Oral Triiodothyronine Supplementation Decreases Low Cardiac Output Syndrome After Pediatric Cardiac Surgery

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Abstract

The oral triiodothyronine for infants and children undergoing cardiopulmonary bypass (OTICC) trial showed that Triiodothyronine (T3) supplementation improved hemodynamic and clinical outcome parameters. We tested the validity of low cardiac output syndrome (LCOS), derived using clinical parameters and laboratory data, by comparing the LCOS diagnosis with objective parameters commonly measured in a cardiac intensive care unit (CCU) setting. OTICC, a randomized, placebo-controlled trial included children younger than 3 years with an Aristotle score between 6 and 9. We used the existing trial data set to compare the LCOS diagnosis with echocardiographic hemodynamic parameters. Additionally, we determined if LCOS, prospectively assigned during a clinical trial, served as an early predictor of clinical outcomes. All LCOS subjects at 6 and 12 h after cross-clamp release later showed significantly lower pulse pressure, stroke volume and cardiac output, and higher systemic vascular resistance. These LCOS patients also had significantly longer time to extubation (TTE) and higher mortality rate. LCOS incidence was significantly lower in the T3 treatment group [$n = 86$ vs. 66, respectively, $p < 0.001$; OR (95% CI) 0.43 (0.36–0.52)] particularly at 6 h. Also, LCOS patients in the placebo group had significantly lower FT3 serum levels over time. These analyses confirm that early clinically defined LCOS successfully predicts cardiac dysfunction determined later by objective hemodynamic echocardiographic parameters. Furthermore, early LCOS significantly impacts TTE and mortality. Finally, the data support prior clinical trial data, showing that oral T3 supplementation decreases early LCOS in concordance with reducing TTE.

Keywords Euthyroid sick syndrome · Congenital heart disease · Cardiopulmonary bypass · Low cardiac output syndrome · Thyroid hormone replacement

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Introduction

Thyroid hormone production is profoundly reduced in children undergoing congenital heart surgery using cardiopulmonary bypass (CPB). This phenomenon has been recognized as “Euthyroid Sick Syndrome” which commonly occurs as a response to critical illness [1, 2]. One of the physiological backgrounds is an impairment of the deiodinase enzyme to convert thyroxine (T4) to triiodothyronine (T3), the biologically active form of thyroid hormone [3]. In general, thyroid hormone acts as inotropic, chronotropic, and vasoactive agent and thereby enhances cardiac output. Thyroid hormone initiates these effects on cardiac performance to cellular and extracellular receptors, which results in an increased calcium uptake and protein transcription and translation [4]. In particular, a developing heart is thyroid-dependent in its metabolic and physiologic activity. Thus, impairment of thyroid hemostasis can severely impact this young population especially during congenital heart surgery with cardiopulmonary bypass [5].

Owing to the importance of thyroid hormone in modulating cardiac function, thyroid supplementation has been evaluated in many clinical trials [6–10]. T3 supplementation demonstrated a number of clinical advantages such as enhancing inotropic drug potency and preventing low cardiac output [6–10]. Intravenous T3 supplementation decreased time to extubation (TTE) and minimized the use of inotropic agents by improving cardiac function in children under 5 months after cardiac surgery [9]. In addition, the “Oral Triiodothyronine for Infants and Children undergoing Cardiopulmonary bypass (OTICC) trial” demonstrated that oral T3 supplementation elevated T3 without evidence of adverse events and showed similar success in reducing TTE [10, 11].

Low cardiac output syndrome (LCOS) occurs frequently in children after cardiac surgery and has been used as a clinical end point in many trials [12–14]. Although the etiology of LCOS is multifactorial, depression of T3 certainly is one of the contributing factors [15]. Oral T3 supplementation has proven to decrease LCOS at 6 h after aortic cross-clamp removal [10].

The assessment of LCOS is based on reproducible hemodynamic measurements using thermodilution catheters within the pulmonary artery in adults. However, due to the risk associated with these indwelling catheters in young patient with congenital heart disease, this approach is not used in children or after congenital heart surgery. As routinely performed in centers worldwide, LCOS is assessed by a combination of clinical parameters and laboratory findings, such as the presence of a minimum of two clinical findings (tachycardia, oliguria, poor peripheral perfusion, or cardiac arrest) and/or a central venous

saturation less than 60% (oxygen extraction ratio higher than 40%), with or without metabolic acidosis or increased lactate levels, resulting in an escalation of therapy.

