Point: Should Lactate Clearance Be Substituted for Central Venous Oxygen Saturation as Goals of Early Severe Sepsis and Septic Shock Therapy? Yes

Quantitative resuscitation in critically ill patients consists of structured cardiovascular interventions, such as intravascular volume expansion and vasoactive agent support, to achieve explicit predefined physiologic parameters or goals. The concept of quantitative resuscitation (also referred to as hemodynamic optimization or goal-directed therapy) as a treatment strategy to improve clinical outcome was first reported in high-risk surgery patients. A recent meta-analysis of randomized clinical trials that compared quantitative resuscitation with standard resuscitation in septic shock found that when therapy was initiated within 24 h of the onset of sepsis (six trials, 740 patients), resuscitation targeting specific physiologic end points improved mortality compared with standard resuscitation (39% vs 57%; OR, 0.50; 95% CI, 0.37-0.69). In contrast, when therapy was initiated >24 h after the onset of sepsis (three trials, 261 patients), resuscitation targeting specific physiologic end points did not improve mortality (64% vs 58% for standard resuscitation; OR, 1.16; 95% CI, 0.60-2.22). Although the data supporting the use of early quantitative resuscitation are robust, the optimal end points or goals of such therapy are controversial.

Currently, consensus guidelines recommend the use of central venous pressure (CVP), mean arterial pressure (MAP), urine output, and central venous oxygen saturation (ScvO₂) as resuscitation goals. These recommendations are based largely on an ED-based clinical trial of quantitative resuscitation for septic shock, an approach termed “early goal-directed therapy,” which was a single-center study published by Rivers et al. in 2001. In this trial, 263 patients with severe sepsis or septic shock were randomly assigned to therapy targeting an ScvO₂ of ≥70% or to conventional therapy that did not target an ScvO₂. In both groups, therapy targeted CVP, MAP, and urine output. Mortality was significantly lower in the group that targeted an ScvO₂ of ≥70% (31% vs 47%). Given that the only difference in the treatment protocols in this trial was the ScvO₂ target, the observed treatment effect appears to hinge on achieving this node of the algorithm. In contrast, earlier studies of critically ill patients that targeted mixed venous oxygen saturation (SvO₂) of ≥70% found no mortality benefit.

Multiple studies have unfortunately documented important barriers to implementing and maintaining an ED-based quantitative resuscitation protocol for septic shock. Among these, the use of a central venous catheter and the need for specialty equipment such as a continuous central venous oxygen spectrophotometer, and the training required for it, were major barriers that limited generalizability. To begin to address these barriers, the Lactate Assessment in the Treatment of Early Sepsis (LACTATES) randomized multicenter noninferiority trial, the largest ED-based early sepsis resuscitation trial completed to date, was designed to compare the use of lactate clearance to ScvO₂ as the final goal of early sepsis resuscitation. In the study, enrolled patients were randomly assigned to one of two groups. Each group received structured quantitative resuscitation while in the ED. The ScvO₂ group (n = 150) was resuscitated by sequentially providing the therapy needed to meet thresholds of CVP, followed by MAP, and then ScvO₂ of ≥70%. The lactate clearance group (n = 150) had similarly targeted thresholds in CVP and MAP, and then lactate clearance of ≥10% or more. The study protocol was continued until all end points were achieved or for a maximum of 6 h. The published results of this study showed a 6% (95% CI, −3% to 14%) in-hospital mortality difference between the two study groups (17% in the lactate clearance group vs 23% in ScvO₂ group), confirming the primary hypothesis of noninferiority.
There are many evidence-based, data-driven, and logical arguments as to why lactate clearance monitoring is a superior therapeutic target to oxygen-derived variables such as \( \text{Scv}_2 \). First, the published experimental (randomized trial) evidence supporting the use of lactate clearance as a therapeutic target is more robust in terms of the number of multicenter studies.\(^9\)\(^{10}\) Similar published experimental evidence supporting \( \text{Scv}_2 \) is derived only from single-center studies.\(^4\)\(^{11}\) Furthermore, multicenter studies have failed to show the use of \( \text{Svo}_2 \) as a resuscitation goal; however, unlike \( \text{Scv}_2 \) or other oxygen-derived variables, the ability to clear lactate has consistently predicted better survival in published studies of sepsis resuscitation.\(^12\)\(^ {13}\)

