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Initial lactate and lactate change in post-cardiac arrest: a multi-center validation study

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Abstract

Introduction—Rate of lactate change is associated with in-hospital mortality in post-cardiac arrest patients. This association has not been validated in a prospective multicenter study.

Objective—To determine the association between percent lactate change and outcomes in post-cardiac arrest patients.

Methods—Four-center prospective observational study conducted from June 2011 to March 2012. Inclusion criteria consisted of adult out-of-hospital non-traumatic cardiac arrest patients who were comatose after return of spontaneous circulation. The primary outcome was survival to hospital discharge, and secondary outcome was good neurological outcome. We compared the absolute lactate levels and the differences in the percent lactate change over 24-hrs between survivors and non-survivors and between subjects with good and bad neurological outcomes.

Results—100 patients were analyzed. The median age was 63 years (IQR: 50 – 75) and 40% were female. 97% received therapeutic hypothermia and overall survival was 46%. Survivors and

patients with good neurological outcome had lower lactate levels at 0, 12 and 24 hours ($p < 0.01$). In adjusted models percent lactate decrease at 12 hours was greater in survivors (OR 2.2 [95% CI 1.1 – 6.2]) and in those with good neurological outcome (OR 2.2 [95% CI 1.1 – 4.4]).

Conclusion—Lower lactate levels at 0, 12 and 24 hours as well as greater percent decrease in lactate over the first 12-hours post-cardiac arrest are associated with survival and good neurologic outcome.

Keywords

lactic acidosis; cardiac arrest; ischemia-reperfusion; lactate; shock; perfusion

Introduction

Out-of-hospital cardiac arrest (OHCA) occurs in approximately 300,000 patients per year in the United States resulting in over 270,000 deaths and substantial neurological morbidity in survivors (1). Guidelines from the American Heart Association (AHA) and the European Resuscitation Council (ERC) emphasize the importance of optimizing intra-arrest treatment, and recent guidelines also emphasize management of patients during the post-arrest period (2–4).

The post-cardiac arrest period includes systemic illness from ischemic-reperfusion injury combined with the pathophysiologic derangements caused by the underlying etiology of arrest. Management of the post-arrest patient includes optimizing ventilation and oxygenation, optimizing tissue and organ perfusion, considering induced hypothermia when appropriate to promote neurological recovery, and treating the underlying etiology of arrest (5). Decrease in lactate is a surrogate marker for adequate tissue perfusion after return of spontaneous circulation (ROSC) and potentially serves as an endpoint for resuscitation. Current guidelines recommend measuring serial lactate levels in post-arrest patients to ensure adequate perfusion, however the International Liaison Committee On Resuscitation (ILCOR) consensus statement recognizes a knowledge gap in this area since these recommendations are based, in part, from extrapolation from other diseases such as sepsis (5–7). Two single-center, retrospective studies have addressed the association between lactate clearance and mortality, and found that effective clearance was associated with decreased mortality (8, 9).

We hypothesize that greater lactate reduction is associated with decreased mortality and good neurological outcome. To test this hypothesis, we performed a pre-planned analysis of a prospective, multicenter observational study of mitochondrial injury in post-arrest patients. We examined the association between early lactate change and mortality and neurologic morbidity in post-arrest patients. Secondly we evaluated the difference in initial and subsequent lactate levels between survivors and non-survivors and between patients with good versus poor neurological outcome.

Methods

Design and Setting

The National Post-Arrest Research Consortium (NPARC) is a clinical research network conducting research in post-cardiac arrest care. The network consists of four urban tertiary care teaching hospitals: ((Beth Israel Deaconess Medical Center (Boston, MA), University of Pennsylvania (Philadelphia, PA), University of Pittsburgh (Pittsburgh, PA), and Virginia Commonwealth University (Richmond, VA)) and was established to evaluate treatment strategies for people who are successfully resuscitated from out-of-hospital cardiac arrest. Patient care protocols for these hospitals have been reported previously (10). The NPARC network was funded initially to characterize mitochondrial injury in the post-arrest period. The current investigation is a preplanned analysis of data collected in the initial prospective observational cohort study.

