Original Article

Changes in myocardial lactate, pyruvate and lactate-pyruvate ratio during cardiopulmonary bypass for elective adult cardiac surgery: Early indicator of morbidity

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Abstract

Background: Myocardial lactate assays have been established as a standard method to compare various myocardial protection strategies. This study was designed to test whether coronary sinus (CS) lactates, pyruvate and lactate-pyruvate (LP) ratio correlates with myocardial dysfunction and predict postoperative outcomes.

Materials and Methods: This prospective observational study was conducted on 40 adult patients undergoing elective cardiac surgery with the aid of cardiopulmonary bypass (CPB). CS blood sampling was done for estimation of myocardial lactate (ML), pyruvate (MP) and lactate-pyruvate ratio (MLPR) namely: pre-CPB (T_1), after removal of aortic cross clamp (T_2) and 30 minutes post-CPB (T_3).

Results: Baseline myocardial LPR strongly correlated with Troponin-I at T1 (σ: 0.6). Patients were sub grouped according to the median value of myocardial lactate (2.9) at baseline T1 into low myocardial lactate (LML) group, mean (2.39 ± 0.4 mmol/l), n = 19 and a high myocardial lactate (HML) group, mean (3.65 ± 0.9 mmol/l), n = 21. A significant increase in PL, ML, MLPR and TropI occurred in both groups as compared to baseline. Patients in HML group had significant longer period of ICU stay. Patients with higher inotrope score had significantly higher ML (T2, T3). ML with a baseline value of 2.9 mmol/l had 70.83% sensitivity and 62.5% specificity (ROC area: 0.7109 Std error: 0.09) while myocardial pyruvate with a baseline value of 0.07 mmol/l has 79.17% sensitivity and 68.75% specificity (ROC area: 0.7852, Std error: 0.0765) for predicting inotrope requirement after CPB.

Conclusion: CS lactate, pyruvate and LP ratio correlate with myocardial function and can predict postoperative outcome.

Key words: Coronary sinus, lactate, lactate-pyruvate ratio, pyruvate

Introduction

Myocardial ischemia is a metabolic phenomenon that occurs in patients undergoing open heart surgery like coronary artery bypass grafting (CAPB), valvular heart surgery, vascular surgeries etc. due to stress imposed during cardiopulmonary bypass (CPB), obligatory interruption of coronary blood flow during aortic cross clamp and reperfusion after aortic cross clamp release. These effects manifest as hemodynamic instability, arrhythmias, greater use of inotropes, difficulty in weaning from CPB, use of intra-aortic balloon pump (IABP)/ventricular assist devices (VADs). The oxygen debt imposed during CPB heralds the onset of postoperative complications in the form of increased need of inotropes, prolonged mechanical ventilation, renal/hepatic dysfunction, prolonged intensive care unit (ICU) stay and adds to the morbidity and mortality of patients.

Hyperlactatemia occurs in aerobic conditions where increased glycolysis occurs with stimulation by endo/exogenous catecholamines.[1] In the absence of other markers of oxygen debt like tissue oxygen delivery index (DO_2I), tissue oxygen extraction ratio (VO_2) or hemodynamic instability serum hyperlactatemia alone has not been correlated with adverse postoperative outcomes.[2] So diagnostic and prognostic implication of serum hyperlactataemia is not always straightforward and it is not a sensitive marker of myocardial ischemia.

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Access this article online	
Quick Response Code:	Website: www.joacp.org
	DOI: 10.4103/0970-9185.81819

Once anerobic conditions prevail, pyruvate a substrate for oxidative phosphorylation cannot be utilized, its level increases and it is diverted to the formation of lactate. Normal lactate to pyruvate ratio (LP ratio) is 10:1, which also occurs in cases of increased metabolism (catecholamine induced) but increases in LP ratio (>10:1) occur in conditions of tissue hypoxia alone.

There is paucity of data in literature about increased serum pyruvate or LP ratio as a marker of redox state of myocardium. Few studies have found out that serum LP ratio is an excellent indicator of adequacy of cellular oxygenation, has shown good correlation with postoperative outcome.[3,4]

Measuring metabolic substrates from interstitium (by microdialysis) or venous outflow (great cardiac vein) of the heart increases reliability and temporal resolution of monitoring myocardial ischemia.[5] Heringlake *et al.* demonstrated a relationship between myocardial lactate (ML) concentration, right ventricular ejection fraction (RVEF) and stroke volume index (SVI).[6]

We hypothesized that ML, pyruvate and LP ratio can be used as markers of myocardial dysfunction during and after CPB and undertook this study to evaluate the correlation of ML, pyruvate and LP ratio with hemodynamic parameters and perioperative outcomes in patients undergoing elective adult cardiac surgery with CPB.

