# Hyperlactatemia after coronary artery bypass surgery: risk factors and effect on mortality

*Koroner arter bypass cerrahisi sonrası hiperlaktatemi: Risk faktörleri ve mortalite ilişkisi*

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***Background:*** This study aims to determine the risk factors for hyperlactatemia developing after coronary artery bypass grafting (CABG) surgery and to analyze its effect on mortality and the morbidity.

***Methods:*** Four-hundred and eighty-two consecutive patients who had undergone elective CABG were prospectively included in the study and divided into two groups: group 1 (n=260), patients who had high blood lactate levels in the first measurement (>3.5 mmol/l) in the intensive care unit (ICU); group 2 (n=222), patients who had normal blood lactate levels (<3.5 mmol/l). The duration of cardiopulmonary bypass (CPB) and cross-clamping (CC), hyperglycemia (blood glucose level >140 mg/dL), the presence of hemodynamic instability and requirement for vasopressors during CPB, inotropic agent administration for more than three hours and the temperature and lactate changes at five different time points during ICU stay were measured. Postoperative neurologic, infectious and renal complications and the durations of ICU stay and mechanical ventilation were recorded.

***Results:*** The blood lactate levels were found significantly higher in patients with longer CPB and CC durations and peroperative hemodynamic instability. Postoperatively, the patients who had high glucose levels and high inotropic agent needs also had higher lactate levels. The patients in group 1 had longer extubation times and ICU stays. There was a significant correlation between blood lactate levels and mortality and morbidity ($p<0.01$).

***Conclusion:*** Having an initial blood lactate concentration higher than 3.5 mmol/l after being transferred to ICU is a bad prognostic indicator. Serial lactate measurements may allow for detection of patients with high risk of developing mortality and morbidity and taking the necessary preventive measures.

*Key words:* Coronary artery bypass graft; hyperlactatemia; mortality.

***Amaç:*** Bu çalışmada, koroner arter bypass greftleme (KABG) ameliyatı sonrası gelişen hiperlaktatemi ile ilişkili risk faktörlerin belirlendi ve hiperlaktateminin mortalite ve morbidite üzerindeki etkileri analiz edildi.

***Çalışma planı:*** Elektif KABG ameliyatı geçiren ardışık 482 hasta ileriye dönük olarak çalışmaya alındı ve iki gruba ayrıldı: Grup 1, yoğun bakım ünitesi (YBÜ)'ndeki ilk ölçümde kan laktat düzeyi yüksek olan 260 hasta (>3.5 mmol/l); grup 2, kan laktat düzeyi normal olan 222 hasta (<3.5 mmol/l). Kardiyopulmoner bypass (KPB) ve kros klemp (KK) süresi, hiperglisemi (kan glukoz düzeyi >140 mg/dL), KPB süresince hemodinamik instabilite varlığı ve vasopressör gereksinimi, üç saatten daha uzun süre inotropik ajan kullanımı, YBÜ'de beş farklı zaman noktasında değerlendirilen ısı ve laktat değişimleri ölçüldü. Ameliyat sonrası nörolojik, infeksiyöz ve renal komplikasyonlar, mekanik ventilasyon ve YBÜ'de kalış süreleri kaydedildi.

***Bulgular:*** Ameliyat sırasında uzun KPB ve KK süreleriyle hemodinamik instabilitesi olan hastaların kan laktat düzeylerinin anlamlı ölçüde daha yüksek olduğu saptandı. Ameliyat sonrasında glukoz düzeyleri yüksek ve inotropik ajan gereksinimi fazla olan hastalarda, laktat düzeyleri de daha yüksek idi. Grup 1'deki hastaların ekstübasyon ve YBÜ'de kalış süreleri daha uzundu. Kan laktat düzeyleri ile mortalite ve morbidite arasında anlamlı bir bağıntı vardı ($p<0.01$).

***Sonuç:*** Hastalar YBÜ'ye transfer edildiğinde ilk ölçülen kan laktat düzeyinin 3.5 mmol/l'nin üzerinde olması kötü bir prognostik göstergedir. Seri laktat takipleri, mortalite ve morbidite gelişmesi riski yüksek olan hastaların belirlenmesine ve gerekli önlemlerin alınmasına olanak sağlayabilir.

