Increased blood lactate levels: a marker of...?

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Since Meakins in 1927 described the relationship between increased blood lactate levels and the presence of oxygen debt (tissue hypoxia) in patients with circulatory shock [1], lactate levels have been used to diagnose and monitor the treatment of these patients.

However, as lactate is a normal (end) product of metabolism the relationship between increased lactate levels in patients and shock could be much more complicated. In the current paper we discuss the metabolism of lactate and its clinical implications.

1. Lactate metabolism

Lactate is a normal end product of glycolysis (**Fig. 1**). It can only be formed from pyruvate mediated by lactate dehydrogenase [1].

$$\text{Pyruvate} + \text{NADH} + \text{H}^+ \xleftrightarrow{\text{Lactate dehydrogenase}} \text{Lactate} + \text{NAD}$$

Equation 1

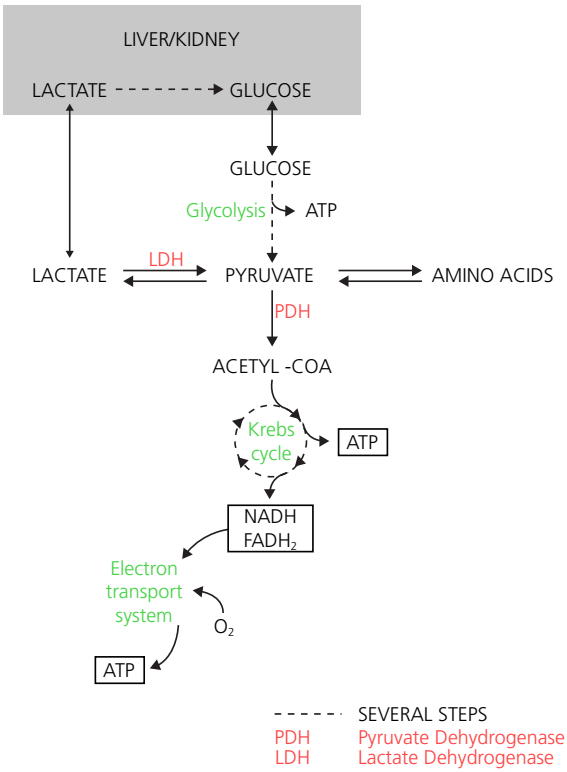

FIG. 1

Under normal conditions this reaction results in a lactate-to-pyruvate ratio of 10:1. All cells are capable of producing lactate. Tissues with a high metabolic rate (gut, brain, skeletal muscle) contribute largely to the daily lactate production.

Normal blood lactate levels are 1.3 mmol/L [2]. Lactate metabolism mainly occurs in the liver and kidney. Lactate can only be metabolized by the conversion to pyruvate. Therefore, blood lactate levels depend on pyruvate metabolism.

The irreversible conversion of pyruvate to Acetyl-CoA (mediated by pyruvate dehydrogenase) that is subsequently metabolized in the Krebs cycle results in the production of adenosine triphosphate (ATP), carbon dioxide and water.

ATP can be seen as a universal energy source that is required in many vital cellular functions. Pyruvate can also be used to regenerate glucose by the conversion to oxaloacetate.

In this way lactate can be converted back to glucose that can subsequently be converted to lactate (Cori cycle). Regeneration of glucose from lactate is an important mechanism in restoring glucose levels and removal of lactate from the systemic circulation following prolonged tissue hypoxia (e.g. diving mammals, cardiac arrest) [3]. Last, pyruvate can be converted to alanine and α-ketoglutarate.

The reverse of this reaction regenerates pyruvate that can thus be used for oxidation or gluconeogenesis. From equation 1 we can conclude that even in the presence of a stable redox state (NAD-to-NADH ratio) and cellular pH, lactate levels will rise whenever the formation of pyruvate exceeds its utilization or the conversion of pyruvate to Acetyl-CoA is limited.

Utilization of pyruvate may decrease when pyruvate dehydrogenase is deficient (inborn error of metabolism).

Dysfunction of the pyruvate dehydrogenase complex may occur during sepsis, resulting in increased pyruvate levels and hence blood lactate levels [4]. The clinically most relevant cause of limited pyruvate utilization is a cellular lack of oxygen.

Both oxidation of pyruvate and gluconeogenesis require the presence of oxygen. Consequently when oxygen levels fall, glucose is mainly converted to lactate.

Although this reaction also produces ATP, it is less effective (two molecules of ATP versus 34 molecules of ATP when metabolized in the Krebs cycle).

Three pathways are involved in the transport of lactate across the cell membrane [5]. First, free diffusion of lactic acid plays a role in lactate efflux and uptake by the cells, especially at higher concentrations.