Materials and Methods

This prospective clinical observational study was conducted at cardiothoracic centre (All India Instititute of Medical Sciences, New Delhi) after obtaining approval of hospital ethics committee and informed consent from the patients. Forty consecutive adult patients of either sex undergoing elective CABG or valve surgery with the aid of CPB were included in this study. Patients with unstable angina, recent myocardial infarction (MI), diabetes mellitus, renal, hepatic or neurological dysfunction, coagulopathy, LV aneurysm, preoperative congestive heart failure (CHF), left ventricular ejection fraction <45%, preoperative hemodynamically unstable arrhythmias and those undergoing concomitant CABG and valvular surgery were excluded from the study. All surgeries were performed by the same anesthesia, surgery and perfusion team.

Anesthesia and CPB

All patients were premedicated with morphine 0.1 mg/kg and promethazine 0.5 mg/kg intramuscularly 30-45 minutes prior to induction of anesthesia. Anesthesia was induced with intravenous thiopentone (3-5 $mg.kg^{-1}$), fentanyl (2-5 $\mu g.kg^{-1}$), and midazolam (1-2 mg). Endotracheal intubation was facilitated with vecuronium (0.8-1.0 $mg.kg^{-1}$). Anesthesia was maintained with oxygen in air (50%), isoflurane and supplemental doses of intravenous fentanyl, midazolam and vecuronium. The lungs were mechanically ventilated to maintain a pH of 7.35-7.45 and normocapnia.

Radial artery line was passed for invasive blood pressure monitoring with Vigileo monitor (version 1.10)[7] and Flotrac sensor (Edward Lifesciences, Irvine, CA, USA) for determination of cardiac output (CO), cardiac index (CI), stroke volume index (SVI), oxygen delivery index (DO_2I), and systemic vascular resistant index (SVRI). The right internal jugular vein was cannulated with 8.5 Fr triple lumen central venous catheter (Arrow International Inc, PA, USA) for central venous pressure (CVP) measurement, fluid and vasopressor/inotrope administration. In addition five lead ECG, pulse oximetry, nasopharyngeal/rectal temperature and urine output were monitored.

Volume replacement was done with Ringer's lactate or hydroxyl ethyl starch (Voluven 6% Fresenius Kabi, Germany) as appropriate to maintain a CVP of 8-12 mmHg. After systemic heparinisation with intravenous heparin 400 IU kg^{-1}, to achieve an activated clotting time (ACT) of >480 sec, aortic and atrial cannulations were done.

A retrograde cardioplegia cannula with self-inflating balloon (RC014, Edward Life sciences) was inserted by the surgeon through right atrium using a blind technique before going on bypass solely for the purpose of the study.[8,9] Its position was confirmed by observing distension of the posterior interventricular vein, maintenance of coronary sinus (CS) pressure, and palpation of the CS cannula. CPB and surgical techniques were standardized and did not change during the study period.

All patients underwent cardiac surgery with a standard CPB protocol under moderate hypothermia at 30-32°C. Pump flow rates and perfusion pressures were maintained at 2.2-2.6 $L/min/m^2$ and 50-80 mmHg, respectively. α-stat strategy was used for blood gas management and blood sugar was maintained between 100 and 200 mg/dl during CPB. A hematocrit ≥ 25% and mixed venous oxygen saturation of >75% was maintained as well. Myocardial protection was achieved with intermittent antegrade cold blood cardioplegia (St Thomas I solution, 4:1), repeated in 20-25-min intervals.

Blood samples were collected from CS by the surgeon for ML, myocardial pyruvate (MP) and Troponin I (Trop I) estimation. CS blood sample (5 ml) for estimation of myocardial pyruvate and Trop I was centrifuged within 20 minutes and plasma was stored at -20°C until analysis.

ML and plasma lactate were determined by blood gas analysis of the respective samples.

Inotropes and vasodilators (dopamine, dobutamine, adrenaline and nitroglycerine) were used as required to maintain hemodynamics. Intravenous adrenaline was started if SBP remained <70 mmHg and CI < 2 $l.min^{-1}.m^{-2}$ with dopamine and dobutamine each at a dose of 10 $\mu g\, kg^{-1}\, min^{-1}$. IABP was inserted if poor hemodynamics along with ECG changes of ischemia, arrhythmia or metabolic acidosis persisted despite adrenaline. Patients were weaned from CPB at a nasopharyngeal temperature of 36°C, CI > 2.5 l. min^{-1} m^{-2}, SBP > 90 mmHg or MAP > 70 mmHg, and if no metabolic acidosis was present.

Sampling methods

Blood samples were taken from CS and arterial line at predetermined times. These time points were as follows:

T_1: Soon after cannulation, before institution of CPB (pre-CPB)
T_2: On removal of aortic cross-clamp (post-AoXCl)
T_3: 30 minutes after completion of CPB (post-CPB)

Hemodynamic parameters

Heart rate (HR), mean arterial pressure (MAP), CVP, CO, CI, SVI, DO_2I and SVRI were recorded following anesthetic induction (t1), pre-CPB (t2), immediate post-CPB (t3) and 30 min after bypass (t4). Hemodynamic parameters were recorded at the same time as the samples were taken.

