Review

Lactate as a marker of energy failure in critically ill patients: hypothesis

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See related commentary by Leverve in this issue, page 622 [http://ccforum.com/content/9/6/622]

Abstract

Lactate measurement in the critically ill has been traditionally used to stratify patients with poor outcome. However, plasma lactate levels are the result of a finely tuned interplay of factors that affect the balance between its production and its clearance. When the oxygen supply does not match its consumption, organisms such as man who are forced to produce ATP for their integrity adapt in many different ways up to the point when energy failure occurs. Lactate, being part of the adaptive response, may then be used to assess the severity of the supply/demand imbalance. In such a scenario, the time to intervention becomes relevant: early and effective treatment may allow the cell to revert to a normal state, as long as the oxygen machinery (i.e. mithocondria) is intact. Conversely, once the mithocondria are deranged, energy failure occurs even in the presence of normoxia. The lactate increase in critically ill patients may therefore be viewed as an early marker of a potentially reversible state.

Lactate in critical illness

The normal reference values for lactate are traditionally considered 1 ± 0.5 mmol/l in normal patients and <2 mmol/l in critically ill patients [1]. Since 1975, values above 2 mmol/l but lower than 5 mmol/l have been separated from values above 5 mmol/l, associated with acidemia, as different clinical entities – referring to hyperlactatemia states in the former situation as opposed to lactic acidosis in the latter situation [2]. A further stratification, initially proposed by Cohen in 1976 [3], has been subsequently used according to the presence (type A) or absence (type B) of 'evident' causes of tissue hypoxia to explain the underlying cause of increased lactate. Over the years, however, more sophisticated means of assessing regional and even local perfusion have changed the aforementioned classification into a more perfusion-oriented vision. In fact, our increased ability to assess tissue oxygenation clearly implies that measured plasma lactate concentration is only a small window of a much more complicated scenario.

Lactate as a clinical marker of hypoxia

As will be described, lactate is one of the intermediate products that increase as a consequence of the rearrangement of metabolism during hypoxia. As such, lactate has been widely considered a marker of tissue hypoxia. There are several examples of the increase of lactate in hypoxic conditions [4,5]. Figure 1 shows our own experimental results. The lactate increase is very fast, a matter of minutes, and is proportional to the defect in the oxidative metabolism [6].

However, measured plasma lactate is the balance between production and clearance. Liver failure does in fact influence the kinetics of lactate increase [7].

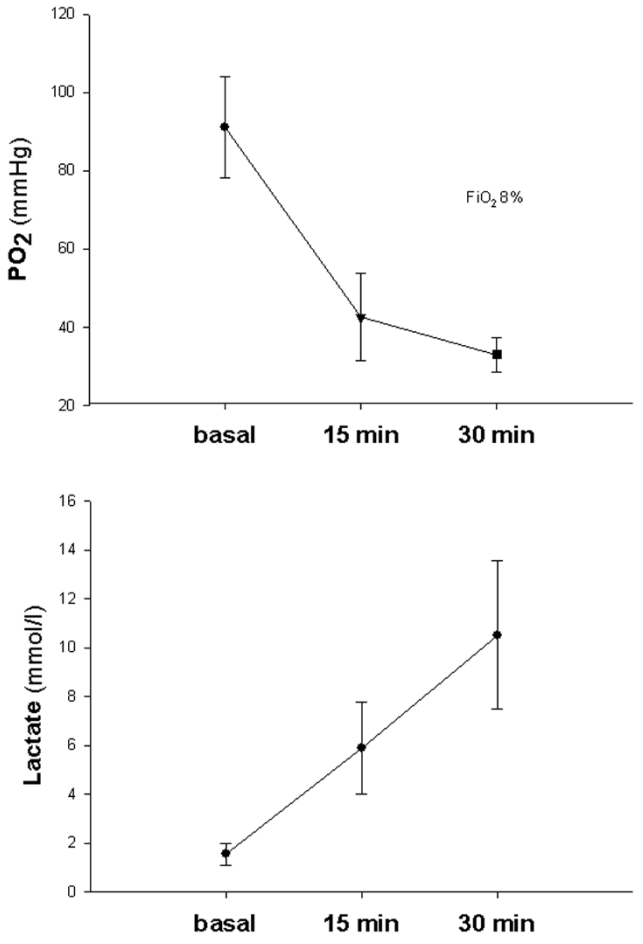
It is also worth note that lactate is an intermediate compound of normal metabolism. Erythrocytes, for instance, which are equivalent to an organ weighing approximately 2500 g, are obligatory anaerobes and 'breathe' via the lactate they produce that is recycled from fatty acid oxidation in the liver. Lactate, in this case, may be considered an energy shuttle rather than a waste compound [8].

