

LACTIC ACIDOSIS AND THE PLACE FOR MEASURING INTERMEDIARY  
METABOLITES

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The concentration of lactic acid in blood is dependent on both production and removal. It is normally found between 0.4 and 1.0 mmol/l in the resting fasting state and there is little diurnal variation so that effective homeostatic mechanisms seem to apply. Blood lactate during maximum exercise exceeds 10mmol/l and, in athletes, reaches values of 22mmol/l. The distribution space is that of total body water. However, because of the large capacity of lactic dehydrogenase, pyruvate exchanges almost quantitatively with lactate. There is no definite evidence for active transport of lactate. The total daily production of lactate is about 1.5mol and the  $T_{1/2}$  9 mins. The renal threshold for lactate is about 7mmol/l. The major organ contribution to lactate production is that of formed elements in the blood, but brain, skeletal muscle, skin, renal medulla and the intestinal mucosa also contribute. Liver and kidneys utilize lactate for gluconeogenesis and the heart takes up lactate as a fuel. The relative contribution of lactate to myocardial oxygen consumption is about 10%.

The hormones catecholamines and insulin increase blood lactate concentrations, but there is a proportionate increase in pyruvate. Huckabee referred to this kind of hyperlactataemia as Type I, by comparison with Type II where the lactate-pyruvate molar ratio exceeded 10. One reservation about regarding lactate:pyruvate ratios as indicative of redox status is that the two carbohydrates have different rates of membrane transport.

Hyperlactataemia less than 5mmol/l is generally not associated with acidosis. This is because below the renal threshold for lactate,

- (i) lactate removed by oxidation or gluconeogenesis involves the utilization of as many hydrogen ions as were formed in its production and
- (ii) there is no loss of cations in the urine to accompany lactate.

Cohen and Woods consider two varieties of lactic acidosis on clinical grounds. Type A occurs in association with circulatory insufficiency and hypoxia. Type B refers to lactic acidosis in situations where poor tissue perfusion or poor oxygenation are not obviously present. Causes of Type B include

- (a) disorders such as diabetes mellitus, renal failure, liver disease, infection, leukaemia
- (b) drugs such as phenformin
- (c) parenteral nutrition with fructose, sorbitol and xylitol
- (d) toxins such as ethanol or methanol and streptozotocin
- (e) hereditary disorders such as glucose-6-phosphatase deficiency (Type I glycogen storage disease).

In view of the considerable capacity of the liver normally to remove lactate, simple overproduction of lactate is unlikely to account for lactic acidosis. Decreased hepatic removal of lactate because of reduced splanchnic blood flow or actual hepatic production of lactate are likely.

Diabetic ketoacidosis and diabetic hyperosmolar coma may both be associated with lactic acidosis. Lactic acidosis may persist when ketoacidosis has been corrected.

Of the biguanides, phenformin may be 50 times more likely than metformin to produce lactic acidosis. In part this may be due to a longer half life for lactate with phenformin, probably reflecting decreased hepatic removal of lactate. Current practice is now to avoid phenformin as an oral antidiabetic agent.

Recognition of lactic acidosis comes by awareness of predisposing circumstances; recognition of Kussmaul breathing; assessment of the anion gap (normally not more than 10 - 18mmol/l except in uraemia, diabetic or starvation ketoacidosis and salicylate poisoning); any unexplained low pH; an unexplained leukocytosis.

Experimental evidence from studies where lactic acid and sodium lactate have been compared suggest that the dangers of lactic acidosis rest with the acidosis rather than the hyperlactataemia. However, prognosis in man is related to the degree of hyperlactataemia. This relationship may simply indicate the severity of, for example, poor tissue perfusion.

Assessment of intermediary metabolites other than lactate and pyruvate will probably have an increasing place in clinical medicine. For example, acetaldehyde is now recognised as the principle toxic agent in alcoholic cardiomyopathy and it may also be of value in assessing alcohol dependence and susceptibility to intoxication.

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