Second, elevated lactate levels reflect the total picture of energy metabolism in the acutely stressed patient with sepsis. Elevated blood lactate has long been known to reflect anaerobic metabolism from tissue hypoxia in critically ill patients.\(^{16}\) However, besides these anaerobic processes, aerobic (metabolic) mechanisms that affect the host’s efficiency of energy transfer contribute to lactate production in sepsis. Cytokine-mediated glucose uptake and catecholamine-stimulated Na-K pump overactivity can both result in increased pyruvate production that eventually will overwhelm the catalytic capacity of pyruvate dehydrogenase (PDH) and result in increased lactate because of either mass effect, sepsis-induced PDH dysfunction, or both. This mechanism may explain part of the lactate production observed from the lungs and WBC in response to the inflammatory stress, rather than tissue hypoxia of sepsis.\(^{17}\) Additionally, reduced lactate clearance may reflect globally impaired metabolic function by the liver and kidney, both of which normally contribute to systemic lactate disposal through anaplerosis, a mechanism that carboxylates lactate and delivers it to the tricarboxylic acid cycle, independent of the action of PDH.\(^{18}\) Recent studies have shown that early lactate clearance is associated with improvement in the biomarkers of inflammation and organ dysfunction.\(^{19}\) Thus, as opposed to \( \text{Scv}_2 \), which is a rudimentary indicator of only the balance between oxygen supply and demand, lactate clearance biologically reflects more of the general homeostasis of the host and provides more meaningful data about the overall adequacy of the resuscitative processes.

Third, in some circumstances the use of \( \text{Scv}_2 \) might erroneously lead a clinician to believe that the physiologic status of the patient has improved, when in fact it may not have improved. A recent multicenter study of 619 patients demonstrated that venous hyperoxia (\( \text{Scv}_2 > 89\% \)) is present in \( 36\% \) of ED patients with septic shock and is associated with an increased risk of death, and, when adjusted for confounders, venous hyperoxia was actually associated with a higher risk of death than venous hypoxia (\( \text{Scv}_2 < 70\% \)).\(^{20}\) In this situation, high \( \text{Scv}_2 \) values represent either an inability to exchange oxygen because of impaired flow in the small vessels from dysfunctional vascular autoregulatory mechanisms and functional shunting of oxygen or the inability of cells to use the oxygen because of derangement of cellular respiration, so-called “cytopathic hypoxia.”\(^{21}\) Although the Rivers et al\(^2\) protocol focuses on the correction of a low \( \text{Scv}_2 \) level signifying impairment in macrovascular oxygen delivery, the algorithm treats venous hyperoxia the same as normoxia (\( \text{Scv}_2 70\% - 90\% \)). The finding that a high \( \text{Scv}_2 \) is associated with increased mortality reminds us that tissue dysoxia may occur despite adequate global oxygen delivery and that this situation is not identified by the presence of normal venous oxygen levels. However, impaired oxygen transfer at any point from the lungs to the nicotinamide adenine dinucleotide dehydrogenase enzyme will cause lactic acidosis, and clearing lactate levels almost always signifies improvement in host oxygen use.\(^6\)

Finally, a recently reported secondary analysis of the LACTATES study\(^9\) reported no significant concordance in achieving lactate clearance and \( \text{Scv}_2 \) goals when measured simultaneously in the same subject, suggesting that these tests may be measuring and/or providing data about physiologically distinct processes. If lactate clearance was < 10%, the mortality was 40%, but if the \( \text{Scv}_2 \) was < 70%, the mortality was 11% (proportion difference 29%; 95% CI, 6%-50%).\(^{22}\)

In conclusion, early sepsis resuscitation remains a dynamic topic of research interest, with many important questions that have yet to be answered. As summarized in this report, the best available evidence suggests that if a clinician has to choose a single goal of early sepsis resuscitation, lactate clearance, as opposed to \( \text{Scv}_2 \), is the more appropriate goal to choose.

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**Financial/nonfinancial disclosures:** The author has reported to CHEST the following conflicts of interest: Dr Jones has received funding from the National Institutes of Health to study lactate clearance in sepsis resuscitation. Dr Jones has never been assigned patents, nor has he received patent royalties, honoraria, consulting fees, or other monetary or nonmonetary payments at any time related to the use of lactate or lactate clearance.

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Counterpoint: Should Lactate Clearance Be Substituted for Central Venous Oxygen Saturation as Goals of Early Severe Sepsis and Septic Shock Therapy? No

In 2001, early goal-directed therapy (EGDT) resulted in a 16% reduction in hospital mortality and, post hoc, a higher lactate clearance in severe sepsis and septic shock.1 Multiple studies have confirmed the validity and generalizability of EGDT, resulting in its adoption into the Surviving Sepsis Campaign Guidelines.2,3 Nguyen et al4-5 examined early lactate clearance and found a significant retrospective association with inflammation, apoptosis, coagulation, organ dysfunction, and mortality. Following this rationale, Jones et al6 modified the EGDT protocol in 2010 using a noninferiority study design and concluded that lactate clearance is equivalent to central venous oxygen saturation (ScvO2) in the management of individual patients.

Before applying the findings of Jones et al6 to one’s next patient, compare the baseline characteristics,
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Before applying the findings of Jones et al6 to one’s next patient, compare the baseline characteristics,
early hemodynamic patterns, and therapeutic interventions between those of Jones et al and the EGDT study. Further, review the complexities of lactate kinetics and the weaknesses of a noninferiority study design. Based on these facts, it is clear that lactate clearance and ScvO2 are not equivalent, but complementary goals for the individual patient.

