The Heart Surgery Forum #2012-1084
16 (2), 2013 [Epub April 2013]
doi: 10.1532/HSF98.20121084

Online address: http://cardenjennings.metapress.com

Evaluation of Positive Inotropic Drug Effects on Thyroid Hormone Levels after Open Heart Surgery

Umit Kervan,[1] Anil Ozen,[1] Utku Unal,[1] Irfan Tasoglu,[1] Mahmut Mustafa Ulas,[1] Kumral Cagli,[2] Alper Uzun,[1] Hasmet Bardakci,[1] Kerim Cagli[1]

Departments of [1]Cardiovascular Surgery and [2]Cardiology, Yuksek Ihtisas Hospital of Turkey, Ankara, Turkey

ABSTRACT

Objective: The aim of this study was to examine the effects of positive inotropic drugs, including adrenaline, dopamine, and dobutamine on thyroid hormone levels following open heart surgery.

Methods: We analyzed free thyroid hormones (FT3 and FT4) and thyroid-stimulating hormones (TSH) in 200 consecutive patients undergoing open heart surgery. Patients were divided into 5 groups according to the inotropic drug administration as follows: Group A (n = 46) received dopamine alone; Group B (n = 40), dopamine and dobutamine; Group C (n = 36), dopamine, dobutamine, and adrenaline; Group D (n = 32), adrenaline alone; and Group E (n = 46), placebo. Procedural factors affecting thyroid hormones were recorded and included cardiopulmonary bypass (CPB) time, cross-clamping time, degree of hypothermia, and the duration and doses of positive inotropic drugs. Blood samples for hormone assays were collected before initiation of inotropic drug therapy (baseline) and postoperatively at 24, 72, and 120 hours after drug therapy.

Results: FT3, FT4, and TSH levels at baseline were similar in all groups. Although there was a trend showing very slight increases in thyroid hormone levels from baseline to the 24th, 72nd, and 120th postoperative hours after drug therapy, these changes were not significant, and there were also no significant differences between the groups. There was also no significant statistical difference in CPB time, cross-clamping time, degree of hypothermia, and duration and doses of positive inotropic drugs between groups.

Conclusion: Although thyroid hormone levels were affected by positive inotropic drug usage after open heart surgery, this effect was not significant and thyroid hormone levels remained within normal ranges.

Received July 10, 2012; accepted March 2, 2013.

Correspondence: Umit Kervan, MD, Department of Cardiovascular Surgery, Yuksek Ihtisas Hospital of Turkey, Sihhiye, Ankara, Turkey; +90 505 256 44 38 (e-mail: drukervan@yahoo.com).

INTRODUCTION

Cardiopulmonary bypass (CPB) is associated with changes in thyroid hormone levels consistent with euthyroid sick syndrome (ESS), a spectrum of hypothalamus-pituitary-thyroid axis dysfunction [Holland 1991]. 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 thyroxine (T4) to its active compound triiodothyronine (T3) has been implicated as the central pathophysiologic mechanism, and there is a concomitant rise in the levels of the inactive compound reverse T3 [Velissaris 2009]. In this syndrome, T3 levels and also T4 levels may be low [De Groot 1999]. ESS has been observed in starvation, sepsis, myocardial infarction, and cardiac and noncardiac surgery and may be encountered in any severe illness [De Groot 1999; Afandi 2000]. Recovery from surgery could be compromised if circulating levels of thyroid hormones are depressed or deficient. We hypothesized that the most commonly used cathecolamines could change the circulating levels of thyroid hormones. The current literature is unclear as to the magnitude or direction of changes in circulating thyroid hormone levels in patients undergoing cardiac surgery with or without inotropic support by cathecolamines. Therefore, the amount and duration of positive inotropic support, and the related thyroid hormone status, becomes very important in cardiac surgery patients [Bettendorf 1997; Reinhardt 1997]. The hypothesis was tested by measuring the serum levels of FT3, FT4, and TSH before and after the initiation of intravenous cathecolamine infusions in 200 cardiac surgery patients.