Second, exchange for another anion such as Cl^- or HCO_3^- facilitates lactate transport across the cell membrane.

The third and most important pathway involves an H^+-linked carrier mechanism (monocarboxylate transporter). This H^+-linked transporter increases lactate flux in the presence of a pH gradient across the membrane.

By this mechanism lactate uptake by the cell (e.g. skeletal muscle and cardiac myocytes) is increased during acidosis. In contrast, lactate efflux will increase during alkalemia, resulting in an increase in lactate levels during systemic alkalemia [6].

The increase in lactate levels during alkalemia could also be related to the stimulation of phosphofructokinase in these conditions, resulting in increased glycolysis and thus increased lactate production.

Although increased blood lactate levels are frequently associated with the presence of a metabolic acidosis (lactic acidosis) the production of lactate does not result in net hydrogen ion (H^+) production as the H^+ ions are reutilized in the production of ATP from adenosine diphosphate (ADP) and adenosine monophosphate (AMP).

$$ATP \rightarrow ADP + Pi + H^+ \rightarrow AMP + 2Pi + 2H^+$$

Equation 2

The inability of the cells to reutilize H^+-ions generated by the hydrolysis of ATP during hypoxia is mainly responsible for the metabolic acidosis in these conditions [7].

2. Relationship between lactate and tissue hypoxia

Clinically, blood lactate levels are frequently used to monitor tissue hypoxia. The rationale for this, as outlined above, is clear: The utilization of pyruvate depends on the presence of oxygen so that decreases in cellular oxygen delivery should result in increased lactate production and thus blood lactate levels (**Fig. 2A**).

Tissue hypoxia is best defined as the presence of an imbalance between the demand for oxygen and the actual delivery of oxygen (DO_2). As DO_2 decreases, tissues maintain their oxygen utilization to meet their oxygen demand by extracting more oxygen.

An increase in the calculated oxygen extraction ratio (O_2ER) and a decrease in the mixed venous oxygen saturation usually reflect this. Global DO_2 is a function of the arterial oxygen content (ctO_2) and the cardiac output (Q_t) (**Equation 3**).

$DO_2 = ctO_2 \times Q_t = (ctHb \times sO_2(a) \times (1 - FCOHb - FMetHb) + \alpha \times pO_2) \times Q_t$

$ctHb$ = hemoglobin level
$sO_2(a)$ = arterial oxygen saturation

Equation 2

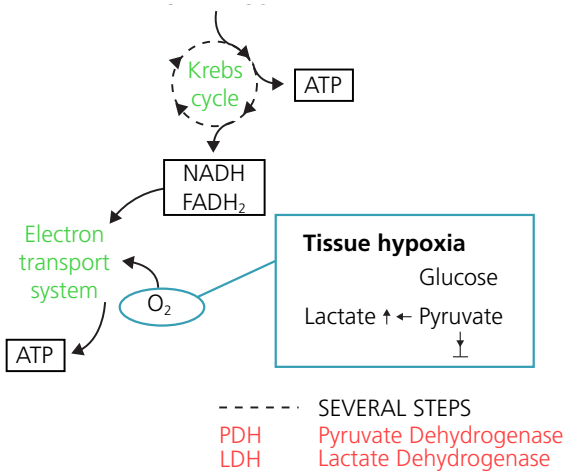

FIG. 2A

Although a decrease in each of the components can cause a decrease in DO_2, decreases in hemoglobin levels and arterial oxygen saturation are usually accompanied by compensatory increases in cardiac output so that DO_2 can be maintained to meet oxygen demand [8] and thus generally do not result in tissue hypoxia [9].

When this compensatory mechanism fails, DO_2 will decrease more rapidly in these conditions [10].

When DO_2 falls below a critical level, oxygen demand can no longer be met and oxygen consumption starts to fall coincided with an increase in blood lactate levels (**Fig. 1**).

This phenomenon (supply dependency) has been demonstrated during experimental decreases in hemoglobin levels, arterial oxygen saturation and cardiac output [11-13]. For obvious reasons, effects of lowering DO_2 to critical levels in humans are not well studied.

In patients and healthy volunteers, acute decreases in hemoglobin levels are met by compensatory increases in cardiac output to maintain tissue oxygen delivery [8]. In two studies, Shibutani, Komatsu and co-workers showed that in cardiac surgery patients supply dependency occurred when DO_2 was below a critical level of 300 mL/min [14, 15].

In patients with increased blood lactate levels, oxygen consumption fell immediately when DO_2 was lowered [14].

