

**ASSESSMENT OF BLOOD LACTATE LEVELS AND LACTATE CLEARANCE IN PATIENTS UNDERGOING CARDIAC SURGERIES WITH CARDIOPULMONARY BYPASS DURING PERIOPERATIVE IN A TERTIARY HOSPITAL –CROSS SECTIONAL STUDY**

**Dr. Harish.G.L.K<sup>1</sup> ,Dr. Preethi Fatima.D<sup>2</sup> , Dr. Abunaya.H.I<sup>3</sup>**

*(1), (2) Junior Resident, Department of Anaesthesia, Sree Mookambika Institute of Medical Sciences, Kanyakumari, Tamilnadu. (3) Senior Resident, Department of Anaesthesia, Sree Mookambika Institute of Medical Sciences, Kanyakumari, Tamilnadu*

**Corresponding author:** Dr. Harish.G.L.K, Junior Resident, Department of Anaesthesia, Sree Mookambika Institute of Medical Sciences, Kanyakumari, Tamilnadu Email: doc.harish.glk@gmail.com

**ABSTRACT:**

**Background:** Cardiopulmonary bypass (CPB) is instituted, during various cardiac operations, to allow for optimal systemic perfusion. Tissue hypoperfusion is associated with lactic acidosis secondary to anaerobic metabolism. Measurement of blood lactate levels can hence be used as a marker to assess the adequacy of tissue perfusion. In this study we tried to find out the association between various preoperative NYHA classes and link their association with perioperative lactate and lactate clearance values.

**Methods:** 100 patients undergoing elective cardiac surgery under cardiopulmonary bypass were included in this prospective observational study. Based on history, the patients were allocated to their respective class as per the New York Heart Association (NYHA) functional classification. Patients aged between 18-80 years posted for elective cardiac surgery under cardiopulmonary bypass were included. For measuring lactate levels, baseline arterial blood was collected from the intra-arterial catheter immediately after induction of anaesthesia. Subsequent samples were collected at intervals of 15 minutes and 45 minutes after institution of CPB, rewarming (at 35°C), immediately after termination of CPB, 24 hours and 48 hours post-surgery.

**Results:** All four NYHA groups were comparable in terms of baseline lactate levels (P value 0.096). Higher mean levels of lactate were seen in NYHA group 4 compared to other three groups during rewarming, termination and post operatively (24 and 48 hours). After 45 minutes of CPB and during rewarming, NYHA 4 group varied significantly from NYHA 1, 2 and 3. In terms of mean lactate clearance, Tukey HSD (Assuming equal variances) post hoc test showed that both NYHA 3 and NYHA 4 were significantly different from each other as well as NYHA group 2. At 24 hours postoperatively, NYHA 2 varied significantly from NYHA 1, 3 and 4. After 48 hours, a significant difference in lactate clearance was seen between NYHA 1 and 2. The duration of inotropic support as well as mechanical ventilation was more in NYHA 3 and 4.

**Conclusion:** There is a definite association between higher mean lactate levels and lactate clearance with a higher NYHA class during the perioperative period. Increased mean lactate levels and lactate clearance is also associated with increased duration of mechanical ventilation and inotropic support. Higher perioperative lactate levels also

prolong the ICU and hospital stay in higher NYHA classes.

