on the microcirculation at a different site than phentolamine, since it has been reported to increase the microvascular blood flow by vasodilating arterioles and venules, and increasing the density of perfused capillaries.19

To test this hypothesis, we evaluated the relationship between changes in \(\dot{V}O_2\), skin microvascular blood flow measured by laser Doppler flowmetry, and whole body \(\dot{V}O_2\) induced by two vasodilating agents, prostacyclin and phentolamine, in septic patients with respiratory failure.

**PATIENTS AND METHODS**

**Patients**

Eleven patients (mean age: 56 ± 6 years) admitted to the surgical...
ICU and studied during the first 48 hours after the onset of septic syndrome were included in the present study (Table 1). The diagnosis of septic syndrome is based on clinical evidence of infection, fever or hypothermia, tachycardia, tachypnea, together with evidence of multiple organ dysfunction as manifested by one of the following criteria: altered mental function, hypoxemia, elevated plasma lactate, decreased urine output. All patients required mechanical ventilatory support using controlled or intermittent mandatory ventilation with positive end-expiratory pressure in order to maintain a PaO\(_2\) greater than 8 kPa and a PaCO\(_2\) between 5.5 and 7.0 kPa with arterial pH between 7.30 and 7.45. Patients were sedated with a continuous intravenous infusion of midazolam and morphine as indicated clinically. None of the patients was receiving vasoactive or inotropic drugs, except for a low dose of dopamine (2 to 3 μg·kg\(^{-1}\)·min\(^{-1}\)). All patients received crystalloid fluids to optimize cardiac filling pressures at values above which there was no further increase in cardiac index. The study was approved by the committee for ethics in human research of our institution and informed consent was obtained from the patient, or if this was not possible because his clinical condition, from the closest relative or treating physician.

**Procedure**

The APACHE II score, derived from 12 clinical and laboratory variables, age, and previous health status, was determined for all patients at the time of admission to the intensive care unit. Two sets of baseline measurements were made, separated by a time interval of 30 minutes, including the following variables: heart rate, mean systemic arterial and mean pulmonary arterial blood pressure, central venous pressure, and pulmonary capillary wedge pressure were measured using a radial arterial cannula and a 7-F triple lumen Swan-Ganz catheter, respectively, connected to calibrated quartz pressure transducers positioned at the midaxillary line. Cardiac output was measured three times at end-expiration by the same operator by thermodilution with ice-cold injectate and using a bedside computer. The coefficient of variation for cardiac output measurements was less than 5 percent. Systemic and pulmonary vascular resistances were calculated using standard formulae. Rectal temperature was measured electronically. Arterial and mixed venous blood samples were drawn for measurement of total hemoglobin concentration by spectrophotometry, oxygen tension, and pH using standard electrodes and corrected for the patient's temperature. Oxygen saturation of hemoglobin in arterial and mixed venous blood were measured using a CO-oximeter. Plasma lactate concentrations were measured by absorption spectrometry. 

Skin microvascular blood flow was measured continuously using a laser Doppler flow meter probe placed on the inner thigh. According to the Doppler principle, moving blood cells in the superficial part of the skin changes the frequency of the back-scattered light. The LDF signal is a function of the product of the number of red cells and their mean velocity. In the present study, the change in LDF signal was expressed as percentage of the maximal internal calibration signal.

After control measurements, patients were assigned to randomly receive a 30-minute infusion of prostacyclin (5 to 10 ng·kg\(^{-1}\)·min\(^{-1}\)) or phentolamine (5 to 10 μg·kg\(^{-1}\)·min\(^{-1}\)) to obtain an increase in cardiac output of at least a 15 percent. A full set of hemodynamic and respiratory measurements was repeated after 30 minutes of drug infusion, and the infusion then terminated. Sixty minutes later, control measurements were repeated, and thereafter, the second vasodilator administered. The VO\(_2\) was calculated using standard formula. The VO\(_2\) was derived from the reverse Fick equation. Oxygen extraction ratio was expressed as the ratio of VO\(_2\) to VO\(_2\).

