16

The Physiology and the Clinical Significance of Postoperative Hyperlactatemia After Pediatric Cardiac Surgery

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1. Introduction

Lactate was first described by Berzelius in 1807 when he discovered it in its modified form in meat juices. It has been used as a marker of cellular hypoxia and tissue malperfusion, and hyperlactatemia has been associated with postoperative complications and mortality. Notably, high blood lactate concentrations have been associated with increased mortality and morbidity in children after cardiac operations (Siegel et al., 1996). Hyperlactatemia associated with metabolic acidosis is a major predictor of mortality of patients with sepsis or after cardiovascular shock, and the evolution of lactate concentration after therapeutic management can more accurately predict the outcome (Bakker et al., 1996; Weil & Afifi, 1970). Blood lactate concentrations are more easily obtained and measured than other monitoring variables, even before any invasive monitoring, such as mean arterial blood pressure, is available. This use of lactate as a clinical endpoint is based on a substantial body of literature, including multiple prospective studies on trauma, surgery or sepsis, patients and in mixed populations of critically ill patients.

2. The physiology of lactate production

Lactate is a glycolytic product that is either used within the cells or transported through the interstitium and vasculature to adjacent and anatomically distributed cells for utilization. As such, lactate is a quantitatively important oxidizable substrate and gluconeogenetic precursor, as well as a means by which metabolism in diverse tissues is coordinated (Brooks, 2002; Stacpoole et al., 1994). Furthermore, lactate measurement in critically ill animals is practical and can provide information on illness severity and prognosis, because a high lactate level is most frequently, but not always, interpreted as resulting from anaerobic metabolism, particularly when associated with metabolic acidosis (Handy, 2006).
Lactic acid is derived from the metabolism of pyruvic acid, a reaction that is catalyzed by lactate dehydrogenase and one that involves the conversion of NADH into NAD+ (reduced

and oxidized nicotine adenine dinucleotide, respectively) (Phypers, 2006). Under aerobic conditions, pyruvate is converted to acetyl CoA to enter the Kreb's cycle. Under anaerobic conditions, pyruvate is converted by lactate dehydrogenase (LDH) to lactic acid. In aqueous solutions, lactic acid dissociates almost completely to lactate and H^+þ (Phypers, 2006). Once having been believed to be the consequence of oxygen lack in contracting skeletal muscle, it is now known that lactate is also formed and utilized continuously under fully aerobic conditions (Brooks, 2002).

Normal plasma lactate concentration is 0.3–1.3 mmol/liter (3-12 mg/dL), and normal basal lactate production is 0.8 mmol/kg/hour (1300 mmol/day) (Phypers, 2006). Normal subjects produce between 15 to 20 mmol/kg of lactic acid/day, most of which is generated either from glucose via the glycolytic pathway or from the deamination of alanine (Huckabee, 1961). Its concentration can rise to over 20 mmol/L (180 mg/dL) during intense exertion or severe illness (Mizock & Falk, 1992).

Lactate has two chemical isomers in nature. The first, D-lactate, is produced from non-absorbed carbohydrates by colonic bacteria (which may also proliferate in the ileum). The D isomer is mostly exogenous from Ringer's lactate solution infusion, and its non-iatrogenic presence in humans is uncommon. In the blood, it is a reflection of bacterial overgrowth in the gastrointestinal tract. Its clearance is much slower than the other chemical isomer, L-lactate, with the clearance mainly depending on liver function (Uribarri et al., 1998). L-lactate is the product of anaerobic glycolysis in humans and has been used as a marker of cellular hypoxia and tissue malperfusion. It can only be produced or consumed from pyruvate via the enzyme LDH in the cytosol, by means of a process of fermentation during normal metabolism and exercise (Mizock, 1989). It does not increase in concentration until the rate of lactate production exceeds the rate of lactate removal, a process which is governed by a number of factors, including monocarboxylate transporters, concentration and isoform of LDH, and oxidative capacity of the tissues.

Both the production and the removal of lactate are active functions of every tissue of the body. Tissue sources of lactate production include erythrocytes, perivenous hepatocytes, skeletal myocytes and skin. The liver is the major organ of lactate utilization, followed by the kidneys (Huckabee, 1961; Mizock, 1989). The liver removes 70% of lactate and less than 5% of lactate is renally excreted. Liver uptake involves both a monocarboxylate transporter and the less efficient process of diffusion, while renal fraction may increase and become more clinically significant during hyperlactatemia. Following the liver, skeletal muscle, brain, erythrocytes, and the renal medulla are considered to be the most important sources of lactate in the body (Phypers, 2006).

3. Causes for hyperlactatemia

Hyperlactatemia is usually defined as more than >4 mmol/liter or 40 mg/dL, a result of conditions in which production exceeds utilization. Hyperlactatemia can be associated with acidosis, alkalosis and normal blood pH, and can also be found in conditions of normoxia, hypoxia and anoxia (Handy, 2006).

