Hypothyroid on cardiopulmonary bypass usage in children with congenital heart disease: A literature review

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ABSTRACT

Congenital heart disease (CHD) is a birth defect that affects the structure or function of the heart. Cardiopulmonary bypass (CPB) is frequently used to treat CHD, which raises the risk of hypothyroidism. Hypothyroidism can cause decreased cardiac output due to poor relaxation of cardiac smooth muscle cells and reduced endothelial nitric oxide accessibility. This causes a chain reaction of increasing arterial stiffness, which raises systemic vascular resistance (SVR). Thyroid hormones also have an effect on the renin-angiotensin-aldosterone pathway, promoting the synthesis of renin substrates in the liver. This causes higher diastolic blood pressure, narrow pulse pressure, and decrease in renin levels in hypothyroid patients. Thyroid hormones also regulate the transcription of pacemaker genes, hence hypothyroid patients have a slower heartbeat. Hypothyroidism raises the likelihood of atrial fibrillation.

INTRODUCTION

Congenital heart disease (CHD) is the most prevalent congenital abnormality, accounting for one in every three live-born congenital malformations.¹ Despite ever-improving diagnostic and therapeutic technologies, CHD remains one of the top causes of death in the first year of life.² CHD care frequently involves the use of a cardiopulmonary bypass (CPB) machine or known as open heart surgery; however the use of CPB is a double-edged sword; on the one hand, it can aid surgery, but on the other hand, it can create hormonal function abnormalities such as hypothyroid. According to prior study, there is a decline in postoperative thyroid hormones compared to baseline values before surgery, there was a decrease in 24 hours after the use of CPB, there was a decrease in 29.1% in free T4 (FT4), 32.1% in total T4 (TT4), 77% in thyroid stimulating hormone (TSH), 46% in free T3 (FT3), and 45% in total T3 (TT3).³

Post-operative open-heart surgery can result in hypothyroidism, which can impair the cardiovascular system, as well as edema and pleural effusion, both of which are symptoms of heart failure. A decrease in heart rate, ventricular filling, and myocardial contractility can explain these symptoms. Children are additionally predisposed to ventricular arrhythmias as a result of the heart's action potential being prolonged.¹ Hypothyroidism can also result in bradycardia, a low-voltage ECG pattern, and prolonged PR and QT intervals.⁴ Low cardiac output syndrome (LCOS) can be caused by hypothyroidism due to poor relaxation of cardiac smooth muscle cells and reduced accessibility of endothelial nitric oxide. This causes a chain reaction of increasing arterial stiffness, which raises systemic vascular resistance (SVR).⁵ Thyroid hormone plays a crucial role in critically ill patients, patients undergoing surgical procedures, and various drugs administered while undergoing intensive care have been reported to suppress the hypothalamic-pituitary-thyroid axis, which can lead to changes in plasma concentrations of thyroid hormones that play a crucial role in regulating growth, nervous system myelination, metabolism, endocrine system, and organ function.⁶ Several theories believe that CPB can cause hypothyroidism due to hemodilution, hypothermia, ultrafiltration, non-pulsatile flow, heparinization, hypothermia, systemic inflammatory response syndrome (SIRS), lowered selenium levels, and cellular hypoxia.⁷

COLLECTING DATA

We collected our references using the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statements (Figure 1).⁷ In addition, we also employed a measurement tool to assess systematic reviews (AMSTAR 2) to analyze the results of our review.⁸

CONGENITAL HEART DISEASE

CHD is a womb-acquired defect in the structure and function of the heart. These defects can occur in the heart wall, heart valves, or blood vessels around the heart. As a result, the patient's blood flow may be hindered, resulting in obstruction or blood flowing into the wrong pathway.⁹ CHD is the most prevalent of the congenital malformation, accounting for one in every three live-born congenital malformations.⁹,¹⁰
Etiology
The exact cause of CHD is unknown, but several factors or conditions in the mother can increase the risk of CHD, including genetic disorders, drugs taken during pregnancy, infectious diseases (e.g. rubella, fever) especially in the first trimester of pregnancy, retinoic acid exposure, obesity, smoking, and being exposed to chemicals or radiation during pregnancy.9

Diagnosis
CHD can be diagnosed with anamnesis, hetero-anamnesis, physical examination, and supporting examination. The symptoms that arise in CHD patients and the timing of their appearance vary substantially depending on their type of CHD encountered. Symptoms can emerge soon after birth, during childhood, or even in maturity. Blueness, particularly in the tongue and mucous membranes of the mouth, interference with breastfeeding, sweating while breastfeeding, palpitations, growth disturbances, activity disturbances (e.g., the patient does not appear as active as their peers), recurrent cold coughs, and shortness of breath are of the symptoms.11,12

