

Acid-Base Physiology

8.1 Lactic Acidosis

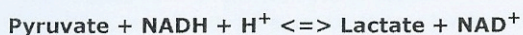
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Lactic acidosis is a common cause of metabolic acidosis. ^{1,2,3}

8.1.1 Daily Production of Lactate

Each day the body has an excess production of about 1500 mmols of lactate (about 20 mmols/kg/day) which enters the blood stream and is subsequently metabolised mostly in the liver. This internal cycling with production by the tissues and transport to and metabolism by the liver and kidney is known as the Cori cycle. This normal process does not represent any net fixed acid production which requires excretion from the body.

All tissues can produce lactate under anaerobic conditions but tissues with active glycolysis produce excess lactate from glucose under normal conditions and this lactate tends to spill over into the blood. Lactate is produced from pyruvate in a reaction catalysed by lactate dehydrogenase:



This reaction is so rapid that pyruvate and lactate can be considered to be always in an equilibrium situation. Normally the ratio of lactate to pyruvate in the cell is 10 to 1. The ratio $[\text{NADH}]/[\text{NAD}^+]$ by the Law of Mass Action determines the balance between lactate and pyruvate. This ratio is also used to denote the redox state within the cytoplasm. Lactic acid has a pK value of about 4 so it is fully dissociated into lactate and H^+ at body pH. In the extracellular fluid, the H^+ titrates bicarbonate on a one for one basis.

8.1.2 Tissue Production & Metabolism

Lactate is released from cells into the ISF and blood.

Tissues Producing Excess Lactate

At rest, the tissues which normally produce excess lactate are:

- skin - 25% of production
- red cells - 20%
- brain - 20%
- muscle - 25%
- gut - 10%

During heavy exercise, the skeletal muscles contribute most of the much increased circulating lactate. ^(4,5)

During pregnancy, the placenta is an important producer of lactate which passes into both the maternal and the foetal circulations.

Lactate is metabolised predominantly in the liver (60%) and kidney (30%)⁶. Half is converted to glucose (gluconeogenesis) and half is further metabolised to CO_2 and water in the citric acid cycle. The result is no net production of H^+ (or of the lactate anion) for excretion from the body. Other tissues can use lactate as a substrate and oxidise it to CO_2 and water but it is only the liver and kidney that have the enzymes that can convert lactate to glucose.

Note:

- The balance between release into the bloodstream and hepatorenal uptake maintains plasma lactate at about one mmol/l.
- The renal threshold for lactate is about 5 to 6 mmols/l so at normal plasma levels, no lactate is excreted into the urine.
- The small amount of lactate that is filtered (180mmol/day) is fully reabsorbed.

8.1.3 Mechanisms involved in Lactic Acidosis

Lactic acidosis can occur due to:

- excessive tissue lactate production
- impaired hepatic metabolism of lactate

In most clinical cases it is probable that both processes are contributing to the development of the acidosis. The liver has a large capacity to metabolise lactate so increased peripheral production alone is unlikely to lead to other than transient acidosis. The situation is analogous to a respiratory acidosis where increased CO_2 production alone is rarely responsible because of the efficient ventilatory regulation of pCO_2 . Impaired ventilation (impaired excretion of CO_2) is almost invariably present and responsible for a respiratory acidosis.

In situations where lactic acidosis is clearly due to excessive production alone (such as severe exercise or convulsions), the acidosis usually resolves (due to hepatic metabolism) within about an hour once the precipitating disorder is no longer present. In severe exercise, lactate levels can rise to very high levels eg up to 30 mmol/l. Respiratory compensation for the acidosis may not be significant because of the short time involved. However, there are other causes of hyperventilation present and arterial pCO_2 is typically reduced providing partial compensation. For example, exercise results in markedly increased ventilation and the cause of this is largely unknown. The arterial pCO_2 usually falls with exercise and this is not considered to be due to the lactic acidosis as it occurs even in less severe exercise where there is little excess lactate produced.

A continuing lactic acidosis means that there is continuing production of lactate that exceeds the liver's capacity to metabolise it. This may be due to clearly very excessive production (eg convulsions) with a normal liver at one extreme, or to increased production in associated with greatly impaired hepatic capacity to metabolise it (eg due to cirrhosis, sepsis, hypoperfusion due hypovolaemia or hypotension, hypothermia, or some combinations of adverse factors) at the other extreme.

8.1.4 Definitions

Definitions differ concerning the blood level at which a lactic acidosis is regarded as 'significant'. For our purposes:

Hyperlactaemia: a level from 2 mmols/l to 5 mmol/l.

