Perioperative & Critical Care Medicine

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Critical review

Lactate clearance as a target of therapy in sepsis: a flawed paradigm

PE Marik[1]*, R Bellomo[2]

Abstract

Introduction

An increased blood lactate level is widely believed to be a marker of inadequate oxygen delivery and an-aerobic metabolism. Furthermore, the rate of decline in lactate concentration (lactate clearance) has been recommended as an end-point of early goal directed therapy in critical ill patients with sepsis. We provide compelling data that an elevated lactate concentration is a consequence of increased aerobic glycolysis as part of the stress response and that titrating therapy to the rate of decline in lactate concentration is a potentially harmful endeavour. Furthermore, an increased lactate concentration may be an important adaptive survival response during critical illness.

Conclusion

An elevated lactate concentration in patients with sepsis is a marker of disease severity and not an indication of anaerobic metabolism. Increasing oxygen delivery to treat a non-existent oxygen debt may be a harmful undertaking. 'Lactate clearance' should not be used as the end-point of resuscitation in patients with sepsis.

Introduction

It is widely believed that in critically ill patients when oxygen delivery fails to meet oxygen demand an oxygen debt with global tissue hypoxia ensues[1–2]. This results in anaerobic metabolism and increased lactate production[1–2]. An increased blood lactate concentration is therefore regarded as irrefutable evidence of anaerobic metabolism and tissue hypoxia[1]. Nguyen reported that 'lactate clearance', defined as the percentage decrease in lactate from emergency department presentation to 6h, was an independent predictor of mortality[1].They concluded that '*lactate clearance in the early hospital course may indicate a resolution of global tissue hypoxia and that this is associ-ated with decreased mortality rates.'* This study popularized the concept of 'lactate clearance' and has led to a number of studies which have used 'lactate clearance' as the major end-point of haemodynamic resuscitation in critically in patients with sepsis[3–5]. In this paper we demonstrate that this logic is scientifically flawed and that attempting to titrate therapy to a blood lactate level may be harmful. We suggest that the degree of elevation of the blood lactate is a reflection of the severity of illness and the degree of activation of the stress response (and release of epinephrine) rather than being a marker of an-aerobic metabolism. Furthermore, an increased lactate concentration may be an important adaptive survival response during critical illness.

Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Lactate metabolism

Lactate is produced by glycolysis and metabolised by the liver and to a lesser degree by the kidney. Lactate is produced in the cytoplasm according to the following reaction (see Figure 1):

Pyruvate + NADH + H+ lactate + NAD+

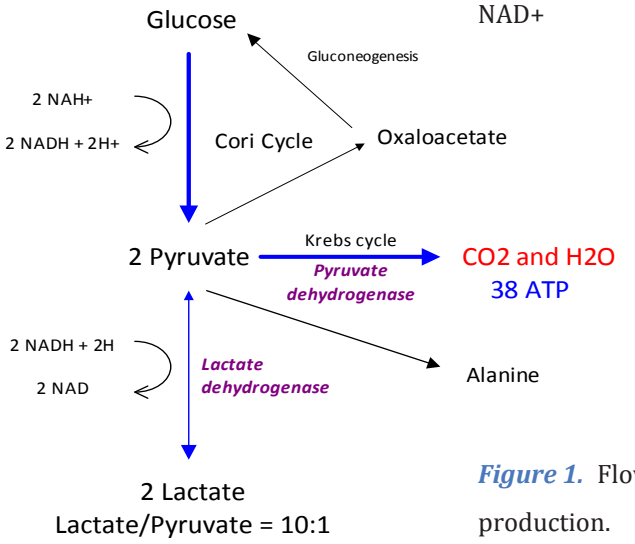

Figure 1. Flow chart of lactate production.

