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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 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,

early hemodynamic patterns, and therapeutic interventions between those of Jones et al[6] and the EGDT study.[1] Further, review the complexities of lactate kinetics and the weaknesses of a noninferiority study design.[7] Based on these facts, it is clear that lactate clearance and $Scvo_2$ 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 (Do_2)-dependent (hypodynamic) phase, a decrease in Do_2 results in a decrease in $Scvo_2$/mixed venous oxygen saturation (Svo_2) and usually an increase in systemic oxygen extraction (OER) or $1 - Scvo_2/Svo_2$ (Fig 1,[8] 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.[9] This gives rise to why some patients may require normal or elevated Do_2 in order to resolve GTH (decreased $Scvo_2/Svo_2$ and increased lactate) (Fig 1, Table 1). GTH is associated with increased morbidity and mortality if not adequately treated.[10,11] Because GTH can occur with normal vital signs, it has been termed "cryptic shock."[12] 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.[13,14] EGDT is associated with a 50% reduction in this adverse event, an issue not addressed by Jones et al.[6]

With adequate volume therapy and myocardial reserve, a hyperdynamic or compensated phase follows. During this compensated phase, Do_2 is in the normal or elevated range, systemic oxygen consumption ($\dot{V}o_2$) is increased, and vascular resistance is generally decreased. In contrast to the hypodynamic phase (patients in the Rivers et al[1] study), Jones et al[6] enrolled patients in this phase with a lower systolic BP, normal central venous pressure (CVP), normal $Scvo_2$, lower lactate levels, and triple the frequency of vasopressor 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.[2]

Pathological Do_2 dependency is a result of a progressive impairment of OER, which is accompanied by a markedly increased $Scvo_2/Svo_2$ (venous hyperoxia) and a hyperdynamic circulation. When Do_2 is insufficient, $\dot{V}o_2$ 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 Do_2 may not result in improvement in $\dot{V}o_2$.

Sepsis may consist of four hemodynamic phases where a decreased $Scvo_2/Svo_2$ 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.[15]

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.[16]

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%.[9,17-19] In fact, many patients develop multisystem organ failure and die without ever having increased lactate levels.[9] Thus, lactate has limitations as a tool for risk stratification and as a guide for resuscitation in individual patients. In the Jones et al[6] study, the lactate clearance goal was at least 10% at $\geq$2 h or normality of both initial and subsequent lactates. Nguyen et al,[20] 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[6] study. Because of the variable expression of lactate, its complicated kinetics, and the limited accuracy of

lactate clearance, Nguyen et al[20] 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 $ScvO_2$ ($66.7\% \pm 8.6\%$) 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.

What if the Patient Requires More Than Fluid and Vasopressors and the Lactate Is Still High?

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 $\dot{V}O_2$ (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 noninferiority, lactate clearance has to be appropriately