Since lactate is a byproduct of anaerobic metabolism, it becomes elevated in hypoperfusion states when pyruvate cannot enter the Krebs cycle due to insufficient oxygen supply and is converted to lactate. Lactate-producing tissues include the skin, erythrocytes, brain, skeletal muscles, leukocytes and the renal medulla. Lactate-consuming tissues include the liver,

renal cortex and heart. Overproduction and under-consumption result in hyperlactatemia, which can be *physiologic* or *pathologic*. Specifically, increased lactate production can be physiologic as a result of postprandial rest, postabsorptive rest, sustained submaximal exercise or catecholamine-stimulated glycolysis (Mizock, 1989). The primary role of lactate overproduction is clear in certain disorders: for example, plasma lactate levels may transiently be as high as 15 mmol/L during a grand mal seizure, and 20-25 mmol/L during maximally intense exercise, with the systemic pH falling to as low as 6.80. Studies on these subjects have demonstrated rapid recovery of acid-base balance with a maximum rate of lactate utilization that can reach as high as 320 mmol/h.

Impairment of oxidative pathways during lactate production results in a net gain of H^+ whereupon acidosis occurs. The pathologic causes of hyperlactatemia were historically divided between those with evidence of one or another of the well-known causes of hypoxia; and those with no detectable disturbance in oxygen transport in the usual sense (Huckabee, 1961). As a result, hyperlactatemia may occur without (primary) or with (secondary) tissue hypoperfusion, a distinction proposed by Cohen and Woods in 1976 (as cited in Mizock, 1989). However, many critically ill patients can have hyperlactatemia as a result from both of those mechanisms (Phypers, 2006).

3.1 Primary (type B)

The more clinically prevalent hyperlactatemia is not associated with poor tissue perfusion (i.e., alkalosis or increased metabolic activity). In such cases, body-buffering mechanisms can compensate for the decreasing pH (Smith et al., 2001). Among the mechanisms that may be involved are a toxin-induced impairment of cellular metabolism or regional areas of ischemia. Primary hyperlactatemia is usually associated with an underlying disease (e.g., diabetes mellitus, liver disease, malignancy, sepsis, pheochromocytoma, and thiamine deficiency), with drugs or toxins (e.g., ethanol, methanol, ethylene glycol, fructose, sorbitol, xylitol, salicylates, acetaminophen, epinephrine, terbutaline, cyanide, nitroprusside, isoniazid and propylene glycol), and with inborn errors of metabolism (e.g., glucose + phosphatase deficiency [van Gierke's disease], fructose-l + diphosphatase deficiency, pyruvate carboxylase deficiency, pyruvate dehydrogenase deficiency, and oxidative phosphorylation defects), or following hypoglycemia (Mizock, 1989). D-lactic acidosis is a unique form of acidosis that occurs in patients with short bowel syndrome or other forms of malabsorption.

3.2 Secondary (type A)

Secondary hyperlactatemia is due to poor tissue perfusion and the body-buffering mechanisms are not able to compensate for the decreasing pH (Smith et al., 2001). This is the common post-cardiac surgery type of hyperlactatemia. The most frequent cause for secondary hyperlactatemia is the hypoperfusion and tissue hypoxia that are associated with significant cardiopulmonary compromise. Either systemic or regional hypoperfusion may result in hyperlactatemia (Mizock & Falk, 1992). The major causes of secondary hyperlactatemia are shock (cardiogenic, septic, hypovolemic), regional hypoperfusion (limb, mesenteric ischemia), severe hypoxemia, severe anemia, carbon monoxide poisoning, and severe respiratory acidosis (asthma) (Juneja et al., 2011; Mizock, 1989).

The relationship between regional oxyhemoglobin saturation ($rS0_2$) and lactate is exponential in nature, as demonstrated in a study which aimed to determine whether there

is a relationship between $rS0_2$ measured at various body locations by near-infrared spectroscopy and blood lactate level in children after cardiac surgery (Chakravarti et al., 2009).

3.3 Summary

Hyperlactatemia may be physiologic or pathologic. It can be caused by increased lactate production (i.e., an increase in the rate of glycolysis or unregulated substrate entry into glycolysis) as well as a decrease in its clearance (i.e., liver or renal insufficiency).
Common causes for type A hyperlactatemia include intense exercise or hypoxemia, anemia, systemic or regional hypoperfusion, shock, CO poisoning and impaired liver blood flow below 25%. This type is more common in postoperative patients.

4. The prevalence and incidence of postoperative hyperlactatemia

The prevalence and incidence of postoperative hyperlactatemia after pediatric cardiac surgery

An increase in serum lactate reflects anaerobic metabolism, and this yardstick has been used in many studies of postoperative management in congenital heart defects (CHD) as a predictor of adverse outcome, given that an elevated serum lactate is common at the time of ICU admission after surgical correction of CHD.
Postoperative hyperlactatemia was seen in 38% of a cohort of 68 patients who underwent isolated atrial septal defect repair at Arkansas Children's Hospital between January 2001 and March 2006 (Abraham et al., 2010).
Our previous studies and validated data of a clinical database encompassing all the consecutive children who underwent surgery for CHD between 1999 and 2001 at the Sheba Medical Center, revealed a prevalence of 41% (89 out of 215 patients) of hyperlactatemia on pediatric cardiac critical-care unit (PCCU) admission, and of 49% in the last blood lactate level taken at the operating room post-CHD repair (our unpublished data). The prevalence declined to 27% and 17% at 6 and 12 hours, respectively, post-PCCU admission after CHD repair. Moreover the mean initial postoperative lactate level was significantly lower for survivors (42.2 ±32.0 mg/dL) than for nonsurvivors (85.4 ± 54.1 mg/dL) ($p<0.01$) (Molina Hazan et al., 2010).
In another study in which 23 pediatric non-cyanotic patients were included, lactate was measured at 0, 2, 4, 6, and 24 hours after admission to the pediatric intensive care unit (PICU), and more often if clinically indicated (Chakravarti et al., 2009). A total of 163 lactate measurements were recorded, of which 18% had a value greater than 3 mmol/L (27 mg/dL).

