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Free triiodothyronine: a novel predictor of postoperative atrial fibrillation

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Abstract

Objective: Despite improved perioperative management, atrial fibrillation (AF) after coronary artery bypass grafting (CABG) remains a relevant clinical problem, whose pathogenetic mechanisms remain incompletely explained. A reduced incidence of postoperative AF has been described in CABG patients receiving IV tri-iodothyronine (T3). This study was designed to define the role of thyroid metabolism on the genesis of postoperative AF. **Methods and results**: Free T3 (fT3), free thyroxine (fT4), and thyroid stimulating hormone were assayed at admission in 107 consecutive patients undergoing isolated CABG surgery. Patients with thyroid disease or taking drugs known to interfere with thyroid function were excluded. A preoperative rhythm other than sinus rhythm was considered an exclusion criterion. Thirty-three patients (30.8%) had postoperative AF. An older age ($P = 0.03$), no therapy with β-blockers ($P = 0.08$), chronic obstructive pulmonary disease ($P = 0.08$), lower left ventricle ejection fraction ($P = 0.09$) and lower fT3 concentration ($P = 0.001$), were univariate predictors of postoperative AF. On multivariate analysis, low fT3 concentration and lack of β-blocking therapy were independently related with the development of postoperative AF (odds ratio, OR, 4.425; 95% confidence interval, CI, 1.745–11.235; $P = 0.001$ and OR 3.107; 95% CI 1.087–8.875; $P = 0.03$, respectively). Postoperative AF significantly prolonged postoperative hospital stay ($P = 0.002$). **Conclusions**: Low basal fT3 concentration can reliably predict the occurrence of postoperative AF in CABG patients.
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Keywords: Atrial fibrillation; Thyroid hormone; Coronary artery bypass grafting

1. Introduction

Postoperative atrial fibrillation (AF) occurs in 30% to 40% of patients undergoing coronary artery bypass grafting (CABG) [1,2], and is associated with higher surgical morbidity and increased hospital costs [1,2]. Several studies have sought to identify baseline predictors of AF, but only increased age has been consistently associated with AF after CABG [1–5].

In a prospective, double-blind, placebo-controlled trial, Klemperer and coworkers demonstrated that IV triiodothyronine (T3) can significantly reduce the incidence of postoperative AF in CABG patients [6], but the proposed mechanisms explaining this effect were mostly speculative. In recent years, the cardiovascular effects of thyroid hormone have been deeply investigated [7], and a strong relationship between low circulating levels of T3 and adverse prognosis of cardiac patients has been recently established [8]. Furthermore, a direct action of T3 on the calcium handling of human atrial cardiomyocytes has been described [9], and altered calcium handling has been indicated as one of the factors underlying the arrhythmogenic ionic remodeling of the atrial myocardium [10,11].

The present study was designed to prospectively evaluate the influence of basal thyroid hormone concentration on the risk of postoperative AF.

2. Methods

2.1. Patients

Thyroid function profile was evaluated at admission in all patients undergoing isolated CABG at our institution

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from October the 1st, 2002, to March the 31st, 2003. Patients with known thyroid disease, and patients taking drugs known to interfere with thyroid function were excluded. Patients with a basal rhythm other than normal sinus rhythm, and patients with a history of paroxysmal AF were not enrolled.

This study was approved by the Ethical Committee of the 'G. Pasquinucci Hospital' and of the 'Institute of Clinical Physiology' of the Italian National Research Council. Written informed consent was obtained from all patients.

2.2. Thyroid hormone sampling

A 5 ml blood sample was obtained from all patients at admission. All samples were collected in serum separator tubes and immediately centrifuged and analyzed. Free T3 (fT3), free thyroxine (fT4) and thyroid stimulating hormone (TSH) were assayed on all samples with the AxSYM® Microparticle Enzyme Immunoassay (MEIA, Abbott Laboratories, Diagnostic Division, Rome, Italy). The reference intervals for our laboratory were as follows: fT3 2.23–5.35 pmol/l, fT4 9.14–23.81 pmol/l, and TSH 0.47–4.64 μIU/ml.

