Value of combined lactate and central venous oxygen saturation measurement in patients with sepsis: a retrospective cohort study

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Abstract

Introduction. Lactate and central venous oxygen saturation (ScvO₂) reflect tissue hypoperfusion but each measure is confounded by many additional factors. These confounding factors differ between lactate and ScvO₂. Objectives. We postulated that combined assessment of lactate and ScvO₂ may yield information beyond that of each measure alone. Specifically we sought to determine whether lactate has different characteristics and predictive value at different levels of ScvO₂. Material and methods. We conducted a retrospective analysis of a Derivation cohort and a Validation Cohort of sepsis patients with lactate and ScvO₂ measured within the first 4 hours of intensive care unit admission and 12 hours after resuscitation. Patients were grouped according to: 1) ScvO₂ < 60 %; 2) 60 % ≤ ScvO₂ < 80 %; 3) ScvO₂ ≥ 80 %.

Results. Lactate was negatively correlated with ScvO₂ in the ScvO₂ < 60 % group in both cohorts but was not correlated with ScvO₂ in the other ScvO₂ groups. Using receiver operator characteristic analysis in the Derivation Cohort, in the ScvO₂ ≥ 80 % group lactate was predictive of 28-day mortality with an area under the ROC curve (AUC) of 0.94 and an optimal threshold lactate of 3.0 mmol/L. Using this threshold in the ScvO₂ ≥ 80 % groups, 28-day mortality was 32.7 %.

Conclusions. Lactate has different characteristics and predictive value at different levels of ScvO₂. When ScvO₂ < 60 % correlation between lactate and ScvO₂ is consistent with a degree of oxygen supply limitation. When ScvO₂ ≥ 80 % lactate > 3.0 mmol/L is predictive of mortality.

Keywords: central venous oxygen saturation, oximetry, lactate, sepsis, septic shock, prognosis, mortality
Introduction

Current guidelines suggest “guiding resuscitation of sepsis and septic shock to decrease lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion” [1]. Earlier guidelines suggested using central venous oxygen saturation (ScvO₂) to guide resuscitation of sepsis and septic shock. Yet both lactate and central venous oxygen saturation are highly confounded by factors other than tissue hypoperfusion [2–4] although both share tissue hypoperfusion as one of their underlying determinants. We therefore postulated that the combination of lactate and ScvO₂ would provide additional information beyond the individual measurement of lactate or ScvO₂.

Lactic acidemia is a biomarker of tissue hypoxia [8–9] and is associated with adverse outcome [9–12]. Regional ischemia (e.g. gut, limb) must be distinguished from inadequate whole body oxygen delivery as the cause of elevated lactate. In the absence or regional ischemia, elevated lactate levels may also be due to accelerated glycolysis driven by sepsis or beta-adrenergic stimulation, reduced entry of pyruvate into the Kreb’s cycle due to thiamine deficiency or other causes, increased conversion of pyruvate to lactate in a reducing environment or, not infrequently, due to decreased lactate clearance due to hepatic dysfunction or other causes. The Hour-1 Surviving Sepsis Campaign Bundle of Care recommends measuring a lactate level. If the initial lactate level is more than 2 mmol/L, it should be re-measured [13]. Previous studies suggest a significant reduction in mortality with “lactate-guided” resuscitation [14–15]. However, these conclusions are clouded because, in a key open-label randomized-controlled trial of early lactate-guided therapy, the treatment algorithm also involved interventions guided by ScvO₂ [14].

Mixed venous oxygen saturation (SvO₂) and its surrogate, ScvO₂, measured from a thoracic central line [16], can be used to evaluate oxygen supply/demand adequacy [17] and estimate cardiac output using the Fick equation [18]. Low ScvO₂ helps identify inadequate oxygen delivery conditions [17]. High ScvO₂ generally indicates adequate oxygen delivery but, importantly, this is not always the case. For example, ScvO₂ may be paradoxically high when tissue oxygen extraction is pathologically impaired due to cellular dysfunction involving mitochondria, cofactors, antioxidants, or membrane stabilizers [19]. Early Goal-Directed Therapy targeting ScvO₂ as part of the initial resuscitation of septic shock improved outcomes in an early study [20] but failed to improve outcomes in later studies [21–24]. The latter studies are clouded because both the intervention and control groups had already received protocolized initial fluid resuscitation; a key component
of Early Goal-Directed Therapy, which was the treatment to be tested.

