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Lactate as a Hemodynamic Marker in the Critically Ill

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Abstract

Purpose of review—An early quantitative resuscitation strategy improves outcome in critically ill patients. The hemodynamic endpoints of such a strategy have been a topic of debate in the literature. This review focuses on the use of lactate as a marker for risk stratification, lactate clearance as a hemodynamic endpoint, and its use compared to mixed venous oxygenation as a resuscitation goal

Recent findings—Lactate clearance is associated with improved outcome across several cohorts of critically ill patients. Lactate levels and central venous oxygen saturations are frequently discordant. Targeting lactate clearance as part of a quantitative resuscitation strategy may be as effective as targeting central venous oxygen saturation.

Summary—Resuscitation of the critically ill patient should be aimed at the reversal of tissue hypoxia. The use of lactate as a hemodynamic marker and resuscitation endpoint makes physiologic sense and is supported by recent data. The use of lactate clearance versus other traditional endpoints of resuscitation, such as mixed venous oxygen saturation, should be based on the clinical characteristics and response of the individual patient.

Keywords

Lactate; lactate clearance; quantitative resuscitation; mixed venous oxygen saturation

Introduction

Historically, hemodynamics refers to a set of parameters that define cardiovascular function and blood flow through the circulation. Classically, these are markers of the macrocirculation, such as cardiac output, mean arterial pressure, mixed venous oxygen saturation, and indices of preload, such as central venous pressure. In the setting of critical illness, improving pathological values is likely beneficial and are common targets for the practicing clinician. However, there is increasing evidence suggesting traditional hemodynamic parameters are unreliable [1], and the ability to apply a set of hemodynamic norms across individual patients with differing physiology can be inappropriate[2]. Also, normalization of hemodynamics often leaves a significant proportion of patients with ongoing tissue hypoperfusion [3]. Given this, there is an increasing trend to monitor and normalize surrogates of cellular perfusion as resuscitation targets. In this fashion, lactate clearance has been proposed as a hemodynamic resuscitation target in the critically ill. As a

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marker of tissue perfusion, it is influenced not only by the macrocirculation, but also by the microcirculation (network of arterioles, capillaries, and venules), as well as mitochondrial function. This review will focus on the use of lactate as a hemodynamic marker and target for resuscitation in the critically ill.

Background and History

The ability to characterize and detect circulatory failure and tissue hypoperfusion has been in evolution for over a century[4]. This has historically hinged on clinical symptoms and physical exam findings, both of which are marred by a lack of sensitivity to detect organ dysfunction. In 1918, Cannon, describing metabolic acidosis, stated “there is a relationship between blood flow, and hence tissue perfusion and blood pH values” [5]. Lactate was first described after isolation from sour milk in 1780 [5]. The first reports of lactate in sepsis were in 1843 by German physician-chemist, Johann-Joseph Scherer (a friend of Rudolph Virchow) when he described the detection of high lactate levels from an autopsy heart puncture in a 23 year old female who died from puerperal septic shock, likely due to a streptococcus pyogenes[6]. The clinical syndrome of lactic acidosis was specifically characterized in 1961, and correlated with poor outcome [7, 8]. The association of lactate accumulation and oxygen debt during shock states has been described for decades [9]. Throughout the years, there has been continued interest in refining clinically important values, resuscitation triggers, and response to therapy.

Normal Lactate Metabolism

Lactate is the metabolic end-product of anaerobic glycolysis. In conditions of low flow or cellular hypoxia, pyruvate cannot enter the mitochondria and is preferentially reduced to lactate, causing arterial lactate concentrations to increase [5, 10]. This is an adaptive process to generate energy, but comes at the expense of worsening acidosis. Lactate is produced in all tissues, but the greatest producers are skeletal muscle, brain, intestine, and red blood cells. During critical illness, increasing lactate production arises from the lungs, as well as white blood cells and splanchnic organs. The daily production of lactate is around 1300 mmol/day and the concentration of arterial lactate is a reflection of net production and clearance, and is generally around 2mmol/L. Metabolism and clearance of lactate is primarily via the liver and kidneys, and dysfunction of these organs has been associated with varying levels of reduced clearance[5, 10].

Lactic acidosis occurs whenever production exceeds utilization and clearance. Type A lactic acidosis describes an inadequate oxygen delivery/consumption match and the presence of anaerobic glycolysis, and type B lactic acidosis describes hyperlactatemia in the absence of anaerobic glycolysis (secondary to altered clearance, malignancy or drugs for example)[5]. Medications that have been associated with hyperlactatemia include nucleoside reverse transcryptase inhibitors, epinephrine, metformin, methanol, cyanide and ethylene glycol. It is also possible that the pro-inflammatory state of sepsis can produce a stress hyperlactatemia in the absence of overt tissue hypoxia. Type A lactic acidosis is likely the most common cause of elevated lactate in the critically ill patient with overt hemodynamic perturbations, however both types likely exist together to some degree in a significant number of patients. For lactate levels to be normal and aerobic metabolism to work, the body needs an intact macrocirculation (and therefore organ perfusion), microcirculation, and mitochondrial function. The clinician must keep this in mind, as an elevated lactate forecasts a poor prognosis, but exactly why it is elevated and where the lactate is coming from is often difficult to elucidate. As one might expect, lactic acidosis, not hyperlactatemia itself, is the primary predictor of inhospital mortality as has been demonstrated in septic patients presenting to the emergency department[11].

