

Lactic acidosis in asthma: Report of two cases and review of the literature

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Lactic acidosis is commonly associated with states of hypoxia and decreased tissue perfusion. Elevated lactic acid levels have also been observed in individuals who are not septic and who are normotensive, but who have received systemic adrenergic agonist therapy. This report presents two patients with acute asthma treated with very large doses of aerosolized and systemic salbutamol, who developed lactic acidosis despite normal systemic hemodynamics and adequate oxygenation. Lactic acidosis was clinically important because it contributed to respiratory failure in one patient, and complicated the assessment and management of acute, severe asthma in the other patient.

Key Words: *Asthma; Beta₂-adrenergic agonists; Catecholamines; Glycolysis; Lactic acidosis; Metabolic acidosis*

Lactic acidosis is a commonly used marker of tissue hypoperfusion and inadequate oxygen delivery (1). Impaired oxygen delivery or consumption leads to increased anaerobic glycolysis, with terminal oxidation of the resulting pyruvate to lactate instead of through the Krebs acid cycle of aerobic metabolism. Indeed, in clinical settings such as sepsis and shock ('type A' lactic acidosis), increased serum lactate is an important prognostic factor for increased mortality (2,3).

Acidose lactique et asthme : deux exposés de cas et examen de la documentation

RÉSUMÉ : L'acidose lactique est souvent associée aux états d'hypoxie et de perfusion insuffisante des tissus. Des taux élevés d'acide lactique ont également été observés chez des personnes non porteuses de germes pathogènes et normotendues mais traitées aux agonistes adrénergiques à action générale. Voici le cas de deux patients en crise d'asthme, qui ont reçu de très fortes doses de salbutamol à action générale, en aérosol et chez qui s'est installée une acidose lactique malgré une hémodynamique générale normale et une oxygénation adéquate. L'acidose lactique a eu des répercussions cliniques suffisamment importantes pour jouer un rôle dans l'apparition de l'insuffisance respiratoire chez un patient et pour compliquer l'évaluation et le traitement de l'asthme, grave et aigu, chez l'autre.

It has long been recognized that certain clinical conditions may be associated with increased lactate levels in the absence of altered systemic hemodynamics or tissue hypoperfusion. In this 'type B' lactic acidosis, there is altered cellular metabolism, with either increased flux of pyruvate to lactate rather than into the Krebs cycle or decreased lactate metabolism. Conditions associated with type B lactic acidosis include inborn errors of metabolism such as pyruvate dehydrogenase deficiency, systemic disorders such as liver

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TABLE 1
Blood gas levels and chemistry data in case 1

| Time after admission (h) | pH | PaCO ₂ (mmHg) | Carbonate (mmol/L) | PaO ₂ (mmHg) | FiO ₂ | Sodium (mmol/L) | Potassium (mmol/L) | Chlorine (mmol/L) | Lactate (mmol/L) | Albumin (g/L) |
|--------------------------|------|--------------------------|--------------------|-------------------------|------------------|-----------------|--------------------|-------------------|------------------|---------------|
| 3 | 7.36 | 37 | 20 | 77 | 0.50 | — | — | — | — | — |
| 7 | 7.29 | 31 | 15 | 100 | 0.50 | — | — | — | — | — |
| 8 | 7.30 | 29 | 14 | 101 | 0.50 | 139 | 3.6 | 110 | 10.0 | 42 |
| 10 | 7.12 | 58 | 18 | 167 | 1.00 | 139 | 4.7 | 112 | 5.4 | — |
| 12 | 7.22 | 37 | 14 | 132 | 0.50 | 139 | 5.0 | 113 | 8.5 | — |
| 18 | 7.34 | 37 | 19 | 107 | 0.40 | 135 | 4.6 | 111 | 3.4 | 38 |
| 41 | 7.38 | 44 | 26 | 94 | — | 137 | 4.1 | 106 | 2.4 | 34 |

FiO₂ Inspired fraction of oxygen; PaCO₂ Arterial partial pressure of carbon dioxide; PaO₂ Arterial partial pressure of oxygen

