

Biomarkers in low cardiac output syndrome after open cardiac surgery in children

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Abstract

Background Corrective cardiac surgery is the standard management for complex congenital heart disease. Cardiopulmonary bypass surgery and post-surgical intensive care may lead to low cardiac output syndrome (LCOS), as a major complication after open heart surgery. To diagnose early LCOS, lactate level, pCO₂ gap, and mixed venous oxygen saturation (SvO₂) are parameters reported to have correlations with decreased cardiac output, morbidity, and post-cardiac surgery mortality.

Objective To determine the usefulness of lactate level, pCO₂ gap (arterial-vein), and SvO₂ for early detection of LCOS in children post-open heart surgery.

Methods This prospective cohort study was done from August to October 2017 in the ICU of the Integrated Cardiac Center, Dr. Cipto Mangunkusumo Hospital, Jakarta. Subjects were pediatric patients who underwent cardiac surgery. After surgery, patients underwent monitoring in the ICU for clinical signs of LCOS and examinations for lactate levels, pCO₂ gap, and SvO₂ at 15 minutes, 4 hours and 8 hours.

Results Thirty-three open heart surgery patients were the subjects. Lactate level at 4 hours and 8 hours post-operative were significantly higher in the LCOS group compared to non-LCOS group. For the pCO₂ gap, only the 4-hour post-operative results were significantly higher in LCOS group compared to non-LCOS groups. In addition, only SvO₂ at 4 hours after surgery was significantly lower in LCOS group compared to non-LCOS group.

Conclusion Elevated lactate, high pCO₂ gap, as well as decreased SvO₂ at 4 hours post-operatively are the most reliable markers of LCOS after pediatric open heart surgery. [Paediatr Indones. 2021;61:223-8; DOI: 10.14238/pi61.4.2021.223-8].

Keywords: LCOS; lactate; pCO₂ gap; SvO₂

Congenital heart disease (CHD) is the common congenital disorder in children, appearing in 0.8% of births or 8-10 of every 1,000 live births. Approximately 2.6 per 1,000 live births with CHD are considered to be in a critical state, as severe malformations requiring corrective cardiac surgery continue in the first year of life.¹⁻³ Corrective heart surgery with cardiopulmonary bypass (CPB) is an option for management of cardiac anomalies, but post-cardiac surgery mortality and morbidity are still reported. Decreased cardiac output is an important problem post-open heart surgery. One such complication is low cardiac output syndrome (LCOS), which is caused by a temporary decrease in systemic perfusion due to cardiac myocardial dysfunction.⁴⁻⁶

The presence of myocardial dysfunction can effect hemodynamic disorders by low diuresis and metabolic acidosis followed by decreased cardiac index (CI) <3.5

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L/min/m, which indicates the occurrence of LCOS.^{7,8} Decreased cardiac output after open heart surgery is a sign to begin treatment in order to increase cardiac contractility and reduce afterload. In the early stages, the body will compensate by high oxygen extraction, hence, the amount of oxygen remaining will be low when returning to the right atrium. The remaining amount of oxygen used by tissue can be evaluated by mixed venous oxygen saturation (SvO₂). In some studies, SvO₂ had correlations with cardiac output, lactate levels, and mortality outcome.^{8,9}

High lactate is a sign of hypoperfusion due to oxygen delivery failure and anaerobic metabolism due to tissue hypoperfusion. Lactate was also reported to increase 0.9 μm per hour post-operatively, and was associated with infant mortality.¹⁰ A previous study found that lactate >3 mmol/L correlated with post-operative global hypoperfusion of the heart.¹¹ Another study found that children who underwent cardiopulmonary pulmonary bypass had higher lactate level and low SvO₂ that were associated with low cardiac output (CO).¹² Another indicator of LCOS is the venous-to-arterial pCO₂ gap, which is the voltage difference between venous pCO₂ and arterial pCO₂. After open heart surgery, a wide pCO₂ gap indicates hypoperfusion.¹³ Studies have shown high pCO₂ gaps in experimental animals, with 60% blood flow reduction and decreased cardiac output. Other studies also reported that pediatric patients undergoing extracorporeal membrane oxygenation (ECMO) with a low pCO₂ gap had significantly better survival rate than patients with a high pCO₂ gap.^{13,4}

We aimed to compare lactate levels, pCO₂ gap, and SvO₂ in LCOS and non-LCOS pediatric patients after open heart surgery.