The primary objective of this study was to test the validity of LCOS, derived using clinical parameters and laboratory data, by comparing the LCOS diagnosis with objective parameters commonly measured in a cardiac intensive care unit (CCU) setting. We used the existing trial data set from the “Oral Triiodothyronine for Infants and Children undergoing Cardiopulmonary bypass (OTICC) trial” [10] to compare the LCOS diagnosis by clinical assessment and laboratory findings which resulted in therapy escalation with echocardiographic and hemodynamic parameters. Additionally, we sought to determine if LCOS, prospectively assigned during the trial, served as a predictor of clinical outcomes, including time to extubation (TTE), length of CCU stay, time to hospital discharge, and mortality. We also aimed to more fully characterize a subgroup, which did not appear to respond to triiodothyronine in OTICC.

Materials and Methods

Study Design

This study is an ancillary analyses of data obtained in the oral triiodothyronine for infants and children undergoing cardiopulmonary bypass (OTICC) trial. OTICC was performed as randomized placebo-controlled double-blind clinical trial [10]. All data were obtained at the National Cardiovascular Center Harapan Kita, Jakarta, Indonesia. The study was approved by ethical research committee and registered on ClinicalTrials.gov under identifier number NCT02521168. The primary intervention was oral triiodothyronine supplementation during and after cardiopulmonary bypass. The protocol including T3 dose and timing are described in the parent study article [10].

Patients

All patients were recruited consecutively and evaluated starting from July 1, 2013 to October 16, 2014. Informed consent by the parents or legal guardians was obtained. Inclusions criteria were children subjected to CPB for Congenital Heart Disease (CHD) repair aged less than 3 years of age with an Aristotle score of 6 to 9. Patients with single-ventricle physiology, birth weight below 2 kg, history of tachyarrhythmia before surgery, pre-surgical sepsis, serum creatinine > 2 mg/dL, and primary thyroid abnormality were excluded from the study. All patients were randomized using a block randomization procedure. The placebo—saccharum lactis—or oral T3 (1 mcg/kgBW) was administered via nasogastric tube

every 6 h starting from anesthesia induction until 60 h after the initial administration (11 doses in total).

Clinical Assessment and Measurements

Low cardiac output syndrome (LCOS) was clinically evaluated every 6 h in series from 6 to 48 h post-aortic cross-clamp removal. A modified version of LCOS criteria, based on the prophylactic intravenous use of milrinone after cardiac operation in pediatrics (PRIMACORP) study, [12] was used in this study. As routinely performed in centers worldwide, LCOS was defined as the presence of a minimum of two clinical findings (tachycardia, oliguria, poor peripheral perfusion, or cardiac arrest) and/or a central venous saturation less than 60% (oxygen extraction ratio higher than 40%), with or without metabolic acidosis and increased lactate levels, resulting in an escalation of therapy at the discretion of the consultant in charge at the time of assessment. As this study was double blinded, the consultant was not aware of treatment assignment.

Hemodynamic monitoring and echocardiography evaluation was performed within 24 h until 48 h after surgery and the results were unrelated to the clinical escalation therapy for LCOS. Cardiac index (CI), ejection fraction (EF), and tricuspid annular plane systolic excursion (TAPSE) were assessed using standard Doppler and echocardiography-derived parameters. Pulse pressure was calculated as difference between systolic and diastolic blood pressure. Blood pressure and central venous pressure were measured by routine invasive hemodynamic monitoring. Cardiac output (CO) was measured by ECHO as commonly described [16]. Other hemodynamic parameters measured and calculated by ECHO were stroke volume (SV) and systemic vascular resistance index (SVRI). Supporting examinations such as blood gas analysis (oxygen extraction and central vein saturation) and lactate concentration were performed starting from the induction of anesthesia to 48 h after surgery. Inotropic and vasoactive-inotropic score [17, 18] were also measured to evaluate the dose inotropes and vasopressors used in both groups. In addition, serial-free T3 (FT3) measurements were performed starting from the induction of anesthesia until 48 h post-surgery.

Time to extubation (TTE) was described as the time from the removal of the aortic cross clamp to the first effective extubation (without re-intubation before discharge), or 7 days or death. The time of intubation, length of ICU, and hospital stay were recorded and evaluated.

