INTENSIVE CARE

Dysoxia and lactate

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Disturbances of oxygen supply or cellular oxygen metabolism are common in critically ill patients. An understanding of dysoxia, or oxygen limited energy depletion, requires an understanding of the normal physiology of cell oxygen metabolism, and the compensatory mechanisms that supply high energy molecules under conditions of hypoxia. Understanding disorders associated with hyperlactataemia requires consideration of the cellular response in dysoxia, and pathology specific derangements in lactate metabolism. Much has recently been discovered about the causes of lactic acidosis in sepsis, and about the role of lactate in monitoring critically ill children.

This review discusses how cells produce energy for metabolism under normal and hypoxic conditions; what happens to lactate produced during these processes; the clinical situations in which lactic acidosis has been described; the reasons why excess lactate may occur in sepsis; the evidence that a high lactate concentration is not simply a surrogate for tissue dysoxia; the relevance of lactate in the management of critically ill children; and suggested strategies to manage high blood lactate.

Normal cellular oxygen metabolism

Cells require oxygen for the production of ATP, the principal energy source. ATP is hydrolysed to ADP and high energy phosphate by adenosine triphosphatases in the cytosol.¹ Energy released is used for the maintenance of membrane integrity, ionic pumps, and other specialised functions, such as contractility of muscle cells, and impulse transmission in neurons. The body's stores of ATP will last no more than a few minutes, so it must be synthesised continuously as it is being used. Under physiological conditions, most ATP is generated from the metabolism of glucose, by the process of oxidative phosphorylation. The first stage of oxidative phosphorylation is the conversion of glucose to pyruvic acid; this occurs in the cytoplasm. The second stage, the oxidation of pyruvic acid, can only occur in the mitochondria as part of the Krebs (citric acid) cycle. Oxidative phosphorylation produces a net 36 molecules of ATP (or 1270 kJ of available energy) for every glucose molecule oxidised.

Under normal conditions some tissues, such as myocytes, preferentially use free fatty acids,

rather than glucose, as the substrate for ATP generation. In myocytes, palmitate forms about 60% of the total substrate metabolised, glucose 10%, and lactate 30%. During cellular hypoxia the consumption of lactate ceases, and that of glucose increases to 90% of the total substrate consumed.² The brain, on the other hand, under any conditions can use only glucose or ketone bodies for ATP production.

Thresholds of hypoxia and cell (dys)function

Oxidative phosphorylation can only occur when the partial pressure of oxygen (PO_2) within the mitochondrion is above a critical level, thought to be in the order of 1 mm Hg (0.13 kPa).³ Although the PO_2 of dry air at sea level is 159 mm Hg, and the alveolar PO_2 is about 100 mm Hg, the mean capillary blood PO_2 is 50 mm Hg. From the capillaries oxygen diffuses down a further concentration gradient from one cell to another, and within cells, such that normal mitochondrial PO_2 is in the order of 4–20 mm Hg (0.5–2.7 kPa).³ Some cells, such as the centrilobular cells in the liver, are particularly susceptible to hypoxia because they are further away from capillaries. These undergo necrosis early under hypoxic conditions.

Connett *et al* defined three theoretical thresholds of cell hypoxia.⁴ The first threshold is crossed when cell oxygen decreases but ATP production is maintained at a level sufficient to match ATP demand by metabolic adaptation. Adaptation involves recruitment of the redox component of electron transport, changes in the phosphorylation states of mitochondria, and increased glycolysis. The critical level of mitochondrial PO_2 for oxidative phosphorylation depends on the cells ability to adapt the phosphorylation process metabolically, and the level of ATP demand.

The second threshold occurs when steady state ATP turnover can only be maintained by supplementary production of ATP from anaerobic glycolysis, by the Embden-Meyerhof pathway. This energy inefficient mechanism for producing high energy molecules generates only two molecules of ATP (67 kJ of available energy) for every molecule of glucose metabolised. The pathway must therefore either consume relatively larger quantities of glucose or, alternatively, yield much less ATP. In high energy consuming organs, such as the brain,

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kidney, and liver, the rapid transfer of such quantities of glucose across cell membranes is not possible. Therefore, these organs develop ATP depletion rapidly under hypoxic conditions. Dysoxia can be defined below the second threshold, where ATP production becomes oxygen limited. The third threshold is crossed when glycolysis becomes insufficient to produce enough ATP to maintain cell function and structural integrity.

