Intensive Care Med (1998) 24: 304–312

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Hyperlactatemia during acute severe asthma

Received: 29 July 1997
Accepted: 26 January 1998

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Abstract *Objective:* To evaluate arterial lactate levels during treatment of acute severe asthma (ASA) and the prognostic value of arterial hyperlactatemia in ASA.
Design: Prospective study.
Setting: A respiratory intensive care unit (ICU) of a university hospital.
Patients: 29 consecutive patients admitted to the ICU for ASA not intubated on admission and with a peak expiratory flow (PEF) < 150 l/min or an arterial carbondioxide tension ($PaCO_2$) > 40 mm Hg. All patients received standardized treatment during the first 24 h including i. v. and nebulized salbutamol, i. v. theophylline, and dexamethasone.
Measurements and results: Arterial lactate levels were serially measured by an enzymatic method during the first 24 h following admission. On admission, the mean arterial lactate level was 3.1 ± 0.38 mmol/l (range 1.1–10.4); 17 patients (59 %) had arterial hyperlactatemia with a lactate level > 2 mmol/l. No difference was found in lactate levels between patients with progressively worsening asthma and those with an acute onset of severe asthma. No correlation was found between arterial lactate levels on admission, on the one hand, and respiratory rate (RR), heart rate, PEF, pH, $PaCO_2$, arterial oxygen tension, potassium, phosphorus, creatine kinase, or transaminase values on admission, on the other hand. All patients developed an important but transient increase in arterial lactate levels during treatment, with a peak at 7.72 ± 0.46 mmol/l and a mean elevation of 4.62 ± 0.45 mmol/l (range 0.4–12.1), from the initial admission value contrasting with a significant clinical improvement assessed by RR, PEF, and arterial blood gas parameters.
Conclusion: This study suggests that, in ASA, arterial hyperlactatemia is frequently present on admission to the ICU. Delayed hyperlactatemia is a constant finding during treatment of ASA. Initial or delayed hyperlactatemia seems of no prognostic value because none of the patients required mechanical ventilation. The effects of therapy for acute asthma on lactate metabolism still need to be studied.

Key words Acute severe asthma · Blood lactate · Bronchodilator therapy

Introduction

Acute asthma is usually associated with hyperventilation and respiratory alkalosis on blood gas analysis [1]. When airway obstruction is more severe or prolonged, respiratory acidosis may develop. Metabolic acidosis has been reported in acute severe asthma [2] and two types of metabolic acidosis have been described: renal loss of bicarbonate as a renal compensatory response to a preceding period of hypercapnia due to

a prolonged period of hyperventilation and lactic acidosis [3].

In critically ill patients, elevation of lactate levels usually reflects tissue hypoxemia and a predominant anaerobic metabolism [4]. Monitoring of lactate levels seems helpful for assessing the effectiveness of therapy and patient prognosis in several clinical situations, such as cardiogenic shock or septic shock [4–7]. A persistent elevated arterial lactate level is often associated with a poor prognosis [5].

An increase in arterial blood lactate has been noticed either on admission or during the course of acute severe asthma (ASA) [8–11]. Hyperlactatemia has been suggested to be a marker of severity of ASA, predicting respiratory failure and the requirement for mechanical ventilation [9]. However, hyperlactatemia in ASA has only been reported in retrospective studies [2, 8–10]. The incidence of arterial hyperlactatemia in ASA and its prognostic value are not well known.

The aim of our prospective study was to evaluate in patients with ASA arterial lactate levels on admission to the ICU and variations during treatment of ASA. Another aim of the study was to assess the prognostic value of hyperlactatemia in ASA by analysing the relationships between an elevated arterial lactate level and patient outcome, especially the occurrence of respiratory failure requiring mechanical ventilation.

Patients and methods

Patients

During a 6-month period all patients admitted to the ICU at Hôtel-Dieu Hospital for ASA were eligible for the study. The diagnosis of asthma was made according to the American Thoracic Society criteria [12]. A diagnosis of ASA was made according to the clinical indices of ASA given in the most recent guidelines for the diagnosis and management of asthma [13–15]. Admission to the ICU was decided on either because of a severe initial clinical status with a near-death state or because of failure of an initial emergency treatment including oxygen therapy, at least 10 mg of a nebulized $beta_2$ agonist (salbutamol), and i.v. corticosteroids. Failure of initial emergency treatment was determined 30 min after the patient had received the treatment by the presence of one or more of the following signs: respiratory rate above 30/min, heart rate above 120/min, severe dyspnea and difficulty speaking, intercostal or tracheosternal retraction, nasal flaring, cyanosis, inaudible breath sounds, pulsus paradoxus above 20 mm Hg, arterial carbon dioxide tension ($PaCO_2$) $\geq$ 40 mm Hg, or peak expiratory flow rate (PEF) $\leq$ 150 l/min.