MATERIALS AND METHODS

Study Design

The study groups enrolled 154 patients who underwent a single operative procedure, such as coronary artery bypass grafting surgery, aortic valve replacement, or mitral valve surgery who in addition required inotropic support. All patients included in the study were receiving beta blocker treatment (metoprolol 25-100 mg/day). Study groups were divided into 5 groups according to their inotropic drug administration as

Table 1. Demographic and Baseline Characteristics of the Patients*

	Group A (n = 46)	Group B (n = 40)	Gropu C (n = 36)	Group D (n = 32)	Group E (n = 46)	*P*
Age, y (mean ± standard deviation)	46.16 ± 12.31	46.14 ± 11.00	50.18 ± 17.01	49.03 ± 15.28	48.20 ± 11.30	>.05
Gender, n (%)						
Male	22 (52.1%)	20 (50%)	20 (55.5%)	20 (62.5%)	23 (50%)	.03
Female	22 (47.9%)	20 (50%)	16 (44.5%)	12 (37.5%)	23 (50%)	
Hypertension, n	10	14	8	8	10	>.05
Preoperative inotropic usage, n	0	0	0	0	0	>.05
Preoperative LVEDd, n						
<6cm	40	32	24	24	42	.004
>6cm	6	8	12	8	4	
Preoperative VS, n						
<12	40	32	24	24	42	.004
>12	6	8	12	8	4	
Preoperative pulmonary edema, n	0	1	0	0	0	>.05
Preoperative cardiogenic shock, n	0	0	0	0	0	>.05
Coronary artery disease, n	28	26	24	18	25	.004
Mitral valve disease, n	14	8	10	10	14	.005
Aortic valve disease, n	4	6	2	4	7	.005

*Group A received dopamine alone; Group B, dopamine and dobutamine; Group C, dopamine, dobutaime, and adrenaline; Group D, adrenaline alone; Group E, placebo. LVEDd indicates left ventricle end-diastolic disorder; VS, ventricle score.

follows: Group A (n = 46) received dopamine alone; Group B (n = 40), dopamine and dobutamine; Group C (n = 36), dopamine, dobutamine, and adrenaline; Group D (n = 32), adrenaline alone; and Group E (n = 46), placebo. The placebo included the group of patients requiring no inotropic support to make a better comparison between the groups in order to see the effects of inotropic agents. The choice and different combinations of inotropic agents was according to the clinical status (i.e., low cardiac output, bradycardia) of the patients. Exclusion criteria included history of thyroid disease, preoperative antithyroid (i.e., lithium, amiodarone, sulfonamides, propylthiouracil) or thyroid drug therapy, severe illness such as pulmonary edema or cardiogenic shock, and urgent procedures.

This study was conducted in accordance with the policies and procedures of the Training and Planning Committee of our hospital. Written informed consent was obtained from all the patients. Demographic characteristics of patients are presented in Table 1.

Data Collection

The patients' demographic and clinical characteristics were recorded and included the following parameters: age, sex, hypertension status, preoperative ventricular score (VS) (greater than or less than 12 on ventriculography), echocardiographic left ventricle end-diastolic diameter (LVEDd) (greater than or less than 6 cm), type of cardiac pathology and operative procedure, cardiopulmonary bypass (CPB) and cross clamping (XCl) duration, degree of hypothermia, presence of postoperative infarction, need for cardiopulmonary resuscitation, and amount and the duration of positive inotropic drug support. Blood samples for hormone assays were collected as applied for all preoperative patients routinely (baseline) and at the 24th, 72nd, and 120th postoperative hour after drug therapy. Each blood sample was stored at 4°C and centrifuged within 6 hours. Levels of FT3, FT4, and TSH were measured by using a chemiluminescence assay. Reference values used in thyroid function tests were 1.5 to 4.1 pg/mL for FT3; 0.8 to 1.9 ng/dL for FT4; and 0.4 to 4.0 IU/mL for TSH. Each patient had only 1 operative procedure, including coronary artery bypass grafting surgery, aortic valve replacement, or mitral valve surgery according to the cardiac pathology.

Statistical Analysis

Data analyses were performed by using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, USA). Continuous variables were shown as mean ± standard deviation, along with their ranges. Analysis of variance (ANOVA) was used to determine significant differences over time. A *P* value less than .05 was considered statistically significant.

RESULTS

The mean preoperative ventricular score was 8.2 ± 1.3, and the mean LVEDd was 5.90 ± 0.88 cm, taking into consideration all groups. ANOVA tests revealed no statistical differences among the age groups. Pearson chi-square tests revealed that the sex, hypertension, preoperative LVEDd,

Table 2. The Dosages and Times of Positive Inotropic Drug Treatments According to the Groups*