Most data on cell dysfunction in hypoxia are from *in vitro* studies; mechanisms are complex and poorly understood, and application to clinical pathophysiology is speculative. Technology, such as nuclear magnetic resonance spectroscopy, which will non-invasively measure cell biochemical changes, is as yet impractical in acute clinical settings.

The effects of ATP depletion on cell function can be divided into those occurring as a result of the initial hypoxic insult, and those that result from reperfusion or reoxygenation. Depletion of ATP results in loss of function of sodium/potassium (Na^+/K^+)⁵ channels, leading to accumulation of intracellular Na^+ . Because cell membrane synthesis is a continuous energy requiring process, ATP depletion leads to loss of cell membrane integrity. This, and the accumulation of intracellular Na^+ , results in cell swelling. Similarly, there is disruption of lysosomal membranes and release of enzymes into the cytosol, causing autolysis. Massive influx of Na^+ inhibits or reverses the sodium/calcium ($\text{Na}^+/\text{Ca}^{2+}$) ion channel, and is one mechanism leading to the intracellular sequestration of Ca^{2+} . Intracellular Ca^{2+} increases during the first 30 minutes of hypoxia, but can decrease to normal when hypoxia is of longer duration. However, during reperfusion there is

a pronounced increase in cytosol Ca^{2+} .⁶⁻⁸ Ca^{2+} activated proteases can destroy the sarcolemma and the cytoskeleton; Ca^{2+} activated phospholipases further degrade membrane phospholipids. Concurrent with the depletion of intracellular ATP there is an accumulation of AMP. AMP is released from the cell into the interstitium, where it is dephosphorylated rapidly to adenosine. Adenosine acts as a vasodilator in most vascular beds, improving blood flow in capillaries, but acts as a vasoconstrictor in the renal vascular bed. During reoxygenation, adenosine is a source of oxygen radicals through the formation of inosine, hypoxanthine, and xanthine. Oxygen radicals cause cell damage by lipid peroxidation, release of excitatory amino acids, and inhibition of enzymes.

Lactate production and elimination

Anaerobic metabolism is not only energy inefficient and unsustainable, but it produces two molecules of lactic acid for every molecule of glucose metabolised. Although lactic acid has energy potential, it is only in the presence of oxygen that it can be reconverted into pyruvic acid, which in turn can be metabolised in the citric acid cycle. Lactic acid can be converted into glucose, by the process of gluconeogenesis (Cori cycle, requiring six molecules of ATP), and stored in the liver as glycogen. This is also an ATP requiring process.

Under normal conditions, the liver has a large capacity for lactate removal, and other organs including the kidneys, gastrointestinal tract, and muscle also remove lactate. Lactate production has to be substantially increased before the metabolic threshold of the liver and other organs is exceeded, and increased blood concentrations occur. Lactate accumulation depends on the rate of glycolysis, the exchange of lactate across cell membranes, washout by the circulation, and consumption and clearance by tissues.⁴ Lactate clearance by the liver and other organs may be reduced in sepsis⁹ and in respiratory alkalosis.¹⁰

Other conditions interfere with lactate production, so that despite tissue hypoxia, blood lactate will be normal. In severe malnutrition—for example, glucose stores are insufficient to sustain glycolysis. Figure 1 outlines the mechanisms of lactate production and elimination.

Most plasma cell membranes contain a symport for lactate and hydrogen ions, and lactic acid produced in cells is released into the circulation. In the brain, however, excess lactate accumulates in neurons, because the blood–brain barrier is relatively impermeable to charged ions. In severe cerebral hypoxia, some of the brain tissue injury might be caused by intracellular acidosis, in addition to the depletion of high energy compounds.

