ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.5336/cardiosci.2019-70462

The Effect of Serum Lactate and Lactate Clearence on Mortality in Cardiac Surgery Patients

Serum Laktatı ve Laktat Klirensinin Kalp Cerrahisi Hastalarında Mortalite Üzerine Etkisi

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Received: 18 Jul 2019
Received in revised form: 29 Sep 2019
Accepted: 02 Oct 2019
Available online: 15 Oct 2019

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ABSTRACT Objective: Lactate levels may increase due to tissue hypoperfusion that may occur during cardiopulmonary bypass. The blood lactate level is a dynamic variable, so a single lactate measurement may not always give sufficient information about the patient. Our aim was to evaluate whether a dynamic parameter such as lactate clearance was more useful in predicting mortality and morbidity after cardiac surgery. **Material and Methods:** A total of 591 patients who underwent cardiovascular surgery between January 2010-September 2018 were respectively included in the study. Among patients; hemodynamic parameters, extubation durations, duration of intensive care unit stay, total duration, of hospital stay and death time of those who died within 28 days were recorded. The patients were classified into two groups:The highest lactate level <4 (Group 1) and ≥ 4 (Group 2). Among the groups; hospital and intensive care stay periods and mortality ratios were compared. 24-hour and 72-hour lactate clearances were measured in all patients. **Results:** Cross clamp duration (86.5±78 vs. 74.4±26.9, p=0.005) and cardiopulmonary bypass duration (122.6±38.3 vs. 112.5±36.8, p=0.002) were significantly longer in Group 2. Lactate clearance level (T1-2) at 24th hour was significantly lower in patients who do not survive compared to the patients who survive [-12.33±81.47 vs 12.56±68.94, p=0.009]. Correlation analysis revealed a weak and positive correlation between 24th hour lactate clearance and duration of hospital stay. **Conclusion:** The addition of dynamic lactate parameters to the evaluation, such as lactate clearance, may be useful in predicting morbidity and mortality after cardiac surgery.

Keywords: Cardiac surgery; intensive care unit; lactate; lactate clearence; mortality

ÖZET Amaç: Kardiyopulmoner baypas sırasında meydana gelebilecek doku hipoperfüzyonu sonucu laktat seviyelerinde artış oluşabilir. Kan laktat düzeyi dinamik bir değişkendir, bu nedenle tek bir laktat ölçümü hasta hakkında her zaman yeterli bilgi vermeyebilir. Amacımız, kardiyak cerrahi sonrası mortalite ve morbidite tahmininde laktat klirensi gibi dinamik bir parametrenin daha faydalı olup olmadığını değerlendirmekti. **Gereç ve Yöntemler:** Ocak 2010-Eylül 2018 yılları arasında kliniğimizde kardiyovasküler cerrahi geçiren 591 hasta retrospektif olarak çalışmaya alındı. Hastalar ameliyat sonrası en yüksek laktat düzeylerine göre, laktat düzeyi<4 (Grup 1) ve≥4 (Grup 2) olmak üzere iki gruba ayrıldı. Tüm hastaların 24. saat ve 72. saat laktat klirensleri ölçüldü. Mortalite ile ilişkileri değerlendirildi. **Bulgular:** Grup 2'deki hastalarda Diyabetes Mellitus sıklığı (%38,9'a karşılık %30,7, p=0,038), kros klemp süresi (86,5±78'e karşılık 74,4±26,9, p=0,005) ve kardiyopulmoner baypas süresi (122,6±38,3'e karşılık 112,5±36,8, p=0,002) anlamlı olarak daha fazla idi. Hastalardan yaşamını yitirenlerde, yaşayanlara göre 24. saat laktat klirens düzeyi (T1-2) anlamlı olarak daha düşük idi [-12,33±81,47'e karşılık 12,56±68,94, p=0,009]. Yirmidördüncü saat laktat klirensi ile hastanede yatış süresi arasında zayıf ve pozitif bir korelasyon tespit edildi. **Sonuç:** Laktat klirensi gibi dinamik laktat parametrelerinin değerlendirmeye eklenmesi, kardiyak cerrahi sonrası morbidite ve mortalitenin öngörü değerini artırmada faydalı olabilir.