Keywords: Cardiopulmonary bypass, lactate, lactate clearance, NYHA class

**INTRODUCTION:**

Cardiopulmonary bypass (CPB) is instituted, during various cardiac operations, to allow for optimal systemic perfusion. No definitive biochemical markers of prognostic significance have been identified yet in patients undergoing cardiac surgery under CPB. Tissue perfusion is always at risk during CPB and in the immediate postoperative period. The duration of CPB, degree of hypothermia, duration of cooling and rewarming, pH status and the haematocrit value are all potential risk factors that may contribute to tissue hypoperfusion during CPB. Many factors like impaired venous drainage or anatomic lesions characterized by reduced splanchnic flow or excessive systemic runoff may limit optimal tissue perfusion. The systemic inflammatory response to CPB may also impair tissue oxygenation and perhaps more specifically, tissue oxygen extraction. <sup>[1]</sup> Improvements in CPB and overall haemodynamic management have reduced the incidence of severe perioperative tissue hypoperfusion. <sup>[2]</sup> It is a recognized fact that tissue hypoperfusion is associated with lactic acidosis secondary to anaerobic metabolism. Measurement of blood lactate levels can hence be used as a marker to assess the adequacy of tissue perfusion. The end product of this pathway is pyruvate, which can then diffuse into mitochondria and get metabolized to carbon dioxide by the Krebs's cycle. <sup>[3]</sup> Metabolic acidosis may accompany an increase in blood lactate. Such hyperlactatemia is usually seen in subclinical tissue hypoperfusion, secondary to elevated blood catecholamine levels. This may be either stress induced, due to administration of catecholamines or due to alkalosis where buffering systems are able to mitigate any fall in the pH. <sup>[4]</sup>

Lactic acidosis may persist despite control of hemorrhage, reflecting flow-demand mismatch or loss of appropriate capillary density as a consequence of shock, vasoconstriction, or other dysfunctional responses.

<sup>[5]</sup> Lactate clearance (LC) has recently emerged as an important concept that aims to reach predefined physiological goals. <sup>[6]</sup> Several studies have shown that poor lactate clearance is associated with increased mortality during septic shock and after cardiac surgery. <sup>[7-10]</sup>

In this prospective observational study, we tried to find out the association between various preoperative NYHA classes and link their association with perioperative lactate and lactate clearance values.

**METHODS:**

100 patients undergoing elective cardiac surgery under cardiopulmonary bypass at Sree Mookambika Institute of Medical Sciences were included in this prospective observational study. Pre-anaesthetic evaluation and necessary investigations were done. Written informed consent from each patient for the study was taken preoperatively. All patients were monitored in CTVS-ICU postoperatively for 48 hours. Based on history, the patients were allocated to their respective class as per the New York Heart Association (NYHA) functional classification. Patients aged between 18-80 years posted for elective cardiac surgery under cardiopulmonary bypass were included in this study. Patients not giving consent, having history of neurological

diseases/deformities, diabetic patients on phenformin, having liver, respiratory or kidney diseases were excluded. Premedication was done with midazolam (1-2.5mg IV) 5 minutes before and ranitidine (1 mg/kg) intravenous about 30-45 minutes prior to induction of anaesthesia. Induction was done with Propofol (1-2.5 mg/ kg) and Vecuronium (0.1 mg/kg) facilitated endotracheal intubation. Maintenance was achieved with 50% oxygen (O<sub>2</sub>) with isoflurane 0.6% to 1.2% along with intermittent vecuronium doses (0.02 mg/kg)

Morphine (0.05 mg/kg) was given prior to incision followed by 0.15 mg/kg added to the pump prime. Additional morphine (0.1 mg/kg) and Vecuronium (0.1 mg/kg) was administered during rewarming. Post- CPB anaesthesia was maintained with 100% O<sub>2</sub>, isoflurane 0.6% to 1.2%, and Vecuronium (1/4th of induction dose). Standard bypass techniques with systemic hypothermia of 28-32°C were employed. Mean arterial pressure (MAP) was continuously monitored and maintained between 50- 60 mm of Hg. The hemoglobin was maintained between 6 -8 gm%. 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%. After completion of surgery, CPB was discontinued and heparin was neutralized with protamine. Patients received inotropic support in the form of dopamine (5-10 µg/Kg/min), dobutamine (2-20 µg/Kg/min), adrenaline (0.06-0.6 µg/Kg/min) and nitroglycerine (0.5-3µg/Kg/min) were added when required. Elective ventilation was done in the intensive care unit with continuous monitoring of hemodynamic parameters and arterial blood gas analysis. For measuring lactate levels, baseline arterial blood was collected from the intra-arterial catheter immediately after induction of anaesthesia. Subsequent samples were collected at intervals of 15 minutes and 45 minutes after institution of CPB, rewarming (at 35°C), immediately after termination of CPB, 24 hours and 48 hours post-surgery. The arterial blood samples were analyzed in ABG machine for lactate. Quality controls checks were performed on the analyzer prior to lactate value determinations.

