Original Article

Effect of Delta Carbon Dioxide and Lactate on Prognosis in Patients Undergoing Open-Heart Surgery

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Abstract

Background: To identify individuals with an increased mortality and morbidity risk after surgery, different parameters showing impaired tissue perfusion/oxygenation have been investigated, and the balance between tissue oxygen consumption and oxygen delivery has been evaluated in detecting organ failure. **Aim:** This study aimed to evaluate the efficacy of central venous–-arterial partial carbon dioxide difference (ΔPCO_2) and lactate (ΔLAC) values within the first week after discharge in predicting mortality in patients undergoing open-heart surgery. **Patients and Methods:** A total of 102 patients between February and April 2020 were included in the study. The patients' data obtained at the end of cardiopulmonary bypass (hour 0) and during the intensive care follow-up (hour 1, hours 6, and 24) data were prospectively recorded. All statistical analyses were performed using SPSS v. 22.0 for Windows (SPSS Inc, Chicago, IL, USA). **Results:** The mean age of the patients was 56.88 ± 11.02 (min 18–max 78) years, and 71.6% of the patients were male. It was observed that the area under the curve was not significant for the four measurements performed for ΔLAC. Although the area under the curve of ΔPCO_2 measured at hour 6 (0.66) was significant. **Conclusion:** The ΔPCO_2 were found to have a poor ability to predict the development of complications during the intensive care and early postoperative period in patients undergoing open-heart surgery.

Keywords: *Cardiopulmonary bypass, lactate, morbidity, oxygen deficiency, perfusion*

Introduction

Tissue hypoxia during surgery and postoperative organ failure are among the leading causes of patient mortality. Failure to meet the increased oxygen demand after surgery may cause tissue hypoxia.[1] To identify individuals with an increased mortality and morbidity risk after surgery, different parameters showing impaired tissue perfusion/oxygenation have been investigated, and the balance between tissue oxygen consumption and oxygen delivery has been evaluated in detecting organ failure. A low central venous oxygen saturation ($ScvO_2$), which is used as one of the indicators of this balance, has been associated with postoperative organ failure.[2] Nevertheless, in the case of decreased oxygen delivery capacity, normal or high values of $ScvO_2$ do not exclude the presence of tissue hypoxia, which limits the benefits and use of this parameter in patient follow-up.[3] In addition, interventions to reduce serum lactate—a stimulating parameter in terms of tissue hypoxia—decrease the length of the patient's hospital stay as well as their risk of mortality.[4] However, increases in lactate levels can be delayed, and the tissue may not be sensitive enough to indicate perfusion failure.[5]

Although measurements of mixed venous and central venous oxygen saturation provide similar results,

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the best approach for these parameters is to monitor measurements taken at different times.[6] The central venous–arterial carbon dioxide difference (delta carbon dioxide, ΔPCO_2) is inversely correlated with cardiac output and indicates whether venous blood flow is sufficient to remove the excess CO_2 formed in tissues as a result of metabolism.[7] Therefore, impaired tissue perfusion during hypoperfusion is the main determinant of the increase in the central venous–arterial carbon dioxide difference.[8]

Considering that patients who have undergone open-heart surgery among other major surgical operations are more prone to early postoperative complications, it is important to develop advanced examinations and investigate their efficacy in these patients.

Aim

In this study, we aimed to evaluate the efficacy of intraoperative and postoperative ΔPCO_2 and the central and arterial–venous lactate difference (ΔLAC) values during a hospital stay and after discharge (within the first week) in predicting mortality and morbidity in patients undergoing open-heart surgery.

Materials and Methods

Data collection

The study was carried out between February 1, 2020, and April 30, 2020, at Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital after obtaining approval from the Clinical Research Ethics Committee of the Health Sciences University Haydarpaşa Numune Training and Research Hospital (HNEAH-KAEK 2019/KK/159). In the sample size, analysis was performed by taking 80% power at a 95% confidence interval as a reference. The minimum sample size to be reached was determined to be 79 (P = 5%), and therefore, 102 patients were included in the study after applying the inclusion and exclusion criteria. The study had a prospective observational design. The patients provided written informed consent during the preoperative evaluation.