A spell is an episode characterized by breathing that appears faster and deeper, whimpering, appears bluish or looks increasingly blue, can be accompanied by loss of consciousness or seizures, and can even result in death in children during feeding activities. During a spell episode, the child will often feel better in a squatting position.11,12

Physical examination may also reveal signs and symptoms of CHD, such as age-appropriate weight and height, blood pressure differences between hands and feet, high heart rate, shortness of breath, abnormal heart sounds, or an enlarged liver. Electrocardiography, chest X-rays, echocardiography, and cardiac catheterization are supportive examinations that can help confirm the diagnosis.11,12

Pathophysiology and Management of Congenital Heart Disease
Clinically, CHD is classified as “non-cyanotic” non-blue abnormalities, indicating a left to right heart shunt (L to R shunts). Atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA), and obstruction of blood flow (e.g., pulmonary valve stenosis, aortic valve stenosis, coarctation of the aorta, and congenital mitral valve malformation) are examples of non-cyanotic congenital heart defects. Tetralogy of Fallot (TOF), transposition of the great vessels (TGA), tricuspid atresia (TA), total anomalous pulmonary venous return (TAPVR), truncus arteriosus, hypoplastic left heart syndrome (HLHS), pulmonary atresia (PA/critical PS), and double outlet right ventricle (DORV) are examples of cyanotic congenital heart defects (blue babies).13,14

Atrial Septal Defect (ASD)
ASD is distinguished by a leaky septum that connects the right atrium to the left atrium as a result of septal formation failure. The defects can occur at the foramen ovale, septum secundum defects, which is the failure of septum secundum closure, venous sinus defect with a defect at the mouth of the superior vena cava, and sinus coronary defect, which result in a shunt from left to right. The direction of the lungs in acyanotic patients with ASD is from left to right, and the size of this shunt is determined by compliance of the right ventricle (RV) and left ventricle (LV); if the RV compliance is larger than the LV, there will be a shunt from left to right. The size of this shunt will affect the enlargement of the heart. The atrial septal defect occurs at the atrial level of ASD pathophysiology.
and dilatation occurs in the right atrium (RA), RV, and pulmonary artery (PA). There is no dilatation of the left atrium (LA) in an atrial septal defect, because the enhanced pulmonary venous return to the left atrium is directly transferred to the right atrium.15

Children getting tired quickly when playing, sweating, rapid breathing, shortness of breath, delayed growth, and frequent respiratory infections are the most typical clinical symptoms of ASD. Some children, however, show no symptoms. History taking, physical examination, and supporting tests such as ECG, chest X-ray, and echocardiography are used to make a diagnosis. Transcutaneous catheterization can be used to close a secundum, however if the defect is too tiny or too wide, or if the ASD lacks a rim, pulmonary hypertension occurs, surgical closure of the ASD is the preferred option.15

Ventricular Septal Defect (VSD)
VSD is an acyanotic heart abnormality characterized by leak in the ventricular septum that causes a left-to-right shunt. The degree of left-to-right shunt resistance in tiny defects depends on the size of the defect and is independent of the level of pulmonary vascular resistance (PVR). In this case, a decrease in PVR is normal. There is little resistance to the left-to-right shunt and is greatly reliant on the extent of PVR. The larger the left-to-right shunt, the smaller the PVR. Even when a large VSD is present in a newborn, the PVR remains elevated, and so a large shunt does not occur until the infant is 6 to 8 weeks old. Congestive heart failure may ensue when the shunt is elevated.15

Management of VSD starts with medication such as diuretics, digoxin, and ace inhibitors. Indications and timing of surgery can be conducted in patients with medication failure, conditions that lead to congestive heart failure, growth delay, patients with pulmonary artery pressure greater than 50% of systemic pressure, and surgical closure at the end of the first year. Older infants with a large VSD and enlarged PVR should be operated on as soon as possible. Surgery is not recommended for minor VSDs with a Qp/Qs ratio less than 1.5:1. Surgery is not recommended for patients who have a pulmonary vascular resistance to systemic ratio greater than 0.5 or who have pulmonary vascular obstructive disease with a dominant right-to-left shunt. Depending on the size of the VSD, surgery can be either direct closure or a dacron patch.15,16

Tetralogy of Fallot (TOF)
TOF is a complicated cardiac condition characterized by VSD, overriding aorta/ aortic shift to the right, infundibular, valvular or both pulmonary stenosis, and right ventricular hypertrophy.13 The degree of RVOT obstruction determines the direction and magnitude of the shunt through the VSD; with mild stenosis, the shunt can occur from left to right, and the clinical picture resembles VSD. This condition is known as acyanotic TOF or pink Fallot; with severe stenosis, the shunt will occur from right to left, giving a clinical “cyanotic” picture.15

