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Lactate reloaded–reevaluation of the importance of lactate monitoring in the management of adult sepsis in the emergency department

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Abstract: For about a quarter of a century, monitoring lactate levels and/or lactate clearance has been an unquestionable cornerstone in sepsis management. The elevated lactate level appeared to be an independent predictor of mortality, and the consequent metabolic acidosis was thought to explain a number of pathophysiological changes seen in septic shock. Recent physiological and clinical findings seem to challenge the adverse role of lactic acidosis in sepsis. Evidence suggests that lactate levels are not necessarily directly proportional to either tissue or cellular hypoxia, and conversely, despite high lactate levels, increased peripheral tissue oxygen pressure can be measured in adult patients with septic shock. According to the most recent understanding of *in vitro* and *in vivo* evidence, the elevated lactate level in sepsis might be a normal reaction due to adrenergic stress with potential beneficial/protective physiological effects, as well. On the one hand, burning lactic may help fuel the body during critical illness, but on the other hand, with a slight drop in pH, the body may counteract certain deleterious changes during the dysregulated host response; reduce the chances of reperfusion myocardial injury, and improve tissue oxygenation by shifting the haemoglobin dissociation curve to the right. Understanding the pathophysiological process in sepsis resulting in elevated lactate levels may aid management in an emergency, medicine, and intensive care settings. With more in-depth physiological knowledge, physicians may inevitably surpass normalisation heuristics and deliver personalized rather than protocolised sepsis resuscitation.

Introduction

Sepsis resuscitation (i.e., interventions aimed at restoring tissue perfusion/oxygenation) in the present emergency and intensive care practice is guided mostly on indirect parameters like absolute arterial or venous lactate levels and/or lactate clearance (temporal changes in serial lactate assessment). Over the past 25 years, several studies have demonstrated that elevated lactate levels, and consequent metabolic acidosis, in sepsis, is an independent predictor of mortality, similar to other states of shock (Szabó *et al.*, 2017; Jenei *et al.*, 2019; Villar *et al.*, 2019). However, recent research seems to challenge the prognostic accuracy of lactate monitoring/clearance during the assessment of tissue perfusion (Singh *et al.*, 2019).

Until now, sepsis-associated hyperlactataemia (SAHL) was considered to be equivalent to tissue hypoperfusion (hypoxia-induced anaerobic glycolysis) (Dellinger *et al.*, 2013; Sterling *et al.*, 2013). Metabolic acidosis was thought to aggravate vasoplegia (pathologic relaxation in the wall of the small blood vessels) and therefore worsen septic shock by three main mechanisms. First, a drop in pH results is not only downregulating the number of surface adrenoceptors (Levy *et al.*, 2012; Ives *et al.*, 2013) of the vascular smooth muscle cells (VSMC) but at the same time is decreasing the intracellular calcium levels (which opens the ATP-sensitive potassium channels, prompting smooth muscle relaxation) (Ishizaka and Kuo, 1996; Kuo *et al.*, 2009); increasing the expression of inducible nitric oxide synthase both in the endothelium and in VSMC (Yaghi *et al.*, 1993; Pedoto *et al.*, 1999;

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Pedoto *et al.*, 2001; Fernandes and Assreuy, 2008). Our primary goal is to review the process of lactate production in sepsis to better understand the prognostic value of it in SAHL.

Lactate production in sepsis

There is a growing body of (overlooked) evidence challenging the unquestionable dogma of "lactic acidosis = tissue hypoxia". Physiologically, a rise in the lactate level could be explained by adrenergic stimulation and secondary aerobic glycolysis in the muscles than by systematic tissue hypoxia driven anaerobic glycolysis. Beta2 stimulation–even in low perfusion shock–is known to increase the NaK-ATPase activity in the skeletal muscles resulting in lactate release (Xantus *et al.*, 2020b). In light of recent findings, SAHL is most likely an integral part of the systemic stress response but could also be a marker of impaired mitochondrial respiration (Garcia-Alvarez *et al.*, 2014).

Lactic acid production in sepsis is a very complex mechanism not completely explained by either primary or secondary glycolysis. It seems that lactate production may also depend on mitochondrial pyruvate dehydrogenase (dys) function, with a not completely understood link with increased glycolysis (Park *et al.*, 2018). Lactate (in anaerobic states) converted to pyruvate during the Cori/Krebs cycle serves as a precursor for glucogenesis (Nuttall *et al.*, 2008) (Fig. 1). Based on the above, it seems that lactate might play a pivotal role in maintaining the homeostasis in sepsis, as it may serve as extra fuel in the oxidation processes (Fig. 2).

