Review

Bench-to-bedside review: Lactate and the lung

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Abstract

The ability of the isolated lung tissue to take up glucose and to release lactate is potentially similar to that of other body tissues. Nonetheless, when lung lactate exchange was assess *in vivo* in normal humans, no measurable lactate production could be detected. Lung lactate production may become clinically evident in disease states especially in the patients with acute lung injury or with acute respiratory distress syndrome. Potential mechanisms of lactate production by the injured lung may include not only the onset of anaerobic metabolism in hypoxic zones, but also direct cytokine effects on pulmonary cells and an accelerated glucose metabolism in both the parenchymal and the inflammatory cells infiltrating lung tissue. In addition, as skeletal muscle, lung tissue may show metabolic adaptations in response to systemic mediators and may contribute to the systemic metabolic response to severe illness even in the absence of direct tissue abnormalities.

Keywords acute respiratory distress syndrome, arteriovenous balance, cytokines, lactate release, pulmonary artery

The respiratory and immune functions of the lung are largely dependent on the activity of a number of metabolic pathways. Surfactants and prostanoids are synthesized from lipid precursors. Protein synthesis is maintained at a high rate to maintain a rapid turnover of the endothelial and parenchymal pulmonary cells and of the immune cells. Energy is produced from glucose, fatty acids and branched chain amino acid oxidation. Lactate, alanine and glutamine are synthesized to shuttle carbon and nitrogen residues derived from glucose and amino acid metabolism.

Despite the importance of these metabolic pathways, the role of the lung in interorgan substrate exchange in physiological and pathological conditions is largely unknown. In humans, substrate exchange across an individual organ is determined according to the Fick principle, by measuring substrate arteriovenous concentrations and local blood flow. This approach has been largely used to determine skeletal muscle metabolism in the human limbs. In the lung, however, the arteriovenous difference of substrate concentrations is usually small compared with a high rate of blood flow through the tissue. This limits the ability of the Fick technique to detect statistically significant rates of substrate exchange across the lung in most circumstances.

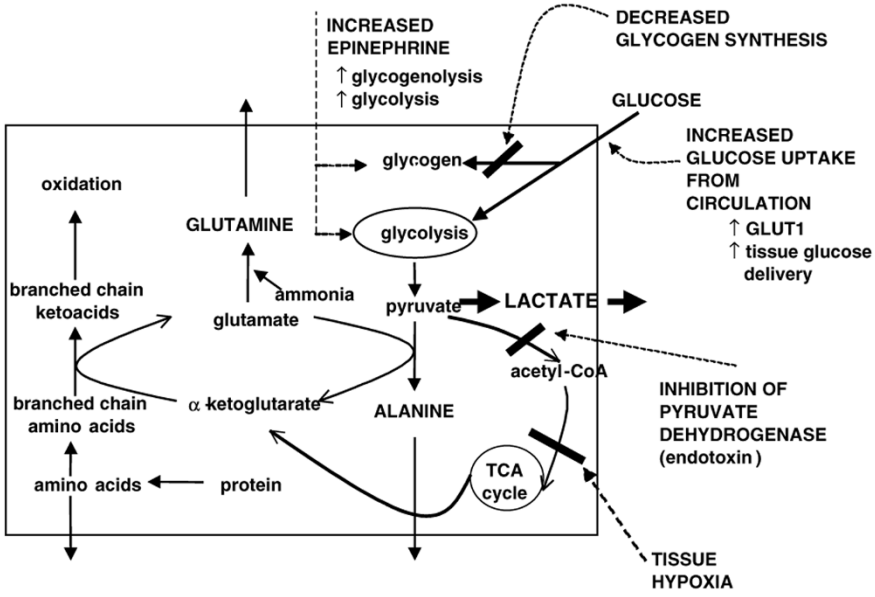
Lung lactate synthesis and release

Virtually all tissues can synthesize or utilize lactate. Lactate is synthesized from the pyruvic acid derived from glycolysis, whereas it can be utilized to form glucose or it can be oxidized through pyruvate and the tricarboxylic acid cycle. In physiological conditions, lactate is mainly produced in the skin, skeletal muscle, leucocytes and red blood cells. It is mainly utilized, however, in the liver and the kidney. Lactate is therefore one of the major carbon shuttles among body tissues.

