Understanding Lactatemia in Human Sepsis
Potential Impact for Early Management

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Abstract

Rationale: Hyperlactatemia in sepsis may derive from a prevalent impairment of oxygen supply/demand and/or oxygen use. Discriminating between these two mechanisms may be relevant for the early fluid resuscitation strategy.

Objectives: To understand the relationship among central venous oxygen saturation (ScvO₂), lactate, and base excess to better determine the origin of lactate.

Methods: This was a post hoc analysis of baseline variables of 1,741 patients with sepsis enrolled in the multicenter trial ALBIOS (Albumin Italian Outcome Sepsis). Variables were analyzed as a function of sextiles of lactate concentration and sextiles of ScvO₂. We defined the “alactic base excess,” as the sum of lactate and standard base excess.

Measurements and Main Results: Organ dysfunction severity scores, physiologic variables of hepatic, metabolic, cardiac, and renal function, and 90-day mortality were measured. ScvO₂ was lower than 70% only in 35% of patients. Mortality, organ dysfunction scores, and lactate were highest in the first and sixth sextiles of ScvO₂. Although lactate level related strongly to mortality, it was associated with acidemia only when kidney function was impaired (creatinine >2 mg/dl), as rapidly detected by a negative alactic base excess. In contrast, positive values of alactic base excess were associated with a relative reduction of fluid balance.

Conclusions: Hyperlactatemia is powerfully correlated with severity of sepsis and, in established sepsis, is caused more frequently by impaired tissue oxygen use, rather than by impaired oxygen transport. Concomitant acidemia was only observed in the presence of renal dysfunction, as rapidly detected by alactic base excess. The current strategy of fluid resuscitation could be modified according to the origin of excess lactate.

Keywords: sepsis; lactic acidosis; venous oxygen saturation; base excess
Hyperlactatemia has historically been associated with adverse outcomes in critically ill patients (1) and still represents the strongest outcome indicator in sepsis. Hyperlactatemia, however, may originate from a variety of causes, such as a deficit in oxygen transport. This common clinical perception often motivates adherence to the current resuscitation approach of aggressive and indiscriminate nonselective administration of fluid. Our expanded interpretation is based on accepted principles that are well known and documented in isolation but have never been grouped together and presented as a unified model. We applied this unifying conceptual interpretation to a large dataset of patients with sepsis, derived from the ALBIOS (Albumin Italian Outcome Sepsis) study (8), using the baseline data collected before randomization. We hypothesized that, after accounting for potentially relevant confounders, hyperlactatemia is present both at high and low values of central venous oxygen saturation (ScvO2) and that the presence or absence of kidney injury determines the final effect of plasma lactate concentration on pH.

Methods

Patients
This study is a secondary analysis of the ALBIOS study (8), a multicenter randomized controlled trial conducted between 2008 and 2012 in 100 Italian ICUs that compared the effects of 20% albumin and crystalloids versus crystalloids alone in severe sepsis and septic shock. In the present study, we included 1,741/1,818 patients for whom both serum lactate and ScvO2 measurements were available at baseline (see Figure E1 in the online supplement). Measurements were collected at baseline (within 24 h from the diagnosis of sepsis) after randomization and before the albumin administration. We do not know the volume or composition of fluids given to the patients in the emergency room and/or in ICU before the randomization. Therefore, our analysis refers to the subsequent phase of sepsis management.

Study Design
We analyzed baseline clinical, physiologic, and hemodynamic variables as functions of lactate concentration, ScvO2 levels, and alactic base excess (BE) (see below). These variables were grouped into sextiles that included similar numbers of patients (<250 each).

