

Short-term prognostic value of perioperative coronary sinus-derived-serum cardiac troponin-I, creatine kinase-MB, lactate, pyruvate, and lactate-pyruvate ratio in adult patients undergoing open heart surgery

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ABSTRACT

Objectives: To investigate the release pattern of different cardiac metabolites and biomarkers directly from the coronary sinus (CS) and to establish the diagnostic discrimination limits of each marker protein and metabolites to evaluate perioperative myocardial injury in patients undergoing cardiac surgery under cardiopulmonary bypass (CPB). **Patients and Methods:** Sixty-eight patients undergoing first mitral and/or aortic valve replacements with/without coronary artery bypass grafting and Bentall procedure under CPB and blood cardioplegic arrest were studied. All cardiac metabolites and biomarkers were measured in serial CS-derived blood samples at pre-CPB, immediate post aortic declamping, 10 minutes post-CPB and 12 hrs post-CPB. **Results:** Receiver operating characteristic curve analysis of cardiac biomarkers indicated lactate-pyruvate ratio as the superior diagnostic discriminator of myocardial injury with an optimal “cut-off” value >10.8 immediately after aortic declamping (AUC, 0.92; 95% CI: 0.85-0.98). Lactate was the second best diagnostic discriminator of myocardial injury with an optimal “cut-off” value >2mmol/l at immediately after aortic declamping (AUC, 0.89; 95% CI: 0.80-0.96). Cardiac troponin-I was the third best diagnostic discriminator of myocardial injury with an optimal “cut-off” value >2.1ng/ml at immediately after aortic declamping (AUC, 0.88; 95% CI: 0.80-0.95). Creatine kinase-MB was the fourth best diagnostic discriminator of myocardial injury with an optimal “cut-off” value >58 log units/ml prior to decanulation (AUC, 0.85; 95% CI: 0.78-0.94). **Conclusions:** Measurable cardiac damage exists in all patients undergoing cardiac surgery under cardioplegic arrest. The degree of myocardial injury is more in patients with poor ventricular function and those requiring longer aortic clamp time. CS-derived lactate-pyruvate ratio, lactate, cTn-I served as superior diagnostic discriminators of peri-operative myocardial damage.

Key words: Biomarkers; Diagnostic discriminators; Metabolites; Myocardial damage; Myocardial injury

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INTRODUCTION

Despite advances in myocardial preservation strategies, surgical techniques, intraoperative hemodynamic monitoring, and perioperative management, subclinical myocardial stunning, damage, and perioperative myocardial infarction are still life-threatening complications after cardiopulmonary bypass (CPB), responsible for early and late major cardiovascular adverse events and mortality.^[1-3]

Khabbaz *et al.* have demonstrated global and regional alterations in the metabolic status of the myocardium throughout the cross-clamp time and reperfusion and concluded that the functional recovery of the myocardium depends on the metabolic status of the heart during these vulnerable periods.^[4] Previous investigators including us have demonstrated that myocardial ischemia during cardiac surgery results in functional and structural changes, development of myocardial tissue acidosis and lactate production, and ultimately in release of cardiospecific marker proteins from injured cardiac myocytes.^[1,5-7] However, published literature does not address or quantitate the comparative release pattern of the cardiac biomarkers after cardioplegic arrest between patients undergoing coronary artery bypass grafting (CABG) and non-CABG procedures.

Although the postischemic recovery of left ventricular (LV) function can be assessed intraoperatively, the usual load-dependent measures of ventricular function are less precise because preload, afterload, and heart rate (HR) cannot be held constant.^[1-6] The primary goal of perioperative biochemical monitoring of cardiac surgical patients is to identify appropriate markers to detect early cardiac cellular injury to prevent postoperative myocardial infarction and its associated cardiac complications.

The importance of coronary sinus (CS) measurements is that they allow for a direct assessment of myocardial outflow of biomarkers of cell injury and metabolites during ischemia and reperfusion. With this background, we hypothesized that an increase in myocardial lactate, lactate-pyruvate ratio (LPR), cardiospecific biomarkers such as creatine kinase-MB (CK-MB) and cardiac troponin-I (cTn-I) may be reflective of inadequacy of myocardial protection and/or myocardial hypoperfusion in patients with advanced New York Heart Association (NYHA) presentation with or without coronary artery obstruction, thereby causing

altered perioperative hemodynamics and postoperative cardiovascular complications.

We tested this hypothesis by sampling blood directly from the CS at different time intervals to measure cardiac metabolites and biomarkers and analyzed their relationship to hemodynamic patterns and major cardiovascular events during and after cardiac surgery.

The aims of this prospective study were (1) to investigate the release kinetics of different CS-derived cardiac metabolic markers and biomarkers (lactate, pyruvate, LPR, cTn-I, and CK-MB) and their relevance to myocardial injury in patients undergoing cardiac surgery under CPB and cardioplegic arrest; (2) to measure the sensitivity, specificity, and likelihood ratio (+) of individual cardiac metabolites and biomarkers to establish the diagnostic discrimination limits of each measured value to evaluate perioperative myocardial injury; (3) to evaluate the effectiveness of myocardial preservation techniques utilized; and (4) to assess the relationship between different grades of elevated cardiac metabolites and biomarkers and postbypass low cardiac output syndrome (LCOS) including other major cardiovascular adverse events in the immediate and late postoperative period.

PATIENTS AND METHODS

Criteria for patient selection

This study conforms to the principles outlined in the Declaration of Helsinki. The sample size was calculated using Stata 9 software and calculated as power >85% with $\alpha = 0.05$. Thus, 68 patients (50 male cases) scheduled to undergo first elective mitral valve replacement (MVR), mitral and aortic valve replacements (AVR), concomitant AVR and CABG, concomitant MVR and CABG, aortic root replacement for annuloaortic ectasia and acute type A aortic

Table 1: Relationship between the operations performed and cardiac output in the study group

Surgical group	n (%)	LCO, n (%)	NCO, n (%)
MVR	15 (22.1)	8 (53.3)	7 (46.7)
AVR + MVR	20 (29.4)	16 (80)	4 (20)
Bentall's procedure	3 (4.4)	3 (100)	0 (0)
CABG + MVR	5 (7.4)	4 (80)	1 (20)
CABG + AVR	3 (4.4)	2 (66.7)	1 (33.3)
CABG	22 (32.3)	15 (68.2)	7 (31.8)

MVR: Mitral valve replacement, AVR: Aortic valve replacement, CABG: Coronary artery bypass grafting, LCO: Low cardiac output, NCO: Normal cardiac output

dissection (Bentall procedure), and isolated CABG with the aid of CPB and blood cardioplegic myocardial preservation between June 2009 and June 2014 were enrolled in this prospective, nonrandomized trial after obtaining the Institutional Ethics Committee approval and written informed consent from each patient. Diagnosis was confirmed on these patients by clinical examination, echocardiography, catheterization, and angiocardiology as necessary. None of the patients received thrombolytic agents [Table 1].

Cardiac metabolites and biomarkers, namely, cTns (I and T) and lactate, are known to be elevated in patients with impaired hepatic clearance, intrinsic renal disease, chronic obstructive airway disease, severe coagulation abnormalities, and treatment with fibrinolytic agents.^[8-12] Therefore, the above subset of patients were excluded from the study group.

