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Status Asthmaticus and Lactic Acidosis
Is There a Toxicologic Link?

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A young man with status asthmaticus has an elevated lactate concentration. What steps should be taken to determine the cause of hyperlactatemia, and how should he be treated?

An 18-year-old man with a history of severe asthma is brought to the emergency department by ambulance for status asthmaticus. Despite multiple treatments with nebulized albuterol administered by the paramedics, the patient is unable to speak due to severe dyspnea. His pulse oximeter reads 81% on high-flow oxygen. He appears distressed, and despite aggressive treatment, he continues to worsen and requires intubation.

The patient is admitted to the intensive care unit, where he continues to receive multiple therapies for his severe asthma. Ten hours after intubation, the critical care team reports his vital signs as follows: blood pressure, 131/46 mm Hg; heart rate, 138 beats/min; respiratory rate, 18 breaths/min; and temperature, 99.1°F. His oxygen saturation is 100%. On physical examination, he is sedated and intubated. His cardiac exam reveals a regular tachycardic rhythm. On auscultation, there is poor air movement and wheezing in all lung fields. His abdomen is soft, with normal bowel sounds.

On laboratory evaluation, the patient is noted to have a rising arterial serum lactic acid concentration, which is now 8 mmol/L (normal range, 0.6-1.7 mmol/L). Laboratory data are significant for a pH of 7.18 with a P_{CO_2} of 57 mm Hg; his serum bicarbonate level is 20 mEq/L, and his anion gap is 20 mEq/L.

What causes an elevated lactate concentration?

There are several routes of lactate production, and the term *lactic acidosis* is frequently used. However, a metabolic acidosis with an elevated lactate concentration typically is associated with an impairment of oxidative metabolism, resulting in the net production of hydrogen ion through the failure to synthesize adenosine triphosphate (ATP) in the mitochondria. Elevated lactate levels can also occur without mitochondrial failure, however, in patients with good tissue perfusion and tissue oxygenation.

Dividing potential causes of hyperlactatemia into two etiologies facilitates understanding and appropriate work-up. *Type A lactic acidosis* is traditionally thought to be the result of hypoxia from either poor perfusion or poor oxygen delivery. A common example is a patient with severe septic shock and hypotension, resulting in impaired tissue perfusion and oxygen utilization. (See the Table for other common examples). These patients usually have clinical signs of poor tissue perfusion, such as hypotension, cyanosis, or peripheral vasoconstriction.

Type B lactic acidosis tends to be more complex and results from nonhypoxic causes. This type may occur in the setting of an underlying disease, such as an inborn error of metabolism, or it may be toxicologic in origin.[1,2] Many nonhypoxic causes, such as ketoacidosis, are the result of an alteration in the NADH/NAD ratio in the face of other causes of metabolic acidosis.

Which medications used to treat asthma can cause an elevated lactate concentration?

Asthma is a complex disease with both a bronchospas-

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Cover Images: Radiograph of an asthma attack: BSIP/Photo Researchers, Inc.; Bronchodilator drug crystals, SEM: David McCarthy/Photo Researchers, Inc.

tic and an inflammatory component. The typical treatment strategy relies on aggressive bronchodilator therapy, followed by anti-inflammatory agents. The bronchodilators most commonly used are β_2-adrenergic agonists, such as albuterol, and occasionally theophylline is used (though much less commonly than in the past).

Methylxanthines are a class of agents that includes theophylline and caffeine. Several distinct mechanisms of action of methylxanthines have been identified. They antagonize adenosine receptors, resulting in bronchodilation, and also stimulate the release of endogenous catecholamines, specifically norepinephrine and epinephrine. Antagonism of adenosine, an inhibitory neurotransmitter, accounts for the sympathomimetic and convulsant effects of this drug class. In addition, methylxanthines, which are structural analogs of adenosine, inhibit phosphodiesterase at supratherapeutic concentrations. The result of inhibition of this enzyme is an increase in cAMP (cyclic adenosine monophosphate), a second messenger involved in adrenergic stimulation.

