Teaching Point
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Lactate in a Laubenpieper

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Abstract
Acid–base disorders seldom kill; however, the mechanisms and associated complications certainly do. We recently encountered a patient with a mysterious lactic acidosis. The patient proved to be a most capable teacher of important lessons.

Keywords: Lactate; Lactate acidosis; Beri Beri; Hyperkalaemia

Introduction
Lactate is the end-product of anaerobic glycolysis and is produced at \( \approx 1 \text{ mmol/kg/h} \) or \( \approx 2000 \text{ mmol/day} \) for an 80 kg adult as follows: glucose + 2 ATP + 2 \( \text{H}_2\text{PO}_4^- \rightarrow 2 \text{lactate} + 2 \text{ADP} + 2 \text{H}_2\text{O} \). The hydrogen ions needed to convert lactate to lactic acid are generated by the hydrolysis of ATP. Skeletal muscle, bowel, brain and erythrocytes are the primary sources. Lactate can be reconverted to glucose or can be used as a primary fuel. The principle causes of hyperlactataemia are tissue hypoxia and disturbed pyruvate oxidation. We recently encountered a challenging patient whose clinical picture imparted several lessons. The physicians were confronted with a life-threatening illness and a flood of clinical and laboratory findings.

Case
The patient is a 47-year-old unemployed man with dyspnoea and lower extremity oedema of 2 weeks duration. He also noted diarrhoea for several days, loss of appetite and decreased urine. He denied ingesting drugs or medications, and denied excessive alcohol (Berliner estimate) intake. The patient was a resident in a typical spring–summer Berlin garden colony. These gardens are commonly granted by allotment to city dwellers (Ger. Lauben). The inhabitants are commonly called 'garden birds' (Ger. Laubenpieper) in the Berliner vernacular. The term is an endearment, not an insult.

His blood pressure was 115/60 mmHg, heart rate 96/min, respiratory rate 36/min, body weight 94 kg, and height 180 cm. The neck veins were distended, there were rales at both bases, the heart sounds could not be distinguished, the abdomen was distended and bowel sounds were diminished. Oedema extended to the sacrum. Neurologically, the eye movements were intact and sensory ability was maintained in the lower extremities. The emergency department’s blood gas analyser provided the initial information. The haemoglobin was 13 g/dl, haematocrit 38 vol%, pH 7.3, \( \text{PaCO}_2 20 \text{ mmHg} \), \( \text{PaO}_2 105 \text{ mmHg} \), \( \text{HCO}_3^- 10 \text{ mmol/l} \). Na 123, K 6.1, Cl 87, glucose 5.6 and lactate 14 (all mmol/l). The admission electrocardiogram is shown in Figure 1.

Are life-threatening features present?
Clinically the patient had severe congestive heart failure with neck vein distension, bibasilar rales and anasarca. He was awake, communicative, not hypoxaemic and not in shock. The circulation appeared hyperdynamic with a widened pulse pressure. The \( \text{PaCO}_2 \) of 20 mmHg and \( \text{PaO}_2 \) of 105 mmHg allowed the quick calculation of an alveolar arterial oxygen gradient from the abbreviated alveolar gas equation (sea level): \( \text{PaO}_2 = 150 \text{ mmHg} - 1.25 \text{PaCO}_2 = 125 \text{ mmHg} \). The \( \text{PaO}_2 \) was 105 mmHg. Thus, the \( \text{PaO}_2 \) to \( \text{PaCO}_2 \) gradient was 20 mmHg, a value only modestly elevated. Death from acute pulmonary oedema or respiratory failure was unlikely in this patient. The low pH in the face of a low \( \text{PaCO}_2 \) and low \( \text{HCO}_3^- \) pointed to a metabolic acidosis. The \( \text{HCO}_3^- \) was reduced by 15 mmol/l; however, the \( \text{PaCO}_2 \) was reduced by 20 mmHg. Wiederseiner et al. recently showed that in acute metabolic acidosis, for every mmol/l decrease in \( \text{HCO}_3^- \), the \( \text{PaCO}_2 \) decreased by 0.85 mmHg [1]. For clinical purposes, a relationship of 1:1 is reasonable. In our patient, the metabolic
Acidosis was slightly ‘overcompensated’. The anion gap \((\text{Na} - \text{Cl} - \text{HCO}_3^-) = 26\text{ mmol/l (normal } 12 \pm 2\text{ mmol/l)}\) was increased by 14 mmol/l. The lactate level was elevated by 13 mmol/l, precisely mirroring the increase in anion gap and decrease in HCO_3^- concentrations. The lactic acidosis was impressive, but since shock was not present probably not lethal. The electrocardiogram revealed a sinus rhythm with a PR interval at the very upper limits of normal. The axis was shifted rightward at \(137^\circ\). The QRS interval was prolonged at 150 ms. The terminal QRS vector was directed right and anterior, indicating a right bundle branch block. The T waves were abnormal but not typically tented. The admitting physician diagnosed hyperkalaemia.

