Clinical significance of lactate in acute cardiac patients

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Abstract

Lactate, as a metabolite of easy and quick assessment, has been studied over time in critically ill patients in order to evaluate its prognostic ability. The present review is focused on the prognostic role of lactate levels in acute cardiac patients (that is with acute coronary syndrome, cardiogenic shock, cardiac arrest, non including post cardiac surgery patients). In patients with ST-elevation myocardial infarction treated with mechanical revascularization, hyperlactatemia identified a subset of patients at higher risk for early death and in-hospital complications, being strictly related mainly to hemodynamic derangement. The prognostic impact of hyperlactatemia on mortality has been documented in patients with cardiogenic shock and in those with cardiac arrest even if there is no cut-off value of lactate to be associated with worse outcome or to guide resuscitation or hemodynamic management. Therapeutic hypothermia seems to affect per se lactate values which have been shown to progressively decrease during hypothermia. The mechanism(s) accounting for lactate levels during hypothermia seem to be multiple ranging from the metabolic effects of reduced temperatures to the hemodynamic effects of hypothermia (i.e., reduced need of vasopressor agents). Serial lactate measurements over time, or lactate clearance, have been reported to be clinically more reliable than lactate absolute value also in acute cardiac patients. Despite differences in study design, timing of lactate measurements and type of acute cardiac conditions (i.e., cardiogenic shock, cardiac arrest, refractory cardiac arrest), available evidence strongly suggests that higher lactate levels can be observed on admission in non-survivors and that higher lactate clearance is associated with better outcome.

Key words: Lactate; Acute coronary syndrome; Cardiogenic shock; Cardiac arrest; Therapeutic hypothermia; Extracorporeal membrane oxygenation; Prognosis

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Core tip: The present review is focused on the prognostic role of lactate levels in acute cardiac patients (acute coronary syndrome, cardiogenic shock, cardiac arrest). The prognostic impact of hyperlactatemia on mortality has been documented in cardiogenic shock and cardiac arrest even if there is no cut-off value of...
lactate to be associated with worse outcome or to guide resuscitation or hemodynamic management. Lactate clearance was reported to be clinically more reliable than lactate absolute value in these patients. Despite differences in study design, timing of lactate measurements and type of acute cardiac conditions (i.e., cardiogenic shock, cardiac arrest, refractory cardiac arrest), available evidence strongly suggests that higher lactate levels can be observed on admission in non-survivors and that a more favorable outcome is observed in patients with higher lactate clearance.

INTRODUCTION

Hyperlactatemia is known to be associated with adverse outcome in critical illness\cite{1-3}. However, the source, patho-physiology and metabolic function of lactate remain unclear probably because lactate is widely produced and it is cardinal to many energy-related pathways\cite{4}.

In recent years, available evidence strongly suggests that stress hyperlactatemia is due to increased aerobic lactate production with or without lactate clearance and that it is probably due to adrenergic stimulation. In other words, increased lactate levels are indicative of a stress response and lactate is a source of energy and not a waste product.

Lactate, since it is easy and quick to measure even at the bedside, has been widely investigated in critically ill patients to assess its prognostic role\cite{5}.

The present review is focused on the prognostic role of lactate levels in acute cardiac patients (acute coronary syndrome, cardiogenic shock, cardiac arrest). Post cardiac surgery patients are not included.

LACTATE IN THE HEART

In a normal heart, at rest, β-oxidation of fatty acids provides about 60%-90% of Adenosine triphosphate (ATP) while pyruvate produces 10%-40% of ATP\cite{6}. However, fatty acids show lower production efficiency and increased intracellular free fatty acids activate uncoupling proteins, so that protons leak into the mitochondria without generating ATP\cite{7}. That is why inhibition of β-oxidation is associated to an increased in mechanical efficiency of the left ventricle.

Lactate is an important fuel for the stressed heart\cite{8}. During exercise the uptake of lactate by the myocardium and its use increase as well as during β-adrenergic stimulation and shock\cite{4,9}.