Lactate clearance was calculated by the equation:  $[(\text{lactate}_{\text{initial}} - \text{lactate}_{\text{follow-up}}) / \text{lactate}_{\text{initial}}] * 100\%$ . Lactate<sub>initial</sub> was defined as the baseline arterial sample, and Lactate<sub>follow-up</sub> was the measurement at 15mins, 45 mins, rewarming, immediately after termination of CPB, 24hrs and 48 hours after lactate<sub>initial</sub>. Lactate clearance was taken as being a deficit of at least 10%. [7,8]

## RESULTS:

One hundred patients (52 males and 48 females) posted for elective cardiac surgery under cardiopulmonary bypass were included in this prospective study from February 2018 to January 2019. There were 13, 30, 36 and 13 patients in NYHA 1, 2, 3 and 4 respectively [Table 1]. Five patients in NYHA 3 and 3 patients in NYHA 4 were excluded from the study as they could not be weaned off bypass. Average age and weight of the patients was 50.4 ±13.27 years and 62.38 ± 6.30 Kgs respectively. [Table 2 and 3] Mitral valve replacement (n=35) was the most commonly performed procedure followed by coronary artery bypass grafting (n=23). [Table 4]

All four NYHA groups were comparable in terms of baseline lactate levels (P value

0.096). [Table 5, Figure 1] Both Tukey HSD (Assuming equal variances) and Tamhane (Assuming unequal variances) post hoc tests revealed significant differences between all four groups in terms of mean lactate levels during and after CPB. Higher mean levels of lactate were seen in NYHA group 4 compared to other three groups during rewarming, termination and post operatively (24 and 48 hours). [Figure 2 and 3]

One way ANOVA with Turkey Kramer post hoc test for pairwise comparison was done to compare the four groups at different time points (Baseline, 15 minutes and 45 minutes after CPB, rewarming, termination, 24 hours and 48 hours post operatively). Fifteen minutes after CPB initiation, the NYHA 3 group was significantly different from both NYHA 1 and NYHA 2. After 45 minutes of CPB and during rewarming, NYHA 4 group varied significantly from NYHA 1, 2 and 3. During termination of CPB as well as post operative (both 24 hours and 48 hours), all four NYHA groups varied significantly from each other. [Table 6]

In terms of mean lactate clearance, Tukey HSD (Assuming equal variances) post hoc test showed that both NYHA 3 and NYHA 4 were significantly different from each other as well as NYHA group 2. Tamhane (Assuming unequal variances) post hoc test also showed that lactate clearance in both NYHA 3 and NYHA 4 were significantly different from each other as well as NYHA group 2. Additionally, lactate clearance in NYHA group 1 was comparable to NYHA group 2. [Table 7] Analysis of Variance (ANOVA) for individual time points (Baseline, 15 minutes and 45 minutes after CPB, rewarming, termination, 24 hours and 48 hours post operatively) showed no difference in lactate clearance 15 minutes after CPB initiation between all four groups. At 45 minutes after CPB initiation, lactate clearance all four groups were significantly different from each other. During rewarming lactate clearance was significantly slower in NYHA group 4 compared to NYHA 1, 2 and 3. Intra group comparison at termination showed significant differences between NYHA group 4 and NYHA group 3. Significant difference was also seen between NYHA group 3 and NYHA group 2 as well as between NYHA group 4 and NYHA group 1. At 24 hours postoperatively, NYHA 2 varied significantly from NYHA 1, 3 and 4. After 48 hours, a significant difference in lactate clearance was seen between NYHA 1 and 2. [Table 6] The mean duration of inotropic support and mechanical ventilation is varied significantly between the groups. As expected, both the duration of inotropic support as well as mechanical ventilation was more in NYHA 3 and 4. [Table 8] The length of ICU stay as well as hospital stay was significantly prolonged in NYHA 3 and 4.

