Review Article

World Journal for Pediatric and Congenital Heart Surgery
2020, Vol. 11(3) 316-324

DOI: 10.1177/2150135120903977
journals.sagepub.com/home/pch
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Hyperlactatemia: An Update on Postoperative Lactate

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Abstract

While hyperlactatemia in postoperative cardiac surgery patients was once believed to solely reflect hypoperfusion, either from the accumulated "oxygen debt" during bypass or ongoing inadequate perfusion, our understanding of lactate generation, clearance, and management has evolved. A contemporary understanding of lactate balance is critical to the management of the postoperative patient with hyperlactatemia. In this review, we summarize the current understanding of lactate metabolism in pediatric patients following cardiac surgery and highlight two types of hyperlactatemia: type A, which is secondary to inadequate oxygen delivery and tissue hypoxia, and type B, which in postoperative pediatric cardiac surgery patients largely reflects increased glycolysis driven by the stress response. Both types may coexist; thus, it is imperative that providers first assess the patient for evidence of hypoperfusion. In patients with evidence of adequate perfusion, a type B component is often associated with a concomitant balanced (normal anion gap) metabolic acidosis and hyperglycemia. These patients will benefit from a more nuanced approach to their type B hyperlactatemia, as many will have a benign course and may be managed expectantly.

Keywords

biochemistry, CPB physiology/pathophysiology, ischemia/reperfusion, inflammation

Submitted September 18, 2019; Accepted January 13, 2020.

Introduction

Lactate represents an important biomarker of tissue perfusion, classically heralding the presence of shock from low-cardiac output syndrome following cardiac surgery.[1] However, our understanding of lactate production and clearance has evolved in recent decades. This review will update the readership on the evaluation and management of hyperlactatemia in the postoperative setting.

In 1964, Broder and Weil published a seminal paper documenting that elevated serum lactate levels correlated with increased mortality in patients with shock.[2] The authors discussed "reversibility" of lactic acidosis as a favorable prognostic indicator.[2] The premise of this and subsequent studies was that tissue hypoxia from inadequate cardiac output led to anaerobic metabolism and lactic acidosis. De Wever et al described the trajectory of lactate clearance as an independent predictor of mortality, supporting the notion that goal-directed resuscitation focusing on lactate clearance would rescue patients.[3] However, it has become clear that lactate metabolism is more complex than initially appreciated, a balance of production, conversion, and clearance. To this end, we briefly review the basics underlying lactate metabolism, our current understanding of hyperlactatemia in postoperative pediatric cardiac surgery patients, and outline key principles to the assessment and management of these patients.

Lactate Metabolism

Glycolysis, occurring in the cytoplasm, converts glucose and nicotinamide adenine dinucleotide (NAD^+) into adenosine triphosphate (ATP) and pyruvate (Figure 1). When sufficient oxygen is present for aerobic metabolism, pyruvate enters the mitochondria and yields additional ATP and regenerates the NAD^+ for glycolysis to continue:

$$\text{Pyruvate}^- + \text{NADH} + \text{H}^+ \leftrightarrow \text{Lactate}^- + \text{NAD}^+.$$

When oxygen tension is insufficient to support anaerobic metabolism, pyruvate is instead shunted to lactate by lactate dehydrogenase in the first part of the Cori cycle as an alternative pathway to regenerate NAD^+ to support further glycolysis. Lactate is then converted in the liver (second half of the Cori