Outcome and stratification of severity

Lactate has been used as a marker in critically ill patients since 1964 [9]. In 1970, Weil and Afifi clearly showed the relationship between lactate concentration and outcome [10]. Several authors have subsequently confirmed those results [11-15]. Interestingly, lactate measurements have also been used to stratify patients. In fact, plasma lactate may be used as

DO_2 = oxygen delivery; VO_2 = oxygen consumption.

Figure 1



Quick response to lactate production following exposure of laboratory animals to hypoxia. The panel on the top represents changes in arterial oxygenation (PO_2) when inspiratory fraction of oxygen (FiO_2) is decreased to 8%. Bottom panel shows corresponding lactate changes.

a tool to discriminate patients with or without hemodynamic failure, a process similar to the early definition of type B lactic acidosis (see earlier). Many of the papers dealing with the oxygen consumption/oxygen delivery (VO_2/DO_2) dependency have included such an approach [16-24].

Therapeutic response

Even more important, however, is the use of lactate measurement as a guide to therapy.

A lactate fall after a volume challenge may reveal a preload-based energy failure. An increase of lactate following a dobutamine challenge test may imply that the oxygen machinery is unable to cope with the new workload [25]. The use of lactate to assess the efficacy of therapy has been recently shown by Rivers and colleagues in their frequently quoted paper [26], and is confirmed by routine clinical use of lactate in many clinical settings such as emergency departments, operating rooms or intensive care units.

Despite the encouraging scenario, however, there are pitfalls for lactate as a clinical marker. Specimen collection, the stability of stored samples, the metabolic effects of blood cells or even technical problems may affect the interpretation of lactate concentrations [27]. Moreover, there are situations in which plasma lactate does not increase despite its local formation (exclusion of the territory from perfusion) or in which the lactate increase does not correspond to energetic failure (neoplastic cells, intoxications, etc.). Nevertheless, we think the use of lactate may be of great value for clinical practice, as long as it is 'interpreted' over time within other signs, symptoms and biophysical measurements.

In the following we will propose a research hypothesis according to which an increase of lactate in critically ill patients may be considered positive when supply dependency occurs. To describe this hypothesis we will first briefly cover the basics of adaptation to tissue hypoxia in order to define 'energy failure'. We will then discuss the role of lactate measurements in the critically ill and the meaning of time to intervention following energy failure.

Adaptation to hypoxia and energy failure

Apart from the easy to understand differences between the fresh water turtle, the hibernating frog and man, there is one major difference: the first two species are able to 'conform' to oxygen deprivation, whereas man definitively needs oxygen to 'regulate' his whole life [28].

The so-called oxygen conformers shut down energy expenditure by arresting transmembrane ion traffic [29]. The energy required for pumping ions across the membrane and against the electrochemical gradient is in fact a great amount of the resting energy expenditure. Ion channel arrest is therefore valuable in decreasing oxygen requirements. Notably, ion channel arrest does not interfere with cell integrity.

Oxygen regulators, such as man, lack this possibility to shut down energy expenditure. They are forced to consume energy irrespective of its supply. Such an imbalance of supply and demand drives the cascade of events that eventually leads the cell to death in the absence of oxygen (i.e. energy substrate) [28].

Man does not always die even in critical hypoxic situations, however, implying that a certain amount of adaptation to hypoxia is possible. Some of the mechanisms of adaptation to acute hypoxia are now described.

