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Original Article

Effect of Low Triiodothyronine (T3) Hormone Levels on The Development of Atrial Fibrillation After Coronary Artery Bypass Surgery

Düşük Triiyodotironin (T3) Hormon Düzeylerinin Koroner Arter Baypas Cerrahisi Sonrası Atriyal Fibrilasyon Gelişimine Etkisi

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ABSTRACT

Objective: Atrial fibrillation (AF) after coronary artery bypass surgery (CABG) is the most common type of arrhythmia and it causes serious morbidity. Low levels of triiodothyronine (T3) hormone are thought to be a strong determinative factor on poor prognosis of cardiac patients. This study was planned to investigate the effect of low levels of T3 on the development of AF after off-pump coronary artery bypass surgery (OPCAB) or conventional CABG surgery.

Method: Sixty patients undergoing CABG surgery were included in this prospective randomized study. Thirty of them were randomly selected among the patients undergoing OPCAB, and the other 30 among the patients undergoing conventional CABG surgery. Thyroid function profiles of all patients were evaluated before the operation and on the first day of postoperative period.

Results: Mean age of the patients was 58.7±8 years. After the operation, 3 patients from each group, 6 patients in total, developed AF. Postoperatively measured Total T3 (TT3) levels of the patients who developed AF after the operation (0.39±0.09 ng/ml) were found to be significantly lower than the preoperatively measured TT3 levels (0.97±0.06 ng/ml) (p=0.042). Moreover, postoperative free T3 (fT3) levels of the patients who developed AF after operation (1.58±0.30 pg/ml) were found to be significantly lower than preoperative fT3 levels (2.95±0.37 pg/ml) (p=0.001). However, by univariate logistic regression analysis, it was seen that the variables that were thought to be risk factors for AF were not significantly effective. Also, when the effects of the variables were examined together by multivariate regression analysis, no significant result was found.

Conclusion: In our study, it was seen that low levels of thyroid hormone in patients undergoing OPCAB and conventional CABG surgery had no effect on AF development.

Keywords: atrial fibrillation, conventional coronary artery bypass, off-pump coronary artery bypass, thyroid hormone

ÖZ

Amaç: Koroner arter baypas cerrahisi (CABG) sonrası atriyal fibrilasyon (AF) en sık görülen aritmi türüdür ve ciddi morbiditeye neden olur. Düşük triiyodotironin (T3) hormonu seviyelerinin, kalp hastalarının kötü prognozu üzerinde güçlü bir belirleyici faktör olduğu düşünülmektedir. Bu çalışma çalışan kalpte koroner arter baypas cerrahisi (OPCAB) ve konvansiyonel CABG sonrası düşük T3 seviyelerinin AF gelişimi üzerindeki etkisini araştırmak için planlandı.

Yöntem: Bu prospektif, randomize çalışmaya CABG uygulanan 60 hasta dahil edildi. Bu hastaların 30'u OPCAB yapılan, diğer 30 hasta ise konvansiyonel CABG yapılan hastalar arasından rastgele olarak seçildi. Tüm hastaların tiroid hormon seviyeleri operasyon öncesi ve postoperatif dönemin ilk gününde değerlendirildi. Tüm hastaların preoperatif ve intraoperatif değerlendirmeleri, postoperatif takipleri kliniğimizin protokolüne göre yapıldı ve veriler kaydedildi.

Bulgular: Hastaların yaş ortalaması 58,7±8 idi. Operasyon sonrası her gruptan 3'er hastada, toplamda 6 hastada AF gelişti. Postoperatif AF gelişen hastaların ameliyat sonrası ölçülen TT3 düzeyleri (0,39±0,09 ng/ml) ameliyat öncesi ölçülen TT3 düzeylerinden (0,97±0,06 ng/ml) anlamlı olarak düşük bulundu (p=0,042). Ayrıca ameliyat sonrası AF gelişen hastaların ameliyat sonrası ölçülen serbest T3 düzeyleri (1.58±0.30 pg/ml) ameliyat öncesi ölçülen serbest T3 düzeylerinden (2.95±0.37 pg/ml) anlamlı olarak düşük bulundu (p=0.001). Ancak tek değişkenli lojistik regresyon analizi ile AF için risk faktörü olduğu düşünülen değişkenlerin anlamlı derecede etkili olmadığı görülmüştür. Ayrıca değişkenlerin etkileri çok değişkenli regresyon analizi ile birlikte incelendiğinde anlamlı bir sonuç bulunamamıştır.