Anesthesia and cardiopulmonary bypass

All patients were premedicated with morphine 0.1 mg/kg and phenergan 0.5 mg/kg intramuscularly, 30–45 min before induction of anesthesia. Anesthesia was induced with intravenous thiopentone (3–5 mg/kg), fentanyl (2–5 µg/kg), and midazolam (1–2 mg). Endotracheal intubation was facilitated with vecuronium (0.8–1.0 mg/kg). Anesthesia was maintained with oxygen in air (50%), isoflurane along with supplemental doses of intravenous fentanyl, midazolam, and vecuronium.

Radial artery line was passed for invasive blood pressure monitoring with Vigileo monitor and FloTrac sensor (Edwards Lifesciences, Irvine, CA, USA) for determination of cardiac output (CO), cardiac index (CI), stroke volume index (SVI), oxygen delivery index, and systemic vascular resistance index.^[13]

Systemic heparinization was done with heparin 4 mg/kg to achieve target activated clotting time between 480 and 600 s. After surgery, heparin was neutralized with protamine in 1.5:1 ratio.

A retrograde cardioplegia cannula with a self-inflating balloon (RCO14, Edwards Lifesciences, Irvine, CA, USA) was inserted by the surgeon through the right atrium (RA) into the CS with a blind technique before going on bypass for retrograde cardioplegia as well as for the purpose of sampling. The correct position was confirmed by observing distension of the posterior interventricular vein, maintenance of CS pressure, and palpation of the CS cannula posteriorly at the base of the

heart. CPB and surgical techniques were standardized and did not change during the study period.

All patients underwent cardiac surgery using CPB under moderate hypothermia at 30°–32° C. The CPB equipment consisted of membrane oxygenator with hard shell venous reservoir (Capiiox SX18, Terumo), roller pump, arterial filter (Affinity, Medtronic), and blood cardioplegia delivery system (Dideco). The circuit was primed with ringer lactate (15 mL/kg), hydroxyethyl starch (Voluven 6%, Fresenius Kabi 10 mL/kg), mannitol (20%, 0.5 g/kg), heparin (50 mg), and sodium bicarbonate (7.5% w/v). α -stat strategy was used for blood gas management on bypass. The blood sugar was maintained between 100 and 200 mg/dl on bypass with the addition of insulin, if required, on bypass. The hematocrit was maintained >25% on bypass with the addition of packed red blood cells if required and mixed venous oxygen saturation >75% was maintained.

Myocardial preservation

All patients were subjected to the same myocardial preservation strategy. Intermittent cold blood cardioplegia (St. Thomas II solution 4:1) at a dose of 150 mL/min/m² along with topical cooling was used on all patients. A combination of antegrade and retrograde cardioplegia was used in all patients in an alternating sequential manner and was repeated every 20 min. The average adult was given a dose between 900 and 1000 mL with approximately 2/3rd being delivered antegrade and the remainder retrograde. The potassium concentration of the cardioplegic solution was between 28 and 30 mmol/L. No patients received continuous or near-continuous retrograde or hot shot cardioplegia.

Inotropes (dopamine, dobutamine, and adrenaline) were used as required to maintain hemodynamics. Intra-aortic balloon pump (IABP) was inserted if the above hemodynamics persisted with adrenaline and/or appearance of additional electrocardiographic (ECG) change of ischemia, arrhythmia with persistent metabolic acidosis [Appendix 1].

Sampling methods

Since blood samples were drawn from the CS in which cardioplegia was administered, the initial 15–20cc of the stagnant blood in the CS catheter was discarded before sample collection. Blood samples were taken from CS and arterial line at predetermined times. These time points were as follows:

- T₁: Soon after cannulation, before institution of CPB (pre-CPB)
- T₂: Immediately after the release of aortic cross-clamp (postaortic cross-clamp)
- T₃: 10 min after coming off CPB, before decannulation (post-CPB)
- T₄: 12 h after coming off CPB in the Intensive Care Unit (ICU) (arterial sample).

The CS blood sample (5 mL) was collected in ethylenediaminetetraacetic acid vial, immediately cooled to 4°C, and centrifuged at 3000 rpm for 10 min at 4°C. Plasma was stored at -70°C until assay.

Biochemical analysis

CS-derived-serum pyruvate, lactate and blood gas analysis were done with commercial gas analyzer (ABL 835 Flex, radiometer Copenhagen, Denmark). CK-MB was estimated by photometric method (Diagnostic Systems GmbH, Alte Strasse 965558 Holzheim, Germany; normal range, 0–24 IU/L); cTn-I level was estimated using Immulite 1000 Troponin-I analyzer using CS blood samples (Diagnostic Product Corporation, Los Angeles, USA). According to the manufacture's information, the minimum detectable concentration of cTn-I was 0.2 µg/L. Levels of cTn-I are undetectable in the apparently healthy individual.

Lactate-pyruvate ratio = myocardial lactate-myocardial pyruvate

The relationship between myocardial lactate level and intraoperative and postoperative clinical variables was evaluated in this study. The intraoperative variables included CPB time, aortic cross-clamp time, and CS-derived CK-MB, cTn-I, lactate, and pyruvate levels. The postoperative variables included post-CPB need for inotropes, requirement for IABP, duration of mechanical ventilation, inotrope usage, ICU stay, and mortality.

Clinical parameters

The patients were also studied for the requirement of inotropes (Inotropic score), duration of ventilation, length of ICU and hospital stay, any events (infection, mortality, etc.), comorbidities, and pre- and post-operative LV functions. Inotropic score was calculated on the basis of number and doses of the individual inotropes. Transthoracic echocardiogram was performed in all patients using the Hewlett-Packard Sonos 1500 or 5500 ultrasound system (Hewlett-Packard Co, Andover, MA, USA) to evaluate the LV function, pre- and post-operatively, before discharge by the same

cardiologist who was blinded to the study. LV function was defined as moderate (ejection fraction [EF] 30–50%) and good (EF >50%).

Hemodynamic parameters

HR, mean arterial pressure, central venous pressure, CO, and CI were recorded following anesthetic induction, pre-CPB (T₁); immediate postaortic cross-clamp release (T₂); 10 min post-CPB (T₃); and 12 h post-CPB in ICU (T₄). Hemodynamic parameters using a FloTrac Vigileo Monitor were recorded at the same time as the samples were taken.

Surgical techniques

CPB was established with ascending aortic cannulation and two-stage venous cannulation of the RA in CABG, isolated aortic valve, and aortic surgeries. Bicaval cannulation was done for mitral valve surgery and with concomitant CABG.

For patients undergoing MVR, total/partial chordal preservation was done as deemed necessary in individual patients. Either a St. Jude mechanical or bioprosthesis (Carpentier-Edwards, Perimount) was used. For patients undergoing modified Bentall procedure, a coronary "button technique" was used in all patients.

The prime objective of patients undergoing CABG was to obtain complete revascularization by bypassing all severe stenoses (at least 50% diameter reduction in all coronary arterial trunks and branches having a diameter of about 1 mm or more). After distal anastomosis and once the left internal mammary artery was unclamped, warm reperfusion composed exclusively of 37° C oxygenated blood was administered through a multiperfusion catheter with a constant flow rate of between 200 and 500 mL/min to minimize myocardial ischemia.

