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WHAT'S NEW IN INTENSIVE CARE

The ten pitfalls of lactate clearance in sepsis

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The problem with clearance

Clearance is the removal of a substance from blood, expressed as a volume (milliliters) over time (minutes). However, changes in lactate levels are the sum of ongoing production and removal from the blood by excretion (e.g., urine, sweat) and its metabolism (e.g., uptake by cells as a direct source of energy, conversion to glucose by the liver). To talk about "lactate clearance" [1] when actually describing a decrease in blood level is wrong and misleading. Following the review of 96 studies, Vincent et al. [1] concluded that given recent evidence, measurements every 1–2 h would give clinically relevant data about the decrease in lactate levels.

Lactate levels: production versus clearance

In clinical practice the change in lactate levels over time is thought to primarily reflect a change in production. As increased levels are generally associated with circulatory dysfunction, we often see a decrease in lactate levels as associated with an improvement in circulatory status and hypothesize (but cannot prove) decreased production. However, as true clearance in both stable septic patients and septic shock animals is significantly decreased in shock states, ongoing hyperlactatemia or even a rise in lactate levels may reflect decreased clearance rather than an increase in production of lactate [2, 3]. This is typically seen in the presence of shock with associated ischemic hepatitis. In addition, the complex inter- and intracellular metabolism of lactate makes our understanding of lactate physiology in shock extremely limited (see Sect. "Lactate as a substrate").

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Lactate and glucose metabolism

As lactate is a normal product of glucose and pyruvate metabolism, any increase in glucose metabolism or decrease in pyruvate metabolism will increase lactate generation and, in some cases, levels, even in the presence of adequate tissue oxygenation (as seen with epinephrine infusion). In sepsis, the inflammatory response appears associated with an increase in glycolysis and impaired pyruvate dehydrogenase (the enzyme critical for pyruvate entry into the Krebs cycle). Thus, cytoplasmic pyruvate increases with greater lactate formation but preserved pyruvate to lactate ratio, and lactate levels rise. In this way, the relationship of increased lactate production with tissue hypoxia as its possible source is confounded by the stress response that increases glucose metabolism and lactate generation [4]. In addition, although lactate levels can be significantly decreased by improving its metabolism by the administration of dichloroacetate, this will not result in improved survival as it does not address the root cause [5]. The same might apply to the correction of acidosis in the presence of increased lactate levels as the relationship between pH, anaerobic glycolysis, and lactate levels is not fully understood and is likely to be complex [6, 7].

Lactate as a substrate

Just like glucose, lactate may also serve as a substrate for metabolism. Especially in stress (such as sepsis), lactate, through several "shuttles", provides a source of cellular energy. The first is the organ-to-organ lactate shuttle. Lactate released by muscle is taken up by the liver to enter the Cori cycle to generate glucose, which then through glycolysis may generate lactate depending on liver bioenergetics. In addition, lactate may be metabolized by the kidneys, accounting for up to 50% of total lactate metabolism. The second is the cell-to-cell lactate shuttle. This shuttle appears particularly important in

