

THE ROLE OF SERUM LACTATE IN POST-CARDIAC ARREST SYNDROME

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ABSTRACT

Cardiopulmonary arrest is a medical emergency with significant mortality. The success of resuscitation led to the emergence of post-cardiac arrest syndrome (PCAS), which originates from ischemia-reperfusion injury and its consequent increase in serum lactate. Despite the robust evidence correlating hyperlactatemia as a prognostic marker in critically ill patients, there is insufficient evidence about the role of serum lactate in the outcome of PCAS. Thus, the purpose of this review is to check the current evidence on the role of lactate in predicting mortality in PCAS.

Keywords: Cardiac arrest; cardiopulmonary resuscitation; lactic acid.

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Cardiopulmonary arrest (CPA) is a medical emergency defined as the sudden and unexpected cessation of vital functions, characterized by the absence of heart beats, respiratory movements, and responsiveness to stimuli (1).

In Canada and in the United States, 200,000 to 350,000 people are estimated to be victims of CPA each year (2). In Brazil, there are few studies with consistent data on the subject. A study from the 1980s, conducted in São Paulo, estimated an annual prevalence of 2.9/1000 people, with 80% of these events attributed to ventricular fibrillation (3).

In the last 50 years, with the rise of cardiopulmonary resuscitation (CPR) and protocols for the management of CPA, many advances were made in emergency cardiac care and in advanced cardiac life support. These interventions contributed to the restoration of spontaneous circulation (RSC) and, consequently, to an increase in survival rates (4).

The success of CPR led to the emergence of post-cardiac arrest syndrome (PCAS), defined as a pathophysiological state, or a post-resuscitation disease, which originates from ischemia-reperfusion injury and from the consequent increase in serum lactate. Clinically, PCAS presents as a myocardial dysfunction, systemic inflammatory response, and post-cardiac arrest brain injury (5).

This study aimed to review current evidence on the role of serum lactate in predicting mortality among patients with PCAS.

METHODS

We conducted a narrative literature review through searches in MEDLINE, Pubmed (U.S. National Library of Medicine), SciELO (Scientific Eletronic Library Online), and BIREME (Biblioteca Regional de Medicina, or Regional Library of Medicine) for the following MeSH (Medical Subject Heading) descriptors: heart arrest, cardiopulmonary resuscitation, and lactic acid. When indicated, these terms were searched in Portuguese as well. In the last review, in May 2013, studies with both experimental and human subjects were analyzed and the most relevant ones were selected.

POST-CARDIAC ARREST SYNDROME

Post-cardiac arrest syndrome was first described in 1953 with a high mortality rate (5). This syndrome, still only partially understood, is considered by some as the most complex phase of CPA (6).

A recent study with 36.902 adult patients, all victims of in-hospital CPA, reported a success rate of 47% for RSC, but only 37.7% of the patients survived hospitalization (7). Another study, with 11.896 victims of out-of-hospital CPA, reported a success rate of 28.2% for RSC. Of these patients, only 28.4% were discharged from the hospital (2). Recently, a meta-analysis with 79 studies on out-of-hospital CPA, including 142.760 patients, identified a success rate of 23.8% for RSC and a mere 7.6% rate for survival to hospitalization.

A Brazilian study from 2001 indicated a 47.6% rate for RSC in CPA victims, with no distinction between locations, and a 34.1% rate of survival for more than one month (9). Another Brazilian study, from 2007, with victims of in-hospital CPA, reported a 43.4% rate for RSC and a 31.7% rate of survival to hospitalization (10). However, a national prospective study yielded different results. After analyzing 452 patients, it registered a 24% success rate for RSC, but only a 5% survival rate. Adrenaline use, initial care in public hospitals, and duration of RSC > 15 minutes were identified as risk factors (11).

The pathophysiology of PCAS is complex and remains a partial mystery. However, there seems to be a predominance of ischemia-reperfusion injuries and a nonspecific activation of the systemic inflammatory response (12). Thus, the high mortality rate may be attributed to a pathophysiological process involving various organs, and, even though

the prolonged global ischemia initially causes damage to organs and tissues, there is additional damage during the reperfusion stage (13).