Statistical analysis

Statistical analysis was performed using Stata 9.0 (College Station, Texas, USA). Data were presented as number (percentages) or mean ± standard deviation (SD)/median (range). Baseline characteristics of the patients were compared between the low and normal cardiac output groups using Chi-square test/Student's *t*-test for independent samples. Receiver operating characteristic curves (ROCs) were constructed to compare the discriminatory ability and to determine the appropriate cutoff value of CS-derived lactate, pyruvate, LPR, cTn-I, and CK-MB for myocardial

dysfunction. The generalized estimating equation was used to find out the difference in means between the groups measured at various time points since the observations were correlated. Statistical significance was set at $P < 0.05$.

RESULTS

Five (10.4%) patients in this study group died between 9 and 15 days following surgery. One patient undergoing Bentall procedure for acute type A aortic dissection died of acute renal failure and low cardiac output on the 11th postoperative day. Two patients undergoing CABG and two patients undergoing concomitant MVR and CABG died of LCOS ($n = 2$) and cerebrovascular accident ($n = 2$) between the 9th and 15th day after surgery, respectively.

Forty-eight (70.6%) patients in this study group had LCOS following surgery. A detailed description of the criteria used to diagnose LCOS can be found in definitions (Electronic) [Appendix 1]. All patients with LCOS following surgery ($n = 48$) were in NYHA functional class IV and had poor LV function (mean left ventricular ejection fraction [LVEF] = $34.79\% \pm 2.29\%$, range 20–40%). Thirty (44.1%) patients with postoperative LCOS were in congestive heart failure (CHF) before surgery. The CPB time, aortic cross-clamp time, number of cardioplegia used, postoperative inotropic score, and requirement of postoperative ventilation were significantly higher in patients with LCOS following surgery as compared to patients with normal cardiac output [Tables 1-3 and Figures 1, 2]. Despite following a standardized protocol for the length of ventilation and institution of inotropes in the setting of LCOS,

Table 2: Baseline characteristics of the study group (n=68)

Variables	LCO	NCO	P
Age (years), mean±SD (range)	46.57±14.52 (15-70)	45.05±13.70 (25-75)	0.42
Male population, n (%)	35 (72.9)	16 (80)	0.38
Weight (kg), mean±SD (range)	58.60±15.29 (35-110)	59.60±18.04 (31-98)	0.54
Height (cm), mean±SD (range)	163.34±9.49 (140-187)	161.05±23.54 (68-182)	0.56
BSA (m ²), mean±SD (range)	1.59±0.14 (1.4-1.9)	1.63±0.14 (1.4-1.9)	0.36
Comorbidities, n (%)	39 (81.3)	12 (60)	0.03
Diabetes mellitus (%)	18 (37.5)	8 (40)	0.53
Hypertension (%)	28 (58.3)	7 (35)	0.06
Preoperative left ventricular ejection fraction (%), mean±SD (range)	34.79±7.29 (25-55)	50.25±4.44 (40-50)	0.01
New York Heart Association Functional Class	3.44±0.62 (2-4)	2.20±0.42 (2-3)	0.01
Congestive heart failure (%)	30 (62.5)	0 (0)	0.01
Atrial fibrillation (%)	24 (50)	8 (40)	0.31

Bold face indicates statistical significance. SD: Standard deviation, LCO: Low cardiac output, NCO: Normal cardiac output, BSA: Body surface area

Table 3: Peri- and post-operative variables of the study group

Variables	LCO (n=48)	NCO (n=20)	P
Aortic cross-clamp time, mean±SD (range)	64.22±20.71 (31-108)	46.41±18.58 (26-91)	0.01
Cardiopulmonary bypass time, mean±SD (range)	102.26±27.95 (50-186)	76.41±23.19 (46-122)	0.01
Number of cardioplegia, mean±SD (range)	2.73±0.75 (1-4)	1.75±0.79 (1-3)	0.03
Postoperative inotropic score, mean±SD (range)	62.94±34.24 (14-114)	19.65±14.02 (10-78)	0.001
Postoperative ventilation (h), mean±SD (range)	21.13±17.49 (6-68)	8.10±2.31 (6-16)	0.001
ICU length of stay (days), mean±SD (range)	3.0±1.21 (1-5)	1.30±0.57 (1-3)	0.001
Hospital stay (days), mean±SD (range)	10.50±3.75 (3-16)	7.10±0.97 (6-10)	0.001
Postoperative LVEF (%), mean±SD (range)	38.64±15.49 (20-45)	53.25±2.94 (45-55)	0.01
IABP, n (%)	16 (33.3)	-	0.01
Death, n (%)	5 (10.41)	-	0.01

Bold face indicates statistical significance. IABP: Intra-aortic balloon pump, MI: Myocardial infarction, LCO: Low cardiac output, NCO: Normal cardiac output, LVEF: Left ventricular ejection fraction, SD: Standard deviation

significant differences were observed between two groups of patients with and without low cardiac output in duration of mechanical ventilation (21.13 ± 17.49 vs 8.10 ± 2.31 ; $P = 0.001$) and ICU stay (3.0 ± 1.21 vs 1.30 ± 0.57 days; $P = 0.001$) [Table 3 and Figures 1, 2].

All 48 patients (70.6%) exhibiting LCOS required moderate inotropic drug support following surgery whereas no patients in the normal cardiac output category required such support following surgery.

In patients undergoing CABG, there was no perioperative myocardial infarction in either group as defined by ECG criteria.^[7] There was transient moderate impairment of LVEF ranging from 0.20 to 0.45 in all patients exhibiting LCOS following surgery. Patients without manifestations of LCOS had postoperative LVEF ranging between 0.45 and 0.55 (mean \pm SD 53.25 ± 2.94 vs 38.64 ± 15.49), ($P = 0.01$). However, there was no noticeable difference in this regard at discharge [Table 3 and Figures 1, 2].

Time course of median concentration of cardiac metabolites and biomarkers

The median values of each marker protein rose from a baseline concentration before CPB to a postoperative peak, indicating myocardial damage to a certain degree in all cases. The total amount of biomarkers released in both groups has not been considered for comparative evaluation of myocardial injury because an initially increased value can take a few days to resolve and would be counted or added to the total amount as high on multiple occasions.

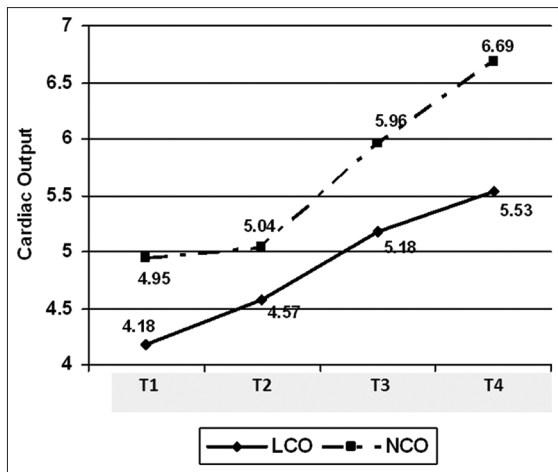


Figure 1: Comparison of cardiac output in two groups of patients with and without low cardiac output at different time intervals. The two measurements at different time intervals differed significantly ($P = 0.001$)

For each sample drawn, the CS-derived-serum lactate was significantly higher in patients exhibiting LCOS than with normal cardiac output at pre-CPB ($P = 0.008$), immediately after aortic cross-clamp release ($P = 0.01$), before coming off bypass ($P = 0.01$), and at 12 h following CPB ($P = 0.004$) [Table 4 and Figure 3].