Patient population

For the 102 patients scheduled for elective open-heart surgery, the following were recorded: age, gender, ejection fraction (EF), EuroSCORE value, chronic diseases, the presence and dosage of postoperative inotrope support, fluid balance at the time of admission to the intensive care unit (ICU) postoperatively and at hour 24, 24-hour urine volume, preoperative hemoglobin/hematocrit values, whether or not blood/blood product replacement was performed perioperatively (if so, hemoglobin/hematocrit value at the time of blood replacement), cardiopulmonary bypass time (CPB), cross-clamp time, postoperative ΔPCO_2 and ΔLAC values simultaneously measured at hour 1 (end of bypass), hour 1 (admission to ICU), hour 6, and hour 24, postoperative complications within the first 24 hours and 7 days; length of ICU and hospital stays, and mortality and morbidity within the first 7 days after discharge of hospital. The inclusion criteria required the patients to be above 18 years of age and under 80, undergo open-heart surgery immediately followed by admission to ICU, and receive intensive care for at least 24 hours. The exclusion criteria were if they were undergoing surgery under emergency conditions and required an intra-aortic balloon pump and extracorporeal membrane oxygenation.

Method

All patients received 0.03–0.05 mg/kg intramuscular midazolam as premedication 30 minutes before the operation. After the patients were taken to the operating room, invasive artery monitoring was provided via electrocardiogram (ECG), pulse oximetry, and radial artery cannulation. All patients received standard anesthetic management. For inducing anesthesia, 2–2.5 mg/kg propofol, 2.5–5 mg/kg fentanyl, and 0.6 mg/kg rocuronium bromide were intravenously administered. Anesthesia was maintained using 6–10 mg/kg/h propofol, 2 mg/kg/h fentanyl, and 0.03 mg/kg/h rocuronium bromide infusions. Ventilation was provided using the volume control mode, and the respiratory rate and tidal volume were adjusted to achieve normocapnia. Right or left internal jugular vein cannulation was performed for central venous pressure monitoring and central venous blood gas assessment after anesthesia induction. The ECG, pulse oximetry, end-tidal CO_2, arterial and central venous pressures, and urine output were monitored during the operation. All patients were operated upon using CPB. Before administering CPB, a cannula was placed and 300–400 IU/kg heparin was intravenously administered. Activated clotting time (ACT) was measured 3 minutes after heparin injection and aimed to be above 400 seconds. The ACT was monitored at 30-minute intervals, and additional heparin doses were administered to maintain the value above 400 seconds. To neutralize the effect of heparin at the termination of CPB, a 3 mg/kg intravenous protamine infusion was administered with the control ACT value within normal limits (100–140 seconds).

During CPB, blood gas monitoring was performed every 30 minutes to evaluate the tissue perfusion and metabolic balance. The pump flow was adjusted to keep the mean arterial pressure within 60–90 mmHg, and vasoactive drugs were administered when necessary.

Urine was monitored and diuretics were administered, when required. After the cross-clamp was removed and the cardiac surgery procedures were completed, the patients were checked for normothermia, regular and normal heart rhythm, arterial blood pressure, arterial blood gas parameters, and electrolyte values. When these values were found to be normal, mechanical ventilation was started and CPB was started and gradually terminated. During this period, the patients' hemodynamic parameters were closely monitored and fluid electrolyte, positive inotropic agent, and vasodilator drug treatment were readjusted. After terminating the CPB, central venous and arterial blood gas samples were simultaneously taken from the patients and the ΔPCO_2 and ΔLAC values were recorded (hour 0).

Upon completing surgery, infusions of anesthetic drugs were stopped and the patients were transferred to the ICU while intubated. Upon arrival at the ICU, central venous and arterial blood gas samples were simultaneously taken from the patients, and the ΔPCO_2 and lactate values were again measured (hour 1). In the postoperative follow-up, a routine treatment protocol was applied based on the heart rate, heart rhythm, arterial blood pressure, central venous pressure, urine output, and blood gas parameters. The patients were extubated after achieving stable hemodynamics, normal arterial blood gas parameters, adequate consciousness, and muscle strength. The ΔPCO_2 and ΔLAC levels were also simultaneously recorded at hours 6 and 24 after admission to the ICU.

Statistical analysis

The SPSS v. 22 was used to analyze the data. The Kolmogorov–Smirnov test was used to test the normality of distribution. Qualitative data were expressed as percentages and numbers, and quantitative data were expressed as mean, standard deviation, and median values. The Chi-square test, Mann–Whitney U test, Kruskal–Wallis test, binary logistic regression analysis, Spearman's correlation analysis, and receiver operating characteristic (ROC) analyses were used to analyze the data.

