Blood lactate level as a predictor of patients' outcome at the Respiratory Intensive Care Unit of Zagazig University Hospitals

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Background Many variables measured in critically ill patients have been used to predict patient outcomes; however, it is unlikely that one measurement can replace all, but lactate levels may come close.

Aim This study aims to evaluate the role of blood lactate level as a predictor of patients' outcome at Respiratory Intensive Care Unit at Zagazig University Hospitals (RICU-ZUH).

Patients and methods A prospective cohort study was conducted on 52 patients recruited from RICU-ZUH. All patients' functional conditions were assessed on admission by the Simplified Acute Physiology Score II scoring system, Glasgow Coma Scale (GCS), and Sequential Organ Failure Assessment scores as well as assessment of sepsis. The blood lactic acid level was measured at H0 (initial blood lactate level), H6, H12, H24, and H48 (in mmol/l). Patients were classified into two groups: (i) normal blood lactate level group, and (ii) hyperlactatemia group. Lactate clearance and lactime were also measured.

Results Out of the 52 cases studied, hyperlactatemia was present in 30 (57.6%) patients, whereas a normal blood lactate level was found in 22 (42.4%) patients. H0 was significantly high ($P<0.01$) in the hyperlactatemia group (4.41 ±1.69 mmol/l), with lactime 42.4±10.5 h; also, lactate clearance at H6 was nonsignificantly high ($P>0.05$). The Simplified Acute Physiology Score II and Sequential Organ Failure Assessment scores were significantly positively correlated with H0 and lactime, but significantly negatively correlated with lactate clearance, whereas GCS was negatively correlated in a significant way with H0 and lactime and positively correlated with lactate clearance. The significant highest mortality risk of 2.86 was reported with lactime more than 48 h, followed by a 2.28 risk of mortality with H0 blood lactate level more than 3.9 mmol/l, and the least risk was reported with GCS less than 10.5.

Conclusion Hyperlactatemia at admission and a prolonged lactime are valuable independent predictors of mortality of RICU patients.

Egypt J Bronchol 2017 11:128–133

Egyptian Journal of Bronchology 2017 11:128–133

Keywords: hyperlactatemia, lactate clearance, lactic acid, lactime

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Received 23 August 2016 **Accepted** 13 October 2016

Introduction

Many variables measured in critically ill patients have been used to predict patient outcomes; however, it is unlikely that one measurement can replace all, but lactate levels may come close [1]. It is frequently measured in critically ill patients to detect tissue hypoxia [2]. Furthermore, microcirculatory processes hampering oxygen utilization at the tissue level may also increase lactate level [2,3]. The correlation between lactate levels in arterial and venous blood was found to be acceptable [4]. Should we routinely monitor lactate in the critically ill? And if so, when should we measure it? What would be the best predictors of patient outcome? Accordingly, the research question was, would monitoring of blood lactate predict patients' outcome in the respiratory intensive care unit (RICU)? We hypothesize that blood lactate level, clearance, and lactime predict patients' outcome in the RICU.

The aim of this work was to assess the role of blood lactate level as a predictor of patients' outcome at Respiratory Intensive Care Unit at Zagazig University Hospitals (RICU-ZUH).

Objectives

(1) To identify blood lactate level at patients' admission.
(2) To monitor lactime and lactate clearance through RICU stay.
(3) To relate previous lactate measures to patients' outcome to determine best predictors of mortality.

Patients and methods

This was a prospective cohort study and was conducted at the RICU of the Chest Department of Zagazig University Hospitals during the period from October 2014 to May 2015 after being approved by the Zagazig University Institutional Review Board.

Study population

Fifty-two patients (selected sample) were enrolled in the study from cases that were admitted to the RICU.

 DOI: 10.4103/ejb.ejb_64_16

They included 33 male and 19 female patients, with an age range of 23–76 years and a mean±SD of 52.4±14.6 years.

