

Lactate and shock state: the metabolic view

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Purpose of review

The conventional view in severe sepsis or septic shock is that most of the lactate that accumulates in the circulation is due to cellular hypoxia and the onset of anaerobic glycolysis. A number of papers have suggested that lactate formation during sepsis is not due to hypoxia. I discuss this hypothesis and outline the recent advances in the understanding of lactate metabolism in shock.

Recent findings

Numerous experimental data have demonstrated that stimulation of aerobic glycolysis – that is, glycolysis not attributable to oxygen deficiency – and glycogenolysis occurs not only in resting, well-oxygenated skeletal muscles but also during experimental haemorrhagic shock and experimental sepsis, and is closely linked to stimulation of sarcolemmal Na^+/K^+ -ATPase under epinephrine stimulation. A human study of hyperkinetic septic shock demonstrated that skeletal muscle is a leading source of lactate production by exaggerated aerobic glycolysis through Na^+/K^+ -ATPase stimulation.

Summary

There is increasing evidence that sepsis is accompanied by a hypermetabolic state, with enhanced glycolysis and hyperlactataemia. This should not be rigorously interpreted as an indication of hypoxia. It now appears, at least in the hyperkinetic state, that increased lactate production and concentration as a result of hypoxia are often the exception rather than the rule.

Keywords

epinephrine, hypoxia, lactate, sepsis, shock

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Abbreviation

PDH pyruvate dehydrogenase

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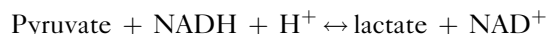
Introduction

Traditionally, hyperlactataemia in critically ill patients and particularly those in shock was normally interpreted as a marker of secondary anaerobic metabolism due to inadequate oxygen supply inducing cellular distress [1]. A number of papers have suggested that lactate formation during sepsis is not due to hypoxia but rather to metabolic processes [2]. This review discusses this hypothesis and outlines the recent advances in the understanding of lactate metabolism in shock.

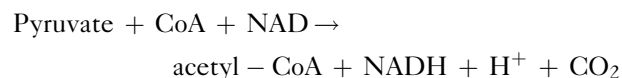
Lactate metabolism

Arterial lactate concentration is dependent on the balance between its production and consumption [3]. In general, this concentration is less than 2 mmol/l, although daily production of lactate is actually 1500 mmol/l. In physiological conditions, lactate is produced by muscles (25%), skin (25%), brain (20%), intestine (10%) and red blood cells (20%), which are devoid of mitochondria. Lactate is essentially metabolized by liver and kidney.

Lactate is produced in the cytoplasm according to the following reaction (Fig. 1):



This reaction favours lactate formation, yielding a 10-fold lactate/pyruvate ratio. Lactate therefore increases when production of pyruvate exceeds its utilization by the mitochondria. Pyruvate is essentially produced via glycolysis; hence any increase in glycolysis, regardless of its origin, can increase lactataemia. Pyruvate is essentially metabolized by the mitochondrial aerobic oxidation pathway via the Krebs cycle:

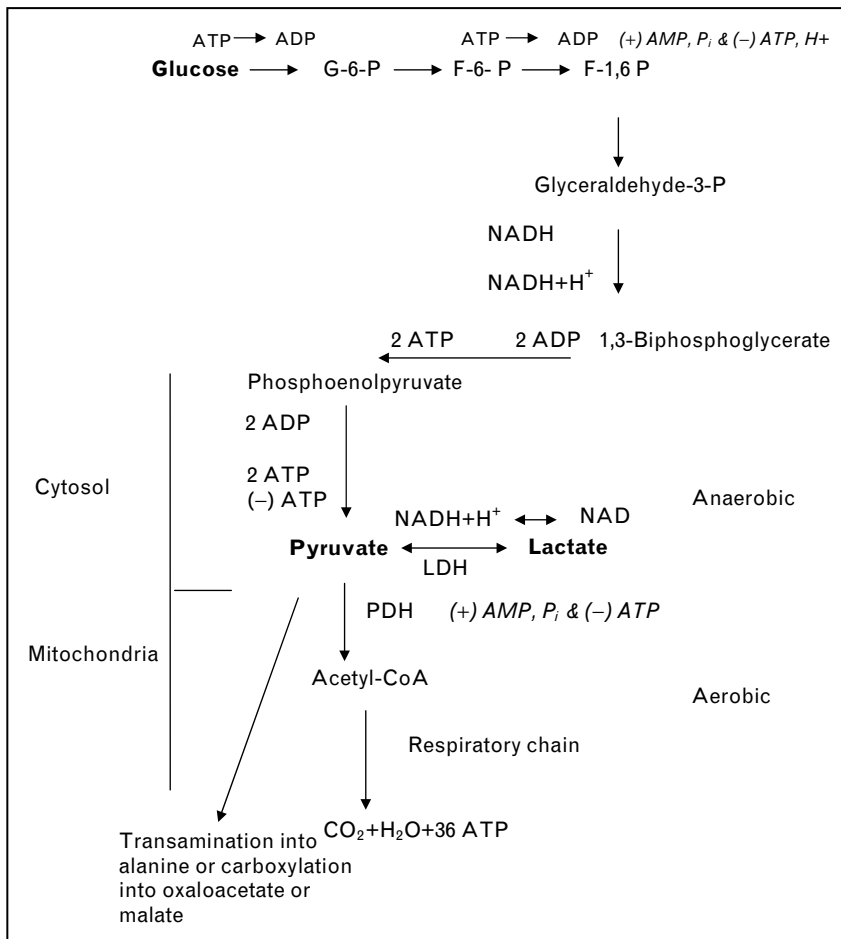


This reaction leads to the production of large quantities of ATP (36 molecules of ATP for one molecule of pyruvate).

Generated lactate can be transformed into oxaloacetate or alanine via the pyruvate pathway or can be utilized directly by periportal hepatocytes (60%) to produce glycogen and glucose (neoglycogenesis and neoglucogenesis; Cori cycle). The kidney also participates in the metabolism of lactate (30%), with the cortex classically acting as the metabolizer by neoglucogenesis and the

Figure 1 An overview of carbohydrate metabolism

F-6-P, fructose 6-phosphate; F-1,6-P, fructose 1,6-bisphosphate; G-6-P, glucose 6-phosphate; Glyceraldehyde-3-P, glyceraldehyde 3-phosphate; P_i, phosphate.



medulla as a producer of lactate. The threshold of renal excretion is 5–6 mmol/l, meaning that, physiologically speaking, lactate is not excreted in the urine.

Hence lactataemia reflects a balance between production and utilization of lactate. Consequently, for the same etiological mechanism producing an increase in lactate, one can either observe hyperlactataemia (if metabolism decreases) or normolactataemia. Understanding this concept is vital, notably to avoid treating solely a numerical value of lactate.

Formation of lactate in cases of tissue hypoxia

By definition, hypoxia blocks mitochondrial oxidative phosphorylation [4], thereby inhibiting ATP synthesis and reoxidation of NADH. This leads to a decrease in the ATP/ADP ratio and an increase of the NADH/NAD ratio. A decrease in the ATP/ADP ratio induces both an accumulation of pyruvate, which cannot be utilized by way of phosphofructokinase stimulation, and a decrease

in pyruvate utilization by inhibiting pyruvate carboxylase, which converts pyruvate into oxaloacetate. An increased NADH/NAD ratio also increases pyruvate by inhibiting pyruvate dehydrogenase (PDH) and hence its conversion into acetyl-CoA.

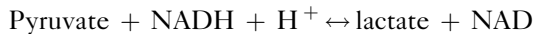
Consequently, the increase in lactate production in an anaerobic setting is the result of an accumulation of pyruvate which is converted into lactate stemming from alterations in the redox potential. This conversion allows for the regeneration of some NAD⁺, enabling the production of ATP by anaerobic glycolysis, although clearly less efficient from an energy standpoint (two molecules of ATP produced compared with 36). It is important to consider that the modification of the redox potential induced by an increase in NADH/NAD ratio activates the transformation of pyruvate into lactate and consequently increases the lactate/pyruvate ratio.