The prevalence and incidence of postoperative hyperlactatemia in adults

Maillet et al. (2003) found immediate postoperative hyperlactatemia in 20.6% patients, and early postoperative hyperlactatemia in 17.2% patients among 325 patients following coronary heart disease repair. Hyperlactatemia was observed in a substantial proportion of patients who had been operated on under extracorporeal circulation in a Russian study which included 270 patients after cardiac surgery (Bakanov et al., 2009).
Ranucci et al. (2006) reported the rate of patients with hyperlactatemia during cardiopulmonary bypass (CPB) as being relatively low (5.7%) when they measured

progressive hyperlactatemia during the procedure (excluding 30 patients who had pre-existing hyperlactatemia). The overall incidence of hyperlactatemia was 11.4%. Non-pre-existing hyperlactatemia during CPB for cardiac operations in adults occurred in approximately 6% of the patients.
O'Connor and Fraser's (2010) single-center review of prospectively collated data from 529 post-cardiac surgical patients in a tertiary Australian cardiac surgical ICU showed 25% late hyperlactatemia (above 2.5 mmol/L [23 mg / dL]).
Demers et al. (2000) reported higher rates: they recorded peak blood lactate levels of 4.0 mmol/L (36 mg/dL) or higher during CPB in 18.0% of their patients

The prevalence and incidence of hyperlactatemia upon general admission to the ICU

Hyperlactatemia was present in 199 of 653 (30.47%) patients, admitted over 15 months to an 8-bed general ICU of a tertiary care hospital in India (Juneja et al., 2011). Khosravani et al. (2009) documented the incidence of hyperlactatemia in critically ill patients and found a significantly variation according to the major admitting diagnostic category. Specifically, the incidence of hyperlactatemia was highest among neuro/trauma patients (1053/2328, 45%), followed by medical (2047/4935, 41%), other surgical (900/2274, 40%), and cardiac surgical (1578/4395, 36%).

5. Predictive factors for hyperlactatemia

Hyperlactatemia appears in association with peripheral circulatory failure (reduced arterial blood pressure, tachycardia, sweating and mental confusion), with low arterial blood 0_2 saturation, and with acid base disturbance. Significant hyperlactatemia and dangerous hypoperfusion can exist despite the lack of acidosis. Patients with hyperlactatemia may have variable blood pyruvate concentrations because renal dysfunction, electrolyte abnormalities serum lactate and base deficits may not always be linked due to alterations in the body's buffer base. Also relevant is whether the patients did or did not undergo treatment.
While they may present clinically with normal vital signs and are hemodynamically stable, many surgical patients have increased blood lactate levels ('occult hypoperfusion' or 'compensated shock') (Jansen et al., 2008; Meregalli et al., 2004).

5.1 Nonoperative factors

Hyperlactatemia could be present in a critically ill patient due to multiple factors that are either secondary to increased production (shock, sepsis, or respiratory failure) or because of reduced lactate clearance (liver or renal failure). Shock was the most common cause for non-surgical hyperlactatemia, followed by respiratory and renal failures in one study (Juneja et al., 2011). Patients with or without shock who had higher blood lactate levels on admission to the ICU were also found to have higher APACHE II scores, and a greater need for vasopressors or renal replacement therapy and mechanical ventilation, (Juneja et al., 2011).

5.2 Operative factors

Lactic acidosis is often observed as being related to cardiac surgery with CPB, low output syndrome and hypoxemia, which usually show clinical evidence of poor tissue oxygen delivery. Early postoperative hyperlactatemia is seen in some children after surgical repair

of CHD despite evidence of good cardiac output. Cardiac arrest or severe hypovolemia triggers anaerobic metabolism and hyperlactatemia, all of which can appear pre-, peri- or postoperatively due to the many cardiac or resuscitation problems found in pediatric patients with CHD.
Changes in lactate levels in post-cardiac surgery patients are not homogenous in nature, due to the fact that early hyperlactatemia and late hyperlactatemia differ in both risk profile and physiological rationale (O'Connor & Fraser, 2010).

