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Lactic Acidosis in Status Asthmaticus* : Three Cases and Review of the Literature

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observed that methimazole can increase the levels of IgE antibodies[3] and interleukin-2, a cytokine with a chemotactic activity on eosinophils.[4]

We postulate that methimazole-induced bronchial hypereosinophilia might have caused an exacerbation of asthma, unresponsive to bronchodilators, and allergy-like symptoms. The failure of β_2-adrenoceptor agonists to produce a clinical improvement after the introduction of methimazole can be explained by a downregulation of β-receptors,[5] possibly induced by this drug and by the inflammatory mediators released in the airways by activated eosinophils.

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Lactic Acidosis in Status Asthmaticus*

Three Cases and Review of the Literature

Constantine A. Manthous, MD, FCCP

Lactic acidosis is a frequent laboratory finding in patients with severe exacerbations of asthma. The pathogenesis of lactic acidosis in asthma is not well understood, but it has been presumed, by some, to be generated by fatiguing respiratory muscles. We herein report the cases of three patients with status asthmaticus and lactic acidosis despite pharmacologic muscle relaxation. No common etiologies were found for lactic acidosis that abated after bronchospasm improved and the intensity of pharmacologic therapies was reduced. We review the literature describing lactic acidosis with asthma and discuss mechanisms by which lactic acidosis may occur in patients with status asthmaticus.

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Key words: albuterol; asthma; bronchodilators; lactate; lactic acid; lactic acidosis; status asthmaticus; sympathomimetic

Abbreviations: cAMP = cyclic adenosine monophosphate; PEEP = positive end-expiratory pressure; SA = status asthmaticus; VT = tidal volume

Lactic acidosis is a well-described phenomenon in patients with severe asthma[1–8] and has been hypothesized, by some, to result from inadequate oxygen delivery to the respiratory muscles to meet an elevated oxygen demand.[1] We report the cases of three patients with status asthmaticus (SA) in whom respiratory muscle activity could not have accounted for lactic acidosis. We then delineate possible mechanisms underlying the pathogenesis of lactic acidosis in SA.

Case Reports

Case 1

A 27-year-old white woman with a history of steroid-dependent asthma, with no previous intubations, presented with an acute exacerbation of asthma. After being found by emergency technicians in extreme respiratory distress at her private physician's office, she was emergently intubated for respiratory arrest. She received two doses of subcutaneous epinephrine and 100 mg of IV cortisol before transport. After transport to the emergency department, her BP was 164/84 mm Hg, heart rate was 100 to 110 beats/min, respiratory rate was 30 breaths/min (with a set ventilatory rate of 12/min), and temperature was 36.1°C. Physical examination of the lungs revealed bilateral diffuse rhonchi and wheezing. Chest radiography demonstrated hyperinflation with mild pneumomediastinum and pneumopericardium. On assist-control mode, with a set respiratory rate of 12/min, an actual rate of 30 breaths/min, tidal volume (VT) of 500 mL, a fraction of inspired oxygen of 40%, and no positive end-expiratory pressure (PEEP), her arterial blood gas levels were pH, 7.20; P_{CO_2}, 43 mm Hg; and P_{O_2}, 200 mm Hg. She received IV methylprednisolone, 125 mg q6h; IV magnesium sulfate, 4 g; and continuously nebulized albuterol. She did not receive parenteral β-agonists in the hospital. She was sedated with midazolam, 1 to 3 mg every 1 to 3 h as needed, and received a muscle relaxant (pancuronium) (with no triggered breaths and a "train of 4" of two twitches) to prevent excessive tachypnea and associated dynamic hyperinflation. With this regimen, her arterial blood gas levels improved to pH, 7.23; Pa_{CO_2}, 35 mm Hg; and Pa_{O_2}, 192 mm Hg on 40% inspired oxygen. Peak airway pressure was 71 cm H_2O, static pressure was 21 cm H_2O, and intrinsic PEEP was 7 to 8 cm H_2O. She became increasingly tachycardic, with a heart rate of 120 to 130 beats/min, and did not respond to 5 mg of lorazepam or 500 mL of normal saline solution infusion (her theophylline level was 2.1 μg/mL, and she had not received theophylline in the hospital). Culture results of urine, blood, and sputum were negative, and she did not demonstrate other signs of sepsis. Her oxygen saturation remained ≥ 90% throughout her ICU stay, and she never exhibited signs of shock. Her anion gap metabolic acidosis was found to be secondary to lactic acid (Table 1), which persisted until the second hospital day, when continuous β-agonist aerosols were reduced to four puffs of albuterol via metered-dose inhaler with holding chamber q4h after airway pressures