In presence of increased lactate concentrations, lactate might represent up to 60% of cardiac oxidative substrate. During shock, lactate is the most important fuel for the heart. Indeed, in laboratory animals, lactate depletion is associated with shock and mortality\cite{10,11} while lactate infusion increased cardiac performance in cardiogenic and septic shock\cite{12}.

Hyperlactatemia can be viewed as part of the stress response including increased metabolic rate, sympathetic nervous system activation, accelerated glycolysis and a modified bioenergetic supply. In animals with cardiogenic shock\cite{13} and in patients with cardiogenic shock, a marked increment in glycolysis and gluconeogenesis associated with hyperlactatemia was described\cite{14}. In healthy subjects and in cardiogenic shock\cite{12}, it was observed, using an infusion of labelled lactate, that 50% of this lactate was oxidized and 20% used for glucose synthesis, without differences between the two subgroups. All these data strongly suggest that lactate is a source of energy in stress conditions.

PROGNOSTIC SIGNIFICANCE OF LACTATE

Acute coronary syndrome

Few investigations assessed whether lactate values are a diagnostic tool in patients with chest pain. In 129 patients with chest pain\cite{15}, lactate values measured on arrival identified those chest pain patients with critical cardiac illness (i.e., severe congestive heart failure) which lactate concentrations within the normal range had a high negative predictive value for diagnosis of acute myocardial infarction (AMI). In patients arriving at the emergency department for suspected AMI\cite{16}, lactate values on arrival were highly sensitive for the diagnosis of AMI, mainly in those patients with more than 2 h of chest pain. In 229 patients admitted to coronary care unit\cite{17}, admission lactate showed the greatest predictive power for shock development.

To date, the prognostic significance of lactate in acute coronary syndrome (ACS), that is unstable angina, no ST elevation myocardial infarction and ST elevation myocardial infarction (STEMI), has been investigated in observational, mainly single-center, studies\cite{18,19}.

In 1176 STEMI patients\cite{20}, hyperlactatemia measured at arrival in the catheterization laboratory was associated with worse outcome measures [increased 30-d mortality, larger enzymatic infarct size and increased use of intra-aortic balloon pump (IABP)]. Among non survivors with admission lactates $\geq 1.8$ mmol/L, the fifty percent died within a day after percutaneous coronary intervention (PCI). Hypotension, higher heart rate, poor Thrombolysis in myocardial infarction-flow, diabetes and non-smoking were independently associated with hyperlactatemia. In 253 STEMI non-diabetic patients with STEMI\cite{21}, lactate, measured after PCI, was an independent predictor of mortality together with C-peptide and homeostatic model assessment, an index of acute insulin resistance.
In 807 STEMI patients treated with PCI\textsuperscript{[22]}, our group observed that lactate values were independently associated with early mortality only in the subgroup of patients in advanced Killip classes. Lactate concentrations (measured in the early phase of STEMI) were influenced by the degree of hemodynamic impairment (as indicated by Killip class), of myocardial ischemia (as inferred by Tn I), and by glucose values.

Moreover, lactate represented an independent marker for complications (acute pulmonary edema and arrhythmia) observed during intensive cardiac care unit (ICCU) stay in 445 STEMI patients\textsuperscript{[19]} and in 481 ACS patients with cardiogenic shock treated with IABP, lactate was an independent predictor of IABP-related complications (hemorrhagic, ischemic events) together with use of inotropes and nadir platelet count\textsuperscript{[22]}. Overall, according to the available evidence hyperlactatemia in STEMI patients submitted to primary PCI identified a subset of patients at higher risk for early death and in-hospital complications, being strictly related mainly to hemodynamic derangement. Similarly in 754 consecutive patients with acute decompensated heart failure (ADHF) (ACS in the 52%)\textsuperscript{[23]} admission lactate values > 3.2 mmol/L were associated with increased in-hospital mortality in ADHF patients either with or without ACS.

