The role of lactate in sepsis and COVID-19: Perspective from contracting skeletal muscle metabolism

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Abstract
In critically ill patients, elevated plasma lactate is often interpreted as a sign of organ hypoperfusion and/or tissue hypoxia. This view on lactate is likely to have been influenced by the pioneering exercise physiologists around 1920. August Krogh identified an oxygen deficit at the onset of exercise that was later related to an oxygen ‘debt’ and lactate accumulation by A. V. Hill. Lactate is considered to be the main gluconeogenetic precursor in the liver and kidneys during submaximal exercise, but hepatic elimination is attenuated by splanchnic vasoconstriction during high-intensity exercise, causing an exponential increase in blood lactate. With the development of stable isotope tracers, lactate has become established as an important energy source for muscle, brain and heart tissue, where it is used for mitochondrial respiration. Plasma lactate $> 4$ mM is strongly associated with mortality in septic shock, with no direct link between lactate release and tissue hypoxia. Herein, we provide evidence for mitochondrial dysfunction and adrenergic stimulation as explanations for the sepsis-induced hyperlactataemia. Despite profound hypoxaemia and intense work of breathing, patients with severe coronavirus disease 2019 (COVID-19) rarely exhibit hyperlactataemia ($> 2.5$ mM), while presenting a systemic hyperinflammatory state much like sepsis. However, lactate dehydrogenase, which controls the formation of lactate, is markedly elevated in plasma and strongly associated with mortality in severe COVID-19. We briefly review the potential mechanisms of the lactate dehydrogenase elevation in COVID-19 and its relationship to lactate metabolism based on mechanisms established in contracting skeletal muscle and the acute respiratory distress syndrome.

KEYWORDS
acute respiratory distress syndrome, cardiovascular system, critical care, exercise, lung injury
Blood lactate is frequently elevated in critically ill patients, especially in patients with sepsis or septic shock, where lactate is prognostic for mortality (Rhodes et al., 2017). In the intensive care setting, lactate is commonly viewed as an indicator of tissue hypoxia attributable to hypoperfusion (Casserly et al., 2015). Accordingly, early fluid resuscitation is recommended for patients with sepsis or septic shock, with the purpose of normalizing plasma lactate (Rhodes et al., 2017). In patients with coronavirus disease 2019 (COVID-19), however, even severe hypoxaemia is typically associated with only a small increase in arterial lactate (< 2.5 mmol/l), both at hospital admission (Castro, McCoy et al., 2020) and during intensive care therapy (Nardi et al., 2020). Lactate dehydrogenase (LDH) facilitates the formation of pyruvate from lactate (Van Hall, 2000), and circulating LDH is elevated in severe COVID-19 to the extent that it is associated with disease severity and even mortality (Henry et al., 2020). If lactate is a marker of tissue hypoxia, why is blood lactate not higher in COVID-19 patients, who typically present with an exceedingly high respiratory rate in response to hypoxaemia and a systemic hyperinflammatory state similar to sepsis (Crucès et al., 2020)?

The clinical use of lactate, measured in plasma or serum, as an indicator for tissue hypoxia has its historical background in exercise physiology. In 1920, the Danish physiologists August Krogh and Johannes Lindhard examined pulmonary oxygen uptake (\( \dot{V}O_2 \)) in response to the transition from rest to submaximal exercise and during recovery. Despite an acute increase in work rate and thus oxygen requirement, \( \dot{V}O_2 \) increases relatively slowly, resulting in an ‘oxygen deficit’, as it takes a minute or so before \( \dot{V}O_2 \) establishes a steady state. The decrease in \( \dot{V}O_2 \) at the cessation of exercise also lags behind, such that it remains elevated well into recovery (Krogh & Lindhard, 1920). It was Archibald V. Hill and co-workers who introduced the concept of an anaerobic contribution to energy production during exercise: ‘use now, pay later’, as opposed to aerobic energy production ‘pay as you go’ (Bassett, 2002). Accordingly, the elevated \( \dot{V}O_2 \) during recovery from exercise was named an ‘oxygen debt’ considered equal to the oxygen deficit at the onset of exercise and suggested to represent the breakdown of lactate (Bassett, 2002).