Sonuç: Çalışmamızda OPCAB ve konvansiyonel CABG uygulanan hastalarda postoperatif dönemde düşük T3 hormon düzeylerinin AF gelişimine etkisinin olmadığı gösterilmiştir.

Anahtar kelimeler: atriyal fibrilasyon, çalışan kalpte koroner baypass, konvensiyonel koroner bypass, tiroid hormonu

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INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia postoperatively seen after cardiac surgery (1). Although this type of arrhythmia is not life-threatening in most cases, it causes serious morbidity. AF causes prolonged hospital and intensive care unit stay after coronary artery bypass grafting (CABG), leading to increases in hospital costs (2,3).

Frequency of AF after CABG varies between 20-40% (4-9). In most cases, AF is self-limiting. However, arrhythmia can cause hemodynamic disturbance and increases the risk of postoperative stroke (8).

AF is found to be mainly associated with factors related to conventional CABG technique. It has been reported that surgical manipulations performed on right atrium, use of cardioplegic solution, and aortic cross-clamping (XCL) trigger development of AF (9). However, it is not exactly known which factors cause AF following off-pump coronary artery bypass surgery (OPCAB). Perioperative ischemic damage is thought to cause electrical irregularity and rhythm disturbance (2).

It has been stated that some factors trigger AF regardless of the operation type, such as beta-blocker withdrawal before the surgery, advanced age, increased sympathetic activation, inadequate atrial protection, and fluid and electrolyte loss (2,10-12).

Cardiovascular system is one of the most important target that thyroid hormones play a role in. In clinical and experimental studies, it has been indicated that triiodothyronine (T3) plays the most crucial role in the adjustment of heart rate, myocardial contractility, and arterial peripheral resistance (13). Consequently, low levels of T3 are among the strong determinants of poor prognosis in patients with cardiac disease.

This study aims to investigate the effect of T3 levels on development of AF after OPCAB and conventional CABG.

MATERIALS AND METHODS

The study was prospectively planned on 60 patients undergoing CABG surgery. All patients were informed about the study, their written consents and approval of the ethics committee were obtained. Thirty patients were randomly selected among the patients undergoing OPCAB, and the other 30 among the patients undergoing conventional CABG surgery. Patients having or receiving treatment for a thyroid disease, patients with abnormal thyroid hormone levels as detected in preoperative thyroid function tests, patients whose heart rates were not in sinus rhythm before CABG and patients with inotropic drug requirement after cardiac surgery were excluded from the study. Thyroid function tests were performed in preoperative period and at the postoperative 24th hour. Daily electrocardiography follow-up was performed in each patient until discharge and when any complaints (palpitations, distress) occurred.

Surgical Methods

The surgical method for coronary bypass to be applied to the patients was decided by the attending surgeon, depending on the risk factors, the extent of coronary artery disease, ventricular function and atherosclerosis of the aorta of the patient. Routine cardiac surgery anesthesia was applied to all patients (Table 1).

Table 1. Anesthetic protocol

Phases of anesthesia	Drug	Dose
Pre-anesthesia	Morphine + Scopolamine	0.08-0.1 mg/kg + 0.3-0.5 mg
Induction	Fentanyl Etomidate Vecuronium	5 µg/kg 0.2 – 0.3 mg /kg 0.1 mg/kg
Maintenance	Fentanyl Vecuronium Midazolam Isoflurane/ Sevoflurane	3-5 µg/kg 0.05 mg/kg 0.03 mg/kg 0.5 – 1 % MAC

MAC: Minimum alveolar concentration

Table 2. Thyroid hormone levels

	Reference interval	Unit
Total T4	4.87-11.72	µg/dl
Free T4	0.70-1.48	ng/dl
Total T3	0.60-1.80	ng/ml
Free T3	1.71-3.71	pg/ml
TSH	0.35-4.94	mIU/ml

T4: Thyroxine, T3: Triiodothyronine, TSH: Thyroid-stimulating hormone

OPCAB technique

This procedure was performed via median sternotomy under general anesthesia. Heparinization was achieved with a dose of 100-150 IU/kg and to maintain activated clotting time (ACT) above 300 sec, additional dose of heparin was administered as required. Coronary artery stabilization was accomplished with the Octopus IV cardiac stabilizer (Medtronic). The target coronary arteries were occluded proximally by using a bulldog clamp and to provide the visibility of the surgical field, a filtrated air blower (< 5 L/min) was used. Proximal anastomoses were performed during a single partial clamping of the ascending aorta. After all anastomoses were completed, protamine [protamin/heparin (unit): 1/1] was given to neutralize the effect of heparin.

