Lactate revisited: is lactate monitoring beneficial for ICU patients?

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Abstract - Blood lactate levels are frequently measured in critically ill patients. Whilst these measurements are known to be accurate, for the correct interpretation of hyperlactataemia, it is essential to have sufficient understanding of anaerobic and aerobic mechanisms of production and clearance. The consistency of the prognostic value emphasizes the place of lactate measurement in the risk-stratification of critically ill patients. However, until recently the clinical benefit of lactate-guided resuscitation in critically ill patients was unknown. By referring to two recent multi-centre randomized controlled trials, this review provides an update on this important topic. The first study showed that lactate clearance was non-inferior to central venous oxygen saturation (ScvO₂) as a goal of early resuscitation in patients with severe sepsis or septic shock who presented to the Emergency Department (ED). The second study showed that in patients with hyperlactataemia on ICU admission, lactate monitoring significantly reduced hospital mortality when adjusting for predefined risk factors, a finding that was consistent with important secondary endpoints. This suggests that lactate monitoring has clinical benefit and that lactate measurement should be incorporated in goal-directed therapy.

Keywords - lactate, lactic acidosis, monitoring, goal-directed therapy

Introduction
Blood lactate was first measured in human blood by the German physician-chemist Johann Joseph Scherer in 1843, when he described a lethal case of fulminant septic shock due to puerperal fever in a young woman [1]. Nowadays, lactate is frequently measured in critically ill patients, usually with the aim of detecting tissue hypoxia [2]. However, other processes not related to tissue hypoxia can also result in increased lactate levels [3], which complicates its clinical interpretation and therapy. Until recently, the clinical benefit of lactate monitoring in critically ill patients had not been subjected to rigorous clinical evaluation. Therefore, the question remains: should we routinely monitor lactate in the critically ill and if so, when should we measure it, what would be the therapeutic consequences and would this improve patient outcome?

Accuracy of lactate measurement
Blood lactate levels can be measured using the hospital’s central laboratory, point-of-care blood gas analyzers or hand-held devices. Generally, all have reported small biases with clinically acceptable limits of agreement [4,5]. Most investigators found satisfactory agreement comparing capillary, venous or central/mixed venous levels with arterial levels [6-8]. Ongoing in-vitro glycolysis might occur after blood sampling, resulting in erroneous elevation of lactate levels [9], particularly in cases of leukocytosis or high hematocrit [10]. To avoid this problem, analysis within 15 minutes, storage <4°C or use of fluoride oxalate tubes are suggested. Infusion of Ringer’s lactate does not hamper the accuracy of lactate measurement [11]. Finally, renal replacement therapy eliminates only negligible amounts of lactate [12], although lactate-containing buffer solutions are able to induce transient hyperlactataemia [13,14].

The level of lactate should not be estimated from other acid base variables, as there is no clinically important relationship with pH, base excess or anion gap [15,16]. Lactate is only responsible for a minor percentage of metabolic acidosis in critically ill patients [17] and lactate or non-lactate etiologies of metabolic acidosis are associated with different mortality rates [18]. Therefore, although hyperlactataemia has often been associated with the presence of a metabolic acidosis, this relationship does not appear to be at all straightforward.

Causes of hyperlactataemia
Traditionally, hyperlactataemia has been associated with tissue hypoxia. This causal relationship has been confirmed by experimental [19] and clinical [2] studies. Furthermore, even when systemic oxygen delivery is sufficient for metabolic demand, microcirculatory processes hampering oxygen utilization at the tissue level may also raise lactate levels. In addition to these anaerobic causes, the following aerobic mechanisms can also contribute to hyperlactataemia:
- Catecholamine-stimulated increased Na-K-pump activity, which increases aerobic glycolysis [3]
- Cytokine-mediated enhanced glycolysis [20,21]
- Mitochondrial dysfunction [22,23]
- Impaired activity of pyruvate dehydrogenase (PDH) in sepsis [24]
- Thiamin deficiency (beri-beri’s disease) [25]
- Liver dysfunction [26-28]
- Pulmonary lactate production [29,30], reflecting metabolic adaptations in response to inflammatory mediators
- Alkalosis; H+-linked carrier transport mechanism across the cell membrane [31]
- Epinephrine [32, 33], metformin, nucleosidic reverse transcriptase inhibitors [34], methanol, cyanide [35] or ethylene-glycol [36].

