

Pathophysiology of lactic acidosis, and its clinical importance after cardiac surgery

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Introduction:

In 1925, Clausen identified the accumulation of lactic acid in blood as a cause of acid-base disorder. Several decades later, Huckabee's seminal work firmly established that lactic acidosis frequently accompanies severe illnesses and that tissue hypoperfusion underlies the pathogenesis. In their classic 1976 monograph, Cohen and Woods classified the causes of lactic acidosis according to the presence or absence of adequate tissue oxygenation. The normal blood lactate concentration in unstressed patients is 0.5-1 mmol/L. Patients with critical illness can be considered to have normal lactate concentrations of less than 2 mmol/L. Hyperlactatemia is defined as a mild-to-moderate persistent increase in blood lactate concentration (2-5 mmol/L) without metabolic acidosis, whereas lactic acidosis is characterized by persistently increased blood lactate levels (usually >5 mmol/L) in association with metabolic acidosis (pH < 7.35).^{1,2} Lactic acidosis is associated with major metabolic dysregulation, tissue hypoperfusion, effects of certain drugs or toxins, or congenital abnormalities in carbohydrate metabolism. Cohen and Woods divided lactic acidosis into 2 categories: "type A", associated with impaired delivery of oxygen to tissues (DO₂) eg, hypotension, cyanosis, cool and clammy extremities, and "type B", where lactic acidosis occurs in the presence of normal DO₂.

Causes: Classification of acquired causes of lactic acidosis is as follows:

• Type A - Due to tissue hypoxia

- Tissue hypoperfusion - Abnormal vascular tone or permeability, left

ventricular failure, decreased cardiac output

- Reduced arterial oxygen content - Asphyxia, hypoxemia (PaO₂ <35 mm Hg), carbon monoxide poisoning, life-threatening anemia

• Type B - Not due to tissue hypoxia

- B1 (common disorders) - Sepsis, hepatic failure, renal failure, diabetes mellitus, cancer, malaria, cholera
- B2 (drugs or toxins) - Biguanides, acetaminophen, ethanol, nalidixic acid, salicylates, isoniazid, methanol, streptozotocin, ethylene glycol, sorbitol, cyanide, parenteral nutrition, nitroprusside, lactulose, niacin, theophylline, catecholamines, cocaine, diethyl ether, vitamin deficiency, papaverine, paraldehyde
- B3 (other conditions) - Strenuous muscular exercise, grand mal seizures, D-lactic acidosis

Pathophysiology:

The anaerobic metabolic pathway known as glycolysis is the first step of glucose metabolism and occurs in the cytoplasm of virtually all cells. The end-product of this pathway is pyruvate, which can then diffuse into the mitochondria and be metabolized to carbon dioxide by another, more energy-efficient metabolic pathway, the Krebs cycle. The metabolism of glucose to pyruvate also results in the chemical reduction of the enzyme cofactor oxidized form nicotinic acid dehydrogenase (NAD⁺) to nicotinic acid dehydrogenase (NADH) (reduced form).



Erythrocytes are capable of carrying out glycolysis; however, these cells do not have mitochondria and cannot use oxygen

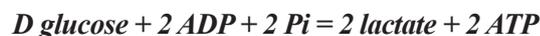


to produce adenosine triphosphate (ATP). The pyruvate formed during glycolysis is metabolized by the enzyme lactate dehydrogenase to lactate. The anaerobic pathway is very inefficient, and only 2 moles of ATP are produced for each molecule of glucose that is converted to lactate. The lactate diffuses out of the cells and is converted to pyruvate and then is aerobically metabolized to carbon dioxide and ATP. The heart, liver, and kidneys use lactate in this manner. Alternatively, hepatic and renal tissues can use lactate to produce glucose via another pathway referred to as gluconeogenesis. Lactate producers are skeletal muscle, the brain, the gut, and erythrocytes. Lactate metabolizers are the liver, the kidneys, and the heart.^{1,2}

Metabolism of glucose to lactate by one tissue, such as red blood cells, and conversion of lactate to glucose by another tissue, such as the liver, is termed the Cori cycle. The ability of the liver to consume lactate is concentration-dependent and progressively decreases as the level of blood lactate increases. Lactate uptake by the liver also is impaired by several other factors, including acidosis, hypoperfusion, and hypoxia. Lactate synthesis increases when the rate of pyruvate formation in the cytosol exceeds its rate of use by the mitochondria. This occurs when a rapid increase in metabolic rate occurs or when oxygen delivery to the mitochondria declines, such as in tissue hypoxia. Lactate synthesis also may occur when the rate of glucose metabolism exceeds the oxidative capacity of the mitochondria, as observed with administration of catecholamines or errors of metabolism.

