Original Article

Hyperlactatemia in patients undergoing adult cardiac surgery under cardiopulmonary bypass: Causative factors and its effect on surgical outcome

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ABSTRACT

Objectives of the Study: To identify the factors causing high lactate levels in patients undergoing cardiac surgery under cardiopulmonary bypass (CPB) and to assess the association between high blood lactate levels and postoperative morbidity and mortality. **Methods:** A retrospective observational study including 370 patients who underwent cardiac surgeries under cardiopulmonary bypass. The patients were divided into 2 groups based on serum lactate levels; those with serum lactate levels greater than or equal to 4 mmol/L considered as hyperlactatemia and those with serum lactate levels less than 4 mmol/L. Blood lactate samples were collected intraoperatively and postoperatively in the ICU. Preoperative and intraoperative risk factors for hyperlactatemia were identified using the highest intraoperative value of lactate. The postoperative morbidity and mortality associated with hyperlactatemia was studied using the overall (intraoperative and postoperative values) peak lactate levels. Preoperative clinical data, perioperative events and postoperative morbidity and mortality were recorded. **Results:** Intraoperative peak blood lactate levels of 4.0 mmol/L or more were present in 158 patients (42.7%). Females had higher peak intra operative lactate levels (P = 0.011). There was significant correlation between CPB time (Pearson correlation coefficient r = 0.024; P = 0.003) and aortic cross clamp time (r = 0.02, P = 0.007) with peak intraoperative blood lactate levels. Patients with hyperlactatemia had significantly higher rate of postoperative morbidity like atrial fibrillation (19.9% vs. 5.3%; P = 0.004), prolonged requirement of inotropes (34% vs. 11.8%; P = 0.001), longer stay in the ICU (P = 0.013) and hospital (P = 0.001). **Conclusions:** Hyperlactatemia had significant association with post-operative morbidity. Detection of hyperlactatemia in the perioperative period should be considered as an indicator of inadequate tissue oxygen delivery and must be aggressively corrected.

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INTRODUCTION

Cardiopulmonary bypass (CPB) is widely preferred for cardiac surgery to maintain systemic perfusion and oxygenation.[1] It is well known that tissue hypoperfusion due to circulatory failure is associated with an increase in lactate levels secondary to anaerobic metabolism.[2-4] This situation is termed as Type A lactic acidosis, which results from an imbalance between tissue oxygen demand and supply.[5-8] Therefore, increase in lactate levels as seen in Type A lactic acidosis

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is closely associated with total oxygen deficit and tissue hypoperfusion.[5-9] Hyperlactatemia (HL) in patients who undergo cardiac surgery with CPB can be due to tissue hypoxia, nonhypoxic causes such as drug therapy, cardioplegia solution, hypothermia, and CPB itself.[10,11] In a recent study done by Demers *et al.*, it was found that in adult patients undergoing cardiac surgery, HL is detected in 10–20% of patients[11,12] and was associated with significant postoperative morbidity and mortality.[11] In a study done by Broder and Weil, more than 88% of patients who had blood a lactate level of > 4.0 mmol/L had a high risk of mortality due to circulatory shock.[6] The same authors documented that the chances of survival from shock declines from 90 to 10% as blood lactate levels escalates from 2.0 to 8.0 mmol/L.[7,13]

The outcome after any cardiac surgery is determined by the preoperative characteristics of the patient as well as intraoperative factors such as surgical technique, strategies of myocardial protection, hemodynamic management of the patient, and duration of CPB, which play a crucial role in determining the postoperative course of the patient.[14-20] Monitoring of such factors during the perioperative period may help in early recognition and treatment, which may improve the overall outcome of the patient. Serum lactate levels have been used frequently in critical care settings as a guide for clinicians to begin and optimize early treatment in patients with shock and thereby help to decrease morbidity and mortality.[11,13-15,20,21] Patients undergoing cardiac surgery under CPB, despite having normal arterial blood gases (ABGs), may still experience lactic acidosis secondary to tissue hypoperfusion. Therefore, monitoring blood lactate levels in cardiac surgery patients might be more sensitive than ABG analysis alone and will thereby help in early detection of an imbalance between oxygen supply and demand.

