

# Perioperative Blood Lactate Levels, Pyruvate levels and Lactate/ Pyruvate Ratio in Children Undergoing Cardiopulmonary Bypass for Congenital Heart Disease

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## Citation

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## Abstract

**Background:** Cardiopulmonary bypass (CPB) affects almost every body system by hypoperfusion either subclinically or clinically and also produces a systemic inflammatory response due to contact of blood with mechanical surfaces. There has been no documentation, with regards to pyruvate, in predicting postoperative mortality and morbidity. This study was carried out to evaluate lactate levels, pyruvate levels and lactate/ pyruvate ratio in pediatric patients undergoing cardiopulmonary bypass (for correction of congenital cardiac anomaly) and their correlation to perioperative outcomes.

**Methods:** 50 consecutive patients (less than 14 years of age) of various congenital heart diseases (CHD) undergoing cardiopulmonary bypass were studied. Patients were classifying into three categories according to their surgical complexity. Arterial blood samples were collected at different stages of CPB to estimate blood lactate and pyruvate levels by using documented spectrophotometric method.

**Results:** The observed mean baseline lactate levels were  $2.24 \pm 0.79$  mmol/L (normal range of 0.9 to 1.7 mmol/L). The mean circulating lactate levels, at 15 minutes and 45 minutes after institution of CPB, increased to  $4.49 \pm 1.2$  mmol/L and  $5.24 \pm 1.02$  mmol/L respectively. A progressive decline, in the mean lactate levels, was noted during rewarming (at  $35^{\circ}\text{C}$ ) and immediately off-bypass which continued steadily even 24 and 48 hours postoperatively. Mean baseline lactate/pyruvate ratio was 24.73, which increased at 15 and 45 minutes after institution of CPB, rewarming (at  $35^{\circ}\text{C}$ ), and immediately off-bypass. As far as the duration of CPB concerned, we found Lactate levels were elevated significantly ( $p < 0.05$ ) as well as lactate/pyruvate ratio were significantly high ( $p < 0.001$ ) during rewarming, off-bypass, 24 hours and 48 hours post CPB in patients requiring CPB for more than 1 hours. The average duration of postoperative mechanical ventilation, inotropic support and Lactate/Pyruvate ratio were significantly higher ( $p < 0.001$ ) in category III of patients in comparisons with category I and II.

**Conclusion:** In patients undergoing cardiopulmonary bypass for congenital heart operation, elevations in lactate/pyruvate ratio can predict the postoperative outcome significantly better in comparison to lactate levels.

## INTRODUCTION

Cardiopulmonary bypass (CPB) is established during various cardiac operations to allow adequate systemic oxygenation and perfusion during the surgical procedure<sup>1</sup>. CPB being a non-physiological condition, affects almost every body system secondary to hypoperfusion, either subclinically or clinically, and also produces a systemic inflammatory response due to contact of blood with mechanical surfaces. Much attention has been focused in

recent years on the adverse effects of CPB, particularly in pediatric patients undergoing surgical repair. Evidence presented has shown significant activation of various inflammatory mediators, including components of the complement cascade, activation of neutrophils and platelets resulting in local and systemic production of circulating proinflammatory cytokines and adhesion molecules.

Tissue perfusion is at risk during cardiac surgery and also in the immediate postoperative period<sup>2</sup>. The development of

predictors of death involves evaluating multiple different cardiorespiratory physiologic indices <sup>2</sup>. This approach is often difficult in infants with congenital heart disease (CHD) because of their small size, which limits invasive monitoring capabilities and reliable diagnostic options. Despite these obstacles, the search for predictors to help direct aggressive interventions in this patient population remains an important goal.

It is a well known fact that tissue hypoperfusion is associated with lactic acidosis due to anaerobic metabolism. Measurement of blood lactate levels can hence be used as a marker to assess the adequacy of tissue perfusion <sup>3</sup>. There are no studies evaluating the use of pyruvate and lactate/ pyruvate ratio as a marker for assessing tissue perfusion. Hence, Measuring perioperative blood lactate levels, pyruvate levels and lactate/ pyruvate ratio, during CPB for congenital cardiac diseases, may provide a diagnostic and prognostic tool.