Notwithstanding the contributions by Hill and co-workers to exercise physiology, lactate does not only represent an anaerobic contribution to metabolism, but is also integrated in the intermediate metabolism of skeletal muscle and is a substrate for various tissues (Poole et al., 2021). Thus, gluconeogenesis from lactate occurs not only in the liver but also in the kidneys, and lactate serves as an energy source for working skeletal muscle, brain and the heart during exercise (Brooks, 2018; Gertz et al., 1988; van Hall et al., 2009). Herein, we review human lactate metabolism during exercise and propose explanations for hyperlactataemia in patients with sepsis. Finally, we focus on lactate metabolism in patients with severe COVID-19 pneumonia, where systemic accumulation of lactate seems unrelated to arterial hypoxaemia and the ventilatory effort.

### New Findings

- **What is the topic of this review?**
  Lactate is considered an important substrate for mitochondria in the muscles, heart and brain during exercise and is the main gluconeogenic precursor in the liver and kidneys. In this light, we review the (patho)physiology of lactate metabolism in sepsis and coronavirus disease 2019 (COVID-19).

- **What advances does it highlight?**
  Elevated blood lactate is strongly associated with mortality in septic patients. Lactate seems unrelated to tissue hypoxia but is likely to reflect mitochondrial dysfunction and high adrenergic stimulation. Patients with severe COVID-19 exhibit near-normal blood lactate, indicating preserved mitochondrial function, despite a systemic hyperinflammatory state similar to sepsis.

### 2 LACTATE DURING EXERCISE

Since the 1920s, blood lactate accumulation has been considered a metabolic consequence of an oxygen deficit at the onset of exercise and subsequently eliminated during recovery from exercise with increased use of oxygen, known as an oxygen debt (Figure 1a). This scheme has, however, undergone revision because lactate during exercise is now viewed primarily as an energy source that is both released from and used within working muscles (Brooks, 2018; Van Hall, 2000).

#### 2.1 Lactate in muscle metabolism

Early evidence of lactate as a metabolically important substrate included the discovery of ‘the Cori cycle’; that is, gluconeogenesis from lactate in the liver (Cori & Cori, 1929). Thus, lactate was considered a ‘waste product’ from exercising muscles that had to be ‘regenerated’ to glucose to become relevant as a substrate for other issues, notably skeletal muscle. Since then, it has been confirmed unequivocally that the liver contributes to substrate mobilization for working muscles during exercise via gluconeogenesis from lactate (Emhoff et al., 2013). Likewise, the kidneys convert circulating lactate to glucose and appear to possess a similar gluconeogenic capacity to the liver (Meyer et al., 2002).

During prolonged (2 h) cycling exercise at ~60% of maximal \( \dot{V}O_2 \) (\( \dot{V}O_2\text{max} \)), a balance between leg muscle release and hepatic uptake is established that maintains blood lactate < 4 mmol/l (Figure 1a) (Nielsen et al., 2007). The release of lactate by the leg muscles is
markedly increased, with peak concentrations of > 10 mmol/l during incremental exercise at ~90% of \( V_{\text{O}_2 \text{max}} \) (Nielsen et al., 2007). This exponential increase in blood lactate is explained, in part, by vasoconstriction in the splanchnic vasculature that reduces hepatic blood flow, while leg muscle blood flow increases with work intensity during incremental exercise (Perko et al., 1998; Nielsen et al., 2007). Thus, the exponential increase in blood lactate with work intensity does not represent an ‘anaerobic threshold’ (Wasserman, 1987), but rather reflects collapse of liver sinusoids because of inadequate blood flow, meaning that less liver tissue is available for lactate elimination (Figure 1b). In contrast, the kidneys appear to maintain lactate uptake during incremental exercise, despite reduced renal blood flow (Volianitis et al., 2012).