We excluded from the study all patients with one of the following conditions: shock or systolic arterial pressure lower than 80 mm Hg, renal failure (creatinine level above 150 μmol/l), severe sepsis, or liver dysfunction [bilirubin > 30 μmol/l, alanine aminotransferase (ALAT) or aspartate aminotransferase (ASAT) exceeding five times the normal value] on admission to the ICU, retrospective diagnosis of chronic obstructive pulmonary disease (after review of clinical history and respiratory function evaluation), previously known endocrine disease (diabetes mellitus, pancreatic or thyroid gland dysfunction), previous severe liver disease (cirrhosis), and pregnancy. We also excluded patients under mechanical ventilation, before ICU admission, as one of the study aims was to evaluate patient outcome and occurrence of respiratory failure with regard to lactate level.

Treatment

During the first 24 h in the ICU, all patients were treated according to a standard protocol, which included oxygen therapy to maintain arterial oxygen saturation (SaO_2) above 92%, intravenous hydration with 4 l per day of 5% dextrose in water with sodium, potassium, and phosphorus according to serum levels, intravenous β_2 agonist (salbutamol 1 mg/h) nebulized β_2 agonist (10 mg salbutamol nebulized on admission, repeated 20 min later and every hour during the first 6 h and then every 4 h), corticosteroids (i.v. dexamethasone, 20-mg bolus followed by 0.15 mg/kg i.v. 4-hourly) and continuous intravenous theophylline infusion adjusted to the individual theophylline clearance [16] in order to obtain a serum concentration of 12 mg/l. In the case of clinical worsening despite medical treatment, intravenous β_2 agonist infusion was progressively increased up to 5 mg per h. If bronchial obstruction still did not improve, intravenous epinephrine 0.1 mg up to 1 mg per h was infused. In the case of refractory bronchial obstruction, a decision to mechanically ventilate could be made. After 24 h, intravenous drugs were progressively withdrawn if clinical status, arterial blood gases, and PEF had improved.

Clinical improvement was assessed by hourly recording of respiratory rate, heart rate, and PEF during the first 24 h (Miniwright Peakflowmeter).

Measurements of arterial blood lactate, serum electrolyte determination, and arterial blood gas analysis

All specimens for blood gas analysis, lactate, electrolytes, creatine kinase (CK), ALAT and ASAT determination, and theophylline blood levels were obtained by collecting blood samples via an arterial catheter aseptically inserted on admission.

A 5-ml sample of arterial blood was obtained anaerobically via the arterial catheter for lactate determination. The specimens were placed on ice and immediately transported and analyzed within 5 min. The lactate level was determined by enzyme assay (Kodak Ektachem 700 Analyzer C series, Rochester, N.Y., USA). Normal arterial lactate values using this technique in resting normal volunteers have been reported to be less than 2 mmol/l. Another 3 ml of arterial blood was drawn anaerobically into a heparinized syringe and placed immediately on ice for arterial blood gas analysis. Arterial blood pH, $PaCO_2$, base excess, arterial oxygen tension (PaO_2), and SaO_2 were determined using an automated blood gas analyzer (Blood Gas Analyzer 1306, Instrumentation Laboratory, Milano, Italy). An additional 10 ml of arterial blood was collected into a non-heparinized syringe for serum potassium, phosphorus, CK, ASAT, and ALAT determination. The serum potassium level was determined by an electrochemical method (Beckman, Brea, Calif., USA). Serum phosphorus levels were determined by a colorimetric method (Kodak Ektachem 700 Analyzer C series, Rochester, N.Y., USA), and CK, ALAT, and ASAT by enzyme assay (Kodak Ektachem 700 Analyzer C series, Rochester, N.Y., USA).

Arterial blood samples for determination of lactate, blood gas analysis, potassium, phosphorus, and CK concentrations were obtained on admission to the ICU (H0) and 3 h (H+3), 6 h (H+6), 14 h (H+14), and 24 h (H+24) after admission. ASAT and ALAT were determined only at H0 and at H+14 and H+24. Theophylline

Table 1 General characteristics of the patients ($n = 29$). Results are expressed as number of patients or mean ± SEM (*NSAID* non-steroidal anti-inflammatory drug, *ASA* acute severe asthma)

Sex	13 F, 16 M
Age (years)	43 ± 2.6
Delay since first diagnosis of asthma (years)	10 ± 1.5
Atopy	10
Intolerance to NSAIDs	3
Previous ASA	16
Usual asthma medication	
Inhaled β_2 agonists	28
Inhaled steroids	12
Oral steroids[a]	14
Theophylline	12
Other drug	3
Triggering factors of ASA	
Bronchitis or pneumonia	6
Total or partial withdrawal of treatment	18
Aspirin- or NSAID-induced crisis	1
Pattern of the crisis	
Delay of worsening (h)	56 ± 11.6
Acute onset severe asthma	13