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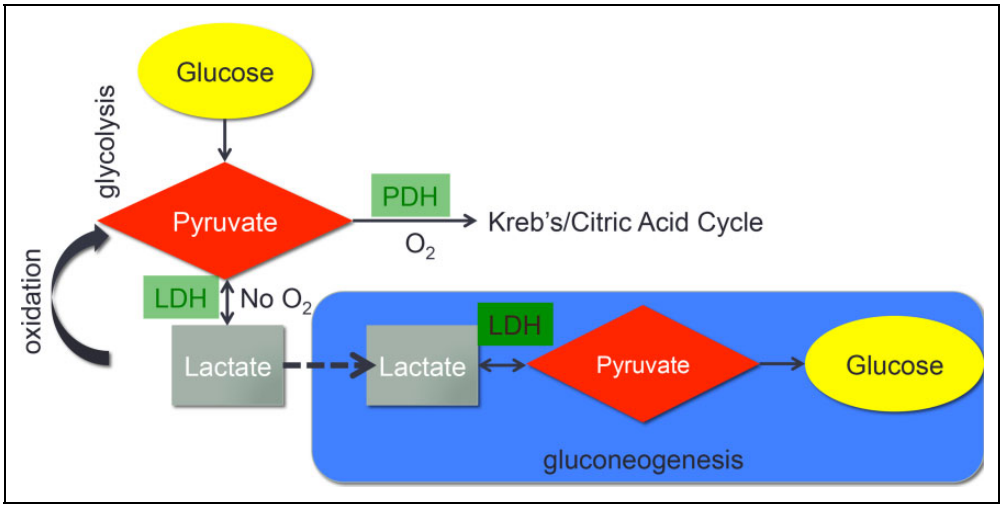

Figure 1. Simplified diagram of the basics of lactate metabolism. LDH, lactate dehydrogenase; O_2, oxygen; PDH, pyruvate dehydrogenase.

Abbreviations and Acronyms

ATP	adenosine triphosphate
A-$\dot{V}O_2$	arteriovenous oxygen
ECMO	extracorporeal membrane oxygenation
ICU	intensive care unit
NAD	Nicotinamide adenine dinucleotide
NEC	necrotizing enterocolitis
NIRS	near-infrared spectroscopy

cycle) to regenerate glucose.[4] Importantly, under baseline physiologic conditions with a normal oxygen tension, lactate is produced from pyruvate following glycolysis in a 10:1 ratio of lactate to pyruvate.[5] Critical to our understanding is that conditions driving glycolysis will increase lactate production yet preserve the lactate–pyruvate ratio. When tissue demands outstrip the supply of oxygen, oxidative phosphorylation (ie, the electronic transport chain) supporting aerobic metabolism falters and pyruvate accumulates, significantly accelerating lactate production.[5] During periods of intense metabolic demand, such as exercise, skeletal muscles will generate lactate to sustain glycolysis, and lactate will later be oxidized by the muscles during recovery.[6]

Lactate is produced exclusively from pyruvate, the end product of glycolysis.[4] Lactate may be converted back into pyruvate via oxidation into glucose through gluconeogenesis.[7] Gluconeogenesis (part of the Cori cycle) principally occurs in hepatocytes, while oxidation occurs in both the renal cortex and skeletal muscles. The liver accounts for 60% of lactate metabolism, while the kidney metabolizes 30%.[5] The serum lactate, therefore, reflects the balance of production, conversion, and clearance. Lactate may accumulate via anaerobic metabolism during periods of tissue hypoxia, via aerobic metabolism with increased glycolysis, and from decreased lactate conversion, such as inhibition or relative deficiency of pyruvate dehydrogenase.

Cardiomyocytes principally use glucose and fatty acids for energy generation but are able to utilize lactate when plentiful, suggesting that hyperlactatemia may be an adaptive as opposed to a maladaptive response.[8] Studies reveal that lactate is the heart's primary energy source in shock states,[9] and blocking lactate utilization caused cardiac decompensation and death in an animal model.[10] Relevantly, patients with a blunted lactate production in response to epinephrine had higher mortality.[11]

Contributors to Type A Lactic Acidosis

Hyperlactatemia can be broadly categorized into type A, which is secondary to inadequate perfusion, and type B, in which perfusion is adequate. Elevated lactate in the setting of inadequate perfusion has classically been termed type A lactic acidosis because of the association with metabolic acidosis.[12,13] Type A lactic acidosis classically occurs in the setting of anaerobic metabolism. Inadequate perfusion can be global, regional, or microcirculatory. Examples of systemic inadequate perfusion include uncompensated shock state and low cardiac output syndrome. An example of regional/local malperfusion is limb ischemia. Type A lactic acidosis will drive up the lactate–pyruvate ratio because, in the setting of hypoxia, pyruvate dehydrogenase is inhibited and pyruvate is diverted to lactate production.[4]

