Superior cava vein saturation and cardiac lactate as cardiac output predictor after cardio-pulmonary bypass on children

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Abstract

***Objective*: to evaluate cardiac heart lactate, superior cava vein saturation and microcirculation dysfunction as cardiac output predictors after surgery on patients with Tetralogy of Fallot (TF) through measuring serum level of sTNFR-1 and IL-6.**

***Design*: cohort study**

***Setting*: Cipto Mangunkusumo Hospital**

***Patient and participants*: Subjects were children aged 1 to 6 years that underwent corrective surgery. Subjects who met the inclusion criteria were divided into 2 groups after ischemia-reperfusion injury (post surgery). The first group was subjects with high cardiac lactate and the second group was subjects with low cardiac lactate.**

***Measurements and results*: Subjects were observed for 24 hours; during surgery, 6 and 24 hours after aortic clamp removed. During July 2012 - December 2013, there were 52 patients who became subjects. There were proportion differences between cardiac lactate and cardiac output change after cardiac surgery. Increase of cardiac lactate has a correlation with increasing levels of sTNFR-1 and IL-6 and decreasing index of Tc, ScvO2 and cardiac output. There were correlations among low index of ScvO2, high index of cardiac lactate and decrease of cardiac output. High sTNFR-1 and IL-6 were correlated to low cardiac output. Cardiac lactate, ScvO2 and MAP can be used as predictors of cardiac output change in patients with cardio-pulmonary bypass. sTNFR-1 and IL-6 levels were correlated with cardiac output changes after cardiac surgery.**

***Conclusion*: Cardiac lactate and $ScvO_2$ are valuable in measuring cardiac output changes on patient with cardio-pulmonary bypass.**

Key words: Cardio-pulmonary bypass, IL-6, cardiac lactate, ScvO2, sTNFR-1, tetralogy of Fallot.

Introduction

Tetralogy of Fallot (TF) is the most common cyanotic congenital heart disease (CHD) in children that require corrective surgery as definitive therapy. (1) Corrective surgery is performed by using the cardio-pulmonary bypass machine (CBM) that put patients on ischemia-reperfusion injury risk. (2)

Pathogenesis of ischemia-reperfusion injury involves pro-inflammatory cytokines. Common cytokines originating from cardiac are tumor necrosis factor alpha (TNF-α) (3) and interleukin 6 (IL-6). (4) TNF-α level is not stable in the circulation and determined by examining the soluble tumor necrosis factor receptor (sTNFR-1), a form of TNF-α active ligand in circulation that bind to its receptor. (5) These cardiac pro-inflammatory cytokines are large enough to induce high lactate level. (6) High levels of cardiac lactate is due to inhibition of pyruvate dehydrogenase (PDH) enzyme in mitochondria persist 2-45 minutes after ischemia-reperfusion injury. Pyruvate dehydrogenase is converting pyruvate into acetyl-CoA and will inhibit PDH enzyme due to persistent high lactate. High levels of cardiac lactate will affect cardiac muscle performance due to insufficiency of cardiac energy metabolism, especially the left ventricle muscle which requires a very high energy and adequate oxygenation in metabolism. The decrease of left ventricle muscle performance will lead to low cardiac output after cardio-pulmonary shunt. (7)

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Low cardiac output, in turn, can cause microcirculation failure. (8) Microcirculation failure that persists in 24 hours will lead to pathogenic cascade activation that can end as organ failure. Monitoring becomes important at the level of microcirculation, oxygen delivery, and tissue oxygenation levels. (9,10)

This study used transcutaneous CO2 monitoring to monitor dysfunction that occurs at the level of microcirculation and ScvO2 that continuously monitor oxygen delivery and tissue oxygenation levels. (11) Microcirculation dysfunction and ScvO2 monitoring are very helpful in evaluating postoperative interventions and also able to predict decrease of cardiac output in the normal hemodynamic condition after surgery. (12,13) This study aimed to answer challenges of monitoring cardiac output performance after the surgery. As far as we know this was the first study that evaluated cardiac lactate and ScvO2 levels to predict microcirculation dysfunction after cardiac correction surgery in children.

