

Association of Weight-indexed Conventional Ultrafiltration Volume with Post-operative Lactate in Patients Undergoing Cardiopulmonary Bypass

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What's Known

- Increased lactate is a common problem in patients undergoing cardiac operations.
- Low hematocrit, bypass duration, low pump flow, blood glucose, and hypothermia were found to have associations with lactate levels in several studies. However, the use of conventional ultrafiltration with peri-operative lactate in cardiac surgery is controversial.

What's New

- The association of weight-indexed conventional ultrafiltration volume and lactate levels in heart surgery was investigated.
- There was a positive association between higher volumes of ultrafiltration and peak post-operative serum lactate levels.

Abstract

Background: Conventional ultrafiltration (CUF) during cardiopulmonary bypass (CPB) is utilized to minimize hemodilution. However, removing high volumes leads to tissue hypoperfusion by activating the anaerobic glycolysis pathways. This study aimed to determine the association between weight-indexed CUF volumes and lactate in patients who underwent coronary artery bypass grafting (CABG).

Methods: In this single-center retrospective study, 641 CABG patients, who were referred to Al-Zahra Hospital (Shiraz, Iran) and underwent CPB, during 2019-2021, were recruited. Peri-operative parameters were extracted from the patient's records. The patients with non-elective status, pre-existing liver and renal diseases, ejection fraction <35%, and repeated sternotomy were excluded from the study. An increase in post-operative lactate level ≥ 4 mmol/L after 6 hours was defined as hyperlactatemia (HL). To predict HL, univariable and multiple logistic regression modeling, while controlling confounding factors, were employed.

Results: The patients' mean age was 58.8 ± 11.1 years, and 39.2% were women. The incidence of HL was 14.5% (93 patients). There was a significant association between weight-indexed CUF volume and HL. The volume removed in the HL patients was almost doubled (43.37 ± 11.32 vs. 21.41 ± 8.15 mL/Kg, $P < 0.001$), and the higher the weight-indexed CUF volume, the more likely to develop an HL at a rate of 1.38 (Odds ratio = 1.38 [1.27-1.49], 95% CI, $P < 0.001$). Furthermore, the multiple logistic regression model showed that HL was associated with the lowest mean arterial pressure (MAP) during CPB.

Conclusion: A higher volume of ultrafiltration was associated with increased post-operative serum lactate levels.

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Keywords • Cardiopulmonary bypass • Ultrafiltration • Hemofiltration • Hyperlactatemia • Lactic acid

Introduction

Hematocrit levels decrease during cardiopulmonary bypass (CPB) due to the administration of sanguineous fluids to maintain hemodynamics and to prime CPB and cardioplegia circuits.¹ Excessive hemodilution reduces the delivery of oxygen to tissues and is associated with side effects, such as kidney

and neurocognitive dysfunction, coagulation disorders, hyperlactatemia, and a higher mortality rate.²⁻⁶

During CPB, conventional ultrafiltration (CUF) is utilized to remove plasma water, reduce inflammatory mediators, and lessen the demand for blood transfusion. Zero-balanced ultrafiltration (ZBU) occurs when the amount of fluid added and removed is the same. The modified ultrafiltration (MUF) technique is utilized after weaning the bypass, which is frequently used in pediatric surgery. It is believed that CUF will have a beneficial effect on organs.^{1, 7, 8} Nonetheless, Paugh and others reported that the protective effect of different filtered volumes during CUF on tissues still remained unclear.⁹ A previous study reported that tissue hypoperfusion following high-volume hemofiltration (HVHF) can cause acute kidney injury (AKI).¹⁰ In multicenter research, Joanne-Boyao and colleagues found no evidence that HVHF (70 mL/Kg/h) could reduce the 28-day mortality rate or enhance hemodynamic parameters or organ perfusion.¹¹ Furthermore, hypoperfusion causes an imbalance in oxygen supply and demand, induces anaerobic metabolism, and increases serum lactate (type A).¹² Hypothermia, coronary artery surgeries, bypass duration, low pump flow, low hematocrit, peak blood glucose, and post-operative hemorrhage are the other causes of elevated lactate in individuals undergoing cardiac surgery.^{13, 14} Rabie Soliman and others reported that CUF could cause metabolic acidosis and elevated lactate.¹⁵ Although, they compared patients with and without CUF, the question of whether there was an association between the extracted volume during the CUF and lactate remained unanswered. Moreover, the indication of the amount filtered during CPB was not clearly established.