*Anahtar sözcükler:* Koroner arter bypass cerrahisi; hiperlaktatemi; mortalite.

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After coronary artery bypass grafting (CABG) surgery, hyperlactatemia is frequently seen in 10-20% ratio and is related with increased postoperative mortality and morbidity.[1] Although higher lactate levels cannot be explained exactly, the likely mechanism suggested is tissue hypoxia in cardiopulmonary bypass (CPB).[2,3] Hemodilution, inappropriate peripheral oxygen distribution and hemodynamic instability could lead to tissue hypoxia and these factors are related to postoperative mortality and morbidity. It is reported that hyperlactatemia after CPB tends to occur commonly in procedures requiring more prolonged CPB times.

When the $O_2$ supply is decreased to a critical level, $O_2$ consumption becomes dependent on supply and begins to decrease until lactic acidosis finally occurs. Also, hemodynamic instability and administration of high dose $\beta_2$ agonist agents are risk factors for hyperlactatemia.[4]

The purpose of our study is to determine the risk factors concerned with hyperlactatemia after elective CABG, and to analyze the mortality and morbidity.

## PATIENTS AND METHODS

After Research, Planning and Coordination Council of the Ministry of Health approval, 482 patients who underwent elective CABG in our cardiovascular surgery clinic between July 2005 and April 2008 were enrolled in the study. Patients who had undergone emergency CABG, required combined procedures and had low ejection fractions (EF <30%) were excluded. Patients were divided into two groups according to their lactate levels; blood lactate levels higher than 3.5 mmol/l, group 1, blood lactate levels lower than 3.5 mmol/l, group 2 as a control group. Physical characteristics (sex, height, weight) and co-morbid diseases (hypertension, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), renal failure (RF; creatinin levels >2 mmol/l), acute myocardial infarction (AMI) within a month were recorded. A single surgical team operated on all the patients and the same anesthetic management techniques were used.

Before anesthesia induction, axillary temperature and basal arterial lactate levels ($T_0$) were measured. Intraoperatively, CPB and aortic CC times, peroperative hemodynamic instability (mean arterial pressure; MAP <50 mmHg) and requirements of vasopressors were recorded. In the intensive care unit (ICU), requirements of inotropic agents more than three hours, hyperglycemia (blood glucose level >140 mg/dl), intubation time, staying period in the ICU, cerebrovascular accident, infections (pneumonia, mediastinitis, bacteremia, local wound infection, catheter infection) and acute renal failure (at least twice the preoperative creatinine levels) were evaluated. Also, body temperatures and arterial lactate levels of all the patients were recorded before anesthesia induction ($T_0$), at the 1st hour in the ICU ($T_1$), and at the 4th, 8th, 16th and 24th hours ($T_2$, $T_3$, $T_4$, $T_5$) respectively.

All data were analyzed by using SPSS (Statistical Package for Social Sciences) for Windows version 15.0 package (SPSS Inc., Chicago, Illinois, USA). Descriptive statistical methods evaluated included mean and standard deviation, the Student t-test in comparisons of quantitative data with normal distribution, and Mann Whitney U-test in the comparison of groups without normal distribution. Wilcoxon signed rank test was used for comparison of parameters within each group. Chi-square and Fisher's exact chi-square tests were used for qualitative data analysis. The results were evaluated at 95% confidential interval (CI) and significance ($p<0.05$) level.

## RESULTS

The demographic, physical characteristics and co-morbid diseases are demonstrated in table 1. There

**Table 1. Assessments of demographic factors and co-morbid diseases**

| | Group 1 | | | Group 2 | | | *p* |
|---|---|---|---|---|---|---|---|
| | n | % | Mean±SD | n | % | Mean±SD | |
| Height | | | 166.6±8.9 | | | 167.9±10.8 | NS |
| Weight | | | 76.5±13.2 | | | 78.2±11.8 | NS |
| Sex | | | | | | | |
| Female | 98 | | | 91 | | | |
| Male | 162 | | | 131 | | | |
| Diabetes | 74 | 28.6 | | 74 | 33.5 | | NS |
| Hypertension | 143 | 55.2 | | 129 | 58.4 | | NS |
| Chronic obstructive pulmonary disease | 31 | 12.0 | | 38 | 17.2 | | NS |
| Renal failure | 4 | 1.5 | | 4 | 1.5 | | NS |
| Acute myocardial infarction | 84 | 32.4 | | 56 | 5.3 | | NS |

SD: Standard deviation; NS: Not significant.

