

Prolonged lactate clearance is associated with increased mortality in the surgical intensive care unit

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Abstract

Background: Failure of arterial serum lactate to achieve normal levels has been associated with an increased mortality among medical and trauma patients. At our institution the ability of the patient to normalize arterial serum lactate has been utilized as an end point of resuscitation. In this study, we examine the correlation between length of time to lactate normalization and mortality.

Methods: The charts of 95 consecutive surgical intensive care unit (SICU) patients requiring hemodynamic monitoring or therapy were reviewed retrospectively. Hemodynamic, demographic, and laboratory data were recorded. Patients were stratified by lactate normalization time, and a subgroup analysis of survivors and nonsurvivors was performed by univariate and multivariate analysis.

Results: Patients not achieving a normal lactate level sustained a 100% hospital mortality rate. Those clearing between 48 and 96 hours sustained a 42.5% mortality rate. Patients normalizing in 24 to 48 hours had a 13.3% mortality rate, and those clearing in less than 24 hours had a mortality rate of 3.9%. Subgroup analysis by survival revealed differences in time to lactate clearance, initial blood pressure, and initial lactate on univariate analysis. On multivariate analysis only time of lactate clearance was found to differ.

Conclusions: Prolongation of lactate clearance is associated with increasing mortality. Failure of a patient to normalize lactate is associated with 100% mortality. Measurement of arterial serum lactate is a simple and effective predictor of outcome and end point of therapy. © 2001 Excerpta Medica, Inc. All rights reserved.

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Failure of serum arterial lactate levels to reach normal values within a specific time interval has been shown to correlate with mortality in the critically ill [1]. Abramson et al [2] have shown that inability to normalize arterial serum lactate within 24 hours of injury correlates with increased mortality in a trauma population. Vincent [3] reported that the inability of patients to return lactate to normal values within 48 hours of intensive care unit (ICU) admission could be used as a reliable predictor of patient outcome in critically ill medical patients. Further, much debate exists as to therapeutic endpoints of resuscitation. Specific physiologic endpoints such as oxygen delivery (DO_2), oxygen consumption (VO_2), and intragastric pH (pHi) have been proposed as possible markers of resuscitation [3-6]. In our

surgical ICU (SICU), a normal arterial serum lactate is used to define adequacy of resuscitation. Because there has not been a study that examines the impact of prolonged lactate clearance on outcome in surgical patients, we determined to investigate whether serial arterial lactate levels and lactate clearance time could be used as predictors of patient outcome in a critically ill surgical patient population. Using arterial serum lactate as a marker of resuscitation, this study examines the correlation between time to normalization of arterial serum lactate and outcome in a series of 95 consecutive postoperative SICU patients.

Methods

The charts of 95 consecutive SICU patients requiring hemodynamic monitoring and resuscitation in the postoperative period were reviewed retrospectively. By definition,

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Table 1
Characteristics of the four groups

	Group 1 (n = 12) No clearance	Group 2 (n = 16) 48–98 hours	Group 3 (n = 15) 24–48 hours	Group 4 (n = 51) <24 hours
Mortality	100%	42.5%	13.3%	3.9%
Age (years)	68.9 ± 8.8	68.7 ± 13.6	67.6 ± 13.0	73.6 ± 10.2
Apache II score	23 ± 6.2	19.6 ± 5.7	17.2 ± 6.2	16.6 ± 4.9
Apache III score	74.4 ± 28.2	73.3 ± 20.7	62.9 ± 24.1	53.9 ± 15.6
Predicted mortality (%)	50.5 ± 24.6	32.8 ± 23.0	30.1 ± 13.9	29.6 ± 15.4
Oxygen delivery (mL · min ⁻¹ · m ⁻²)	497.6 ± 134.2	519.4 ± 203.6	641.7 ± 330.9	557.7 ± 144.9
Oxygen consumption (mL · min ⁻¹ · m ⁻²)	133.9 ± 55.7	137 ± 44.4	109 ± 12.1	130 ± 51.2
Initial systolic blood pressure (mm Hg)	84.7 ± 14.1	97.4 ± 38.3	105.8 ± 44.5	135.2 ± 50.9
pH	7.23 ± 0.15	7.29 ± 0.06	7.33 ± 0.13	7.38 ± 0.07
Initial lactate level (mmol/L)	9.5 ± 6.1	6.15 ± 2.5	5.26 ± 2.4	2.26 ± 1.09

