

DIAGNOSIS

Acid–base patterns in acute severe asthmaGuillermo A. Raimondi, MD¹, Silvia Gonzalez, PhD², Jorge Zaltsman, PhD², Guillermo Menga, MD², and Horacio J. Adrogué, MD³¹Department of Pulmonology, Instituto de Investigaciones Neurológicas Raúl Carrea (FLENI), Buenos Aires, Argentina, ²Department of Pulmonology and Clinical Laboratory, Hospital María Ferrer, Buenos Aires, Argentina, and ³Department of Medicine, Baylor College of Medicine, Methodist Hospital, and Renal Section, Veterans Affairs Medical Center, Houston, TX, USA**Abstract**

Background and objectives: Acid–base status in acute severe asthma (ASA) remains undefined; some studies report complete absence of metabolic acidosis, whereas others describe it as present in one fourth of patients or more. Conclusion discrepancies would therefore appear to derive from differences in assessment methodology. Only a systematic approach centering on patient clinical findings can correctly establish true acid–base disorder prevalence levels. **Methods:** This study examines acid–base patterns in ASA (314 patients), taking into account both natural history of disease and treatment, in patients free of other diseases altering acid–base status. Data were collected from patients admitted for ASA without prior history of chronic bronchitis, emphysema, kidney or liver disease, heart failure, uncontrolled diabetes mellitus or gastrointestinal illness. Informed consent was obtained for all patients, after study protocol approval by the Institutional Review Board. **Results:** Arterial blood gases, plasma electrolytes, lactate levels, and FEV₁ were measured on arrival. Severe airway obstruction was found with FEV₁ values of $25.6 \pm 10.0\%$, substantial hypoxemia (PaO_2 66.1 ± 11.9 mmHg) and increased A-a O₂ gradient (39.3 ± 12.3 mmHg) breathing room air. While respiratory alkalosis occurred in patients with better preservation of FEV₁, respiratory acidosis was observed with more severe airway obstruction, as was increased lactate in the majority of patients, independent of PaO_2 and PaCO_2 levels. **Conclusions:** Predominant acid–base patterns observed in ASA in this patient population included primary hypocapnia, or less frequently, primary hypercapnia. Lactic acidosis occurred in 11% of patients and presented consistently as a mixed acid–base disorder. These findings suggest lactic acidosis results from the combined effects of both ASA and medication-related sympathetic effects.

Keywords

Acid–base balance, airway obstruction, asthma, lactic acidosis, metabolic acidosis

History

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Introduction

Arterial blood gas analysis is a valuable tool in the assessment and management of acute severe asthma (ASA). Blood acid–base status and oxygenation are routinely measured in the emergency department setting and on hospital admission [1,2].

It has by now been well established that hypoxemia arising from alterations in ventilation-perfusion ratios is a constant feature in ASA [3–6]. In addition, carbon dioxide retention is considered an ominous sign, since it is commonly indicative of severe airway obstruction, complicated by respiratory muscle fatigue and ventilatory depression [7–9]. However, conflicting reports in current literature do not allow acid–base status in patients with ASA to be well defined.

Some studies reporting acid–base profiles in acute asthma describe complete absence of metabolic acidosis [7]. Conversely, others report metabolic acidosis developing in as much of one-fourth or more patients with acute asthma

[10,11]. Closer examination of these publications provides an explanation for the discrepancy. Some authors have used acid–base “maps” with confidence bands relating PaCO_2 and pH for the primary acid–base disorders, while others applied rules of thumb for estimating compensatory responses. These two approaches can lead to misdiagnosis, since data falling within a given region of the acid–base “map” or within a compensatory band for any one disorder, do not necessarily confirm the presence of the disorder [12,13].

Only a systematic approach to acid–base diagnosis centered on clinical findings can provide correct diagnosis of disorders in the buffering system [13,14]. This study examines acid–base patterns in ASA taking into account disease natural history, including therapeutic interventions, in patients free of concomitant diseases known to alter acid–base homeostasis.

