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Lactate Clearance for Assessing Response to Resuscitation in Severe Sepsis

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Abstract

Severe sepsis remains a major public health problem both with a high hospital mortality rate and with staggering associated health care expenditures. The past decade has seen new insights into the early resuscitation of severe sepsis and this is an important, controversial, and constantly changing topic to emergency physicians. In this article, the recent support for lactate clearance as a measure of early sepsis resuscitation effectiveness is summarized, lactate-derived to oxygen-derived resuscitation variables are compared, and the shortcomings of lactate-derived variables are described. As summarized in this article, the best available experimental evidence suggests that lactate clearance of at least 10% at a minimum of 2 hours after resuscitation initiation is a valid way to assess initial response to resuscitation in severe sepsis. Associative data suggest that lactate normalization during resuscitation is a more powerful indicator of resuscitative adequacy; however, further research on the optimal lactate clearance parameters to use during resuscitation is needed, and many other important questions have yet to be answered.

Quantitative resuscitation in patients with sepsis is undertaken to achieve explicit predefined physiologic parameters or goals. A meta-analysis of randomized clinical trials that compared quantitative resuscitation to standard resuscitation in septic shock found that when therapy was initiated within 24 hours of the onset of sepsis, resuscitation targeting specific physiologic endpoints improved mortality compared to standard resuscitation (odds ratio [OR] = 0.50, 95% confidence interval [CI] = 0.37 to 0.69).[1] Quantitative resuscitation is recommended by the Surviving Sepsis Campaign as the best practice treatment strategy to improve clinical outcome in patients with severe sepsis.[2] Although the data supporting the use of early quantitative resuscitation are solid, the optimal endpoints or goals of such therapy are more controversial.

The Surviving Sepsis Campaign recommends the use of central venous pressure (CVP), mean arterial pressure (MAP), urine output, and central venous oxygen saturation ($ScvO_2$) as resuscitation goals.[2] These recommendations are based almost entirely on one clinical trial of quantitative resuscitation for septic shock, an approach termed “early goal-directed therapy,” which was published in 2001 by Rivers et al.[3] In this single-center trial, 263 patients with criteria for systemic inflammation and shock were randomized to therapy targeting $ScvO_2$ of 70% or more or conventional therapy that did not target $ScvO_2$. In both groups, therapy targeted CVP, MAP, and urine output. The study reported a significantly lower mortality in the group that targeted $ScvO_2$ of 70% or more as compared to conventional therapy (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. Of note, an earlier study of critically ill patients that

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targeted mixed venous oxygen saturation (SvO_2) of 70% or more found no mortality benefit.[4]

Several studies have reported important barriers to implementing and maintaining an emergency department (ED)-based quantitative resuscitation protocol for septic shock.[5,6] Among hospitals implementing protocols complying with best practice guidelines, measuring $ScvO_2$ via an indwelling catheter, and the need for specialty equipment and training, such as the use of a continuous central venous oxygen spectrophotometer, are major barriers to implementing and maintaining such a protocol. Thus in the decade since the Rivers et al.[3] publication, investigators have searched for less invasive resuscitative goals or surrogate indicators of resuscitation adequacy other than those proposed by Rivers and collegues.[7] This leads to the main question of this report, namely, the question, “Is lactate clearance a valid way to assess response to resuscitation in severe sepsis?”

SUPPORT FOR LACTATE CLEARANCE

The prognostic value of initial lactate measurements in sepsis has been previously described.[8,9] Several decades ago, Bakker et al.[10] demonstrated that delayed clearance of lactate in the initial days of intensive care unit (ICU) treatment of septic shock was associated with poor outcome. In a substudy of the publication by Rivers et al., Nguyen et al.[11] demonstrated that early lactate clearance in ED patients undergoing early goal-directed therapy was associated with improved outcome. In that study, a relative lactate clearance of 10% was associated with the best combination of sensitivity and specificity for predicting survival, after adjusting for other predictors of mortality. Finally, Arnold et al.[12] confirmed the value of a relative lactate clearance of 10% in a multicenter observational study of ED patients undergoing resuscitation for severe sepsis as the strongest predictor of mortality among five variables. Their study reported a mortality rate of 60% for lactate nonclearance versus 19% for lactate clearance ($p < 0.001$) and that lactate nonclearance was an independent predictor of death (OR = 4.9, 95% CI = 1.5 to 15.9). These data provide associative data that lactate clearance is a viable surrogate marker of resuscitation adequacy in severe sepsis.