Measurements

ML, plasma lactate and blood gas analysis was done with commercial gas analyzer (ABL 835 Flex, radiometer Copenhegen, Denmark). Pyruvate estimation was done by ELISA method, using Pyruvate Assay Kit (Biovision Research Product, CA USA). Trop I level was estimated using Immolite 1000 Troponin I analyzer (Diagnostic product corporation, LA, USA).

Myocardial lactate – pyruvate ratio (MLPR) was calculated as:
MLPR = myocardial lactate/myocardial pyruvate.

The intraoperative variables recorded included CPB time and aortic cross clamp time (AOXCt). The postoperative variables observed included post-CPB need for inotropes, duration of mechanical ventilation, inotrope usage and ICU stay.

Statistical analysis

The sample size was calculated using Stata-9 software with $\alpha = 0.05$ establishing the power of study as 85. Statistical analysis was performed using SPSS version-15 software. Data were checked for normality before statistical analysis. Continuous variables were expressed as mean ± SD or median (range) according to normality, and categorical variables were presented as either absolute numbers or percentage. Spearman sign - rank test was applied to see correlation between CS lactate, pyruvate and LPR and perioperative variables. Receiver operating characteristic (ROC) curves were constructed to compare the performance of CS lactate, pyruvate, LP ratio and determine appropriate cutoff value of the markers for myocardial dysfunction. Normally distributed continuous variables were compared using the unpaired Student's *t*-test, whereas the Mann-Whitney *U*-test was used to compare non-normally distributed data. Categorical variables were analyzed using χ^2 test. One-way analysis of variance (ANOVA) for repeated measures with posthoc Bonferroni correction was used for intragroup comparison. Statistical significance was set at *P*-value < 0.05.

Results

Patients were sub grouped according to the median value of ML (2.9) at baseline T_1 into low myocardial lactate (LML) group, mean (2.39 ± 0.4 mmol/l), $n = 19$ and high myocardial lactate (HML) group, mean (3.65 ± 0.9 mmol/l), $n = 21$, respectively. Patient characteristics were comparable in both LML and HML groups [Table 1]. CPB time, AOXCt, inotope score, duration of mechanical ventilation and inotrope usage were similar in both the groups. The length of stay in ICU was significantly less in LML group.

The baseline hemodynamic parameters (postinduction; t1) were comparable between both the groups. Post-CPB (t4), CVP was significantly higher in HML group [Table 2]. Also, in HML group, at t4 (30 min post-CPB) there was a significant increase in HR, CI and SVI, and a significant decrease in MAP and SVRI as compared to T1 values.

ML and PL were significantly higher in the HML group at T_1, T_2 and T_3 [Table 3]. There was no difference in myocardial pyruvate (MP), MLPR and TropI in both the groups. A statistically significant increase in PL, ML, MLPR and TropI in both groups was observed at T2 as compared to baseline (T1). At T3, ML significantly decreased, in HML group, in comparison to T2 whereas PL and TropI increased. In LML group PL decreased at T3, and ML, MLPR and TropI increased.

Patients with longer CPB duration (>60 min) had significantly higher PL levels at T2 (immediate post-CPB) and T3

(30 min post-CPB) as compared to those with CPB < 60 min [Table 4]. MLPR was higher at T_1 and T_3 and there was a prolonged duration of inotrope usage (in ICU) in patients with CPB duration >60 min [Table 5].

Patients with an inotrope score of 2 had significantly longer median CPB duration, higher baseline CVP (t1), higher PL level (T_2, T_3), ML (T_2, T_3), significantly longer duration of mechanical ventilation, inotrope administration and ICU stay as compared to patients with inotrope score of 1.

On receiver operator characteristic curve a baseline value (T1) of 2.9 mmol/l of ML was found to have a sensitivity of 70.83% and a specificity of 62.5% for predicting inotrope requirement. A value of 3 mmol/l raised the specificity to 66.67%. (ROC area: 0.7109 std error: 0.09) [Figure 1a]. Similarly, a baseline value (T1) of 0.07 mmol/l of myocardial pyruvate had a 79.17% sensitivity and 68.75% specificity. An increase in value to 0.09 mmol/l raised its specificity to 81.25% but decreased sensitivity to 58.33% for predicting inotrope requirement. (ROC area: 0.7852, std error: 0.0765.) [Figure 1b].

Discussion

Evaluation of myocardial metabolism quantifies the degree of physiologic impairment at various stages of cardiac operations e.g., on initiation of CPB, aortic cross-clamping and reperfusion.[10] Clinically applicable methods for metabolic analyses include myocardial tissue assays, myocardial markers, intramyocardial gas tensions or pH and direct cannulation for evaluation of CS metabolites to measure coronary blood flow and analyze substrate use.[11] In order to develop strategies against perioperative infarction or ischemia-reperfusion injury, we need to study and describe the metabolism in regional myocardial ischemia and its global circulatory consequences, concomitantly.

