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

Abbreviations: CVP = central venous pressure; Do_2 = systemic oxygen delivery; EGDT = early goal-directed therapy; GTH = global tissue hypoxia; MAP = mean arterial pressure; OER = systemic oxygen extraction; PDH = pyruvate dehydrogenase; $Scvo_2$ = central venous oxygen saturation; Svo_2 = mixed venous oxygen saturation; $\dot{V}o_2$ = oxygen consumption

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.[1] 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).[2] 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 ($Scvo_2$) as resuscitation goals.[3] 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[4] in 2001. In this trial, 263 patients with severe sepsis or septic shock were randomly assigned to therapy targeting an $Scvo_2$ of ≥ 70% or to conventional therapy that did not target an $Scvo_2$. In both groups, therapy targeted CVP, MAP, and urine output. Mortality was significantly lower in the group that targeted an $Scvo_2$ of ≥ 70% (31% vs 47%). Given that the only difference in the treatment protocols in this trial was the $Scvo_2$ 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 (Svo_2) of ≥ 70% found no mortality benefit.[5]

Multiple studies have unfortunately documented important barriers to implementing and maintaining an ED-based quantitative resuscitation protocol for septic shock.[6-8] 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 $Scvo_2$ as the final goal of early sepsis resuscitation.[9] In the study, enrolled patients were randomly assigned to one of two groups. Each group received structured quantitative resuscitation while in the ED. The $Scvo_2$ group (n = 150) was resuscitated by sequentially providing the therapy needed to meet thresholds of CVP, followed by MAP, and then $Scvo_2$ 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 $Scvo_2$ 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 $Scvo_2$. 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 $Scvo_2$ is derived only from single-center studies.[4,11] Furthermore, multicenter studies have failed to show the use of Svo_2 as a resuscitation goal[5]; however, unlike $Scvo_2$ or other oxygen-derived variables, the ability to clear lactate has consistently predicted better survival in published studies of sepsis resuscitation.[12-15]

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 $Scvo_2$, 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 $Scvo_2$ 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 ($Scvo_2 > 89\%$) 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 ($Scvo_2 < 70\%$).[20] In this situation, high $Scvo_2$ 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[4] protocol focuses on the correction of a low $Scvo_2$ level signifying impairment in macrovascular oxygen delivery, the algorithm treats venous hyperoxia the same as normoxia ($Scvo_2$ 70%-90%). The finding that a high $Scvo_2$ 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 $Scvo_2$ 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 $Scvo_2$ 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 $Scvo_2$, 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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DOI: 10.1378/chest.11-2560