Methods

Data collected from 314 patients (90 men and 224 women, 18- to 83-years-old) admitted for ASA was analyzed, based on raw data previously published elsewhere relating to outpatient management of acute asthma in Argentina [15,16]. Time elapsed between symptom onset and hospital admission was

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over 72 h in 63% of patients, between 24 and 72 h in 23%, between 3 and 24 h in 13% and less than 3 h in 2% of study patients. All patients met diagnostic criteria for bronchial asthma. Patients presenting bronchitis or emphysema were excluded [17], as were those with significant medical conditions other than bronchial asthma including: kidney or liver disease, heart failure, uncontrolled diabetes mellitus, or symptomatic gastrointestinal illness. Prior to admission 98.4% of patients had been prescribed inhaled beta agonist bronchodilators, 60.7%, inhaled corticosteroids, 11.8% aminophylline and 7.0% systemic corticosteroids. Informed consent was obtained from all patients after approval of the study protocol by the Institutional Review Board (Comité de Bioética, Hospital María Ferrer, 035/11). Blood samples were collected under anaerobic conditions from the radial or brachial artery in the ED. Arterial carbon dioxide tension, oxygen tension, and pH were measured using standard electrodes (Radiometer ABL 520). Plasma electrolytes and lactate were evaluated with Radiometer EML 105 electrodes and plasma anion gap calculated as $\text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)$. One-second forced expiratory volume (FEV_1) (Vitalograph) was measured in the Emergency Department, and expressed as a percentage of predicted normal value normalized to patient age, gender, and height [18]. At least three maneuvers were performed and the highest result was taken as valid. Many patients failed to complete spirometry, in some cases because of poor general physical condition as judged by the attending physician, in others due to other underlying conditions. Relationship between FEV_1 values and arterial blood gases was examined. Correlations of carbon dioxide tension and other acid-base parameters, as well as between serum lactate and other laboratory results were evaluated.

All findings are presented as mean values $\pm$ standard deviation. Student *t* test or Mann-Whitney *U* test were used to compare normally distributed and skewed continuous variables, as appropriate. Correlations were analyzed using Pearson's correlation coefficient of linear regression analysis, and *p* values <0.05 considered statistically significant.

Results

Corresponding acid-base composition, plasma anion gap, and serum lactate results for all patients are listed in Table 1. Three groups are shown, total patient population, patients able to complete spirometry and patients unable to do so. Mean blood arterial pH, PaCO_2 , bicarbonate and base excess levels remained within normal limits, even after a wide range of data point acquisitions, ranging from very low to very high values for each parameter. Mild increase in serum lactate and anion gap was also found. Severe airway obstruction was encountered with FEV_1 values of $25.6 \pm 10.0\%$ (264 patients), as well as substantial hypoxemia (PaO_2 66.1 ± 11.9 mmHg) and increased alveolo-arterial oxygen tension difference (39.3 ± 12.3 mmHg), in 237 patients breathing room air (for mmHg conversion to kilopascals, SI units must be multiplied by a factor of 0.133). Comparison between patients able to successfully complete spirometry and those unable to perform the evaluation revealed hypocapnia and alkalemia (i.e. respiratory alkalosis) in the former, and hypercapnia and acidemia (i.e. respiratory acidosis) in the latter, although

Table 1. Laboratory data on admission for acute severe asthma.

	Blood pH	PaCO_2	$[\text{HCO}_3^-]$, mEq/L	BE, mEq/L	AG, mEq/L	Lactate
All patients	7.42 ± 0.09 (314)	37.5 ± 12.5 (314)	23.4 ± 3.6 (314)	-0.4 ± 3.9 (314)	14.1 ± 3.2 (238)	3.0 ± 1.5 (160)
Group I	7.44 ± 0.04 (266)	35.1 ± 6.5 (266)	23.4 ± 3.5 (266)	0.1 ± 3.1 (266)	14.1 ± 3.2 (196)	2.9 ± 1.4 (126)
Group II	7.31 ± 0.18 ($p < 0.00000$) [48]	50.9 ± 24.3 ($p < 0.00000$) [48]	23.4 ± 4.2 (NS) [48]	-3.2 ± 5.6 ($p < 0.0001$) [48]	13.9 ± 3.4 (NS) [42]	3.1 ± 2.0 (NS) [34]

Groups I and II, refer to patients who could perform spirometry, and those who could not perform this evaluation, respectively. A comparison of Group I versus II and the statistical significance are indicated with the respective *p* values. BE, base excess; AG, plasma anion gap ($\text{Na}^+ - \text{Cl}^- - \text{HCO}_3^-$); values in parenthesis indicate number of patients for each determination. To convert mmHg to kilopascals (SI units) multiply by 0.133.