PCAS may be divided into four phases after RSC. The immediate phase comprises the first 20 minutes after RSC; the early phase starts at 20 minutes and lasts up to 6–12 hours, when early interventions are more effective; the intermediate phase spans between the early phase and 72 hours after restoration, when injury pathways are still active and more aggressive treatment is used; and the recovery phase comes after 72 hours, when prognosis becomes reliable (14).

PCAS is potentially treatable, and early therapeutic interventions may improve outcome. Therapeutic hypothermia, for instance, has been shown to improve neurological outcome and survival rates for CPA victims. Although there are no effective pharmacological therapies in this case, minimizing risk factors (hypotension, hyper- or hypoglycemia, hypoxemia, hypocapnia, hyperthermia, electrolyte disturbances), optimizing cerebral perfusion pressure, and using therapeutic hypothermia may improve prognosis (15-20).

LACTATE METABOLISM

Lactate is a product of glycolysis, a metabolic pathway consisting of ten steps catalyzed by free enzymes found in the cytosol, where glucose is oxidized. Initially, under aerobic conditions, enzymatic reactions in the cytoplasm convert 1 glycolysis molecule into 2 pyruvate molecules, 2 adenosine triphosphate (ATP) molecules, and two reduced equivalents of coenzyme NADH⁺ (reduced nicotinamide adenine dinucleotide). This aerobic process occurs even during states of low tissue perfusion. From then on, pyruvate follows one of two metabolic routes. The first option is a second series of aerobic enzymatic reactions, called the Krebs cycle, which occurs in the mitochondria. This is where pyruvate is oxidized, generating water and carbon dioxide, which results in 18 ATPs. Alternatively, if there is no oxygen, pyruvate is converted into lactate (Figure 1). Finally, lactate is metabolized in the liver and kidneys. At a basal metabolic rate, serum arterial lactate levels range from 0.5 to 1 mEq/L. This balance indicates lactate production and metabolism (21).

Animal models of ischemia and reperfusion showed that, during the first 10 minutes of total ischemia, ATP levels decrease around 25% when compared to basal levels. After 60 minutes,

