# Lactate

*Ricardo Castro, David Carpio, and Glenn Hernández*

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**Learning Objectives**

The purpose of this chapter is to review the physiological basis of lactate production and clearance, its major determinants during shock states, and to provide some clues to aid in the interpretation of lactate levels in the intensive care unit (ICU) setting.

## 17.1 Introduction

Lactate is a key metabolic parameter that has traditionally been related to hypoperfusion and hypoxia during acute circulatory dysfunction [1–4]. In fact, persistent hyperlactatemia is a strong adverse prognostic factor during shock states, and on the contrary, a decrease in lactate levels during resuscitation is associated with enhanced change of recovery and has been considered as a marker of reperfusion [5–9]. For these reasons, lactate assessment is recommended as a fundamental part of the monitoring of the critically ill patient. Moreover, hyperlactatemia was incorporated into the latest septic shock definition [10] and proposed as a resuscitation goal by the Surviving Sepsis Campaign (SSC) [11].

In this chapter, we will review the physiological basis of lactate generation and clearance, its major determinants during shock states, and provide some clues to aid in the interpretation of lactate levels in the critically ill patient.

## 17.2 Anaerobic Lactate Generation

Lactate is produced in all human cells as part of intracellular handling of glucose [12–14]. The metabolism of glucose into two molecules of pyruvate generates two net adenosine triphosphate (ATP) molecules and does not require oxygen ($O_2$), thus being called anaerobic glycolysis. Pyruvate can be metabolized through different pathways, being the most relevant its conversion to lactate by the lactate dehydrogenase (LDH) or the mitochondrial Krebs cycle depending on the activity of the pyruvate dehydrogenase complex (PDH) and $O_2$ availability. The conversion of pyruvate into lactate regenerates nicotinamide adenine dinucleotide (NAD), a key cofactor to maintain glycolysis [12].

Anaerobic glycolysis is the mechanism by which hypoperfused cells can produce ATP, and its rate can increase several times compensating up to some point the actual decrease in mitochondrial function (Fig. 17.1). During overt or occult hypoperfusion, increased anaerobically generated lactate is released into the circulation and can alert physicians on the presence of under-resuscitated tissues. Classical experimental data suggested that anaerobic lactate production increases when $O_2$ delivery falls below a critical threshold upon which $O_2$ consumption becomes supply dependent [3, 15]. In this context, when systemic and regional flow and tissue oxygenation are restored, lactate can be removed through specific monocarboxylate transporters (MCT) by the same cells where it was released and reconverted into pyruvate and enters the Krebs cycle, signaling a successful resuscitation [12]. However, severe microcirculatory abnormalities might preclude restoration of tissue oxygenation, and several studies have found a good correlation between these abnormalities and progressive hyperlactatemia [16, 17, 18].

Two clinically measurable variables that have been proposed as closely representing tissue hypoxia are the venous-arterial $CO_2$ to arterial-venous $O_2$ content difference ratio ($Cv\text{-}aCO_2/Da\text{-}vO_2$) [19] and the lactate/pyruvate (L/P) ratio [20]. Both ratios might constitute an expression of anaerobic metabolism at the cellular level and thus can be linked to hypoxia. Thus, they might aid in suggesting a hypoxic source of lactate.