Flow redistribution

Blood flows to distal organs according to simple physical laws. Hagen Pousille's law clearly shows that flow depends on the pressure gradient from the initial to the distal point of

flow and on the length and size of the vessels (i.e. resistances). Given an initial pressure (i.e. heart function and vessel tone), the flow distributes according to the least pressure encountered downstream. Basically this is the background for flow distribution to organs, given the local neural control of vessel size that translates into resistance to flow. The vasoconstriction and/or vasodilatation of different vessels in critical conditions therefore allows blood flow to redistribute to first-line organs, the function of which is necessary to maintain integrity of the whole body to survive. This simple yet sophisticated possibility is one of the fundamentals of adaptation to hypoxia.

Flow redistribution, by increasing the number of capillaries per tissue unit, is also one of the cornerstone mechanisms of an oxygen extraction ratio increase.

Partial oxygen 'shut down'

Years ago many authors and clinicians spent much time dealing with the so-called VO_2/DO_2 dependency [30]. This dependency is defined as the critical point below which VO_2 depends on DO_2. The VO_2/DO_2 dependency may be viewed as an adaptive mechanism: the organism, due to a lack of energy, consumes less energy. Perhaps this state was for a long time considered 'bad', but we may provocatively think of it as 'good' (i.e. as a strategy to survive).

This phenomenon may be viewed as an adaptation, thus assimilating man, at least in part, to oxygen conformers.

Metabolic rearrangement

Metabolic rearrangement is impressive. Our complicated metabolic machinery, once the substrate for energy production decreases or even ceases, shifts its pathways to overcome the problem.

One of the most known and important metabolic rearrangements is the Pasteur effect. Under a lack of oxygen, pyruvate derived from the anaerobic conversion of glucose cannot enter the Krebs' cycle via acetyl-coenzyme A to produce energy. The conversion of pyruvate to lactate, despite unfavorable stechiometry, thus allows energy production without oxygen. This is a major adaptive mechanism to survive hypoxia.

Meanwhile, a whole interplay of metabolic pathways favors lactate utilization for gluconeogenesis in the liver [31], decreases glucose oxidation via insulin resistance [32] and even redirects the compartmentalization of glucose/lactate metabolism between different types of cells within the same organ [33].

Acid–base status

According to Stewart's view, lactate production modifies the strong ion difference thus influencing one of the determinants of H^+ concentration. The resulting addition of protons drives the CO_2 dissociation equation, $CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+$, to the left causing CO_2 to dissolve (even if the CO_2 content does not change). Both CO_2 and the protons move the dissociation curve of hemoglobin to the right, thus allowing a better transfer of oxygen to the tissue.

The influence of pH on the adaptive response, however, is possibly even more important. Indeed, while extreme values of acidemia (perhaps below 7.2) interfere with hemodynamic stability, a pH value lower than normal is somewhat essential for adaptation. In fact, while there are tissues whose metabolic rearranged pathways need lactate as an intermediate metabolite to survive [34], the production of lactate itself depends on the pH level [35].

Interestingly, the inhibition of phosphofructokinase by low pH, decreasing the utilization of glucose, may serve as a strategy to spare metabolic fuel avoiding rapid consumption and exhaustion of glucose [36]. Moreover, the pH value controls the rate of lactate uptake from blood by hypoxic skeletal muscles [37].

Gene regulation

Metabolic pathways are driven by dissociation constants and are under tight enzymatic control. However, as we are increasingly learning, several kinds of 'regulations' (adaptive not excluded) are under gene control.

Interestingly, possibly via the amount of reactive oxygen species or directly via the mitochondria [38], cells sense hypoxia and trigger the upregulation of a powerful factor, hypoxia inducible factor-1 [39]. This inducible factor, which is constitutively expressed and rapidly degraded in normoxic conditions, is accumulated during hypoxia. The increased protein stability can activate many of the aforementioned mechanisms of adaptation, including the Pasteur effect [40]. Table 1 summarizes some of the cellular and systemic responses in which hypoxia inducible factor-1 is involved, all of which are of importance in preventing energy failure by rearranging more favorable fuel utilization and by increasing local oxygen delivery.