Lactate for Risk Stratification

Lactate has been studied as a marker of critical illness severity for decades [9]. The pathophysiology of lactate production, clearance, and kinetics are not always straightforward, but hyperlactatemia is typically present with delivery-dependant oxygen consumption. However there is no precise critical level of oxygen delivery or central venous oxygen saturation that is associated with hyperlactatemia. This is thought to be related to the importance of regional, not just global, oxygen delivery in tissue perfusion. Even after normalization of the macrocirculation, a significant number of patients remain in “cryptic” or “occult” shock, secondary to persistent cellular hypoperfusion [3, 12–15]. For this reason, a low threshold for checking lactate levels should be maintained, as the correlation between lactate elevation and surrogate markers of hypoperfusion, such as physical exam, and anion gap, is low[16].

The exact level pointing to a worse outcome can be debated, depending on the patient cohort and trial quoted. However, general themes in the literature exist: 1) the higher the lactate elevation, the higher the mortality tends to be; 2) even mild elevations of lactate identify patients groups at higher risk for worse outcome. This data is consistent over several patient populations, to include: severe sepsis and septic shock[17], cardiac arrest[18], and trauma[19, 20]. In fact, in the setting of severe sepsis, a mild elevation (2–3.9 mmol/L) in lactate is associated with mortality, independent of shock or organ failure [21]. These data strongly suggest that any elevation in lactate in the patient with sepsis should raise concern for increased mortality, but the accepted threshold for initiation of formal early goal-directed therapy, treatment protocols, and care bundles has traditionally been 4mmol/L [17, 22, 23].

Lactate Clearance as a Hemodynamic Endpoint

Similar to all monitoring devices or biomarkers, unless linked with a therapy that improves outcome, merely checking or monitoring lactate levels will not improve outcome. The aim of any therapy should be reversal of global tissue hypoxia, and a decrease in lactate values to normal levels can serve as a surrogate in this regard. The data on lactate clearance is also fairly consistent: 1) compared with non-clearers of lactate, patients who clear elevated lactate levels have improved outcomes; and 2) the slower that lactate clearance is achieved, the worse the outcome[19, 24–28].

In surgical ICU patients, persistent hyperlactatemia was 100% predictive of mortality in a single-center study [27]. In patients achieving lactate clearance within 24 hours, mortality fell to 3.9%. In elective cardiac surgical patients, a protocol aimed at lactate clearance was associated with decreased hospital stay[29]. In critically ill septic patients, an early and more pronounced lactate clearance is associated with reduced mortality [3, 24]. Also in septic patients, a multicenter trial showed patients with lactate clearance (≥10% decrease in lactate from initial measurement) had a 41% decrease in absolute mortality compared to non-clearers of lactate[26]. In another multicenter trial from a mixed ICU population, serial lactate monitoring, along with a protocolized treatment algorithm aimed at reversing both macrocirculatory and microcirculatory dysfunction, resulted in a decrease in mortality, organ failure, and ICU days[25].

The measurement of lactate serves three purposes: (1) to establish the diagnosis of severe sepsis (infection plus elevated lactate); (2) if ≥4 mmol/L may trigger early goal-directed therapy; and (3) if elevated may provide the baseline for targeting resuscitation to lactate clearance. It is clear from the literature that elevated lactate should be a cause for concern and serial lactate monitoring, with aim for clearance, should be a target for resuscitation in the critically ill.

What is less clear is what the therapeutic plan should be in patients with a persistently elevated lactate, as the literature is less robust in certain arenas. As another therapeutic potential, lactate-guided resuscitation may afford the clinician the ability to know when to cease aggressive resuscitation and to decrease potentially harmful interventions. Table 1 summarizes the measured parameters and potential interventions to achieve lactate clearance.

Lactate Clearance versus Mixed Venous Oxygenation as a Resuscitation Goal

Quantitative resuscitation involves a protocol-driven delivery of care targeting predefined physiological goals. Data supports an early quantitative resuscitation strategy to improve outcome in the critically ill [36]. While the optimal targets are of debate and the data suggests a lack of consensus, what is clear is that some sort of quantitative resuscitation strategy should be used [36, 37]. Despite robust clinical data showing improved outcome associated with serial lactate monitoring and lactate-guided resuscitation, current guidelines do not include this as a therapeutic endpoint[23]. This topic has been the focus of intense debate recently[38]. Each parameter has limitations, as well as certain attractions physiologically. Each parameter has capability for obtaining values through bedside measurement (continual measurement for mixed venous oxygenation (S_vO_2) and point of care measurement for lactate). Both values can also be measured by sending blood to the laboratory.