**Table 1: Comparability check between the four NYHA groups**

**Gender**

NYHA	Female	(%)	Male	(%)	n	Significance <sup>1</sup>
1	8	61.54%	5	38.46%	13	P=0.0897*
2	12	40.00%	18	60.00%	30	
3	21	58.33%	15	41.67%	36	
4	3	23.08%	10	76.92%	13	
<b>Total</b>	<b>44</b>	<b>47.83%</b>	<b>48</b>	<b>52.17%</b>	<b>92</b>	<b>P=0.6772*</b>

\*Not significant (Gender distribution is comparable)

<sup>1</sup>Using Chi-square test & Test for one proportion respectively

**Table 2: Age**

NYHA	Mean (yrs)	Std. deviation	n	Significance <sup>1</sup>
1	54.077	11.543	13	P=0.584*
2	48.867	10.881	30	
3	49.500	15.148	36	
4	52.769	14.771	13	
<b>Total</b>	<b>50.402</b>	<b>13.272</b>	<b>92</b>	

\*Not significant (Age distribution is comparable)

<sup>1</sup>Using ANOVA test

**Table 3: Weight**

NYHA	Mean (kg)	Std. deviation	n	Significance <sup>1</sup>
1	60.385	5.650	13	P=0.041*
2	61.267	5.426	30	
3	62.500	6.465	36	
4	66.615	7.042	13	
<b>Total</b>	<b>62.380</b>	<b>6.305</b>	<b>92</b>	

\*Significant (Significantly heavier subjects were seen in NYHA 4 when compared to NYHA 2 group)

<sup>1</sup>Using ANOVA test

**Table 4: Types of Surgery**

Surgery	Number of patients
CABG	23
MVR	35
AVR	10
DVR	12
ASD Closure	7
VSD Closure	8
Redo MVR	2
TOF Repair	1
Atrial tumour	2

**Table 5: Baseline lactate levels of subjects in four NYHA groups**

NYHA	Mean (mmol/l)	Std. deviation	N	Significance <sup>1</sup>
1	2.3154	0.4625	13	P=0.096*
2	2.4133	0.5455	30	
3	2.6297	0.3509	36	
4	2.5577	0.4254	13	

\*Not significant (baseline lactate levels are comparable)

<sup>1</sup>Using ANOVA test

**Table 6: Comparison of lactate levels between four NYHA groups**

**1. Repeated measures ANOVA**

a. Tests of within-subjects effects

Time factor (p<0.0001)

Time factor \* NYHA (p<0.0001)

b. Tests of between-subjects effects

NYHA ( p<0.0001)

c. Post-hoc tests

**Tukey HSD**

	Mean difference	Std. Error	Significance
NYHA 1 Vs NYHA 2	0.5829	0.10889	P<0.0001*
NYHA 1 Vs NYHA 3	-0.4587	0.10611	P=0.0002*
NYHA 1 Vs NYHA 4	-1.1857	0.12863	P<0.0001*
NYHA 2 Vs NYHA 3	-1.0417	0.08107	P<0.0001*
NYHA 2 Vs NYHA 4	-1.7686	0.10889	P<0.0001*
NYHA 3 Vs NYHA 4	-0.7270	0.10611	P<0.0001*