Methods

This prospective cohort study was done in CHD patients aged 1 month to 18 years who underwent open heart surgery with cardiopulmonary bypass (CPB) at the Integrated Cardiac Center, Dr. Cipto Mangunkusumo Hospital, Jakarta. Post-operative patients were monitored for clinical signs of LCOS for 12 hours post-surgery, at 4-hour intervals (15 minutes, 4 hours, 4-8 hours, and 8-12 hours). Low cardiac output syndrome (LCOS) was defined as decreasing of cardiac

index (CI) in the absence of relative hypovolemia due to left ventricular and/or right ventricular failure that usually occurs after cardiac surgery and other clinical conditions. Cardiac index (CI) was cardiac output divided by total body surface area, normal value CI are <3.5-5.5 L/min/m². Identification of LCOS manifestations in ICU included CI <3.5L/minute/m², central venous pressure <8 mmHg, capillary filling >3 seconds, tachycardia, hypotension, hypothermia (T<36.5°C), and urine output <1mL/kg/hour. The CI measurements using trans-thoracic echocardiography (*Philips Affiniti 60*) were performed by the pediatric cardiologist or intensivist on duty after open heart surgery. Blood specimens were taken from the femoral artery catheter for assessment of lactate level and central venous catheters at the internal jugular vein into the superior vena cava for assessment of pCO₂ venous-to-arterial gap and SvO₂ at 15 minutes, as well as 4 and 8 hours post-cardiac surgery. Blood specimens were analyzed using a blood gas analysis machine. Lactate level, pCO₂ gap, and SvO₂ in the LCOS and non-LCOS groups after cardiac surgery were analyzed by independent T-test and Mann-Whitney test. Results with P values <0.05 were considered to be statistically significant.

This study was approved by the Health Research Ethics Commission at the Universitas Indonesia Medical School/Dr. Cipto Mangunkusumo Hospital, Jakarta.

Results

A total of 33 post-cardiac surgery subjects were evaluated from August to October 2017. The basic characteristics of subjects are described in **Table 1**. Subjects' mean age was 64.5 months and most were female 17 (51.5%). The most prevalent CHD type was TF in 15 (45.5%) patients, followed by VSD in 4 (12.1%) patients. There were 15 children (45.5%) with LCOS. The mean timing of LCOS was 3.93 hours (SD 1.792) post-operatively.

Subjects with LCOS had longer mean CPB and duration of surgery, but the differences were not statistically (**Table 2**). With regards to hemodynamic assessment and cardiac afterload ability, cardiac index (CI) was lower in the LCOS than in the non-LCOS group at 15 minutes post-operatively [3.54 (SD 2.59)

Table 1. Baseline characteristics of subjects

Characteristics	N=33
Sex, n	
Male	16
Female	17
Mean age (SD), months	64.55 (50.531)
Mean body weight (SD), kg	15.14 (9.581)
Mean height (SD), cm	98.82 (26.752)
Nutritional status, n	
Normal	11
Underweight	19
Malnourished	2
Overweight	1
CHD type, n	
Absent pulmonary valve	1
ASD	1
ASD+MR+TR	1
PA-VSD	1
Partial AVSD	1
PS+PDA	1
TF	15
TF+ASD	2
VSD	4
Residual VSD	1
VSD+ASD+PDA	1
VSD+PDA	3
VSD+PS	1
Comorbidities, n	
Down syndrome	1
Underweight	19
Malnourished	2
Noonan syndrome	1
None	9
Surgical procedure, n	
ASD closure+MV repair	1
ASD closure+MV repair +TV repair	1
Comisurotomy+PDA ligasi	1
Rastelli procedure	4
Repair of partial AVSD	1
TF correction	14
TF correction +ASD closure	2
VSD closure+ASD closure+PDA ligation	1
VSD closure	4
VSD closure+excision PS	1
VSD closure+PDA ligation	3
LCOS, n	
Yes	15
No	18

Mean timing of LCOS occurrence (SD), hours 3.93 (1.792)

ASD: atrial septal defect, MR: mitral regurgitation, TR: tricuspid regurgitation, VSD: ventricular septal defect, PDA: patent ductus arteriosus, TF: tetralogy of Fallot, PH: pulmonary hypertension, AVSD: atrioventricular septal defect, PS: pulmonary stenosis

vs. 3.84 (SD 1.18) L/minute/m², respectively]. In addition, at 4 hours and 8 hours post-surgery, CIs were lower in the LCOS group than in the non-LCOS group.

However, CI was not significantly different between groups at any time point.

Table 3 shows the distribution of lactate level, pCO₂ gap, and SvO₂ among subjects after open heart surgery. Mean lactate levels were not significantly different in the LCOS and non-LCOS groups at 15 minutes post-operatively (P=0.060). However, at 4 hours post-operatively, mean lactate level was significantly higher in the LCOS group than in the non-LCOS group [5.44 (SD 8.843) vs. 1.94 (SD 0.849) mmol/L, respectively (P=0.021)]. At 8 hours post-operatively, lactate levels decreased in both groups, but remained significantly higher in the LCOS group [2.25 (SD 0.622) vs. 1.28 (SD 0.635) mmol/L, respectively (P<0.0001)].