Materials and methods

This was a cohort study on patients with TF aged 1 to 6 years that underwent an open surgery at Cipto Mangunkusumo Hospital. The study was conducted in three phases, the first phase was a cross-sectional study, phase II was a cohort study, and phase III was cohort study with multivariate analysis. Subjects were children aged 1 to 6 years that underwent corrective surgery. Subjects who met the inclusion criteria were divided into 2 groups after ischemia-reperfusion injury (post surgery). The first group was subjects with high cardiac lactate and the second group was subjects with low cardiac lactate. The study had been approved by the Ethics Committee of Medical School of University of Indonesia/Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Cardiac lactate samples were obtained during the cross-clamp period and at prespecified during reperfusion. Lactate level was measured from serum obtained from cardio-pulmonary bypass machine using Stat Profil® Critical Care xpress (Nova Biomedical) in mmol/L. Cardiac lactate was difference of lactate level from coronary and serum on 5-10 minutes reperfusion. Both groups were followed for 24-hour monitoring with clinical and laboratory parameters that regularly used. Regular monitoring was added with ScvO2 and transcutaneous CO2. Value of ScvO2 was performed with fiber optic double lumen central venous catheter (CVC) that inserted from internal jugular vein. Both groups were assessed in two phases: first phase on 6 hours and second phase on 24 hours after the ischemia-reperfusion injury. Value of ScvO2 and transcutaneous CO2 level (in the form of Tc index and Δ CO2) were taken just before patient underwent surgery, on 6 hours of monitoring, and 24 hours monitoring. Subjects were divided into 2 groups: group with normal cardiac output and decreased cardiac output. Cardiac output was obtained by assessing cardiac index (CI) using echocardiography on the 6 hour and 24 hour monitoring. Blood samples for pro-inflammatory cytokines examination were performed in three consecutive times; prior surgery, 6 hours, and 24 hours of monitoring.

Subject characteristics were assessed on phase I and II to see whether there were differences in the characteristics of the two groups that affected study. Continuous data with normal distribution were analyzed with independent t-test, while abnormal data were analyzed with non-parametric Mann Whitney test. Multivariate analysis was performed to identify factors that could predict cardiac output and formula quality was assessed by using Anova test. Assessment of mean difference in each group was performed by using GLM test.

Results

There were 52 patients participated in this study with age ranged between 1 year and 4 months to 6 years and 3 months. A total of 22 patients included in the group of low cardiac lactate (≤0.8 mmol/L) and 30 others in the group of high cardiac lactate. This study showed a new cut off point for cardiac lactate derived in 5-10 minutes post ischemia-reperfusion injury: 0.8 mmol/L with area under the curve (AUC) of 86.8% (95% CI:76-98%, p<0.001) (**Figure 1**).

In the first phase we found that the average level of ScvO2 showed significant correlation in both groups of cardiac lactate. In the group of higher cardiac lactate, ScvO2 levels were lower. While the association of pro-inflammatory cytokines (sTNFR-1 and IL-6) with cardiac lactate only showed by sTNFR-1. Subjects with higher sTNFR-1 level also showed higher cardiac lactate levels. The correlation between postoperative cardiac lactate and microcirculation dysfunction (Tc index and ΔCO2) were only found in the Tc index alone. Higher postoperative Tc index was obtained in lower cardiac lactate levels (**Table 1**).

In the phase II study, we found that cardiac lactate showed a significant correlation in both groups of cardiac output, higher cardiac lactate was significantly correlated with low cardiac output group. ScvO2 levels also showed a significant correlation

with cardiac output. Lower ScvO2 was obtained in the lower cardiac output group. Pro-inflammatory cytokines (sTNFR-1 and IL-6) and cardiac output group showed significant correlation (**Figures 2 and 3**). High pro-inflammatory cytokines significantly correlated with low cardiac output group. Microcirculation dysfunction (Tc index and ΔCO2) with postoperative cardiac output showed no significant correlation in both groups.