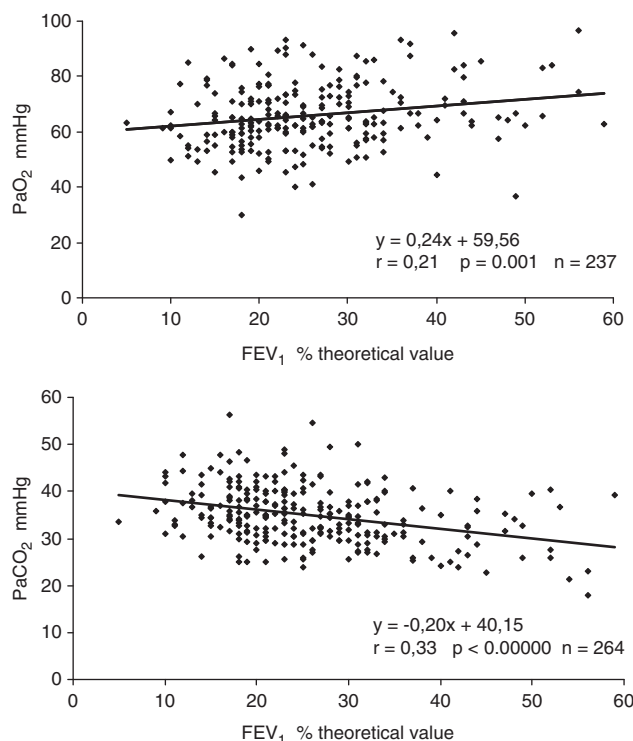


Figure 1. Relationships between FEV₁% and PaO₂ (upper panel) and FEV₁% and PaCO₂ (lower panel) in patients with acute severe asthma on admission. A significant positive correlation was found between FEV₁% and PaO₂; thus, the more severe the airway obstruction led to lower oxygen levels in patient's breathing room air. By contrast, a significant negative correlation was detected between FEV₁% and PaCO₂; thus, the more severe the airway obstruction resulted in higher carbon dioxide tension (to convert mmHg to kilopascals, SI units, multiply by 0.133).

serum lactate levels and anion gap values did not differ between these two groups (Table 1).

Severity of airway obstruction and arterial blood gas levels

Significant positive correlation was found between the FEV₁ and PaO₂ (Figure 1, upper panel). Conversely, significant negative correlation was detected between the FEV₁ and PaCO₂ (Figure 1, lower panel), as well as between PaCO₂ and PaO₂ (Figure 2, upper panel), such that carbon dioxide retention was associated with lower levels of blood oxygenation.

Correlation between carbon dioxide tension and other acid–base parameters

A statistically significant negative correlation (Figure 2, lower panel) was found between PaCO₂ and blood pH. Figure 3 depicts the relationship between PaCO₂ and plasma HCO₃[−] for all patients (upper panel) and for patients not exceeding 45 mmHg (middle panel). The relationship between PaCO₂ and plasma [HCO₃[−]], corrected for bicarbonate-depleting effects of lactic acidosis, was examined adding serum lactate to plasma [HCO₃[−]]. $\Delta\text{HCO}_3^-/\Delta\text{PaCO}_2$ derived using “corrected” HCO₃[−], and demonstrated that for each mmHg decrease in PaCO₂, plasma [HCO₃[−]] decreased by 0.44 mEq/L. (Figure 3, lower panel).