All in all, anaerobic energy metabolism is characterized by hyperlactataemia associated with an elevated lactate/

pyruvate ratio, greater glucose utilization and low energy production.

Lactate/pyruvate ratio

Lactate/pyruvate interconversion can be described by the following equation:



And, at equilibrium

$$\text{Lactate/pyruvate} = K \times (\text{NADH/NAD}) \times \text{H}^+$$

Where K represents the dissociation constant. Therefore, an increase in the NADH/NAD ratio or a drop in cytosolic pH triggers an increase in lactate/pyruvate ratio. The use of this ratio has been advocated for differentiating hypoxia-related hyperlactataemia from hyperlactataemia resulting from an increase in glycolytic flux without hypoxic stress.

However, the above equation clearly demonstrates that this NADH/NAD ratio can be altered by factors other than the inability to transfer electrons to oxygen. Furthermore, for the plasma lactate/pyruvate ratio to properly reflect the redox potential, one would need to demonstrate that this ratio is identical to both cytosolic and mitochondrial ratios and that the rate of cell efflux of pyruvate and lactate also be identical [5]. Lastly, use of a pyruvate assay is precarious since the latter is quickly degraded and can therefore lead to falsely elevated lactate/pyruvate levels.

We have nonetheless demonstrated [6] that this ratio is very high (40 ± 6) in comparison with controls (8 ± 2) in cardiogenic shock patients with low cardiac output, with these patients representing a clinical model of tissue hypoxia (we will see further that this notion can in fact be debated). We also found a definite increase of this ratio in patients with refractory septic shock characterized by elevated catecholamine dosages, low blood pressure, metabolic acidosis and normokinetic state. On the other hand, in stabilized patients with septic shock, this ratio was slightly increased (14 ± 1) or otherwise normal when corrected for pH. Interestingly, for equal concentrations of lactate, septic patients, with the exception of refractory septic-shock patients, have higher pyruvate levels, thus implying a mechanism other than hypoxia. In the end, the prognostic value of the lactate/pyruvate ratio was no better than that of lactate and failed to provide any additional information.

Lactate and shock state

Classically, hyperlactataemia in shock state is considered secondary to tissue hypoxia induced by a decrease in tissue perfusion. This notion is potentially true in certain clinical situations.

Situations where hyperlactataemia is predominantly a reflection of tissue hypoperfusion

Shock states induced by low cardiac output should theoretically be accompanied by a hypoxic hyperlactataemia. Cardiogenic shock, as demonstrated previously, is associated with hyperlactataemia with a very high lactate/pyruvate ratio. In theory, haemorrhagic shock should behave in an identical fashion.

The problem encountered with sepsis is more complex, although at least two situations are usually accompanied with hypoxia-associated hyperlactataemia. The first is septic shock with catecholamine-resistant cardiocirculatory failure, especially in situations of low cardiac output [6]. The second circumstance is septic shock pre-emptively observed prior to volumetric expansion, as illustrated in the study of Rivers *et al.* [7] in which hyperlactataemia was associated with signs of poor oxygen delivery. These two situations are nonetheless close to low output states.