**Statistical Analysis**

All recorded variables (mean ± SE) were compared within each treatment using a one-way analysis of variance for repeated measurements followed by Bonferroni's multicomparisons test. Comparison between both treatments was performed with a paired Student's t-test. The Pearson's square correlation coefficient was used to detect any significant association between changes of VO\(_2\), VO\(_2\), and hemodynamic, respiratory or biochemical variables. A p value <0.05 was considered as statistically significant.

**RESULTS**

The main clinical characteristics of each patient are reported in Table 1. Positive blood cultures were found in eight of 11 patients studied with a sepsis syndrome (three patients with Gram-negative microorganisms and five patients with Gram-positive cocci). Five patients died of a multiple organ failure syndrome associated with sepsis, and six survived to hospital discharge. No significant difference was found in any of the recorded variables between patients with positive blood cultures and those without. All patients had a hyperdynamic cardiocirculatory state characterized by an elevated CI associated with a low SVR and tachycardia. Plasma lactate values were above the normal range, i.e., 1.9 mmol/L, in eight of 11 patients. All patients required mechanical ventilation and presented an increased alveo-arterial O\(_2\) gradient/inspired O\(_2\) concentration ratio ([PA-a]O\(_2\)/FiO\(_2\)), an elevated venous admixture, and increased QO\(_2\) and VO\(_2\).
Table 2—Hemodynamic Variables and Lactate Values*

<table>
<thead>
<tr>
<th></th>
<th>Control 1</th>
<th>Control 2</th>
<th>Experimental</th>
<th>Control 1</th>
<th>Control 2</th>
<th>Experimental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats·min⁻¹</td>
<td>110 ± 10</td>
<td>111 ± 10</td>
<td>114 ± 11</td>
<td>108 ± 9</td>
<td>108 ± 8</td>
<td>116 ± 10</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>67 ± 3</td>
<td>68 ± 4</td>
<td>67 ± 4</td>
<td>73 ± 3</td>
<td>71 ± 4</td>
<td>57 ± 3†</td>
</tr>
<tr>
<td>CVP, mm Hg</td>
<td>11 ± 1</td>
<td>10 ± 1</td>
<td>13 ± 1</td>
<td>11 ± 1</td>
<td>11 ± 1</td>
<td>12 ± 2</td>
</tr>
<tr>
<td>MPAP, mm Hg</td>
<td>26 ± 2</td>
<td>26 ± 2</td>
<td>27 ± 2</td>
<td>26 ± 1</td>
<td>26 ± 2</td>
<td>26 ± 2</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>12 ± 1</td>
<td>12 ± 1</td>
<td>14 ± 2</td>
<td>13 ± 1</td>
<td>13 ± 1</td>
<td>14 ± 1</td>
</tr>
<tr>
<td>Cardiac index, L·min⁻¹·m⁻²⁻¹</td>
<td>4.9 ± 0.5</td>
<td>4.6 ± 0.6</td>
<td>6.0 ± 0.7†</td>
<td>4.1 ± 0.5</td>
<td>4.1 ± 0.5</td>
<td>5.5 ± 0.6†</td>
</tr>
<tr>
<td>SVR, dyn·sec·cm⁻²</td>
<td>515 ± 45</td>
<td>564 ± 50</td>
<td>409 ± 40†</td>
<td>690 ± 90</td>
<td>690 ± 100</td>
<td>381 ± 42†</td>
</tr>
<tr>
<td>PVR, dyn·sec·cm⁻³</td>
<td>125 ± 18</td>
<td>129 ± 17</td>
<td>95 ± 14†</td>
<td>138 ± 16</td>
<td>134 ± 12</td>
<td>102 ± 12†</td>
</tr>
<tr>
<td>Arterial lactate, mmol/L</td>
<td>2.9 ± 0.6</td>
<td>2.8 ± 0.6</td>
<td>2.9 ± 0.5</td>
<td>2.8 ± 0.5</td>
<td>2.8 ± 0.5</td>
<td>3.1 ± 0.6</td>
</tr>
</tbody>
</table>

*p ± SE; n = 11; MAP, mean arterial pressure; CVP, central venous pressure; MPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance.
†Significantly different from control 2 values (p<0.05).