**Are initial therapeutic steps required now?**

Hyperkalaemia warrants prompt treatment. The options available are infusions of glucose and insulin, calcium, bicarbonate or \(\beta\)-adrenergic agonists. Alternatively, a potassium-binding resin could be considered. A sodium bicarbonate infusion might have appeal in this patient with a HCO_3^- of 10 mol/l and hyperkalaemia, with the thought that metabolic acidosis and hyperkalaemia could be combated simultaneously. In a randomized prospective trial, bicarbonate was hardly effective in lowering the serum potassium concentration [2]. Instead, the admitting physicians selected a calcium gluconate infusion followed by glucose and insulin infusion [3]. The blood gas analyser had measured the ionized Ca concentration, which was low-normal at 1.13 mmol/l. Calcium gluconate and calcium chloride are highly effective and offer protection in minutes. Profound hypocalcaemia in the face of metabolic acidosis and hyperkalaemia has been described as a sequel to citric acid ingestion [4]. In that particular patient, a calcium infusion was life saving. With resolution of hyperkalaemia, the PR interval decreased to 136 ms, the QRS interval normalized at 116 ms, the axis shifted to a normal \(-15^\circ\), but an incomplete right bundle branch block persisted.

The platelet count was normal. The leukocytes numbered 16,000/\(\mu\)m\(^3\). The D dimer value was 0.48 mg/dl. Troponin T was 0.05 \(\mu\)g/l. The physicians performed echocardiography and the pulmonary artery pressure was not inordinately elevated. The international normalized ratio (INR) was 1.48 and the aPTT was >180 s. ALAT was 60 U/l, ASAT was 107 U/l and total bilirubin was 47 \(\mu\)mol/l. The creatinine concentration was 243 \(\mu\)mol/l, while the urea concentration was 19 mmol/l. The serum osmolality was 287 mosm/kg H_2O. Ethanol levels were zero. A urinary catheter had been placed and a urinalysis was done, revealing a specific gravity of 1.030, pH 5, protein 1.5 g/l and ketones <0.5 mmol/l. The urine Na concentration was 10 mmol/l, the Cl was 15 mmol/l and the K was 65 mmol/l.

The physicians calculated the serum osmolarity from the laboratory values, \(2(\text{Na} + \text{K}) + \text{glucose} + \text{urea},\) which yielded \(2(129) + 5.6 + 19 = 283\), only 4 mmosm/l lower than the measured osmolality. Ethanol is the most common cause of an ‘osmolar gap’. With no osmolar gap, the physicians were comfortable that the patient had not ingested methanol or ethylene glycol. Both are associated with elevated lactate levels, albeit not to this degree. The lack of ketones in the urine and the absence of uraemia eliminated two other causes of anion gap metabolic acidosis. The patient could have conceivably ingested aspirin since he had some respiratory alkalosis accompanying his metabolic acidosis. Lactate levels can be elevated in aspirin poisoning. However, that possibility was exceedingly remote. The sum of UNa^+ and UK^+ was 75 mmol/l, less than the serum Na^+ concentration. Thus, the physicians knew that the effective free water clearance...
had to be positive and that the hyponatraemia would improve.

What was driving this lactic acidosis?