**Table 2. Assessments of perioperative and postoperative variables**

| | Group 1 | | | Group 2 | | | *p* |
|---|---|---|---|---|---|---|---|
| | n | % | Mean±SD | n | % | Mean±SD | |
| Pump time (min) | | | 102.5±37.5 | | | 89.1±30.7 | <0.05 |
| Pump balance (cc) | | | 1236.8±701.9 | | | 1164.6±737.9 | NS |
| Cross-clamp time (min) | | | 72.3±58.1 | | | 60.0±26.1 | <0.05 |
| MAP <50 mmHg | 27 | 10.4 | | 4 | 1.8 | | <0.05 |
| Vasopressor agent administration | 62 | 23.9 | | 44 | 19.9 | | NS |
| Hyperglycemia | 110 | 42.47 | | 73 | 33.03 | | <0.05 |
| Need of inotropic agents | 44 | 16.9 | | 20 | 9 | | <0.05 |
| Neurological complications | 8 | 3.1 | | 2 | 0.9 | | NS |
| Infections | 6 | 2.3 | | 3 | 1.4 | | NS |
| Postoperative acute renal failure | 9 | 3.5 | | 3 | 1.4 | | NS |

MAP: Mean arterial pressure; SD: Standard deviation; NS: Not significant.

were no statistically significant differences between the groups.

In group 1, CPB and aortic cross-clamp times were longer and hemodynamic instability (MAP <50 mmHg) incidences were higher (p<0.01). During the postoperative period hyperglycemia was seen more frequently in group 1 and was noted to be significant (p<0.05). Also in group 1 patients, the need for inotropic agents was found to be significantly higher (p<0.05). There was no statistically-significant difference between the groups with regard to the other variables (Table 2).

Preoperative lactate levels were noted to be statistically insignificant between the groups (p>0.05). In group 1, except for the basal lactate level ($T_0$), all the lactate levels measured at $T_1$, $T_2$, $T_3$, $T_4$, $T_5$ were found significantly higher than group 2 (p<0.05). Also, in both groups, the lactate levels measured at $T_0$ time were noted to be significantly lower than the lactate levels at $T_1$, $T_2$, $T_3$, $T_4$, $T_5$ times (p<0.05; Fig. 1).

In comparisons of postoperative temperatures, there were no statistically significant difference between the groups at the $T_0$, $T_1$, $T_2$, $T_3$, $T_4$, $T_5$ times, (p>0.05). In both groups, temperatures measured at $T_1$ were significantly lower than $T_0$, $T_2$, $T_3$, $T_4$, $T_5$ period, (p<0.05; Fig. 2).

In group 1, intubation and postoperative staying period were longer than group 2 (p<0.05) but there were no statistically significant differences in hospitalization periods between the groups. In group 1, mortality ratio was found significantly higher than in group 2 (p<0.05; Table 3).

## DISCUSSION

Although increased blood lactate levels in the ICU after cardiac surgery are frequently seen as a metabolic