[a] More than 5 mg per day of equivalent of prednisone for at least 1 month during the 12 previous months

Table 2 Characteristics of the patients on admission to the ICU (*SAPS* simplified acute physiology score, *RR* respiratory rate, *HR* heart rate, *PEF* peak expiratory flow, *pH* arterial pH value, PaO_2 arterial oxygen partial pressure, $PaCO_2$ arterial carbon dioxide partial pressure, HCO_3 bicarbonate level, *BE* arterial base excess, *Lactate* arterial blood lactate level, K^+ serum potassium level, *CK* creatine kinase, *ALAT* alanine aminotransferase, *ASAT* aspartate aminotransferase)

	Mean value ± SEM
SAPS	8.2 ± 0.5
RR (/min)	30 ± 1
HR (/min)	118 ± 3.3
PEF (l/min)	135 ± 10.6
Pulsus paradoxus > 20 mm Hg (n)	9
pH	7.36 ± 0.01
$PaCO_2$ (mm Hg)	42 ± 1.2
PaO_2 (mm Hg)	89.2 ± 5.7
HCO_3 (mmol/l)	23.2 ± 0.53
BE (mmol/l)	0.18 ± 0.55
Lactate (mmol/l)	3.11 ± 0.38
Lactate ≤ 2 mmol/l (n)	12
Lactate > 2 mmol/l (n)	17
Anion gap (mmol/l)	14.25 ± 0.38
K^+ (mmol/l)	3.38 ± 0.08
$K^+ \leq 3.5$ mmol/l (n)	19
$K^+ > 3.5$ mmol/l (n)	10
Phosphorus (mmol/l)	1.02 ± 0.04
P ≤ 0.75 mmol/l (n)	5
P > 0.75 mmol/l (n)	24
CK (IU/l)	214 ± 35
ASAT (IU/l)	19 ± 2.6
ALAT (IU/l)	23 ± 2.9

blood levels were determined at H0, at the end of the loading dose (20 min), and at H+3, H+6, H+14, and H+24, as described previously [16].

Based on recent consensus conferences on the management of ASA [13–15], written guidelines for hospital or ICU admission, treatment, and clinical and biological monitoring of patients with ASA are routinely used in our hospital. For this study, arterial lactate measurement was the only additional biological parameter we monitored.

The study design was in accordance with the revised Helsinki Declaration of 1983.

Statistical analysis

Statistical analysis was performed using the Statview SE software (Abaccus Concept, Berkeley, Calif., USA). All results are expressed as mean values ± standard error of the mean. Continuous variables were compared using parametric and nonparametric tests according to the distribution of the values. The parametric tests used were Student's t-test for paired or unpaired values and the nonparametric tests used were the Wilcoxon rank sum test and the Mann–Whitney test. The chi-square test was used for discontinuous variables. A p value < 0.05 was considered as statistically significant. Associations between variables were assessed using simple regression and Spearman's correlation analyses.

Results

The general characteristics and clinical pattern of the severe asthmatic crisis that the 29 patients included in the study had are given Table 1. Most had a long history of asthma, with first clinical symptoms 10 ± 1.5 years earlier (range 2–33 years). Of the 29 patients, 18 had severe chronic asthma [15]. Atopy, defined by an elevated immunoglobulin E level, a positive skin test, or a previous allergic manifestation such as Quincke's edema, allergic rhinitis, or eczema, was patent in 10 patients. The usual asthma medication was extremely variable including 0 to 6 drugs for each patient.

Thirteen patients had a sudden asphyxic asthma attack which worsened in less than an hour and they were admitted to the ICU within 2 h of the crisis. Admission to the ICU was decided on either because of the severe initial clinical status ($n = 14$) or because of lack of response to initial treatment ($n = 15$).

The medical treatment given before admission to the ICU included oxygen for 29 patients, nebulized salbutamol for 29 patients: 15 ± 3 mg (range 10–20 mg), i.v. salbutamol for 9 patients (0.25–1 mg/h), subcutaneous terbutaline for 8 patients (0.25–1 mg), and i.v. corticosteroids for 25 patients. None of the patients had received epinephrine or i.v. theophylline before ICU admission.

The characteristics of the patients on admission to the ICU are given in Table 2. In the group of patients

Table 3 Treatment in first 24 h. Values are numbers on mean ± SEM

i. v. Salbutamol (n)	29
(μg/kg per min)	0.24 ± 0.012
Nebulized salbutamol (n)	29
Number of nebulizations (10 mg)/day	12 ± 0.5
i. v. Dexamethasone (n)	29
(mg/kg per day)	1.2 ± 0.1
i. v. Theophylline (n)	29
(mg/kg per h)	0.8 ± 0.2
Serum theophylline level (mg/l)	
H+3	9.7 ± 0.7
H+6	11.2 ± 0.4
H+24	11.1 ± 0.3
Mechanical ventilation (n)	0

with acute onset of severe asthma ($n = 13$) and severe clinical signs when ICU referral was made, 5 patients had a rapidly reversible bronchial spasm after initial treatment and presented almost no wheezing on admission.