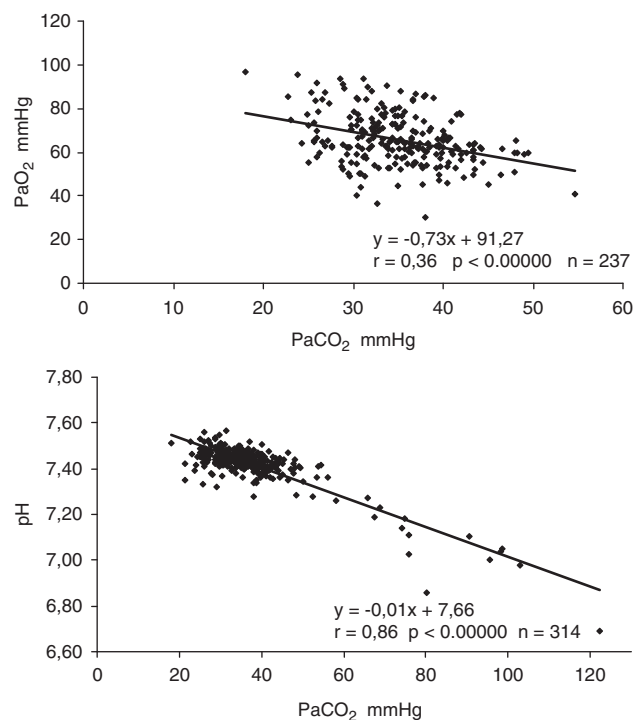


Figure 2. Relationships between PaCO₂ and PaO₂ (upper panel) and PaCO₂ and blood pH (lower panel) in patients with acute severe asthma on admission. A significant negative correlation was found between PaCO₂ and PaO₂; thus, carbon dioxide retention was associated with lower oxygen levels. As expected, a significant negative correlation between PaCO₂ and pH was detected that resembled the experimental *in vivo* CO₂ titration curve in normal man (to convert mmHg to kilopascals, SI units, multiply by 0.133).

Correlation of serum lactate levels to other laboratory results

Significant positive correlation between serum lactate levels and plasma anion gap was observed (Figure 4). The corresponding equation, $\text{AG} = 11.2 + 0.98 \times \text{lactate}$, demonstrated that the rise in anion gap was fully accounted for by the rise in serum lactate; consequently, no retention of other acids occurred in these patients. Reliable diagnosis of lactic acidosis requires serum lactate levels ≥ 5 mEq/L, although slightly lower values have been used by some investigators. No strong correlation between PaCO₂ and serum lactate was observed, but lactate values ≥ 5 mEq/L were detected in 18 patients (11% of study subjects in whom lactate was measured) with variable PaCO₂ ranging from hypocapnia to hypercapnia. Table 2 shows acid–base data in patients with hypocapnia, eucapnia, and hypercapnia with lactate levels ≥ 5 mEq/L. To further examine acid–base homeostasis in these groups, the Henderson–Hasselbalch equation was applied to estimate expected blood pH using measured PaCO₂ together with calculated and “corrected” [HCO₃[−]]. Measured and estimated blood pH values found were 7.43 and 7.56 (hypocapnia), pH 7.40 and 7.51 (eucapnia), and pH 6.91 and 7.08 (hypercapnia), respectively. Substantial alkalemia and high levels of “corrected” bicarbonate estimated for the hypocapnia and eucapnia groups were indicative of a coexistent metabolic alkalosis participating in mixed type acid–base disorders.