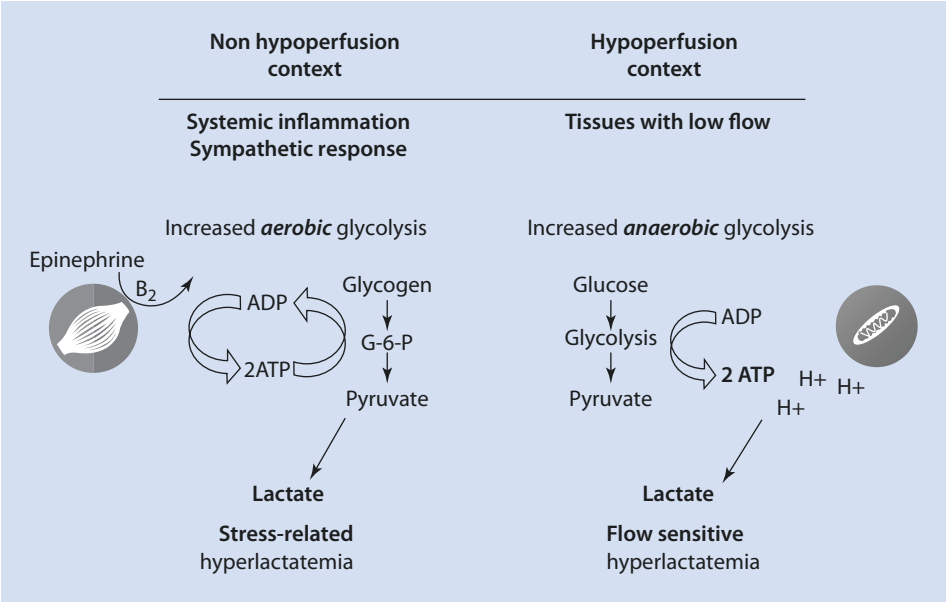


**Fig. 17.1** The figure shows the two main mechanisms involved in lactate generation: anaerobic glycolysis in hypoperfused tissues and adrenergic-driven aerobic glycolysis at the muscle level

This Cv-a$CO_2$/Da-v$O_2$ ratio might be useful as a surrogate of the respiratory quotient [19, 21, 22]. A ratio ≥1.4 could identify anaerobic $CO_2$ generation [19, 21, 22]. A high Cv-a$CO_2$/Da-v$O_2$ ratio in the setting of hyperlactatemia may favor anaerobic metabolism as the possible source of lactate, while a normal Cv-a$CO_2$/Da-v$O_2$ ratio may suggest that lactate accumulation is due to non- hypoperfusion-related causes [19, 21, 22]. In a recent study, we observed that persistent hyperlactatemia combined with a high Cv-a$CO_2$/Da-v$O_2$ ratio was associated with severe organ dysfunctions and mortality, while simultaneous normalization of lactate and Cv-a$CO_2$/Da-v$O_2$ ratio was associated with the best outcome [19].

Several authors have suggested that pyruvate should be measured together with lactate to discriminate hypoxic from non-hypoxic sources of lactate [20, 23]. In anaerobic conditions, pyruvate is transformed to lactate, and thus the L/P ratio increases to ≥18 [23]. The L/P ratio might be one of the most reliable indexes of hypoxia in critically ill patients, but it has never been extensively used because of technical difficulties with measuring pyruvate.

## 17.3 Aerobic Lactate Generation

During systemic inflammation, sepsis, and shock states, activation of the compensatory adrenergic neurohormonal complex leads to an increase in epinephrine levels which is proportional to the magnitude of the injury. Epinephrine stimulates skeletal muscle beta-2 adrenergic receptors increasing cyclic AMP activity, thus promoting glycogenolysis and aerobic glycolysis with concomitant activation of the Na+/K+-ATPase pump [12, 14] (Fig. 17.1). Generated pyruvate eventually overwhelms PDH capacity during severe stress and inflammation, therefore increasing conversion to lactate. Lactate is exported

and can be used as a metabolic fuel by other groups of muscle cells or remote organs such as the brain and the heart during stress and shock conditions [12].

Adrenergic-driven lactate production is an aerobic process, since it occurs in the presence of adequate muscle oxygenation and constitutes a fundamental metabolic shuttle. It can be modulated in experimental and clinical settings by blocking the Na+/K+-ATPase pump or by decreasing adrenergic tone [24, 25] (◘ Fig. 17.1).

Additionally, many other causes such as the presence of necrotic or infected tissue, and PDH inhibition by inflammatory mediators, might contribute to enhanced lactate production during systemic inflammation [12].