The clinical relevance of high blood lactate

High lactate concentrations are seen in the setting of circulatory shock as a result of haemorrhage, myocardial failure, burns, and sepsis¹¹⁻¹⁶; after cardiopulmonary bypass¹⁷⁻¹⁹; and after liver transplantation.²⁰ Lactic acidosis might exist not only in the presence of hypotension

Figure 1 The effect of decreasing mitochondrial partial pressure of O_2 (PO_2) on cellular ATP production, and mechanisms of lactate production and elimination. Factors influencing lactate clearance are in boxes. Critical levels of mitochondrial PO_2 for dysoxia depend upon ATP demand. GI, gastrointestinal.

and low cardiac output, but also in normotensive patients with a normal or high cardiac output.²¹⁻²² Situations where the rate of glycolysis exceeds the rate of pyruvate utilisation by the Krebs cycle include alkalosis, and excess catecholamine release, and are also associated with hyperlactataemia.²³ Drugs and chemicals that interfere with gluconeogenesis, such as ethanol, methanol, ethylene glycol, salicylates, and phenformin, can also raise lactate concentrations.²³ Congenital defects of mitochondrial function also present with hyperlactataemia.

The association of lactic acidosis with increased mortality in critically ill patients is well recognised.¹⁶⁻²⁴⁻²⁶ In a heterogeneous group of 126 severely ill adults with metabolic acidosis, defined as a lactate ≥ 5 mmol/l, and either an arterial pH ≤ 7.35 or a base deficit > 6 mmol/l, Stacpoole and colleagues¹¹ found higher lactate concentrations in non-survivors (mean, 12.2; SD, 5.9 mmol/l) than survivors (mean, 9.2; SD, 4.9 mmol/l; $p = 0.004$). Less than 17% of the patients in this series survived to hospital discharge.¹³

Mild hyperlactataemia with respiratory alkalosis might not have the same adverse prognostic value as hyperlactataemia with acidosis. Some authors have proposed that mild rises in lactate are not indicative of serious pathology, depending on the mechanism involved.⁹⁻¹⁰⁻²⁶

In critically ill patients, there is some value in the trend of change in lactate as a means of assessing response to treatment, and prognosis.¹⁵⁻¹⁸⁻²⁷⁻²⁹ Vincent *et al* described the time course of blood lactate in adults who responded to rapid volume resuscitation for circulatory shock.¹⁵ In all cases, during the first hour there was at least a 10% reduction in blood lactate. This contrasted with patients who died during circulatory shock, in whom lactate concentrations did not change with resuscitation. In a study of adults with sepsis, Tuchschiidt and colleagues³⁰ observed that despite the similarity in oxygen consumption (VO_2) after the initial resuscitation period among survivors and non-survivors, lactate concentrations decreased in the survivors, but not in those who died.

Cause of hyperlactataemia in sepsis

The traditional distinction between type A (where there is clinical evidence of tissue hypoxia) and type B lactic acidosis (where there is no clinical evidence of tissue hypoxia) proposed by Cohen and Woods³¹ is simplistic in sepsis. Several mechanisms are involved. Clinical application of this distinction also implies that there is a valid gold standard for the measurement of tissue hypoxia, which is arguable.

Tissue hypoxia can occur because of a decrease in oxygen delivery in hypodynamic sepsis. Sepsis with low cardiac output and peripheral vasoconstriction might be more common in young children, and is a well described feature of severe meningococcal sepsis.³²⁻³³ Even a normal or raised cardiac output might not supply sufficient oxygen to tissues that have an increased metabolic rate.

Hypoxia induced hyperlactataemia might also occur because of the formation of peripheral arterio-venous shunts, or the regional redistribution of blood away from the hepatosplanchnic vascular bed. The true role of impaired cellular oxygen delivery (DO_2) in sepsis is uncertain, however, because covert tissue hypoxia might not be a common antecedent for lactic acidosis or adverse sequelae in sepsis.³⁴

Although there is some evidence for a relation between delivery dependent oxygen consumption and lactate, this has not been shown in all studies, and cannot be generalised to all septic patients. In support of lactate reflecting delivery dependent oxygen consumption, Gilbert and colleagues³⁵ showed that patients with a high lactate had significant increases in VO_2 in response to colloid fluid volume expansion and packed red cell transfusion, whereas patients with normal lactate had no such increase in VO_2 . Against these findings are those of Silverman,¹⁴ who used intravenous fluids, packed red cell transfusion, and dobutamine infusion to improve DO_2 in 17 adults with sepsis. Of 52 interventions that improved DO_2 and VO_2 in the 17 patients, about one third were associated with an unchanged, or increased, blood lactate. There was no predictable relation between improvements in VO_2 and reductions in blood lactate.

