Lactate and Venoarterial Carbon Dioxide Difference/Arterial-Venous Oxygen Difference Ratio, but Not Central Venous Oxygen Saturation, Predict Increase in Oxygen Consumption in Fluid Responders

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**Objectives:** During circulatory failure, the ultimate goal of treatments that increase cardiac output is to reduce tissue hypoxia. This can only occur if oxygen consumption depends on oxygen delivery. We compared the ability of central venous oxygen saturation and markers of anaerobic metabolism to predict whether a fluid-induced increase in oxygen delivery results in an increase in oxygen consumption.

**Design:** Prospective study.

**Setting:** ICU.

**Patients:** Fifty-one patients with an acute circulatory failure (78\% of septic origin).

**Measurements:** Before and after a volume expansion (500 mL of saline), we measured cardiac index, \(o_{2}\)- and \(CO_{2}\)-derived variables and lactate.

**Main Results:** Volume expansion increased cardiac index \(\geq 15\%\) in 49\% of patients ("volume-responders"). Oxygen delivery significantly increased in these 25 patients \((-1-32\% \pm 16\%\), \(p < 0.0001\)). An increase in oxygen consumption \(\geq 15\%\) concomitantly occurred in 56\% of these 25 volume-responders (+38\% \pm 28\%). Compared with the volume-responders in whom oxygen consumption did not increase, the volume-responders in whom oxygen consumption increased \(\geq 15\%\) were characterized by a higher lactate (2.3 \(\pm 1.1\) mmol/L vs. 5.5 \(\pm 4.0\) mmol/L, respectively) and a higher ratio of the veno-arterial carbon dioxide tension difference \((P(v - a)CO_{2})\) over the arteriovenous oxygen content difference \((C(a - v)O_{2})\). A fluid-induced increase in oxygen consumption greater than or equal to 15\% was not predicted by baseline central venous oxygen saturation but by high baseline lactate and \((P(v - a)CO_{2})/(C(a - v)O_{2})\) ratio (areas under the receiving operating characteristics curves: 0.68 \(\pm 0.11\), 0.94 \(\pm 0.05\), and 0.91 \(\pm 0.06\)). In volume-nonresponders, volume expansion did not significantly change cardiac index, but the oxygen delivery decreased due to a hemodilution-induced decrease in hematocrit.

**Conclusions:** In volume-responders, unlike markers of anaerobic metabolism, central venous oxygen saturation did not allow the prediction of whether a fluid-induced increase in oxygen delivery would result in an increase in oxygen consumption. This suggests that along with indicators of volume-responsiveness, the indicators of anaerobic metabolism should be considered instead of central venous oxygen saturation for starting hemodynamic resuscitation. (Crit Care Med 2013; 41:1412–1420)

**Key Words:** fluid challenge; oxygen consumption; shock; tissue oxygenation; veno-arterial carbon dioxide gap; venous oxygen saturation

Volume expansion is the first-line treatment in many cases of hemodynamic failure. The main reason to administer volume, by conventional thinking, is to increase preload and optimize cardiac output with the subsequent effect being increasing oxygen delivery and reducing...
tissue hypoxia. For predicting whether fluid administration will possibly increase cardiac output, many predictive indices have been developed during the last years (1). However, reliable indices indicating whether an increase in oxygen delivery might result in a reduction of tissue hypoxia, that is, indices indicating that an oxygen debt is present (2, 3), are lacking.

Based on the results of a large-scale study conducted in patients with early septic shock (4), the Surviving Sepsis Campaign recommends that the treatment of septic shock should be guided by the central venous oxygen saturation ($\text{Scvo}_2$), the goal being to elevate it above 70% (5). Some authors also suggested that a low mixed venous oxygen saturation value should be the trigger for starting hemodynamic resuscitation (6). Nevertheless, whereas several studies now support the notion of a low $\text{Scvo}_2$ being indicative of standard oxygen delivery, a value of $\text{Scvo}_2$ greater than 70% has the potential to be misleading (3). Indeed, during septic shock, due to impairment of oxygen extraction, $\text{Scvo}_2$ is often elevated in spite of oxygen delivery/oxygen consumption ($D_O^2/\dot{V}O_2$) dependence. In this respect, some studies showed that in a majority of septic shock patients who have been already resuscitated, $\text{Scvo}_2$ was elevated while tissue hypoxia was still present (7–11). Thus, $\text{Scvo}_2$ does not always reflect tissue hypoxia and might not be the best trigger for starting hemodynamic resuscitation (12). In the present study, we compared $\text{Scvo}_2$ with alternative resuscitation targets in patients with multiple etiologies of tissue hypoperfusion, the majority with sepsis.