Statistical Analysis

The difference in the incidence of LCOS and other categorical data was analyzed by the Chi-square or Fischer exact test. Bivariate analysis was performed on potential factors

influencing LCOS such as age, nutritional status, CPB duration, aortic cross-clamp duration, Aristotle score, PRISM III score, and inotropic dose and the use of vasoactive-inotropics. All variables with $p < 0.25$ were pooled together in a multivariate analysis model using logistic regression. Repeated analysis of variance was used to evaluate serial hemodynamic measurements and echocardiography results. Differences between the groups at each time point of measurements were analyzed by the t test if the data were normally distributed and by the Mann–Whitney test if they were not normally distributed. Multivariate analysis using cox regression was performed between time to extubation (TTE), length of ICU, and hospital stay with LCOS 6 h and 12 h after aortic cross clamp, and this analysis was adjusted by age and nutritional status.

Results

Patient Characteristics

A total of 208 out of 292 screened patients were randomized into the placebo group ($n = 104$) and drug group ($n = 104$). Patients were not included if the T3 oral medication was unavailable ($n = 40$), if they were septic or on ventilator support prior to surgery ($n = 16$), no researcher was available for informed consent ($n = 15$) or parent's refused participation, or screening error ($n = 1$). Additionally, five patients in the placebo group were excluded from the analysis due to incomplete LCOS and TTE data. The majority of diagnoses were Ventricular Septal Defect (VSD) and Tetralogy of Fallot (TOF).

Low Cardiac Output Syndrome Profile

The total number of patients exhibiting LCOS at anytime between 6 and 48 h after cross-clamp removal was significantly higher in the placebo group [$n = 86$ vs. 66, respectively, $p < 0.001$; OR (95% CI) 0.43 (0.36–0.52)]. Analysis at specific time points showed that treated patients showed a lower LCOS rate at 6 h compared to placebo [$p = 0.02$; 18/89 (20%) vs. 30/82 (37%), OR (95% CI) 0.44 (0.22–0.87)] (Fig. 1), but the difference decreased with time (Fig. 1).

Baseline characteristics of the patients with LCOS at 6 h are shown in Table 1. The majority of patients with LCOS at 6 and 12 h were in the placebo group (37 vs 20; 32 vs 25, respectively). Most of the patients in the treatment group with LCOS at 6 and 12 h were younger and malnourished. Patients > 5 months old, female, aristotle score > 7–8, and TOF repair showed a significantly lower LCOS rate at 6 h after cross-clamp removal in T3 group compared to placebo group.

Fig. 1 LCOS at the 6, 12, 18, 24, and 48 h after aortic cross-clamp removal in placebo versus T3 treatment group. Note: * $p < 0.05$, *** $p < 0.001$

Based on a bivariate analysis model, age, duration of CPB, total inotropic score, total vasoactive-inotropic score, and intervention mode (drug vs placebo) showed a significant relationship to the occurrence of LCOS ($p < 0.25$). A multivariate analysis was performed to evaluate confounders upon any etiological correlation between interventions given and LCOS at 6 h after aortic clamp removal. The result of the multivariate analysis using logistic regression showed that the odds ratio of LCOS at 6 h after aortic cross-clamp removal was 2.31 higher in the placebo group as compared to the treatment group (OR 2.31; 95% CI 1.14–4.71).

Thyroid Hormone Measurement

T3 levels at induction, 1, 12, and 24 h after cross-clamp removal for LCOS subjects at 6 and 12 h after cross-clamp removal were significantly lower than comparable non-LCOS in both treatment groups, but this effect reached significance only in placebo and not in treatment (Table 2).

Table 1 Demographic and surgical characteristics of subjects with and without low cardiac output syndrome at the 6 h after aortic cross-clamp removal in placebo and treatment group