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Table 1—*Parameters Associated With Lactic Acidosis in Case 1

Day	Time	Aerosol Administration	Heart Rate, beats/min	pH	P_{CO_2}, mm Hg	Lactate, mmol/L
1	9:30 PM	Continuous	130–140	7.20	43	6.0
2	4 AM	Continuous	130–140	7.23	35	6.2
2	5 PM	Every 2 to 4 h	90–100	7.37	31	0.9

*At 11 AM on day 2, continuous nebulization of albuterol treatment was stopped and she was started on four puffs of metered-dose inhaler albuterol q4h. No therapies were changed except that just before 4 AM on her second hospital day, pancuronium treatment was stopped and she continued to receive midazolam to maintain synchrony/comfort with the ventilator. Lactic acidosis improved around the time of her clinical improvement (which allowed reversal of permissive hypercapnia and reduction of β-agonist treatments). Normal values of lactate are up to 2.1 mmol/L. Times are indexed to lactate levels and arterial blood gas levels reflect gas exchange within an hour or two of lactates.

had further decreased. By this time, she had received in excess of 100 mg (cumulatively) of aerosolized albuterol > 24 h. Her tachycardia and lactic acidosis promptly improved, and she was extubated successfully on her third hospital day without complications.

Case 2

A 36-year-old Hispanic woman with a history of heroin and tobacco abuse and severe asthma requiring hospitalizations on several previous occasions presented with 3 days of upper-respiratory-tract infection and increasing shortness of breath. On physical examination, she had severe wheezing and peak flows < 200 L/min. After treatment with eight nebulized treatments of albuterol, 2.5 mg, and IV methylprednisolone, 125 mg, she continued to worsen. A trial of heliox also failed to alleviate her severe dyspnea, and she was electively intubated for increasing respiratory extremis (respiratory rate > 40 breaths/min; pulsus paradoxus, 25 mm Hg). After intubation, with initial VT of 500 mL delivered with 60 L/min constant inspiratory flow, peak inspiratory pressure was 52 cm H_2O with a static airway pressure of 25 cm H_2O and intrinsic PEEP of 4 cm H_2O. Tachypnea while receiving mechanical ventilation led to administration of benzodiazepines, and, subsequently, vecuronium was also added to control her ventilation and avoid barotrauma. She was sedated with midazolam, 1 to 3 mg every 1 to 3 h as needed, and received a muscle relaxant (pancuronium) (with no triggered breaths and a "train of 4" of two twitches). A strategy of permissive hypercapnia was required to maintain static airway pressures < 35 cm H_2O; a consequent pH of 7.10 and P_{CO_2} of 59 mm Hg prompted institution of IV bicarbonate therapy. She remained hemodynamically stable throughout. A lactic acid level drawn 8 h after intubation was 5.0 mmol/L. On her second hospital day, airway pressures remained elevated despite muscle relaxation and nebulized albuterol at 2.5 mg/h; lactic acid remained elevated at 3.1 mmol/L (Table 2). After doses of vecuronium, lorazepam, and morphine sulfate, she experienced an acute increase in airway pressures (peak > 90 cm H_2O; static, 33 cm H_2O on 60 L/min constant flow). A chest radiograph did not reveal pneumothorax. Shortly thereafter, her systolic BP dropped from the 120 to 130 mm Hg range to 50 mm Hg. IV fluids were administered acutely at maximal rates but failed to retrieve her BP. Caregivers entertained a diagnosis of acute hypotension secondary to dynamic hyperinflation. One milligram of IV epinephrine was administered, leading to an abrupt increase in her BP and a gradual decrease in her airway pressures. Five hours later, while she continued to receive hourly aerosolized β-agonists, airway pressures had decreased to peak of 44 cm H_2O and static of 26 cm H_2O on continuous inspiratory flows of 60 L/min. A lactic acid drawn 6 h later was 0.6 mmol/L and remained normal for the remainder of her stay. Airway pressures remained in a similar range for the next 36 h, and permissive hypercapnia was reversed. She was awakened and successfully extubated without difficulty.