	Group A	Group B	Group C	Group D	Group E
Adrenaline					
Dosage, μg/kg per min	—	—	1.5 ± 0.36	1.4 ± 0.31	—
Time, h	—	—	33.1 ± 10.11	29.4 ± 9.67	—
Dopamine					
Dosage, μg/kg per min	6.7 ± 1.21	8.7 ± 1.74	7.61 ± 1.48	—	—
Time, h	28.1 ± 9.89	30.9 ± 10.6	33.8 ± 11.29	—	—
Dobutamine					
Dosage, μg/kg per min	—	14.7 ± 2.81	12.0 ± 2.04	—	—
Time, h	—	25.3 ± 7.80	29.1 ± 9.90	—	—

*All data presented as mean ± standard deviation. Group A received dopamine alone; Group B, dopamine and dobutamine; Group C, dopamine, dobutaimen, and adrenaline; Group D, adrenaline alone; Group E, placebo.

preoperative VS, coronary artery disease, mitral valve disease, aortic valve disease variables, and the groups were independent from each other (Table 1).

Postoperative ischemia was evident for 2 patients in Group A and 2 patients in Group B. Cardiopulmonary resuscitation was required for only 1 patient in Group C. In Table 2, the dosage and the duration of positive inotropic supports are shown. There were no significant differences between the groups regarding the positive inotropic drug doses and the infusion time. In Group D, the rationale for using adrenaline alone was to achieve an adequate heart rate.

Comparison of CPB and XCl times and the degree of hypothermia between the groups are presented in Table 3. There were no significant differences between the groups regarding these parameters ($P > .05$).

Thyroid hormone levels were compared within the groups, and the data are shown in Table 4. At baseline, FT3, FT4, and TSH levels were similar in all groups and were within the normal ranges. Although there was a trend showing very slight increases in the thyroid hormone levels from baseline to the 24th, 72nd, and 120th postoperative hours after drug therapy, these changes were not significant, and there were also no significant differences between the groups.

DISCUSSION

In open heart surgery, non-physiological procedures have negative effects on the cardiac tissue, and this, along with thyroid hormone deficiency, can result in a delayed recovery [Vander Salm 1997]. Low thyroid hormone levels are considered to contribute to cardiac decompensation [Mitchell 1992; Bennett-Guerrero 1996; Saatvedt 1998]. In the postoperative period, they cause an increase in the ventilatory support time, an increase in the duration of the intensive care unit stay, and the possibility of cardiac decompensation; all of these effects can result in increased mortality and morbidity [Reinhardt 1997]. Although low thyroid hormone levels may be noted in the first following days after CPB, the description of perioperative thyroid hormone changes led to several animal and clinical studies that investigated the impact of T3 administration during or after CPB with conflicting results [Thrush 1995]. In our study, there was no significant difference between the groups regarding the baseline and the postoperative levels of the thyroid hormones. Consistent with these findings, a prospective study by Thrush et al also revealed no differences in total T3, total T4, FT3, reverse triiodothyronine (rT3), and TSH concentrations in the group of patients undergoing either hypothermic or normothermic CPB [Thrush 1995].

There are some mechanisms related to the effects of positive inotropic drugs on thyroid hormone levels, but much is still unknown. According to some reports, dopamine has a hypophysiotropic effect and decreases the concentration of all the hormones in the circulation that are associated with the anterior pituitary gland [Van den Berghe 1996]. Dopamine decreases the response of TSH to thyrotropin releasing hormone (TRH) by affecting the hypothalamus-pituitary axis [Coiro 2000] and demonstrates this effect in the 2-5 μg/kg per minute dose range [Van den Berge 1994]. Suppression begins on the thyroid axis within 24 hours of dopamine

Table 3. The Duration of Extraphysiological Procedures and the Degree of Hypothermia According to the Groups*

	Group A	Group B	Group C	Group D	Group E	*P*
XCl time, min	46.5 ± 14.65	46.01 ± 13.90	42.3 ± 11.01	44.2 ± 13.16	43.5 ± 10.15	>.05
CPB time, min	64.66 ± 19.83	66.28 ± 19.70	62.31 ± 14.89	68.49 ± 20.98	66.50 ± 18.42	>.05
Hypothermia, °C	30.5 ± 1.52	30.2 ± 1.38	31.3 ± 2.11	30.02 ± 1.78	30.5 ± 1.58	>.05

*All data presented as mean ± standard deviation. Group A received dopamine alone; Group B, dopamine and dobutamine; Group C, dopamine, dobutamine, and adrenaline; Group D, adrenaline alone; Group E, placebo. XCl indicates cross-clamping; CPB, cardiopulmonary bypass.