Further evidence has been used to argue against tissue hypoxia as the major cause of lactic acidosis, namely: (1) the effect of sodium dichloroacetate (DCA) on lactate concentrations in sepsis³⁶; (2) the finding that in patients with mild rises of blood lactate, clearance is reduced rather than lactate production increased⁹; (3) in clinical studies, efforts to drive DO_2 to supranormal levels do not consistently improve outcome³⁷ or lower blood lactate³⁸; (4) in some models of sepsis, organ failure occurs despite levels of VO_2 and DO_2 within the physiological range³⁹; and (5) in some studies, tissue oxygen tension has been measured in septic patients and found not to be low.

DCA, in the presence of oxygen, stimulates pyruvate dehydrogenase activity and increases oxidation of pyruvate to acetyl coenzyme A and carbon dioxide, thereby increasing pyruvate and lactate metabolism. DCA reduces blood lactate in septic patients. Some have argued, therefore, that deficits in cellular oxygen cannot be the rate limiting step in lactate accumulation,³⁶ but instead there is increased pyruvate production or decreased lactate clearance.⁹ Lactate reductions in septic patients treated with DCA are modest, however. In one study, with of a pretreatment mean value of 11.6 mmol/l, the reduction was between 1 and 3 mmol/l, and one third of patients had less than a 20% decrease in blood lactate concentration.¹³ There was still an excess of lactate that was not eliminated by this DCA induced aerobic process, which might be attributable to cell hypoxia.

The absence of an apparent delivery dependent relation between DO_2 , VO_2 , and lactate does not exclude dysoxia as the cause of high lactate in sepsis. Supply dependent oxygen

consumption at a tissue level might be poorly detected by the global values of VO_2 and DO_2 , even if independent and valid methods are used to measure each variable. It is untested whether regional measures of dysoxia, such as the hepatic venous β -hydroxybutyrate to acetoacetate ratio,⁴⁰ would better determine whether supply dependent oxygen consumption exists in sepsis, and how sensitive high blood lactate is at reflecting this.

If tissue hypoxia is not the major cause of lactate accumulation in sepsis, then what other mechanisms are involved? Levraut *et al* showed that haemodynamically stable adults with sepsis and mildly raised blood lactate had more than a 50% reduced lactate clearance compared with septic adults who had normal lactate, whereas lactate production was similar in the two groups.⁹ Reduced activation of the pyruvate dehydrogenase complex in sepsis⁴¹ might cause the accumulation of pyruvate and formation of lactate.

Although mitochondrial PO_2 might be normal in sepsis, theoretically, ATP production would be reduced by impaired delivery of pyruvate into the Krebs cycle, inhibition of mitochondrial enzymes in the Krebs cycle or electron transport chain, or other disruption of mitochondrial function.⁴² What has been termed “cytopathic hypoxia” might really be a cytopathic inability to use available oxygen. This is well defined—for example, in cyanide poisoning, where cytochromes are inhibited and aerobic metabolism ceases. Whether a similar mechanism operates in clinical sepsis, what causes it, and whether it contributes to hyperlactataemia are uncertain.

Lactate and prediction of outcome in critically ill children

Whatever the causes of hyperlactataemia, high or rising blood lactate might help identify children at high risk of mortality.