Anahtar Kelimeler: Kardiyak cerrahi; laktat; laktat klirensi; mortalite; yoğun bakım ünitesi

Cardiopulmonary bypass (CPB) is widely preferred to maintain systemic perfusion and oxygenation during cardiac surgery. Tissue hypoperfusion due to circulatory failure during CPB may lead to an increase in lactate levels secondary to anaerobic metabolism.[1,2] Studies have shown that high lactate levels are associated with poor outcomes in many clinical conditions, including cardiac surgery.[3] Blood lactate levels are also

frequently used to guide interventions such as fluid administration or inotropic therapy, and decreased lactate clearance is associated with prolonged mechanical ventilation and prolonged intensive care unit (ICU) stay.[4-6]

The blood lactate level is a dynamic variable, so a single lactate measurement may not always give sufficient information about the patient. Recent studies have shown that single measurement of lactate level has limited clinical benefit for outcome estimation.[7] Long-term high levels of lactate in postoperative patients are associated with increased mortality rate.[8] Therefore, the calculation of lactate clearance by serial lactate measurements may be a better biomarker than a single lactate level measurement in predicting mortality.

Our hypothesis was that static blood lactate after cardiac surgery was not useful enough to predict mortality and major adverse events. The addition of a dynamic parameter, such as lactate clearance, could be more beneficial in patients requiring intensive intervention.

MATERIAL AND METHODS

After the approval of the hospital ethics committee (Harran University Ethics Committee approval dated 21/12/2018 and numbered 10996); the files of 685 patients who underwent cardiac surgery between January 2010 and September 2018 in Health Sciences University Mehmet Akif İnan Education Research Hospital were reviewed retrospectively. This study was carried out in accordance with the principles of Helsinki Declaration. Patients with hepatic dysfunction (AST, ALT values that are 2 times higher than normal values), those with renal dysfunction (creatinine value that is 1.5 times more than normal values),patients with peripheral artery disease, patients who underwent dissection surgeries and revision surgeries, patients who died within 72 hours postoperatively were excluded from the study. In conclusion, 591 patients whose data were available and who met the study criteria were included in the study.

Demographic characteristics, comorbidities, ejection fractions (EF), type of surgery, presence of an urgent operation or not, cross clamp duration and cardiopulmonary bypass time were recorded in all patients.

Invasive arterial blood pressure, electrocardiography (ECG), peripheral oxygen saturation, end-tidal CO_2, central venous pressure (from the internal jugular vein) and nasopharyngeal heat monitoring were performed just before the operation. After standard induction of anesthesia, patients were intubated and anesthesia was maintained with inhalation anesthetics. The mean arterial pressure was maintained between 60-80 mmHg during cardiopulmonary bypass.

Among patients undergoing intensive care for postoperative follow-up; hemodynamic parameters, extubation durations, duration of intensive care unit stay, total duration of hospital stay and death time of those who died within 28 days were recorded.

The highest lactate levels of all patients were recorded in the postoperative period and the patients were classified into two groups according to their highest lactate levels: The highest lactate level <4 (Group 1, n=270) and the highest lactate level ≥4 (Group 2, n=321). Among the identified groups; hospital and intensive care stay periods and mortality ratios were compared. In addition, 24-hour and 72-hour lactate clearances were measured in all patients. The lactate clearance of the patients was calculated according to the following formula "Lactate clearance = [(first lactate level-second lactate level)/first lactate level] x 100". According to this formula; 24th hour lactate clearence [Basal-24th hour lactate clearance (T1-2)] and 72th hour lactate clearence [Basal-72th hour lactate clearance (T1-3)] were calculated.

