Thyroid Hormones Predict ICU Mortality After Cardiopulmonary Bypass in Congenital Heart Disease Patients Under 3 Months Old

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Abstract

Backgroup: To study the effectiveness of thyroid hormones in predicting intensive care unit (ICU) mortality after cardiopulmonary bypass (CPB) in infants with congenital heart disease (CHD).

Methods: We retrospective observational analyzed data from 133 patients under 3 months old who underwent cardiac surgery with CPB from June 2017 to November 2019. ICU mortality prediction was assessed by multivariate binary logistic regression analysis and area under the curve (AUC) analysis.

Results: Non-survivors were younger (17.46±17.10 days vs. 38.63±26.87 days, P=0.006), with a higher proportion of neonates (9/13 vs. 41/120, P=0.017) and a higher proportion of individuals with Risk Adjustment in Congenital Heart Surgery-1 (RACHS-1) score ≥4 (8/13 vs. 31/120, P=0.020). No significant difference was found in CPB and aortic cross-clamping (ACC) time. The levels of free triiodothyronine (FT3) (3.91±0.99 pmol/L vs. 5.11±1.55 pmol/L, P=0.007) and total triiodothyronine (TT3) (1.55±0.35 nmol/L vs. 1.90±0.57 nmol/L, P=0.032) were higher in survivors compared with non-survivors. In the ICU mortality prediction assessment, only FT3 was an independent mortality predictor and showed a good AUC (0.856 ± 0.040).

Conclusion: FT3 was a powerful and the only independent predictor of ICU mortality in CHD infants under 3 months old after CPB.

Backgroud

Congenital heart disease (CHD) is the most common congenital malformation among live births, accounting for approximately one-third of birth defects [1]. A systematic review showed that the prevalence of CHD increased from 0.6‰ in the 1930s to 9.1‰ at the end of the 20th century [2]. Cardiopulmonary bypass (CPB) is often used for surgery in complex CHD cases. However, hemodilution, hypothermia and ultrafiltration during CPB have been identified as inducing a temporary hypothyroid state, especially in infants [3, 4].

The thyroid hormones triiodothyronine (T3) and thyroxin (T4) have permissive effects on β1-adrenergic receptors, which enhance heart contractility and reduce systemic vascular resistance [5, 6]. Additionally, thyroid hormones increase preload and decrease afterload, leading to increase cardiac output [7]. Several studies have shown that the hypothyroid state, which affects the metabolism of myocardial energy, is associated with poor prognosis after cardiac surgery with CPB [8, 9]. Correspondingly, thyroid hormone replacement therapy could provide clinical benefits in infants undergoing CPB [8–10].

A study was conducted to assess the effects of CPB on thyroid function in infants weighing less than 5 kg, and the results showed that low T3 and T4 were both predictors of high mortality [13]. Talwar et al [14] found that low levels of postoperative TT4 were correlated with postoperative morbidity, a prolonged postoperative course, and prolonged MV in open heart surgery with CPB. Since the levels of thyroid

hormones play a critical role in recovery from cardiac surgery and thyroid hormones decreased after CPB, the preoperative level of thyroid hormones could be a predictor of ICU mortality after CPB in CHD patients. Therefore, we conducted a retrospective study to evaluate the effect of thyroid hormones in relation to survival in patients after cardiac surgery with CPB.

Methods

We retrospectively reviewed the medical records of patients with CHD under 3 months old in our hospital between June 2017 and November 2019. This study protocol was approved by the Institutional Ethical Committees of the hospital (201912257-1). We excluded patients who were over 90 days old at the time of surgery, patients without CPB, patients with primary thyroid gland disease, and patients with trisomy 21 syndrome. Clinical data included gender; age; weight; Risk Adjustment in Congenital Heart Surgery-1 (RACHS-1) score [15]; type of CHD; preoperative levels of thyroid hormones [total T3 (TT3, normal range: 1.29–3.11 nmol/L), free T3 (FT3, normal range: 2.8–7.1 pmol/L), total T4 (TT4, normal range: 66-187.4 nmol/L), free T4 (FT4, normal range: 12.1–22 pmol/L), thyroid stimulating hormone (TSH, normal range: 0.2-5 μIU/ml)], which is a routine examination for patients with CHD in our clinic; CPB time; aortic cross-clamping (ACC) time; and ICU mortality.