Mean PaO_2 value while receiving oxygen was 89 ± 5.7 mm Hg (range 59–188), mean pH 7.36 ± 0.01 (7.25–7.45), and mean $PaCO_2$ 42.03 ± 1.2 (33–55); 16 patients had a $PaCO_2 > 40$ mm Hg and the mean bicarbonate level was 23.2 ± 0.53 mmol/l. Three patients had a pH value above 7.40 with decreased $PaCO_2$ (< 37 mm Hg). Eleven patients (38%) had acidosis with an arterial pH lower than 7.35. Two types of acidosis were noted: respiratory acidosis with a $PaCO_2$ above 45 mm Hg in 7 patients (24%) and metabolic acidosis with an increased anion gap (≥ 16 mmol/l) in 4 patients (14%).

Nineteen patients (66%) had hypokalemia ($K^+ \leq 3.50$ mmol/l). Serum phosphorus levels were within the normal range (0.90–1.25 mmol/l) in 20 patients, only 5 had significant hypophosphatemia ($\leq$ 0.75 mmol/l). CK was slightly elevated (normal < 150 IU/l) in 15 patients (50%), but the MB fraction was always below 5% of the total CK value. Only 1 patient had a moderate increase in transaminase values but less than twice the upper limit of usual values (normal range: ASAT 14–50 IU/l, ALAT 21–72 IU/l).

The mean arterial lactate level on admission (Table 2), was 3.1 ± 0.38 mmol/l (range 1.1–10.4); 17 patients (59%) had arterial hyperlactatemia with a lactate level above 2 mmol/l. No statistically significant difference was found in lactate levels between the groups with progressively worsening asthma and acute onset of severe asthma. No statistically significant correlation was found between arterial lactate levels on admission and the following parameters: respiratory rate, heart rate, PEF, pH, $PaCO_2$, PaO_2, potassium, phosphorus, CK, or transaminase values on admission.

During the first 24 h in the ICU, all patients were treated according to our standard therapy described above (Table 3). Neither mechanical ventilation nor increasing i. v. salbutamol infusion rate was necessary.

Significant clinical improvement was noted in all patients during the first 24 h of treatment (Table 4). Clinical signs of severe bronchial spasm, as mentionned above, were absent in all patients after 24 h of treatment. A statistically significant improvement in PEF was noted at the end of the third hour of treatment. After 6 h of treatment, PEF increased significantly compared to the admission value (HO 234 ± 18 versus 135 ± 11 l/min, $p < 0.005$, PEF (H+6) > 150 l/min: $n = 27/29$). The mean PEF H+24 was 273 ± 17 l/min (130–500), $p < 0.001$ vs H0. At this time, only 6 patients had a PEF lower than 200 l/min.

The consecutive arterial blood gas analyses (Table 4) showed pH values to be normal and $PaCO_2$ values decreased. PaO_2 values, with oxygen supply, remained within the normal range in all patients. After 6 hours of treatment, mean $PaCO_2$ had significantly decreased (35.6 ± 0.9 vs 42 ± 1.2 mm Hg, $p < 0.005$) and 25 patients had values < 45 mm Hg.

A marked decrease in phosphorus (P) and potassium (K^+) values was noted (Table 4) after 3 h of treatment: P = 0.81 ± 0.04 mmol/l (0.32–1.29), K^+ = 3.15 ± 0.08 mmol/l, $p < 0.005$ vs H0. Potassium and

Table 4 Clinical and biological evolution during the first 24 h of treatment. Values are mean ± SEM

	H0	H+3	H+6	H+14	H+24
Lactate (mmol/l)	3.1 ± 0.38	5.45 ± 0.39*	7.38 ± 0.38*	4.97 ± 0.54*	2.96 ± 0.22
PEF (l/mn)	135 ± 11	209 ± 19*	234 ± 18*	251 ± 18*	273 ± 17*
RR (/min)	30 ± 1	32 ± 2	25 ± 3*	24 ± 2*	20 ± 1*
pH	7.36 ± 0.01	7.36 ± 0.01	7.35 ± 0.01	7.39 ± 0.01*	7.42 ± 0.01*
$PaCO_2$ (mm Hg)	42 ± 1.2	38.2 ± 0.9*	35.6 ± 0.9*	34.3 ± 0.9*	33.9 ± 0.7*
PaO_2 (mm Hg)	89.2 ± 5.7	95.7 ± 4.2	99.3 ± 4.1	99.1 ± 4.5	91.3 ± 3.7
K^+ (mmol/l)	3.38 ± 0.08	3.16 ± 0.08*	3.43 ± 0.09	3.70 ± 0.11*	3.85 ± 0.1*
Phosphorus (mmol/l)	1.02 ± 0.04	0.81 ± 0.04*	0.83 ± 0.04*	0.89 ± 0.05*	1.01 ± 0.06