5.2.1 Preoperative

The Risk-Adjusted Classification for Congenital Heart Surgery (RACHS-1) system for mortality risk adjustment has recently been proposed as a universal objective score for adjusting differences in case mix when examining in-hospital death rates after congenital heart surgery, and for predicting the risk involved in specific types of cardiac surgery (Jenkins & Gauvreau, 2002; Jenkins et al., 2002). RACHS-1 assigns congenital heart surgical cases to one of six risk categories based on the presence or absence of specific diagnosis and procedure codes, where category 1 has the lowest risk of death and category 6 has the highest. When the mean lactate level was measured at four time points for each RACHS-1 subgroup, blood lactate levels absolutely correlated with the RACHS-1 subgroups at each of the time points (r^2>0.89 for all) (Molina Hazan et al., 2010). In addition, the progression of lactate levels over time differs significantly between patients with different RACHS-1 scores (P = 0.029).
The patient's age affects the risk for postoperative hyperlactatemia. Children younger than 1 year of age would be primed with banked red blood cells and have comparatively more banked blood peri-operatively and higher risk for developing postoperative hyperlactatemia and lactic acidosis (Zhou & Liu, 2011). The adult patient's age is not a predictor for hyperlactatemia.
The electivity/urgency of the surgery are also influential: the more elective the surgery, the lower the postoperative blood lactate levels are expected (Maillet et al., 2003). Urgent or emergency surgery is usually performed for patients who are hemodynamically unstable, and so the preoperative lactate values might have already been abnormal in some of them.
Non-pre-existing hyperlactatemia during CPB for cardiac operations in *adults* is favored by the preoperative risk profile (high serum creatinine values and active endocarditis) and by prolonged (> 96 minutes) CPB times, in addition to being associated with hyperglycemia (Ranucci et al., 2006). Patients with a blood lactate level of 4.0 mmol/L (36 mg/dL) or higher were older and were more often females. The prevalence of congestive heart failure, left ventricular ejection fraction less than 30%, and arteriosclerosis was significantly higher among the patients with hyperlactatemia (Demers et al., 2000).

5.2.2 Peri-operative

Hyperlactatemia occurring early after CPB may represent intra-operative or early postoperative tissue oxygen debt, impaired lactate clearance, or both. It may, however, follow CPB despite well-maintained oxygen delivery and a normal perioperative course. The duration of CPB and, especially, the occurrence of hypotension at the start of the bypass period appears to be related to the development of lactic acidosis. Non-pulsatile, hypothermic CPB itself has a potential for impairment of peripheral perfusion and thus of metabolic balance, since it is associated with collapse and sludging in capillary vessels

according to duration of the CPB and to lactate concentration fluctuations (increase after the start of CPB, remaining elevated during CPB, decreasing after CPB, and increasing again after surgery).

Patients with lactate levels of 4.0 mmol/L (36 mg/dL) or higher had significantly longer CPB time and aortic cross-clamping time, and the lowest hemoglobin value recorded during CPB tended to be lower in patients with lactate levels of 4.0 mmol/L (36 mg/dL) or higher (Demers et al., 2000).

Postoperative hyperlactatemia following cardiac surgery was associated with the longest CPB duration and the more frequent intraoperative administration of vasopressors (Maillet et al., 2003). A significant association was found between either duration of CPB or arterial pH and lactate in a retrospective study (Duke et al., 1997). Type A lactic acidosis during CPB appears to be multifactorial.

In a retrospective study where hyperlactatemia was defined as 5 mmol/L (45 mg/dL) or more, CPB duration in the hyperlactatemia group was significantly longer than for the normal lactatemia group in adults undergoing cardiac surgery. Moreover, significant elevations of serum lactate were observed after the start of CPB in the hyperlactatemia group, while other intraoperative variables, including the degree of induced hypothermia, were similar between the two groups (Inoue et al., 2001). In that study, significant correlations between maximal lactate concentration and duration of CPB and aortic cross-clamping were observed as well.

Abraham et al. (2010) compared perioperative factors in 26 patients with postoperative hyperlactatemia (lactate greater than 3 mmol/L (27 mg/dL))) to 42 patients with low-normal lactatemia, including bypass time, crossclamp time, mixed venous oxygen levels, peripheral oxygen saturation, pump flow, intraoperative mean arterial blood pressure, lowest intraoperative core temperature, rewarming time, duration of surgery, duration of anesthesia, average intraoperative hemoglobin, intraoperative oxygen content, and intraoperative oxygen delivery. Of all these intra-operative measurements, the authors found the two groups to differ significantly only in pump flow and intra-operative oxygen delivery. The weight-indexed CPB flow rate was an independent predictor of postoperative high lactate ($P<.007$), and the odds ratio was 7.67 for postoperative hyperlactatemia when it was less than 100 mL/kg/min. Higher mean arterial blood pressure was associated with a reduced risk of high lactate blood levels. An increase of 1 mm Hg, with a fixed CPB flow, resulted with odds ratio for postoperative hyperlactatemia of 0.8343 ($P<.009$) (Abraham et al., 2010). The nadir temperature, duration of cooling and rewarming, hematocrit during and after CPB, and systemic inflammatory response to CPB were also proposed as being likely predictors for postoperative hyperlactatemia (Abraham et al., 2010; Cheung et al., 2005; Munoz et al., 2000).

An association was found between the duration of extracorporeal circulation and the magnitude of hyperlactatemia developing in the early post-pediatric cardiac operation period in Bakanov et al.'s (2009) work as well.

Finally, massive exogenous D-lactate Ringer's solution infusion during surgery can also cause iatrogenic hyperlactatemia in infants with immature liver function (Zhou & Liu, 2011).