Ronco *et al* [16] also showed that lowering DO_2 below a critical level resulted in a decrease in oxygen consumption and a rise in blood lactate levels.

In critically ill patients, Vincent *et al* [17] showed that oxygen consumption increased only in patients with increased blood lactate levels when DO_2 was increased by the infusion of dobutamine. Interpretation of increased blood lactate levels in patients with sepsis can be difficult [7].

However, in the early phase of septic shock, increased blood lactate levels have also been associated with the presence of supply dependency and thus tissue hypoxia [18]. Should we therefore conclude that in clinical practice, increased blood lactate levels should be regarded as an indicator of the presence of tissue hypoxia [19]?

3. Other causes of increased lactate levels

In the absence of cellular hypoxia, dysfunction of the PDH enzyme complex also results in an increase in pyruvate levels (**Fig. 2B**). Increased aerobic glycolysis increases intracellular pyruvate levels when there is no need for increased ATP production (i.e. when oxygen demand is not increased).

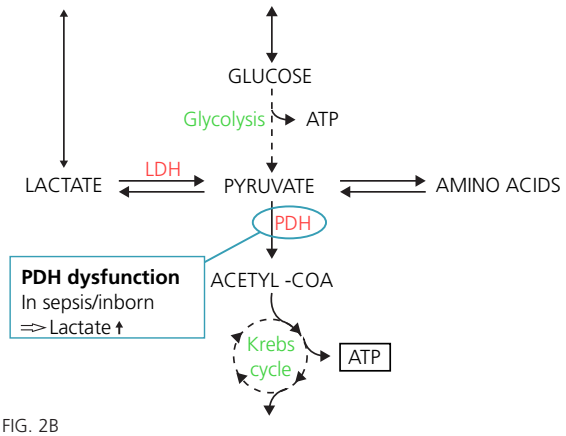

FIG. 2B

Increased activity of the Na^+-K^+-ATPase in the presence of cellular normoxia has been related to this pathway of aerobic lactate production [20]. Protein breakdown results in an increased amino acid disposal that may increase pyruvate levels in the process of gluconeogenesis (**Fig. 2C**).

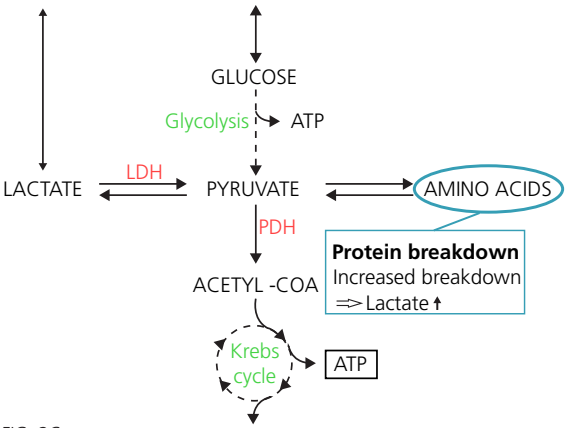

FIG. 2C

Increased lactate production in the absence of cellular hypoxia has been documented in clinically relevant experimental settings (sepsis, chatecholamine treatment) and in patients [21, 22]. Dysfunction of the PDH enzyme has been documented in experimental and clinical sepsis and could also be related to the decreased lactate clearance in septic patients.

In addition, decreased blood flow (decreased delivery of lactate) to liver and kidney could influence lactate clearance. Finally, persistent cellular hypoxia in the presence of a hemodynamically stable condition could be related to decreased clearance (**Fig. 2D**).

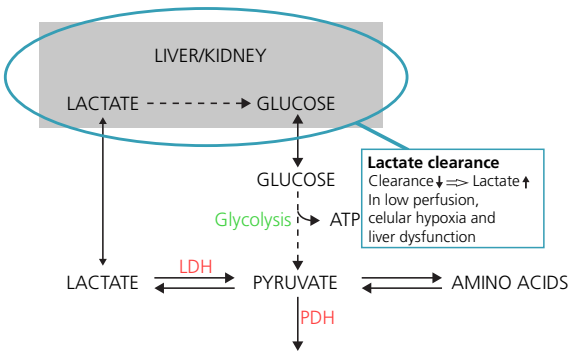

FIG. 2D

Plasma levels of lactate not only result from the production of the molecule but also from its clearance. Lactate clearance occurs predominantly in the liver and kidney, whereas during hyperlactatemia muscles also metabolize lactate.

Decreased lactate clearance rather than increased production could be an important cause of increased blood lactate levels in septic patients following hemodynamic stabilization [23]. However, also in patients following cardiac surgery and in patients with liver dysfunction, clearance of blood lactate is deranged [24, 25].

