Acid-Base Disturbances in Acute Asthma*

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The clinical features, arterial blood gases, and acid-base profile were examined in 229 consecutive episodes of acute asthma in 170 patients who required hospitalization. A simple respiratory alkalosis was the most common acid-base disturbance, occurring in 48 percent of the episodes. Metabolic acidosis, either alone or as part of a mixed disturbance, was noted in 28 percent. Of 60 episodes presenting with respiratory acidosis, 37 (62 percent) had a coexistent metabolic acidosis. Metabolic acidosis was more likely to occur in male subjects and in patients with evidence of more severe airflow obstruction. Patients with metabolic acidosis had an average anion gap of 15.8 mEq/L; these patients were more hypoxemic than those without metabolic acidosis and there was a significant inverse correlation between the anion gap and the degree of hypoxemia. We conclude that metabolic acidosis is a common finding in acute, severe asthma and suggest that the pathogenesis of lactic acidosis is multifactorial and includes contributions from lactate production by respiratory muscles, tissue hypoxia, and intracellular alkalosis.

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The typical arterial blood gas and acid-base profile in acute asthma is hypoxemia, hypocapnia, and respiratory alkalosis.[1] Metabolic acidosis in adults with acute asthma is thought to be uncommon[2]; however, when acute asthma is severe, metabolic acidosis may occur.[3,4] We examined the clinical features, arterial blood gases, and acid-base profile in 229 consecutive episodes of acute asthma in 170 patients who required hospitalization and found that metabolic acidosis with and without an increase in the anion gap occurred in 28.0 percent of these episodes. Patients with metabolic acidosis were more hypoxemic and had evidence of greater airflow obstruction compared with those without metabolic acidosis. It appears that the metabolic acidosis of acute asthma is due primarily to lactic acidosis caused by a variable contribution of lactate production by respiratory muscles, tissue hypoxia, and intracellular alkalosis; the nonanion gap metabolic acidosis of acute asthma most likely represents a metabolic acidosis superimposed on the tendency to hyperchloremia seen with hyperventilation.

Patients and Methods

The clinical records of all adult patients (age 18 years or older) admitted to the University Hospital of the University of Colorado Health Sciences Center, Denver, with a diagnosis of asthma from July 1975 through June 1981 were reviewed; this search found 229 consecutive episodes in 170 patients. All patients fulfilled the American Thoracic Society diagnostic criteria for asthma.[5] Severe acute asthma was the primary reason for hospital admission in all patients. Patients with any feature of emphysema or chronic bronchitis were excluded. Patients with pneumonia, organic heart disease, diabetes mellitus, or renal failure also were excluded. None of the patients had a recent history of diarrhea, starvation, excess alcohol consumption, salicylate ingestion, or toxin ingestion. Thirty-four episodes otherwise fulfilling inclusion criteria did not have arterial blood gases on admission and were excluded.

Pertinent historic and physical examination data were obtained from the clinical records. Hyperinflation was considered present if it was mentioned on the chest roentgenogram report. Initial spirometry using a portable wedge bellows spirometer (Vitalograph) was done in 54 of the 229 episodes.

Arterial blood gas measurements within an hour of initial evaluation were available in all patients. Blood was collected anaerobically in a heparinized syringe from the radial or brachial artery and pH, $PaCO_2$, and PaO_2 were measured with standard electrodes (Radiometer MK2 or Radiometer ABL2). Initial measurement of serum electrolytes was made in 209 of the 229 episodes. Sodium and potassium values were measured with flame photometry; colorimetric methods were used to measure chloride and total carbon dioxide content. The anion gap was calculated as $Na^+ - (Cl^- + HCO_3^-)$. The normal anion gap in our clinical laboratory is 10 to 14 mEq/L.

