

Review Article

Hyperlactatemia and Cardiac Surgery

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Abstract: The normal blood lactate level is 0–2 mmol/L, and a value above 3–5 mmol/L is variably used to define hyperlactatemia. In cardiac surgical patients, hyperlactatemia can arise from both hypoxic and non-hypoxic mechanisms. The major non-hypoxic mechanism is likely stress-induced accelerated aerobic metabolism, in which elevated lactate results from a mass effect on the lactate/pyruvate equilibrium. The lactate/pyruvate ratio is normal (<20) in this circumstance. Hyperlactatemia can also result from impaired global or regional oxygen delivery, in which case the lactate/pyruvate ratio is typically elevated (>20). Lactate is a strong anion that is virtually fully dissociated at physiological pH. As such, increased lactate concentration reduces the strong ion difference and exerts an acidifying effect on the blood. Hyperlactatemia in cardiac surgery patients has been categorized as either early or late onset. Early-onset hyperlactatemia is that which develops in the operating room or very early following intensive care unit (ICU) admission. Early-onset hyperlactatemia is strongly

associated with adverse outcome and probably arises as a consequence of both hypoxic (e.g., microcirculatory shock) and non-hypoxic (accelerated aerobic metabolism) mechanisms. By contrast, late-onset hyperlactatemia is a benign, self-limiting condition that typically arises within 6–12 hours of ICU admission and spontaneously resolves within 24 hours. Late onset hyperlactatemia occurs in the absence of any evidence of global or regional tissue hypoxia. The mechanism of late onset hyperlactatemia is not understood. Hyperlactatemia is a common accompaniment to treatment with β_2 -agonists such as epinephrine. Epinephrine-induced hyperlactatemia is thought to be due to accelerated aerobic metabolism and requires no specific intervention. Irrespective of the cause, the presence of hyperlactatemia should trigger a search for remedial causes of impaired tissue oxygenation, bearing in mind that normal—or even supranormal—indices of global oxygen delivery may exist despite regional tissue hypoperfusion. **Keywords:** acidosis, lactate, cardiac surgery, outcome. *J Extra Corpor Technol. 2017;49:7–15*

Hyperlactatemia occurs in 10–20% of patients following cardiac surgery and is associated with increased mortality and morbidity (1,2). Clinically, elevated blood lactate concentration is frequently used as a marker of tissue hypoxia. However, lactate metabolism during the perioperative period is complex, dynamic, and incompletely understood. The causes of perioperative hyperlactatemia are varied and include hypoxic as well as non-hypoxic causes (1,3–6).

The purpose of this article is to review lactate metabolism in health and critical illness with an emphasis on cardiac surgical patients. In addition, an approach to investigating and treating patients with hyperlactatemia is described.

NORMAL LACTATE METABOLISM

Lactate ($\text{CH}_3\text{CH}(\text{OH})\text{CO}_2^-$) is the conjugate base of lactic acid. Lactic acid has a pK_a of 3.86, meaning it is virtually fully ionized at physiological pH. Lactate occurs in two optical isomeric forms: levo (*L*) and dextro (*D*). The endogenous form of lactate is predominantly *L*-lactate. *D*-lactate is produced by certain bacterial microorganisms, including those in the gastrointestinal tract, but is not produced by mammalian cells. Only *L*-lactate is considered in this review, as this is the form of lactate that is responsible

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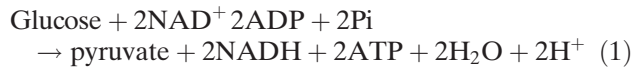
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for perioperative hyperlactatemia and is the form that is measured clinically.

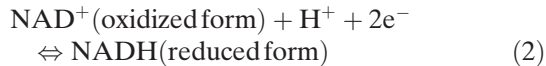
To understand the mechanisms responsible for hyperlactatemia, it is necessary to have a working knowledge of normal lactate metabolism.

GLYCOLYSIS

Lactate is produced exclusively from pyruvate that is itself the end product of glycolysis. In the cytoplasm, one molecule of glucose is metabolized to two molecules of pyruvate. In the process, two molecules of high-energy adenosine triphosphate (ATP) are produced and two molecules of nicotinamide adenine dinucleotide (NAD) are reduced:



ATP is formed by the addition of a high-energy phosphate (Pi) group to adenosine diphosphate (ADP). NAD is a co-enzyme that functions as an electron carrier. It is involved in many redox reactions in intermediary metabolism, being reversibly oxidized and reduced:



For continued glycolysis, it is necessary to regenerate NAD⁺. Regeneration of NAD⁺ occurs by one of two processes: oxidative phosphorylation and the conversion of pyruvate to lactate.