5.2.3 Postoperative

Metabolic disturbances, such as changes in blood acid-base balance and electrolytic composition, hyperglycemia and hyperlactatemia, are factors that frequently complicate the

early postoperative period in patients after cardiac surgery under extracorporeal circulation. Post-cardiac surgery hyperlactatemia is mostly the consequence of excess lactate production, although a reduction of hepatic lactate clearance may contribute to the condition. Early postoperative measurable adverse effects, such as base deficit, maximal anion gap and bicarbonate levels, were significantly different between patients with postoperative hyperlactatemia and patients with low-normal lactatemia in the early postoperative period (i.e., less than 12 hours after admission to the ICU), while postoperative lactate and glucose levels were significantly correlated (Abraham et al., 2010; Chiolero et al., 2000).

Inadequate tissue oxygen delivery because of impaired cardiac output after pediatric cardiac surgery is a relatively common problem which can be expressed in early stages by hyperlactatemia, and one that has been associated with significant morbidity and mortality (Chakravarti et al., 2009).

Elevated lactate concentrations were associated with metabolic acidosis following cardiac surgery. Moreover, postoperative episodes of hypotension, hyperglycemia, and epinephrine, norepinephrine or dobutamine consumption were more frequent in patients with hyperlactatemia following cardiac surgery compared to patients with non-elevated blood lactate levels (Maillet et al., 2003).

Clinical indicators used for diagnosing decreased cardiac output other than hyperlactatemia include a low peripheral temperature/core temperature gradient, long capillary refill time, high pulse and low blood pressure, decreased urine output and base deficit (Bohn, 2011). Most of these indicators do not reflect cardiovascular performance very well (Tibby et al., 1997).

Averaged cerebral and renal $rS0_2$ levels of less than 65% as measured by near-infrared spectroscopy (NIRS) predict hyperlactatemia (>3 mmol/L, 27 mg/dL) in acyanotic children after congenital heart surgery (Chakravarti et al., 2009). The averaged cerebral and renal $rS0_2$ was a good predictor of the lactate status, with a value less than or equal to 65%, predicting a lactate level of greater than or equal to 3.0 mmol/L (27 mg per dL), with a sensitivity of 95% and a specificity of 83% in the studied patients. Consequently, monitoring of $rS0_2$ could aid in the prompt identification of patients at risk for hyperlactatemia and low-cardiac-output syndrome (Chakravarti et al., 2009). A combination of cerebral and renal $rS0_2$ with an average value less than 65% using the intravenous NIRS device could, therefore, predict hyperlactatemia (>3 mmol/L (>27 mg/dL)) in acyanotic children after congenital heart surgery.

Patients with higher blood lactate levels during CPB were also more likely to have myocardial infarction and postoperative neurologic, hemodynamic, pulmonary, digestive, or renal complications (Demers et al., 2000).

Moreover, sepsis as postoperative complication, can be the cause for late postoperative hyperlactatemia.

5.3 Summary

Patients without signs of clinical shock can still be hypoperfused and are at high risk for pre-peri- and postoperative complications. They tend to develop postoperative hyperlactatemia. Patients undergoing surgery with a RACHS-1 score of IV and higher are not expected to maintain good cardiac output in the postoperative period, emphasizing the importance of combining pre- peri- and postoperative prognosis predictors, especially for the so called "preoperative good prognosis" groups.

6. Blood lactate levels as a biomarker

6.1 General

Biomarkers that are sensitive and rapidly measurable could allow early intervention and improve patient outcomes. Efforts are aimed at developing novel biomarkers and surrogates for disease severity to indicate conditions associated with organ dysfunction early on and by early intervention lead to improved outcome. Lactate levels are commonly used to stratify risk and to assess adequacy of resuscitation among high risk patients in the ICU (Smith et al., 2001). Lactate may have prognostic value in critically ill patients with either observed or occult tissue hypoperfusion.

Lactate levels higher than 2 mmol/L (18 mg/dL) after 48 hours predicted mortality with a specificity of 86% and poor neurologic outcome with a specificity of 87%. Sensitivity for both end points was 31%. Lactate at 48 hours after cardiac arrest is an independent predictor of mortality and unfavorable neurologic outcome. Persisting hyperlactatemia over 48 hours. predicts a poor prognosis (Kliegel et al., 2004). Sensitivity and specificity of lactate >2 mmol/L (18 mg/dL) to predict ICU mortality was 74.8% and 77.8%, respectively. The odds ratio for dying in patients with hyperlactatemia was 10.39 (95% CI, 6.378-16.925), with a relative risk of 1.538 (95% CI, 1.374-1.721) (Juneja et al., 2011). In one multicenter, open-label randomized controlled study on patients who had hyperlactatemia on general ICU admission, lactate monitoring followed by hyperlactatemia-targeted treatment significantly reduced length of stay in the ICU. In addition, ICU and hospital mortality were reduced when adjusting for predefined risk factors (Jansen et al., 2010). In that study, the time of the first available lactate level immediately after ICU admission was taken as the baseline and patients were randomly allocated to either treatment aimed to decrease lactate levels by at least 20%/2 hours or to standard therapy for the following 8 hours.

Elevated blood lactate levels in the presence of normal vital signs (occult hypoperfusion) are good markers of mortality in surgical patients. It is therefore important to identify the high-risk surgical patients who have had a stable hemodynamic course during surgery and immediately after admission to the ICU. Blood lactate levels are superior to several clinical markers of shock or organ failure, including the heart rate, diuresis and the mean arterial pressure, or indices of metabolic acidosis.