Thus, lactate and ScvO₂ both reflect tissue hypoperfusion but each measure is confounded by many additional factors that have not been fully addressed in any study. Importantly, the confounding factors differ between lactate and ScvO₂. Thus, it is possible that combined assessment of lactate and ScvO₂ may yield information beyond that of each measure alone. Accordingly, we explored the relationship between combined lactate and ScvO₂ measurements and clinical outcomes. Specifically, we sought to determine whether serum lactate concentration has different characteristics and predictive value at different levels of central venous oxygen saturation (ScvO₂).

Materials and Methods

Patient cohorts

Derivation Cohort. All patients admitted to the Intensive Care Unit at St Paul’s Hospital (SPH) in Vancouver, British Columbia, Canada, between 2004–2009 were screened for sepsis (n = 754). Sepsis was defined by an acute change in total Sequential Organ Failure Assessment (SOFA) score ≥ 2 points due to infection [25]. Of these, 274 patients who had lactate and ScvO₂ measurements within the first 4 hours of study enrollment were included in this analysis as a Derivation Cohort. The study was approved by the University of British Columbia Research Ethics Board (H02-50076-A027).

Validation Cohort. To reduce the possibility of false positive results from the Derivation Cohort we tested for replication of findings in a Validation Cohort. All patients admitted to the Intensive Care Unit at SPH from 2010 to 2018 were screened for sepsis (n = 855). Sepsis was defined using the same consensus definition as above [25]. Of these, 289 patients had lactate and ScvO₂ measurements within 4 hours of study enrollment. The study was approved by the University of British Columbia Research Ethics Board (H02-50076-A027).

Measurements in both cohorts. Baseline characteristics and medical comorbidities were assessed at the time of enrollment. Laboratory variables (lactate, ScvO₂, hemoglobin, white blood cell count, platelet count, alanine aminotransferase, total bilirubin, creatinine) were measured. Previous studies have used 60 % as a cutoff value for a low ScvO₂ and 80 % as a cutoff value for a high ScvO₂ [26–27]. Therefore, we classified patients into three groups according to ScvO₂ measured within the first 4 hours: 1) ScvO₂ < 60 %; 2) 60 % ≤ ScvO₂ < 80 %; 3) ScvO₂ ≥ 80 %.

Statistical analysis

Median (interquartile range) was employed for continuous variables and percentage was used for categorical variables. Chi square tests were utilized for comparison between groups of categorical variables. Kruskal-Wallis tests were used for non-normally distributed continuous data and ANOVA was used for normally distributed continuous data. Group differences associated with a p-value of ≤ 0.05 were considered statistically significant. A linear regression analysis was used to assess the correlation of ScvO₂ and lactate. The receiver operator characteristic (ROC) curve with area under the ROC curve (AUC) was used to derived an optimal lactate threshold predictive of 28-day mortality in the Derivation Cohort. This lactate threshold was then tested for prognostic value in the combined cohorts. Statistical analysis was performed using SPSS Version 23 (SPSS Inc., Chicago, IL).

Results

Patient characteristics

The Derivation Cohort was comprised of 274 sepsis patients having both lactate and ScvO₂ measurements within 4 hours of study enrollment. Baseline characteristics are shown in Table 1 A classified by ScvO₂ at time of enrollment: 1) ScvO₂ < 60 %; 2) 60 % ≤ ScvO₂ < 80 %; 3) ScvO₂ ≥ 80 %. Patients in the ScvO₂ < 60 % group had significantly higher baseline lactate levels (2.5 mmol/L) compared with the other groups (ScvO₂ ≥ 60 and < 80 % lactate 1.7 mmol/L; ScvO₂ ≥ 80 % lactate 1.3 mmol/L, p = 0.01). Patients having ScvO₂ ≥ 80 % were younger (p = 0.02) and had significantly higher creatinine concentrations (p = 0.04). Sex, comorbidities, APACHE II score, and other laboratory measurements at presentation were not different between the three groups. There was no significant difference in primary infection sites of sepsis (Table 1 A).