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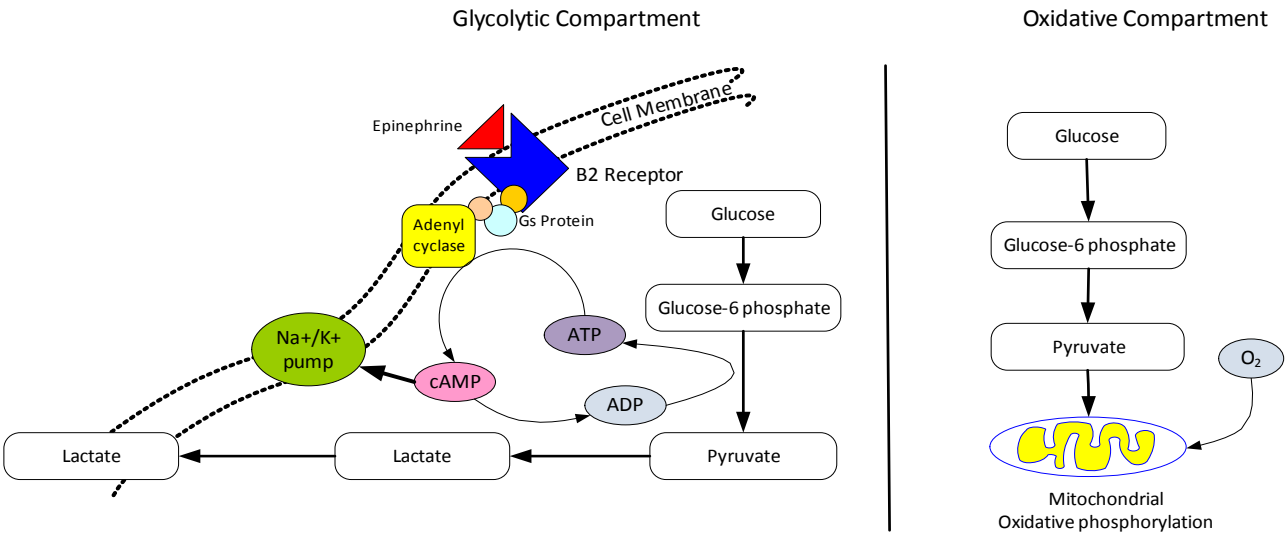

Figure 2. Glycolytic pathway. Epinephrine-increased glycolysis is coupled to Na^+/K^+ ATPase activity. *From James et al*[39].

This reaction favours lactate formation, yielding a ten-fold lactate/pyruvate ratio. In physiological conditions, lactate is produced by muscles (25%), skin (25%), brain (20%), intestine (10%) and red blood cells (20%)[6]. Increased glycolysis results in increased lactate formation. Arterial lactate concentration is dependent on the balancebetween its production and consumption. Ingeneral, this concentration is less than 2 mmol/l, although daily production of lactate is actually 1500 mmol/l[6]. Generated lactate can be transformed into oxaloacetate oralanine via the pyruvate pathway or can be utilized directly by periportal hepatocytes (60%) to produce glycogen and glucose (glycogenesis and glucogenesis; Cori cycle). The kidney also participates in the metabolism of lactate (30%), with the cortex classically acting as the metabolizer by glucogenesis and the medulla as a producer of lactate. Pyruvate is metabolized by the mitochondrial aerobic oxidation pathway via the Krebs cycle. This reaction leads to the production of large quantities of ATP (36 molecules of ATP for one molecule of pyruvate) (see Figure 2).

Hypoxia blocks mitochondrial oxidative phosphorylation, thereby inhibiting ATP synthesis and reoxidation of NADH. This leads to a decrease in the ATP/ADP ratio and an increase in the NADH/NAD ratio. A decrease in the ATP/ADP ratio induces bothan accumulation of pyruvate, which cannot be utilised by way of phosphofructokinase stimulation, and a decreasein pyruvate utilization by inhibiting pyruvate carboxylase, which converts pyruvate into oxaloacetate.[6] Consequently, the increase in lactate production in ana-erobic setting is the result of an accumulation of pyruvate which is converted into lactate stemming from alterations in the redox potential; this results in an increase in the lactate/pyruvate ratio.

Classic teaching suggests that increased production of lactate results in acidosis, known widely as lactic acidosis.7Close examination ofglycolysis reveals that complete metabolism of glucose to lactate results in no net release of protons and, thus, does not contribute to acidosis. In fact, during the production of lactate from pyruvate, protons are consumed and acidosis isinhibited (Figure 1)[8]. Furthermore, lactate oxidationand lactate consumption via gluconeogenesis consume hydrogen ions and are alkalinizing processes. This implies that 'lactic acidosis' is a condition that does not exist[8].