In different conditions, the rate of lactate synthesis is dependent on the activity of the glycolytic pathway relative to the oxidative capacity of the pyruvate dehydrogenase enzymatic

ALI = acute lung injury; ARDS = acute respiratory distress syndrome.

Figure 1



Potential mechanisms of increased tissue lactate production in sepsis. GLUT1, glucose transporter 1; TCA, tricarboxylive acid cycle; acetyl-CoA, acetyle-coenzyme A.

complex. An acceleration of lactate synthesis may be observed in conditions of increased glucose uptake from circulation, of increased glycogenolysis and glycolysis due to enhanced epinephrine secretion, of inhibition of pyruvate dehydrogenase or of glycogen synthesis in sepsis and, finally, during tissue hypoxia (Fig. 1).

Early *in vitro* studies [1] demonstrated that the ability of the isolated lung tissue to take up glucose and to release lactate was potentially similar to that of other body tissues such as skeletal muscle, skin, red blood cells, leucocytes, and so on. Nonetheless, when lung lactate exchange was assessed *in vivo* in normal humans, no measurable lactate production could be detected by the Fick method. It was concluded, therefore, that the rate of lactate synthesis in the normal lung is approximately equal to the rate of lactate utilization, leading to a net lactate balance close to zero [2–4]. In many pathological conditions, in contrast, the arteriovenous lactate concentration difference across the lung has often been found consistently negative, suggesting that a net lactate production from the lung may become clinically evident in disease states. In animals, Bellomo *et al*. observed an early lactate release from the lung following endotoxin administration [5]. In humans, a net lung lactate production was measured in patients with different types of acute lung injuries by many authors, including ourselves [6–10].

The largest number of patients has been studied by De Backer *et al*. [6]. They compared the transpulmunary lactate exchange in 43 patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS), as defined according to the American–European Consensus Conference, with that in other patients affected by acute cardiogenic pulmonary oedema ($n = 9$), pneumonia ($n = 37$), lung transplantation ($n = 7$) or other causes of respiratory failure ($n = 26$). De Backer *et al*. observed that lung lactate production was greater in the patients with ALI/ARDS that in those with other disease states. Furthermore, lung lactate production was related with the ratio between arterial oxygen pressure and the fraction of inspired oxygen (PaO_2/FiO_2; inverse correlation) and with the pulmonary injury score (direct correlation). In patients with high lactate plasma levels, lung lactate production was not related to the arterial lactate concentration.

These observations have been confirmed in other smaller groups of patients affected by ALI or ARDS [7–10]. Several considerations can be made on the basis of these studies. A lung inflammatory condition is always associated with an increased lung lactate production. Also, the extent of lactate release is related to the severity of the lung injury. A third consideration is that the presence of pulmonary infection does not increase lactate production. Also, the inflammatory process should be severe and should involve the entire organ since lactate production is not increased in localized inflammatory processes. In fact, it has been observed in lung carcinoma that lung lactate production is increased only in the affected districts [2]. Finally, the lung is not the only major source of lactate in conditions of severe increase of plasma lactate.

Potential mechanisms of lung lactate production by the injured lung may include not only the onset of anaerobic metabolism in hypoxic zones, but also direct cytokine effects on pulmonary cells and an accelerated glucose metabolism in both the parenchymal and the inflammatory cells infiltrating the lung tissue. Experimental evidence *in vitro* [11] and *in vivo* [12,13] indicates that lung metabolism tolerates severe reductions of intracellular oxygen availability, suggesting that lung hypoxia is not the main factor responsible for increasing lactate release from the injured lung. In severe cardiac failure [14] and during acute hepatic failure [15], an increased lung lactate production appeared to be directly related to systemic lactate levels. In addition, preliminary data from our laboratory indicate that septic ARDS patients with no direct lung injuries and with normal oxygen tissue delivery release lactate from lung tissue at rates three to four times greater than that from skeletal muscle [16]. These patients also exhibited a negative lung protein balance and a large lung release of neoglucogenic amino acids [17].

These observations suggest that, as skeletal muscle, lung tissue may show metabolic adaptations in response to systemic mediators (e.g. cytokines) and may contribute to the systemic metabolic response to severe illness even in the absence of direct tissue abnormalities.

Competing interests

None declared.

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