The Validation Cohort was similarly defined and was comprised of 289 sepsis patients. Patients in the ScvO₂ < 60 % group had a higher prevalence of ischemic heart disease and had a higher lactate level point estimate, although not statistically significantly higher (Table 1 B). As in the Derivation Cohort, patients having ScvO₂ ≥ 80 % were younger (p = 0.04). Again, sex, comorbidities, APACHE II score, and other laboratory measurements at presentation were not different between the three groups. Similarly, primary infection sites were not different between groups (Table 1, B).

IQR is Interquartile range. APACHE II score is Acute physiology and chronic health evaluation II score.
### Table 1. Baseline characteristic in two cohorts of sepsis patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Derivation Cohort</th>
<th>Validation Cohort</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ScvO₂ &lt; 60 % (n=38)</td>
<td>ScvO₂ 60–80 % (n=172)</td>
<td>ScvO₂ &gt; 80 % (n=64)</td>
</tr>
<tr>
<td>Age, yr, median (IQR)</td>
<td>66.9 (48.7–76.1)</td>
<td>60.4 (48.5–69.8)</td>
<td>56.6 (42.1–68.6)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>22 (57.9)</td>
<td>113 (65.7)</td>
<td>44 (68.8)</td>
</tr>
<tr>
<td><strong>Comorbidities, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>0 (0)</td>
<td>4 (2.3)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Other liver disease</td>
<td>3 (7.9)</td>
<td>19 (11.0)</td>
<td>8 (12.5)</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>4 (11.1)</td>
<td>23 (13.9)</td>
<td>7 (12.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5 (13.2)</td>
<td>19 (11)</td>
<td>2 (3.1)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>3 (7.9)</td>
<td>13 (7.6)</td>
<td>8 (12.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 (2.6)</td>
<td>12 (7.0)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>4 (10.5)</td>
<td>20 (11.6)</td>
<td>3 (4.7)</td>
</tr>
<tr>
<td>APACHE II score, median (IQR)</td>
<td>23 (16–30)</td>
<td>22 (18–27)</td>
<td>24 (19–27)</td>
</tr>
<tr>
<td><strong>Laboratory variables, median (IQR)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline lactate (mmol/L)</td>
<td>2.5 (1.5–5.1)</td>
<td>1.7 (1.1–4)</td>
<td>1.3 (1–3)</td>
</tr>
<tr>
<td>Baseline ScvO₂ (%)</td>
<td>53 (47–57)</td>
<td>72 (67–76)</td>
<td>84 (82–88)</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>126 (80.5–202.5)</td>
<td>128.5 (74–234)</td>
<td>210 (93–362)</td>
</tr>
<tr>
<td>White blood cell count, × 10³ μL</td>
<td>13.9 (6.8–19.5)</td>
<td>11.6 (5.7–17.7)</td>
<td>11.2 (6.4–16.5)</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>99.5 (83–113)</td>
<td>98 (83.5–119.5)</td>
<td>101 (82.5–116.5)</td>
</tr>
<tr>
<td>Platelet count, × 10³ μL</td>
<td>196.5 (146–252)</td>
<td>153.5 (73.5–209)</td>
<td>165 (88.5–231.5)</td>
</tr>
<tr>
<td>Total bilirubin, μmol/L</td>
<td>12 (9–15.5)</td>
<td>14 (6–32.5)</td>
<td>15 (7–29)</td>
</tr>
<tr>
<td>Alanine aminotransferase, μmol/L</td>
<td>50.5 (31–125)</td>
<td>37 (22–74)</td>
<td>33 (16–86)</td>
</tr>
<tr>
<td><strong>Infection sites, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>24 (63.2)</td>
<td>100 (62.5)</td>
<td>36 (56.3)</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>1 (2.6)</td>
<td>3 (1.7)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Abdominal</td>
<td>4 (10.5)</td>
<td>19 (11)</td>
<td>11 (17.2)</td>
</tr>
<tr>
<td>Skin and soft tissue</td>
<td>1 (2.6)</td>
<td>8 (4.7)</td>
<td>2 (3.1)</td>
</tr>
<tr>
<td>Others (central venous system, bone, blood)</td>
<td>2 (5.2)</td>
<td>11 (6.3)</td>
<td>3 (4.7)</td>
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</tbody>
</table>