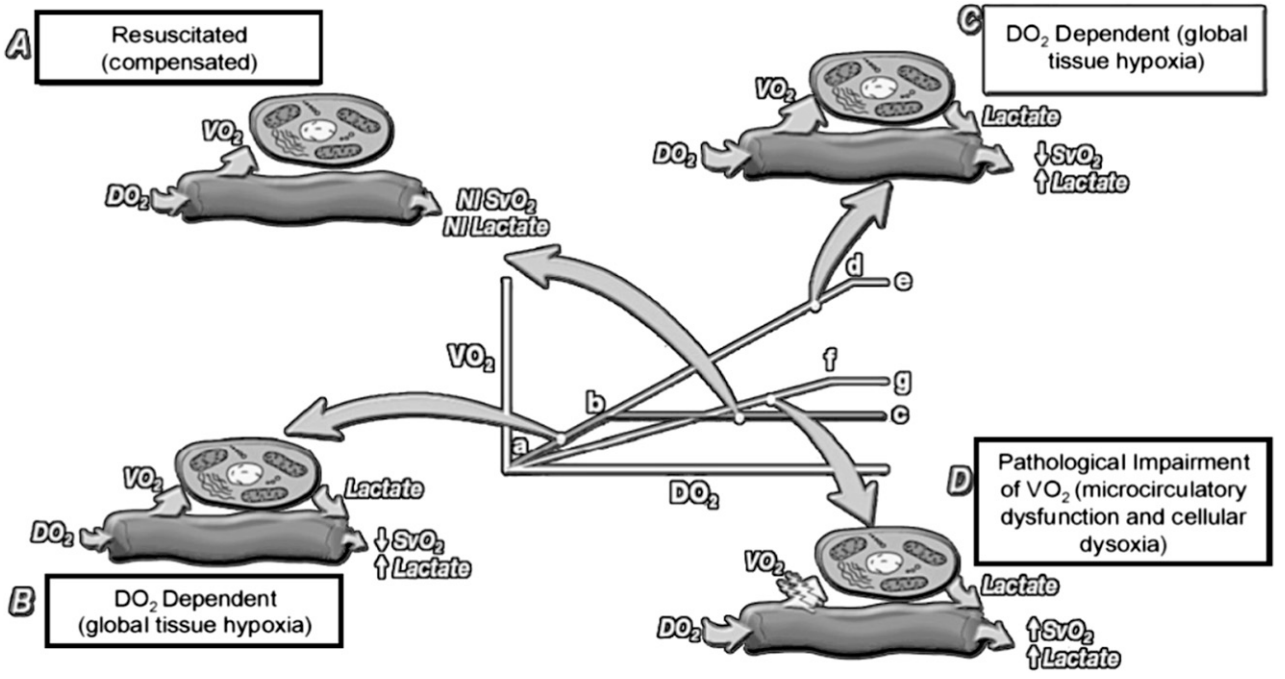

Figure 1. The hemodynamic phases of sepsis. DO_2 = systemic oxygen delivery; NI = normal; SvO_2 = mixed venous oxygen saturation; VO_2 = oxygen consumption. Reprinted with permission from Kruse.[8]

Table 1—*Hemodynamic Phases of Sepsis*

Stage	Hemodynamic Picture	SBP	CVP	Treatment and Comments
B	Hypovolemia	Variable	↓	Volume
	Myocardial suppression	Variable	↑	Correct anemia, inotropic therapy
A	Resuscitated, compensated, and vasodilatory	Variable	Normal	Vasopressors, low-dose corticosteroids
C	Supranormal DO_2 dependency	Variable	↑ to normal	Increased $\dot{V}O_2$ after augmentation of DO_2
D	Impairment of tissue O_2 utilization	Variable	Normal	r-APC
	Decreased $\dot{V}O_2$	Variable	Normal	Resuscitated

CVP = central venous pressure; DO_2 = systemic oxygen delivery; r-APC = recombinant activated protein C; SBP = systolic BP; SvO_2 = mixed venous oxygen saturation; $\dot{V}O_2$ = oxygen consumption.

Table 2—*Comparison of Clinical Variables Between Jones et al[6] and Rivers et al[1]*

	Jones et al[6]		Rivers et al[1]	
	Lactate Clearance	$ScvO_2$ Guided	Standard Therapy	EGDT
Comorbidities				
Congestive heart failure	…	…	30.2	36.7
Coronary artery disease	…	…	23.5	26.5
Liver disease	…	…	23.5	23.1
Alcohol use	…	…	38.7	38.5
Baseline hemodynamics				
Lactate,[a] mmol/L	3.9 ± 3.1	4.2 ± 3.1	6.9 ± 4.5	7.7 ± 4.7
CVP,[a] mm Hg	11 ± 6.5	11 ± 6.2	6.1 ± 7.7	5.3 ± 9.3
Systolic BP,[a] mm Hg	91 ± 24.6	92 ± 21.0	109 ± 34	106 ± 36
$ScvO_2$[a]	…	74 ± 12.3	49.2 ± 13.3	48.6 ± 11.2
Treatments (0-6-h ranges)				
RBC transfusions	7	3	18.5	64.1
P Value	.2	…	< .001	…
Vasopressors[a]	72	75	30.3	27.4
Inotropes	3	5	0.8	13.7
P Value	.57	…	< .001	…
Mechanical ventilation[a]	27	26	53.8	53.0
6 h hemodynamics				
Lactate, mmol/L	…	…	4.9 ± 4.7	4.3 ± 4.2
P Value			.01	
Lactate clearance (0-6 h)	…	…	29	44.2
P Value			.01	
CVP, mm Hg	…	…	11.8 ± 6.8	13.8 ± 4.4
P Value			.007	
$ScvO_2$	…	…	66.0 ± 15.5	77.3 ± 10.0
P Value			< .001	
Sudden cardiopulmonary collapse	…	…	21.0	10.3
P Value			.02	
SAPS II scores (baseline)[a]	44.8 ± 18.4	44.1 ± 17.3	48.8 ± 11.1	51.2 ± 11.1
Predicted mortality (approximate)	34.8	32.8	48.4	48.7
Actual in-hospital mortality	23	17	46.5	30.5
P Value	NS	…	.009	…