The hypothesis of this study is that patients with high blood lactate levels in the perioperative period are at a higher risk for postoperative complications. The goal of this study was to identify possible risk factors that can cause HL in patients undergoing cardiac surgery under CPB; furthermore, to evaluate the association of HL during the perioperative period with postoperative morbidity and mortality in an adult cardiac surgical population.

MATERIALS AND METHODS

Study population

This retrospective observational study was conducted on adult patients who underwent elective cardiac surgery under CPB in our institution, a tertiary referral center, between July 2013 and June 2014. A total of 452 adult patients were assessed for eligibility. However, 82 patients did not meet the inclusion criteria; hence 370 patients were studied. The patients were divided into two groups based on serum lactate levels; those with serum lactate levels ≥4 mmol/L considered as HL and those with serum lactate levels <4 mmol/L [Figure 1]. All intraoperative (operation theater) and postoperative (Intensive Care Unit [ICU]) data were collected by means of a standardized data collection sheet which was later used for analysis by appropriate statistical methods. The research proposal was discussed and approved by our Institutional Review Board (No. 8998).

All patients posted for elective cardiac surgery under CPB between the ages of 18–75 years, with an ejection fraction ≥40% were included in the study. Patients who had off-pump surgery, preoperative ejection fraction <40%, preoperative serum creatinine >2.0 mg/dL, or with active congestive cardiac failure were not included in the study. Patients with intraoperative death and all emergency cardiac surgeries were also excluded from the study.

Demers *et al*. considered a lactate level of up to 2.0 mmol/L as normal. Patients with blood lactate levels between 2 and 4 mmol/L were categorized as having mild to moderate HL and those with blood lactate levels higher than 4.0 mmol/L were categorized as severe HL.[11] In this study, a blood lactate level of ≥4.0 mmol/L was taken as the threshold consistent with the previous studies.[11] Our patients were divided into two groups; those with serum lactate levels ≥4 mmol/L, which was considered as HL and those with serum lactate levels < 4 mmol/L.

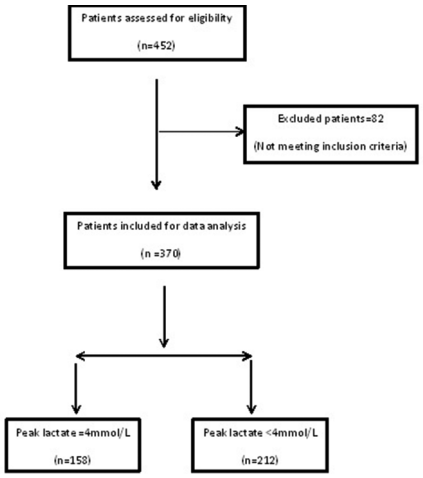

Figure 1: Consort diagram showing inclusion of patients for the study

To identify possible preoperative and intraoperative risk factors for HL, the highest intraoperative lactate value was taken. The postoperative morbidity and mortality associated with HL was studied using the overall (including intraoperative and postoperative values) peak lactate levels. Various risk factors for HL and the relationship of HL with intraoperative and postoperative clinical variables were evaluated.

Anesthesia and cardiopulmonary bypass

All patients included in the study had a standardized anesthesia technique as per our cardiac anesthesia unit protocol. A balanced anesthesia technique with midazolam (0.05–0.1 mg/kg), etomidate (0.1–0.3 mg/kg), or propofol (1 mg/kg) with fentanyl (5–10 mcg/kg) and nondepolarizing muscle relaxants (rocuronium, pancuronium, or vecuronium) and sevoflurane were used for induction of anesthesia. Anesthesia was maintained with air, oxygen, and isoflurane with incremental doses of fentanyl and muscle relaxant. The standard American Society of Anesthesiologist monitoring was used together with central venous pressure monitoring, invasive arterial pressure monitoring, and transesophageal echocardiography.

The CPB circuit was primed with a mixture of Ringer's lactate, mannitol, and sodium bicarbonate solution to make the priming volume to 1200 ml. Standard CPB techniques were employed. Extracorporeal circulation with pump flows of 2.0–2.4 L/min/m^2 of body surface area and mild systemic hypothermia and intermittent antegrade cold blood cardioplegia were used.