**ScvO₂ is correlated with serum lactate only when ScvO₂ < 60 %**

In the Derivation cohort we observed a correlation between higher serum lactate at lower ScvO₂ (p = 0.01) in the ScvO₂ < 60 % group (Table 2). This negative correlation replicated in the Validation Cohort for the ScvO₂ < 60 % group (p = 0.004) (Table 2) suggesting that this finding was not a false positive result. In contrast, no correlation was observed in either the Derivation or Validation Cohorts between lactate levels and ScvO₂ for patients in the 60 %≤ScvO₂ < 80 % group nor in the ScvO₂ ≥ 80 % group (Table 2). Thus, lactate arising from global inadequate oxygen delivery is only evident when ScvO₂ < 60 %.

**Lactate predicts mortality only when ScvO₂ ≥ 80 %**

In the Derivation Cohort, lactate was not predictive of 28-day mortality in the ScvO₂ < 60 % group (AUC = 0.64, 95% confidence interval [95% CI], 0.40–0.89,
### Table 1. Continued

<table>
<thead>
<tr>
<th>Variable</th>
<th>Validation Cohort</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ScvO₂ &lt; 60 % (n = 44)</td>
<td>ScvO₂ 60–80 % (n = 187)</td>
</tr>
<tr>
<td>Age, yr, median (IQR)</td>
<td>62.3 (32.5–81.1)</td>
<td>65.0 (52.8–71.1)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>28 (63.6)</td>
<td>118 (63.1)</td>
</tr>
<tr>
<td>Comorbidities, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>0 (0)</td>
<td>9 (4.8)</td>
</tr>
<tr>
<td>Other liver disease</td>
<td>5 (11.4)</td>
<td>27 (14.4)</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>8 (18.2)</td>
<td>26 (13.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (22.7)</td>
<td>50 (26.7)</td>
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<td>Chronic obstructive pulmonary disease</td>
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<td>21 (11.2)</td>
</tr>
<tr>
<td>APACHE II score, median (IQR)</td>
<td>20 (17–22)</td>
<td>19 (16–24)</td>
</tr>
<tr>
<td>Laboratory variables, median (IQR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline lactate (mmol/L)</td>
<td>3.8 (1.8–7.7)</td>
<td>2.8 (1.0–5.9)</td>
</tr>
<tr>
<td>Baseline ScvO₂ (%)</td>
<td>52 (43–56)</td>
<td>71 (67–76)</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>118 (97–139)</td>
<td>98.5 (72–182.5)</td>
</tr>
<tr>
<td>White blood cell count, × 10⁶ μL</td>
<td>13 (10–21.4)</td>
<td>14.3 (7.9–19.3)</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>106 (89–134)</td>
<td>107 (93.5–126)</td>
</tr>
<tr>
<td>Platelet count, × 10⁹ μL</td>
<td>152 (108–240)</td>
<td>207 (129–291)</td>
</tr>
<tr>
<td>Total bilirubin, μmol/L</td>
<td>25 (11–33)</td>
<td>13 (6–22.5)</td>
</tr>
<tr>
<td>Alanine aminotransferase, u/L</td>
<td>43 (26–297)</td>
<td>35 (20–76.5)</td>
</tr>
<tr>
<td>Infection sites, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>11 (25.0)</td>
<td>64 (34.2)</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>2 (4.5)</td>
<td>20 (10.7)</td>
</tr>
<tr>
<td>Abdominal</td>
<td>6 (13.6)</td>
<td>31 (16.6)</td>
</tr>
<tr>
<td>Skin and soft tissue</td>
<td>2 (4.5)</td>
<td>7 (3.7)</td>
</tr>
<tr>
<td>Others (central venous system, bone, blood)</td>
<td>5 (11.4)</td>
<td>7 (3.7)</td>
</tr>
</tbody>
</table>