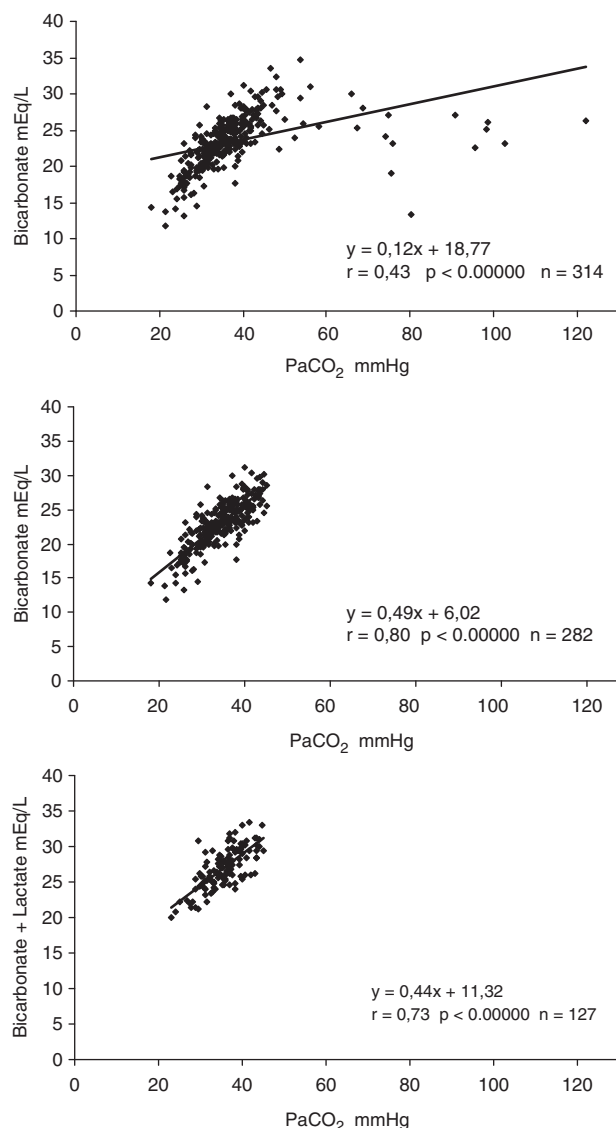


Figure 3. Relationships between PaCO_2 and HCO_3^- including all patients (upper panel) and between PaCO_2 and HCO_3^- in patients with PaCO_2 not exceeding 45 mmHg (middle panel). Significant positive correlations between these variables were detected, but the slope was higher when patients with hypercapnia were excluded. The relationship between PaCO_2 and “corrected” HCO_3^- for lactate (lower panel) demonstrates that the $\Delta[\text{HCO}_3^-]/\Delta\text{PaCO}_2$ of patients with hypocapnia was close to that described in experimental chronic hypocapnia in normal man (to convert mmHg to kilopascals, SI units, multiply by 0.133).

Discussion

Accurate diagnosis of alterations in acid-base balance requires a systematic approach centering on patient clinical findings [12,13]. Unraveling which acid-base pattern is present in ASA cases requires as a fundamental step, to link acid-base data collected to natural history of causal disease, as well as to other associated factors including therapeutic interventions. Common practice, which currently involves simply plotting laboratory values into a published acid-base template, significantly increases risk of misinterpretation of true patient acid-base status. Similarly, any attempt to identify a primary underlying clinical condition by direct comparison of patient acid-base data to four simple cardinal disorders with expected secondary responses is inappropriate,

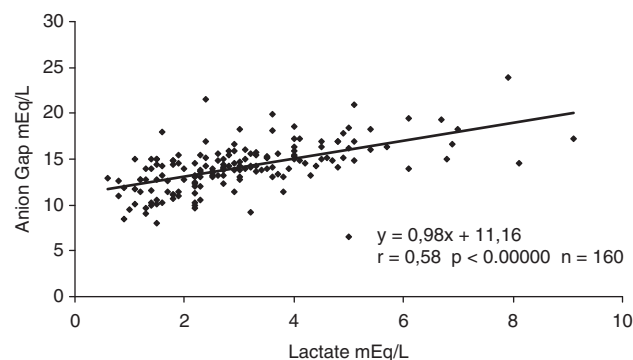


Figure 4. Relationship between lactate levels and plasma anion gap in patients with acute severe asthma on admission. A significant positive correlation between these variables was found; the corresponding equation had a slope of 0.98 mEq/L increase in anion gap per one mEq/L increase in serum lactate. Thus, 98% of the rise in anion gap was accounted for by retention of lactate, a finding supporting that there were no retention of other acids.

and may also represent an additional source of diagnostic error [14].