**Prognosis of hyperlactataemia**

In a recent systematic Health Technology Assessment, all available studies that addressed the prognostic value of lactate in the ED or the ICU were searched [37]. In the ED setting, the area under the receiver operating characteristic curve (AUROC) for mortality varied from 0.67 [38] to 0.98 [39], which indicates moderate to excellent capability of discriminating non-survivors from survivors. In the ICU setting, AUROC varied from 0.53 [40] and 0.58 [41] to 0.86 [42]. To answer the question whether or not a hyperlactataemic patient will die, which is what clinicians want to know when individually assessing patients, the positive predictive value or post-test probability is important. In some of the studies included in the Health Technology Assessment, this value was very low (4-15% [38,43,44]). However, comparison of the pre-test probability (population mortality rate) with the post-test probability determines the value that lactate can add in risk-
stratification. From the evaluated studies, it is clear that lactate generally increased the ability to predict non-survival, both in the ED and the ICU settings. The consistency of this finding means that lactate certainly has a place in the risk-stratification of critically ill patients.

As early identification of critical illness is widely acknowledged as a vital step towards improving survival [45-47], recent studies have transferred the prognostic ability of lactate monitoring from the hospital to the pre-hospital setting, with promising results [48,49]. These recent data indicate a new avenue of research into the hospital to the pre-hospital setting, with promising results.

In 2010, two multi-centre clinical trials were published on the clinical value of lactate-directed therapy [53,54].

**Lactate-guided therapy: The USA**

Jones et al. tested the hypothesis of non-inferiority between lactate clearance and central venous oxygen saturation (SvO2) as goals of early resuscitation in patients presenting to the ED with severe sepsis or septic shock [53]. In their three-centre, open-label, randomized controlled study, 300 patients were randomized to either a goal of ScvO2 of at least 70% or a decrease in lactate of at least 10%, both in combination with normalization of central venous pressure (CVP) and mean arterial pressure (MAP). The intervention lasted until all goals were achieved or for up to 6 hours. There were no differences found in treatments administered during the initial 72 hours of hospitalization. In-hospital mortality in the lactate group was non-inferior to the ScvO2 group (17% vs. 23%, 95% CI for the 6% difference -3% to 15%).

Early goal-directed therapy is resource intensive, and the relative contributions of the individual components to the overall treatment effect are not well characterized. This has become particularly relevant since controversy has been generated [55,56] regarding the results of the reference trial of Rivers [57]. The study of Jones et al. provides the first step in identifying the key components responsible for the efficacy of this strategy, with the goal of reducing the burden of implementation without loss of benefit [58].

Time, expertise, and specialized equipment required to continuously measure ScvO2 might pose a barrier to the implementation of ScvO2-driven resuscitation programmes in the ED [59,60]. However, although the study of Jones et al. possibly eliminates the need for a specialized catheter and its associated electronic instrumentation, it does not prevent the need for a central venous