Inclusion criteria

Patients aged 18 years or more, who had primary respiratory diseases with or without respiratory failure were included in the study.

Exclusion criteria

Patients with known chronic organ failure – for example, liver cell failure, renal failure, heart failure, pregnancy, recent trauma, diabetic ketoacidosis, and patients on chemotherapy and/or radiotherapy were excluded.

Informed consent was obtained either from the patients or their relatives. All patients were subjected to the following:

(1) Initial diagnosis which was based on the following: medical history, clinical examination (general and local chest examination), radiological chest assessment [plain radiograph posteroanterior view and chest computed tomography when needed], and laboratory assessment (complete blood count (CBC), random blood sugar (RBS), kidney function test (KFT), liver function test (LFT), and arterial blood gases).
(2) Assessment of patients' functional condition at admission by calculating the following scores:
    (a) The Simplified Acute Physiology Score II (SAPS II) scoring system for assessing severity of the disease [5].
    (b) The Glasgow Coma Scale (GCS) for assessing the neurological condition of the patients [6].
    (c) The Sequential Organ Failure Assessment (SOFA) score for assessing organ failure [7].
(3) Assessment for the presence of sepsis: sepsis is suspected infection in the presence of two or more systemic inflammatory response syndrome criteria [8,9]:
    (a) Body temperature less than 36°C or more than 38°C.
    (b) Heart rate more than 90 beats/min.
    (c) Tachypnea with more than 20 breaths/min or $PaCO_2$ less than 32 mmHg.
    (d) White blood cell count less than 4000 cells/mm^3 or more than 12 000 cells/mm^3, or the presence of more than 10% immature neutrophils (band forms). Band forms more than 3% is called bandemia or a 'left-shift'.
(4) Plan of treatment: conventional treatment according to the diagnosis of each patient with the guidelines in RICU-ZUH.
(5) Measurement of lactic acid blood level:
    (a) Type of sample: arterial sample.
    (b) Time of sampling: lactic acid was measured on RICU admission (H0, initial blood lactate level), 6 h later (H6), 12 h later (H12), 24 h later (H24), and 48 h later (H48) (in mmol/l) using the arterial blood gases analysis device (Epoc BGEM Blood Test; Epocal Inc. 2060 Walkley Road Ottawa, ON K1G 3P5 Canada).
    (c) According to H0, the patients were classified as follows:
        (1) Normal blood lactate group (lactic acid blood level <2 mmol/l).
        (2) Hyperlactatemia group (lactic acid blood level >2 mmol) [10].
    (d) 'Lactime' was measured and defined as the time during which blood lactate was more than 2.0 mmol/l [10].
    (e) Lactate clearance at 6 h was measured using blood lactate level at RICU admission (H0) and blood lactate level at H6 according to the following equation: [(lactate initial (H0)–lactate delayed (H6)/lactate initial (H0)]×100% [11].
(3) End point of the study: patient death (nonsurvivors) or discharge home or to inpatient ward where continuation of conventional treatment was carried out.
(4) Outcome assessment: survival or death (nonsurvivors).

Statistical analysis

The data were tabled and statistically analyzed. Data were collected and analyzed using Microsoft Excel software (Microsoft Excel 2016 16.0.6741.2048 free download http://microsoft_excel.en.downloadastro.com/). Data were then imported into statistical package for the social sciences (SPSS, version 20.0; SPSS Inc., Chicago, Illinois, USA) software for analysis. According to the type of data, the following tests were used to test differences in significance; differences between frequencies (qualitative variables) and percentages in groups were compared by the χ^2-test. Differences between means (quantitative variables) in parametric multiple groups were compared by the analysis of variance test, in parametric two groups by the *t*-test and in nonparametric variables by the Mann–Whitney test. Receiver operating characteristic curves were used for the assessment of sensitivity and specificity and cutoff, and logistic regression for independent predictors. *P* value was set at less than 0.05 for significant results, at less than 0.001 for highly significant results, and at less than 0.05 for nonsignificant results.

