Lack of Oxygen Supply Dependency in Patients With Severe Sepsis*
A Study of Oxygen Delivery Increased by Military Antishock Trouser and Dobutamine

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Background: During severe sepsis, the existence of a pathologic oxygen supply dependency remains controversial.

Study objective: To evaluate the relationship between oxygen delivery (Do2) and oxygen consumption (Vo2) during severe sepsis and to compare, in this respect, survivors and nonsurvivors and patients with normal or increased concentration of plasma lactate.

Study design: Cohort analytic study.

Setting: Three European ICUs in university hospitals.

Patients: Seventeen mechanically ventilated patients with severe sepsis (six with high blood lactate levels) studied within the first day of diagnosis.

Interventions and measurements: Pulmonary elimination of carbon dioxide, or carbon dioxide production (Vco2) and Vo2 were measured by indirect calorimetry before and after two interventions designed to increase Do2 (calculated from the Fick equation): inflation of a military antishock trouser (MAST) and infusion of dobutamine.

Results: During MAST inflation, Do2 increased by 19% in patients with a normal concentration of plasma lactate (p <0.01), but remained unchanged in patients with high lactate levels. During dobutamine infusion, Do2 increased in both groups by 16% (p <0.01) and 20% (p <0.05), respectively. In both groups, we found that the Vo2 and Vco2 were not affected by either the MAST or the dobutamine-induced increase in Do2. There was no difference between survivors and nonsurvivors.

Conclusion: There was no evidence of a pathologic oxygen supply dependency in patients with severe sepsis, even in those who had an elevated concentration of plasma lactate and in those who ultimately died. These results do not favor the conclusion that maximizing Do2 is a primary therapeutic objective in such patients.

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ARDS=adult respiratory distress syndrome; Do2=oxygen delivery; CI=cardiac index; MAST=military antishock trouser; RQ=Respiratory quotient; SAPS=simplified acute physiologic score; Vco2=carbon dioxide production; Vo2=oxygen consumption

Key words: dobutamine; indirect calorimetry; military antishock trouser; oxygen consumption; oxygen delivery; sepsis

At least seven studies1-8 suggest that, during severe sepsis, aerobic metabolism becomes limited by oxygen supply at normal or even increased levels of oxygen delivery (Do2) with a relative fixed oxygen extraction when Do2 falls. This abnormal positive relationship between Do2 and oxygen consumption (Vo2) has been termed pathologic supply dependency.9 It has been interpreted as reflecting substantial oxygen debt contributing to the development of irreversible multiple organ failure and subsequent death.4,7 The presence of an elevated concentration of plasma lactate, presumed to be a marker of anaerobic metabolism, predicted this supply dependency.3,8,10 These observations have led several intensive care practitioners to propose maximizing Do2 of patients with sepsis in order to improve tissue oxygenation.8,11,12

However, two lines of arguments have been raised against this conventional interpretation. The first is dealing with the observation that oxygen supply dependency has been described in quite different groups of patients, including not only patients with sepsis, but also patients with adult respiratory distress syndrome (ARDS), COPD, pneumonia, or congestive heart failure.13 Therefore, it has been suggested that the dependency of Vo2 on Do2 is not "pathologic," but represents the "normal" relationship in humans and expresses a difference between human and animal physiology: in the case of a decrease in Do2, hu-
mans might be unable to achieve values of tissue oxygen extraction as high as those observed in anesthetized animals. The second line of arguments deals with the presence of methodologic weaknesses in most previous clinical studies. Indeed, in these studies, $D_O_2$ and $V_O_2$ were calculated from a common set of measured variables, cardiac output, and arterial blood oxygen content.

Consequently, the observed oxygen supply dependency might be artefactual, resulting from pure mathematical coupling. Despite the demonstration that the strength of the correlation observed in some of these studies between $D_O_2$ and $V_O_2$ cannot be ascribed only to mathematical coupling, it should be noted that studies that used independent methods to measure $D_O_2$ and $V_O_2$ failed to demonstrate this supply dependency in patients with severe sepsis or ARDS. However, these last observations themselves have been challenged for three main reasons. First, patients might not have been ill enough for oxygen debt to be detected. Second, the delay between the onset of the sepsis process and the beginning of the investigation might have been too long. Third, imposed changes in $D_O_2$ might not have been large enough to demonstrate oxygen supply dependency.

