

Occasional essay

Varying clinical significance of hyperlactataemia

Lactate levels are frequently cited as an indicator of inadequate tissue perfusion or oxygenation. However, due to the variety of mechanisms by which an elevated plasma lactate level can occur, the diagnostic and prognostic implications of hyperlactataemia are not always straightforward. Although extensively described and differentiated from type A lactic acidosis,¹ the clinical and prognostic significance of hyperlactataemia in the absence of impaired oxygen delivery (DO_2) has not been well defined.

Hyperlactataemia is defined by a measured blood lactate level above the normal range ($> 2\text{mmol/L}$), while lactic acidosis is defined by the presence of a blood lactate concentration $> 5\text{mmol/L}$ concurrent with a metabolic acidaemia ($\text{pH} < 7.35$).² Lactic acidosis has been divided into “type A”, associated with impaired delivery of oxygen to tissues (DO_2), and “type B”, where lactic acidosis occurs in the presence of normal DO_2 . Lactic acidosis occurring in the setting of normal DO_2 may represent increased cellular production of lactate, reduced tissue uptake or utilisation of oxygen, or reduced lactate clearance.

There is increasing recognition that hyperlactataemia and lactic acidosis may occur in the absence of tissue hypoxia. However, interpretation of hyperlactataemia as an indication of inadequate tissue perfusion or oxygenation continues, resulting in interventions aimed at increasing tissue oxygen delivery (DO_2). Glucose (85%) and amino acids (15%) are metabolised to pyruvate in all cells, generating ATP and NADH. The Krebs cycle and oxidative phosphorylation within the mitochondria generates ATP via metabolism of pyruvate to CO_2 and water. This process is dependent on the maintenance of a minimum local concentration of oxygen. Normal aerobic metabolism generates 36 mol of ATP for every 1 mol of glucose. Any process impairing metabolism of pyruvate, particularly tissue hypoxia, leads to accumulation of pyruvate and its alternative metabolite, lactate. This process provides a mechanism where ATP production can continue in states of tissue hypoxia, but is far less efficient than aerobic metabolism. Anaerobic metabolism produces 2 mol of ATP for every 1 mol of glucose utilised. The lactate produced in erythrocytes (which lack mitochondria) and by anaerobic metabolism is metabolised mainly in the liver. Each molecule of lactate

metabolised also regenerates a molecule of bicarbonate, replacing that used in initially buffering lactic acidosis.

Lactate accumulates in the presence of tissue hypoxia, but may also increase in aerobic conditions where increased glycolysis occurs, as with stimulation by endogenous or exogenous catecholamines. Measurement of the ratio between lactate and pyruvate concentrations may distinguish between situations of increased cellular metabolism (ratio normal - 10:1) and tissue hypoxia (ratio elevated - $> 10:1$).

Clinically, moderate hyperlactataemia may also occur in the absence of acidosis - as in patients receiving renal replacement therapy (RRT) with lactate-containing dialysate. However, increasing hyperlactataemia will inevitably result in metabolic acidosis, by virtue of the increased presence of the strong ion lactate.³

Hyperlactataemia in the critically ill may then take one of three forms:

1. Moderate hyperlactataemia without acidosis.
2. Lactic acidosis associated with impaired DO_2 (Type A).
3. Lactic acidosis associated with preserved DO_2 (Type B).

Hyperlactataemia and lactic acidosis are common findings in critically ill patients, and have significant prognostic implications. Lactic acidosis as a result of poor tissue oxygenation or redox state has been shown to be a predictor of poor outcome in the critically ill. Overall, the severity and duration of lactic acidosis in critically ill patients correlates with overall oxygen debt, potential organ dysfunction and mortality.^{4,5} If representative of impaired DO_2 , serial lactate measurements may also aid in assessing the adequacy of resuscitation. However, it is conceivable that findings of isolated hyperlactataemia, or of type B lactic acidosis may have different prognostic implications to those of type A lactic acidosis.

However, the prognostic implications of isolated hyperlactataemia in the absence of acidosis, or of type B lactic acidosis, do not seem to be widely appreciated by the clinician. Different forms of hyperlactataemia may represent very different pathophysiologic states, with differing implications for therapy and prognosis. Tissue hypoperfusion or hypoxia associated with type A lactic acidosis may contribute to subsequent organ failure or mortality. Depending on underlying mechanisms, type B lactic acidosis may be indicative of the patient's capacity to increase metabolism in response to stress, and so may correlate with improved prognosis. In sepsis, the ability to increase DO_2 in response to dobutamine administration has been associated with decreased mortality.⁶ Conversely, impaired lactate clearance, associated with either normal lactate levels or

type B lactic acidosis, is a significant predictor of mortality.^{7,8}

Iatrogenic hyperlactataemia may result from interventions such as dialysis using lactate-containing fluids, and administration of exogenous β -adrenergic agonists such as salbutamol, or adrenaline post cardiopulmonary bypass.⁹ Lactic acidosis is well described as a complication of β -agonist therapy in asthma.^{10,11} B_2 -adrenergic stimulation increases glycogenolysis and skeletal muscle Na-K-ATPase activity,^{9,12} increasing both pyruvate and lactate production but maintaining a normal lactate/pyruvate ratio.

