

Take my breath away: a case of lactic acidosis in an asthma exacerbation

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ABSTRACT

A 36-year-old male with a history of chronic asthma presented to an emergency department with shortness of breath consistent with an asthma exacerbation. He had persistent tachypnea following inhaled bronchodilator treatment; thus, the workup and differential diagnosis were expanded. He was found to have a mixed respiratory alkalosis and metabolic acidosis with elevated serum lactate without an obvious cause and was admitted to hospital. His case was reviewed, and the lactic acidosis was thought to be caused by inhaled β_2 -agonist use. Emergency physicians should be aware of the potential side effects of inhaled β_2 -agonists as lactic acidosis may complicate clinical assessment and management of asthma exacerbations and lead to unnecessary and potentially dangerous escalations in therapy.

RÉSUMÉ

Un patient de sexe masculin de 36 ans ayant de antécédents d'asthme chronique s'est présenté aux urgences et affichait des difficultés respiratoires compatibles avec une aggravation de l'asthme. Il présentait une tachypnée persistante à la suite d'un traitement au bronchodilatateur en inhalation; ainsi, le bilan et le diagnostic différentiel ont été élargis. Il s'est avéré qu'il avait une alcalose respiratoire et une acidose métabolique mixte accompagnée d'une élévation de lactates sériques sans cause évidente, et il fut admis à l'hôpital. Son cas fut examiné, et on a établi que l'acidose lactique était due à l'emploi d'un agoniste β_2 en inhalation. Les urgentologues devraient être au courant des effets secondaires possibles des agonistes β_2 inhalés, car l'acidose lactique peut compliquer l'évaluation clinique, et la prise en charge de l'aggravation de l'asthme, et conduire à une augmentation inutile et potentiellement dangereuse du traitement.

Keywords: asthma, β_2 -agonist, lactic acidosis, metabolic acidosis, salbutamol

Asthma is a common emergency department (ED) presentation, treated in most cases with corticosteroids, salbutamol, and ipratropium bromide (IB).¹⁻³ This case report describes a mild to moderate asthma exacerbation complicated by lactic acidosis and respiratory alkalosis. Although arterial blood gas (ABG) abnormalities are not uncommon in asthma exacerbations in the ED, elevated serum lactate is less common, particularly in mild presentations. We review the literature surrounding elevated lactate associated with asthma exacerbations and discuss the potential etiologies of this association, including the underrecognized complications of inhaled β_2 -agonist therapy.

CASE REPORT

A 36-year-old male with a history of asthma arrived via ambulance at an ED at 12:35 with a chief complaint of shortness of breath. His vital signs at triage were temperature = 36.2°C (97.1°F); heart rate = 108 beats/min; blood pressure = 137/74 mm Hg; respiratory rate = 28 breaths/min; and O₂ saturation = 99% on room air. He was triaged as a CTAS (Canadian Triage and Assessment Scale) level 4.

He described a 4-day history of progressive worsening shortness of breath associated with productive cough, fever and chills, and intermittent chest pains. The patient had been using a salbutamol metered-dose inhaler three to four puffs four times per day for several days. His past medical history was significant for chronic asthma and allergic rhinitis, for which he

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normally used salbutamol three times per week and fluticasone 3 days per week, although he ran out of his inhaled corticosteroid several weeks earlier. Two months earlier, he presented to an ED with a mild asthma exacerbation; however, no investigations were performed, and he received no treatment. He reported having asthma for 8 to 9 years and denied previous hospitalizations for any asthma exacerbations. He admitted to being a 60-pack-year cigarette smoker who quit 5 years previously. Neither spirometry nor pulmonary function testing had ever been performed.

His stated medical history included chronic back pain and anxiety, and his hospital chart reported bipolar affective disorder. He had no thromboembolic risk factors. He denied any substance abuse. His other medications included diclofenac 75 mg daily, quetiapine 75 mg as needed (PRN) at night, and acetaminophen PRN.

On examination at 13:25, the patient was in mild to moderate respiratory distress with a respiratory rate of 28 breaths/min. He had wheezes bilaterally. His cardiovascular and abdominal examinations were normal. His peak flow with suboptimal technique was 270 L/min prior to any treatment (43% of predicted).