Table 4. Thyroid Hormone Levels over Time in All Groups*

Parameter	Time point†	Group A	Group B	Gropu C	Group D	Group E	*P*
FT3, pg/mL (normal value 1.5-4.1 pg/mL)	baseline	2.08 ± 0.09	2.0 ± 0.23	1.73 ± 1.06	2.61 ± 0.75	2.05 ± 0.75	>.05
	24th hour	2.03 ± 0.36	2.01 ± 0.24	1.72 ± 1.0	2.60 ± 0.70	2.03 ± 0.68	
	72nd hour	2.43 ± 0.56	2.5 ± 0.58	2.1 ± 0.24	2.75 ± 0.78	2.08 ± 0.72	
	120th hour	2.58 ± 0.68	2.4 ± 0.39	2.1 ± 0.42	2.56 ± 0.62	2.06 ± 0.56	
FT4, ng/dL (normal value 0.8-1.9 ng/dL)	baseline	1.15 ± 0.27	1.10 ± 0.10	1.10 ± 0.09	1.40 ± 0.52	1.10 ± 0.50	>.05
	24th hour	1.16 ± 0.28	1.13 ± 0.12	1.10 ± 0.09	1.40 ± 0.50	1.10 ± 0.65	
	72nd hour	1.21 ± 0.30	1.23 ± 0.34	1.20 ± 0.21	1.69 ± 0.84	1.12 ± 0.78	
	120th hour	1.34 ± 0.51	1.28 ± 0.51	1.20 ± 0.54	1.78 ± 0.92	1.14 ± 0.54	
TSH, IU/mL (normal value 0.4-4 IU/mL)	baseline	0.76 ± 0.75	0.82 ± 0.71	0.40 ± 0.49	1.03 ± 1.21	0.80 ± 0.70	>.05
	24th hour	0.77 ± 0.76	0.50 ± 0.80	0.41 ± 0.28	1.04 ± 1.20	0.81 ± 0.20	
	72nd hour	1.61 ± 1.11	1.45 ± 1.07	0.63 ± 0.69	1.84 ± 1.35	0.79 ± 0.62	
	120th hour	1.78 ± 1.33	1.92 ± 1.41	0.66 ± 0.64	1.88 ± 1.44	0.79 ± 0.68	

*All data presented as mean ± standard deviation. Group A received dopamine alone; Group B, dopamine and dobutamine; Group C, dopamine, dobutamine, and adrenaline; Group D, adrenaline alone; Group E, placebo.

†Postoperative time points after drug therapy.

administration, and thyroid hormone levels return to normal within 24 hours of dopamine infusion discontinuation [Van den Berge 1994]. Return to normal value is 82% for T3 and 57% for T4. Dopamine infusion can also lead to ESS in critically ill patients. This is rather an iatrogenic hypothyroidism than an adaptive situation [Van den Berge 1994]. Dopamine as a neurotransmitter also has the effect of lowering the T3, T4, and TSH levels [Roth-Härer 2001]. In our study, we used dopamine above 5 µg/kg per minute for our patients, and infusion time was over 24 hours, but no significant changes were observed in the hormone levels. Is reported that high-dose dobutamine also affects thyroid hormone levels [Heinen 1983; Cerillo 2005]. Specifically, when dobutamine is administered at doses of 20 µg/kg per minute or above, decrease in TSH levels are observed due to mechanisms not fully elucidated [Buttrick 1988; Velissaris 2009]. Although the affect of long period dobutamine usage on the thyroid hormone levels is not fully understood, it is thought to have an overall decreasing affect [Lee 1999; Eggum 2010]. In our study, dobutamine did not affect the hormone levels, probably due to the use of lower doses, below 20 µg/kg per minute.

According to some reports, adrenaline has a minimal effect on the thyroid hormone levels [Reinhardt 1997]. In agreement with this, adrenaline also did not affect the thyroid hormone levels in this study.

In open heart surgery, the release of proteolytic enzymes and edema formation resulting from non-physiological procedures lead to a decrease in the hormone levels, via affecting the hypothalamus-pituitary axis [Mitchell 1992; Saatvedt 1998] or the thyroid gland. Generally, hormone levels remain within the physiological ranges, but when operative and postoperative procedures are prolonged, pathological changes may be observed. In this study, XCl and CPB times were short, and hypothermia degrees were moderate. Therefore, a major deviation in hormonal status would not be expected.

In the current study, we demonstrated that FT3, FT4, and TSH levels did not change significantly from the baseline to the 24th, 72nd, and 120th postoperative hours after inotropic drug supports. Furthermore, there was no significant difference in thyroid hormone levels between the patients using different inotropic supports. We believe that using positive inotropic drugs, such as adrenaline, dopamine, and dobutamine, in acceptable doses in cardiac surgery patients do not influence these hormone levels.