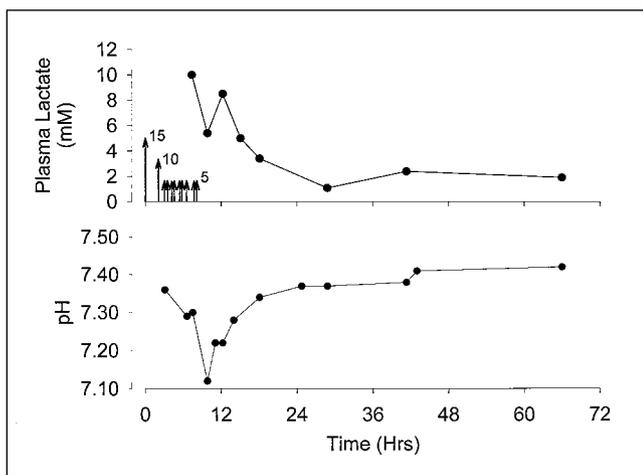


Figure 1 Time course of beta₂-agonist therapy, blood gas pH and plasma lactate levels in case 1. Arrows indicate timing and dose of aerosolized salbutamol (mg)

failure, and adverse effects of medications such as biguanides (eg, metformin) and nucleoside reverse transcriptase inhibitors (eg, stavudine, lamivudine) (1).

It has recently been suggested that conditions characterized by excessive adrenergic stimulation may similarly be associated with increased conversion of pyruvate to lactate (4). For example, lactate can arise in well-oxygenated tissues (eg, skeletal muscle) through adrenaline-stimulated glycolysis and glycogenolysis during exercise and after cardiac surgery (4,5). Lactic acidosis of uncertain significance has also been reported in cases of beta₂-adrenergic agonist therapy for tocolysis in premature labour and in acute asthma (6-8). The present report describes two patients with exacerbations of severe, persistent asthma, in whom significant lactic acidosis developed in the absence of hypoperfusion or significant tissue hypoxia. We hypothesize that lactic acidosis was due to large doses of beta₂-adrenergic agonists administered both by nebulization and parenterally, and perhaps was also due to elevated endogenous catecholamine levels related to marked respiratory distress. Lactic acidosis had a significant impact on the assessment and management of asthma in these two patients. We sug-

gest that lactic acidosis should be considered in patients with asthma exacerbations who are receiving large doses of beta₂-adrenergic agonists, and who fail to improve or manifest metabolic acidosis.

CASE PRESENTATIONS

Case 1

A 45-year-old white woman was intubated and admitted to the intensive care unit, with an exacerbation of her severe persistent asthma. Regular therapy of her asthma consisted of high-dose inhaled corticosteroids (ICSs), inhaled, long-acting beta₂-agonists, and salbutamol via both metered-dose inhaler (MDI) and nebulizer several times daily. She had had increased exertional dyspnea, nocturnal symptoms and awakening over the previous few days. She had required treatment with nebulized salbutamol (2.5 mg) at 4 to 6 h intervals and two to four puffs of salbutamol (100 µg) via MDI at 1 to 2 h intervals, with minimal relief. On the morning of admission, she had presented to her family physician's office, where she was found to be in severe distress, speaking in single-word phrases, and had decreased breath sounds bilaterally on auscultation. During the subsequent 90 min, nebulized salbutamol (2.5 mg) was administered three times, as well as a single oral dose of 50 mg of prednisone. She was then transported to hospital via ambulance while she received 5 mg of nebulized salbutamol.

On presentation, she was very anxious, and had marked accessory muscle recruitment and diffusely decreased breath sounds with occasional expiratory wheezes. Her vital signs were: heart rate 120 beats/min, respiratory rate 40 breaths/min and blood pressure 160/110 mmHg with a pulsus paradoxus of 30 mmHg. An initial assessment of arterial blood gases (Table 1) showed a severe gas exchange defect and mild metabolic acidosis. Over the next 7 h, she was administered supplemental oxygen, 125 mg of intravenous methylprednisolone, repeated doses of nebulized salbutamol and, subsequently, an intravenous infusion of salbutamol (Figure 1). Despite aggressive bronchodilator therapy, she remained in respiratory distress, but was hemodynamically stable, with her blood pressure between 140/100 and 170/120 mmHg. The initial metabolic acidosis worsened, associated with a rising lactate level and an

