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Original Article

Effects of Cardiopulmonary Bypass on Thyroid Function and Need of Prophylactic Low-Dose Thyroxine for Post-operative Cardiac Surgery Patient

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Abstract

Introduction: Cardiopulmonary bypass (CPB) is associated with well-described changes in thyroid hormone levels, consistent with what is described as the euthyroid sick syndrome.

Aim: This study aims to evaluate thyroid hormone changes and their association with post-operative care in low-risk patients undergoing cardiac surgery with CPB.

Materials and Methods: Fifty patients with euthyroid were included; no one received drugs with a known influence on thyroid status at the time of the operation. Eighteen of the patients had coronary artery bypass surgery, 29 had a single valve replaced, and 3 had both valve replacement. Blood samples were collected 6 h after surgery and on the 3rd postoperative days (POD).

Results: Thyroid-stimulating hormone (TSH) levels were raised in 10 patients and free T3 level reduced in 14 patients in the early post-operative period and TSH raised in 4 patients and free T3 reduced in 6 patients during the 3rd POD. Number of the cases with normal TSH is 36, free thyroxine [T4] remained within the normal range in all patients throughout the study.

Conclusion: There is an advantage of prophylactic administration low dose of thyroxine to all cardiac patients, especially female patient who undergoes surgery to improve the general condition of the post-cardiac surgery patients.

Key words: Cardiopulmonary bypass, Euthyroid sick syndrome, Thyroid hormone

INTRODUCTION

Cardiopulmonary bypass (CPB) is associated with well-described changes in thyroid hormone levels, consistent with what is described as the euthyroid sick syndrome.[1-3] The syndrome is characterized by depressed total (TT3) and free (fT3) triiodothyronine levels despite normal concentrations of thyroid-stimulating hormone (TSH) and total (TT4) and free (fT4) thyroxine. Decreased deiodination of T4 to its active compound T3 has been implicated as the central pathophysiologic mechanism, while there is a concomitant rise in the levels of the inactive compound reverse T3.[4] After CPB, some patients have low cardiac output, responding poorly to conventional inotropic stimulation. Recently, it has been claimed that acutely administered triiodothyronine (T3) may benefit cardiac performance by several mechanisms independent of *de novo* protein synthesis. It seems likely that a severely depressed thyroid state at the end of the operation might contribute to acute heart failure. A low T3 syndrome is often seen in patients with serious diseases and those having an operation.[5-8] Very sparse and indeed, conflicting results concerning thyroid hormonal state have been presented in this specific category of patients undergoing CPB.[3,8-11]

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The possible hemodynamic consequences of the respective findings have been discussed only sparsely.

Aim

This study aims to evaluate thyroid hormone changes and their association with post-operative care in low-risk patients undergoing cardiac surgery with CPB and to assess whether free thyroid hormone concentrations are decreased to a degree indicating the need for T3 substitution to restore cardiac performance perioperatively.

MATERIALS AND METHODS

Fifty preoperatively euthyroid patients, 28 men and 22 women, ranging in age from 28 to 64 years (median 48 years), were included in the study after giving written and informed consent. No one received drugs with a known influence on thyroid status at the time of the operation. Eighteen of the patients had coronary artery bypass surgery, 29 had a single valve replaced, and 3 had both valve replacement. The priming solution for the heart-lung machine was composed of 2000 ml Ringer's lactate solution and heparin (5000 IE). Heparin was further administered to the patients before CPB, according to the activated clotting time (about 300 IE/kg body weight). When required during perfusion, bicarbonate was added to the heart-lung machine. Aortic cross-clamp time ranged from 41 to 115 min (62 ± 21 min). Local and universal cooling to 28°C was performed, and blood cardioplegic solution was used and by lowering the temperature in the heart-lung circuit. The flow was kept at 60 ml/kg/min, and blood pressure ranged from 40 to 60 mmHg (by our standard non-pulsatile system). All patients received a single unit of blood and two units of plasma at the end of the procedure. Dobutamine and adrenaline infusion (3 ~g/kg/min) was started at the end of the operation in all patients. Patients have treated with thyroxine 50 μg/day. Blood samples were collected 6 h after surgery and on the 3rd postoperative days (POD).

RESULTS

TSH levels were raised in 10 patients (female 6 and male 4) and free T3 level reduced in 14 patients (female 8 and male 6) in the early post-operative period [Figure 1] and TSH raised in 4 patients (female 1 and male 3) and free T3 reduced in 6 patients (female 3 and male 3) during the 3rd POD [Figure 2]. The number of the case with normal TSH is 36, free thyroxine [T4] remained within the normal range in all patients throughout the study. Total patients with abnormal thyroid levels and treated with tablet thyroxine 50 μg/day through oral are 30 [Figure 3]. Of the 30 patients, 4 develop low cardiac output and high inotropic supports and 3 of them improved from low cardiac output after administration thyroxine.