### Table 2. Correlation of lactate with ScvO₂

<table>
<thead>
<tr>
<th>ScvO₂</th>
<th>Derivation cohort</th>
<th>Validation cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correlation with lactate</td>
<td>p</td>
</tr>
<tr>
<td>&lt; 60 %</td>
<td>R² = 0.16</td>
<td>0.01</td>
</tr>
<tr>
<td>60–80 %</td>
<td>R² &lt; 0.001</td>
<td>0.83</td>
</tr>
<tr>
<td>≥ 80 %</td>
<td>R² = 0.009</td>
<td>0.45</td>
</tr>
</tbody>
</table>
p = 0.3) and also not predictive in the 60 % ≤ ScvO₂ < 80 % group (AUC = 0.65, 95% CI, 0.56–0.74, p = 0.3). This lack of predictive power was also observed in the Validation Cohort. In contrast, in the ScvO₂ ≥ 80 % group from the Derivation Cohort ROC curve analysis showed that the AUC for predicting 28-day mortality was 0.94 (95% CI, 0.88–1.0) (Fig. 1). A lactate level of 3 mmol/L in the group was the optimal threshold in the Derivation Cohort. Using this lactate threshold in the combined Derivation and Validation Cohorts 28-day mortality was 32.7 % when lactate > 3.0 mmol/L while 28-day mortality was 5.6 % when lactate ≤ 3 mmol/L (p = 0.00002) (Fig. 2). Thus, lactate is predictive of 28-day mortality only when ScvO₂ ≥ 80 %.

**Response to resuscitation**

Since lactate arising from global inadequate oxygen delivery is only evident when ScvO₂ < 60 % we postulated that lactate clearance in response to resuscitation would be more marked in this group. We further postulated that lactate clearance in response to resuscitation may be less evident at higher ScvO₂, which would then suggest that at higher ScvO₂, lactate levels may be more heavily influenced by processes other than global tissue hypoxia. To test these hypotheses, we assumed that most resuscitation would have occurred within the first 12 hours after intensive care unit (ICU) admission and we combined Derivation and Validation Cohorts in order to have adequate numbers in subgroups (survivors versus non-survivors in each of three ScvO₂ groups). In the ScvO₂ < 60 % group lactate clearance was positive (levels decreased from baseline to 12 hours) in survivors but negative in non-survivors. Thus, for ScvO₂ < 60 % the difference in lactate clearance between survivors and non-survivors was 3.2 ± 3.0 mmol/L over 12 hours (p < 0.001). In contrast, no significant difference in lactate clearance was found between survivors and non-survivors in the 60 % ≤ ScvO₂ < 80 % group (difference between survivors and non-survivors 1.2 ± 2.1 mmol/L over 12 hours, p = 0.75) nor in the ScvO₂ ≥ 80 % group (difference between survivors and non-survivors 1.6 ± 2.4 mmol/L over 12 hours, p = 0.14).

**Discussion**

In our study, we found a correlation between lactate and ScvO₂ only when ScvO₂ < 60 %. Since both lactate and ScvO₂ are (imperfect) markers of tissue hypoperfusion, this correlation is consistent with elevated lactate reflecting tissue hypoperfusion due to inadequate oxygen delivery when ScvO₂ < 60 % (Fig. 3a). Resuscitation over the first 12 hours of ICU admission in this ScvO₂ group resulted in decreasing lactate in survivors while lactate rose in non-survivors. These results suggest that current guidelines may be appropriate for this ScvO₂ group of patients. That is, when ScvO₂ < 60 % our results support “guiding resuscitation of sepsis and septic shock to decrease serum lactate in patients with elevated lactate level as a marker of tissue hypoperfusion” [1].

In contrast, absence of a correlation between lactate and ScvO₂ when ScvO₂ ≥ 60 % suggests that lactate may not be particularly reflective of inadequate whole body oxygen delivery for higher values of ScvO₂ (Fig. 3b). Specifically, there is no correlation between lactate and ScvO₂ when ScvO₂ ≥ 60 % and, furthermore, resuscitation over the first 12 hours of ICU admission does not result in significantly greater lactate clearance in survivors versus non-survivors.
Thus, elevated lactate when ScvO$_2$ ≥ 60 % may be heavily influenced by other processes such as accelerated glycolysis driven by sepsis or beta-adrenergic stimulation, reduced entry of pyruvate into the Kreb’s cycle, increased conversion of pyruvate to lactate in a reducing environment or decreased lactate clearance. Thus, when ScvO$_2$ ≥ 60 %, our results question the current guidelines that resuscitation should be guided by lactate clearance.