2.3. Preoperative and postoperative medications

Preoperative medications, including β-blockers and calcium channel blockers, were routinely omitted on the day of surgery. When not contraindicated, preoperative medications were again administered on the first postoperative day.

2.4. Anesthetic technique and surgical management

The anesthetic technique and surgical management employed in this series have been previously described [12]. Total intravenous anesthesia with diazepam, fentanyl, pancuronium and propofol, was used in all cases. The decision to use or not cardiopulmonary bypass was left to the operating surgeon, and was mostly based on the severity and extension of disease of the target vessels. Cardiopulmonary bypass (CPB) was conducted on moderate hypothermia (34°C), and myocardial protection was achieved by using intermittent anterograde hyperkalemic warm blood cardioplegia. The final goal of CABG surgery was to obtain a complete myocardial revascularization.

2.5. Electrocardiographic (ECG) monitoring

Postoperatively, patients were routinely monitored for the occurrence of arrhythmias by bedside monitors during intensive care unit stay (ICU), and by telemetry after ICU discharge. Automatic arrhythmia detection and printed strip report were employed in all cases. The occurrence of AF was confirmed by a complete, 12 lead ECG in all cases. Only sustained episodes of postoperative AF, as previously defined [3,4], and documented by 12 lead ECG, were included in the analysis.

2.6. Statistical analysis

Continuous variables are expressed as mean ± standard deviation. Dichotomous variables are expressed as percentages. The association of preoperative, intraoperative and postoperative variables with the occurrence of postoperative AF was investigated by the Fisher's exact test (dichotomous variables), or by the unpaired Student's *t*-test (continuous variables). Non-normally distributed continuous variables were analyzed by the Mann–Whitney *U*-test. The tested variables are listed and defined in the Appendix A. Factors resulting significantly associated to the development of AF were then included in a logistic multivariate regression model to ascertain their independent role. Also factors for which the univariate analysis gave a P value ≤ 0.1, or of known biologic significance, but failing to meet the critical α level, were included. Odds ratio (OR) and 95% confidence interval (CI) were calculated. Receiver operating characteristic (ROC) curves were calculated to single out the best cutoff value of fT3 predicting postoperative AF. The accuracy of the test was assessed measuring the area under the ROC curve (AUC). The AUC was assessed by the non-parametric method of DeLong and Clarke-Pearson [13]. The non-symmetric 95% CI for AUC was computed using the Bootstrap Percentile Method [14], with 1000 bootstrap replications. The statistical significance of difference of AUC from that of the 'line of no information' was evaluated by Mann–Whitney *U*-statistic. A P value < 0.05 was considered significant. Statistical analysis was conducted using SPSS software version 10.1 (SPSS Inc, Chicago, IL).

3. Results

3.1. Patients population

One-hundred and seven patients were included. Mean age was 67.2 ± 9.9 years, and 77 patients (71.9%) were male. Preoperatively, 66 (61.6%) patients were on β-blockers. Sixty-seven patients (62.6%) had a previous acute myocardial infarction (AMI), and 23 (21.4%) had a recent AMI. Mean left ventricle ejection fraction (LVEF) was 53 ± 10%, and nine patients (8.4%) had a LVEF ≤40%. Most patients (74.7%) had three-vessels disease. Mean fT3 at admission was 3.3 ± 0.7 pmol/l, mean fT4 was 14.1 ± 2.6 pmol/l, and mean TSH was 1.9 ± 1.6 μIU/ml. Demographic data are depicted in Table 1.