THE CITRIC ACID CYCLE AND OXIDATIVE PHOSPHORYLATION

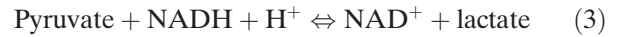
Under normal circumstances, most of the pyruvate formed from glycolysis is fully oxidized to carbon dioxide and water within mitochondria. Pyruvate combines with co-enzyme A and is converted to acetate (acetyl-CoA) under the influence of *pyruvate dehydrogenase*. The metabolism of acetate in the citric acid cycle generates further NADH (along with other reduced co-enzymes). In the presence of oxygen, NADH produced by glycolysis and the citric acid cycle is oxidized to NAD⁺ by the mitochondrial electron transport chain, and produces a large amount of ATP. The complete oxidation of one mole of glucose to carbon dioxide and water has a net yield of approximately 32 molecules of ATP.

The intracellular oxygen tension (PO₂) threshold for oxidative phosphorylation is unknown; however, cellular respiration is clearly inhibited at PO₂ values below 1 mmHg (3). As tissue PO₂ falls and oxidative phosphorylation is inhibited, there is a progressive increase in the ratios of ADP/ATP and NADH/NAD⁺, which in turn inhibit

pyruvate dehydrogenase, blocking entry of pyruvate to the citric acid cycle.

LACTATE DEHYDROGENASE AND THE CORI CYCLE

The second mechanism for the regeneration of NAD⁺ is through the conversion of pyruvate to lactate under the influence of *lactate dehydrogenase*:



The reversible production of lactate from pyruvate allows ongoing glycolysis in the absence of oxygen but yields only two molecules of ATP per molecule of glucose (i.e., much less than by oxidative phosphorylation).

Lactate generated by anaerobic glycolysis in tissues (e.g., skeletal muscle during maximal exercise) may be recycled back to glucose (gluconeogenesis) in the liver. Each molecule of glucose produced from two lactate molecules requires six molecules of ATP. Collectively, the anaerobic production of lactate in muscle, transfer via blood, and regeneration of glucose in the liver is known as the Cori cycle. The Cori cycle serves an important function in working muscle, as it decouples ATP utilization (muscle) from production (liver), allowing ongoing muscular activity despite inadequate oxygen delivery for full aerobic respiration. However, the process is much less efficient in terms of ATP production than oxidative phosphorylation.

LACTATE AS AN AEROBIC FUEL

The traditional view of lactate is as a waste product of anaerobic metabolism. However, under aerobic conditions, lactate is a precursor for oxidative phosphorylation, through its conversion to pyruvate (Equation 3) and then entry to the citric acid cycle. Indeed, most lactate produced in the body is ultimately oxidized rather than recycled to glucose in the Cori cycle (4).

During high-intensity exercise, skeletal muscle releases lactate into blood. However, during recovery from intense exercise or during sustained low-intensity exercise, there is a net uptake of lactate into skeletal muscle where it is removed by oxidation (3). At rest, cardiac muscle utilizes glucose and fatty acids as its primary fuels. However, cardiac muscle can use many energy sources, including lactate. The uptake of lactate by cardiac muscle and other organs is proportional to the plasma concentration of lactate (5), which is normally low (≈1 mmol/L). Conversely, during high-intensity exercise, when blood lactate increases substantially, glucose utilization by myocytes decreases and lactate becomes an important fuel for aerobic metabolism (6). Studies using radiolabeled lactate indicate that virtually

all of the lactate taken up by cardiac myocytes during exercise is fully oxidized (7). There is also evidence that during exercise, there is uptake and oxidization of lactate by the brain (8).

Thus, lactate appears to be an important mobile fuel for aerobic metabolism, particularly during exercise, being able to be rapidly exchanged between tissues depending on the local PO_2 and workload (3).

LACTATE METABOLISM DURING STRESS

During states of metabolic stress, such as sepsis, blood lactate concentration increases. The primary source of lactate in this circumstance is probably skeletal muscle (9). Traditionally, hyperlactatemia during sepsis has been attributed to tissue hypoxia. However, there is clear evidence that oxygen and ATP levels in skeletal muscle are not reduced in this circumstance (10–12). Furthermore, dichloroacetate reduces blood lactate concentration in humans with septic shock (12,13), which also suggests aerobic respiration is not limited by tissue hypoxia. Dichloroacetate is an activator of *pyruvate dehydrogenase*, increasing entry of pyruvate into the citric acid cycle but only in the presence of adequate tissue PO_2 .