Human clinical observations also seemingly challenge the role of lactate in predicting tissue hypoxia. Boekstegers *et al.* (1994) found no association between higher lactate levels nor tissue or cellular hypoxia. Partial oxygen pressure (PtO2) of the biceps muscle was measured in three groups of adult ICU patients. Their status ranged from severe sepsis to septic shock (with a third subgroup in cardiogenic shock). The results demonstrated no statistically significant correlation between serum lactate levels and brachial PtO_2. The clinical significance of this observation is yet to be explored fully. However, their findings were confirmed later by Sair *et al.* (2001), who compared PtO_2 values in both the forearm musculature and subcutaneous tissue of patients with severe sepsis vs healthy volunteers. This study showed that in septic patients, despite increased serum lactate concentration, an increase in tissue oxygenation was measured compared to those healthy volunteers. Both papers concluded that elevated lactate levels do not correlate with upper limb peripheral tissue hypoxia.

Another approach used fluoromomisonidazole isotope to detect hypoxia. This agent was originally developed for Positron Emission Tomography however, the isotope is now also widely used outside radiology both in translational and clinical diagnostics (Hotchkiss *et al.*, 1991). Animal studies of induced sepsis found no evidence of tissue hypoxia in either skeletal or myocardial muscle, lung, or brain despite higher lactate concentrations (Hotchkiss and Karl, 1992). A recent review of in-vitro and animal evidence (Jeger *et al.*, 2013) concluded that mitochondrial dysfunction does not necessarily result in multi-organ failure in severe sepsis and/or septic shock. Unfortunately, the inferential value of these conclusions (based on observations of mostly young and healthy animals) is unknown in the elderly septic population.

Regueira *et al.* (2012) further demonstrated that the expression of the hypoxia-induced factor (HIF-1) was not proportionate with the rise in lactate level during the course of sepsis, in either skeletal and cardiac muscle or in other vital organs such as the liver, pancreas, lung, kidney. It seemed that even though serum lactate level doubled up during disease progression, in the porcine model the

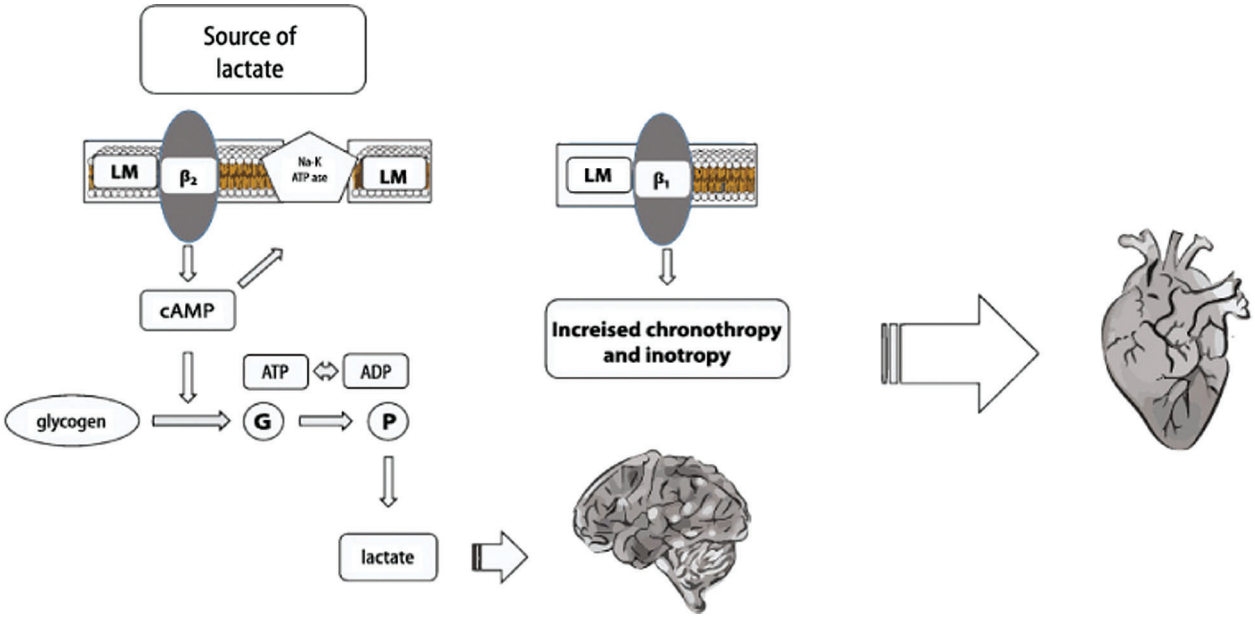

FIGURE 1. Lactate production under aerobic condition.
Lactate production under anaerobic conditions can be part of the Pasteur effect, whereby anaerobiosis accelerates glucose uptake and glycolysis, and pyruvate, instead of entering the citrate cycle, forms lactate. Lactate then can be utilised by the cardiac muscle and the brain–especially under circumstances when there is an overspillage of lactate such as in shock. Therefore lactate is perceived as an "opportunistic", glucose sparing substance. G: Glucose, P: Pyruvate, LM: Lipid Membrane.