In 2010, the LactATES randomized multicenter noninferiority trial, the largest ED-based early sepsis resuscitation trial completed to date, provided the experimental data needed to confirm lactate clearance as a robust target for early sepsis resuscitation.[7] LactATES was designed to compare the use of lactate clearance to $ScvO_2$ 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 $ScvO_2$ group (n = 150) was resuscitated by sequentially providing therapy needed to meet thresholds of CVP, followed by MAP, and then $ScvO_2$ of 70% or more. The lactate clearance group (n = 150) had similarly targeted thresholds in CVP, MAP, and then lactate clearance of 10% or more. The study protocol was continued until all endpoints were achieved or a maximum of 6 hours. 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 lactate clearance group vs. 23% in $ScvO_2$ group), confirming the primary hypothesis of noninferiority. Another ICU-based randomized controlled trial published in 2010 by Jansen et al.[13] reported that the addition of a relative lactate clearance goal of 20% improved survival in patients with shock, although in should be noted that these patients received a comprehensive resuscitation strategy including $ScvO_2$. These data provide experimental evidence that support lactate clearance as an appropriate target to gauge the adequacy of early sepsis resuscitation.

Despite the published evidence (observational and experimental) indicating that clearing lactate during early sepsis resuscitation results in improved survival,[7,10–14] and assuming

that lactate clearance reflects tissue oxygenation, this raises the second major question: "Which is a preferable endpoint, lactate-derived variables or oxygen-derived variables?"

LACTATE-DERIVED VARIABLES VERSUS OXYGEN-DERIVED VARIABLES

There are several logical arguments that are supported by published data as to why lactate clearance monitoring is a superior therapeutic target to oxygen-derived variables such as $ScvO_2$. First, as has been outlined above, 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 and number subjects.[7,13] The experimental data supporting the clinical effectiveness of oxygen-derived variables such as $ScvO_2$ and SvO_2 have demonstrated mixed results.[3,4,15]

Second, lactate parameters provide more data about the total body homeostasis than do oxygen-derived variables. It is widely accepted that elevated blood lactate can 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 also contribute to lactate production in sepsis. Cytokine-mediated glucose uptake and catecholamine-stimulated Na-K pump overactivity both can result in increased pyruvate production that eventually will overwhelm the catalytic capacity of pyruvate dehydrogenase (PDH) and result in increased lactate due either to mass effect, sepsis-induced PDH dysfunction, or both. Additionally, reduced lactate clearance may reflect globally impaired metabolic function by the liver and kidney, both of which normally contribute to systemic lactate disposal. In fact, data derived from the original study by Rivers et al. have shown that early lactate clearance is associated with improvement in the biomarkers of inflammation and organ dysfunction.[17] Thus, as opposed to oxygen-derived variables such as $ScvO_2$, which is a rudimentary indicator of only balance between oxygen supply and demand, lactate clearance biologically reflects more of the total body metabolic processes of the host and provides more meaningful data about the overall adequacy of the resuscitative processes.

Third, the use of oxygen-derived variables might erroneously lead a clinician to believe that the physiologic status of the patient has improved. In a multicenter study of 619 patients, Pope et al.[18] demonstrated that venous hyperoxia ($ScvO_2 > 89\%$) is present in more than one-third of ED patients with septic shock and is associated with a higher mortality rate, and when confounders are considered, venous hyperoxia is actually prognostically worse than venous hypoxia ($ScvO_2 < 70\%$). These high $ScvO_2$ values probably represent an inability to exchange oxygen because of impaired flow in the small vessels from dysfunctional microvasculature or the inability of cells to use the oxygen because of derangement of mitochondrial cellular respiration. This point highlights the shortcoming of sepsis resuscitation protocols that focus on the correction of a low $ScvO_2$ level, signifying impairment in macrovascular oxygen delivery. These protocols treat venous hyperoxia the same as normoxia ($ScvO_2$ 70% to 90%). Thus, clinicians may be led to erroneously believe that they have performed adequate resuscitation if venous hyperoxia is present. Such a situation does not occur if lactate parameters are evaluated, because biochemically, impaired oxygen transfer at any point from the lungs to the NADH oxidase enzyme will cause lactic acidosis, and clearing lactate levels almost always signifies improvement in host oxygen utilization.

Finally, a recently reported secondary analysis of the LactATES study by Puskarich et al.[19] measured lactate clearance and $ScvO_2$ goals simultaneously in the same subjects. Achievement of the $ScvO_2$ goal only was associated with a mortality rate of 41% (nine of 22), while achievement of the lactate clearance goal only was associated with a mortality

rate of 8% (two of 25; proportion difference = 33%; 95% CI = 9% to 55%). Furthermore, no agreement was found between goal achievements. These data suggest that these variables are most likely measuring physiologically distinct processes, allowing for the potential argument that both $ScvO_2$ and lactate clearance are better than either measurement alone. However, if one endpoint were to have to be chosen as superior, lactate clearance clearly is more robust and advantageous.