In cyanotic patients with severe pulmonary stenosis who do not meet the criteria total correction, palliative surgery in the form of a Blalock-Taussig shunt (BT-shunt) or its modification by creating an artificial shunt from the subclavian artery to the pulmonary artery is required. With the introduction of the heart-lung bypass machine and the advancement of medical technology, it is now possible to totally repair the complex anomaly.13,15

Transposition of Great Artery (TGA)
A cyanotic congenital heart abnormality is transposition of the great arteries (TGA). The aorta exits the RV and the PA exits the LV in this scenario. Whereas the aorta is in front and the PA is on the left in levotransposition of the great arteries (L-TGA), the atria and ventricles are in a stable relationship. As in a normal heart, coronary arteries emerge through the aorta. Desaturated blood returning to the right atrium from the body flows out of the aorta without oxygenation from the lungs and then returns to the right atrium. As a result, vital organs including the brain and heart are perfused with blood that has a low oxygen saturation. Well-oxygenated blood, on the other hand, will return to the LA and flow out of the pulmonary artery and back into the left atrium. This condition is made up of two independent circuits that cannot maintain life unless there is a connection or shunt between the two circuits to supply the body’s oxygen needs. This shunting link can occur in the atria, ventricle, or ductus arteriosus.15,16

CARDIOPULMONARY BYPASS
CPB is a surgical method in which a machine temporarily replaces the heart and lungs. The CPB machine’s primary duty is to assist in circulation, respiration, and temperature regulation in order to ease surgery on the heart and major blood vessels. The invention of CPB equipment has allowed for advancements in cardiac surgery. With the availability of CPB equipment, heart surgery can now be performed in a blood-free surgical environment.17,18

Mechanism of action
The CPB circuit comprises Cannula (veins and arteries), a reservoir, a blood pump, an oxygenator, a heat exchanger, an arterial filter, and a cardioplegia system. Tubes of various sizes connect the full. The CPB circuit directs blood away from the heart and lungs via venous cannula, while arterial cannula returns oxygenated blood to systemic circulation. The blood pump forces the blood volume forward via the oxygenator membrane, allowing oxygenated blood to returned to systemic circulation.17,18

To preserve the organs, the temperature is continuously monitored during surgery. The ideal temperature during CPB machine surgery is still being discussed. The primary purpose for hypothermia in CPB machine surgery is to preserve the brain and other organs by reducing the metabolic rate of oxygen consumption. Hypothermia reduces the risk of cerebral ischemia due to embolism by lowering the cerebral blood flow requirements.18

Adequate anesthesia is critical during surgery with a CPB machine. Anesthesia can be maintained through inhalation or intravenous routes. Anticoagulant drug delivery is required before initiating CPB to prevent blood clotting in the system, which can be accomplished by delivering 300 IU/kg. The most often utilized diagnostic method for determining heparin adequacy is activated clotting time (ACT). ACT should be monitored on a frequent basis during CPB.19
Complications Due to Cardiopulmonary Bypass Machine

Various complications can develop, including CPB insertion complications as well as systemic complications.17 The following is a description of mechanical and systemic complications.

Mechanical Complications

Several complications can occur during the arterial cannulation procedure, including hemorrhage, aortic dissection, atherosclerotic plaque separation, or malpositioning that impairs brain perfusion. Low arterial blood pressure, high arterial line pressure, loss of venous return, and bluish discoloration of the veins are all symptoms of aortic dissection. Hemorrhage may develop during the venous cannulation process, and malposition may result in insufficient blood return, resulting in cerebral congestion. Another issue that can develop is air embolism as resulting in pumping from an empty reservoir.17,18

Systemic Complications

a. Systemic Inflammation: Blood contact with machine surfaces, ischemia-reperfusion injury, endotoxemia, or surgical trauma can all cause systemic inflammation. The acute phase reaction begins with the production of cytokines, complement, and nitric oxide (NO), which increases blood vessel capillary permeability.20

b. Platelet Dysfunction: CPB machine induces both qualitative and quantitative thrombocyte dysfunction. Hemodilution reduces pro-coagulant concentration. The coagulation, complement, and fibrinolytic pathways are all activated. Bleeding is increased by extended CPB use, reoperation, and preoperative anticoagulant use.21