Table 3—Gas Exchange, Venous Admixture, Oxygen Transport, Oxygen Consumption and Oxygen Extraction Ratio During Short Intravenous Infusions of Prostacyclin and Phentolamine*

<table>
<thead>
<tr>
<th></th>
<th>Control 1</th>
<th>Control 2</th>
<th>Experimental</th>
<th>Control 1</th>
<th>Control 2</th>
<th>Experimental</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH, units</td>
<td>7.38 ± 0.01</td>
<td>7.36 ± 0.01</td>
<td>7.34 ± 0.02</td>
<td>7.37 ± 0.01</td>
<td>7.37 ± 0.01</td>
<td>7.36 ± 0.01</td>
</tr>
<tr>
<td>PaCO₂, kPa</td>
<td>6.8 ± 0.6</td>
<td>6.7 ± 0.7</td>
<td>7.1 ± 0.7†</td>
<td>6.4 ± 0.5</td>
<td>6.4 ± 0.6</td>
<td>6.5 ± 0.5†</td>
</tr>
<tr>
<td>PaO₂, kPa</td>
<td>13.9 ± 1.2</td>
<td>14.0 ± 1.1</td>
<td>9.7 ± 0.5¹</td>
<td>13.1 ± 1.2</td>
<td>13.3 ± 1.3</td>
<td>12.4 ± 1.5</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>94.2 ± 0.4</td>
<td>94.3 ± 0.4</td>
<td>91.1 ± 1.0†</td>
<td>94.1 ± 0.6</td>
<td>93.9 ± 0.8</td>
<td>93.0 ± 0.9</td>
</tr>
<tr>
<td>SvO₂, %</td>
<td>68.4 ± 2.6</td>
<td>68.9 ± 2.5</td>
<td>67.3 ± 2.6</td>
<td>67.0 ± 2.4</td>
<td>66.5 ± 2.4</td>
<td>70.1 ± 2.7</td>
</tr>
<tr>
<td>F(A-a)O₂/FIO₂, kPa</td>
<td>62.4 ± 2.0</td>
<td>62.0 ± 2.0</td>
<td>68.1 ± 1.7†</td>
<td>62.0 ± 2.5</td>
<td>62.0 ± 2.0</td>
<td>63.3 ± 2.0</td>
</tr>
<tr>
<td>Venous admixture, %</td>
<td>35.0 ± 3.3</td>
<td>35.1 ± 3.3</td>
<td>42.8 ± 3.6†</td>
<td>33.3 ± 3.1</td>
<td>33.5 ± 3.7</td>
<td>39.5 ± 3.3†</td>
</tr>
<tr>
<td>Oxygen transport, ml·min⁻¹·kg⁻¹</td>
<td>15.5 ± 1.7</td>
<td>14.7 ± 1.5</td>
<td>18.4 ± 2.1†</td>
<td>13.6 ± 1.3</td>
<td>13.6 ± 1.4</td>
<td>17.6 ± 2.1†</td>
</tr>
<tr>
<td>Oxygen consumption, ml·min⁻¹·kg⁻¹</td>
<td>4.1 ± 0.4</td>
<td>3.9 ± 0.3</td>
<td>4.6 ± 0.4</td>
<td>3.8 ± 0.2</td>
<td>3.9 ± 0.4</td>
<td>4.2 ± 0.5</td>
</tr>
<tr>
<td>Oxygen extraction ratio, %</td>
<td>28.3 ± 2.6</td>
<td>27.9 ± 2.5</td>
<td>26.6 ± 2.7</td>
<td>29.7 ± 2.5</td>
<td>30.0 ± 2.6</td>
<td>25.5 ± 2.7†</td>
</tr>
</tbody>
</table>

*p ± SE; n = 11; SaO₂, arterial O₂ saturation of hemoglobin; SvO₂, mixed venous O₂ saturation of hemoglobin; F(A-a)O₂/FIO₂, alveolo-arterial O₂ gradient/inspired O₂ concentration ratio.
†Significantly different from control 2 values (p<0.05).