Notably, lactate appears to convey very different clinical information when ScvO$_2$ ≥ 80 %. When ScvO$_2$ ≥ 80 % elevated lactate is predictive of mortality, possibly by discriminating between surviving patients with adequate oxygen delivery versus non-survivors with mitochondrial or other causes of histotoxic hypoxia. This is an important distinction so lactate measurement is helpful. Yet, lactate levels may not be sufficiently reflective of inadequate oxygen delivery (tissue hypoperfusion) in these ScvO$_2$ ≥ 80 % patients (Fig. 3 c) to provide a firm guide to resuscitation.

Metabolic acidosis is common in patients with sepsis and septic shock and is a prognostic predictor of poor outcome [5]. For example, negative base excess and lactate measurements are associated with adverse clinical outcome [6–7]. However, normal lactate levels are common

**Fig 3.** Postulated explanations for observations

**A.** ScvO$_2$ < 60 %. Some of the patients in this group have approximately normal tissue oxygen extraction capacity and, therefore, normal Vo$_2$–Do$_2$ (oxygen consumption — oxygen delivery) relationships (solid line). Pre-resuscitation the problem is that some of these patients have a Vo$_2$–Do$_2$ point that falls below the critical oxygen extraction ratio so that oxygen supply limitation exists (anaerobic metabolism = shock) so that ScvO$_2$ (~1 — Vo$_2$/Do$_2$) is decreased and lactate (dashed line) is increased. Following resuscitation (bold arrow) aerobic metabolism is restored so that ScvO$_2$ increases and lactate decreases. Thus, lactate correlates with ScvO$_2$ in this group (slope of solid line).

**B.** 60 ≤ ScvO$_2$ < 80. These patients have a relatively normal Vo$_2$–Do$_2$ relationship (solid line) and a normal-range ScvO$_2$, but lactate (dashed line) is elevated, dominated by causes other than inadequate whole body oxygen delivery (including regional ischemia) so that lactate is not decreased by resuscitation. Resuscitation may drive Do$_2$, a bit higher but this does not impact tissue oxygenation and lactate may even rise due to factors such as catecholamine-driven increases in glycolysis.

**C.** ScvO$_2$ ≥ 80. This category may be comprised of two types of patients with high ScvO$_2$, for different reasons: 1) those with relatively normal oxygen extraction (Vo$_2$–Do$_2$ relationships, solid line) and high oxygen delivery with relatively normal lactate levels and 2) those with very impaired oxygen extraction capacity (dotted line) who have high lactate levels. Resuscitation increases an already high oxygen delivery in 1) with little effect on their relatively normal lactate. However, resuscitation in 2) may further impair tissue oxygen extraction capacity, for example, by worsening tissue edema and oxygen diffusion distances. The key differentiating feature between 1) and 2) is lactate. Using survival versus non-survival as a surrogate marker of 1) versus 2), we found a lactate level of 3 mmol/L as the optimal threshold for distinguishing these two groups.
in patients with septic shock and lactate alone is not sufficient
to judge success or failure of treatment because it can
be affected by many factors. For example, an increase
in blood lactate following infusion of adrenaline in septic
shock was associated with better survival (31–34). Thus,
lactate is an imperfect measure. ScvO₂ is also imperfect.
Low ScvO₂ may be a marker for macrocirculatory failure
(inadequate whole body oxygen delivery) and high ScvO₂ values may reflect microcirculatory
or mitochondrial failure. Both abnormally low and high
ScvO₂ are associated with increased mortality [36].
Thus, ScvO₂ is not, by itself, a good predictor of sepsis
mortality [28, 37]. Some studies have demonstrated that
venous-to-arterial carbon dioxide difference (vaCO₂ gap)
might be help to identify patients with persistent global
hypoperfusion and guide resuscitation process [42].
A vaCO₂ > 6 mmHg reflects a low output state with
hypoperfusion and a low vaCO₂ of < 6 mmHg reflects
impaired utilization of oxygen and low CO₂ production
due to mitochondrial dysfunction [43, 44]. Additionally,
central venous-to-arterial carbon dioxide difference
(PvaCO₂ gap) is associated with lactate clearance since
PvaCO₂ gap has moderate accuracy for predicting lactate
improvement [45]. Therefore, it is likely that adding vaCO₂
gap measurements to the lactate / ScvO₂ assessment
provide additional information. We did not have vaCO₂
gap measurements consistently measured in these cohorts
to address this issue here.

