CASE REPORT

Inhaled β -agonist therapy and respiratory muscle fatigue as under-recognised causes of lactic acidosis

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SUMMARY

A 49-year-old man with chronic obstructive pulmonary disease (COPD) presented with significant tachypnoea, fevers, productive cough and increased work of breathing for the previous 4 days. Laboratory data showed elevated lactate of 3.2 mEq/L. Continuous inhaled ipratropium and albuterol nebuliser treatments were administered. Lactate levels increased to 5.5 and 3.9 mEq/L, at 6 and 12 h, respectively. No infectious source was found and the lactic acidosis cleared as the patient improved. The lactic acidosis was determined to be secondary to respiratory muscle fatigue and inhaled β -agonist therapy, two under-recognised causes of lactic acidosis in patients presenting with respiratory distress. Lactic acidosis is commonly used as a clinical marker for sepsis and shock, but in the absence of tissue hypoperfusion and severe hypoxia, alternative aetiologies for elevated levels should be sought to avoid unnecessary and potentially harmful medical interventions.

BACKGROUND

Lactic acidosis is a common marker of tissue hypoperfusion and hypoxia, most frequently associated with sepsis and systemic shock.¹ Two commonly overlooked aetiologies of lactic acidosis in patients presenting with respiratory distress are lactate production from respiratory muscle fatigue and inhaled β -agonist therapy targeted at improving respiratory symptoms.²

CASE PRESENTATION

A 49-year-old man with a history of severe chronic obstructive pulmonary disease (COPD) and obstructive sleep apnoea status post-tracheostomy placement presents to the emergency department with 4 days of progressive tachypnoea, subjective fevers, productive cough and increased work of breathing. On examination, he was afebrile and haemodynamically stable, but visibly tachypnoeic with a respiratory rate of 40/min and an oxygen saturation of 98% on 28% oxygen through tracheostomy mask.

INVESTIGATIONS

Initial laboratory data revealed a bicarbonate level of 24 mEq/L with an anion gap of 15 mEq/L, normal white cell count (WCC) 9.8, and an elevated lactate 3.2 mEq/L (normal reference range 0.3–2.2 mEq/L). Venous blood pH showed 7.42 and a pCO₂ 44 mmHg. Chest X-ray revealed cardiomegaly, but no acute pulmonary process (figure 1). Blood and urine cultures showed no growth.

DIFFERENTIAL DIAGNOSIS

The causes of lactic acidosis are extensive and can be classified as either type A or B (box 1).

Type A lactic acidosis is associated with tissue hypoperfusion and systemic shock; in the presence of impaired oxygen delivery, aerobic metabolism is impaired, resulting in increased conversion of pyruvate to lactate through anaerobic glycolysis. Precipitants include sepsis, cardiac failure, hypovolaemia and complete cardiopulmonary arrest.^{3–4} In cases of sepsis and shock, elevated lactate is an important clinical marker of increased mortality and disease severity.⁵

Alternatively, type B lactic acidosis is a result of altered cellular function, in the absence of tissue hypoperfusion or hypoxia, either due to increased flux of pyruvate to lactate rather than through the Krebs cycle or decreased lactate metabolism.⁵ Conditions associated with type B lactic acidosis include inborn errors of metabolism, systemic disorders including liver and kidney dysfunction, haematological malignancy and adverse effects of medications (biguanides, nucleoside reverse transcriptase inhibitors and ethanol).^{5–6} Recently, β -agonist therapy used in the treatment of preterm labour and asthma has also been implicated.⁷ Finally, fatiguing skeletal muscle from excessive exercise is a well-known but often overlooked trigger.⁸

TREATMENT

A presumptive diagnosis of COPD exacerbation was made. The patient was admitted to the intensive care unit for concern for sepsis in the setting of an elevated lactate, worsening tachypnoea and

Figure 1 X-ray of the patient on presentation showing no acute cardiopulmonary process. A tracheostomy tube is present.

