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Influence of mechanical ventilation on blood lactate in patients with acute respiratory failure

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Abstract *Objectives:* To determine whether mechanical ventilation (MV) may affect blood lactate concentration in patients with acute respiratory failure.
Design: Prospective observational study with follow-up to hospital discharge.
Setting: A 17-bed medical and coronary intensive care unit in a 650-bed general hospital.
Patients: 55 adult patients mechanically ventilated for acute respiratory failure between May 1996 and April 1997 were recruited.
Measurements and results: Arterial blood samples for determination of plasma lactate and blood gas analysis were taken just before tracheal intubation on spontaneous breathing, and 20 and 60 min after the initiation of controlled MV. Cuff systemic arterial pressure was measured before tracheal intubation and every 10 min during the first h of MV. Hyperlactatemia (arterial blood lactate ≥ 2 mmol/l) was present in 21 of the 55 patients studied. After 20 min of MV, there was a decrease in blood lactate from 4.74 ± 1.78 to 3.07 ± 1.69 mmol/l ($p < 0.01$); 40 min later there was a further decrease to 2.63 ± 1.35 mmol/l ($p < 0.05$). The decrease in blood lactate was also observed in those patients who after starting MV developed systemic arterial hypotension ($p < 0.01$). In patients with a normal lactate concentration at the entry to the study, lactate remained the same after 60 min on MV (NS).
Conclusions: Controlled MV decreases substantially the severity of hyperlactatemia in patients with acute respiratory failure, and any adverse circulatory effects of MV do not alter this beneficial outcome.

Key words Arterial lactate · Mechanical ventilation · Respiratory failure · Arterial hypotension · Respiratory mechanics · Work of breathing

Introduction

Sepsis and shock are the most frequent causes of increased blood lactate concentration in the critically ill patient, but respiratory failure has also been associated with elevated blood lactate in this population [1, 2]. Thus, hyperlactatemia has been reported in patients with cardiogenic pulmonary edema (CPE) [3], acute exacerbation of chronic obstructive pulmonary disease (COPD) [4], and acute severe asthma [5]. Recently, several reports have in fact shown that in patients with acute lung injury the lung is a major source of lactate and lung lactate release is related to the extent of lung injury [6–9].

Favorable effects of mechanical ventilation (MV) on blood lactate were reported by Aubier et al. [10] in an animal model of cardiogenic shock. They demonstrated that during low cardiac output the working respiratory muscles contribute substantially to lactate production, and a reduction in blood lactate and an increased surviv-

al time were obtained by resting respiratory muscles with MV. However, whether this effect of MV on blood lactate can also be observed in patients with respiratory failure has not been investigated.

During the initiation of MV support, arterial hypotension due to a reduction in systemic venous return induced by positive airway pressure is commonly observed [11, 12]. Although under most circumstances hypotension is readily corrected, when severe or prolongued tissue hypoperfusion results and oxygen delivery becomes compromised, and lactate metabolism may be affected [13].

The purpose of this study was twofold: (1) to find out if the beneficial effects of MV on blood lactate reported in the laboratory are seen in clinical practice in patients with respiratory failure, and (2) whether arterial hypotension commonly observed at the start of MV could influence this effect.

Materials and methods

Patients

Fifty five adult patients (36 males, 19 females) who were admitted to the intensive care unit for the management of acute respiratory failure between May 1996 and April 1997, and who required mechanical ventilatory support were recruited for the study. Exclusion criteria were: age < 18 years, pregnancy, stroke, renal insufficiency (indicated by a serum creatinine of > 3.5 mg/dl), hepatic insufficiency (indicated by a serum total protein concentration of < 3 g/l and a total bilirubin of > 5 mg/dl), treatment with catecholamines or intravenous terbutaline [14], and arterial hypotension (defined as systemic systolic pressure < 90 mmHg) before tracheal intubation on spontaneous breathing.