The Hemodynamic Phases of Severe Sepsis and Septic Shock

The early stages of sepsis are accompanied by circulatory insufficiency that results from hypovolemia, vasomotor dysfunction, myocardial depression, and increased metabolic demands. In the systemic oxygen delivery (Do2)-dependent (hypodynamic) phase, a decrease in Do2 results in a decrease in Scvo2/mixed venous oxygen saturation (Svo2) and usually an increase in systemic oxygen extraction (OER) or 1 − ScvO2/SvO2 (Fig 1, Table 1). When the limits of the OER (anaerobic threshold) are reached, lactate is produced, signifying the development of global tissue hypoxia (GTH).

There is significant individual variation in the anaerobic threshold leading to variable lactate production. This gives rise to why some patients may require normal or elevated Do2 in order to resolve GTH (decreased ScvO2/SvO2 and increased lactate) (Fig 1, Table 1). GTH is associated with increased morbidity and mortality if not adequately treated. Because GTH can occur with normal vital signs, it has been termed “cryptic shock.” GTH or cardiovascular insufficiency is a significant part of the natural history of sepsis and responsible for the sudden cardiopulmonary deterioration seen in 12% to 21% of patients. EGDT is associated with a 50% reduction in this adverse event, an issue not addressed by Jones et al. With adequate volume therapy and myocardial reserve, a hyperdynamic or compensated phase follows. During this compensated phase, Do2 is in the normal or elevated range, systemic oxygen consumption (Vo2) is increased, and vascular resistance is generally decreased. In contrast to the hypodynamic phase (patients in the Rivers et al study), Jones et al enrolled patients in this phase with a lower systolic BP, normal central venous pressure (CVP), normal Scvo2, lower lactate levels, and triple the frequency of vaspressor dependence (Fig 1; Tables 1, 2). These patients also had corresponding Simplified Acute Physiology Score II scores and predicted mortality that was nearly 14% lower than that in patients receiving EGDT (34.8% vs 48.4%) and other studies.

Pathological Do2 dependency is a result of a progressive impairment of OER, which is accompanied by a markedly increased Scvo2/SvO2 (venous hyperoxia) and a hyperdynamic circulation. When Do2 is insufficient, Vo2 decreases, and increased lactate levels accompany venous hyperoxia. The phase of tissue dysoxia can be the result of microcirculatory dysfunction causing maldistribution of blood flow or mitochondrial dysfunction with defects in substrate utilization. In this phase, improvement in Do2 may not result in improvement in Vo2.

Sepsis may consist of four hemodynamic phases where a decreased Scvo2/SvO2 always precedes the appearance of lactate, making them complementary and nonexclusive end points, (Fig 1, Table 1). These hemodynamic phases are not always distinct and may overlap depending on the timing and quality of the resuscitation. By characterizing these phases in hemodynamic outcome studies, future trials can be conducted with the appropriate research design and interpreted with clarity, facilitating generalizability and external validation in clinical management.

Lactate Kinetics Are Complex and Limit the Interpretation of Lactate Levels and Lactate Clearance in the Individual Patient

Lactate elevation may indicate stress-induced upregulation in epinephrine-stimulated sodium-potassium adenosine triphosphatase activity in skeletal muscle and inhibition of pyruvate metabolism rather than, or in addition to, the traditionally implicated cellular hypoxia. Other confounding influences may include exogenous lactate sources (Ringers lactate or packed RBC transfusions), lactate shuttles and transport, delayed washout from underperfused tissue, variable lactate clearance by a number of organs, and dilution (large-volume resuscitations) (Fig 2). These interactions are not in a steady state and depend on the pathophysiology, timing, and quality of the resuscitation in the individual case.

Normal lactate levels occur in up to 45% of cases of septic shock, and although there is significant variability, the associated mortality can be up to 52%. In fact, many patients develop multisystem organ failure and die without ever having increased lactate levels. Thus, lactate has limitations as a tool for risk stratification and as a guide for resuscitation in individual patients. In the Jones et al study, the lactate clearance goal was at least 10% at ≥ 2 h or normality of both initial and subsequent lactates. However, found an optimal lactate clearance cutoff of < 10% after 6 h of intervention to have a sensitivity of 44.7%, specificity of 84.4%, and accuracy of only 67.6% for predicting in-hospital mortality. Additionally, lactate clearance was less predictive of outcome in septic shock, the predominant feature of the patients in the Jones et al study. Because of the variable expression of lactate, its complicated kinetics, and the limited accuracy of
lactate clearance, Nguyen et al\(^2\) did not recommend lactate clearance as a sole therapeutic end point. Serum lactate levels may rise or fluctuate during therapy. Of patients with increased initial lactate levels, 41\% have delayed peak values (20 ± 12 h) after the initial presentation.\(^11\,\(^17\) Of patients with normal initial lactates, 15\% will later demonstrate elevations. These patients have abnormal ScvO\(_2\) (66.7\% ± 8.6\%) at baseline compared with their counterparts with normal levels.\(^17\) Lactate levels over time can increase (negative clearance), stay the same, or decrease (positive clearance) after intervention (Fig 2). Not only is the direction of clearance important but also the magnitude of change. There are significantly different clinical and outcome implications in patients whose lactate levels decrease from 10 to 9 mmol/L vs 4 to 3.6 mmol/L. Although both represent clearance of 10\%, the implications for illness severity and prognostic significance are much different.