The purpose of the present study was to reevaluate the relationship between $D_O_2$ and $V_O_2$ in patients with severe sepsis who were studied as soon as possible after the resuscitation phase. We used two methods to increase $D_O_2$: inflation of a military antishock trouser (MAST) and infusion of a vasoactive agent, dobutamine. Comparisons also were carried out between patients with a normal or increased concentration of plasma lactate and between those who survived and those who ultimately died.

**METHODS**

**Patients**

Seventeen patients admitted to one of the three centers between July 1991 and July 1992 were studied. The centers were the ICU of the Cochin Port-Royal University Hospital in Paris, France, the Sabadell University Hospital in Sabadell, Spain, and the Gustave Roussy Institute in Villejuif, France. Patients were included if they had severe sepsis according to the recent definitions of consensus conference or were mechanically ventilated and needed pulmonary and radial artery catheters. The exclusion criteria were hemorrhagic or cardiogenic shock, ARDS (score >2.5), fraction of inspired oxygen of 0.8 or more, and gas leaks. This study was approved by the ethical committee of Cochin Port-Royal and Sabadell University Hospitals.

**Protocol**

Patients were studied within the first day of the diagnosis of severe sepsis, as soon as hemodynamic stability was achieved with intravenous fluids (to obtain a pulmonary artery balloon-occluded pressure of at least 13 mm Hg) and vasoressor agents, excluding dobutamine. The protocol included the two following periods. The first period, data collection, included hemodynamic measurements and arterial and mixed venous blood sampling. The $D_O_2$, $V_O_2$, and carbon dioxide production ($V_CO_2$) measurements were performed at baseline and 20 min after placement of a MAST inflated at a constant pressure of 50 cm H$_2$O around the legs. The MAST was then gradually deflated. The second period started with a new baseline data collection performed 20 min after the complete MAST deflation. A dobutamine infusion was started at 5 $\mu g$/kg/min and was gradually increased up to 15 $\mu g$/kg/min. Twenty minutes after reaching the highest infusion rate, the data were again collected. In summary, $D_O_2$ and $V_O_2$ were simultaneously assessed at the first baseline, during MAST inflation, at the second baseline after MAST deflation, and finally during dobutamine infusion at 15 $\mu g$/kg/min. Dobutamine infusion was well tolerated in all patients with no episodes of arrhythmias or severe hypotension.

All patients received continuous infusion of phenoperidine and flunitrazepam, and when needed for clinical reasons, pancuronium bromide for muscle relaxation. During the study period, ventilatory setting, fluid infusion rate, and vasoactive support were not modified. Moreover, patients were neither suctioned nor turned within 30 min prior to acquisition of the first baseline measurements and throughout the study period. Core temperature remained stable in all patients during the study.

**Measurements**

The main characteristics and simplified acute physiologic score (SAPS) were collected at admission of the patients in the ICU. Hemodynamic measurements were obtained using radial and pulmonary artery catheters connected to pressure transducers (Baxter-Edwards Laboratories, Santa Ana, Calif). Pressure signals were transmitted to a polygraph recorder and presented as the average phasic values over an entire respiratory cycle. Heart rate, temperature, and intravascular pressures were continuously monitored. Cardiac output was measured by thermodilution technique (Computer 9520A; Baxter-Edwards Laboratories) using 10 mL of cold 5% dextrose in water and a closed system (CO-set system; Baxter-Edwards Laboratories). Five measurements throughout the respiratory cycle were averaged to obtain each cardiac output value. All values were within 10% of each other. In each blood sample, oxygen tension (ABL3; Radiometer, Copenhagen, Denmark), hemoglobin concentration, and hemoglobin saturations (OSM3; Radiometer) were determined. The arterial lactate concentration was measured enzymatically with an automated analyzer (Roche Lactate analyzer 640) with a normal range of 0.5 to 2 mmol/L.

The $V_CO_2$, $V_O_2$, and respiratory quotient (RQ) were continuously measured using a system of indirect calorimetry (Deltatrac Metabolic Monitor, Datex Instrumentarium, Helsinki, Finland). A thorough description and validation has been published elsewhere.