Study Population

The study population of interest consisted of OHCA patients who presented to the Emergency Department (ED) at one of the four NPARC centers during the period from 6/2011 to 3/2012. We included all persons 18 years of age or older who had suffered OHCA with sustained ROSC (defined as the presence of palpable pulses for > 20 minutes) and were comatose (Glasgow Coma Scale < 8) immediately after the arrest. Patients were excluded if they had blunt or penetrating injury as the primary cause of arrest, if they were pregnant, or if they were prisoners. The study was approved by the Institutional Review Board at each participating site and the designated legally authorized surrogate provided written informed consent for each subject.

Data Collection and Data Management

Data were abstracted from the Emergency Medical Service reports, emergency department charts and hospital records using standardized definitions (11). We collected demographics and other baseline characteristics including initial cardiac arrest rhythm, initial vital signs, and laboratory results. We assessed the presence or absence of bystander cardiopulmonary resuscitation and subject downtimes. We recorded pharmacologic interventions including the use of vasoactive agents, sedatives or neuromuscular blocking agents, and anti-epileptic medications. We recorded the results of diagnostic testing including x-ray, echocardiogram and computed tomography results. Therapeutic hypothermia data and the results of cardiac catheterization procedures were recorded. Vital signs and laboratory data including lactate levels were collected at baseline (within 3 hours of sustained ROSC) and every 12 hours up to a maximum of 48 hours after the arrest.

Neurologic examinations were performed serially and at hospital discharge. Data were collected locally, removed of any personal identifying information and entered into a secure electronic database that was shared across participating sites.

Outcome Measures

For the current analysis the primary outcome measure was difference in percent lactate change at 12 hours between in-hospital survivors vs. non-survivors similar to previous

investigation (9). Secondary outcome measures included association of initial lactate with mortality, association of lactate change with good neurological outcome, and differences in lactate between survivors and non-survivors at additional time points. We defined percent lactate change at X hour as: $((\text{Lactate at 0 hour} - \text{lactate at X hour}) / \text{lactate at 0 hour}) \times 100\%$. We used the modified Rankin scale to assess neurological outcome as recommended per recent AHA outcome guidelines (12, 13). This is a validated scale, ranging from 0 to 6, that is used for measuring the performance of daily activities by patients who have suffered a stroke and is used commonly in cardiac arrest investigations (14, 15). Lower scores represent better performance; scores of 4 or greater represent severe disability or death. Good neurological outcome was defined as a modified Rankin scale of 0–3 and bad neurological outcome as a modified Rankin scale of 4–6. In addition to the primary analyses, we tested the difference in median lactate values between survivors and non survivors at the 0, 12 and 24 hour time points. For the purpose of this analysis, downtime is defined as the time of recognition of cardiac arrest to the time of return of spontaneous circulation (ROSC).

Statistical Analysis

Simple descriptive statistics were used to summarize the study population. Data for continuous variables are presented as means with standard deviations (SD) or median with inter-quartile ranges (IQR) depending on normality of the data. Categorical data are presented as frequencies with percentages. Lactate levels between groups were compared using Wilcoxon signed rank test. We used Bonferroni's method to account for multiple comparisons. In order to normalize the data lactate values were log transformed prior to calculating the lactate change variable. A logistic regression was performed to determine the ability of lactate change at 12 hours to predict in-hospital mortality and favorable neurologic outcome. All explanatory variables were tested and those which were significant ($p < 0.05$) were then included in multiple logistic regression models for the purpose of assessing the significance of percent lactate change at 12 hour. Initial lactate was forced into the model. The percent lactate change was also examined at the 24-hour time point. In order to account for missing data we conducted a sensitivity analysis with multiple imputations for the primary outcome of lactate change at 12 hour. The results from this analysis were not different from the primary analysis and the primary analysis is presented here.

In order to analyze lactate levels ability to predict mortality and neurological outcome at different time points we created the receiver operating characteristic (ROC) curve and calculating the area under the curve (AUC).

Patients were divided into six groups based on initial lactate levels (< 5 , $5 - 10$ and > 10 mmol/L) and initial vasopressor support versus no vasopressor support within 1 hour after ROSC for a subgroup analysis using lactate in a model to predict survival. All tests of the data were performed in SAS v. 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 111 out-of-hospital cardiac arrest patients were enrolled (see Figure 1). One hundred patients had initial lactate levels measured and were included in the analysis.

Baseline characteristics for these patients are shown in Table 1. Overall survival was 46% and overall good neurological outcome was 30%. Of those who survived to discharge, 65% had a good neurological outcome. Ninety-seven percent of patients received therapeutic hypothermia. Baseline characteristics for the overall population and for survivors and non-survivors are shown in Table 1.