all patients included into the study required hemodynamic monitoring with a pulmonary artery catheter and active resuscitation with fluids, pressors, or inotropes. Patients admitted to the SICU for reasons other than resuscitation (eg, observation, optimization) were not included in this study. Treatment with fluids, pressors or inotropes was as indicated by the patient's clinical and hemodynamic parameters. Clinical management was by surgical residents under the direction of surgical intensivists in a closed SICU. Beginning at time of SICU admission, arterial lactate levels were drawn at 8-hour intervals until the patient reached and maintained a serum lactate level less than 2 mmol/L on two repeated measurements. A value of less than or equal to 2.0 mMol/L is defined as the normal institutional arterial serum lactate level. At this point, end points of resuscitation were achieved. Arterial serum lactates were drawn until two normal values were obtained, the patient died, or 120 hours (5 days) from the time of initial lactate had elapsed. Lactate levels and times of sampling were entered into a database. Other values recorded into the ICU database (SICU Assistant, Levy and Assoc., Houston Texas) included demographic data, hemodynamic readings, serum chemistries, operative diagnosis, Apache (Acute Physiology and Chronic Health Evaluation) II, Apache III, and predicted mortality by Apache II. DO₂, and VO₂ were recorded at 24 hours after ICU admission. As this study was a retrospective chart review, Institutional Review Board approval was not required.

Patients were stratified by time of lactate clearance into four groups. Group 1 (n = 12) included all patients who did not achieve normal values of lactate at any time in their SICU stay. Group 2 (n = 16) included patients who cleared their lactate between 48 hours and 96 hours. Group 3 (n = 15) normalized their lactate between 24 and 48 hours, and group 4 (n = 51) included patients whose lactate reached normal values in less than 24 hours. Patients' outcomes in the four groups were compared. A subgroup analysis comparing survivors and nonsurvivors was then performed. Variables examined included age, initial blood pressure (BPi), initial lactate (LACTi), time to lactate clearance

(LCT), DO₂I, VO₂I, Apache II, Apache III, and their predicted mortality by Apache II (PM). The groups were initially contrasted by univariate analysis. Variables identified as different between the two groups were then examined in a step-wise regression multivariate analysis utilizing survival as the dependant variable. All data are presented as means ± standard deviation. Data were analyzed with Student's *t* test, Mann-Whitney *U* test, and analysis of variance (ANOVA). Statistical significance was accepted to correspond to a *P* value less than 0.05.

Results

When stratified by time to lactate clearance, mortality in the four groups was significantly different (Table 1). Group 1 patients who did not clear lactate postoperatively had 100% (12 of 12) hospital mortality rate. This subset of patients either died before lactate normalization or persisted with an elevated arterial serum lactate at greater than 96 hours. In this study, no patient whose lactate was still greater than 2.0 mmol/dL at 96 hours reached normal values. Of note, 33% (4 of 12) of these patients expired late in their postoperative course (after postoperative day 50) as a result of a sequelae of events directly attributable to their initial illness. While some of the patients were discharged from the SICU, they did not progress further than a step-down or subacute chronic care unit. None of the patients achieved an adequate degree of independence. Group 2 patients, whose lactate levels returned to normal values between 48 and 96 hours, had a hospital mortality of 42.5% (7 of 16). All deaths in group 2 were also caused by sequelae of their initial illness. Five of the 7 deaths occurred in the late postoperative period (after 30 days). When serum lactate cleared between 24 and 48 hours, the mortality fell to 13.3% (2 of 15). Both deaths were again from multiorgan dysfunction syndrome (MODS) and occurred on postoperative day 9 and 10. If lactate normalized in less than 24 hours, the hospital mortality fell to 3.9% (2 of 51; *P* < 0.00001). The four groups did not differ with regard to

Table 2
Characteristics of survivors and nonsurvivors

	Survivors (n = 72)	Nonsurvivors (n = 23)
Age (years)	70.6 ± 12.0	71.5 ± 8.9 (NS)
Time to lactate clearance (hours)	17.0 ± 22.3	48.0 ± 30 (<i>P</i> < 0.0001)
Predicted mortality (%)	28.5 ± 15.5	44.6 ± 26.0 (<i>P</i> < 0.01)
Oxygen delivery (mL · min ⁻¹ · m ⁻²)	576.1 ± 193.0	492.0 ± 118.3 (NS)
Oxygen consumption (mL · min ⁻¹ · m ⁻²)	144.6 ± 47.2	119.5 ± 47.3 (NS)
Apache II score	17.1 ± 5.2	25.0 ± 13.6 (<i>P</i> < 0.001)
Apache III score	56.8 ± 22.2	72.2 ± 25.9 (<i>P</i> < 0.01)
Initial blood pressure (mm Hg)	128.3 ± 51.1	84 ± 12.7 (<i>P</i> < 0.01)
Initial lactate level (mmol/L)	4.3 ± 2.1	7.3 ± 5.4 (<i>P</i> < 0.01)

NS = not significant.

age and gender. Although there was an association between elevated Apache II scores increasing lactate clearance times, the difference was not statistically significantly different except between group 1 and group 4 (*P* < 0.01). The Apache III scores showed a significant differences between groups 1 and 3 as well as groups 1 and 4 (*P* < 0.05).