Classic teaching is that S_vO_2 and lactate are concordant variables: as oxygen consumption becomes delivery-dependent, S_vO_2 will decrease, the patient will reach their anaerobic threshold, and lactate levels will increase. However, in a multicenter trial of severe sepsis patients receiving quantitative resuscitation, 79% of patients with persistently elevated lactate values had central venous oxygen saturation ($S_{cv}O_2$) values ≥ 70%[26]. Lactate clearance was a stronger predictor of in-hospital mortality when compared to optimization of $S_{cv}O_2$, and $S_{cv}O_2$ values of ≥70% could not exclude lactate non-clearance. The authors concluded that “serial lactate measurement may provide unique and important information on resuscitation effectiveness”[26]. Furthermore, a significant percentage of patients with sepsis present with venous hyperoxia ($S_{cv}O_2$ >89%), which may be a worse prognostic indicator than venous hypoxia, and for which there are currently no therapeutic options [39]. In another multicenter trial involving severe sepsis and septic shock patients, protocolized resuscitation targeting ≥10% lactate clearance versus $S_{cv}O_2$ values ≥ 70% produced similar in hospital mortality (17% lactate clearance group vs. 23% $S_{cv}O_2$ group), using a noninferiority clinical trial design[40]. However, many knowledgeable individuals in this research area, despite the results of this study, would take little comfort in knowing their resuscitation efforts had lowered an initially very high lactate by only 10%.

In the setting of a quantitative resuscitation strategy, enough data does not exist to strongly recommend targeting lactate clearance over $S_{cv}O_2$ or vice versa. Enough data does exist to recommend a quantitative resuscitation strategy, targeting either lactate clearance, $S_{cv}O_2$ ≥ 70%, and perhaps a combination [36]. These parameters should be viewed not as rivals, but as complimentary to resuscitation goals. The wise clinician will titrate resuscitative efforts to individual patient response and cease aggressive resuscitation when tissue hypoxia has been reversed. It is these authors’ opinion that in patients more likely to require inotropic support (history of congestive heart failure, inadequate myocardial reserve, myocardial depression secondary to sepsis), continuous monitoring of S_vO_2 or $S_{cv}O_2$ should be favored. Table 2 summarizes some of the pros and cons associated with each approach.

Conclusion

The resuscitation of the critically ill patient should be aimed at reversing early tissue hypoxia, not at strictly achieving predefined static hemodynamic parameters. While hyperlactatemia can be complex in etiology, robust data associates its presence with increased morbidity and mortality across a wide array of critically ill patients. Similarly, lactate values have been shown to be accurate for risk stratification, and lactate clearance is associated with improved outcome. A quantitative resuscitation strategy is recommended to reverse global tissue hypoxia in the early stages of shock. The clinician should choose to follow lactate clearance and/or $S_{cv}O_2$ based on individual patient characteristics and response to therapy. When global tissue hypoxia is reversed, aggressive resuscitation should be stopped, thereby preventing unnecessary interventions.

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Key Points

- In the setting of critical illness, lactate elevation, even to a mild degree, is associated with worse outcome.
- Lactate levels should be checked to identify patients with occult tissue hypoperfusion, and for risk stratification.
- Lactate clearance is associated with improved outcomes in the setting of early resuscitation.
- The use of lactate clearance may be as beneficial as mixed venous oxygenation in select patient populations, and should be viewed as a complementary resuscitation target.

Table 1

Parameters and targets to achieve lactate clearance

Hemodynamic Target	Measured Parameter	Suggested Therapy	Comment
Macrocirculation	Preload responsiveness	Crystalloid or colloid	Hydroxyethyl starch should be avoided in patients with sepsis[30]
	Decreased myocardial contractility	Inotropic agent Afterload reduction	
	Oxygen consumption	Endotracheal intubation Sedation Paralysis	Should be weighed against potential side effects of neuromuscular blockade
	Anemia	Packed red blood cell transfusion	The ability for stored cells to efficiently improve oxygen consumption is limited[31]
	Hypoxemia	Supplemental oxygen Endotracheal intubation	
Microcirculation	$S_{cv}O_2 \geq 70\%$ Microcirculatory dysfunction	Nitroglycerin infusion	Controversial Limited data[25, 32–34]
Mitochondrial dysfunction	Various substrate, cofactor, antioxidant, and membrane stabilizer species[35]	Human trials lacking	Physiologically attractive, but no available therapies at this time

Table 2

Comparison of central venous oxygen saturation versus lactate clearance

	Central Venous Oxygen Saturation	**Lactate Clearance**
Pro	Generalizability of this resuscitation strategy has been shown[41]	Supported by two multicenter studies[25, 40]
	Supported by guideline recommendations[23]	Consistent data support survival benefit in multiple patient cohorts
	Can detect early hemodynamic deterioration in dynamic fashion	
	Better surrogate for myocardial performance	Better surrogate for cellular stress
Con	Normal to high values common in septic shock [39]	Normal values common in septic shock [42]
	No therapy for elevated values	Lactate elevation not solely due to oxygen delivery- consumption mismatch
		Different prognostic implications depending on initial value