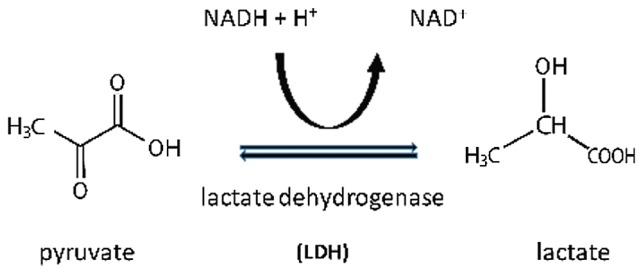

FIGURE 2. Lactate production under anaerobic condition.
Under aerobic conditions pyruvate is metabolised in the Cory/Krebs cycle to acetyl CoA. If anaerobic conditions apply pyruvate can be converted to lactate by the mechanism above. In states of shock, this mechanism prevails and lactate is produced, which can serve as extra the fuel for the brain and the heart.

mitochondrial respiration remained intact regardless of sepsis severity (Regueira *et al.*, 2012). HIF-1 is a protein complex that plays a key role in the body's response to low oxygen concentrations; numerous processes like hypoxia-related re-vascularization, systemic immune response, HIF-1 assay may not only be useful in experimental models, but it is also likely to be a feasible diagnostic method in human practice as well, this is because HIF-1 related mRNA serum concentrations are consistently and significantly higher in patients with septic shock vs healthy controls (Textoris *et al.*, 2012). One clinical study assessed the correlation between serum lactate and HIF-1 mRNA level in septic patients and found no significant association between the two (van Hall, 2010), questioning the predictive role of lactate.

Reinterpretation of lactate in sepsis

Clinical and *in vitro* models seem to suggest that SAHL is not exclusively a sign of mitochondrial hypoxia, but elevated lactate production could be a part of the systemic response to sepsis. Furthermore, hyperlactataemia is not directly proportional to tissue level hypoxia, as presumed previously. Animal experiments investigating muscle metabolism in induced sepsis, by means of phosphorus 31 nuclear magnetic resonance spectroscopy, found no evidence of a drop in either the intracellular NDPH level or overall pH, even in significant hyperlactataemia (Gilles *et al.*, 1994). However, the clinical significance of this finding is yet to be determined.

Clinical observations consistently found elevated lactate levels in asthmatics on beta-agonist treatment, which could not be explained with the previously unquestioned "hypoxia = lactate elevations" theory (Jee and Brownlow, 2007). A recently published placebo-controlled, randomized clinical trial investigated the hemodynamic effects of esmolol infusion (an ultra-short acting beta-blocker) in adult patients with sepsis. The administration of esmolol was associated with a significant decrease in serum lactate level. This finding was unexpected in view of the fact that esmolol reduces cellular oxygen demand (Bouglé and Mira, 2014). Should SAHL be caused by abnormal perfusion/oxygenation only, hyperlactatemia would have been corrected by supranormal values of systemic and/or regional oxygen delivery; however, this study proved the contrary.

A strong correlation between adrenergic stress and lactic acidosis was also confirmed on isolated human left ventricular cardiac myocytes (Schotola *et al.*, 2012). This is in line with previous observations that proved that mild metabolic acidosis reduced inotrope provoked beta-adrenergic response (Marsh *et al.*, 1988; Keiichi *et al.*, 2013), even when serum lactate levels were elevated. It seems that a slight drop in pH may positively affect cardiac relaxation in diastole (Toller *et al.*, 2005; McCaul *et al.*, 2006). Such a response may explain the beneficial effect of beta-antagonist on mortality in septic shock.

In addition to mitigating the adverse effects of adrenergic stress, metabolic acidosis may also play a protective role in preventing reperfusion injury. Fujita *et al.* (2007) reported that transient episodes of metabolic acidosis may reduce early cardiac reperfusion injury (Mitchell *et al.*, 1972). Lastly, metabolic acidosis may also be important in meeting the increased tissue O_2 demand in the critically ill, as at lower pH, the haemoglobin (HbO_2) dissociation curve shifts to the right, resulting in a decrease in SaO_2 and consequently increase PO_2. Due to the sigmoid shape of the HbO_2 curve, the effect of such a shift is generally insignificant at normal PO_2 levels. Such a shift may be particularly important at low PO_2 levels seen in septic shock (Refsum *et al.*, 1997; Fujita *et al.*, 2007). In-depth physiological knowledge may inevitably surpass normalisation heuristics, correct certain parameters to physiological levels in a pathophysiological situation, and deliver personalized rather than protocolised sepsis resuscitation (Xantus *et al.*, 2020a).

Conclusion

To the best of our knowledge, elevated lactate levels in septic adults with consequent mild metabolic acidosis are likely to be a consequence of a not yet completely understood systemic adrenergic response to stress as opposed to a simple marker of tissue hypoxia. Resuscitative interventions in sepsis aimed to correct lactate levels and subsequent metabolic acidosis may deprive the body of additional energy and may counteract certain potential defensive responses intended to mitigate some of the potentially detrimental effects of the dysregulated adrenergic response and secondary reperfusion injury; or conversely, even impaired tissue oxygenation by shifting the haemoglobin dissociation curve to the right. Understanding the complex physiological basis of SAHL can help emergency physicians to revisit sepsis resuscitation goals aiming at correcting serum lactate levels at all costs.

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