Markers of anaerobic metabolism, such as blood lactate, are likely to be elevated in case of oxygen debt. Thus, these markers might be better than $\text{Scvo}_2$ for guiding hemodynamic resuscitation, as recently emphasized (13, 14). In a previous study of our group, the ratio between the venoarterial carbon dioxide ($C_{O_2}$) tension gradient ($P(\text{v-a})C_{O_2}$) and the arteriovenous $O_2$ content gradient ($C(a-v)O_2$) was suggested to reflect the occurrence of anaerobic metabolism and to be correlated with lactate (15). In that study, the ratio was calculated using the mixed venous blood. A possible advantage of this indicator of anaerobic metabolism over lactate would be to have a faster response to treatments. Another advantage would be that, unlike lactate (16), it would be a pure marker of anaerobic metabolism during sepsis.

The main goal of the present study was to compare the respective ability of $\text{Scvo}_2$, $P(\text{v-a})C_{O_2}/C(a-v)O_2$ ratio calculated from the central venous blood, and lactate to predict whether a fluid-induced increase in cardiac output will reduce the oxygen debt assessed by an increase in $\dot{V}O_2$.

PATIENTS AND METHODS

Patients

As approved by the institutional review board of our institution, patients’ relatives were informed about the study at the time the patient was included. Possibility was given to them to refuse patient’s participation at that time. If not, patients were informed as soon as their mental status enabled it and possibility was given to them to refuse to participate. Patients were prospectively included if they met all the following criteria:

- Presence of a circulatory failure defined by a systolic arterial pressure less than or equal to 90 mm Hg (or fall of systolic arterial pressure 250 mm Hg in known hypertensive patients) and one or more of the following signs: 1) urinary flow less than or equal to 0.5 mL/kg/min for greater than or equal to 2 hours, 2) tachycardia greater than or equal to 100 beats/min, or 3) presence of skin mottling.

- Need for a fluid challenge, as decided by the attending physician.

- Jugular venous and femoral arterial catheters in place. Investigators (F.J., N.A.-H., M.L., C.G., M.J., R.P.) checked that the position of the tip of the venous catheter was in the upper part of the right atrium on chest radiograph.

- Hemodynamic monitoring with a PiCCO$_2$ (Pulsion Medical Systems, Munich, Germany) in place.

Measurements and Study Design

At baseline, we measured arterial lactate and hemodynamic and tissue oxygenation variables. The hemodynamic variables included heart rate, blood pressure, and cardiac index measured by transpulmonary thermodilution. Tissue oxygenation variables were measured after arterial and central venous blood sampling and analysis (ABL 800flex, Radiometer, Copenhagen, Denmark). $C_{ao_2}$ was calculated as follows: $C_{ao_2} = 1.34 \times S_{ao_2} \times Hb + 0.003 \times P_{ao_2}$, where $S_{ao_2}$ is the oxygen saturation of arterial blood, $Hb$ the hemoglobin concentration, and $P_{ao_2}$ the oxygen tension of the arterial blood. $C_{vo_2}$ was calculated using the same formula but using the $O_2$ saturation and tension of the venous blood. The $D_O^2$ was calculated using the following formula: $D_O^2 = \text{cardiac index} \times C_{ao_2} \times 10$. The $\dot{V}O_2$ was calculated using the formula: $\dot{V}O_2 = 10 \times \text{cardiac index} \times C(a-v)O_2$. The $P(\text{v-a})C_{O_2}$ was calculated as $P(\text{v-a})C_{O_2} = P_{vO_2} - P_{aO_2}$. Arterial lactate was measured by a Modular device (Roche, Meylan, France).