SEPSIS

We prospectively compared the predictive value of several variables for mortality and major sequelae in 31 children admitted to the intensive care unit (ICU) with severe sepsis. Those variables were: mean arterial pressure, heart rate, arterial pH, base deficit, gastric intramucosal pH, and blood lactate.⁴³ These were measured at the time of admission and 12, 24, and 48 hours later. There were 10 deaths and 21 survivors. Blood lactate was the earliest predictor of mortality, and identified survivors from those who subsequently died, when measured as early as 12 hours after admission. Twelve hours after admission a blood lactate > 3 mmol/l had a positive predictive value for death of 56%, and a lactate of 3 mmol/l or less had a positive predictive value for survival of 84%. At 24 hours, a lactate > 3 mmol/l had a positive predictive value for death of 71%, and a lactate of 3 mmol/l or less had a positive predictive value for survival of 86%. No other variable identified deaths from survivors as early as 12 hours.

CARDIAC SURGERY

Siegel and colleagues¹⁸ measured arterial blood lactate in 41 children after cardiopulmonary bypass. The mean (SD) lactate concentration for survivors was significantly lower than for the seven who died (2.38 (0.13) mmol/l *v* 6.86 (0.79) mmol/l). Higher lactate concentrations on admission to the ICU were significantly associated with an increased number of extra-cardiac organ systems failing in the postoperative period, and were positively correlated with total bypass and circulatory arrest times.

We compared the predictive power of markers of cardiovascular function for clinically important major postoperative adverse events in a prospective cohort study of 90 children after cardiopulmonary bypass.¹⁹ Heart rate, blood pressure, cardiac output by thermodilution, oxygen delivery, base deficit, mixed venous oxygen saturation, blood lactate, gastric intramucosal pH, and toe core temperature gradient were measured at the time of admission to the ICU, and every four hours thereafter. We also recorded the duration of cardiopulmonary bypass, aortic cross clamping, and circulatory arrest. The major postoperative adverse events of interest were cardiac arrest, need for emergency chest opening, need for commencement of extracorporeal life support, development of multiple organ failure, and death. The subjects were selected for their high risk for major postoperative adverse events, and included 23 neonates having the arterial switch procedure, and 23 infants undergoing repair of multiple ventricular septal defects. In the series, 12 children had major postoperative adverse events and three died. The variables that were the earliest predictors of major postoperative adverse events were the duration of cardiopulmonary bypass, the blood lactate at the time of admission to the ICU, and admission hypotension. Blood lactate was the most consistent predictor of major postoperative adverse events, identifying subsequent major postoperative adverse events when measured also at four and eight hours after admission. Gastric intramucosal pH was also predictive of major postoperative adverse events, but was a later predictor than lactate. At no time in the first 24 hours after ICU admission were cardiac output, oxygen delivery, mixed venous oxygen saturation, or the toe core temperature gradient predictive of major postoperative adverse events. Lactate might be a useful indicator of children at risk of major morbidity and mortality after cardiac surgery. Of note, a high lactate did not predict more than one third of all major postoperative adverse events so, although a specific marker of risk of such events, it had poor sensitivity.

NEONATAL INTENSIVE CARE

Hyperlactataemia has been described as an early marker of sepsis⁴⁴ and necrotising enterocolitis⁴⁵ in preterm neonates. Deshpande *et al* measured lactate, arterial pH, and base excess in 75 mechanically ventilated newborns, most of whom were premature.²⁹ They found significantly higher blood lactate in those who died compared with survivors. After a

neonate developed hyperlactataemia (defined as a blood lactate > 2.5 mmol/l), a substantial fall in lactate was more likely to occur in survivors. There might be an element of survivor bias in this finding. The time frame that this reduction occurred in is not specified and if the second lactate concentration was recorded at a variable time interval from the first, this might have allowed the lactate of those who survived to fall. This study could demonstrate no predictable relation between lactate concentrations, arterial pH, or base excess. Lactate was a better predictor of outcome than the other acid-base variables.