The research protocol was approved by the ethics committee of the hospital. Data collected included patient demographics, first 24-h Simplified Acute Physiology Score II (SAPS II), etiology of the respiratory failure, arterial blood gases (ABGs), arterial plasma lactate, systemic blood pressure, respiratory mechanics (RM), and follow-up to hospital discharge. A portable chest X-ray was taken after tracheal intubation.

Study protocol

MV was started when at least one of two criteria was present: namely (i) arterial oxygen saturation measured by pulse oximetry or ABGs below 90% in spite of a maximum oxygen concentration administered through a face mask, (ii) extreme work of breathing with respiratory acidosis (defined as higher arterial carbon dioxide tension ($PaCO_2$) than expected for the plasma bicarbonate concentration and pH ≤ 7.30) or alterated of conscious level.

Simultaneous arterial blood samples for determination of plasma lactate and blood gas analysis were drawn in anaerobic conditions by radial arterial puncture just before tracheal intubation, and 20 and 60 min after the start of MV. Samples were immediately transported to the laboratory and plasma lactate concentration was determined by the radiative energy attenuation (REA) method on the TDx system (Abbot Laboratories, Abbot Park, Ill., USA) and blood gas measurements by an automated blood gas analyzer (Radiometer ABL 500 blood gas analyzer, Copenhagen, Denmark).

Cardiac frequency and cuff systemic blood pressure were measured before tracheal intubation on spontaneous breathing and every 10 min during the first h on MV. Arterial hypotension under MV was treated with i.v. fluids [normal saline and gelatin (Hemoce) solutions] until a systolic pressure ≥ 90 mmHg was achieved, unless the primary attending physician considered treatment with catecolamines or modification of the ventilatory support.

Patients were intubated (Portex cuffed endotracheal tube, internal diameter 8–8.5 mm), adequately sedated (0.1–0.2 mg/kg of midazolam or 1—2 mg/kg propofol administered as an i.v. bolus prior to tracheal intubation and followed by a continuous i.v. infusion of midazolam or propofol), paralysed (0.1 mg/kg i.v. vecuronium), and mechanically ventilated using the volume control mandatory mode of the Servo 900°C ventilator (Siemens-Elema, Solna, Sweden) with constant inspiratory flow, and 100% fractional inspired oxygen FIO_2 until the third sample of arterial blood was taken. The inspiratory flow rate was the same in all patients (40 l/min).

All measures of RM were obtained, following airway suctioning, immediately after tracheal intubation. In each patient we reproduced airway tracings and flow shape using the pressure transducers incorporated into the Servo 900 C and the Siemens ventilator device Sirecust 400 (Siemens Sirecust 400 Ventilator Cartridge, Siemens, Erlangen, Germany) [15]. All variables were recorded on a four-channel recorder (Siemens-Sideroc, Erlangen, Germay) at a paper speed of 25 mm/s. The electrocardiogram, heart rate, and arterial O_2 saturation were continuously monitored (Siemens Sirecust 404 EKG Cartridge and Ohmeda Biox 2740, Louisville, Ky., USA).

Measures of airway pressure included peak inflation pressure (Ppeak), plateau end-inspiratory pressure (Pplateau), plateau end-expiratory pressure (PEEPi), and mean airway pressure ($\bar{P}$). To obtain PEEPi airway opening was occluded by pressing the end-expiratory button incorporated in the ventilator until a plateau on the airway tracing was achieved [16]. After five regular breaths, the airway occlusion maneuvre was performed once again, but this time at end-inspiration, using the end-inspiratory hold button for direct measurement of Pplateau; $\bar{P}$ was obtained by measuring the inflation pressure at midcycle on a tracing of airway presure against time [17].

The static inflation compliance of the total respiratory system (Cst,rs) was computed by dividing the inflation volume of the lung (difference between volume delivered from the ventilator and volume collected at standard low-compliance adult circuit) (V_t) by the difference between Pplateau and PEEPi. Total inspiratory resistance (Ri,rs) was calculated by dividing the difference between Ppeak and Pplateau by the preceding inspiratory flow [18]. Since the subjects were ventilated with constant inflation flow, $\bar{P}$ was considered numerically equivalent to the mechanical work of breathing per liter of ventilation (Wi/V_t), and the mechanical work per tidal breath (Wi) was calculated by multiplying $\bar{P}$ by the inflation volume of the lung [19].