A fluid challenge was then intravenously administered (500 mL of saline over 30 min) (17). Immediately after the fluid challenge, we again measured hemodynamic and tissue oxygenation variables. The dose of norepinephrine was kept unchanged during the fluid challenge. The arterial lactate was measured (average + SD) 3.0 ± 1.5 hours later. In the meantime, resuscitation was continued without protocolized algorithm, aiming to achieve a lactate value less than or equal to 1.7 mmol/L and a $\text{Scvo}_2$ value greater than or equal to 70%. This resuscitation included continued volume expansion, blood transfusion, catecholamine administration, and continuous veno-venous hemofiltration depending on the situation.

Statistical Analysis

Patients in whom the fluid challenge induced an increase in cardiac index greater than or equal to 15% were defined as "volume-responders" and the remaining ones as "volume-nonresponders" (18). By analogy, because $\dot{V}O_2$ is proportional to cardiac index, we defined a clinically significant increase in $\dot{V}O_2$...
by a VO₂ augmentation ≥15%. Liver failure was defined by the Sepsis-related Organ Failure Assessment score (19). Data are expressed as mean ± SD or as median (interquartile range), as appropriate. The areas under receiving operating characteristics (ROC) curves are expressed as mean (95% confidence interval). The comparison of data before vs. after fluid challenge was performed by paired Student t test or Wilcoxon paired test as appropriate. The comparison of data among different groups of patients was performed by a two-tailed Student t test or a Mann-Whitney U test as appropriate. The absolute change in variables over time was also analyzed by performing an analysis of covariance with the change in variable as dependent variable, the group of patients as a factor, and the baseline value as a covariate. Proportions were compared with the chi-square test. We constructed ROC curves for testing the ability of ScvO₂, the lactate level, and the \( \frac{(P(v-a)CO_2)}{(C(a-v)O_2)} \) ratio at baseline to predict an increase in VO₂ greater than or equal to 15% with volume expansion in volume-responders. The comparison among the areas under the ROC curves was performed using the Hanley-McNeil test. Correlations were analyzed using the Spearman coefficient. A \( p \) value of less than 0.05 was considered statistically significant. The statistical analysis was performed using MedCalc 8.1.0.0 (Mariakerke, Belgium).

RESULTS

Study Population

Fifty-one patients were included in the study. Their characteristics at baseline before volume expansion are summarized in Table 1. Forty-six patients were mechanically ventilated (all in the assist control mode). Forty patients suffered from septic shock. The source of infection in these patients was pneumonia in 33, urinary tract infection in three, infection of acute pancreatitis in two, and unknown in two. ScvO₂ value was greater than 70% (78% ± 5%) in 25 patients. All of them suffered from septic shock. ScvO₂ value was less than 70% (62% ± 8%) in the remaining 26 patients. Among the 40 septic shock patients, ScvO₂ value was greater than 70% in 25 at baseline. Norepinephrine was administered in 86% of patients. Patients did not receive any other catecholamine or any paralyzing agent.

Effects of Volume Expansion in the Whole Population

Considering the population as a whole, volume expansion significantly increased cardiac index (21% ± 22% paired \( t \) test, \( p = 0.04 \)) and DO₂ (14% ± 22% paired \( t \) test, \( p < 0.001 \)). VO₂ did not change significantly (10% ± 24% paired \( t \) test, \( p = 0.62 \)).

There was a significant correlation between the baseline lactate and the \( \frac{(P(v-a)CO_2)}{(C(a-v)O_2)} \) ratio (\( r = 0.56, p < 0.0001 \)). This correlation was tested only at baseline because the second values of lactate and \( O_2^- \) and \( CO_2^- \)-derived variables were not measured simultaneously after volume expansion. There was a significant correlation between the \( (P(v-a)CO_2) \) gradient and the cardiac index (\( r = -0.36, p = 0.0002 \)) but not between \( (P(v-a)CO_2) \) and lactate at baseline (\( p = 0.58 \)). The fluid-induced changes in the \( (P(v-a)CO_2) \) gradient and in the cardiac index were significantly correlated (\( r = -0.59, p < 0.0001 \)).

Differences Between Volume-Responders and Volume-Nonresponders

Volume expansion increased cardiac index by more than 15% in 25 "volume-responders" (49% of the whole population; Fig. 1). In these volume-responders, cardiac index increased by 39% ± 17% (paired \( t \) test, \( p < 0.001 \)), DO₂ increased by 32% ± 16% (paired \( t \) test, \( p < 0.001 \)), and VO₂ increased by 32% ± 16% (paired \( t \) test, \( p < 0.001 \), Supplemental Table 2, Supplemental Digital Content 1, http://links.lww.com/CCM/A577). Among these 25 volume-responders, volume expansion increased VO₂ by more than 15% (38% ± 28%, paired \( t \) test, \( p < 0.001 \)) in 14 "VO₂-responders," whereas it did not change VO₂ in 11 of the volume-responders (Table 2, Fig. 1).