EXTRACORPOREAL LIFE SUPPORT

Cheung and Finer⁴⁶ described 28 neonates requiring extracorporeal membrane oxygenation, in whom lactate concentrations were higher on admission among non-survivors than survivors. Twelve hours after the start of extracorporeal membrane oxygenation, lactate concentrations had fallen significantly in survivors, but not in those who died. These authors also demonstrated absence of a close relation between lactate and other acid-base variables. In an underpowered study we found lactate was not useful in discriminating survivors from deaths on extracorporeal life support but that DCO_2 (measured by gastric tonometry) was.⁴⁷

Management of lactic acidosis

A monitoring variable with predictive power becomes truly valuable to the clinician at the bedside if treatment can be adjusted, based on the variable, and adverse events avoided or outcome improved. To my knowledge, there is only one controlled trial with adequate power that has tested an intervention based on blood lactate and measured important clinical outcomes.¹³ Several other trials, using empirical interventions to increase DO_2 , allow limited conclusions to be made about the management of hyperlactataemia in circulatory failure.

DICHLOROACETATE

Stacpoole *et al* tested whether specific treatment of the lactic acidosis of circulatory shock with DCA could reduce mortality.¹³ There was a significant, but clinically small, reduction in lactate concentrations and an increase in arterial pH in the treatment group; however, there were no improvements either in haemodynamics or survival. Only 12% of the DCA treated group survived to hospital discharge, compared with 17% of the group who received placebo.

BICARBONATE

The treatment of lactic acidosis with bicarbonate is based on the notion that: (1) the cardiovascular or metabolic effects of acidosis or hyperlactataemia are harmful per se; and (2) there are net cardiovascular or metabolic benefits when bicarbonate is given.

Does metabolic acidosis depress myocardial performance and responses to catecholamines? Although there is evidence to support this,^{48 49} bicarbonate might worsen intracellular acidosis by generated CO_2 , which enters the cytoplasm,⁵⁰ and might further depress myo-

cardial function.^{49 51 52} However, the evidence that bicarbonate administration causes paradoxical intracellular acidosis is contentious. In cell preparations, the effect on intracellular pH of adding bicarbonate to extracellular fluid depends on the starting pH of the system, the size of the bicarbonate boluses added to the system, and the type of buffering solutions used as the extracellular suspension. In vitro studies that have reproduced metabolic acidosis,^{53 54} which used physiological solutions buffering the extracellular fluid,⁵³ and added bicarbonate as a series of small boluses,⁵⁴ have shown only small and transient reductions in intracellular pH.

What of the effect of bicarbonate on myocardial function? Two canine studies found transient increases in coronary venous CO_2 and decreases in myocardial contractility at the beginning of an infusion of sodium bicarbonate.^{52 55} This was followed by improved contractile function beyond baseline levels. One study documented a reduction in intracellular pH,⁵² whereas the other study showed no change in intracellular pH, but a decrease in serum free Ca^{2+} , coinciding with myocardial depression.⁵⁵ These investigators proposed that myocardial depression after bicarbonate infusion might be caused by reduced availability of free Ca^{2+} , rather than intracellular acidosis.⁵⁵

The effect of bicarbonate on the intracellular pH in other organs is similarly contentious. In a rabbit model of hypoxic lactic acidosis, brain intracellular acidosis was partially corrected by bicarbonate administration⁵⁶; however, in a study of five normal adult humans, intravenous sodium bicarbonate resulted in a reduction in brain intracellular pH, measured by magnetic resonance imaging spectroscopy.⁵⁷ Despite all this, it is not known whether the therapeutic correction of intracellular acidosis is without adverse effects, and one experimental study shows that intracellular acidosis might protect against reperfusion injury.⁸

It has been proposed that the effect of bicarbonate in shifting the haemoglobin-oxygen dissociation curve to the left will result in delayed tissue reoxygenation. In a porcine model of haemorrhagic shock, bicarbonate delayed increases in tissue PO_2 , and delayed falls in plasma lactate.⁵⁸ This study used small patient numbers, and repeated measures over time, but analysed differences in the data at time intervals that were not predetermined. Therefore, the conclusions are not strongly supported.