3.2. Early outcome and complications

Two patients (1.8%) died, both for multiorgan failure, on the 7th and 11th postoperative day, respectively. Both

Table 1
Baseline, operative and postoperative characteristics of patients with and without postoperative AF

Factor	AF ($n = 33$)	Non-AF ($n = 74$)	P*
fT3 (pmol/l)	3.0 ± 0.4	3.5 ± 0.7	0.005**
fT4 (pmol/l)	14.2 ± 2.9	14.0 ± 2.4	0.76
TSH μIU/ml	2.2 ± 1.9	1.8 ± 1.4	0.24
Age, years	70.2 ± 9.4	65.8 ± 9.8	0.03**
Sex (male, %)	26 (78.8)	51 (68.9)	0.35**
Hypertension, *n* (%)	23 (69.7)	53 (71.6)	0.82
Diabetes, *n* (%)	11 (33.3)	20 (27.0)	0.50
Smokers, *n* (%)	16 (48.5)	46 (62.2)	0.20
Dyslipemia, *n* (%)	25 (75.7)	55 (74.3)	0.32
LVEF %	50.5 ± 9.0	53.9 ± 9.7	0.09**
Left atrial size (mm)	39.3 ± 2.2	38.8 ± 2.2	0.24**
Previous AMI, *n* (%)	19 (57.5)	48 (64.8)	0.52
Recent AMI, *n* (%)	8 (24.2)	15 (20.3)	0.62
3-vessels disease	26 (78.8)	53 (71.6)	0.34
β-blockers, *n* (%)	16 (48.5)	50 (67.6)	0.08**
Ca^{2+} channel blockers	18 (54.5)	31 (41.9)	0.29
COPD, *n* (%)	8 (24.2)	8 (10.8)	0.08**
Renal failure, *n* (%)	2 (6.1)	2 (2.7)	0.58
Non-elective surgery, *n* (%)	16 (48.4)	29 (39.2)	0.29
CPB, *n* (%)	24 (72.7)	64 (86.4)	0.10**
Operative time (min)	216.2 ± 46.8	217.3 ± 59.4	0.93
CPB time (min)	94.4 ± 23.9	96.1 ± 29.5	0.82
Cross clamp time (min)	56.0 ± 13.5	53.8 ± 14.5	0.59
Graft (*n*)	2.3 ± 0.8	2.6 ± 1.0	0.43
Complete revascularization, *n* (%)	30 (90.9)	67 (90.5)	>0.99
POMI, *n* (%)	–	2 (2.7)	>0.99
Major bleeding, *n* (%)	2 (6.1)	3 (4.0)	0.64
Need for inotropes, *n* (%)	6 (18.2)	6 (8.1)	0.18
LOS, *n* (%)	2 (6.1)	1 (1.3)	0.23
Acute renal failure, *n* (%)	3 (9.1)	3 (4.1)	0.37
Acute respiratory failure, *n* (%)	5 (15.1)	3 (4.1)	0.10
ICU stay (h)	30.7 ± 27.7	23.7 ± 13.1	0.08
MAV (h)	9.2 ± 4.3	7.9 ± 3.7	0.10
Postoperative stay	9.4 ± 4.5	7.4 ± 1.8	0.002

See Appendix A for variables definition. LVEF, left ventricle ejection fraction. AMI, acute myocardial infarction. COPD, chronic obstructive pulmonary disease. CPB, cardiopulmonary bypass. POMI, perioperative myocardial infarction. LOS, low output syndrome. ICU, intensive care unit. MAV, mechanical assisted ventilation. *Fisher's exact test, unpaired Student's *t*-test, Mann–Whitney *U*-test. **Factors included in the multivariate logistic regression model.

patients had chronic renal failure requiring dialysis, and the first one had undergone emergency CABG for acute, evolving myocardial infarction. This second patient developed AF on postoperative day 2.

Four patients (3.7%) had myocardial ischemia postoperatively. Two of these (1.8%) developed a perioperative myocardial infarction (POMI). Twelve patients (11.2%) needed inotropic support for ≥24 h. Other major postoperative complications included major bleeding (4.6%), severe low output syndrome (2.7%), acute respiratory failure (7.4%), acute renal failure (5.6%), and cerebrovascular accident (0.9%). Postoperative complications were not related to the occurrence of postoperative AF (Table 1).