Cellular energy metabolism and lactate production

During cellular hypoxia, the hydrolysis of ATP leads to accumulation of H and Pi in the cytosol. Therefore, ATP hydrolysis is the source of cellular acidosis during hypoxia and not the formation of lactate from glucose, which neither consumes nor generates H⁺. The glycolytic process may be viewed as the following:



The hydrolysis of 2 ATP molecules formed from the metabolism of glucose produces H⁺, ADP, and Pi.



If the oxygen supply is adequate, the metabolites of ATP are recycled in the mitochondria and the cytosolic lactate concentration rises without acidosis. On the other hand,

with cellular hypoxia, the equation of anaerobic glycolysis becomes the following:



Cellular transport of lactate

Lactate leaves the cell in exchange for a hydroxyl anion (OH⁻), a membrane-associated, pH-dependent, antiport system. The source of extracellular OH⁻ is the dissociation of water into OH⁻ and H⁺. Extracellular H⁺ combines with lactate leaving the cell, forming lactic acid, while intracellular OH⁻ binds to H⁺ generated during the hydrolysis of ATP to form water.

Cellular response to hypoxia

Declines in cellular oxygen delivery lead to more oxygen extraction from the capillary blood. This action redistributes the cardiac output to organs according to their ability to recruit capillaries and also decreases the distance from the capillaries to the cells. With severe decreases in oxygen transport, compensatory increase in the oxygen extraction ratio is insufficient to sustain aerobic metabolism. Therefore, the cell must employ anaerobic sources of energy to produce ATP, resulting in generation of lactate and H⁺.

Clinical importance :

Elevated blood lactate level associated with metabolic acidosis is common among ill patients with systemic hypoperfusion and tissue hypoxia. This situation represents type A lactic acidosis, resulting from an imbalance between supply and demand for tissue oxygen. Lactate production results from cellular metabolism of pyruvate into lactate under anaerobic conditions. Therefore, blood lactate level in type A lactic acidosis is related to the total oxygen debt and the magnitude of tissue hypoperfusion.^{6,7,8} Several studies have suggested that blood lactate concentration has prognostic value in patients with circulatory shock.^{7,8,9}

Lactate acidosis as a metabolic monitor of myocardial dysfunction during and after heart surgery:

Identification of predictors of morbidity and mortality is an important issue for the optimal management of cardiac surgical patients. The accurate identification of patients who have the potential to further deteriorate after cardiac surgery is difficult. Stratification of risk in the cardiac surgical population involves mainly preoperative factors.

However, intraoperative events related to surgical technique, myocardial protection, and cardiopulmonary bypass (CPB) may modify the postoperative course.¹⁰

*ischemia-reperfusion-induced injury*_ When an imbalance between oxygen supply and demand exists, anaerobic respiration commences and metabolic acidosis develops. This metabolic acidosis can be quantified from direct arterial blood gas analysis by examination of the base excess and the serum lactate concentration. Although there are a variety of other causes for metabolic acidosis, the early identification of those patients with tissue dysoxia would enable better triage decisions to be made with regard to future management. Hyperlactatemia may occur with or without concomitant metabolic acidosis. When hyperlactatemia occurs in the setting of good tissue perfusion, for example, catecholamine administration, alkalosis, or increased metabolic activity due to sepsis, the buffering mechanisms can compensate for any fall in pH. When lactate levels are increased because of poor tissue perfusion, however, the buffering systems are unable to cope and acidosis develops. Postischemic myocardial dysfunction is attributable, in part, to a phenomenon known as *ischemia-reperfusion-induced injury*. Clinically, it manifests by low cardiac output and hypotension and may be subdivided into two subgroups: reversible injury and irreversible injury. The two typically are differentiated by the presence of electrocardiographic abnormalities, elevations in the levels of specific plasma enzymes or proteins such as creatine kinase and troponin I or T, and/or the presence of regional or global echocardiographic wall motion abnormalities. With respect to coronary artery bypass grafting (CABG) alone, 10% of patients may experience myocardial infarction (MI), severe ventricular dysfunction, heart failure, and/or death despite advances in surgical technique.⁹