The aim of the study was to establish the relationship of lactate levels, pyruvate levels and lactate/ pyruvate ratios in patients undergoing cardiopulmonary bypass for correction of congenital cardiac anomaly and their correlation to perioperative outcome, morbidity and mortality.

## MATERIALS AND METHODS

50 consecutive patients undergoing cardiopulmonary bypass for congenital heart disease were included in this study. All were elective procedures.

The institutional ethics committee gave approval and informed consent was obtained from every patient.

On the basis of the surgical complexity, the patients were allocated into categories as described by Jenkins and Colleagues <sup>2</sup>.

### Figure 1

**Category I** – ASD (Atrial Septal defect)  
**Category II** -- VSD (Ventricular Septal Defect)  
 AVC (Atrio Ventricular Canal)  
 Sub aortic stenosis  
 Open pulmonary valvotomy  
**Category III** –TOF (Tetralogy of Fallot)  
 TAPVC (Total Anomalous Pulmonary Venous Connection)  
 Truncus Arteriosus  
 Aorto Pulmonary Window

## ANAESTHESIA TECHNIQUE

All were premedicated with injection morphine (0.2 mg/kg) and promethazine (0.5 mg/kg) intramuscularly about 30 minutes prior to induction of anaesthesia.

Anaesthesia was induced with injection thiopentone (5mg/kg) followed by assisted ventilation with a mixture of 50% oxygen (O<sub>2</sub>) and 50% nitrous oxide (N<sub>2</sub>O)] followed by injection vecuronium (0.1 mg/Kg). Ryles tube and nasopharyngeal probes were inserted and then endotracheal intubation, using an appropriate sized portex tube, was carried out. Anaesthesia was maintained with a mixture of 50% O<sub>2</sub>, 50% N<sub>2</sub>O, halothane (0.5% to 1%) and I.V fentanyl 5-10 µg/kg/hr.

Morphine (0.05 mg/Kg) was administered before incision and 0.15 mg/Kg was added to the priming solution. The bypass circuit was primed with a mixture of ringer lactate and plasma. If required blood was added to the prime to maintain a circulating haematocrit of 25-30%.

CPB was instituted after systemic heparinisation (using 3000 IU/Kg of porcine lung heparin) and cardioplegia was administered (using cold hyperkalemic blood containing solution) via the aortic root after the application of aortic cross clamp. Nasopharyngeal temperature was decreased during CPB. Flow rate of 2.4 X body surface area (in L/min/m<sup>2</sup>) were maintained at 32°C. Mean arterial pressure was maintained between 60 and 65 mm Hg through an invasive arterial line. Urine output was monitored throughout the procedure. Blood sugar was monitored using a glucometer intraoperatively and the sugar levels were maintained between 180 and 240 mg%. Anaesthesia on bypass was maintained with a fentanyl drip. During rewarming 0.1mg/kg morphine and 0.1mg/kg vecuronium were added to the reservoir. CPB was discontinued and heparin neutralized with protamine. Patients received inotropic support, if required. The inotrope of choice was dobutamine (5- 10 µg/ Kg/ min) followed by adrenaline (0.06 µg/ Kg – 0.6 µg/ Kg). Post CPB anaesthesia was maintained using 50% O<sub>2</sub>, 50% N<sub>2</sub>O, halothane 0.5 to 1%, and vecuronium (1/4th of induction dose) as and when needed. Before shifting the patient to cardiac intensive care unit, morphine 0.1 mg/Kg was given intravenously. In the intensive care unit the patients were electively ventilated while continuous monitoring of haemodynamic parameters and arterial blood gas analysis was followed.

## BLOOD LACTATE AND PYRUVATE LEVEL MEASUREMENT

For measuring lactate and pyruvate levels, arterial blood was collected through the intra-arterial catheter (inserted for blood pressure monitoring) immediately after induction of anaesthesia. This was termed as the baseline sample.

Subsequent samples were collected at 15 minutes after institution of CPB, 45 minutes after institution of CPB (if any), rewarming (at 35°C), immediately after cessation of CPB, 24 hours post surgery and 48 hours post surgery.