* $p < 0.05$ versus H0

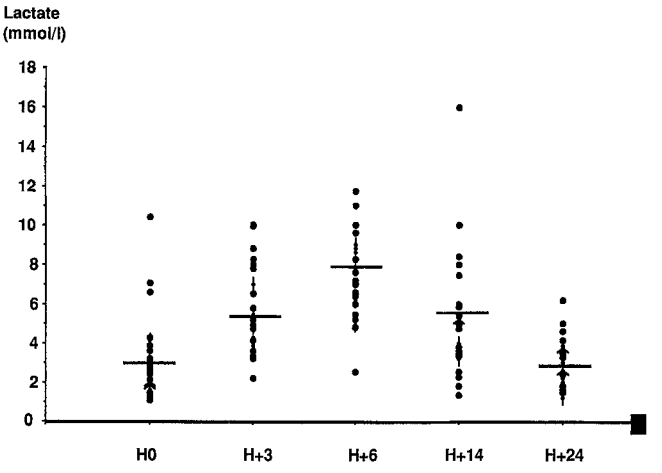

Fig. 1 Individual arterial blood lactate levels. *Horizontal bars* indicate mean values on admission *H0*, and at 3 *H+3*, 6 *H+6*, 14 *H+14*, and 24 h *H+24* after admission

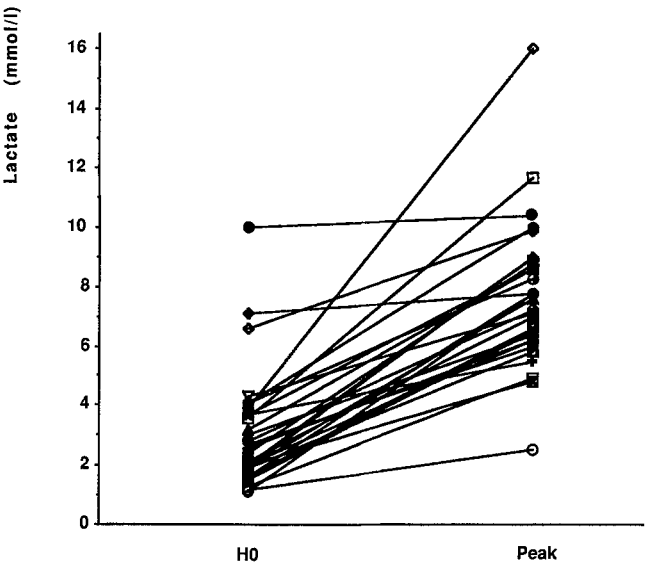

Fig. 2 Maximum increase in arterial blood lactate levels. *H0* at admission, *Peak* maximum value of arterial blood lactate levels obtained after admission (after 3 h in 3 patients, 6 h in 24 patients and 14 h in 2 patients)

phosphorus values were within the normal range at H+24. Ten patients had elevated creatine phosphokinase (CPK) at H+24. One patient had a CPK above 1000 IU/l with no clinical or renal function impairment. Transaminase values were within the normal range in all patients at H+24.

The kinetics of arterial lactate is shown in Table 4 and Figs. 1 and 2. In all patients arterial lactate levels increased. The mean arterial lactate peak was 7.7 ± 0.46 mmol/l (2.5–16) with a mean increase from the admission value (peak lactate–lactate H0) of 4.62 ± 0.45 mmol/l (0.4–12.1). The peak lactate level was reached in all patients after admission at: H+3 in 3 patients, H+6 in 24 patients, and H+14 in 2 patients.

At H+6, all patients had appreciable arterial hyperlactatemia [lactate 7.38 ± 0.38 mmol/l (2.5–11), $p <$ 0.001 vs H0], with a mean arterial lactate variation from admission of 4.28 ± 0.41 mmol/l (–1.9–+8.1). After 24 h of treatment, levels decreased progressively and returned to baseline values in most of the patients.

No statistically significant difference was found in the peak lactate level or in lactate levels at H+3, H+6, H+14, or H+24 between patients with progressively worsening asthma ($n = 16$) and those with acute onset of severe asthma ($n = 13$) (Table 5). No statistically significant difference was found in peak levels or in levels at H+3, H+6, H+14, and H+24 between patients with a normal $PaCO_2$ on admission (< 40 mm Hg, $n = 11$) and those with an elevated $PaCO_2$ on admission (≥ 40 mm Hg, $n = 18$) (Table 6).