Statistical analysis

The statistical analysis was performed with SPSS version 20.0 software (Chicago, IL, USA). Continuous variables are expressed as the mean ± standard deviation, while categorical variables are summarized as frequencies and percentages. Comparisons between groups were made using unpaired Student's t-test for continuous variables and χ^2 or Fisher's exact test for categorical variables. Multivariate binary logistic regression analysis was further conducted to assess the independent ICU mortality predictors. Receiver operating characteristic (ROC) curves were generated to examine the variables for predicting ICU mortality, and the area under the curve (AUC) was calculated from the ROC curve. Youden's index, which maximized the sum of the sensitivity and specificity, was used to define the optimal cut-off value. Statistical significance was defined as $P < 0.05$.

Results

Patient characteristics

This study enrolled 133 patients under 3 months old (with a mean age of 36.56 ± 26.78 days), including 50 neonates (37.6%). Among the participants, 39 patients (29.3%) had a RACHS-1 operative risk score ≥ 4. Based on the normal ranges mentioned above, 10(7.5%), 1(0.8%), 23(17.3%), 2(1.5%) and 48(36.1%) patients had low FT3, low FT4, low TT3, low TT4 and high TSH, respectively. A total of 13 patients (9.8%) died in the ICU; their causes of death were low cardiac output syndrome (8/133, 6.0%), sepsis (3/133, 2.3%), and brain injury (2/133, 1.5%). The demographic and physiological characteristics of the patients are presented in Table 1.

Table 1
Characteristics of enrolled patients with congenital heart disease

Characteristic	All patients (n = 133)
Age (days)	36.56 ± 26.78
≤28 days	50 (37.6%)
>28 days and ≤ 90 days	83 (62.4%)
Gender	
Male	89 (66.9%)
Female	44 (33.1%)
Weight (kg)	3.89 ± 0.91
RACHS-1	
Score-1	4 (3.0%)
Score-2	46 (34.6%)
Score-3	44 (33.1%)
Score-4	38 (28.6%)
Score-5	1 (0.7%)
Score-6	0(0%)
Type of Surgery	
ASD	2 (1.5%)
VSD	12 (9.0%)
VSD + ASD	50 (37.6%)
COA/IAA	15(11.3%)
TAPVC	21(15.8%)
TGA	19 (14.3%)
PA-VSD	3 (2.2%)
DORV	2 (1.5%)

RACHS-1, Risk Adjustment in Congenital Heart Surgery-1; ASD, atrial septal defect; VSD, ventricular septal defect; COA, coarctation of aorta; IAA, interrupter aortic arch; TAPVC, total anomalous pulmonary venous connection; TGA, transposition of the great arteries; PA, pulmonary atresia; DORV, double outlet right ventricular; CPB, cardiopulmonary bypass; ACC, aortic cross-clamping; FT3, free triiodothyronine; FT4, free thyroxin; TT3, total triiodothyronine; TT4, total thyroxin; TSH, thyroid stimulating hormone.

Characteristic	All patients (n = 133)
Other	9 (6.8%)
Operative factors	
CPB time (min)	114.23 ± 81.98
ACC time (min)	46.03 ± 21.59
ICU mortality	13 (9.8%)
Pre-operative thyroid function	
FT3 (pmol/L)	4.99 ± 1.54
FT4 (pmol/L)	21.28 ± 5.82
TT3 (nmol/L)	1.87 ± 0.56
TT4 (nmol/L)	120.25 ± 34.61
TSH (μIU/ml)	5.72 ± 5.95

RACHS-1, Risk Adjustment in Congenital Heart Surgery-1; ASD, atrial septal defect; VSD, ventricular septal defect; COA, coarctation of aorta; IAA, interrupter aortic arch; TAPVC, total anomalous pulmonary venous connection; TGA, transposition of the great arteries; PA, pulmonary atresia; DORV, double outlet right ventricular; CPB, cardiopulmonary bypass; ACC, aortic cross-clamping; FT3, free triiodothyronine; FT4, free thyroxin; TT3, total triiodothyronine; TT4, total thyroxin; TSH, thyroid stimulating hormone.