(Tables 2 and 3).

There was no significant change in any of the recorded variables between the two control measurements taken before administration of either vasodilator. The 30-minute intravenous infusion of prostacyclin produced a 24 percent increase in QO₂ (from 14.7 ± 1.5 to 18.4 ± 2.1 ml·min⁻¹·kg⁻¹, p<0.05) with a 18 percent increase in VO₂ (from 3.9 ± 0.4 to 4.6 ± 0.4 ml·min⁻¹·kg⁻¹, p<0.05) (Fig 1) but without significant change in QO₂/ER. This was associated with a significant decrease in SVR and PVR but with no significant change in MAP (Table 2). Prostacyclin also decreased PaO₂ (from 14.0 ± 1.1 to 9.7 ± 0.5 kPa, p<0.05), SaO₂ (from 94.3 ± 0.4 to 91.1 ± 1.0 percent, p<0.05), and increased the P(A-a)O₂/FIO₂ ratio (from 62.0 ± 2.0 to 68.1 ± 1.7 kPa, p<0.05) and pulmonary venous admixture (from 35.1 ± 3.3 to 42.8 ± 3.6 percent, p<0.05) (Table 3).

The 30-minute intravenous infusion of phentolamine produced a 25 percent increase in QO₂ (from 13.6 ± 1.4 to 17.6 ± 2.1 ml·min⁻¹·kg⁻¹, p<0.05) with...
The results of the present study demonstrate that, for a similar increase in \( \dot{Q}_O_2 \), prostacyclin compared to phentolamine produced a significantly greater increase in the skin microvascular blood flow of septic patients with respiratory failure. We also observed a supply dependency of \( \dot{V}_O_2 \) with prostacyclin, but not with phentolamine.

Our data confirm the results of previous studies where a dependency of \( \dot{Q}_O_2 \) on \( \dot{V}_O_2 \) had been reported in septic patients, when \( \dot{Q}_O_2 \) was increased by fluid loading.\(^{12,13,23}\) Our study suggests that the site of action of the vasodilator used to increase \( \dot{Q}_O_2 \) could be important when trying to demonstrate a peripheral \( O_2 \) deficit in sepsis. The sequence of drug administration probably did not influence the effect of the vasodilators on \( \dot{Q}_O_2 \) and \( \dot{V}_O_2 \). The vasodilators were randomly administered in each patient in a sequential manner. We did not find any significant difference in the control measurements taken 1 h after stopping the first drug infusion between patients receiving prostacyclin or phentolamine as the first drug.

The difference in \( \dot{V}_O_2 \) and \( O_2 \)ER changes induced by both vasodilators is most probably related to their different site of action. In the present study, prostacyclin increased \( \dot{V}_O_2 \) without changing \( O_2 \)ER in all patients. Such a supply dependency of \( \dot{V}_O_2 \) has been reported in critically ill patients with respiratory failure\(^{17}\) or acute liver failure\(^{24}\) receiving a short intravenous infusion of prostacyclin. The effect of prostacyclin on \( \dot{V}_O_2 \) and \( O_2 \)ER may probably be explained by its particular effect on the microcirculation, i.e., a vasodilation of arterioles and venules, and an increase in the