Results

The study included a total of 102 patients (71.6% male and 28.4% female). The patients' mean age was 56.88 ± 11.02 (min: 18, max: 78) years, with 86.3% being over 45. The sociodemographic, clinical operative characteristics of the patients, their ΔPCO_2 and ΔLAC values, complications, and morbidity and mortality rates are presented in Table 1. The descriptive statistics of the investigated parameters and medications administered are shown in Table 2. When the distribution of the patients' comorbidities was examined, 77.5% had additional diseases (diabetes in 34.3% and hypertension in 47.1%). Concerning complications, bleeding developed on the first day in 44% of the patients and on the seventh day in 5.9% (bleeding in 1%, respiratory problems in 2%, and

Table 1: Sociodemographic data, chronic disease distribution, ΔPCO_2 measurements, FFP and platelet supplementation, first- and seventh-day morbidity, post-discharge morbidity, and EuroSCORE groups

Parameters	*n* / %
Gender	
Female	29 (28.4%)
Male	73 (71.6%)
Age, years	
18-30	2 (2%)
31-45	12 (11.8%)
46-60	47 (46.1%)
61 and above	41 (40.2%)
Chronic diseases	
Respiratory disease	8 (7.8%)
Diabetes mellitus	35 (34.3%)
Hypertension	48 (47.1%)
Thyroid disorder	5 (4.9%)
Renal failure	3 (2.9%)
Other	19 (18.6%)
ΔPCO_2 at hour 0	
<6	56 (54.9%)
≥6	46 (45.1%)
ΔPCO_2 at hour 1	
<6	41 (40.2%)
≥6	61 (59.8%)
ΔPCO_2 at hour 6	
<6	53 (52%)
≥6	49 (48%)
ΔPCO_2 at hour 24	
<6	59 (57.8%)
≥6	43 (42.2%)
Complications on the first day	
FFP	46 (45.1%)
Platelet supplementation	1 (1%)
Bleeding	45 (44.1%)
Complications on the seventh day	
Bleeding	1 (1%)
Respiratory problems	2 (2%)
Renal failure	4 (3.9%)
Post-discharge morbidity	
Renal failure	1 (1%)
EuroSCORE	
Low risk	72 (70.6%)
Moderate risk	28 (27.5%)
High risk	2 (2%)
Total	102 (100%)

(FFP: Fresh frozen plasma, ΔPCO_2: central venous-arterial partial carbon dioxide difference)

Table 2: Descriptive statistics (EF, ΔPCO_2, andΔLAC), mean values of the medication and other infusions administered during and after the operation, and postoperative length of ICU and hospital stay

	Min	Max	X	SD
EF%	25	65	52.94	8.68
ΔPCO_2 at hour 0	−3.5	24.8	6.17	4.35
ΔLAC at hour 0	−0.7	1.1	0.05	0.26
ΔPCO_2 at hour 1	−1.3	89	7.69	8.89
ΔLAC at hour 1	−1.2	1	0.03	0.26
ΔPCO_2 at hour 6	−2	17.4	6.19	3.23
ΔLAC at hour 6	−1.4	0.6	0.03	0.22
ΔPCO_2 at hour 24	−10	14.2	5.8	2.94
ΔLAC at hour 24	−0.3	0.3	−0.009	0.11
Noradrenalin	0	0.5	0.01	0.06
Adrenalin	0	0.5	0	0.05
Dopamine	0	20	2.65	4.56
Dobutamine	0	0	0	0
Fluid balance at hour 0	−1150	2000	497.45	551.69
Fluid balance at hour 24	−1400	1900	69.6	458.8
Urine output at hour 24	1000	4150	2836.17	505.69
Preoperative HB	8.4	17	13.5	1.84
Preoperative HTC	25.5	50.5	40.51	5.16
Erythrocyte suspension (units)	0	2	0.34	0.6
Perioperative HB	0	11	2.15	3.55
Perioperative HTC	0	35	6.7	11.07
Duration of pump use (minutes)	43	251	117	42.2
Duration of cross-clamp use (minutes)	15	180	76	32.6
ICU stay (days)	1	6	1.3	0.7
Hospital stay (days)	6	45	8	4.1

(X: Arithmetic mean, SD: Standard deviation, EF: Ejection fraction, ΔPCO_2: central venous-arterial partial carbon dioxide difference, ΔLAC: lactate, HB: hemoglobin, HTC: hematocrit, ICU: intensive care unit)

Table 3: Results of the logistic regression analysis for the prediction of complication development within 24 hours

