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PHYSIOLOGICAL NOTE

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Lactic acidosis

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Introduction

Hyperlactatemia is considered a hallmark of ongoing tissue hypoxia, but this is not always the case, and erroneous conclusions may sometimes be drawn that lead to unjustified therapeutic interventions. In this note we discuss the possible implications of hyperlactatemia

Lactate metabolism

Lactate is a byproduct of glycolysis. In the energy-producing metabolism of glucose two distinct processes occur. The first series of enzymatic reactions (Enden-Mierhoff pathway), occurring in the cytoplasm of cells, anaerobically transforms 1 molecule of glucose into 2 molecules of pyruvate, generating 2 molecules of ATP. This is the primary energy process for all cells functioning in a low oxygen environment, such as in poorly perfused tissues. Pyruvate may either be converted to lactate, producing one additional molecule of ATP, or move into the second series of reactions. The second series of enzymatic reactions (Krebs cycle) takes place in the mitochondria and requires oxygen: pyruvate is oxidized into CO_2 and H_2O producing 18 ATP molecules. In the absence of oxygen, pyruvate cannot enter the Krebs cycle and is preferentially transformed into lactate to maintain ATP production. This causes the lactate to pyruvate ratio to increase (normal ratio 10/1). Once molecular oxygen is again available, assuming that mitochondrial function is preserved, the excess lactate is rapidly metabolized back through pyruvate into CO_2 and H_2O via the Krebs cycle. Some cells, such as red blood cells, do not have mitochondria and thus are primary lactate producers. Since lactate is rapidly metabolized by liver and skeletal muscle, these functional anaerobic cells result in minimal blood lactate levels.

Lactate in the blood is metabolized mainly by the liver (50%) and kidneys (20%). Liver function and liver blood flow influence hepatic lactate clearance, but extreme conditions of pH can also decrease lactate clearance. Renal lactate clearance occurs in the cortex, and this area is very sensitive to a reduction in blood flow. Striated muscle, the heart, and the brain also metabolize lactate and in some conditions this clearance can be significant. In basal metabolic conditions arterial lactate levels are between 0.5 and 1 mEq/l, and this value represents the balance between lactate production and consumption. Traditionally, elevated blood lactate levels in hemodynamically unstable subjects are often taken to reflect circulatory shock, arterial hypoxemia or both. However, other factors may coexist, complicating the interpretation of hyperlactatemia.

Lactate vs. pH measurements in assessing anaerobic metabolism?

Monitoring the blood pH, base deficit, or anion gap may fail to detect hyperlactatemia. Hyperventilation corrects arterial pH. Measurements of base excess and anion gap reflect lactate levels in pure lactic acidosis, buts may be influenced by other factors in complex situations. Concomitant renal failure, preexisting acid base disorders, and decreased albumin levels alter the specificity and sensitivity of base excess. Hence measurements of

blood lactate levels are mandatory to detect hyperlactatemia.

Lactate measurements

Measurement has long involved sampling blood on iced fluoride tubes to inhibit in vitro red blood cells lactate production. Lactate is then measured on plasma using enzymatic colorimetry with lactate dehydrogenase. More recent analyzers use enzymatic amperometry with lactate oxidase generating H_2O_2, which is detected by the electrode. The time response with these two methods is approximately 1 h. Alternatively, blood lactate levels can be measured by a blood gas analyzer using the same enzymatic amperometry technique. The time response is only 2 min. To be valid, blood gas analyzer measurements must be made with a short delay between sampling and analysis (less than 5 min, with the syringe stored on ice). Blood lactate concentrations overestimate plasma concentrations by 1 or 2 decimals. Measurement of plasma lactate with enzymatic amperometry is the reference method, which should be used when accurate measurements are required (especially for estimating arteriovenous lactate differences). Pyruvate measurements may be useful to identify anaerobic lactate production, but these are cumbersome, time consuming, and subject to many errors.