STATISTICAL ANALYSIS

The data were analyzed with "SPSS for Windows 23.0 version". For the data with normal distribution in the descriptive statistics of the continuous variables, the results are expressed as mean±standard deviation (SD), and for those without normal distribution, the results are expressed as median (minimum-maximum). Normal distribution was evaluated by Kolmogorov Smirnov test. Mann-Whitney-U test was used for binary group compa-

TABLE 1: Demographic features, preoperative and intraoperative data.

	Group 1 (n =321)	Group 2 (n =321)	
	mean±SD/n (%)		p
Age (year)	60.3±10.6	59.2±10.9	0.243*
Gender			0.161**
	Female	105 (38.9%)	107 (33.3%)
	Male	165 (61.1%)	214 (66.7%)
BMI (kg/m2)	1.8±0.26	1.82±0.2	0.178*
DM	83 (30.7%)	125 (38.9%)	**0.038****
HT	133 (49.3%)	165 (51.4%)	0.604**
Smoking	67 (24.8%)	74 (23.1%)	0.617**
EF (%)	50.9±7.2	50.7±7.5	0.642*
Elective/Urgent			0.139**
Elective	240 (88.9%)	272 (84.7%)	
Urgent	30 (11.1%)	49 (15.3%)	
Type of Operation			0.853**
Valve op	22 (8.1%)	25 (7.8%)	
CABG+Valve op	0 (0%)	5 (1.6%)	
CABG	248 (91.9)	291 (90.7%)	
Cross-clemp duration (min)	74.4±26.9	86.5±78	**0.005***
Bypass duration (min)	112.5±36.8	122.6±38.3	**0.002***

*Mann-Whitney-U test; ** Chi-square test; DM: Diabetes mellitus; EF: Ejection fraction; HT: Hypertension; CABG: Coronary artery bypass graft; op: Operation; SD: Standard deviation; BMI: Body mass index.

risons. For the categorical variables, Chi-squared test was used in the comparisons between the groups. Regression analysis was performed to determine the independent effects of the factors that may affect mortality. ROC analysis was performed because lactate clearance T1-2 was low in patients with mortality. $p<0.05$ was considered as statistically significant.

RESULTS

In our study, 591 patients with cardiac surgery were evaluated. In 270 of these patients, the highest lactate level was below 4 (Group 1) and in 321 patients the lactate level was equal to 4 or higher than 4 (Group 2). The demographic data of the patients and the data about the surgery are shown in Table 1. There was no significant difference between the two groups in terms of age, gender, body mass index, hypertension, smoking, ejection fraction, urgency status of operation and types of patients ($p>0.005$). In Group 2, Diabetes Mellitus (DM) frequency was higher (38.9% versus 30.7%, $p=0.038$), cross clamp duration (86.5±78 vs. 74.4 ± 26.9, $p=0.005$) and CPB duration (122.6±38.3 vs. 112.5±36.8, $p=0.002$) were significantly longer.

When the total amount of blood products given to the patients in the intraoperative and postoperative period was examined; there was no statistical difference between two groups in terms of red blood cell and fresh frozen plasma (Table 2).

The postoperative data and mortality rates of the patients are shown in Table 3. There was no

TABLE 2: Amount of total given blood products.

	Group 1 (n=270)	Group 2 (n=321)	
	mean±SD		p*
RBC	5.03±2.88	5.22±3.09	0.084
FFP	5.27±2.61	5.27±2.76	0.574

*Mann-Whitney-U test; RBC: Red blood cell; SD: Standard deviation; FFP: Fresh frozen plasma.

TABLE 3: Postoperative data.

	Group 1 (n= 270)	Group 2 (n= 321)	
	mean±SD/n (%)		p
AMean intubation time (hr)	11.8±17.5	11±16.4	0.127*
ICU Stay (day)	3.3±2.88	3.37±3.29	0.398*
Hospital Stay (day)	8.06±3.98	8.39±4.41	0.078*
Exitus			0.517**
No	241 (89.3%)	281 (87.5%)	
Yes	29 (10.7%)	40 (12.5%)	
Exitus (day)	4.8±5.2	6.7±7.3	0.575*

*Mann-Whitney-U test, ** Chi-Square test; hr: hour, sd: standard deviation; ICU: Intensive Care Unit.