It is of note that absolute oxygen deprivation at the mitochondria site is the trigger for cell apoptosis [39]. This is another key factor in the genetic regulation of adaptation to hypoxia, allowing programmed cell death (apoptosis) as opposed to the much more harmful cell necrosis.

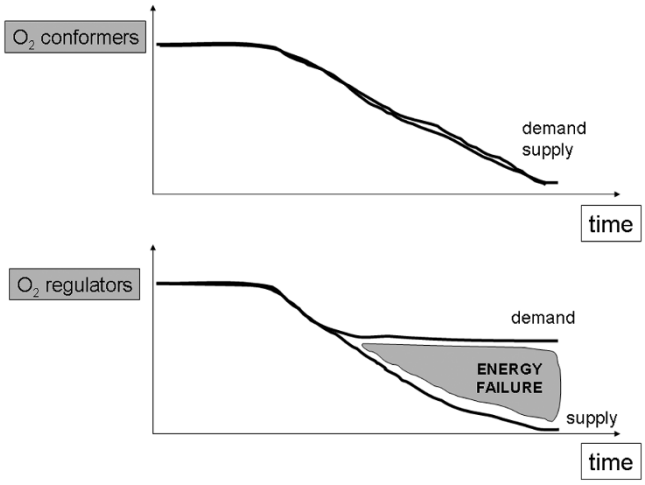
In conclusion, there are several mechanisms by which oxygen regulators may initially adapt to an imbalance between energy supply and energy demand. However, as shown in Fig. 2, contrary to oxygen conformers, man is only able to cope with an energy imbalance to a limited extent. Once the threshold of adaptation is overcome, the obligate need for energy leads to 'energy failure'. This may be accounted for as an unfavorable balance between ATP production and ATP utilization (i.e. ATP turnover) according to the formula

Table 1

Responses to acute and/or chronic hypoxia in which hypoxia inducible factor-1 is involved

Pathway involved	Gene controlled	References of interest
Glycolysis	Aldolase A–C	[46,47]
	Enolase 1	
	Glucose transporter 1–3	
	Glyceraldehyde phosphate dehydrogenase	
	Hexokinase 1–2	
	Lactate dehydrogenase A	
	Phosphofructokinase L	
	Pyruvate kinase 1-M	
Erythropoiesis	Erythropoietin	[48]
Angiogenesis	Vascular endothelial growth factor	[49]
Vascular tone	Endothelin-1	[50-52]
	Hemeoxygenase-1	
	Nitric oxide synthase 2	

Figure 2



Different responses of oxygen conformers and oxygen regulators to oxygen deprivation. Once a threshold of adaptation is reached, oxygen regulators undergo an imbalance between energy supply and energy consumption that leads to 'energy failure'.

describing energy charge: Energy charge = ([ATP] + 0.5[ADP]) / ([ATP] + [ADP] + [AMP]). A ratio between 0.8 and 0.95 is considered normal to survive, implying normal supply for ATP synthesis and structurally intact machinery (i.e. mithocondria).

Energy failure, lactate and time-course of illness

As already mentioned, a hypoxic insult may lead an oxygen-regulated organism to death or to survival according to its ability to adapt to hypoxia. However, even for a given genetic trait, an individual may undergo adaptation or energy failure, depending on time. In fact, if one expressed ATP turnover over time there may be a scenario in which forced hypometabolism rapidly decreases ATP turnover, eventually leading to cell death. On the contrary, a slow decrease of ATP turnover may allow a much longer survival (Fig. 3).

In the acute setting, oxygen conformance is unlikely because a decrease of VO_2 is accompanied by an increase in lactate levels. On the contrary, in the subacute settings, down-regulation of some tissue metabolic activities is possible in order to preserve more essential reactions [41]. There is also evidence that oxygen conformance may exist in chronic diseases in humans: Schumaker and colleagues reported that VO_2, determined indirectly by calorimetry, rapidly increases after percutaneous valvuloplasty in patients with severe aortic stenosis and cardiac cachexia [42].