### Table 1—Hemodynamic Phases of Sepsis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Hemodynamic Picture</th>
<th>SBP</th>
<th>CVP</th>
<th>Treatment and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Hypovolemia</td>
<td>Variable</td>
<td>↓</td>
<td>Volume</td>
</tr>
<tr>
<td></td>
<td>Myocardial suppression</td>
<td>Variable</td>
<td>↑</td>
<td>Correct anemia, inotropic therapy</td>
</tr>
<tr>
<td>A</td>
<td>Resuscitated, compensated, and vasodilatory</td>
<td>Variable</td>
<td>Normal</td>
<td>Vasopressors, low-dose corticosteroids</td>
</tr>
<tr>
<td>C</td>
<td>Supranormal Do(_2) dependence</td>
<td>Variable</td>
<td>↑ to normal</td>
<td>Increased Yo(_2) after augmentation of Do(_2)</td>
</tr>
<tr>
<td>D</td>
<td>Impairment of tissue O(_2) utilization</td>
<td>Variable</td>
<td>Normal</td>
<td>r-APC</td>
</tr>
<tr>
<td></td>
<td>Decreased Yo(_2)</td>
<td>Variable</td>
<td>Normal</td>
<td>Resuscitated</td>
</tr>
</tbody>
</table>

CVP = central venous pressure; Do\(_2\) = systemic oxygen delivery; r-APC = recombinant activated protein C; SBP = systolic BP; SvO\(_2\) = mixed venous oxygen saturation; Vo\(_2\) = oxygen consumption.

What if the Patient Requires More Than Fluid and Vasopressors and the Lactate Is Still High?\(^2\)

Optimization of preload (CVP) and afterload (mean arterial pressure) were addressed by Jones et al;\(^6\) however, the remaining components of EGDT, including optimizing Do\(_2\) (oxygen carrying capacity [supplemental oxygen and hemoglobin], cardiac output) and decreasing Vo\(_2\) (mechanical ventilation and sedation) to prevent delayed cardiopulmonary complications, were not elicited or examined.\(^15\) Over the past decade, numerous studies have validated the clinical utility of ScvO\(_2\) in recognizing supply dependency, need for a transfusion, detection of myocardial dysfunction, response to oxygen and mechanical ventilation, early cardiopulmonary complications, and overall influence on mortality. To establish non-inferiority, lactate clearance has to be appropriately

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FIGURE 1. The hemodynamic phases of sepsis. Do\(_2\) = systemic oxygen delivery; Ni = normal; Scvo\(_2\) = mixed venous oxygen saturation; Vo\(_2\) = oxygen consumption. Reprinted with permission from Kruse.\(^5\)

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examined in these scenarios in order to be generalizable to all hemodynamic phases of sepsis and these facets of care. The discrepancy between ScvO₂-triggered interventions in the Rivers et al study vs the 30 interventions (10% of patients) guided by lactate clearance reflects significant differences in hemodynamic phases, patient populations, and frequency and timing of interventions (Fig 2). This undermines the conclusion of equivalency from a noninferiority research design. Patients more likely to require inotropes (congestive heart failure or coronary artery disease) or patients with reduced lactate clearance (liver failure) were not described by Jones et al (Table 2). This lower number of interventions reflects a lower illness severity compared with other studies, the possibility of poor compliance to the protocol, or a study design that is not equivalent to EGDT. The threefold greater use of vasopressors by Jones et al may have resulted in higher lactate levels (catecholamines), CVP (increased afterload and venous tone), and ScvO₂ (decreased OER). As a result, triggers for more fluid administration, RBC transfusion, inotropes, and mechanical ventilation may have been obscured by catecholamines. In this vasodilatory phase of sepsis, one would expect a higher use of corticosteroids; however, they were only used in 37% and 35% of eligible patients in the lactate clearance and ScvO₂ groups, respectively.

**Real-World Clinical Practice**

Central venous catheterization is recommended for patients with septic shock, and this was indeed the practice in the Jones et al study. However, this study often is misinterpreted to imply that lactate clearance precludes the need for central venous catheterization altogether. This could result in a delay in a safer route for administration of vasopressors and achievement of EGDT goals within 6 h. The Surviving Sepsis Campaign recommendations include intermittent...
or continuous ScvO₂ sampling. It is a simple matter to add intermittent ScvO₂ to lactate measurements in the absence of continuous monitoring. Bundle compliance and socioeconomic costs improve significantly with continuous monitoring.

Conclusions

ScvO₂ provides immediate feedback to the VO₂/DO₂ relationship but requires interpretation that depends on the phase of sepsis. Lactate is a delayed indicator of tissue perfusion and is subject to complex kinetics that are never clear in the individual case. Lactate levels may be normal or fluctuate, leading to inappropriate risk stratification and therapy. Lactate clearance and ScvO₂, therefore, are complementary and not mutually exclusive end points.