c. Organ Injury: The usage of CPB equipment can harm multiple organs, including the brain, kidneys, and heart. Cerebral injuries include anything from cognitive impairment to stroke. Acute kidney injury (AKI) can occur as a result of inflammatory reactions and hypotensive circumstances, with risk factors including extended use of the CPB machines, sepsis, and diabetes. Aortic cross-clamps dislodging following cardioplegia may cause subclinical myocardial injury. Metabolic acidosis, preoperative ventricular function, reperfusion injury and inflammatory mediators are all risk factors for myocardial injury.22

d. Acute respiratory distress syndrome (ARDS) may arise as a result of CPB machine’s effects. Atelectasis caused by anesthesia and decreased mucociliary clearance contribute to acute lung injury. Following cardiac surgery, frequent pulmonary abnormalities include atelectasis and pleural effusion.23

e. Vasoplegia is characterized by severe vasodilatation and resistance to vasopressors, which occurs due to activation of NO synthesis, vascular smooth muscle ATP-sensitive potassium channels, and relative vasopressin deficiency.24

THE IMPACT OF CARDIOPULMONARY BYPASS SURGERY ON THE HORMONAL SYSTEM

CPB-assisted surgery may cause physiologic abnormalities that have not been observed in prior major surgeries. The heart and lungs are not perfused as they would be in normal circulation, therefore they cannot secrete hormones, execute their functions, or contribute to drug metabolism. The oxygenator pump can harm biological constituents in the blood, causing plasma proteins to be adsorbed and removed from circulation, which might stimulate an immunological response. During CPB usage, hemodilution (from blood-free priming fluids) and anticoagulation disturb the concentration of electrolytes, hormones, and serum proteins in the blood. Finally, hypothermic approaches can slow down biological reactions and impair hormonal response.25

Several of the extracorporeal perfusion components cause electrolyte, endocrine, and metabolic disturbances. The effect of non-pulsatile perfusion on organ circulatory flow is different. As a result, pulsatile perfusion can reduce or eliminate some hormonal disturbances after CPB use. The use of CPB may increase hormonal stress that is already uneven in the physiological state, for reasons that are unknown. Following the cessation CPB and restoration of normothermic pulsatile circulation to the endocrine organs, some hormone concentrations rise above normal.26

Thyroid hormone is a hormone that influences the control of circulatory hemodynamics in general. Hyperthyroidism can result in lower systemic vascular resistance, increased heart rate, higher preload, cardiac output, and decreased atrial function. This can result in systolic hypertension caused by increased preload, cardiac output, and decreased arterial function. Furthermore, hyperthyroidism can cause heart rhythm problems, such as atrial fibrillation. Hypothyroid, on the other hand, can raise systemic vascular resistance, decrease heart rate, contractility, and cardiac output. This causes an increase in diastolic pressure and a decrease in pulse pressure. Hypothyroidism can also result in bradycardia, a low-voltage ECG, and prolonged PR and QT intervals.4

Hypothyroidism after cardiac surgery using Cardiopulmonary Bypass

Pediatric hypothyroid patients may exhibit symptoms of shortness of breath, edema, and pleural effusion, all of which are indicators of heart failure. A decrease in heart rate, ventricular filling, and myocardial contractility can explain these symptoms. Children are additionally predisposed to ventricular arrhythmias as a result of the prolonged cardiac action potential. Supplementation with thyroid hormone may help to improve these cardiovascular problem.9

Thyroid hormones serve a key role in controlling growth, nervous system myelination, metabolism, and organ function. The hypothalamus-pituitary-thyroid axis has been documented to be suppressed in severe illness, individuals having surgical procedures, and various drugs given while receiving intensive care. Changes in thyroid hormone plasma concentrations have been linked to euthyroid sick syndrome and contributes to critical disease. Cardiac surgery with CPB causes changes in the central nervous system and several endocrine
systems, although the significance of these changes is uncertain. Postoperative intensive care sequelae in children with congenital heart defects following cardiac surgery, such as LCOS, left ventricular dysfunction, increased vascular resistance, and inadequate ventilation, mimic those associated with hypothyroidism. Transient hypothyroidism after cardiac surgery in children may not only be dangerous immediately after surgery, but it may also jeopardize future central nervous system development. Long-term follow-up studies of the association between children’s neurodevelopmental outcomes in children with CHD and thyroid function after cardiac surgery, on the other hand, are lacking.27

