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# Hormonal changes in the first 24 postoperative hours after cardiac surgical procedures

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## ABSTRACT

*Background:* Hormone level changes after heart surgeries are a widely observed phenomenon due to neurohormonal feedback mechanisms that may affect postoperative morbidity and mortality. The current study aimed to analyze the changes in thyroid and sex hormones in the first 24 postoperative hours after heart surgery. *Methods:* This prospective, observational study (registered on ClinicalTrials.gov: NCT03736499; 09/11/2018) included 49 patients who underwent elective cardiac surgical procedures at a tertiary heart center between March 2019 and December 2019. Thyroid hormones, including thyroid-stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4), and sex hormones, including prolactin (PRL) and total testosterone, were measured preoperatively and at 24 h postoperatively. *Results:* Significant decreases in serum TSH ($P < 0.001$), T3 ($P < 0.001$) and total testosterone ($P < 0.001$) levels were noted, whereas T4 ($P = 0.554$) and PRL ($P = 0.616$) did not significantly change. Intensive care unit (ICU) hours ($P < 0.001$), mechanical ventilation ($P < 0.001$) and Vasoactive-Inotropic Score (VIS) ($P = 0.006$) were associated with postoperative T3 level. ICU hours were associated with postoperative T4 level ($P = 0.028$). Postoperative and delta testosterone levels were in connection with lengths of stay in ICU ($P = 0.032$, $P = 0.010$ respectively). Model for End-Stage Liver Disease (MELD) scores were associated

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with thyroid hormone levels and serum testosterone. *Conclusions:* T3 may represent a marker of non-thyroidal illness syndrome and testosterone may reflect hepatic dysfunction. In addition, PRL may act as a stress hormone in female patients.

**KEYWORDS**

cardiac surgical procedures, thyroid function, nonthyroidal illness, prolactin, testosterone

# INTRODUCTION

Cardiac surgical procedures results in major stress and can cause disturbances in the physiological regulation of homeostasis [1]. Reacting to stress automatically activates a cascade that is controlled by the hypothalamic-pituitary axis and results in a great number of physiological and neurohormonal responses [2]. Altered central regulation of the hypothalamic–pituitary–adrenal and hypothalamic-pituitary-thyroid axes are the most notable factors that are frequently investigated and might be responsible for a complex range of acute and chronic changes and neurohormonal responses [3, 4].

Nonthyroidal illness syndrome (NTIS) appears in several critical conditions, including starvation, sepsis and postoperative conditions that require intensive care. NTIS is hallmarked by low plasma triiodothyronine (T3) and reduced plasma thyroxin (T4) that are not followed by an increase in plasma thyroid-stimulating hormone (TSH); missing or reduced response of the hypothalamic-pituitary-thyroid axis; and tissue-specific changes in the expression of deiodinase enzymes, catalyzing thyroid hormone metabolism [5, 6]. These hormonal changes can lead to reduced cardiac output, increased vascular resistance, tachyarrhythmia, immune dysfunction, delayed recovery, coronary spasm and higher oxygen demand [7]. However, whether these hormonal changes are adaptive mechanisms that contribute to recovery or more of a maladaptive response of a dysregulated reaction still remains a matter of debate [8, 9].

On the other hand, other hormones, such as testosterone serum hormone levels, have a modest impact on cardiac function by presenting androgen receptors in cardiac myocytes. Cross-sectional data have shown that coronary heart disease might be associated with reduced testosterone serum levels in men [10]. Prolactin (PRL) potentially has a hypertensive impact via a positive chronotropic effect in animal studies [11].

The aim of the recent study was to investigate the patterns and trends of hormonal changes in the perioperative period of cardiac surgical procedures. In addition, we tried to explore possible cofactors associated with the hormonal changes. Therefore, we designed our study to focus on perioperative trends and tendencies in addition to current values, as this may provide a more exhaustive assessment for independent cofactors and predictors of adverse outcomes after cardiac surgical procedures.

# METHODS

## Design and setting

The study was performed in accordance with the latest regulations and guidelines regarding the Declaration of Helsinki (as revised in 2013). This observational, single-center, prospective cohort study was registered on Clinical Trials.gov (NCT03736499; 09/11/2018) and was reviewed and ethically approved by the Regional Ethics Committee, Semmelweis University, Budapest (TUKEB No. 35287-2/2018/EKU). Informed consent was obtained from each patient.

