International Journal of Scientific Advances
ISSN: 2708-7972
Volume: 6 | Issue: 6 | Nov – Dec 2025 Available Online: www.ijscia.com
DOI: 10.51542/ijscia.v6i6.28

Thyroid Response to Cardiopulmonary Bypass in Children with Congenital Heart Disease: A Literature Review

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ABSTRACT

Congenital heart disease (CHD) correction frequently requires open-heart surgery with cardiopulmonary bypass (CPB), a procedure that can trigger hormonal disruption and hemodynamic instability. CPB is known to cause Non-Thyroidal Illness Syndrome (NTIS) through decreased perfusion, hemodilution, and the release of inflammatory cytokines that suppress the hypothalamic-pituitary-thyroid axis. This literature review aims to describe the mechanisms of thyroid response to CPB in children with CHD and their association with postoperative outcomes. A search of six databases (2010–2025) yielded six relevant studies. All studies demonstrated significant decreases in T3, T4, and TSH within 24–48 hours postoperatively, particularly in neonates and in patients undergoing high-complexity procedures. These changes are associated with increased inotropic requirements, the risk of low cardiac output syndrome, longer ventilation duration, and length of ICU stay. This confirms that CPB significantly impacts thyroid function and hemodynamic stability in children, requiring careful postoperative clinical and hormonal monitoring to minimize the risk of complications. Thyroid hormone supplementation may help stabilize levels, although its benefits on primary outcomes remain inconsistent.

Keywords: congenital heart disease; cardiopulmonary bypass; aortic cross-clamping; thyroid-stimulating hormone; pediatric; cardiac surgery

INTRODUCTION

Congenital heart disease (CHD) is an anatomical abnormality of the cardiac structures and great vessels that develops during embryogenesis. These defects may involve the aorta, pulmonary trunk, vena cava, and pulmonary veins, and represent one of the leading causes of morbidity and mortality in infants and children [1]. The global incidence of congenital heart disease (CHD) in newborns has been estimated to range from 0.8% to 1.2%, with Asia reported as the region with the highest prevalence, reaching 9.3 to 50 per 1,000 live births [2,3]. In Indonesia, the prevalence is similarly high, estimated at 8–10 per 1,000 live births [4].

The definitive management for most CHD cases is open-heart surgery performed with the assistance of cardiopulmonary bypass (CPB). This technique enables blood circulation and oxygenation to continue while the heart is temporarily arrested to allow correction of intracardiac anomalies. During this process, aortic cross-clamping (ACC) is typically applied to create a blood-free surgical field. Although CPB and ACC are essential for surgical success, both can elicit complex physiological responses that may adversely affect multiple organ systems, including the endocrine system [5,6].

The post-CPB physiological response often resembles hypothyroid-like manifestations such as hypotension, bradycardia, hypothermia, and metabolic disturbances [7]. The thyroid system plays a crucial role in regulating metabolism and cardiovascular function. During CPB, reduced tissue perfusion, hemodilution, and the release of pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α),

can suppress thyroid-stimulating hormone (TSH) secretion and inhibit peripheral conversion of thyroxine (T4) to triiodothyronine (T3) by inhibiting deiodinase activity [8]. These changes result in the development of non-thyroidal illness syndrome (NTIS), an adaptive response to severe physiological stress characterized by reduced T3 levels without a compensatory increase in TSH.

Studies have consistently demonstrated significant postoperative reductions in TSH, FT3, and FT4 among pediatric patients with CHD undergoing open-heart surgery with CPB [7]. However, most available evidence has focused primarily on hormonal profiles, with limited exploration of the molecular and physiological mechanisms underlying these changes.

This literature review aims to provide a comprehensive assessment of the thyroid response to cardiopulmonary bypass (CPB) in children with congenital heart disease (CHD) and to integrate these hormonal alterations with postoperative clinical outcomes. A more detailed understanding of these mechanisms is expected to support the development of targeted preventive and therapeutic strategies to mitigate thyroid dysfunction in the pediatric CHD population.