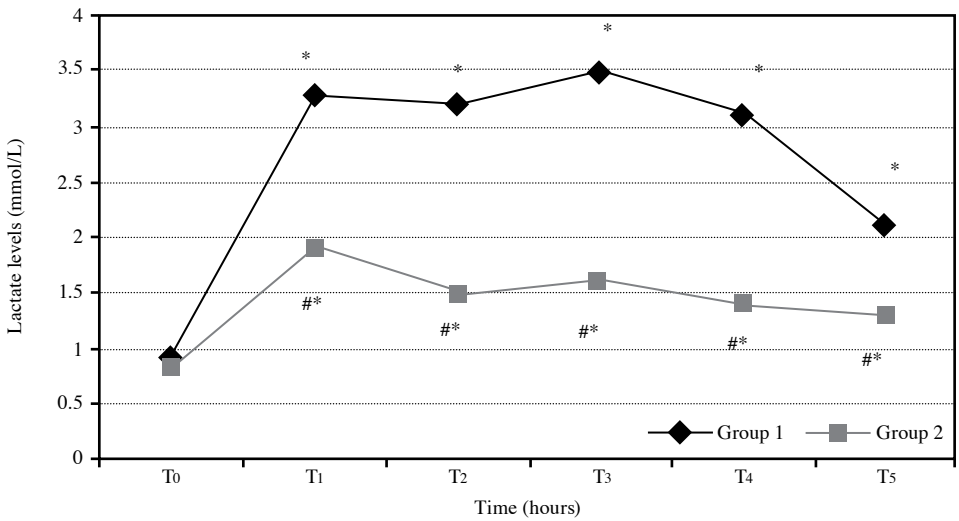


**Fig. 1.** Relation of lactate levels and postoperative course in both groups.

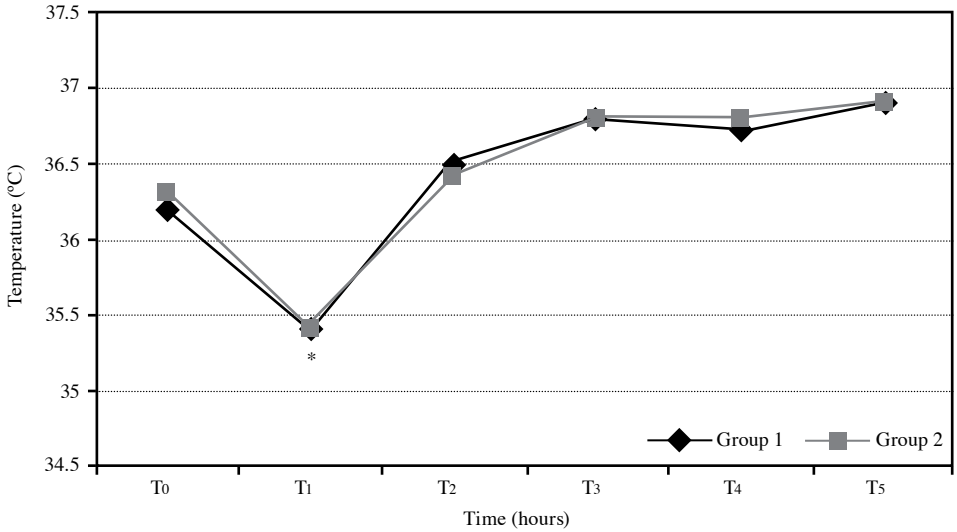


**Fig. 2.** Relation of body temperature in postoperative course.

disorder, the pathophysiology has not been explained clearly.[1] Hyperlactatemia occurs due to tissue hypoxia (Type A hyperlactatemia), and it can also be seen in some cases without tissue hypoxia (Type B hyperlactatemia). Especially after cardiac surgery, type B hyperlactatemia could be seen frequently in the early postoperative period.[5]

Demers et al.[6] supposed that many different preoperative factors and co-morbidities produced the favorable medium for the hyperlactatemia seen during CPB. They reported that age, congestive heart failure, low left ventricle ejection fraction, hypertension, DM, reexploration and emergency interventions were risk factors for hyperlactatemia. Contrary to the study of Demers, we did not find age, hypertension or DM as risk factors for hyperlactatemia. Probably, it was found that myocardial infarction (MI), COPD, RF did not increase the risk of hyperlactatemia. In order to standardize the variables and conditions that may lead to abnormal hyperlactatemia, the patients who underwent re-exploration or emergency interventions were excluded from the study- hence no interpretations could be made for these conditions.

The principal reason for hyperlactatemia seen during CPB is excessive hemodilution and organ hypoxia due to low peripheral $O_2$ supply.[7] It was found that hyperlactatemia more commonly occurred after cardiac procedures that required prolonged CPB time and was independently related with low oxygen supply and almost always correlated with hyperglycemia.[8,9] When $O_2$ supply decreases below a critical level, $O_2$ consumption becomes dependent on supply and begins to decrease and leads to the lactic acidosis. It has been demonstrated that in patients whose $O_2$ supplies decrease below 260 ml/min/m$^2$, the lactate levels begin to increase.[10]