For each sample drawn, the CS-derived-serum pyruvate concentrations were significantly higher in patients exhibiting LCOS than those with normal cardiac output at immediate post-aortic cross-clamp release ($P = 0.002$), before coming off CPB ($P = 0.01$), and at 12 h following surgery ($P = 0.01$) [Table 4 and Figure 4].

For each sample drawn, the CS-derived LPR was significantly higher in patients with LCOS than those with normal cardiac output at pre-CPB ($P = 0.001$) immediately after aortic cross-clamp release ($P = 0.001$), before coming off CPB ($P = 0.001$), and at 12 h following surgery ($P = 0.001$) [Table 4 and Figure 5].

For each sample drawn, the CS-derived CKMB concentration was significantly higher in patients with LCOS at pre-CPB ($P = 0.001$), immediately after aortic cross-clamp release ($P = 0.001$), before coming off CPB ($P = 0.001$), and at 12 h following surgery ($P = 0.001$) [Table 4 and Figure 6].

For each sample drawn, the CS-derived cTn-I was significantly higher in patients with LCOS at pre-CPB ($P = 0.001$), immediate post-aortic cross-clamp release ($P = 0.002$), before coming off CPB ($P = 0.01$), and at 12 h following surgery ($P = 0.01$) [Table 4 and Figure 7].

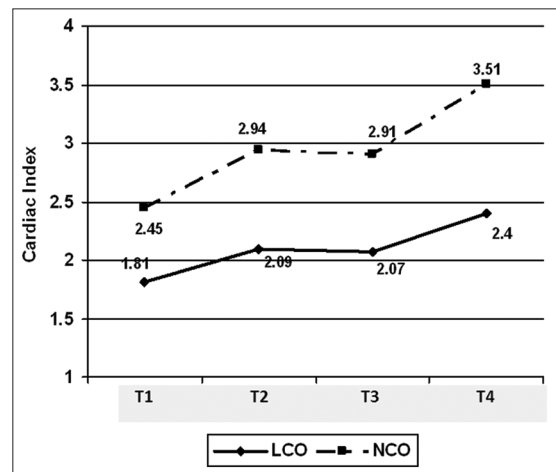


Figure 2: Comparison of cardiac indices in two groups of patients at different time intervals. The two measurements at different time intervals differed significantly ($P = 0.001$)

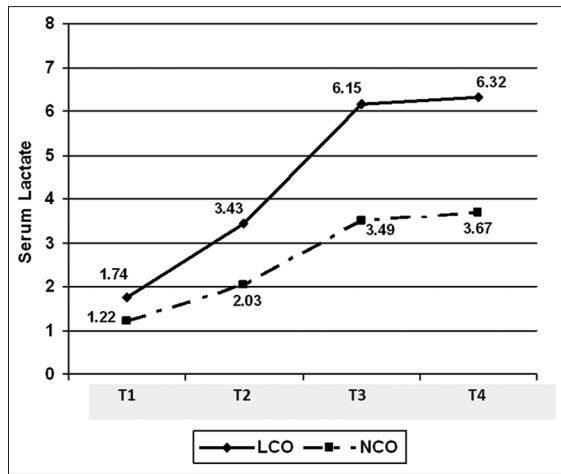


Figure 3: Comparison of coronary sinus-derived-serum lactate in two groups of patients at different time intervals. The two measurements differed significantly ($P = 0.01$). The serum lactate values were significantly higher in the low cardiac output group than in the normal cardiac output group at precardiopulmonary bypass ($P = 0.008$), postaortic clamp release ($P = 0.001$), before aortic decannulation ($P = 0.01$), and 12 h after coming off cardiopulmonary bypass ($P = 0.004$)

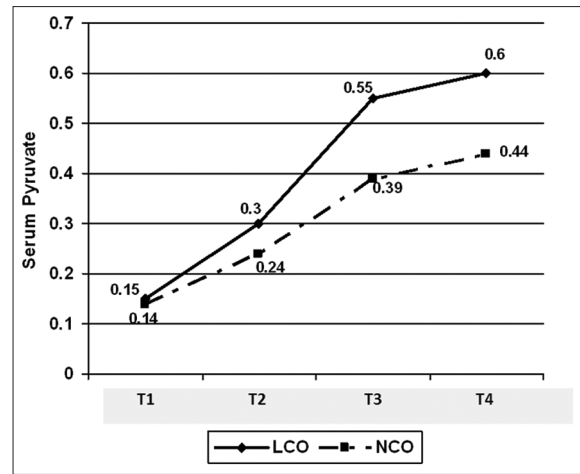


Figure 4: Comparison of coronary sinus-derived-serum pyruvate in two groups of patients at different time intervals. The two measurements differed significantly ($P = 0.01$). The serum pyruvate values were significantly higher in the low cardiac output group than in the normal cardiac output group at postaortic clamp release ($P = 0.002$), before aortic decannulation ($P = 0.01$), and 12 h after coming off cardiopulmonary bypass ($P = 0.01$)

Table 4: Comparative values of coronary sinus-derived cardiac metabolites and biomarkers between two groups of patients

Sample time	Mean±SD (median; range)		P
	LCO	NCO	
Serum lactate			
T ₁	1.73±0.76 (1.5; 0.8-3.9)	1.22±0.48 (1.2; 0.7-2.5)	0.008
T ₂	3.42±1.35 (3.1; 1.6-6.5)	2.03±0.63 (2.1; 0.9-3.8)	0.01
T ₃	6.14±2.11 (5.6; 2.6-9.8)	3.48±0.99 (3.5; 1.8-5.7)	0.01
T ₄	6.17±2.13 (5.9; 2.4-9.9)	3.48±0.97 (3.2; 1.6-5.9)	0.004
Serum pyruvate			
T ₁	0.15±0.07 (0.14; 0.06-0.36)	0.13±0.04 (0.13; 0.08-0.28)	0.38
T ₂	0.30±0.10 (0.28; 0.18-0.54)	0.23±0.06 (0.24; 0.10-0.42)	0.002
T ₃	0.55±0.19 (0.49; 0.24-0.89)	0.38±0.08 (0.38; 0.22-0.61)	0.01
T ₄	0.55±0.18 (0.46; 0.26-0.88)	0.39±0.09 (0.39; 0.24-0.65)	0.01
Lactate/pyruvate ratio			
T ₁	11.24±3.55 (10.4; 5.5-22.5)	8.77±1.81 (8.7; 3.8-12.8)	0.001
T ₂	9.99±1.66 (10; 7-14)	8.50±1.64 (8; 5-14)	0.001
T ₃	11.79±1.45 (12.1; 7.6-14.6)	9.09±1.06 (8.8; 7.7-11.2)	0.001
T ₄	13.63±2.69 (14.3; 7.8-18.4)	9.00±1.13 (8.2; 7.4-11.5)	0.002
Creatine kinase-MB			
T ₁	7.45±5.30 (7.0; 1.4-22.0)	2.01±0.32 (2.1; 1.4-2.8)	0.001
T ₂	77.27±51.27 (76; 16-280)	22.85±6.51 (22; 14-38)	0.001
T ₃	142.25±72.47 (160; 24-280)	36.50±6.51 (36; 28-52)	0.001
T ₄	189.91±95.67 (212; 26-386)	51.10±6.91 (50; 32-64)	0.001
Cardiac troponin I			
T ₁	1.10±0.94 (0.9; 0.1-3.8)	0.25±0.28 (0.2; 0.1-1.4)	0.001
T ₂	3.80±2.46 (3.8; 0.4-9.8)	0.69±0.45 (0.6; 0.3-2.4)	0.001
T ₃	8.74±5.11 (9.8; 0.9-21.2)	1.55±0.78 (1.4; 0.8-4.2)	0.001
T ₄	10.34±6.44 (10.25; 0.90-23.20)	1.57±0.78 (1.45; 0.80-4.20)	0.001