## 17.4 Lactate Generation During Acute Circulatory Dysfunction

The distinction between anaerobic and aerobic lactate generation is somehow artificial and didactic. Increased lactate production is always multifactorial during shock states. In fact, as tissue hypoperfusion evolves, the cells shift ATP generation to anaerobic glycolysis as a basic survival mechanism, and simultaneously the compensatory neurohormonal response activates aerobic glycolysis at the muscle level. In successfully resuscitated patients, lactate production decreases in relation both to reperfusion and deactivation of the adrenergic response [1]. On the contrary, persistent and progressive hyperlactatemia is a hallmark of refractory shock probably representing the sum of hypoxia, toxic hyperadrenergia, and other mechanisms [1].

## 17.5 Lactate Clearance and Kinetics

Approximately 1500 mmol of lactate is produced daily under physiological conditions, and the most relevant metabolizing organs are the liver and the kidneys. Together these organs account for more than 90% of systemic clearance, either by oxidation or neoglucogenesis through the Cori cycle [12–14].

Lactate clearance has been defined by a change of lactate levels between two time points and expressed as a 10–20% hourly lactate reduction or a decrease of at least 10% in 6 h during early resuscitation [12–14]. However, clearance is more strictly a pharmacokinetic term used to describe drug or endogenous substance elimination from the organism. In this sense, the term "lactate clearance" has been incorrectly used in the medical literature since a decrease in lactate levels could be induced either by a decreased aerobic or anaerobic generation or increased lactate clearance [1, 26]. Therefore, it is better to use the term "lactate kinetics" or "time course" [26].

A recent systematic review on lactate kinetics found a heterogeneous pattern of evolution of lactate levels in critically ill patients, where some patients decrease, others increase, and others exhibit a stable course over time in response to therapy [26]. Based on these observations, it appears that reassessing lactate every 1 or 2 h is sufficient in most clinical conditions.

The liver which is responsible for 60% of systemic lactate clearance is a vulnerable organ during sepsis-related acute circulatory dysfunction. Liver dysfunction in the context of uncontrolled sepsis or hepatosplanchnic hypoperfusion in septic shock could affect lactate handling by the liver [12, 27–29]. However, it is noteworthy that persistent hyperlactatemia has only been related to a liver dysfunction in the setting of severe shock with clear ischemia as expressed by an increase in liver enzymes or hypoglycemia or in advanced

cirrhosis [27, 28]. Indeed, there is a relative lack of comprehensive physiological studies addressing the role of the liver in persistent hyperlactatemia, and experimental and clinical studies so far have provided conflicting results.

In a recent physiological study, we addressed the role of hepatosplanchnic perfusion in lactate kinetics during resuscitation [27]. A cohort of 15 hyperdynamic septic shock patients under active resuscitation were subjected to a special monitoring including serial lactate assessments, together with gastric tonometry and plasma disappearance rate of indocyanine green (ICG-PDR (LiMON, Pulsion Medical Systems, Munich, Germany)). ICG-PDR depends on liver flow and function, but since function does not change in short periods of time, a decrease in PDR from a normal range of 20–30%/min is assumed to reflect hypoperfusion. Patients with versus without an impaired lactate decrease at 6 h exhibited hepatosplanchnic hypoperfusion as revealed by both techniques (ICG-PDR (9.7 vs 19.6%/min, $p < 0.05$) and $pCO_2$ gap (33 vs 7.7 mmHg, $p < 0.05$)). Systemic hemodynamics was comparable between groups, once again highlighting the fact that normal macrohemodynamics does not rule out the presence of hepatosplanchnic hypoperfusion. However, the most interesting aspect is that liver enzymes including transaminases did not differentiate patients that decreased or not lactate [27]. This could mean that a potential role for liver dysfunction in abnormal lactate kinetics cannot be ruled out just by looking at systemic parameters of any kind.

A moderate impairment of whole body lactate clearance was demonstrated by Levraut et al. in a cohort of stable septic patients with mildly elevated lactate levels but without vasopressors [30]. For real clearance assessment, a bolus of 1 mmol/kg of sodium lactate was infused via a central venous catheter over 15 min. Serial arterial blood samples for lactate assessment were taken at baseline, during the infusion, and, then, sequentially for 40 min after the lactate bolus. Clearance was later analyzed using the least squares method with semi-logarithmic coordinates [30]. This study demonstrated that lactate clearance can be impaired in septic patients in a subclinical way even without evident circulatory dysfunction, suggesting a metabolic dysfunction.