In the present study, CUF is a routine practice in our center, which is performed for all patients undergoing heart surgery. The differences in the surgery team's perspectives on weaning the bypass, hemodynamic conditions, acceptable final hematocrit, and the purpose of hemofiltration could all affect the expected volume. Therefore, the volume that is removed is not the only function of the volume in the reservoir. Based on the clinical observations, we hypothesized that a higher volume of ultrafiltration would be associated with increased post-operative serum lactate levels. Therefore, the purpose of this study was to verify this hypothesis and investigate the association between weight-indexed CUF volume and post-operative serum lactate in patients who underwent coronary artery bypass grafting (CABG).

Patients and Methods

This observational study was approved by the Local Ethics and Review Committee of Shiraz University of Medical Sciences (code: IR.SUMS.REC.1400.130). The Research Ethics Committee did not require the patient's written informed consent due to the retrospective observational nature of the study, and the anonymous confidential use of the data.

In this retrospective cohort study, 800 patients over the age of 18, who were eligible for elective CABG surgery at Al-Zahra Hospital (Shiraz, Iran), between March 21, 2019, and March 19, 2021, were reviewed. Out of the 800 participants, 159 patients were excluded, and 641 patients were included in the final analysis. The exclusion criteria were patients with non-elective status, repeated sternotomy, off-pump surgeries, serum creatinine concentration greater than 1.5 mg/dL, pre-existing renal and liver diseases, ejection fraction (EF) less than 35%, pre-operative intra-aortic balloon pump (IABP), and incomplete records.

Moreover, the data related to pre-intra-post-operative parameters; including demographic, risk factors, hematocrit (Hct), creatinine, mean arterial pressure (MAP), blood transfusion, urinary output (UOP), use of inotropes, bypass and cross-clamp times were collected.

All patients underwent CUF, and the volume depletion in CUF was recorded. To calculate weight-indexed CUF (mL/Kg), the CUF volume (mL) was divided by weight (Kg) for each patient.

Serum lactate was measured pre-CPB (T_0), 15 min after CPB (T_1), upon arrival in the ICU (T_2), and at 6 (T_3), 24 (T_4), and 48 (T_5) hours after their admission in the ICU. Hyperlactatemia (HL) was taken into consideration for patients with serum lactate levels ≥ 4 mmol/L. Lactate levels at the T_3 point were used to dichotomize patients into two groups ($<$ and ≥ 4 mmol/L).

The patient's information was collected using anesthesia and perfusion registration forms, as well as the available notes in the intensive care unit (ICU). Data collection was executed by experienced nurses who were blinded to the objective of this study.

The Procedure of Anesthesia and CPB

All patients underwent standard general anesthesia. The roller-type heart-lung machine was primed with 1300 mL Ringer's, 10 mg furosemide, 50 mL mannitol 20%, and 100 units/Kg heparin. A cardiac index of 2.2 to 2.5 L/min/m² with non-pulsatile perfusion was used to maintain MAP between 50 and 80 mmHg and Hct between 24-28% during CPB. Conventional

ultrafiltration was performed during CPB, and the volume was removed based on the patient's condition. If the Hct remained below 20% during CPB, packed red blood cells (PRBC) would be injected into the circuit. Inotropes, trinitroglycerin, and IABP were used to manage hypotension and CPB weaning.

Statistical Analysis

The collected data was analyzed using SPSS software, version 25 (IBM Statistics, Chicago, USA). Quantitative variables were expressed as mean±SD for normally distributed data. The median, first, and third quartiles (Q1, Q3) were used to express non-normal distributed data. The independent samples *t* test and Mann-Whitney U test were used to compare patients with lactate levels of ≥4 and <4 mmol/L with normal or non-normal distribution. Categorical variables were expressed as frequency and percentage, and the Chi square test was used to compare the groups. Univariate and multiple logistic regression analyses were used to determine the association between lactate and weight-indexed CUF volume. Univariate analysis was used to identify potential confounding variables associated with lactate. Variables with P<0.2 were eligible to be included in the multiple logistic model. Using the