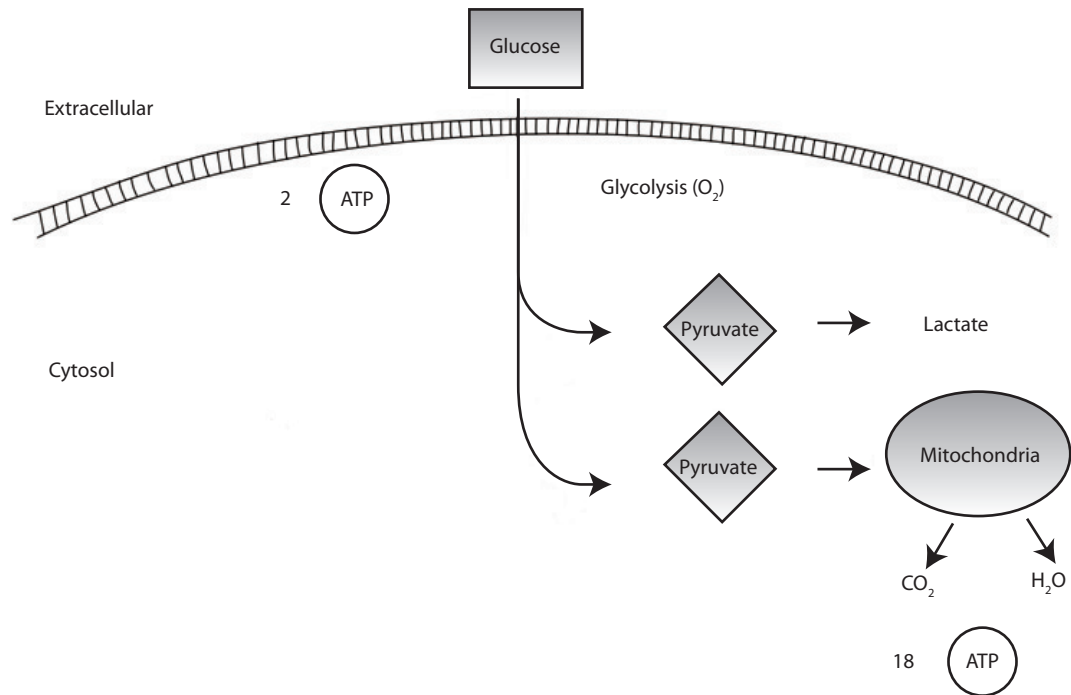


Figure 1: Serum lactate metabolism. ATP – adenosine triphosphate, (O₂) – oxygen-dependent reaction, CO₂ – Carbon dioxide, H₂O – Water.

ATP levels are reduced to 5% and remain so up until 120 minutes, when serum lactate levels increase by up to 20-fold compared to initial levels. After 15 minutes of ischemia followed by 120 minutes of reperfusion, ATP and lactate levels return to normal (22).

CLINICAL USE OF LACTATE

In 1843, German physician and chemist Johann Joseph Scherer measured lactate levels for the first time in two patients with septic shock associated with puerperal fever (23). Since then, hyperlactatemia is used as a marker of hypoxia and tissue hypoperfusion in critically ill patients (24). In a 1990s clinical trial, lactate overcame oxygen-dependent variables such as oxygen delivery rate (DO₂), oxygen consumption rate (VO₂), and mixed venous oxygen saturation as a predictor of mortality in patients with septic shock (25).

Serum lactate clearance (LaCl) was also associated with a reduction in mortality and multiple organ failure in septic, burned, polytraumatized, and critically ill surgical patients (26-30). Recent studies suggest LaCl is tantamount, or even superior, to central venous

oxygen saturation as a predictor of mortality in patients with severe sepsis or septic shock (31,32). LaCl should be assessed with caution in cases of acute renal failure (33), postictal states, heart surgeries, acute liver failure, hypothermia, and alkalosis (34).

In the last years, lactate has evolved from being considered a mere metabolic waste product (“bad lactate”) to being considered a good temporary energy source (“good lactate”). This means hyperlactatemia should be viewed in many clinical situations as an adaptive response to a critical state, not only as a marker of tissue hypoxia. Nevertheless, regardless of its formation mechanism, hyperlactatemia remains an excellent prognostic marker for critically ill patients (35).

LACTATE IN POST-CARDIAC ARREST SYNDROME

CPA is the most severe shock state, during which DO₂ to the tissues and production of metabolic substrates are dramatically reduced. Inadequate DO₂ may persist even after RSC due to myocardial dysfunction, hemodynamic instability, and microcirculatory failure (14). Buildup of the derivatives of oxidative metabolism leads to endothelial

activation and systemic inflammation, both predictive of subsequent multiple organ failure and death (36).

Experimental studies in the 1980s demonstrated for the first time the increase in serum lactate levels during CPA and the correlation between this metabolite and survival after CPR. A canine model of CPA induced by ventricular fibrillation established an association between lactate and timing and accuracy of CPR maneuvers. Lactate levels increased significantly only after CPR maneuvers had begun (37). Another experimental study, one in a porcine model, demonstrated that serum lactate levels decreased around 50% over 60-90 minutes after *tissue perfusion restoration*.

Serum lactate levels increase progressively after CPA due to global ischemia and are one of the main causes of metabolic acidosis in the post-cardiac arrest state (Figure 2). This limits the mere measurement of this marker during the early hemodynamic optimization after CPA (39-40).

LACTATE AS A PREDICTOR OF MORTALITY IN POST-CARDIAC ARREST SYNDROME

Kliegel et al. (2004) compared the serial levels of serum lactate with the outcomes of 394 victims of out-of-hospital CPA and found that hyperlactatemia, which persisted during the 48 hours following CPA,

was an independent predictor of mortality Odds Ratio 1,49; IC 95% 1.17-1.89 (39). A retrospective study with 79 patients in post-cardiac arrest state (out-of-hospital CPA) reported a statistically significant difference in Lacl after 6 and 12 hours between survivors and non survivors. After statistical adjustment with logistic regression, only the 12-hour Lacl remained significantly different between both groups (42).