Mean arterial pressure was monitored continuously and maintained between 50 and 60 mmHg during CPB. The hemoglobin on pump was maintained between 6 and 8 gm%. Intraoperative blood glucose was maintained between 100 and 140 mg/dL. Insulin infusion was started when blood sugar exceeded 180 mg/dL. Adrenaline was the first line inotrope with doses ranging from 0.01–0.2 mcg/kg/min, and noradrenaline was added to attain the desired hemodynamics. Milrinone was added if there was impaired left or right ventricular function or pulmonary artery hypertension. Postoperatively, all the patients were shifted to the cardiac ICU where they were electively ventilated, and continuous monitoring of hemodynamic parameters and ABG analysis were done at regular intervals.

Measurement of blood lactate

Blood lactate levels were measured at fixed time intervals. The blood sample was drawn from an intra-arterial catheter. Blood lactate values were obtained from standard arterial blood gas analyzer (GEM Premier 3000 Blood Gas Analyzer). The first sample (baseline) was taken as soon as the catheter was inserted. Subsequent samples were collected at the following intervals: 10 min after institution of CPB, 10 min after aortic cross-clamp release, 10 min after protamine administration, immediately on arrival into the ICU (0 h), 6 h later, 12 h later, and 24 h later.

Data collection

The following data were collected for all the patients and entered in the standardized pro forma; demographic data - age, weight, body surface area; gender; type of surgical operation; preoperative comorbid illness; preoperative laboratory data - hemoglobin and serum creatinine; and CPB data - CPB duration, aortic cross-clamp duration, flow rate, lactate values, and on-pump Hb. Lactate values were collected as specified earlier.

The outcome data were documented as atrial fibrillation; low cardiac output syndrome - use of inotropic drugs for >24 h, use of intra-aortic balloon pump (IABP); central nervous system - stroke, focal neurologic deficits, seizures, or severely altered mental status; respiratory - mechanical ventilation for >24 h, acute respiratory failure requiring reintubation; gastrointestinal (GI) - peritonitis, acute GI bleed, and paralytic ileus; renal - increase in serum creatinine >2 mg/dL; Infection - wound infection, septicemia, or pneumonia; length of stay in the ICU and in the hospital; and mortality - death occurring in the hospital.

Statistical methods

Descriptive data were expressed as mean, standard deviation of the mean, quartiles, frequencies, or as absolute numbers and percentage when appropriate. Univariate comparisons were computed using Chi-square test for categorical variables and *t*-tests for continuous variables. Mean lactate level (with standard deviation) at different time points was derived using error plot. A two group comparison for postoperative length of stay in intensive care and hospital was performed using the Mann–Whitney U-test and represented graphically using box plots. Pearson correlation coefficient was used to determine the correlation of serum lactate levels with intraoperative variables and was represented by scatter plot graphs.

Odds ratio and 95% confidence interval for the presence of postoperative complications according

to lactate levels after surgery were calculated using logistic regression analysis. The statistical analysis was performed using SPSS 17.O (Statistical Package for Social Sciences) and R- software (R for Windows 3.1.2). $P < 0.05$ was considered statistically significant for all of the statistical tests.

RESULTS

Preoperative risk factors

Of the 370 patients studied, 158 were found to have intraoperative peak lactate levels ≥4 mmol/L and 212 patients had these lactate levels <4 mmol/L. On comparing the 2 groups, age distribution was almost the same with no statistical significance ($P = 0.815$). Females had higher lactate levels as compared to males, and this was statistically significant ($P = 0.011$). The other comorbidities such as diabetes, hypertension, ischemic heart disease, bronchial asthma, and chronic obstructive pulmonary disease did not have any statistical significance in relation to the peak intraoperative blood lactate levels [Table 1].