Data are presented as mean ± SD or %. EGDT = early goal-directed therapy; NS = not significant; SAPS = Simplified Acute Physiology Score; $ScvO_2$ = central venous oxygen saturation. See Table 1 legend for expansion of other abbreviations.

[a]No statistical significance.

examined in these scenarios in order to be generalizable to all hemodynamic phases of sepsis and these facets of care.[7] The discrepancy between $ScvO_2$-triggered interventions in the Rivers et al[1] 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.[7] 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[6] (Table 2). This lower number of interventions reflects a lower illness severity compared with other studies,[2] 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[6] may have resulted in higher lactate levels (catecholamines), CVP (increased afterload and venous tone), and $ScvO_2$ (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[3]; however, they were only used in 37% and 35% of eligible patients in the lactate clearance and $ScvO_2$ 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[6] 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

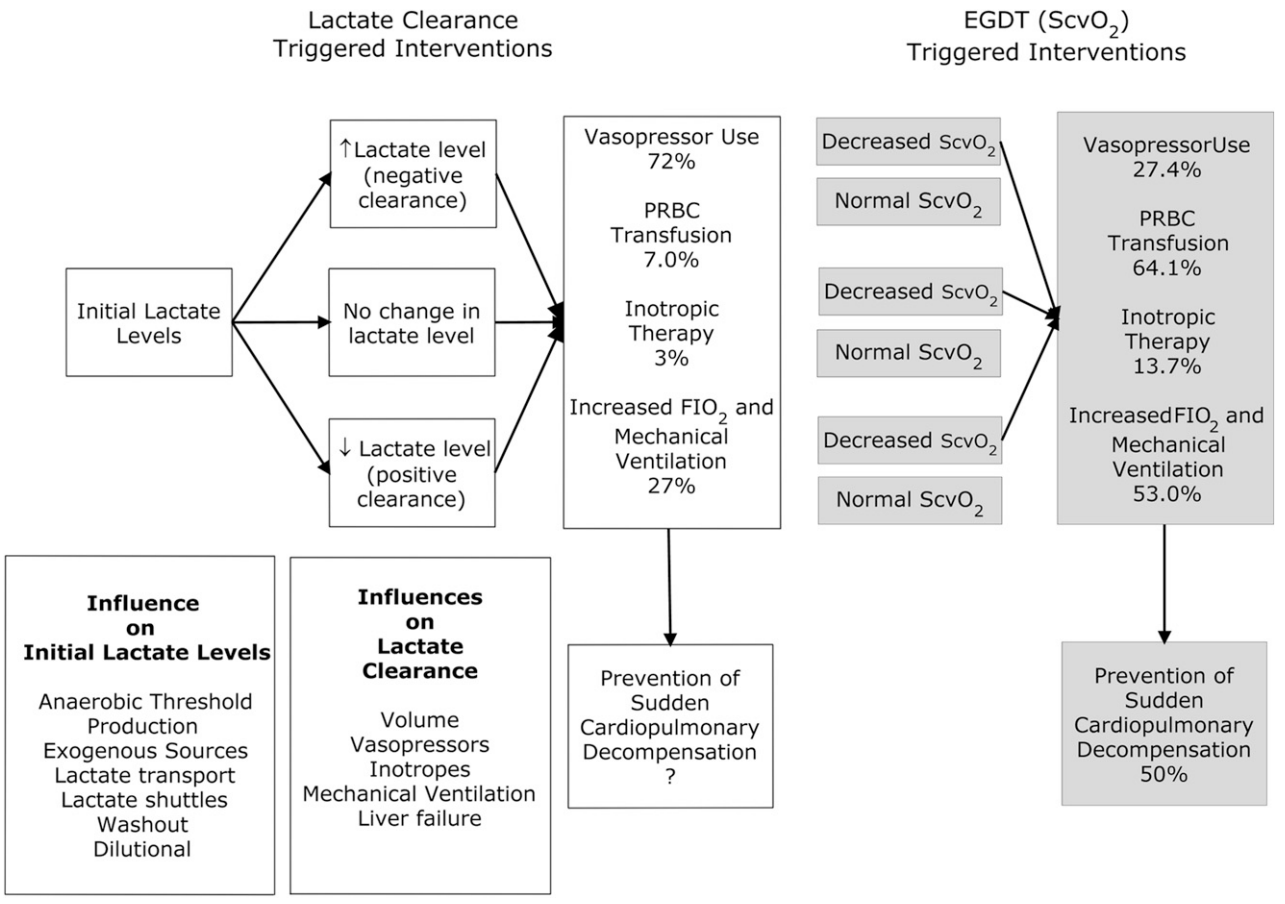

FIGURE 2. The kinetics, diagnostic, and therapeutic clinical scenarios of lactate. EGDT = early goal-directed therapy; PRBC = packed RBC; $ScvO_2$ = central venous oxygen saturation. See Figure 1 legend for expansion of other abbreviation.

or continuous $ScvO_2$ sampling.[3] It is a simple matter to add intermittent $ScvO_2$ to lactate measurements in the absence of continuous monitoring. Bundle compliance and socioeconomic costs improve significantly with continuous monitoring.[21]

CONCLUSIONS

$ScvO_2$ provides immediate feedback to the $\dot{V}O_2/DO_2$ 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 $ScvO_2$, therefore, are complementary and not mutually exclusive end points.