## Population and sampling

Inclusion criteria applied were patients aged between 18 years old and 80 years old who underwent elective cardiac surgical procedures. Pregnancy, acute surgery, lack of consent and exposure to iodine-containing material formed the exclusion criteria. In addition, patients without markable perioperative data and with missing hormone panels were excluded. Forty-nine patients provided written informed consent and were enrolled in our final analysis at the Heart and Vascular Centre of Semmelweis University and the Department of Anesthesiology and Intensive Therapy of Semmelweis University, Budapest, Hungary between March 2019 and November 2019.

## Procedure

Serum concentrations of TSH (normal range [NR]: 0.350–4.940 μIU $mL^{-1}$), free triiodothyronine (fT3) (NR: 2.63–5.70 pmol $L^{-1}$), free thyroxine (fT4) (NR: 9.00–23.20 pmol $L^{-1}$), PRL (NR: male: <330 μIU $mL^{-1}$; nonpregnant female: <500 μIU $mL^{-1}$) and total testosterone (NR: male: 1.8–25.0 ng mL; female: 1.8–15.0 ng $mL^{-1}$) were measured in addition to routine parameters, such as complete blood count and biomarkers of kidney and liver function. Serum samples were collected from blood samples in the early morning hours preoperatively and 24 h after the first sample was taken.

## Hormone assays

TSH, fT3, fT4, PRL and total testosterone were measured using ARCHITECT (Abbott Diagnostics) chemiluminescence microparticle immunoassays (CMIA) based on protocols described by Chemiflex. One-step CMIA was applied for testosterone, and two-step CMIA was used for TSH, fT3, fT4 and PRL. All measurements were conducted according to the manufacturer's instructions.

## Study data and variables

Demographic data and clinical factors, such as sex, age, height, weight, body mass index (BMI), medical history, preoperative medications, heart failure classifications (NYHA New York Heart Association (NYHA) classification [12], European System for Cardiac Risk Evaluation (EuroSCORE) II [13], Canadian Cardiovascular Society (CCS) grading [14], preoperative blood test (complete blood count (CBC), renal and liver function, hormone panels) and types of cardiac surgical procedures, were collected [15]. In addition, the standard Model for End-Stage Liver Disease (MELD) score [16] and MELD XI [17] and MELD albumin [18] scores were calculated to assess the probability of liver and kidney function deficiency prior to the operation. For values less than 1, a number of 1 was given to avoid negative values. The formulas for calculating standard and modified MELD scores are presented below:

$$\mathrm{MELD} = 5.11 * \ln(\mathrm{INR}) + 3.78 * \ln(\mathrm{TotalBilirubin}) + 9.57 * \ln(\mathrm{Creatinine}) + 6.43 \; [16]$$

$$\text{MELD XI} = 5.11 \ * \ \ln(\text{TotalBilirubin}) + 11.76 \ * \ \ln(\text{Creatinine}) + 9.44 \ [17]$$

$$\text{MELD albumin} = 11.2 \ * \ \ln(1) + 3.78 \ * \ \ln(\text{TotalBilirubin}) + 9.57 \ * \ \ln(\text{Creatinine}) + 6.43 \ (\text{Albumin} \geq 4.1\text{g/dL}) \ [18]$$

Inotropic Score (IS) and Vasoactive-Inotropic Score (VIS) were calculated on the first postoperative day based on the data extracted from intensive care unit (ICU) charts and were reported as μg $kg^{-1}$ $min^{-1}$ [19]. Formulas for calculating IS and VIS are presented below:

$$\text{IS} = \text{dopamine dose } (\mu g/kg/min) + \text{dobutamine dose } (\mu g/kg/min) + 100 * \text{epinephrine dose } (\mu g/kg/min)$$

$$\text{VIS} = \text{IS} + 10 * \text{PDE inhibitor (milrinone or olprinone) dose } (\mu g/kg/min) + 100 * \text{norepinephrine dose } (\mu g/kg/min) + 10000 * \text{vasopressin dose } (U/kg/min) \ [19]$$

Intraoperative factors, including cardiopulmonary bypass (CPB) time, cross-clamp time and fluid balance ([fluid input + transfusion] - [fluid output + bleeding]), were measured. Bretschneider (Custodiol ©) cardioplegia solution was used in case of crystalloid cardioplegic procedures and Calafiore cardioplegia solution were applied in case of blood cardioplegic procedures [20]. Mild intraoperative hypothermia (34.5 °C) was applied during most of the procedures to prevent vital organs from ischemic injury, however, for some aortic surgeries deep hypothermic circulatory arrest (20 °C) was used for effective cerebral protection based on our institutional protocols [21, 22].

