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EDITORIAL

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Lactate in shock: a high-octane fuel for the heart?

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Lactic acid was first discovered in sour milk by the Swedish chemist Carl Wilhelm Scheele in 1780 [1]. Since then the role of lactate (lactic acid) has fascinated physiologists, biochemists, and intensive care physicians. Hyperlactatemia is one of the most common metabolic abnormalities in critically ill patients, and numerous studies have established the use of blood lactate levels and/or lactate clearance as a diagnostic, therapeutic, and prognostic marker of tissue hypoxia in circulatory shock [2, 3, 4]. Lactate can accumulate when lactate production is increased and/or lactate utilization diminished [5]. Both overproduction and decreased lactate clearance appear to be operative in most patients. In certain disorders the origin of elevated lactate is clear. For example, plasma lactate levels may transiently be as high as 15 mmol/l during a grand mal seizure [6], and it proportionally reflects the cumulative oxygen debt in hemorrhagic shock [7]. In this context, lactate was traditionally considered a metabolic dead-end waste product of glycolysis due to hypoxia. This lactate paradigm, however, has recently been challenged, and both the source of lactate production and its role as a mobile fuel have been reinvestigated [8, 9] particularly in complex disorders such as systemic inflammation and sepsis [10, 11]. If ATP produced by oxidative phosphorylation and ATP coming from glycolysis are similar molecules, intracellular architecture and complex metabolic networks favor a channeling of energetic metabolism. Several lines of evidence do suggest that numerous membrane enzymes (including the Na^+/K^+-ATPase) electively consume glycolytic ATP. Lactate overproduction in sepsis therefore may not necessarily be related to anaerobic metabolism (i.e., tissue hypoxia) but may also be produced during adequate oxygen provision due to epinephrine effect on Na^+/K^+-ATPase activity [11, 12, 13]. In this process ADP generated by the Na^+/K^+-ATPase accelerates aerobic glycolysis, and thus increases lactate concentration. Another important discovery is the recognition of lactate acting as a mobile metabolite distributed via the systemic circulation to various organs, tissues, and cells for oxiation or recycling, allowing the maintenance of ATP provision [8, 9, 10]. Finally, lactate also represents a signaling molecule involved in the regulation of cellular redox state and oxidative defense [14].

A contribution to *Intensive Care Medicine* now provides further insights into this enigmatic molecule. In their complex experimental study in a short-term, lethal model of endotoxic shock in anesthetized and ventilated rats Levy et al. [15] sought to determine whether (a) muscle lactate production is linked to β_2-adrenergic stimulation, and (b) limited systemic lactate availability alters car-

diovascular performance. The first hypothesis was tested using selective blockade of the β_2-adrenergic pathway in the tissues by ICI-118551 administration via microdialysis catheters, which allowed the authors to determine that local muscle lactate production is indeed related to an epinephrine-stimulation via β_2-adrenoreceptors of Na^+/K^+-ATPase-mediated aerobic glycolysis. To test the second hypothesis systemic lactate deprivation was achieved by intravenous administration of either the selective β_2-inhibitor (ICI-118551), dichloracetate (DCA), an activator of pyruvate dehydrogenase or the combination of these two drugs.

The authors found that inhibition of β_2-adrenoreceptors significantly reduced the otherwise progressive endotoxemia-induced increase in local muscle lactate production, thereby supporting the notion that stimulation of lactate production by epinephrine is secondary to Na^+/K^+-ATPase activation. Most strikingly, limited availability in circulating lactate concentrations induced both by ICI-118551 and DCA was associated with altered heart bioenergetics, as documented by decreased ATP and phosphocreatine content in the heart. Moreover, a further decrease in lactate availability resulting from the combined administration of ICI-118551 and DCA caused a pronounced low flow state with profound hypotension and early lethality. Importantly, the correction of this systemic "lactate deficit" by adding sodium lactate to ICI-118551 or DCA reversed the hemodynamic disturbances, thus supporting the authors' conclusion that the obtained results are truly related to lactate deprivation.