T₁: Soon after cannulation, before institution of CPB, T₂: Immediately after the release of aortic cross-clamp, T₃: 10 min after coming off CPB, before decannulation, T₄: 12 h after coming off CPB in the ICU (arterial sample). ICU: Intensive Care Unit, CPB: Cardiopulmonary bypass, LCO: Low cardiac output, NCO: Normal cardiac output, SD: Standard deviation

Thus, the degree of increase of all cardiac metabolites and biomarkers was significantly higher in patients exhibiting LCOS at all levels of measurements as compared to the other groups.

Diagnostic performance of coronary sinus-derived-serum lactate, pyruvate, lactate-pyruvate ratio, creatine kinase-MB, and cardiac troponin-I

To determine the optimal “cutoff” value and test characteristics of the above-mentioned cardiac metabolites and biomarkers at each postoperative time

point in patients undergoing cardiac surgery under CPB with St. Thomas based blood cardioplegic myocardial preservation, ROC analysis revealed the following:

- LPR was the best diagnostic discriminator of myocardial injury with an optimal “cutoff” value of >10.8 at immediately after aortic declamping (area under the curve [AUC], 0.92 [\pm standard error (SE) 0.03, 95% confidence interval (CI): 0.85–0.98]; sensitivity 83.3%; specificity 85%; likelihood ratio (+) 5.55 [Table 4 and Figures 5, 8])
- Lactate was the second best diagnostic discriminator of myocardial injury with an optimal “cutoff”

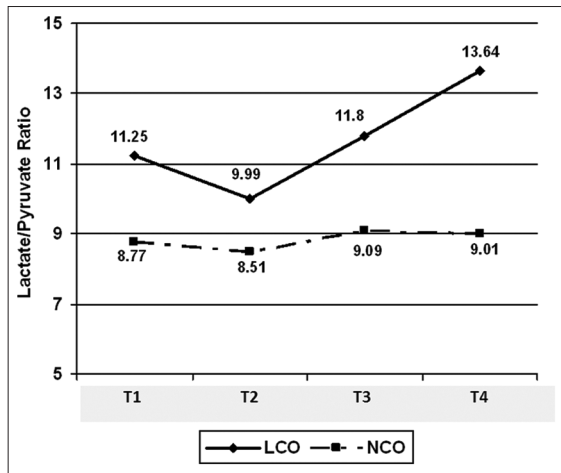


Figure 5: Comparison of coronary sinus-derived-lactate-pyruvate ratio in two groups of patients at different time intervals. The two measurements differed significantly ($P = 0.01$). The serum lactate-pyruvate ratio was significantly higher in the low cardiac output group than in the normal cardiac output group at precardiopulmonary bypass ($P = 0.001$), post-aortic clamp release ($P = 0.001$), before aortic decannulation ($P = 0.001$), and 12 h after coming off cardiopulmonary bypass ($P = 0.002$)

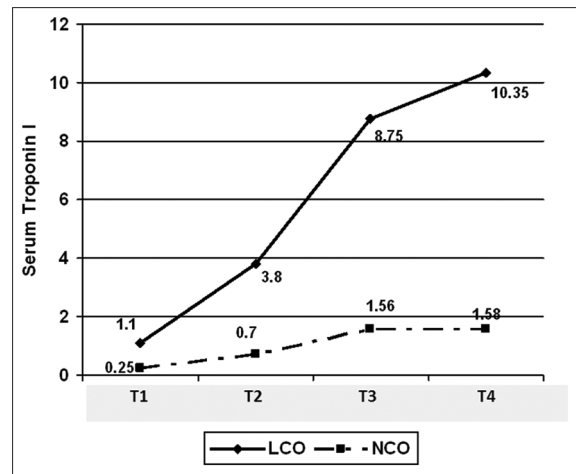


Figure 6: Comparison of coronary sinus-derived-cardiac troponin-I in two groups of patients at different time intervals. The cardiac troponin-I ratio was significantly higher in the low cardiac output group than in the normal cardiac output group at precardiopulmonary bypass ($P = 0.001$), post-aortic clamp release ($P = 0.001$), before aortic decannulation ($P = 0.001$), and 12 h after coming off cardiopulmonary bypass ($P = 0.001$)

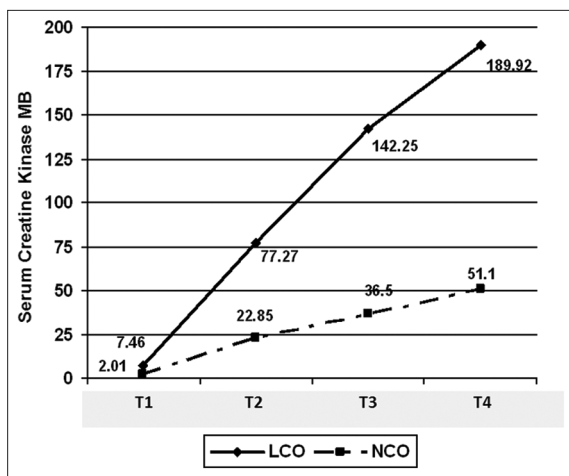


Figure 7: Comparison of coronary sinus-derived-serum creatine kinase-MB in two groups of patients at different time intervals. The serum creatine kinase-MB ratio was significantly higher in the low cardiac output group than in the normal cardiac output group at precardiopulmonary bypass ($P = 0.001$), post-aortic clamp release ($P = 0.001$), prior to aortic decannulation ($P = 0.001$), and 12 h after coming off cardiopulmonary bypass ($P = 0.001$)

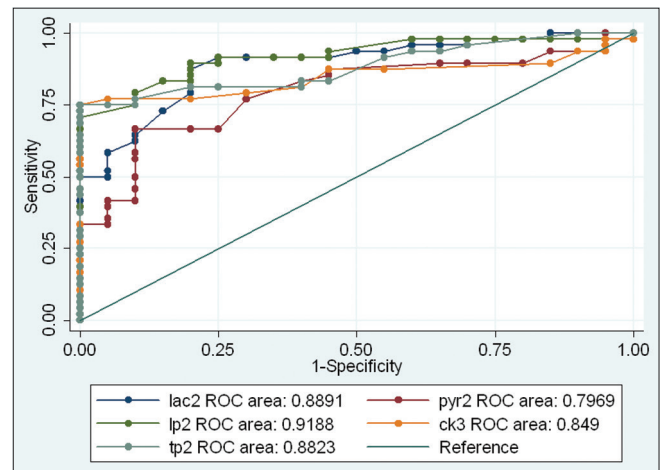


Figure 8: The receiver operating characteristic curve of the study group to compare the tradeoffs between the true-positive rate and false-positive rate of increase of all cardiac biomarker levels to identify all the diagnostic discrimination limits for each marker (lactate, pyruvate, lactate-pyruvate ratio, cardiac troponin-I, and creatine kinase)

value of >2 mmol/L at immediately after aortic declamping (AUC, 0.89 [\pm SE 0.04, 95% CI: 0.80–0.96]; sensitivity 83.33%; specificity 80%; likelihood ratio (+) 4.16) [Table 4 and Figures 3, 8]