Survivors had lower median lactate levels at 0, 12, and 24 hours compared to non-survivors (see Table 2 and Figure 2). Patients with good neurological outcome had lower median lactate levels at 0, 12, and 24 hours compared to patients with poor neurological outcome (see Table 2). For the endpoint of percent lactate change at 12 hours, the unadjusted model revealed a change of 44% [10 – 67] versus 32% [–24 – 54] ($p = 0.21$) for survivors and non-survivors respectively. After step-wise adjustment for variables found to be independent predictors of mortality (including initial lactate levels), percent reduction in lactate at 12 hours was statistically significantly associated with higher mortality (OR 2.2 [95% CI 1.1 – 6.2], $p = 0.02$ Figure 3). Between patients with good versus bad neurological outcome, unadjusted models showed a percent lactate change of 44% [15 – 67] versus 32% [–21 – 56] ($p = 0.25$) respectively. In the adjusted model, we found that less percent lactate change at 12 hours was statistically significantly associated with higher rate of bad neurological outcome (OR 2.2 [95% CI 1.1 – 4.4], $p = 0.02$ Figure 4). There was a difference in percent lactate change between survivors and non-survivors at 24 hour (62% [27 – 74] vs. 36% [–9 – 59]; $p = 0.03$). There was a trend toward larger percent lactate change at 24 hours in those with good neurological outcome but this did not reach statistical significance (62% [35 – 70] vs. 37% [–9 – 63]; $p = 0.08$). We analyzed the ability of lactate to predict mortality and neurological outcome at different time points by creating the receiver operating characteristic (ROC) curve (not shown) and calculating the area under the curve (AUC). The AUC for predicting mortality was 0.67 (0 hour), 0.76 (12 hour), and 0.78 (24 hour) The AUC for predicting bad neurological was 0.67 (0 hour), 0.72 (12 hour), and 0.77 (24 hour).

Patients were divided into six groups based on initial lactate levels (< 5, 5 – 10 and > 10 mmol/L) and initial vasopressor support versus no vasopressor support within 1 hour after ROSC. Figure 5 illustrates mortality that was significantly different between the groups ($p = 0.002$).

The amount of intra-arrest epinephrine (mg) was correlated with the initial lactate level ($r = 0.22$, $p = 0.03$), however this relationship was no longer present after adjusting for downtime ($r = 0.19$, $p = 0.08$).

Discussion

We found that greater percent lactate change over the first 12 hours post-arrest was associated with lower mortality and better neurological outcome in a cohort of OHCA patients. These differences held up after adjusting for potential confounders indicating that early lactate reduction is an independent predictor of mortality in post-arrest patients. In addition, the initial lactate level was higher in non-survivors and those who had poor neurological outcome as compared to survivors and those with good neurological outcome. Survivors had lower lactate measurements at all time points (0, 12, and 24 hours) (Figure 2).

Our findings are consistent with those previously reported in retrospective single-center studies of post-arrest patients and consistent with findings from other disease states.

Effective lactate clearance and lower initial lactate have been associated with reduced mortality in a variety of critical ill patients including patients with trauma, burns, and sepsis (16–18). In post cardiac arrest patients, previous investigators have demonstrated an association between lactate clearance and in-hospital mortality. Kliegel *et al.* retrospectively studied cardiac arrest patients with survival beyond 48h and found that lactate levels at 48 hours were an independent predictor of mortality. Moreover, they showed that survivors had lower initial lactate levels (8) which was confirmed by the current study. In a retrospective study of 79 patients, Donnino et al. found that lactate clearance at 12 hours was associated with 24-hour survival. However, initial lactate was not different between survivors and non-survivors (9). The initial lactate levels reported by Donnino et al. were substantially higher than the current average from our multi-center study likely reflecting an overall sicker population in that study. Patients reported by Donnino et al. had longer downtimes, were less likely to receive bystander CPR, and had overall higher mortality levels. Thus, the lack of a statistically different initial lactate level may reflect a clustering of patients with severe post-arrest syndrome and not an inability of initial lactate to differentiate outcomes for the broader population.