Characteristics	Placebo ($N=99$)*		p	Triiodothyronine ($N=104$)		p
	LCOS	No LCOS		LCOS	No LCOS	
All patients, N (%)	37 (37.4)	62 (62.6)		20 (19.2)	84 (80.8)	< 0.01
Sex, n (%)						
Male, 122 (60.1)	16 (28.1)	41 (71.9)		12 (18.5)	53 (81.5)	0.21
Female, 81 (39.9)	21 (50.0)	21 (50.0)		8 (20.5)	31 (79.5)	< 0.01
Age, median (IQR), month	9.0 (5.0–15.0)	10.0 (7.0–17.0)	0.11	5.5 (5.0–9.0)	13.0 (7.0–22.0)	< 0.01
Age group, n (%)						
≤ 5 months, 47 (23.2)	13 (59.1)	9 (40.9)		10 (40.0)	15 (60.0)	0.19
> 5 months, 156 (76.8)	24 (31.2)	53 (68.8)		10 (12.7)	69 (87.3)	< 0.01
Z-score (BW/H), Mean (SD)	− 2.53 (1.6)	− 2.31 (1.7)	0.53	− 2.71 (1.3)	− 2.14 (1.2)	0.09
Aristotle complexity score, n (%)						
6–7, 117 (57.6)	20 (35.1)	37 (64.9)		12 (20)	48 (80)	0.07
> 7–8, 61 (30.1)	11 (36.7)	19 (63.3)		2 (6.5)	29 (93.5)	< 0.01
> 8–9, 25 (12.3)	6 (50.0)	6 (50.0)		6 (46.2)	7 (53.8)	0.85
Surgical diagnosis; procedure, n (%)						
VSD, ASD, 113 (55.7)	19 (35.8)	34 (64.2)		12 (20)	48 (80)	0.06
AVSD, I/CAVSD repair, 12 (5.9)	2 (28.6)	5 (71.4)		2 (40.0)	3 (60.0)	1
TOF repair, 49 (24.1)	9 (37.5)	15 (62.5)		2 (8.0)	23 (92.0)	0.013
PAPVD, TAPVD repair, 17 (8.4)	3 (37.5)	5 (62.5)		3 (33.3)	6 (66.7)	1
Others, 12 (5.9)	4 (57.1)	3 (42.9)		1 (20.0)	4 (80.0)	0.293
Cardiopulmonary bypass duration, median (IQR), minute	76.0 (60.0–107.0)	73.0 (57.0–104.0)	0.90	90.0 (56.5–108.0)	74.0 (55.0–92.0)	0.13
Aortic cross-clamp duration, median (IQR), minute	39.0 (31.5–64.5)	41.0 (30.8–60.3)	0.78	47.0 (29.3–65.0)	40.5 (28.0–59.8)	0.36

Bold values indicate statistical significance ($p < 0.05$)

ASD atrioventricular septal defect, Aox cross-clamp removal, BW/H body weight to height, FT3 free triiodothyronine, I/CAVSD intermediate or complete atrioventricular septal defect, IQR interquartile, LCOS low cardiac output syndrome, TOF tetralogy of Fallot, VSD ventricular septal defect

*There were 5 patients in Placebo group that had no complete data for LCOS. The p values were calculated from chi-square analysis on the categorical data and Mann–Whitney analysis for numeric data

Table 2 Serum-free triiodothyronine levels at the 1st, 12th, 24th, 48th hours after cross-clamp removal in patients with and without LCOS at the 6 and 12 h after cross-clamp removal in ALL patients, placebo, and treatment groups