Situations where hyperlactataemia reflects a metabolic adjustment, such as in sepsis

Many argue against tissue hypoxia as the major cause of hyperlactataemia in septic shock. Theoretically, if septic-shock hyperlactataemia was indeed induced by tissue hypoxia caused by hypoperfusion, then (i) hyperlactataemic septic patients should display collapsed oxygen delivery, which should be corrected with increased O_2 transport, which is not the case [8]; (ii) tissue PO_2 should be low, although, and in contrast to cardiogenic shock, muscle PO_2 measured in septic-shock patients is actually elevated [9]; (iii) ATP levels should be decreased, yet these levels were found to be normal when measured in human muscle, as in many animal models [10]; (iv) dichloroacetate, a PDH activator, should not lower lactataemia in septic patients or animals since it increases the conversion of pyruvate into acetyl-CoA used in the respiratory chain; however, numerous animal models and several human studies have shown that dichloroacetate significantly decreased lactataemia in septic states [11]; and (v) finally, it has been postulated that lactate may originate from a regional source. Splanchnic circulation was initially targeted but De Backer *et al.* [12] demonstrated that the splanchnic area in general consumed lactate and that splanchnic production was uncommon and in no case quantitatively sufficient to explain systemic hyperlactataemia. The lungs can also produce lactate, essentially in acute respiratory distress syndrome, although this is mostly explained by the presence of infiltrating inflammatory cells [13] and not by hypoxia.

Aerobic production of lactate

On a biochemical point of view, aerobic is defined as any situation involving oxygen. Lactate formation occurring during the first part of glycolysis is termed anaerobic, as it

does not require the presence of oxygen. Here aerobic will be defined by any situation in which oxygen is available.

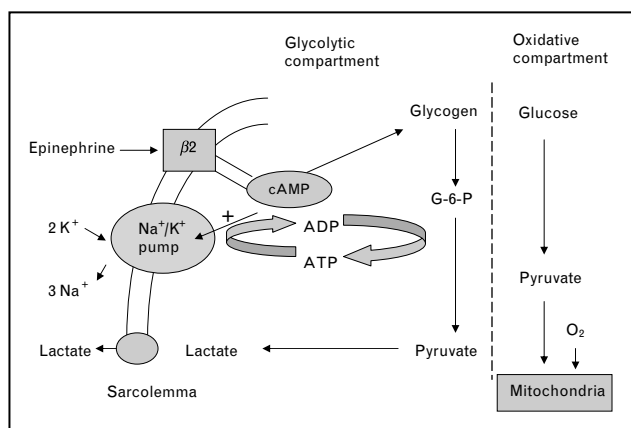
A sepsis-associated inflammatory state induces an increase in pyruvate production combined with accrued synthesis of mRNA of the glucose transporter GLUT-1 [14]. This state, called accelerated aerobic glycolysis, occurs when the rate of carbohydrate metabolism exceeds the oxidative capacity of the mitochondria. Pyruvate is produced by an increased influx of glucose [15] but also via muscle protein catabolism, releasing amino acids subsequently transformed into pyruvate and thereafter lactate. Accelerated aerobic glycolysis is induced by endogenous/exogenous catecholamine and inflammatory state. The hypothesis was further sustained by Gore *et al.* [15], who demonstrated that pyruvate production and oxidation are increased in septic patients. Moreover, PDH dysfunction has been described in sepsis and thus may participate in the accumulation of pyruvate [16].

Compartmentalization of glycolysis, epinephrine, muscle and Na^+/K^+ -ATPase pump

Cytosolic glycolytic flux is functionally divided into two distinct compartments. There are two distinctive glycolytic pathways utilizing separate glycolytic enzyme pools. The first pathway participates in oxidative metabolism via the Krebs cycle. The second pathway is linked to activity of the Na^+/K^+ -ATPase pump (Fig. 2 [17]). Indeed, ATP produced by this pathway is used to fuel this membrane pump [18,19].

Numerous studies [20,21] have demonstrated that epinephrine, via β_2 -adrenoceptor stimulation, increases

Figure 2 Epinephrine-increased glycolysis is coupled to Na^+/K^+ -ATPase activity



The ATP furnished by the glycolysis under epinephrine stimulation is used to fuel Na^+/K^+ -ATPase activity. β_2 , β_2 -adrenoceptor; G-6-P, glucose 6-phosphate. From [17].

cAMP production, inducing the stimulation of glycogenolysis and glycolysis (ATP production) as well as activation of the Na^+/K^+ -ATPase pump, which in turn will consume this ATP, thereby producing ADP. This generated ADP via phosphofructokinase stimulation will reactivate glycolysis and hence generate more pyruvate and thereafter lactate. Muscle tissue, which represents approximately 40% of total cell mass in the body, is particularly implicated in this mechanism, not to mention that over 99% of muscle adrenergic receptors are β_2 receptors [22].