METHOD

This study employed a literature review methodology to identify and synthesize relevant evidence. Scientific articles were searched across six major databases: PubMed, ScienceDirect, ProQuest, Cochrane Library, ResearchGate, and Google Scholar, using combinations of the keywords "cardiopulmonary bypass," "aortic cross-clamping," "thyroid function," "thyroid-stimulating hormone," "thyroid hormones," "non-thyroidal illness syndrome," "pediatric," and "congenital heart disease," connected with the Boolean operators AND and OR. Studies were included based on their relevance to the thyroid response to cardiopulmonary bypass in children with congenital heart disease, availability in full-text format, and publication between 2010 and 2025. The 15-year time frame was selected because restricting the search to the most recent 10 years yielded only two eligible articles, whereas extending the range provided a more representative and comprehensive evidence base. Articles that did not meet these criteria were excluded from the review.

RESULT

The authors conducted a literature search on the thyroid response to cardiopulmonary bypass in children with congenital heart disease. They identified six articles that met the inclusion criteria and were relevant to the study topic. The results of the literature search are presented in Table 1.

TABLE 1: Findings from the Literature Search.

No.	Title	Study (Year)	Summary of Study Results
1	Changes of serum TSH, FT3, and FT4 levels in infants who received surgical correction of congenital heart disease under cardiopulmonary bypass	Lin et al. (2023)	• Differences in sex, age, body length, and body weight between CHD groups were not statistically significant ($P > 0.05$). • Postoperatively, the simple CHD group demonstrated better ejection fraction ($P = 0.003$) and fewer complications ($P < 0.05$). No significant differences were observed in the rates of hepatic or renal failure. • Thyroid hormone levels (TSH, FT3, FT4) decreased significantly after surgery (T1) compared with preoperative values (T0), increased at T3, but remained below baseline levels ($P < 0.01$). • No group differences were observed at T0 and T1 ($P > 0.05$). However, at T2 and T3, thyroid hormone levels were significantly higher in the simple CHD group ($P < 0.05$).
2	Patterns and Determinants of Change in Cortisol Levels and Thyroid Function as a Function of Cardiac Risk in Children Undergoing Cardiac Surgery	Al-Sofyani et al. (2022)	• This study included 46 children (54.3% male; mean age 12 months, range 1 month to 14 years). Six patients (13%) had undergone prior cardiac surgery, and 56.5% were classified as RACHS ≥ 3 before surgery. • All patients required mechanical ventilation, and delayed sternal closure occurred in 17.4%. The median durations of mechanical ventilation, PICU stay, and hospital stay were 1.5, 5.5, and 8.5 days, respectively. • Most patients (60.9%) had preserved cardiac function. Common postoperative complications included hypotension, low cardiac output syndrome (37.0%), and acute kidney injury (26.1%). One patient (2.2%) died. • Thyroid hormone levels (TSH, FT3, FT4) showed a U-shaped pattern, with significant decreases at 24 and 48 hours after surgery, reaching the lowest values at 48 hours. At 72 hours, TSH, FT4, and cortisol had returned to baseline levels, whereas FT3 remained low (−1.67 pmol/L; $P < 0.001$). Cortisol peaked at 24 hours and returned to baseline at 72 hours.