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**Table 1. Mortality**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>CONTROL GROUP (N=177)</th>
<th>LACTATE GROUP (N=171)</th>
<th>RELATIVE RISK (95%CI)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality</td>
<td>43.5% (77/177)</td>
<td>33.9% (58/171)</td>
<td>0.78 (0.60-1.02)</td>
<td>0.067</td>
</tr>
<tr>
<td>28-day mortality</td>
<td>35.6% (63/177)</td>
<td>30.4% (52/171)</td>
<td>0.85 (0.63-1.16)</td>
<td>0.30</td>
</tr>
<tr>
<td>ICU-mortality</td>
<td>34.5% (61/177)</td>
<td>28.7% (49/171)</td>
<td>0.83 (0.61-1.14)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Jansen J. et al. [54] *Chi-square test. § Cox proportional hazard analysis with adjustment for age, sex, APACHE II (modified; at baseline) and SOFA (modified; at baseline), and stratified for centre and sepsis group, as predefined in the study protocol.*
catheter. Furthermore, measuring lactate without venous oxygen saturations might put some patients at risk as S(c)vO2 can be a valuable tool to differentiate anaerobic from aerobic hyperlactataemia, which often requires different treatment [61]. In addition, it seems questionable whether the target of a 10% reduction in lactate in 6 hours is sufficient to guarantee adequate resuscitation; e.g., has a patient been treated well enough when the lactate level has decreased from 6.7 to 6.0 mmol/l after 6 hours of resuscitation?

Another important limitation is that only 10% of the patients received either dobutamine or red blood cell transfusion. Because fluids and vasopressor administration were guided by CVP and MAP in both groups, this means that the potential difference in protocol actions directly attributable to either lactate clearance or ScvO2 was very small. This complicates the interpretation of the study. Changes in lactate levels (except for the admission value) during the first eight hours of ICU stay (figure 1A). In the lactate group, treatment was guided by lactate levels with the objective to decrease lactate by 20% or more per two hours (figure 1B); in the control group the treatment team had no knowledge of lactate levels except for the admission value. This resulted in administration of more fluids and vasodilators in the lactate group. A non-significant 9.6% absolute mortality reduction was found in the unadjusted primary outcome analysis (p=0.067) (table 1), which was consistent with a highly significant mortality reduction in the pre-defined multivariable analysis (p=0.006) and with a decrease in important secondary outcome measures such as organ failure, duration of mechanical ventilation and length of ICU stay.

Two results of this study need further attention. First, there was a discrepancy in the significance between the unadjusted and adjusted primary outcome analysis. The statistical method of predefined covariate adjustment increased the power of the study without requiring increased sample size [62]. This technique made treatment effect estimation more individualized, reduced noise in the analysis and thereby improved the statistical power, i.e., the ability to identify a smaller treatment effect when it really exists. The second study finding that needs attention is the similar course of lactate levels in the two groups. This suggests no causal relationship between the administered therapy (i.e., additional fluid resuscitation and vasodilator therapy) and hyperlactataemia. Instead, lactate might be an epiphenomenon of severity of disease. By acting as a warning signal, clinicians might have interpreted hyperlactataemia as a warning that their patients did not clinically improve or even deteriorate in the presence of stable hemodynamic parameters. This could have triggered intensified resuscitation or attention to other causes than inadequate tissue perfusion of impaired lactate reduction (e.g., non-controlled septic focus). Additionally, ScvO2 monitoring, which was mandatory in the lactate group and facultative in the control group, might have had an impact on the observed outcome as well. Unfortunately, the design of the study does not allow definite conclusions on the mechanism behind the outcome benefit to be drawn.

The strengths of the study include the immediate start of the study treatment following ICU admission, the use of hospital mortality as the primary endpoint and its multi-centre design, particularly as growing concerns have been raised regarding adoption of single-centre studies in clinical guidelines [63]. Finally, the results extend the concept of River’s early-goal-directed therapy from the ED to the ICU and to other patient groups besides severe sepsis or septic shock.

Conclusion

Lactate measurement is accurate and clinicians at the bedside can trust the numerical value they collect. However, sufficient understanding of anaerobic and aerobic mechanisms of production and clearance is essential for the correct interpretation of hyperlactataemia. Although the prognostic value of lactate can vary considerably depending on the patient population, lactate generally increases the ability to predict non-survival, both in the ED and ICU. Until recently, there was a lack of clinical trials investigating the value of lactate-guided resuscitation therapy. Two recent multi-centre trials have confirmed that the use of lactate levels in goal-directed therapy improves clinical outcome [53,54]. These findings suggest that lactate monitoring is beneficial for ICU patients and that it should be incorporated in early resuscitation strategies for critically ill patients.

References