To confirm this hypothesis, we utilized muscle microdialysis in hyperlactataemic septic-shock patients under catecholamine treatment. This technique consists of inserting into the quadriceps muscle a very fine catheter perfused with a liquid similar to the extracellular medium, but lactate-free. The catheter is comprised of a membrane similar to a dialysis membrane, therefore enabling one to retrieve, following an equilibrium period, a fluid that is in equilibrium with the interstitial fluid. When the liquid is perfused very slowly ($0.3 \mu\text{l}/\text{min}$), the composition of the collected fluid is equal to the composition of the interstitial fluid. Furthermore, it is possible to add a biologically active substance to the perfusate whose effect will be strictly limited to cells surrounding the catheter. Finally, by measuring the arterial concentration of the compound of interest, one can establish an interstitial muscular-arterial gradient which, if positive, indicates production by the muscles.

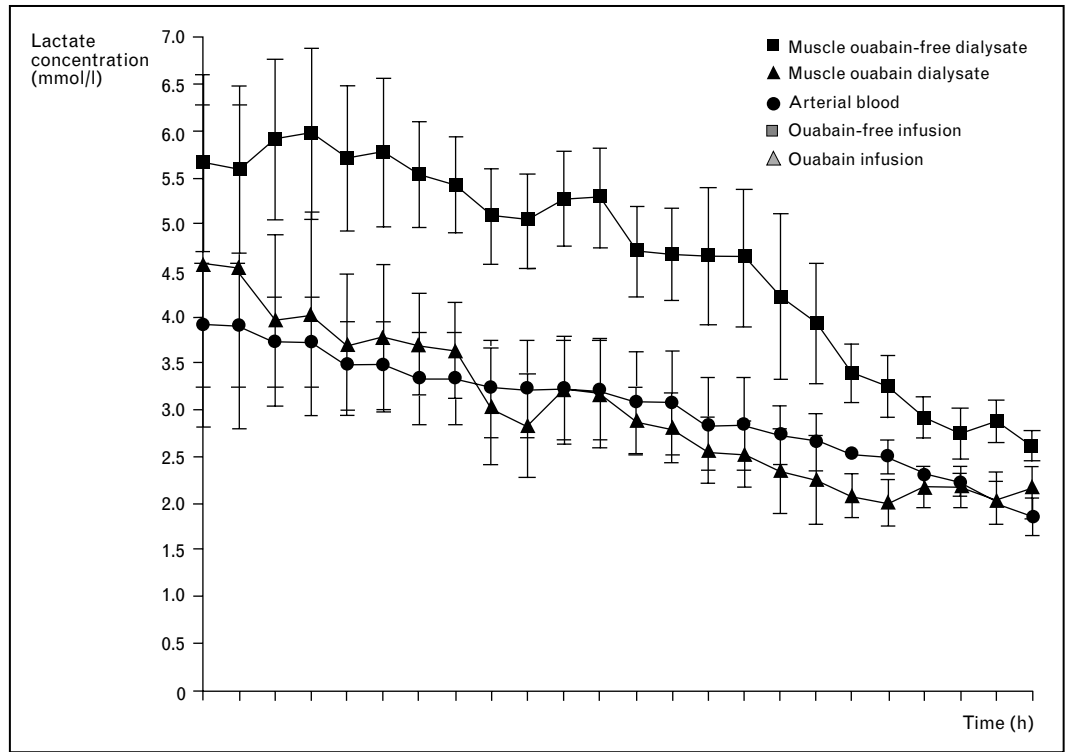
Our working hypothesis stipulated that epinephrine, secreted in response to a shock state, boosted production of muscle lactate by activating the Na^+/K^+ -ATPase pump. We therefore introduced two microdialysis catheters, the first perfused with lactate-free Ringer's and the second perfused with the same solution in combination with ouabain, a selective inhibitor of the Na^+/K^+ -ATPase pump. A key finding revealed that muscle lactate was consistently greater than arterial lactate, thus indicating muscle production and that this production was totally inhibited by ouabain, confirming a Na^+/K^+ -ATPase-dependent mechanism, but independent of tissue hypoxia [23**] (Fig. 3).