Statistical analysis

Normal distribution of data was checked for each of the tested parameters. Continuous data were compared by Student's *t*-test if the variables had a normal distribution, and by the Mann-Whitney U test if not. Changes in lactate concentration were assessed by analysis of variance for repeated measurements. When the *F* value was significant, a post-hoc adjustment of the Neuman-Keuls test was applied. To quantify the strength of the association between lactate and other variables, the Pearson correlation coefficient was calculated for values with a normal distribution, and the Sperman correlation coefficient for data not showing normal distribu-

Table 1 Characteristics and outcome for 55 patients with acute respiratory failure (*Lactate* Lactate on spontaneous breathing before tracheal intubation, *PaO_2* PaO_2on spontaneous breathing just before tracheal intubation, *S* survived, *D* died, *CPE* cardiogenic pulmonary edema, *COPD* chronic obstructive pulmonary disease, *ALI* acute lung injury, *BMT* bone marrow transplantation)

Patient No.	Diagnosis	Age (years)	Lactate (mmol/l)	PaO_2 (mm Hg)	Outcome
Group 1 (lactate ≥ 2 mmol/l)					
1	CPE	64	4.41	44	S
2	CPE	62	4.65	60	S
3	Lobar pneumonia	72	4.97	56	S
4	CPE	63	4.69	30	D
5	COPD	77	3.46	50	S
6	COPD	65	5.21	83	D
7[a]	CPE	66	2.66	57	S
8	Upper airway obstruction	75	4.26	58	S
9	ALI, abdominal sepsis	33	4.23	53	D
10	ALI, gastric aspiration	25	6.79	47	S
11	Postoperative atelectasis	79	4	–	S
12	Lobar pneumonia	70	5.29	44	D
13	COPD	75	3.84	60	S
14	Lobar pneumonia	63	10.28	51	D
15[a]	CPE	72	3.30	48	D
16	ALI, autologous BMT	25	2.46	59	D
17	Lobar pneumonia	70	6.91	48	S
18	ALI, bronchopneumonia	47	2.24	43	S
19	ALI, bronchopneumonia	56	4.11	44	D
20	ALI, caustic inhalation	71	4.87	72	D
21	ALI, abdominal sepsis	45	3.45	62	S
Group 2 (lactate < 2 mmol/l)					
22	Neuromuscular disorder	38	1.35	124	S
23	Neuromuscular disorder	72	1.45	67	S
24	Pancreatitis	78	0.41	121	D
25	COPD, lobar pneumonia	62	1.98	76	D
26	COPD	71	0.90	78	S
27	ALI, bronchopneumonia	69	1.17	33	D
28	COPD	70	0.60	128	S
29	CPE	57	1.92	67	S
30	COPD, lobar pneumonia	73	1.12	56	S
31	COPD	61	1.21	72	S
32	ALI, pancreatitis	51	1.35	61	D
33	ALI, caustic inhalation	58	1.54	59	D
34	COPD, lobar pneumonia	70	0.63	60	D
35	Disseminated tuberculosis	61	0.83	74	S
36	COPD	56	1.65	57	S
37	COPD	60	0.97	70	S
38	CPE	72	0.68	90	D
39	COPD	74	0.72	64	D
40	CPE	70	0.97	47	S
41	COPD	74	0.16	70	S
42	COPD	75	0.74	101	S
43	COPD	75	1.01	98	S
44	CPE	70	1.03	127	S
45	Lobar pneumonia	78	1.62	77	D
46	Abdominal sepsis	76	1.02	58	D
47[a]	Thoracic trauma	68	1.96	69	S
48	COPD	76	0.39	120	S
49	Upper airway obstruction	58	1.45	78	S
50	COPD	71	1.67	98	S
51	COPD, lung cancer	77	0.82	83	D
52	Thoracic trauma	48	1.20	53	S
53	Neuromuscular disorder	35	1.18	51	S
54	COPD	65	0.76	83	S
55	COPD	68	0.72	95	S

[a] Patients excluded for analysis of lactate variations

tion. Categorical data were compared using chi-square analysis, and, when groups were small, by Fisher's exact test. A p-value < 0.05 was considered to be statistically significant. All data are presented as mean ± standard deviation in text and tables, unless otherwise stated.