Table 1: Preoperative risk factors for hyperlactatemia

Variable	Lactate, *n* (%)		*P*
	≥4	<4	
Age			
>50	69 (43.4)	90 (56.6)	0.815
<50	89 (42.2)	122 (57.8)	
Sex			
Male	91 (37.9)	149 (62.1)	0.011*
Female	67 (51.5)	63 (48.5)	
Diabetes mellitus	54	79	0.540
Hypertension	61 (39.6)	93 (60.4)	0.310
Bronchial asthma	1	3	0.837
COPD	2	1	0.798

*P<0.05. COPD: Chronic obstructive pulmonary disease

Table 2: Types of surgery performed

Types of surgery	Number of patients
CABG*	183
CABG + MVR	10
CABG + MVR + TAP	2
MVR	80
MVR + TAP	10
AVR	23
DVR	35
Redo MVR	4
Redo DVR	1
ICR	15
ASD closure	3
VSD closure	1
Miscellaneous	3

*CABG: Coronary artery bypass graft, MVR: Mitral valve replacement, AVR: Aortic valve replacement, DVR: Double valve replacement, TAP: Tricuspid annuloplasty, ASD: Atrial septal defect, VSD; Ventricular septal defect, ICR: Intracardiac repair

Intraoperative data

From the total number of surgeries performed, isolated coronary artery bypass grafting (CABG) constituted almost 50% of the total surgeries. The miscellaneous group comprised Bentall's procedure, pacemaker lead reimplantation, and repair of rupture of sinus of Valsalva [Table 2].

There was a gradual increase in lactate levels during the course of CPB which continued to remain high into the postoperative period in the ICU up to the first 6 h and then steadily declined. There was no bimodal distribution of lactate levels as was observed in some of the previous studies.[17] The mean and standard deviation of blood lactate levels at different time intervals both intraoperatively and in the ICU are shown in Table 3. The graph [Figure 2] depicts the mean values of the blood lactate levels during the perioperative period.

Patients with HL had significantly longer CPB time (92.40 ± 26.0 vs. 83.96 ± 28.18 min; $P = 0.003$) and aortic cross-clamp time (55.8 ± 18.2 vs. 48.4 ± 19.8 min; $P = 0.007$). There was no significant difference in the lowest hemoglobin on pump or flow rate between the two groups [Table 4].

The scatter plot diagram [Figure 3] shows that as CPB duration increases, the blood lactate level

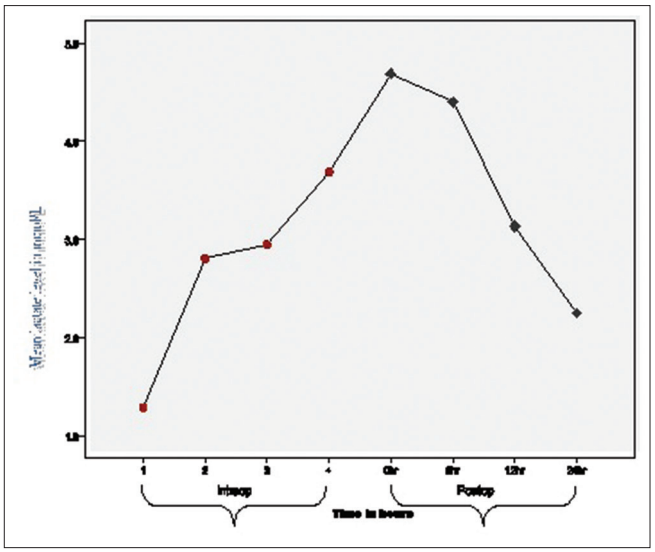

Figure 2: Graphical distribution of mean lactate levels during the perioperative period

Table 3: Mean±standard deviation of blood lactate levels during the perioperative period

n=370	Baseline	10 min			ICU			
		Post-CPB	Post-AOX*	Postprotamine	0 h	6 h	12 h	24 h
Mean±SD lactate levels	1.28±0.6	2.80±1.6	2.94±1.0	3.68±1.3	4.6±3.2	4.3±2.1	3.12±1.7	2.24±1.3

*AOX: Aortic cross clamp, CPB: Cardiopulmonary bypass, ICU: Intensive Care Unit, SD: Standard deviation