Significance

Muscle lactate, produced under the effect of epinephrine and released into the bloodstream, is utilized by the liver to produce glucose through neoglucogenesis (the Cori cycle; Fig. 4 [24]) or by other cells for oxidative purposes. Neoglucogenesis is associated with a lower energetic efficiency since two ATP molecules are produced per molecule of glucose to generate lactate, while six molecules of ATP are consumed for every molecule of glucose generated from lactate. This

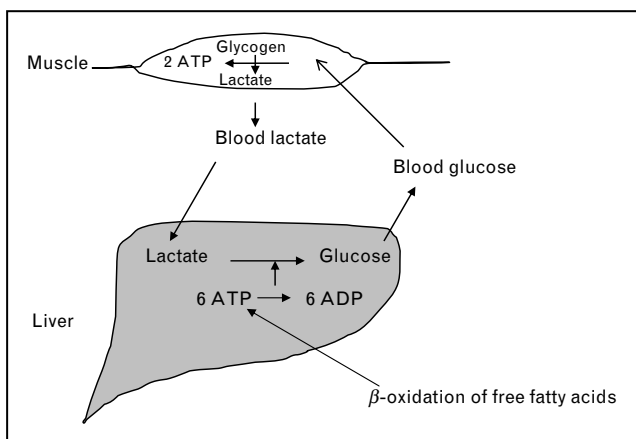
Figure 3 Lactate concentration in 14 patients with septic shock in 24 h of study

From [23**] with permission.



process nonetheless allows the liver to use the ATP generated by fatty acid β -oxidation to produce glucose. Hence, fatty acids which supply large quantities of

Figure 4 Cori cycle: lactate is produced by muscle and released into the blood



Lactate reaches the liver where it enters the Cori cycle and becomes glucose. The energy for such gluconeogenesis is supplied by β -oxidation of fatty acids. The glucose produced by this mechanism is either used locally or recycled to supply fast energy to cells. These pathways ensure conversion of slow energy stored as fat into fast energy that is readily available as glucose. Such fast energy is used to sustain the increased glycolytic flux necessary to meet the metabolic demands of severe sepsis [24].

available energy, albeit in a slow process, are used to produce limited stocks of glucose. This mechanism underscores the pivotal role of lactate during aerobic energy metabolism. The 'lactate shuttle' theory suggests that aerobic production of lactate represents an important mechanism by which various tissues share a common source of carbons for oxidation and other biochemical processes such as neoglucogenesis. Hyperlactataemia in shock states may therefore constitute an adaptive protective mechanism by favouring the oxidation of lactate rather than that of glucose in tissues where oxygen content is rare. Thus an elevated lactate/pyruvate ratio is an indicator of a cytoplasmic accumulation of reduced equivalents (NADH) from which NADH can be used to regenerate ATP ($ADP + NADH + H^+ \rightarrow ATP + NAD$). Henceforth, the combination of lactate/pyruvate could be considered as an adaptive energetic substrate, able to navigate from cell to cell or from organ to organ [25].

This hypothesis is largely supported by several experimental studies demonstrating for example that the brain [26] or heart can utilize lactate as a preferred source of energy in certain situations of stress. It was also demonstrated that lactate depletion in the myocardium resulting from haemorrhagic shock reduced myocardial performance [27].

Other aetiologies of non-hypoxic hyperlactataemia

Increased lactate requires a thoughtful differential diagnosis in the critically ill.