Increased plasma lactate levels reflect the onset of anaerobic metabolism secondary to inadequate cellular oxygen uptake. However, it is surprising that a progressive rise in plasma lactate concentration has been shown to occur after CPB despite a rise in cardiac index and oxygen uptake.²³ The possible explanations for this observation are, first, the hypermetabolic response after cardiac surgery, which may increase oxygen demand over and above what appears to be an adequate O₂ delivery (DO₂). Lactate synthesis also may occur when the rate of glucose metabolism exceeds the oxidative capacity of the mitochondria, as observed

with administration of catecholamines.¹ Furthermore, an increase in oxygen extraction ratio in these circumstances may also reflect the inability of the myocardium to respond rapidly to the increased demands of the immediate postoperative period. Second, a fall in DO₂ could result in rise in lactate in parallel with a rise in cardiac index, provided that hemoglobin levels fall sufficiently. Third, a delay in the tissue washout of lactate, such that plasma levels increased only after rewarming, with a consequent increase in tissue perfusion, could have occurred. Fourth, systemic microvascular control may become disordered in CPB, resulting in peripheral arteriovenous shunting and a rise in tissue lactate levels despite an apparently adequate cardiac output. Impaired cellular use of oxygen due to similar mechanisms has been proposed to occur after major abdominal surgery.²⁶ Finally, the elevation in lactate could be due to impaired clearance.

Limitations of lactic acidosis as a monitor:

The use of lactate as an index of tissue perfusion has several limitations. The presence of liver disease causes a decreased ability to clear lactate during periods of increased production. Various causes of type B lactate acidosis may produce hyperlactatemia and lactate acidosis in the absence of tissue perfusion. For significant increase in blood lactate to occur, lactate must be released into the systemic circulation and the rate of production must exceed hepatic, renal, and skeletal muscle uptake. Therefore, regional hypoperfusion of tissues may be present despite normal blood lactate concentrations.

Lactate assay: In the past, lactate assays were difficult and tedious. Newer autoanalyzers can rapidly and accurately measure blood, serum, or plasma lactate levels within minutes. Either arterial blood or a mixed venous sample is preferable because the peripheral venous specimen may reflect regional, rather than systemic, lactate concentrations. The blood specimen should be immediately transported on ice and analyzed without delay because blood cells continue to produce lactate in vitro and falsely elevate the concentration. In some instances, the sample can be collected in special tubes containing glycolytic inhibitor such as sodium fluoride or iodoacetic acid. In patients with circulatory shock, lactate elevation above 2.5 mmol/L is associated with excessive mortality. If circulatory failure develops, serial lactate values are helpful in following in

the course of the hypoperfusion state and the response to therapeutic interventions.

Special Concerns in treatment:

Lactic acidosis is observed frequently in patients who are critically ill. Despite a large number of potential etiologies, tissue hyperfusion is by far the most common etiology.

- Aggressive cardiorespiratory resuscitation designed to restore tissue perfusion is the fundamental approach to these patients.

- Titrating therapies to traditional endpoints may not ensure that the microvascular bed is reperfused. Monitoring blood lactate concentration not only allows for prognostication but also serves as an indicator of when supportive therapies are restoring tissue perfusion.

Cardiovascular collapse should be treated with fluid replacement, preferably with isotonic sodium chloride preparations, avoiding solutions containing lactate. vasoconstrictor drugs have potential to exacerbate ischemia in critical tissue beds. Severe metabolic acidosis with arterial pH of less than 7.2 is associated with impaired cardiac contractility and suboptimal response to exogenous catecholamines. Elevation of serum lactate concentration may have negative inotropic effects independent of serum pH. Furthermore, bicarbonate therapy may lead to electrolyte disturbances, such as hypokalemia and hypocalcaemia. Controversy continues to surround the use of alkali in treating lactic acidosis. As sodium bicarbonate (NaHCO_3) breaks down into carbon dioxide and water in the tissues, patients must have effective ventilation to eliminate carbon dioxide and should be able to handle additional sodium and volume load. The animal models of lactic acidosis have shown that intravenous administration of NaHCO_3 may increase lactate production (particularly by splanchnic bed), decrease portal vein flow, lower intracellular pH in muscle and liver, lower arterial pH, and worsen the cardiac output. The improvement noted in hemodynamic status when bicarbonate is administered during acidosis may be caused by other mechanisms than correction of acidosis (eg, increased preload, effect of tonicity).^{32,33}

The arterial pH could always be corrected by lowering the PaCO_2 by increasing the rate of ventilation. This may correct both the extracellular and intracellular acidosis. The use of bicarbonate in patients with severe metabolic acidosis and arterial pH less than 7.15 should be reserved to maintain the pH above 7.15 until the underlying process is corrected.