variance inflation factor (VIF), the collinearity among explanatory variables was evaluated. From highly correlated pairs of variables, one of them was selected for inclusion in the final model based on the stronger relationship with serum lactate level. A backward elimination approach was used to fit the final model. In the final model, P<0.05 was considered to be statistically significant. Evaluation of the logistic models were performed using -2 log-likelihood change and goodness of fit Chi square test. By indexing CUF volume using weight and CPB time together, which was reported as mL/Kg/hour, additional analyses were performed. Moreover, a generalized linear model (GLM) was conducted to predict the final peak lactate controlling the starting lactate, weight-indexed CUF volume, and the other covariates. In addition, a receiver operating characteristic (ROC) analysis was performed to determine how accurately weight-indexed CUF volume can predict serum lactate ≥4 mmol/L. Pearson's correlation and simple linear regression were performed to determine the association between the cross-clamp and bypass times with T₃ lactate. Finally, the correlation between serum lactate at 6 hours post-operative with both pre-operative Hct and weight-indexed CUF volume was examined.

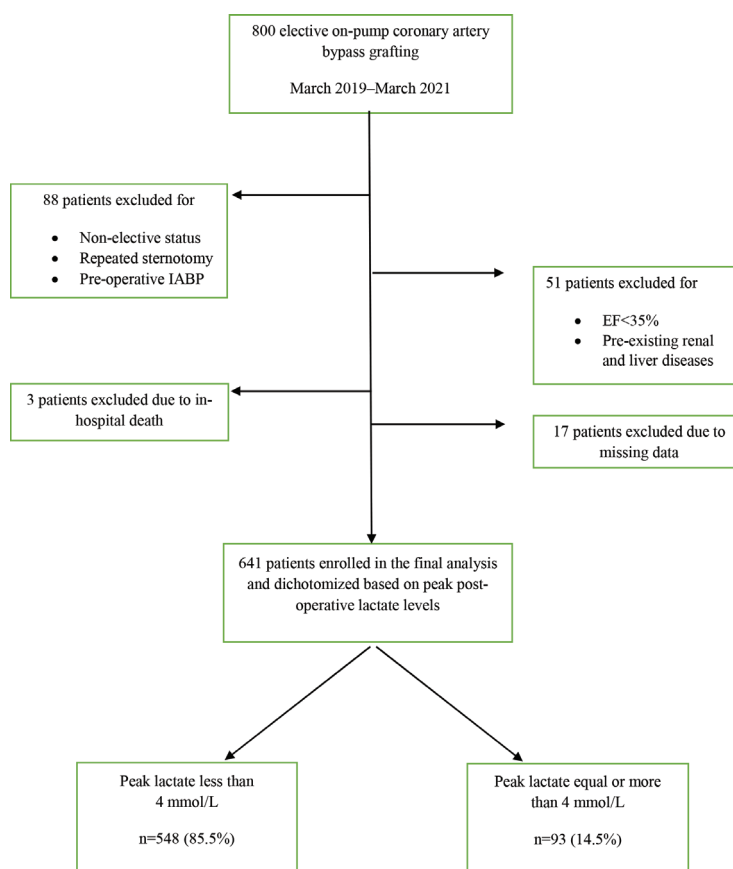


Figure 1: A total of 641 patients were selected from the initial cohort of 800 patients based on the inclusion and exclusion criteria.

Results

Out of the 800 participants, 159 patients were excluded, and 641 patients were included in the final analysis (figure 1). From 641 patients, 93 (14.5%) patients had peak lactate levels ≥ 4 mmol/L, and 548 (85.5%) patients had peak lactate levels < 4 mmol/L. The highest serum lactate levels were observed at T_3 , 6 hours after ICU admission. The mean and standard deviation for serum lactate levels in the two groups in different peri-operative times are shown in figure 2. The difference between the two groups was significant at all time points. However, it was small in magnitude until arrival to the ICU and reached its peak at 6 hours after admission.

The intergroup comparison indicated that comorbidities, such as diabetic mellitus (DM), hypertension, and hyperlipidemia had a significant negative association with post-operative lactate levels (table 1). Hyperlactatemia (HL) group had significantly lower hemoglobin (Hb) (11.3 ± 1.7 vs. 11.9 ± 1.7 , $P=0.003$) and Hct (32.9 ± 5.0 vs. 35.5 ± 5.2 , $P<0.001$).