4. Lactate and acidosis

The relationship between lactate and hydrogen ion concentration is far from straightforward. Recent reviews have stressed that, especially in sepsis, the production of lactate and H^+-ions can be unrelated [7]. In addition, physical chemistry has stressed the importance of the strong-ion difference as an important cause of changes in H^+-ion concentration and free water as the major source of these H^+-ions [26].

Although the relationship between lactate levels and indices of metabolic acidosis are reasonable in low-flow states, the production of unmeasured ions, the presence of renal dysfunction and the arterial pCO_2 (simply influenced by manipulating the mechanical ventilator) are probably related to the weak-to-absent correlation between arterial pH, base excess or base deficit and lactate levels in the general intensive care population and patients with sepsis in particular [27, 28].

Groeneveld *et al* [29] already showed that despite similar lactate levels, patients with septic shock had a lower arterial pH than patients with non-septic shock. In this study the severity of sepsis, as related to ultimate survival, also influenced the relationship between lactate level and arterial pH.

5. Lactate levels in clinical practice

From the above we can conclude that increased blood lactate levels with or without concomitant acidosis reflect a complex metabolic disturbance in which increased aerobic and anaerobic production and decreased clearance are important elements.

Furthermore, the importance of these elements differs in different disease states. It is therefore no surprise that the reflection of such a complex metabolic disturbance is not met by clinical signs of critical illness, including the classical signs of shock [30].

Also, other laboratory abnormalities, usually coinciding critical illness, do not reflect blood lactate levels or changes in blood lactate levels [28, 31]. In addition, a given level of oxygen delivery or oxygen consumption also cannot predict the presence of oxygen supply dependency or increased blood lactate levels [32]. This underlines the importance of measuring lactate levels rather than estimating them from other (biochemical) variables.

5.1 Measurement techniques and sampling site

When first described (Gaglio 1886), the measurement of lactate levels required the collection of 100-200 mL blood and took several days to complete. In 1964, Broder and Weil [33] were the first to use a photospectrometric method to measure lactate levels in whole blood, decreasing turnaround time substantially.

With this they set a trend in the monitoring of blood lactate levels in critically ill patients. The labor-intensive aspect of the early measurement technique limited the widespread use, as results were usually available long (hours) after therapeutic decisions had to be made.

The availability of a substrate-specific electrode now enables the clinician to measure lactate concentrations rapidly (within two minutes) in a minimal amount (130 µL) of plasma or whole blood, using a blood gas analyzer. Using a device like this can simultaneously provide information on hemoglobin levels, oxygen saturation and blood lactate levels.

Recently a handheld device using a reflective photometry method has been introduced and validated in emergency department patients [34] and ICU patients [35].

With this handheld device blood lactate measurements can be made using one drop of whole blood, and results are available within 60 seconds. This relatively cheap and easy-to-perform method can be used for rapid lactate measurements in emergency situations [36].

In the intensive care unit, blood drawn from an arterial line is usually used to measure blood lactate levels. However, (mixed) venous blood can also be used to measure blood lactate levels in critically ill patients [37, 38].

When capillary or peripheral venous blood is used, damming of blood and muscle activity should be avoided [39].

Collected blood samples should be stored on ice and measurements of blood lactate levels should be performed rapidly when metabolism of red and white blood cells is not stopped by the addition of e.g. fluoride to the sample [40].

5.2 Increased lactate in relation to clinically relevant endpoints

Lactate monitoring needs to be incorporated into an interventional and therapeutic plan in order for the patient to benefit from these measurements. Could such an easily obtainable parameter of complex abnormalities then be used to assign patients to an interventional plan?

More specifically, could lactate levels be used to identify patients that would benefit from intensive care admission?

For this, lactate levels should be related to risk of morbidity and mortality from a disease state that is best managed in an intensive care unit.

For more than 25 years, blood lactate levels have discriminated patients with less morbidity from patients with more morbidity and survivors from non-survivors in many forms of surgical interventions, trauma and critical illness [33, 41-45]. Also, most patients with increased lactate levels have a high risk of compromised vital organ functions [2].

In addition, limited clearance of lactate in patients without circulatory failure is still related to increased mortality in patients with sepsis [46]. Although the relationship between lactate and acidosis is complex, the combination of increased lactate levels and acidosis bears a high mortality [44].

Some studies showed that in specific patient groups, lactate levels were better predictors of survival and development of organ failure than complex scoring systems like APACHE II [47].

In a recent study, Smith *et al* [48] showed that blood lactate levels could discriminate patients with high risk of morbidity and mortality from patients with relative low risk.