Salbutamol 2.5 mg and IB 250 µg were administered via nebulization by staff prior to physician assessment; no treatment was given earlier by the ambulance staff. Salbutamol 5 mg and IB 500 µg were nebulized every 20 minutes for three doses, and 50 mg oral prednisone was administered. No investigations were initially ordered.

At 16:30, his O₂ saturation was 96% on room air and his wheeze had resolved; however, his respiratory rate remained at 28 to 30 breaths/min. The patient felt slightly better but still complained of shortness of breath. Investigations including ABG, chest radiography, and electrocardiography (ECG) were ordered. Additional doses of salbutamol and IB were ordered, as well as 2 g IV MgSO₄ and 250 mg oral clarithromycin. A total of 22.5 mg of nebulized salbutamol was

administered in the ED prior to blood work and an ABG being drawn.

The initial laboratory investigations at 17:42 were as follows: hemoglobin 153 g/L, white blood cell count $8.95 \times 10^9/L$ with neutrophils $8.01 \times 10^9/L$, platelets $240 \times 10^9/L$, international normalized ratio 1.1, partial thromboplastin time 35 seconds, sodium 139 mmol/L, chloride 103 mmol/L, CO₂ 20 mmol/L, potassium 2.8 mmol/L, glucose 11.1 mmol/L, creatinine 101 µmol/L, and anion gap 16.

The chest radiograph revealed normal lung volumes with prominent bilateral perihilar thickening, compatible with lower airway inflammation.

The ECG showed normal sinus rhythm at a rate of 87, right axis deviation, early transition in the precordial leads, borderline right ventricular hypertrophy, and incomplete right bundle branch block.

The ABG showed a mixed acid-base disturbance with pH of 7.44, oxygen partial pressure (pO₂) 76 mm Hg, carbon dioxide partial pressure (pCO₂) 27 mm Hg, bicarbonate 18 mmol/L, and lactate 5.3 mmol/L (Table 1). Based on the elevated lactate, antibiotic coverage was broadened to cefotaxime 1 g IV for possible occult sepsis. In the presence of both a primary metabolic acidosis and a primary respiratory alkalosis (based on an expected pCO₂ of 35 mm Hg), acetylsalicylic acid (ASA) toxicity was suspected, and an IV bicarbonate infusion with potassium supplementation was initiated at 18:45. Additional blood work and a repeat ABG were ordered. Internal Medicine was consulted for further workup.

At 20:15, he was afebrile, with a heart rate of 98 beats/min, O₂ saturation of 98% on room air, and respiratory rate of 24 to 30 breaths/min. He appeared anxious and had difficulty speaking in complete sentences. Respiratory examination revealed minimal wheeze with good air entry bilaterally. Examinations of the head and neck and cardiovascular, abdominal, dermatologic, and peripheral systems were unremarkable.

Table 1. Serial arterial blood gas results

| Time from ED presentation | pH | pO ₂ (mm Hg) | pCO ₂ (mm Hg) | HCO ₃ ⁻ (mmol/L) | Anion gap | Lactate (mmol/L) | Glucose (mmol/L) |
|---------------------------|------|-------------------------|--------------------------|--|-----------|------------------|------------------|
| 5 h 10 min | 7.44 | 76 | 27 | 18 | 16 | 5.3 | 12.0 |
| 7 h 55 min | 7.48 | 106 | 19 | 14 | 18 | 6.1 | 12.5 |
| 20 h 10 min | 7.53 | 114 | 22 | 19 | 12 | 1.2 | 6.6 |

ED = emergency department; pCO₂ = carbon dioxide partial pressure; pO₂ = oxygen partial pressure.

The repeat ABG demonstrated a worsening of both his metabolic acidosis, with bicarbonate of 14 mmol/L and lactate of 6.1 mmol/L, and his respiratory alkalosis, with pCO₂ of 19 mm Hg (see Table 1). Additional blood work showed aspartate aminotransferase (AST) 35 U/L, creatinine kinase 191 U/L, lipase 36 U/L, troponin < 0.02 µg/L, and salicylate level < 0.03 mmol/L. Blood culture results obtained later revealed no growth.