All patients						
Serum FT3 levels after cross-clamp removal, median (IQR), pg/mL	6th hour		<i>p</i>	12th hour		<i>p</i>
	LCOS <i>N</i> =56*	No LCOS <i>N</i> =141**		LCOS <i>N</i> =56*	No LCOS <i>N</i> =141**	
On induction	2.80 (2.26–3.24)	3.11 (2.77–3.64)	0.003	2.88 (2.37–3.24)	3.09 (2.74–3.63)	0.012
1st hour	2.78 (2.38–3.17)	3.36 (2.86–3.80)	<0.001	2.48 (2.07–4.71)	3.22 (2.84–3.80)	0.003
12th hour	2.55 (2.07–4.90)	3.09 (2.52–6.53)	0.001	2.50 (2.07–4.85)	3.09 (2.52–6.53)	0.001
24th hour	2.16 (1.72–5.21)	4.21 (2.16–7.45)	0.001	2.33 (1.71–6.05)	4.03 (2.15–7.16)	0.008
48th hour	2.32 (1.48–5.00)	3.80 (1.91–6.63)	0.015	2.45 (1.48–6.21)	3.30 (1.91–6.66)	0.094
Placebo group	<i>n</i> =36	<i>n</i> =58		<i>n</i> =31	<i>n</i> =63	
On induction	2.81 (2.26–3.24)	3.19 (2.84–3.63)	0.004	2.88 (2.47–3.22)	3.11 (2.75–3.57)	0.035
1st hour	2.71 (2.19–3.11)	3.09 (2.67–3.46)	0.005	2.71 (2.26–3.13)	3.06 (2.65–3.43)	0.064
12th hour	2.16 (1.83–2.48)	2.54 (2.28–2.81)	0.002	2.12 (1.83–2.38)	2.54 (2.29–2.84)	<0.001
24th hour	1.79 (1.50–2.17)	2.10 (1.78–2.37)	0.033	1.74 (1.49–2.03)	2.12 (1.79–2.37)	0.002
48th hour	1.81 (1.09–2.29)	1.91 (1.50–2.27)	0.327	1.70 (1.08–2.21)	1.91 (1.51–2.34)	0.062
Treatment group	<i>n</i> =20	<i>n</i> =83		<i>n</i> =25	<i>n</i> =78	
On induction	2.80 (1.98–3.55)	3.09 (2.72–3.64)	0.258	2.84 (2.09–3.35)	3.09 (2.60–3.67)	0.163
1st hour	3.11(2.64–4.03)	3.63 (2.90–4.47)	0.102	3.07 (2.65–3.85)	3.64 (2.97–4.67)	0.043
12th hour	5.56(3.61–6.57)	5.69 (3.80–8.09)	0.407	4.90 (3.20–5.93)	5.97 (4.13–8.08)	0.059
24th hour	6.95 (4.88–7.72)	6.93 (4.65–8.37))	0.757	6.48 (4.62–8.06)	7.00 (5.07–8.38)	0.484
48th hour	6.01(3.25–8.39)	6.30(4.26–7.54)	0.920	6.30 (3.97–7.01)	6.18 (4.13–8.02)	0.561

Bold values indicate statistical significance ($p < 0.05$)

FT3 free triiodothyronine

*1 patient in placebo group with LCOS and **4 patients without LCOS in placebo group and 1 patient in T3 group had missing FT3 levels data

FT3 levels from induction of anesthesia until 24 h post-surgery were significantly lower in placebo group patients with LCOS at 6 and 12 h after aortic cross-clamp removal compared to non-LCOS ($p < 0.05$) (Table 2)

Hemodynamic Measurements

There were no significant differences for the hemodynamic parameters such as ejection fraction, stroke volume (SV), and cardiac output (CO) between the treatment and placebo group prior to surgery, but SV and CO in patients without LCOS were significantly higher compared to LCOS patients at 6 and 12 h after aortic clamp removal. Higher systemic vascular resistance index (SVRI) and lower cardiac index (CI) were found in LCOS than non-LCOS patients at 12 h ($p = 0.04$), whereas pulse pressure was significantly lower in patients with LCOS at 6 h ($p = 0.004$) after aortic clamp removal (Table 3). When LCOS and non-LCOS patients were compared separately in the treatment and placebo group, SV, CI, and SVRI were significantly different in the placebo group ($p = 0.001$; $p = 0.001$; and $p = 0.002$; and $p = 0.03$, respectively) between LCOS and non-LCOS, but no difference was found in the treatment group.

Blood gas analyses showed that central vein saturation and oxygen extraction were significantly lower in LCOS than non-LCOS patients at 6 and 12 h after aortic clamp removal ($p < 0.001$), but no difference was found for lactate levels (Table 3). In addition, patients with LCOS 6 h after aortic cross-clamp removal required more inotropic and vasoactive agents as reflected by a significant difference in the total inotropic score and vasoactive score 6 h after aortic clamp removal ($p = 0.009$ and 0.029 , respectively). The difference in the total vasoactive-inotropic score in LCOS and non-LCOS sample at 12 h after aortic cross-clamp removal was significant ($p = 0.001$) (Table 3).