In the setting of postoperative cardiac surgery, studies have shown that bypass itself appears to be a source of type A lactic acidosis. Tissue microdialysis studies in uncomplicated adult cardiac patients have shown that cardiopulmonary bypass itself causes increased lactate and increase in lactate–pyruvate levels in myocardium and peripheral tissues.[14,15] Interestingly, despite bypass delivering adequate calculated tissue perfusion for a given patient, select patients develop early-onset elevated lactate, likely related to variable inflammatory, microcirculatory, and mitochondrial responses during hypothermia and cardiopulmonary bypass. Alternatively, a component of this elevated lactate could be secondary to inadequate delivery despite calculated perfusion needs. During bypass, it is unclear which tissue beds contribute significantly to serum lactate generation; the myocardium, lungs, intestines, and skeletal

muscles have all been implicated.[16] Elevated lactate within the myocardium has specifically been associated with postoperative myocardial dysfunction, perhaps suggesting inadequate cardioplegia and/or ongoing tissue ischemia.[17,18] In normal physiologic states, the myocardium extracts lactate for fuel,[19,20] but during surgery and/or perioperatively, lactate utilization decreases[21,22] despite lactate production increasing.[7] Once coronary perfusion is restored, 30 minutes is required for the cellular machinery to convert from anaerobic to aerobic metabolism in the heart.[23] There is also a time period of "washout" of lactate from tissue[24–26]; therefore, an increase in lactate after the cross-clamp has been released may reflect improved tissue perfusion.[7] Release of lactate from the pulmonary system postbypass is significant and continues up to six hours postoperatively.[27,28] This lactate level has been shown to correlate with the postoperative alveolar–arterial oxygen gradient and systemic plasma lactate levels.[27] However, as some authors have pointed out, the concept of lactate "clearance" is fundamentally flawed in that clearance is technically the rate of decline in serum lactate.[5] This fails to take into account that serum lactate levels represent a dynamic process and ultimately are the net result of production, conversion, dilution, and clearance.[5]

Additionally, cardiopulmonary bypass elicits a robust systemic inflammatory response, including the creation of reactive oxidative species and free radicals. These changes, coupled with any ischemic/reperfusion injury, contribute to mitochondrial dysfunction,[29,30] decreasing their capacity for oxidative phosphorylation which shunts pyruvate to lactate,[7,31] thus contributing to a type B hyperlactatemia. Further, the stress response of cardiac surgery leads to endogenous catecholamine release that increases glycolysis and gluconeogenesis, driving glucose and lactate production.[31,32]

Hyperlactatemia Does Not Always Equate With Inadequate Perfusion

While initial studies suggested elevated lactate primarily occurred in the setting of inadequate oxygen delivery, research has expanded our understanding. Stress states increase endogenous catecholamines and cortisol, altering both glycolysis and the mitochondrial flux of pyruvate independent of tissue hypoxia. In an animal model of hemorrhagic shock, lactate accumulation was prevented by pretreatment with α- and β-adrenergic blockers.[33] Subsequent studies support that hyperlactatemia may be driven by stimulation of β2 adrenergic receptors. A role for the adrenergic system has been confirmed in shock states using epinephrine infusion to drive adrenergic pathways and adrenergic blockade, then to inhibit them.[10,11,33–35] Endogenous catecholamines (eg, epinephrine) are released during stress, driving Na^+/K^+ ATPase activity and increasing lactate production even in well-oxygenated conditions.[36,37] A study by Levy et al in adults with septic shock demonstrated that inhibition of Na^+/K^+ ATPase prevented elevations in both lactate and pyruvate.[38] These studies support that adrenergic signaling, such as that occurs under stressful conditions (ie, cardiac surgery), drives glycolysis and secondarily lactate production.