- cTn-I was the third best diagnostic discriminator of myocardial injury with an optimal “cutoff” value of >2.1 ng/mL at immediately after aortic declamping (AUC, 0.88 [\pm SE 0.04, 95% CI: 0.80–0.95]; sensitivity 81.25%; specificity 80%; likelihood ratio (+) 4.06) [Table 4 and Figures 7, 8]
- CK-MB was the fourth best diagnostic discriminator of myocardial injury with an optimal “cutoff” value of >58 log units/mL after coming off bypass before decannulation (AUC, 0.85 [\pm SE 0.05, 95% CI: 0.78–0.94]; sensitivity 77.08%; specificity 80%; likelihood ratio (+) 3.85) [Table 4 and Figures 6, 8]
- CS-derived pyruvate was the fifth best diagnostic discriminator of myocardial injury with an optimal “cutoff” value of >0.44 mmol/L after coming off bypass before decannulation (AUC, 0.79 [\pm SE 0.05, 95% CI: 0.68–0.90]; sensitivity 66.67%; specificity 75%; likelihood ratio (+) 2.66) [Table 4 and Figures 4, 8].

Thus, LPR, lactate, and cTn-I were independent predictors of perioperative cardiac injury.

DISCUSSION

As far as we could establish, there are no published studies in English literature addressing specifically the comparative release pattern, and optimal cutoff values of CS-derived different cardiac biomarkers, namely, serum pyruvate, lactate, LPR, CK-MB, and cTn-I for evaluating myocardial injury after cardiac surgery using CPB and cardioplegic arrest.

The diagnostic discrimination limits of the cardiac metabolites and biomarkers and the ability to predict the risk of myocardial injury after cardioplegic arrest using the degree of increased cardiac biomarkers levels also have not been established.

The major findings of this investigation were consistently higher increases of CS-derived myocardial pyruvate, lactate, LPR, CK-MB, and cTn-I in patients exhibiting LCOS following cardiac surgery than those with postoperatively normal cardiac output.

The second important finding was the finding of greater levels of CS-derived cardiac metabolites and biomarkers in patients with preoperatively advanced

NYHA functional class, CHF and poor LV function, and those requiring longer aortic cross-clamp time.

The third important finding was the ability to predict the risk of perioperative myocardial injury in patients with raised pre-CPB values of CS-derived cardiac metabolites and biomarkers.

The fourth important finding was the ability to predict the risk of myocardial injury using the degree of increase of CS-derived cardiac metabolites and biomarkers, namely, pyruvate, lactate, LPR, CK-MB, and cTn-I.

Cardiac biomarkers and metabolites of myocardial damage: Characteristics and practical application for detection of myocardial injury after cardioplegic arrest Cardiac biomarkers

Cardiospecific marker proteins are intracellular molecules bound to subcellular structures that are released into the extracellular space after the damage of the myocardial cell membrane. Plasma levels of specific marker proteins follow a typical pattern. Small water-soluble molecules are more rapidly washed out and detectable in the serum earlier than proteins with a larger molecular mass, mainly because of the permeability of the endothelial layer.^[8,14-16]

An ideal marker of myocardial injury would (1) be found in high concentrations in myocardium; (2) not be found in other tissues, even in trace amounts; (3) be released rapidly and completely after myocardial injury; (4) be released in direct proportion to the extent of myocardial injury; and (5) persist in plasma for several hours to provide a convenient diagnostic time window but not so long that recurrent injury would not be identified. Thus, markers with improved sensitivity and specificity are required for accurate and reliable information concerning myocardial biochemistry.^[8,14-16]

CK-isoenzymes are dimers composed of 39,000- to 42,000-D subunits synthesized in the cytosol of myocytes. The disadvantage of CK-MB as a cytosolic marker of perioperative myocardial cellular injury compared with troponins is not only its lower sensitivity and specificity but also the short diagnostic window of approximately 24 h.^[8,14-16]

Troponins are regulatory proteins (I, C, or T) located in the striated muscle. They regulate actinomyosin interactions. cTn-I and cTn-T have small cytosol distribution and are tightly complexed to the contractile apparatus. These are more specific markers of

myocardial injury and have been shown to predict the risk of mortality and cardiac events in patients with unstable angina and lower release pattern in patients with off-pump CABG compared with on-pump CABG.^[7,14-16]

Several investigators have investigated the release pattern of troponin I for 24 h and found lower troponin I release in off-pump CABG as compared to on-pump CABG.^[17,18]

Metabolites of myocardial damage

The myocardium has the highest oxygen extraction capability in the body, at a rate of nearly 70%. Under conditions of normal metabolism and adequate myocardial perfusion, the production and washout of H⁺ ions are in equilibrium, resulting in a normal acid-base balance. Glycolysis, glycogenolysis, hydrolysis of ATP, hydrolysis of triglycerides, and the synthesis of triglycerides from palmitate are all sources of H⁺ ion production in the myocardial cell.^[19] Under conditions of ischemia, the hydrogen ion (H⁺) and lactate accumulate in the myocardial tissue in proportion to the magnitude of ischemic insult. The accumulation of H⁺ is the result of both increased anaerobic production of H⁺ secondary to decreased substrate and decreased washout of H⁺ secondary to decreased coronary perfusion.

Hypoxic-anaerobic production of lactate may be global or focal. A nonhypoxic increase in lactate concentration may result from an impaired hepatic clearance, a dysfunction of pyruvate dehydrogenase, and an increased protein degradation causing amino acid conversion to pyruvate.^[11,12,20,21]

Among plasma biochemical markers of tissue hypoxia, LPR represents NADH/NAD⁺ ratio which is linked to phosphorylation potential of the cell (ATP/[ADP + Pi]). Because it cannot be readily measured, NADH/NAD⁺ ratio can be estimated into cytosol from the LPR. Some investigators have demonstrated that hyperlactatemia with a normal LPR <10 reflects nonhypoxic origin whereas an LPR >10 indicates tissue hypoxia.^[11,12,20-24]

Clinically applicable methods for metabolic analysis include the following: Myocardial tissue assays; serial collection of myocardial-specific biomarkers, online measurement of intramyocardial gas tensions or pH, or direct cannulation of the CS metabolites to measure coronary blood flow and to analyze substrate use.^[11,12,20-25]

Myocardial tissue acidosis can be quantitated by measurement of tissue PCO₂ or H⁺ concentration. Although reliable data could be obtained experimentally using mass spectrometry, it could not be used in the operating room because of its long stabilization and response times. Perioperative changes in lactate metabolism in CABG were first described by Carlson *et al.*^[20] Several investigators have revealed an inverse correlation between the degree of metabolic acidosis during aortic cross-clamp and postoperative LCOS.^[11,12,14,20,22-25]

Metabolites and biomarkers of myocardial damage: Diagnostic performance and clinical application

Perioperative myocardial injury after CPB and cardioplegic arrest is associated with a high risk of early and late mortality, as well as poor long-term outcome.^[1-7] The reported incidence varies between 5% and 20% in different publications.^[1-7,10-13,20] However, its prevalence depends on the tests and diagnostic criteria used. ECG criteria remain uncertain and lack diagnostic accuracy in perioperative periods. The primary goal of perioperative biochemical monitoring of cardiac patients is to detect early cardiac cellular injury and prevent postoperative myocardial infarction which has prognostic implications. Therefore, diagnosis depends on assessment of plasma levels of cardiospecific marker proteins.