In adults following cardiac surgery, blood lactate levels at admission to the ICU were the best predictors of ICU mortality (AUC, 0.84; 95% CI, 0.73 to 0.95), compared to lactatemia measured during the ICU stay (Maillet et al., 2003). Early postoperative hyperlactatemia is associated with adverse outcome of surgery. When they were compared with patients with a normal lactate profile, patients with late hyperlactatemia showed no increase in hospital mortality (OR 0.57, 95%CI 0.07 to 5.05) (O'Connor & Fraser 2010). However, Nichol et al. (2010) reported that early (at admission) and late (post-admission) hyperlactatemia were both strongly associated with mortality in cardiac/vascular surgical patients of whom a significant number were postoperative cardiac patients).

Boyd et al. (1993) demonstrated a 75% reduction in postoperative mortality in adults when targeted therapy was guided by blood lactate levels as predictors for poor prognosis.

Moreover, Kliegel et al. (2004) claimed that sequential measurements during therapy may be more useful than a single measurement since the rapidity at which lactate is cleared from the blood during resuscitation correlates better with outcome — including mortality or organ failure — than a single measure. They showed that survivors' blood lactate levels decreased significantly with time, while those levels remained stable in the non-survivor group.

Among a cohort of 9107 first admissions with an ICU stay of at least one day, both hyperlactatemia at presentation and its later development were associated with significantly increased fatality rates compared with patients without elevated lactate (20% vs. 5%; P < 0.001 and 27% vs. 4%; P < 0.001, respectively). After controlling for confounding effects in multivariable logistic regression analyses, hyperlactatemia was an independent risk factor for death (Khosravani et al., 2009). When broadly implemented in routine practice, measurement of lactate in patients with infection and possible sepsis can affect assessment of mortality risk. Specifically, an initial lactate level equal to or greater than 4.0 mmol/l (36 mg/dL) substantially increases the probability of acute phase death (Trzeciak et al., 2007).

Blood lactate concentrations greater than 5 mmol/L in patients with severe acidosis (pH less than 7.35 or base deficit greater than 6) carries a mortality of 80% (Stacpoole et al., 1994).

It is well established that hyperlactatemia is also a postoperative prognostic factor. Historically, a rise in blood lactate levels was associated with a decrease in survival rates (Weil & Afifi 1970). These results were recently repeated by a number of investigators. The severity of hyperlactatemia was shown to correlate with oxygen debt and poor survival (Mizock & Falk, 1992), and sustained presence of hyperlactatemia was confirmed as being an important risk factor for poor outcome of critically ill patients (Abubacker et al., 2003; Bakker et al., 1996; Gogos et al., 2003; Kobayashi et al., 2001).

Patients with lactic acidosis were shown to have a higher mortality rate and are at a greater risk of developing multiple organ failure (Bakker et al. 1996). ICU mortality was significantly increased in patients with hyperlactatemia who did not have hypotension (P = .009) (Juneja et al., 2011). Similarly to other changes in blood acid-base balance and electrolytic composition, this metabolic disturbance is a factor that frequently complicates the early postoperative period in patients after cardiac surgery under extracorporeal circulation.

6.2 Post-pediatric congenital heart disease repair

An elevated lactate level has been associated with an increased risk for morbidity and mortality after pediatric cardiac surgery (Basaran et al., 2006; Charpie et al., 2000; Cheifetz et al., 1997; Duke et al., 1997). Elevated blood lactate levels were associated with a higher mortality rate and postoperative complications in hemodynamically stable surgical patients, and failure of serum lactate levels to reach normal values within a specific time during critical illness could be even more closely related to survival than the initial level (Meregalli et al., 2004). Hyperlactatemia during and after CPB has been linked to increased morbidity and mortality in children undergoing surgical repair of complex CHD (Cheung et al., 2005; Munoz et al., 2000). Several factors contribute to lactic acidosis because of global ischemia occurring during circulatory arrest and the hypocirculatory state during cardiopulmonary resuscitation. Oxygen deficiency leads to anaerobic metabolism and therefore to overproduction of lactate. At the same time, the profound ischemic state may impair liver function, leading to reduced lactate elimination. Basaran et al. (2006) reported that mean lactate levels correlated significantly with inotrope score, intubation time, and duration of intensive care unit stay.

In their prospective cohort study of 90 children post-congenital heart surgery, Duke et al.'s (1997) multivariable logistic regression analysis showed that lactate levels were an independent predictor of major adverse events. These adverse events included death,

cardiac arrest, emergency chest reopening, and an increased risk of failure of 3 or more organ systems. The only measurement that those authors found to consistently predict major adverse events was an elevated serum lactate concentration at the time of ICU admission and at 4, 8, 12, and 24 hours postoperatively (Duke et al., 1997). Of the all variables tested by Seear et al. by stepwise discriminant analysis, serum lactate and $Scv0_2$ emerged as the only ones with significant predictive power for major adverse events. This predictive effect was present at all measurement time points (3, 6, 9, 12, and 24 hours, postoperatively) (Seear et al., 2008). Initial postoperative lactate levels above 4.2 mmol/L (38 mg/dL), above 4.5 mmol/L (40.5 mg/dL), and above 6 mmol/L (54 mg/dL) were associated with a positive predictive value for mortality of 16.7%, 32% and 100% respectively (Hatherill et al., 2000; Siegel et al., 1996).