The blood samples were collected in a sample tube containing 3 ml of 5% metaphosphoric acid. Samples were stored in ice carriers and transferred to the laboratory where they were immediately centrifuged. The protein free filtrate was then collected in another tube for the estimation of lactate and pyruvate (Using the spectrophotometer method at 340 nm) <sup>4</sup>.

The endpoint of the study was predetermined with the last sample being collected at 48 hours after termination of CPB. The one-way ANOVA was used for statistical analysis.

## RESULTS

The average age was  $6.3 \pm 4.1$  years and average weight was  $15.1 \pm 7.6$  kg. There are 39 male and 11 females. There was one mortality.

Table 1 shows distribution of the patients according to the surgical complexity. Maximum patients 25 (i.e. 50% of the patients) belonged to category II.

### Figure 2

Table 1: Categories Of Patients According To Surgical Complexity

Category	No. of patients	Percentage
I	10	20%
II	25	50%
III	15	30%

The distributions of individual surgical procedures are shown in table 2. Most patients underwent a ventricular septal defect closure.

### Figure 3

Table 2: Types of surgery

Type of surgery	No. of Patients
ASD closure	10
VSD closure	23
TOF repair	14
A-V Canal Closure	2
TGV correction	1

Mean lactate, pyruvate and lactate/pyruvate ratio in various categories of patients are shown in table 3. No statistically significant difference in the elevation in Lactate, pyruvate levels (in mmol/L) and lactate/pyruvate ratio (during CPB), in various categories, was seen.

### Figure 4

Table 3: Mean Lactate, Pyruvate Level (mmol/L) and Lactate/Pyruvate ratio in various categories of patients

Category	Base Line			15 min.			45 min.			Rewarming		
	L	P	L/P	L	P	L/P	L	P	L/P	L	P	L/P
I	2.08 ± 0.98	0.09 ± 0.001	23.1 ± 10.9	4.7 ± 0.8	0.11 ± 0.02	43.1 ± 8.03	5.1 ± 1.8	0.2 ± 0.01	31.3 ± 13.2	6.9 ± 1.9	0.29 ± 0.01	14.6 ± 3.67
II	2.2 ± 0.83	0.12 ± 0.02	24.4 ± 10.7	4.2 ± 1.3	0.1 ± 0.02	42.6 ± 15.6	5.15 ± 1.5	0.19 ± 0.01	32.4 ± 11.2	7.7 ± 3.1	0.3 ± 0.02	13.0 ± 4.6
III	2.2 ± 0.59	0.09 ± 0.005	26.2 ± 7.7	4.6 ± 1.2	0.1 ± 0.01	46.3 ± 14.2	5.2 ± 1.4	0.19 ± 0.01	31.7 ± 8.6	8.0 ± 3.0	0.29 ± 0.02	11.3 ± 4.5
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

Category	Off-Bypass		24 hrs.		48 hrs.							
	L	P	L/P	L	P	L/P	L	P	L/P	L	P	L/P
I	6.4 ± 1.9	0.33 ± 0.01	15.3 ± 1.3	4.0 ± 1.4	0.19 ± 0.01	15.8 ± 2.3	2.8 ± 0.74	0.1 ± 0.01	26.7 ± 1.6			
II	6.3 ± 3.5	0.33 ± 0.02	12.4 ± 5.0	4.4 ± 2.5	0.19 ± 0.02	15.3 ± 6.6	3.1 ± 1.5	0.1 ± 0.01	25.4 ± 10			
III	6.3 ± 2.7	0.33 ± 0.02	10.8 ± 3.6	5.1 ± 2.7	0.19 ± 0.02	15.3 ± 6.5	3.4 ± 1.8	0.1 ± 0.02	26.4 ± 8.3			
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

L: Lactate; P: Pyruvate; L/P: Lactate/Pyruvate ratio

Values Expressed as Mean ± SD.

NS: Non significant (Multiple Comparison by using One-way ANOVA)

Comparison of duration of CPB versus changes in perioperative lactate, pyruvate levels and lactate/pyruvate ratio are shown in table 4.

