Lactate and lactate clearance in acute cardiac care patients

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European Heart Journal: Acute Cardiovascular Care
1(2) 115–121

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DOI: 10.1177/2048872612451168

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Abstract

Hyperlactataemia is commonly used as a diagnostic and prognostic tool in intensive care settings. Recent studies documented that serial lactate measurements over time (or lactate clearance), may be clinically more reliable than lactate absolute value for risk stratification in different pathological conditions. While the negative prognostic role of hyperlactataemia in several critical ill diseases (such as sepsis and trauma) is well established, data in patients with acute cardiac conditions (i.e. acute coronary syndromes) are scarce and controversial. The present paper provides an overview of the current available evidence on the clinical role of lactic acid levels and lactate clearance in acute cardiac settings (acute coronary syndromes, cardiogenic shock, cardiac surgery), focusing on its prognostic role.

Keywords

Acute cardiac setting, lactate, lactate clearance

Received: 16 February 2012; accepted: 19 May 2012

Introduction

First isolated in 1780 by Carl Wilhelm Scheele,¹ lactic acid (LA) is still recognized as a gauge of metabolic function and has a diagnostic and/or prognostic role in different clinical settings.²

While the negative prognostic role of hyperlactataemia in several critical ill diseases (such as sepsis and trauma) is well established,^{3–5} data in patients with acute cardiac conditions (i.e. acute myocardial ischaemia) are scarce and controversial.^{6,7}

The present manuscript is aimed at summarizing available evidence on the clinical role of LA levels and lactate clearance in acute cardiac settings (that is acute coronary syndromes, cardiogenic shock, and cardiac surgery), focusing on its prognostic role.

Hyperlactataemia in physiological conditions

In physiological conditions, approximately 1500 mmol of lactate (whose normal value is 2 mmol/l) are produced daily, primarily from skeletal muscle, skin, brain, intestine, and red blood cells.⁸

LA is considered one of the most crucial intermediates of carbohydrates and non-essential amino-acid metabolism⁹ and its levels are related to the balance between its production and clearance. In all tissues, LA is produced through an anaerobic reaction from pyruvate metabolism; at physiological pH, it is more than 99% dissociated into LA-anions and protons (H⁺)¹⁰ and it is converted to glucose (via the Cori or lactic acid cycle) in the liver (Figure 1), so that it can be used as an energy source during hypoxia.⁸ This metabolic re-arrangement, known as the Pasteur effect, represents the major adaptive mechanism to survive hypoxia.¹¹ The most common physiological condition of hypoxia is physical exercise. During moderate intensity exercise, muscles produce lactate rapidly, while lactate clearance is slowed, resulting in an increased net lactate output from the muscle to the blood. In this setting, blood

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Figure 1. The Cori cycle.

lactate flux may exceed glucose flux, thus underlying the role of lactate acid as a carbohydrate fuel source.

During recovery from short-term exercise or during prolonged exercise, there is instead lactate uptake from the blood by resting muscles or by other muscles exercising at lower intensity, leading to a physiological dynamic process of lactate interchange.¹⁰ In these conditions, lactate blood concentrations could be physiologically increased.

Hyperlactataemia in the critical illness

Hyperlactataemia associated to disease conditions can be related to excess LA production, reduced removal, or both as a consequence of different disease states. Tissue dysoxia (i.e. during hypoperfusion) favours accumulation of pyruvate and generation of lactate, as a consequence of a mitochondrial oxidative capacity impairment.¹² Increased lactate production may also be stimulated in the absence of dysoxia, as a response to inflammatory mediators, catecholamines, and other factors stimulating Na/K adenosine triphosphatase activity (as happens during sepsis, even in the early phases).^{13–15} Moreover, the persistence of increased lactate values may occur in presence of microcirculatory disarray, which could hamper oxygen utilization at the tissue level¹⁶ and in presence of a compromised renal function (i.e. during shock).

LA, as a metabolite of easy and quick assessment (even at the bedside), has been studied over time in critically ill patients in order to evaluate its diagnostic and prognostic ability, even at early phases of disease.³

The clinical role (and weight) of absolute LA values is strictly related to the specific disease. While in sepsis and trauma, lactate values of 2 mmol/l are considered 'not alarming', in surgical patients the lactate cut-off values to be considered 'clinically relevant' are still under debate. Some authors suggested that a level up to 4 mmol/l lactate should be adopted as a cut off in these kinds of patient.⁴ In contrast, Nichol et al.¹⁷ recently demonstrated that relative hyperlactataemia, defined as blood lactate concentrations >0.75 mmol/l could also identify patients at higher risk of death. They furthermore confirmed that lactate concentrations >2 mmol/l remained strongly associated with higher hospital mortality.