Comparison of survivor and non-survivor groups

Compared with survivors, non-survivors were younger (17.46 ± 17.10 days vs. 38.63 ± 26.87 days, P = 0.006), were more likely to be neonates (9/13 vs. 41/120, P = 0.017), and had a higher proportion of RACHS ≥ 4 (8/13 vs. 31/120, P = 0.020). CPB and ACC time were slightly longer in the non-survivors, while no significant difference was found compared with the survivors. The levels of FT3, FT4, TT3 and TT4 were low and TSH was high in non-survivors; however, only FT3 (3.91 ± 0.99 pmol/L vs. 5.11 ± 1.55 pmol/L, P = 0.007) and TT3 (1.55 ± 0.35 nmol/L vs. 1.90 ± 0.57 nmol/L, P = 0.032) showed a significant difference between survivors and non-survivors. Interestingly, all non-survivors were male (Table 2).

Table 2
Characteristics of patients according to survivors and non-survivors

Characteristic	Survivors (N = 120)	Non-survivors (N = 13)	P value
Age (days)	38.63 ± 26.87	17.46 ± 17.10	**0.006**
≤28 days	41 (34.1%)	9(69.2)	**0.017**
Female	44 (36.7%)	0 (0%)	**0.005**
Weight (kg)	3.92 ± 0.93	3.61 ± 0.63	0.234
RACHS-1 ≥ 4	31(25.8%)	8(61.5%)	**0.020**
Pre-operative thyroid function			
FT3 (pmol/L)	5.11 ± 1.55	3.91 ± 0.99	**0.007**
FT4 (pmol/L)	21.52 ± 5.79	19.02 ± 5.85	0.142
TT3 (nmol/L)	1.90 ± 0.57	1.55 ± 0.35	**0.032**
TT4 (nmol/L)	122.07 ± 34.77	103.47 ± 29.10	0.066
TSH (μIU/ml)	5.48 ± 4.94	7.89 ± 11.90	0.483
Operative factors			
CPB time (min)	111.53 ± 83.87	139.07 ± 58.61	0.251
ACC time (min)	45.01 ± 21.61	55.40 ± 19.73	0.100
Abbreviations as in Tables 1.			

Independent predictors of ICU mortality

Predictors with p-valves less than 0.1 were enrolled in the multivariate binary logistic regression analysis to determine the independent predictors of ICU mortality, except gender. As shown in Table 3, FT3 was the only independent predictor.

Table 3
Multivariate logistic regression, odds ratio of variables for predicting ICU mortality in patients with congenital heart disease after cardiopulmonary bypass

Variables	B	S.E.	Wald	df	P value	OR	95% C.I. for OR	
							Lower	Upper
Age	-0.036	0.016	3.406	1	0.065	0.965	0.929	1.002
RASCH-1 ≥ 4	-1.002	0.528	1.621	1	0.203	0.367	0.078	1.717
ACC	-0.003	0.016	0.038	1	0.846	0.997	0.966	1.028
FT3	-1.112	0.528	4.429	1	**0.035**	**0.329**	**0.117**	**0.926**
TT3	2.227	1.437	2.400	1	0.121	9.268	0.554	155.017
TT4	-0.017	0.012	2.121	1	0.145	0.983	0.960	1.006
Constant	2.560	1.693	2.286	1	0.131	12.937		
Abbreviations as in Tables 1.								

Value of FT3 in predicting ICU morality

ROC curves were constructed to examine the performance of FT3 as a predictor of ICU mortality (Fig. 1). The AUC was 0.856 ± 0.040, optimal cutoff value was 4.89 pmol/L, and sensitivity and specificity were 100% and 63.3%, respectively (Table 4).