Conventional CABG technique

All patients were operated using a median sternotomy approach. According to baseline ACT, 350 IU/kg IV heparin was administered to maintain ACT greater than 450 sec during surgery. CABG was performed through arterial cannulation of the ascending aorta and two-stage vein cannulation of right atrial appendage. Cardiopulmonary bypass (CPB) was initiated and XCL was applied. Cardioplegic solution was reinfused every 15 minutes. After all anastomoses were performed, CPB was discontinued. Protamine [protamin/heparin (unit): 1/1] was administered to neutralize the effect of heparin.

Patients in both groups were transferred to the cardiovascular surgery intensive care unit as intubated and connected to a volume-controlled respirator.

Hemodynamic Measurements

ECG was performed on all patients daily in the preoperative period. Blood pressure and heart rate were monitored every four hours. As standard, radial, central venous, and Swan-Ganz catheters were placed in all patients before the operation. In the postoperative period, blood pressure and heart rate were recorded hourly in the intensive care unit and every four hours in the clinic.

Metabolic Measurements

Venous blood samples were taken in preoperative period and on the first postoperative day. Measurements were performed in Abbott ARCHITECT ® analyzer using ARCHITECT TSH, total T4 (TT4), free T4 (fT4), total T3 (TT3), free T3 (fT3) reactive kits, by Chemiluminescent Microparticle Enzyme Immunoassay (CMIA) method. Reference values of Uludag University Faculty of Medicine Central Laboratory were used (Table 2).

Statistical Analysis

Statistical analysis was performed by using SPSS for Windows Version 11.0 statistics package program. Data with continuous values were presented as mean (± standard deviation - SD), as median values when necessary, and categorical data as frequencies and percentages (n,%). For continuous variables asessed after normality analysis, t-test and Mann-Whitney U test were used in independent groups for the comparison of the groups, whereas t-test and Wilcoxon rank sum test were used in pairs of groups before and after comparison of each group. Comparison of changes over time between groups was performed by using the Mann-Whitney U test. Pearson's chi-square test, Fisher's exact chi-square test and Kolmogorov-Smirnov test were used to compare the distribution of the groups for categorical variables. Correlation coefficients were calculated using Spearman and Pearson correlation analysis to examine the co-changes of variables. Univariate and multivariate logistic regression analysis were

Table 3. Clinical features of the patients

Clinical Characteristics	OPCAB (n=30)	Conventional (n=30)	p value
Male	25	20	0.136
Preoperative use of beta blockers	22	19	0.405
Postoperative use of beta blockers	24	20	0.243
COPD	0	3	0.237*
HT	21	22	0.774
DM	8	10	0.573
Postoperative AF	3	3	1.000*

OPCAB: Off-pump coronary artery bypass, COPD: Chronic obstructive pulmonary disease, HT: Hypertension, DM: Diabetes mellitus, AF: Atrial fibrillation

p value: Pearson chi-square test
*p value: Fisher's exact chi-square test

Table 4. Preoperative and postoperative TT3 levels of the patients

Group	Preop TT3(ng/ml)	Postop TT3(ng/ml)	p value
OPCAB	0.96±0.28	0.43±0.24	<0.001°
Conventional	0.86±0.33	0.73±0.43	0.439¨
p value	0.210ˆ	0.001 ˇ	

OPCAB: Off-pump coronary artery bypass, TT3: Total triiodothyronine, preop: preoperative, postop: postoperative

° p value: paired t-test
¨p value: Wilcoxon rank sum
ˆ p value: t –test
ˇ p value: Mann Whitney U test

performed for variables considered to be risk factors in the development of atrial fibrillation. The level of statistical significance was taken as 0.05.