The patient’s oxygen saturation was normal. The physicians placed a pulmonary artery catheter for detailed measurements and found the following at a systemic pressure of 118/46 mmHg: central venous pressure 28 mmHg, pulmonary capillary wedge pressure 22 mmHg, cardiac output 91/min, systemic vascular resistance 336 dyn/cm². The patient’s arterial oxygen content at a saturation of 100% was: 1.34 × Hb = 17.4 ml/dl or 174 ml/l. The oxygen delivery (DO₂) was 174 ml/l × 91/min or 1566 ml/min, a generous amount. The mixed venous PvO₂ was 63 mmHg with a saturation of 90%. Thus, the oxygen content of mixed venous blood was 15.6 ml/dl or 156 ml/l. The oxygen uptake (VO₂) can be calculated from the relationship: VO₂ = DO₂ × (SaO₂ – SvO₂) or = 156.6 ml/min. The oxygen extraction ratio was calculated from O₂ER = VO₂/DO₂ × 100 and revealed a value of only 10%. The normal O₂ER is 20–30% and our patient’s value was sharply reduced. The pulmonary artery catheter confirmed the presence of a ‘high output’ form of heart failure (filling pressures were markedly increased while cardiac output was also increased) with a hyperdynamic circulation (peripheral vascular resistance was markedly reduced with high pulse pressures). The oxygen delivery was high while consumption was reduced in the face of an elevated mixed venous PvO₂ (normal 40 mmHg with saturation at 75%). Either systemic shunts were present, oxygen uptake was sharply reduced or both in this patient. In any event, the lactic acidosis was not being driven by oxygen deprivation or tissue hypoxia.

How else can oxidative phosphorylation be inhibited?

Oxidative phosphorylation can be inhibited at many stages. Our main considerations are outlined in Figure 2. Pyruvate dehydrogenase complex can be inhibited by endotoxin, which can produce lactic acidosis without shock. We considered this possibility; however, blood cultures were negative, we had no infection source, and our patient did not have the acquired immune deficiency syndrome. The electron flow in cytochrome c oxidase can be blocked by cyanide, azide and carbon monoxide. These possibilities were excluded in our patient. The tight coupling of electron transport and phosphorylation in mitochondria can be disrupted by 2,4-dinitrophenol and certain other acidic aromatic compounds. Our patient had not received metformin and had not been exposed to atracyloside (a plant glycoside) or bongkrekic acid (an antibiotic from a mould) to our knowledge. He did not suffer from defects in uncoupling proteins or mitochondrial genes. We were left with something far more common.

What is your best diagnosis?

The normal vitamin B1 (thiamine) level for our laboratory is 28–85 µg/l. Our patient’s value was 22 µg/l, which was not zero but very consistent with a patient described with wet beriberi in a recent publication [5]. We gave our patient intravenous thiamine shortly after admission and, within ~12 h, his acidosis was gone and his lactate level had returned to normal (1 mmol/l). The signs of heart and renal failure rapidly abated and the patient was transferred to the ward. Shortly thereafter, the patient left the hospital against medical advice.

We believe our patient had wet beriberi, a disorder caused by thiamine deficiency. Beriberi is occasionally seen in alcoholics. Thiamine pyrophosphate is the prosthetic group of three important enzymes: pyruvate dehydrogenase, α-ketoglutarate dehydrogenase and transketolase. The transketolase levels in erythrocytes are reduced in beriberi and would have been a reliable diagnostic indicator in our patient. Rice, the major food in the Far East, has a rather low thiamine content that is reduced even further when the skin is removed. Jacob Bonitus, a Dutch physician working in Java,
first described the disease in 1630. Christiaan Eijkman was awarded the 1929 Nobel Prize in Physiology or Medicine for first identifying a substance in rice skin, which was later to be known as vitamin B1.

**Teaching points**

- Lactic acidosis without shock points to endotoxin, thiamine and other uncouplers.
- The value of invasive intensive care unit monitoring extends far beyond pressure measurements and lies instead in determining oxygen delivery and utilization.

*Conflict of interest statement.* None declared.

**References**


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