The combination of initial lactate and the need for vasopressor support has been showed to accurately predict mortality in one retrospective study of post-cardiac arrest patients (19). We conducted the same analysis and found similar results. All groups except the group with lactate 5 – 10 mmol/L and no vasopressor had similar mortality in the two studies showing that the simple combination of initial lactate and the use of vasopressors immediately post-arrest accurately predict mortality.

The pathophysiology of elevated lactate in post-cardiac arrest is complex and likely multifactorial. Pre-arrest, intra-arrest, and post-arrest factors influence lactate levels and potentially lactate clearance. The initially elevated lactate likely reflects the ischemia-reperfusion injury combined with any tissue hypoperfusion that may be present from the underlying etiology of arrest. For example, a pulmonary embolism may cause underlying lactic acidosis prior to arrest from tissue hypoperfusion that is then markedly accentuated after the ischemia-perfusion insult of the arrest. The persistent elevation of lactate or the effective change in lactate likely depends on the factors governing the initial elevation in conjunction with post-arrest conditions. In the post-arrest period, tissue hypoperfusion may persist for multiple reasons including the lack of resolution of the underlying insult, a post-arrest systemic inflammatory response (20, 21), myocardial depression with resultant cardiogenic shock (22), microcirculatory dysfunction (23–25), and mitochondrial injury (26, 27). The development of other complications such as sepsis (28), bowel ischemia (29, 30), seizures (31), and/or adrenal insufficiency causing shock (32) could play a role if present. Another potential cause of elevated lactate levels in the post-arrest period may be the presence of a hyper metabolic state with accelerated aerobic glycolysis potentially caused by activation of the Na⁺ K⁺ ATPase by endogenous epinephrine (33, 34).

The use of epinephrine has been suggested to cause elevated lactate (35), but an earlier study did not find a correlation between intra-arrest epinephrine and early lactate clearance (9). The current study found a weak correlation between the amount of intra-arrest epinephrine and initial lactate but the difference was not significant when adjusting for downtime. Whether lactate clearance is affected by the use of induced hypothermia could not be examined in this current study since almost all patients (97%) received induced hypothermia.

The ideal endpoints of resuscitation in post arrest remain controversial (7). While our data (and that of others) show that lactate is associated with worse outcome, utilization of lactate as an endpoint of resuscitation remains unproven though physiologically plausible. If elevated lactate post-arrest mostly represents injury from the initial ischemia-reperfusion injury to cells or from irreversible damage, the value of lactate would seemingly be less useful as a barometer for success of post-arrest treatments. In contrast, if persistence of lactate in represents ongoing correctable tissue hypoxia, one could conceivably adjust care based on lactate levels. Given that change in lactate at 12 hours is an independent predictor of survival after adjustment for arrest characteristics, our data suggest that at least some component of lactate change is dependent on the post-arrest course and therefore potentially useful as an endpoint of resuscitation. Future research could be targeted at adjunctive therapies to improve lactate clearance, and investigators might consider lactate change as an intermediary endpoint in post-arrest trials. In addition, lactate change could be evaluated as part of a severity of illness model in future prospective studies.

The current study has some limitations. The measurement of lactate levels were not part of the overall protocol and lactate levels were only ordered if deemed appropriate by the treating physician. That said, 90% (100/111) had an initial lactate drawn. Table 2 illustrates the number of lactate levels at each time point within those who had lactate drawn initially and our primary endpoint of lactate change between 0 and 12 hours had 85/100 (85%) of lactate measurements available. Thus, some selection bias may have occurred but we believe this was minimized by the strong majority of patients with this measurement available. We furthermore conducted a sensitivity analysis using a multiple imputations method for our primary analysis that did not alter our main results. The lactate samples were not all drawn from either arterial or venous sites, however studies have shown that there is a high correlation between arterial and venous lactate levels(36) Lactate analyzers were not standardized across the centers. However, differences in centers were evaluated in the multivariable model. Finally, while the study was multi-center, the sample size was relatively small.

Conclusion

Lower lactate levels at 0, 12, and 24 hours and greater percentage lactate reduction at 12 hours is associated with improved survival and good neurological outcome in post-cardiac arrest patients. The use of percent lactate change as an endpoint of resuscitation warrants further research.

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Figure 1.
Patient Flow Chart

Figure 2.
Median Lactate Levels with IQR in Survivors vs. Non-survivors for the First 24 Hours Post-Cardiac Arrest

Figure 3.