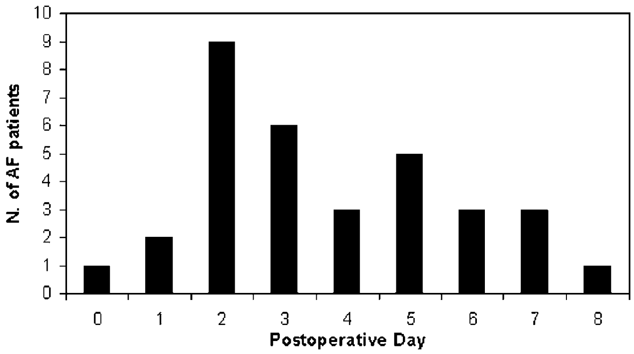

Fig. 1. Time of occurrence of AF.

Mean postoperative ICU stay was 25.9 ± 19.0 h. Mean postoperative hospital stay was 8.0 ± 3.0 days. Postoperative AF significantly prolonged postoperative hospital stay (Table 1).

3.3. Predictors of AF

Thirty-three (30.8%) patients developed AF during the postoperative period, with a peak incidence during postoperative day 2 (Fig. 1). An older age, and lower fT3 at admission were significantly associated with postoperative AF. Other factors included in the multivariate logistic regression model included male sex, LVEF, left atrial size, therapy with β-blockers, chronic obstructive pulmonary disease (COPD), and use of CPB. Outcome variables significantly related to postoperative AF were not included in the multivariate logistic regression analysis, since they were considered as a consequence, rather than as a possible causative factor, of AF (Table 1).

The results of the multivariate logistic regression analysis are depicted in Table 2. Low fT3 at admission resulted to be the single, most important, independent predictor of postoperative AF. Furthermore, therapy with β-blockers was independently associated with a reduction of the risk of postoperative AF.

According to the ROC curve analysis, the best threshold value of fT3 for predicting the occurrence of postoperative AF was 3.34 pmol/l (ROC area, 0.698; 95% CI 0.587–0.785; $P < 0.001$, Fig. 2). This cutoff value showed a sensitivity of 0.85 and a specificity of 0.51.

3.4. fT3 and β-blockers

Serum fT3 concentration was similar in patients receiving and not receiving therapy with β-blockers

Table 2
Predictors of postoperative AF

Variables	C	OR (95% CI)	P
fT3	−1.488	0.226 (0.089–0.573)	0.001
β-blockers (no)	1.134	3.107 (1.087–8.875)	0.03

Multivariate logistic regression analysis.

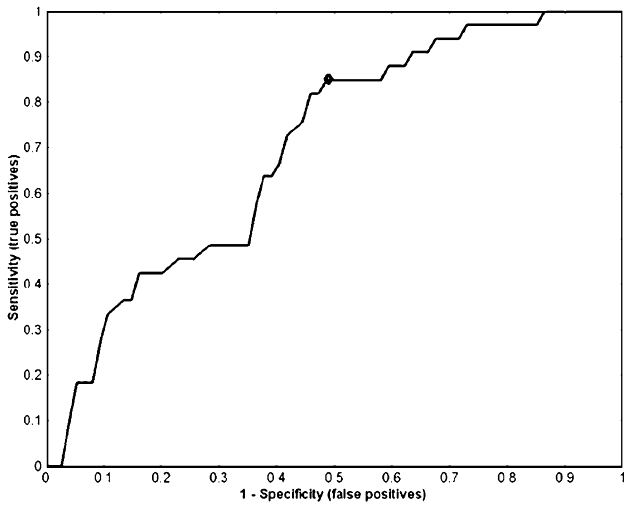

Fig. 2. Receiver operating characteristic curve for the prediction of postoperative AF. The rhomboid point shows the best predictive value of fT3 (3.34 pmol/l). AUC = 0.698; 95% CI = 0.587–0.785. $P < 0.001$.