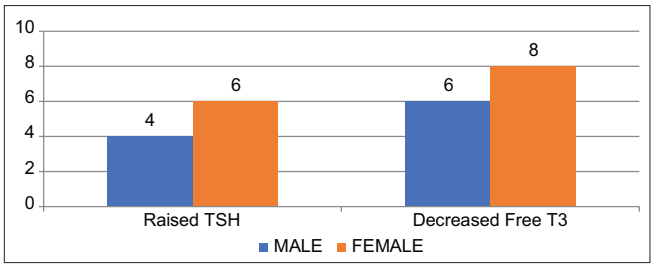

Figure 1: Thyroid status on postoperative days 0

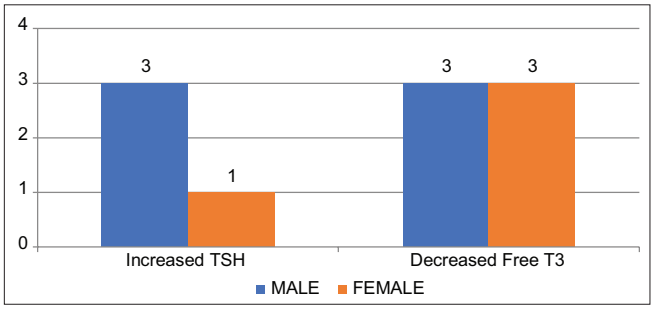

Figure 2: Thyroid status on postoperative days 3

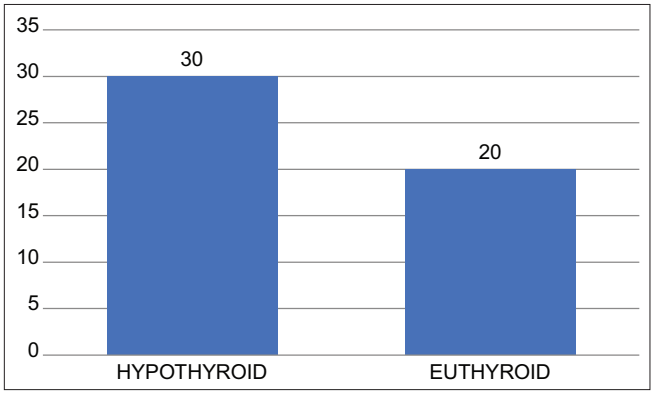

Figure 3: Total patient distribution

DISCUSSION

The study confirms the previous findings of significant thyroid hormone changes after CPB.[1-3,12] The results shows that, a progressive decline in fT3 levels in the early post-operative phase, despite preserved fT4 level. These thyroid hormone changes are consistent with what is known as a euthyroid sick syndrome, which is also characterized by raised levels of the inactive compound reverse T3 (rT3). The previous studies have confirmed the presence of elevated rT3 during and after CPB.

The mechanism responsible for the development of euthyroid sick syndrome involves the regulation of two deiodinases that control T4 metabolism.[2,12] Thyroxine is

3 times less potent than T3 and is entirely secreted by the thyroid gland. Approximately 40% of T4 is deiodinated to the active compound, T3, in the peripheral tissues. Two deiodinases are involved in this process: 5'deiodinase converts T4 to T3 and rT3 to 3,3'T2, and 5-deiodinase converts T4 to rT3 and T3 to 3,3'T2. It is thought that reduced activity of 5'deiodinase results in decreased formation of T3, allowing increased conversion of T4 to rT3 by 5-deiodinase. Moreover, there is concomitantly reduced metabolism of rT3 to 3,3'T2, which contributes to the raised levels of rT3.[4]

There is an obvious difference between euthyroid sick state and primary hypothyroidism, in that the latter is usually characterized by decreased levels of T4 and fT4, raised concentrations of TSH and normal levels of T3 and fT3. Furthermore, primary hypothyroidism is a chronic illness, while euthyroid sick syndrome has been observed as an acute response of the thyroid axis to a variety of insults. These include general surgical operations,[8,9] acute and chronic systemic illnesses, fasting, and major trauma.[13]

It is interesting to note that post-surgical euthyroid sick syndrome occurs in the early post-operative phase, at a time, when the patient is in a catabolic state with increased whole-body oxygen consumption and global oxygen extraction fraction. Similarly, Aun *et al.*[13] observed that in trauma patients, there was a reduction in T3 levels despite increased oxygen extraction by muscular tissue. All this would suggest that the euthyroid sick syndrome represents an adaptive mechanism of the body in an attempt to reduce catabolism,[2,4] rather than a true hypothyroid state.