	B	*P*	OR	95% CI OR	
				Lower	Upper
Gender	−0.914	0.06	0.401	0.155	1.038
Age	0.021	0.305	1.021	0.981	1.062
Ejection fraction	−0.065	0.015	0.937	0.89	0.987
Chronic diseases	−0.914	0.086	0.401	0.141	1.139
Constant	2.434	0.196	11.404		
ΔPCO_2 at hour 0	0.595	0.192	1.813	0.741	4.436
ΔPCO_2 at hour 1	0.489	0.376	1.63	0.552	4.811
ΔPCO_2 at hour 6	1.962	0.001	7.092	2.341	21.739
ΔPCO_2 at hour 24	0.087	0.867	1.091	0.392	3.038
Constant	−0.235	0.307	0.79		

(OR: Odds Ratio, ΔPCO_2: central venous-arterial partial carbon dioxide difference)

renal failure in 3.9%). After discharge from the hospital, 1% of the patients developed a morbid condition, but no mortality occurred.

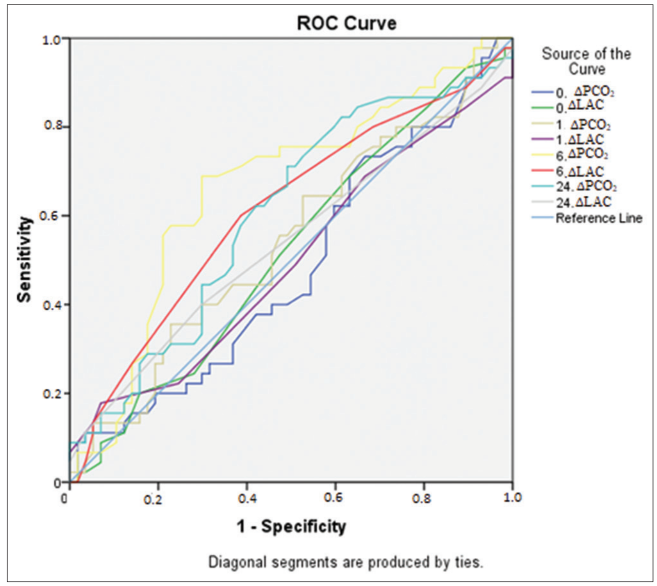

Figure 1: ROC analysis of ΔPCO_2 and ΔLAC

A weak significant positive correlation was found between the ΔPCO_2 and ΔLAC levels measured at hour 6 (Spearman's correlation analysis, r = 0.275, *P* = 0.005 and r = 0.294, *P* = 0.003, respectively). At hour 24, there was a weak significant positive relationship between ΔPCO_2 and venous ΔLAC levels (r = 0.205, *P* = 0.038). No significant correlation was observed between the ΔPCO2 values measured at different times and the duration of the pump requirement and cross-clamp times. There was also no significant correlation between any of the ΔPCO_2 values and preoperative hemoglobin and hematocrit. A weak significant negative correlation was found between ΔPCO_2 at hour 24 and EF (r = −0.315, *P* = 0.001). When the correlations between the ΔPCO_2 values measured at all four hours were examined, there was a weak positive correlation between hours 0 and 1 (r = 0.233, *P* = 0.018), and a moderate significant positive correlation between hour 1 and hours 6 and 24 (r = 0.424, *P* < 0.00 and r = 0.462, *P* < 0.001, respectively), and between hour 6 and hour 24 (0.505, *P* < 0.001). No significant correlation was determined between the medication doses given and the ΔPCO_2 values. There was also no significant difference in any of the ΔPCO_2 values according to gender, age, and presence or absence of chronic diseases.

The independent variables of gender, age, EF, and chronic disease status were included in a logistic regression analysis to predict the patients' risk of developing complications within the first 24 hours postoperatively. The results were statistically significant (omnibus test *P* = 0.028), with the total percentage of accurate prediction calculated as 59.8% [Table 2]. It was determined that EF significantly contributed to the model, and as this parameter increased, the risk of complications decreased by 1.03 times. The ΔPCO_2 values were included in a second logistic regression analysis to predict the risk of developing complications within the first 24 hours. The results were significant (omnibus test $P = 0.002$) with the total percentage of accurate prediction being 68.6% [Table 2]. Among the variables included in the second model, $\Delta PCO_2 > 6$ at hour 6 had a significant contribution, and as this value increased, the risk of complications increased by 7.09 times.