References

1. Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee TS. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. *Chest*. 1988;94(6):1176-1186.
2. Jones AE, Brown MD, Trzeciak S, et al; Emergency Medicine Shock Research Network investigators. The effect of a quantitative resuscitation strategy on mortality in patients with sepsis: a meta-analysis. *Crit Care Med*. 2008;36(10):2734-2739.
3. Dellinger RP, Levy MM, Carlet JM, et al; International Surviving Sepsis Campaign Guidelines Committee; American Association of Critical-Care Nurses; American College of Chest Physicians; American College of Emergency Physicians; Canadian Critical Care Society; European Society of Clinical Microbiology and Infectious Diseases; European Society of Intensive Care Medicine; European Respiratory Society; International Sepsis Forum; Japanese Association for Acute Medicine; Japanese Society of Intensive Care Medicine; Society of Critical Care Medicine; Society of Hospital Medicine; Surgical Infection Society; World Federation of Societies of Intensive and Critical Care Medicine. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med*. 2008;36(1):296-327.
4. Rivers E, Nguyen B, Havstad S, et al; Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345(19):1368-1377.
5. Gattinoni L, Brazzi L, Pelosi P, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO2 Collaborative Group. *N Engl J Med*. 1995;333(16):1025-1032.
6. Carlbom DJ, Rubenfeld GD. Barriers to implementing protocol-based sepsis resuscitation in the emergency department—results of a national survey. *Crit Care Med*. 2007;35(11):2525-2532.
7. Jones AE, Kline JA. Use of goal-directed therapy for severe sepsis and septic shock in academic emergency departments. *Crit Care Med*. 2005;33(8):1888-1889.
8. Jones AE, Shapiro NI, Roshon M. Implementing early goal-directed therapy in the emergency setting: the challenges and experiences of translating research innovations into clinical reality in academic and community settings. *Acad Emerg Med*. 2007;14(11):1072-1078.
9. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA; Emergency Medicine Shock Research Network (EMShockNet) Investigators. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA*. 2010;303(8):739-746.
10. Jansen TC, van Bommel J, Schoonderbeek FJ, et al; LACTATE study group. Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. *Am J Respir Crit Care Med*. 2010;182(6):752-761.
11. Wang XC, Lü CJ, Gao FQ, Li XH, Yan WF, Ning Fw. Efficacy of goal-directed therapy in the treatment of septic shock [in Chinese]. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue*. 2006;18(11):661-664.
12. Arnold RC, Shapiro NI, Jones AE, et al; on behalf of the Emergency Medicine Shock Research Network (EMShockNet) Investigators. Multi-center study of early lactate clearance as a determinant of survival in patients with presumed sepsis. *Shock*. 2008;32:36-39.
13. Nguyen HB, Rivers EP, Knoblich BP, et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. *Crit Care Med*. 2004;32(8):1637-1642.
14. Bakker J, Coffernils M, Leon M, Gris P, Vincent J-L. Blood lactate levels are superior to oxygen-derived variables in predicting outcome in human septic shock. *Chest*. 1991;99(4):956-962.
15. Bakker J, Gris P, Coffernils M, Kahn RJ, Vincent J-L. Serial blood lactate levels can predict the development of multiple organ failure following septic shock. *Am J Surg*. 1996;171(2):221-226.
16. Weil MH, Afifi AA. Experimental and clinical studies on lactate and pyruvate as indicators of the severity of acute circulatory failure (shock). *Circulation*. 1970;41(6):989-1001.
17. De Backer D. Lactic acidosis. *Intensive Care Med*. 2003;29(5):699-702.
18. Russell RR III, Taegtmeyer H. Changes in citric acid cycle flux and anaplerosis antedate the functional decline in isolated rat hearts utilizing acetoacetate. *J Clin Invest*. 1991;87(2):384-390.
19. Nguyen HB, Loomba M, Yang JJ, et al. Early lactate clearance is associated with biomarkers of inflammation, coagulation, apoptosis, organ dysfunction and mortality in severe sepsis and septic shock. *J Inflamm (Lond)*. 2010;7:6.
20. Pope JV, Jones AE, Gaieski DF, Arnold RC, Trzeciak S, Shapiro NI; Emergency Medicine Shock Research Network (EMShockNet) Investigators. Multicenter study of central venous oxygen saturation ($ScvO_2$) as a predictor of mortality in patients with sepsis. *Ann Emerg Med*. 2010;55(1):40-46, e1.
21. Fink MP. Bench-to-bedside review: cytopathic hypoxia. *Crit Care*. 2002;6(6):491-499.
22. Puskarich M, Trzeciak S, Shapiro N, Kline J, Jones AE. Concordance and prognostic value of central venous oxygen saturation and lactate clearance in emergency department patients with septic shock. *Acad Emerg Med*. 2011;18(5):S159-S160.

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 al[4,5] examined early lactate clearance and found a significant retrospective association with inflammation, apoptosis, coagulation, organ dysfunction, and mortality. Following this rationale, Jones et al[6] modified the EGDT protocol in 2010 using a noninferiority study design and concluded that lactate clearance is equivalent to central venous oxygen saturation ($ScvO_2$) in the management of individual patients.

Before applying the findings of Jones et al[6] to one's next patient, compare the baseline characteristics,