Similarly, lactic acidosis can also develop in cardiac surgical patients following cardiopulmonary bypass (CPB) in the absence of tissue hypoxia (14–16).

The likely explanation for the hyperlactatemia that occurs in the absence of tissue hypoxia is “accelerated glycolysis,” in which stress-induced increased uptake of glucose by peripheral tissues leads to enhanced glycolysis and increased pyruvate production (17). Enhanced pyruvate production from accelerated glycolysis leads to increased lactate production by a simple mass effect on the lactate–pyruvate equilibrium (Equation 3). Furthermore, enhanced pyruvate production in sepsis is also associated with greatly enhanced oxidation of pyruvate via the citric acid cycle (12). Thus, rather than reduced aerobic respiration, the hyperlactatemia seen in septic patients is actually associated with *increased* aerobic respiration.

LACTATE/PYRUVATE RATIO

One potential way to distinguish aerobic from anaerobic lactate production is the lactate/pyruvate (L/P) ratio. Under normal circumstances, the ratio is approximately 10:1; i.e., the equilibrium shown in Equation 3 greatly favors lactate over pyruvate. If the primary mechanism of hyperlactatemia is increased pyruvate production (i.e., accelerated aerobic glycolysis), the lactate concentration will increase proportionally to pyruvate, and the L/P ratio will remain relatively unchanged.

By contrast, if hyperlactatemia is caused by tissue hypoxia, pyruvate will be preferentially converted to lactate, and the lactate/pyruvate ratio will be increased. Recall that tissue hypoxia leads to increased ADP/ATP and NADH/NAD⁺ ratios, inhibiting *pyruvate dehydrogenase* and blocking entry of pyruvate to the citric acid cycle.

Levy and colleagues have investigated the evolution of lactate and L/P ratios in patients with cardiogenic and septic shock admitted to their intensive care unit (ICU) (18). Very high L/P ratios (40 ± 6) were identified in patients with cardiogenic shock, and this was associated with a high (60%) early mortality. The authors found the situation with septic shock to be more complex. Among early non-survivors, similarly high L/P ratios were identified (37 ± 4). Beyond 24 hours, L/P ratios were higher in patients who subsequently died (22 ± 1) than in survivors (14 ± 1). By contrast, L/P ratios in controls (non-septic ICU patients) were 8 ± 2 . In another study, Suistomaa and colleagues measured lactate and L/P ratios in 98 consecutive patients admitted to a medical ICU (19). Median peak lactate levels on admission were higher in non-survivors (5.3 [interquartile range 1.9–7.5]) than survivors vs. (1.9 [1.3–2.9]). Furthermore, hyperlactatemia with an elevated L/P ratio (>18) was associated with higher mortality than hyperlactatemia with normal L/P ratio (<18) (37.5% vs. 12.5%, respectively, $p = .03$), and was found mainly in patients who had severe circulatory failure rather than sepsis.

The likely explanation for these findings is that in patients with shock (either cardiogenic or septic), a high lactate in association with a high L/P ratio is indicative of circulatory failure and anaerobic glycolysis. Hyperlactatemia from this cause is associated with high mortality. However, in patients with “stable” septic shock, elevated lactate in association with a relatively normal L/P ratio is indicative of accelerated aerobic metabolism, which is not, of itself, predictive of adverse outcome. Nevertheless, higher lactates are typically found in patients with tissue hypoxia and are associated with increased mortality.

CATECHOLAMINES AND HYPERLACTATEMIA

A key mechanism for increased lactate during metabolic stress is likely the endogenous release (or exogenous administration) of epinephrine leading to β_2 -mediated receptor uptake of glucose into cells and accelerated glycolysis via a mass effect (20).

Of the commonly used catecholamines, only epinephrine, isoproterenol, and salbutamol exert a potent effect on peripheral β_2 -receptors. In one study, 6 of 19 patients randomized to receive epinephrine following cardiac surgery developed lactic acidosis compared to 0 of 17 patients randomized to receive norepinephrine (21). Epinephrine-induced lactic acidosis has been demonstrated by several

other authors (22–24), and forms part of day-to-day clinical experience. In keeping with the purported mechanism of accelerated glycolysis, such lactic acidosis is associated with normal (or increased) oxygen delivery and has a benign course.

Unsurprisingly, hyperglycemia is a common accompaniment to hyperlactatemia associated with accelerated glycolysis (14–16,21).

LACTATE CLEARANCE

Approximately 60% of lactate is cleared by the liver with contributions from the kidneys, heart, and skeletal muscle (25). Metabolism of lactate involves conversion to pyruvate (Equation 3) and then either oxidation to carbon dioxide and water or gluconeogenesis in the liver via the Cori cycle. In addition to its role as a site of lactate metabolism, in the presence of hyperlactatemia, renal excretion of lactate becomes clinically important (26).