To explore this subject more profoundly, we performed a series of experimental studies [31, 32]. Our objectives were to establish the kinetics and severity of exogenous lactate clearance impairment during endotoxic (LPS) shock and to explore a potential role for liver hypoperfusion in the early phase of shock [31]. After anesthesia, 12 sheep were subjected to hemodynamic/perfusion monitoring including hepatic vein and portal catheterization, and a hepatic ultrasound flow probe, and then randomized to LPS or sham. After 60 min of shock, the LPS animals were resuscitated with fluid and vasopressors. Serial assessments of all parameters including repeated exogenous lactate and sorbitol clearances were performed up to 2 h after shock resuscitation. Progressive hyperlactatemia was observed in LPS animals reaching 10.2 mmol/L at 2 h. In parallel, exogenous lactate clearance decreased to 10% of the value of sham animals at the end of the experiment. This severe impairment was not related to liver hypoperfusion since hepatic oxygen transport, consumption and extraction, total hepatic blood flow, ex vivo mitochondrial respiration, transaminases, and sorbitol clearance (a flow-related parameter) were comparable between LPS and sham animals [31]. In a subsequent study using the same model, we demonstrated that abnormalities in exogenous whole body and hepatic lactate clearance could be attenuated with the use of adrenergic modulators such as dexmedetomidine and esmolol [32]. In this later study, parallel samples of hepatic vein and portal and arterial catheters were taken for serial lactate assessment after the sodium lactate bolus, finding that there was no gradient between hepatic vein and portal lactate levels, suggesting a negligible liver extraction (non-published observations on study [31]).

In summary, it appears that the contribution of the liver to persistent hyperlactatemia might be much higher than previously thought, and the mechanisms are probably multifactorial. Doubtlessly, hepatosplanchnic ischemia could contribute in some cases especially in, but not limited to, severe septic shock and with or without alterations in classic liver enzymes.

On the other hand, a severe impairment of exogenous lactate clearance not related to liver hypoperfusion has been shown in experimental conditions. If this is adaptive or maladaptive, a metabolic dysfunction or eventually is caused by liver microcirculatory abnormalities is a matter for further research.

## 17.6 Transition to Hyperlactatemia

The balance between production and clearance maintains normal lactate levels even under conditions of increased lactate generation as in systemic inflammation or mild circulatory dysfunction. The transition from normal lactate levels to hyperlactatemia reflects the transition from a physiological equilibrium to a pathophysiological decompensated state affecting one or more of the mechanisms involved in normal lactate metabolism [1].

Therefore, and not surprisingly, progressive hyperlactatemia is associated to a bad prognosis in different clinical settings [2, 4, 6, 7, 33]. Indeed, since the report by Scherer in 1843, a significant amount of evidence accumulated in the literature demonstrates that progressive hyperlactatemia is associated with significant morbidity and mortality [33–35]. Many studies have emphasized the prognostic relevance of either a single elevated lactate level or impaired lactate decrease during resuscitation. Remarkably, the prognostic value of lactate levels seems to be independent from the underlying critical illness and the presence of shock and is superior to macrohemodynamic parameters in predicting outcome in different critical patients' populations, including sepsis. More recently, an analysis of a large SSC dataset confirmed that persistent hyperlactatemia is a useful predictor of outcome in severe sepsis and septic shock patients [33].

**Practical Implications**

1. Both the recent Sepsis-3 consensus [10] and the fourth hemodynamic recommendations of the SSC [11] fail to address a key issue: the heterogeneity of the mechanisms that can lead to progressive hyperlactatemia in patients with sepsis-related acute circulatory dysfunction [36, 37]. The apparently homogeneous risk of death among septic shock patients brought by the Sepsis-3 definition and the proposal of lactate normalization as the main resuscitation goal by SSC guidelines are highly controversial issues that lack strong physiologic foundations [35–37].