Circulating lactate released by the leg muscles during ergometer cycling is also extracted by the relatively inactive musculature of the arms (Stanley et al., 1986). During arm exercise, the working muscles release lactate and continue to do so when leg cycling exercise is added. Conversely, leg muscles shift from lactate release to lactate uptake when arm exercise is added (Secher et al., 1977). There may also be an exchange of lactate within the contracting muscle, where type II (fast-twitch) muscle fibres secrete lactate (Mizuno et al., 1994) and type I (slow-twitch) muscle fibres extract lactate. Thus, lactate becomes a linkage between aerobic and anaerobic muscle fibre metabolism within an exercising muscle, but an excess of lactate develops when workload increases, maybe because the local rate of lactate production via glycolysis becomes higher than mitochondrial uptake (Brooks, 2018), and lactate is transported to remote tissue, such as arm muscle (Figure 1b).

### 2.2 Oxidation of lactate by heart and brain

The development of stable isotope tracers has made it possible to refine the study of lactate metabolism during exercise in humans. Carbon (C) has two stable isotopes, \(^{12}\text{C} \) (98.9%) and \(^{13}\text{C} \) (1.1%). A common model to study lactate metabolism is venous infusion of \(^{13}\text{C} \)-labelled lactate (tracer), which is incorporated into the body’s depot of lactate (tracee). The rate of release and uptake of lactate can then be quantified by measuring the ratio between tracer and tracee in arterial and venous blood across organs or muscles, while determining the regional blood flow. The oxidation rate of lactate is then quantified by the ratio of the tracer to tracee in CO₂ of exhaled air, where the total amount of CO₂ released per minute is determined, for example, by indirect calorimetry (Kim et al., 2016). By these methods, it has been shown that lactate accounts for ~25% of brain energy consumption during ergometer cycling at a moderate intensity (75%
Intracellular lactate metabolism in muscle and transport to other organs during exercise. Type II muscle fibres (fast-twitch) are considered to be producers of lactate, whereas type I (slow-twitch) fibres mainly consume lactate, and there may be an exchange of lactate within a working muscle bed. Lactate is likely to be the end-product of glycolysis and transported into the mitochondria or out of the muscle fibre. The lactate produced by contracting muscles is transported via the blood to the heart and the brain (bottom right), where it is used as a substrate for mitochondrial respiration, and to the liver and the kidneys (top right), where it is converted to glucose. Abbreviations: Acetyl CoA, acetyl coenzyme A; Glucose-6-P, glucose-6-phosphate; LDH, lactate dehydrogenase; TCA, tricarboxylic acid cycle.

Collectively, the accumulation of lactate during exercise serves several purposes for whole-body metabolism, and it is not merely a waste product related to the oxygen deficit. There is an exchange of lactate between muscle groups and between fibre types within the contracting muscles. Lactate is transported to other organs, including the heart and the brain, where it serves as a substrate for mitochondrial respiration. In the liver and kidneys, lactate is converted to glucose and then used for energy by other organs, including working muscles (Figure 2).

3 SEPSIS-INDUCED HYPERLACTATAEMIA

The prevailing explanation for hyperlactataemia in sepsis is a mismatch between oxygen supply ($D_{O_2}$) and oxygen demand ($V_{O_2}$), whereby tissue hypoxia induces release of lactate. This probably originates from A. V. Hill’s oxygen debt theory, because the formation and release of lactate may be considered a consequence of the oxygen deficit caused by local relative hypoperfusion and anaerobic metabolism (Figure 1). International sepsis guidelines recommend fluid resuscitation to normalize lactate in patients with elevated lactate concentrations (> 2 mmol/l) as a biomarker for occult tissue hypoperfusion (Rhodes et al., 2017). As such, the hyperlactataemia seen in sepsis is associated with, and not causative for, the poor outcome, and indices of tissue hypoxia are predictive of poor outcome independent of hyperlactataemia (Garcia-Alvarez et al., 2014; Osipn-Tascón et al., 2015). Accordingly, recent studies found only a weak link between lactate concentrations and the $V_{O_2}/D_{O_2}$ ratio in patients with sepsis (Gattinoni et al., 2019) and found a similar effect of fluid resuscitation based on skin perfusion (capillary refill time) compared with a lactate-targeted strategy (Castro, Kattan, Ferri et al., 2020).