Table 4: Comparison of intraoperative variables between the two groups

Variables	Lactate levels		*P*
	≥4.0 (mmol/l), *n*=158	<4.0 (mmol/l), *n*=212	
CPB time (min)	92.40±26.0	83.96±28.18	0.003*
AOX time (min)	55.8±18.2	48.4±19.8	0.007*
Lowest Hb (mg/dl) on pump	7.03±1.20	7.04±1.47	0.510
Flow rate (L/min/m^2)	3.5±2.1-3.8±1.8	3.3±1.9-3.7±1.8	0.921

*P<0.05. CPB: Cardiopulmonary bypass, Hb: Hemoglobin, AOX: Aortic cross clamp

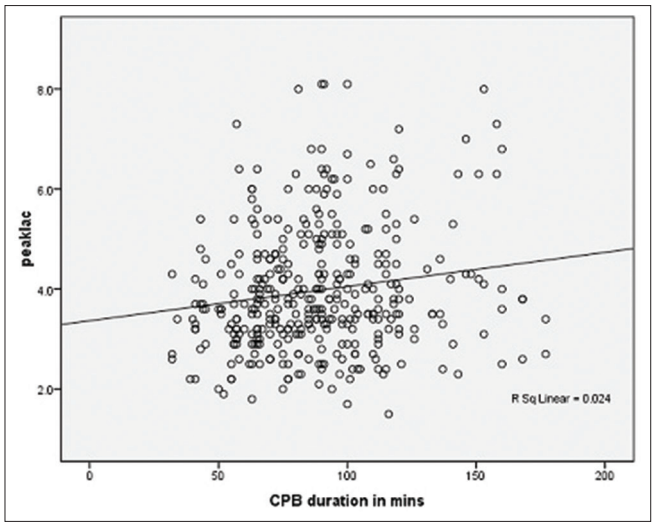

Figure 3: Correlation between peak lactate level and the cardiopulmonary bypass time

rises. The correlation between CPB time and peak intraoperative lactate level was found to be statistically significant (Pearson correlation coefficient $r = 0.024$; $P = 0.003$).

There also was a strong correlation between aortic cross-clamp time and peak lactate level which was statistically significant ($r = 0.02$, $P = 0.007$). The scatter plot diagram [Figure 4] depicts the same.

The incidence of atrial fibrillation was found to be more common in the HL group (19.9% vs. 5.3%; $P = 0.004$). Patients in the HL group required more inotropic supports (34% vs. 11.8%; $P = 0.001$). However, on comparing mechanical ventilator support, renal dysfunction, GI bleed, and postoperative infections, there was no statistically significant difference between the two groups. Although patients with paralytic ileus had higher lactate levels, it was statistically not significant, probably because of the small number.

The length of ICU stay (<3 days - 215 [76.5%] vs. 66 [23.5%]; ≥3 days - 79 [88.8%] vs. 10 [11.2%]; $P = 0.013$) and hospital stay (<7 days - 148 [50.3%] vs. 53 [69.7%]; ≥7 days - 146 [49%] vs. 23 [30.3%]; $P = 0.001$) were found to be significantly higher in the HL group [Table 5]. There were no neurological complications. One patient died of left ventricular rupture following mitral valve replacement, but this patient did not have raised lactate levels.

Patients in the HL group had 3.5 times the risk of developing atrial fibrillation in the postoperative period as compared to those with lower lactate levels. Similarly, the requirement for inotropic supports was 5.66 times more in the HL group [Table 6].

DISCUSSION

HL and lactic acidosis are known to be associated with increased morbidity and mortality. Published literature shows a correlation between the postoperative peak lactate concentration and postoperative morbidity without considering intraoperative variables.[10,11,13,22,23] Early HL is defined as high lactate occurring during the first 4 h of surgery, and late HL is defined as increase in lactate from 4 to 24 h postsurgery.[10] We wanted to observe whether early HL, including also intraoperative lactate values, could be used as a predictor for postoperative morbidity and mortality.