Although oxygen transport variables have been correlated with outcome in other studies [7,8], we found no significant difference in DO₂I or VO₂I between the four groups. The mean DO₂I varied from 497 ± 134 mL · min⁻¹ · m⁻² in group 1 to 642 ± 331 in group 3. The difference was not statistically significant and no trend was apparent. Similarly, VO₂I varied only from 134 ± 56 mL · min⁻¹ · m⁻² in group 1 to 130 ± 51 in group 4, again with no apparent trend (Table 1).

Some statistical differences were found between groups when initial systolic blood pressure, initial lactate, and pH were compared by ANOVA analysis. The values between the groups when systolic blood pressure was examined was significant by ANOVA (Table 1; *P* < 0.05); however, the Bonferroni *P* values between the groups were significant only between groups 1 and 4, and groups 2 and 4. (*P* < 0.01, *P* < 0.05) Similarly, the initial pH was found to be significantly different by ANOVA (*P* < 0.0001). Bonferroni analysis of initial pH revealed differences between groups 1 and 4 (*P* < 0.05) and groups 2 and 4 (*P* < 0.05). The difference in initial serum lactate showed a significant decrease with decreasing clearance time. Patients taking longer to clear lactate were found to have higher initial lactates. Those patients in group 1 (never cleared) had an initial lactate of 9.5 ± 6.1, while those in group 4 (<24 hours) had an average initial lactate of 2.26 ± 1.09 (*P* < 0.0001; Table 1).

Table 3
Predictors of survival

	Survivors	Nonsurvivors	Univariate analysis	Multivariate analysis
Time to lactate clearance (hours)	17.0 ± 22.3	48.0 ± 30	<i>P</i> < 0.0001	<i>P</i> < 0.0001
Initial blood pressure (mm Hg)	128.3 ± 51.1	84 ± 12.7	<i>P</i> < 0.01	NS
Initial lactate level (mmol/L)	4.3 ± 2.1	7.3 ± 5.4	<i>P</i> < 0.01	NS

NS = not significant.

On subgroup analysis, the average lactate clearance time was significantly longer in nonsurvivors by univariate analysis. In nonsurvivors, the average lactate clearance time was 48 ± 30 hours, while survivor's lactate clearance time was 17 ± 22 hours (*P* < 0.0001; Table 2).

In contrast to lactate, a statistically significant difference in DO₂I and VO₂I was not found between our survivors and nonsurvivors. The average DO₂I for non survivors was 492 ± 118 mL · min⁻¹ · m⁻², while survivors had a DO₂I of 576 ± 193 (Table 1; *P* > 0.05). The average VO₂I of nonsurvivors was 120 ± 47 mL · min⁻¹ · m⁻² while the VO₂I for survivors was 145 ± 47 (*P* > 0.05). The Apache II and Apache III scores differed between the two groups (*P* < 0.001, *P* < 0.01) as did the predicted mortality (*P* < 0.01; Table 2). Nonsurvivors were found to have a higher initial lactate and lower systolic blood pressure than survivors (*P* < 0.01, *P* < 0.005; Table 2). On multivariate analysis, only lactate clearance time factored out as significant (*P* < 0.0001). Neither initial lactate nor initial BP were found to be predictive of mortality (Table 3).

Comments

Lactate is formed through the reduction of pyruvate which is the end product of glycolysis. This reaction is driven by the enzymatic action of lactate dehydrogenase. Under aerobic conditions, pyruvate is oxidized via pyruvate dehydrogenase (PDH) to acetyl-CoA, which in turn enters the Krebs's cycle. If the action of PDH is inhibited, as in the anaerobic milieu, pyruvate will be converted to lactate. Thus, tissue hypoperfusion will lead to a cellular hypoxia which causes accumulation of lactate. Hypoperfusion with

its associated ischemia/reperfusion phase, may prime cells to produce cytokines responsible for the events leading to MODS [9]. Cairns et al [5] noted an association between early mitochondrial dysfunction and MODS in a series of trauma patients. Mitochondrial dysfunction, as measured by redox decoupling, and elevated serum lactate were found to differ significantly in nonsurvivors as compared with survivors; however, he found no statistical difference in VO_2I or DO_2I between survivors and nonsurvivors.

