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### Lactate Monitoring in the ICU



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The use of lactate measurements in critically ill patients has steadily increased to a level where in some cases it may be considered lactate monitoring. In this brief review we discuss the central metabolic role of lactate in animal metabolism, and address important misconceptions as well as why lactate is mainly a marker of stress and how this translates into its unique diagnostic utility in many acute conditions. Finally several interesting future perspectives in lactate monitoring are discussed.

#### **Elucidation of Lactate Metabolism and Misconceptions about Lactate**

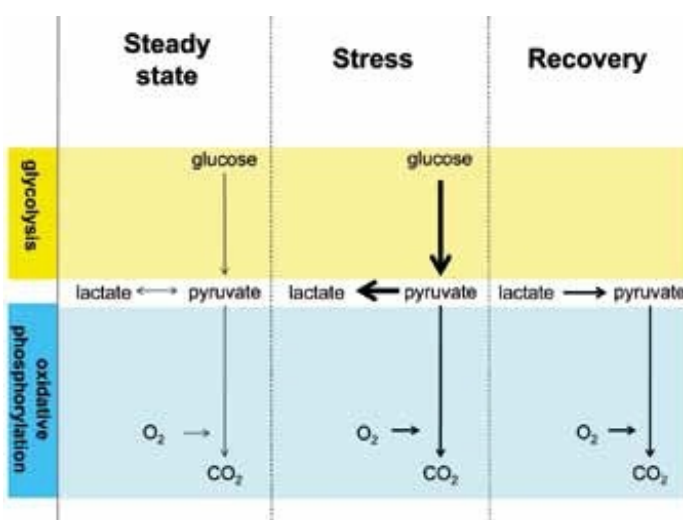
The history of lactate measurement and lactate metabolism is a fascinating story (Kompanje et al. 2007), having important relevance for current views on lactate, as some misunderstandings persist. From the moment it was recognised that lactic acid is generated when milk sours, some of the keenest investigators studied lactate metabolism. Several Nobel prize winners, including Otto Meyerhof, Otto Warburg, Hans Krebs, Carl Cori and Gerty Cori (Voet and Voet 2011) helped elucidate

lactate metabolism. Although often interchangeably used, lactic acid (HLA) and lactate (La-) are of course different entities, but for brevity we will not address this topic. Even at extreme physiological conditions HLa is fully dissociated into H+ and La-. When cells produce and export H+ and La-, the H+ will be partially buffered in the extracellular space.

Early in the 20th century it was recognised that glucose is a fuel used by virtually all living organisms. In the middle of the 20th century it was discovered that in animals mitochondria are able to fully oxidise carbohydrate and fat to CO<sub>2</sub> and thereby generate far more ATP (adenosine triphosphate) with so-called oxidative phosphorylation than is possible by conversion of glucose to pyruvate (glycolysis) alone. In the complete absence of oxygen, cells or tissues that are capable of both glycolysis and oxidative phosphorylation can only use glycolysis. When glycolysis produces pyruvate that cannot be further metabolised by mitochondria, this pyruvate must be converted into lactate in order for glycolysis to continue. This lactate must then be transported out of the cell, and can then be converted back to pyruvate and metabolised by mitochondria elsewhere in the body.

Although all oxygen-consuming tissues possess the ability to consume lactate, the liver and kidneys also possess the ability to convert this lactate back into glucose (gluconeogenesis) and export this glucose into the circulation. The Cori cycle describes the conversion of glucose to lactate by muscles, the subsequent transport of lactate to the liver, regeneration of glucose by gluconeogenesis in the liver and then transport of glucose back to the muscle. This cycle is an important example of acute whole-body metabolic interaction between two organs. The Cori cycle allows muscles to perform longer during strenuous exercise, since the liver offloads the lactate-producing muscle. This cycle comes at a metabolic 'cost', however. When glycolysis generates two ATP from a glucose molecule in the muscle, the liver must spend six ATP to regenerate glucose from lactate. Thus at the whole-body level the Cori cycle entails a loss of four ATP for each recycled glucose. In contrast to the Cori cycle, the direct reuse of lactate by the mitochondria of other cells carries no energy penalty (Voet and Voet 2011).