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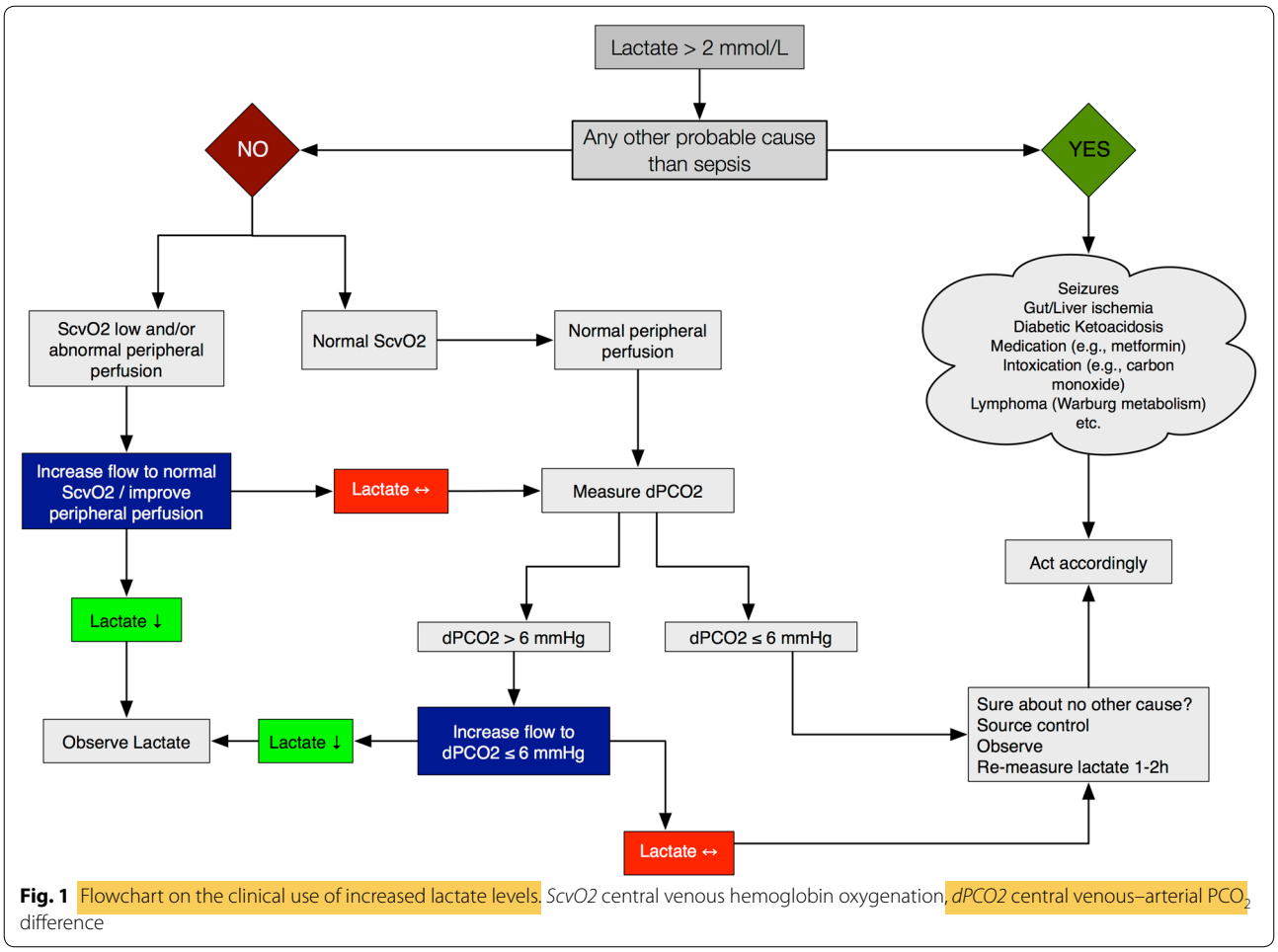

Fig. 1 Flowchart on the clinical use of increased lactate levels. *ScvO2* central venous hemoglobin oxygenation, *dPCO2* central venous–arterial PCO_2 difference

the brain, where lactate can become a more important energy substrate than glucose [8]. Lactate is transported from astrocytes into neurons by dedicated transporters and then transformed into pyruvate by lactate dehydrogenase type 1. Pyruvate then enters the Krebs cycle to produce ATP. The third is the intracellular shuttle where lactate, generated by glycolysis in the cytoplasm, is used through mitochondrial membrane shuttles to increase the concentration of reduced NAD (NADH), which provides a proton gradient to generate energy by the electron transport chain.

Lactate and liver dysfunction

The liver, which is responsible for 60% of systemic lactate metabolism, is a vulnerable organ during sepsis-related acute circulatory dysfunction. The contribution of the liver to persistent hyperlactatemia might be much higher than previously thought, and the mechanisms are probably multifactorial. Without doubt, hepatosplanchnic ischemia could contribute in some cases especially in, but not limited to, severe septic shock [9]. On the other hand, early and severe impairment of exogenous lactate clearance not related to liver hypoperfusion has been shown in experimental conditions [3].

Lactate concentration in resuscitation fluids

Intravenous administration of lactated Ringer's solution does not seem to increase circulating lactate concentrations in hemodynamically stable adults, nor worsen metabolic acidosis during an infusion of 1 L in 60 min [10]. Only when infusing large volumes (180 mL/kg/h) do lactate levels rise significantly [11]. On the contrary, the buffering effect of Ringer's solution, with a more physiologic strong anion difference, might have a positive effect on blood pH.

Lactate and its confounders

As every increase in glucose metabolism may increase lactate levels, many elements confound the clinical use of lactate. Best known in clinical practice is the use

of catecholamines in septic shock patients, alkalosis-induced increases in glucose metabolism, lactate buffered continuous hemofiltration, liver dysfunction, and lung lactate production. Also, the use of specific drugs has been associated with increased lactate levels (nucleoside reverse transcriptase inhibitors for treatment of HIV, metformin) as are some intoxications (ethylene glycol, methanol, and steroids) [4, 12].