Acid-base disturbances at presentation were classified according to the approach outlined by Harrington and associates.[6] That is, a simple acid-base disturbance was assumed to be present if the changes in $PaCO_2$ and bicarbonate fell within the 95 percent confidence limits established by controlled experimental studies,[7-9] whereas a mixed acid-base disturbance was assumed if the changes in $PaCO_2$ and bicarbonate were beyond the 95 percent confidence limits. The bicarbonate increase in response to acute hypercapnia in man is well defined[7] allowing relatively confident classification of hypercapnic patients into either acute respiratory acidosis, mixed respiratory-metabolic acidosis, or incomplete renal compensation in chronic hypercapnia. The decrement in the bicarbonate level in response to acute hypocapnia in man also is established;[8] however, the expected renal response to chronic hypocapnia is based on studies in dogs.[9] No attempt was made to differentiate acute and chronic respiratory alkalosis in the present study. This approach is likely to underestimate the presence of metabolic acidosis, since a patient with acute respiratory alkalosis and metabolic acidosis may be difficult to differentiate from a patient with chronic respiratory alkalosis alone and would be classified only as "respiratory alkalosis." A normal or increased hydrogen ion activity would suggest a superimposed metabolic acidosis.

Results

The classification of acid-base disturbances at presentation is shown in Table 1. Simple respiratory

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Table 1—*Acid-Base Status at Presentation in 229 Episodes of Acute Asthma*

Acid-Base Status	No. (% of Episodes)
Normal	28 (12.2)
Respiratory alkalosis	109 (47.6)
Respiratory alkalosis + metabolic acidosis	14 (6.1)
Metabolic acidosis	13 (5.7)
Respiratory acidosis	23 (10.0)
Respiratory acidosis + metabolic acidosis	37 (16.2)
Respiratory alkalosis + metabolic alkalosis	5 (2.2)

alkalosis was the most common acid-base disturbance, occurring in 47.6 percent of the episodes. Metabolic acidosis, either alone or as part of a mixed disturbance, occurred in 28.0 percent of the episodes. Of 60 episodes presenting with respiratory acidosis, 37 (61.7 percent) had a coexistent metabolic acidosis. Furthermore, of 30 episodes presenting with an initial pH of less than 7.30, 27 (90 percent) had a coexistent metabolic acidosis. A mixed respiratory-metabolic alkalosis was noted in five episodes; three of these episodes were associated with hypochloremia and hypokalemia, whereas two episodes remained unexplained.

Selected clinical features of episodes associated with metabolic acidosis are presented in Table 2 and compared to episodes without metabolic acidosis. Metabolic acidosis was more likely to occur in male subjects and in patients with ancillary evidence of greater airflow obstruction, including hyperinflation on chest roentgenogram and larger degrees of pulsus paradoxus. Also, the initial FEV_1 tended to be lower in patients with metabolic acidosis, although because of a limited number of measurements this difference did not reach statistical significance ($.05<p<.10$). Patients with metabolic acidosis had an average anion gap of 15.8 mEq/L (normal, 10 to 14 mEq/L). Specific anion gap data for each acid-base disturbance are presented in Figure 1. Patients presenting with metabolic acidosis were more hypoxemic than the remaining patients (Table 2). Furthermore, there was a significant inverse correlation between the anion gap and the degree of hypoxemia ($p<.001$) (Fig 2).

Discussion

Previous studies[1,10,11] have reported conflicting results concerning the occurrence of metabolic acidosis in acute asthma (Table 3). We found that simple or combined metabolic acidosis occurred in 28 percent of 229 episodes of acute asthma. In contrast, McFadden and Lyons[1] did not observe any instance of metabolic acidosis in 101 episodes of acute asthma. This study underlies the commonly accepted percep-