No significant correlation was found at any time (H+3, H+6, H+14, H+24) between arterial lactate level respiratory rate, and heart rate, or PEF. Nor was a significant correlation found at any time, between arterial lactate variations and variations in heart rate, respiratory rate, or PEF. The maximum increase in arterial lactate level during treatment (peak lactate–lactate H0) was correlated neither to respiratory rate, heart rate, or PEF baseline values nor to their respective variations.

No correlation was found at any time between arterial lactate level and pH, PaO_2, $PaCO_2$, or phosphorus values. No correlation was found at any time between lactate variation and variations in pH, PaO_2, $PaCO_2$, potassium, or phosphorus. The maximum increase in lactate values during treatment (peak lactate–lactate H0) was positively correlated with the $PaCO_2$ value on admission ($r = 0.51$, $p = 0.005$) (Fig. 3) and negatively correlated with the phophorus value on admission ($r =$ 0.49, $p = 0.007$) (Fig. 4) and potassium value at H+3 ($r = 0.41$, $p = 0.027$).

No correlation was found at any time between arterial lactate levels or maximal increases in lactate during treatment (peak lactate–lactate H0) and the amount of drug (mg/kg per h) received by the patients.

The duration of ICU stay was 4 ± 0.3 days (2–9) and was correlated neither to arterial lactate level on admission nor to peak lactate level. None of those patients required mechanical ventilation. No complication was related to arterial catheterization. On discharge from the ICU the patients had a mean PEF of 295 ± 16 l/min. All patients were alive at discharge from hospital 6.2 ± 0.5 days after admission.

Discussion

This study demonstrates that a significant increase in the arterial lactate level is a constant finding during

Table 5 Evolution of arterial blood lactate level in patients with progressively worsening or acute onset of severe asthma

	Lactate (mmol/l)			
	H0	H+6	Peak	H+24
Progressively worsening ($n = 16$)	3.19 ± 0.55	7.28 ± 0.46	7.64 ± 0.69	2.6 ± 0.27
Acute onset ($n = 13$)	3.02 ± 0.52	7.50 ± 0.66	7.79 ± 0.61	3.4 ± 0.33

Table 6 Evolution of arterial blood lactate level according to $PaCO_2$ on admission

	Lactate (mmol/l)			
	H0	H+6	Peak	H+24
$PaCO_2 < 40$ mm Hg ($n = 11$)	3.45 ± 0.86	6.66 ± 0.7	6.9 ± 0.69	2.78 ± 0.38
$PaCO_2 > 40$ mm Hg ($n = 18$)	2.91 ± 0.32	7.79 ± 0.42	8.21 ± 0.59	3.07 ± 0.27

treatment of patients with ASA. A moderate but not constant arterial hyperlactatemia might be present on admission ($n = 17/29$, 59% of the patients), but all patients developed a considerable but transient increase in lactate levels during treatment, with a peak arterial lactate level of 7.72 ± 0.46 mmol/l and a mean elevation of 4.62 ± 0.45 mmol/l (range 0.4–12.1) from the baseline value. Arterial hyperlactatemia appeared despite a significant clinical improvement assessed by the favorable evolution of respiratory rate, PEF, and arterial blood gas values.

Several studies [1–3, 10, 17] have focused on acid–base disturbances in ASA. In a retrospective study [2] of 229 consecutive episodes of acute asthma in 170 patients, Mountain and co-workers found that metabolic acidosis either alone or as part of a mixed disturbance was noted in 28% with a mean anion gap of 15.8 ± 0.4 mEq/l but arterial lactate levels were not available in that study. In the report of McFadden and Lyons [1], metabolic acidosis was documented in 20.8% of 24 episodes. Roncoroni and co-workers [10] found that simple or combined metabolic acidosis occurred in 37.9% of 103 episodes of acute asthma. In the latter study, arterial lactate levels were measured only in 27 patients with simple or combined metabolic acidosis and were always found to be elevated with a mean value of 4.16 mEq/l. Appel et al. [9] have documented lactic acidosis in 12 (20%) of 60 patients with ASA. Okrent and co-workers [3] found metabolic acidosis in 10 of 22 patients with acute severe asthma in the emergency department. Only one of those 10 patients had an elevated lactate value on admission. Lissac and co-workers [17] found that 62 out of 94 patients with ASA had acidosis on admission (pH < 7.36): 24 patients had respiratory acidosis, 22 mixed acidosis, and 16 metabolic acidosis. On admission, the mean blood lactate level was 3.6 ± 1.9 mmol/l. These results are similar to our findings.

To our knowledge, no prospective study has monitored the kinetics of arterial blood lactate in ASA. The timing of the determination of the arterial lactate level could explain the discrepancy in the results regarding the frequency of hyperlactatemia in the various published studies.