Table 4
Value of FT3 in predicting ICU morality

Variable	AUC	P valve	Cutoff value	Sensitivity (%)	Specificity (%)
FT3	0.856 ± 0.040	0.000	4.89	100	63.3
FT3, free triiodothyronine; AUC, area under the curve.					

Discussion

To our best knowledge, the present study is the first clinical retrospective analysis of the predictable value of thyroid hormones in patients with CHD undergoing CPB. In our study of 133 consecutive patients, we found that FT3 may be an independent predictor of ICU mortality based on multivariate binary logistic regression and ROC curves. Previous studies [16] have reported that low T3 was an independent predictor of ICU mortality, which is consistent with our finding. However, for CHD patients, especially children, RACHS-1 scores could predict ICU mortality, length of ICU stay and duration of MV [17–20]. In our study, compared with survivors, non-survivors had a higher RACHS-1 score. However, in the additional multivariate binary logistic regression, it was not an independent mortality predictor. We suggest that RACHS-1 scores on the basis of CHD subtype should not consider the relationship of year, weight, and

levels of thyroid hormone as confounding factors [21]. Additionally, the small sample size of children with RACHS-1 scores of 5 or 6 may be another reason for the reduced statistical power. Although the CPB and ACC time were high in non-survivors, no significant difference was found compared with survivors, which demonstrates the improvement of cardiac surgery techniques and perfusion mode of CPB in China.

We found an interesting phenomenon in our study, namely, that all the non-survivors were male. This could be related to the preference for sons over daughters, which is very common in China. Thus, when a child is diagnosed with complex CHD, based on the gender, operative risk and economic status of the parents, girls may not have the opportunity to undergo the operation, especially in rural areas [22, 23]. Due to this bias, we removed gender from the multivariate binary logistic regression.

Thyroid hormones have important effects on the cardiovascular system, such as increasing cardiac output and decreasing systemic vascular resistance, which are predictive of good outcomes [24, 25]. However, several studies have verified that cardiac surgery with CPB induces a marked depression of thyroid hormones [14, 26, 27]. Researchers have found that low levels of T3 [28] or T4 [14] were correlated with postoperative morbidity in open heart surgery with CPB. A study was conducted to assess the effects of CPB on thyroid function in infants weighing less than 5 kg, and the results showed that low T3 and T4 were both predictors of high mortality [13]. Since postoperative low levels of thyroid hormones could lead to a poor prognosis, a preoperative increase in thyroid hormones may improve the prognosis. A multicenter randomized controlled trial (RCT) of T3 supplementation of patients undergoing heart surgery with CPB (TRICC) showed that T3 supplementation provides clinical advantages in patients younger than 5 months, but not in older patients [29]. Talwar et al [30] performed an RCT study of perioperative oral T4 in patients younger than 6 months who underwent open heart surgery with CPB and found that thyroid hormone levels reduced postoperative and that T4 supplementation reduced the duration of MV and ICU and hospital stays. Therefore, the preoperative level of thyroid hormones may predict the prognosis of patients with CHD undergoing CPB. Kumar et al [31] found that low T3 is an important marker of mortality in critically ill patients, while low T4 and TSH did not increase the predictability. In a large-scale prospective, observational study of unselected ICU patients, they found that FT3 was the most powerful and only independent predictor of ICU mortality among the thyroid hormone indicators [16]. However, Quispe et al [32] found that the FT3 level was not significantly different between survivors and non-survivors and was not a mortality predictor.

Our study showed that only FT3 is the independent predictor of ICU mortality with a good AUC. Thyroid hormones include T4, which represents the major form of circulating thyroid hormones (> 80%), and T3, which accounts for a small portion (< 20%) of circulating thyroid hormones and has a major biological effect on the heart. Moreover, the levels of TT3 and TT4 can be affected by the concentration of thyroxine-binding globulin (TBG) or the binding ability of TBG, which may be affected by several drugs, including furosemide and heparin [16]. In contrast, FT3 and FT4 were not affected in these conditions. Thus, the level of FT3 may be better than other thyroid hormones as a predictor of ICU mortality, which is consistent with our findings.