The clinical management of cross-matched red blood cell (RBC) transfusion was used based on the institutional criteria. During CPB procedure hemoglobin <7.0 g $dL^{-1}$, for the post-CPB period hemoglobin <8.5 g $dL^{-1}$ were defined as institutional trigger criteria [23].

Postoperative variables, such as 30-day and all-cause mortality, lengths of ICU stay, lengths of in-hospital stay, lengths of mechanical ventilation (MV), adverse outcomes, need for inotropic and vasoactive medications, postoperative fluid intake and output, and postoperative blood test (CBC, renal and liver function, hormone panels) were collected.

## Outcome

Our primary outcome was to model hormonal changes in the early postoperative period after cardiac surgical procedures. Each patient underwent cardiac surgical procedure with CPB. The secondary outcome was to analyze the correlation between the pre- and postoperative hormone levels and to explore possible predictors and cofactors for hormonal changes.

## Statistical analysis

All coded data were recorded in IBM SPSS Statistics software (IBM Corp, released 2013, IBM SPSS Statistics for Windows, Version 23.0.; Armonk, NY) to perform proper statistical analysis. Categorical data are presented as quantities and percentages, whereas Kolmogorov–Smirnov and Shapiro–Wilk tests were used to assess normality regarding continuous data. In the case of a normal distribution, means and standard deviations (SD) were presented. For data with a skewed distribution, medians and interquartile range (IQR; 25th and 75th percentiles) were presented. Chi-square and Fisher's exact tests were applied for categorical variables, whereas nonparametric tests, such as the Mann–Whitney *U* test, were used to evaluate continuous data.

A paired *t* test was applied to analyze changes in hormone levels (TSH, T3, T4, PRL, and testosterone) 24 h postop with respect to the preop values. In addition to analyzing raw, digital values, we created new variables based on the following equation:

$$\Delta X = \text{Xpostop} - \text{Xpreop}$$

where X indicates the investigated hormone (TSH, T3, T4, PRL, and testosterone) and Δ refers to the actual change. Here, $X_{preop}$ and $X_{postop}$ specify the analyzed hormone levels preoperatively and postoperatively. Odds ratios (ORs), correlation coefficients ($R^2$) and confidence intervals (CIs) were reported. Changes as a percentage compared to the baseline ratio were also analyzed.

Linear regression was conducted to explore the possible predictors that are independently associated with changes in TSH, fT3, fT4, PRL and testosterone. Cubic spline interpolation and the *F* test were applied to assess the linearity of continuous values. All values were used in linear form, as significant deviation from linearity was not presented. Enter mode was applied, and the results are reported as beta, $R^2$ and *P* values.

Cox regression analysis was conducted to assess one-year mortality with the evaluated hormone levels. Based on the results of univariate analysis, variables with a *P* value <0.10 were included in the multivariate models. Multivariate models were created to assign hormones independently associated with mortality and were adjusted for age, BMI, and operation time. All implemented tests were two-sided, and a *P* value <0.05 was considered statistically significant.

# RESULTS

## Demographic data and baseline characteristics

A total of 49 patients who underwent cardiac surgical procedure were enrolled in the current study. Of the 49 surgeries, 26 were isolated valve surgeries (53.1%), 14 were isolated coronary artery bypass graft (CABG) (28.6%), 5 were CABG combined with valve (10.2%), 2 were combined valve and aortic (4.1%) and 2 were other types of surgeries (4.1%). Nine patients (18.4%) were female. The median follow-up time was 584 days (IQR 25–75: 564–614 days). The median age was 67 years (IQR 25–75: 60.5–72.0 years), and the median BMI was 28.4 (IQR 25–75: 25.2–32.0). The median values of NYHA classification, EuroSCORE II and CCS grading were 2.5 (IQR 25–75: 2.0–3.0), 1.7 (IQR 25–75: 1.1–2.7) and 1.0 (IQR 25–75: 0–2.0), respectively. All anamnestic data and preexisting conditions are presented in Table 1.