According to the distribution of the patients according to EuroSCORE grouping [Table 1], 2% of the patients were at high risk, 27.5% at moderate risk, and 70.6% at low risk. No significant correlation was detected between the ΔPCO_2 and EuroSCORE values of the patients. There was also no significant correlation between the EuroSCORE results and the patients' ΔLAC levels. However, a significant difference was observed in the length of ICU and hospital stays, according to the EuroSCORE results. The duration of ICU and hospital stays of the moderate-risk individuals were significantly longer than the low-risk group ($P < 0.001$). However, there was no significant difference between the EuroSCORE groups in terms of the development of complications within the first 24 hours.

No significant difference was found when the 24-hour complications were compared according to the presence of chronic diseases ($P < 0.001$). The patients who developed complications within 24 hours had significantly higher ΔPCO_2 and ΔLAC values at hour 6 compared to those without complications ($P < 0.001$). In the ROC analysis performed to examine the ability of the ΔPCO_2 and ΔLAC values measured at hour 6 to predict the development of complications within the first 24 hours, it was found that the area under the curve (AUC) was significant for ΔPCO_2 but not for ΔLAC. The value AUC was not significant for any of the four measurements performed for ΔLAC. For ΔPCO_2, the AUC value was significant only for the hour 6 measurement (0.66), but it indicated a poor predictive ability. Therefore, this parameter was also considered inappropriate for use as a diagnostic test [Table 3] [Figure 1].

Discussion

A high ΔPCO_2 value indicates that the cardiac output cannot meet general metabolic activities, and there is anomalous microcirculation.[9] This parameter correlates with the cardiac output and arterial lactate values of the patients undergoing abdominal surgery and experiencing septic shock.[10] According to our study's results, which investigated whether a high ΔPCO_2 value was associated with the development of postoperative complications, the ΔPCO_2 and ΔLAC levels measured at hours 0, 1, 6, and 24 had a poor ability to predict the development of complications during an ICU stay and the early postoperative period (first 10 days). In addition, the ΔPCO_2 and ΔLAC levels measured at hour 6 were significantly higher in patients who developed complications within the first 24 hours, ΔPCO_2 levels measured at hour 6 increased the complication risk 7.09 times. The length of ICU and hospital stays was longer in the moderate-risk group compared to the low-risk patients, according to the EuroSCORE grouping. However, gender, age, and presence of chronic diseases did not lead to a significant difference in complication development.

Guinot *et al*.[11] conducted a study with 393 patients who underwent cardiac surgery to investigate the relationship between postoperative complications and ΔPCO_2. The patients were first evaluated collectively and then divided into four subgroups (1: continuously normal ΔPCO_2, 2: increasing ΔPCO_2, 3: decreasing ΔPCO_2, and 4: continuously high ΔPCO_2). According to the results of that study, postoperative complications developed in 61% of the patients. The rates of major postoperative complications were not different (53–62%) between the four groups. The authors concluded that ΔPCO_2 was poorly correlated with perfusion parameters. In a study by Habicher *et al*.[12] investigating the significance of ΔPCO_2 in cardiac surgery patients with normal central venous oxygen saturation in terms of complication development and hospital stay, those with high ΔPCO_2 (>8) required longer ICU stays and longer mechanical ventilation, as well as a higher rate of complications between days 3 and 5 postoperatively. The authors observed a relationship between the coexistence of $ScvO_2 > 70$ and high ΔPCO_2 (>8 mmHg) and increased lactate levels and reduced spleen function postoperatively.

Robin *et al*.[13] found that raised ΔPCO_2 was associated with increased postoperative complications. Complications developed in 47% of high-risk surgery patients. More postoperative complications were observed in the group with a mean PCO_2 of 8.76 mmHg and a median lactate value of 1.54 at the end of 12 hours after surgery. In another study, Du *et al*.[14] investigated the ratio of venous–arterial carbon dioxide and arterial–venous oxygen difference in patients undergoing cardiac surgery with increased lactate values and normal $ScvO_2$ values. This ratio being above 1.6 could be used to predict increased oxygen requirement (DO_2) in the postoperative period. Morel *et al*.[15] studied 220 elective cardiac surgery patients, with the ΔPCO_2 values at the time of ICU admission and at hours 6, 24, and 48 used to evaluate postoperative complications. In the low ΔPCO_2 group, the sequential organ failure assessment score, as well as the mortality rates during the hospitalization period and 6 months postoperatively, were higher. For cardiac surgery, ΔPCO_2 was determined to be of low significance in predicting postoperative outcomes.