Type B lactic acidosis developing in patients undergoing cardiac surgery, with the aid of CPB, is related to various factors eg high NYHA class, duration of CPB, depth of intraoperative hypothermia, episode of hypotension at commencement of CPB, endotoxemia, etc.[2,12-15] The significant increase in lactate level during perioperative period is directly proportional to the duration of mechanical ventilation, requirement for vasopressors and impending major adverse events.[13,14,16] In the present study we found that longer period of CPB > 60 min was associated with significantly higher PL levels, without significant difference

Table 1: Patient characteristics, post-CPB need for inotropes (inotrope score) and postoperative outcomes in patients undergoing elective adult cardiac surgery under cardiopulmonary bypass

Groups	LML (n = 19)	HML (n = 21)	*P*-value
Age (yr)	39.2 ± 12.5	40.6 ± 14.7	ns
Sex (m/f)	14/5	14/7	ns
Weight (kg)	61.1 ± 13.6	56.9 ± 13.1	ns
BSA (m^2)	1.66 ± 0.2	1.52 ± 0.2	ns
EF (%)	56.3 ± 6.63	57.9 ± 4.9	ns
Surgery (CABG/valves)	9/10	13/8	ns
AoXCl (min)	52(30-204)	51(28-104)	ns
CPB (min)	81(59-282)	102(59-230)	ns
Inot score (1: 2)	8/11	8/13	ns
Mech Vent (hours)	16(7-24)	18(8-51)	ns
Inot duration(hours)	30(0-192)	36(0-144)	ns
ICU stay (days)	3.79 ± 1.23	4.86 ± 1.54	0.042

Continuous variables are expressed as mean ± SD or median (range) according to normalcy and categorical variables are presented as either absolute numbers or percentage. Normally distributed continuous variables are compared using the unpaired Student's t-test, whereas the Mann-Whitney U-test is used to compare non-normally distributed data. Categorical variables are analysed using χ^2) test. LML = Low myocardial lactate, HML = High myocardial lactate, BSA = body surface area, EF = ejection fraction, CABG = coronary artery bypass graft, AoXCl = aortic cross clamp time, CPB = cardiopulmonary bypass time, Inot score = inotropic score, Mech Vent = duration of mechanical ventilation, Inot duration = duration of inotropic usage, ICU stay = duration of intensive care unit stay P-value < 0.05 statistically significant.*
Inotrope Score: score 1 = (dopamine + /- dobutamine + nitroglycerine), score2 = (dopamine + dobutamine+/ - NTG + Adrenaline)

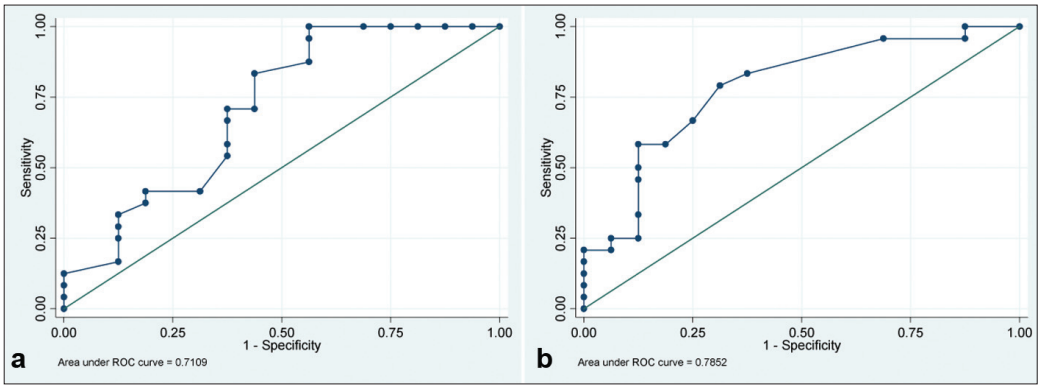

Figure 1: Receiver operator characteristic curve showing sensitivity and (1-specificity) of precardiopulmonary bypass coronary sinus myocardial lactate and pyruvate for inotropic requirement after ca rdiopulmonary bypass. (a) ROC area: 0.7109 (ML); Std error: 0.09 (b) ROC area: 0.7852 (MP); Std error: 0.0765

in tissue oxygen delivery index. This increased lactate levels was associated with significantly longer period of ICU stay. Longer period of bypass > 60 min was associated with rising MLPR from baseline to post-CPB although ML value decreased from peak level after AoXCl release to post-CPB, which indicates that MLPR is better indicator of residual ischemia than ML.[4]

The increasing trend in myocardial TropI in both groups was associated with increasing levels of ML, which shows that it is a more specific marker for myocardial injury and subtle myocardial injury occurs in otherwise uneventful cardiac surgery under CPB. Raman *et al.* observed a positive correlation between CS cTnI and CS lactate in patients undergoing primary CABG under CPB.[17] T W Koh *et al.* found that CS cTnT concentration increased earlier and were greater than arterial concentration during CABG both on beating heart and surgery on CPB and suggested that CS sampling method would be a more sensitive method of intraoperative assessment of myocardial injury.[18]

The longer period of ICU stay in patients with higher baseline ML indicates that presurgery higher myocardial levels may predict postoperative outcome. Rao *et al.* found that persistent ML release during reperfusion occurs in a significant proportion of low-risk patients undergoing isolated CABG and is a predictor of postoperative low cardiac output syndrome.[19]

