

The laboratory investigation of lactic acidaemia

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Reference range

Typical ranges for blood lactate are:

Newborn	0.3 - 2.2 mmol/L	Nielsen J et al 1994
1-12mo	0.9 - 1.8 mmol/L	Bonnefont et al 1990
1-8y	0.7 - 1.6 mmol/L	Bonnefont et al 1990
6-18y	0.6 - 0.9 mmol/L	Bonnefont et al 1990
CSF lactate	0.8 - 2.2 mmol/L	Hutchesson et al 1997

Collection

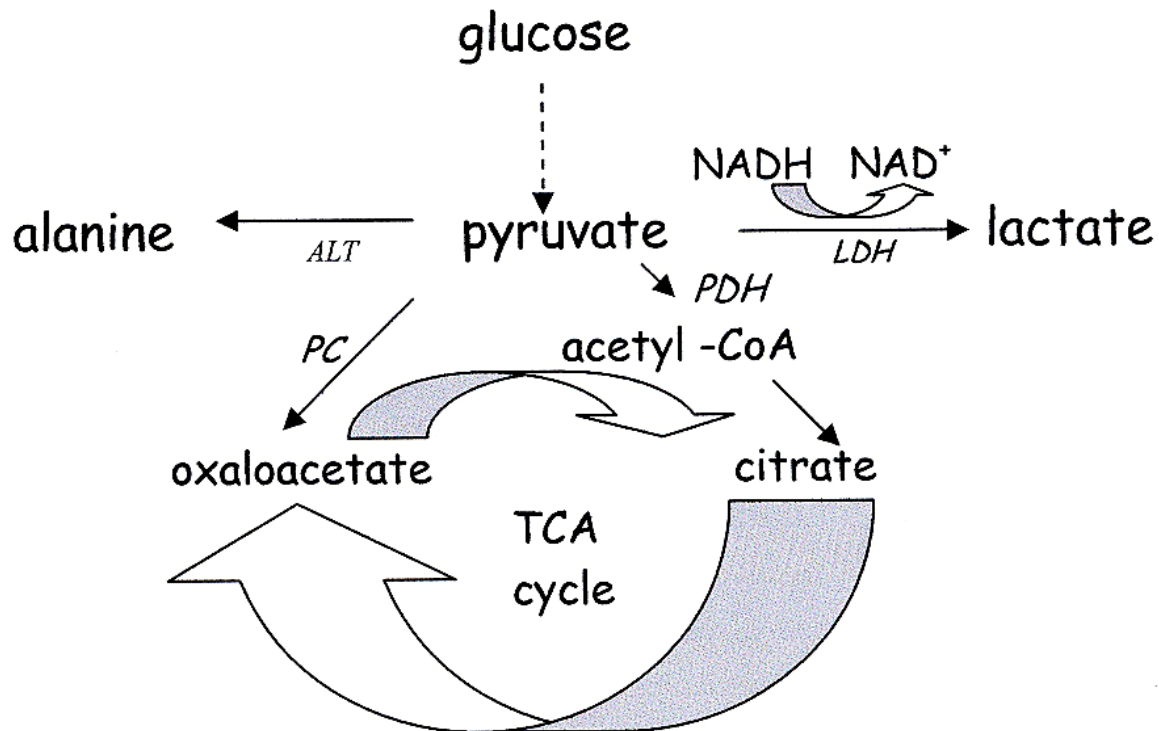
- A short period of venous stasis when using a tourniquet in older children does not appear to increase lactate significantly although muscle activity including hand clenching should be avoided.
- In younger children or when repeated samples are required using an indwelling cannula will provide the most reliable results.
- Continued glycolysis after blood collection can elevate lactate, this can be inhibited by using fluoride tubes or prevented by enzyme denaturation by addition of perchloric acid. The samples should be separated within 12 hour and plasma is stable for 24 hours when refrigerated at 4°C or for 1 month at -20°C, PCA samples may be stable when frozen for even longer periods.
- In un-separated samples lactate can be increased by around 10% within 30 min rising quickly after this when Li Heparin or EDTA is used as an anticoagulant and this should be avoided.

Measurement

- Most methods rely upon the enzymatic conversion of lactate to pyruvate by lactate dehydrogenase. Pyruvate formation is favoured at high pH (9.0-9.6) and in the presence of excess NAD
- The linked production of NADH can be measured spectro-photometrically or fluorimetrically
- $\text{lactate} + \text{NAD}^+ \rightleftharpoons \text{pyruvate} + \text{NADH} + \text{H}^+$

Biochemistry

- Lactate is eliminated and formed via pyruvate and maintains a balanced equilibrium with this compound.



