

# Is Hypothyroidism Overlooked in Cardiac Surgery Patients?\*

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## ABSTRACT

**Objectives:** To analyze adequacy of preoperative thyroid screening of cardiac surgery patients (pts) with hypothyroidism (HT) and compare with pts without HT by demographic data, EuroSCORE (ES) scores, early and late outcomes. **Patients:** From 1000 cardiac surgery pts from Jan 1999 through May 2000 pts with HT were identified (Group 1, n = 80). 920 pts (Group 2) had no HT. **Results:** Group 1 pts were older ( $p < 0.0001$ ), had more females ( $p < 0.0001$ ), more pts with CHF  $p < 0.0001$ , more pts in NYHA class III-IV ( $p = 0.01$ ) and higher ES risk scores by both algorithms ( $p = 0.003$  and  $p < 0.0001$  consecutively) than Group 2 pts. ES variables demonstrated higher number of pts  $> 60$  years ( $p = 0.004$ ), more females ( $p < 0.0001$ ) and higher number of other than CABG surgery pts ( $p = 0.01$ ) in Group 1. 47 (58.8%) had adequate laboratory tests. 15 (18.8%) had no tests and 18 (22.5%) inadequate tests. 10 (12.5%) pts had no replacement therapy. There was no operative mortality in Group 1 and 14 (1.5%) in Group 2 ( $p = 0.70$ ). Hospital mortality was higher in Group 1 (6/7.5% vs. 37/4.5%),  $p = 0.03$ . Stay in postoperative intensive care unit and hospital were similar ( $p = 0.66$  and  $0.53$ ). More pts in Group 1 needed prolonged ICU and LOS ( $p < 0.0001$  for both). Occurrence of postoperative AF was higher in Group 1,  $p < 0.02$ . Seventeen pts (23.0%) were not discharged home in Group 1 and 87 (10.2%) in Group 2, ( $p = 0.002$ ). Follow-up mortality was higher in Group 1 (45/58.1% vs. 378/43.5%,  $p = 0.02$ ). **Conclusions:** HT is overlooked in cardiac surgery patients. Long-term mortality is higher in pts with HT. Resource utilization is higher in pts with HT.

**Keywords:** Hypothyroidism; Cardiac Surgery; Outcome Differences

## 1. Introduction

Hypothyroidism (HT) is common finding in elderly people. Most often it is a sequel of Hashimoto's thyroiditis although a history of the disease is often lacking. It is more common in females (about 4 to 1) and the prevalence in general population is 4% - 6%. It has been reported that approximately 10% of females aged 70 years or older have some degree of thyroid impairment [1].

With the ongoing increase in ages of patients (pts) presenting for cardiac surgery more pts with HT will inevitably be encountered.

Symptoms of HT are often subtle and easy to be overlooked specially in pts with a heart disease and symptoms are thought to be from the existing cardiac condition.

There is a consensus that patients (pts) with known HT should have thyroid screening before any major surgery

including cardiac surgery [2-4] and if indicated should be made euthyroid before surgery.

HT has many negative effects on long-term fate of pts, it increases cholesterol levels and accelerate development of arteriosclerosis both peripheral and coronary [5] the cardiac output may decrease up to 50% by decreased preload, increased afterload and decreased left ventricular systolic function and subsequently make pts more vulnerable to congestive heart failure [6,7] and has negative effects on kidney function [8-10] among other functions.

The aim of this study is to assess the adequacy of thyroid screening in pts with known HT before cardiac surgery and to report the differences in presentation and outcomes after cardiac surgery in pts with and without preoperatively diagnosed HT.

## 2. Material and Methods

One thousand consecutive pts who underwent cardiac surgery in our unit between 1999 through May 2000

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were retrospectively studied. Pts with a preoperative diagnosis of HT were identified and made the study group (Group 1,  $n = 80$ ). The remaining 920 pts served as controls. Preoperative, operative and postoperative details were introduced into a database. EuroSCORE (ES) risk profiling for all pts for comparison purposes was allocated using the online calculator ([www.euroscore.org](http://www.euroscore.org)) and added to the database. Follow-up all cause mortality was achieved from Social Security Main Death Index and follow-up for all pts was 10 years or over.