Moussa *et al*.[16] evaluated patients that underwent CPB and collected data at hours 0, 2, 6, and 24. Of the 330 patients, 56% developed major postoperative complications. In the ROC analysis, the AUC of ΔPCO_2 was 0.64 for predicting major postoperative complication development. In addition, in the regression model established to predict the development of major postoperative complications, there was a change in ΔPCO_2 which increased the complication risk by 1.11 times. However, although ΔPCO_2 was associated with the development of major postoperative complications, this parameter was limited in complication prediction performance. Similarly, in our study, we observed that ΔPCO_2 and ΔLAC had low performances in predicting postoperative morbidity. Hour 6 ΔPCO_2 values were significant but limited in predicting the risk of developing complications within 24 hours.

In a study conducted by Akamatsu *et al*.[17] with 114 patients who underwent cardiac surgery, there was no relationship between the ΔPCO_2 value being below or above 6 and the duration of extubation and hospital stay. In addition, no mortality was observed in the 30-day follow-up. This is consistent with our study, in which no significant relationship was detected between ΔPCO_2 and the length of ICU and hospital stay.

Terashima *et al*.[18] evaluated 55 dialysis patients who underwent cardiac surgery and reported no strong correlation between the ΔPCO_2 and serum lactate values. The authors also noted no significant difference between the patients with and without complications in terms of the ΔPCO_2 and serum lactate values. In contrast, in a study that Denault *et al*.[19] conducted with 58 patients who underwent bypass surgery, it was stated that 65% of the patients had a high ΔPCO_2 value (>6 mmHg) throughout the surgery and that this parameter could be used as a marker for the follow-up of adequate tissue perfusion during cardiac surgery. In our study, the ΔPCO_2 values were monitored following the termination of CPB instead of during surgery.

Renew *et al*.[20] examined the lactate values of 9,580 patients who underwent elective cardiac surgery and reported the development of postoperative hyperlactatemia in 1.26% of the patients. Postoperative mortality was observed at a rate of up to 40% in the presence of hyperlactatemia. In another evaluation undertaken by Cobianchi *et al*.,[21] an increased lactate level was found to generally reflect increased morbidity and higher mortality. The authors stated that they considered lactate monitoring to be a valuable tool in critically ill patients but emphasized the need for further studies to systematize the use of this parameter. Zante *et al*.[22] investigated the postoperative mortality estimation of lactate values in patients who underwent cardiac surgery and found that a one-unit increase in the lactate level increased the risk of death by 1.16 times. In addition, in their ROC analysis aiming to predict mortality using lactate and base excess, it was found that the AUC was not significant for the lactate values. In our study, we also determined that the AUC of lactate was not significant ($P > 0.005$).

Ammannaya *et al*.[23] retrospectively analyzed the data of 350 patients who underwent cardiac surgery. In the early postoperative period, the serum lactate level was measured in all patients in the ICU at the time of admission to the unit (hour 0) and at hours 6 and 12. The 30-day mortality and morbidity results were also compared. The complications were mostly associated with prolonged mechanical ventilation and length of stay in the ICU. A main result of the study found that hyperlactatemia was associated with a large number of adverse events after bypass surgery. In contrast, in our study, the postoperative lactate levels were not found to be related to mortality.

In a study including 100 patients who underwent cardiac bypass, Azad *et al*.[24] assessed the role of blood lactate levels in predicting postoperative outcomes. The blood lactate level measured at hour 6 after ICU transfer was reported as an independent risk factor for adverse outcomes, including mortality after cardiac surgery under CPB in adult patients. In another study, Lopez-Delgado *et al*.[25] examined the role of lactate in predicting long-term mortality in 2,935 patients who underwent cardiac surgery. The patients were followed up for an average of 6.3 years. A comparison of the data of the surviving and deceased patients showed that the arterial blood lactate levels were significantly higher in the mortality group for all measurements (hours 0, 6, 12, and 24). Hyperlactatemia (arterial lactate > 3) was an independent predictor of both hospital mortality and long-term mortality. In our study, we determined that the ΔLAC level measured at different times was not suitable as a diagnostic tool for predicting complication development within 24 hours.

Conclusion

In this study, ΔPCO_2 was evaluated together with ΔLAC in predicting mortality and morbidity after cardiac surgery in patients who underwent open-heart surgery. Given the widespread availability of ΔPCO_2, we support the inclusion of this parameter in indices used for the monitoring and risk assessment of this specific ICU population, and we recommend larger prospective analyses on this subject.

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Conflicts of interest

There are no conflicts of interest.

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