Based on these and other studies, hyperlactatemia is perhaps best understood as a biomarker of the stress response, which is a multifactorial process and not solely reflexively as a measure of tissue hypoxia. In addition to tissue hypoxia triggering the stress response, many other conditions, such as systemic inflammation, fever, and tissue injury driving cortisol and adrenergic signaling, contribute even in states of adequate cardiac output and tissue perfusion.

Type B Lactic Acidosis

Elevated lactate in the setting of adequate perfusion is termed type B lactic acidosis, although type B hyperlactatemia is the more appropriate term, since metabolic acidosis is not always present. Stress states driving glycolysis will generate more lactate (Figure 2) yet preserve the lactate–pyruvate ratio at 10:1 because a balanced, albeit increased, amount of pyruvate will be shunted into the Krebs cycle and transformed into lactate.[4] In cases of type B hyperlactatemia, patients are generally less acidemic than expected (may even have a normal pH, very much depending on the degree of hyperchloremia or bicarbonate deficiency), are warm and well perfused on examination, have adequate end-organ function (urine output, mentation), and have a normal or narrow arteriovenous oxygen ($A\text{-}\dot{V}O_2$) difference.

Hyperglycemia is interrelated to hyperlactatemia in the setting of type B lactic acidosis, and studies show that glucose and lactate levels rise and fall together in these patients.[32] The stress response, along with exogenous steroids, leads to gluconeogenesis and catabolism, and serum glucose represents an independent biomarker of the stressed state.[39–42] Studies have shown that exogenous epinephrine in patients with sepsis increased lactate levels, despite increased cardiac output and improved tissue perfusion, and was associated with hyperglycemia.[43,44] Hyperlactatemia actually contributes to insulin resistance,[45] and given insulin is a stimulator of pyruvate dehydrogenase,[46] it is postulated that the insulin resistance seen after surgery further increases serum lactate.[21] Further glucose metabolites act via free fatty acids to further inhibit pyruvate dehydrogenase resulting in increased lactate.[32,47]

A second classification scheme based on the time of onset (early or late) has been used to describe elevated postoperative lactate. Early onset is defined as from bypass until intensive care unit (ICU) admission, while late onset is defined as 6 to 12 hours after ICU admission.[4] Early-onset elevations in lactate have been associated with increased mortality. In two studies of adult cardiac surgery patients, Maillet et al reported a 14.9% mortality in patients with a lactate >3 mmol/L at the time of ICU admission compared to 1.5% in those <3 mmol/L,[41] and Ranucci et al found that lactate >3 mmol/L during cardiopulmonary bypass was associated with increased intra-aortic balloon pump usage, longer postoperative mechanical ventilation, and longer length of stay in the ICU.[48]

