

## Commentary

# Lactate in the intensive care unit: pyromaniac, sentinel or fireman?

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See related review by Valenza *et al.* in this issue, page 588 [<http://ccforum.com/content/9/6/588>]

## Abstract

Lactate, indispensable substrate of mammalian intermediary metabolism, allows shuttling of carbons and reducing power between cells and organs at a high turnover rate. Lactate is, therefore, not deleterious, although an increase in its concentration is often a sensitive sign of alteration in energy homeostasis, a rise in it being frequently related to poor prognosis. Such an increase, however, actually signifies an attempt by the body to cope with a new energy status. Hyperlactatemia, therefore, most often represents an adaptive response to an acute energy disorder. Investigation of lactate metabolism at the bedside is limited to the determination of its concentration. Lactate metabolism and acid-base homeostasis are both closely linked to cellular energy metabolism, acidosis being potentially a cause or a consequence of cellular energy deficit.

Lactate is certainly not a pyromaniac: it is not toxic and possesses no harmful effect *per se*. It is probably a trustworthy sentinel because it sensitively indicates that fire is potentially in the house and numerous works have already shown a good relationship between lactate level and outcome [1]. Above all, it is an indispensable soldier that actively acts as a major intermediate involved in the vast cellular and organ energy interplay, allowing the body to cope with a wide range of metabolic disorders (for example, exercise, hypoxia, ischemia, severe sepsis, shock) [2].

Based on their broad experience in the management of the profound metabolic derangements observed in critical illnesses, associated with some experimental data, Valenza *et al.* [3] propose, in a review-hypothesis paper in this issue of *Critical Care*, to regard lactate increase in the intensive care unit as a marker of a metabolic adaptation requiring a therapeutic aid ("possibly indicating that 'there is still room' to boost fast intervention") rather than a sign of irreversible end-stage energy failure. In this context, these authors propose to take the decrease in blood lactate following a therapeutic challenge as a major indicator of the efficacy of such

treatment. This proposal seems absolutely correct and very close to what has been already proposed regarding oxygen consumption ( $VO_2$ ), but with a simple bedside parameter of metabolic integration. Indeed, whatever the cause of derangement and the metabolic environment, any rise in blood lactate indicates an attempt by the body to adapt to an unusual energetic situation, which may affect redox state, phosphate potential or pH [4]. Moreover, as indicated by the authors, lactate production requires a complete glycolytic pathway, that is, an intact cell with sufficient glucose supply or glycogen storage. Therefore, in ischemic tissues, which don't have a sustained supply of blood glucose, a substantial amount of lactate can be released as long as glucose is present in the interstitial fluid or in the cells (glycogen). Thus, it should be noted that a decrease in lactate might imply 'a correction' of the initial disorder but also an exhaustion of the precursor (glucose) or a destruction of tissues.

In fact, as for any metabolite, lactate concentration depends on the ratio between production and consumption. Because these two parameters are not routinely assessed at the bedside, however, the pathophysiological view is mostly based on lactate concentration only, which may represent a sometimes hazardous shortcut. Lactate metabolism is intimately linked to the three major potentials of living systems, all strictly related to energy metabolism: redox potential ((NADH, H<sup>+</sup>)/NAD<sup>+</sup>); phosphate potential (ATP/(ADP × Pi)); and hydrogen potential or pH ( $6.1 + \log(\text{HCO}_3^- / 0.03 \times \text{PaCO}_2)$ ). The first indicates a potential deficit in oxidation (oxygen or oxidative capacity), the second shortage in energy and the third, which is closely linked to these parameters, could be viewed as a metabolic tool allowing the exact matching between them. ATP turnover is controlled by pH [5-10]: acidosis decreases ATP turnover and oxygen demand, representing an adapted or deleterious event depending on how deep, how long and how reversible.

Although there is no doubt about the fact that a change in lactate metabolism is linked to energy imbalance, the complete picture of the mechanisms involved in lactate regulation, which represents just a piece of a very complex puzzle, triggering or inducing an adaptive response is not completely clear as yet. However, anaerobic ATP supply from a glycolytic anaerobic source is limited in terms of its sustained rate of ATP production, except for a very acute and short muscle contraction. As a matter of fact, 300 ml/minute oxygen consumption ( $VO_2 = 13.4 \text{ mmol O}_2$ ) represents an ATP turnover of approximately 80 mmol/minute, which costs about 1.6 mmol/minute (0.3 g) of glucose when oxidized and 40 mmol/minute (7.2 g) when metabolized anaerobically. Hence, the entirety of liver glycogen would be consumed in about 15 minutes as there is no glucose release from glycogen in muscle cells because of the lack of glucose-6 phosphatase. With the exception of initial muscle contraction, increased anaerobic glycolytic ATP production is adaptive for a fall in mitochondrial (aerobic) ATP supply only when associated with a decrease in ATP consumption, imposing a new hierarchical setting on the different ATP consuming pathways. In other words, lactate-associated (anaerobic) ATP production is an appropriate response to ischemia, anoxia or any kind of energy crisis only when the body can simultaneously save energy. The consequences of these changes in cell priorities represent a major aspect of understanding metabolic derangement in acute organ failure. Acidosis is linked to energy metabolism and lactate homeostasis is related to both pH and energy status. When metabolic or respiratory acidosis is the initial event, it depresses energy expenditure and lactate might rise, but only modestly. Correction of acidosis improves the energetic derangement. In contrast, when the primary defect concerns energy homeostasis, pH decrease is adaptive: lowering energy expenditure allows matching a decrease in oxidative ATP synthesis capacity and the rise in lactate concentration and turnover is part of this adaptation. It should also be considered that rises in lactate also occur frequently in the absence of acidosis, or even simultaneously with alkalosis. Indeed, several causes of hyperlactatemia encountered in intensive care unit patients appear to be independent of any defect in cellular energy status [11,12]. In these situations, the significance and prognostic value of such hyperlactatemia are very different from those associated with acidosis.

In conclusion, the significance of hyperlactatemia depends on the concomitant acid-base status because of a common link with energy metabolism. When acidosis is the primary cause of the metabolic abnormalities, cellular energy deficit is a consequence, lactate rise is modest and correction of pH improves the metabolic disorder. When the cellular energy defect is the *primum movens*, hyperlactatemia and acidosis are its consequences and pH correction without simultaneous improvement of the energy defect impairs the adaptive response to energy failure, as represented by acidosis. When lactate increases in the absence of acidosis, it probably indicates a lack of a relationship with energy deficit.

## Competing interests

The author(s) declare that they have no competing interests.

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