TABLE 4: Comparison of lactate clearance in dying and surviving patients.

	Died (+)	Survived (-)	p*
Lactate clearence (T1-2)	**-12.33±81.47**	**12.56±68.94**	**0.009**
Lactate clearence (T1-3)	**48.34±52.58**	**52.69±32.58**	0.595

*Mann-Whitney-U test; T1-2: between 1st time to 2nd time; T1-3: between 1st time to 3rd time; 1. Time: Intensive Care Entry; 2. Time: 24th Hour; 3.Time: 72th Hour.

significant difference between the two groups in terms of the mean duration of intubated patients, the duration of intensive care and hospital stay, rate of mortality and the day average of the deaths.

The levels of lactate clearance at 24 hours and 72 hours in patients who do not survive and patients who survive are given in Table 4. Lactate clearance level (T1-2) at 24th hour was significantly higher in patients who survive [12.56±68.94 vs -12.33±81.47, p=0.009]. However, there was no significant difference in lactate clearance between patients who survive and who do not survive at 72 hours [48.34±52.58 vs 52.69±32.58]. Correlation analysis revealed a weak and positive correlation between 24th hour lactate clearance and duration of hospital stay (r= 0.102, p= 0.016) (Table 5).

In multivariate logistic regression analysis, lactate clearence T1-2 was demonstrated to be an independent predictor for mortality after CPB (OR: 0.985; 95% CI 0.973-0.998; p= 0.021) (Table 6). In ROC analysis, a clear cut-off point could not be determined because the curve was very close to the normal curve and there was multiple points. The area under curve for lactate clearence T1-2 was 0.587 (0.506-0.668; %95 CI, p= 0.032) (Figure 1).

TABLE 5: Correlation analysis between lactate clearance and length of hospital stay and length of intensive care unit stay.

		Lactate clearence (T1-2)	Lactate clearence (T1-3)
ICU Stay (day)	r*	0.056	-0.017
	p*	0.182	0.700
Hospital Stay (day)	r*	**0.102**	0.050
	p*	**0.016**	0.241

*Spearman Rho correlation; r: correlation coefficient; ICU: Intensive care unit; T1-2: between 1st time to 2nd time; T1-3: between 1st time to 3rd time; 1.Time: Intensive Care Entry; 2.Time: 24th Hour; 3.Time: 72th Hour.

DISCUSSION

In our study, the effect of serial lactate measurements on mortality in patients undergoing cardiac surgery was investigated. The main finding of our study was as follows; there was no significant correlation between peak lactate levels and mortality after cardiac surgery, whereas lactate clearance at 24th hour was significantly lower in patients who do not survive.

The plasma lactate level is traditionally indicative of tissue hypoxia and is widely used in the

TABLE 6: Comparison of lactate clearance in dying and surviving patients.

	OR	95% CI	p*
Age (year)	1.006	0.932-1.084	0.886
Gender (male gender)	0.953	0.23-3.947	0.947
EF (%)	0.899	0.831-0.972	0.008
CPB duration (min)	0.998	0.982-1.015	0.815
Cross clemp duration (min)	1	0.988-1.012	0.978
Peak creatinine	1.392	0.581-3.335	0.458
Peak lactate	0.97	0.722-1.304	0.840
Lactate clearence T1-2	0.985	0.973-0.998	0.021
Lactate clearence T1-3	1.014	0.989-1.041	0.275
DM	1.046	0.202-5417	0.957
HT	0.829	0.151-4.544	0.829
Smoking	0.541	0.091-3.216	0.500

CPB: Cardiopulmonary bypass; CI: Confidence interval; DM: Diabetes mellitus; EF: Ejection Fraction; HT: Hypertension; T1-2: between 1st time to 2nd time; T1-3: between 1st time to 3rd time; 1. Time: Intensive Care Entry, 2. Time: 24th Hour; 3.Time: 72th Hour.