The study was approved by hospital research committee and need for informed consent waived because no pt was personally contacted Operative technique.

Operations were performed using standard median sternotomy in moderate hypothermia to 34°C using antegrade and retrograde cold whole blood cardioplegia. All pts received preoperatively 600 mg of allopurinol and 1000 mg vitamin C as antioxidants and 750 mg methylprednisolone to mitigate the postoperative systemic inflammation reaction syndrome.

### Statistical Analysis

Covariables were tested for their association with HT using t-test (continuous variables) or chi-square test (categorical variables) as appropriate. Outcomes included operative mortality, hospital/30 day mortality, length of hospitalization (LOS), length of stay in the postoperative intensive care unit (ICU), LOS > 5 days, ICU > 2 days, appearance of postoperative atrial fibrillation, appearance of postoperative renal failure (rise of s-crea > 2.25 mg/dl with or without need of renal replacement therapy) and whether pts were discharged home or to other facilities for rehabilitation/extended care. Long-term survival was estimated using Kaplan-Meier plots and survival difference tested by log-rank test. Both groups were tested for propensity scores and tests of difference in the outcome variables were done within the same strata and inferences combined across strata for an overall treatment effect. Groups were compared on outcomes using t- or chi-square tests as appropriate.

Computations were done in R version 2.10.0 (R Development Core team 2009).

### 3. Results

Eighty pts had a preoperative diagnosis of HT, 8%, which is higher than in general population with a prevalence of 4% - 6%.

Group 1 pts were older ( $p < 0.0001$ ) and there were more females ( $p < 0.0001$ ).

More pts in Group 1 had history of congestive heart failure (CHF) ( $p = 0.001$ ) and more pts were in NYHA class III-IV ( $p = 0.01$ ). The incidence of diabetes was similar between the Groups.

There were more pts with main operative diagnosis of coronary artery disease (CAD) in Group 2 ( $p = 0.01$ ) and more pts with valvular main operative diagnosis in Group 1 ( $p = 0.003$ ).

Additive EuroSCORE (AES) and logistic EuroSCORE (LES) were significantly higher in Group 1 pts: AES 8.54 vs. 6.6,  $p = 0.003$  and LES 18.4% vs. 11.5%,  $p < 0.0001$ . Demographics are summarized in **Table 1**.

For individual ES variables in Group 1 pts ages, number of females, high pulmonary artery pressure and other than CABG only pts were significantly higher compared to Group 2 pts but differences between other variables did not reach statistical significance. ES variables are summarized in **Table 2**.

At the time of surgery the routine thyroid screening included thyroid stimulating hormone (TSH), total T4 (T4), free T4 index (FT4index) and thyroid uptake (TU) the minimum requirement was TSH and T4.

Of the 80 pts with diagnosis of HT 18 (22.5%) pts did not have any thyroid screening before cleared for surgery. 16 of them were on thyroid replacement and two not. 47 pts (58.8%) had both T4 and TSH measured before surgery, 10 pts had TSH only and 5 pts T4 only. Altogether 11 pts (13.8%) had no replacement therapy when admitted. Of these one pt had overt HT and the surgery delayed for weeks and performed when the pt was euthyroid. One pt with ongoing replacement still had overt HT, the replacement dose was adjusted and surgery performed when the pt was euthyroid. Both pts had coronary artery disease but no adverse effects were observed with higher doses of levothyroxine.

Sixty two pts had TSH and T4, or TSH, or T4 measured. Of these 37 were euthyroid (59.7%), three pts were overtreated (TSH < 0.35 Iu/ml), two had overt HT and 20 (32.3%) TSH values over the reference limit (>5.5 Iu/ml). Medication adjustments were done only to the 2 pts with overt HT.

Twenty three pts in Group 2 had preoperative laboratory test made. One pt was hyperthyroid with adequate medication and 22 pts were euthyroid. 2 pts were on replacement for reasons unknown to us without having HT.