## Intraoperative and postoperative data

MV was required during all surgeries. The median CPB time was 180 min (IQR 25–75: 170–210 min), and the median aorta cross-clamp was 58 min (IQR 25–75: 0–73.5 min). The median length of in-hospital stay was 8 days (IQR 25–75: 0–18.2 days), whereas the lengths of MV and ICU stay were 5 h (IQR 25–75: 0–14.5 h) and 23 h (IQR 25–75: 10.6–52 h), respectively. Seven patients (14.3%) spent more than 72 h in the ICU, and 4 patients (8.2%) needed more than 24 h on a MV device. Five patients (10.2%) died in the first postoperative year. The most

*Table 1.* Demographic and clinical data of the population

| | *N* Median | % IQR | *N* Median | % IQR | *P* |
|---|---|---|---|---|---|
| *Demographic characteristics* | | | | | |
| Age (years) | 67.0 | 60.5–72.0 | | | |
| BMI (kg $m^{-2}$) | 28.4 | 25.2–32.0 | | | |
| Gender - male | 40 | 81.6 | | | |
| Gender - female | 9 | 18.4 | | | |
| *Categories of surgeries* | | | | | |
| Isolated valve | 26 | 53.1 | | | |
| *Isolated AVR* | 15 | 30.6 | | | |
| *Isolated MVR* | 11 | 22.4 | | | |
| Isolated CABG | 14 | 28.6 | | | |
| CABG + AVR | 5 | 10.2 | | | |
| AVR + aortic | 2 | 4.1 | | | |
| Other (turtle cage, AV fistula closure) | 2 | 4.1 | | | |
| *Anamnestic and laboratory data* | | *Preop* | | *24 h* | |
| NYHA Classification | 2.5 | 2.0–3.0 | | | |
| EuroSCORE II | 1.7 | 1.1–2.7 | | | |
| CCS grading | 1.0 | 0.0–2.0 | | | |
| MELD score | 7.2 | 6.6–9.0 | | | |
| Hemoglobin (g $L^{-1}$) | 141.0 | 130.5–149.0 | 108.0 | 96.5–113.0 | <0.001 |
| WBC (G $L^{-1}$) | 7.2 | 5.7–8.8 | 11.5 | 9.1–13.8 | <0.001 |
| Thrombocyte (G $L^{-1}$) | 210.0 | 181.5–250.0 | 153.0 | 125.0–196.0 | <0.001 |
| Lymphocyte (G $L^{-1}$) | 1.72 | 1.35–2.24 | 0.7 | 0.6–0.85 | <0.001 |
| GFR (mL $min^{-1}$) | 81.6 | 63.6–88.2 | 76.9 | 59.4–94.5 | 0.756 |
| Creatinine (μmol $L^{-1}$) | 87.0 | 73.0–101.5 | 87.0 | 73.0–106.5 | 0.816 |
| BUN (mmol $L^{-1}$) | 6.3 | 5.4–7.8 | 5.4 | 4.5–6.3 | 0.001 |
| Sodium (mmol $L^{-1}$) | 140.0 | 137.0–141.0 | 138.0 | 136.0–140.0 | 0.021 |
| Potassium (mmol $L^{-1}$) | 4.4 | 4.0–4.7 | 4.4 | 4.3–4.8 | 0.058 |
| Total protein (g $L^{-1}$) | 68.4 | 64.7–71.5 | 48.0 | 45.3–50.6 | <0.001 |
| Albumin (g $L^{-1}$) | 45.5 | 43.1–48.2 | 31.7 | 30.2–33.3 | <0.001 |
| Total bilirubin (μmol $L^{-1}$) | 9.6 | 7.8–12.6 | 8.0 | 6.0–12.2 | 0.047 |
| INR | 1.1 | 1.0–1.2 | 1.3 | 1.2–1.5 | 0.034 |
| CRP (mg $L^{-1}$) | 2.0 | 0.9–4.7 | 63.7 | 40.1–76.0 | <0.001 |
| *Preexisting conditions* | | | | | |
| History of acute myocardial infarction | 13 | 26.5 | | | |
| Chronic heart disease | 19 | 38.8 | | | |
| COPD | 14 | 28.6 | | | |
| Asthma | 2 | 4.1 | | | |
| Smoke | 10 | 20.4 | | | |
| Stroke | 6 | 12.2 | | | |
| Hypertension | 41 | 83.7 | | | |
| Diabetes mellitus | 19 | 38.8 | | | |
| Neoplasia | 4 | 8.2 | | | |
| Atrial fibrillation | 11 | 22.4 | | | |
| Coronary artery disease | 17 | 34.7 | | | |