Causes of lactic acidaemia

- Increased glycolytic flux resulting in an increased production of pyruvate eg glycogen storage disease type 1 or hereditary fructose intolerance
- Reduced utilisation of pyruvate eg pyruvate dehydrogenase deficiency or pyruvate carboxylase deficiency
- Increased H^+ concentration eg renal tubular acidosis
- Reduced availability of NAD^+ due to inadequate oxidation of $NADH$ eg poor perfusion, hypoxia, mitochondrial disorders

Acquired causes of lactic acidaemia

Hypoxia/Hypoperfusion	<i>hypovolaemic shock, endotoxic shock, cardiogenic shock, asphxia, severe anaemia</i>
Systemic disease	<i>diabetes mellitus, liver failure, renal disease, neoplastic disease, seizure disorder</i>
Drugs and toxins	<i>carbon monoxide, salicylates, methanol, ethylene glycol, ethanol, nitroprusside, terbutaline, epinephrine, aetaminophen, gucose infusion</i>

Secondary increases in lactate are also seen as a result of muscle activity following strenuous activity or seizures

Heritable or non-acquired disorders resulting in lactic acidaemia

Secondary lactic acidaemia	Organic acidaemias: <i>methylmalonic acidaemia, propionic acidaemia isovaleric acidaemia, pyroglutamic aciduria, 3-hydroxy-methyl-glutaryl CoA lyase deficiency</i>
	Fatty acid oxidation defects: <i>VLCAD deficiency, LCHAD deficiency, β -ketothiolase deficiency</i>
	Urea cycle disorders: <i>citrullinaemia, OTC deficiency</i>

Heritable or non-acquired disorders resulting in lactic acidaemia

Primary lactic acidaemia	Glycogen metabolism defects <i>GSD0, GSD1, GSD3, GSD6</i>
	Gluconeogenic defects <i>fructose 1:6 biphosphatase defn</i> <i>phosphenol pyruvate carboxykinase defn</i>
	Disorders of pyruvate metabolism <i>PDH defn, PC defn, multiple carboxylase defn</i>
	TCA cycle defects <i>fumarase defn, α-ketoglutarate defn, E3 defn</i>
	Mitochondrial respiratory chain defects

Laboratory investigation

- **First line tests**

- U&E
- Blood glucose
- Blood gas
- Full blood count
- CK

Laboratory investigation

- **Second line tests**

- Urinary organic acids
- Dried blood spot acyl carnitine profile
- Intermediary metabolites (FFA, 3-hydroxybutyrate, lactate, glucose) performed pre- and 1 hour post-prandially
- Plasma aminoacids
- Plasma ammonium
- MtDNA analysis for MELAS, MERFF, Kearns Sayre and Pearson syndrome
- Blood and urine toxicology including ethanol, salicylate and paracetamol
- CSF lactate in neurologically presenting cases

Laboratory investigation

- **Third line tests**

- Lactate : pyruvate ratio if the lactate is increased and a change in the redox state needs to be confirmed
- Fasting test possibly with glucagon stimulation
- Muscle biopsy for respiratory chain enzyme assay
- Skin biopsy for PDH measurement where this is a possibility and for fat oxidation where respiratory chain defects are suspected

Interpretation of results

- Variation in lactate concentration due to sampling artefacts and the changing clinical and physiological condition of the patient often makes interpretation difficult.
- It is important to know and understand the clinical context in which sampling took place and if possible to make multiple determinations of lactate concentration under carefully controlled conditions before making a diagnosis of lactic acidaemia and progressing to further tests.

Interpretation of results

- Modest elevation (perhaps up to 3.5 mmol/L) of plasma lactate in sick children is not uncommon and in the majority of these cases no cause can be identified
- Persistent or recurrent lactic acidemia should be documented in carefully obtained samples before further investigations are initiated
- In neurologically presenting cases CSF lactate is an important investigation and may be elevated when plasma lactate is normal or near normal. Results >3.0 mmol/L may be significant and should prompt further investigation

Interpretation of results

- Lactate:pyruvate ratio is only useful when the lactate is itself elevated and a modestly increased ratio ie <30:1 may not be significant
- In general but not invariably secondary lactic acidaemia due to organic acidaemias or fatty acid oxidation defects are less profound (often in the range 3.0 - 6.0 mmol/L) than primary defects such as GSD1, PDH defn, PC defn or respiratory chain disease where the concentration often exceeds 5.0 mmol/L at least during periods of illness.

Interpretation of results

- In glycogen storage disorders and gluconeogenic defects in particular the lactate concentration is very dependent upon the time of feeding and may be normal at times in GSD0, GSD3, GSD6 and even GSD 1
- CSF lactate may be increased in non-ketotic hyperglycinaemia probably related to seizure activity
- An elevated lactate is not an invariable finding in the majority of the candidate metabolic disorders, for instance in one series the sensitivity of an elevated CSF lactate > 3.0 mmol/L was only 67% for the detection of mitochondrial disease. This increased to 73% if a lower cut-off of 2.2 mmol/L was used and to 91% when an elevated plasma lactate > 2.4 mmol/L was included. In practice however, using these cut-offs would result in a very low positive predictive value