In the remaining 26 volume-nonresponders, the arterial Hb decreased by 8% ± 4% during volume expansion (paired \( t \) test, \( p < 0.001 \)). Concomitantly, DO₂ decreased by 4% ± 7% (paired \( t \) test, \( p < 0.001 \)), and VO₂ decreased by 4% ± 11% (paired \( t \) test, \( p < 0.001 \)).

Volume-responders and volume-nonresponders did not differ in terms of baseline ScvO₂, lactate, or \( (P(v-a)CO_2) \) ratio (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/CCM/A577). When considering both volume-responders and volume-nonresponders, ScvO₂, lactate, or the \( (P(v-a)CO_2) \) ratio did not predict whether fluid administration would result in an increase in VO₂ ≥15% (areas under the ROC curves not significantly different from 0.5).

The mortality rate was 43% in VO₂-responders and 73% in VO₂-nonresponders (chi-square test, \( p = 0.27 \)).

Prediction of the Response of VO₂ to Volume Expansion in the Subgroup of Volume-Responders

In the 14 patients who were both volume-responders and VO₂-responders, mean ScvO₂ value at baseline was 70% ± 15% and did not significantly change with volume expansion (paired \( t \) test, \( p = 0.20 \), Table 2 and Figs. 1 and 2). In four of these patients, ScvO₂ value at baseline was less than 70% (47% ± 4%). Shock was of septic origin in three of them. In all the remaining patients who were both volume- and VO₂-responders, ScvO₂ value at baseline was greater than 70% and shock was of septic origin. In volume- and VO₂-responders, the \( (P(v-a)CO_2) \) ratio was 2.3 ± 0.8 mm Hg/mL at baseline and significantly decreased by 42% ± 30% with volume expansion (paired \( t \) test, \( p < 0.01 \), Table 2). The lactate value was 5.5 ± 4.0 mmol/L at baseline (Table 2).

In the 11 patients who were volume-responders but VO₂-nonresponders, shock had a nonseptic origin. Compared with patients who were both volume-responders and VO₂-responders, these patients were characterized by both lower baseline \( (P(v-a)CO_2) \) and lactate (two-tailed \( t \) tests, \( p = 0.01 \) and 0.02, respectively; Table 2 and Fig. 1). ScvO₂ value at baseline was 64% ± 4%, and it significantly increased to
TABLE 1. Characteristics of Patients at Baseline and did not significantly change with volume expansion (paired t test, p < 0.01, Table 2). The \( P(v - a)C_O/C(a - v)O_2 \) ratio was 1.3 ± 0.5 mm Hg/mL at baseline and did not significantly change with volume expansion (paired t test, \( p = 0.58 \), Table 2). Lactate value was 2.3 ± 1.1 mmol/L at baseline (Table 2). Among the subgroup of volume-responders, the fluid-induced changes in the \( P(v - a)C_O/C(a - v)O_2 \) ratio (analysis of covariance, \( p < 0.001 \) ) but neither in ScvO, \( (p = 0.28) \) nor in lactate \( (p = 0.41) \) were significantly lower in Vo2, nonresponders than in Vo2, responders.

Considering the population of volume-responders pooled, the value of ScvO, at baseline did not predict the Vo2 increase ≥15% (area under the ROC curve not significantly different from 0.5). Nevertheless, among volume-responders whose ScvO, value was less than or equal to 70%, the four who were Vo2, responders had a baseline ScvO, value ranging between 40% and 50% (Supplemental Table 2, Supplemental Digital Content 1, http://links.lww.com/CCM/A577). In addition, all volume-responders who were Vo2, nonresponders had a baseline ScvO, > 50%. Thus, in volume-responders, a ScvO, value ≤50% was always associated with a fluid-induced increase in Vo2 ≥15%.