Results

Immediately before tracheal intubation, plasma lactate was raised (≥ 2 mmol/l) in 21 of the 55 patients studied (group 1: mean value 4.57 ± 1.77 mmol/l), and was normal in 34 patients (group 2: mean 1.09 ± 0.45 mmol/l; $p < 0.001$). At this time, cardiac frequency was higher in group 1 (124 ± 26 vs 110 ± 17 bpm; $p < 0.05$), and no patient had systemic arterial hypotension; systolic and diastolic blood pressures were similar in both groups (136 ± 22 vs 140 ± 29 mmHg and 76 ± 13 vs 79 ± 15 mmHg; NS).

Raised lactate was observed both in patients with alveolar disease and in patients with airway disease, but while most of the patients with acute lung injury (ALI) [20] had hyperlactatemia ($p < 0.05$), the majority of COPD patients had a normal blood lactate concentration ($p < 0.01$). No patient with neuromuscular disease had raised lactate, and sepsis [21] was present in 7 patients in group 1, and in 7 patients in group 2 (NS).

Overall mortality was 43 and 32% in groups 1 and 2, respectively, but this difference was not statistically significant; not were there statistically significant differences in age (61 ± 16 years vs 65 ± 11 years; NS) and median first 24-h SAPS II score (50 ± 16 vs 43 ± 13, NS). Causes of the respiratory failure, age, plasma lactate level, and arterial oxygen tension (PaO_2) before tracheal intubation at entry to the study, and outcome for the patients studied are summarized in Table 1.

Before tracheal intubation, 14 patients in group 1 had respiratory and metabolic acidosis, 4 patients had metabolic acidosis and respiratory alkalosis, 2 patients had respiratory acidosis, and in 1 patient (patient 11) ABGs could not be obtained. At this time, patients with hyperlactatemia had a lower PaO_2 ($p < 0.001$) and bicarbonate ($p < 0.01$) than patients with normal lactate levels (Table 2). There was no correlation between ABGs on spontaneous breathing and lactate, except for bicarbonate in patients with hyperlactatemia ($r = 0.58$, $p < 0.01$). After 20 min on MV, the PaO_2/FIO_2 ratio was lower in patients with hyperlactatemia ($p < 0.001$) (Table 2). Patients in group 1 had a lower Cst,rs and Ri,rs than patients in group 2, but these differences were not statistically significant (Table 3); mechanical work of breathing was similar in both groups (Table 3). There was no correlation between blood lactate and any measure of RM (NS) or work of breathing (NS).

To analyse variations in lactate concentration after beginning MV, two CPE patients from group 1 (patients 7 and 15), who developed arterial hypotension under MV and were treated with catecholamines, and one patient from group 2 (patient 47), who required cardiopulmonary resucitation at the time of tracheal intubation, were excluded.

In patients from group 1, lactate decreased after 20 min of the start of MV from 4.74 ± 1.78 to 3.07 ± 1.69 mmol/l ($p < 0.01$); 40 min later, there was a further decrease to 2.63 ± 1.35 mmol/l ($p < 0.05$) (Fig. 1). At this time lactate had decreased in all patients and had returned to normal values (< 2 mmol/l) in 8 of them (42%) (Fig. 2). Consequently, although before tracheal intubation lactate was higher in acute lung injury than in COPD patients (3.22 ± 1.8 vs 1.42 ± 1.29 mmol/l; $p < 0.01$), after 60 min on controlled MV it was the same in both groups (1.77 ± 0.98 vs 1.25 ± 0.84 mmol/l; NS). On the other hand, in patients from group 2, after 20 min on MV there was a slight increase from 1.06 ± 0.44 to 1.26 ± 0.59 mmol/l ($p < 0.05$) that returned to previous values 40 min later (1.11 ± 0.47 mmol/l; NS) (Fig. 1).