Table 1 shows the comparison of pre-operative and intra-operative parameters between the two lactate groups. Although the volume of cardioplegia was significantly higher ($P<0.001$), the patients in the HL group had significantly lower MAP, central venous pressure (CVP), and UOP during CPB ($P<0.001$). During CPB, the minimum Hct value was recorded for each patient. As indicated in table 1, no significant difference was found between the two groups in terms of the lowest Hct levels. The removed volume by CUF was significantly higher among the HL patients, and weight-indexed CUF volume was 43.3 ± 11.3 vs. 21.4 ± 8.1 mL/Kg ($P<0.001$). As shown in figure 3, the correlation between weight-indexed CUF volume and 6-hour peak post-operative lactate was statistically significant (Pearson correlation coefficient $r=0.695$; $P<0.001$). Furthermore, HL patients required more intra-operative inotropic support (epinephrine, norepinephrine, and dopamine) (table 1). The correlation between serum lactate with pre-operative Hct ($r=-0.18$, $P=0.003$) was lower than the correlation with weight-indexed CUF ($r=-0.67$, $P<0.001$).

Investigation of collinearity among the explanatory variables showed that there was a high correlation between bypass time and cross-clamp time (VIF=4.4). Therefore, between these two variables, cross-clamp time was selected for the final model. Besides, the intra-operative inotropes (norepinephrine, epinephrine, and

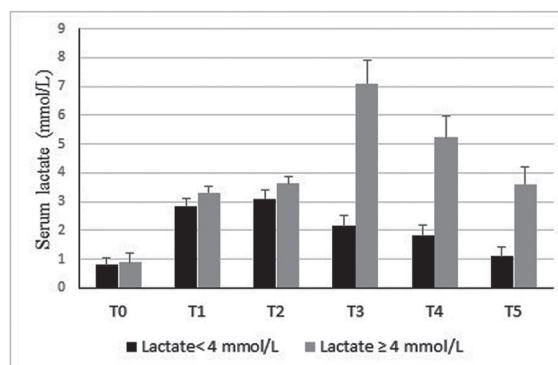


Figure 2: The mean and standard deviation for serum lactate levels in two groups (< 4 and ≥ 4 mmol/L at 6 hours postoperatively) at different peri-operative times were compared. Two groups were significantly different at all times ($P=0.045$ at T_0 and $P<0.001$ at other times); baseline (T_0), 15 minutes after cardiopulmonary bypass (T_1), immediately on the arrival to ICU (T_2), at 6 (T_3), 24 (T_4) and 48 (T_5) hours after ICU admission. ICU: Intensive care unit

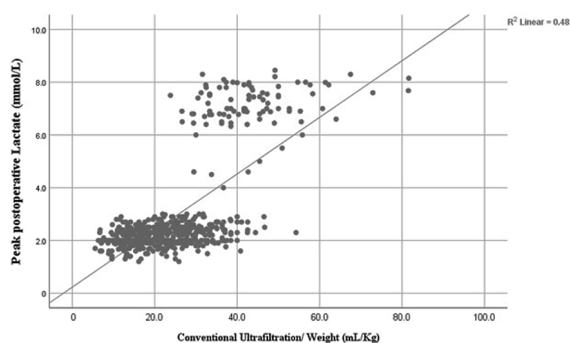


Figure 3: Weight-indexed conventional ultrafiltration volume shows a positive correlation with peak post-operative lactate. Pearson correlation coefficient $r=0.695$; Coefficient of determination. $R^2=0.483$; $P<0.001$

dopamine) indicated significant associations with each other and with hemofilter volume ($P<0.001$) and were excluded from the multiple logistic models. Additionally, pre-operative hemoglobin, pre-operative Hct, and the highest and lowest hematocrits during CPB, and blood transfusion had linear correlations with each other (VIFs up to 24). Accordingly, only pre-operative Hct was selected to include in the multiple logistic model. In the remaining cases, no significant collinearity was found between variables (all VIF <1). Variables included in the multiple logistic model and significant variables in the final model are shown in table 2. In multiple logistic regression analysis (table 2), in addition to CUF volume based on weight-indexed (OR=1.29, 95% CI=1.22-1.35, $P<0.001$), the lowest MAP on CPB was found to be another predictor of post-operative lactate level at six hours after CABG procedure. The results revealed a relatively similar outcome when indexing CUF volume by weight, and CPB time was introduced simultaneously into the multiple logistic models (table 3).