Although the hyperlactatemia seen in critical illness is primarily related to increased production, there is also evidence that reduced hepatic clearance contributes to hyperlactatemia in stable septic patients (27). Certainly, in the presence of severe hepatic hypoperfusion or acute liver failure, reduced hepatic metabolism almost certainly contributes to acidosis and hyperlactatemia.

LACTATE AND ACIDOSIS

As noted earlier, at physiological pH, lactic acid is virtually completely dissociated. Thus, it is commonly assumed that each molecule of lactate leads to the production of one hydrogen ion, which in turn causes acidosis. This assumption is incorrect. Understanding why requires a (brief) review of the Stewart methodology of acid–base physiology (28).

THE STEWART FORMULATION OF ACID–BASE PHYSIOLOGY

The Stewart analysis is based on the principle of electroneutrality, whereby the total number of cations in solution must always equal the total number of anions. Only strong ions (i.e., ions fully dissociated at physiological pH), $p\text{CO}_2$, and weak acids (predominantly plasma proteins such as albumin) can change pH directly. This has led to the concept of the strong ion difference (SID). The SID is the sum of the strong cations (Na^+ , K^+ , Ca^{2+} , Mg^{2+}) minus the strong anions (predominantly Cl^- but also lactate⁻). In health, the plasma concentration of strong cations exceeds the plasma concentration of strong anions, resulting in an SID of around +40 mEq/L (Figure 1). The remaining

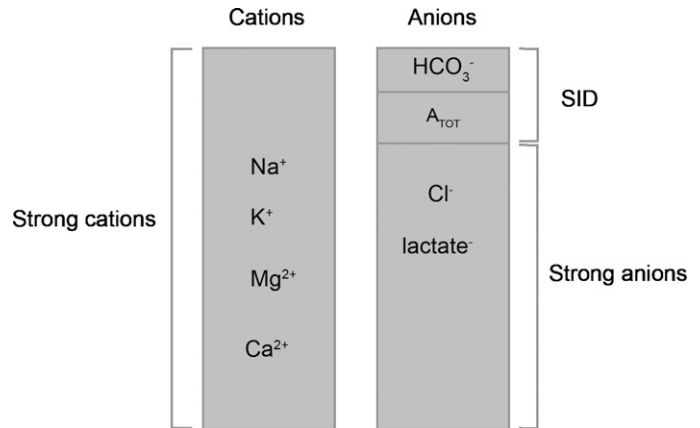


Figure 1. The SID. The SID is the difference between the strong cations and anions in extracellular fluid. The SID is primarily comprised of the concentration of bicarbonate and the negative charge from dissociated plasma proteins (A_{TOT}). This display format for the SID, in which the two columns are used to demonstrate the cations and anions, is known as a gamblegram, after the pediatrician Dr. J.L. Gamble.

anions are predominantly comprised of HCO_3^- and the negative charge from dissociated plasma proteins, notably albumin, termed A_{TOT} .

Changes in SID, $p\text{CO}_2$, and A_{TOT} alter pH via their effect on the dependent variables HCO_3^- and H^+ , which alter their concentrations to maintain electrical neutrality (29). The relationship between pH, bicarbonate, and $p\text{CO}_2$ is characterized by the Henderson–Hasselbalch equation, which may be formulated as:

$$\text{pH} \propto \log_{10} \left(\frac{[\text{HCO}_3^-]}{p\text{CO}_2} \right) \quad (4)$$

Given the bicarbonate contribution to the anion total is $\text{SID} - A_{\text{TOT}}$ (Figure 1), the Henderson–Hasselbalch equation may be reformulated as (29):

$$\text{pH} \propto \log_{10} \left(\frac{(\text{SID} - A_{\text{TOT}})}{p\text{CO}_2} \right) \quad (5)$$

In simple terms, any condition that reduces the SID results in a metabolic acidosis and any condition that increases the SID results in a metabolic alkalosis through alterations in the bicarbonate buffer system.

The concept of the SID readily explains the phenomenon of saline-induced hyperchloremic metabolic acidosis. When .9% saline is administered to a patient, equal amounts of sodium and chloride ions are delivered to the extracellular fluid. However, since the plasma $[\text{Cl}^-]$ is less than $[\text{Na}^+]$, plasma chloride concentration increases proportionally more than the plasma sodium concentration, reducing the SID and therefore causing an acidosis. Similarly, chloride loss in excess of sodium (e.g., the vomiting of gastric contents) increases the SID and causes a (hypochloremic) alkalosis.