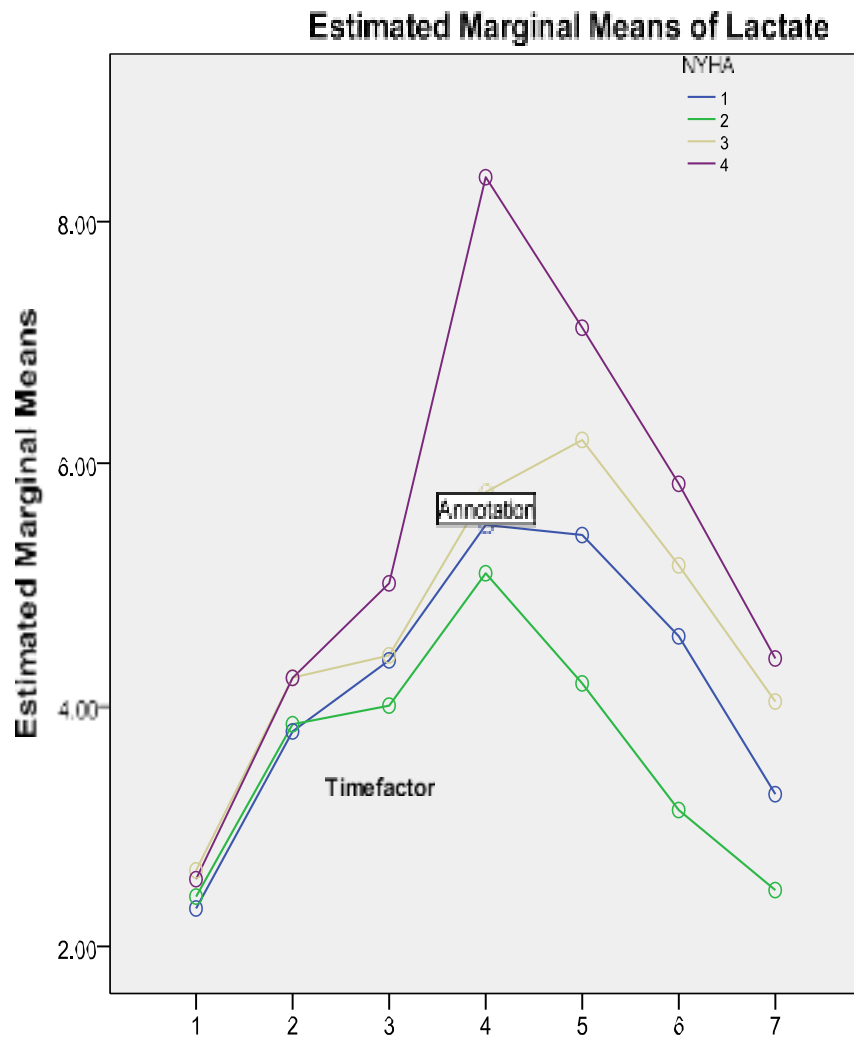
\*Significant

**Tamhane**

	Mean difference	Std. Error	Significance
NYHA 1 Vs NYHA 2	0.5829	0.11016	P=0.0003*
NYHA 1 Vs NYHA 3	-0.4587	0.11475	P=0.004*
NYHA 1 Vs NYHA 4	-1.1857	0.13263	P<0.0001*
NYHA 2 Vs NYHA 3	-1.0417	0.07824	P<0.0001*
NYHA 2 Vs NYHA 4	-1.7686	0.10269	P<0.0001*
NYHA 3 Vs NYHA 4	-0.7270	0.10759	P<0.0001*

\*Significant

Figure 2: Line diagram showing the estimated marginal means of lactate levels of four NYHA groups over different time points (Time \* NYHA)



<b>Time factor</b>	<b>NYHA</b>	<b>Mean</b>	<b>Std. Dev</b>	<b>N</b>	<b>Significance<sup>1</sup></b>	<b>Significantly different NYHA pairs<sup>2</sup></b>
<b>Baseline</b>	1	2.3154	.46249	13	P=0.096	N/A
	2	2.4133	.54549	30		
	3	2.6297	.35088	36		
	4	2.5577	.42540	13		
	Total	2.5046	.45684	92		
<b>Min_15</b>	1	3.7815	.54963	13	P=0.003	3 vs 1, 3 vs 2
	2	3.8407	.55854	30		
	3	4.2267	.41759	36		
	4	4.2238	.51684	13		
	Total	4.0375	.53179	92		
<b>Min_45</b>	1	4.3700	.62252	13	P<0.001	4 vs 1, 4 vs 2, 4 vs 3, 3 vs 2
	2	3.9950	.43990	30		
	3	4.4103	.43257	36		
	4	5.0069	.98253	13		
	Total	4.3535	.64554	92		
<b>Rewarm</b>	1	5.4908	.43893	13	P<0.001	4 vs 1, 4 vs 2, 4 vs 3, 3 vs 2
	2	5.0910	.48136	30		
	3	5.7628	.82942	36		
	4	8.3692	.48198	13		
	Total	5.8736	1.22960	92		
<b>Termin</b>	1	5.4077	.49238	13	P<0.001	All pairs are significantly different from each other
	2	4.1787	.29910	30		
	3	6.1944	.67483	36		
	4	7.1231	.62471	13		
	Total	5.5572	1.19487	92		
<b>Hr_24</b>	1	4.5692	.69208	13	P<0.001	All pairs are significantly different from each other
	2	3.1300	.27057	30		
	3	5.1556	.47476	36		
	4	5.8308	.31724	13		