No.	Title	Study (Year)	Summary of Study Results
3	Non-thyroidal illness syndrome and cardiopulmonary bypass in children with congenital heart disease	Babazadeh et al. (2014)	• A total of 135 pediatric cardiac surgery patients were evaluated, with three postoperative deaths excluded from the analysis. • All patients showed decreases in TSH, T3, and T4 levels and an increase in T3RU after cardiopulmonary bypass. Repeated-measures ANOVA confirmed significant reductions in TSH, T3, and T4 ($p < 0.001$). T3 levels decreased significantly up to 24 hours after surgery and then reached a peak. T4 demonstrated a similar decline during the first postoperative day, with no further changes thereafter. T3RU peaked immediately after surgery and then decreased to values below baseline. TSH levels fell up to 12 hours postoperatively, remained stable for the next 12 hours, and then began to rise, likely reflecting recovery of T3 and T4 levels.
4	Thyroid and Brain Natriuretic Peptide Response in Children Undergoing Cardiac Surgery for Congenital Heart Disease	Cantinotti et al. (2013)	• Patients were divided into three age groups: neonates, infants, and children. The severity of congenital heart disease was classified using the ABC Aristotle score. • Neonates had more complex disease and poorer postoperative outcomes, including longer ICU stay, prolonged transthoracic echocardiography monitoring, greater inotropic support requirements, and higher rates of adverse events ($P \leq 0.001$). • Although not statistically significant, major complications were more frequent in neonates (19%) compared with older children (6%). • TSH, fT3, and fT4 levels decreased significantly after surgery ($P < 0.001$), with recovery beginning within 48 to 72 hours. In neonates, TSH remained suppressed until 108 hours and normalized only by day 15. In older children, recovery started on day 2 and was complete within 84 hours. The nadir of fT3 occurred later in neonates (84 hours versus 36 hours; $P = 0.002$). Despite having lower preoperative thyroid levels, neonates demonstrated higher postoperative fT3 and fT4 levels up to 60 hours ($P < 0.01$). BNP levels rose 6 to 12 hours after surgery ($P < 0.001$), peaked at 108 hours, and returned to baseline by day 7, showing an age-related pattern similar to thyroid hormones.
5	Cardiopulmonary Bypass and Serum Thyroid Hormone Profile in Pediatric Patients with Congenital Heart Disease	Talwar et al. (2012)	• This study examined 100 children (71 males and 29 females) who underwent open-heart surgery for the correction of congenital heart disease. • Postoperatively, 3 children developed transient mild left ventricular dysfunction, and 7 experienced severe ventricular dysfunction, predominantly right ventricular dysfunction, following tetralogy of Fallot repair. There were 12 deaths, mainly due to low cardiac output syndrome, sepsis, and pulmonary hypertensive crises. • All baseline thyroid hormone levels were within normal ranges. Significant declines occurred within 24 hours after CPB: FT4 decreased by 29.1%, TT4 by 32.1%, TSH by 77%, FT3 by 46%, and TT3 by 45% ($P < 0.0001$). Serum TSH was the first hormone to rise during recovery. Although levels began to improve at 48 and 72 hours, they remained below baseline values. All values stayed within physiological limits.
6	Perfusion temperature, thyroid hormones, and inflammation during pediatric cardiac surgery	Eggum et al. (2010)	• The median age was 6 months (range 2 to 14) in the mild hypothermia group (Group A) and 7 months (range 1 to 18) in the moderate hypothermia group (Group B). The median weights were 5950 g (range 4040 to 9599) and 6300 g (range 4720 to 9900), respectively. • No significant differences were found between groups in these parameters or in clinical outcomes, including ventilation time, urine output, packed red cell transfusion, inotropic support, ICU stay, and mortality. • Both groups demonstrated reductions in T3, fT4, and TSH, reaching their lowest values at 24 hours. TSH increased thereafter, while T3 and fT4 remained low at 48 hours.

No significant hormonal differences were observed between groups. IL-6 and RANTES correlated with lower T3 levels, and MCP-1 correlated with lower fT4 levels. These correlations were present in Group B but not in Group A. Complement markers correlated positively with fT4 (TCC) and TSH (C3bc) in all patients, including those in Group A.

DISCUSSION

Definition and Pathophysiology of NTIS

Non-thyroidal illness syndrome (NTIS), also referred to as sick euthyroid syndrome (SES), represents an adaptive physiological response to severe systemic stress. The condition is characterized by decreases in triiodothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone (TSH), despite the absence of intrinsic thyroid pathology [8]. Across the six studies analyzed in this review, children undergoing open-heart surgery with cardiopulmonary bypass (CPB) consistently demonstrated this classic NTIS profile, most notably during the first 24 to 48 hours after surgery.

Altered thyroid regulation in this setting is largely driven by surgical stress, tissue hypoperfusion, and inflammatory activation. These mechanisms align closely with the postoperative hormonal trends reported across the included studies, supporting the concept of NTIS as a regulated metabolic adaptation to major physiological stress rather than a manifestation of intrinsic thyroid dysfunction [9].

Age-Related Variability in Postoperative Thyroid Function

Age significantly influences the depth and duration of postoperative thyroid suppression. Neonates exhibit the greatest reductions in TSH and fT3 and the slowest recovery compared with infants and older children [10]. This vulnerability is consistent with the relative immaturity of the neonatal hypothalamic–pituitary–thyroid axis, including limited TSH responsiveness and reduced peripheral T4-to-T3 conversion.