Clinical trials of bicarbonate in children are few. Fanconi *et al*,⁵⁹ in an open non-randomised, "before and after" trial in neonates with metabolic acidosis, examined the cardiovascular effects of bicarbonate infusion. Sodium bicarbonate induced a transient increase in cardiac output and a fall in systemic vascular resistance. Although this appears at odds with the animal models described above,^{52 55} from this clinical study there is no way of telling whether the effect was because of bicarbonate correction of acidosis, or because

Table 1 Protocol to manage high blood lactate in sepsis*

Give intravenous fluid volume bolus of 10–20 ml/kg of colloid or normal saline
Continuously monitor
<ul style="list-style-type: none"> • arterial blood pressure • central venous pressure (CVP) • heart rate • cutaneous oxygen saturation (SpO₂) • urine output
Maintain CVP at 8–12 mm Hg with fluid volume
Up to 40–60 ml/kg might be required in the first six hours
Optimise SpO ₂ with oxygen and mechanical ventilation
Transfuse with packed cells if haemoglobin < 100 g/l
Give clotting products as volume if there is a coagulopathy, but beware of hypotension caused by fresh frozen plasma
Repeat lactate; if still high or blood pressure low, add dopamine at 5 µg/kg/min
Apply mechanical ventilation to reduce respiratory muscle oxygen consumption and allow redistribution of cardiac output to vital organs
Increase inotropic support if lactate still rising
Consider that catecholamines, especially adrenaline (epinephrine), might also cause high lactate concentrations
If the child is receiving adrenaline, and has an acceptable blood pressure but a rising lactate, reducing the adrenaline infusion rate might lower lactate
Titrate the inotrope to the lowest infusion rate that will maintain
<ul style="list-style-type: none"> • a blood pressure in the normal range for age • a urine output > 1 ml/kg/hour • a reduction in lactate
If lactate continues to rise despite these measures, consider the use of extracorporeal life support

*Assumes appropriate antibiotics have been given.

Table 2 Protocol to manage high blood lactate after cardiopulmonary bypass

Correct deficits in oxygen delivery
<ul style="list-style-type: none"> • maintain adequate circulating volume • maintain haemoglobin at 120–140 g/l • do not stop dopamine on first postoperative night • optimise arterial oxygen saturation
Give paracetamol for fever and use other cooling methods as necessary (to normothermia)
Do not stop neuromuscular blocking drugs or wean off ventilation on first postoperative night unless there is a specific reason (for example, Fontan, Glenn), and then only with frequent reassessment of perfusion
Start peritoneal dialysis early if the child has generalised oedema, oliguria, or large volumes of fluid are required to maintain circulation
Repeat lactate at four and eight hours after intensive care unit (ICU) admission
If lactate is rising, or > 4 mmol/l
<ul style="list-style-type: none"> • notify the ICU consultant and cardiac surgeon • check cardiac rhythm and perform echocardiography to examine cardiac function and exclude pericardial effusion • optimise intravascular volume
Consider the following
<ul style="list-style-type: none"> • increasing dopamine to 7.5–10 µg/kg/min • adding another inotrope if mean arterial pressure is low • the possible detrimental effects of high dose catecholamine constrictors • the need for vasodilators • cardiac tamponade (as a result of mediastinal oedema or haemorrhage)
Frequent assessment of the child is required

ICU admission lactate > 5 mmol/l has a 30% risk of major adverse events. Lactate at four hours > 4 mmol/l has a 45% risk of major adverse events.

of fluid volume, or infusion of a hyperosmolar solution.

Therefore, the theoretical disadvantages of administered bicarbonate are: (1) complications of hyperosmolar solutions, particularly an increased risk of intraventricular haemorrhages in neonates; (2) ventilatory failure and arterial hypercarbia in patients with compromised pulmonary function; (3) worsening of intracellular acidosis; and (4) delayed tissue reoxygenation.