Case 3

A 28-year-old black woman with a history of severe asthma, who was most recently intubated 2 months before admission, presented with a 2-day history of increasing shortness of breath and nonproductive cough. Her symptoms failed to improve after self-administration of three "back-to-back" treatments of albuterol. She was brought to the hospital by ambulance, where personnel administered 125 mg of IV methylprednisolone, two more albuterol nebulizers, and one dose of 1:1,000 subcutaneous epinephrine. In the emergency department, she was very short of breath and was intubated because of extremis; arterial blood gas values were: pH, 7.10; P_{CO_2}, 86 mm Hg. She was sedated and received a muscle relaxant (vecuronium); on initial ventilator settings of 14/min, 400-mL VT, and 100% oxygen, her pH increased to 7.17 and P_{CO_2} was 63 mm Hg. Airway pressures were very high (peaks > 70 cm H_2O), airway resistance was 65 cm H_2O/L/s, and plateau airway pressure was 27 cm H_2O with an auto-PEEP of 6 cm H_2O. Treatment with propofol was started at 0.005 mg/kg/min for sedation, and vecuronium was continuously infused to maintain the minimal dose that prevented triggering of the ventilator. She continued to receive hourly nebulized albuterol; every 4 h, ipratropium bromide was added to nebulized treatments. She also received a second dose of 125 mg of methylprednisolone 6 h after intubation. Airway pressures improved dramatically, allowing gradual increases in VT (maintaining static airway pressures < 25 cm H_2O). Nearly 14 h after

Table 2—*Parameters Associated With Lactic Acidosis in Case 2

Day	Time	Aerosol Administration	Heart Rate, beats/min	pH	P_{CO_2}, mm Hg	Lactate, mmol/L
1	10 PM	Hourly	123	7.15	68	5.0
2	4:30 AM	Hourly	118	7.16	68	5.6
2	2 PM	Hourly	129	7.24	64	3.1
3	4:45 PM	Hourly	109	7.31	58	0.6

*Note that lactic acidemia improved, despite nearly continuously nebulized albuterol, around the time of improvement sufficient to reverse permissive hypercapnia.

Table 3—*Parameters Associated With Lactic Acidosis in Case 3

Day	Time	Aerosol Administration	Heart Rate, beats/min	pH	P_{CO_2}, mm Hg	Lactate, mmol/L
1	5:10 PM	Hourly	132	7.22	57	–
1	11:40 PM	Hourly	117	7.23	40	4.9
2	3:45 PM	Every 4 h	127	7.34	36	2.4
3	4:58 AM	Every 4 h	120	None	None	1.0

*As with the other patients, improvements in lactic acid corresponded to improvements in bronchospasm.

intubation, she was eucapnic (pH, 7.23; P_{CO_2}, 40 cm H_2O) with airway resistance of 29 cm H_2O/L/s and static airway pressures of 21 cm H_2O. Hourly nebulized treatments were reduced in frequency to every 4 h, and vecuronium treatment was stopped. The lactic acid level, drawn before cessation of vecuronium to define the etiology of her metabolic acidosis, was 4.9 mmol/L. She continued to improve clinically; the next morning, treatment with propofol was stopped and 45 min later she was successfully extubated. She continued to improve with nebulized treatments every 4 to 6 h and methylprednisolone, 60 mg q6h. Her lactic acidosis abated over the next 24 h (Table 3), and she was discharged home on the sixth hospital day.