High CVP persisting post-CPB in HML group shows

Table 2: The time course of hemodynamics in patients undergoing adult cardiac surgery under cardiopulmonary bypass

Hemodynamics		t1	t2	t3	t4
HR	LML	89.6 ± 30.9	91.3 ± 22.8	98.2 ± 16.9	97.4 ± 18
	HML	85.7 ± 24	82.6 ± 19.8	99.6 ± 8.6 §	104.5 ± 7.1 §
MAP	LML	81.5 ± 16.4	77.4 ± 14.3	69.7 ± 16.6	70.2 ± 12.6
	HML	85.3 ± 18.7	72.9 ± 14.8§	69.3 ± 14.5§	74.1 ± 12.5
CVP	LML	10(0-33)	8(1-18)	7(1-15)	7.5(0-16)
	HML	12(0-23)	10(1-21)	10(5-17)	14(2-28)*
CI	LML	2.8 ± 1.14	2.9 ± 0.9	3.3 ± 1.2	3.3 ± 0.9
	HML	3 ± 1.12	2.57 ± 0.8	3.35 ± 1.3	3.76 ± 1.1§
SVI	LML	38.5 ± 13.9	40.1 ± 22.2	33.6 ± 5.2	33 ± 5.8
	HML	36.5 ± 10.5	31.8 ± 11.3	33.2 ± 8.6 §	36.3 ± 10.8§
DO2I	LML	485.9 ± 183.9	477.7 ± 140.4	427.5 ± 174.7	484.4 ± 189.5
	HML	459.3 ± 128.8	406.2 ± 128.7	438.8 ± 146.6	478 ± 93.4
SVRI	LML	2071 ± 790.8	2176 ± 1054.6	1260.3 ±268.4 §	1390.9 ± 336.8 §
	HML	2301.7 ± 887.5	2128.2 ±966.6	1479.2 ±489.6 §	1418.5 ± 387.9§

*Continuous variables were expressed as mean ± SD or median (range) according to normalcy. Normally distributed continuous variables were compared using the unpaired Student's t-test, whereas the Mann-Whitney U-test was used to compare non-normally distributed data. One-way analysis of variance (ANOVA) for repeated measures with posthoc Bonferroni correction was used for intra group comparison. *P-value < 0.05 statistically significant. §P-value < 0.05 statistically significant. (intragroup); HR = Heart rate, MAP = Mean arterial pressure, CVP = Central venous pressure, CI= Cardiac index, SVI = Stroke volume index, DO2I = Oxygen delivery index, SVRI = Systemic vascular resistance index, LML = Low myocardial lactate, HML = High myocardial lactate, t1 = Postinduction, t2 = Pre-CPB, t3 = Immediate post-CPB, t4 = 30 min post-CPB*

Table 3: The time course of plasma lactate, myocardial lactate, pyruvate and lactate – pyruvate ratio, myocardial enzymes in patients undergoing adult cardiac surgery under cardiopulmonary bypass

Markers		T_1	T_2	T_3
PL	LML	2.49 ± 0.6	3.64 ± 1.25*§	3.37 ± 1.04*§
	HML	3.39 ± 1.03 *	4.63 ± 1.04*§	4.77 ± 1.2*§
ML	LML	2.39 ± 0.4	3.93 ± 1.2§	4.18 ± 1.2§
	HML	3.65 ± 0.9*	5.28 ± 1.27*§	4.76 ± 1.2*§
MP	LML	0.07(0.02 – 0.28)	0.07(0.03 – 0.34)	0.06(0.02 – 0.19)
	HML	0.08(0.03 – 0.58)	0.08(0.01 – 0.32)	0.08(0.01 – 0.24)
MLPR	LML	37.14(10 – 115)	58(12 – 103)§	60(32 – 127)§
	HML	51.6(5 – 120)	72.5(11 – 420)	62(14 – 600)
TROP – I	LML	0.21(0.08 – 3.2)	1.8(0.2 – 11.6)§	2.2(0.2 – 11.5)§
	HML	0.22 (0.17 – 0.35)	1.1(2 – 6.3)§	2.6(0.2 – 13.8)§

*Continuous variables were expressed as mean ± SD or median (range) according to normalcy. Normally distributed continuous variables were compared using the unpaired Student's t – test, whereas the Mann – Whitney U – test was used to compare non – normally distributed data. One – way analysis of variance (ANOVA) for repeated measures with posthoc Bonferroni correction was used for intra group comparison. *P – value < 0.05 statistically significant. §P – value < 0.05 statistically significant. (intragroup); PL = Plasma lactate, ML = Myocardial lactate, MP = Myocardial pyruvate, MLPR = Myocardial lactate pyruvate ratio, TROP – I = Troponin I, LML = Low myocardial lactate, HML = High myocardial lactate, T1 = pre – CPB, T2 = immediately post – CPB, T3 = 30 min post – CPB*