Severe Lactic Acidosis: when levels are greater than 5 mmols/l

As levels rise above 5mmols/l, the associated mortality rate can become very high. A serious lactic acidosis can be present without much noticeable elevation of the anion gap. This is because the lactate levels associated with high mortality (say 6 to 10 mmols/l) may not cause much change in a derived variable (the anion gap) which has a 95% reference range of +/-5mmols/l.

The brief and often very high lactate levels that occur with severe exercise or generalised convulsions (eg up to 30 mmol/l) are associated with an extremely low mortality rate. Indeed the mortality rate in these causes is usually extremely low. A lactate level of 15 mmols/l in an elderly ill septic patient in an Intensive Care Unit would be associated with a very high risk of death.

The absolute lactate level (alone) is not a good predictor of outcome unless the cause of the high level is also considered.

Lactate can be converted to glucose in the liver and kidney. This part of the Cori cycle is an example of gluconeogenesis.

Anaerobic glycolysis produces lactate and equivalent amounts of H^+ from ATP hydrolysis. If both these reactions are combined, then there is effectively a net production of equal amounts of lactate and H^+ but the low pKa of lactic acid dissociation means that lactic acid (the undissociated form) is present only in miniscule amounts.

8.1.5 Causes of Lactic Acidosis

Lactic acidosis is commonly classified into either Type A or Type B (Cohen & Woods, 1976) with the main differentiating point being the adequacy of tissue oxygen delivery. In both types, the fundamental problem is the inability of the mitochondria to deal with the amount of pyruvate with which they are presented.

Type A lactic acidosis refers to circumstances where the clinical assessment is that tissue oxygen delivery is inadequate. This is the most common clinical situation. The inadequate oxygen supply slows mitochondrial metabolism and pyruvate is converted to lactate (and NADH to NAD^+). The conversion of NADH to NAD^+ is important as it regenerates NAD^+ needed for glycolysis to continue. This situation is known as anaerobic metabolism and results in a small net ATP production: two moles of ATP per mole of glucose. The mitochondrial reactions are presumed to be intact but unable to function because of inadequate oxygen. If hypoxaemia is the only factor present, it needs to be severe (eg $paO_2 < 35\text{mmHg}$) to precipitate lactic acidosis because of the protection afforded by the body's compensatory mechanisms which increase tissue blood flow. Similarly anaemia needs to be severe (eg $[Hb] < 5\text{G\%}$) if present alone because tissue blood flow is increased in compensation.

Reduced perfusion is the most important factor in causing impaired oxygen delivery in type A lactic acidosis.

Anaemia or hypoxaemia alone is not sufficient unless severe or associated with reduced perfusion.

Type B lactic acidosis refers to situations in which there is no clinical evidence of reduction in tissue oxygen delivery. Carbohydrate metabolism is disordered for some reason and excess lactic acid is formed. Research using more sophisticated methods to assess tissue perfusion have now shown that occult tissue hypoperfusion is present in many cases of Type B acidosis.

An **ischaemic bowel** can produce large amounts of lactate. Mesenteric ischaemia can cause a severe lactic acidosis even if perfusion in the rest of the body is adequate. This situation can easily be overlooked especially in those cases where abdominal clinical signs are minimal.

Phenformin is a biguanide oral hypoglycaemic agent which was associated with a severe form of Type B lactic acidosis. The incidence was highest among diabetics with renal insufficiency where blood levels are highest. The mechanism of action is not fully established but the drug probably interferes with mitochondrial function. High levels of phenformin significantly depress myocardial contractility. The decrease in cardiac output undoubtedly contributes a major component of tissue hypoperfusion to many cases.

Other factors predisposing to development of lactic acidosis are sepsis, liver failure and some malignancies.

Patients with cirrhosis often have a much reduced ability to take up and metabolise lactate. Despite this, patients with chronic hepatic disease alone do not commonly develop lactic acidosis unless other factors such as sepsis, shock, bleeding or ethanol abuse are also present. So, the development of lactic acidosis in patients with cirrhosis suggests severe liver damage and the presence of other factors. In this setting, death rates are high.

Any factor which stimulates glycolysis (eg catecholamine administration, cocaine) will lead to an increased lactate production. Lactic acidosis occurs in up to 10% of patients presenting with diabetic ketoacidosis. This may be due to poor peripheral perfusion or phenformin administration but may occur without the presence of these factors.