Measured Variables

Clinical. We recorded Sequential Organ Failure Assessment score (SOFA) (9), Simplified Acute Physiology Score II (10), 90-day mortality, bilirubin, glucose, creatinine, albumin, platelet and leukocyte count, percentage of patients fulfilling the Sepsis-2 definition (as defined by the ALBIOS study entry criteria [8]) or Sepsis-3 criteria (i.e., vasopressor requirement to maintain mean arterial pressure ≥ 65 mm Hg with lactate levels >2 mmol/L) (11, 12), and proportion of patients requiring renal replacement therapy (RRT).

Physiologic. Physiologic measurements included FIO2, arterial and venous partial pressures of oxygen and carbon dioxide, arterial and venous pH, arterial BE, sodium, chloride and potassium, diuresis, and fluid balance in the first 6 hours after admission.

Hemodynamic. Hemodynamic measurements included central venous and mean arterial pressures, heart rate, use and dosing of epinephrine, norepinephrine, ScvO2, arteriovenous difference in oxygen content, vеноarterial difference of CO2 partial pressures, and Hb concentration.

Computed Variables
We computed the standard BE as

\[
\text{standard BE (mmol/L)} = [\text{HCO}_3^\text{-}} \text{(mmol/L)} - 24.8 \text{ mmol/L}] + 16.2 \text{ mmol/L} \times (\text{pH} - 7.4).
\]

We used standard BE rather than actual as better representative of the buffer base status of the extracellular fluid (13). See the online supplement for details.

To better understand the relationship between hyperlactatemia and acidemia, we introduce the concept of alactic BE, which helps in the rapid discrimination between metabolic acidosis secondary to lactate accumulation from that caused by an increase in fixed acids (unmeasured strong anions):

\[
\text{alactic BE (mmol/L)} = \text{standard base excess (mmol/L)} + \text{lactate (mmol/L)}.
\]

This variable focuses on the role of fixed acids other than lactate in the sepsis scenario (fixed acids refer to the acids...
balance deteriorated progressively ($P < 0.001$); $P_{\text{aO}_2}$ and $P_{\text{aCO}_2}$ values were similar across all lactate sextiles. There was no obvious relationship between alactic BE and lactate level.

**ScvO$_2$, Lactate, and Tissue Hypoxia**

As shown in Figure 2, the ScvO$_2$ as recorded in all the patients with sepsis without exclusions, ranged from 24% to 98% (median, 73%; interquartile range, 67–79%). As shown in Figure 3, several clinical variables, including lactate, SOFA score, and mortality, showed a U-shaped relationship with the ScvO$_2$. Indeed, the worst values of these variables were observed at the lowest and highest levels of ScvO$_2$. Among the other clinical, hemodynamic, and laboratory variables, the lactate levels showed similar $P$ values less than 0.05 was considered statistically significant. All statistical analyses were performed using R and GraphPad Prism Software.

**Study Approval**

The protocol of the original ALBIOS study and the informed-consent process were approved by the ethics committee at each participating institution. Written informed consent or deferred consent was obtained from each patient.

**Results**

**Lactate and Clinical Variables**

As shown in Figure 1, mortality and SOFA score progressively increased across the sextiles of lactate. In contrast, the ScvO$_2$ remained remarkably similar (ScvO$_2$ ~72%) throughout the first five sextiles of lactate (i.e., lactate levels ranging from 0.1 to 5.6 mmol/L) and slightly, but significantly, decreased to 69.7% in the highest lactate sextile (i.e., lactate levels from 5.6 to 27 mmol/L). Similarly, pH remained similar and in the normal range within the first five sextiles of lactate and decreased significantly to a mean ± SD of 7.31 ± 0.14 only in the terminal lactate sextile. Most of the other measured clinical, physiologic, and hemodynamic variables deteriorated with increasing lactate levels, as reported in Table E1. Briefly, central venous pressure ($P = 0.01$), heart rate ($P < 0.001$), norepinephrine requirements, mean arterial pressure ($P < 0.001$), diuresis, and fluid $RRT$. Accordingly, with worsening renal function, the concentration of fixed acids other than lactate increased in the plasma. This dysfunction led to worsening acidemia, as reflected in more negative values of alactic BE. Conversely, an alactic BE near 0 suggested that acidemia was fully explained by the lactate, because no other acids were present in excess, whereas a positive alactic BE suggested either that the kidney fully compensated for metabolic acidosis or that additional mechanisms contributed to metabolic alkalosis (e.g., diuretic usage, contraction of the extracellular volume). Actually, the alactic BE was strongly associated to the fluid balance (see Figure E5).