(3.3 ± 0.6 pmol/l and 3.3 ± 0.8, respectively, $P = 0.79$). Of the 62 patients with serum fT3 <3.34 pmol/l, 27 (43.5%) had postoperative AF. Considering only this particular subgroup, AF occurred in 31.4% of patients receiving β-blockers and in 59.2% of patients not receiving β-blockers ($P = 0.03$). Logistic regression analysis confirmed this observation (OR: 3.174; 95% CI, 1.112–9.053; $P = 0.03$). On the other hand, the protective effect of β-blockers was negligible in patients with serum fT3 >3.34 pmol/l (OR: 0.4; 95% CI, 0.042–3.788; $P = 0.42$).

4. Discussion

Low serum T3 is a common finding in patients with heart disease, and recent evidence suggests that altered thyroid metabolism may significantly worsen the prognosis of cardiac patients [8]. The results of previous research indicate that the administration of exogenous T3 has a favorable impact on the outcome of CABG patients [15,16], and that it is associated with a reduced incidence of postoperative AF [6]. Nevertheless, the evidence for a negative role of low T3 on the postoperative course of CABG patients is lacking [17]. Our data show that low serum fT3 at admission is strongly predictive of postoperative AF, and that a unit reduction of the fT3 concentration is associated with more than 4-fold increase of postoperative AF risk.

4.1. Association between thyroid function and postoperative AF

In light of the known association between chronic hyperthyroidism and AF, the finding that low fT3 is associated with an increased incidence of atrial fibrillation after CABG may appear unexpected. Nonetheless, some argument exists that could potentially explain the result of our study.

Thyroid hormone actively participates to cardiomyocytes calcium handling. In particular, it increases the expression of the Ca^{2+} adenosine triphosphatase of the sarcoplasmic reticulum (SERCA 2) [9,18]. Depressed SERCA 2 expression, as observed in T3-deprived human cardiomyocytes in culture, results in a reduced Ca^{2+} load inside the intracellular compartment [9], a figure similar to that observed in arrhytmogenic ionic remodeling [10,11]. Furthermore, a reduction in L-type Ca^{2+} current (I_{ca}) has been described in the ventricular myocytes of hypothyroid guinea pigs [19], and down regulation of L-type Ca^{2+} current has been consistently reported in animal and human models of AF [1,2,10,11]. T3 also exerts important effects on the density ant the kinetics of other ionic currents flowing during the action potential of cardiomyocytes [20]. According to these observations, normal thyroid hormone availability should be considered as one of the factors needed to maintain the normal electrophysiological properties of the atrium. Consequentially, low T3 could potentially predispose to atrial arrythmias. The already mentioned finding that the administration of exogenous T3 reduces the incidence of AF in CABG patients [6] also seems to support this hypothesis, especially if one considers that cardiac surgery decreases the circulating levels of fT3 [12,21], thus potentially augmenting the adverse effect of a lower basal serum fT3 concentration.

4.2. Predictors of atrial fibrillation: limitations of the study

Although the only factor consistently associated with the occurrence of AF by previous literature is patients age, several other baseline predictors of postoperative AF in CABG patients have been identified by well-designed and rigorous clinical trials [1–5]. Surprisingly, most of these were not significant in our analysis.

Patients age had a significant effect at univariate analysis (Table 1), but resulted non-significant at multivariate logistic regression, although a trend in this direction was observed ($P = 0.1$). This was likely due to the fact that our study was conducted on a relatively small number of patients. A larger series would have probably evidenced the effect of older age. Similar observations may be formulated with regard to the effect of LVEF ($P = 0.09$).

CPB has been reported to be the most important cause of postoperative AF in CABG patients [4]. We found no relationship between CPB and postoperative AF (Table 1), but only 19 patients (17.6%) in our series underwent off-pump CABG, and our results should be considered inconclusive in this regard. Similarly, only nine patients (8.4%) in our series had a LVEF ≤40%, and we can not draw conclusions about the effect of depressed LV function.