3.1 Adrenergic stimulation

Studies of experimentally induced sepsis in healthy human subjects injected i.v. with purified lipopolysaccharide (LPS) have shown that circulating adrenaline and noradrenaline concentrations are often increased (Sayk et al., 2008). Despite the endogenous catecholamine response, mean arterial pressure decreases, and subjects experience chills in response to a rise in core temperature (Bundgaard et al., 2003; Sayk et al., 2008). Lactate is released from the leg muscles, whereas potassium is absorbed, and at the same time the blood flow to the leg muscles increases, while arterial and venous oxygen saturations are maintained at pre-LPS levels (Bundgaard et al., 2003). Thus, these data from LPS-induced sepsis suggest that adrenergic stimulation activates
the Na\(^+\)-K\(^+\)-ATPase and accelerates glycolysis in the musculature, leading to an excess of lactate being transported out of the cells (Figure 3b).

Although skeletal muscle is the main producer of lactate during exercise, there is no evidence of exaggerated lactate release from muscle tissue in response to hypoperfusion or hypoxia in human sepsis models (Brassard et al., 2016; Bundgaard et al., 2003). Organ hypoperfusion is one of the main concerns in clinical sepsis and can be manifested as hypotension; however, in LPS-induced sepsis, oxygen delivery to the leg muscles and leg oxygen consumption are preserved (Brassard et al., 2016). The ability to blunt sympathetic vasoconstriction in exercising muscle vasculature (functional sympatholysis) ensures adequate perfusion to the active muscle (Mortensen & Saltin, 2014). Likewise, in LPS models of sepsis, the vascular \(\alpha\)-adrenergic responsiveness is low in the leg, causing vasodilatation and attenuated mean arterial pressure even though circulating catecholamine concentrations are high (Brassard et al., 2016). It is, however, possible that the high adrenergic stimulation during clinical sepsis might attenuate lactate elimination by the liver if its blood supply is impaired by splanchnic vasoconstriction as seen during high-intensity exercise (Nielsen et al., 2007). Likewise, the contribution of the kidneys to gluconeogenesis could be attenuated by lower renal perfusion in response to attenuated mean arterial pressure or by the presence of acute kidney injury; consequently, lactate (the main gluconeogenic precursor) accumulates systemically in the septic patient.

3.2 Mitochondrial dysfunction

Another explanation for sepsis-induced hyperlactataemia is mitochondrial dysfunction (Brealey et al., 2002), appreciating lactate as the ‘normal’ product of glycolysis in the cell as described during exercise (Figure 2), in both aerobic and anaerobic conditions. Although glycolytic (type II) muscle fibres, in particular, release lactate as an anaerobic consequence of exercise, other cells consume excess lactate...
during fully aerobic conditions, including those of the brain and heart. In the mitochondria of these cells, lactate probably crosses the outer mitochondrial membrane, where it is converted into pyruvate by mitochondrial LDH anchored in the inner mitochondrial membrane, and pyruvate is then included in Krebs cycle to release ATP, H₂O and CO₂ (Brooks, 2018). Thus, sepsis-associated mitochondrial dysfunction in an organ that normally converts lactate into energy could result in a shunt of lactate across the affected organ and cause hyperlactataemia (Figure 3a; García-Alvarez et al., 2014; Gattinoni et al., 2019). The appealing aspect about this theory is that low oxygen availability will eventually also lead to mitochondrial dysfunction and thereby reduced lactate utilization in the mitochondria. However, cellular hypoxia is not a prerequisite for lactate production, which is pivotal for understanding the pathophysiology of sepsis, where hypoxia is not always present (Gattinoni et al., 2019).