A persistent misconception about lactate metabolism is that lactate production automatically implies "anaerobic glycolysis". However, in the majority of conditions lactate production occurs in the presence of sufficient oxygen and fully functioning mitochondria. This is both the case in physiology (e.g. during maximal exercise) and in pathophysiology (e.g. sepsis). A related popular misconception is that muscle ache is the result of accumulation of lactic acid. Thus lactate has long been considered a detrimental waste product, in particular since regeneration of glucose from it by the Cori cycle involves loss of ATP. But lactate is far from a waste product. Just like glucose, lactate is a fuel with an ATP yield on par with glucose upon complete oxidation. Given lactate's central metabolic role, the body can metabolise hundreds up to thousands of millimoles of lactate per day (Cole 2003). The use of the term 'clearance' in the case of lactate is not appropriate, since its concentration is the net result of the rapidly varying production and consumption by many tissues (see Figure 1).



**Figure 1.** three Metabolic states with Respect to Lactate Production and Consumption  
source: Adapted from Bakker 2013

In most (patho)physiological conditions, acute energy requirements are a key driver of local or systemic lactate levels, irrespective of local oxygen tension. The left panel depicts non-stressed steady-state conditions where glucose is converted to pyruvate, which is subsequently fully oxidised

to  $\text{Co}_2$ , generating approximately 36 ATP (adenosine tri-phosphate) per glucose molecule.

The mid panel depicts a stressed situation where tissue immediately requires more ATP. Glycolysis generates only 2 ATP but can very rapidly increase by a two or three orders of magnitude. Even with optimal mitochondrial oxygenation and function, this rate of pyruvate production will saturate the much more complex but much less flexible process of oxidative phosphorylation. Thus for glycolysis to continue, pyruvate must be converted to lactate.

The right panel depicts the post stress situation when lactate is converted back to pyruvate and fully oxidised. Since lactate can be transported both at micro and at macro scales, lactate shuttles exist that allow the simultaneous production and consumption of lactate by different cells or tissues.

## Hyperlactataemia and Stress

Although severe hypoxia or anoxia induce lactic acidosis, the relation cannot be used in reverse, because in the majority of cases in the ICU hyperlactataemia is not caused by hypoxia but by stress. The three main conditions regarding lactate production and consumption are depicted in Figure 1. During resting steady state conditions glycolysis and oxidative phosphorylation are balanced, with no production of lactate. During stress, when increased ATP production is required, glycolysis can increase manifold. In these conditions excessive lactate production is not an indicator of tissue hypoxia, but simply reflects the ability of glycolysis to vastly outrun mitochondrial oxidative phosphorylation (Gladden 2004). The poor relation of increased  $[\text{La}^-]$  with oxygen delivery parameters underscores that stress, not hypoxia, is the common driver of hyperlactataemia (Bakker 1991).

It is well known that adrenergic  $\beta_2$ -activation can directly induce production of lactate (Levy 2008) and glucose. In addition, a recent study showed that hyperlactataemia and hyperglycaemia are closely associated and related to mortality in a large patient cohort (Kaukonen 2014). The well-established univariate relation of hyperglycaemia with mortality disappeared when hyperlactataemia was included. The investigators concluded that stress is the common denominator of both hyperlactataemia and hyperglycaemia (Kaukonen 2014).

In animal studies, treatment of healthy dogs with prednisone dose dependently increased blood lactate levels (Boysen et al. 2009). Furthermore a prospective controlled trial in cardiac surgery patients (Ottens 2015) showed that the synthetic glucocorticoid dexamethasone both induces hyperglycaemia and hyperlactataemia, underscoring the deep connection between both the adrenergic and the corticoid stress response and subsequent elevations of both lactate and glucose.