Discussion

The most common acid-base abnormality accompanying an acute exacerbation of asthma is respiratory alkalosis.[2] However, concurrent metabolic acidosis occurs in upwards of 28% of patients with severe exacerbations of asthma. The pathogenesis of lactic acidosis in asthma has been hypothesized to be related to production by the respiratory muscles and/or tissue hypoxia.[2]

As discussed in a recent review,[9] lactic acidosis results from overproduction and/or inadequate clearance of lactic acid. Therefore, lactic acidosis of SA could result (1) if patients were in occult shock, (2) if produced by overloaded respiratory muscles (*ie*, respiratory muscle oxygen demand outstripping oxygen supply), (3) if produced by the lung parenchyma, or (4) if changes in glycolysis were caused by β-agonist administration. Lactic acid could also be undermetabolized by the liver.

We cannot discount the possibility that the three patients in this report were in occult shock, although they continued to urinate, had mean arterial pressures that were normal or high, and experienced no clinical signs of end-organ dysfunction typical of shock. Because all three patients had received muscle relaxants, it is not tenable to attribute their lactic acidemia to respiratory muscle production. One previous case report[4] has similarly ruled out the possibility of lactic acid production by the respiratory muscles in patients with SA. Although the lungs of patients with ARDS may produce lactate,[10] this has not been described in SA. Our patients showed no laboratory evidence of liver or renal dysfunction during their hospitalizations, reducing the likelihood that underclearance contributed to these findings.

We performed a literature search and found that no other medications administered to our patients have been associated with lactic acidemia. One author[8] states, "This finding [lactic acidosis] is, as a rule, related to massive doses of β_2 adrenergic agents given parenterally: subsequent elevated lactate is in no way a marker of cellular hypoxia and has no pejorative meaning in this event." However, there are no convincing data to substantiate this claim. Previous studies have suggested that administration of β-agonists can lead to lactic acidemia in the absence of hypoxia or shock. Ensinger et al[11] infused epinephrine into eight normal volunteers and found that consequent hypertension and tachycardia were associated with a more than fivefold increase in plasma lactate concentrations. Stevenson et al[12] demonstrated that epinephrine infusion in dogs resulted in increased lactate levels despite increased uptake of lactate by the liver. They also demonstrated that epinephrine caused a dose-dependent increase in glucose production via stimulation of glycogenolysis and gluconeogenesis. Reverte et al[13] demonstrated that salbutamol infusion in rabbits caused an increase in lactate that was attenuated by prazosin. Sympathomimetic agents used for tocolysis have also been associated with lactic acidemia.[14,15] We could find no experimental studies of the effects of injected, ingested, or inhaled albuterol on plasma lactate levels. However, oral carbuterol, another selective β-agonist, has been associated with lactic acidosis in stable asthmatic patients.[16]

The mechanisms by which β-agonists may cause lactic acidemia remain uncertain.[1,2] Stimulation of β-adrenergic receptors leads to a variety of metabolic effects, including increases in glycogenolysis, gluconeogenesis, and lipolysis.[12,17] Stimulation of β-adrenergic receptors increases activity of adenylate cyclase activity, which in turn leads to increased intracellular cyclic adenosine monophosphate (cAMP). The mechanism by which cAMP leads to additional metabolic events is unclear. Stimulation of β-adrenoceptors increases lipolysis[17,18]; and β_2 stimulation appears to increase lipolysis to a greater degree than does β_1 stimulation. Increased free fatty acids inhibit conversion of pyruvate to acetyl-coenzyme A with consequent increases in lactic acid. Moreover, stimulation of β-adrenergic receptors increases plasma glucose concentrations,[12] thus increasing substrate for glycolysis. Thus, a number of mechanisms may explain lactic acidemia in patients with asthma who receive high doses of β-agonists. Finally, glucocorticoids and theophylline, frequently used concomitantly with β-agonist inhalants in patients with obstructive airways disease, also increase the level of intracellular cAMP and may enhance the sensitivity of β-receptors to β-adrenergic agents that may further amplify the above-described events.[4]