Reduction in lactate clearance

Levrant *et al.* [28] have elegantly demonstrated through the use of labelled lactate that persistent hyperlactataemia in haemodynamically stable septic-shock patients not treated by catecholamine was due to a reduction in lactate clearance and not an increase in lactate production. Reduced lactate utilization in stable patients with sepsis therefore may contribute to mild hyperlactataemia. On the other hand, using a similar method, Revely *et al.* [29**] recently demonstrated that in sepsis and cardiogenic shock, hyperlactataemia was mainly related to increased production, whereas lactate clearance was similar to healthy subjects. Increased lactate production was concomitant to hyperglycaemia and increased glucose turnover, suggesting that the latter substantially influences lactate metabolism during critical illness. The differences between the two studies might be explained by methodological differences in measuring lactate clearance. Revely and colleagues [29**] used a continuous-infusion method, as opposed by the bolus injection method used by Levrant *et al.* [28]. More likely explanations are that the lactate level was higher in Revely *et al.*'s [29**] study (3.2 ± 2.6 compared to 2.6 ± 0.6 mmol/l) and that patients in Levrant *et al.*'s [28] study were weaned from catecholamines.

Pyruvate dehydrogenase dysfunction

PDH converts pyruvate into acetyl-CoA, allowing pyruvate to enter the mitochondria. PDH activity was found to be lower in septic muscle and restored by dichloroacetate. Dichloroacetate lowers lactataemia in septic patients. It is therefore likely that there is a certain degree of dysfunction or saturation of PDH activity in septic states [30], although this phenomenon remains secondary.

Protein degradation

Protein catabolism generates the release of amino acids, which are converted into pyruvate and thereafter into lactate.

The prognostic value of lactate

Regardless of the mechanism of production, hyperlactataemia and especially the persistence of hyperlactataemia remains a major prognostic factor in diseases with aetiologies as varied as polytrauma or shock, whether it be septic, haemorrhagic or cardiogenic [31,32]. Persistence of an elevated lactate level can be due to an incessant overproduction related to a persistence of the initiator mechanism but also to a lowering of lactate, clearance notably due to hepatic dysfunction.

Line of conduct when facing hyperlactataemia

Lactate must be assayed in all predisposing situations leading to its formation and particularly in the diagnosis and follow-up of shock states, including all cases of severe sepsis. Rivers *et al.* [7] demonstrated for example that a large proportion of patients with severe sepsis without hypotension exhibited hyperlactataemia and low central venous oxygen saturation (ScVO₂) and that this hyperlactataemia was corrected during ensuing care management.

Initiated treatment should be based on alleged mechanisms of formation but mostly on observed physiopathological disorders as they relate to objective parameters warranted by the situation: cardiac output, blood pressure, echocardiography, mixed venous oxygen saturation (SVO₂) and abdominal pressure. Lactate can be used to monitor efficiency of initiated therapy in so far as confounding factors such as catecholamines and particularly epinephrine and also hepatic function are taken into account. The major concern of the treating critical-care specialist when facing hyperlactataemia – and even more so when it is accompanied by metabolic acidosis – is cardiovascular dysfunction, regardless of its origin. Once this diagnosis is eliminated, when warranted, by treatment aimed at increasing oxygen delivery, the aetiological diagnosis will rest on knowledge of the various aetiologies involved. To date, there is no specific treatment available; furthermore, several physiopathological components as mentioned above actually suggest that hyperlactataemia could even be beneficial.

Conclusion

Measurement of plasma lactate remains a primordial component for a sound diagnostic and therapeutic line of conduct in critical care. The concept of lactate merely as a metabolic waste product (bad lactate) has now evolved towards lactate being viewed as an energy shuttle (good lactate). In most clinical critical-care situations, hyperlactataemia must be perceived as an adaptive response to an aggressive state and not as a marker of tissue hypoxia. Nevertheless, irrespective of its mechanism of formation, hyperlactataemia remains an excellent prognostic marker.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 370–371).

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