After calibration, we measured $V_CO_2$, $V_O_2$, and RQ minute by minute throughout the study period. A period of 10 min in which variations in minute by minute measured $V_O_2$ and RQ were less than 5% was required to identify a stable metabolic rate in each patient and to begin baseline measurements. The mean of ten values was registered for each part of the protocol over a 10-min period, with an average coefficient of variation of 2.8±1.7%.

**Calculations**

Arterial and mixed venous contents were calculated according to the following formula: $[\text{hemoglobin}] \times [\text{arteriovenous saturation}] + [\text{oxygen tension}]$. Oxygen delivery was calculated as the product of cardiac index (CI) cardiac output/body surface area) and arterial oxygen content. We also calculated indirect $V_O_2$ from the Fick equation as the product of CI and arteriovenous oxygen content difference. Oxygen extraction was calculated as the ration between arteriovenous oxygen content difference and...
Table 1—Clinical Characteristics of the Patients With Normal or High Lactate Concentration at Entry

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, yr</th>
<th>Sex</th>
<th>SAPS</th>
<th>Diagnosis</th>
<th>Lactate Level, mmol/l</th>
<th>Outcome*</th>
<th>Inotropic Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal lactate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>72</td>
<td>M</td>
<td>18</td>
<td>Peritonitis</td>
<td>1.2</td>
<td>D</td>
<td>Epinephrine, 1.5 mg/h</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>M</td>
<td>11</td>
<td>Liver abscess</td>
<td>1.2</td>
<td>S</td>
<td>Dopamine, 25 mg/kg/min</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>M</td>
<td>15</td>
<td>Pneumonia</td>
<td>1</td>
<td>S</td>
<td>Dopamine, 12.5 mg/kg/min</td>
</tr>
<tr>
<td>4</td>
<td>74</td>
<td>F</td>
<td>22</td>
<td>Pneumonia</td>
<td>0.9</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>M</td>
<td>25</td>
<td>Septic shock</td>
<td>1.3</td>
<td>S</td>
<td>Dopamine, 8 mg/kg/min</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>M</td>
<td>26</td>
<td>Pneumonia</td>
<td>1.4</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>69</td>
<td>M</td>
<td>24</td>
<td>Pneumonia</td>
<td>1</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>M</td>
<td>26</td>
<td>Pneumonia</td>
<td>1.3</td>
<td>S</td>
<td>Norepinephrine, 0.4 mg/hr; dopamine, 3 mg/kg/min</td>
</tr>
<tr>
<td>9</td>
<td>64</td>
<td>M</td>
<td>15</td>
<td>Peritonitis</td>
<td>1.7</td>
<td>S</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>58</td>
<td>M</td>
<td>21</td>
<td>Mediastinitis</td>
<td>1.4</td>
<td>D</td>
<td>Epinephrine, 0.5 mg; dopamine, 10 mg/kg/min</td>
</tr>
<tr>
<td>11</td>
<td>55</td>
<td>M</td>
<td>23</td>
<td>Peritonitis</td>
<td>1.4</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>64.2 ± 6.2</td>
<td>203 ± 4.9</td>
<td>1.3 ± 0.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| High lactate |        |     |      |               |                       |          |                                  |
| 12       | 67     | M   | 17   | Pneumonia     | 2.9                   | D        | Epinephrine, 3.5 mg/h; dopamine, 5 mg/kg/min |
| 13       | 52     | M   | 25   | Meningococcemia | 9                     | D        | Dopamine, 15 mg/kg/min           |
| 14       | 66     | M   | 25   | Peritonitis   | 2.5                   | S        | Norepinephrine, 0.3 mg/hr; dopamine, 3 mg/kg/min |
| 15       | 57     | M   | 15   | Cholecystitis | 3.4                   | S        | Dopamine, 18 mg/kg/min           |
| 16       | 65     | M   | 15   | Pericarditis  | 6                     | D        | Epinephrine, 1.5 mg/hr; dopamine, 3 mg/kg/min |
| 17       | 49     | F   | 18   | Osteoarthrosis| 3.2                   | D        | Epinephrine, 0.5 mg/hr; dopamine, 3 mg/kg/min |
| Mean ± SD | 59.3 ± 7.8 | 19.2 ± 4.7 | 4.5 ± 2.6 |          |          |          |                                  |

*S=survivor; D=deceased.