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Box 1 Causes of lactic acidosis. Modified from Dodd and Spiro.²**Type A lactic acidosis**

Global hypoxia
 Hypoperfusion/ischaemia/shock
 Local ischaemia
 Severe asthma or chronic obstructive pulmonary disease
 Cardiopulmonary arrest
 Carbon monoxide poisoning

Type B lactic acidosis

Drugs
 Metformin
 Catecholamines
 Isonicotinylhydrazine
 Ethylene glycol
 Salicylates
 Nucleoside reverse transcriptase inhibitors
 Alcoholic and diabetic ketoacidosis
 Thiamine deficiency
 Large fructose loads
 Increased muscular effort
 Renal/hepatic failure
 Inborn errors of metabolism (pyruvate dehydrogenase deficiency)
 Malignancy
 Seizures
 Cyanide poisoning

increased work of breathing, although no infectious aetiology was ascertained. The patient received ipratropium and albuterol nebuliser treatments every 4 h with improvement in his respiratory symptoms.

OUTCOME AND FOLLOW-UP

Throughout his hospitalisation, the patient remained afebrile, WCC count remained normal, and all blood and urine cultures were negative for infection. Repeat lactate levels, 6 and 12 h later, were increased to 5.5 and 3.9, respectively. In the setting of a negative infectious workup and continued haemodynamic stability, lactic acidosis was determined to be secondary to respiratory muscle fatigue and inhaled β -agonist therapy. Ultimately, the patient's tachypnoea and work of breathing improved, and he was discharged home.

DISCUSSION

Lactic acidosis in the setting of asthma and COPD exacerbations, as presented in this case, should warrant careful search for infectious source and sepsis. However, in the presence of continued haemodynamic stability and negative infectious workup, alternative aetiologies including respiratory muscle fatigue and medication effect should be considered to avoid unnecessary and potentially harmful medical interventions.

Fatiguing respiratory muscles has long been recognised as a cause of lactic acidosis in patients with obstructive lung diseases, but little evidence is available regarding the relative contribution of respiratory muscles to lactic acidosis.⁸ There has been indirect evidence to suggest that exercising respiratory muscles are capable of producing lactic acid sufficient to alter blood lactate levels in both normal patients working against sustained

maximal voluntary ventilation⁹ and patients with airflow obstruction in respiratory distress.¹⁰ However only modest elevations of serum lactate levels have been observed in these studies, which underscores that the pathogenesis of lactic acidosis in patients with respiratory distress is multifactorial.

Importantly, the use of β -adrenergic therapy targeted at improving respiratory symptoms is a significant factor contributing to lactic acidosis. Several case reports have documented the link between β -agonist therapy and lactic acidosis in the absence of tissue hypoperfusion or hypoxia in acute asthma and in tocolysis for premature labour.^{7–11} While reports have more consistently described elevated lactate from intravenous β -agonist therapy,^{7–12–13} there have been a few reports of inhaled β -agonist therapy linked to lactic acidosis in the absence of hypoxia.^{14–16} Stimulation of β -adrenergic receptors is hypothesised to increase lipolysis, producing free fatty acids which inhibit conversion of pyruvate to coenzyme A. Similarly, catecholamines stimulate glycolysis and glycogenolysis, increasing pyruvate generation and overwhelming oxidative metabolism. Consequently, increased pyruvate is shunted through anaerobic glycolysis, producing increased lactate.¹⁷

In this case, we believe that excessive respiratory muscle activity contributed to the elevated lactate level found on admission, but the further increase in lactate levels was likely due to the increased doses of inhaled β -agonist therapy. The patient's lactate level later improved with decreased doses of β -agonist therapy although his symptoms had improved long before resolution of the lactic acidosis.

Lactic acidosis secondary to respiratory muscle fatigue and inhaled β -agonist therapy are two common scenarios in patients presenting in acute respiratory distress that can complicate the clinical evaluation of patients with acute COPD exacerbations.

Learning points

- ▶ Type B lactic acidosis occurs in the absence of tissue hypoperfusion and hypoxia.
- ▶ Respiratory muscle fatigue and β -agonist therapy are two under-recognised causes of lactic acidosis that can complicate clinical evaluation and management of patients with acute chronic obstructive pulmonary disease exacerbations.
- ▶ In the absence of tissue hypoperfusion and severe hypoxia, consider alternative aetiologies for elevated lactate levels.

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Competing interests None.

Patient consent Obtained.

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