He was admitted to the medical ward with a diagnosis of asthma exacerbation and lactic acidosis of unknown cause. With ASA being undetectable, his bicarbonate infusion was stopped. His overnight treatment included IV potassium replacement and minimal O₂ supplementation. He received prednisone 50 mg, clarithromycin 250 mg, and diclofenac-misoprostol 75 mg. He had salbutamol 2.5 mg with IB by nebulization at midnight and salbutamol 5 mg at 06:00.

The next morning, the ABG on 1 L O₂ revealed a persistent respiratory alkalosis with pH 7.53 and pCO₂ 22 mm Hg. The bicarbonate increased to 19 mmol/L; the serum lactate and glucose decreased to 1.2 mmol/L and 6.6 mmol/L, respectively (see Table 1). Complete blood count, electrolytes, and renal function values were all within normal limits. No recorded vital signs or physical examination findings were available in the chart from the morning. The patient was discharged home with a prescription for IB inhaler twice a day, clarithromycin for 10 days, and salbutamol PRN. He was instructed to follow up with his family doctor.

DISCUSSION

Shortness of breath owing to asthma exacerbation is among the most common presentations in Canadian EDs. Physician-diagnosed asthma affects approximately 3 million Canadians, and asthma is a major cause of hospitalization, particularly in children.¹ In the United States, there are approximately 1.8 million ED visits annually for acute asthma. In Canada, asthma patients who present to the ED with exacerbations represent a poorly controlled group; 51% report unscheduled visits related to their asthma, and 30% report one or more visits to the ED within the past year.² A recent publication reports that an adult asthmatic visits an ED every 30 minutes in Alberta.³ The total costs of asthma in Canada are over \$1 billion annually, of which approximately one-quarter is related to acute care.⁴ Mortality rates in Canada have fallen

consistently over the past 20 years. In 2001, there were 299 deaths; 5% were children, whereas 62% were adults over 70 years of age.⁵

We present a case of a moderately severe asthma exacerbation with persistent shortness of breath and tachypnea after initial treatment with bronchodilators. Blood gas analysis revealed a mixed acid-base disorder with an elevated lactate. In mild asthma exacerbations, ABGs are not indicated; however, when obtained, the results are either normal or demonstrate a simple respiratory alkalosis. In one study of adults with acute asthma in the ED with more evidence of outflow obstruction and hypoxia than our patient had, isolated respiratory alkalosis was present in almost half of the patients, whereas a mixed metabolic acidosis with respiratory alkalosis was present in only 6.1% of the patients.⁶

Lactic acidosis may be classified as either type A or B. Type A occurs with tissue hypoperfusion; precipitating conditions include systemic shock, carbon monoxide poisoning, or even intense exercise. Type B lactic acidosis is a result of altered cellular function, which either increases the conversion of pyruvate to lactate or decreases lactate metabolism. This may result from inborn errors of metabolism, liver failure, or metabolic changes induced by medications or toxins.

Lactic acidosis has been well described in severe asthma exacerbations in adults and children. Causative hypotheses have included tissue hypoxia, excessive respiratory muscle use, and/or altered liver metabolism; however, it has become increasingly accepted that it is primarily an effect of β₂-agonist use.⁷⁻¹¹ Although the mechanism is not completely understood, β₂-agonists are known to stimulate cyclic adenosine monophosphate (cAMP)-mediated glycogenolysis and lipolysis. Hyperglycemia and free fatty acid inhibition of pyruvate dehydrogenase lead to anaerobic metabolism of pyruvate to lactate.^{9,11,12} Some researchers have postulated that hyperadrenergic states, owing to endogenous catecholamine release secondary to respiratory distress and/or anxiety, and cotreatment with corticosteroids predispose patients to lactic acidosis with the administration of β₂-agonists.^{10,13} β₂-Agonist-induced lactic acidosis has most often been reported in severe asthma exacerbations treated with intravenous therapy; however, there are case reports of patients treated with inhaled therapy alone.^{7,13-19} The prevalence of lactic acidosis has been reported between

16 and 40% in severe asthma exacerbations, more commonly in the intensive care unit setting than in the ED.¹³ It remains unclear, however, if lactic acidosis is a marker of asthma severity in this setting or if it is iatrogenic. One recent ED-based prospective study demonstrated hyperlactatemia shortly following inhaled salbutamol therapy and suggested that it is likely underrecognized in the ED.¹³