Still considering the population of volume-responders pooled, a lactate value at baseline ≥2.7 mmol/L predicted the Vo2 increase ≥15% with a sensitivity of 93% (66–100) and a specificity of 82% (48–98). A \( P(v - a)C_O/C(a - v)O_2 \) ratio at baseline ≥1.8 mm Hg/mL predicted the Vo2 increase ≥15% with a sensitivity of 86% (57–98) and a specificity of 91% (59–100) (Fig. 2). The area under the ROC curve for the baseline lactate and \( P(v - a)C_O/C(a - v)O_2 \) ratio were both significantly larger than the area under the ROC curve for baseline ScvO, \( (0.91 ± 0.06, 0.94 ± 0.05, \) and \( 0.68 ± 0.11; \) Fig. 2).

**Difference Between Patients With Baseline ScvO, > 70% and Patients With Baseline ScvO, ≤ 70%**

When data were analyzed depending on the level of ScvO, at baseline (Supplemental Table 2, Supplemental Digital Content 1, http://links.lww.com/CCM/A577), we observed that Vo2 increased ≥15% in patients with a baseline ScvO, > 70%, while it did not change in patients with a baseline ScvO, ≤ 70%. Compared with patients with a baseline ScvO, > 70%, patients with a baseline ScvO, ≤ 70% were characterized by a higher baseline \( \text{VO}_2 \) \( (88 ± 36 \text{ mL/min/m^2}) \) vs. \( 143 ± 79 \text{ mL/min/m^2} \), respectively, two-tailed \( t \) test, \( p = 0.002 \), a nonsignificantly lower baseline \( \text{DO}_2 \) \( (450 ± 161 \text{ mL/min/m^2}) \) vs. \( 374 ± 188 \text{ mL/min/m^2} \), respectively, two-tailed \( t \) test, \( p = 0.13 \), and a lower baseline lactate \( (5.4 ± 4.2 \text{ vs. } 2.2 ± 1.4 \text{ mmol/L}) \), respectively, two-tailed \( t \) test, \( p < 0.001 \).

**DISCUSSION**

Although this study showed that none of the three studied variables were predictors of increase in \( \text{Vo}_2 \) in the total population studied, the lactate and the \( P(v - a)C_O/C(a - v)O_2 \) ratio at baseline were good predictors of increase in \( \text{Vo}_2 \) in those patients whose \( \text{Do}_2 \) increased with fluid administration. This was not the case for ScvO, except for values ≤50%.

**The Concept of Vo2/Do2 Dependence as an Indicator of Oxygen Debt**

\( \text{Vo}_2/\text{Do}_2 \) dependence has been demonstrated to be a marker of tissue hypoxia (20) and poor outcome (21). As a marker of anaerobic metabolism, lactate increases in case of \( \text{Vo}_2/\text{Do}_2 \) dependence (22). As a first result, the present study shows that calculating the oxygen-derived variables from the central instead of the mixed venous blood also allows detecting tissue hypoxia through \( \text{Vo}_2/\text{Do}_2 \) dependence. Indeed, baseline lactate value was elevated in patients in whom fluid increased both \( \text{Do}_2 \) and \( \text{Vo}_2 \) and lower in patients without \( \text{Vo}_2/\text{Do}_2 \) dependence.

Years ago, the concept of \( \text{Do}_2/\text{Vo}_2 \) dependence during sepsis was a matter of debate (23). Some argued that a mathematical coupling was responsible for the \( \text{Do}_2/\text{Vo}_2 \) relationship (24). Nevertheless, the fact that in our study, lactate was elevated at baseline and decreased after fluid administration does not support that such a phenomenon is responsible for the \( \text{Vo}_2 \) increase in our study. It was suggested that therapy increasing \( \text{Do}_2 \) (e.g., beta-adrenergic agents) might increase \( \text{Vo}_2 \) through a thermogenic effect (25). Nevertheless, this probably did not occur in our study because \( \text{Do}_2 \) was increased by saline. Finally,
one cannot exclude that an increase in VO$_2$ could result from
an increase in nonoxidative oxygen use once tissue hypoxia has
resolved (26).

Patients with ScvO$_2$ value greater than 70% were character-
ized by a relatively lower VO$_2$ and higher DO$_2$, than patients with
a ScvO$_2$ value less than or equal to 70%. This suggests that the
DO$_2$/VO$_2$ relationship was steeper in patients with ScvO$_2$ value
>70%, that is, a typical septic pattern of DO$_2$/VO$_2$ dependence.
This typical septic condition could also explain why ScvO$_2$ was
higher (due to the oxygen extraction impairment) and lactate
was higher (possible nonanaerobic production of lactate) (27)
in these patients. This group of patient is likely characterized
by a greater alteration of oxygen extraction capacities than
patients with a low ScvO$_2$ value.