Lactate Levels and Mortality in Patients Administered Vasopressors vs. Patients not Administered Vasopressors

Figure 4.
Multivariable Logistics Regression Showing Variables Associated with Survival

Figure 5.
Multivariable Logistic Regression Showing Variables Associated with Good Neurologic Outcome

Table 1**Baseline characteristics**

(All continuous variables are expressed as medians (inter quartile range))

	All patients (n = 100)	Survivors (n = 46)	Non-survivors (n = 54)	P-value
Demographics				
Sex (% female)	40	37	43	0.57
Age (years)	63 (50 – 75)	63 (47 – 74)	64 (54 – 77)	0.25
Race (% white)	62	62	62	0.94
Body mass index (kg/(m ² m))	26.9 (22.8 – 32.2)	28.3 (22.8 – 32.1)	26.5 (22.9 – 32.3)	0.6
Co-morbidities (%)				
Coronary artery disease	32	26	37	0.24
Congestive heart failure	11	9	13	0.5
COPD	17	11	22	0.13
Diabetes	32	20	43	0.01
Prior myocardial infarct	18	13	22	0.23
Hypertension	57	54	59	0.62
Arrest details				
Witnessed (%)	80	89	72	0.04
Bystander CPR (%)	40	49	33	0.1
Initial rhythm (% shockable)	55	75	38	<0.001
Downtime (minutes)	21 (12 – 30)	15 (10 – 25)	26 (18 – 37)	0.004
Intra-arrest epinephrine (mg)	2 (1 – 3)	2 (0 – 2)	2 (2 – 4)	<0.001
Initial vital signs				
Temperature (C)	35.7 (35.3 – 36.3)	35.9 (35.4 – 36.4)	35.4 (34.8 – 35.8)	0.14
Heart rate (minutes ⁻¹)	96 (78 – 118)	96 (84 – 112)	93 (77 – 123)	0.94
Systolic blood pressure (mm Hg)	131 (112 – 154)	140 (125 – 161)	120 (103 – 137)	0.03
Initial laboratory values				
Hemoglobin	12.8 (10.9 – 14.4)	13.1 (10.9 – 14.6)	12.3 (10.8 – 14.0)	0.43
White blood count (K/ μ L)	13.7 (9.8 – 18.0)	12.9 (9.8 – 17.1)	15.0 (10.2 – 18.3)	0.45
INR	1.2 (1.1 – 1.4)	1.2 (1.1 – 1.2)	1.3 (1.1 – 1.6)	0.001
Bicarbonate (mEq/L)	20.1 (16.2 – 23.2)	20.7 (18.0 – 22.1)	20.0 (15.5 – 24.0)	0.45
Creatinine (mg/dL)	1.2 (1.0 – 1.7)	1.1 (0.9 – 1.4)	1.3 (1.1 – 1.8)	0.008
Bilirubin	0.7 (0.4 – 1.1)	0.7 (0.4 – 1.1)	0.6 (0.4 – 0.9)	0.52
Glucose (mg/dL)	229 (161 – 279)	195 (160 – 248)	246 (177 – 308)	0.04
pH	7.2 (7.1 – 7.3)	7.3 (7.2 – 7.3)	7.2 (7.1 – 7.3)	0.02
Base excess (mEq/L)	-6.1 (-12.0 – -3.1)	-5.8 (-10.0 – -3.9)	-8.8 (-15.0 – -3.1)	0.11
Post-arrest vasopressor support (%)	49	30	65	<0.001

Table 2

Lactate levels in survivors vs. non-survivors and in patients with good neurological outcome (mRS 0–3) vs. bad functional outcome (mRS 4–6)

Time point	Alive	Dead	p-value	mRS 0-3	mRS 4-6	p-value
0 hour (n=100)	4.1 (2.6 – 7.7)	7.3 (3.4 – 10.9)	0.004	3.9 (2.7 – 6.1)	7.0 (3.0 – 10.4)	0.009
12 hour (n=85)	2.2 (1.4 – 3.5)	6.0 (3.2 – 7.9)	< 0.001	2.2 (1.2 – 3.4)	5.1 (2.2 – 7.0)	0.001
24 hour (n=72)	1.6 (1.1 – 2.5)	4.4 (2.9 – 8.2)	< 0.001	1.5 (1.1 – 2.1)	3.9 (1.9 – 5.8)	< 0.001

All lactate levels are expressed as median (Inter quartile range)