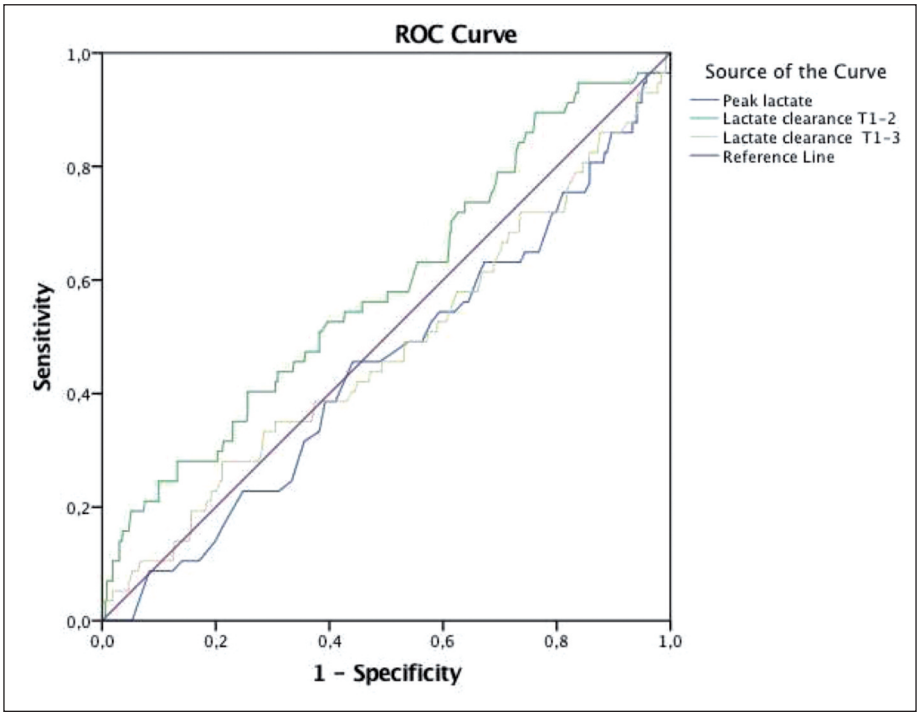

FIGURE 1: Peak lactate and lactate clearance change according to mortality; T1-2: between 1st time to 2nd time; T1-3: between 1st time to 3rd time; 1. Time: Intensive Care Entry; 2. Time: 24th Hour; 3. Time: 72th Hour.

follow-up of critically ill patients.[4] Lactate elevation has been reported to be associated with increased morbidity and mortality regardless of the etiology of this elevation.[9,10] The relationship between increased lactate level and mortality is independent of intraoperative variables.[11,12] The normal blood lactate level is defined as 0.4 to 2.0 mmol/L. The lactate level from 2.0 mmol/L to 4.0 mmol/L is considered to be a mild to moderate elevated lactate level and the lactate level above 4.0 mmol/L is defined as the severely elevated lactate.[12] However, the values referenced in each study for the definition of hyperlactatemia may vary.[13,14] In our study, we considered the most accepted value of 4.0 mmol/L as the reference value.

Hyperglycemia has been shown to be an independent risk factor for lactate elevation in many studies.[11,15] Glucose elevation may increase lactate levels by glycolysis and, conversly, increased lactate levels may generate glucose via the Cori cycle.[16] Lactate levels were found to be significantly higher in diabetic patients in our study, in support of current studies.

Studies have shown that the highest postoperative lactate level in cardiac surgery patients is an independent risk factor for early and late mortality.[11,17,18] However, in our study, no significant correlation was found between the highest lactate level and mortality. This unexpected result is probably due to the different patient profile in our study. In our study, unlike most other studies, we excluded patients with renal and hepatic dysfunction, aortic dissection surgeries, revision surgeries and patients who died within 72 hours postoperatively. Because these comorbidities and complex surgeries may cause lactate elevation on their own and may contribute to the increase of mortality so that they can alter the results of the study. In support of our study, Naik et al. did not find any correlation between lactate elevation and mortality.[19] Therefore, in order to clarify the relationship between lactate level and mortality, we think that the above-mentioned conditions should be taken into consideration.