TABLE 2
Blood gas levels and chemistry data in case 2

| Time after admission | pH | PaCO ₂ (mmHg) | Carbonate (mmol/L) | PaO ₂ (mmHg) | FiO ₂ | Sodium (mmol/L) | Potassium (mmol/L) | Chlorine (mmol/L) | Lactate (mmol/L) |
|----------------------|------|--------------------------|--------------------|-------------------------|------------------|-----------------|--------------------|-------------------|------------------|
| 0 h | 7.44 | 31 | 21 | 113 | 1.00 | 140 | 2.8 | 109 | – |
| 8 h | 7.34 | 34 | 18 | 104 | 0.40 | 142 | 3.2 | 111 | – |
| 12 h | 7.30 | 27 | 13 | 82 | 0.40 | – | – | – | – |
| 14 h | 7.37 | 29 | 16 | 87 | 0.40 | 137 | 3.9 | 111 | 3.6 |
| 14 days | 7.42 | 36 | 23 | 78 | 0.21 | 137 | 3.3 | 100 | 2.4 |

FiO₂ Inspired fraction of oxygen; PaCO₂ Arterial partial pressure of carbon dioxide; PaO₂ Arterial partial pressure of oxygen

increased plasma anion gap, and she exhibited appropriate respiratory compensation (Table 1, Figure 1). This metabolic acidosis was associated with a fall in her serum potassium level (Table 1). She appeared to be increasingly fatigued, became hypercapnic and developed severe, mixed acidosis (ie, metabolic acidosis and superimposed acute respiratory acidosis), for which she was intubated.

She was transferred to the intensive care unit, where she was mechanically ventilated quite easily at the following settings: assist-control mode, respiratory rate 25 breaths/min, tidal volume 410 mL, positive end expiratory pressure (PEEP) 5 cm H₂O and inspiratory flow 90 L/min. She was initially administered six puffs of salbutamol (100 µg) at 2 h intervals, six puffs of ipratropium bromide (20 µg) at 4 h intervals and 125 mg of methylprednisolone intravenously at 6 h intervals. Over the next 36 h, the bronchodilators were tapered to administration at 6 h intervals, corticosteroid therapy was switched to 50 mg oral prednisone daily, and she was extubated. The systemic lactic acidosis persisted during the initial 12 h after intubation, but then resolved slowly over the next 48 h, coincident with tapering of beta₂-agonist therapy. She achieved a normal acid-base status by the time of discharge on day 3.

Case 2

A 24-year-old white woman was admitted to the hospital for an exacerbation of her severe, persistent asthma. Her usual medications were salbutamol 200 µg four times daily via MDI, high dose ICSs, zafirlukast and oral prednisone 30 mg daily during spring and summer over the previous few years.

An upper respiratory tract infection had led to increasing dyspnea with audible wheezing on the day before admission. On the day of admission, her symptoms worsened and were minimally relieved, despite taking 21 puffs of salbutamol. When she presented to the emergency department, she was in significant respiratory distress and was only able to speak in brief, three-word phrases. Her vital signs were: blood pressure 171/127 mmHg, heart rate 148 beats/min, respiratory rate 36 breaths/min and arterial oxygen saturation via pulse oximetry 85% while breathing room air. She had marked recruitment of accessory muscles of inspiration, and diffuse inspiratory and expiratory wheezes. Over the initial 2 h, she received supplemental oxygen, multiple doses of 5 mg of

nebulized salbutamol (total 45 mg), 0.5 mg ipratropium bromide and 125 mg of methylprednisolone intravenously. Her vital signs at the time were: blood pressure 150/84 mmHg with a pulsus paradoxus of 45 mmHg, heart rate 164 beats/min and arterial oxygen saturation 95% to 98%.

Laboratory investigations on admission revealed a serum potassium level of 2.8 mmol/L, albumin level of 42 g/L and a white blood cell count of 21.1×10⁹ cells/L. The rest of the electrolyte, blood urea nitrogen, creatinine and hemoglobin levels were within the normal range. Capillary blood gas and electrolyte levels on admission and during the subsequent 12 h are shown in Table 2. Her initial blood gas showed a partially compensated mild respiratory alkalosis and adequate oxygenation on 100% oxygen.