There were no operative mortality in Group 1 and 14 (1.5%) in Group 2,  $p = 0.7$ .

ES algorithms overestimated hospital mortality in both Groups. Hospital mortality was higher in Group 1: 6 pts, 7.5% versus Group 2: 31 pts, 3.4%,  $p = 0.03$ . ES risk scores were very high in the hospital mortality pts, mean AES  $12.2 \pm 5.08$  and LES  $39.1\% \pm 30.1\%$  in Group 1 pts,  $14.5 \pm 4.51$  and  $49.9\% \pm 30.62\%$  in Group 2 pts with no statistical difference.

Comments about fatigue or extreme fatigue and other signs which could be connected to HT (unexplained gastroenterological disturbances, confusion or psychiatric problems, pulmonary problems due to weak respiratory

**Table 1. Patient demographics: Group 1 pts with HT (n = 80), Group 2 no HT (n = 920).**

Variable	Group 1 Mean ± SD/n (%)	Group 2 Mean ± SD/n (%)	p-value
Age	71.4 ± 9.2	68.5 ± 11.7	<0.0001
Females	54 (67.5)	290 (31.5)	<0.0001
BMI (kg/m <sup>2</sup> )	28.7 ± 6.3	27.4 ± 5.0	0.08
History of CHF	35 (43.6)	265 (28.8)	<0.0001
Diabetics	35 (43.8)	372 (40.4)	0.56
S-crea (mg/dl)	1.28 ± 1.1	1.23 ± 1.1	0.85
Preoperative AF	4 (5.0)	60 (6.5)	0.59
NYHA I-II	27 (33.8)	447 (48.6)	0.01
NYHA III-IV	53 (66.2)	473 (51.4)	0.01
Primary operative dg:			
CAD	53 (66.3)	728 (79.1)	0.01
AS/AI	12 (15.0)	89 (9.7)	0.17
MR/MS	14 (17.5)	68 (7.4)	0.004
TR	0	4 (0.4)	-
Miscellaneous	1 (1.25)	31 (3.4)	-
AES	8.5 ± 4.4	6.6 ± 4.1	0.003
LES	18.4 ± 21.7	11.5 ± 15.2	<0.0001

BMI: Body Mass Index; CHF: Congestive Heart Failure; S-Crea: Serum Creatinine Level; AF: Atrial Fibrillation; NYHA: New York Heart Association Functional Classification; CAD: Coronary Artery Disease; AS/AI: Aortic Valve Stenosis/Insufficiency; MR/MS: Mitral Valve Regurgitation/Stenosis; TR: Tricuspid Valve Regurgitation; AES: Additive EuroSCORE Points; LES: Logistic EuroSCORE %.

effort/muscles etc.) were documented in 35 pts (43.8%) in Group 1 but comments like these were not seen in Group 2 pts. 33 pts of these (94.3%) had LOS > 5 days and 14 (40.0%) ICU > 2 days. 5 out of 6 hospital deaths had comments about severe fatigue and very weak respiratory muscles.

Mean ICU and LOS were similar. Group 1: ICU 2.5 days vs. 2.1 days,  $p = 0.47$  and LOS 8.7 days vs 7.8 days,  $p = 0.30$ . Normal ICU was 1 - 2 days and LOS 4 - 5 days. In Group 1 there was higher number of pts needing prolonged ICU (>2 days): 17/23.0% vs. 118/13.8%,  $p < 0.0001$ . The reasons were predominantly respiratory problems in Group 1 and hemodynamic instability in Group 2. The number of pts needing prolonged LOS was also higher in Group 1: 57/72.2% vs. 411/48%,  $p < 0.0001$ . The main reasons for this were respiratory problems and difficulties in mobilization due to weakness in Group 1. In Group 2 there was more variability in causes with no definite main cause.

Cardiac surgical pts were discharged home in about 90% of cases. Extended care and/or rehabilitation was needed in 17/23.0% of Group 1 pts and in 87/10.2% in Group 2 ( $p = 0.002$ ).