Left atrial dilation increases the risk of AF in the general population [11]. We found no relationship between left atrial size and postoperative AF, and this result is consistent with previous literature on postoperative AF in CABG patients [3].

4.3. Clinical relevance of the present study

Despite increased knowledge of the mechanisms underlying the development of atrial arrythmias and despite the improved anesthetic and surgical management of CABG patients, postoperative AF remains a relevant clinical problem, and the increasing number of proposed strategies to prevent AF onset is testament to this [22].

On the other hand, the previous observation that T3 administration improves the outcome of cardiac surgery mostly relied on a theoretical basis, and, apart from the above mentioned results [6,15,16], a real clinical benefit deriving from T3 supplementation has not been proven, at least in adult patients undergoing CABG [17,23].

Our study demonstrates the existence of a strong, previously unrecognized, relationship between preoperative thyroid metabolism and the occurrence of postoperative AF. According to our results, patients with a basal fT3 concentration <3.34 pmol/l should be considered at higher risk of postoperative AF, and should receive antiarrythmic prophylaxis. Consequentially, thyroid function profile evaluation should be recommended in patients scheduled for CABG surgery.

The appreciation of the thyroid hormone role in the regulation of the cardiovascular system function, and the recognition of cardiac surgery as a possible cause of the so-called 'euthyroid sick syndrome' [24], have led, in the past decade, to the development of several protocols involving perioperative T3 supplementation. Indeed, the results of the two largest randomized, placebo-controlled trials on IV T3 administration in CABG patients [15,16] showed only marginal in-hospital benefit. Our data, in conjunction with the results of other investigations [6,8,9,15,16], are likely to stimulate further research in this field. We are convinced that careful selection of patients, based on preoperative thyroid function profile assessment, will result in increased statistical power, reduced consumption of hospital resources, and, possibly, in increased clinical benefit for the treated patients, with a marginal increase of the hospital costs.

4.4. Conclusion

Low fT3 at admission is a strong independent risk factor of postoperative AF after CABG. Therapy with β-blockers is effective in reducing the risk of postoperative AF, and should be employed in patients with basal fT3 <3.34 pmol/l. Prospective double-blind, placebo-controlled trials, enrolling only patients with low basal fT3, are needed to define the efficacy of T3 supplementation in preventing the onset of postoperative AF after CABG.

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Appendix A

Variables employed in the univariate analysis (Fisher's exact test, unpaired Student's *t*-test, Mann–Whitney *U*-test): fT3 concentration, fT4 concentration, TSH concentration, age, sex, arterial hypertension, diabetes, smoking history, dyslipidemia, LVEF, left atrial size, previous AMI, recent AMI (≤ 1 month prior to hospital admission), therapy with β-blockers, therapy with calcium channel blockers, chronic obstructive pulmonary disease (COPD, defined by a positive bronchospirometric test), chronic renal failure (basal creatinine ≥ 2 mg/dl), surgical priority (elective versus urgent), use of CPB, operative time, CPB time, aortic cross-clamp time, number of grafts per patient, completeness of the revascularization, POMI defined as the presence of two or more of the following criteria: enzymatic elevation (CK-MB $>10\%$ of total CK or Troponine I >0.5 ng/ml), new Q waves greater than 0.03 ms or a reduction in R waves greater than 25% in two leads, and new akinetic segment(s) shown at echocardiogram), postoperative bleeding (>800 ml/12 h), need for inotropes (dopamine or dobutamine for ≥ 24 h), low output syndrome (requirement for more than one of the above mentioned drugs or for adrenaline, noradrenaline, enoximone, or IABP), acute renal failure (postoperative creatinine >2 mg/dl with a serum creatinine rise ≥ 0.7 mg/dl versus baseline), acute respiratory failure (need of mechanical assisted ventilation (MAV) for more than 24 h or the need of reintubation), ICU length of stay, MAV time, and postoperative hospital stay.