Inhaled bronchodilators are a mainstay of ED asthma management regardless of the severity.²⁰ In addition to bronchodilation, commonly seen effects include mild tachycardia and tremor. However, less obvious adverse effects are well documented in the literature and may have a deleterious effect on patient management and outcomes. For emergency physicians, reactive airway disease pathophysiology and medication-induced alterations in cellular metabolism have very real clinical implications. Salbutamol-induced lactic acidosis may complicate clinical assessment and management of asthma exacerbations in the ED. Persistent tachypnea, which usually indicates persistent airway obstruction but may indicate respiratory compensation of metabolic acidosis, commonly leads to increased doses of salbutamol. Increased minute ventilation decreases expiration time and increases dead space, leading to CO₂ retention and decreased cardiac output in severe cases.²¹ Metabolic acidosis and hypokalemia may further contribute to cardiorespiratory decompensation and even failure.

Serum lactate has become a critical screening tool in the ED, especially for sepsis. Rivers's *Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock* used systemic inflammatory response syndrome (SIRS) criteria (including tachycardia and tachypnea, which our patient had on presentation) plus hypotension or a lactate > 4 mmol/L as inclusion criteria.²² Asthmatics are not immune to sepsis, and an elevated lactate puts physicians in a diagnostic and treatment dilemma. As elevated serum lactate is an important marker of tissue hypoxia and hypoperfusion in critically ill patients and a marker of poor prognosis, its presence in an asthma exacerbation requires very careful attention.

CONCLUSION

Our case is an example of lactic acidosis in a relatively moderately severe asthma exacerbation that complicated patient management and disposition. We suspect that the metabolic effects were induced by salbutamol therapy. The presentation and workup did not reveal any other cause for the acidosis. Concomitant hyperglycemia and hypokalemia are consistent with the effects of β_2 -agonists. Finally, the metabolic abnormalities, including the elevated lactate, resolved with decreased salbutamol use and without significant additional intervention. Our patient may have been

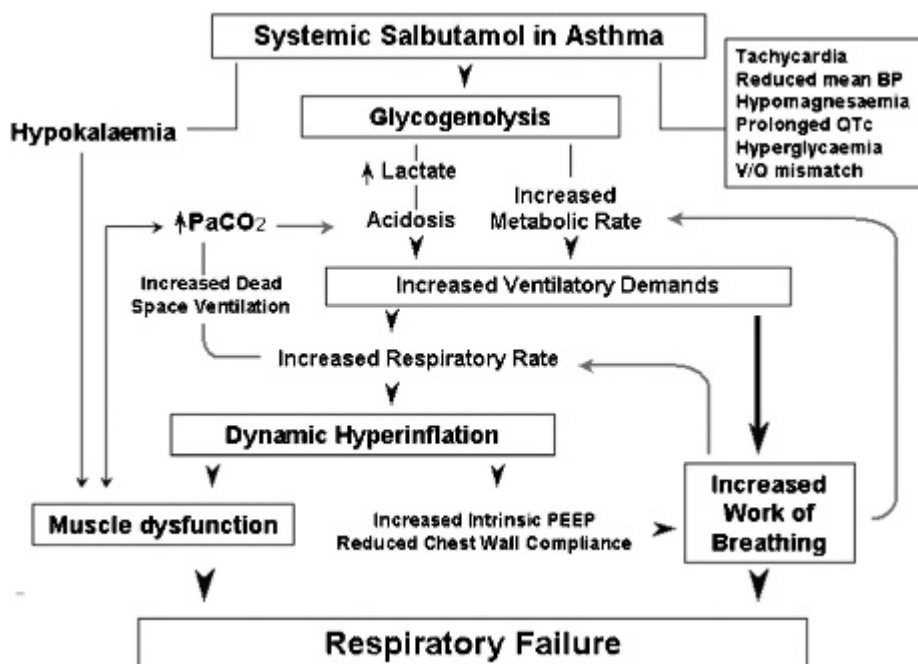


Figure 1. Clinical implications of systemic salbutamol. Reproduced with permission from Tobin A.²¹ PaCO₂ = arterial carbon dioxide tension; PEEP = peak end-expiratory pressure.

sensitive to the effects of salbutamol owing to his anxious state; this may account for the persistent respiratory alkalosis prior to discharge from the ward.