In several critical conditions, admission hyperlactataemia has been demonstrated to be a predictor of death, independently of its cut-off values. Duke et al.¹⁸ demonstrated that blood lactate level was the earliest predictor of outcome in children with sepsis. In a retrospective study, Khosravani et al.¹⁹ classified patients in four groups (cardiac surgical patients, trauma/neuro patients, other surgical patients admitted directly from the operating room, or those who were classified as having a surgical diagnosis as defined for the APACHE II score but excluding cardiovascular surgery, neurosurgical, neuro/trauma patients, and medical patients) and evaluated lactate concentration at admission and during intensive care unit (ICU) stay. They found that hyperlactataemia at presentation and its later development was an independent risk factor for death.

Similarly, in the population described by Juneja et al.⁵ (including patients with shock or respiratory and renal failure), hyperlactataemia was related to an increased ICU mortality, irrespective of hypotension persistence. Moreover, in surgical patients, Singhal et al.²⁰ observed that lactate ≥ 4.0 mmol/l and base deficit ≤ -7 mmol/l were associated with a 94.5% probability of death after ruptured abdominal aortic aneurysm repair.

Hyperlactataemia in acute cardiac care setting

Hyperlactataemia in acute coronary syndromes

Acute coronary syndromes (ACS) – unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI) – are conditions caused by coronary vessel obstruction and thrombotic occlusions from rupture or erosion of a plaque. The subsequent blood flow impairment causes a precarious balance between myocardial oxygen supply and demand. When oxygen demand exceeds what the diseased vessel can supply, oxygen deprivation forces the myocardium to shift from aerobic to anaerobic metabolism, leading to accumulation of LA and reduction of cellular pH.

The clinical role of lactate in ACS is not definitively assessed. Few studies investigated whether LA values could represent a diagnostic tool in patients with suspected

ACS. Schmiechen et al.,²¹ in a study performed in 129 patients with chest pain, tested the usefulness of blood lactate values as a diagnostic tool. According to their data, the blood lactate concentration obtained on emergency department arrival identified those chest pain patients with critical cardiac illness [e.g. acute myocardial infarction (AMI), severe congestive heart failure, decompensated arrhythmias] while a normal blood lactate had a high negative predictive value for AMI diagnosis. Mavrić et al.²² evaluated the capability of blood lactate concentration to predict shock development in a group of 229 patients admitted to coronary care unit and found that admission blood lactate was the variable with the greatest predictive power for shock development. Moreover Gatién et al.²³ demonstrated that venous lactate level at presentation is highly sensitive for the diagnosis of AMI, particularly in patients with more than 2 hours of chest pain.

Data on hyperlactataemia as a prognostic tool in ACS are scarce and controversial. In 1982, Henning et al.⁶ observed that, in patients with AMI, persistent hyperlactataemia was associated with a ominous prognosis; no patients whose arterial blood lactate was greater than 4 mmol/l for more than 12 h survived, regardless of the magnitude of the stroke volume, the left ventricular filling pressure, or the cardiac work.

In STEMI patients, Vermeulen et al.²⁴ detected that higher lactate values were independently related to an increased 30-day mortality and worse percutaneous coronary intervention (PCI) outcome. Moreover, in a recent study performed on 253 consecutive non-diabetic patients with STEMI submitted to PCI, Lazzeri et al.²⁵ found that admission lactic acid was an independent predictor of intensive cardiac care unit (ICCU) mortality. In a larger cohort (807 diabetic and non-diabetic STEMI patients submitted to PCI), the same study group found that blood lactate concentration was a prognostic marker for early mortality only in patients with advanced Killip class.⁷

Hyperlactataemia in cardiogenic shock

Cardiogenic shock (CS) is defined as a condition of inadequate tissue perfusion that results in an increase in anaerobic metabolism and lactate production as a consequence of regional hypoxia. In this setting, hyperlactataemia could be simply explained by the increased regional LA production, which could be also induced by inotrope administration and microvascular impairment. Renal and splanchnic hypoperfusion, with the consequent functional impairment, could justify lactic acidosis persistence, irrespective of increased LA production.