Results

The study included 52 patients, of whom 63.5% were male and 36.5% female, with a mean age of 52.4±14.6 years (Table 1). The median (range) of SAPS II score was 25 (8–120) and SOFA score was 7 (3–20), whereas GCS had a mean of 10.5±0.98. Sepsis was present only in 11 (21.2%) patients and no patients developed severe sepsis or septic shock (Table 2). The most common disease was chronic obstructive pulmonary disease (COPD) in 15 (28.8%) patients, whereas other diagnoses varied: overlap syndrome (COPD and obstructive sleep apnea (OSA)) in two (3.8%) patients, bronchial asthma in five (9.6%) patients, pneumonia in 12 (23.1%) patients, pulmonary embolism in six (11.55%) patients, pneumothorax in two (3.8%) patients, interstitial lung diseases in seven (13.5%) patients, acute respiratory distress syndrome (ARDS) in three (5.8%) patients. The normal lactate blood level group included 22 (42.4%) patients and all survived (100%), whereas the hyperlactatemia group included 30 (57.6%) patients out of whom 18 (60%) survived and 12 (40%) did not survive, with a very high statistically significant difference ($P<0.001$). Initial blood lactate levels (H0) revealed 30 (57.6%) patients with hyperlactatemia and 22 (42.4%) patients with a normal blood lactate level (Table 3). There was significant difference between groups regarding initial blood lactate levels (H0), where it was 4.41±1.69 mmol/l in the hyperlactatemia group, whereas 1.81±0.09 mmol/l in the normal lactate group. Lactime, measured only in the hyperlactatemia group, was 42.4±10.5/h. Lactate clearance at H6 was higher in the hyperlactatemia group than in the normal group. The death rate reported in this work was 12 out of 52 (23.08%) patients, and all of them were in the hyperlactatemia group [representing 12/30 (40%)], whereas 18 patients [18/30 (60%)] survived. SAPS II was highly significantly positively correlated with H0 ($r=0.71$, $P<0.001$) and significantly positively correlated with lactate time ($r=0.42$, $P<0.05$), but highly significantly negatively correlated with lactate clearance ($r=-0.62$, $P<0.001$) as well as SOFA scores, where it was highly significantly positively correlated with H0 ($r=0.75$, $P<0.001$) and significantly positively correlated with lactate time ($r=0.51$, $P<0.05$), but highly significantly negatively correlated with lactate clearance ($r=-0.62$, $P<0.001$), whereas GCS was negatively correlated with H0 ($r=-0.5$, $P<0.05$) and lactate time ($r=-0.38$, $P<0.05$) and positively correlated with lactate clearance ($r=0.68$, $P<0.001$) (Table 4). All the cutoff values for SAPS II (cutoff value >30.5), SOFA (cutoff value >7), GCS (cutoff value <10.5), initial blood lactate level (H0) (cutoff value >3.9), lactime (cutoff value >48 h),

Table 1 Characteristics of the studied patients

Patients' criteria (n=52)	
Sex [*N* (%)]	
Male	33 (63.5)
Female	19 (36.5)
Age (mean±SD) (years)	52.4±14.6
ABGs	
pH (mean±SD)	7.4±1.4
PaO_2 (mean±SD)	56.9±5.4
$PaCO_2$ [median (range)]	27.5 (12–102)
HCO_3 [median (range)]	20.0 (11.0–46.0)
SAPS II [median (range)]	25 (8–120)
SOFA [median (range)]	7 (3–20)
GCS (mean±SD)	10.5±0.98
WBCs (mean±SD)	16.1±3.8
Temperature (°C) (mean±SD)	38±2.1
RR (breaths/min) (mean±SD)	30.9±2.9
Systolic blood pressure (mean±SD) (mmHg)	99.8±19.8
Diastolic blood pressure (mean±SD) (mmHg)	60.4±12.03
HR (mean±SD) (beats/min)	124.6±11.1
Urine output (mean±SD) (ml/24 h)	516.3±158.03

ABG, arterial blood gas; GCS, Glasgow Coma Scale; HR, heart rate; RR, respiratory rate; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; WBCs, white blood cells count.