After the start of MV, 11 of the 19 patients in group 1 and 18 of the 33 in group 2 developed arterial hypotension, which was treated with i.v. fluids. Duration of hypotension was similar in both groups (36 ± 14 vs 35 ± 15 min; NS), and the amount of fluids used to treat it

Table 2 ABGs obtained before tracheal intubation on spontaneous breathing, except for PaO_2/FIO_2 that was calculated from ABGs obtained 20 min after beginning MV, on 100% of FIO_2. Values are mean ± SD

	Group 1 ($n = 21$)	Group 2 ($n = 34$)	p
pH	7.22 ± 0.13	7.23 ± 14	NS[a]
$PaCO_2$ (mm Hg)	59 ± 23	68 ± 24	NS[a]
PaO_2 (mm Hg)	53 ± 11	79 ± 24	$p < 0.001$[a]
Bicarbonate (mEq/l)	22 ± 4	28 ± 8	$p < 0.01$[a]
PaO_2/FIO_2 (mm Hg)	158 ± 93	254 ± 97	$p < 0.001$[a]

[a] Student's t-test

Table 3 Respiratory mechanics and work of breathing. Values are mean ± SD (*Ppeak* peak inflation pressure, *Cst,rs* static inflation compliance of the total respiratory system, *Ri,rs* total inspiratory resistance of the respiratory system, *PEEPi* intrinsic positive end-expiratory pressure, Wi/V_t work per liter of ventilation, *Wi* work per tidal breath)

	Group 1 ($n = 21$)	Group 2 ($n = 34$)	p
Ppeak (cmH_2O)	33 ± 6	32 ± 8	NS[a]
Cst,rs (ml/cmH_2O)	38 ± 13	45 ± 17	NS[a]
Rir,rs (cmH_2O/l per s)	15 ± 6	19 ± 16	NS[b]
PEEPi (cmH_2O)	6 ± 4	7 ± 4	NS[a]
Wi/V_t (J/l)	2.599 ± 0.622	2.560 ± 0.821	NS[a]
Wi (J)	1.499 ± 0.076	1.458 ± 0.434	NS[a]

[a] Student's t-test
[b] Mann-Whitney U test

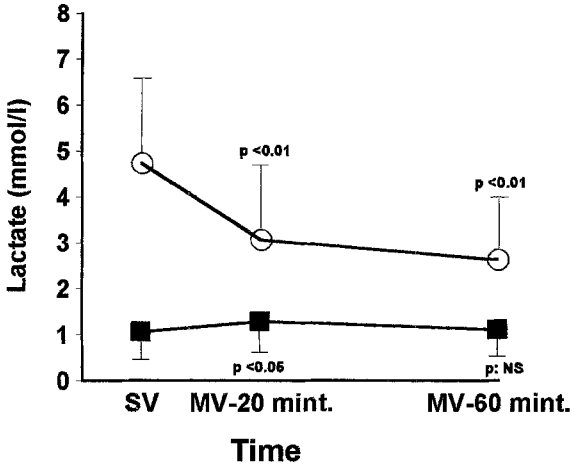
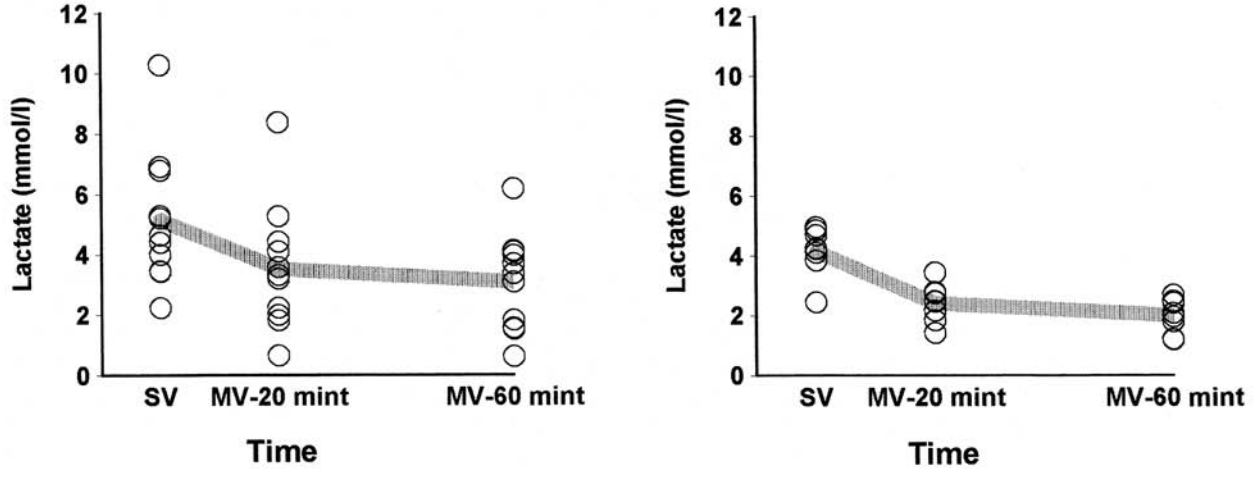