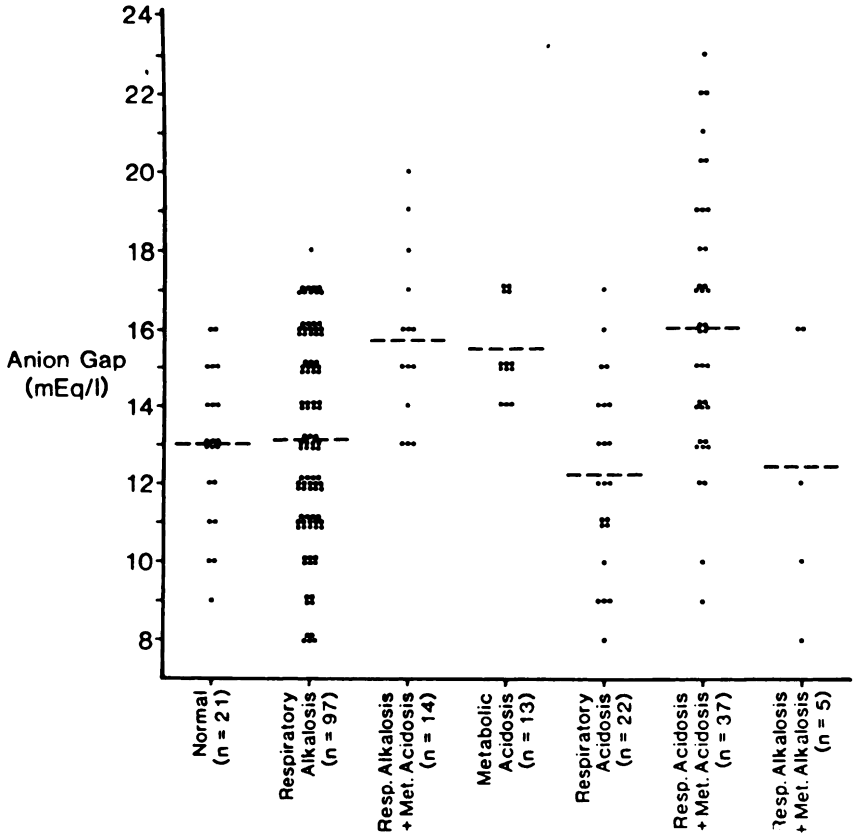

Figure 1. Individual anion gap data for each acid-base disturbance listed in Table 1. Data were available in 209 of the 229 episodes. Dash lines represent mean anion gap for each disturbance.

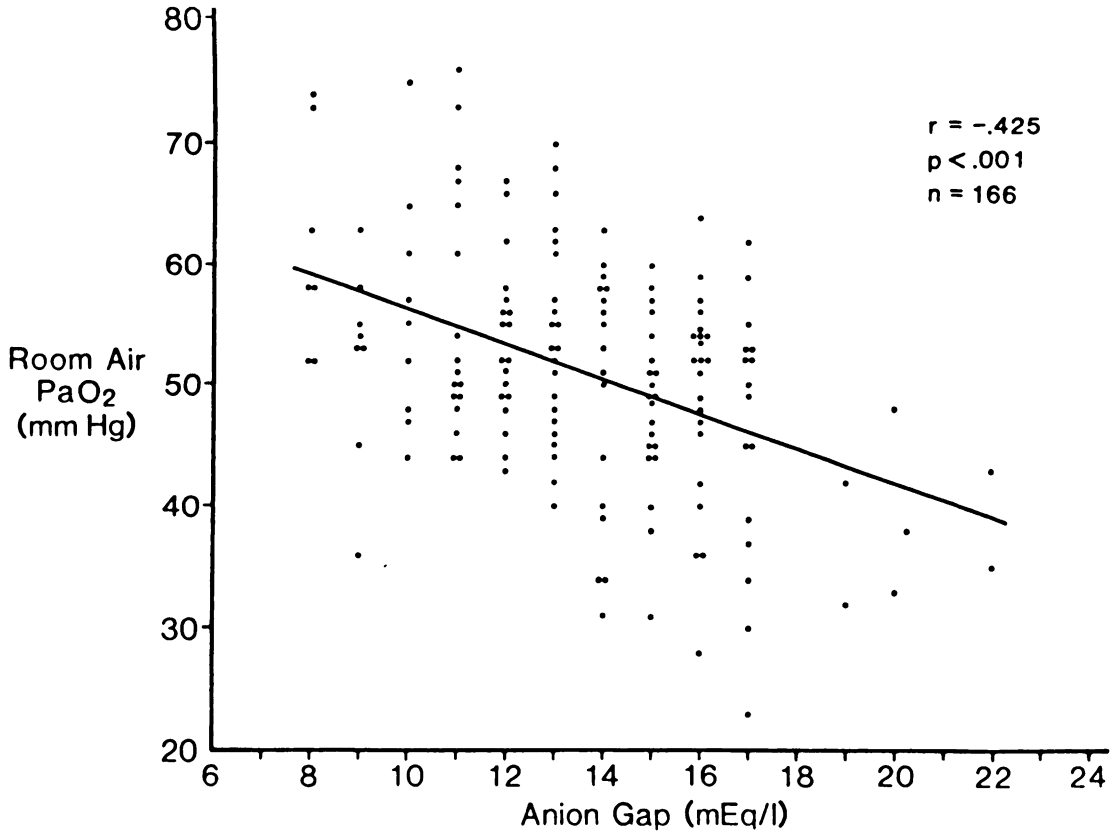

FIGURE 2. Relationship between room air PaO_2 at presentation and anion gap at presentation. Solid line is least squares linear regression relationship.