Table 2 Characteristics of the studied patients with regard to critical illness, presence of sepsis, and diagnosis

Patients' criteria (n=52)	*N* (%)
Sepsis	
Sepsis	11 (21.2)
No	41 (78.8)
Diagnosis	
COPD	15 (28.8)
Bronchial asthma	5 (9.6)
Pneumonia	12 (23.1)
Pulmonary embolism	6 (11.55)
Pneumothorax	2 (3.8)
Interstitial lung diseases	7 (13.5)
Overlap syndrome (COPD+OSA)	2 (3.8)
ARDS	3 (5.8)

Table 3 Survival, initial lactate levels (H0), lactime, and lactate clearance at H6 in the hyperlactatemia group in comparison with the normal lactate group

	Normal lactate (n=22)	Hyper lactatemia (n=30)	χ^2 (t/MW)	P
Survived (n=40) [*N* (%)]	22 (100.0)	18 (60)	11.4	<0.001**
Nonsurvived (n=12) [*N* (%)]	0 (0.0)	12 (40)	–	–
Initial lactate (H0) (mean±SD) (mmol/l)	1.81±0.09	4.41±1.69	6.53	<0.01**
Lactime (h)	0.0	42.4±10.5	–	–
Lactate clearance H6 [median (range)] (%)	14.08 (11.1–29.4)	16.6 (0–40)	Z=0.41	>0.05

Z, Mann–Whitney (MW) test. **Highly significant.

and lactate clearance (cutoff value <13.6) were significantly valid for the detection of mortality (Table 5).

The most sensitive variables were the SOFA score, GCS, lactime, and lactate clearance at H6 (91.7%) and the most specific variables were the initial lactate level (H0) (95%) and SAPS II (92.5%); also, Table 6 showed the superiority of lactate over studied scores in mortality prediction such as area under the curve (AUC), which was 0.93 for initial lactate (H0) against 0.85 for SOFA, 0.91 for SAPS II, and 0.44 for GCS. The significant ($P<0.05$) highest mortality risk (odds ratio=2.869) was reported with lactime cutoff value more than 48, followed by the risk of mortality with initial blood lactate level (H0) cutoff value more than 3.9 mm/l (odds ratio=2.28), and the least risk reported was with GCS cutoff value less than 10.5 (odds ratio=0.109). Accordingly, the best independent predictors of mortality in RICU-ZUH were initial blood lactate level (H0) more than 3.9, lactime more than 48 h, and GCS less than 10.5.

Discussion

To understand the importance of an increased lactate level, it is important not only to consider anaerobic production, but also aerobic mechanisms and changes in lactate clearance. Despite this complex evaluation, increased lactate levels usually reflect increased morbidity and high mortality [1]. Physicians need accurate and very early indications concerning the prognosis, and both initial blood lactate levels and early lactate clearance were appropriate tools [12]. In trauma patients, alcohol or drug use, which are frequently encountered conditions, do not modify the predictive accuracy of initial blood lactate levels [13]. Blood lactate level can be measured using various devices (central laboratory, point-of-care blood gas analyzers, hand-held devices), and generally most devices used at the bed side have acceptable limits of agreement

Table 4 Correlation between Simplified Acute Physiology Score II, Glasgow Coma Scale, Sequential Organ Failure Assessment, and initial lactate levels, lactime, and lactate clearance in the hyperlactatemia group

Lactate levels	SAPS II		SOFA		GCS	
	r	*P*	*r*	*P*	*r*	*P*
Initial lactate (H0) (mmol/l)	0.71	0.00**	0.75	0.00**	–0.5	0.005*
Lactime (h)	0.42	0.02*	0.51	0.003*	–0.38	0.03*
Lactate clearance H6 (%)	–0.62	0.00**	–0.62	0.00**	0.68	0.00**

GCS, Glasgow Coma Scale; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment. *Significant. **Highly significant.