**Prediction of the VO$_2$ Increase in Response to the
Fluid-Induced Increase in DO$_2$**

During shock, fluid administration aims not only at increasing
cardiac output but also at reducing tissue hypoxia. It was
recently reported that ScvO$_2$ did not predict whether fluid
administration will increase cardiac output or not (28). The
present study further suggests that ScvO$_2$ cannot predict
whether a DO$_2$ increase will increase VO$_2$.

Indeed, in a large proportion of volume-responders, VO$_2$
increased while baseline ScvO$_2$ was high. All these patients were
in septic shock with high lactate, confirming that, during septic
shock, oxygen extraction is impaired (i.e., ScvO$_2$ is high) (29).
It is in agreement with previous studies showing that ScvO$_2$ is
greater than 70% despite obvious tissue hypoxia in a large pro-
portion of septic shock patients who have been already resus-
citated (8, 10).

In only few patients in whom the fluid-induced increase in
DO$_2$ increased VO$_2$, ScvO$_2$ was very low at baseline (between 40% and 50%). In other words, only ScvO$_2$ values ≤50% were infor-
mative and allowed to predict that VO$_2$ would increase with DO$_2$.
Nevertheless, such ScvO$_2$ values were rare in our population in
which septic shock patients were the majority. These patients with
very low ScvO$_2$ values were similar to those of the study by Rivers
et al. before resuscitation (4) but constituted a minority of our
patients. By contrast, a large proportion of volume-responders
with a baseline ScvO$_2$ value less than 70% did not respond to fluid
by increasing VO$_2$. Hence, recommendations to guide resuscitation
TABLE 2. Hemodynamic and Tissue Oxygenation Variables During Volume Expansion in Volume Responders According to the Response of VO$_2$ Change ≥ 15% (n = 14) and VO$_2$ Change < 15% (n = 11)

<table>
<thead>
<tr>
<th>Variable</th>
<th>VO$_2$ Change ≥ 15% (n = 14)</th>
<th>VO$_2$ Change &lt; 15% (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Volume Expansion</td>
<td>After Volume Expansion</td>
</tr>
<tr>
<td>Heart rate (mean ± so, beats/min)</td>
<td>90 ± 15</td>
<td>88 ± 12</td>
</tr>
<tr>
<td>Mean arterial pressure (mean ± so, mm Hg)</td>
<td>76 ± 11</td>
<td>83 ± 13$^b$</td>
</tr>
<tr>
<td>Cardiac index (mean ± so, L/min/m$^2$)</td>
<td>2.7 ± 1.2</td>
<td>3.7 ± 1.5$^b$</td>
</tr>
<tr>
<td>Stroke index (mean ± so, mL/m$^2$)</td>
<td>31 ± 17</td>
<td>44 ± 21$^b$</td>
</tr>
<tr>
<td>Dose of norepinephrine (median [interquartile range], µg/kg/min)</td>
<td>0.28 [0.23-0.40]</td>
<td>0.28 [0.23-0.40]</td>
</tr>
<tr>
<td>Arterial pH (mean ± so)</td>
<td>7.32 ± 0.14</td>
<td>7.32 ± 0.14</td>
</tr>
<tr>
<td>Arterial oxygen saturation (mean ± so, %)</td>
<td>98 ± 2</td>
<td>98 ± 2</td>
</tr>
<tr>
<td>Arterial Hb (mean ± so, g/dL)</td>
<td>10.5 ± 2.2</td>
<td>9.9 ± 2.0$^a$</td>
</tr>
<tr>
<td>Arterial oxygen content (mean ± so, mL)</td>
<td>14.2 ± 2.7</td>
<td>13.7 ± 1.8$^b$</td>
</tr>
<tr>
<td>Arterial carbon dioxide tension (mean ± so, mm Hg)</td>
<td>32 ± 7</td>
<td>31 ± 8</td>
</tr>
<tr>
<td>Venous pH (mean ± so)</td>
<td>7.31 ± 0.18</td>
<td>7.30 ± 0.11</td>
</tr>
<tr>
<td>Central venous oxygen saturation (mean ± so, %)</td>
<td>70 ± 15</td>
<td>71 ± 13</td>
</tr>
<tr>
<td>Venous Hb (mean ± so, g/dL)</td>
<td>10.7 ± 2.2</td>
<td>10.0 ± 2.2$^b$</td>
</tr>
<tr>
<td>Central venous oxygen content (mean ± so, mL)</td>
<td>10.1 ± 3.4</td>
<td>9.7 ± 3.2</td>
</tr>
<tr>
<td>Central venous carbon dioxide tension (mean ± so, mm Hg)</td>
<td>40 ± 7</td>
<td>36 ± 8$^b$</td>
</tr>
<tr>
<td>Oxygen delivery (mean ± so, mL/min/m$^2$)</td>
<td>388 ± 197</td>
<td>502 ± 229$^b$</td>
</tr>
<tr>
<td>VO$_2$ (mean ± so, mL/min/m$^2$)</td>
<td>103 ± 51</td>
<td>135 ± 58$^b$</td>
</tr>
<tr>
<td>(V-a)CO$_2$ (mean ± so, mm Hg)</td>
<td>8.5 ± 2.8</td>
<td>4.9 ± 3.1$^b$</td>
</tr>
<tr>
<td>C(a-v)O$_2$ (mean ± so, mL)</td>
<td>3.6 ± 1.9</td>
<td>3.4 ± 1.1</td>
</tr>
<tr>
<td>(V-a)CO$_2$ / C(a-v)O$_2$ (mean ± so, mm Hg/mL)</td>
<td>2.3 ± 0.8</td>
<td>1.3 ± 0.8$^b$</td>
</tr>
</tbody>
</table>