Classification of Some Causes of Lactic Acidosis (Cohen & Woods, 1976)**Type A Lactic Acidosis : Clinical Evidence of Inadequate Tissue Oxygen Delivery**

- Anaerobic muscular activity (eg sprinting⁷, generalised convulsions)
- Tissue hypoperfusion (eg shock -septic, cardiogenic or hypovolaemic; hypotension; cardiac arrest; acute heart failure; regional hypoperfusion esp mesenteric ischaemia; malaria^{8,9})
- Reduced tissue oxygen delivery or utilisation (eg hypoxaemia, carbon monoxide poisoning, severe anaemia)

Type B Lactic Acidosis: No Clinical Evidence of Inadequate Tissue Oxygen Delivery

- **type B1** : Associated with underlying diseases (eg ketoacidosis, leukaemia, lymphoma, AIDS)
- **type B2**: Assoc with drugs & toxins (eg phenformin, cyanide, beta-agonists, methanol, nitroprusside infusion, ethanol intoxication in chronic alcoholics, anti-retroviral drugs)
- **type B3**: Assoc with inborn errors of metabolism (eg congenital forms of lactic acidosis with various enzyme defects eg pyruvate dehydrogenase deficiency)

Note: This list does not include all causes of lactic acidosis

8.1.6 Diagnosis

The condition is often suspected on the history and examination (eg shock, heart failure) and is easily confirmed and quantified by measuring the blood lactate level. A particular problem is the diagnosis of the condition when present as part of a mixed acid-base disorder. It may be associated with other causes of a high anion gap acidosis (eg ketoacidosis, uraemic acidosis) and not be suspected. Coexistent lactic acidosis and metabolic alkalosis may result in minimally altered plasma bicarbonate level. A high anion gap may be a clue in this later situation but the anion gap is not invariably elevated out of the reference range.

Why do clinicians have difficulty diagnosing lactic acidosis?

The main reason is that traditionally a lactate level was an uncommon investigation and the diagnosis of lactic acidosis was by exclusion in patients with a high anion gap metabolic acidosis and some evidence of impaired perfusion. Other factors were a low index of clinical suspicion and a tendency to not appreciate the significance of an elevated lactate result.

The basic investigations needed to supplement the history, examination and electrolyte results in differentiating the causes of a high anion gap acidosis are:

- blood glucose level
- urinary ketones
- urea & creatinine
- urine output
- blood lactate level
- calculation of osmolar gap

8.1.7 Management

The principles of management of patients with lactic acidosis are:

- Diagnose and correct the underlying condition (if possible)
- Restore adequate tissue oxygen delivery (esp restore adequate perfusion)
- Avoid sodium bicarbonate (except possibly for treatment of associated severe hyperkalaemia)

When the circulation is restored, the liver can metabolise the circulating lactate. If lactic acidosis is severe and the cause cannot be corrected, the mortality can be quite high.

What is the role of IV bicarbonate?

Quite large doses of bicarbonate (eg 1,000 to 3,000 mmols/day!) have traditionally been administered to severe cases but the success rate is low. Interestingly, metabolic alkalosis induced by administration of sodium bicarbonate can lead to a substantial increase in the production of lactate. This may be because the intracellular acidosis strongly inhibits phosphofructokinase which is the rate-limiting enzyme in glycolysis. This suggests that bicarbonate therapy could result in induction of alkalosis intracellularly which could release this inhibition and increase pyruvate and lactate production (& thus a vicious cycle). No wonder massive doses of bicarbonate seem necessary and why the outcome is so poor.

[See also: [Use of Bicarbonate in Metabolic Acidosis](#)]

References

1. Kruse JA and Carlson RW. *Lactate metabolism*. Crit Care Clin 1987 Oct; 3(4) 725-46. [PubMed](#)
2. Luft FC. *Lactic acidosis update for critical care clinicians*. J Am Soc Nephrol 2001 Feb; 12 Suppl 17 S15-9. [PubMed](#)
3. Stacpoole PW. *Lactic acidosis*. Endocrinol Metab Clin North Am 1993 Jun; 22(2) 221-45. pmid:8325284. [PubMed](#)
4. Juel C. *Muscle pH regulation: role of training*. Acta Physiol Scand 1998 Mar; 162(3) 359-66. [PubMed](#)
5. Juel C. *Lactate-proton cotransport in skeletal muscle*. Physiol Rev 1997 Apr; 77(2) 321-58. [PubMed](#)
6. Bellomo R. *Bench-to-bedside review: lactate and the kidney*. Crit Care 2002 Aug; 6(4) 322-6. [PubMed](#)
7. Robergs RA, Ghiasvand F, and Parker D. *Biochemistry of exercise-induced metabolic acidosis*. Am J Physiol Regul Integr Comp Physiol 2004 Sep; 287(3) R502-16. [PubMed](#)
8. Pasvol G. *The treatment of complicated and severe malaria*. Br Med Bull 2005; 75-76 29-47. [PubMed](#)
9. Maitland K and Newton CR. *Acidosis of severe falciparum malaria: heading for a shock?*. Trends Parasitol 2005 Jan; 21(1) 11-6. [PubMed](#)

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