Table 4: Comparison of duration of CPB versus changes in myocardial lactate, pyruvate and lactate–pyruvate ratio

Dur of CPB	PL T_1	PL T_2	PL T_3	ML T_1	ML T_2	ML T_3	MP T_1	MP T_2	MP T_3
< 60 min	1.7(1–2.4)	3.65(3.1–4.2)	2.9 (2.8–3)	4.2 (2.8–5.5)	5.1(4–6)	4.8(3.5–6)	0.22(0.16–0.28)	0.2(0.06–0.34)	0.13(0.1–0.15)
> 60 min	3.1(1.2–5.9)	4.2(1.3–7.3)*	4 (1.2–6.8)*	2.9 (1.6–6.3)	4.5(2–9)	4.2(1.9–6.8)	0.07(0.02–0.07)†	0.08(0.01–0.32)	0.07(0.01–0.24)
MLPR T1	**MLPR T2**	**MLPR T3**	**DO2I t1**	**DO2I t2**	**DO2I t3**	**DO2I t4**	**Mech vent**	**Inot duration**	**ICU stay**
22.2 (10–34.3)	57.6 (12–103)	41.7 (23–60)	600 (450–751)	495 (391–599)	525(380–669)	525(380–669)	10.5(10–11)	12(0–24)	3(3–3)
40.7 (5–120)	59 (11–420)	62.11 (14–600)	427 (169–858)	453 (128–976)	391(236–985)	461(236–1025)	18(7–51)	36(0–192) *	4(2–12)

Continuous variables were expressed as median (range) according to normalcy. Mann–Whitney U–test was used to compare non–normally distributed data.

**P– value < 0.05 statistically significant.*

PL = Plasma lactate, ML = Myocardial lactate, MP = Myocardial pyruvate, MLPR = Myocardial lactate pyruvate ratio, DO2I = Oxygen delivery index, Mech Vent = Duration of mechanical ventilation, Inot duration = Duration of inotropic usage, ICU stay = Duration of intensive care unit stay, T1 = Pre–CPB, T2 = Immediately post–CPB, T3 = 30 min post–CPB, t1 = Postinduction, t3 =Immediate post–CPB, t4 = 30 min post–CPB

myocardial dysfunction while higher HR, CI, SVI in face of low MAP and SVRI may be because of increased inotrope use.[6] The higher baseline ML level in HML group may be expressive of tissue ischemia and may predict postoperative myocardial dysfunction as seen by significantly longer ICU stay and higher need for inotropes in that group. Patients who needed greater inotropic support had longer CPB time, higher baseline CVP, lower post-CPB MAP, SVI and CI and higher postaortic cross-clamp release and post-CPB plasma and ML levels, higher myocardial pyruvate and lower LP ratio at all three time points. This indicates that there was delay in crossover from anerobic to aerobic metabolism indicating poorer myocardial function pre-CPB which continued post-CPB despite use of higher inotropes. These patients also had longer duration of mechanical ventilation, inotropic usage and ICU stay.

ML production is a good and well-established marker of anerobic metabolism and correlates well to the degree of ischemia. Pyruvate levels show cyclic changes which are not synchronous to lactate levels.[20] The early increase in pyruvate levels at reperfusion could be due to wash-out of protons, favoring anerobic glycolysis resulting in transient pyruvate accumulation. In the later phase of reperfusion, the oxygen supply becomes high enough to allow mitochondrial metabolism, leading to consumption of pyruvate. During the short period following ischemia, pyruvate metabolism was diverted to lactate as evidenced by the increase in microdialysate lactate concentration.[20] In our study, we found that in patients with higher baseline ML, it increased till aortic cross clamp release and decreased 30 minutes after coming off CPB and was associated with no decrease in MP and MLPR post-CPB suggesting delayed return in aerobic metabolism of heart in this group of patients. Whereas in patients with lower baseline ML, there was gradual increase in ML and MLPR levels till 30 min post-CPB although the absolute values remained lower than the HML group and was associated with decrease in myocardial pyruvate level post-CPB suggesting return of aerobic metabolism with utilization of pyruvate. This suggests that MLPR can be utilized as a marker of aerobic metabolism.

Tissue lactate or MLPR have been found to be good markers of ischemic injury and may even correlate inversely with post-ischemic recovery.[21] Many studies in different clinical conditions have demonstrated that a rise in both serum as well as myocardial LP ratio is associated with organ dysfunction and has a better predictive value for postoperative outcomes as compared to lactate level.[4,3,22] Backstrom *et al.* demonstrated relatively larger increase of lactate and LP ratio in great cardiac vein than intramyocardially which rapidly and reliably detect local myocardial ischemia and they concluded that coronary

Table 5: Hemodynamics and baseline myocardial lactate, pyruvate and lactate–pyruvate ratio in cardiac surgery patients needing inotropes after cardiopulmonary bypass