   In fact, persistent hyperlactatemia is particularly difficult to interpret in the clinical setting. As stated above, at least three possible pathogenic mechanisms might be involved: anaerobic glycolysis in hypoperfused territories especially in the presence of severe microcirculatory abnormalities [1, 17, 18, 38], stress-related adrenergic-induced aerobic glycolysis [12], and impaired hepatic lactate clearance [30–32]. The most crucial challenge is to try to identify the predominant mechanism for each patient. This is a key aspect since only some of these mechanisms such as persistent hypoperfusion might respond to systemic flow optimization, a condition that we call flow sensitivity, and others will clearly not.

To recognize a clinical pattern of hypoperfusion-related hyperlactatemia is highly relevant since optimizing systemic blood flow in this setting could revert ongoing hypoperfusion and improve prognosis. In contrast, pursuing additional resuscitation in non-hypoperfusion-related cases might lead to the toxicity of fluid overload and excessive vasoactive drugs, eventually increasing morbidity or mortality [1].

2. The rate of lactate decrease or normalization has been related to survival and tested as a goal in two important studies with conflicting results [9, 39]. More recently, Shapiro et al. reported that lactate normalization was the strongest predictor of survival (adjusted OR, 5.2; 95% CI, 1.7–15.8), followed by lactate decrease >50% in 6 h (OR, 4.0; 95% CI, 1.6–10.0) in a cohort of 187 septic shock patients subjected to early resuscitation [40].

   However, there are several unresolved aspects and concerns about the role of lactate as an appropriate resuscitation target. First, it is not clear if selecting lactate decrease versus lactate normalization as resuscitation goals is equivalent but, more importantly, if this decision leads to similar timely resolution of tissue hypoperfusion or hypoxia. Eventually, only lactate normalization may assure the absence of hypoxia, although this is controversial [40]. Second, since non-hypoperfusion-related causes of hyperlactatemia might predominate in an unknown number of patients, this could lead to over-resuscitation in at least some of them as stated above. Third, the kinetics of recovery of lactate might exhibit a biphasic pattern, and therefore, the real-time response of lactate to fluid challenges could be not straightforward depending on the hypoperfusion context [41]. Some survivors might even normalize lactate only after 24 h of evolution [41].
3. We recently proposed that a simultaneous analysis of central venous $O_2$ saturation ($ScvO_2$), central venous-arterial $pCO_2$ gradient ($P(cv\text{-}a)CO_2$), and peripheral perfusion assessed by the capillary refill time (CRT) might be helpful in suggesting a hypoperfusion context for patients with or without hyperlactatemia [1] (◘ Fig. 17.2). The presence of a low $ScvO_2$ clearly indicates an imbalance in the $O_2$ transport/$O_2$ consumption relationship [1]. In the case of $P(cv\text{-}a)CO_2$, an inverse curvilinear relationship between $Pcv\text{-}aCO_2$ and cardiac output exists, highlighting the importance of blood flow on venous $CO_2$ accumulation [1, 42]. Even more, high $Pcv\text{-}aCO_2$ could potentially identify septic patients who remain inadequately resuscitated despite achieving oxygen metabolism targets, reinforcing the notion of $P(cv\text{-}a)CO_2$ as a better marker of global perfusion [42]. The assessment of peripheral perfusion may provide additional physiological information. An abnormal peripheral perfusion may be caused by adrenergic-induced skin vasoconstriction secondary to a low systemic blood flow and should prompt at least a reassessment of preload status [43].

   In a retrospective proof-of-concept study in 90 hyperlactatemic septic shock patients, we tested if these criteria could effectively identify a subgroup with higher risk [44]. Patients exhibiting either a $ScvO_2 < 70\%$, a $P(cv\text{-}a)CO_2 \geq 6$ mmHg, or a CRT $\geq 4$ sec at ICU admission were categorized as patients with a hypoperfusion context. Seventy patients met this category and required more vasopressors and inodilators. They also tended to have higher ICU and hospital length of stay, mechanical ventilation days, positive fluid balance, and rescue therapy requirements. Only 1 of 20 hyperlactatemic patients without a hypoperfusion context died (5%) compared to 11 of the 70 with hypoperfusion-related hyperlactatemia (16%), although this difference fell short of significance [44].