An elevated serum lactate is not uniformly accepted, as a marker of cellular hypoxia. Gore et al [4] states that the increase in serum lactate seen during stressed states is the result of accelerated pyruvate oxidation, accelerated glycolysis, and decreased hepatic clearance. Studies by both Hayes et al [10] and Steffes et al [11] failed to establish a correlation between DO_2I , both global and regional, and altered lactate levels. Boekstegers et al [12] could not establish a correlation between tissue hypoxia and elevated lactate in a cohort of septic patients. The prognostic value of serum lactate, however, has been advocated in other articles [13–15]. Similarly, the time to normalization of arterial serum lactate has been identified as a superior predictive variable to isolated levels in determination of outcome [3,13,14]. Although we demonstrate a higher overall initial lactate in nonsurvivors on univariate analysis, this is not borne out in multivariate analysis, indicating that initial lactates are not predictive of patient outcome in our patient group as well. Our data show that lactate clearance time is a valuable predictor of ICU and hospital mortality in surgical patients. Failure to clear lactate is associated with a 100% mortality in this patient population. Univariate and multivariate analysis demonstrate a significantly longer time to clearance in nonsurvivors.

Bishop et al [6], Boyd et al [7], and Shoemaker et al [8] all demonstrated a correlation between maximal optimization of oxygen delivery and decreased mortality in surgical and trauma patients. Holm et al [16] similarly demonstrated a correlation between increased DO_2I , increased VO_2I , lactate clearance, and increased survival, although a critical DO_2I was not identified. These observations, however, have not been universally corroborated. Shapiro et al [17] noted no difference in mortality between patients whose resuscitation was guided by DO_2I and VO_2I and those patients who were managed with conventional parameters. Steltzer et al [18] also could not establish an association between an optimal oxygen delivery value and survival, nor could they establish a statistical correlation between VO_2I and survival. Clearance of arterial serum lactate levels may be a superior independent predictive variable than DO_2I and VO_2I . Indeed, Abramson et al [2] identified lactate clearance time as more predictive of outcome in trauma patients than DO_2I . Our findings would seem to confirm this. Our study, however, may lack adequate sample size to draw definitive conclusions concerning DO_2I and VO_2I . Further, the values of DO_2I and VO_2I in our study were values obtained only at 24 hours, and were not uniformly obtained. Cryer et al [19]

reported an increased survival with adult respiratory distress syndrome (ARDS) in patients who achieved maximal DO_2I on day 3. Perhaps, if DO_2I and VO_2I had been measured serially or at 72 hours a correlation may have been established. While a correlation may have been demonstrated by trending DO_2I and VO_2I or increasing sample size, it is the authors' belief that monitoring the arterial serum lactate is a simpler and more cost-effective technique to achieve the same end.

The demonstrated correlation between lactate clearance time and survival in the SICU is in keeping with previously reports in the medical and trauma setting. Further, it appears that the normalization of arterial serum lactate may be an efficacious and simple marker to gauge end points of resuscitation. The longer the lactate clearance time the higher the patient mortality. Failure to clear lactate within 96 hours was predictive of certain mortality. In our unit, lactate continues to be utilized as a marker of resuscitation. An elevated lactate is interpreted as generally reflective of ongoing hypoperfusion at the tissue/cellular level. The response to an elevated lactate entails measures aimed at maximization of oxygen delivery. These measures are guided by the patient's hemodynamic profile and vary with each clinical situation. Whether optimizing oxygen delivery in itself is sufficient to establish an adequate end point of resuscitation is unclear in the literature, as mentioned above, and not supported by our data. Indeed, just what constitutes an optimal DO_2 in a given patient is variable and is dependent on factors such as patient reserve and the ability increase oxygen extraction to maintain an adequate oxygen consumption. The normalization of an arterial serum lactate would indicate adequate tissue perfusion at the cellular level, correction of the oxygen debt, and adequate oxygen extraction whereas a failure to reach end points of resuscitation is associated with an inability to bring arterial lactate to normal levels. One might argue that some of our patients may have, with more aggressive therapy, been able to be shifted to a more favorable group. While possible, this does not alter the observation that as lactate clearance time increased, so did mortality.

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