Why measure lactate on the ICU?

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Introduction. Blood lactate monitoring in the ICU has been done for decades. However, its value remains a matter for debate, which is reflected by its variable clinical use in hospitals worldwide. In intensive care medicine hyperlactataemia has been regarded mainly as a sign of tissue hypoxia. However, as lactate is a normal end product of metabolism, other processes unrelated to tissue hypoxia may also cause lactate levels to rise. Therefore the exact aetiology of hyperlactataemia needs to be assessed at the bedside, requiring sufficient understanding of lactate metabolism.

Other factors should also be clearly understood when lactate monitoring is put into practice. First, hyperlactataemia and lactic acidosis although often used interchangeably, do not necessarily co-exist. Second, although lactate is widely associated with mortality, its prognostic potential needs to be clarified. Finally, as monitoring itself does not change outcome, the measurement of lactate levels requires a treatment algorithm in order to provide benefit to the patient.

In this “questions and answers”-document we aim to provide answers concerning the value of lactate measurements and lactate-guided treatment in critically ill patients.

What is the aetiology of hyperlactataemia?

Lactate is a normal end product of glycolysis and can be formed only from pyruvate. The lactate – pyruvate equilibrium shifts towards lactate in anaerobic circumstances (Figure 1). Experimental studies have confirmed that lactate accurately detects tissue hypoxia [1-2]. In these studies the components of oxygen delivery (haemoglobin level, oxygen saturation and cardiac output) were reduced until oxygen demand could no longer be met. Below this critical level of oxygen delivery, oxygen consumption is limited by oxygen delivery and this coincides with a sharp increase in lactate levels.

In addition to a macrocirculatory (global) demand/supply mismatch, microcirculatory derangement can prevent adequate oxygen extraction at the tissue level, particularly in sepsis. Capillaries that are poorly perfused pass through functional tissue units and consequently, insufficient oxygen is delivered to the cell. Improving capillary perfusion has recently been correlated to a reduction in lactate levels in patients with septic shock, independent of changes in systemic haemodynamic variables [3].

In addition to macrocirculatory and microcirculatory supply/demand mismatches, aerobic processes may also account for hyperlactataemia in the critically ill. As lactate is an end product of carbohydrate metabolism, increased aerobic glycolysis could lead to hyperlactataemia by mass effect. Elevated cellular uptake of glucose that is mediated by cytokines, is a stimulus for such increased glycolysis [4]. Likewise, increased Na- K- ATP-ase activity that is mediated by catecholamines, enhances aerobic glycolysis. In septic shock, in particular, evidence is accumulating that aerobic glycolysis through Na- K- ATP-ase stimulation is an important cause of hyperlactataemia [5]. Pyruvate dehydrogenase dysfunction is another aerobic mechanism of hyperlactataemia in sepsis [6].

The liver primarily clears lactate and consequently liver failure [8] and liver surgery [9] can impair this process.

Finally, medication (e.g. reverse transcriptase inhibitors in the treatment of HIV [10], intoxications (alcohol, methanol and ethylene glycol [11]) or vitamin deficiency (thiamine deficiency in the disease beriberi[12]) can seriously interfere with lactate metabolism.

Is lactic acidosis different from hyperlactataemia?

Although hyperlactataemia is often associated with the presence of a metabolic acidosis (lactic acidosis), this relationship is not straightforward. The conversion of pyruvate into lactate does not directly result in net production of H+ ions. H+ ions are generated during the hydrolysis of adenosine triphosphate (ATP) and some studies have stressed that only if H+ ions cannot be recycled in the mitochondria (e.g. in anaerobic conditions), does acidosis coincide with the increase in lactate level [13].

Moreover, Stewart’s modern acid-base classification emphasizes the role of water dissociation as a source of protons [14]. In the Stewart methodology, three independent variables control pH: strong ion difference (SID), pCO2 and the sum of the weak acids and proteins in plasma [15]. Lactate is considered a strong anion and hyperlactataemia results in a reduced strong ion difference. This would in turn generate protons and result in acidosis. It is important to realize that in Stewart’s method, lactate contributes to the strong ion difference but does not necessarily relate to net formation of H+ ions. Other alterations in SID, the number of weak acids and proteins and changes in pCO2 (manipulations of the mechanical ventilator) all probably contribute to the weak relationship between lactate and acidosis and its different prognostic value in critically ill patients.