**A Comprehensive Synthesis of the Results**

In Figure 5 we present an integrated view of our results. As shown, hyperlactatemia was increased quite independently from $V_{O_2}/$ oxygen delivery ($D_{O_2}$) (see Figure E6A). In contrast the $V_{O_2}/D_{O_2}$, viewed as an independent variable, strictly determines the ScvO$_2$ levels: low when the oxygen transport is low (high $V_{O_2}/D_{O_2}$) and high when oxygen use is impaired (low $V_{O_2}/D_{O_2}$). The physiologically sound ScvO$_2$–$V_{O_2}/D_{O_2}$ relationship, unfortunately, is biased by mathematical coupling, which prevents a rigorous analysis of possible confounders. In addition, it is worth emphasizing that ScvO$_2$ might not be representative of the whole-body average oxygen venous saturation, even though it is a broadly accepted surrogate of the mixed venous oxygen saturation (15). The second independent variable is renal function, on which we hypothesize that acidemia should primarily depend. Among several variables, we found that $P_{\text{aCO}_2}$, SOFA without its renal component, and mean arterial pressure acted as real confounders both on creatinine and pH. Including these variables in a multiple linear regression model, the creatinine remained the variable most strongly independently related to the pH (see online supplement for complete analysis).

**Discussion**

Over recent decades there has been a growing evidence that lactate in sepsis and...
shock state may increase for several reasons other than tissue hypoxia (16). The possible heterogenous sources of lactate in septic shock, however, have rarely been quantified. Alegria and colleagues (17) in a retrospective analysis of 90 patients with septic shock, found that 70 patients presented elevated lactate in association with signs of hypoperfusion (including ScvO₂ < 70%). In our analysis on 1,741 patients, after admission in ICU, we found that only 35% of the patients had an ScvO₂ lower than 70%, whereas 65% had high lactate coexisting with normal or increased ScvO₂. This finding suggests that high lactate levels, as observed in an ICU setting after initial fluid resuscitation made in the emergency department, are caused by a macrocirculatory oxygen transport defect only in a minority of cases. Furthermore, we found that hyperlactatemia in this setting is reliably associated with acidemia only if renal dysfunction is simultaneously present. Finally, the estimation of the alactic BE is a useful tool by which the degree of renal compensation of the acid-base disorder can be rapidly determined.

**Lactate and Tissue Hypoxia**

Despite its limitations, ScvO₂ is one of the best surrogates for the assessment of tissue oxygen availability (i.e., the relationship between oxygen delivery and demand) and is widely used in clinical practice. We found that, on admission, only approximately 35% of our patients had ScvO₂ lower than 70%. This finding is consistent with what has been observed in most large clinical trials performed for sepsis (18–20). Although, admittedly, ScvO₂ is an imperfect indicator of the cellular oxygen environment, it is reasonable to associate extreme values of ScvO₂ either to a predominant oxygen transport insufficiency (low ScvO₂) or to a predominant oxygen use impairment (high ScvO₂). These two extremes of ScvO₂ are indeed associated with the highest lactate levels, renal dysfunction, disease severity, and mortality, so that ScvO₂ has a U-shaped relationship with these characteristics. This interpretation is supported by other findings: the highest arteriovenous oxygen content difference and the greatest venoarterial difference in PCO₂ were found in the first ScvO₂ sextile (24–62%).