Some limitations exist in our study. First, this was a retrospective study with a small sample size, which limited the statistical power. Therefore, additional cases need to be enrolled, and a prospective randomized multicenter study should be conducted. Second, patients with RACHS-1 scores of 5 or 6 are rare, which reduced the ability of RACHS-1 to predict ICU mortality in CHD children. Finally, we did not consider the relationship of thyroid hormones with albumin and dopamine, which may provide more robust evidence to assess the predominant predictor.

Conclusion

Thyroid hormones play an important role in the recovery of patients with CHD undergoing CPB, and FT3 level was the most powerful and only independent predictor of ICU mortality.

Abbreviations

ACC: Aortic Cross-Clamping, **AUC:** Area Under the Curve, **CHD**: Congenital Heart Disease, **FT3**: Free Triiodothyronine, **FT4**: Free Thyroxin, **ICU:** Intensive Care Unit, **MV**: Mechanical Ventilation, **RACHS-1**: Risk Adjustment in Congenital Heart Surgery-1, **ROC**: Receiver Operating Characteristic, **TBG**: Thyroxine-Binding Globulin, **T3**: Triiodothyronine, **T4**: Thyroxin, **TT3**: Total Triiodothyronine, **TT4**: Total Thyroxin, **TSH**: Thyroid Stimulating Hormone

Declarations

Acknowledge

None declared.

Author contributions

X.M.M. and Y.Q.S. designed the study. D.Y. and L.Z. wrote the manuscript. D.Y., L.Z. and Y.S.C. collected the data, and Y.P.L. and Q.F.W. analyzed the data. All authors reviewed the manuscript.

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Availability of data and material

Please contact the author for data requests.

Ethics approval and consent to participate

Study approval and ethical clearance was obtained from the Institutional Ethical Committees of Children's Hospital of Nanjing Medical University (201912257-1).

Consent for publication

Not applicable

Competing interests

The authors declare that they have no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Figures

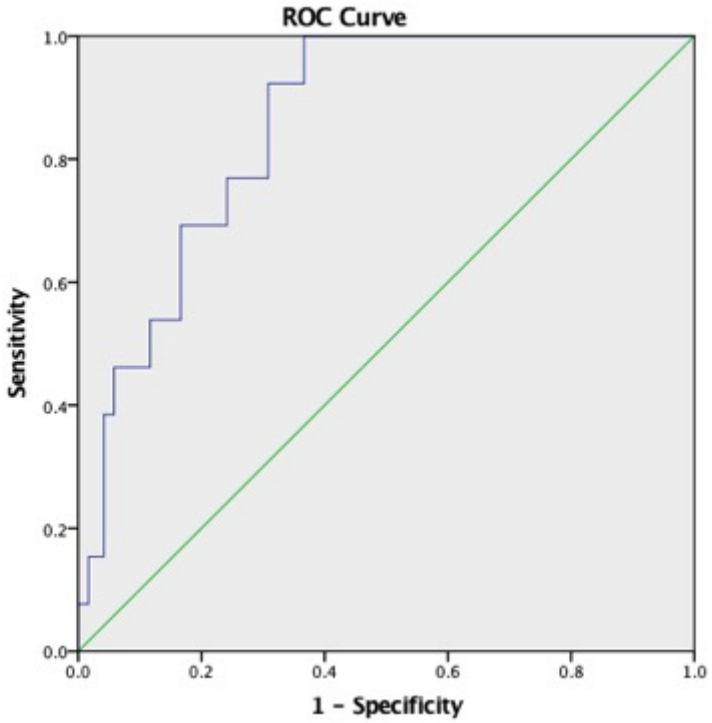

Figure 1

Receiver operating characteristic curves for free triiodothyronine (FT3)