Phase III study aimed to determine the predictive model of decreased cardiac output in TF patients postoperative. Bivariate analysis was conducted to determine any factors that included in the multivariate analysis and the final results of multivariate analysis showed that mean arterial pressure (MAP), cardiac lactate, and ScvO2 values could be used as a predictor of cardiac output decrease after surgery (**Table 2**). Anova test for formula quality indicated that the formula had decent quality with adjusted R-square value of 52.7%.

Discussions

This study got a new cut off point for cardiac lactate of 0.8 mmol/L. Studies in children generally give higher lactate values than those in adults. This new cut off point obtained was relatively strong. The correlation among each variable in this study further referred on the 6 hour examination, because the 24 hour results were influenced by interventions that performed in 6th until 24th hours. Intervention on the monitoring period must be performed in order to uphold a code of conduct in the safety of patient's manner during study period.

The correlation of cardiac lactate and ScvO2 levels in this study showed that the magnitude increased of cardiac lactate during post ischemia-reperfusion injury would affect cardiac muscle performance at a later time. The role of pro-inflammatory cytokines (sTNFR-1 and IL-6) on cardiac lactate production on this study only showed by sTNFR-1, because IL-6 was still influenced by other factors. Values of sTNFR-1 showed significant correlation in both cardiac lactate groups as TNF-α works directly on the myocardium through sphingosine. The greater the exposure to cardiac muscle, the greater the production of TNF-α and lactate levels. Correlation of cardiac lactate and microcirculation dysfunction (Tc index and ΔCO2) was indicated significantly only by Tc index. Higher cardiac lactate level was significantly correlated with lower Tc index. This showed that the manipulation of the cardiac during the reperfusion injury was able to cause microcirculation disorders resembling sepsis. 24-hour monitoring of patients in the ICU showed improvement in ScvO2 levels, pro-inflammatory cytokines, and microcirculation dysfunction in both cardiac output groups. The improvement was a result from drugs and other interventions that were performed at the time of 6-24 hours of observation in the ICU, and this implicated on better results after 24 hours monitoring.

The correlation between cardiac lactate, ScvO2, pro-inflammatory cytokines (sTNFR-1 and IL-6), microcirculation dysfunction (index ΔTc and CO2) with cardiac output decrease were only indicated by cardiac lactate, ScvO2, and pro-inflammatory cytokines. The difference in the new microcirculation evident within 24 hours after treatment started. Subsequent monitoring after 24 hours of observation and hemodynamic interventions showed microcirculation improvement of both groups. Microcirculation differences in both groups were very likely due to three subjects that had decreased cardiac output syndrome, although the values were not significant.

The final assessment to determine predictor of decreased cardiac output was performed in two steps using bivariate and multivariate analyzes. Clinical and laboratory standard parameters were also included as a predictor factors of cardiac output due to those factors were act as a parameter used in the ICU. Multivariate analysis showed that MAP, cardiac lactate, and ScvO2 could be used as a predictor of cardiac output decreased in TF patients after surgery. However, equation (**Figure 4**) that was obtained only determined 52.7% predictors of decreased cardiac output, while the remaining 47.3% was explained by other variables that was not examined, this would lead to further study need to assess decreased cardiac output causes in children with cardio-pulmonary bypass surgery.

Conclusions

Cardiac lactate and ScvO2 are valuable in measuring cardiac output changes on patient with heart-pulmonary bypass.

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Conflict of interest

The authors affirm no conflict of interest on this study.

Table 1. Differences in sTNFR-1, IL-6, Tc index and ΔCO2 within 24 hours with cardiac lactate on TF patients

	Cardiac lactate ≤0.8 mmol/L n=22	Cardiac lactate >0.8 mmol/L n=30	Hypothetical test*
ScvO2 Mean (SD)	74.86 (4)	74.15 (5.9)	p=0.05
sTNFR-1 (ng/mL) Median (P25-P75)	929.9 (546-4851.86)	1359.9 (703.43-5643.86)	p<0.001
IL-6 (pg/mL) Median (P25-P75)	49.9 (22.62-267)	58.6 (11.67-482.53)	p=0.08
Tc index (torr) Median (P25-P75)	0.67 (0.4-0.79)	0.66 (0.23-0.89)	p=0.07
ΔCO2 (torr) Median (P25-P75)	11.1 (5.6-13.1)	11.6 (9.2-14.2)	p=0.3

Legend: *=Mann-Whitney test for unpaired median group.