## Timescales on which Changes in $[\text{La}^-]$ can Occur

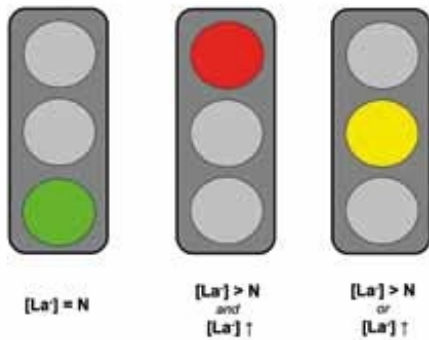
In many institutions  $[\text{La}^-]$  is measured on ED admission and upon ICU admission and thereafter daily or only on indication. In other institutions all glucose measurements performed for ICU glucose-control are combined with lactate and blood gas analysis, resulting in many  $[\text{La}^-]$  values per day.

Theoretically even a far higher frequency of measurement of circulating  $[\text{La}^-]$  might be informative. The known relevant biological variation of a specific signal in relation to the accuracy of measurement determines the minimal timescales of scientific or clinical interest. In the case of  $[\text{La}^-]$  an interval of one minute makes sense, since modern detectors achieve 0.1 mmol/L accuracy and  $[\text{La}^-]$  can decrease by  $>0.1$  mmol/L/min during recovery and increase by  $>1$  mmol/L/min during severe stress. The rate of recovery of hyperlactataemia differs per condition. A decrease of 20% per hour suggests successful sepsis treatment (Jansen 2010), but after cardiopulmonary resuscitation or generalised seizures faster recovery rates are the rule (Vincent et al. 1983).

## Monitoring of Lactate and its Clinical Utility as a Strong Marker of Outcome

It is now well-established that of all available laboratory measurements circulating lactate has the strongest univariate relation with outcome. It is quite unlikely that another routine laboratory measure will emerge that will outperform lactate in this respect. It should be noted that obviously no single laboratory value, including lactate, should serve as the sole value to interpret the condition of a patient. As transpires from its function during stress, a high  $[\text{La}^-]$  is not harmful by itself, but represents a compensatory response to a variety of severe underlying conditions (Kraut 2014). Thus

[La<sup>-</sup>] may be considered the ultimate example of a biochemical marker and not a mediator of poor outcome. The considerable clinical utility (Jansen 2009) of [La<sup>-</sup>] rests particularly on its specificity and less on its sensitivity, as illustrated by the traffic light cartoon (see Figure 2).



**Figure 2.** The Practical importance of Lactate Monitoring

A large amount of information must be integrated (sub) consciously by intensivists when assessing ICU patients. Some parameters serve as a generic alert that something is wrong, although it may not immediately be clear what is wrong. An abnormally high [La<sup>-</sup>] or  $\Delta$ [La<sup>-</sup>] serves as such a warning to critically assess the condition of the patient and consider alternative diagnoses and additional interventions. The red colour signifies the most alarming condition since [La<sup>-</sup>] is elevated and still rising. Obviously, a normal [La<sup>-</sup>] (green sign) makes severe conditions less likely, but can never exclude them.

A marker that highlights situations that entails increased risk can help physicians and nurses to focus their diagnostic and therapeutic resources on those who stand to benefit most. In our experience it is possible in most patients with marked hyperlactataemia to correctly identify the underlying cause. When the cause is not immediately evident, it may trigger appropriate additional investigations. The prospective randomised LACTATE trial was the first to demonstrate the benefit of [La<sup>-</sup>] guidance during early sepsis treatment (Jansen 2010).

### Future Perspectives - Decision Support

We anticipate several developments concerning lactate monitoring. Continuous lactate monitoring holds great promise as suggested by first clinical studies in cardiac surgery patients with a continuous intravascular microdialysis system that allows ex vivo detection of circulating lactate and glucose levels (Schierenbeck 2014). Measuring [La<sup>-</sup>] on timescales of minutes will likely uncover important hitherto undetected phenomena.