RESULTS

The mean age of 60 patients was 58.7±8 years. Forty-five of them were male. AF developed in only 6 patients during the follow-up. Twenty patients in the conventional CABG and 25 of the patients in OPCAB group were male (Table 3). Mean ages of the patients in the OPCAB and conventional CABG groups were 58±9, and 59.3±6.4 years, respectively.

Postoperative TT3 levels in the OPCAB surgery group were statistically significantly lower than the preoperative TT3 levels (t-test in paired groups p<0.001). In addition, the postoperative TT3 levels of the patients undergoing OPCAB were found to be statistically significantly lower than the postoperative TT3 levels of the patients who had conventional CABG (Mann-Whitney U test p=0.001) (Table 4).

Postoperative fT3 levels of the patients who underwent OPCAB surgery were statistically significantly lower than the preoperative fT3 levels. Likewise, postoperative fT3 levels of the patients who had conventional CABG surgery were statistically lower than the preoperative fT3 levels (p=0.003). Preoperative fT3 levels of patients who underwent conventional CABG surgery were found to be statistically lower than the preoperative fT3 levels of patients who underwent OPCAB (p=0.004) (Table 5).

In addition, percentage changes of TT3 and fT3 levels showed statistically significant difference between conventional method and OPCAB. In the conventional method, the levels of fT3 and TT3 percentage changes were statistically significantly lower than those in OPCAB (p<0.001, p=0.015, respectively).

Table 5. Preoperative and postoperative fT3 levels of patients

Group	Preop fT3(pg/ml)	Postop fT3(pg/ml)	° p value
OPCAB	2.79±0.47	1.67±0.40	<0.001
Conventional	2.34±0.65	1.83±0.61	0.003
ˆ p value	0.004	0.249	

OPCAB: Off-pump coronary artery bypass, fT3: Free triiodothyronine, preop: preoperative, postop: postoperative

ˆ p value: t-test

° p value: paired t -test

Table 6. Factors that have a role in the development of atrial fibrillation

	AF (+) (n=6)	**AF (-) (n=54)**	**p value**
Male	5	40	1.000*
Preoperative use of beta blockers	5	36	0.654*
Postoperative use of beta blockers	5	39	1.000*
COPD	0	3	1.000*
HT	6	37	0.170*
DM	1	17	1.000*

AF: Atrial fibrillation, COPD: Chronic obstructive pulmonary disease, HT: Hypertension, DM: Diabetes mellitus

*p value: Fisher's exact chi-square test

Table 7. TT3 levels among patients with and without atrial fibrillation

AF	Preop TT3 (ng/ml)	Postop TT3 (ng/ml)	¨p value
AF(+)	0.97±0.06	0.39±0.09	0.042
AF(-)	0.90±0.32	0.60±0.39	<0.0001
p value	0.222 ˆ	0.210 ˇ	

AF: Atrial fibrillation, TT3: Total triiodothyronine, preop: preoperative, postop: postoperative

¨p value: Wilcoxon rank sum ˇ p value: Mann-Whitney U test

ˆ p value: t-test

Table 8. fT3 levels among patients with and without atrial fibrillation

AF	Preop fT3 (pg/ml)	Postop fT3 (pg/ml)	°p value
AF(+)	2.95±0.37	1.58±0.30	0.001
AF(-)	2.52±0.61	1.77±0.53	<0.001
ˆ p value	0.103	0.555	

AF: Atrial fibrillation, fT3: Free triiodothyronine, preop: preoperative, postop: postoperative

° p value: paired t –test ˆ p value: t-test

Atrial fibrillation developed in 6 (10%) of the cases after CABG surgery including 5 male patients (Table 6). Three of the patients who developed AF were in conventional CABG group, and the other 3 patients in OPCAB group. The mean ages of the patients who did and did not develop AF were 60±5.1 and 58.5±8.2 years, respectively.

Postoperative TT3 levels in the patients who developed AF after surgery were statistically significantly lower than preoperative TT3 levels (p=0.042) (Table 7).

Postoperative fT3 levels in patients who developed AF after the operation were found to be statistically significantly lower than the preoperative fT3 levels (p=0.001) (Table 8).

When all of the percentage changes in thyroid hormones over time were examined in patients who did and did not develop AF, no statistically significant difference was found. In the univariate logistic regression analysis, it was seen that the variables that were thought to constitute risk factors for AF had no statistically significant effect. When the combined effects of multivariate logistic regression variables were examined, no significant results were found.