Assessment of patient's cardiac output and other hemodynamic parameters usually involves placement of a catheter in the pulmonary artery (PA) and performing thermodilution assessment.^[26-28] This is an invasive procedure requiring balloon flotation of the catheter through the right heart and an elaborate protocol of intermittent injection into the PA catheter for thermodilution calculation. Second, surgical manipulation of the heart during open heart surgery can make thermodilution, PA, central venous monitoring, and transesophageal echocardiography unreliable as monitors.^[26-28]

The emergence of new modalities of semi-invasive hemodynamic monitoring has opened up newer frontiers for evaluation of such patients.^[13,26-28] The FloTrac™ sensor and Vigileo™ monitor system introduced by Edwards Lifesciences allow continuous measurement of cardiac output without requiring thermodilution or dye dilution. It bases its calculations on arterial waveform characteristics in conjunction with patients' demographic data and does not require external calibration.

All patients in this study developed atrial fibrillation on the 2nd or 3rd postoperative day. Only patients diagnosed to have LCOS received IABP in addition. Vigileo monitor is known for its inaccuracy in the setting of atrial fibrillation and IABP, and thermodilution assessment is an ideal methodology in this setting. Since three of four samples were taken intraoperatively before the institution of IABP, use of Vigileo monitor did not affect the data analysis.

The aim of this prospective, nonrandomized study was to determine the release kinetics of the cardiac biomarkers and other myocardial metabolites, namely, lactate, pyruvate, and LPR directly from the CS after cardioplegic arrest.

In this study, there were consistently higher increases of all cardiac biomarkers in patients undergoing different types of cardiac surgery under cardioplegic arrest. The release kinetics of the cardiac biomarkers and other myocardial metabolites revealed an elevated level at baseline before surgery in patients with advanced NYHA class, preoperatively poor LVEF and/or CHF implying the existence of subclinical cardiac damage before surgery. The degree of rise of the above cardiac biomarkers and metabolites was statistically significant in the low output group than in the normal output group, indicating a greater degree of myocardial injury during cardioplegic arrest despite optimal cardioprotection in the above-mentioned subset of patients. It is noteworthy that LPR, lactate, and cTn-I were independent predictors of perioperative myocardial injury [Table 4].

Although the cutoff values of cardiac markers have been reported elaborately for patients presenting with chest pain, these values are not well-established for assessment of myocardial injury in patients undergoing surgical revascularization with or without CPB. Based on the data in the present study, we found optimal cutoff values and test characteristics of all available cardiac biomarkers using ROC curves in patients undergoing CABG and non-CABG procedures under CPB and cold blood cardioplegic myocardial preservation.

ROC analysis of cardiac metabolites and biomarkers indicated LPR as the best diagnostic discriminator of myocardial injury with an optimal “cutoff” value of >10.8 at immediately after aortic declamping (AUC, 0.92 [\pm SE 0.03, 95% CI: 0.85–0.98]; sensitivity 83.3%; specificity 85%; likelihood ratio (+) 5.55) [Figure 8]. Lactate was the second best diagnostic discriminator

of myocardial injury with an optimal “cutoff” value of >2 mmol/L at immediately after aortic declamping (AUC, 0.89 [\pm SE 0.04, 95% CI: 0.80–0.96]; sensitivity 83.33%; specificity 80%; likelihood ratio (+) 4.16) [Figure 8].^[29-31] cTn-I was the third best diagnostic discriminator of myocardial injury with an optimal “cutoff” value of > 2.1 ng/mL at immediately after aortic declamping (AUC, 0.88 [\pm SE 0.04, 95% CI: 0.80–0.95]; sensitivity 81.25%; specificity 80%; likelihood ratio (+) 4.06) [Figure 8]. CK-MB was the fourth best diagnostic discriminator of myocardial injury with an optimal “cutoff” value of > 58 log units/mL after coming off bypass before decannulation (AUC, 0.85 [\pm SE 0.05, 95% CI: 0.78–0.94]; sensitivity 77.08%; specificity 80%; likelihood ratio (+) 3.85) [Table 4 and Figure 8].

The above observations have important implications in the management of patients undergoing open heart surgery with CPB in the early postoperative period. Although most patients have an uneventful postoperative period after cardiac surgery, irrespective of technique, and few have clinically significant myocardial infarction, intensive care specialists are often confronted with a group of patients with borderline clinical situations (nonspecific ECG changes and mild hypotension with or without inotropes). Routine intraoperative CS-derived biochemical monitoring will be useful to establish preventive strategies to reduce further myocardial damage.

Limitations

Our study had its limitations in the evaluation of postoperative LV function. Transthoracic echocardiography might not be a sufficient tool for evaluation of LV function because of a poor window in the immediate postoperative period. Radionuclide studies or magnetic resonance imaging (MRI) for assessment of LV function would have consolidated our findings, and better distinction between the two groups could have been established. Second, the population studied in this study was heterogeneous and the number of patients in each subgroup was small.

Third, it is unknown whether this reduction in release of myocardial enzymes after CPB and cardioplegic arrest is associated with reduced perioperative myocardial stunning (reversible) or necrosis (irreversible) because enzyme release might be partly due to increased turnover of cytoplasmic pools. A comparative quantification of myonecrosis in patients undergoing cardioplegic arrest under CPB using cine-MRI and contrast-enhanced MRI

would have assessed the functional significance of these biochemical markers in discriminating perioperative myocardial damage.

Fourth, a paired analysis of arterial-CS difference of released biomarkers would have determined the myocardial contribution to the biomarker of interest and integrated the total release of each marker over the time course of study.

Fifth, patients who received adrenaline may have a higher than average serum lactate level which may have confounded our interpretation.

Finally, when assessing the utility of a biochemical test, the ability to compare it with an established gold standard is paramount. Unfortunately, there is no easily applicable gold standard for the diagnosis of postoperative myocardial infarction in patients undergoing CABG. Like us, most authors used ECG criteria of newly developed Q-waves, left bundle branch block, ST-T changes, and/or echocardiographically detected and newly developed wall-motion abnormalities. Of note, ECG or echocardiographic changes would not allow the diagnosis of smaller or nontransmural infarcts to be tested.

CONCLUSIONS

We conclude that measurable transient subclinical cardiac damage exists in all patients undergoing cardiac surgery under CPB and cold blood cardioplegic myocardial protection strategy despite advances in myocardial preservation and CPB conduction. CS-derived LPR peaks earlier than CK-MB and there was a trend toward myocardial LPR, lactate, cTn-I, CK-MB, and pyruvate being the reliable diagnostic discriminators of perioperative myocardial damage. Serial determination of CS-derived-serum LPR, cTn-I, and CK-MB values at immediately after reperfusion before coming off bypass is useful in the rapid detection of perioperative myocardial injury.