The number of pts needing prolonged LOS (>5 days) was also higher in Group 1: 57/72.2% vs. 411/48%,  $p < 0.0001$ . The main reasons for this were respiratory problems and difficulties in mobilization due to weakness in Group 1. In Group 2 there was more variability in causes with no definite main cause.

The incidence of preoperative AF was similar but the occurrence of postoperative AF was higher in Group 1 pts: 19/25.0% vs. 121/14.1%,  $p = 0.02$ .

Preoperative renal failure defined as s-crea > 2.2 mg/dl with or without need for renal replacement therapy was observed in 6/7.5% of Group 1 pts and in 60/6.5% pts of Group 2 pts,  $p = 0.89$ . There was no difference in the mean preoperative s-crea levels between the groups. Postoperative renal failure was defined as postoperative increase of s-crea > 2.2 mg/dl in patients with preoperative s-crea < 2.2 mg/dl with or without dialysis support.

Postoperative renal failure developed in 15/20.3% pts in Group 1 and 122/13.5% in Group 2 pts,  $p = 0.12$ . Outcomes are summarized in **Table 3**.

Total follow-up for hospital survivors was 5449 months for Group 1 pts and 95,669 months for Group 2 pts with no difference in the mean follow-up time (Group 1

**Table 2. EuroSCORE variables.**

Variable	Group 1 n (%)	Group 2 n (%)	p	OR <sup>1</sup>	95% CI
Age > 60 years	70 (87.5)	623 (67.7)	0.0004	3.30	1.8 - 7.0
Females	54 (67.5)	290 (31.5)	<0.0001	4.5	2.8 - 7.5
Chronic pulmonary dis.	11 (13.8)	124 (13.5)	0.95	1.02	0.5 - 1.9
Extracardiac arteriopathy	18 (23.0)	183 (20.0)	0.54	1.20	0.7 - 2.0
Neurological dysfunction	5 (6.2)	54 (5.9)	0.89	1.10	0.4 - 2.5
Previous cardiac surgery	8 (10.0)	99 (10.8)	0.92	0.92	0.4 - 1.9
S-creatinine > 200 µmol/l	6 (7.5)	60 (6.5)	0.89	1.10	0.4 - 2.5
Active endocarditis	2 (2.5)	7 (0.8)	0.14	3.30	0.5 - 4.1
Critical preop. state	7 (8.7)	47 (5.1)	0.17	1.80	0.7 - 3.8
Unstable angina	15 (18.8)	131 (14.2)	0.28	1.40	0.7 - 2.4
EF 0.3 - 0.5	33 (41.2)	363 (39.5)	0.75	1.10	0.7 - 1.7
EF < 0.3	11 (13.8)	128 (13.9)	0.97	0.99	0.5 - 1.8
AMI within 90 days	16 (20.0)	229 (24.9)	0.33	0.75	0.4 - 3.0
Pulmonary hypertension <sup>2</sup>	7 (8.7)	35 (3.8)	0.04	2.40	0.96 - 5.3
Emergency operation	8 (10.0)	70 (7.6)	0.45	1.30	0.6 - 2.8
Other than isolated CABG	33 (41.2)	254 (27.6)	0.01	1.80	1.1 - 3.0
Surgery on thoracic aorta	1 (0.1)	17 (0.2)	0.71	0.68	0.4 - 3.4
Postinf. septal rupture	0	3 (0.3)			

EF: Left Ventricular Ejection Fraction; AMI: Acute Myocardial Infarction; CABG: Coronary Artery By-Pass Graft; <sup>1</sup>OR: Odds of Event in Group 1/Odds of Event in Group 2; <sup>2</sup>Systolic Pulmonary Artery Pressure > 60 mmHg.