REFERENCES

Afandi B, Schussler GC, Arafeh AH, Boutros A, Yap MG, Finkelstein A. 2000. Selective consumption of thyroxine-binding globulin during cardiac bypass surgery. Metabolism 49:270-4.

Bennett-Guerrero E, Jimenez JL, White WD, D'Amico EB, Baldwin BI, Schwin DA. 1996. Cardiovascular effects of intravenous triiodothyronine in patients undergoing coronary artery bypass graft surgery. A randomized, double-blind, placebo-controlled trial. Duke T3 study group. JAMA 275:687-92.

Bettendorf M, Schmidt KG, Tiefenbacher U, Grulich-Henn J, Heinrich UE, Schönberg DK. 1997. Transient secondary hypothyroidism in children after cardiac surgery. Pediatr Res 41:375-9.

Buttrick P, Malhotra A, Factor S, Geenen D, Scheuer J. 1988. Effects of chronic dobutamine administration on hearts of normal and hypertensive rats. Circ Res 63:173-81.

Cerillo AG, Storti S, Mariani M, et al. 2005. The non-thyroidal illness syndrome after coronary artery bypass grafting: a 6-month follow-up study. Clin Chem Lab Med 43:289-93.

Coiro V, Volpi R, Cataldo S, et al. 2000. Dopaminergic and cholinergic involvement in the inhibitory effect of dexamethasone on the TSH response to TRH. J Investig Med 48:133-6.

De Groot LJ. 1999. Dangerous dogmas in medicine: the nonthyroidal illness syndrome. J Clin Endocrinol Metab 84:151-64.

Eggum R, Ueland T, Mollnes TE, et al. 2010. Perfusion temperature, thyroid hormones and inflammation during pediatric cardiac surgery. Interact Cardiovasc Thorac Surg 10:76-80.

Heinen E, Herrmann J, Lippe J, Dudek M, Krüskemper HL. 1983. Effect of dopamine and dobutamine on thyroid hormone concentration [in German]. Med Welt 34:696-9.

Holland FW 2nd, Brown PS Jr, Weintraub BD, Clark RE. 1991. Cardiopulmonary bypass and thyroid function: a "euthyroid sick syndrome." Ann Thorac Surg 52:46-50.

Lee E, Chen P, Rao H, Lee J, Burmeister LA. 1999. Effect of acute high dose dobutamine administration on serum thyrotrophin (TSH). Clin Endocrinol (Oxf) 50:487-92.

Mitchell IM, Pollock JC, Jamieson MP, Donaghey SF, Paton RD, Logan RW. 1992. The effects of cardiopulmonary bypass on thyroid function in infants weighing less than five kilograms. J Thorac Cardiovasc Surg 103:800-5.

Reinhardt W, Mocker V, Jockenhövel F, et al. 1997. Influence of coronary artery bypass surgery on thyroid hormone parameters. Horm Res 47:1-8.

Roth-Härer A, Lilienthal H, Bubser M, et al. 2001. Neurotransmitter concentrations and binding at dopamine receptors in rats after maternal exposure to 3,4,3,4-tetrachlorobiphenyl: the role of reduced thyroid hormone concentrations. Environ Toxicol Pharmacol 9:103-15.

Saatvedt K, Lindberg H, Geiran OR, et al. 1998. Thyroid function during and after cardiopulmonary bypass in children. Acta Anaesthesiol Scand 42:1100-3.

Thrush DN, Austin D, Burdash N. 1995. Cardiopulmonary bypass temperature does not affect postoperative euthyroid sick syndrome? Chest 108:1541-5.

Van den Berghe G, de Zegher F, Lauwers P. 1994. Dopamine and the sick euthyroid syndrome in critical illness. Clin Endocrinol (Oxf) 41:731-7.

Van den Berghe G, de Zegher F. 1996. Anterior pituitary function during critical illness and dopamine treatment. Crit Care Med 24:1580-90.

Vander Salm TJ, Stahl RS. Early postoperative care. In: Edmunds LH, ed. Cardiac surgery in the adult. 1st ed. Philadelphia: The McGraw-Hill Companies; 1997: 339-67.

Velissaris T, Tang AT, Wood PJ, Hett DA, Ohri S.K 2009. Thyroid function during coronary surgery with and without cardiopulmonary bypass. Eur J Cardiothorac Surg 36:148-54.