There is increasing evidence supporting the use of lactate as a diagnostic, therapeutic, and prognostic marker of global tissue hypoxia in cases of circulatory shock. Wail and Afifi²⁶ corroborate the hypothesis that LA concentration serves as a reliable prognosticator of survival in acute

circulatory failure. Müllner et al.²⁷ demonstrated that, in patients resuscitated from ventricular fibrillation, high admission lactate levels were associated with severe neurological impairment, even if this parameter presented poor prognostic value for individual estimation of the severity of subsequent functional neurological impairment. Moreover, Valente et al.,²⁸ in a study performed on 45 consecutive patients with CS complicating STEMI treated with PCI, found that hyperlactataemia (defined as lactate >6.5 mmol/l) was an independent indicator of in-hospital death in this kind of patient.

Even if elevated serum lactate concentrations is believed as an indicator of global tissue hypoxia in CS, there is no established cut-off value to guide resuscitation and the use of lactate as a resuscitation end point to improve survival has yet to be demonstrated.²⁹

Hyperlactataemia in cardiac surgery

During and after cardiac surgery, hyperlactataemia is a relative common finding and several mechanisms have been advocated to explain it. Some authors attributed hyperlactataemia to the haemodilution degree and a low peripheral oxygen delivery leading to tissue hypoxia.^{30,31} Myocardial ischaemia, as a phenomenon which could occur in open heart surgery (i.e. in case of obligatory interruption of blood coronary flow during aortic crossing clamp), could be involved in determining hyperlactataemia. Similarly, splanchnic and renal hypoperfusion could lead to a reduced lactate clearance, sustaining the persistence of hyperlactataemia. Otherwise, various preoperative factors or comorbidities, such as diabetes or renal impairment, could justify the onset and persistence of high lactate concentration in patients undergoing cardiac surgery.

Irrespective of its origin, hyperlactataemia and its persistence have been demonstrated to be an early indicator of worse outcome in cardiac surgical patients.³² Kapoor et al.,³³ in a recent study, demonstrated that lactate and other myocardial markers, as pyruvate and lactate/pyruvate ratio, were related to myocardial function and can predict post-operative outcome. Moreover Maillet et al.³⁴ identified a lactate blood concentration threshold up to 3 mmol/l as an indicator of higher risk of mortality and morbidity after cardiac surgery. More specifically, Rocha et al.³⁵ recently evaluated lactate trend in infants after Jatene's operation and found that, in this paediatric population, serum lactate levels can assess morbidity and mortality; increased lactate levels in the third hour appeared to be suggestive of worse prognosis.

Lactate clearance: physiopathology

Lactate clearance is the organic capability to reduce lactate blood concentration and it is derived from the balance of lactate production and lactate removal. Lactate production

(as physiological condition or as a consequence of disease states) has been previously described in this paper. Concerning lactate removal, in normal subjects it occurs principally in the liver (60%) with an important contribution from the kidney (30%) and, to a lesser extent, from other organs (such as the heart and skeletal muscle).³⁶ Under conditions of normal lactate blood concentrations, the most important mechanism of renal lactate removal is the lactate re-uptake, which could remove up to the 20–30% of lactate load. In condition of hyperlactataemia, when lactate blood concentrations exceed the renal threshold of 5 mmol/l, renal lactate removal switches to lactate urinary excretion mechanism, which can remove up to the 10–12% of total lactate load.³⁷

Lactate clearance: prognostic role in acute cardiac settings

Serial lactate measurements over time or lactate clearance may be clinically more reliable as a surrogate for the magnitude and duration of global tissue hypoxia,^{38–42} basically as a prognostic tool.

Lactate clearance in critically ill patients

The first advances on assessment of the role of lactate clearance and the utility of continuous lactate monitoring concerned sepsis. Nguyen et al.⁴³ documented that, in patients with sepsis and septic shock, lactate clearance early in the hospital course is associated with decreased mortality rate, since it may indicate a resolution of global tissue hypoxia. Furthermore, Nguyen et al.⁴⁴ also demonstrated that an early lactate clearance is significantly related to decreased levels of pro-inflammatory biomarkers, indirectly supporting the role of lactate clearance as a marker of prognosis and therapeutic responses. In a multicentre cohort of patients with septic shock, Arnold et al.⁴⁵ observed that lactate non-clearance (i.e. lactate decreased by <10% from initial) was an independent predictor of death.