Inotrope score	CPB	AoXCl	HR t1	HR t3	HR t4	MAP t1	MAP t3	MAP t4
1	72(59 – 144)	44.5(30 – 93)	78.5(51 – 126)	100(69 – 110)	100(64 – 110)	83.5(60 – 118)	74(40 – 100)	72(54 – 100)
2	102(61 – 282)*	53.5(28 – 204)	85(50 – 170)	100(82 – 140)	100(84 – 140)	79(52 – 120)	62(50 – 101)	72(47 – 87)
Inotrope score	**CVP t1**	**CVP t3**	**CVP t4**	**CI t1**	**CI t3**	**CI t4**		
1	9(0 – 16)	8(1 – 15)	7(2 – 15)	2.6(1.6 – 6.1)	3.1(2 – 7.1)	3.6(1.9 – 6.4)		
2	12(1 – 33)*	9(2 – 17)	8(0 – 28)	2.6(1.1 – 5.3)	3.2(1.2 – 5.5)	3.3(2.2 – 4.7)		
Inotrope score	**SVI t1**	**SVI t3**	**SVI t4**	**PL T1**	**PL T2**	**PL T3**		
1	38.5(29 – 80)	32(17 – 42)	37(21 – 58)	2.55(1 – 4.4)	3.8(1.3 – 5.3)	3.1(1.2 – 5.9)		
2	35(9 – 57)	35(16 – 53)	32(22 – 60)	3.15(1.7 – 5.9)	4.6(2.1 – 7.3)*	4.2(2.6 – 6.8)*		
Inotrope score	**ML T1**	**ML T2**	**ML T3**	**MP T1**	**MP T2**	**MP T3**		
1	3(1.6 – 5.5)	3.9(2 – 6)	4(1.9 – 6)	0.06(0.02 – 0.28)	0.06(0.01 – 0.34)	0.06(0.02 – 0.22)		
2	2.9(1.7 – 6.3)	5.2(2 – 9)*	4.7(2.7 – 6.8)*	0.08(0.03 – 0.58)	0.09(0.04 – 0.26)	0.08(0.01 – 0.24)		
Inotrope score	**MLPR T1**	**MLPR T2**	**MLPR T3**	**Mech Vent**	**Inot dur**	**ICU Stay**		
1	44.2(10 – 115)	60(12 – 420)	65.4(20 – 127)	10.5(8 – 18)	24(0 – 48)	3(2 – 4)		
2	37.8(5 – 120)	51.5(11 – 25)	56.4(14 – 600)	18(7 – 51)*	48(24 – 192)*	4(3 – 12)*		

Continuous variables were expressed as median (range) according to normalcy. Mann – Whitney U – test was used to compare non – normally distributed data.
** P – value < 0.05 statistically significant.*
PL = Plasma lactate, ML = Myocardial lactate, MP = Myocardial pyruvate, MLPR = Myocardial lactate pyruvate ratio, DO2I = Oxygen delivery index, Mech Vent = Duration of mechanical ventilation, Inot duration = Duration of inotropic usage, ICU stay = Duration of intensive care unit stay, T1 = pre – CPB, T2 = Immediately post – CPB, T3 = 30 min post – CPB, HR = Heart rate, MAP = Mean arterial pressure, CVP = Central venous pressure, CI= Cardiac index, SVI = Stroke volume index, t1 = Postinduction, t2 = pre – CPB, t3 = Immediate post – CPB, t4 = 30 min post – CPB

venous outflow sampling is superior to intramyocardial microdialysis. [5]

Rao *et al.* found that lactate release is a better marker of myocardial metabolism and a value of 0.4 mmol/l post-AoXCl release has 33% sensitivity and 86% specificity of predicting postoperative low cardiac output syndrome.[19] In our study, we found that pre-CPB ML value of 2.9 mmol/l has 70.83% sensitivity and 62.5% specificity (ROC area: 0.7109) of predicting inotropic requirement post-CPB. Pre-CPB myocardial pyruvate value of 0.07 mmol/l has 79.1% sensitivity and 68.75% specificity (ROC area: 0.7852) of predicting post-CPB inotropic requirement which is better than ML.

Limitations

Because of non-randomized method of patient selection the population studied was heterogenous. The sample size was probably not adequate to detect the subtle changes in myocardial pyruvate levels. We did not use pulmonary artery catheter or transesophageal echocardiography for monitoring which would have been more accurate in assessment of the hemodynamics and myocardial dysfunction. CS does not represent global changes in metabolism of heart. A more accurate sampling method from great cardiac vein or microdialysis would have been more appropriate. The wide time interval between sampling points probably could not show the real changes in ischemic myocardium as on line or frequent sampling could have done.

Conclusions

The sampling of CS blood via cannula in CS is a simple, cheap, easy technique and can be performed routinely. Myocardial markers like lactate, pyruvate and LP ratio may be effective in predicting postoperative outcomes e.g., need for inotropes, postoperative myocardial dysfunction, prolonged postoperative ventilation, ICU stay. Pre-CPB myocardial lactate value of 2.9 mmol/l and myocardial pyruvate value of 0.07 mmol/l can predict inotropic requirement post-CPB with good sensitivity and specificity.