A recent retrospective analysis of 128 survivors of out-of-hospital CPA showed that, in patients using vasopressor agents, a progressive increase in lactate levels was associated with higher hospital mortality rates, with an area of 0.82 (IC 95% 0.75-0.90) under the ROC (receiver operating characteristic) curve (43).

Finally, a retrospective study by Seeger et al. with 206 patients in post-cardiac arrest state, both in-hospital and out-of-hospital, showed that, upon admission, serum lactate levels > 6.94 mmol/L, pH levels < 7.21, and age \geq 65 years had 100% sensitivity and predictive value for death or unfavorable neurological outcome in 30 days (44).

CONCLUSION

The success of CPR led to the emergence of PCAS, which originates from ischemia-reperfusion injury.

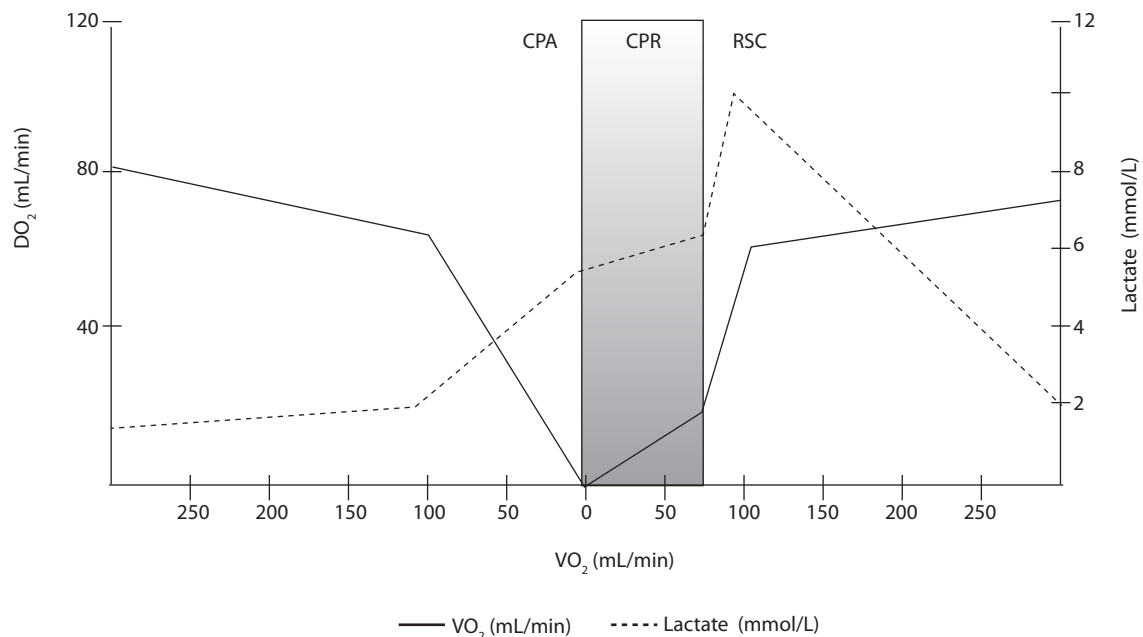


Figure 2: Relationship between serum lactate, oxygen delivery rate (DO_2), and oxygen consumption rate (VO_2) at different moments following CPA. CPA – cardiopulmonary arrest, CPR – cardiopulmonary resuscitation, RSC – restoration of spontaneous circulation.

Lactate, a product of anaerobic metabolism, is elevated after return of spontaneous circulation in the post-cardiac arrest state, and current evidence indicates a

correlation between hyperlactatemia and mortality in this population. Using this biomarker in the prognostic assessment of CPA survivors seems appropriate.

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