Emanuel P. Rivers, MD, MPH, FCCP
Detroit, MI
Ronald Elkin, MD
San Francisco, CA
Chad M. Cannon, MD
Kansas City, KS

Affiliations: From the Department of Emergency Medicine and Surgery (Dr Rivers), Henry Ford Hospital, Wayne State University; Department of Medicine (Dr Elkin), Pulmonary and Critical Care Medicine, California Pacific Medical Center; and Department of Emergency Medicine (Dr Cannon), University of Kansas Hospital.
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Correspondence to: Emanuel P. Rivers, MD, MPH, FCCP, Department of Emergency Medicine, Wayne State University, 270 Clara Ford Pavilion, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202; e-mail: erivers1@hfhs.org

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Rebuttal From Dr Jones

In their counterpoint, Dr Rivers and colleagues[1] present the theoretical view that patients with septic shock present in very distinct "hemodynamic phases" and that Jones et al[2] enrolled patients in a different phase of septic shock than did Rivers et al.[3] According to their theory, decreased central venous oxygen saturation ($Scv\overline{O}_2$) 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 $Scv\overline{O}_2$. Furthermore, as shown in Table 1,[2-10] the hemodynamic patterns of the subjects enrolled by Rivers et al[3] are markedly different from any other reported populations of patients with septic shock treated with quantitative resuscitation. The study by Rivers et al[3] patients had much higher lactate, much lower $Scv\overline{O}_2$, 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[3] study was 20% higher than any septic shock mortality reported in the recent literature, leaving one to question exactly what care they received.[3] Little evidence supports the contention that Jones et al[2] enrolled patients in a different phase of septic shock