### Figure 5

Table 4: Comparison of Duration of CPB and Change in Perioperative Lactate, Pyruvate levels (mmol/L) and Lactate/Pyruvate Ratio

Duration Of CPB	Base Line			15 min.			45 min.			Rewarming		
	L	P	L/P	L	P	L/P	L	P	L/P	L	P	L/P
< 1 hrs.	2.42 ± 0.87	0.1 ± 0.02	24.2 ± 9.98	4.6 ± 1.27	0.1 ± 0.0	38. ± 16.5	5. ± 1.0	0.1 ± 0.0	49 ± 16	7.2 ± 2.6	0.20 ± 0.07	36 ± 9.3
1-2 hrs.	2.04 ± 0.63	0.09 ± 0.02	22.7 ± 8.5	4.2 ± 1.15	0.1 ± 0.0	38. ± 16.6	6. ± 2.3	0.1 ± 0.0	52 ± 13	8.2 ± 3.4	0.30 ± 0.1	27 ± 12
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	*	**

Duration Of CPB	Off- Bypass	24 hrs.	48 hrs.					
	P	L/P	L	P	L/P	L	P	L/P
< 1 hrs.	0.15 ± 0.08	38 ± 16	3.8 ± 1.1	0.2 ± 0.09	20 ± 6.4	2.8 ± 1.0	0.1 ± 0.03	28.3 ± 10.2
1-2 hrs.	0.40 ± 0.13	18 ± 10	5.3 ± 2.9	0.18 ± 0.07	29 ± 11	3.9 ± 2.1	0.1 ± 0.02	45.1 ± 20.2
Significance	NS	**	*	NS	**	*	NS	**

L: Lactate; P: Pyruvate; L/P: Lactate/Pyruvate ratio

Values Expressed as Mean ± SD.

\* P < 0.05 as compared to < 1 hours, duration of CPB.

\*\* P < 0.001 as compared to < 1 hours of CPB

Lactate levels were elevated significantly ( $p < 0.05$ ) and lactate/pyruvate ratio were significantly high ( $p < 0.001$ ) during rewarming, off-bypass, 24 hours and 48 hours post CPB in patients requiring CPB for more than 1 hours.

Pyruvate was significantly elevated during rewarming in patients requiring CPB for more than 1 hour. The rise in lactate/ pyruvate levels was more significant in comparison with absolute lactate or pyruvate levels.

Table 5 shows a comparison of the various surgical categories with mean duration of postoperative inotropic and mechanical support and the associated elevations in lactate and pyruvate levels. The average duration of postoperative mechanical ventilation, inotropic support and Lactate/Pyruvate ratio were significantly higher ( $p<0.001$ ) in category III of patients in comparisons with category I and II. Lactate was less significant ( $p<0.05$ ) in category III.

### Figure 6

Table 5: Comparison in various surgical categories, Lactate, Lactate/pyruvate ratio with mean duration of postoperative Iontropic and Mechanical support

Categories	Lactate (mmol/L)	Lactate/Pyruvate Ratio	Iontropic Support (hrs.)	Mechanical Support (hrs.)
I	4.5±0.98	19.2±8.8	9.8±3.1	10.6 ± 2.6
II	4.6±1.0	17.7±9.8	15.8±9.0	17.08±7.58
III	5.0±1.1**	27.8±10.5 *	28±9.7 *	18.67±9.2 *

Values Expressed as Mean ± SD.

\*  $P<0.001$  as compared with category I and II

\*\*  $P<0.05$  as compared with category I and II

## DISCUSSION

Advances in pediatric cardiac surgery for complex congenital heart diseases continue. It is essential to identify patients who have an increased risk for postoperative morbidity and mortality and may benefit from early aggressive intervention. A small but substantial number of patients with complex congenital heart disease continue to die in the immediate postoperative period <sup>5</sup>. Lactate is a marker of anaerobic metabolism and tissue oxygen deficit. The severity of lactic acidosis in critically ill patients correlates with overall oxygen debt and survival <sup>6</sup>. As lactate concentration increased from 2 to 8 mmol/L the estimated probability of survival decreased from 90% to 10% <sup>7</sup>.