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Rebuttal From Dr Jones

In their counterpoint, Dr Rivers and colleagues present the theoretical view that patients with septic shock present in very distinct “hemodynamic phases” and that Jones et al enrolled patients in a different phase of septic shock than did Rivers et al. According to their theory, decreased central venous oxygen saturation (ScvO2) always precedes the appearance of lactate—a concept not observed in my clinical practice. Clinicians who routinely care for the critically ill encounter patients with elevated lactate and normal ScvO2. Furthermore, as shown in Table 1, the hemodynamic patterns of the subjects enrolled by Rivers et al are markedly different from any other reported populations of patients with septic shock treated with quantitative resuscitation. The study by Rivers et al patients had much higher lactate, much lower ScvO2, and much higher mortality than described elsewhere. Possible explanations for this discrepancy may include that patients with septic shock in Detroit between 1997 and 2000 were markedly different than any other septic shock population reported in the world’s literature and/or that systematic selection bias was a significant problem in the their study. In such a scenario, their results have questionable external validity. Supporting either of these assertions is the fact that mortality in the control group of the Rivers et al study was 20% higher than any septic shock mortality reported in the recent literature, leaving one to question exactly what care they received. Little evidence supports the contention that Jones et al enrolled patients in a different phase of septic shock.
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Table 1—Summary of Initial Clinical Characteristics and Mortality Rates of Recent Studies of Quantitative Resuscitation for Septic Shock

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Lactate, mmol/L</th>
<th>ScvO₂, %</th>
<th>Mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivers et al(^1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGDT group</td>
<td>130</td>
<td>7.7</td>
<td>48.6</td>
<td>30.5</td>
</tr>
<tr>
<td>Control group</td>
<td>133</td>
<td>6.9</td>
<td>49.2</td>
<td>46.5</td>
</tr>
<tr>
<td>Jones et al(^2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ScvO₂ group</td>
<td>150</td>
<td>4.2</td>
<td></td>
<td>74</td>
</tr>
<tr>
<td>LC group</td>
<td>150</td>
<td>3.9</td>
<td></td>
<td>23</td>
</tr>
<tr>
<td>Shapiro et al(^3)</td>
<td>116</td>
<td>4.4</td>
<td></td>
<td>72</td>
</tr>
<tr>
<td>Jones et al(^5)</td>
<td>77</td>
<td>3.6</td>
<td>69-81</td>
<td>18</td>
</tr>
<tr>
<td>Nguyen et al(^6)</td>
<td>197</td>
<td>3.4-4.4</td>
<td></td>
<td>62-69</td>
</tr>
<tr>
<td>Kortgen et al(^7)</td>
<td>30</td>
<td>2.6</td>
<td></td>
<td>27</td>
</tr>
<tr>
<td>van Beest et al(^8)</td>
<td>125</td>
<td>2.7</td>
<td>74</td>
<td>26</td>
</tr>
<tr>
<td>Peake et al(^9)</td>
<td>324</td>
<td>6.9(^*)</td>
<td></td>
<td>23</td>
</tr>
<tr>
<td>Xiao-Zhi et al(^10)</td>
<td>16</td>
<td>5.3</td>
<td></td>
<td>18</td>
</tr>
</tbody>
</table>

The most abnormal values in each column are present in bold and italic text. EGDT = early goal-directed therapy; LC = lactate clearance; ScvO₂ = central venous oxygen saturation.

\(^*\)Only 98 had lactate measured.

Because data from an experimental clinical trial are the only way to scientifically deduce the clinical efficacy of lactate clearance vs ScvO₂ and because data from a large multicenter clinical trial demonstrated that lactate clearance is not inferior to ScvO₂ as an end point of early sepsis resuscitation, as described herein, lactate clearance has principles that may make it the more appropriate end point to choose.

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Rebuttal From Dr Rivers et al

An End Point Must Be Consistently Present to Be Generalized

Levrant et al1 stated, “It is common knowledge that many septic patients develop multiple organ failure and die despite normal blood lactate levels.” Below the critical systemic oxygen delivery, central venous oxygen saturation (SvO2) decreases; however, lactate level elevation may not occur. More importantly, an SvO2 ≥ 70% is not the only goal, as achievement of all early goal-directed therapy (EGDT) goals actually resulted in an SvO2 ≥ 77.3%. According to Dr Jones,2 a study by Gattinoni et al3 did not show an outcome benefit of reaching a mixed venous oxygen saturation of 70% up to 48 h after ICU admission. However, Chamberlain et al4 found in a meta-analysis that patients resuscitated to this end point within a more reasonable 6 h were twice as likely to survive than without it.