Table 1: Comparison of pre-operative and intra-operative parameters for hyperlactatemia

Variables	Lactate<4 (mmol/L)	Lactate≥4 (mmol/L)	P value
Number of patients (%)	548 (85.5)	93 (14.5)	
Age (year, mean±SD)	59.02±11.05	57.38±11.5	0.190
Sex n (%)	Male	320 (59.7)	62 (67.4)
	Female	221 (40.3)	30 (32.6)
Weight (Kg, mean±SD)	68.07±12.1	69.49±13.5	0.306
Body surface area (Kg/m ² , mean±SD)	1.7±0.1	1.7±0.1	0.183
Euro score II (mean±SD)	2.1±1.6	1.9±1.3	0.240
Diabetes mellitus n (%)	191 (34.8)	22 (23.9)	0.04
Hypertension n (%)	347 (63.2)	48 (52.2)	0.044
Hyperlipidemia n (%)	274 (49.9)	35 (38.0)	0.035
COPD n (%)	20 (3.6)	6 (6.5)	0.195
Atrial fibrillation n (%)	48 (8.7)	7 (7.6)	0.719
Smoking/addiction n (%)	211 (38.4)	34 (37.0)	0.787
Unstable angina n (%)	7 (1.3)	1 (1.1)	0.880
Heart failure n (%)	17 (3.1)	0 (0)	0.087
CVA n (%)	13 (2.4)	1 (1.1)	0.437
Hyper-/hypo-thyroid n (%)	13 (2.4)	2 (2.2)	0.909
Asthma n (%)	15 (2.7)	6 (6.5)	0.059
Ejection fraction (% , mean±SD)	51.1±8.4	51.6±8.3	0.546
Hemoglobin (gr/dL, mean±SD)	11.9±1.7	11.3±1.7	0.003
Hematocrit (% , mean±SD)	35.5±5.2	32.9±5.0	<0.001
Creatinine (mg/dL, mean±SD)	1.02±0.2	1.03±0.2	0.538
Lactate 6 h ICU (mean±SD)	2.1±0.3	7.08±0.8	<0.001
Lowest MAP (mmHg, mean±SD)	59.6±10.09	53.4±7.6	<0.001
Lowest CVP (mmHg, mean±SD)	9.5±4.8	6.8±4.3	<0.001
Temperature (°C, mean±SD)	33.07±0.9	32.9±1.3	0.142
Cardioplegia volume (mL, mean±SD)	1082.9±233.3	1305.9±318.2	<0.001
Urine output (mL, mean±SD)	568.03±393.5	357.06±390.3	<0.001
Lowest hematocrit (%)	21.3±4.6	21.13±4.2	0.665
Highest hematocrit (%)	26.3±3.7	27.1±3.5	0.05
Blood transfusion n (%)	402 (73.4)	62 (67.4)	0.236
Blood transfusion (mL, mean±SD)	336.8±270.2	290.3±253.4	0.122
CUF volume (mL, mean±SD)	1407.4±449.4	2911.8±578.5	<0.001
CUF / weight (mL/Kg, mean±SD)	21.4±8.1	43.3±11.3	<0.001
Intraoperative inotropes			
Norepinephrine n (%)	364 (66.3)	85 (92.4)	<0.001
Epinephrine n (%)	221 (40.3)	59 (64.1)	<0.001
Dopamine n (%)	26 (4.7)	10 (10.9)	0.018
Bypass time (min, mean±SD)	68.7±19.3	73.6±23.07	0.03
Cross-clamp time (min, mean±SD)	39.1±12.5	43.7±15.4	0.002
IABP n (%)	4 (0.7)	1 (1.1)	0.718

COPD: Chronic obstruction pulmonary diseases; CVA: Cerebrovascular accident; ICU: Intensive care unit; MAP: Mean arterial pressure; CVP: Central venous pressure; CUF: Conventional ultrafiltration; IABP: Intra-aortic balloon pump. For both groups, continuous variables were compared using two independent samples *t* tests, and categorical variables were compared using the Chi square test.