Fig. 1 Mean values of arterial lactate at the time periods studied. In patients with hyperlactatemia *open circles* there was a decrease in lactate after 20 min on controlled MV ($p < 0.01$)* that continued 40 min later ($p < 0.01$)*. In patients with normal lactate at entry to study *solid squares*, there was a slight increase in lactate 20 min after the initiation of MV ($p < 0.05$)*, but 40 min later arterial lactate had returned to previous values (NS)*. *SV* spontaneous ventilation, *MV* mechanical ventilation. * Analysis of variance for repeated measurements

were also the same [600 ± 129 vs 541 ± 128 ml of normal saline and 300 ± 258 vs 263 ± 234 ml gelatin (Hemoce); NS]. After 60 min on MV, blood lactate had decreased in both hypotensive (from 5.15 ± 2.20 to 3.09 ± 1.59 mmol/l; $p < 0.01$) and nonhypotensive patients (from 4.17 ± 0.79 mmol/l to 2 ± 0.53 mmol/l; $p < 0.01$) in group 1 (Fig. 2), and remained unchanged in group 2 (from 1.15 ± 0.49 to 1.14 ± 0.54 mmol/l in patients who developed hypotension, and from 0.97 ± 35 to 1.08 ± 0.39 mmol/l in those who did not; NS).

Fig. 2 Individual values *open circles* and mean values *gray line* of arterial lactate at the time periods studied in patients with hyperlactatemia. After 20 min of commencing MV there was a decrease in lactate that remained 40 min later ($p < 0.01$)* both in patients who developed arterial hypotension under MV *left* and in those who remained hemodynamically stable *right*. *SV* spontaneous ventilation, *MV* mechanical ventilation.* Analysis of variance for repeated measurements



Discussion

The results of this study show that in patients with respiratory failure: 1) elevated blood lactate is not an unusual finding (38% in the present study), 2) controlled MV with neuromuscular paralysis decreases the severity of hyperlactatemia, and 3) adverse circulatory effects of positive pressure ventilation, when treatment includes i. v. fluids, do not affect this decrease.

Hyperlactatemia has rarely been reported in patients with respiratory failure. Fulop et al. [3] demonstrated that metabolic acidosis in CPE was due to lactic acidosis. They found a lactate concentration ≥ 2 mmol/l in 15 of 18 patients studied. As pulmonary edema regressed, hyperlactatemia decreased considerably. Treatment with MV was not mentioned. Appel et al. [5] reported lactic acidosis in 12 patients with severe asthma. All patients improved, and as the asthma became less severe the metabolic acidosis disappeared. Although 6 of the patients required tracheal intubation and MV, lactate after starting MV was not measured.

We have studied arterial lactate in a wide group of patients with respiratory failure of different etiologies (Table 1). No patient with a systolic blood pressure < 90 mmHg on spontaneous breathing was included. Raised lactate was observed in patients with alveolar and airway disease, but not in patients with neuromuscular disease.