Statistical Analysis

The relationship between Do2 and Vo2 (evaluated by the two methods described: analysis of respiratory gases and Fick equation) was assessed using random-effects linear models.33,34 These models permitted us to test null hypotheses that slope are equal to 0 within a specific group of patients, as well as the null hypothesis that there are no differences in slope between two groups of patients, ie, patients with normal and high lactate levels, survivors and nonsurvivors. The mixed models also gave estimations of within-group mean slopes (and SDs). Restricted maximum likelihood was used as the optimal criterion to fit the data.35

Data are reported as mean ± 1 SD. The computations were performed using the Proc Mixed procedure of the SAS package.

Table 2—Physiologic Changes in 17 Patients With Sepsis After MAST Inflation or Dobutamine Infusion*

<table>
<thead>
<tr>
<th>Normal Lactate Group (n=11)</th>
<th>High Lactate Group (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base 1</td>
</tr>
<tr>
<td>Heart rate, beats per minute</td>
<td>98±14</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>88±11</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure, mm Hg</td>
<td>29±5.8</td>
</tr>
<tr>
<td>Pulmonary wedge pressure, mm Hg</td>
<td>16±2.2</td>
</tr>
<tr>
<td>CI, L/min/m²²</td>
<td>4.5±1.4</td>
</tr>
<tr>
<td>DO₂ mL/min/m²²</td>
<td>541±171</td>
</tr>
<tr>
<td>Measured VO₂ mL/min/m²²</td>
<td>150±20</td>
</tr>
<tr>
<td>EO₂ %</td>
<td>30±10</td>
</tr>
<tr>
<td>Fick equation VO₂ mL/min/m²²</td>
<td>147±34</td>
</tr>
<tr>
<td>RQ</td>
<td>0.86±0.08</td>
</tr>
</tbody>
</table>

*Measured by Deltatrac.
†MAST inflation vs base 1, p≤0.05.
‡MAST inflation vs base 1, p≤0.005.
§Dobutamine infusion vs base 2, p≤0.01.
‖Dobutamine infusion vs base 2, p≤0.05.
¶MAST inflation vs base 1, p≤0.01.
EO₂=oxygen extraction.
lactate: an increase in mean pulmonary arterial pressure (+14%), pulmonary wedge pressure (+19%), cardiac output (+11%), and DO₂ (+19%), and a decrease in tissue oxygen extraction (−11%). In patients with high lactate levels, none of these physiologic variables (except mean pulmonary artery pressure) was significantly affected by MAST inflation. In both groups, VO₂ (Fig 1) and RQ remained unchanged during MAST inflation.

There was no significant difference between physiologic values measured after MAST deflation (baseline 2) and those measured before MAST inflation (baseline 1). After dobutamine infusion, cardiac output and DO₂ increased in patients with normal lactate levels by 15 and 16%, respectively, and in patients with high lactate levels, by 15 and 19%, respectively (Table 2). The VO₂ (Fig 1) and RQ values were unaffected by dobutamine infusion in both groups.

During both periods of MAST inflation, and dobutamine infusion, there was no significant difference between survivors and nonsurvivors for VO₂ and DO₂ values (Table 3).

When VO₂ evaluated by the Fick method was considered (VO₂F), instead of VO₂ measured by expired gas analysis, it was found to be significantly and positively correlated to DO₂ in most patients of both groups, during MAST inflation as well as during dobutamine infusion (Fig 2). Among patients, the slope of this relationship ranged from 0.06 to 0.17, with a mean of 0.12 (p < 0.001).

### RESULTS

As shown in Table 1, all 17 patients were severely ill, with high SAPS and mortality rate (53%). In the group with elevated plasma lactate values, all patients required vasoactive support, which was necessary in only 6 out of the 11 patients in the normal lactate level group.