Medications with β-adrenergic effects can, by themselves, cause elevated serum lactate concentrations. There have been many case reports in which β agonists, such as albuterol or salbutamol, caused transiently elevated lactate concentrations, which can be as high as 10 mmol/L.[3,4]

The increased β_2-adrenergic stimulation causes smooth muscle relaxation, peripheral vasodilation, and excitability.[5] Note that this is distinct from the effects of sympathomimetics (also α-adrenergic agonists), which produce potent vasoconstriction. While the exact mechanism of elevated lactate levels in a patient with profound β_2 agonism is not known, several mechanisms are postulated. One of the most commonly cited mechanisms is the increased efflux of lactate from the skeletal muscle due to increased glycogenolysis and glycolysis from increased sympathetic stimulation (β_2-agonist effects). Muscle biopsies from healthy volunteers who received infusions of the β agonist epinephrine showed decreased amounts of glycogen during the infusions.[6]

Table
Classification of Metabolic Acidosis with Elevated Lactate

Hypoxic (Type A)	Nonhypoxic (Type B)
Increased anaerobic activity (seizures or extreme physical action)	Underlying illnesses (renal or hepatic dysfunction, short bowel syndrome, infection)
Global hypoxia (shock, respiratory failure)	Inborn errors of metabolism (pyruvate dehydrogenase deficiency, glycogen storage disease)
Regional hypoperfusion (mesenteric ischemia, limb ischemia)	Acquired metabolic errors (thiamine deficiency, alcoholic or diabetic ketoacidosis)
Functional hypoxia by altering oxygen-carrying capacity or oxygen delivery*(carbon monoxide, methemoglobin)	Accelerated aerobic glycogenolysis and glycolysis (catecholamine excess)*
	Mitochondrial toxins (cyanide, carbon monoxide, salicylates, antiretroviral drugs, metformin)

*May account for the effects of extreme β_2-adrenergic agonism

Another potential cause of increased plasma lactate concentration in a patient with excessive β_2-agonist stimulation is poor oxygen extraction from a functionally shunted capillary bed. The development of the low-resistance circuit due to arteriolar dilation allows blood to traverse the capillary bed without adequate time for oxygen extraction, resulting in tissue hypoxia and venous hyperoxia. On physical examination, vital signs may show a widened pulse pressure due to β_2-receptor–mediated vasodilation and enhanced inotropy, reflected by the reduced diastolic and elevated systolic blood pressures, respectively. This constellation of symptoms was seen during an outbreak of exposures to clenbuterol-tainted heroin.[7] Clenbuterol is a long-acting β_2 and β_3 agonist that is used medically to treat asthma in some countries. Bodybuilders have ingested it, and ranchers have used it on cattle, both illicitly, for its purported lipolytic and anabolic effects. In a 2005 epidemic, treating physicians were concerned about possible cyanide poisoning in a cluster of intravenous drug users presenting with hypotension, profound hyperlactatemia, and venous hyperoxia. Before providers identified the causative agent as

clenbuterol, cyanide antidote was administered without significant improvement.[7]

What other medications or toxins can cause hyperlactatemia?

Many toxins and medications cause elevated lactic acid concentrations. Convulsions are among the most common causes of an elevated lactate concentration, whether they are toxicologic or not. The lactic acidosis is a result of increased anaerobic metabolism due to motor movement in the setting of hypoxemia from respiratory failure during the event. The lactate is expected to clear quickly once the seizure terminates, as the liver converts the lactate to pyruvate to glucose (Cori cycle).