References

1. Baker S, Cadogan M. Varying clinical significance of hyperlactatemia. Critical Care Resusc 2005;7:57-9.
2. Raper RF, Cameron G, Walker D, Bowey JC. Type B lactic acidosis following cardiopulmonary bypass. Crit Care Med 1997;25:46-51.
3. Levy B, Sadoune LO, Gelot AM, Bollaert P, Nabet PG, Larcan A. Evolution of lactate/pyruvate and arterial ketone body ratios in the early course of catecholamine-treated septic shock. Crit Care Med 2000;28:114-9.
4. Shinde S, Golam K, Patil N, Kumar P, Kesevan. Perioperative blood lactate levels, pyruvate levels and lactate/pyruvate ratio in children undergoing cardiopulmonary bypass for congenital heart disease. Internet J Anaesthesiol 2006;10:1-6.

5. Bäckström T, Franco-Cereceda A. Intravasal microdialysis is superior to intramyocardial microdialysis in detecting local ischaemia in experimental porcine myocardial infarction. Acta Physiol Scand 2004;180:5-12.
6. Heringlake M, Bahlmann L, Misfeld M, Poeling J, Leptien A, Kraatz E, *et al.* High myocardial lactate concentration is associated poor myocardial function prior to cardiopulmonary bypass. Minerva Anestesiol 2005;71:775-83.
7. Mayer J, Boldt J, Wolf WM, Lang J, Suttner S. Cardiac output derived arterial pressure waveform analysis in patients undergoing cardiac surgery: Validity of a second generation device. Anesth Analg 2008;106:867-72.
8. Gundry SR, Sequiera A, Razzouk AM, McLaughlin JS, Bailey LL. Facile retrograde cardioplegia: transatrial cannulation of the coronary sinus. Ann Thorac Surg 1990;50:882-7.
9. Onorati F, Cristodoro L, Caroleo S, Esposito A, Amantea B, Santangelo E, *et al.* Troponin I and lactate from coronary sinus predict cardiac complication after myocardial revascularisation. Ann Thorac Surg 2007;83:1016-23.
10. Crittenden MD. Intraoperative metabolic monitoring of the heart: Clinical assessment of coronary sinus metabolites. Ann Thorac Surg 2001;72:S2220-6.
11. Siouffi SY, Kwanik EM, Khuri SF. Methods for the metabolic quantification of regional myocardial ischemia. J Surg Res 1987;43:360-78.
12. Inoue S, Kuro M, Furuya H. What factors are associated with hyperlactatemia after cardiac surgery characterized by well-maintained oxygen delivery and a normal postoperative course? A retrospective study. Eur J Anaesthesiol 2001;18:576-84.
13. Shinde SB, Golam KK, Kumar P, Patil ND. Blood lactate levels during cardiopulmonary bypass for valvular heart surgery. Ann Card Anaesth 2005;8:38-44.
14. Duke T, Butt W, South M, Karl TR. Early markers of major adverse events in children after cardiac operation. J Thorac Cardiovasc Surg 1997;114:1042-52.
15. Andersen LW, Landow L, Baek L, Jansen E, Baker S. Association between gastric intramucosal pH and splanchnic endotoxin, antibody to endotoxin, and tumor necrosis factor – α concentrations in patients undergoing cardiopulmonary bypass. Crit Care Med 1993;21:210-7.
16. Hatherill M, Sajjanhar T, Tibby SM, Champion MP, Andersopn D, Marsh MJ, *et al.* Serum lactate as a predictor of mortality after paediatric cardiac surgery. Arch Dis Child 1997;77:235-8.
17. Raman JS, Bellomo R, Hayhoe M, Tsamitros M, Buxton BF. Metabolic changes and myocardial injury during cardioplegia: A pilot study. Ann Thorac Surg 2001;72:1566-71.
18. Koh TW, Carr-White GS, DeSouza AC, Ferdinand FD, Hooper J, Kemp M, *et al.* Intraoperative cardiac Troponin T release and lactate metabolism during coronary artery surgery: Comparision of beating heart with conventional coronary artery surgery with cardiopulmonary bypass. Heart 1999;81:495-500.
19. Rao V, Ivanov J, Weisel RD, Cohen G, Borger MA, Mickle DA. Lactate release during reperfusion predicts low cardiac output syndrome after coronary bypass surgery. Ann Thorac Surg 2001;71:1925-30.
20. Wikstrom BG, Ronquist G, Waldenstrom A. Dynamics of myocardial metabolism in the preconditioned porcine heart studied using continuous microdialysis. Eur Heart J 1995;16:563-9.
21. Cross HR, Clarke K, Opie LH, Radda GK. Is lactate-induced myocardial ischemia injury mediated by decreased pH or increased intracellular lactate? J Mol Cell Cardiol 1995;27:1369-81.
22. Metzsch C, Liao Q, Steen S, Algotsson L. Myocardial glycerol release, arrhythmias and hemodynamic instability during regional ischemia-reperfusion in an open chest pig model. Acta Anaesthesiol Scand 2006;50:99-107.

Source of Support: Nil, **Conflict of Interest:** None declared.