DISCUSSION

AF is seen with a frequency of 20-40% after cardiac surgery (8,9,14). Postoperative AF increases hemodynamic disturbances and thromboembolic events and prolongs the duration of intensive care and hospital stay (15). Despite all the studies conducted to reveal the risk factors in the development of AF, its pathophysiological mechanism has not been fully elucidated. Suggested risk factors are structural changes in the heart like aging, beta-blocker withdrawal before the operation and increased sympathetic activation in the postoperative period, the effects of cardiopulmonary bypass and cardioplegics, postoperative hypoxia, hypovolemia and electrolyte imbalance (9). In addition, it is known that low levels of T3 thyroid hormone have negative effects on the prognosis of cardiac diseases (16-18).

In the general population, advanced age increases the risk of developing AF related to both OPCAB and conventional CABG surgeries. Dilatation and fibrosis of the atrium increase with age and causes loss of electrical conduction between atrial muscle fibers. Thus, the slowed down electrical conduction leads to development of atrial arrhythmias. However, in most cases, this mainly occurs in the 8th decade (8). In our study, the mean age at the onset of atrial arrhytmias was 58.5±7.76. Therefore, we think that age has no role in our results.

The use of preoperative beta blocker therapy reduces the incidence of postoperative AF. Supraventricular tachycardia is triggered as a result of atrial hypersensitivity due to adrenergic stimulation after discontinuation of beta blocker therapy (15). Preoperative beta blocker use decreased the development of AF in both groups. However, it did not cause a significant difference between groups. In our study, patients using beta blocker therapy continued to use beta blockers in the postoperative period. In the group that did not use beta blockers preoperatively, beta blocker treatment was started in the presence of postoperative indications. When the groups in the off-pump and conventional CABG surgeries were evaluated according to the use of beta blocker therapy with the indication of AF development, no significant difference was detected between the groups.

In our study, hypertension, COPD and DM which are considered as predisposing factors, were not significantly different between the OPCAB and conventional CABG surgery groups.

It is known that various intraoperative factors also affect the development of AF. During the conventional CABG surgery, the risk of AF development increases during XCL time. Conventional CABG operation triggers systemic inflammatory response and can cause insufficient myocardial protection and ischemia during cardioplegic arrest. In addition, prolonged XCL and inadequate cooling also increase this risk (15,19). As a result of our study, when the groups undergoing OPCAB and conventional CABG operation were compared in terms of operation techniques, no statistically significant difference was found. Increased thyroid

hormone metabolism is observed due to low T3 levels in circulation after acute myocardial infarction, heart failure and CABG surgery. This condition negatively affects the prognosis of cardiac patients. It is claimed that low T3 hormone levels are independent and strong risk factors affecting the development of AF in the postoperative period (14). In another study, T3 treatment was shown to reduce the incidence of AF development after cardiac operations (20).

Decrease in T3 and fT3 levels without any significant change in serum TSH and fT4 values during the conventional CABG surgery and until 24 hours after the operation has been shown in various studies (16,17). When fT3 measurements were evaluated in our study, postoperative levels were found to be statistically significantly lower than the preoperative levels in both groups with and without AF development. However, fT3 values were not significant regarding the development of AF. According to these results, it was seen that low levels of T3 hormone in the postoperative period had no effect on AF development.

In the conventional CABG surgery group, TSH levels were found to be significantly higher in the postoperative period. Studies show that increased TSH levels are due to low T3 hormone values. Conventional CABG operation and TSH levels can be significant in terms of AF development when evaluated in multivariate analysis. The fact that no significance was found regarding AF development in our study can be attributed to the low sample size. Postoperative levels of T3 hormone were significantly lower in the OPCAB group than the conventional CABG surgery group. However, no statistically significant difference was found between the groups in terms of AF development.

According to these results, even though T3 hormone levels in the OPCAB surgery group were comparable to those reported in the literature, no similarity was found in terms of AF development.

In conclusion, in our study, it was seen that low levels of thyroid hormone in patients undergoing OPCAB and conventional CABG surgery had no effect on AF development. However, we believe that investigating this issue in a wide range of patients would be more appropriate.

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