The current role of bicarbonate that is supported by an arguable balance of evidence is as small titrated doses to achieve a pH compatible with optimal cardiovascular responsiveness, while attempts to improve oxygenation are continued.⁵¹

GENERAL MEASURES TO IMPROVE OXYGEN DELIVERY

Several randomised, controlled trials in adults have tested whether the empirical driving of DO₂ to levels seen in survivors of critical illness will have a survival benefit for all patients. Results are conflicting, reflecting the

heterogeneity of patients enrolled, differences in interventions used, and the timing of interventions. In a meta-analysis of these studies it was concluded that interventions designed to achieve supraphysiological goals of oxygen transport variables did not reduce mortality.³⁷ There are dangers of massive dose inotropic support, such as was used in some of these trials. High dose catecholamines can cause tachyarrhythmia, myocardial ischaemia,⁶⁰ and worsen lactic acidosis.⁶¹

What therefore is a rational approach to the problem of hyperlactataemia if it is not solely caused by impaired tissue oxygenation, and if no specific treatment has been proved to be beneficial? Tables 1 and 2 suggest guidelines for the management of high lactate in children with sepsis and after cardiac surgery. For many patients with hyperlactataemia, management that includes fluid volume expansion will produce a fall in lactate and a favourable clinical response.¹⁵ Large volumes of fluid might need to be given early in the treatment of children with septic shock.⁶² Titrating inotropic drugs to the lowest infusion dose that will achieve an acceptable blood pressure, a urine output of > 1 ml/kg/hour, improve peripheral perfusion, and correct acidosis might be as precise as can be currently achieved.

In children with severe circulatory failure, mechanical ventilation can result in a redistribution of 15–20% of the cardiac output away from the muscles of respiration to other vital organs.

Effective management requires non-specific treatment based on considerations of the following: the underlying pathology; the child's fluid volume status, cardiovascular, and respiratory function; liver function and drugs; and the effects of dysoxia on the brain, gastrointestinal tract, and kidneys.

A normal blood lactate in children with severe circulatory failure might also have clinical relevance; it should prompt consideration of associated conditions that might impair lactate production, such as depletion of glucose stores in malnutrition. It remains untested whether there is any metabolic abnormality common to children with fatal septic shock who never have hyperlactataemia.

Future directions in the monitoring of dysoxia

The earliest detection of dysoxia might be found by specific measures of the redox state of cells. The β-hydroxybutyrate to acetoacetate (ketone body) ratio estimates liver mitochondrial NADH/NAD, and has been shown to be a marker of oxygen limited ATP flux in liver,⁴⁰ and a predictor of adverse events after liver transplantation. What role it may have in other pathologies is unclear. Near infrared spectroscopy might be useful to monitor cytochrome redox states.⁶³ The lactate to pyruvate ratio, reflecting the redox potential of the cytosol, might be a more specific marker of dysoxia than lactate alone. Before any new technique is adopted for practice, careful clinical studies in critically ill children, which compare the

predictive value for major adverse events, and the cost effectiveness, with those of established techniques, will be needed.

Conclusions

In dysoxia, oxygen limited ATP production produces lactic acid, but this is not the only mechanism for excess lactate in critically ill patients. There is not a direct relation between lactate concentrations and supply dependent oxygen consumption in all patients, although current techniques to test this are imprecise. One of the causes of mild hyperlactataemia in sepsis is impaired lactate removal. The role of lactate in the management of critically ill children is in alerting clinicians to a higher risk of mortality or adverse events, and it is but one useful tool to monitor response to treatment. The immediate management depends on consideration of the aetiology of hyperlactataemia. High blood lactate does not suggest a universal therapeutic response, but indicates severe physiological derangement associated with an increased risk of mortality. Lactate concentrations are not well predicted by other acid-base variables, and lactate is a better predictor of adverse outcomes, including mortality. Hyperlactataemia might be a specific predictor of morbidity risk, but in a population of critically ill children, has low sensitivity.

In children with hyperlactataemia it is sensible to consider whether there are correctable deficits in oxygen delivery. Current treatment aimed at lowering the lactate concentration by specifically altering a biochemical pathway does not improve survival, and neither does driving DO_2 to supranormal levels with inotropes. Bicarbonate infusion has a limited role, and is only effective in normalising blood pH when generated CO_2 is eliminated from the body. In many cases there will be identifiable and avoidable causes of insufficient tissue oxygen delivery, such as hypovolaemia or inadequate cardiac output.

Further research is required to define more sensitive, and equally inexpensive and non-invasive, markers of tissue dysoxia.

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