In our study, the initial or delayed hyperlactatemia does not seem to have any significant prognostic value as no patient developed respiratory failure requiring mechanical ventilation. The peak lactate level was not correlated with the initial $PaCO_2$ or PEF. No correlation could be found between the level of lactate elevation and the period from the start of the crisis to ICU admission. Only the initial $PaCO_2$ correlated slightly positively with the maximum increase in lactate level during treatment ($r = 0.51$, $p = 0.005$). The increase in lactate level did not correlate with improvement in PEF under treatment.

To our knowledge, no prospective study has assessed specifically the prognostic value of arterial hyperlactatemia in ASA. In a retrospective study [9], Appel et al. have reported on 12 patients with severe asthma and lactic acidosis. The lactic acidosis was considered as a poor prognostic factor because 8 of those patients subsequently developed respiratory acidosis and 6 required mechanical ventilation. The results of that study are questionable because the arterial blood lactate level was not determined on admission and at regular intervals but only if arterial blood gas analysis, either on admission or subsequently, revealed a pH value lower than expected. In a study including 56 patients. Iberty et al. [18] reported the low sensitivity of the anion gap as a screen to detect hyperlactatemia in critically ill patients. In patients with ASA, Lissac et al. [17] did not find any significant correlation between arterial blood lactate level and anion gap on admission.

Several mechanisms accounting for the development of hyperlactatemia may interact during treatment of a severe asthma attack and need to be discussed. Severe tissue hypoperfusion is unlikely to be responsible for lactate elevation in those patients because none developed hypotension, severe hypoxemia, or sepsis during

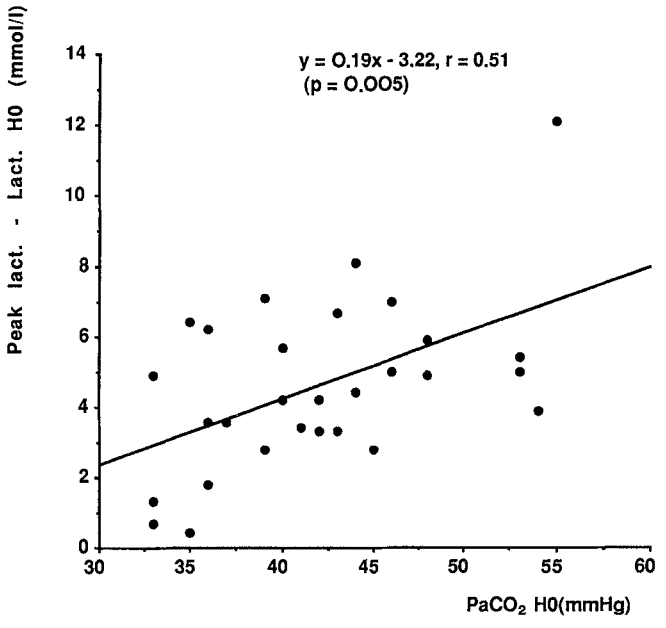

Fig. 3 Relationship between $PaCO_2$ on admission *H0* and maximum increase in arterial blood lactate level peak). *Peak lact–lact. H0* maximum increase in arterial lactate level from admission value *$PaCO_2$ H0* $PaCO_2$ on admission

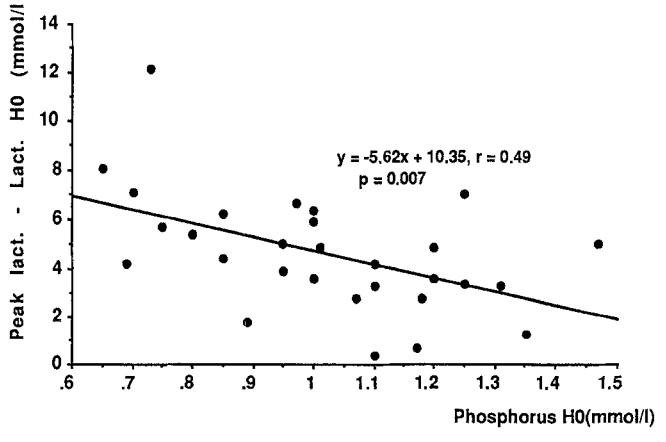

Fig. 4 Relationship between phosphorus on admission *H0* and maximum increase in arterial blood lactate level (peak). *Peak lact–lact. H0* maximum increase in arterial lactate level from admission value, *Phosphorus H0* serum phosphorus concentration on admission

the study period. Also, all patients with severe organ dysfunction on admission were excluded.

Lactate elevation could result from lactate production by respiratory muscles. In ASA, respiratory muscles are exhausted because of the increased inspiratory and expiratory work [19]. The fact that a positive correlation was found between the initial $PaCO_2$ value and the peak arterial lactate level could reflect a respiratory muscle origin for the increase in lactate. Rhabdomyolysis was not noted and CPK elevation was always moderate. On the other hand, lactate levels increased despite significant clinical improvement, and when peak lactate levels were reached no patient showed clinical respiratory muscle dysfunction.