Younger age groups consistently demonstrate more pronounced hormonal suppression and delayed normalization of thyroid function [7]. These findings indicate that age is a critical biological determinant of postoperative endocrine response, shaping the severity of NTIS after CPB.

Influence of Surgical Complexity and Clinical Outcomes

Surgical complexity contributes substantially to postoperative thyroid alterations. Children undergoing more complex procedures show lower postoperative thyroid hormone levels and sharper early declines. Longer CPB duration and extended aortic cross-clamping intensify inflammatory responses, which in turn influence thyroid hormone metabolism [7,11,12].

Inflammatory mediators such as interleukin-6 (IL-6), regulated on activation normal T-cell expressed and secreted (RANTES), and monocyte chemoattractant protein-1 (MCP-1) correlate with reductions in T3 and fT4, reinforcing the role of systemic inflammation and deiodinase modulation in NTIS [13]. These hormonal disturbances have meaningful clinical implications. Marked reductions in T3 impair myocardial contractility and energy utilization, and declines of approximately 45-46% have been associated with postoperative ventricular dysfunction and hemodynamic instability [12].

Neonates undergoing complex procedures also experience poorer clinical outcomes, likely reflecting a combination of greater surgical burden and heightened susceptibility of the immature endocrine system [10].

Systemic Stress Responses to NTIS

Endocrine changes after CPB extend beyond the thyroid axis. Activation of the hypothalamic–pituitary–adrenal (HPA) axis leads to early cortisol elevation, which helps maintain hemodynamic stability during acute stress. Higher postoperative cortisol levels are associated with increased inotropic support, longer mechanical ventilation, and prolonged PICU stays [14]. These elevations frequently occur in patients exposed to longer CPB times or delayed sternal closure, linking adrenal activation to surgical and inflammatory stress.

Systemic inflammation and hemodynamic instability further stimulate the HPA axis, serving as compensatory mechanisms to maintain vascular tone [15]. Cardiac biomarkers provide additional insight: postoperative BNP correlates with ICU stay, inotropic requirements, and ventricular function, and its inverse relationship with fT3 and TSH indicates that cardiovascular stress parallels the degree of endocrine disturbance [10,16]. These findings highlight NTIS as one component of an integrated multisystem stress response involving inflammatory, cardiovascular, and adrenal pathways.

Management Implications

Therapeutic use of thyroid hormone has been explored as a potential strategy to counteract the hemodynamic effects of NTIS after pediatric cardiac surgery. Several studies indicate that supplementation with T3 or T4 may reduce the need for inotropic support, although consistent benefits on ventilatory duration, intensive care stay, overall hospitalization, cardiac index, or mortality have not been observed [17]. Additional evidence shows that postoperative administration of T4 can help preserve circulating T3, FT3, and FT4 concentrations and may modestly reduce the risk of low cardiac output syndrome, yet without translating into significant improvements in ICU length of stay [18].

Overall, the available data suggest that while clinicians often anticipate hemodynamic improvement with thyroid hormone therapy, controlled clinical evidence remains insufficient to support its routine use, underscoring the need for more targeted and well-designed trials to determine which pediatric subgroups may benefit most.

CONCLUSION

Cardiopulmonary bypass (CPB) in pediatric cardiac surgery is associated with significant thyroid dysfunction and a characteristic NTIS pattern, particularly in neonates and in high-complexity procedures, with potential implications for postoperative hemodynamic stability. Vigilant preoperative assessment and postoperative monitoring of thyroid function are therefore essential. Although thyroid hormone supplementation may reduce inotropic requirements and help preserve postoperative hormone levels, current evidence does not consistently demonstrate improvements in primary clinical outcomes. Further studies with larger cohorts and structured hormonal surveillance are needed to refine management strategies and identify patient groups most likely to benefit from targeted therapy.

ACKNOWLEDGMENT

The authors would like to acknowledge all researchers whose work has contributed to the current understanding of thyroid physiology, cardiopulmonary bypass, and postoperative endocrine responses in pediatric cardiac surgery. The evidence and insights provided by previous clinical, physiologic, and perioperative studies were essential in supporting the completion of this literature review.

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