There was no significant correlation between plasma lactate concentrations, APACHE II score and individual patient slopes of the relationship between the changes in \( \dot{V}_O_2 \) and \( \dot{Q}_O_2 \) produced by the administration of both vasodilators.
density of perfused capillaries. In the present study, we found that the prostacyclin-induced increase in the skin microvascular blood flow was out of proportion to the concurrent increase in systemic blood flow. Moreover, prostacyclin produced a three times greater increase in the skin microvascular blood flow than phentolamine (35 and 13 percent, respectively) for a similar increase in cardiac output. Prostacyclin has been shown to increase the perfusion in the rabbit skin microcirculation and in the dermis of healthy volunteers. Prostacyclin has also been reported to increase the gastric mucosal blood flow in rats. A vasodilator which increases microvascular blood flow but has no effect on the density of perfused capillaries, does not increase tissue \(O_2\)ER, since the tissue \(O_2\)ER at constant metabolic rate is mainly a function of the ratio of perfused capillary surface to blood flow. Prostacyclin has been reported to increase capillary recruitment and should, therefore, produce an increase in tissue \(O_2\)ER and \(V_0\).

Contrary to prostacyclin, phentolamine did not significantly change \(V_0\) but decreased \(O_2\)ER in the septic patients included in the present study. This confirms our previous study designed to examine the variability of the supply dependency of \(V_0\) over time by increasing \(Q_0\) with phentolamine. In the latter study, \(V_0\) changes measured after administration of a short intravenous infusion of phentolamine varied within patients from day to day and were not related to plasma lactate concentrations. There is little evidence that phentolamine, like other conventional vasodilators, could reduce the maldistribution of blood flow observed in sepsis and then increase tissue \(V_0\). It has been demonstrated that such vasodilators may themselves produce a pathologic disturbance of the local oxygen supply, perhaps by depressing the capillary surface area or increasing the nonnutritional arteriovenous shunts. The 13 percent mean increase in the perfusion of the skin microcirculation produced by phentolamine is probably due to its arteriolar vasodilator effect. The LDF signal used to assess cutaneous microcirculation measures the blood flow in resistance and capacitance vessels as well as in capillaries of the skin within 1-mm depth of the laser field. An increase in the skin LDF signal in healthy volunteers has also been reported with prazosin, a selective alpha-1 adrenergic receptor antagonist which has mainly an arteriolar vasodilator effect.

In our investigation, prostacyclin did not produce a fall in plasma lactate concentrations despite a significant increase in \(V_0\). This may be explained by the short duration of the prostacyclin infusion (30 minutes) used in this study. A significant decrease in plasma lactate levels of critically ill patients has only been detected after a longer infusion of prostacyclin and also in septic patients receiving a fluid infusion for more than 6 h in order to increase \(Q_0\). The lack of changes in plasma lactate levels in our study could also be due to a delayed hepatic clearance of lactate, as reported in patients after resuscitation from circulatory shock.

In conclusion, the present study demonstrates that a short intravenous infusion of prostacyclin, but not of phentolamine, significantly increases \(V_0\) and the microvascular blood flow of the skin in patients with sepsis and respiratory failure. This difference between both vasodilator agents may be related to the fact that prostacyclin but not phentolamine could improve the distribution of microcirculatory flow in sepsis. However, further studies are required to determine whether the prostacyclin-induced changes in skin microcirculation may also be observed in more vital organs of septic patients.

ACKNOWLEDGMENT: We gratefully acknowledge the technical assistance of Julian Lopez.

REFERENCES

7. Cain SM, King CE, Chapter CK. Effects of time and microembolism on \(O_2\) extraction by dog hindlimb in hypoxia. J Crit Care 1988; 3:89-95


18 Palazzo M, Pirenne B, Morel DR, Suter PM. Relationship between \( O_2 \) consumption and \( O_2 \) delivery in severely ill patients with reference to their hormonal status and outcome [abstract]. Schweiz Med Wschr 1989; 119:380


10 Cain SM. Effects of time and vasoconstrictor tone on \( O_2 \) extraction during hypoxic hypoxia. J Appl Physiol 1977; 45:219-24