3.3 Other sources of lactate

A major source of lactate in sepsis is the activated population of immune cells, which are mobilized as part of the inflammatory response (Certo et al., 2021). This probably explains why substantial amounts of lactate are released from the lungs in a manner that depends on the severity of lung injury (De Backer et al., 1997); that is, when sepsis is complicated by the acute respiratory distress syndrome (ARDS), which is characterized by diffuse alveolar damage, with protein-rich alveolar oedema and accumulation of neutrophils and macrophages (Matthay & Zemans, 2011). However, even when this occurs, blood lactate concentrations may still be within the normal range (De Backer et al., 1997), suggesting that the presence of mitochondrial dysfunction and/or liver and kidney dysfunction might be necessary for lactate accumulation.

4 LACTATE METABOLISM IN COVID-19

Unlike sepsis, blood lactate is usually within the normal range in severe COVID-19 pneumonia or manifest ARDS despite grave hypoxaemia, which might indicate preserved mitochondrial function (Figure 3c). Given that immune cells are recruited to the alveolar and interstitial compartments, similar to non-COVID-19 ARDS (Ronit et al., 2021), lactate production from the lungs is likely also to be increased in COVID-19-related ARDS (De Backer et al., 1997). If so, lactate consumption is concurrently increased, which is supported by studies showing substantial increases in plasma LDH (Henry et al., 2020). Hence, at the time of hospitalization, LDH is positively associated with mortality in COVID-19 (Castro, McCoy et al., 2020b; Henry et al., 2020). Moreover, (Zeng et al., 2021) followed a cohort of severe COVID-19 patients and found serum LDH ≥ 360 U/l to be an independent risk factor for mortality [hazard ratio: 21.6 [95% confidence interval: 9.7 to 47.7]] at day 10–15 from symptom onset. Lactate dehydrogenase is found in virtually all cells of the human body, especially in the heart and skeletal muscle, but also in the lung. There are different isoforms of LDH, and the predominant LDH isoform in skeletal muscle is considered to favour the formation of lactate from pyruvate, whereas the heart LDH isoform primarily catalyses the conversion of lactate to pyruvate (Van Hall, 2000). Immunohistochemical studies have shown that LDH is present both in the cytoplasm and in the mitochondria of skeletal muscle (Figure 2; Brooks et al., 1999). Moreover, endurance training upregulates the mitochondria-rich type I fibres and the heart-specific LDH isoform in skeletal muscle, suggesting a higher capacity for intracellular oxidation of lactate (Doubuchaud et al., 2000), whereas the activity of the skeletal muscle LDH isoform is upregulated in type II fibres (Saltin et al., 1995). This corresponds to the cell-to-cell lactate shuttle theory described above, whereby lactate is produced by type II fibres and consumed by type I fibres during exercise (Brooks, 2018).

4.1 Pulmonary or cardiac release of LDH

It is still unclear which cells release LDH in COVID-19 (Nardi et al., 2020). Lactate dehydrogenase can be released from cells upon injury, but in severe COVID-19 most probably heart or lung tissue, given the cardiorespiratory symptoms. In favour of pulmonary-derived LDH, electron microscopy has revealed extensive damage of the alveolar epithelium and of the blood–gas membrane during the acute phase of non-COVID-19 ARDS (Thompson et al., 2017). Bronchoalveolar lavage from patients with pneumocystis pneumonia shows higher bronchoalveolar-to-blood LDH ratios compared with non-pneumocystic lung disease, suggesting that LDH flows back through the alveolocapillary membrane into the pulmonary capillaries (Smith et al., 1988). Nonetheless, myocardial injury is also observed frequently in patients with COVID-19 and is associated with increased risk of death (Sandoval et al., 2020). However, if LDH reflects alveolar and/or myocardial injury in severe COVID-19, why is plasma LDH still elevated in survivors after several weeks of admission (Zeng et al., 2021), and why is plasma lactate mostly kept within the normal range?