Continuous combined lactate and glucose monitoring may provide a powerful tool to monitor liver function, something currently not possible. When serial measurements show that [La<sup>-</sup>] rises whilst [Glu] is 'normal' or decreases, gluconeogenesis may be impaired, indicating partial (de Felice 2014) or complete liver failure (Oldenbeuving 2014). Likewise the time course of [La<sup>-</sup>] after an IV lactate bolus can be used to quantify the liver's metabolic ability in real time and repeatedly (Tapia et al. 2015).

Eventual incorporation of [La<sup>-</sup>] into scoring systems that predict mortality such as APACHE or SAPS seems inevitable, since [La<sup>-</sup>] univariately outperforms all known biochemical markers for predicting mortality. Inclusion of [La<sup>-</sup>] is long overdue, because these scoring systems already incorporate many less powerful but equally available predictors such as potassium, leukocyte count or glucose.

An important conceptual challenge is to translate the predictive power of [La<sup>-</sup>] and  $\Delta$ [La<sup>-</sup>]/ $\Delta$ t for specific conditions to sufficient pathophysiological understanding, so that an increased [La<sup>-</sup>] can be optimally interpreted in individual cases. Because many different acute conditions can lead to hyperlactataemia, we believe structured decision support to best interpret increased [La<sup>-</sup>] may be of use. Building on the principles set out in the LACTATE study (Jansen 2010), we are currently developing such a decision support system. Optimal interpretation of a rise in [La<sup>-</sup>] within a specific clinical context may also prevent incorrect reflexes of caregivers. Unfortunately, even in our ICUs we frequently discover that a fluid bolus is administered when [La<sup>-</sup>] rises, even if hyperlactataemia does

not result from hypovolaemia, but for example from anxiety (ter Avest 2011). Designing lactate computer support will be inherently more complex than computerised glucose or potassium control, since in glucose or potassium control measurement and therapeutic corrections can to a large extent be fully 'outsourced' to the computer and the ICU nurse (Vogelzang 2008; Hoekstra 2010). The first goal for computerised lactate support should be to improve understanding of [La-] dynamics and leave the specific diagnostic and therapeutic actions to the intensivists.

Lactate sensors employ technology very similar to glucose sensors. Thus many measurement techniques developed for glucose can be ported to lactate. Although [La-] is currently mostly determined in critically ill patients, this measurement may also be employed in patients on general wards or even in outpatients. A potentially very important example of the latter group may be type II diabetics who usually use metformin. Metformin is a key oral antidiabetic drug used by maybe 100 million patients worldwide. A small but important minority of these patients can develop metformin associated lactic acidosis (MALA). Hand-held combined lactate and glucose measurements would be very useful for timely detection of emerging MALA in this very large population of chronic patients.

## Conclusion

Lactate is a central intermediate metabolite that allows the flexible integration of the two ATP generating systems that animals possess. Increases in lactate may usually reflect metabolic stress rather than tissue hypoxia. Increased lactate levels have a stronger relation to mortality than observed for any other biochemical marker.

The scientific and clinical rationale for more frequent measurements of [La-] is supported by a growing body of evidence and facilitated by advanced analysers. The emerging technology of continuous lactate measurements also holds large scientific and clinical promise for critically ill patients. We will study the impact of continuous lactate monitoring on outcome in future trials.

## Key Messages

- Lactate is a central intermediate metabolite that is usually increased because of stress.
- Of all laboratory parameters, in the spectrum of critically ill patients, lactate has the strongest relation with outcome.
- The rate of change of circulating lactate is also of prognostic importance.
- Monitoring of lactate on short timescales is both scientifically and clinically useful.
- Future trials may establish whether continuous lactate monitoring improves outcome.

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