Table 2. Differences at 6 hours ScvO2, cardiac lactate and cytokines in open surgery children with cardiac index <2.5 L/min/m2 and ≥2.5 L/min/m2

	Cardiac index <2,5 L/min/m2 n=23	Cardiac index ≥2,5 L/min/m2 n=29	Hypothetical test*
ScvO2 (%) Mean (SD)	65 (56-79)	72 (59-87)	p<0.0001
Cardiac lactate (mmol/L) Mean (SD)	1 (0.2-2.1)	0.6 (0.1-1.3)	p<0.0001
sTNFR-1 (ng/mL) Median (P25-P75)	1120.3 (665.65-3319.88)	862.04 (381.76-1903.77)	p<0.0001
IL-6 (pg/mL) Median (P25-P75)	146.1 (52.5-300)	97.0 (21.13-300)	p=0.01

Legend: *=Mann-Whitney test for unpaired median.

Figure 1. Receiver-operating-characteristic of cardiac lactate as a predictor of cardiac output

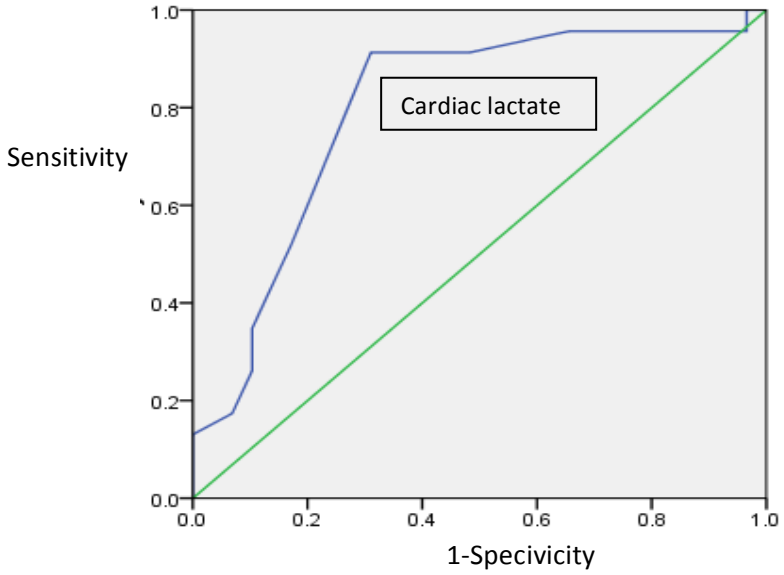

Figure 2. IL-6 pattern within 24 hours after open cardiac surgery on TF children with decreased cardiac output