T3 hormone concentration decreases after CPB due to lower T4 to T3 conversion. T3 hormone deficiency reduces intracellular Ca2+ ion levels in cardiomyocytes.28 CPB is linked to the occurrence of pathological situations such as endothelial damage, reperfusion ischemia, and the production of inflammatory cytokines, adhesion molecules, and tumor necrosis factor (TNF), all of which can disrupt homeostasis. Endothelial dysfunction following CPB surgery is caused by neutrophils interacting with proinflammatory molecules.5,28 Thyroid hormone levels in post-CPB patients fall dramatically in 50-75% of patients peri-operatively, according to changes in thyroid hormones. Thyroid hormone levels continue to fall until postoperative days 1-4. Hypothyremia, hemodilution, caloric restriction, and activation of inflammatory mediators such as Interleukin-6 (IL-6) following cardiac surgery causes a reproduction in T3 hormone levels. These conditions result in lower T4 to T3 conversion, a smaller distribution volume, and a shorter half-life of T3 hormones.5,28

Previous studies have found decrease in total T3 and free T3 levels hormone levels following CPB surgery.36 Another study discovered a substantial decrease in T4, T3, and FT3 hormone levels after CPB surgery. The decline was inducted by a decrease in T4 conversion to T3 as a result of metabolic reaction. TSH and fT4 concentrations, on the other hand, did not change significantly following CPB procedure in this study.37 Meanwhile, CHD patients used CPB for longer periods, which was related with lower levels of the FT3 and TSH hormones.32

There is an increase in proinflammatory cytokines that disrupt cardiac function due to alterations in thyroid function with CPB use. An increase in cytokines results in a decrease in T3 hormone levels. T3 hormone treatment improves cardiac function after CPB usage in children. After CPB weaning, T3 hormone supplementation is reported to improve left ventricular systolic and diastolic pressures.3,35 Abnormal thyroid hormone levels after cardiac surgery in a pediatric population have been linked CPB use and physiological stress caused by inflammation. Sick euthyroid syndrome (ESS) is the clinical term for this illness. In ESS type 1, total T3 and FT3 levels are lower, but TSH levels are normal, indicating an inflammatory response, elevated steroid hormone levels due to surgical stress, or hypoxia during the perioperative phase due to poor cardiac output. T3 and T4 hormone levels fall in type 2 ESS due to decreased thyroid-binding globulin levels. Thyroid hormone levels decreased 24-48 hours after surgery and returned to normal on days 5 to 7, particularly in uncomplicated patients receiving critical care in the ICU. T3 hormone supplementation minimizes the need for inotropic use from 72 hours postoperatively. Supplementation is also more beneficial in children under the age of 6 months who have major cardiac surgery.2,34

Thyroid hormone concentrations may vary in pediatric patients with CHD who have cardiac surgery with CPB. TSH hormone levels will rise in response to decreasing T3 hormone levels at the start of CPB administration in surgery. Thyroid hormone levels return to normal after a few days. Routine thyroid replacement hormone in children following congenital heart surgery may provide therapeutic benefits. These advantages include a decrease in the usage of postoperative inotropes.35

Thyroid response patterns differ in the pediatric patients undergoing cardiac surgery. There is a link between patient age, CPB use length, surgical morbidity, and the degree of thyroid response. Cardiac surgery, with or without CPB, induces post-operative depression of circulating thyroid hormones in both adult and pediatric populations. Cardiac surgery using CPB procedures SIRS, which leads to increased morbidity and mortality as well as organ failure. Inflammatory cytokines, especially IL-6, have been linked to the suppression of T4 to T3 hormone conversion. TSH, T3, and T4 hormone levels in neonates are lowest on the first and second postoperative days, but return to normal by the fifth or seventh day.36

Hypothyroid Effects on Cardiac Physiology
Thyroid hormones play critical roles in cardiac and vascular physiology. Hypothyroidism can result in lower cardiac output due to poor relaxation of cardiac smooth muscle cells and decreased endothelial nitric oxide accessibility. This causes a chain reaction of increased arterial stiffness, which raises SVR. Thyroid hormone also influences the renin-angiotensin-aldosterone pathway, causing the liver to produce renin substrates. As a result, hypothyroidism causes increased diastolic blood pressure, narrow pulse pressure, and decreased renin levels. The thyroid hormone also regulates the transcription of pacemaker genes, therefore hypothyroid patients have a slower heartbeat.3 Hypothyroidism patients have a reduced risk of atrial fibrillation than euthyroid patients, and corrected hypothyroid patients stay in the hospital for less time than euthyroid patients.35,36

CONFLICT OF INTEREST
The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTION
Agil Al Jufri: Data curation, Data Analysis, Visualization, Manuscript Preparation; Heroe Soebroto: Research concept, Methodology, Review, Manuscript Preparation, Editing, Revision, Supervision; I Ketut Alit Utayayas: Review, Manuscript Preparation, Supervision.
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