tion that metabolic acidosis is unusual in acute adult asthma. In a smaller study published in the same year as the report of McFadden and Lyons, metabolic acidosis was documented in 20.8 percent of 24 episodes.[11] In the largest series prior to our study, Roncoroni et al[10] found that simple or combined metabolic acidosis occurred in 37.9 percent of 103 episodes of severe acute asthma. More recently, other investigators have documented lactic acidosis in 12 (20 percent) of 60 patients[3] and a nonanion gap metabolic acidosis in ten (45 percent) of 22 patients[4] with severe acute asthma. As noted in Table 3, the patients studied by McFadden and Lyons were less hypoxemic than our patients or the patients of Rees et al[11] and this may partially explain the absence of metabolic acidosis in their series.[1] Although Denver's altitude (1,600 m) contributed to the hypoxemia in our patients, the studies of Roncoroni et al[10] (Buenos Aires) and Rees

Table 2—*Clinical Features at Presentation in 229 Episodes of Acute Asthma with (n = 64) and without (n = 165) Metabolic Acidosis*

	Metabolic Acidosis		No Metabolic Acidosis		
Age, yr	34.3 ± 1.9*	64†	37.2 ± 1.2	165	NS‡
Episodes in male subjects, n (%)	26 (40.6)	64	40 (24.2)	165	<.05§
Using accessory muscles, n (%)	60 (93.7)	64	141 (85.2)	165	.05<p<.10
Hyperinflation on chest roentgenogram, n (%)	33 (53.2)	62	48 (29.8)	161	<.01
Pulsus paradoxus, mm Hg	23.2 ± 1.5	58	13.9 ± 0.8	118	<.001
FEV_1, ml	756 ± 92	13	982 ± 94	41	.05<p<.10
pH	7.30 ± .01	64	7.44 ± .01	165	<.001
Room air PaO_2, mm Hg	43.5 ± 1.4	38	53.9 ± 0.7	146	<.001
$PaCO_2$, mm Hg	44.8 ± 2.0	64	33.6 ± 0.9	165	<.001
Anion gap, mEq/L	15.8 ± 0.4	64	12.9 ± 0.2	145	<.001

*Mean ± standard error.
†Number of observations.
‡NS = not significant.
§P value determined by two-tailed *t* test or χ^2 analysis.

Table 3—*Comparison of Studies of Acid-Base Disturbances in Acute Asthma*

Finding	Present Study	Roncoroni et al[10]	McFadden and Lyons[1]	Rees et al[11]
No. of episodes	229	103	101	24
Mean room air PaO_2, mm Hg	52	NA*	70	51
Mean FEV_1 (ml or % pred)	930	NA	28.2%	460
Acid-base disturbance (% of episodes)				
Normal	12.2	25.2	15.8	25.0
Respiratory alkalosis	47.6	12.6	75.3	25.0
Respiratory alkalosis + metabolic acidosis	6.1	0	0	8.3
Metabolic acidosis	5.7	24.3	0	8.3
Respiratory acidosis	10.0	24.3	8.9	12.5
Respiratory acidosis + metabolic acidosis	16.2	13.6	0	4.2
Other	2.2	0	0	16.7

*NA = not available.

et al[11] (Edinburgh) were performed near sea level.

Roncoroni and coworkers[10] provided direct evidence that the metabolic acidosis of acute asthma is a lactic acidosis. Arterial lactate levels were measured in 27 patients with simple or combined metabolic acidosis and found to be elevated in all with a mean value of 4.16 mEq/L.[8] The majority of our subjects with simple or combined metabolic acidosis had a modest increase in the anion gap (Fig 1) consistent with lactic acidosis. Furthermore, none of our subjects had any other apparent cause of anion gap acidosis, including diabetic ketoacidosis, starvation, alcohol ingestion, renal failure, drug ingestion, or toxin ingestion.