Normal lactate is defined as blood lactate level between 0.4 and 2.0 mmol/L. Lactate level between 2 mmol/L and 4.0 mmol/L is considered as mild to moderate HL and blood lactate >4.0 mmol/L is classified as severe HL.[11] Mirmohammad-Sadeghi *et al*. had defined HL as a lactate level more than 3 mmol/L.[24] For our study, we used a lactate value of ≥4 mmol/L as HL. The percentage of severe HL was less in male patients compared to female patients. Our results support

Demers *et al*. who identified female sex as a risk factor for postoperative HL.[11]

Patient comorbidities such as hypertension, diabetes mellitus, or ischemic heart disease did not have a statistically significant association with HL. Several investigators have identified hyperglycemia as a risk factor for HL.[10,17] We had practiced a tight control regimen for blood glucose homeostasis (120–160 mg/dL) using human insulin infusion perioperatively. This could explain why we could not obtain a statistically significant difference between diabetes and HL. Contrary to published literature, we could not find an association between preoperative anemia and preoperative creatinine with HL.[10,12,13,16] This could be because we excluded patients with preoperative serum creatinine of more than 2 mg/dL. Furthermore, the mean preoperative hemoglobin of our study population was 12.68 ± 2.84. The number of severely anemic patients was few to derive any statistical correlation.

Mirmohammad-Sadeghi *et al*. reported a 76% incidence of HL in his study with a definition of HL having a value of more than 3 mmol/L.[24] In this study with our criteria for HL (lactate value ≥4 mmol/L) when peak intraoperative lactate values were considered, there was an incidence of 42.7% (158 out of 370 patients). When overall peak lactate for all observed values was considered, there was an incidence of 79.5% (294 out of 370 patients). The reported incidence of HL is about 10–20%.[10,25] We had a higher incidence of HL probably due to adrenaline being our inotrope of choice. Increased circulating catecholamines secondary to the stress response to surgery, in combination with the use of adrenaline perioperatively, have been reported to result in increased blood lactate levels.[26]

Serum lactate levels increased from the onset of CPB to peak and remain high up to 6 h in the ICU and returned

Table 5: Postoperative morbidity

Variable	Lactate level		*P*
	≥4 (%)	<4 (%)	
Atrial fibrillation			
+	57 (19.4)	4 (5.3)	0.004*
−	237 (80.6)	72 (94.7)	
Inotropic support			
+	100 (34)	9 (11.8)	0.001*
−	194 (66)	67 (88.2)	
Ventilation			
+	21 (7.1)	3 (3.9)	0.447
−	273 (92.9)	73 (96.1)	
Renal dysfunction			
+	22 (7.5)	0	0.029
−	272 (92.5)	76 (100)	
Gastrointestinal bleed			
+	2 (0.7)	0	1.000
−	292 (99.3)	76 (100)	
Paralytic ileus			
+	3 (1)	0	0.868
−	291 (99)	76 (100)	
Infection			
+	10 (34)	3 (3.9)	1.000
−	284 (96)	73 (96.1)	
Length of stay			
ICU (days)			
<3	215 (76.5)	66 (23.5)	0.013*
≥3	79 (88.8)	10 (11.2)	
Hospital (days)			
<7	148 (50.3)	53 (69.7)	0.001*
≥7	146 (49)	23 (30.3)	

*P<0.05. ICU: Intensive Care Unit

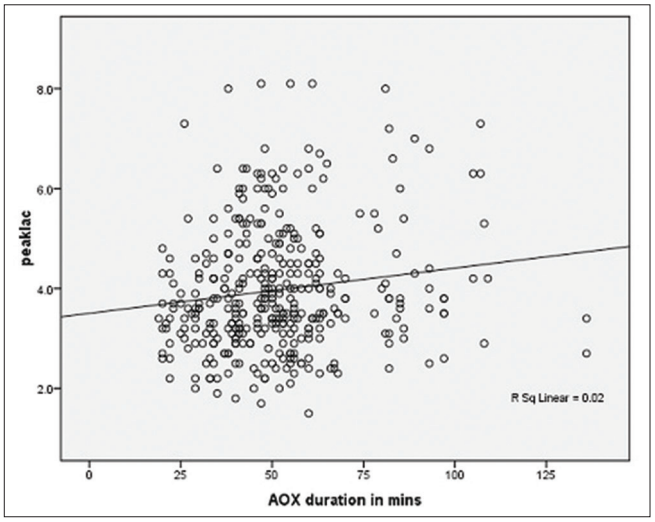

Figure 4: Correlation between aortic cross clamp time and peak blood lactate level during cardiopulmonary bypass