Over the subsequent 8 to 12 h, she showed significant improvement after administration of nebulized salbutamol (5 mg) every 30 min and methylprednisolone 125 mg intravenously at 8 h intervals. Her blood pressure was 118/48 mmHg with no pulsus paradoxus, her respiratory rate was 16 breaths/min and her arterial oxygen saturation was 95% while breathing 40% oxygen. However, she developed a progressive metabolic acidosis with respiratory compensation, which was found to be associated with an elevated plasma lactate level of 3.6 mmol/L (drawn 16 h after presentation), which remained elevated at 4.2 mmol/L 36 h after admission. The frequency of administration of nebulized salbutamol was reduced to 4 h intervals, and 40 mg of prednisone was administered orally. Two days later, the patient had no signs of respiratory distress, and was discharged on high dose ICSs and oral prednisone.

The patient continued to take salbutamol 200 µg four times daily by MDI and two to three times daily on an as-needed basis, but she was clinically well when reassessed two weeks later, with a forced expiratory volume in 1 s of 2.68 L (88% predicted). Her serum potassium level was 3.3 mmol/L and her serum lactate level was 2.4 mmol/L (normal range 0.5 to 2.2 mmol/L). She was encouraged to use salbutamol only on an as-needed basis, and formoterol was prescribed at 12 µg twice daily.

DISCUSSION

The most important acid-base abnormality in acute asthma is respiratory acidosis due to severe airflow limitation, inadequate minute ventilation and progressive hypercapnia.

TABLE 3
Details of etiology and consequences of lactic acidosis in published cases of acute asthma

| Reference | n | Peak lactate level (mmol/L) (range) | Suggested etiology of lactic acidosis | Effect of lactic acidosis |
|-------------------------------|----|-------------------------------------|--|---|
| Roncoroni et al, 1976 (11) | 25 | 4.2 (3.4 to 5.0)* | Uncertain: increased respiratory muscle production and/or decreased muscle or liver metabolism | None observed; potential impaired beta ₂ -agonist-mediated bronchodilation |
| Appel et al, 1983 (7) | 12 | 6.8 (2.9 to 9.4) | Marker of severe asthma: increased respiratory muscle production and/or decreased muscle or liver metabolism | Eight of 12 developed respiratory acidosis, six of whom required mechanical ventilation |
| Braden et al, 1985 (12) | 1 | 7.2 | Beta ₂ -agonist, theophylline and steroid therapy | None |
| O'Connell and Iber, 1990 (13) | 3 | 6.4 (2.8 to 9.5) | Uncertain: intravenous beta ₂ -agonists versus severe asthma | None |
| Mountain et al, 1990 (8) | 27 | – | Hypoxia and increased respiratory muscle production | None |
| Maury, 1997 (36) | 1 | 10 | Beta ₂ -agonist therapy | Inappropriate intensification of beta ₂ -agonist therapy |
| Prakash and Mehta, 2001 | 2 | (3.6 to 10.0) | Beta ₂ -agonist therapy | Contributed to hypercapnic respiratory failure and respiratory acidosis |

*95% CI, not range

Asthma can also be associated with several other acid-base abnormalities. For example, in patients with mild or moderate acute asthma, the most common acid-base finding is respiratory alkalosis. This intracellular alkalosis can also be associated with nonanion gap metabolic acidosis through renal bicarbonate wasting (8-11). As well, increased anion gap metabolic acidosis has also been reported, due to either presumed or measured lactic acidosis (Table 3) (7,8,12,13).

Lactic acidosis most commonly signifies an impaired ability to meet tissue oxygen demands such as those that can result during shock, hypotension and hypoxemia. Hypoxemia in patients with acute, severe asthma may lead to lactic acidosis. For example, during 229 episodes of acute asthma in 170 patients assessed in Denver, Colorado (mean altitude 1600 m), metabolic acidosis was found in 28%; in the majority of these patients, the anion gap was elevated, but lactate levels were not measured (8). In these patients, the anion gap was correlated with the arterial partial pressure of oxygen. In contrast, in 101 episodes of acute, severe asthma during which hypoxemia was rigorously assessed and treated, metabolic (lactic) acidosis was not observed in a single cases (14). In the present two cases, although hypoxemia was noted on presentation, this was clearly not a factor in the later development or worsening of lactic acidosis.