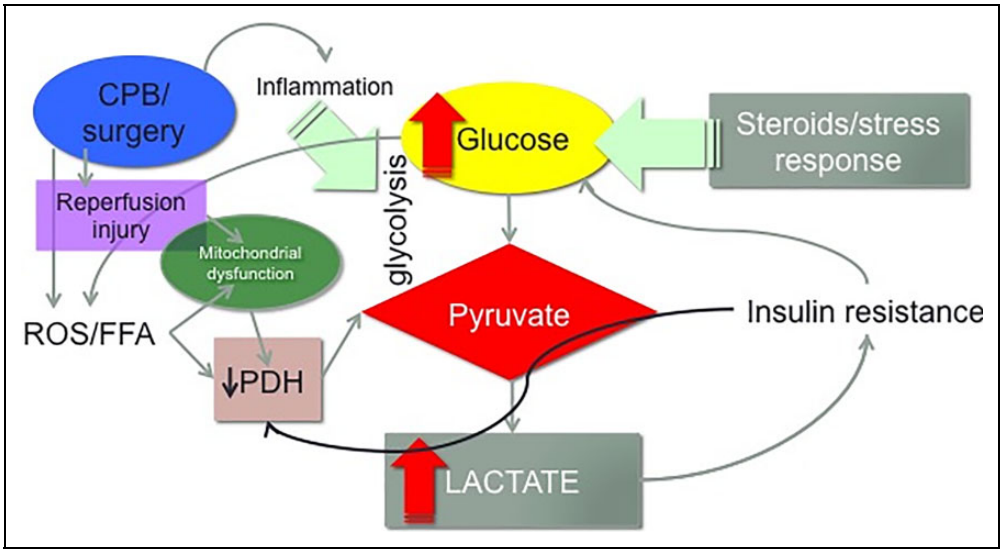

Figure 2. Contributing factors to hyperlactatemia and hyperglycemia in type B lactic acidosis. CPB indicates cardiopulmonary bypass; PDH, pyruvate dehydrogenase; ROS/FFA, reactive oxygen species/free fatty acids.

Late-onset hyperlactatemia occurs in approximately 10% to 20% of adult cardiac surgery postoperative patients.[4,48,49] These patients typically have normal cardiac output, adequate perfusion, and frequently have an associated hyperglycemia.[39–41] The lactate–pyruvate ratio remains normal.[40] These patients have a benign course, and the elevated lactate spontaneously will resolve within 24 hours.[4,16,39,41] While associations between late-onset elevated lactate and exogenous epinephrine have been identified,[42] the cause in many patients is likely multifactorial resulting from inflammatory changes during tissue injury and cardiopulmonary bypass as well as increased exogenous and endogenous catecholamines and steroids. Studies in pediatric patients support findings from adult studies.[50] In one retrospective study of pediatric postoperative cardiac surgery patients by Palermo et al,[32] 10% of the population developed evidence of type B hyperlactatemia with an associated hyperglycemia. The median time to onset of elevated lactate ($\geq$3.5 mEq/L) was 4.4 hours after cardiopulmonary bypass, and median time to onset of hyperglycemia ($\geq$200 mg/dL) was 4.9 hours. The timing of the elevation in lactate and glucose closely correlated with one another. Lactate and glucose levels decreased together, resolving spontaneously after a median of 14 hours. There was no mortality reported. Importantly, postcardiac surgical pediatric patients with an isolated type B hyperlactatemia have reassuring outcomes, and neither the lactate nor the associated hyperglycemia requires treatment except for time.

Other considerations for a type B hyperlactatemia without evidence of inadequate perfusion include diabetic ketoacidosis, hepatic dysfunction reducing lactate conversion, thiamine deficiency reducing pyruvate dehydrogenase function, and toxins such as cyanide and salicylate.[4] Key factors differentiating type A and B lactic acidosis are shown in Table 1.

Evaluation and Management of Hyperlactatemia

When evaluating the postoperative pediatric cardiac patient with an elevated lactate, the first and most critical step is to determine whether tissue perfusion is adequate (Figure 3). It is important to note that postoperative cardiac surgery patients often have both type A and type B mechanisms simultaneously following cardiac surgery. The goal is to rule out type A lactic acidosis, as failure to identify and reverse tissue hypoxia may result in end-organ damage and even ultimately death. In certain settings, there should be a higher index for suspicion for a type A lactic acidosis, such as a persistent hyperlactatemia beyond postoperative days 2 and 3 and in patients with lactate levels that had normalized and subsequently became elevated. Various measures of perfusion are used in postoperative patients, such as clinical examination, blood pressure and heart rate, urine output, mental status, near-infrared spectroscopy (NIRS), central A-$\dot{V}O_2$ difference, and core-to-peripheral temperature gradient. While pyruvate–lactate ratios can be useful in theory and experimental studies, such measurements are not routinely used as they are difficult to use in real time (at the bedside); pyruvate is unstable and such laboratory tests must be processed immediately; furthermore, the results can be imprecise depending on laboratory processing.