A Repeat Look at a Previously Quoted Study

Dr Jones2 cites the study by Jansen et al5 as supportive of lactate clearance, but not all patients in that study were septic. Furthermore, the reduction of lactate was no faster when the control group therapy was compared with the lactate-guided aggressive resuscitation group. In fact, these authors concluded that “this observation might actually argue against lactate level as a target of hemodynamic therapy. However, given that SvO2 monitoring was mandatory in the lactate group and control group, we cannot exclude the possibility that this had an impact on the observed outcome difference.”5

Does Noninferiority Mean Equivalency? Be Careful What You Read

Noninferiority is a double negative that may confuse clinicians because of the complexity of study design. Noninferiority trials are controversial and difficult to design, conduct, analyze, and interpret for trialists, clinicians, reviewers, and editors.6 The low number of interventions observed by Jones et al7 bias toward the conclusion of noninferiority. Thus, for appropriate interpretation, one must be aware of and apply the CONSORT (Consolidated Standards of Reporting Trials) recommendations on noninferiority and equivalence trials (Table 1).6–10

Responding to Perceived Barriers

Barriers specified by Dr Jones2 are unacceptable as excuses for our failure to save lives. We do not avoid complex interventions for trauma, stroke, or myocardial infarction. Severe sepsis carries a mortality risk far in excess of these acknowledged emergencies. Surely, placement of central lines, as well as continuous or intermittent venous saturation measurement, should be well within the capabilities of competent emergency and critical care practitioners.

Conclusion

Today’s clinical tools for assessing tissue perfusion, including SvO2 and lactate level, have benefits and limitations. SvO2 has a half-life of seconds, providing value as an early goal of resuscitation with interpretation potentially confounded by changes in systemic oxygen delivery, tissue extraction, and distribution of blood flow at both the macrocirculatory and microcirculatory levels. Serum lactate levels may remain normal before and throughout resuscitation or fluctuate due to the complexities of lactate kinetics, causing one to question the clinical usefulness of lactate clearance. Moreover, a 10% drop in serum lactate level has different implications if the initial value is 12 mmol/L rather than 4 mmol/L. The concept of lactate clearance as the single goal of resuscitation is, therefore, flawed and potentially dangerous. Today’s prudent clinician will use both normalization of SvO2 and lactate levels to guide resuscitation rather than rely on one parameter alone.

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Financial/nonfinancial disclosures: The authors have reported to CHEST the following conflicts of interest: In the past 3 years, Dr Rivers has received funding from the National Institutes of Health, Aggennix AG, and Alere Corporation. He has been a one-time consultant for Aggennix AG; Eisai Co, Ltd; Idaho Technologies Inc; AstraZeneca; Massimo; and Sangard. He is a consultant to the Institute of Medicine, National Academies. The Early Goal-Directed Therapy (EGDT) study was performed without external industry support or funding of any kind. Any intellectual properties associated with Dr Rivers’ research are exclusively owned by Henry Ford Hospital. Dr Rivers holds no past or present intellectual properties and has never received royalties or stock interest related to technologies in EGDT research and practice. Dr Elkin has received funding from the Gordon and Betty Moore Foundation, has been a one-time consultant for Eisai Co, Ltd, and participated on the speaker’s bureau for Edwards Lifesciences LLC on three occasions. Dr Cannon has been a one-time consultant for Aggennix AG and Eisai Co, Ltd.

**Rebuttal From Dr Rivers et al**

**An End Point Must Be Consistently Present to Be Generalized**

Levrault et al\(^1\) stated, “It is common knowledge that many septic patients develop multiple organ failure and die despite normal blood lactate levels.” Below the critical systemic oxygen delivery, central venous oxygen saturation (Scv\(_o_2\)) decreases; however, lactate level elevation may not occur. More importantly, an Scv\(_o_2\) ≥ 70% is not the only goal, as achievement of all early goal-directed therapy (EGDT) goals actually resulted in an Scv\(_o_2\) ≥ 77.3%. According to Dr Jones,\(^2\) a study by Gattinoni et al\(^3\) did not show an outcome benefit of reaching a mixed venous oxygen saturation of 70% up to 48 h after ICU admission. However, Chamberlain et al\(^4\) found in a meta-analysis that patients resuscitated to this end point within a more reasonable 6 h were twice as likely to survive than without it.

**A Repeat Look at a Previously Quoted Study**

Dr Jones\(^2\) cites the study by Jansen et al\(^5\) as supportive of lactate clearance, but not all patients in that study were septic. Furthermore, the reduction of lactate was no faster when the control group therapy was compared with the lactate-guided aggressive resuscitation group. In fact, these authors concluded that “this observation might actually argue against lactate level as a target of hemodynamic therapy. However, given that Scv\(_o_2\) monitoring was mandatory in the lactate group and control group, we cannot exclude the possibility that this had an impact on the observed outcome difference.”\(^5\)

**Does Noninferiority Mean Equivalency? Be Careful What You Read**

Noninferiority is a double negative that may confuse clinicians because of the complexity of study design. Noninferiority trials are controversial and difficult to design, conduct, analyze, and interpret for trialists, clinicians, reviewers, and editors.\(^6\) The low number of interventions observed by Jones et al\(^7\) bias toward the conclusion of noninferiority. Thus, for appropriate interpretation, one must be aware of and apply the CONSORT (Consolidated Standards of Reporting Trials) recommendations on noninferiority and equivalence trials (Table 1).\(^6\)-\(^10\)

**Responding to Perceived Barriers**

Barriers specified by Dr Jones\(^2\) are unacceptable as excuses for our failure to save lives. We do not avoid complex interventions for trauma, stroke, or myocardial infarction. Severe sepsis carries a mortality risk far in excess of these acknowledged emergencies. Surely, placement of central lines, as well as continuous or intermittent venous saturation measurement, should be well within the capabilities of competent emergency and critical care practitioners.