Lactate accumulation may occur in patients with respiratory failure whenever there is either an increase in its production or a decrease in its clearance. Factors that may have contributed to the hyperlactatemia in

these patients include acute hypoxia [3, 13], increased work of breathing [10], sepsis [21], increased secretion of catecholamines [22, 23], respiratory alkalosis [24], abnormal pulmonary lactate metabolism [6–9], and decreased lactate metabolism in hepatic and skeletal muscle [25]. Lastly, although we tried to exclude patients with shock by not recruiting patients with arterial hypotension on spontaneous breathing at entry to the study, we can not disregard the fact that some patients with shock and occult tissue hypoperfusion but no arterial hypotension might have been included [26].

MV may affect lactate metabolism by improving blood gases and decreasing systemic oxygen consumption [27–29]; the addition of a paralytic agent when respiratory muscle exertion continues during assisted ventilation may produce a further decrease in oxygen consumption and increase in gastric intramucosal pH, presumably by redistributing the blood flow from the respiratory muscles to the splanchnic and other vascular beds [30].

At entry to the study, most of the patients with hyperlactatemia had hypoxemia (Table 1), clinical indications of overloaded respiratory muscles [31], and increased work of breathing measured at the ventilator (Table 3). Therefore, it is very possible that MV and neuromuscular paralysis affected lactate metabolism by improving blood gases (Table 2), decreasing oxygen consumption by putting respiratory muscles at rest, and redistributing systemic blood flow [32].

There are several methodological limitations in our study: first, the lack of a controlled period of preintubation measurement of lactate. Second, hemodynamic parameters like systemic oxygen delivery, systemic oxygen consumption, and gastric intramucosal pH were not measured. Lastly, we quantified the mechanical work performed by the ventilator that is not representative of the work of breathing during spontaneous ventilation [33, 34]. Therefore, we are uncertain why controlled MV with neuromuscular paralysis affected lactate metabolism in these patients.

Hypotension after the start of MV was present in more than half of the patients in both groups, and it was energetically treated by administering i.v. fluids. The causes of hypotension at the start of MV are varied, but a reduction in systemic venous return and in cardiac output are the most commonly observed ones [11]. It is possible that in some patients in group 1 lactic acidosis could be related to normotensive or impending shock [26] prior to MV, and the fluids administered after MV was started improved cardiac output and systemic oxygen delivery, and, as a consequence, lactate metabolism. However, only four patients in group 1 (patients 1, 2, 14, and 18) received cardiovascular drugs during the next 24 h, while the other 15 remained hemodynamically stable with appropriate perfusion and diuresis. Therefore, we are of the opinion that in most of the patients hypotension was related to positive pressure ventilation and deep sedation, although the adequacy of intravascular volume was not confirmed.

Patients with normal lactate values at entry to the study showed a slight transitory increase in lactate after 20 min of MV, although 40 min later the lactate concentration had returned to previous values (Fig. 1). Most of these patients had respiratory acidosis before tracheal intubation, and after 20 min on MV there was a significant increase in pH (from 7.23 ± 0.14 to 7.35 ± 0.09; $p < 0.001$) due to a decrease in $PaCO_2$ (from 68 ± 24 to 48 ± 12 mmHg; $p < 0.001$). It is known that, due to the dependence on blood pH of the membrane-associated lactate transporters [20, 35, 36], hepatic lactate uptake decreases as pH increases [37]. Therefore, it is probable that the increase in pH after the start of MV could have influenced the cellular uptake of lactate and contributed to the slight increase we observed [24].

In conclusion, our study suggests that controlled MV with neuromuscular paralysis decreases blood lactate in patients with hyperlactatemia and severe respiratory failure, and this favorable effect is not influenced by the hypotension associated to MV when i.v. fluids are quickly administered. We believe that in this population it may be justifiable to attempt controlled MV to improve lactate metabolism when hyperlactatemia persists despite oxygen administration and specific therapy.

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