LACTATE AS A CAUSE OF ACIDOSIS

As a strong anion, excess lactate production reduces the SID and causes a metabolic acidosis in a manner similar to chloride excess. This is certainly the mechanism by which tissue hypoxia, which is associated with a greatly increased lactate production, causes a metabolic acidosis. However, for other conditions, the relationship between elevated lactate and acidosis is less straightforward.

Lactated Ringer's solution is a balanced salt solution containing sodium (130 mmol/L), chloride (109 mmol/L), lactate (28 mmol/L), and small amounts of potassium and calcium. Lactated Ringer's has a SID of 28 mEq/L, closer to the normal value of 40 mEq/L than .9% saline, which has a SID of 0 mEq/L. Rapid administration of large amounts of lactated Ringers can reduce the SID of plasma, transiently causing a metabolic acidosis. However, typically the lactate is rapidly metabolized by the liver, negating this effect. Metabolism of lactate yields a relative excess of sodium that, as a strong cation, increases the SID of plasma, exerting an alkalinizing effect (30). Similar effects on plasma SID and pH can be expected in patients receiving renal replacement therapy (RRT) with lactate-buffered replacement solution.

The situation in patients with accelerated glycolysis (metabolic stress, endogenous or exogenous catecholamine administration) is incompletely understood. In general, hyperlactatemia due to metabolic stress is associated with lower lactate levels (typically in the range of 3–6 mmol/L) than that associated with tissue hypoxia. Modest elevations in plasma lactate are not necessarily associated with acidosis.

In an attempt to resolve the issue of whether hyperlactatemia can occur in the absence of metabolic acidosis, Morgan and Hall performed an in vitro experiment in which fresh whole blood was diluted in a 3:1 with nine different crystalloid solutions of varying SID (–5 to 40 mEq/L), created by varying the concentrations of chloride, bicarbonate, and lactate (31). All crystalloids had a sodium concentration of 140 mmol/L. The blood-crystalloid solutions were equilibrated with carbon dioxide and air to obtain normocarbica. The main findings of the simulation were twofold. First, there was a close correlation between SID and pH, regardless of whether the strong anion was lactate or chloride. Second, only when the plasma lactate concentration exceeded 10 mmol/L did values of base excess and normocarbic pH fall outside the reference ranges. Although this is an in vitro simulation that has not been verified in vivo, it seems reasonable to conclude that lactate, like any strong anion (e.g., chloride, ketoacids, sulfates), exerts an acidifying effect due to its effect on the SID. However, only high levels of lactate—greater than the levels typically found with stress-induced aerobic glycolysis—cause signifi-

cant acidosis. It is also worth remembering that shock states (hypovolemic, cardiogenic, septic) are frequently associated with renal failure, which in turn results in the buildup of strong anions, notably sulfates. Such anions also contribute to a reduced SID and metabolic acidosis.

RRT, HYPERLACTATEMIA, AND ACIDOSIS

The effect of RRT on lactate metabolism and acid–base status is complex and incompletely understood (26). In patients with lactic acidosis and acute renal failure, RRT with a bicarbonate-buffered replacement fluid corrects acidosis and avoids exacerbating hyperlactatemia (32,33). As a small, non-protein bound molecule, lactate is cleared by both hemofiltration (convective clearance) and dialysis (diffusive clearance). However, clinically, lactate clearance by RRT represents only a small proportion of total body lactate clearance—less than 3% in one study (34)—and is insufficient to treat overproduction.

If lactate-buffered replacement fluid is used, moderate hyperlactatemia can occur; however, in the absence of liver failure this is not associated with acidosis (26).

CLASSIFICATION OF LACTIC ACIDOSIS

Lactic acidosis that occurs in the context of impaired tissue oxygenation is termed Type-A, whereas lactic acidosis that occurs in the absence of tissue hypoxia is termed Type-B. Type-A lactic acidosis implies either a global or regional impairment of tissue oxygen delivery and is typically associated with an elevated L/P ratio. Causes of regional impairment of oxygen delivery include limb, hepatic, and mesenteric ischemia. Accelerated aerobic glycolysis is an example of Type-B lactic acidosis, and is typically associated with a normal L/P ratio. Other causes of Type-B acidosis include drug toxicity and poisonings (cyanide, methanol, salicylates), diabetic ketoacidosis, hepatic dysfunction (reduced lactate clearance), and thiamine deficiency (impaired *pyruvate dehydrogenase* function). Depending on the specific etiology, the L/P ratio may be normal or elevated.