Multiple potential causes of lactic acidosis in severe acute asthma exist and include synergistic contributions from intracellular alkalosis, lactic production by respiratory muscles, and tissue hypoxia. Early in the course of acute asthma, hyperventilation leads to hypocapnia and respiratory alkalosis. *In vitro* studies[12] have confirmed that alkalosis stimulates lactate production probably by accelerating glycolytic production of pyruvate and NADH since alkalosis stimulates phosphofructokinase,[13] the rate-limiting enzyme for glycolysis. Controlled *in vivo* studies in normal dogs have confirmed that respiratory alkalosis results in small increments in arterial lactate levels.[14] Many of our patients with apparent respiratory alkalosis alone had small elevations of the anion gap (Fig 1) suggesting a mild lactic acidosis in those subjects as well. Okrent et al,[4] however, found that a nonanion gap metabolic acidosis occurs in acute asthma; they concluded that this was due to excessive renal bicarbonate excretion due to a period of hyperventilation.

Vigorous skeletal muscle exercise is a known cause of transient lactic acidosis.[15] Studies using isocapnic voluntary ventilation have shown that respiratory muscles can produce lactic acid.[16] Furthermore, lactic acidosis may be an important factor in respiratory muscle fatigue.[17] Thus, it seems reasonable to assume that lactate production by respiratory muscles working against the resistive load of increased airflow obstruction contributed to the metabolic acidosis seen in some of our patients. Our findings of increased pulsus paradoxus and other ancillary evidence of greater airflow obstruction with resultant increased work of breathing in patients with metabolic acidosis (Table 2) are consistent with this hypothesis.

Tissue hypoxia may contribute to the lactic acidosis of severe acute asthma. The majority of experimental studies indicate that severe degrees of arterial hypoxemia (PaO_2 30 to 35 mm Hg) are required to reduce arterial oxygen content enough to result in lactic acidosis in the absence of reduced tissue perfusion.[18] None of the patients in our study presented with clinical evidence of hypotension or reduced cardiac output; 11 patients had a room air PaO_2 level of 35 mm Hg or less. Nevertheless, the anion gap correlated inversely with the degree of hypoxemia (Fig 2) suggesting that tissue hypoxia may be an important contributing factor to lactate accumulation and metabolic acidosis. Increasing hypoxemia may reflect increasing airflow obstruction and increased lactate production by respiratory muscles. Furthermore, moderate hypoxia appears to enhance lactate production by respiratory muscles.[17]

In summary, severe hypoxemia in acute asthma may result directly in tissue hypoxia and in an increase in serum lactate levels; however, the moderate degree of hypoxemia more commonly encountered in acute asthma probably acts synergistically with changes in blood pH to facilitate lactate production by respiratory muscles.[17,19] While these modest increases in serum lactate levels may not result in acidemia, it probably contributes to the appropriate compensatory response to acute respiratory alkalosis. It is important to emphasize, however, that complete compensation does

not occur in a primary acid-base disturbance. Thus, a primary respiratory alkalosis would (within the measurement and biologic variability) be associated with a decrease in hydrogen ion activity, whereas the finding of an increase in hydrogen ion activity would imply an associated acidosis. The relevance of the anion gap is variable, since the decrease in the bicarbonate level in cases of metabolic acidosis does not always agree with the change in the anion gap.

Our findings have potential implications for the therapy of severe acute asthma, particularly since 90 percent of our patients with an initial pH of less than 7.30 had a coexistent metabolic acidosis. Previous anecdotal reports[20-22] have called attention to the use of sodium bicarbonate in severe acute asthma; presumed benefits include amelioration of life-threatening acidosis, restoration of responsiveness to adrenergic bronchodilators,[21] and decreasing ventilation, peak inflation pressures, and the risk of barotrauma in patients requiring mechanical ventilation.[22] We think that judicious use of sodium bicarbonate may be an appropriate therapeutic adjunct in patients with severe acute asthma and potentially life-threatening acidosis ($pH<7.20$). Potential complications of alkali therapy, including fluid overload, hyperosmolarity, and rebound alkalosis may be avoided by monitoring the patient's clinical status and arterial blood gases.

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