Although β_2 -agonist-induced lactic acidosis has been described, our case is unique in the literature given the severity of the disease and the relatively low doses of exclusively inhaled salbutamol. The existing literature does not offer any evidence-based recommendations for clinicians who may encounter this scenario. Future research should be directed toward identifying which patients may be predisposed to this phenomenon and determining what should be done when there is a clinical need for bronchodilation in an asthma exacerbation complicated by lactic acidosis. Emergency physicians should be aware of the underrecognized potential of inhaled salbutamol to complicate the management of asthma exacerbations.

Competing interests: None declared.

REFERENCES

1. *Life and breath: respiratory disease in Canada*. Ottawa (ON): Public Health Agency of Canada; 2007. Available at: www.phac-aspc.gc.ca/publicat/2007/lbrdc-vsmrc/index-eng.php (accessed Oct 6, 2009).
2. Rowe BH, Villa-Roel C, Abu-Laban RB, et al. Admission to Canadian hospitals for acute asthma: a prospective, multi-center study. *Can Respir J* 2010;17:25-30.
3. Rowe BH, Voaklander DC, Wang D, et al. Asthma presentations by adults to emergency departments in Alberta Canada: a large population-based study. *Chest* 2009; 135:57-65.
4. Kaplan AG, Balter MS, Bell AD, et al. Diagnosis of asthma in adults. *CMAJ* 2009. DOI: 10.1503/cmaj.080006.
5. Chen Y, Johansen H, Thillaiampalam S, et al. Asthma. *Health Rep* 2005;16(2):45-8.
6. Mountain R, Heffner J, Bracjett N, et al. Acid-base disturbances in acute asthma. *Chest* 1990;98:651-5.
7. Manthous CA. Lactic acidosis in status asthmaticus: three cases and review of the literature. *Chest* 2001;119:1599-602.
8. Braden GL, Johnson SS, Germain MJ, et al. Lactic acidosis associated with the therapy of acute bronchospasm. *N Engl J Med* 1985;313:380.
9. Phillips PJ, Vedig AE, Jones MG, et al. Metabolic and cardiovascular side effects of the beta-2 adrenoceptor agonists salbutamol and rimiterol. *Br J Clin Pharmacol* 1980;9:483-91.
10. Maury F, Ioos V, Lepeq B, et al. A paradoxical effect of bronchodilators. *Chest* 1997;111:1766-7.
11. Meert KL, Clark J, Sarnaik AP, et al. Metabolic acidosis as an underlying mechanism of respiratory distress in children with severe acute asthma. *Pediatr Crit Care Med* 2007;8:519-23.
12. Haffner CA, Kendall MJ. Metabolic effects of beta-2 agonists. *J Clin Pharm Ther* 1992;17:155-64.
13. Rodrigo GJ, Rodrigo C. Elevated plasma lactate level associated with high dose inhaled albuterol therapy in acute severe asthma. *Emerg Med J* 2005;22:404-8.
14. Prakash S, Mehta S. Lactic acidosis in asthma: report of two cases and review of the literature. *Can Respir J* 2002;9:203-8.
15. Gomez Bustos MD, Garcia Ron A, Ibarra de la Rosa I, Pérez Navero JL. Lactic acidosis following high-dose inhaled salbutamol. *An Pediatr (Barc)* 2008;69:586-7.
16. Gonzalez Jimenez D, Concha Torre A, Menendez Cuervo S, García Hernández I. Lactic acidosis secondary to inhaled salbutamol in children with acute severe asthma. *An Pediatr (Barc)* 2009;71:82-3.
17. Stratakos G, Kolomenidis J, Routsis C, et al. Transient lactic acidosis as a side effect of inhaled salbutamol. *Chest* 2002; 122:385-6.
18. Creagh-Brown B, Ball J. An under-recognized complication of treatment of acute severe asthma. *Am J Emerg Med* 2008; 26:514.e1-3.
19. Jee R, Brownlow H. Hyperlactaemia due to nebulised salbutamol. *Anaesthesia* 2007;62:744-55.
20. Hodder R, Lougheed D, Rowe BH, et al. Management of acute asthma in adults in the emergency department: nonventilatory management. *CMAJ* 2010;182:E55-67.
21. Tobin A. Intravenous salbutamol: too much of a good thing? *Crit Care Resusc* 2005;7:119-27.
22. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368-77.