In trauma, all patients who reduced their serum lactate level to initial values by 24 hours survived and those who cleared by 48 hours had a 75% chance of survival; in this population, the ability to reduce lactate to <2 mmol/l was able to significantly predict survival.³⁹ Surgical critically ill patients who showed persistent elevated lactate values had a mortality rate of 100%, while those who cleared their lactate (lactate <2 mmol/l) in the first 24 hours had a mortality of 3.9%.⁴⁶ In a large randomized trial including 300 patients with severe sepsis and septic shock, a protocol targeting lactate clearance of at least 10% as a marker of adequate tissue oxygen delivery produces results in terms of short-term survival rate similar to a protocol using central venous oxygen saturation, suggesting that lactate clearance may be used also as a therapeutic target.⁴¹ In this setting, Soliman and Vincent⁴⁷ recently demonstrated that serum lactate

levels on ICU admission are directly related not only to mortality, but also to the length of ICU stay.

Lactate clearance in acute cardiac patients

The role of lactate clearance in acute cardiac settings is so far not assessed, basically for lack of data in this scenario. The persistence of elevated lactate concentrations could reflect the persistence of tissue hypoxia irrespective of haemodynamic restoration. Several mechanisms, leading to microperfusion impairment, could be involved in determining this phenomenon.⁴⁸ Kliegel et al.,⁴⁹ in a retrospective study, analysed serum lactate levels on admission and over 48 hours in 394 patients surviving after cardiac arrest. They observed that serum lactate levels on admission and over 48 hours were significantly lower in patients surviving the first 6 months after successful cardiopulmonary resuscitation than in non-survivors. According to their data, they concluded that persisting hyperlactataemia over 48 hours seemed to be a predictor of poor outcome in successful resuscitated patients after cardiac arrest. In a recent review article, Jansen et al.⁵⁰ confirmed the role of lactate monitoring for risk stratification in critically ill patients but concluded that it is unknown whether the routine use of lactate as a resuscitation end point really improves outcome.

Recently, we assessed the role of lactate clearance in predicting early death in CS following STEMI submitted to PCI.⁵¹ Fifty-one patients with CS following STEMI all submitted to PCI and free of infection were consecutively enrolled. We observed that, at 12 hours from admission, lactate clearance was higher in survivors. In our series, 12-hour lactate clearance <10% identified a subset of patients at higher risk for death, since it was an independent predictor of ICCU death and it was also associated with poor survival rate at follow up. In our investigation, because patients with 12-hour lactate clearance <10% had a more compromised renal failure (as indicated by a lower estimated glomerular filtration rate) with a lack of significant differences of haemodynamic parameters (such as left-ventricular ejection fraction and mean arterial pressure) and transaminase values (as indexes of liver function), we hypothesized that a more compromised renal function may contribute to persistent hyperlactataemia in these patients, thus underscoring the pivotal role of kidneys in affecting prognosis in STEMI complicated by CS.

Take-home messages for cardiologists

Based on the available evidence and our experience, serum lactate (in absolute values) provides usefulness insight in the haemodynamic status of the single patient (in particular in terms of systemic perfusion), thus allowing an early risk stratification and tailoring of monitoring and therapy. In unstable ACS patients and in those with CS, dynamic changes in serum lactate values helps in monitoring the

Figure 2. Flow-chart of lactate in acute cardiac settings.

therapeutic strategy. In our centre, according to available data and our experience, we follow a care pathway from ICU admission, as shown in the flow chart in Figure 2.

In ACS patients without haemodynamic instability, in presence of an admission lactate concentration >2 mmol/l, we perform a strict monitoring of haemodynamic parameters (such as mean arterial pressure, *glomerular filtration rate*, left ventricular ejection fraction). According to policy of our institution, infection indexes (leucocyte count, *erythro sedimentation rate*, C-reactive protein, and pro-calcitonine) are measured on admission in all patients; in critically ill patients (admission lactate concentration >2 mmol/l), infection indexes are measured at least once a day, for at least 7 days.

Microbiological examinations as urinary and blood cultures are performed in all patients, with microbiological examinations of tracheal aspirate in mechanically ventilated patients. Furthermore in these patients we perform serial lactate measurements (every 6 hours, just for the first 24 hours if no clinical variations).

In patients with haemodynamic instability, as well as a strict monitoring of haemodynamic parameters and of infections indexes and microbiological examinations, we perform serial lactate measurements (every 3 hours, if no clinical variations). In most cases, diagnostic and therapeutic approaches take into account even lactate variations. According to our policy and clinical experiences, lactate-guided therapy has the following therapeutic targets:

- optimizing mean arterial pressure (i.e. tissue perfusion) by means of fluid therapy/inotrope administration;
- multi-organ protection (by means of early implementation of renal replacement therapy/early enteral nutrition);
- optimizing metabolic control (by means of insulin infusion therapy);
- prevention/treatment of infections.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest

None.

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