Table 2 shows that MAST inflation led to the following significant changes in patients with normal

![Image](https://i.imgur.com/3J5Q5Q5.png)

**Figure 1.** Individual responses in measured VO₂ (VO₂m) (top), and in VO₂ calculated with Fick equation (VO₂F) (bottom), to increases in DO₂ by MAST inflation in patients with normal (circles) or elevated (squares) plasma lactate concentrations.

### DISCUSSION

The main finding of this multiple center study was that VO₂ remained unchanged when DO₂ was increased in patients with severe sepsis, even in those who had an elevated concentration of plasma lactate and in those who ultimately died, thus showing a lack of oxygen supply dependency.

This study is the first in which the relationship between VO₂ and DO₂ was observed during the

### Table 3—Effect of MAST Inflation or Dobutamine on Oxygen Delivery and Consumption in 17 Patients With Sepsis

<table>
<thead>
<tr>
<th></th>
<th>MAST</th>
<th>Dobutamine*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DO₂</td>
<td>Fick VO₂</td>
</tr>
<tr>
<td></td>
<td>Base 1</td>
<td>MAST</td>
</tr>
<tr>
<td>Survivors</td>
<td>514</td>
<td>718</td>
</tr>
<tr>
<td>(n=8)</td>
<td>p=0.01</td>
<td>p=0.01</td>
</tr>
<tr>
<td>Nonsurvivors</td>
<td>532</td>
<td>596</td>
</tr>
<tr>
<td>(n=9)</td>
<td>p=0.01</td>
<td>p=0.2</td>
</tr>
</tbody>
</table>

*Dobutamine was infused at 15 μg/kg/min.
†Measured by Deltatrac.
application of two different methods to increase \( \text{DO}_2 \), i.e., MAST inflation and dobutamine infusion. The MAST inflation is a convenient and reversible way to increase cardiac output, and thus \( \text{DO}_2 \), with no effect on whole-body oxygen demand.\(^{35-36} \) Indeed, Ng et al.\(^{37} \) have shown that inflating MAST at 50 mm Hg has no significant effect on \( \text{VO}_2 \) in normal subjects, at rest as well as during muscular exercise.

We also used dobutamine because infusion of this drug can be titrated to produce a large increase in \( \text{DO}_2 \), even in patients unresponsive to volume loading.\(^{37} \) The dobutamine test was used after MAST inflation. Indeed, in a preliminary study in severely ill patients, we observed that after cessation of dobutamine infusion, a relatively long period of time (usually 30 min to 2 h) was most often necessary for a new period of hemodynamic stability to be obtained. In contrast, following MAST deflation, hemodynamic variables return rapidly to baseline values. Therefore, in the present study, randomization of the two interventions aimed at increasing \( \text{DO}_2 \) would have prolonged study time, and thus might have represented a potential source of unstable oxygen demand and delayed treatment for the patients.

With both interventions, the increase in \( \text{DO}_2 \) ranged from 16 to 20%, except for the patients with high blood lactate levels who failed to respond to MAST inflation. In these patients, the lack of MAST-induced increase in cardiac output and \( \text{DO}_2 \) likely reflects myocardial dysfunction, a common feature of severe sepsis.\(^{38} \)

In none of our patients, did the \( \text{VO}_2 \) parallel changes in \( \text{DO}_2 \). Similar observations recently have been published concerning patients with sepsis when \( \text{DO}_2 \) was changed by administration of inotropic drugs, fluid loading, blood transfusion, or use of positive end-expiratory pressure.\(^{19-22} \) On the other hand, our findings are in contrast to other studies who found that the \( \text{VO}_2 \) was linearly related to \( \text{DO}_2 \) during sepsis.\(^{1-8} \) This discrepancy could be related to three main factors which require further discussion: severity of the illness, study protocol, and methods used to measure \( \text{VO}_2 \).