Since lactate and ScvO₂ both share the underlying
determinant of tissue hypoperfusion, we reasoned that
the combination of lactate and ScvO₂ may be superior
to the single measurement of either lactate or ScvO₂.
We observed that serum lactate and ScvO₂ were negatively
correlated when ScvO₂ < 60 %. There was no correlation
between lactate and ScvO₂ for patients with mid-range
and high ScvO₂. This finding is consistent with a previous
study, showing that these variables were correlated when
oxygen extraction was high (hence low ScvO₂) [38].
Correlation suggests that both parameters share
an underlying determinant which, from existing knowledge of
the determinants of both lactate and ScvO₂, implicates
tissue hypoperfusion. Patients who responded to initial
resuscitation (survived) had a notably greater decrease
in lactate in parallel with an increase in ScvO₂, further
supporting the notion that the combination of high lactate
and low ScvO₂ reflected tissue hypoperfusion.

Lactate clearance has been shown to be associated
with improved survival in critical ill patients [40]. Previous
studies demonstrated that a relative lactate clearance of 10 %
and early lactate normalization within 6 hours was associated
with decreased mortality rate [30, 41]. Consistent with this,
our study revealed that in the ScvO₂ < 60 % group lactate
levels decreased from baseline to 12 hours in survivors
but increased in non-survivors. However, lactate clearance
was not as useful in distinguishing survivors from non-
survivors in the groups with higher ScvO₂ and, arguably,
maybe not as helpful in guiding resuscitation.

We found that when ScvO₂ ≥ 80 %, lactate was predictive
of 28-day mortality and a lactate level at 3 mmol/L
was the optimal discriminatory threshold. However, lactate
was not predictive of mortality in the other ScvO₂ groups.
We postulate that when ScvO₂ ≥ 80 %, lactate is predictive
of mortality, possibly by discriminating between surviving
patients with adequate oxygen delivery versus non-survivors
with mitochondrial or other causes of histotoxic hypoxia that
led to elevated lactate levels (Fig. 3c). That is, ScvO₂ > 70 %
(and, hence, ScvO₂ ≥ 80 %) generally reflects adequate
oxygen delivery and cellular metabolism. On the other
hand, in the case of extreme vasodilatory shock where
lactate is rising, high ScvO₂ suggests severely impaired
tissue oxygen extraction ability due to microcirculatory
dysfunction or mitochondrial dysfunction [18]. In this
setting lactate discriminates between these two physiologic
states; normal lactate when oxygen delivery is adequate
but elevated lactate when tissue oxygen extraction capacity
is impaired. This is consistent with a previous clinical trial
which suggested that high ScvO₂ levels were associated with
increased mortality because high ScvO₂ may reflect impaired
extractions of oxygen [27]. Patients with high ScvO₂ and high
lactate levels had significantly higher rates of mortality [36].
Even with adequate resuscitation of the macro-circulation,
tissue hypoxia may persist [39].

Limitations to this study are, first, this a retrospective
analysis in two cohorts from different time periods. Second,
lactate and ScvO₂ were not simultaneously measured
in all patients sepsis patients admitted to the ICU so that
many screened patients were excluded from analysis.
This may result in a risk of selection bias. Third, we were
unable to fully evaluate clinical factors and therapeutic
interventions including amount of fluid resuscitation
and doses of vasopressors that might affect levels of ScvO₂
and lactate. Finally, this is a single center study, therefore,
our findings may not be generalizable to other settings.

Conclusions

Serum lactate concentration has different characteristics
and predictive value at different levels of ScvO₂. A high
lactate when ScvO₂ < 60 % suggests inadequate whole
body oxygen delivery (tissue hypoperfusion). However,
an elevated lactate does not accurately identify tissue
hypoperfusion at higher ScvO₂. When ScvO₂ ≥ 80 %
lactate > 3 mmol/L is predictive of mortality. However,
an elevated lactate is not a good predictor of mortality
for lower values of ScvO₂. Serum lactate concentration
has different characteristics and predictive value at different
levels of central venous oxygen saturation. The combination
of lactate and ScvO₂ gives insight into the underlying state
of shock and potential causes of elevated lactate levels.
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