**Table 3. Outcomes.**

Outcome	Group 1 Mean ± SD/n (%)	Group 2 Mean ± SD/n (%)	Effect <sup>1</sup>	p-value
Operative mort.	0	14 (1.5)	-	-
Hospital/30 day mort	6 (7.5)	37 (4.1)	0.97	0.03
ICU days	2.5 ± 4.0	2.1 ± 4.6	0.04	0.47
LOS days	8.7 ± 6.2	7.8 ± 6.4	0.42	0.30
ICU > 2 days	17 (23.0)	118 (13.8)	1.44	<0.0001
LOS > 5 days	57 (72.2)	411 (48.2)	1.56	<0.0001
Postoperative AF	19 (25.7) <sup>2</sup>	121 (14.1) <sup>2</sup>	1.91	0.02
Postoperative RF	15 (20.3) <sup>3</sup>	122 (13.5) <sup>3</sup>	0.03	0.12
Disch to other inst.	17 (23.0)	87 (10.2)	2.17	0.002
Follow-up deaths	43 (58.1)	378 (43.5)	0.96	0.02

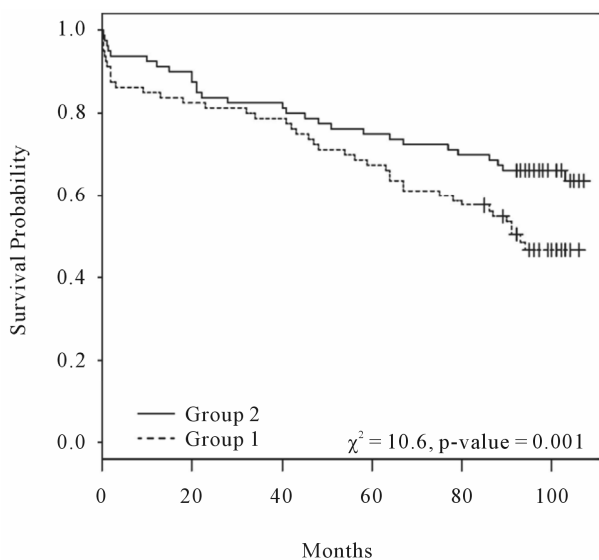
<sup>1</sup>Propensity score adjusted; <sup>2</sup>Of operative survivors with preoperative sinus rhythm (Group 1 n = 74, Group 2 n = 846); <sup>3</sup>Of operative survivors with preoperative s-crea < 2.25 mg/dl (Group 1 n = 74, Group 2 n = 906); ICU: Days in the Postoperative Intensive Care Unit; LOS: Length of Stay; AF: Atrial Fibrillation; RF: Renal Failure. Increase of postoperative s-crea > 2.2 mg/dl (200 µmol/l) with or without dialysis support.

122.1 months, Group 2 110.3 months,  $p = 0.42$ ).

Follow-up all-cause mortality up to 153 months was significantly higher in Group 1 pts: 41/56.9% versus 378/43.5% in Group 2,  $p = 0.02$ . Follow-up mortality is illustrated in the Kaplan-Meier survival estimate in **Figure 1**.

#### 4. Comments

HT is common finding in mixed cardiac surgery population, 8% in our series. The percentage is rising with cardiac surgery patients being older. The risks of cardiac or any major surgery in HT pts has been known for decades [3,11] but in Western world severe HT with typical clinical signs are a rarity or rather do not exist anymore. Most pts with HT are detected and most are being treated and the typical signs may be eliminated. Some symptoms like tiredness/muscle weakness, declining renal function and difficulties in stabilizing CHF are often regarded as symptoms from the underlying cardiac disease only and the role of HT is overlooked. This is quite evident in this series also, only 47 pts (58.8%) had adequate laboratory screening done preoperatively (including TSH and T4) although pts with known (or suspected) HT should have adequate screening done prior to any major surgery. 10 pts (13%) did not have ongoing medication although they had diagnosis of HT. Explanation of this could not be found from the hospital charts. 13 pts had only TSH or T4 measured before being cleared for surgery and an additional 20 pts did not have any or inadequate tests done. 20 pts were undertreated or had no treatment at all with TSH over the reference limit and replacement started preoperatively only on two pts. No adjustments were made to other pts.