The enrolled patients may not be ill enough to show any oxygen debt. The severity of illness of our patients with sepsis, as assessed by SAPS (20 ± 4) and mortality rate (55%), was equal or higher to that in studies that did find pathologic supply dependency.\(^{1-8} \) Moreover, we cannot study patients after a prolonged phase of hemodynamic stabilization because patients might not be ill enough to demonstrate pathologic supply dependency, even in the presence of increased concentration of plasma lactate. Indeed, when \( \text{DO}_2 \) is rapidly restored, the decrease in plasma lactate level usually is progressive,\(^{39} \) particularly in the presence of liver dysfunction, which was present in all patients in the study by Ronco and colleagues.\(^{21} \) Conversely, we also excluded patients with a clearly irreversible condition in whom all therapeutic interventions are doomed to failure. Since our patients were sufficiently ill and were also studied during the first day of severe sepsis, as soon as possible after fluid resuscitation and hemodynamic stabilization, we would have expected to find oxygen supply dependence, if it was present.

Regarding the study protocol, special care has to be made to study patients with a stable oxygen demand. To minimize changes in oxygen demand, all patients were sedated and a baseline period (20 min) in which variation of minute-by-minute measurement of \( \text{VO}_2 \) and RQ were less than 5% was used to identify a stable metabolic rate in each patient. Moreover, the RQ remained stable throughout the study period and ranged from 0.7 to 1. Several other investigators\(^{8,21} \) also have chosen dobutamine, a well tolerated adrenergic agent. However, this drug can increase oxygen demand by direct metabolic effects, but it has not been evaluated in patients with sepsis.\(^{40} \) In our study, we did not find any dobutamine-induced increase in \( \text{VO}_2 \). In contrast, Ronco et al.\(^{21} \) found a small but statistically significant increase in \( \text{VO}_2 \) (8 ± 6 mL · min\(^{-1} \))
1·m⁻²) after dobutamine infusion in the group with normal lactate levels, although they used the same entry criteria for their patients, the same method to assess VO₂, similar statistical analysis, and a comparable dose of dobutamine. A possible explanation could be the lower dobutamine-induced increase in DO₂ observed in our study (16 vs 53%). This modest increase in DO₂ is unlikely to enhance the metabolic demand in organs which VO₂ depends on blood flow, such as the kidney and heart.31-42 The higher requirement of inotropic support observed at entry in our study (6 of 11 vs 1 of 6 in the Ronco et al study)21) provides evidence for a more pronounced decrease in cardiac responsiveness of catecholamines, and is probably the cause of the lower response to dobutamine observed in the present study.43

Second, the magnitude of change in DO₂ has to be quite large. In our study, both MAST and dobutamine produced a significant increase in DO₂ similar or higher than previously reported in sepsis, ranging from 9 to 36%,1,3,5,6 except in the patient group with a high concentration in plasma lactate only when MAST inflation was used, as discussed above.

Third, the range of initial values of DO₂ needs to be large. Indeed, an elevated baseline level of DO₂ higher than the hypothetical critical delivery (the point where oxygen uptake begins to fall) could make it impossible to show pathologic supply dependency, since the critical DO₂ is lower than the studied level. In sedated humans, the critical value of DO₂ is about 330 mL/min/m² or about 8.2 mL/min/kg.44,45 From the data reported, the patients had a plateau VO₂ averaging 85 mL/min/m². In patients with sepsis and ARDS, Ranieri et al46 reported that the critical value of DO₂ was higher, about 640 mL/min/m², with a plateau VO₂ averaging 146 mL/min/m². Our patients with sepsis had a wide range in basal DO₂ from 260 to 540 mL/min/m². Consequently, most of our patients had a basal DO₂ lower than this reported critical value.

If the relationship indicated by such a grouped analysis of many individual patients is representative of what would be found in a single subject, then they imply a critical oxygen extraction ratio near 33% in healthy subjects and patients with sepsis, or about half that in anesthetized dogs.47 Moreover, it is difficult to determine if parallel changes in DO₂ and VO₂ seen in a patient with critical illness reflect pathologic supply dependency, or just the normal cardiovascular response to acute changes in oxygen demand in patients with varying oxygen demand. Actually, the clear identification of a critical DO₂ in humans is problematic, since lowering tissue DO₂ beyond the point where VO₂ becomes limited is likely to be injurious. However, Ronco et al,22 measuring VO₂ by expired gas analysis, found a markedly lower critical value of DO₂ (4 mL/min/kg) in patients with sepsis and those without who died during withdrawal of active care. This threshold is close to that observed in dogs.47 Moreover, pathologic dependence was not found at normal or high levels of DO₂. Finally, significant doubt still exists regarding the physiologic existence of an elevated critical DO₂ in patients with sepsis.