At 15 minutes post-operatively, the mean pCO₂ gap was not significantly different between LCOS and non-LCOS patients [4.36 (SD 4.768) vs. 5.29 (SD 3.566) mmHg, respectively]. At 4 hours post-operatively, the pCO₂ gap was significantly higher in the LCOS group [8.67 (SD 2.389) mmHg] than in the non-LCOS group [5.80 (SD 3.566) mmHg], with a moderate correlation (R=0.543). At 8 hours post-operatively, the pCO₂ gap decreased in both groups, but was not significantly different [5.56 (SD 3.061) vs. 5.80 (SD 3.566) mmHg, respectively].

Mean SvO₂ at 15 minutes post-operatively was higher in the LCOS group [80.43 (SD 11.033) %] compared to the non-LCOS group [79.60 (SD 8.400) %], but the difference was not significant. At 4 hours post-operatively, mean SvO₂ decreased in both groups, and was significantly lower in the LCOS group compared to the non-LCOS group [70.44 (SD 4.110) vs. 76.50 (SD 4.387) %, respectively]. At 8 hours post-operatively, SvO₂ was decreased in both groups but the difference was not significant.

Discussion

Low cardiac output syndrome is one of the major cardiovascular complications associated with complex cardiac surgery. This condition is due to an imbalance between oxygen delivery and oxygen consumption at the cellular level, resulting in hypoxia-ischemia caused by decreased cardiac output associated with post-surgical myocardial injury. Factors contributing to LCOS are longer durations of surgery, cardiopulmonary

Table 2. Characteristics of surgical procedures and hemodynamics after cardiac surgery in the LCOS and non-LCOS groups

Characteristics	Groups		P value
	Non-LCOS (n=18)	LCOS (n=15)	
Mean duration CPB (SD), min	78.50 (24.88)	100.33 (48.07)	0.103 ^a
Mean duration ACC (SD), min	44.33 (26.17)	40.87 (19.04)	0.842 ^b
Mean duration of surgery (SD), min	189.94 (29.15)	225.13 (70.49)	0.073 ^b
Mean post-operative arterial pressure (SD), mmHg			
15 minutes	77.27 (16.50)	59.00 (10.39)	0.01 ^a
4 hours	76.22 (15.94)	61.66 (10.45)	0.05 ^a
8 hours	67.94 (19.55)	60.33 (9.39)	0.016 ^b
Mean post-operative SVRI (SD), dyne*sec/cm ⁵ *m ²			
15 minutes	1,543 (719.25)	1,288.22(841.18)	0.270 ^b
4 hours	1,400.47 (701.63)	1,404 (692.86)	0.857 ^b
8 hours	1,559.11 (800.85)	1,268.86 (725.90)	0.262 ^b
Mean cardiac index (SD), L/min/m ²			
15 minutes	3.84 (1.18)	3.54 (2.59)	0.096 ^b
4 hours	3.98 (1.34)	3.32 (1.60)	0.209 ^a
8 hours	3.53 (1.20)	3.47 (1.93)	0.375 ^b

^aindependent T-test, ^bMann-Whitney test, ^cPearson's correlation test, ^dSpearman's correlation, CPB=cardiopulmonary bypass, ACC=aortic cross clamp, SVRI=systemic vascular resistance index

Table 3. Analysis of lactate, pCO₂ gap, and SvO₂ in LCOS after open heart surgery in patients with and without LCOS

Variables	Groups		R	P value
	Non-LCOS (n=18)	LCOS (n=15)		
Mean post-operative lactate (SD), mmol/L				
15 minutes	1.81 (0.998)	2.72 (1.627)	0.333 ^d	0.060 ^b
4 hours	1.93 (0.849)	5.44 (8.843)	0.407 ^d	0.021 ^b
8 hours	1.28 (0.635)	2.25 (0.622)	0.621 ^c	<0.0001 ^a
Mean post-operative pCO ₂ gap (SD), mmHg				
15 minutes	5.29 (3.566)	4.36 (4.768)	-0.114 ^c	0.526 ^a
4 hours	5.80 (3.566)	8.67 (2.389)	0.543 ^d	0.002 ^b
8 hours	7.38 (3.872)	5.56 (3.061)	-0.256 ^c	0.150 ^a
Mean post-operative SvO ₂ (SD), %				
15 minutes	79.60 (8.400)	80.43 (11.033)	0.195 ^d	0.270 ^b
4 hours	76.50 (4.387)	70.44 (4.110)	-0.681 ^d	<0.0001 ^b
8 hours	77.92 (4.905)	75.22 (4.391)	-0.284 ^c	0.109 ^a