Table 2: Univariate analysis and multiple logistic regression to predict peak post-operative hyperlactatemia

Variable	OR (95% CI)	P value
Lowest MAP (mmHg)	0.956 (0.925-0.988)	0.008
Cross-clamp (min)	1.091 (1.066-1.117)	0.001
Urine output (mL)	0.999 (0.998-1.00)	0.03
CUF to Bypass time (mg/Kg/hours)	1.163 (1.128-1.200)	<0.001

MAP: Mean arterial pressure; CVP: Central venous pressure; CUF: Conventional ultrafiltration; OR: Odds ratio; CI: Confidence interval

Table 3: The association between weight-indexed conventional ultrafiltration and bypass time with 6 hours post-operative serum lactate levels

Variables	Univariate analysis OR (95% CI)	Multiple logistic regression OR (95% CI)	P value
Age (year)	0.99 (0.97-1.01)		
Hypertension n (%)	0.64 (0.41-0.99)		
Hyperlipidemia n (%)	0.62 (0.39-0.97)		
Asthma n (%)	2.48 (0.94-6.58)		
Hematocrit (%)	0.90 (0.86-0.95)		
Lowest MAP (mmHg)	0.93 (0.91-0.96)	0.953 (0.917-0.991)	0.015
Lowest CVP (mmHg)	0.88 (0.83-0.92)		
Temperature (°C)	0.86 (0.70-1.05)		
Urine output (mL)	0.998 (0.997-0.999)		
CUF/weight (mL/Kg)	1.29 (1.23-1.36)	1.29 (1.226-1.357)	<0.001
Cross-clamp time (min)	1.02 (1.01-1.04)		

Multiple logistic regression analysis was done. MAP: Mean arterial pressure; CUF: Conventional ultrafiltration

Table 4: Results of a general linear model to predict peak post-operative hyperlactatemia controlling for baseline lactate

Parameters	B	Standard Error	Wald Chi square	P value
Bypass time (min)	-0.002	0.003	0.727	0.394
CUF/weight (mL/Kg)	0.107	0.004	0.579.391	<0.001
Baseline lactate (mmol/L)	0.407	0.201	4.106	0.043

B: Coefficient estimate; CUF: conventional ultrafiltration

Six hours after the CABG procedure, the conventional ultrafiltration volume (mL/Kg/hour CPB time) was significantly associated with peak post-operative lactate level (OR=1.16, 95% CI=1.13-1.20, P<0.001). Based on the results of GLM analysis, the regression coefficient for peak lactate was 0.107, SE=0.004, P<0.001, which indicated that each 1 mL/Kg increase in the weight-indexed CUF volume resulted in a 0.1 increase in the peak serum lactate (table 4). Based on the ROC analysis, weight-indexed CUF volume was a good predictor of high serum lactate (figure 4). The cutoff point was 29 mL/Kg, and the area under the curve was 0.975 (P<0.001), with high sensitivity (97%) and relatively high specificity (83%).

Discussion

In this study, we investigated the association between weight-indexed CUF volume and post-operative serum lactate levels in patients undergoing elective CABG operation. This study revealed an HL incidence rate of 14.5%. The CUF volume differed significantly between the patients with and without HL, which served as a predictor of post-operative increase in lactate levels. The lowest MAP during CPB was another independent risk factor for the development of post-operative HL.

Hyperlactatemia and lactic acidosis were associated with increased risk of morbidity and mortality.^{13, 16} Depending on how long it took, early and late HL were defined by when the elevated

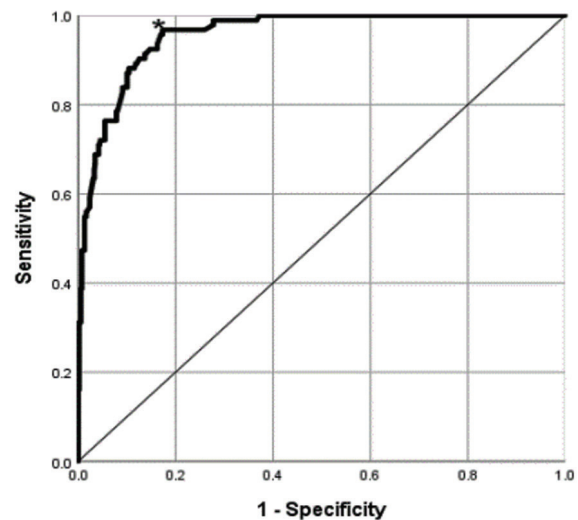


Figure 4: Based on ROC analysis, weight-indexed CUF volume is a good predictor of high serum lactate. The cut-off point is 29 mL/Kg, and the area under the curve is 0.975 (P<0.001). The weight-indexed CUF volume had high sensitivity (97%) and relatively high specificity (83%).