2. Analysis of variance(ANOVA) test – for individual time factors

Descriptive Statistics ( Time factor \* NYHA)

Tamhane

	Mean difference	Std. Error	Significance
NYHA 1 Vs NYHA 2	-5.8970	2.78340	P=0.258 <sup>#</sup>
NYHA 1 Vs NYHA 3	0.0548	2.63400	P=1.000 <sup>#</sup>
NYHA 1 Vs NYHA 4	5.4239	2.78941	P=0.346 <sup>#</sup>
NYHA 2 Vs NYHA 3	5.9518	1.43880	P=0.001 <sup>*</sup>
NYHA 2 Vs NYHA 4	11.3210	1.70675	P<0.0001 <sup>*</sup>
NYHA 3 Vs NYHA 4	5.3691	1.45040	P=0.007 <sup>*</sup>

\*Significant; <sup>#</sup>Not significant

Figure 4: Line diagram showing the estimated marginal means of lactate clearance rate of four NYHA groups over different time points (Time \* NYHA)

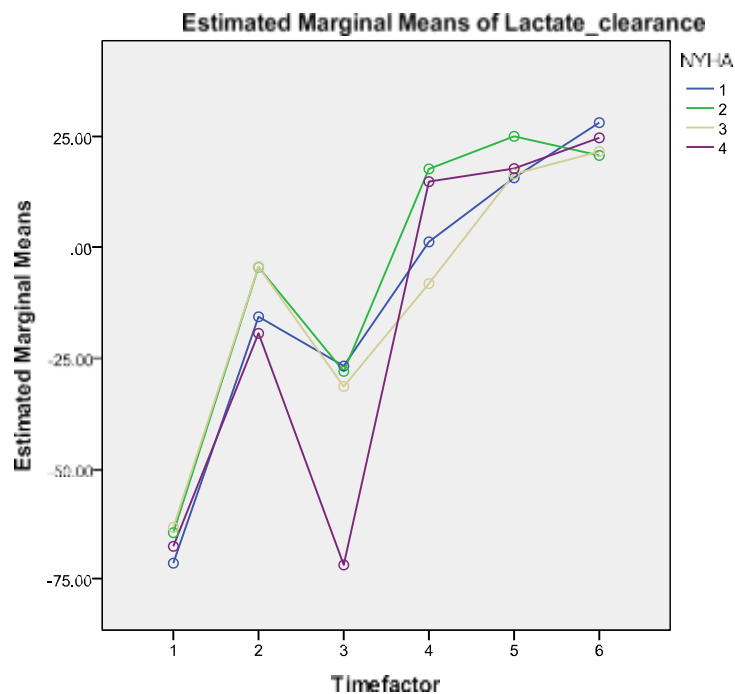


Figure 5: Clustered bar diagram showing the changes in lactate clearance rate between four NYHA groups at different time points

Table 8: Duration of inotropic support and mechanical ventilation

NYHA Class	Mean duration of inotropic support(hrs)	Mean duration of mechanical ventilation(hrs)
1	14± 1.52	6.38± 1.13
2	15± 1.23	6.55± 1.17
3	16.27± 1.99	8.95±1.83
4	18.69± 2.09	14.38±2.9
P value	< 0.0001 <sup>*</sup>	<0.0001 <sup>*</sup>