Near-infrared spectroscopy measures the average hemoglobin saturation within a volume of tissue and is a useful surrogate to trend changes that correlate with venous blood saturation. The cerebral NIRS can be analogous to a continuous mixed venous saturation.[51] In a study of 50 Norwood patients, a cerebral NIRS <56% in the first 48 postoperative hours was predictive of adverse outcomes including death, extracorporeal membrane oxygenation (ECMO), or ICU length of stay >30 days.[52] Similarly, somatic NIRs can assist in evaluating the adequacy of perfusion. In a study of 329

Table 1. Differentiating Type A and Type B Hyperlactatemia.

	Type A	Type B
pH	Metabolic acidosis	Less acidemic pH or normal pH
Perfusion status	Evidence of hypoperfusion (regional or global low cardiac output)	Adequate perfusion
Serum glucose	Variable	Hyperglycemia correlating with rise in lactate
Lactate–pyruvate ratio	Elevated (>10:1)	Remains 10:1
Onset	Early onset	Late onset (6-12 hours post ICU admission)

Abbreviation: ICU, intensive care unit.

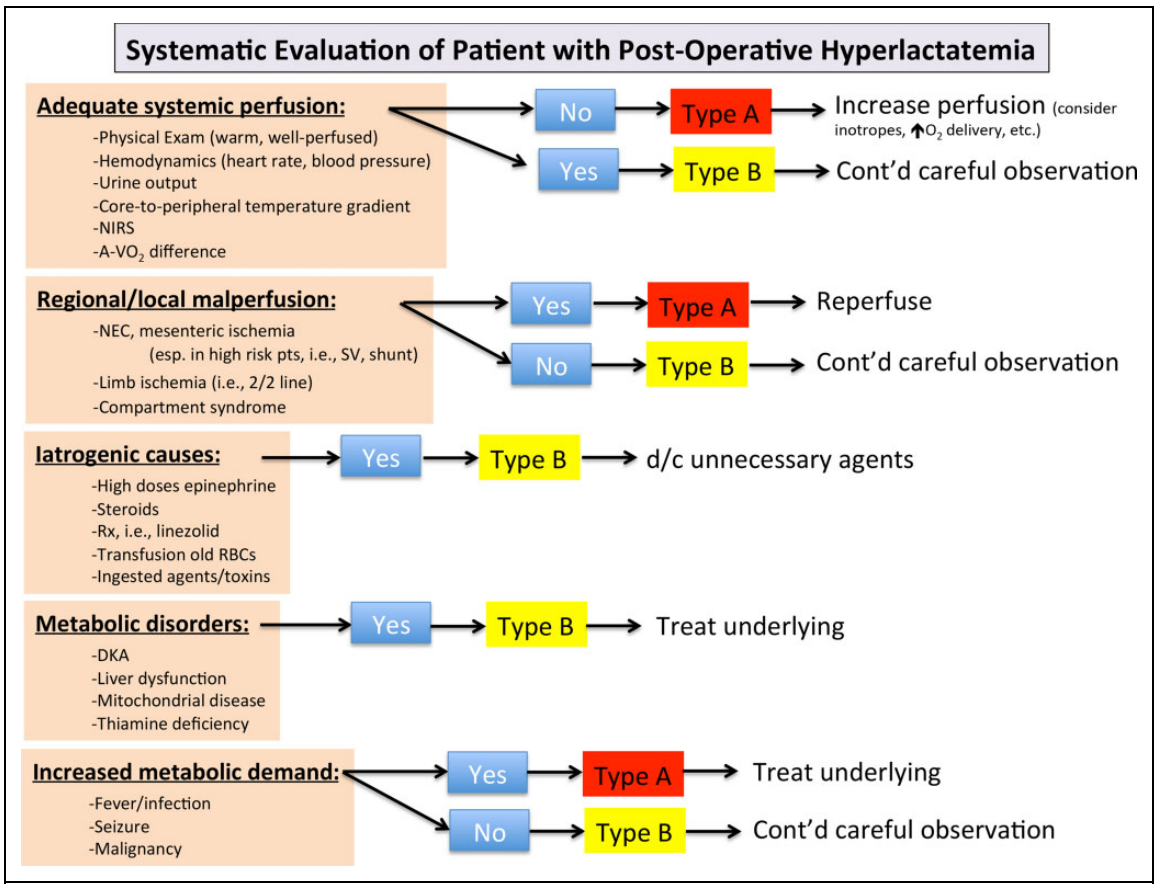

Figure 3. Algorithm for evaluating postoperative patients with hyperlactatemia. Within the evaluation process, certain elements of the assessment may be consistent with type B lactic acidosis; however, all elements must be evaluated to rule out any other components of type A lactic acidosis contributing to the patient's clinical picture, and the practitioner must be vigilant for evolution of type A lactic acidosis. A-$\dot{V}O_2$ indicates arteriovenous oxygen difference; cont'd, continued; d/c, discontinue; DKA, diabetic ketoacidosis; esp., especially; NEC, necrotizing enterocolitis; NIRS, near-infrared spectroscopy; O_2, oxygen; pts, patients; SV, single ventricle; RBCs, red blood cells; Rx, drugs; 2/2, secondary to.

patients undergoing a stage I palliation, investigators found on multivariable analysis that cerebral and somatic NIRs were predictive of outcome, particularly when assessed early post-operatively (during the first six hours).[53]

The Fick equation calculates cardiac output using the arterial and venous oxygen saturation. Specifically, cardiac output $= \dot{V}O_2/(CaO_2 - mSvO_2)$, where $\dot{V}O_2$ is oxygen utilization by the tissues, CaO_2 is the oxygen content of arterial blood, and $mSvO_2$ is the oxygen content of venous blood, also known as mixed venous saturation. Therefore, when oxygen consumption and hemoglobin are constant, the mixed venous saturation can be used as a surrogate for cardiac output, since supply–demand coupling will attempt to compensation and maintain homeostasis.[51] Historically, $mSvO_2$ has been used as an indicator of adequate oxygen delivery, with a widening arteriovenous saturation difference indicating decreased cardiac output, assuming an unchanging saturation of the pulmonary veins. Studies have demonstrated increased mortality in biventricular pediatric cardiac patients with saturations less than 50%.[54–56] Tweddell et al[57] utilized goal-directed therapy