*(continued)*

**Table 1.** Continued

| | *N* Median | % IQR | *N* Median | % IQR | *P* |
|---|---|---|---|---|---|
| Peripheral vascular disease | 5 | 10.2 | | | |
| Arthritis | 10 | 20.4 | | | |

Arteriovenous, AVR: aortic valve replacement, BMI: body mass index, BUN: blood urea nitrogen, CABG: coronary artery bypass graft, CCS: Canadian Cardiovascular Society, COPD: chronic obstructive pulmonary disease, CRP: C-reactive protein, EuroSCORE: European System for Cardiac Risk Evaluation, GFR: glomerular filtration rate, INR: international normalized ratio, IQR: interquartile range, MELD: Model for End-Stage Liver Disease, MVR: mitral valve replacement, NYHA: New York Heart Association, WBC: white blood cell

frequent postoperative complications were postoperative infection (6.1%), reoperation (2.0%) and reintubation (2.0%). The most frequently administered vasoactive medication and positive inotropic agent were norepinephrine (55.1%) and dobutamine (22.4%), respectively. All intraoperatively and postoperatively administered data and complications are presented in Table 2.

## Postoperative hormonal changes

Preoperative and postoperative blood samples were obtained within 24 h to evaluate the hormonal changes. Significant decreases in TSH, T3 and serum testosterone levels were observed in the first 24 h, whereas serum T4 and PRL levels did not change significantly. TSH showed a significantly decreasing trend from mean value 2.03 μU/mL (SD ± 1.87) preoperatively to mean 1.22 μU/mL (SD ± 2.11) postoperatively ($P < 0.001$). The FT3 level exhibited a significant decrease from mean 4.87 pmol $L^{-1}$ (SD ± 0.79) preoperatively to mean 3.19 pmol $L^{-1}$ (SD ± 1.21) postoperatively ($P < 0.001$). Total testosterone decreased in the first 24 h after the surgery (from mean 3.62 ng $mL^{-1}$ [SD ± 2.08] to mean 1.57 ng $mL^{-1}$ [SD ± 1.40] [$P < 0.001$]) (Table 3, Fig. 1A–E).

Visual representation of hormonal changes (TSH: thyroid stimulating hormone, fT3: free triiodothyronine, fT4: free thyroxine, PRL: prolactin, TTE: testosterone) in the perioperative period of cardiac surgical procedures regarding preoperative and postoperative mean values using bar plot.

Meanwhile all of the hormonal preoperative values were in the normal range the postoperative distribution of the values was the following: 6 patients (12.2%) had low serum TSH level, 16 patients (32.7%) had low serum T3 level and 24 patients (49.0%), who were all male, had low serum testosterone level; serum T4 and PRL level were in the normal range postoperatively.

These changes were generally similar in male and female subgroups. However, testosterone and PRL levels exhibited increasing trends in the female group, and reductions in serum testosterone were more profound in the male group (Supplement Table S1).