The amount of NaHCO_3 can be calculated by the following formula:

NaHCO_3 required = (bicarbonate desired - bicarbonate observed) x 0.4 x body weight (kg)

Prognostic issues:

Reperfusion of an ischemic myocardium results in altered myocardial metabolism, which in turn may contribute to delayed functional recovery. Likewise, the activity of mitochondrial pyruvate dehydrogenase (PDH) is inhibited by 40% after ischemia and remains depressed for up to 30 minutes after reperfusion.^{12,13} In addition, the recovery of postischemic myocardial function is dependent on the recovery of PDH activity. These results suggest that persistent anaerobic metabolism may be an important contributor to inadequate postoperative ventricular function; improving the recovery of aerobic myocardial metabolism during reperfusion may serve as an important target for reperfusion injury. Persistent lactate release during reperfusion suggests a delayed recovery of aerobic myocardial metabolism and may be related to intraoperative misadventure or inadequate myocardial protection.¹⁴

It has been speculated that blood lactate concentration monitoring during CPB might be a sensitive tool to detect an imbalance between oxygen supply and demand.¹⁵ Mortality can be predicted by the presence of elevated serum lactate, elevated base deficit, hypotension, oliguria and large vasopressor doses. It was shown that serum lactate more than 10 mmol/L in the first 8 hours of IABP support predicts a 100% mortality. Base deficit more than 10 mmol/L, mean arterial pressure less than 60 mm Hg, urine output less than 30 ml/h for 2 hours, and dose of epinephrine or norepinephrine more than 10 $\mu\text{g}/\text{min}$ were other highly predictive prognostic markers.⁵

In another studies, it has been demonstrated that as the lactate level rises from 2.0 to 8.0 mmol/L, the probability of survival decreases from 90% to 10%, but this prognostic implication is dependent on the cause of the rise in lactate.^{8,9} High lactate levels due to hemorrhagic shock appear to be associated with better outcomes than increases in lactate due to either cardiogenic or septic shock, and this finding can be attributed to a potentially reversible cause of the shock due to hemorrhage.⁹ Morbidity related to CPB, frequently referred to as the postpump syndrome, ranges from mild capillary leakage to multiple organ system failure. The postpump syndrome has been attributed to

exposure of blood cells to foreign surfaces and the release of inflammatory mediators.^{17,18,19,20} In addition to postpump syndrome, many patients develop metabolic acidosis and increased serum lactate levels during and just after CPB.^{15,20,21} This acidosis is secondary to tissue hypoperfusion, which occurs despite the use of hypothermia to reduce metabolic demands and the maintenance of normal mixed venous oxygen saturation levels during CPB.^{15,22,23} Some studies have demonstrated that metabolic acidosis occurs during CPB through peripheral hypoperfusion^{15,24,25} and persists in the early postoperative period.²³ These findings are similar to those of other workers studying patients after both cardiac¹⁵ and major abdominal surgery.²⁶ Siegel and coworkers have demonstrated in pediatric patients a strong correlation between the initial post-CPB serum lactate levels and capillary leakage (maximal weight gain), duration of intravenous inotropic support, duration of ventilatory support, and length of hospital stay.²⁷ They have also shown that serum lactate level was the best predictor of mortality, and a rule predicting mortality at a serum lactate level of >4.2 mmol/L had a positive predictive value of 100% and a negative predictive value of 97%. Maillet and colleagues have demonstrated that nonelective surgery, prolonged CPB, and intraoperative use of vasopressors were independent risk factors for immediate hyperlactatemia after cardiac surgery and also have shown that immediate hyperlactatemia more accurately predicted ICU mortality than late hyperlactatemia.²⁸ Increased cross-clamp and CPB times and highly positive fluid balance at the end of the operation are associated with an early rise in postoperative lactate levels, which is associated with increases in need for IABP support, length of ICU stay, need for red blood cell transfusion, length of hospital stay, and mortality rates.^{29,30} The lungs were found to be a significant source of lactate, and this pulmonary lactate flux was accentuated by CPB. The PLR correlated with systemic hyperlactatemia as well as the A-a O₂ gradient, and was found to be higher in patients requiring prolonged mechanical ventilatory support.³¹ Persistent lactate release during reperfusion occurs in a significant proportion of low-risk patients undergoing isolated CABG and is an independent predictor of postoperative low cardiac output syndrome. It suggests a delayed recovery of aerobic myocardial metabolism and may predict postoperative ventricular dysfunction requiring intra-aortic balloon pump support.¹⁴

Increase in the blood lactate level is associated with adverse outcome during and after cardiac surgery, so monitoring blood lactate level seems to be a valuable tool in identifying the patients who have the potential to deteriorate.^{34,35,36,37}

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