Lactate can also be elevated in situations in which cardiac output is impaired. Impaired left ventricular stroke volume in patients with severe upper airway obstruction has been described, related to the cardiovascular effects of excessive inspiratory falls in pleural pressure (15-18). Acute asthma may also decrease stroke volume via similar mechanisms, as evidenced by the presence of pulsus paradoxus, one of the cardinal manifestations of severe asthma. As well, pulmonary edema has been described in patients with acute asthma (19,20). Moreover, gas trapping and the generation of intrinsic

PEEP (PEEPi) may directly reduce thoracic venous return and further impair cardiac function (16,20). In the two cases presented, it is unlikely that cardiovascular alterations were the cause of lactic acidosis, given that the patients had not only stable, but hyperdynamic cardiovascular function. Moreover, the improvement, rather than worsening, of the lactic acidosis in case 1 after institution of mechanical ventilation further supports our conclusion, given that mechanical ventilation in patients with airflow obstruction is often associated with worsening gas trapping, increasing PEEPi and worsening cardiovascular function (13,16).

Type B lactic acidosis is not due to tissue hypoperfusion or hypoxia, but is rather due to decreased lactate metabolism in the setting of liver disease, inborn errors of metabolism or exposure to certain drugs. In the cases presented, the patients had no evidence of pre-existing liver disease or any acute liver dysfunction, and were not being treated with any medications known to produce lactic acidosis. Although hepatic dysfunction related to the cardiovascular effects of acute asthma may contribute to lactic acidosis in asthma, this is very unlikely (7,10). The liver has a large capacity to metabolize lactate, such that despite a 50% to 70% reduction in hepatic blood flow during intense, upright exercise in normal humans, splanchnic lactate removal was preserved (21). Furthermore, lactate was minimally increased in normal subjects, despite breathing for 10 min during inspiratory or expiratory loading at levels requiring the generation of at least 70% of maximum static mouth pressures (22). Thus, large positive and negative changes in intrathoracic pressure during loaded breathing had insignificant effects on hepatic lactate clearance.

Lactate can arise in well-oxygenated skeletal muscle during vigorous contraction such as during exercise. Although increased levels of lactate during exercise had been consid-

ered a marker of anaerobic metabolism, exercise studies have shown a poor correlation between oxygen saturation of muscle myoglobin and circulating lactate concentration (23-25). Indeed, under either hypoxic or normoxic exercise conditions, net muscle lactate efflux is independent of the intracellular partial pressure of oxygen (25). In contrast, other studies have demonstrated an excellent correlation between adrenalin and plasma lactate levels during exercise (23,24). Hence, increased skeletal muscle lactate efflux during exercise is likely a result of adrenalin-stimulated glycogenolysis and glycolysis (4,26,27). Similarly, enhanced respiratory muscle efflux of lactate may contribute to lactic acidosis during mechanical ventilatory loading such as during episodes of respiratory distress (28). However, only small changes in blood lactate levels have been observed despite sustained maximal voluntary ventilation or loaded breathing in normal subjects, or during respiratory failure in subjects with airflow obstruction (22,29). Thus, it is unlikely that the increased lactate levels observed in the two present cases were simply due to increased respiratory muscle lactate efflux.

Lactic acidosis due to a hyperadrenergic state occurs in conditions other than exercise, including sepsis, lung injury and cardiopulmonary bypass (4,30-32). It has been hypothesized that catecholaminergic stimulation of increased glycolysis and glycogenolysis is associated with increased pyruvate generation and increased conversion to lactate because of either overwhelmed or coincidentally disturbed oxidative metabolism (4). Indeed, catecholamines have been shown to stimulate phosphorylation and the resulting activation of muscle glycogen phosphorylase, leading to increased pyruvate flux (26).