for patients with hypoplastic left heart syndrome based on continuous monitoring of $mSvO_2$, using a threshold of >50% and A-$\dot{V}O_2$ content difference $\leq$5mL/dL.[58] Survivors had a higher $mSvO_2$ than nonsurvivors (59% $\pm$ 9% vs 53% $\pm$ 10%), and patients with lower $mSvO_2$ were more likely to require ECMO.[57] Analysis of stage I palliation patients found that use of continuous $mSvO_2$ monitoring was associated with improved patient survival.[59]

Elevated systemic vascular resistance, often reflective of compensated shock, tends to decrease peripheral perfusion and secondarily reduce skin temperature. Whether subjectively assessed by caretakers or objectively measured using a temperature probe comparing the core to an extremity (eg, the toe), a widening core-to-peripheral temperature differential can indicate compensation for decreased cardiac output and decreasing perfusion. However, there is mixed evidence supporting the reliability of measuring the core to peripheral temperature gradient. Early studies showed a strong correlation between toe temperature and cardiac output, cardiac index, and oxygen transport,[60,61] and another found toe temperature was a better predictor of mortality than cardiac index or arterial pressure in patients with shock.[62] However, other studies have found no correlation between toe temperature and cardiac index or systemic vascular resistance in pediatric cardiac patients postoperatively.[63,64] Moreover, a review of the adult literature did not support for the use of peripheral temperature as a marker of adequate perfusion.[65] A recent survey of members of the Pediatric Cardiac Intensive Care Society found that only 32% of responders used core-to-peripheral temperature differential in the assessment of postoperative patients.[66]

While systemic perfusion may appear adequate based on the markers listed earlier, clinicians also must evaluate for conditions that can cause regional or local tissue malperfusion, such as a line causing limb ischemia, an infiltrate causing compartment syndrome, and necrotizing enterocolitis (NEC) or other types of bowel ischemia. A particularly high index of suspicion for NEC and mesenteric ischemia should be paid for patients at risk for these complications, such as the premature neonates and those with shunted physiology.