Blood lactate level is a dynamic variable and the mechanism of increased lactate level may be caused by many different etiologies.[6] Therefore, the measurement of a single lactate level may not always give sufficient information about the patient. In order to improve the results when treating patients, it is necessary to distinguish the relatively benign and transient causes of lactate elevation from tissue hypoxia. Therefore, in recent studies, researchers mostly focused on more dynamic parameters such as lactate accumulation and lactate clearance.[4,20,21]

In a study evaluating patients undergoing surgery for mitral valve replacement, it was shown that the significantly increased early blood lactate levels were generally well tolerated as long as they were normalized within the first 24 hours.[14] Therefore, it was found that the evaluation of lactate elevation alone was not effective, and dynamic parameters such as lactate clearance could be more effective in predicting adverse outcomes after mitral valve surgery. Similarly, in another study evaluating children who were operated for tetralogy of fallot, it was stated that postoperative early lactate clearance can be used to predict hospital mortality and in patients with lactate clearance higher than 10% in the first 6 hours; less ventilation time, less inotropic requirement, and less ICU stay durations were detected.[6] In a recent meta-analysis, it was found that lactate clearance predicts mortality reliably.[22] Finally, Lopez et al. also demonstrated that low lactate clearance (<3 mmol/L) is the best predictor of morbidity and mortality in patients with heart failure.[23] In our study, it was shown that 24-hour lactate clearance was significantly lower in patients who developed mortality, supporting these findings. These results indicate that serial lactate monitoring in patients undergoing CPB surgery is a more valuable parameter than static lactate measurement. Therefore, it can be said that the use of lactate clearance may be more useful in predicting mortality in patients undergoing cardiac surgery.

LIMITATIONS

The limitations of our study can be listed as follows. First, our study was a retrospective study and data were collected from a single center. More precise data can be obtained by making larger studies. Secondly, although lactate levels were observed more frequently during the first 24 hours postoperatively, the hours of blood gases taken were found to vary among patients, so we tried to determine the lactate level in all patients at a certain time and in this study, lactate level at 24th hour was evaluated. Determination of lactate clearances at 6th and 12th hours may provide additional contribution to our study. Thirdly, the reason why there is no difference between in duration of intensive care stay may be due to that patients are not allowed to leave intensive care unit (ICU) before 3 days after cardiac surgery as a procedure in our hospital. Finally, patient management and selection of inotropic/vasoactive drugs were left to the physician's choice. Since data were collected retrospectively, the inotropic/vasoselective drug selection could not be standardized.

CONCLUSION

High blood lactate level is not a rare clinical condition in cardiac surgery patients and is generally well tolerated. Therefore, the elevated blood lactate level after surgery has limited possibilities for predicting poor patient outcomes. The addition of dynamic lactate parameters to the evaluation, such as lactate clearance, may be useful in predicting morbidity and mortality after cardiac surgery.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Gülçin Patmano, Tuğba Bingöl Tanrıverdi;* ***Design:*** *Gülçin Patmano, Tuğba Bingöl Tanrıverdi;* ***Control/Supervision:*** *Gülçin Patmano, Mehmet Tercan;* ***Data Collection and/or Processing:*** *Gülçin Patmano, Mehmet Tercan, Ahmet Kaya;* ***Analysis and/or Interpretation:*** *Gülçin Patmano, Ahmet Kaya;* ***Literature Review:*** *Gülçin Patmano, Ahmet Kaya;* ***Writing the Article:*** *Gülçin Patmano, Tuğba Bingöl Tanrıverdi;* ***Critical Review:*** *Gülçin Patmano, Mehmet Tercan, Ahmet Kaya;* ***References and Fundings:*** *Gülçin Patmano, Mehmet Tercan, Ahmet Kaya;* ***Materials:*** *Gülçin Patmano, Tuğba Bingöl Tanrıverdi.*

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