SHORTCOMINGS OF LACTATE-DERIVED VARIABLES

Despite the compelling evidence for the use of lactate-derived variables in early sepsis resuscitation, one must also acknowledge some important shortcomings of employing lactate-based resuscitation strategies. First, perhaps as many as 20% to 30% of subjects with criteria for septic shock will have normal (<2 mmol/L) lactate levels. Thus there is no utility in measuring clearance in these subjects. Second, lactate measurements can be confounded by several important scenarios such as use of Ringer's lactate as a resuscitative fluid; the presence of cirrhosis, which may delay (but not eliminate) the observation of lactate clearance; exogenous causes of lactate production such as the use of metformin; or large-volume packed red blood cell transfusion. Third, the optimal lactate-derived parameter to guide resuscitation is still a subject of intense study. A recent publication by Puskarich et al.[20] reported that lactate normalization during early sepsis resuscitation was the strongest predictor of survival (OR = 5.2, 95% CI = 1.7 to 15.8), compared to any other absolute value or absolute or relative change in lactate. However, these are only associative data, and future experimental studies should address if strategies targeting lactate normalization compared to other lactate parameters leads to improved outcomes.

CONCLUSIONS

Early sepsis resuscitation remains an important, controversial, and constantly changing topic of research. As summarized in this article, the best available experimental evidence suggests that lactate clearance of at least 10% at a minimum of 2 hours after resuscitation initiation is a valid way to assess initial response to resuscitation in severe sepsis. Associative data suggest that lactate normalization during resuscitation is a more powerful indicator of resuscitative adequacy; however, further research on the optimal lactate clearance parameters to use during resuscitation and many other important questions have yet to be answered.

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References

1. Jones AE, Brown MD, Trzeciak S, et al. The effect of a quantitative resuscitation strategy on mortality in patients with sepsis: a meta-analysis. Crit Care Med. 2008; 36:2734–9. [PubMed: 18766093]
2. Dellinger RP, Levy MM, Carlet JM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med. 2008; 36:296–327. [PubMed: 18158437]
3. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001; 345:1368–77. [PubMed: 11794169]
4. 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; 333:1025–32. [PubMed: 7675044]

5. Jones AE, Kline JA. Use of goal-directed therapy for severe sepsis and septic shock in academic emergency departments. Crit Care Med. 2005; 33:1888–9. [PubMed: 16096485]
6. 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; 14:1072–8. [PubMed: 17630356]
7. Jones AE, Shapiro NI, Trzeciak S, et al. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. JAMA. 2010; 303:739–46. [PubMed: 20179283]
8. Shapiro NI, Howell MD, Talmor D, et al. Serum lactate as a predictor of mortality in emergency department patients with infection. Ann Emerg Med. 2005; 45:524–8. [PubMed: 15855951]
9. Mikkelsen M, Miltiades A, Gaieski D, et al. Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. Crit Care Med. 2009; 37:1670–7. [PubMed: 19325467]
10. Bakker J, Gris P, Coffernils M, Kahn R, Vincent JL. Serial blood lactate levels can predict the development of multiple organ failure following septic shock. Am J Surg. 1996; 171:221–6. [PubMed: 8619454]
11. Nguyen H, Rivers E, Knoblich B, et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. Crit Care Med. 2004; 32:1637–42. [PubMed: 15286537]
12. Arnold RC, Shapiro NI, Jones AE, et al. Multi-center study of early lactate clearance as a determinant of survival in patients with presumed sepsis. Shock. 2009; 32:36–9.
13. Jansen TC, van Bommel J, Schoonderbeek FJ, et al. Early lactate-guided therapy in intensive care unit patients a multicenter, open-label, randomized controlled trial. Am J Respir Crit Care Med. 2010; 182:752–61. [PubMed: 20463176]
14. Bakker J, Coffernils M, Leon M, Gris P, Vincent JL. Blood lactate levels are superior to oxygen-derived variables in predicting outcome in human septic shock. Chest. 1991; 99:956–62. [PubMed: 2009802]
15. Xiao-zhi W, Chang-jun L, Fu-quan GA. Efficacy of goal-directed therapy in the treatment of septic shock. Chin Crit Care Med. 2007; 18:661–4.
16. Weil M, Afifi A. Experimental and clinical studies on lactate and pyruvate as indicators of the severity of acute circulatory failure (shock). Circulation. 1970; 41:989–1001. [PubMed: 5482913]
17. Nguyen HB, Loomba M, Yang J, et al. Early lactate clearance is associated with biomarkers of inflammation, coagulation, apoptosis, organ dysfunction and mortality in severe sepsis and septic shock. J Inflam (Lond). 2010; 7:6.
18. Pope JV, Jones AE, Gaieski DF, Arnold RC, Trzeciak S, Shapiro NI. Multicenter study of central venous oxygen saturation (ScvO(2)) as a predictor of mortality in patients with sepsis. Ann Emerg Med. 2010; 55:40–6. [PubMed: 19854541]
19. Puskarich M, Trzeciak S, Shapiro N, et al. Concordance and prognostic value of central venous oxygen saturation and lactate clearance in emergency department patients with septic shock. Acad Emerg Med. 2012; 19:252–8. [PubMed: 22435856]
20. Puskarich MA, Trzeciak S, Shapiro NI, et al. Whole blood lacatate kinetics in patients undergoing quantitative resuscitation for severe sepsis and septic shock. Chest. 2013; 143:1548–53. [PubMed: 23740148]