lactate levels occurred either in the first 4 hours following the operation or 4 to 24 hours post-operation, respectively. Normal serum lactate levels can range from 0.4 to 2 mmol/L. However, numerous studies defined hyperlactatemia as being between 3 to 5 mmol/L.^{17, 18} In the present study, lactate level ≥ 4 mmol/L at 6 hours post-operation was considered as HL. The incidence of HL in this study was 14.5%, which was consistent with the findings of a previous study.¹⁹ As previously reported in the literature, with the onset of bypass, the mean lactate level gradually increased and reached its peak, and then

gradually decreased during the post-operative period.^{15, 19} Patients in the HL group had longer bypass and cross-clamp times. A significant but weak association between bypass and cross-clamp times with increased lactate suggested the involvement of other pre-operative and intra-operative variables.

This study showed that CUF and the difference in the removed volume were associated with post-operative lactate levels, and the removed volume based on body weight index in patients with HL, according to the definition presented in this study, was almost twice that of patients without HL. Due to the conditions of each patient and several factors that may affect the volume removed, an optimal cut-off point could not be determined, and there was no specific cut-off point in similar previous studies. However, based on the ROC analysis in this study, the volume of 29 mL/Kg was determined as a cut-off point for the onset and prediction of HL. Manning and others proposed a critical volume of 2239 mL to predict CUF-associated AKI.¹⁰

In the present study, the composition of the prime was identical for all patients, and it was Ringer's solution. Patients in the HL group had lower UOP, CVP, and MAP during CPB. Excessive ultrafiltration by removing the effective circulating volume could cause hypovolemia and hypotension.¹⁵ Inotropes were used to manage hypotension during and after CPB.^{15, 19} The patients in the HL group required significantly more intra-operative inotropes than the other group (peak lactate <4 mmol/L). In the present study, epinephrine and dopamine were mainly used after weaning of CPB. An increase in the level of catecholamine could lead to an excessive increase in glycolysis, and lactate was one of the end products of glycolysis.²⁰ Yessayan and others reported the possibility of lactic acidosis following the use of continuous renal replacement therapy (CRRT), which could be attributed to the discharge of bicarbonate ions through the hemofilter created by Gibbs-Donnan phenomenon and the repulsion of negative charges due to increased plasma protein concentrations.²¹ Cheungpasitporn and others reported that lactate clearance by HVHF was insufficient and ineffective compared to lactate production in septic shock. Moreover, Levraut and others reported that only 3% of the lactate produced was cleared through hemofiltration.^{22, 23} Since lactate levels are associated with post-operative mortality and morbidity, it is essential to understand the potential causes of lactate level elevation. This study evaluated the volume of ultrafiltration based on the weight index, which could lead to new possibilities in clinical settings.

Finally, it is recommended that CUF be limited to patients with renal dysfunction, fluid overload, and patients resistant to diuretics. Other helpful techniques include reducing the volume of prime and administering minimal fluid to maintain sufficient pump flow, using ultrafiltration after bypass weaning, and frequent monitoring of blood gas parameters during bypass.¹⁵ One of the limitations of the present study was that due to the retrospective nature of the present study, confounding factors and unmeasured biases might have affected the findings, and their causality requires further confirmation. Therefore, it is recommended that future research employ a well-designed interventional study.

Conclusion

Hyperlactatemia patients had lower pre-operative Hct and lower MAP, CVP, and UOP during CPB and required more intra-operative inotropic support. Higher weight-indexed CUF volume during CPB was associated with elevated post-operative serum lactate levels. Furthermore, the lowest MAP during CPB was associated with increased post-operative lactate. Prospective studies based on volume differences are required to completely understand the role of CUF in post-operative HL. By predicting the HL, patients undergoing CPB could benefit from better post-operative management with more satisfactory outcomes.

Authors' Contribution

H.G.; literature search, clinical studies, and manuscript preparation, J.S.; data analysis, manuscript preparation, editing, review, B.Gh; concept, design, the definition of intellectual content, editing, and reviewing, M.A.L; data & statistical analysis, editing and reviewing. All authors contributed to the article and approved the submitted version. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of Interest: None declared.

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