Lactate with or without hypoperfusion vs tissue hypoxia

Persistent hyperlactatemia is particularly difficult to interpret. At least four possible pathogenic mechanisms might be involved: anaerobic glycolysis in hypoperfused territories, especially in the presence of severe microcirculatory abnormalities [13]; stress-related adrenergic-induced aerobic glycolysis; impaired hepatic lactate clearance; and mitochondrial dysfunction limiting pyruvate metabolism [14, 15]. Recognizing a clinical pattern of hypoperfusion-related hyperlactatemia is important since optimizing systemic blood flow in this setting could revert ongoing hypoperfusion and improve prognosis. In contrast, pursuing additional resuscitation in non-hypoperfusion-related cases might lead to the toxicity of over-resuscitation. We recently proposed that a simultaneous analysis of three flow-sensitive parameters such as central venous O_2 saturation, central venous–arterial pCO_2 gradient (Pcv-aCO_2), and peripheral perfusion (capillary refill time, peripheral perfusion index, skin temperature, mottling) might be helpful in suggesting the presence of hypoperfusion in the context of hyperlactatemia [15, 16]. In addition to the Pcv-aCO_2 one could use the Pcv-aCO_2 to arterial–venous O_2 content difference as a marker of tissue hypoperfusion as a cause of hyperlactatemia [17]. Persistent hyperlactatemia without a hypoperfusion context is associated with a better prognosis and might suggest non-hypoperfusion-related sources [15] (Fig. 1).

Lactate as a marker of severity

The evidence that lactate is a marker of illness severity in all situations of physiological stress is overwhelming. In sepsis it is a powerful predictor of mortality. In the recent ARISE trial, data were prospectively collected on lactate levels at randomization [18]. Approximately, one-third of patients were randomized because of isolated hyperlactatemia and compared with patients randomized because of isolated hypotension. Despite similar age and sources of infection, patients with isolated hyperlactatemia had 1.7 times the risk of 90-day mortality and were less likely to be discharged alive form ICU and hospital. This predictive value has been recognized by the SEPSIS-3 consensus definition of shock, which requires the presence of hyperlactatemia [19].

Lactate as a goal of what?

The complexity of lactate as a molecule, substrate, biomarker, energy source, component of some intravenous fluids, and major modulator of cellular bioenergetics during physiological stress is formidable [20]. Such complexity makes it impossible to define what goal it should be a marker or target of. Seeking to lower lactate levels (by whatever means given the multiple events that regulate its blood levels) has no credibility and no logic in terms of hemodynamics, bioenergetics, or tissue protection. In fact, it could make more biological sense to assist the natural process of lactate utilization and generation during sepsis or during other physiological stress situations by administering lactate. Until we are able to define the goals that we wish to achieve by manipulating lactate and have the means of measuring whether we have achieved such goals or not, the idea of seeking to lower lactate by increasing its "clearance" in sepsis is both an illusion and a folly.

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CORRESPONDENCE

The 11th pitfall: thiamine deficiency

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Dear Editor,

We read with great interest the article by Hernandez et al. [1]. We think that, regarding lactate and glucose metabolism, the occurrence of thiamine deficit is worth mentioning since it is frequently overlooked in critically ill (septic) patients [2].

Thiamine (or vitamin B1) active form is thiamine pyrophosphate or thiamine diphosphate and represents a co-factor of pyruvate dehydrogenase, alpha-ketoglutaric acid dehydrogenase, and transketolase, three critical enzymes of carbohydrate metabolism. The first of these, pyruvate dehydrogenase, catalyzes the conversion of pyruvate to acetyl-CoA. Thus, glucose metabolism requires thiamine as a mandatory element to avoid lactate accumulation. In thiamine deficiency or depletion, lactic acid will accumulate to produce severe lactic acidosis, and thiamine supplementation implies a rapid lactate decrease (not clearance) [3].

Thiamine deficit may occur in critically ill patients in case of increased glucose metabolism (i.e., in septic states or post-surgical phases), sudden or aggressive nutrition delivery to malnourished patients (refeeding syndrome), or excessive removal (as during continuous renal replacement therapy, especially in case of high-dose prescription) [2]. Pediatric critically ill patients, especially in case of infection, have shown a thiamine deficit incidence of about 25% upon intensive care unit admission [2]. In any case, to avoid lactic acidosis secondary to thiamine deficiency, adequate supplementation with parenteral or enteral nutrition is crucial. In general, the daily maintenance requirement in adults ranges from 1.1 to 1.2 mg orally and 3 mg parenterally, but this dose can be increased up to 100–300 mg/day in patients with signs of thiamine deficit [2].

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