In our study, during the CPB, the requirement for vasopressor agents and hemodynamic instability occurred in more patients of group 1 in whom it may be supposed there was an imbalance of $O_2$ supply and consumption ratio. Reports in the literature support our results that prolonged CPB time leads to lactic acidosis.[2] Moreover, in this study the importance of intraoperative hypothermia was mentioned, and it was found that nonpulsatile hypothermic CPB led to regional, particularly, splanchnic hypoperfusion. Furthermore, it was found that rewarming led to imbalance between $O_2$ supply and consumption. Consequently, this imbalance was more distinctive in

**Table 3. Assessments of intubation period, intensive care unit staying, hospitalization period and mortality**

| | Group 1 | | | Group 2 | | | *p* |
|---|---|---|---|---|---|---|---|
| | n | % | Mean±SD | n | % | Mean±SD | |
| Intubation period (hours) | | | 16.4±11.6 | | | 14.3±4.1 | <0.05 |
| ICU staying period (hours) | | | 39.7±105.6 | | | 26.2±18.0 | <0.05 |
| Hospitalization period (days) | | | 10.0±11.2 | | | 8.1±4.5 | NS |
| Mortality | 14 | 5.4 | | 1 | 0.5 | | <0.05 |

SD: Standard deviation; ICU: Intensive care unit; NS: Not significant.

patients with prolonged hypothermic CPB. Ranucci et al.[8] supposed that the relation of CPB time and peak lactate levels were not linearly correlated and the cut-off value of CPB time for peak lactate level was 96 minutes. In our study, CPB time was 102 minutes in the hyperlactatemia group (Group 1), and 89 minutes in the low lactate group (Group 2), supporting the above-mentioned study.

Totaro and Raper[4] described increasing lactic acidosis with the administration of β2 agonists such as ritodrine and terbutaline and high doses of adrenaline. Lactic acidosis can also be seen in serious hyperadrenergic states such as pheochromocytoma and acute asthma.[11-13] Caruso et al.,[14] reported that hyperlactatemia was related to hyperglycemia and insulin resistance, and hyperlactatemia recovered after the cessation of epinephrine treatment. Epinephrine induces glycogenolysis by increasing pyruvate production. This mechanism leads to stimulation of muscle and liver phosphorylase enzymes and inhibition of glycogen synthase. Additionally, epinephrine increases insulin release, and, glyconeogenesis and metabolization of proteins. The response of these metabolic derangements in diabetic patients is more severe; and can be observed as much more hyperglycemia. Ranucci et al.[10] reported a peak blood glucose level of 160 mg/dl as a cut-off value for hyperlactatemia. In our study, the cut-off value was recognized as 140 mg/dl and found that blood glucose levels were higher in more patients in the hyperlactatemia group. There are many factors that increase the blood glucose level during CPB and the postoperative period. Particularly, inflammatory responses to surgery and extracorporeal circulation, endocrinological factors such as growth hormone, adrenocorticotropin (ACTH), epinephrine, and insulin resistance increase the blood glucose level.[10]

Although there were no differences in demographical data between both groups, for DM it was found that blood glucose levels were higher in more patients in the hyperlactatemia group and it may be related to the inflammatory response to secondarily developing surgical trauma. Even if lactate concentration is a good marker for severity of the disorder in ICU patients, the prognostic significance after cardiac surgery cannot be revealed exactly. Moderate levels of hyperlactatemia could be generally assessed as benign.[10] In our study, a lactate concentration >3.5 mmol/l for patients just transported into the ICU was accepted as a bad prognostic marker. These patients had more prolonged times of intubation and ICU stay when compared with group 2 patients. It was found predictably that the mortality rates of these patients were higher than the normal lactate group.

As a consequence, serial measuring of the lactate levels in the postoperative period may be very beneficial clinically. Prevention of hyperlactatemia, which is accepted as a bad prognostic marker, is very important and we have to provide hemodynamic stabilization during CPB, to avoid severe hypothermia, hemodilution and hypotension as much as possible. Weaning of CPB could be easier by using modern myocardial preservation techniques and meticulous surgical techniques, so CPB and cross-clamp times may be relatively shorter. Blood glucose levels should be closely monitored and hyperglycemia should be treated urgently perioperatively in ICU. Serial lactate follow-ups may be provided to detect the patients having possible high risk of mortality and morbidity and to initiate the required preventive therapeutic modalities.

**Declaration of conflicting interests**

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