Other Measurements

The incidence of a clinically diagnosed LCOS 6 h and 12 h after aortic cross-clamp removal was significantly associated with time to extubation (TTE). LCOS at 6 h after aortic cross-clamp removal was predictive to TTE with a hazard ratio (HR) of (95% CI) 0.62 (0.45–0.86), $p = 0.004$. The LCOS at 12 h after aortic cross-clamp removal was also a significant predictor for TTE with HR = 0.47; 95% CI 0.34–0.65; $p < 0.0001$) (Fig. 2a and b). No significant difference was found on length of ICU and hospital stay

Table 3 Pulse pressure, central vein saturation, oxygen extraction ratio, lactate levels, total inotropic, and vasoactive-inotropic scores at the 6 and 12 h after cross-clamp removal; and echocardiographic parameters within 24 h post-surgery of subjects with and without Low Cardiac Output Syndrome at the 6 and 12 h after aortic cross-clamp release

Characteristics	6th hour		12th hour		<i>p</i>
	LCOS <i>n</i> = 57	No LCOS <i>n</i> = 146	LCOS <i>n</i> = 33	No LCOS <i>n</i> = 170	
Pulse pressure, median (IQR), mmHg	36.00 (30.50–44.00)	42.00 (35.00–49.50)	35.00 (29.00–40.00)	37.00 (31.00–45.00)	0.115
Central vein saturation, median (IQR), %	64.85 (50.40–71.78)	72.30 (60.85–79.05)	53.9 (40.00–58.80)	68.30 (64.05–74.03)	<0.001
Oxygen extraction ratio, median (IQR)	0.33 (0.26–0.43)	0.25 (0.19–0.31)	0.43 (0.40–0.47)	0.29 (0.24–0.33)	<0.001
Lactate, median (IQR), mmol/L	1.30 (0.93–1.88)	1.40 (1.10–1.95)	1.30 (0.90–1.70)	1.10 (0.88–1.80)	0.086
1st day SV, median (IQR), mL	6.28 (4.85–9.61)	8.83 (6.09–12.70)	6.39 (4.05–8.83)	9.27 (6.05–13.01)	<0.001
1st day CO, median (IQR), L/min	0.92 (0.58–1.33)	1.17 (0.85–1.67)	0.89 (0.53–1.16)	1.20 (0.86–1.73)	<0.001
1st day CI, median (IQR), L/min/m ²	2.84 (1.94–3.89)	3.41 (2.41–4.72)	2.63 (1.73–3.62)	3.47 (2.63–4.72)	0.001
1st day SVRI, median (IQR), dyne-s/cm ⁵ /m ²	1,602.96 (1,176.92–2,037.05)	1,325.25 (1,005.06–1,916.65)	1,658.22 (1,172.61–2,281.75)	1,332.03 (1,006.84–1,807.98)	0.046
Inotropic score, median (IQR),	2.25 (0.00–5.00)	0.00 (0.00–4.00)	0.00 (0.00–5.00)	0.00 (0.00–3.00)	0.071
Vasoactive-inotropic score, median (IQR)	5.00 (3.75–10.00)	5.00 (3.75–7.50)	7.50 (5.00–12.50)	5.00 (3.75–7.50)	0.001

Bold values indicate statistical significance (*p* < 0.05)*CI* cardiac index, *CO* cardiac output, *FT3* free triiodothyronine, *SV* stroke volume, *SVRI* systemic vascular resistance

Fig. 2 Kaplan–Meier curve of time to extubation in ALL subjects with and without LCOS at the 6 h (a) and 12 h (b) after aortic cross-clamp removal

between LCOS and non-LCOS patients. Overall mortality was low in the entire study (7/203). Nevertheless, mortality rate was significantly higher in LCOS patients at 6 and 12 h than patients without LCOS [6/57 (10.5%) vs. 1/146 (0.7%), $p=0.001$, OR = 17.06 (2.01–145.12); 5/57 (8.8%) vs. 2/146 (1.4%), $p=0.009$, OR = 6.92 (1.30–36.78), respectively]. Mortality in the treatment group was too low to evaluate impact of LCOS.

Compared to those patients without LCOS in the same group, most of the patients from the treatment group diagnosed with LCOS were significantly younger [5.5 (5–10) vs. 13 (7–23) months, $p=0.004$] and more moderate to severely malnourished (72.2% vs. 53.5%). During randomization, CAVSD and TAPVD were equally distributed between the treatment groups. There were 7 patients with CAVSD in the placebo group and 5 patients in the T3 group. For TAPVD, 8 patients were in the placebo and 9 in the T3 group. Analyses revealed that those patients who still had LCOS after surgery despite T3 supplementation were those CAVSD and TAPVD patients with pulmonary hypertension.