**Conclusion**

Today’s clinical tools for assessing tissue perfusion, including Scv\(_o_2\) and lactate level, have benefits and limitations. Scv\(_o_2\) has a half-life of seconds, providing value as an early goal of resuscitation with interpretation potentially confounded by changes in systemic oxygen delivery, tissue extraction, and distribution of blood flow at both the macrocirculatory and microcirculatory levels. Serum lactate levels may remain normal before and throughout resuscitation or fluctuate due to the complexities of lactate kinetics, causing one to question the clinical usefulness of lactate clearance. Moreover, a 10% drop in serum lactate level has different implications if the initial value is 12 mmol/L rather than 4 mmol/L. The concept of lactate clearance as the single goal of resuscitation is, therefore, flawed and potentially dangerous. Today’s prudent clinician will use both normalization of Scv\(_o_2\) and lactate levels to guide resuscitation rather than rely on one parameter alone.

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Table 1—CONSORT Checklist for Reporting Noninferiority or Equivalence Trials in Rivers et al and Jones et al

<table>
<thead>
<tr>
<th>Topic</th>
<th>Requirements and Considerations</th>
<th>Jones et al</th>
<th>Rivers et al</th>
</tr>
</thead>
</table>
| Background | Scientific background and explanation of rationale, including the rationale for using a noninferiority or equivalence design. | Intermittent or continuous ScvO₂ as part of EGDT and recommended by the SSC is not generalizable because of the following issues:  
- The need for specialty equipment and training, such as continuous ScvO₂ spectrophotometer and catheter.  
- This technology is described as “technically difficult, unavailable in many tertiary care EDs, too complex, costly and takes time away from the patient.”  
- ScvO₂ is a “controversial” method of determining tissue oxygen delivery. | Background of EGDT:  
- It has been replicated in various multiple studies comprising >40 studies totaling >10,000 patients.  
- Reduces absolute mortality by 16%-18% in patients of equal illness severity.  
- It is cost effective and decreases health-care resource consumption.  
- The ScvO₂ technology is >40 y old, requires seconds to calibrate, and is optional with intermittent sampling according to the SSC recommendations. |
| Methods | Precise details of the interventions intended for each group, detailing whether the reference treatment in the noninferiority or equivalence trial is identical (or very similar) to that in any trials (s) that established efficacy and how and when they were actually administered. | LC triggered interventions:  
- Blood transfusions to hematocrit of 30%  
- Dobutamine to a 10% decrease in LC | EGDT triggered interventions over 6 h:  
- Supplemental oxygen  
- Fluid therapy  
- Vasopressor therapy  
- Blood transfusions  
- Inotropes use  
- Mechanical ventilation  
- Prevention of sudden cardiopulmonary complications |
| Objectives | Specific objectives and hypotheses, including the hypothesis concerning noninferiority or equivalence. | Objective:  
- To address the potential utility of LC as a substitute for ScvO₂.  
Hypothesis:  
- Targeting LC as the marker of adequacy of Do₂ was noninferior to the currently recommended ScvO₂ monitoring for the outcome of in-hospital mortality. | (Continued) |
Table 1—Continued

<table>
<thead>
<tr>
<th>Topic</th>
<th>Requirements and Considerations</th>
<th>Commentary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other objectives:</td>
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<tr>
<td>• Disassemble a protocol “too complex” for the providers of care.</td>
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<tr>
<td>• Prove evidence that checking serial lactates is easier and a reliable equivalent to ScvO₂.</td>
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<tr>
<td>• Find a simpler and more generalizable method to monitor the adequacy of Do₂ as a research imperative in the treatment of patients with severe infection.</td>
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<tr>
<td>• The primary endpoint was absolute in-hospital mortality rate.</td>
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<tr>
<td>• Secondary endpoints were ICU length of stay, hospital length of stay, ventilator-free days, and new onset multiple organ failure.</td>
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<tr>
<td>• Other endpoints assessed were the number of resuscitative goals achieved, administered treatments, and predefined protocol-related serious adverse events.</td>
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<tr>
<td>• Using a one-sided test of noninferiority, assuming a control group mortality rate of 25% and α = 0.05, a sample size of 150 per group gave 71% power to determine the intervention did not increase mortality by &gt; 10%.</td>
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<tr>
<td>• The required size of noninferiority trials is usually larger than that for superiority trials.⁶</td>
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<tr>
<td>• Blinding does not protect against bias nearly as well in a noninferiority trial as it does in a superiority trial.</td>
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<tr>
<td>Outcomes</td>
<td>Clearly defined primary and secondary outcome measures, detailing whether the outcomes in the noninferiority or equivalence trial are identical (or very similar) to those in any trial(s) that established efficacy of the reference treatment and, when applicable, any methods used to enhance the quality of measurements (eg, multiple observations, training of assessors).</td>
<td></td>
</tr>
<tr>
<td>Sample size and statistical methods</td>
<td>How sample size was determined, detailing whether it was calculated using a noninferiority or equivalence criterion and specifying the margin of equivalence with the rationale for its choice. When applicable, explanation of any interim analyses and stopping rules (and whether related to a noninferiority or equivalence hypothesis).</td>
<td></td>
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<tr>
<td>Blinding (masking)</td>
<td>Whether participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. When relevant, how the success of blinding was evaluated.</td>
<td></td>
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<tr>
<td>Results</td>
<td>Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the trial protocol, and analyzed for the primary outcome. Describe protocol deviations from trial as planned, together with reasons.</td>
<td></td>
</tr>
<tr>
<td>Baseline data of the participants</td>
<td>Baseline demographic and clinical characteristics of each group. Eligibility criteria for participants (detailing whether participants in the noninferiority or equivalence trial are similar to those in any trial[s] that established efficacy of the reference treatment) and the settings and locations where the data were collected.</td>
<td></td>
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</tbody>
</table>