**Cardiogenic shock**

In 2006, in 38 patients with cardiogenic shock (CS) following acute myocardial infarction and retrospectively analyzed, interleukin-6 concentrations were independently associated with increased 30-d mortality while lactate values were not\textsuperscript{[24]}. In the following years, increasing evidence supported the notion of lactate as a prognostic factor in circulatory shock\textsuperscript{[14-25]}. In 45 CS patients complicating STEMI\textsuperscript{[26]}, increased lactate values (that is > 6.5 mmol/L) were independently associated with in-hospital death. Similar results were reported in other investigations\textsuperscript{[27,28]}.

The strict relationship relation between lactate and hemodynamic impairment was documented in 25 CS patients in whom a short-term increase in mean arterial pressure with norepinephrine was associated with a significant reduction in lactate levels, better cardiac performance and improved microcirculatory variables\textsuperscript{[29]}.

So far there is no cut-off value of lactate associated with worse outcome\textsuperscript{[30]}. Lactate values higher than 2.0 mmol per liter was one of the diagnostic criteria for impaired end-organ perfusion (together with altered mental status; cold, clammy skin and extremities; oliguria with urine output of less than 30 mL/h) in a randomized multicenter trial, including 600 CS patients complicating AMI randomized to intraaortic balloon counterpulsation (301 patients) or no intraaortic balloon counterpulsation (299 patients). Intra-aortic balloon pump did not affect serum lactate concentration as well as the length of ICU stay, catecholamine therapy (dose and duration), and renal function and its use was not associated with a reduced 30-d mortality.

**Cardiac arrest**

The prognostic significance of lactate levels in cardiac arrest was investigated mainly in observational studies, not homogeneous for study design, inclusion criteria (cardiac arrest of cardiac/not cardiac origin) and time and number of lactate determination. The influence on lactate value of treatments such as mild hypothermia and support therapy like extracorporeal membrane oxygenation (ECMO) are so far not completely elucidated. Thus, there is no cut-off of lactate values in post-cardiac arrest patients to be associated with increased mortality and/or neurological impairment or to be use to guide resuscitation or post-resuscitation hemodynamic management.

Hyperlactatemia observed in the early phase in cardiac arrest patients may be related to both the ischaemia that occurs during arrest and to the inflammation resulting from ischaemia-reperfusion injury\textsuperscript{[31-34]}.

Hyperlactatemia in post cardiac patients has been reported in several investigations\textsuperscript{[31-34]}. In 128 out-of-hospital cardiac arrest patients\textsuperscript{[33]} it was reported a progressive increased mortality associated with hyperlactatemia (39% lactate < 5 mmol/L, 67% lactate 5 mmol/L to 10 mmol/L, and 92% lactate ≥ 10 mmol/L; \( P < 0.001 \)). In out-of-hospital cardiac arrest (OHCA) patients\textsuperscript{[35]} blood ammonia and lactate on arrival were independent prognostic factors and, when combining both biomarkers, the positive predictive value was nearly 100%.

An association between lactate levels and neurological outcome has been documented in recent investigations\textsuperscript{[36]}. In 930 cardiac arrest patients who underwent therapeutic hypothermia (TH) collected from the Korean Hypothermia Network\textsuperscript{[27]} high levels of lactate measured 1 h after return of spontaneous circulation were related to early mortality and poor neurological outcome. In 184 OHCA patients\textsuperscript{[36]}, lactate levels < 5 mmol/L and lower epinephrine doses (< 1.5 mg) were predictors of a normal Glasgow Coma Scale. Lactate concentrations measured at 6, 12, 24 and 48 h were significantly lower in the good neurological outcome group than in the poor neurological outcome group, while admission lactate values were comparable between the two subgroups. Moreover, in 76 OHCA patients submitted to TH, lactate clearance (6-h and 12-h) was related to good neurological outcome also when adjusted for confounding factors\textsuperscript{[39]}.