^aindependent T-test, ^bMann-Whitney test, ^cPearson's correlation test, ^dSpearman's correlation

bypass, and aortic cross clamp, as well as complex cardiac abnormalities accompanied by residual lesions, comorbid cyanosis and malnutrition, surgical reperfusion injury, in addition to post-surgical comorbidities such as inflammation, infection, renal failure, and arrhythmias. Mortality rates for LCOS are reported to be around 20% and mostly occur in the 12-hour post-operative period.^{19,20}

We evaluated 33 children who underwent cardiac surgery. Most subjects were female (51.5%); the overall mean age was 64.55 (SD 50.53) months. There were 15 children (45.5%) who experienced LCOS, at a mean time of 3.93 (SD 1.792) hours post-operatively. The most common CHD type was TF (15/33), whom

11/33 subjects had experienced LCOS.

Lactate levels were significantly higher in the LCOS group at 4 and 8 hours post-operatively. Higher lactate and the occurrence of LCOS in the initial period after surgery were also noted by a study which explained that lactate contributes to myocardial dysfunction, global hypoperfusion, and low cardiac output that manifests as worsening hemodynamics after pediatric cardiac surgery.^{10,12-14} Another study also found that in children who underwent cardiac surgery, 43.3% had a mean serum lactate level of more than 4.8 mmol/L. Increased risk of morbidity and mortality was found in those with lactate concentrations of >4.8 mmol/L in the early post-operative hours. Lactate concentration of

4.8 mmol/L or higher in the early post-operative hours was able to identify risk of morbidity and mortality.¹⁵ Several studies also reported that lactate values >3 mmol/L after cardiac surgery were able to predict post-surgical cardiac complications. In early 4 hours until advance phase of 12 hour in the ICU, an increase in lactate > 3mmol/L at 4 to 12 hours was also significantly related to shock (MAP <70mmHg), complex post-surgical complications, and mortality.¹⁶⁻¹⁸

In children undergoing complex corrective heart surgery, myocardial dysfunction often occurs in the form of low cardiac output. When cardiac output falls, metabolic changes occur due to inadequate perfusion at the cellular level. The presence of perfusion disorders leads to cellular hypoxic ischemia, triggering different partial carbon dioxide levels, which is reflected by the increased pCO₂ gap.¹⁹

The significant difference in pCO₂ gap at 4 hours post-operatively indicates that this variable may be useful as a biomarker to predict the occurrence of LCOS. Post-surgical pCO₂ gap has often been used, with a high pCO₂ gap > 6mmHg reported to be significantly associated with increased post-surgical complications in high-risk surgical patients. A high pCO₂ gap was correlated with increased hypoperfusion due to post-operative bradycardia. Furqan *et al.*²¹ also reported that a pCO₂ gap > 7mmHg correlated with SvO₂ reduction to <70% and was useful for identifying LCOS after complex cardiac surgery.

The SvO₂ levels are affected by hemoglobin levels and the oxygen extraction process at the cellular level. Myocardial dysfunction leads to low cardiac output, followed by more oxygen extraction at the tissue and cellular levels as an effect of reduced oxygen delivery. Ultimately, this process leads to a decrease in the saturation value of oxygen returning to the vein.²² In our study, the significant difference in SvO₂ at 4 hours post-operatively (r=0.681; P<0.0001) suggests that SvO₂ may be predictive of LCOS at this time point. Another study suggested that low SvO₂ correlated with increased lactate and pCO₂ gap, as effects in hemodynamic disorders after complex pediatric cardiac surgery.²³ In another study of hypoplastic cardiac surgery, most subjects with cardiac complications such as CHF and arrhythmia had lower SvO₂ of < 59%. The SvO₂ in LCOS was also explained in patients who took levosimendan. Patients with higher SvO₂ and low lactate values were reported have better outcomes

after CPB.²³

Our findings suggest that a combination of lactate level, pCO₂ gap, and SvO₂ at 4 hours post-cardiac surgery in children could be used as a screening tool for LCOS. A limitation of our study was that most subjects had poor nutritional status, which might have affected outcomes. In addition, the mean time of LCOS occurrence was 3.93 (SD 1.79) hours post-operatively. Yet the examinations were not done at the time of LCOS clinical signs, but at 15 minutes, 4 hours, and 8 hours post-operative. The lactate level, pCO₂ gap, and SvO₂ might have changed after resuscitation and inotropic administration for LCOS management. In conclusion the increasing of lactate level and pCO₂ gap followed low level of SvO₂ become indicator to diagnose low cardiac output syndrome post-open heart surgery. Further study may needed regarding about therapeutic response, effect other factor pre-operative nutritional status, comorbidities, intraoperative cardiac factors, cardiac index and other hemodynamic markers that may influence the occurrence of LCOS.

Conflict of Interest

None declared.

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