We suggest that the lactic acidosis in the two present cases of acute asthma was likely the result of excess beta₂-adrenergic agonist therapy. A hyperadrenergic state in asthma could be due to either endogenous or exogenous catecholamines. The presence of distress or anxiety in acute asthma can be associated with neurohumoral sympathetic activation, as manifested by tachycardia and hypertension (10). Large doses of aerosolized and systemic beta₂-adrenergic agonists might also have contributed to such a state of excess adrenergic stimulation, leading to lactic acidosis. A similar beta₂-agonist-induced lactic acidosis has been recognized during beta₂-agonist tocolytic therapy for premature labour (6). In patients with asthma, many of the adverse effects of beta₂-agonists, such as tachycardia, tremulousness and hypokalemia, are related to excess adrenergic stimulation (33). Indeed, both of our patients manifested hypokalemia concomitant with the lactic acidosis. Beta₂-agonist therapy has also been shown to cause hyperglycemia putatively through adrenergic stimulation induced gluconeogenesis and glycogenolysis (33-35).

The presence of a lactic acidosis adversely affected the management of asthma in at least two ways in the cases presented. First, the acute management of asthma depends on the objective assessment of the severity of respiratory distress, including respiratory rate, pulsus paradoxus and the

recruitment of accessory muscles of respiration. It is assumed that tachypnea and increased respiratory effort are related to increased airflow resistance and decreased lung compliance due to gas trapping. In the presence of lactic acidosis, increased respiratory effort may be related, in part, to acidosis-induced stimulation of ventilation, ie, respiratory compensation. Thus, the appropriate response to this respiratory distress would be less, rather than more, aggressive beta₂-agonist therapy (36).

Second, the presence of lactic acidosis also complicated the decision to institute mechanical ventilation in the two cases presented. Assisted ventilation is a valuable therapeutic modality in life-threatening asthma exacerbations. The decision to institute assisted ventilation in acute asthma is based, in part, on the presence of certain features, such as a decreasing level of consciousness, failure to protect the airway, progressive hypercapnia and respiratory acidosis, and severe respiratory distress. In case 1, the increased ventilatory demands due to the concomitant lactic acidosis may have contributed to eventual respiratory fatigue, leading to hypercapnia and respiratory acidosis. Indeed, in a previous report, respiratory acidosis developed in eight of 12 patients with metabolic acidosis in acute asthma, of whom six required intubation and mechanical ventilation (7). Finally, acidosis can impair smooth muscle response to catecholamines, suggesting that metabolic acidosis in asthma may impair bronchodilation in response to exogenous beta₂-agonists, as well as endogenous catecholamines (11,37).

Although ICSs are the first-line therapy in the vast majority of patients with asthma, beta₂-agonists are an important component of the management of stable asthma and acute asthma exacerbations. Regular second-line therapy with long-acting beta₂-agonists has been shown to reduce asthma symptoms, increase lung function and exercise capacity, and decrease asthma exacerbations. As well, the majority of subjects with asthma use beta₂-agonists on an as-needed basis for intermittent symptoms. Although good asthma control is suggested by a need for beta₂-agonists for symptoms three times weekly or less, many studies suggest far greater use by most patients (38). Indeed, in a recent survey of asthma control in Canada, 67% of subjects with asthma used beta₂-agonists at least once daily. A recommended daily 'maximal' dose of beta₂-agonists may be approximately 200 µg of salbutamol six times daily, but many patients take two to four doses at 1 to 2 h intervals when acutely ill. Moreover, aggressive, high dose beta₂-agonist therapy, eg, four to six doses of salbutamol via MDI or 5 mg of nebulized salbutamol every 15 min, is one of the cornerstones of acute management of a severe asthma exacerbation. As well, adjuvant asthma therapy such as theophylline and corticosteroids may accentuate beta₂-agonist-mediated effects through mechanisms such as phosphodiesterase inhibition (increased cyclic adenosine 3',5'-monophosphate half-life) or enhanced beta-adrenergic receptor sensitivity (12,39). Thus, we suggest that clinically significant lactic acidosis may be more frequent than currently appreciated.

Type B lactic acidosis – increased plasma lactate in the absence of tissue hypoxia or hypotension – can occur in acute asthma, possibly due to aggressive beta₂-adrenergic agonist therapy. Respiratory compensation for this primary metabolic acidosis, characterized by increased respiratory

rate and effort, may be mistaken for worsening respiratory distress due to asthma. Lactic acidosis in acute asthma can lead to inappropriate management, including unwarranted intensification of beta₂-agonist therapy and the institution of mechanical ventilation prematurely or unnecessarily.

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