Lactate as a marker of illness severity

It has been well established that an increased blood lactate concentration is a powerful predictor of mortality in critically ill patients. Over 50 years ago Weil and colleagues demonstrated an exponential increase in the mortality of critically ill patients with increasing blood lactate concentrations[9–10]. More recently, studies in both septic and trauma patients have demonstrated an independent association between increasing serum lactate concentration with organ failure and mortality[11–19]. These studies suggest that the mortality increases linearly above a lactate concentration of approximately 1 mmol/l and that this association is independent of organ dysfunction or the presence of shock[11–20]. In patients with sepsis, a serum lactate concentration of more than 4 mmol/l is used as a marker of severe disease with an associated high risk of death[2,14].

Lactate clearance

A number of studies performed during the 1980s demonstrated that the ability to 'clear lactate' to normal in

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patients suffering from both septic and cardiogenic shock was associated with an improved outcome. These authors coined the term 'lactate clearance[21–23]' In 1993 Abramson et al. reported that 'lactate clearance', defined as a decrease of lactate to less than 2mmol/l by 24h, was a predictor of survival following traumatic injury[24]. These authors suggested increasing oxygen delivery in those patients in whom lactate fails to clear. The concept of lactate clearance was subsequently popularized by Nguyen and colleagues[1]. While lactate clearance has been reported to be prognostic of outcome[1,12,18,23–26], not all studies have replicated this finding[27].

Lactate as a marker of metabolic stress

Cytosolic glycolytic flux is functionally divided into two distinct compartments. There are two distinctive glycolytic pathways utilizing separate glycolytic enzyme pools. The first pathway participates in oxidative metabolism via the Krebs cycle. The second pathway is linked to activity of the Na^+/K^+-ATPase pump (see Figure 2)[6]. ATP produced by this pathway is used to fuel this membrane pump. Numerous studies have demonstrated that epinephrine,via β2-adrenoceptor stimulation, incAMP production, inducing the stimulation of glycogenolysis and glycolysis (ATP production) as well as activationof the Na^+/K^+-ATPase pump, which in turn will consume this ATP, thereby producing ADP[28–29]. This generated ADP via phosphofructokinase stimulation will reactivateglycolysis and hence generate more pyruvate- and thereafter lactate.

Several studies performed over four decades ago provide strong evidence that hyperlactacidemia noted during shock states was unlikely to be caused by tissue hypoxia[30–31]. These studies showed that hyperlactacidemia accompanying haemorrhage could be largely prevented by pretreatment with combined alpha and beta adrenergic-receptor blockade[32]. Subsequent experimental studies confirmed that elevated arterial lactate in shock was not due to lack of oxygen but due to increased lactate production that could be mimicked by epinephrine infusion and blocked by adrenergic receptor blockade[33–37]. In these studies plasma lactate correlated well with plasma catecholamines concentrations. Furthermore, animal models of sepsis have demonstrated that despite shock and organ hypoperfusion tissue hypoxia is not a major pathophysiological finding[38]. It has now been well established that epinephrine released as part of the stress response in patients with shock stimulates Na^+/K^+-ATPase activity. Increased activity of Na^+/K^+-ATPase leads to increased lactate production under well-oxygenated conditions in various cells, including erythrocytes, vascular smooth muscle, neurons, glia, and skeletal muscle[29,39]. This concept was confirmed by Levy et al. who in patients with septic shock demonstrated that skeletal muscle was the leading source of lactate formation as a result of exaggerated *aerobic* glycolysis through Na^+/K^+-ATPase stimulation[40]. Selective inhibition of Na^+/K^+-ATPase with ouabain infusion stopped over-production of muscle lactate and pyruvate. This study demonstrated that increased aerobic glycolysis in skeletal muscle secondary to epinephrine-stimulated Na^+/K^+-ATPase activity and not anaerobic glycolysis (due to tissue hypoxia) is the major source of increased lactate in sepsis.

The hypermetabolic state with increased Na^+/K^+-ATPase activity results in accelerated glycolysis and generates pyruvate and lactate at an increased rate. If glycolysis occurs at a rate that exceeds that of oxidative metabolism, some pyruvate may not be oxidatively metabolized in the Krebs cycle and will be converted to lactate. The result will be a concomitant increase in both pyruvate and lactate with an unchanged lactate/pyruvate ratio (L/P). This observation has been demonstrated in patients with sepsis[41]. Gore measured lactate and pyruvate concentrations and the rates of pyruvate production and oxidation prior to and after dichloroacetate (DCA) administration in septic patients with severe lactic acidosis[42]. The patients in this report had significantly elevated levels of glucose, lactate and pyruvate (normal L/P ratio), with an increase in oxygen consumption and a significant decrease in glucose, lactate and pyruvate (unchanged L/P ratio) after the administration of DCA. This study confirmed the rate limiting effect of oxidative metabolism. Revelly et al. studied lactate kinetics in patients with severe sepsis. These authors demonstrated that hyperlactemia was related to increased production whereas lactate clearance was similar to that of healthy subjects[43].