At the opposite extreme, the presence of hyperlactatemia at the most elevated ScvO₂ levels (78–98%) strongly suggests mechanisms other than an oxygen transport deficit. In sepsis, elevated lactate levels with high ScvO₂ may be explained by a variety of mechanisms ranging from the lack of pyruvate decarboxylation caused by thiamine deficiency (21–24) to the impairment of the electron transport chain caused by dysfunctional structure of the respiratory mitochondrial enzymes, induced, for example, by nitric oxide (25) or oxygen radicals (26). Another possible explanation for this association, although physiologically indistinguishable from the aforementioned mechanisms, entails the dysregulation of the microcirculation leading to peripheral shunting (3, 27).

**Lactate and Metabolic Acidosis**

An increase in the concentration of lactate results in metabolic acidosis (i.e., a process leading to an excess of negative strong ions) (14, 28). However, acidemia (i.e., an abnormally high proton concentration [low pH]) is not necessarily present if other processes simultaneously promote a compensatory decrease in negative strong ions, with consequent widening of strong ion difference and restoration of pH toward normality. The kidney has a pivotal role in correcting for the excess of lactate. Indeed, given that PaCO₂ in our population was similar across lactate sextiles, the compensatory mechanisms when present were mainly caused by an offsetting increase in the strong ion difference by the kidney.
To better understand the relation between hyperlactatemia and acidemia, we have introduced the concept of alactic BE, which helps to quickly discriminate between metabolic acidosis secondary to lactate from metabolic acidosis caused, for example, by an accumulation of fixed acids (unmeasured strong anions). The role of renal function on the acid–base balance in sepsis is explicitly quantified by the alactic BE.

The association of a negative alactic BE with creatinine >2 mg/dl indicates that fixed acids other than lactate are retained in the plasma, meaning that the kidney is no longer able to compensate for the lactic acidosis because of an associated renal dysfunction. An alactic BE of zero (observed at creatinine ~2 mg/dl) suggests that the kidney is still able to clear fixed acids but cannot fully “compensate” for the acidosis induced by lactate.

A positive alactic BE (generally with a creatinine <2 mg/dl) suggests the presence of metabolic alkalosis, usually caused by diuretics or volume contraction (29). In summary, although an abnormally high lactate per se nearly always indicates acidosis of some severity, the degree of associated acidemia depends on renal ability to compensate. The concept of alactic BE is a simple, novel, and potentially useful method to immediately detect and track these phenomena over time. The classical BE includes all the information given by the alactic BE. However, alactic BE has more practical diagnostic and therapeutic potential. Indeed, a negative alactic BE, observed in these patients with sepsis, alerts the physician to that fact that the renal function is impaired (unable to compensate for an excess of negative strong ions), whereas a positive alactic BE may indicate an additional process leading to metabolic alkalosis (e.g., excess use of diuretics and volume contraction). It should be noted that the alactic BE clearly differs from the anion gap [i.e., (sodium + potassium) – (chloride + bicarbonate)], because this latter variable does not distinguish between lactate and other fixed acids. If the lactate is added to the anion gap computation, the alactic BE differs

Figure 2. Observed frequency of distribution of central venous oxygen saturation (ScvO2) at baseline measured in the whole population at ICU admission. As shown, only a minority of patients presented an ScvO2 consistent with oxygen transport deficit. Note, however, that the extreme values of ScvO2 (one patient <25% and three patients >95%) are likely artifactual.

Figure 3. (A–C) Lactate (A), Sequential Organ Failure Assessment score (B), and mortality (C) as a function of central venous oxygen saturation sextiles at baseline (ICU admission). Data are presented as mean ± SE. ScvO2 = central venous oxygen saturation; SOFA = Sequential Organ Failure Assessment score.
Lactate metabolism and kidney response. The arrows’ direction indicates increase (↑) or decrease (↓) of the given variable. See text and online supplement for further details. ScvO₂ = central venous oxygen saturation; SID = strong ion difference.