## Determinants of hormonal changes in the first 24 h

The postoperative T4 level was significantly higher in the subgroup where dobutamine was administered for longer than 24 h ($P = 0.026$); however, ΔT4 was not influenced by dobutamine administration. Preoperative and postoperative testosterone levels were significantly elevated

*Table 2.* Intra- and postoperative data

| | *N*<br>Median | %<br>IQR |
|---|---|---|
| *Vasoactive support and fluid balance* | | |
| Norepinephrine | 27 | 55.1 |
| Milrinone | 6 | 12.2 |
| Dobutamine | 11 | 22.4 |
| Terlipressin | 1 | 2.0 |
| Epinephrine | 5 | 10.2 |
| Insulin | 21 | 42.9 |
| RBC transfusion | 9 | 18.4 |
| Bleeding (ml) | 300 | 200–500 |
| Fluid input (ml) | 3,572 | 2,824–4,350 |
| Fluid output (ml) | 2,000 | 1,455–2,422 |
| *Intraoperative and Postoperative data* | | |
| CPB time (min) | 180 | 170–210 |
| Aorta cross-clamp time (min) | 58 | 0–73.5 |
| MV (hours) | 5 | 0–14.5 |
| MV > 24 h | 4 | 8.2 |
| Hospital LOS (days) | 8 | 0–18.2 |
| ICU LOS (hours) | 23 | 10.6–52 |
| ICU LOS >72 h | 7 | 14.3 |
| IS | 0.0 | 0.0–2.6 |
| VIS | 2.7 | 0.2–7.5 |
| *Complications* | | |
| Infection | 3 | 6.1 |
| Reoperation | 1 | 2.0 |
| Reintubation | 1 | 2.0 |

CPB: cardiopulmonary bypass, ICU: intensive care unit, IQR: interquartile range, IS: Inotropic Score, LOS: length of stay, MV: mechanical ventilation, RBC: red blood cell, VIS: Vasoactive Inotropic Score

*Table 3.* Pre- and postoperative hormonal values for all patients

| | Mean | Std. Dev. | S.E. mean | R | Sig. (two-tailed) |
|---|---|---|---|---|---|
| TSH pre (μU $mL^{-1}$) | 2.03 | 1.87 | 0.31 | 0.85 | <0.001 |
| TSH post (μU $mL^{-1}$) | 1.22 | 2.11 | 0.35 | | |
| fT3 pre (pmol $L^{-1}$) | 4.87 | 0.79 | 0.12 | 0.14 | <0.001 |
| fT3 post (pmol $L^{-1}$) | 3.19 | 1.21 | 0.18 | | |
| fT4 pre (pmol $L^{-1}$) | 17.40 | 3.02 | 0.45 | 0.67 | 0.554 |
| fT4 post (pmol $L^{-1}$) | 17.62 | 3.09 | 0.45 | | |
| PRL pre (μU $mL^{-1}$) | 299.36 | 297.67 | 43.89 | 0.20 | 0.616 |
| PRL post (μU $mL^{-1}$) | 276.52 | 153.77 | 22.67 | | |
| Testosterone pre (ng $mL^{-1}$) | 3.62 | 2.08 | 0.31 | 0.42 | <0.001 |
| Testosterone post (ng $mL^{-1}$) | 1.57 | 1.40 | 0.21 | | |

fT3: free triiodothyronine, fT4: free thyroxine, PRL: prolactin, R: correlation coefficient, S.E.: standard error, Sig.: significance, Std. Dev.: standard deviation, TSH: thyroid-stimulating hormone