4.2 Lactate dehydrogenase from respiratory muscles

Alternatively, the elevation of LDH in COVID-19 patients is related to the lactate shuttle theory (Brooks, 2018). Thus, LDH might represent a high oxidative metabolism of lactate that is used as energy by the respiratory muscles (Figure 2). In particular, the diaphragm has great potential for lactate oxidation, with its high proportion of type I fibres (Levine et al., 1997). Although little is known about muscle metabolism during COVID-19, critically ill sepsis patients requiring mechanical ventilation may lose oxidative capacity in the leg muscles, indicated by low intramuscular ATP (Puthucheary et al., 2018) and high lactate content (Fredriksson et al., 2006). In contrast, the intercostal muscle content of ATP and lactate can be within the normal range (Fredriksson et al., 2006), suggesting that respiratory muscles could be net lactate consumers during sepsis-induced respiratory failure.
During maximal ergometer exercise, the respiratory muscles demand ~15% of VO₂ (Harms et al., 1997). The work of breathing during maximal isocapnic hyperventilation corresponds to a respiratory muscle O₂ consumption of ~250–350 ml O₂/min in young, healthy subjects, which is somewhat similar to that of maximal exercise (Coast et al., 1993). Patients with COVID-19 typically perform a large work of breathing (Sartini et al., 2020), and the respiratory effort and high ventilatory minute volume associated with severe COVID-19 can cause patient self-inflicted lung injury by vigorous spontaneous respiration (Cruces et al., 2020; Esnault et al., 2020). In non-COVID-19 ARDS, low tidal volumes during mechanical ventilation reduce mortality, and the mechanism is thought to be avoidance of alveolar overdistention and barotrauma (Brower et al., 2000). Thus, excessive LDH production and spillover into the bloodstream from the contracting respiratory muscles during breathing with high tidal volumes could be an indirect marker of patient self-inflicted lung injury.

5 IMPLICATIONS

The pathophysiology of lactate release during critical illness remains unclear. However, based on evidence from contracting skeletal muscle, lactate is considered an important substrate for the mitochondria within the muscles, the heart and the brain during exercise, and lactate is the main gluconeogenetic precursor in the liver and kidneys. In this light, interventions with the purpose of normalizing lactate should be examined, with fluid resuscitation as the main point of clinical interest.

Lactate metabolism is impaired in patients with sepsis, probably owing to mitochondrial dysfunction and high adrenergic stimulation, but seems unrelated to tissue hypoxia, although lactate is strongly associated with the severity of disease. In contrast, patients with severe COVID-19 pneumonia exhibit near-normal blood lactate, which might indicate preserved mitochondrial function, and the prognostic ability of lactate for clinical outcome is low. Thus, future work might focus on direct measures of mitochondrial function in critically ill patients with sepsis and COVID-19; that is, by respirometry of skeletal muscle tissue.

The origin of the LDH release is not well described in COVID-19 but could be linked to lung injury via patient self-inflicted lung injury or direct alveolar cell damage. Determining regional arterial–venous concentration differences for LDH isoforms could provide insight into the pathophysiology and might explain why high LDH is associated with mortality in COVID-19. Likewise, knowledge on the dynamic kinetics of lactate metabolism in septic patients is lacking and could be quantified by stable isotope tracer methodology.

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U.W.I., R.R.P. and N.H.S. conceived the study. U.W.I. wrote the initial draft of the manuscript. U.W.I. and C.K.R. prepared figures. R.R.P., R.M.G.B. and N.H.S. were involved in drafting and editing subsequent versions of the manuscript. K.T., N.B.F., C.S.M., C.K.R., R.M.G.B. and N.H.S. provided critical input at all stages and critically revised the manuscript. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

COMPETING INTERESTS

None declared.

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