Discussion

Thermodilution using a pulmonary artery catheter remains the standard technique for measuring cardiac output in the adult cardiac intensive care unit. This method then provides an objective measure for assessing for low cardiac output

syndrome. However, thermodilution can provide inaccurate cardiac output readings in patients with congenital heart defects with residual shunts. Paired with the increased risk for an indwelling catheter in the pulmonary artery for these very often small and young patients, thermodilution is not used in pediatric intensive care units on a routine basis. Accordingly, the diagnosis of LCOS in postoperative pediatric patients is based on a compendium of clinical and laboratory parameters as performed in the PRIMACORP study [12]. Echocardiography is also used either independently or in combination with clinical parameters. Echo-derived parameters correlate with thermodilution data in adults, although continuous or frequent monitoring in the PCICU is logistically impossible.

Due to reliance on multiple, often subjective parameters, identification of LCOS in pediatric patients then poses many challenges. We therefore sought to assess the validity and importance of the LCOS diagnosis in a fairly large cohort undergoing a controlled, randomized, and double-blind clinical trial. The principal objective was to determine if early onset of low cardiac output syndrome, 6 or 12 h after cross-clamp release, was associated with poor cardiac function assessed primarily by echocardiogram and available hemodynamic parameters after 24 h. We found that patients with clinically derived LCOS at these time points exhibited later poor myocardial function manifest by low echocardiographically determined cardiac index and high systemic vascular resistance. Importantly, the non-LCOS patients

exhibited superior functional parameters despite a marked reduction in inotropic usage. Thus early clinical diagnosis of LCOS identifies patients, who will demonstrate persistent cardiac dysfunction [17, 19]. The delay in extubation noted in the LCOS stresses the importance of this finding and the relationship to later clinical outcomes.

Prior studies have indicated that LCOS generally emerges between 6 and 18 h after open heart surgery with cardiac index reaching nadir usually between 9 and 12 h [17, 19]. In OTICC, we found that T3 reduced the LCOS incidence at 6 h after cross-clamp removal. Further analyses in the current study showed that T3 also altered distribution for LCOS across the postoperative period (Fig. 1). Thus, T3 substantially reduced overall risk of LCOS although the predominant effect occurred early in the postoperative period. The diagnosis for LCOS by clinical judgement and laboratory findings was supported by the subsequent echocardiographic measurements in this treatment group. This reduction in early LCOS also corresponded to the reduction in TTE noted in OTICC [10] and also decreased mortality rate. We also found that LCOS subjects in the placebo group showed significantly lower T3 levels than those not exhibiting LCOS. The superior clinical state in patients with higher T3 levels was not due to more aggressive use of inotropic and vasoactive agents. Particularly in the younger patients, T3 impact appeared to be confounded by factors other than cardiac function, such as pulmonary hypertension. Most patients with LCOS in the treatment group had surgery for TAPVD or CAVSD, and had postoperative pulmonary hypertension.

This study is subjected to limitations due to the post hoc analyses, although trial data were collected prospectively. Accordingly, cardiac function by echocardiography was only performed after 24 h in the original protocol. Although echocardiography is a standard for monitoring cardiac function in the PICU, data acquisition can be operator dependent, and also impacted by limited access for ultrasound postoperatively in small children.

In summary, this study provides some validation for early LCOS, as a predictor of later cardiac function and clinical outcomes in pediatric patients undergoing surgery for CHD. Additionally, we confirmed that T3 supplementation reduces the risk of early LCOS, which corresponds to a reduction in TTE. Importantly, the findings also suggest that LCOS incidence occurs more frequently in patients with lower T3 levels postoperatively. Overall, the data indicate that the predominant benefit for T3 occurs in the early postoperative period, and relates to the prevention of LCOS. The impact of T3 appears to be mitigated somewhat by other factors such as postoperative pulmonary hypertension.

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Compliance with Ethical Standards

Conflict of interest All authors declare that there is no potential financial or non-financial conflict of interests regarding this paper.

Ethical Approval The study was approved by Ethical Research Committee at the National Cardiovascular Center Harapan Kita with Protocol Number LB 05.01/1.4/235/2010 and registered on ClinicalTrials.gov under Identifier Number NCT02521168. The complete study was performed according to the guidelines of the Helsinki Declaration.

Informed Consent All patients, their parents, or legal guardians have been informed about the study, and informed written consent was obtained before potential enrollment in the study.