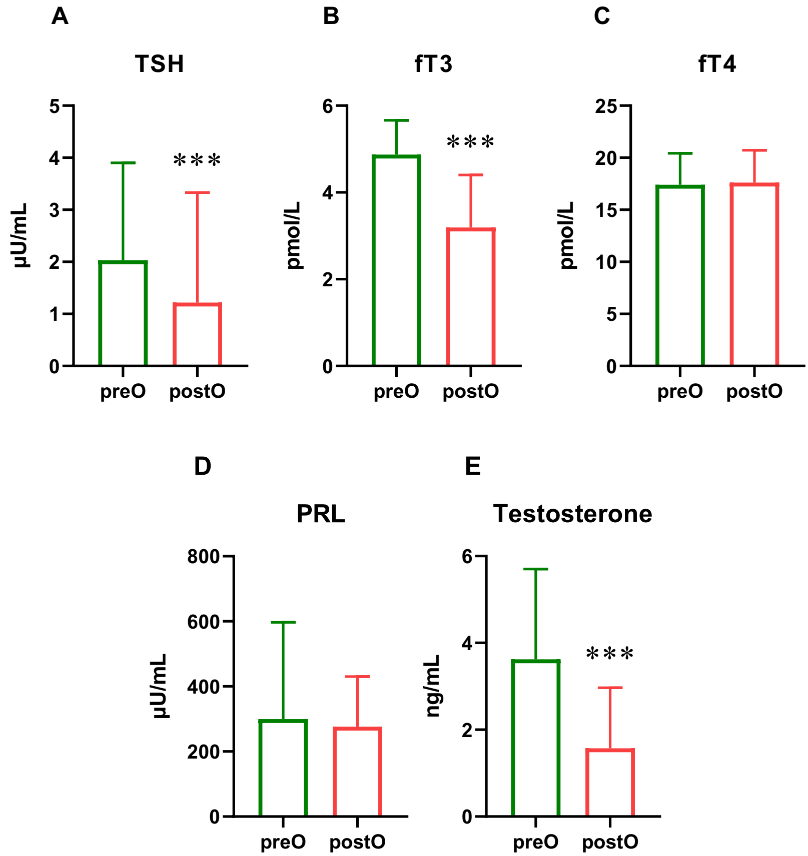


*Fig. 1.* Serum TSH (A) fT3 (B) fT4 (C) PRL (D) and testosterone (E) changes in the perioperative period of cardiac surgical procedures. preO: preoperative, postO: postoperative, TSH: thyroid-stimulating hormone, fT3: free triiodothyronine, fT4: free thyroxine, PRL: prolactin; ***: $P < 0.001$

in the subgroup with a MELD score greater than 9 compared to the subgroup of patients with a MELD less than 9 ($P = 0.028$, $P = 0.035$, respectively), although Δtestosterone was not associated with the MELD score. Patients who spent more than 72 h in the ICU had lower post-operative and Δtestosterone levels than patients with a shorter ICU stay ($P = 0.032$, $P = 0.010$, respectively). The postoperative T4 level was significantly lower in the subgroup where patients were mechanically ventilated for more than 24 h in the ICU ($P = 0.012$); however, MV did not show any association with ΔT4. All statistical associations are shown in Supplement Table S2.

## Associations regarding thyroid hormones and testosterone levels

Univariable linear regression was used to assess the relationship between hormone levels and postoperative parameters. In the univariable model, ICU hours ($P < 0.001$), MV hours ($P < 0.001$) and VIS score ($P = 0.004$) were associated with the postoperative level of fT3.

The postoperative fT4 level was associated with the IS score ($P = 0.041$) and ICU hours ($P = 0.031$) (Table 4).

Variables were adjusted for age, sex, EuroSCORE, fluid balance and operation time in the multivariable model. ICU hours ($P < 0.001$), MV hours ($P < 0.001$) and VIS ($P = 0.008$) were independently associated with the postoperative level of fT3. ICU hours ($P = 0.028$) and MELD albumin score ($P = 0.010$) were independently associated with postoperative level of fT4 (Table 4).

The standard MELD score was associated with the preoperative level of TSH ($P = 0.048$) and the preoperative level of testosterone ($P = 0.050$). MELD XI was significantly associated with preoperative fT4 ($P = 0.036$) and the preoperative level of testosterone ($P = 0.030$). In addition, the MELD albumin score was associated with the preoperative level of TSH ($P = 0.036$) and the postoperative level of fT4 ($P = 0.016$). The results regarding MELD scores are shown in Supplement Table S3.

The reduction in the albumin level was associated with ΔTSH ($P = 0.036$), and the decrease in hemoglobin level was associated with Δtestosterone in the first 24 postoperative hours ($P = 0.026$). The results are shown in Supplement Table S4.

## Impact of hormonal changes on mortality

Univariate and multivariate Cox regression analyses were applied to assess the impact of hormonal changes on mortality. In the univariate model, ΔT4 was associated with 1-year mortality ($P = 0.006$) as well as ΔPRL ($P = 0.016$). After adjusting the model for age, BMI and operation time, ΔT4 showed an independent association with the risk of 1-year mortality ($P = 0.002$).