**Table 9: Post operative morbidity**

Complication	NYHA 1(n=13)	NYHA 2(n=30)	NYHA 3(n=36)	NYHA 4(n=13)	P value
Renal dysfunction	0	2	4	2	NS
GI bleed	0	0	1	1	NS
Paralytic ileus	0	0	1	3	<0.05*
Infection	1	2	2	1	NS
Length of ICU stay(days)	2.53±0.66	3.3±0.95	5.02±1.1	6.53±1.8	< 0.0001*
Length of hospital stay(days)	5.61±0.86	5.9±0.95	8.13±0.93	11.61±1.98	<0.0001*

## DISCUSSION:

Cardiopulmonary bypass (CPB) is a form of extracorporeal circulation whose function is circulatory and respiratory support along with temperature management to facilitate surgery on the heart and great vessels. The normal physiologic functions of the heart and lungs, including circulation of blood, oxygenation, and ventilation, are temporarily taken over by the CPB machine. The procedure results in the deterioration of normal vascular physiologic fragments of blood cells, tubing, and plaques. Tissue perfusion monitoring during CPB is challenging because, as well as the release of a variety of debris into the bloodstream, including mixed venous oxygen saturation (SvO<sub>2</sub>) cannot be measured during CPB, and pulse oximetry does not function correctly in a hypothermic state. Therefore, conventional methods like mean blood pressure (MAP) measurement, blood gas analysis, and intake/output often fail to detect occult hypoperfusion. Serum lactate sampling can be utilized to detect occult hypoperfusion in these cases. [11] Both increased production and decreased clearance of lactate lead to increased lactate in blood. Tissue hypoperfusion, release of catecholamine from gluconeogenesis and glycolysis, systemic inflammatory reaction, and lactate load from blood transfusion all contribute to lactate production. Hypothermia attenuated pyruvate metabolism, variable hepatic or renal functions and anesthetics affect lactate clearance during cardiac surgery. [12]

In our study we tried to observe the changes in blood lactate levels during and after CPB in patients of different preoperative clinical conditions, according to the NYHA classification. There was an increase in mean lactate levels in NYHA 4 patients during rewarming, termination and postoperatively. Shinde et al (2005) also found statistically significant increase in the lactate levels in NYHA Class IV patients. [13] Similar observations were also made by Munoz et al. (2000) and Noval-Padillo et al. (2011) with the largest increment in lactate level occurring during cardiopulmonary bypass. [1] While surgery and anesthesia per se do not seem to alter lactate metabolism, CPB significantly decreased lactate clearance, this effect being possibly related to a mild liver dysfunction even in uncomplicated elective surgery. [14] The Effective use of serial lactate measurements have been used in predicting morbidity and mortality in sepsis, septic shock, trauma and cardiac arrest patients in several studies before. Prolongation of lactate clearance has been associated with increase in mortality in all these patients. [15,16,17,18]

In our study, lactate clearance was significantly slower in NYHA 4 compared to

the other classes in the rewarming phase, possibly due to suboptimal hepatic status in this class of patients.

The mean duration of mechanical ventilation and inotropic support was higher in NYHA class 3 and

4. Similar findings were noted by Shinde et al. (2005) with statistically significant increase in the average duration of mechanical ventilation and inotropic support in patients of increased cardiac surgical complexity compared to less complex groups. [13] Our study found higher classes of NYHA (Class 3 and 4) to be associated with increased length of ICU and hospital stay. Similar results were also observed by Algarni et al. (2020) while comparing 305 consecutive adult patients who underwent cardiac surgeries. [19]

### CONCLUSION:

There is a definite association between higher mean lactate levels and lactate clearance with a higher NYHA class during the perioperative period. Increased mean lactate levels and lactate clearance is also associated with increased duration of mechanical ventilation and inotropic support. Higher perioperative lactate levels also prolong the ICU and hospital stay in higher NYHA classes.

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