The Low Triiodothyronine Syndrome: A Strong Predictor of Low Cardiac Output and Death in Patients Undergoing Coronary Artery Bypass Grafting

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Background. **There is strong clinical and experimental evidence that altered thyroid homeostasis negatively affects survival in cardiac patients, but a negative effect of the low triiodothyronine (T3) syndrome on the outcome of coronary artery bypass grafting (CABG) has not been demonstrated. This study was designed to evaluate the prognostic significance of low T3 syndrome in patients undergoing CABG.**

Methods. **The thyroid profile was evaluated at hospital admission in 806 consecutive CABG patients. Known thyroid disease, severe systemic illness, and use of drugs interfering with thyroid metabolism were considered exclusion criteria. The effect of the baseline free T3 (fT3) concentration and of preoperative low T3 syndrome (fT3 <2.23 pmol/L) on the risk of low cardiac output (CO) and death was analyzed in a logistic regression model.**

Results. **There were 19 (2.3%) deaths, and 64 (7.8%) patients experienced major complications. After univariate analysis, fT3, low T3, New York Heart Association class greater than II, low left ventricular ejection fraction (LVEF), and emergency were associated with low CO and hospital death. History of atrial fibrillation, cardiopulmonary bypass time, and peripheral vascular disease were associated only with low CO. At multivariate analysis, only fT3, low T3, emergency, and LVEF were associated with low CO, and fT3 (odds ratio, 0.172, 95% confidence interval, 0.078 to 0.379; $p < 0.0001$) and LVEF (odds ratio, 0.934, 95% confidence interval, 0.894 to 0.987; $p = 0.03$) were the only independent predictors of death.**

Conclusions. **Our study demonstrates that low T3 is a strong predictor of death and low CO in CABG patients. For this reason, the thyroid profile should be evaluated before CABG, and patients with low T3 should be considered at higher risk and treated accordingly.**

(Ann Thorac Surg 2014;■:■–■)

Patients with heart disease frequently display a typical pattern of altered thyroid hormone metabolism, characterized by low circulating triiodothyronine (T3) levels in the absence of an intrinsic thyroid disease. This condition, variously known as the "low T3 syndrome" [1], the "nonthyroidal illness syndrome" [2], or the "euthyroid sick syndrome" [3], is mainly due to the reduced peripheral conversion of T4 into T3 and has been observed in patients with myocardial infarction [4], heart failure [5], and after cardiac operations with and without cardiopulmonary bypass (CPB) [6, 7].

The T3 has a strong influence on the expression of several structural and regulatory proteins of the cardiac myocyte. Because thyroid hormone-regulated transcription is essential to maintain the physiologic cardiac phenotype, T3 deficiency has been recently proposed as a causative factor in the pathophysiology of heart failure [5, 8]. Furthermore, the low T3 syndrome has been shown to be associated with increased death in the cardiac nonsurgical patient [1, 9]. All these facts led us to hypothesize that the presence of a low T3 syndrome at hospital admission, as can be frequently observed in patients undergoing coronary artery bypass grafting

Accepted for publication Jan 14, 2014.

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Appendix A can be viewed in the online version of this article [http://dx.10.1016/j.athoracsur.2014.01.049] on http://www.annalsthoracicsurgery.org

Published by Elsevier Inc

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2014.01.049

Abbreviations and Acronyms

AF = atrial fibrillation
AKI = acute kidney injury
AMI = acute myocardial infarction
AUC = area under the curve
CABG = coronary artery bypass grafting
CI = confidence interval
CO = cardiac output
COPD = chronic obstructive pulmonary disease
CPB = cardiopulmonary bypass
CVA = cerebrovascular accident
Cx = circumflex artery
fT3 = free triiodothyronine
fT4 = free thyroxine
ICU = intensive care unit
LAD = left anterior descending artery
LIMA = left interior mammary artery
LM = left main
LVEF = ejection fraction
MAV = mechanical assisted ventilation
MOF = multiorgan failure
NYHA = New York Heart Association
OR = odds ratio
POMI = perioperative myocardial infarction
PTCA = percutaneous coronary angioplasty
PVD = peripheral vascular disease
RF = respiratory failure
ROC = receiver operating characteristic
SD = standard deviation
T3 = triiodothyronine
T4 = thyroxine
TSH = thyroid-stimulating hormone

(CABG), could be associated with a worse postoperative course and with increased death. The present study was undertaken to test this hypothesis.

Patients and Methods

This study was approved by the Ethical Committee of the Fondazione Gabriele Monasterio, Massa, Italy. Informed consent was obtained from all patients.

Patients

The effect of the baseline free T3 (fT3) concentration and of preoperative low T3 syndrome (defined as an fT3 concentration <2.23 pmol/L) on the risk of postoperative low cardiac output (CO) and hospital death was prospectively analyzed in 806 consecutive patients undergoing CABG at our institution. The following end points were considered: need for inotropes (dopamine or dobutamine for $\geq$12 h), low CO (requirement for one of the above mentioned drugs plus adrenaline, noradrenaline, enoximone, or an intraaortic balloon pump to maintain an adequate cardiocirculatory function with adequate end-organ perfusion), and hospital death. Patients with a known thyroid disease, patients with an acute, predominant severe systemic illness, and patients taking drugs known to interfere with thyroid function were excluded. In particular, preoperative amiodarone therapy was considered an exclusion criteria.

Thyroid Hormone Sampling

The thyroid profile has been routinely studied as a part of the baseline, preoperative evaluation at our institution since January 2002. A 5 mL blood sample is obtained from all patients at admission. Samples are collected in serum separator tubes and immediately centrifuged and analyzed. For the present study, the fT3, free thyroxine (fT4), and thyroid-stimulating hormone (TSH) were assayed on all samples with the AxSYMw Microparticle Enzyme Immunoassay (Abbott Laboratories, Diagnostic Division, Rome, Italy). The reference intervals for our laboratory were fT3, 2.23 to 5.35 pmol/L; fT4, 9.14 to 23.81 pmol/L; and TSH, 0.47 to 4.64 μIU/mL.

Anesthetic Technique and Surgical Management

The anesthetic technique and surgical management used in this series have been previously described [10]. Total intravenous anesthesia with midazolam, sufentanil, rocuronium, and propofol was used in all cases. The decision to use CPB was left to the operating surgeon and was mostly based on the severity and extent of disease of the target vessels. 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 was to obtain a complete myocardial revascularization.

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 postoperative low CO and hospital death was investigated by the Fisher exact test (dichotomous variables) or by the unpaired Student *t* test (continuous variables). Nonnormally distributed continuous variables were analyzed by the Mann-Whitney *U* test. The tested variables are listed and defined in Appendix A (available online). Factors significantly associated with the end point of the study were included in a logistic multivariate regression model to ascertain their independent role. Also included were factors for which the univariate analysis gave a *p* value of 0.1 or less or were of known biologic significance but failed to meet the critical α level. The 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 low CO and hospital death. The accuracy of the test was assessed measuring the area under the ROC curve (AUC). The AUC was assessed by the nonparametric method of DeLong and Clarke-Pearson [11]. The nonsymmetric 95% CI for AUC was computed using the bootstrap percentile method [12], with 1,000 bootstrap replications. The statistical significance of difference of AUC from that of the "line of no information" was evaluated by the Mann-Whitney *U* statistic. A p value of less