Table 5 Validity of cutoff values of Simplified Acute Physiology Score II, Sequential Organ Failure Assessment, Glasgow Coma Scale, initial blood lactate level (H0), lactime, and clearance as predictors for mortality

Items	Cutoff value	AUC	*P*	Sensitivity (%)	Specificity (%)
SAPS II	>30.5	0.91	0.00**	75.0	92.5
SOFA	>7	0.85	0.00**	91.7	62.5
GCS	<10.5	0.44	0.02*	91.7	65.0
Initial lactate (H0) (mmol/l)	>3.9	0.93	0.00**	83.3	95.0
Lactime (h)	>48	0.9	0.00**	91.7	84.6
Lactate clearance H6 (%)	<13.6	0.48	0.00**	91.7	77.5

AUC, area under the curve; GCS, Glasgow Coma Scale; SAPS II, Simplified Acute Physiology Score II; Sequential Organ Failure Assessment. *Significant. **Highly significant.

Table 6 Multivariate logistic regression for independent predictors of mortality

Cutoff value	Wald	*P*	OR	95% CI	
				Lower	Upper
SAPS II>30.5	0.436	0.509	1.059	0.894	1.254
GCS<10.5	3.946	0.032*	0.109	0.010	0.815
SOFA>7	0.331	0.565	1.146	0.720	1.826
Initial blood lactate (H0)>3.9 mm/l	3.535	0.041*	2.287	1.456	8.663
Lactime>48 h	3.774	0.033*	2.869	1.969	11.180
Lactate clearance<13.6%	1.854	0.067	0.547	0.025	2.542

CI, confidence interval; GCS, Glasgow Coma Scale; OR, odds ratio; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment. *Significant.