References

1. Rubinfeld S (1978) Euthyroid sick syndrome. *N Engl J Med* 299:1414
2. Haas NA, Camphausen CK, Kececioglu D (2006) Clinical review: thyroid hormone replacement in children after cardiac surgery—is it worth a try? *Crit Care* 10:213–220
3. Mebis L, van den Berghe G (2009) The hypothalamus-pituitary-thyroid axis in critical illness. *Neth J Med* 67:332–340
4. Klein I, Danzi S (2007) Thyroid disease and the heart. *Circulation* 116:1725–1735
5. Mainwaring RD, Lamberti JJ, Billman GF, Nelson JC (1994) Suppression of the pituitary thyroid axis after cardiopulmonary bypass in the neonate. *Ann Thorac Surg* 58:1078–1082
6. Bettendorf M, Schmidt KG, Grulich-Henn J, Ulmer HE, Heinrich UE (2000) Tri-iodothyronine treatment in children after cardiac surgery: a double-blind, randomised, placebo-controlled study. *Lancet* 356:529–534
7. Chowdhury D, Ojamaa K, Parnell VA, McMahon C, Sison CP, Klein I (2001) A prospective randomized clinical study of thyroid hormone treatment after operations for complex congenital heart disease. *J Thorac Cardiovasc Surg* 122:1023–1025
8. Mackie AS, Booth KL, Newburger JW, Gauvreau K, Huang SA, Laussen PC et al (2005) A randomized, double-blind, placebo-controlled pilot trial of triiodothyronine in neonatal heart surgery. *J Thorac Cardiovasc Surg* 130:810–816
9. Portman MA, Slee A, Olson AK, Cohen G, Karl T, Tong E et al (2010) Triiodothyronine supplementation in infants and children undergoing cardiopulmonary bypass (TRICC): a multicenter placebo-controlled randomized trial: age analysis. *Circulation* 122:S224–S233
10. Marwali EM, Boom CE, Budiwardhana N, Fakhri D, Roebiono PS, Santoso A et al (2017) Oral triiodothyronine for infants and children undergoing cardiopulmonary bypass. *Ann Thorac Surg* 104:688–695
11. Marwali EM, Boom CE, Sakidjan I, Santoso A, Fakhri D, Kartini A et al (2013) Oral triiodothyronine normalizes triiodothyronine levels after surgery for pediatric congenital heart disease. *Pediatr Crit Care Med* 14:701–708
12. Hoffman TM, Wernovsky G, Atz AM, Kulik TJ, Nelson DP, Chang AC et al (2003) Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. *Circulation* 107:996–1002
13. Freeman RK, Daily PO, Dembitsky WP, Adamson RM, Moreno-Cabral RJ (1997) The treatment of low cardiac output syndrome following cardiopulmonary bypass using delayed sternal closure. *Am Surg* 63:882–884

14. Robert SM, Borasino S, Dabal RJ, Cleveland DC, Hock KM, Alten JA (2015) Postoperative hydrocortisone infusion reduces the prevalence of low cardiac output syndrome after neonatal cardiopulmonary bypass. *Pediatr Crit Care Med* 16:629–636
15. Plumpton K, Haas NA (2005) Identifying infants at risk of marked thyroid suppression post-cardiopulmonary bypass. *Intensive Care Med* 31:581–587
16. Lewis JF, Kuo LC, Nelson JG, Limacher MC, Quinones MA (1984) Pulsed Doppler echocardiographic determination of stroke volume and cardiac output: clinical validation of two new methods using the apical window. *Circulation* 70:425–431
17. Wernovsky G, Wypij D, Jonas RA, Mayer JE Jr, Hanley FL, Hickey PR et al (1995) Postoperative course and hemodynamic profile after the arterial switch operation in neonates and infants. A comparison of low-flow cardiopulmonary bypass and circulatory arrest. *Circulation* 92:2226–2235
18. Gaies MG, Gurney JG, Yen AH, Napoli ML, Gajarski RJ, Ohye RG et al (2010) Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. *Pediatr Crit Care Med* 11:234–238
19. Boehne M, Sasse M, Karch A, Dziuba F, Horke A, Kaussen T et al (2017) Systemic inflammatory response syndrome after pediatric congenital heart surgery: Incidence, risk factors, and clinical outcome. *J Card Surg* 32:116–125

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