The portability of the lactate measuring devices, the ease and speed of the measurements could thus be important factors in the clinical utility of lactate levels as indicators for intensive care admission.

5.3. Treatment of increased lactate levels

Correction of hyperlactatemia by increasing the metabolism of pyruvate and hence lactate has no significant effect on mortality in critically ill patients. Dichloroacetate enhances the activity of the pyruvate dehydrogenase complex, thus decreasing blood lactate levels.

Both experimental and clinical studies have shown that administration of dichloroacetate decreases blood lactate levels during sepsis and septic shock [49, 50, 50].

However, in a recent controlled clinical trial (252 patients), administration of dichloroacetate in critically ill patients with hyperlactatemia and metabolic acidosis had no significant effect on hemodynamics and survival [51].

Also correction of the metabolic acidosis accompanying hyperlactatemia has not been shown to improve hemodynamics, tissue hypoxia and survival in critically ill patients [52, 53].

The mainstay of therapy in patients with increased blood lactate levels is improvement of tissue oxygen delivery. This is usually accomplished by increases in DO_2. Fluid resuscitation, hemoglobin substitution and maintenance of arterial oxygen saturation are frequently used to improve tissue oxygen delivery.

However, fluid resuscitation and inotropes to increase cardiac output have consistently been found to improve tissue oxygen delivery in patients with tissue hypoxia

and thus remain the mainstay of therapy in these circumstances [54-58].

Few studies have prospectively studied the effect of using lactate levels to guide therapy. Blow *et al* [59] vigorously resuscitated trauma patients with persistent hyperlactatemia to normalize blood lactate levels.

Patients who failed to normalize lactate levels within 24 hours had a poor outcome whereas with patients in whom blood lactate levels returned to normal within 24 hours outcome was improved when compared with a historic control group.

Similar findings have been reported by others. In a prospective randomized study of goal-oriented hemodynamic therapy in cardiac surgery patients aimed at maintaining normal blood lactate levels, Pölönen *et al* [60] showed that patients in the protocol group had lower hospital stay and mortality than patients in the control group.

5.4. Clinical application of lactate measurements

A measurement of blood lactate should be part of the evaluation of every critically ill patient unless the diagnosis is obvious and immediate intervention (surgery) is necessary (like in ruptured aneurysm). Especially in the early stages of critical illness, increased blood lactate levels indicate tissue hypoxia and insufficient compensatory mechanisms.

A sad but illustrative case will clarify this. A young trauma victim was admitted to our emergency department with fractures of his upper and lower legs. He was conscious, adequate and oriented in time, place and persons.

He was hemodynamically stable with a blood pressure of 130/80 and a heart rate of 115 b/min. Blood was drawn for routine evaluation including a blood lactate level. An echo of the abdomen was immediately performed and showed no abnormalities.

Within 15 minutes of arrival the patient developed a circulatory collapse and subsequent arrest.

CPR was ineffective and the patient died in the ER. Minutes after he died the laboratory results showed a blood lactate level on arrival of 15 mmol/L. Despite his adequate conscious and stable hemodynamics this patient was running out of compensatory mechanism and from this lactate level it was clear that something dramatic was about to happen.

In addition to the initial measurement of blood lactate levels, subsequent measurements inform the treating physician on the adequacy of the resuscitation [61]. Persisting increased blood lactate levels or a failure to decrease lactate levels should be followed by increasing oxygen delivery.

This could be accomplished by increasing cardiac output [62, 63] or microcirculatory blood flow with vasodilating agents like prostacyclin [64] or nitroglycerin [65].

In postoperative care we measure lactate levels routinely and increase oxygen delivery whenever lactate levels rise above 2.0 mmol/L, or when levels are increased upon admission to the intensive care [60].

6. Conclusion

Increased blood lactate levels serve well as a marker of a complex metabolic derangement related to increased production, decreased clearance or a combination of both. Clinicians should understand these complex processes, appreciate the usefulness and the limitations of monitoring blood lactate levels.

Measurements of blood lactate levels should never replace a complete clinical evaluation. Rather, adding lactate measurements to clinical judgment and easily obtainable clinical variables enhances its predictive power [66, 67].

The presence of increased blood lactate levels, especially in combination with acidosis, should urge the clinician to restore a probable imbalance between oxygen demand and oxygen delivery to the tissues, as this is the most frequent cause of increased blood lactate levels.

Increased lactate levels have been consistently associated with morbidity and mortality in a wide range of disease states for many years.

Therefore the presence of increased blood lactate levels should prompt the clinician to initiate both diagnostic and immediate therapeutic actions and intensive care admission should be considered.

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