compared with laboratory devices [14,15]. In addition, the sampling site of the blood (arterial, venous, capillary, etc.) also does not seem to affect the results much [16,17]. The current study revealed that the initial blood lactate level (H0) was highly significantly ($P<0.01$) elevated in the hyperlactatemia group, which concurs with the study of Régnier *et al.* [12] and van Beest *et al.* [18], who worked on a heterogeneous ICU population including cases with respiratory failure as well as Zhang *et al.* [19] who used initial lactate (H0) with normalization time (lactate clearance) to assess the predictive value of lactate in unselected critically ill patients. In contrast, the lactime in the hyperlactatemia group ($P>0.05$) as well as lactate clearance at H6 were nonsignificant. The current study selected H6 based on the study of Nguyen *et al.* [20] and van Beest *et al.* [18] who found that normalization of lactate less than 6 h (lactate clearance at H6) after ICU admission revealed better survival compared with normalization of lactate at greater than 6 h; moreover, Zhang *et al.* [19] stated that most studies defined lactate clearance as the relative reduction in serum lactate levels within 6 h. Also, the study of Marty *et al.* [11] showed that there is a significant difference between the H0 lactate value and H6, H12, or H24 lactate values in the survivor group. No significant difference was found in the nonsurvivor group between H6, H12, and H24 lactate values compared with H0. Hyperlactatemia in the current study was reported to be associated significantly with increased severity of disease as assessed by SAPS II, and was highly significantly positively correlated with H0 and significantly positively correlated with lactate time, but highly significantly negatively correlated with lactate clearance as well as SOFA scores, where it was highly significantly positively correlated with H0 and significantly positively correlated with lactate time, but highly significantly negatively correlated with lactate clearance, whereas GCS was negatively correlated with H0 and lactate time and positively correlated with lactate clearance; these findings concurred those of Zhang *et al.* [19] about the predictive value of lactate in critically ill patients, where nonsurvivors had higher SAPS II SOFA scores than survivors, and there was a significant correlation between H0 and lactime with the SOFA score and the SAPS II score, whereas Yolbaş *et al.* [21] showed that there is a considerably significance difference between lactate level and GCS in a study about the relationship between different lactate levels and mortality rate. The current study reported 100% survival rate in the normal lactate group, whereas it was 60% in the hyperlactatemia group, and this is nearly matched with the results of van Beest *et al.* [18] where hospital mortality of their population was 18% and was higher in patients with hyperlactatemia during ICU stay compared with those without hyperlactatemia. Also, in the Pasha *et al.*'s [22] study there were 25% nonsurvivors out of 125 patients, and was higher in patients with hyperlactatemia during ICU stay when compared with those without hyperlactatemia. The current study determined that the most sensitive variables as predictors of mortality were the SOFA score, GCS, lactime, and lactate clearance at H6 (91.7%) and the most specific variables were the initial lactate level (H0) (95%) and SAPS II (92.5%); also, the superiority of lactate over studied scores in mortality prediction such as AUC was 0.93 for initial lactate (H0) against 0.85 for SOFA, 0.91 for SAPS II, and 0.44 for GCS. This is matched with the results of Bakker *et al.* [10] where among patients with septic shock, the lactime was the best predictor of outcome in a multiple regression analysis. Similarly, in trauma patients, lactate normalization within 24 h was associated with 100% survival [2]. Further data showed that a decrease in lactate of at least 10% during the first 6 h of septic shock was associated with an improved outcome, and an 11% decrease in mortality was observed with each 10% increase in lactate clearance [20]. Badreldin *et al.* [23] compared the predictive value of lactate with complex physiological scores in a cohort of cardiothoracic surgery patients, where they found that the diagnostic performance of lactate was significantly superior to these scores, as reflected by an AUC of 0.88 for lactate against 0.83, 0.79, and 0.76 for SOFA, SAPS II, and APACHE II, respectively, which are in accordance with the current study. The current study reported that by multivariate logistic regression analysis, significant independent predictors of mortality were initial lactate (H0) more than 3.9 mmol/l with odds ratio 2.28, lactime (>48 h) with odds ratio 2.86, and GCS (<10.5) with odds ratio 0.109. In agreement with the current study, Maarslet *et al.* [24] found that an increased initial lactate (H0) more than 4.5 mmol/l resulted in an odds ratio of 8.4 (95% confidence interval: 1.5–46.1) for mortality and this is also confirmed in the study of Hajjar *et al.* [25] in which the lactate level measured at 6 h after ICU admission was also found to be an independent predictor of complications after major cardiothoracic surgery, whereas the study of Régnier *et al.* [12] showed that the best cutoffs for initial blood lactate (H0) level was 4.7 mm/l (95% confidence interval: 3.4–5.6). Although the normalization time used for predicting mortality commonly ranged from 6 to 72 h, Marty *et al.* [11], Puskarich *et al.* [26], and Zhang *et al.* [19] showed that a normalization time (lactate clearance) within 100 h was positively associated with the hazard. This difference between cutoffs values in different studies can be

explained by the differences in sample size, excluded patients, and the specialty of the study. Our study showed that lactate clearance did not have the same value as H0 and lactime in predicting outcome. In contrast, Nguyen *et al.* [20] reported that lactate clearance was an independent predictor of mortality. According to a recent study on patients with hyperlactatemia in ICU admission, lactate-guided therapy significantly reduced hospital fatal outcomes, which suggests that initial lactate monitoring has much clinical benefit [27]. In conclusion, initial blood lactate levels and lactime are valuable prognostic tools for the prediction of RICU outcomes.

We can recommend the measurement of blood lactate level on RICU admission, and monitoring lactime and lactate clearance during ICU stay for (a) prediction of outcome and (b) application of lactate-guided therapy.

Financial support and sponsorship
Nil.

Conflicts of interest
There is no conflict of interest.

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