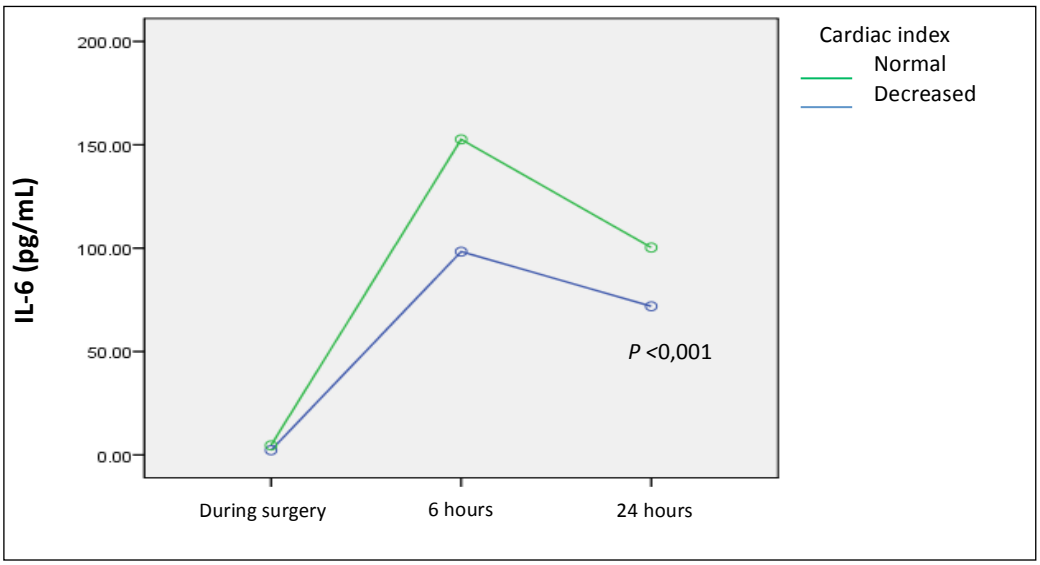

Figure 3. sTNFR-1 pattern within 24 hours after open heart surgery on TF children with decreased cardiac index

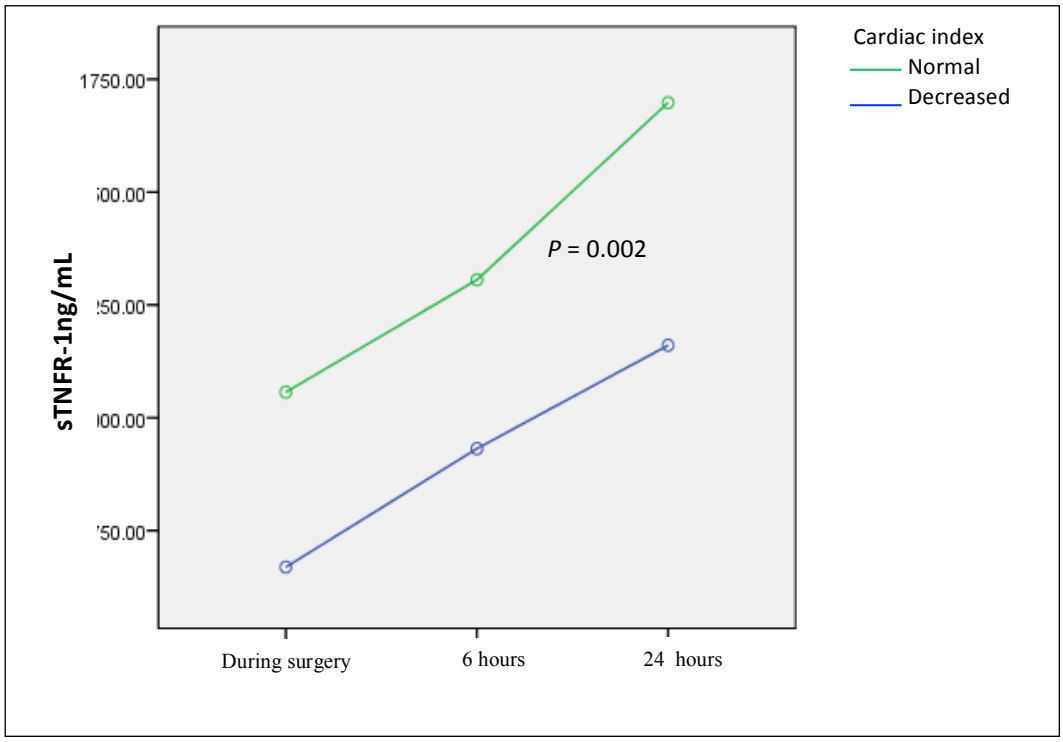

Figure 4. Formula of decreased cardiac output

Decreased cardiac output = -1.620 (constant) + (0.018*MAP) – (0.652*cardiac lactate) + (0.06*ScvO2)

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