As previously reported in ASA [20], mild hypophosphatemia was found in many of our patients during treatment. Hypophosphatemia seemed to precede hyperlactatemia in most of our patients and the peak arterial lactate level showed a negative correlation with the phosphorus level on admission. In patients with ASA. Lissac et al. [17] found a weak but significant negative correlation between arterial lactate level and phosphatemia on admission ($n = 34$, $r = -0.39$, $p = 0.02$). This finding is of interest because hypophosphatemia decreases diaphragm contractility [21] and increases hemoglobin affinity to oxygen as a consequence of a decrease in red cell 2–3 diphosphoglycerate concentration [22] resulting in tissue oxygenation impairment. This may account for lactate production by respiratory muscles. Against this hypothesis is the fact that hypophosphatemia was moderate in most patients and all patients were supplemented with intravenous phosphorus.

Lactate production could result from hepatic dysfunction during ASA. Increased right ventricular afterload and reduced left ventricular compliance due to septal shift might result in a decrease in cardiac output and liver perfusion [23]. Impairment of right ventricular function might also account for increased right ventricular filling pressure resulting in hepatic venous congestion [24], which could impair liver metabolic functions and lactate metabolism [25]. Our study cannot rule out this hypothesis as right ventricular function and liver blood flow were not assessed because they require invasive procedures. Nevertheless, clinical evidence for right ventricular dysfunction was uncommon in those patients and pulsus paradoxus above 20 mm Hg was found in only 9 patients. Liver enzymes remained within the normal range in almost all patients.

Lactate elevation could result from a washout process after clinical improvement with bronchodilator therapy. Reperfusion of previously ischemic organs such as respiratory muscles or liver could result in lactate liberation. This hypothesis is advocated by several authors such as Appel et al. [9] and Villard et al. [26], but their patients had more severe bronchial spasm when admitted to the ICU and often required mechanical ventilation.

Lissac and co-workers [17] found a positive correlation between noradrenaline and lactate values on admission in patients with ASA ($n = 20$, $r = 0.60$, $p < 0.05$), and for this author, the increase in plasma noradrenaline level could lead to a hypermetabolic state that could account for hyperlactatemia without cellular hypoxia. We did not measure plasma catecholamine levels in our study to confirm this hypothesis. In several

animal studies, catecholamine perfusion was reported to induce hyperglycemia and pyruvate and lactate accumulation by several mechanisms: liver and muscle glycogenolysis, increased gluconeogenesis, decreased glucose utilization, inhibition of insulin, and stimulation of glucagon. But none of our patients received epinephrine in our study.

Because all our patients receiving the same treatment developed arterial hyperlactatemia, a potential effect of the treatment must be questioned [27]. In conscious fasting rabbits, i.v. infusion of salbutamol 3 μg/kg per min during 30 min mediated an increase in plasma lactate levels at 60 min up to 6 mmol/l, comparable to the values we found in our patients treated with lower doses of a continuous infusion of salbutamol. In this animal study [28] of the effects of salbutamol on glucose metabolism, plasma lactate elevation was clearly related to β_2 adrenoreceptor stimulation, as the increase in lactate level was significantly reduced by pretreatment with an adrenoreceptor blocking drug. In humans, salbutamol has been questioned as responsible for the increase in arterial lactate in the treatment of preterm labor [29]. In 20 patients in premature labor who received ritodrine, a beta-mimetic tocolytic agent, Richards et al. [29] reported an increase in lactate blood levels (baseline 1 ± 0.1 vs 3.5 ± 0.3 mmol/l after 6 h of i.v. infusion). Theophylline might potentiate the effects of beta-adrenergic agents by raising the intracellular concentration of cyclic AMP through inhibition of 5' phosphodiesterase [30]. Glucocorticoids are known to enhance the sensitivity of beta-adrenergic receptors [31]. Unfortunatly, no significant correlation was found in our study between lactate levels or variations in lactate levels and the amount of drug received by the patients. Nevertheless, delayed hyperlactatemia, noted in our patients despite clinical improvement in all of them, suggests that treatment of ASA with salbutamol, theophylline, and glucocorticoids could be responsible for the increase in the arterial blood lactate level. Only a study of lactate kinetics with serial blood concentrations of each drug could confirm this hypothesis.

In conclusion, this prospective study provides evidence that delayed arterial hyperlactatemia is a common finding during treatment of ASA. Hyperlactatemia is not predictive of respiratory failure. The mechanisms of lactate elevation remain to be determined. Overproduction by overworked respiratory muscles, reduced clearance by the liver, and a metabolic effect of bronchodilor therapy, such as beta-agonist drugs, are possible mechanisms of increased plasma lactate levels in ASA. Other metabolic abnormalities, such as hypokalemia, hypophosphatemia, hyperglycemia, and their relationship with lactate level increase during treatment of ASA, also need further study.

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