Notwithstanding these discussions, patient 2 kept receiving continuously aerosolized β-agonists at a time when lactic acid levels had returned to normal, which argues against β-agonist–induced lactic acidosis. Another event that corresponded to resolution of lactic acidosis in all these patients was improvement in bronchospasm, as measured by reductions in resistive airway pressures, and gradual increases in minute ventilation, *ie*, reversal of permissive hypercapnia. One study[10] demonstrated that lactic acidosis can be produced by the lung parenchyma in patients with ARDS; it is not clear whether this is a result of altered substrate metabolism because of lung injury itself or to mechanical effects engendered by mechanical ventilation. Accordingly, another potential hypothesis, albeit far-flung, is that the lungs of patients with severe asthma produce lactic acid. We were unable to find *in vitro* data to examine this hypothesis. This would be difficult to prove in humans because most patients with SA do not undergo right-heart catheterization that could allow determination of gradients of lactic acid concentration across the lungs. Finally, permissive hypercapnia, which was reversed in these patients (arguably in patient 1) as respiratory pressures (and lactic acid) diminished, has been associated with improved systemic oxygenation of tissues and reduced lactic acid production.[19]

In conclusion, our cases demonstrate that lactic acidemia associated with severe exacerbations of asthma may occur in the absence of respiratory muscle action. These data do not preclude the possibility that the respiratory muscles of nonintubated patients with severe SA contribute to lactic acidosis, only that lactic acid can be produced even during pharmacologic muscle relaxation. The mechanism by which this occurs in not evident from these cases. Although both animal and human data suggest that β-agonists could theoretically contribute to lactic acidosis in severe asthma, one of our cases suggests that this is not the sole explanation. Accordingly, further studies are required to delineate the mechanisms that account for lactic acidosis in patients with SA.

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Iatrogenic Paradoxical Air Embolism in Pulmonary Hypertension*

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Paradoxical systemic air embolism (PAE) occurring as a complication of right-to-left intracardiac shunting during evaluation and treatment of pulmonary hypertension (PH) has not been previously reported. We report four cases of PH-associated PAE recently encountered at our center. Two patients with PH experienced transient neurologic deficits during agitated-saline contrast echocardiography (ASCE), and a patent foramen ovale was subsequently diagnosed in both patients. Two patients with Eisenmenger's syndrome (ES), while receiving epoprostenol via multilumen catheters, experienced transient neurologic deficits while flushing the unused port of the catheter. No patient experienced permanent neurologic deficits. We conclude that ASCE poses a risk for PAE in patients with PH and clinically silent, previously undetected, right-to-left intracardiac shunts, and that multilumen catheters used for long-term epoprostenol therapy in ES carry a risk of PAE. ***(CHEST 2001; 119:1602–1605)***

Key words: contrast echocardiography; Eisenmenger's syndrome; paradoxical systemic air embolism; patent foramen ovale; pulmonary hypertension

Abbreviations: ASCE = agitated-saline contrast echocardiography; ASD = atrial septal defect; ES = Eisenmenger's syndrome; INR = international normalized ratio; PAE = paradoxical systemic air embolism; PFO = patent foramen ovale; PH = pulmonary hypertension; PPH = primary pulmonary hypertension; RV = right ventricular; Sa_{O_2} = arterial oxygen saturation

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