It should be clear from the foregoing discussion that there is much overlap between Types A and B lactic acidosis. For instance, low cardiac output following CPB treated with epinephrine may be associated with global tissue hypoxia (low cardiac output) and accelerated metabolism (epinephrine, systemic inflammatory response syndrome). Other causes of hyperlactatemia that may occur in such a patient include limb ischemia (secondary to an intraaortic balloon pump [IABP]), hepatic ischemia (which may result in reduced lactate clearance and increased lactate production), and mesenteric ischemia.

THE MICROCIRCULATION

An important finding in patients with septic shock is that while global oxygen delivery may be normal—or in fact, often supernormal—regional blood flow may be severely impaired (35,36). Bacterial components and inflammatory proteins cause a range of effects on the microcirculation including vasoconstriction, altered red blood cell deformity, and activation of platelets and the coagulation cascade. Functional shunting occurs in which oxygenated blood bypasses capillary beds resulting in tissue ischemia despite normal (or high) mixed venous oxygen saturation (S_{vO_2}). Research has focused on specific organs, notably the kidney, gut, liver, skin, but blood flow is also heterogeneous within organs. Thus, changes in sublingual (assessed via side-stream dark-field imaging) or gastric (assessed via tonometry) perfusion may not be reflective of blood flow in other parts of the gastrointestinal tract, notably small and large bowel mucosa. Although less well established than in septic shock, CPB and cardiac surgery are also associated with deleterious effects on the microcirculation (37).

A key feature of microcirculatory shock is that normalization or optimization of global indices of oxygen delivery (cardiac output, S_{vO_2}) with fluid and inotrope therapy does not necessarily correlate with restoration of microcirculatory flow. Bedside tools for assessing microcirculatory function (skin mottling, peripheral-to-central temperature gradient, and urine output) are relatively crude, and are likely to be particularly unhelpful during the post-CPB period.

Blood lactate is a useful index of both global and regional tissue perfusion and severe hyperlactatemia portends a high

likelihood of adverse outcome. Clinically, lactate is used to titrate resuscitation therapy; however, there are no outcome data demonstrating the efficacy of this approach.

LACTIC ACIDOSIS AND CARDIAC SURGERY

Numerous studies have identified an association between hyperlactatemia and adverse outcome among cardiac surgical patients (2,16,38–41). A lactate level of 0–2 mmol/L is considered normal but most authors use a cutoff of 3–5 mmol/L to define hyperlactatemia. However, in one study, even lactate levels at the higher end of the reference range (0.75–2 mmol/L) were associated with increased in-hospital mortality (42).

The causes of hyperlactatemia following cardiac surgery are varied and include both hypoxic and non-hypoxic causes (Table 1). Several authors have demonstrated a biphasic distribution of cardiac surgery-associated hyperlactatemia, with important differences in the genesis and outcome from the two different types (1,14–16).

EARLY-ONSET HYPERLACTATEMIA

Early-onset hyperlactatemia is that which occurs from the onset of CPB to arrival in the ICU. Early-onset hyperlactatemia is associated with a greatly increased likelihood of adverse outcome (16,43,44). For instance, Maillet and colleagues documented a mortality of 14.9% with a lactate >3 mmol/L at ICU admission compared to 1.5% in patients with a lactate <3 mmol/L (16). Tissue microdialysis studies have demonstrated that CPB is associated with increased

Table 1. Potential causes of hyperlactatemia in cardiac surgical patients.

| Cause | Mechanism(s) | Onset |
|---|--|---------------|
| Inadequate oxygen delivery during CPB | Tissue hypoxia (Type-A) | Early |
| Low cardiac output | Tissue hypoxia (Type-A) | Early or late |
| Severe anemia/hemodilution | Tissue hypoxia (Type-A) | Early or late |
| Systemic inflammatory response syndrome | Accelerated glycolysis (Type-B) | Early |
| | Impaired tissue perfusion due to microcirculatory failure (Type-A) (e.g., due to prolonged CPB, massive transfusion) | Early |
| Exogenous catecholamines (epinephrine, salbutamol, isoproterenol) | Accelerated glycolysis (Type-B) | Early or late |
| Hepatic ischemia | Tissue hypoxia (Type-A) | Early or late |
| | Reduced lactate clearance (Type-B) | Early or late |
| Limb ischemia | Tissue hypoxia (Type-A) (e.g., IABP) | Early |
| Mesenteric ischemia | Tissue hypoxia (Type-A) (e.g., due to NOMI or arterial embolus) | Late |
| Septic shock | As per systemic inflammatory response syndrome | Late |
| Administration of lactated Ringer's solution | Increased lactate load (sodium lactate) (Type-B) | Early or late |
| Lactate-buffered renal replacement fluid | Increased lactate load (sodium lactate) (Type-B) | Late |
| Grand mal seizure | Accelerated aerobic glycolysis (Type-B) | Late |
| Renal failure | Reduced lactate clearance (Type-B) | Late |
| | Tissue hypoxia (Type-A) | |
| Pancreatitis | As per systemic inflammatory response syndrome | Late |
| Drug related | Propofol syndrome (Type-B) | Late |
| | Sodium nitroprusside (Type-A) | |