Severity of airway obstruction

Natural history of ASA is characterized by symptoms of airway obstruction that may persist for days or even weeks in spite of sustained bronchodilator use [2]. Failure to respond to rescue medication and progressive clinical deterioration are the main reasons patients consult the Emergency Department. In the cohort presented in this study, initial evaluation revealed severe airway obstruction (FEV_1 of approximately 26%) with hypoxemia and increased alveolar-arterial oxygen tension difference, findings largely resembling those described in other studies. Weak relationship between PaO_2 and degree of airway obstruction was found, an observation not entirely unexpected, considering the lack of correlation between VA/Q mismatch and air flow rates previously reported in the literature during acute asthma attacks [19–22]. Also important to consider in this setting are the opposing effects of β agonists on measured air flow and gas exchange, that can lead to reduction in airway obstruction with simultaneous worsening of gas exchange parameters [23,24].

Severity of both airway obstruction and general clinical condition were reflected in blood acid-base values measured, findings supported by the statistically significant negative correlation found between FEV_1 and PaCO_2 . Additionally, and most importantly, patients unable to complete spirometry tests, largely reflecting the presence of a critically ill and incapacitating condition, also exhibited respiratory acidosis. Conversely, patients having less severe acute asthma presented respiratory alkalosis. Approximately 10% of patients exhibited hypercapnia, with PaCO_2 levels exceeding 45 mmHg; mean values were PaCO_2 65.5 mmHg, HCO_3^- 26.8 mEq/L and pH 7.24.

Acid-base diagnosis

To determine baseline plasma bicarbonate levels in the absence of lactic acidosis, we examined the relationship of PaCO_2 and bicarbonate corrected for the effect of lactate on

Table 2. Laboratory data from patients with lactic acidosis in association with hypocapnia, eucapnia and hypercapnia.

	Hypocapnia (PaCO ₂ <35 mmHg)	Eucapnia (PaCO ₂ 35–45 mmHg)	Hypercapnia (PaCO ₂ >45 mmHg)
Measured parameters			
PaCO ₂ mmHg	28.5 ± 4.3	39.3 ± 1.7	95.3 ± 18.7
pH	7.43 ± 0.05	7.40 ± 0.03	6.91 ± 0.14
[HCO ₃ ⁻] mEq/L	18.8 ± 4.2	24.5 ± 1.4	20.9 ± 4.9
Lactate mEq/L	5.9 ± 3.7	6.1 ± 0.8	6.8 ± 1.8
Derived parameters			
PaCO ₂ mmHg	28.5 ± 4.3	39.3 ± 1.7	95.3 ± 18.7
pH	7.56 ± 0.04	7.51 ± 0.02	7.08 ± 0.08
“corrected” [HCO ₃ ⁻] mEq/L	24.8 ± 3.7 (9)	30.5 ± 0.8 (4)	27.6 ± 5.1 (5)

Patients with serum lactate ≥ 5 mEq/L are included. “Corrected” [HCO₃⁻] represents the sum of [HCO₃⁻] and lactate; measured PaCO₂ and “corrected” [HCO₃⁻] allowed to obtain the expected blood pH with the use of the Henderson–Hasselbalch equation. Values in parenthesis indicate number of patients in each group. To convert mmHg to kilopascals (SI units) multiply by 0.133.

plasma bicarbonate. A statistically significant relationship between PaCO₂ and “corrected bicarbonate” was found having a $\Delta[\text{HCO}_3^-]/\Delta\text{PaCO}_2$ slope of 0.44 mEq/L per mmHg. Slope gradient was close to that present in uncomplicated chronic hypocapnia, a finding supporting respiratory alkalosis lasting 48 h or more, as the dominant acid–base disorder present in most of these patients [25–27].

Mild increase in serum lactate of 3.0 ± 1.5 mEq/L was observed when all study patients were included, but values varied widely from low to substantially high values. Earlier studies have indicated that patients with ASA suffering greater airflow obstruction and hypoxemia were likely to develop metabolic acidosis caused by lactate accumulation [10]. The current study does not support this view. We found no relationship between airway obstruction severity or blood oxygenation, and serum lactate or anion gap. Furthermore, patients with less severe clinical presentation who could perform spirometry showed similar serum lactate and anion gap levels, to those measured in patients who could not perform the test. Consequently, factors other than blood oxygenation and airway obstruction are most likely responsible for the hyperlactatemia observed in ASA.