Anaerobic lactate production

In experimental conditions blood lactate concentrations rise when O_2 consumption becomes dependent on O_2 delivery (VO_2/DO_2 dependency), reflecting anaerobic metabolism. In critically ill patients in low flow states hyperlactatemia is mostly of hypoxic origin, although some impairment in liver metabolism may coexist. Tissue wash out may also be present following acute resuscitation.

In septic conditions hyperlactatemia can also be observed, but its hypoxic origin is less clear. In patients with acute circulatory failure treated with high doses of vasoactive agents there is a strong suspicion that hyperlactatemia is related to tissue hypoxia [1]. However, tissue hypoxia and anaerobic metabolism cannot be sustained for long periods of time without inducing cell death, as the energy produced by anaerobic metabolism is quite low compared to aerobic metabolism. Mild hyperlactatemia (2–4 mEq/l) in hemodynamically stable septic patients is probably not related to tissue hypoxia.

Aerobic lactate production

Experimental studies in rodents have reported that pyruvate dehydrogenase, an enzyme essential for the incorporation of pyruvate into the Krebs cycle, is inhibited after endotoxin administration or cecal ligation. However, the impact of pyruvate dehydrogenase inhibition in septic patients remains to be determined as the administration of dichloroacetate, bypassing pyruvate dehydrogenase, results in small and clinically insignificant changes in blood lactate levels and arterial pH [2].

More importantly, sepsis-induced inflammatory mediators accelerate aerobic glycolysis, increasing pyruvate availability. In hemodynamically stable septic patients Gore et al. [3] reported that lactate and pyruvate were both markedly increased and related to an accelerated glucose turnover, as glucose production was fourfold higher in septic patients than in healthy volunteers.

Regional lactate production

Animal studies have reported that the lungs are major lactate producers in sepsis [4]. In patients with acute lung injury, several groups have reported that lung lactate production is markedly increased and proportional to the severity of lung injury. The amount of lactate produced by the lungs in acute lung injury is tremendous and can higher than basal endogenous lactate production by the entire body. De Backer et al. [5] demonstrated that lung lactate production occurs in subjects with acute lung injury states but not in patients with normal lungs, cardiogenic pulmonary edema, or pneumonia. Thus lung lactate production requires a diffuse inflammatory process.

Other organs can also produce lactate. Experimental studies suggest that the gut can produce lactate in sepsis, which is likely from anaerobic metabolism as portal lactate to pyruvate ratio is increased. The investigation of splanchnic lactate turnover in humans is much more complicated as access to the portal vein is not possible outside the operating room. Since the liver is usually able to clear this small amount of gut-produced lactate, splanchnic ischemia may go unsuspected. Accordingly, De Backer et al. [6] reported that splanchnic lactate release is uncommon in patients with severe sepsis and was not related to arterial lactate concentrations, abdominal infection or signs of gut or liver dysoxia.

Finally, white blood cells may also take an active part in the increased tissue lactate production. Under basal conditions, only 10% of ATP production is of mitochondrial origin; hence anaerobic glycolysis provides most of the additional energy requirements when white blood cells are activated, producing large amounts of lactate. Although generated by anaerobic metabolism, this increase in lactate production is not due to O_2 deprivation. After exposure to endotoxin in vitro, whole blood lactate production almost doubles, and this is due exclusively to an increase in white blood cell lactate production [7], as red blood cell lactate production is not modified. Hence

large amounts of lactate can be produced in inflammatory processes even in the absence of tissue hypoxia. Presumably this is the cause of the positive lactate flux from the lung in acute lung injury.

Decreased lactate clearance

Blood lactate concentrations are the result of the balance between lactate production and clearance. In normal conditions at rest the liver accounts for more than one-half of lactate clearance, with kidneys and muscles accounting for the remaining part. The respective contribution of these organs can be influenced by several factors including exercise, liver dysfunction and glucose and O_2 availability.