NOMI, non-occlusive mesenteric ischemia.

myocardial and peripheral tissue increases in lactate and L/P ratio (45,46). Although these studies were performed in “normal” patients, without systemic hyperlactatemia, they nevertheless indicate that CPB is associated with impaired tissue oxygenation, and suggest that tissue hypoxia may be involved in the genesis of early-onset hyperlactatemia. Although data are lacking, it makes intuitive sense that microcirculatory dysfunction, secondary to the pro-inflammatory effects of CPB, contributes to early-onset hyperlactatemia. Hyperlactatemia probably also arises from accelerated aerobic metabolism as a consequence of increased circulating epinephrine and inflammatory proteins. The relative contribution of hypoxic and non-hypoxic causes of hyperlactatemia has not been fully defined in this circumstance. Irrespective of the etiology, early-onset hyperlactatemia should be considered a potent biomarker of adverse outcome.

Ranucci and colleagues demonstrated that hyperlactatemia (>3 mmol/L) during CPB was associated with higher postoperative IABP usage, longer duration of ICU stay, and longer postoperative mechanical ventilation (2). Independent predictors of developing hyperlactatemia included longer CPB duration and reduced oxygen delivery (DO_2) during CPB. Peak lactate increased sharply when DO_2 fell below about 250 mL/min/m², although data were insufficient to provide a critical cutoff value (Figure 2).

In another study, Ranucci and colleagues demonstrated that a $DO_2 < 272$ mL/min/m² and a nadir hematocrit of 26% were predictive of postoperative renal failure in patients undergoing coronary artery bypass surgery (47).

Various tissues have been implicated as sources of lactate during CPB including the heart, the lungs, the gastrointestinal tract, and skeletal muscle (1). In particular, elevated myocardial lactate levels are strongly associated with postoperative cardiac dysfunction (48,49). However, although it is possible to identify increased production of lactate in specific organs, it is less clear which of these is primarily responsible for elevated blood lactate levels.

LATE-ONSET HYPERLACTATEMIA

Within the first 6–12 hours of ICU admission, 15–20% of cardiac surgical patients also develop de novo hyperlactatemia. This, so-called, “late-onset hyperlactatemia” is characterized by normal cardiac output and an absence of impaired tissue oxygen delivery (14,15,21). The condition typically spontaneously resolves within 24 hours. Tissue lactate and pyruvate levels increase proportionally to blood lactate levels resulting in a relatively normal tissue L/P ratio (15). Importantly, late-onset hyperlactatemia is associated with a benign postoperative course. In the study by Maillet and colleagues outlined earlier, late-onset hyperlactatemia was associated with a mortality of 3.6% compared to 14.9%