Figure 4.  (A–D) Creatinine (A), diuresis (B), renal-replacement therapy (C), and simplified strong ion difference ([Na⁺ + K⁺] – Cl⁻) (D) as a function of alactic base excess sextiles at baseline (ICU admission). Data are presented as mean ± SE. BE = base excess; RRT = renal-replacement therapy; SID = strong ion difference.

Figure 5.  Lactate metabolic pathways and kidney response. The arrows’ direction indicates increase (↑) or decrease (↓) of the given variable. See text and online supplement for further details. ScvO₂ = central venous oxygen saturation; SID = strong ion difference.

The plasma concentration of lactate reaches a plateau if the rate of lactate production in the nonfunctioning metabolic units equals the rate of lactate oxidation by the metabolically active functioning units. Most organs, primarily the liver, may “clear” circulating lactate (i.e., completely oxidize lactate) and the rate of oxidation in the functioning metabolic units increases with the lactate input. Indeed, a strong relationship has been shown between exogenous lactate input and its oxidation in patients during dialysis (32), and the same phenomenon has been observed in experimental animal models (33).

Therefore, we may hypothesize that in sepsis, the lactate oxidation capability of the functioning metabolic units (see Figure E10) increases with the increased availability of lactate (34) (see Figures E8 and E11). Interestingly, other metabolites that normally are oxidized by the Krebs cycle within the mitochondria (e.g., nonesterified fatty acids) behave in sepsis as does lactate: increased levels promote higher rates of oxidation (35).

Clinical Implications
Our findings may help account for the ability of lactate to predict the severity and outcome of patients with sepsis. Indeed, we showed that whatever the prevalent mechanism underlying the deterioration in organ function in sepsis (i.e., impairment in the oxygen transport or oxygen use), the end result is an increase in the production of lactates and a decrease in their oxidation, leading to hyperlactatemia. However, despite this apparent similarity in outcome, a better understanding of the primary mechanism of hyperlactatemia, as we suggest in this model, might guide a more targeted and less indiscriminate approach to the management of sepsis. In strictly following the management guidance currently advocated, all patients with overt sepsis would receive similar amounts of fluids, regardless of their mixed venous oxygen saturation (36).

Actually, a deficit in the oxygen transport, as suggested by low ScvO₂, may justify a therapeutic approach aiming at increasing it, such as early goal-directed therapy (37), and, even better, correcting, if possible, the precise cause of oxygen transport impairment. In contrast, at high ScvO₂ (impaired oxygen use) the same therapeutic approach may seem, at best, ineffective, as suggested by recent
randomized controlled trials (18–20). We may rationally wonder whether, in such cases, the mandated use of a fixed amount of fluid has a sound pathophysiologic rationale, and whether this approach is devoid of adverse consequences, as suggested by studies reporting positive fluid balance, renal dysfunction, and worse outcome after aggressive fluid replacement in sepsis (38, 39).

We suggest that patients might be first stratified on the basis of ScvO₂, to understand the origin of lactate production, and then on the basis of the alactic BE to better understand organ (i.e., kidney) perfusion and volemia. Changes in this simple parameter over time may facilitate early restoration of appropriate fluid balance and/or prompt the use of RRT.

Conclusions
Our results indicate that in patients with sepsis: 1) lactate is a powerful marker of illness severity; 2) abnormal lactate levels, in established sepsis, seem to be generated primarily by impaired oxygen transport in the minority of cases, whereas in the majority, high lactate more likely results from impaired tissue oxygen use; and 3) the degree of acidemia or alkalalemia depends primarily on renal function. The alactic BE offers a potentially useful way to estimate renal capability of handling the disturbance to acid–base equilibrium. A clear recognition of the mechanisms underlying lactate elevation should result in an improved therapeutic approach for the individual, particularly regarding the aggressiveness of fluid administration.

Author disclosures
are available with the text of this article at www.atsjournals.org.

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