| Variable                                      | Before Volume Expansion       | 3.5 ± 1.0 Hr Later          | Before Volume Expansion       | 3.5 ± 1.0 Hr Later          |
| Lactate (mean ± so, mmol/L)                   | 5.5 ± 4.0                     | 3.6 ± 1.7$^b$              | 2.3 ± 1.1$^a$               | 2.0 ± 1.0$^{ab}$           |

Hb = hemoglobin; VO$_2$ = oxygen consumption; (V-v)CO$_2$ = venoarterial carbon dioxide tension difference; C(a-v)O$_2$: arteriovenous oxygen content difference.

$^a$p < 0.05 patients with a VO$_2$ change < 15% vs. patients with a VO$_2$ change ≥ 15%.

$^b$p < 0.05 after vs. before volume expansion.

with ScvO$_2$ (5) may only apply to a minority of patients (12). The only interest of ScvO$_2$ would be to predict a fluid-induced increase in VO$_2$ with a high sensitivity when it is low.

By contrast to ScvO$_2$, markers of anaerobic metabolism predicted the fluid-induced increase in VO$_2$ provided that patients were volume-responders. In the whole population of volume-responders and volume-nonresponders, these markers of anaerobic metabolism were unable to predict the effects of volume expansion on VO$_2$. This result is logical because the VO$_2$ challenge can be interpreted as a test for detecting tissue hypoxia only if VO$_2$ increases during the intervention. In other words, one cannot expect any predicting value of markers of anaerobic metabolism if DO$_2$, does not increase with fluid administration. Thus, predicting whether volume expansion will eventually increase VO$_2$ should follow a two-step approach: first to detect preload responsiveness (using proper dynamic tests [1]) and then, if the test is positive, to predict whether fluid administration will increase VO$_2$ (using markers of anaerobic metabolism).

Importantly, increasing VO$_2$ should not be the only therapeutic goal. Indeed, if the DO$_2$/VO$_2$ relationship is on its plateau,
fluid administration might securely move the $D_o/V_o$ relationship far from the critical $D_o$ value and add a margin of safety in case of further decreases of $V_o$. Also, increasing $D_o$ could improve perfusion and reverse tissue hypoxia in a relatively small vascular bed so that global $V_o$ could not change appreciably.