Taken together these data allow two considerations. First, evidence is now accumulating that during endotoxemia/sepsis not only is lactate produced as a result of tissue hypoxia, but also that its formation relates to exaggerated epinephrine-driven aerobic glycolysis through Na^+/K^+-ATPase stimulation. Second, the observed detrimental consequences of lactate starvation on heart energy metabolism and hemodynamic performance clearly support the role of lactate as an important fuel for tissue energetics, further forcing the perception of increased lactate formation as an adaptive event aimed at counteracting the energetic crisis [9]. In this context, particularly the heart is an organ extremely susceptible to derangements in substrate delivery. The myocardium is a highly oxidative tissue that produces more than 90% of its energy from mitochondrial respiration. Optimal cellular energetics and hence the contractile capacity of the heart are determined by many factors, including adequate delivery of oxygen and substrates, the oxidative capacity of mitochondria, and adequate amounts of high-energy phosphate and the phosphocreatine/ATP ratio. Under physiological conditions the heart is a metabolic omnivore able to use a wide range of substrates, which include fatty acids, glucose, lactate, and other oxidizable substrates [16, 17]. In healthy heart 60–90% of the acetyl-coenzyme A comes from β-oxidation of fatty acids and 10–40% from the oxidation of pyruvate that is derived from glycolysis and lactate oxidation [16]. Unfortunately, only limited data are available regarding the preferential use of either lactate, glucose, fatty acids, or other substrates in this organ during sepsis, particularly when all these potential substrates are available. Hence the important issue illustrated by Levy et al. [15] is that we now have better idea of what happens to animals challenged with endotoxin that are unable to increase their lactate production. In support of this notion, evidence derived from studies in failing hearts indicates that switch away from chief myocardial energy substrates (fatty acids β-oxidation) to glycolysis may preserve or even improve myocardial performance [18, 19]. A switch from lipid to preferential carbohydrate oxidation improved the relationship between myocardial oxygen consumption and mechanical work [20], i.e., the mechanical yield of the caloric energy expenditure. This effect mirrors the higher yield of the mitochondrial respiration when glucose is used as a fuel, which is the metabolic adaptation to conditions of limited oxygen availability [21]. Moreover, the overexpression of the lactate transporter MCT1, i.e., the monocarboxylate transporter protein shuttle system allowing the entry of lactate into the cells, in an experimental model of heart failure also suggests such a metabolic adaptation favoring preferential lactate metabolism [22]. Finally, the notion that lactate is an important fuel for myocardial energy metabolism particularly under conditions of compromised substrate supply is also supported by the findings of both experimental and human studies: high lactate levels preserved hemodynamic functions in hemorrhaged rats and dogs [23, 24], and exogenous lactate increased cardiac index in patients after cardiac surgery [25].

Although we have learned a great deal from the study by Levy et al. [15], the findings should be interpreted in the context of the limitations of the study. As for all short-term rodent models of acute, lethal endotoxemic shock, clinical relevance of the result remains equivocal. Without better assessment of cardiac function or precise knowledge of the real ATP turnover and the fate of myocardial lactate metabolism, it is not possible to interpret somewhat contradictory findings, i.e., heart ATP and phosphocreatine content markedly decreased, but strikingly this was not affiliated with compromised aortic blood flow when the two drugs are given separately. Hence further studies are needed to determine the exact molecular mechanisms responsible for changes in myocardial metabolic phenotype that occur during sepsis and shock.

In conclusion, the study by Levy et al. [15] moves forward the concept of lactate acting as an important fuel in shock states. We are just beginning to understand the multifaceted role of lactate in critically ill patients, which may ultimately result in new approaches targeted at increasing the energetic efficiency of the heart and other organs. To

"feed a tired energy-starved horse" rather than "whip the horse" with inotropic and vasopressor agents seems to be a worthwhile road ahead [26].

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