4. From a theoretical point of view, these three easily assessable perfusion-related variables offer an important advantage over lactate as potential targets for fluid resuscitation in septic shock patients: they are clearly flow-sensitive and exhibit a faster recovery rate after systemic blood flow optimization. In other words, these parameters might clear in minutes in fluid-responsive patients as compared to lactate which sometimes takes hours to recover. We demonstrated this point by analyzing the kinetics of recovery of these parameters in a cohort of ultimately surviving septic shock patients. $ScvO_2$, $P(cv\text{-}a)CO_2$, and CRT were already normal in almost 70% of the patients after 2 h of fluid resuscitation, as compared with only 15% in the case of lactate [41].

   However, there are also a couple of drawbacks for some of these perfusion-related flow-sensitive parameters. $ScvO_2$ is a complex physiological variable. It was widely used until recently as the resuscitation goal in critically ill patients [1], although several limitations may preclude a straightforward interpretation of its changes [1]. For instance, normal or even supranormal $ScvO_2$ values do not rule out global or regional tissue hypoxia for several reasons that have been highlighted elsewhere, but that include severe microcirculatory derangements impairing tissue $O_2$ extraction capabilities [1]. Vallee et al. found persistent abnormal $P(cv\text{-}a)CO_2$ values in 50% of septic shock patients who had already achieved normal $ScvO_2$ values after initial resuscitation [42]. Nevertheless, in some hyperdynamic states, a high efferent venous blood flow could be sufficient to wash out the global $CO_2$ generation from hypoperfused tissues, and thus, $Pcv\text{-}aCO_2$ could be normal despite the presence of tissue hypoxia [1]. Another problem for these two variables is that they necessarily require a central venous catheterization to be assessed, a task that might be complex to perform in limited-resource settings or emergency departments (ED).

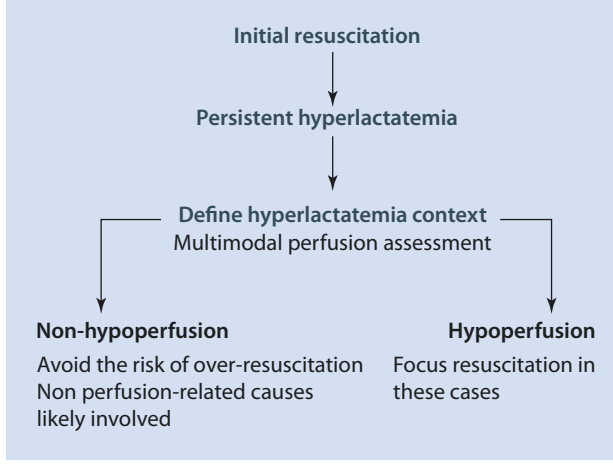


**Fig. 17.2** A simple algorithm to approach persistent hyperlactatemia based on the presence of a hypoperfusion context

### Conclusions

Persistent hyperlactatemia after shock resuscitation is associated to increased morbidity and mortality but is particularly difficult to interpret in the clinical setting. At least three possible pathogenic mechanisms might be involved: anaerobic glycolysis in hypoperfused territories, stress-related aerobic glycolysis, and impaired hepatic lactate clearance. A multimodal perfusion assessment might aid in suggesting a hypoperfusion context in patients with hyperlactatemia to focus resuscitation in these cases and avoid the risk of over-resuscitation when other non-perfusion-related causes are likely involved.

### Take-Home Messages

- Lactate is a key metabolic parameter that has traditionally been related to hypoperfusion and hypoxia during acute circulatory dysfunction.
- Lactate assessment is recommended as a fundamental part of the monitoring of the critically ill patient.
- Persistent hyperlactatemia after shock resuscitation is associated to increased morbidity and mortality.
- Persistent hyperlactatemia is particularly difficult to interpret in the clinical setting. At least three possible pathogenic mechanisms might be involved: anaerobic glycolysis in hypoperfused territories, stress-related adrenergic-induced aerobic glycolysis, and impaired hepatic lactate clearance.
- A multimodal perfusion assessment might aid in suggesting a hypoperfusion context in patients with persistent hyperlactatemia.

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