Another important group of toxins that cause an elevated lactate concentration are those that specifically poison the mitochondria. Mitochondrial toxins inhibit oxidative phosphorylation through various mechanisms. These toxins are also called *chemical asphyxiants* since they inhibit aerobic metabolism and stop the production of ATP. To continue the production of ATP and the regeneration of NAD^+ (nicotinamide adenine dinucleotide), pyruvate is converted to lactate via the anaerobic glycolysis. Following mitochondrial failure, diffuse cellular dysfunction can cause death. Examples of potent mitochondrial toxins include cyanide, carbon monoxide, hydrogen sulfide, and sodium azide.[8] In 2010, a restaurant in Dallas, Texas, served customers iced tea that was contaminated with sodium azide.[9] Moments after drinking the tea, all of the patrons developed diaphoresis and vomiting, and most of them developed hypotension (which is also an effect of azide itself). All of the patients were transported to the emergency department and survived.

Cyanide is a particularly potent mitochondrial toxin, and death occurs moments to minutes after exposure without antidotal therapy. Former Wall Street trader Michael Marin recently committed suicide by ingesting cyanide immediately after he was convicted of arson. Minutes after discreetly swallowing the poison in an Arizona courtroom, he collapsed and died. Salicylates, on the other hand, uncouple oxidative phosphorylation, which slows ATP production but does not halt it, and is sometimes accompanied by an elevated lactic acid concentration in severe salicylate poisoning.

Medications or toxins that cause methemoglobinemia, carboxyhemoglobinemia, or sulfhemoglobinemia can also be considered chemical asphyxiants, although they inhibit aerobic metabolism by either altering the oxygen-carrying capacity or oxygen-unloading ability of hemoglobin. This produces a functional hypoxia in which the circulating blood cells are normal in number but do not function properly. Carbon monoxide also functions like cyanide at the mitochondrial level.

The biguanide antidiabetic medication metformin causes hyperlactatemia via several mechanisms, including interference with oxidative metabolism and suppression of hepatic gluconeogenesis from pyruvate.[10]

Administration of lactate or agents that are metabolized to lactate may cause hyperlactatemia. Propylene glycol, found as an intravenous medication diluent and in "environmentally friendly antifreeze," is metabolized to lactate. The liver should be able to convert this excessive lactate to pyruvate, but this mechanism may be overwhelmed or poorly functional. This may occur in sick patients given large amounts of propylene glycol in medications such as lorazepam for sedation while intubated.

Occasionally, lactate elevations detected by the laboratory are actually false-positives. In ethylene glycol poisoning, some laboratories will report an elevated lactate level when in fact the laboratory analyzer is measuring glycolic acid, a metabolite of ethylene glycol. These laboratory analyzers use the enzyme lactate oxidase to detect lactate. However, glycolic acid cross-reacts with the enzyme, resulting in a false-positive lactate level that is proportional to the amount of glycolic acid present.[11]

Should this patient be given sodium bicarbonate?

There is no clear evidence that administration of intravenous sodium bicarbonate to patients with metabolic acidosis and an elevated lactate concentration results in any significant improvement in mortality or morbidity. Those who advocate use of intravenous sodium bicarbonate believe that a low pH is harmful and capable of causing end-organ dysfunction. Although acidosis may increase the potential for dysrhythmia,[1] it is important to consider that a low blood pH may not be reflective of organ, cellular, or organelle pH. Acidemia also causes decreased cardiac responsiveness to sympathetic stimulation by decreasing the number of available β receptors. This potentially decreases the effectiveness of catechol-

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amines and the ability to resuscitate patients with cardiac dysrhythmias or dysfunction.[12] However, despite increased pH and serum bicarbonate concentrations in studied patients who received sodium bicarbonate for acidemia, no benefit to catecholamine response has been demonstrated.[12]

Additionally, sodium bicarbonate can potentially cause adverse effects, such as fluid overload, electrolyte abnormalities, hyperosmolality, increase in intracranial pressure, paradoxical central nervous system acidosis, and metabolic alkalemia, worsening oxygen delivery.[1,12] Current opinion is that sodium bicarbonate administration to acidemic patients with sepsis may actually worsen outcome. [13]

Case Conclusion

Over the course of the next day, the patient's respiratory status improved and albuterol nebulizations and theophylline administration were tapered off. As these medications were weaned, the patient's serum lactate concentrations and clinical status normalized. **EM**

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