Clinicians should also be aware of iatrogenic causes of increased lactate, such as the administration of exogenous catecholamines and steroids. Certain drugs, such as metformin and linezolid, can also lead to elevated lactate.[67] Ingested toxins, such as cocaine or carbon monoxide poisoning, can similarly cause hyperlactatemia.[67] Studies have also shown that red blood cells that have been stored for one week have a lactate of over 5 and a pH of $\sim$6.8.[68]

Metabolic contributions to elevated lactate must also be considered in evaluating postoperative patients with hyperlactatemia. This can include diabetic ketoacidosis, liver dysfunction, mitochondrial diseases, and thiamine deficiency. Finally, clinicians should consider conditions causing increased metabolic demand, such as seizure, malignancy, fevers, and infection.

Once iatrogenic and metabolic causes, as well as type A lactic acidosis, have been ruled out, patients who have evidence of adequate perfusion, with an elevated lactate and associated hyperglycemia, can be managed with "masterly inactivity, catlike observation," as noted by Minton and Sidebotham.[4]

With respect to the hyperglycemia associated with type B lactic acidosis, in contrast to adult cardiac surgical patients, tight glucose control in children after cardiac surgery has not been shown to be helpful and may in fact be harmful. While the first randomized study related to glucose management in pediatric cardiac surgery patients showed a benefit of tight glycemic control, this has not been substantiated in subsequent studies. Vlasselaers et al[69] randomized 700 critically ill children (75% were postoperative cardiac surgery patients) to intensive glucose management versus conventional treatment. In this study, there was decreased length of stay and mortality in the intensive glucose management cohort, but 25% of patients had at least one episode of severe hypoglycemia compared to 1% of the conventional treatment group.[69] However, subsequent studies have not shown such advantages. In a large, multicentered study of pediatric cardiac surgery patients, there was no difference in infection rate, ICU length of stay, or mortality between the tight glycemic control group and standard treatment group.[70] Further, a meta-analysis of tight glycemic control in critically ill pediatric patients demonstrated no decrease in morality or sepsis and was associated with increased incidence of severe hypoglycemia.[71]

While it may seem beneficial to try to increase cardiac output in patients with type B lactic acidosis, there is no role in increasing oxygen delivery in patients with adequate cardiac output and type B lactic acidosis, and in fact studies have shown increasing mortality with such measures.[72] In patients with type B lactic acidosis, there is not an underlying problem of hypoperfusion that increasing cardiac output would address. Similarly, while severe anemia should be treated, in type B lactic acidosis, transfusions of red blood cells for increasing oxygen carrying capacity is not warranted based on studies in adult patients in septic shock.[73] Therefore, for patients without any evidence of type A lactic acidosis, the optimum management is continued reassessment.

Conclusions

Hyperlactatemia in postoperative pediatric cardiac surgery patients is often of mixed etiology and does not necessarily equate with hypoperfusion. Approximately 10% of postoperative pediatric cardiac patients will have an isolated type B hyperlactatemia that occurs approximately four hours after bypass and is accompanied by hyperglycemia and a less acidemic pH than expected in the setting of increased glycolysis.[32] These patients have a benign course and should be managed expectantly. However, type A lactic acidosis associated with hypoperfusion has a worse prognosis and must be rectified. Importantly, both type A and type B mechanisms may be operative in postoperative patients with hyperlactatemia; therefore, a thoughtful and careful assessment of the patient is essential.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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