Type B lactic acidosis may result from a stress response and release of endogenous catecholamines. Exercise and seizures lead to hyperlactataemia via increased circulating catecholamine concentrations and aerobic glycolysis, rather than by conversion to anaerobic metabolism in muscle once a maximal DO_2 is reached.¹² Lactate concentrations in these situations correlate with circulating catecholamine concentrations.¹³ This "stress hyperlactataemia" is seen in sepsis and post trauma. Type B lactic acidosis in burns patients may be decreased or limited by administration of β -blockers,¹⁴ suggesting that stress-release of endogenous catecholamines and β -adrenergic stimulation is responsible. The magnitude of "stress hyperlactataemia" post trauma and sepsis may be representative of the degree of stress response and catecholamine release, rather than tissue hypoxia. If so, then hyperlactataemia may still correlate with poor prognosis, but perhaps to a different extent than when hyperlactataemia is associated with tissue hypoperfusion and organ failure.

Metabolic acidosis occurs commonly post cardiopulmonary bypass, often related to raised concentrations of unmeasured strong anions¹⁵ and may be related to the pump prime used. Hyperlactataemia may also occur and may be related to regional hypoperfusion associated with non-pulsatile flow during and after cardiopulmonary bypass, altered metabolism with temperature changes, exogenous catecholamines and altered lactate clearance. Based on current knowledge, the presence of a lactic acidosis post cardiopulmonary bypass should be taken as representing impaired DO_2 and attempts should be made to correct this. However, lactic acidosis post cardiopulmonary bypass may not always be associated with impaired DO_2 . Raper¹⁵ demonstrated the occurrence of a type B lactic acidosis in a group of patients post cardiopulmonary bypass, which was not associated with worse outcomes. Another study⁹ also related development of type B lactic acidosis to administration of adrenaline post cardiopulmonary bypass. They did not report patient survival but suggested that this type B lactic acidosis did not have the same unfavourable implications associated with hypoxia.

In the absence of other markers of oxygen debt or cardiovascular instability, hyperlactataemia alone has not been correlated with adverse postoperative outcomes.¹⁶ Hyperlactataemia becomes a prognostic factor when it becomes lactic acidosis and there are other indicators of impaired DO_2 . Overall, the presence of lactic acidosis is associated with an increased incidence of adverse events and death.¹⁷⁻¹⁹ Duke *et al.*,¹⁹ showed that hyperlactataemia (> 4 mmol/L) post cardiac surgery was a predictor of adverse events in paediatric patients, but sensitivity was low, with hyperlactataemia predicting less than a third of adverse events.

In sepsis, hyperlactataemia may occur via a number of mechanisms. Type A lactic acidosis has been demonstrated early in the course of sepsis with haemodynamic instability,²⁰ the severity of which correlates with mortality. Later on lactate levels do not correlate as well with outcomes and Hotchkiss and Karl²¹ showed that hyperlactataemia might then represent a type B lactic acidosis. This may be due to combinations of catecholamine-induced glycogenolysis, increased skeletal muscle Na-K-ATPase activity^{1,5,21}, mitochondrial dysfunction and impaired lactate clearance.

The liver's capacity for lactate clearance is large, but may be reduced in sepsis or with hepatic hypoperfusion. Decreased lactate clearance in stabilised patients with normal lactate levels correlates strongly with mortality.^{7,8}

Hyperlactataemia is commonly seen in patients receiving renal replacement (RRT) using lactate-containing dialysate, especially in those with shock, hepatic dysfunction and impaired lactate clearance.^{22, 23} Hyperlactataemia may or may not be associated with acidosis. Lactic acidosis, but not isolated hyperlactataemia, in critically ill patients receiving RRT has been shown to correlate with increased mortality.^{23, 24}

In addition to dialysis fluids, administration of exogenous lactate in intravenous fluids has been thought to increase blood lactate levels in patients with impaired clearance. Administration of such fluids has been found to produce no change in lactate concentrations in normal subjects²⁵ and those with haemorrhagic shock.¹²

It may now be important to add more clinical data to the large amount of literature on the increasingly complex subject of hyperlactataemia. Clinical studies should aim to characterise hyperlactataemia occurring in various clinical situations as occurring with or without concurrent metabolic acidaemia and by the type and mechanism of acidosis if present. Measurements such as the lactate/pyruvate ratio establish whether tissue hypoxia or increased metabolism are present. Responses to an exogenous lactate load have been used to measure lactate clearance and measurements such as the acetoacetate: β -hydroxybutyrate ratio have been described as measures of mitochondrial function.²⁶

Delineation of the pathophysiology of hyperlactataemia in various clinical settings, in conjunction with outcome data, could then be used to further elucidate the significance of different forms of hyperlactataemia and provide more accurate therapeutic and prognostic guidance. Clearly, to always equate hyperlactataemia with lactic acidosis and consequently with poor outcome is not always correct.

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