Table 6: Logistic regression analysis of the complications among the two groups

Complications	Total number	Lactate		*P*	OR (95% CI)
		≥4	<4		
Atrial fibrillation	61	57	4	0.004*	3.5 (1.53-8.13)
Inotropic support	109	100	9	0.001*	5.66 (3.06-10.48)

*P<0.05. CI: Confidence interval, OR: Odds ratio

to normal by 24 h. There was no bimodal distribution of serum lactate as reported by other researchers.[17] Patients in the HL group had significantly longer CPB time (92.40 ± 26.0 vs. 83.96 ± 28.18 min) and aortic cross-clamping time (55.8 ± 18.2 vs. 48.4 ± 19.8 min). The correlation between CPB time and peak blood lactate level was found to be statistically significant (Pearson correlation coefficient $r = 0.22$; $P = 0.003$). There was also a strong correlation between aortic cross-clamp time and peak blood lactate level which was also found to be statistically significant ($r = 0.281$; $P = 0.007$). These similar findings were seen in the study on lactate and postoperative morbidity and mortality by Demers *et al*.[11]

We found increased lactate levels during and after rewarming. This may be due to increased oxygen demands on reperfusion, and this was similar to the observation made by Ranucci *et al*.[27]

Increased intraoperative peak blood lactate levels (early HL) and blood lactate levels at 6 h postsurgery (late HL) were both highly predictive of major cardiac morbidity such as atrial fibrillation and requirement for prolonged inotropic support. Serum lactate levels >4 mmol/L were associated with 3.5 times higher risk of developing AF and 5.66 times higher risk of prolonged inotropic support requirement compared to patients with serum lactate <4 mmol/L. Our results were similar to those demonstrated by Basaran *et al*.[28] However, HL was not associated with increased IABP requirement as observed by Toraman *et al*.[25] This may be because we excluded patients with low EF of <40% resulting in none of the study patients requiring IABP perioperatively.

We also observed a statistically significant difference in the duration of ICU stay and hospital stay in patients with HL. Peak serum lactate ≥4 mmol/L was associated with a significantly longer ICU stay ($P = 0.013$) and hospital stay ($P = 0.001$) compared to patients with lactate <4 mmol/L. However, we failed to see any difference in the duration of mechanical ventilation days between the two groups. This could be due to our ICU protocol of electively ventilating most patients overnight.

One patient died in the study population. This patient had left ventricular rupture after a mitral valve surgery. Observed lactate levels were not raised and thus did not predict mortality in this patient though lactate level at the end of resuscitation was high. Our result was different from Maillet *et al*. who observed increased mortality in patients with HL.[10] This may be due to the different patient profile in our study. We excluded patients with renal failure, emergency surgery, extremes of age, and active congestive heart failure. This probably resulted in our 0.27% mortality (1 out of 370 patients) and a causal association could not be derived.

Complex surgeries such as redo surgeries, aortic root replacement, and intracardiac repairs were associated with a higher serum lactate. However, as the numbers were very small, we could not derive any statistical association between the complexity of surgery and HL.

We studied 370 patients who underwent a wide variety of cardiac surgeries which included coronary artery bypass grafting, valve surgeries, and adult congenital cardiac surgeries. Unlike other studies, we excluded patients who had raised creatinine or low ejection fraction, as these by themselves could cause HL and also contribute to increased morbidity and mortality, thus confounding the results of the study. This makes our study unique.

Limitations

Our assessment of the impact of HL on postoperative mechanical ventilation days was flawed as we routinely did not extubate any patient during the night as a department protocol.

We could not make any correlation between HL and blood sugar levels, which is a known risk factor for HL, as we followed a strict glycemic control using the insulin sliding scale.

CONCLUSION

HL has a significant association with postoperative morbidity. Detection of HL in the perioperative period should be taken as an indicator of inadequate tissue oxygen delivery and should be aggressively corrected.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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