Liver dysfunction is frequent in critically ill patients and can affect blood lactate concentrations. Using an external lactate load in hemodynamically stable septic patients, Levraut et al. [8] reported that lactate clearance was altered in patients with mildly elevated blood lactate levels (2–4 mEq/l) but not in patients with normal blood lactate concentrations. However, blood lactate concentrations are within normal values in patients with very severely impaired liver function such as in ambulatory cirrhotic patients. Hence, an increased blood lactate concentration suggests that lactate is actively, or has been recently, produced in increased amounts; the impairment in liver function being responsible for a delayed clearance.

Interpretation of blood lactate concentrations

Increased blood lactate can only be caused by increased anaerobic or aerobic lactate production, eventually combined with decreased lactate clearance (Fig. 1). Hence tissue hypoxia should always be excluded first, as persistent tissue hypoxia can lead to multiple organ failure and death. Tissue hypoxia can be global, especially in low flow states and hypoxemia, but it can also be localized, especially within the gut microcirculation. Sometimes impaired mitochondrial performance can induce hyperlactemia. In particular, antiretroviral therapies can induce uncoupling of cytochrome energy transfer, leading to severe and often lethal lactic acidosis. Aerobic lactate production, either global or focal (especially in the lungs), is the result of activation of the inflammation cascade. Hence hyperlactatemia may be a warning indicator of a very severe inflammatory state. One should examine any patient with unexplained lactic acidosis in order to ensure that no focus of infection remains uncovered. When an altered lactate clearance is involved, it can be due to an altered liver metabolism, usually insensitive to hemodynamic manipulations, but also to a decreased perfusion of the liver, which can be improved by hemodynamic interventions.

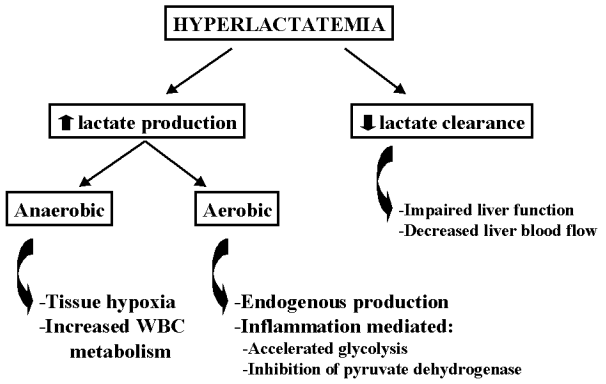

Fig. 1 Interpretation of hyperlactatemia. Blood lactate concentrations reflect the balance between lactate production, either anaerobic (mainly in tissue hypoxia) or aerobic, and lactate clearance (i.e., the sum of the endogenous oxidative-phosphorylation lactate production and the additional lactate production under the influence of overwhelming inflammation, and lactate clearance, mainly by the liver). *WBC* White blood cells

Prognostic value

Whatever its source, lactic acidosis is associated with impaired survival. Admission blood lactate levels are strongly associated with outcome [9]. Interestingly, the prognostic value is better for lactate than for pyruvate or the lactate to pyruvate ratio, suggesting that the prognostic value is not related to tissue hypoxia alone. The course of blood lactate concentrations give the best prognostic value. A decrease in blood lactate levels during the first 24 h is associated with a better outcome while persistent hyperlactatemia and increasing lactate levels are associated with a worse outcome.

Early recognition of hyperlactatemia is essential, as early interventions targeted on hemodynamic endpoints can decrease mortality in patients with severe sepsis and elevated blood lactate levels [10]. However, it has not been confirmed that interventions targeted specifically to normalize blood lactate concentrations can improve outcome.

Conclusions

Measurements of blood lactate concentrations are useful to detect occult tissue hypoxia and to monitor the effects of therapy. However, hyperlactatemia can be due to other causes than tissue hypoxia, in particular inflammatory processes, and therefore hemodynamic interventions in subjects with elevated blood lactate levels may not always be warranted.

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