Hyperlactatemia during CPB is relatively frequent and is associated with an increased postoperative morbidity. Hyperlactatemia has an independently predictive value for major adverse events post-CHD surgical repair, when measured at ICU admission and at 4 and 8 hours, with an odds ratio of 5.1, 8.3 and 9.3 respectively, and with a specificity of 91%, 94% and 95%, respectively (Duke et al., 1997). Death was predicted at ICU admission only by the patient's blood lactate value ($p = 0.03$) and not by any of the other physiologic measures. The odds ratio for death was 29.3 (with a confidence interval of 2.7 to 315) when the admission blood lactate level was greater than 4.5 mmol/L (40.5 mg/dL). However, it should be emphasized that the finding of a normal lactate level did not preclude the possibility of a major adverse event. A lactate level greater than 3 mmol/L (27 mg/dL) at the time of admission to the ICU identified only 50% of those who subsequently had a major complication, thus the sensitivity was relatively low but the specificity was very high (Duke et al., 1997).

As noted earlier, hyperlactatemia post-CHD repair is usually due to decreased cardiac output and hypoperfusion (secondary, type A). Basaran et al. (2006) prospectively studied 60 infants undergoing surgery for CHD and showed that mortality was higher in the group with a mean lactate of greater than 4.8 in the early postoperative period. In another group of 46 infants, the mean initial lactate level was significantly higher in patients who had a poor outcome (as defined as death or the need for extracorporeal membrane oxygenation in the first 72 Hours) than in patients with a good outcome (Charpie et al., 2000).

Studies have shown that blood lactate levels are even superior to mixed venous oxygen saturation in predicting outcome (Duke et al., 1997). Our previous work has validated the measurement of lactate levels as a reliable tool for predicting the postoperative survival of children undergoing cardiac surgery (Molina Hazan et al., 2010). The progression of lactate levels with time was significantly different between the patients in different RACHS-1 subgroups ($p = 0.029$), and the lower the RACHS-1 score at each time point, the lower were the mean lactate levels for each time point ($p < 0.001$). Moreover, postoperative blood lactate levels differed significantly between survivors and non-survivors within the same RACHS-1 subgroup. The lactate level at admission to the PCCU compared with the postoperative lactate level was the most significant parameter for predicting non-survival (odds ratio = 1.038, AUC =0.881, $p < 0.001$). Lactate levels above 53 mg/dL had the sensitivity for non-survival of 88.9% and specificity of 23.4%: accordingly, a patient admitted to the PCCU with lactate levels higher than 53 mg/dL would have an almost 90% risk of dying. Patients who died or survived with complications had higher admission lactate levels compared with survivors without complications (8.5 vs. 4.6 vs. 2.0 mmol/L) (Munoz et al., 2000).

Serum lactate best predicted major adverse events for values greater than 8 mmol/L (>72 mg/dL) with a low sensitivity (73.7%), a high specificity (96.3%) and a low positive predictive value (63.6%) in high risk cases (Seear et al., 2008). The ratio of central venous oxygen sampling (Scv02, measured in %) per lactate (measured in mmol/L) had a better predictive value for major adverse events than each individual value measured alone (if the value of the ratio fell below 5 at any time after surgery, the positive predictive value for major adverse events was above 90%).

The length of time it took for serum lactate levels to reach normal values was a useful predictor of mortality in children undergoing repair or palliation of CHD under CPB, while initial and peak lactate levels had a poor positive predictive value for mortality in that retrospective study (Kalyanaraman et al., 2008). Hyperlactatemia was described as the only predictor of persistent renal impairment at 48 hours at the time of admission to the intensive care unit was the admission blood lactate level ($p = 0.018$) (Duke et al., 1997). The odds ratio for renal impairment was 3.2 (with a confidence interval of 1.1 to 9.5) for patients whose admission lactate level was greater than 4 mmol/L (36 mg/dL) (Duke et al., 1997). According to the results of a retrospective review of children aged 0-21 years who had been admitted to a cardiac ICU, the length of time during which the lactate level remained greater than 2 mmol/L (18 mg/dL) was associated with the number of ventilator days and hospital days for the survivors. They all had surgery for CHD and required CPB (DeCampli & Burke, 2009; Kalyanaraman et al., 2008).

The lactate level was also considered as being a risk factor for cerebral damage, which was defined as the development of seizures, movement disorders, developmental disorders, cerebral hemorrhage, infarction, hydrocephalus, or marked cerebral atrophy in children after they had undergone cardiac surgery (Trittenwein et al., 2003).

6.3 Summary

Measurements of blood lactate reflect oxygen delivery to tissues and, therefore, are useful in guiding clinical management. Levels of serum lactate are indirect markers of tissue hypoxia secondary to insufficient peripheral oxygen delivery. They have been used to monitor progress after pediatric heart surgery and to report positive predictive values (Duke et al., 1997; Hatherill et al., 2000; Munoz et al., 2000).