Prevailing mortality in previous before and after intervention studies show a higher mortality.⁸
- Baseline mortality of 47.6% ± 5%
- After intervention mortality of 27.5% ± 13%

One should avoid features that might dilute true differences between EGDT and LC, thereby enhancing the risk of erroneously concluding noninferiority:
- Poor adherence to the protocol
- Dropouts
- Recruitment of patients unlikely to need or respond to interventions (low illness severity and mortality) treatment crossovers.

At baseline compared to the Rivers et al⁸ study, Jones et al⁷ patients were characterized by:
- Younger age
- Fewer comorbidities
- Lower illness severity
- Lower mortality risk
- Lower lactate levels
- Higher ScvO₂ (normal range)
- Higher CVP (normal range)

(Continued)
Table 1—Continued

<table>
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<tr>
<td><strong>Numbers analyzed</strong></td>
<td>Number of participants (denominator) in each group included in each analysis and whether “intention-to-treat” and/or alternative analyses were conducted. State the results in absolute numbers when feasible (e.g., 10 of 20, not 50%).</td>
<td>Jones et al reported 30 interventions in 300 patients randomized: 10% (n = 29) got to the point in the protocol where one of the two treatments being evaluated were administered (Scvo2; n = 13) and (LC; n = 16).</td>
</tr>
<tr>
<td><strong>Outcomes and estimation</strong></td>
<td>For each primary and secondary outcome, a summary of results for each group and the estimated effect size and its precision (e.g., 95% CI). For the outcome(s) for which noninferiority or equivalence is hypothesized, a figure showing confidence intervals and margins of equivalence may be useful.</td>
<td>Patients were treated in the ED from the time of randomization until all treatment goals were achieved or 6 h had elapsed: No 6-h hemodynamic end points are reported. Although hematocrit was a therapeutic end point, no data were reported in reaching this end point in either group. There was no method to assess whether an indicated therapeutic action was performed in response to a parameter below the intended goal. 6-h end points are provided in the Rivers et al study.</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>All important adverse events or side effects in each intervention group.</td>
<td>Delayed hemodynamic deterioration was not reported. Delayed hemodynamic deterioration is an important feature in up to 20% of patients which was reduced to 10% with EGDT.</td>
</tr>
<tr>
<td><strong>Interpretation and generalizability</strong></td>
<td>Generalizability (external validity) of the trial findings.</td>
<td>LC cannot be used in patients with nonelevated lactate levels. LC is unproven in patients with more complex presentations who require multiple interventions. This study is underpowered to provide enough evidence to use LC as a replacement of Scvo2.</td>
</tr>
<tr>
<td><strong>Overall evidence</strong></td>
<td>General interpretation of the results in the context of current evidence.</td>
<td>• Is there an outcome difference between a LC from 10 to 9 vs 4 to 3.6, both 10% clearance but different outcomes? • How many lactate level were required per patient to complete therapy and the time duration? • Is LC cost effective as shown in EGDT? • What is the technology assessment comparing the clinical utility of a precalibrated Scvo2 and hourly or even more frequent lactate levels? • The section editor of the journal where Jones et al is published is a principle investigator for competing research on EGDT. • The author of the accompanying editorial is participating in competing research on EGDT.</td>
</tr>
<tr>
<td><strong>Additional contributions</strong></td>
<td>Clinicians must be confident that the new treatment would have been shown to be efficacious if a placebo-controlled trial had been performed.</td>
<td></td>
</tr>
<tr>
<td><strong>Competing interests</strong></td>
<td>This may potentially influence the editorial process and interpretation of the results.</td>
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</tbody>
</table>

CONSORT = Consolidated Standards of Reporting Trials; CVP = central venous pressure; Do2 = systemic oxygen delivery; EGDT = early goal directed therapy; LC = lactate clearance; Scvo2 = central venous oxygen saturation; SSC = surviving sepsis campaign.
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References