The documentation of low T3 levels after CPB led to a number of studies that investigated the possible beneficial effect of perioperative T3 administration. Several randomized clinical studies have been undertaken.[5-7,14,15] Despite methodological differences between individual studies, the majority of evidence appears to demonstrate improved hemodynamic performance with T3 administration but no difference in clinical outcome [Table 1].

Hemodilution by the CPB circuit priming volume is unlikely to be a major factor affecting thyroid hormone changes postoperatively since albumin concentrations return to normal by 2 h after CPB, while changes in thyroid hormone levels persist for several days.[1,2,11] Moreover, thyroid hormone changes move in opposite directions during and after CPB, suggesting that despite their structural similarity, they are affected by hemodilution in a different way. Even after correcting for hemodilution, Bremner *et al.* reported thyroid hormone changes of a euthyroid sick response.[12] All this indicates that hemodilution is not a major factor affecting thyroid hormone levels.[2]

The lack of pulsatile flow is perhaps the only factor that has been shown to significantly affect the magnitude of thyroid hormone changes during CPB. Buket *et al.*[3] examined thyroid hormone changes in 30 low-risk patients undergoing CABG with hypothermic (26–30°C) CPB using pulsatile versus non-pulsatile flow. The authors observed the development of euthyroid sick syndrome in both groups. However, total T3 and fT3 concentrations declined significantly less with pulsatile CPB. Immediately relevant to these findings is the pioneering work by Taylor and Bremner *et al.* in the late 1970s. Their group investigated the hypothalamic-pituitary-thyroid axis function during CPB.[12] They found a blunted TSH response to thyrotropin-releasing hormone (TRH) during both the early and late phases of CPB, in contrast to heparinized and non-heparinized patients undergoing major surgery.[12] This led them to repeat the study of TRH administration in 20 patients undergoing normothermic pulsatile versus non-pulsatile CPB. There was a marked difference between the groups, with non-pulsatile patients

Table 1: Summary of T3 administration studies

Author, year	Study design	N	T3 protocol	Main findings
Mullis-Jansson *et al*., 1999[7]	DB, randomized placebo controlled	170	1 mg/kg bolus+1 mg/kg over 6 h	↓ inotropic use, ↓ myocardial ischemia, ↓ pacemaker dependence, ↓ LV mechanical assistance
Bennett-Guerrero *et al*., 1996[6]	DB, randomized placebo-controlled positive control (dopamine)	211	0.8 mg/kg bolus+0.12 mg/kg h for 6 h	No differences in hemodynamics or inotropic use
Klemperer *et al*., 1995[5]	DB, randomized placebo controlled	142	0.8 mg/kg bolus+0.113 mg/kg h for 6 h outcome or inotropic use	↑ CO, ↓ SVR, no difference in
Teiger *et al.,* 1993[15]	DB, randomized placebo controlled	20	Total 0.55 mg/kg in 5 boluses over 20 h	No differences
Novitzky *et al.,* 1989[14]	DB, randomized placebo-controlled LVEF < 30%	24	Total 0.275 mg/kg in 4 boluses over 8 h	↓ inotropic and diuretic requirements, no difference in outcome
	DB, randomized placebo-controlled LVEF > 40%	24	Total 0.55 mg/kg in 5 boluses over 20 h	↑ CO, ↓ SVR, ↓ PVR, no difference in outcome, inotropes, diuretics

*DB: Double blind, LV: Left ventricular, CO: Cardiac output, SVR: Systemic vascular resistance, LVEF: Left ventricular ejection fraction, PVR: Pulmonary vascular resistance

demonstrating the previously reported subnormal response to TRH, while pulsatile CPB resulted in a normal pituitary response to TRH in nine out of 10 patients. These studies provide strong evidence that pulsatile flow during CPB is a major factor contributing to the preservation of a euthyroid hormonal environment.

CONCLUSION

This study has demonstrated the presence of thyroid hormone changes after CPB and consistent with the post-surgical euthyroid sick syndrome. Thyroid function is the result of all effects acting sometimes on the direct production of hormones by the gland and, on the hypothalamic-pituitary-thyroid axis, decreasing TSH, and sometimes on peripheral thyroid hormones metabolism. These manifestations, if transient, determine the presence of euthyroid disease, characterized by reversible but sometimes prolonged thyroid function disorders, particularly in females with extremely relevant post-operative effects such as low cardiac output and high inotropic supports, which are improved well after administration of thyroxine. Through this study, we concluded that there is an advantage of prophylactic administration low dose of thyroxine to all cardiac patients, especially female patient who undergoes surgery to improve the general condition of the post-cardiac surgery patients.

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