The $(P(v - a)Co)/C(a - v)O_2$ Ratio As a Marker of Global Anaerobic Metabolism

We found a significant relationship between the $(P(v - a)Co)/C(a - v)O_2$ ratio and the lactate at baseline, confirming previous results of a study that used the pulmonary artery catheter (15). Under conditions of tissue hypoxia, a decrease in global $V_o$ is associated with a decrease in aerobic $C_o$ production and a potential increase in anaerobic production of $C_o$, which is due to acid buffering (30). Thus, the total $C_o$ production ($V_{Co}$) should be less reduced than $V_o$. According to the Fick equation, $V_o$ is equal to the product of cardiac output and $(C(a - v)O_2)$. Similarly, $V_{Co}$ is equal to the product of cardiac output and veno-arterial $C_o$ content difference. Therefore, the $V_{Co}/V_o$ ratio is equal to the veno-arterial $C_o$ content difference/$(C(a - v)O_2)$ ratio. Over the physiological range of $C_o$ contents, $C_o$ tension is linearly related to $C_o$ content (31). Therefore, under anaerobic conditions and provided that the amount of acid to buffer is only related to anaerobism, the increased $V_{Co}/V_o$ ratio should be reflected by the increased $(P(v - a)Co)/C(a - v)O_2$.

One of the advantages of $(P(v - a)Co)/C(a - v)O_2$ over lactate might be to react faster to short-term hemodynamic changes. We observed that the $(P(v - a)Co)/C(a - v)O_2$ ratio decreased as soon as volume expansion ended in volume-responders. An important limitation of our study is that we did not re-assess the $(P(v - a)Co)/C(a - v)O_2$ ratio at the precise time when lactate was measured again, precluding to test whether the trends of both markers are linked.

Relationship Between Changes in Scvo₂ and in Cardiac Index

We found no significant relationship between changes in cardiac index and in Scvo₂, what is in discrepancy with recent findings (32). The latter study included cardiac patients while we included a majority of septic patients. In this septic population, the absence of correlation between the changes in Scvo₂ and cardiac index during volume expansion might be mainly explained by the fact that $V_o/D_o$ dependence was present in a large proportion of our patients, explaining why Scvo₂ did not change when a $D_o$ and $V_o$ increased concomitantly.

The Value of $(P(v - a)Co)$ Gradient

In volume-responders in whom $V_o$ increased, the $(P(v - a)Co)$ gradient was elevated at baseline and decreased with fluid infusion. Like Vallée et al (9), we suggest that an elevated $(P(v - a)Co)$ gradient might be useful to identify patients who
remain inadequately resuscitated. Confirming previous results (9, 15), we observed that the \((P(v - a)C_0)/C(v - a)O_2\) gradient was not correlated with lactate at baseline. These findings reinforce the message that the \((P(v - a)C_0)/C(v - a)O_2\) gradient better reflects the ability of cardiac output to wash out the accumulated \(C_0\), than the presence of anaerobic metabolism (33, 34).

**Effect of Volume Expansion on Do\(_2\) and Vo\(_2\) in Volume Nonresponders**

Importantly, in volume nonresponders, \(D_O\) decreased due to a decrease in the Hb level related to hemodilution, as previously reported (35). Although this did not decrease the \((P(v - a)C_0)/C(v - a)O_2\) level, likely because the decrease in \(D_O\) was not of sufficient magnitude, this suggests that administering fluids in nonpreload-dependent patients is harmful. This supports that testing volume responsiveness first should be an essential step in fluid management strategy.

**Limitations**

A first limitation of the present study is that we assessed \(D_O\), and \(C_0\)-derived variables from the central venous blood and not from the mixed venous blood, what might miss changes in oxygenation of the splanchnic territory. Second, we found that lactate was a marker of \(V/O_2\) dependence. However, lactate is not a pure marker of anaerobism (13, 16, 27, 36). In our study, conditions in which lactate is elevated without hypoxia (e.g., epinephrine administration, liver failure) were absent or rare, what might limit the generalizability of our findings. Third, our patients might not be representative of all septic shock patients because of their high severity. Finally, our study was not designed for testing whether increasing \(D_O\) even when \(S_cvo\) is already ≥70% could influence prognosis.

In conclusion, in volume-responders, unlike markers of anaerobic metabolism, \(S_cvo\) did not allow the prediction of whether a fluid-induced increase in \(D_O\) would result in an increase in \(V/O_2\). This suggests that markers of tissue hypoxia should be included in decisional algorithms rather than \(S_cvo\), as indicators for targeting hemodynamic resuscitation.

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