Increases in tissue lactate concentration and acidosis correlates with depletion of high-energy phosphate compounds and with cellular dysfunction. Because lactic acid is a product of anaerobic metabolism, elevated lactate levels represent inadequate tissue oxygen delivery. This decrease in oxygen delivery represents a combination of tissue hypoperfusion and hypoxemia prompting a systematic diagnostic evaluation. Several studies have shown a strong correlation between blood lactate levels and the risk of morbidity and mortality in varying clinical situations such as circulatory shock, septic shock, severe hypoxemia, liver

failure, diabetes mellitus and others <sup>6,8,9,10</sup>. To the best of our knowledge no study has been undertaken evaluate pyruvate in predicting postoperative mortality and morbidity. When tissue hypoxia is present, pyruvate oxidation in the Krebs cycle is decreased. Lactate production is increased and ATP formation continues via glycolysis. Hence in this study, instead of measuring only lactate levels we decided to also measure pyruvate levels in predicting the postoperative outcomes.

In adults most of the studies compared the preoperative clinical condition according to the NYHA classification to the changes in lactate levels during cardiopulmonary bypass <sup>11</sup>. However, in children NYHA classification is not applicable. So we decided to categorize the patients according to the complexity of surgery <sup>2</sup>. In our study of 50 patients 10 (20% of the patients) belonged to category I, 25 (50% of the patients) belonged to category II, and 15 (30% of the patients) belonged to Category III.

An early recognition of patients at risk for the development of hyperlactemia may allow intervention in a timely manner hence reducing the postoperative morbidity. Potential interventions that may alter organ perfusion and tissue oxygenation during CPB include the following:

- Manipulation of perfusion pressure and flow rates
- Levels of hypothermia and duration of cooling and rewarming
- Alteration in the circuit prime to ensure optimal hematocrit value and oncotic pressure
- The use of agents to specifically modify the systemic inflammatory response
- Optimal institution of inotropes and vasodilators.

In our study, the mean baseline lactate level was  $2.24 \pm 0.79$  mmol/L and the level increased 15 and 45 minutes after institution of CPB to  $4.49 \pm 1.2$  mmol/L and  $5.24 \pm 1.02$  mmol/L respectively. As contrary to other studies <sup>2,5</sup> lactate levels remained high during rewarming and off bypass. Thereafter the levels began to decline 24 hours and 48 hours postoperatively with mean values of  $4.5 \pm 1.3$  mmol/L and  $3.36 \pm 1.72$  mmol/L respectively. We found no significant difference in elevations of lactate levels between various surgeries. Even when the lactate levels exceeded in the study by Munoz et al <sup>2</sup> there was no significant change in the

postoperative outcomes.

Mean baseline lactate/pyruvate ratio was 24.73 which increased during CPB. Thereafter that ratio began to decline during rewarming and off bypass to 26.2 and 19.3 respectively. The lactate/pyruvate ratio remained elevated even after 24 hours and 48 hours in those who had postoperative morbidity and mortality. Out of 50 patients, one patient expired. It was a case of VSD with severe pH. In this child the lactate/pyruvate ratio at 48 hours was 88.67.

We compared the mean lactate levels and lactate/pyruvate ratio perioperatively with the duration of CPB. Patients were distributed into two groups, those with bypass duration of less than one hour and the others with duration of more than one hour. We found that elevation in lactate levels and lactate/pyruvate ratio was significantly higher in the group where the duration of CPB exceeded one hour. This is similar to the study done by Munoz et al who analyzed the duration of CPB and circulatory arrest with a change in lactate levels. However the elevations in lactate/ pyruvate ratio were more significant than elevation in absolute lactate level values.

The relationship between lactate, pyruvate and the different categories of patients and duration of postoperative inotropic support and ventilation was studied. The average duration of postoperative mechanical ventilation, inotropic support and Lactate/Pyruvate ratio were significantly higher ( $p<0.001$ ) in category III of patients in comparisons with category I and II. Lactate was less significant ( $p<0.05$ ) in category III.

Hence, we found that lactate/pyruvate ratio is more valuable in CHD patients undergoing corrective surgery with CPB as compared to lactate levels alone.

## CONCLUSION

We conclude that, in patients undergoing cardiopulmonary bypass for congenital heart operation, lactate/pyruvate ratio have a good predictive value for postoperative outcome as compared to lactate level.

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