The method we used to measure VO₂ is a critical issue. This system has been validated extensively both in vitro and in vivo in lung models.39-32 It is easy to use, accurate, sensitive, and reproducible with a fraction of inspired oxygen lower than 0.8. The protocol was designed to minimize spontaneous variation of VO₂, and consequently our average coefficient of variation was of 3%, similar to those reported in other studies.21,29-31 We are, therefore, confident that we were able to detect small changes in VO₂, since this was observed when starting dobutamine infusion (the first 60 s) in few patients.

It seems difficult to reconcile the findings of investigators who found a pathologic supply dependency by calculating VO₂ by the Fick principle with those (including us) who did not find it by measuring VO₂ by expired gas analysis. However, it is important to note that the use of dependent measurements on two axes predisposes to a spurious discovery of supply dependence (a type 1 error) just as use of independent measurements predisposes to a failure to disclose pathologic supply dependence (a type 2 error). However, because we used a very sensitive, accurate, and reproducible method to measure VO₂ after large changes in DO₂, a type 2 error is unlikely in our study.

It also is interesting to note that, while Ronco et al,21,22 Wysocki et al,30 as well as our own studies were unable to establish a pathologic supply dependency between VO₂ and DO₂, the same investigators found such a dependence when VO₂ was indirectly determined as the product of thermodilution cardiac output and arteriovenous oxygen difference.1-8 Indeed, after dobutamine infusion, Fick VO₂ increased significantly 12% in the group with normal lactate levels and 8% in the group with high lactate values (Table 2), as well as in the survivors and nonsurvivors, 16 and 10%, respectively (Table 3). Consequently, an increase in Fick VO₂ simultaneously with lack of change in VO₂ measured by expired gas analysis after increasing DO₂ leads to the speculation that previous reports of dependence of VO₂ on DO₂ in sepsis could be due to methologic type 1 error. Although there have been reports that Fick VO₂ does not correlate with DO₂, the literature generally confirms the consistent presence of such a correlation, as do the findings of this study in which the Fick VO₂ rose as DO₂ was increased.
Usually, the largest error in the determining oxygen parameters concerns the assessment of cardiac output by thermodilution technique. Random errors in the estimate of thermal cardiac output will affect both derived variables in proportion. For example, if two sequential measurements are made in the same patient in exactly the same physiologic state, then if the cardiac output measurement was correct the first time, but 10% too high the second, then both DO2 and VO2 would appear to have risen by approximately 10%, suggesting pathologic supply dependence. A similar problem arises if the measurement error is in the opposite direction. The only way to avoid these difficulties is to measure the VO2 by another method, as we did with an analysis of expired gas.

Several groups have reported that pathologic supply dependence accompanies sepsis in patients with lactic acidosis, but not in patients without lactic acidosis, suggesting that pathologic supply dependency is really an indicator of tissue hypoxia. The investigators who measured VO2 by expired gas analysis including ourselves found no difference between these two patient groups. Lactic acidosis alone must be interpreted with caution, since even in the absence of anaerobic metabolism, elevations in lactate may occur as a consequence of increased metabolic rate of glycolysis from increased levels of catecholamines, delayed clearance of plasma lactate related to liver dysfunction, inhibition of pyruvate dehydrogenase by endotoxin, or the combination of several of these mechanisms.

We also analyzed our results in terms of survival, as suggested by Gutierrez and Pohli and Bihari et al. The last investigators found that an infusion of a vasodilator, prostacyclin, was associated with a greater increase in Fick VO2 in patients with acute respiratory failure who died as compared with the survivors. In the present study, we did not find evidence for supply dependency either in the survivors or in those who died from their sepsis episode, despite a greater MAST inflation-induced increase in DO2 in the survivors than in the nonsurvivors.

CONCLUSION
No evidence of pathologic oxygen supply dependency was found in patients with severe sepsis. Analysis of the DO2-Vo2 relationship is not useful to guide therapy and does not favor the view that maximizing DO2 is a primary therapeutic objective in such patients.

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