Lactate levels differed significantly between survivors and non-survivors even within the same preoperative prognosis subgroup. As such, a combination of preoperative scores and postoperative serial lactate measurements is needed in order to serve as a useful marker for the postoperative course of cardiac patients, allowing the targeting of appropriately intensive interventions and therapies for the sickest among them, especially for the apparently low risk groups whose poorer perioperative course and worse outcome may not have been predictable from the preoperative scores alone. A cutoff threshold of 3 mmol/L (27 mg/dL) at ICU admission will identify a subpopulation of patients at higher postoperative risk.

7. Treatment of postoperative hyperlactatemia after pediatric cardiac surgery

Poor outcome was associated with multi-organ involvement, as reflected by high blood lactate values, and the need for ventilatory or inotropic support. The therapy for type A hyperlactatemia is optimal hemodynamic resuscitation combined with supportive treatment, such as alkalinization, thiamine, dialysis, and dichloroacetate (Mizock 1989).

Resuscitation of surgical patients has traditionally been guided by the normalization of vital signs, e.g., blood pressure, urine output, and heart rate. A goal-oriented protocol targeting a normal blood lactate level can shorten the length of hospitalization among cardiac surgical patients (Polonen et al., 2000). Polonen et al. showed that therapy aimed at achieving an $Sv0_2$ level greater than 70% and a lactate concentration less than 2 mmol/L (18 mg/dL) immediately after cardiac surgery improves outcome. Specifically, early monitoring of lactate levels with the added target to reduce levels by 20%/2 hours on top of currently recommended resuscitation guidelines significantly reduced the length of ICU stay of patients with a lactate level at or above 3.0 mmol/L on admission (Jansen et al., 2010). The deliberate increasing of peri- and postoperative oxygen delivery ($D0_2I$) for the guided postoperative therapy which decreased mortality by 75%, was monitored by lactate levels, and that maneuver was maintained in the protocol group until blood lactate levels had fallen below 1.5 mmol/L (13.5 mg/dL) for 2 consecutive measurements (Boyd et al., 1993).
Early postoperative supply of oxygen improved the outcome during the early stages of surgery-related sepsis in cases of late postoperative hyperlactatemia. This was accomplished by the administration of D02I and by the use of intravenous dopexamine, a novel dopamine analogue with action at b2-adrenoceptors and DA1 receptors.
Dichloroacetate enhanced the activity of pyruvate dehydrogenase and lowered blood lactate concentrations in these septic patients but had no effect on hemodynamics or survival (Stacpoole et al., 1994).

8. Recommendations - The function of lactate as a warning signal

Serial lactate monitoring can be used to assess the severity of illness and response to therapy. Although conventional monitoring with blood gases during CPB may detect inadequate tissue oxygenation, blood lactate concentration monitoring during CPB might be more sensitive for detecting an imbalance between oxygen supply and demand. Monitoring alone, however, cannot improve outcome, and the therapeutic plan shares equal importance.
When high blood lactate levels are identified, consideration must be given to the ratio of lactate production to lactate metabolism, oxygen status and blood pH before those levels can be meaningfully interpreted. Normal levels do not exclude and high levels do not confirm the presence of critical illness.
We recommend the administration of additional fluids and the increased use of vasodilators in patients considered as having higher lactate levels. Another recommendation is the perioperative increase of oxygen delivery with dopexamine hydrochloride, in agreement with Boyd et al. (Boyd et al., 1993).
In summary, the combination of serial measurements of postoperative lactate levels after surgical repair for CHD in children assigned to a preoperative risk subgroup was predictive of prognosis after surgery. Lactate levels differed significantly between survivors and non-survivors in the same subgroup. This combination should serve as a useful marker for the child's postoperative course, allowing the targeting of appropriately intensive interventions and therapies for the sickest patients. It should be borne in mind, however, that although the measurement of blood lactate level is relatively a low invasive procedure, it is carried out intermittently, whereupon an acute deterioration may be missed. Finally, frequent blood sampling leads to increased blood loss and an increased risk of infection (Chakravarti, Mittnacht, Katz, Nguyen, Joashi and Srivastava 2009).

9. Conclusions

We recommend maintaining a high level of vigilance for the earliest signs of developing multiorgan involvement, as reflected by high lactate levels. We also recommend priority triage of these postoperative children to the PICU for the purpose of taking measures to prevent systemic complications and reduce mortality rates.

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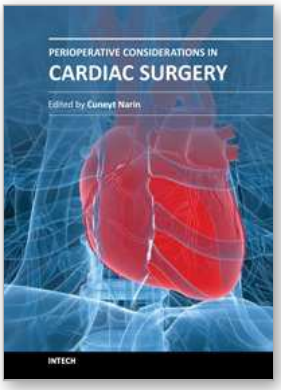

Perioperative Considerations in Cardiac Surgery

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This book considers mainly the current perioperative care, as well as progresses in new cardiac surgery technologies. Perioperative strategies and new technologies in the field of cardiac surgery will continue to contribute to improvements in postoperative outcomes and enable the cardiac surgical society to optimize surgical procedures. This book should prove to be a useful reference for trainees, senior surgeons and nurses in cardiac surgery, as well as anesthesiologists, perfusionists, and all the related health care workers who are involved in taking care of patients with heart disease which require surgical therapy. I hope these internationally cumulative and diligent efforts will provide patients undergoing cardiac surgery with meticulous perioperative care methods.

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