These studies suggest that both increased lactate production and hyperglycemia are a consequence of activation of the stress response and are likely an essential evolutionary-preserved survival response[44]. Under stable conditions the heart oxidizes free fatty acids for 70%–90% of its bioenergetic needs[45]. However, the heart subjected to shock undergoes a shift in substrate utilisation such that it oxidizes lactate for the majority of its energy needs[46]. Accelerated lactate clearance could therefore compromise cardiac performance during shock[47]. In a rat endotoxin model, Levy et al. inhibited lactate production with a selective β2-adrenergic blocker, enhanced its metabolism with dichloroacetate or studied a combination on both interventions[37]. In this study lactate deprivation was associated with cardiovascular collapse and early death of the animals. Conversely, Revelly et al. demonstrated that an infusion of sodium lactate increased cardiac performance in patients with both cardiogenic and septic shock[43]. These studies confirmed that lactate serves as an important energy source during acute haemo-

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dynamic stress. Furthermore, while glucose serves as the major energy source for the brain increased brain lactate oxidation may occur with acute stress[48].

The concept that an epinephrine induced hypermetabolic state is responsible for increased lactate concentrations is supported by two randomized controlled trials, which investigated the haemodynamic effects and outcome of patients with septic shock treated with epinephrine or norepinephrine[49–50]. In both these trials, epinephrine was associated with an initial increase in serum lactate concentration despite an increase in cardiac output and oxygen delivery. Furthermore, the magnitude of the increase in lactate and glucose following an infusion of epinephrine appears to be of prognostic importance with those patients with a blunted response having a significantly higher mortality[36]. In addition to epinephrine induction increased lactate production may impair the activity of the pyruvate dehydrogenase enzyme complex, which in the setting of accelerated aerobic glycolysis, further increases lactate levels[42,51].

Increasing oxygen delivery may be harmful

Current evidence suggests that most of the increase in blood lactate levels in patients with severe sepsis is unrelated to poor tissue perfusion and is therefore unlikely to respond to iatrogenic attempts to increase oxygen delivery. Driving up oxygen delivery in patients without an oxygen debt will not increase oxygen consumption, and it is likely to be harmful. Hayes et al. performed a randomized controlled trial in which patients were randomized to 'supranormal oxygen delivery' or standard therapy[52]. Despite a significant increase in oxygen delivery in the supranormal group, oxygen consumption remained unchanged, while the mortality was significantly higher than in the control group. Similarly, Marik and Sibbald demonstrated that blood transfusion is septic patients with an increased lactate concentration did not result in an increase in oxygen consumption[53]. These data demonstrates that patients with sepsis and an increased lactate do not have an oxygen debt and that increasing oxygen delivery will not increase oxygen consumption and that such an approach is unlikely to be beneficial[54] and may be harmful[52]. Furthermore, we believe that the term 'lactate clearance' is scientifically incorrect. Clearance in medicine is expressed as milliliter per minute. What the authors who have popularized this term presumably mean is the rate of decline in the serum lactate concentration[1]. Furthermore, it is impossible to know if the rate of decline is due to (i) increased removal (metabolism), (ii) decreased production, (iii) dilution due to fluid resuscitation or (iv) all of the above in variable combinations.

We believe that a fall in lactate concentration following the initiation of treatment for sepsis is due to an attenuation of the stress response and not due to correction of an oxygen debt. Furthermore, while a failure of blood lactate levels to decline after the initiation of treatment is an ominous sign, adequate lactate clearance does not guarantee survival. Our review demonstrates that the concept of 'lactate clearance' is fundamentally flawed, and as such, 'lactate clearance' should not be used as the end-point of resuscitation in patients with sepsis.

Conclusion

We believe that a fall in lactate concentration following the initiation of treatment for sepsis is due to an attenuation of the stress response and not due to correction of an oxygen debt. Furthermore, while a failure of blood lactate levels to decline after the initiation of treatment is an ominous sign, adequate lactate clearance does not guarantee survival. Our review demonstrates that the concept of 'lactate clearance' is fundamentally flawed, and as such, 'lactate clearance' should not be used as the end-point of resuscitation in patients with sepsis

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