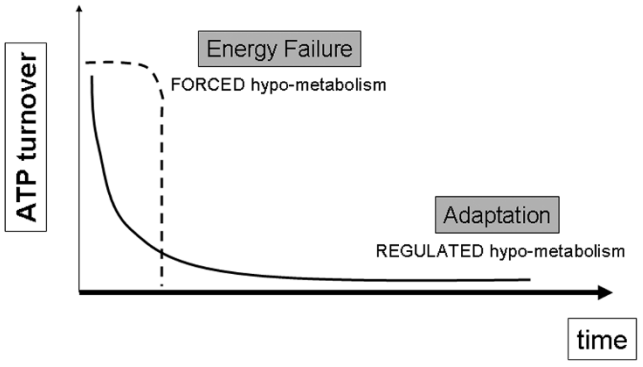
When dealing with energy failure, time is the essence also under a different perspective. In fact, there is a time window in which the hypoxic cell, despite suffering, will revert to a normal state if oxygen is supplied. After a time threshold, however, an energy supply will be of no use. This time frame is our therapeutic opportunity.

Let us consider hemorrhage as an example. Hemorrhage is an acute preload hemodynamic impairment. Provided DO_2 is the product of stroke volume and heart rate (cardiac output) times the oxygen content (respiratory function – arterial oxygen content), the energy failure during hemorrhage is due to a stroke volume deficiency that eventually leads to cell hypoxia. In the presence of normal adaptation processes, however, the cell may cope with hypoxia for a while. If preload is restored meanwhile, once oxygen is back the cell will be able to utilize it because the oxygen machinery (i.e. mitochondria) is still intact.

However, if the lack of oxygen persists, necrosis occurs and organ failure emerges late during the course of illness. At that time, even if an acid load due to cell lysis may persist, the adaptive metabolic rearrangement that previously was responsible for the increase of lactate (see earlier) my cease. Plasma lactate may then decrease over time, provided clearance is not impaired.

Similarly, an exaggerated aerobic glycolysis through Na^+K^+-ATPase stimulation during septic shock may lead to hyperlactatemia [43,44]. However, severe patients with poor outcome have been shown to have mitochondrial dysfunction. In fact, mediators such as nitric oxide may inhibit the respiratory chain in the presence of normoxia or even hyperoxia [45].

Figure 3



ATP turnover expressed over time. The fate of a cell exposed to a decreased ATP turnover is shown. Time is essential to adaptation, the lack of which brings the cell to death.

It thus seems that once oxygen machinery is out of order, whether the initial insult was hemorrhage or sepsis, the therapeutic opportunity is lost. This view may be applied to the literature on the hemodynamic supranormal target. If we consider the paper by Rivers and colleagues [26], it is clear that their intervention was very early in the course of the energy failure process and was very effective (see sections on mixed venous saturation of oxygen and lactate changes over time – few hours), as opposed to the late (third day in the intensive care unit) and ineffective (see section on venous saturation of oxygen) treatment by Gattinoni and colleagues [25].

Conclusion

The metabolic fate of lactate in the body is under sophisticated and finely tuned control. Many different conditions may alter the balance between its production and clearance. This *per se* is a limitation for the use of lactate as a clinical marker in critically ill patients.

Nevertheless, when energy failure becomes relevant, lactate measurement over time may be used as a metabolic marker of energy failure. Contrary to what one may think, an increase of lactate in critically ill patients in the presence of supply dependency may be viewed as a positive feature, indicating the presence of functioning adaptive metabolic pathways! Increased lactate levels may be considered an early marker of a potentially reversible state, possibly indicating that 'there is still room' to boost fast intervention.

Competing interests

Franco Valenza received an honorarium of €500.00 in December 2004 for his presentation on lactate and mitochondria injury in an event organized by Instrumentation Laboratories S.p.a. There are no other financial or non-financial conflicts of interest.

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