**Figure 1.** Kaplan-Meier survival estimates of Group 1 and 2 patients.

HT is easily diagnosed by simple laboratory testing. When pts are treated with levothyroxine the tests often become difficult to interpret. Endocrinology consultation should always be done if the results are aberrant and difficult to make a simple interpretation.

There are basically no differences in demographics and ES risk factors which further points out the difficulties to detect possible symptoms of HT in mixed population of pts with heart disease. There was not a single variable which could have been pointed out as a sign of HT.

HT pts can be operated safely as seen in this and other series [12] with no operative deaths.

In Group 1 the reason(s) for prolonged LOS (and often also ICU) was weakness/extreme weakness and weak respiratory muscles causing respiratory problems without pre-existing lung disease. There were no correlation whether the pt was euthyroid, was on replacement or not, and independent of level of TSH in patients who had TSH measured. It seems that HT itself regardless of normal or abnormal laboratory tests and treatment is a reason for fatigue in the postoperative period. Very few comments of weakness or fatigue were noted in Group 2 pts and usually in very old pts. Fatigue and subsequent slow mobilization were also the main reason for pts being discharged to other facilities for further treatment and mobilization in Group 1 pts.

HT has negative effects on renal function [8-10] but the effects may be mitigated by adequate replacement therapy. No difference was noted in preoperative s-crea values or in appearance of postoperative renal failure. The reason for this may be the replacement therapy—although not always adequate—for most of the HT pts.

Occurrence of postoperative AF is multifactorial but may also be caused by HT (and hyperthyroidism). Guidelines by American College of Chest Physicians to prevent postoperative AF [13] do not give much credit to HT caused postoperative AF perhaps because it occurs even in adequately treated pts. T3 administration during and immediately after surgery has been shown to decrease incidence of AF at least in euthyroid pts [14] but routine use of T3 is regarded obsolete. Almost 10% of contemporary cardiac surgery pts have some degree of thyroid impairment which goes hand in hand with the aging cardiac surgery population with a higher incidence of AF postoperatively [15].

Hospital mortality was equal. There were no difference in ages between pts expired in the hospital vs hospital survivors ( $p = 0.78$ ) but ES risk scores were very high in pts expired in hospital: Group 1 pts ( $n = 6$ ) median AES 14.0 and median LES 70.5%. In Group 2 pts ( $n = 37$ ) median AES 14.5 and median LES 77.5%. Serious comorbidities as reflected by high ES scores were contributors to death in all pts and HT was not regarded as a

causative factor. Zindrou *et al.* [16] demonstrated increased mortality in women after coronary artery surgery who were on thyroid replacement therapy for HT. It was concluded that undertreatment of HT would be a reason for increased deaths. Many pts in this series were undertreated and this may contribute to the significantly higher follow-up mortality in our series. In this series there were no difference in mortality between males and females.

It seems that guidelines of HT treatment and prevention or mitigating its negative prognostic effects in pts with cardiac disease are in a need of aggressive refinement and new studies are needed with larger number of patients preferably in a multicenter setting and blinded if possible.

## 5. Drawbacks

This is a retrospective observational study from a single center with rather limited number of pts. The aim was to report the observed negligence in handling pts with HT and report the observed differences between euthyroid pts and pts with HT. These goals were achieved.

## 6. Conclusions

HT was severely overlooked in cardiac surgery pts.

Although pts with HT may be operated safely the problems appear in the postoperative period. The incidence may well be decreased by adequate preoperative screening and treatment of the pts.

Resource utilization is higher in HT pts.

Long-term mortality is significantly increased in HT pts. This is partly explained by the age, effects on cardiac function, accelerated atherosclerotic changes and effects on renal function if HT is undertreated.

HT pts need close follow-up and adequate replacement therapy in the postoperative period in order to mitigate the long-term effects of HT.

New guidelines for preoperative thyroid screening are needed for pts with and without HT and subjected to cardiac surgery.

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### **Addendum**

After these results all pts who were admitted for cardiac surgery were requested to have thyroid screening (TSH and T4/ft4) and cleared for surgery by cardiologist and endocrinologist. The findings and follow up of first 500 pts is reported separately.