The degree of myocardial damage is more in patients with advanced NYHA functional class, preoperatively poor LVEF, and/or CHF and those requiring increased aortic cross-clamp time during cardiac surgery.

The high cardiospecificity of LPR, cTn-I, and CK-MB could make these reliable diagnostic tools in the diagnosis of perioperative myocardial injury, the comparison of different myocardial preservation

strategies, and further decisions about diagnostic and therapeutic options in these patients.

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Conflicts of interest

There are no conflicts of interest.

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Appendix 1

DEFINITIONS (ELECTRONICS)

PERIOPERATIVE MYOCARDIAL INJURY

Perioperative myocardial infarction represents the most severe complication at the end of an adverse cascade, usually initiated by episodes of prolonged subendocardial ischemia, which might occur as a reversible or irreversible event and is no longer viewed as a binary event. It is now held that there exists a spectrum of myocardial injury characterized by increasing release of cardiac biomarkers to a full-blown picture of myocardial infarction. The reported incidence of perioperative myocardial injury after coronary artery bypass grafting (CABG) has varied considerably, ranging between 5% and 20%, partly as a result of the use of different definitions and diagnostic criteria. Published literature does not address the incidence of perioperative myocardial injury after routine CPB and cardioplegic arrest in non-CABG patients. The pathogenesis of perioperative myocardial injury after CABG is based on a variety of graft- and nongraft-related mechanisms. The graft-related reasons are graft occlusion, graft kinking or overstretching, subtotal anastomotic stenosis, or graft spasm. Nongraft-related causes include direct myocardial trauma by means of surgical manipulation, inadequate cardioplegic perfusion and myocardial protection, incomplete revascularization, and distal coronary microembolization caused by surgical manipulation. The gap between reversible myocardial ischemia and definite death of myocardial cells of a major area might be linked by the appropriate assessment of minor myocardial cellular injury, which could help to prevent myocardial infarction.

For uniformity with other studies in patients undergoing CABG with or without concomitant valve replacements, perioperative myocardial injury was considered to be present in the presence of one of the following criteria: (1) appearance of a new and persistent Q-wave with a duration of >40 ms in at least two adjacent leads; (2) disappearance of an R-wave or 25% reduction of R-waves in two leads; (3) appearance of ST-segment deviations at the J-point in two or more contiguous leads with cutoff points of greater than 0.2 mV in leads V1, V2, or V3 and greater than 0.1 mV in other leads or T-wave abnormalities in two or more continuous leads; (4) appearance of a new-onset left bundle branch block; (5) new and persistent wall-motion

abnormalities on transesophageal echocardiography; and (6) requirement of inotropic support to maintain stable hemodynamics as stated in the absence of mechanical external compression.

LOW OUTPUT SYNDROME AFTER CARDIOPULMONARY BYPASS AND CARDIOPLEGIC ARREST

Low output syndrome after CPB was diagnosed if the patient required inotropic support in the Intensive Care Unit (ICU) and/or intra-aortic balloon assistance postoperatively. It was diagnosed if the patient required inotropic support (dopamine, 4–10 µg/kg/min; dobutamine, 5–10 µg/kg/min, epinephrine, 0.01–0.1 µg/kg/min, milrinone, 50 µg/kg intravenous bolus, followed by 0.375–0.75 µg/kg/min), either isolated or in combination, in the operating room or in the ICU to maintain stable hemodynamics in the absence of mechanical external compression after correction of all electrolytes or blood gas abnormalities and after adjusting the preload to its optimal value.

Low output syndrome was also diagnosed if there was an increasing requirement of the above-mentioned inotropes along with afterload reduction using sodium nitroprusside. Patients who received <4 µg/kg/min of dopamine to increase renal perfusion were not considered to have low output syndrome.

Invasive monitors to measure cardiac output (CO) directly (Swan-Ganz Catheter [Edwards Lifesciences, Irvine, CA, USA], pulmonary artery pressure line, and thermistors) are cumbersome and hazardous at times due to the requirement of surgical manipulation.

In general, under the definition of low output syndrome after cardiac surgery, an integration of relevant clinical, laboratory, and bedside echocardiographic criteria were used. The criteria for diagnosis were cold extremities, absent pedal pulses, decreased toe temperature, reduced systolic pressure (<90 mmHg), decreased CO (<2.2 L/min/m²) or at least 30 min in the operating room or ICU, impaired renal function and oliguria (<1.0 mL/kg/h), metabolic acidosis, increased serum lactate levels (>2 mmol/L for >2 h), low mixed venous oxygen saturation (<50%), and blunt sensorium.

Stroke volume (SV) is the amount of blood pumped per heartbeat. SV variance (SVV) is variation in the

beat-to-beat SV around the mean during a respiratory cycle.

Normal acceptable range of measured variables: cardiac index (CI): 2.5–4.2 L/min/m²; stroke volume index (SVI): 30–65 mL/beat/m²; systemic vascular resistance index (SVRI): 1500–2500 dynes/s/cm⁵/m²; oxygen delivery index (DO₂I): 450–600 mL/min/m²; SVV: less than 10%; central venous pressure (CVP): 6–8 mmHg; blood lactate levels: 5 mmole/L; systemic arterial oxygen saturation >95%; arterial blood gas analysis: pH: 7.35–7.45; partial arterial oxygen tension: >100 mmHg; partial arterial carbon dioxide tension: 35–45 mmHg.

FLOTRAC™ SENSOR AND VIGILEO™ MONITOR (EDWARDS LIFESCIENCES, IRVINE, CA, USA)

The system consists of Flotrac™ sensor and processing/display unit (Vigileo, Edwards LLC). The sensor is a transducer that preprocesses and sends a signal to both the cardiovascular monitor (for real-time waveform display) and Vigileo monitor.^[13] The Vigileo is a small instrument, weighing 2.1 kg, and can be mounted on an intravenous pole. The processing unit applies a proprietary algorithm to the digitized arterial pressure wave, and reports CO, CI, SV, SVI, and SVV. If a CVP catheter has been placed, its signal can be interfaced with the Vigileo, allowing for the calculation of systemic

vascular resistance and SVRI. When used with a central venous oximetry catheter, the Vigileo also provides continuous central venous oxygen saturation. The rear panel of the Vigileo allows interfacing with CVP and oximetry, external video, and a printer (USB). The Vigileo reports hemodynamic parameters at 20 s intervals, performing its calculations on the most recent 20 s of data.

The system calculates the arterial pressure using arterial pulsatility, resistance, and compliance according to the following equation: stroke volume = $K * Pulsatility$, where K is a constant quantifying arterial compliance and vascular resistance, and pulsatility is proportional to the standard deviation of the arterial pressure wave over a 20 s interval. K is derived from patient characteristics (age, gender, height, and weight) as well as waveform characteristics. This calibration constant is recalculated every 10 min.

This advanced technology assesses all hemodynamic variables without requiring external calibration allowing its use in emergency room, medical/surgical ICU, and operation theater. It also reports SVV, i.e., the variation in the beat-to-beat stroke volume around the mean during a respiratory cycle. Patients suffering from hypovolemia exhibit an exaggerated SVV (>10%). However, SVV may be affected by other factors, such as vasodilator therapy, lung disease, and mechanical ventilation.