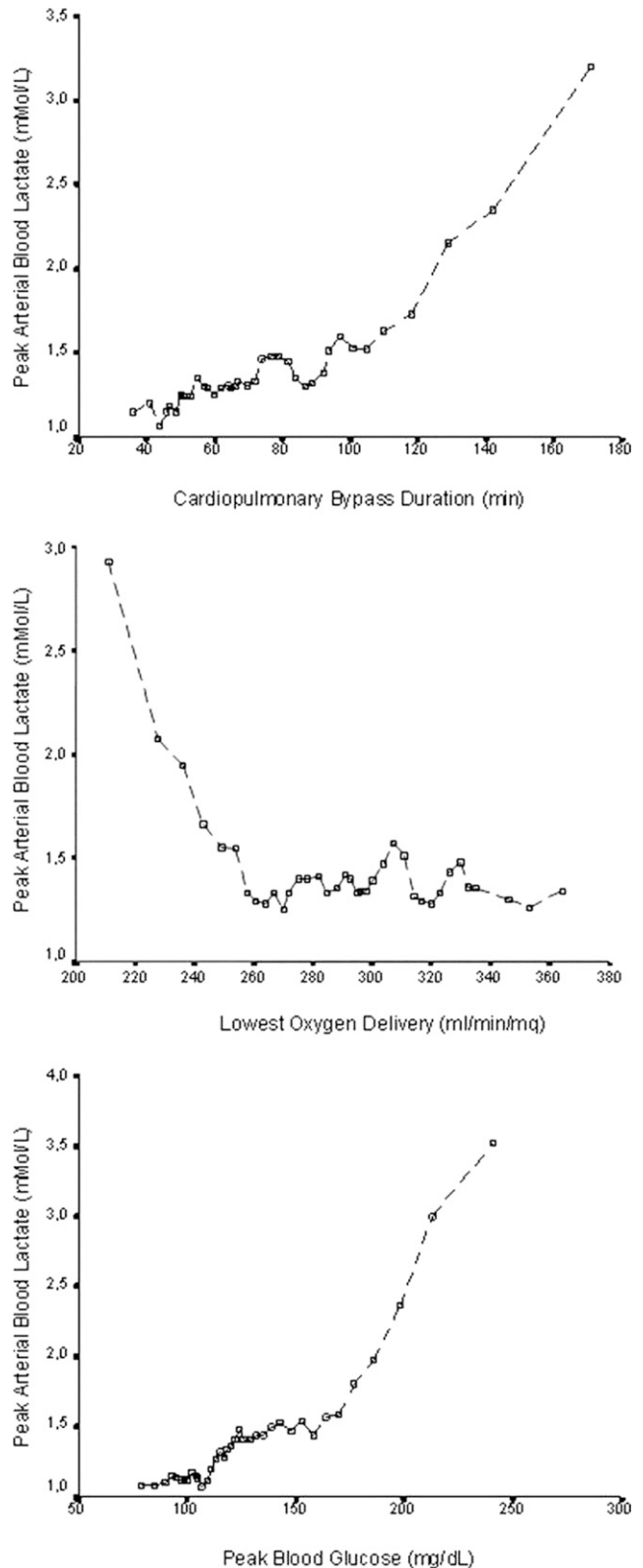


Figure 2. Peak arterial blood lactate values during CPB according to the CPB duration, the lowest oxygen delivery, and the peak blood glucose. Data are shown as rolling deciles (75% overlapping). Symbols (open boxes) represent the mean value recorded for each decile (from Ranucci et al.,² Figure 1 with permission).

for patients with early-onset hyperlactatemia and 1.5% for patients with a normal lactate (16). A similarly benign course for late-onset hyperlactatemia has been identified by other investigators (14,41).

The etiology of late-onset hyperlactatemia is poorly defined. Strong associations between hyperglycemia and exogenous epinephrine administration have been identified (14–16,21); however, these findings do not fully explain the phenomenon. Not all patients with late onset hyperlactatemia receive β_2 -agonists, and hyperglycemia may be considered an accompaniment to accelerated aerobic glycolysis rather than a primary driver.

However, it is important to remember that not all de novo hyperlactatemia that develops during the postoperative period is benign. Complications such as septic shock, cardiac tamponade, and ischemia related to muscle necrosis or mesenteric infarction can all present with hyperlactatemia and acidosis.

AN APPROACH TO HYPERLACTATEMIA IN CARDIAC SURGICAL PATIENTS

Transient increases in blood lactate can occur (e.g., due to blood product administration) during the perioperative period. Thus, it is important that a single high reading be confirmed by repeat testing. Given the increased risk of adverse outcome and the potential contributory role of tissue hypoperfusion, patients with early-onset hyperlactatemia (>3 mmol/L) should have indices of global oxygen delivery measured and, where possible, normalized. Severe anemia should be treated and either low cardiac output (off pump) or low CPB flows (on pump) corrected. During CPB, measuring and maintaining DO_2 above a critical threshold (e.g., >270 mL/min/m²) is probably indicated. Information from a pulmonary artery catheter (cardiac output, mixed venous oxygen saturation) and a transesophageal echocardiogram (ventricular and valvular function) are invaluable to identify remedial problems (e.g., cardiac tamponade), to help guide fluid therapy and inotropic therapy, and to identify patients requiring mechanical cardiovascular support (intraaortic balloon counter pulsation, extracorporeal membrane oxygenation). However, is important to recognize that, just as with sepsis, there is likely an uncoupling of global and regional oxygen delivery. Thus, augmenting oxygen delivery to supernormal levels does not necessarily restore microvascular flow, and is therefore not justified as a “treatment” for hyperlactatemia.

Similarly, hyperlactatemia that develops de novo in the ICU warrants a search for signs of global or regional tissue hypoperfusion. However, in the absence of such signs, the acronym MICLO (masterly inactivity, cat-like observation) is a useful guide. Later in the ICU course—typically beyond the first 2–3 days—the development of hyperlactatemia

warrants a careful search for evidence of mesenteric ischemia or sepsis.

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