However, data on the effect of therapeutic hypothermia on lactate values are so far not uniform. In a prospective trial comparing moderate induced hypothermia with normothermia in OHCA survivors\textsuperscript{[40]} during hypothermia it was reported an increment in lactate values, together with reduced \( P \) values, reduced MAP and increased glucose levels. On the other hand, when comparing therapeutic hypothermia and normothermia\textsuperscript{[41]}, no significant difference in peak lactate values, arterial pressure, and need of vasopressors was reported in comatose survivors of ventricular fibrillation with STEMI. On the other hand,
Lactate clearance have been reported to be more reliable on clinical grounds than absolute value of lactate for risk stratification in different critically ill conditions, ranging from sepsis to trauma[62-99].

Lactate clearance in acute cardiac patients has been investigated to date in few reports, all including observational single-center investigations performed in different populations of acute cardiac patients. Despite differences in study design, timing of lactate measurements and type of acute cardiac conditions (i.e., cardiogenic shock, cardiac arrest, refractory cardiac arrest), available evidence strongly suggests that higher lactate levels can be observed on admission in non-survivors and that higher lactate clearance is related to more favourable outcome.

In 394 survivors from cardiac arrest[60], serum lactate levels, measured on admission and at 48 h, was retrospectively analyzed. Lactate values were lower in survivors at 6-mo after cardiac arrest than in non-survivors.

In 51 CS patients complicating STEM[61], we observed that a 12-h lactate clearance < 10% was independently associated with early death and with poor survival rate at follow up. Since a more compromised renal failure (as indicated by a lower estimated glomerular filtration rate) was observed in patients with a low lactate clearance, associated with a lack of differences in haemodynamics (left-ventricular ejection fraction and mean arterial pressure) and transaminase values (as indexes of liver function), we supposed that a more compromised renal function may have a role in the development of persistent hyperlactataemia in these patients. Since no differences were observed in mean arterial pressure, left ventricular ejection fraction, and incidence of PCI failure between patients with 12 lactate clearance < 10% and those with 12 lactate clearance ≥ 10%, it cannot be ruled out that microvascular alterations (despite global hemodynamic restoration) may be responsible for persistent increased lactate values in patients who exhibited a 12 lactate clearance < 10%.

Similarly, in 96 CS patients following AMI treated with percutaneous cardiopulmonary support, lactate clearance calculated at 48 h < 70% was one of the independent predictors for in-hospital mortality[62] (together with older age ≥ 67 years and unsuccessful revascularization).

Data on the lactate clearance in patients with cardiac arrest supported by ECMO are quite scarce and not uniform.

In a heterogeneous series of 43 patients supported by ECMO for cardiogenic shock or cardiac arrest, hyperlactatemia at 6 h after ECMO implantation were observed in patients who died within 30 d[63].

In 51 patients who had witnessed out-of-hospital refractory cardiac arrest and were supported by ECMO upon arrival in the hospital[64], lactate clearance (values were measured before and 1-2 h after ECMO implantation) was greater in patients who survived. Conversely, in 24 patients with refractory cardiac arrest supported by ECMO[65] lactate values, measured on
admission, at 12 h and at 24 h, significantly decreased over time, with no differences between non-survivors and survivors and with no influence on outcome. A strict relation was documented between lactate and mean arterial (that is system perfusion) which increased both in survivors and in non-survivors. This relation probably explains why no difference was detectable in the dynamic behavior of lactate values during the first 24 h since admission between survivors and non-survivors. Moreover, since lactate values can be related to mean arterial pressure (and not to renal function or gluycemia) it can be supposed that they may be considered a marker of perfusion, that is ECMO support efficacy in these patients.

CONCLUSION

In patients with acute coronary syndrome, cardiogenic shock and/or cardiac arrest, data on the prognostic impact of hyperlactatemia mainly stem from observational investigations. However, hyperlactatemia in these patients is associated with worse outcome, even if a cut-off value of lactate is so far not available.

Serial lactate measurements or lactate clearance have been reported to be more reliable for risk stratification in acute cardiac patients and, on a clinical ground, repeated measurement of lactate is highly advisable especially in those patients who showed increased values on admission (Figure 1). Further investigations are needed to identify the cut-off value of lactate to guide hemodynamic management.

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