How and where should we measure lactate?

Lactate measurement nowadays only requires the collection of a minimal amount of plasma or whole blood. Blood gas analyzers and hand-held devices accurately measure lactate and point-of-care testing with these devices enables lactate measurement within 60 seconds [16]. Lactate can be measured using arterial, (central or
mixed) venous or capillary blood. Although minor discrepancies can be found when analyzing blood from the different sample sites, they fall within clinically acceptable limits of agreement (16;17). Ongoing in-vitro glycolysis after the blood sample has been drawn can result in erroneous increases in lactate levels (18). Immediate analysis (within 15 minutes) or cool storage are the preferred options for avoiding this (18;19).

**Does lactate perform well as a prognostic marker?**

In various clinical conditions and over decades of research, increased blood lactate levels and a failure to normalize these levels during treatment have been associated with increased morbidity and mortality (20-22). Even in haemodynamically stable patients with hyperlactataemia, a condition referred to as compensated shock or occult hypoperfusion, lactate levels are associated with a poor outcome (23;24).

Although base excess (BE) also correlates with survival, the fluid resuscitation state must be taken into account as this may influence the prognostic value of BE (25). Moreover, it has been shown that lactate enhances the prognostic capabilities of BE (22). Collected evidence thus unanimously regards lactate as an important warning signal in all ICU patients (20-24;26).

**Should we apply lactate-guided therapy in patients with hyperlactataemia?**

As hyperlactataemia indicates an unfavourable clinical outcome, all efforts need to be directed at improvement of this undesirable scenario. What kind of treatment should be initiated in this case and could serial lactate measurements guide this therapy?

Reducing lactate levels with dichloroacetate, for instance, showed no clinical benefit (27), indicating that the detrimental outcome of hyperlactataemia is determined by the underlying cause instead of the level of hyperlactataemia itself.

In haemodynamically stable trauma patients with increased lactate levels (occult hypoperfusion), Blow et al. implemented a treatment protocol to increase oxygen delivery that was guided by blood lactate levels (28). Failure to correct hyperlactataemia during their lactate-guided therapy correlated with increased mortality. Rossi et al. studied lactate-guided therapy in children undergoing surgery for congenital heart disease and found a reduction in morbidity and mortality on comparison with a historical subgroup (29). However, their study design was subject to a high probability of introducing bias. Although Rivers et al. did not specifically aim at evaluating a lactate-guided treatment protocol, they did show that lactate levels were significantly lower after six hours in patients receiving early goal-directed therapy compared to those receiving control group therapy, while lactate levels were equal at baseline (30).

To date only one randomized controlled trial evaluating lactate-directed therapy has been performed. Polonen et al. (31) showed a decrease in morbidity and length of stay in post-cardiac surgery patients using lactate < 2.0 mmol/l (and mixed venous oxygen saturation (SvO2) > 70%) as a goal of therapy.

Further randomized controlled evidence thus needs to be collected in order to properly assess efficacy of lactate-guided therapy in all critically ill patients in ICU. Until then, the important clinical question of what to do when lactate levels are elevated remains unanswered. It should however be noted that a hyperlactataemic patient with other signs of circulatory derangement (e.g. low SvO2, oliguria, altered mental state and poor peripheral perfusion) will most likely benefit from increased oxygen delivery.

**Conclusion**

Tissue hypoxia, as well as aerobic processes, cause hyperlactataemia. Hyperlactataemia should not be confused with lactic acidosis, as increased lactate levels do not always coincide with the presence of metabolic acidosis. Lactate can accurately be measured in arterial, venous or capillary blood using a blood gas analyzer or a hand-held device. As hyperlactataemia consistently and strongly predicts outcome, it is an important warning signal on the ICU. Adequate understanding of lactate metabolism is required to facilitate the correct interpretation of increased lactate levels. Nevertheless, increasing oxygen delivery is likely to benefit patients with high lactate levels and other signs of circulatory derangement such as a low SvO2. However, there is not yet a relevant body of clinical evidence to support the use of lactate-guided therapy in all hyperlactataemic patients in the ICU.

**References**