Isolated lactic acidosis or simple metabolic alkalosis was not detected in any of the study patients presenting ASA. However, lactate levels exceeding 5 mEq/L were found in 11% of patients exhibiting a mixed acid–base disorder. Further evaluation of these cases in each of the three patient groups based on corresponding PaCO₂ levels, provided insights in terms of the significance of lactic acidosis in the context of mixed acid–base disorders. Estimation of “corrected” bicarbonate and application of the Henderson–Hasselbalch equation, to calculate anticipated blood pH level in the absence of lactic acidosis unveiled the possible presence of a “hidden” metabolic alkalosis of mild severity in some patients with lactic acidosis (Table 2). Pathogenesis of this condition might include unreported antacid intake, use of corticosteroids, vomiting, or other mechanisms. Large plasma anion gaps substantially exceeding values expected for plasma lactate levels observed, documented in experimental lactic acidosis [28], suggest the possibility of coexisting metabolic alkalosis. However, this observation cannot explain the findings we describe, since in this study, increase in anion

gap was almost identical to increase in serum lactate ($\Delta\text{AG}/\Delta\text{lactate} = 1.0$).

Causes of lactic acidosis

Since respiratory alkalosis was the dominant acid–base disorder observed in this group of patients, we examined its possible role in hyperlactatemia. Alkalosis stimulates glycolysis leading to increased serum lactate, whereas acidosis exerts the exact opposite effect [29–32]. Overall magnitude of this effect is only up to 3 mEq/L in general, but may increase in settings where other factors lead to hyperlactatemia [33]. Both passive and voluntary hyperventilation in humans inducing hypocapnia increase serum lactate by 2–3 mEq/L [34–36]. Conversely, isocapnic hyperventilation achieved with supplementary carbon dioxide administration while exerting a similar workload on respiratory muscles is not accompanied by a rise in serum lactate [37].

Epinephrine administration in animals and humans increasing plasma lactate, as well as salbutamol infusion in rabbits, all lead to lactic acidosis [38–40]. Stimulation of Na⁺/K⁺ ATPase by β agonists has been linked to increased lactic acid production [29,41]. Additionally, several studies have linked lactic acidosis to inhaled β agonists in patients with acute asthma [42–45]. In fact, a prospective study of patients with acute asthma treated in the Emergency Department with high doses of inhaled salbutamol showed that increase in blood lactate levels was associated with improvement of respiratory function [46]. The authors concluded that high lactate concentrations can develop within the first hours of inhaled β -agonist treatment and that the presence of a previous a hyperadrenergic state may predispose to the development of hyperlactatemia.

Significant correlation between PaCO₂ and serum lactate was not observed. Lactate levels ≥5 mEq/L, i.e. lactic acidosis, were found in patients with PaCO₂ levels ranging from hypocapnia to hypercapnia. Consequently, sympathetic stimulation resulting from ASA irrespective of PaCO₂ levels, in combination with β -agonist adrenergic medications used for treatment are both thought to be dominant and key factors responsible for increased serum lactate levels observed in patients like those described. Our view, that high serum

lactate in ASA results from sympathetic activation is also supported by previous observations in patients with this disease, who after treatment with large doses of β -adrenergic agonists present substantial hyperlactatemia without tissue hypoxia.

In summary, acid-base patterns that emerged in the vast majority of study subjects included the primary respiratory disorder as the dominant abnormality. Severity of airway obstruction determined whether hypocapnia or hypercapnia developed. Respiratory alkalosis was detected in patients with better preservation of FEV₁, whereas respiratory acidosis developed in those with more severe airway obstruction. Increased lactate levels were observed in a large fraction of patients, independent of either carbon dioxide or blood oxygen tension levels. Only a small fraction of study patients exhibited lactate levels ≥ 5 mEq/L, evenly distributed between those with high and low level airway obstruction. Thus, high lactate levels were not indicative of acute asthma severity. Although simple lactic acidosis as an isolated disturbance was not observed, mixed acid-base disorder resulting from a combined respiratory acidosis, respiratory alkalosis, or metabolic alkalosis, with lactic acidosis developed in 11% of patients. These data suggest in this study population, lactic acidosis resulted from the combined effects of ASA and medication-related sympathetic effects.

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Declaration of interest

The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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