*Table 4.* The results of univariate and multiple regression analysis of postoperative thyroid parameters

| Dependent variable | Independent variable | Univariate linear regression | | | Multiple linear regression | | |
|---|---|---|---|---|---|---|---|
| | | Beta | CI (95%) | *P* value | Beta | CI (95%) | *P* value |
| TSH post | ICU hours | 0.007 | 0.000–0.013 | 0.037 | | | |
| fT3 post | ICU hours | 0.007 | 0.004–0.010 | <0.001 | 0.007 | 0.004–0.011 | <0.001 |
| | MV hours | 0.010 | 0.007–0.014 | <0.001 | 0.010 | 0.006–0.013 | <0.001 |
| | VIS | 0.047 | 0.015–0.079 | 0.004 | 0.052 | 0.016–0.088 | 0.006 |
| fT4 post | ICU hours | 0.010 | 0.001–0.019 | 0.031 | 0.011 | 0.001–0.021 | 0.028 |
| | IS | 0.434 | 0.019–0.849 | 0.041 | | | |

$R^2$ adj. for fT3 post = 0.181, including age, sex, EuroSCORE, fluid balance and operation time; $R^2$ adj. for fT3 post = 0.421 including ICU hours, F change $P < 0.0001$.
$R^2$ adj. for fT3 post = 0.181, including age, sex, EuroSCORE, fluid balance and operation time; $R^2$ adj. for fT3 post = 0.535 including MV hours, F change $P < 0.0001$.
$R^2$ adj. for fT3 post = 0.181, including age, sex, EuroSCORE, fluid balance and operation time; $R^2$ adj. for fT3 post = 0.334 including VIS score, F change $P < 0.0001$.
$R^2$ adj. for fT4 post = 0.247, including age, sex, EuroSCORE, fluid balance and operation time; $R^2$ adj. for fT4 post = 0.557 including ICU hours, F change $P < 0.0001$.
CI: confidence interval, EuroSCORE: European System for Cardiac Risk Evaluation, fT3: free triiodothyronine, fT4: free thyroxine, ICU: intensive care unit, MELD: Model for End-Stage Liver Disease, MV: mechanical ventilation, post: postoperative, pre: preoperative, $R^2$: correlation coefficient, TSH: thyroid-stimulating hormone, VIS: vasoactive-inotropic score

The results of univariate and multivariate Cox regression analyses have insufficient power for 1-year mortality given the current sample size. The results of Cox regression analysis are presented in Supplement Table S5.

# DISCUSSION

## Summary of recent findings

We found that TSH, T3 and testosterone were significantly decreased in the first 24 h after cardiac surgical procedure with CPB. Prolonged inotropic support and length of MV were associated with significantly lower postoperative T4 levels. In the multivariable model, the postoperative T3 level was inversely associated with longer ICU stay, prolonged MV and higher VIS score. Preoperative and postoperative testosterone levels, but not the changes, were independently associated with higher MELD scores. Postoperative testosterone level and Δtestosterone were associated with an ICU stay longer than 72 h. Changes in glomerular filtration rate, creatinine level or fluid balance were not correlated with hormone changes. In addition, ΔT4 was independently associated with 1-year mortality after cardiac interventions, but the analysis had insufficient power.

## Hormonal responses in cardiac surgical procedures

The stress caused by invasive cardiac interventions generates a modest disturbance in the precise regulation of homeostasis [1]. Adaptive responses of the neuroendocrine system are mediated by the hypothalamic-pituitary axis, which aims to maintain normal physiological processes [24]. It is widely known that thyroid hormones have a modest effect on the heart and peripheral vascular system [7]. In patients with end-stage heart failure, a chronic maladaptive response can be observed [25]. Our population represented a general patient group with a low –mid cardiac surgical procedure severity score. Therefore, the preoperative levels were in the normal range.

The decrease in serum T3 levels in the context of maintained T4 levels and inappropriately normal or slightly elevated TSH levels can be explained by NTIS. Cardiac surgical procedures with CPB result in a substantial stress response for the human body that may result in the presence of euthyroid sick syndrome [1, 26]. Wang et al. highlight the fact that NTIS is associated with multi organ failure in critically ill patients [27]. The proper pathophysiological mechanism remains unknown. However, proinflammatory cytokines may have an impact on the derangement of deiodinase enzymes, and oxidative stress might disrupt deiodinase function [6, 9, 25, 28]. Unlike classical laboratory manifestation of NTIS, in our study population serum TSH showed a decreasing tendency, however it remained in the normal range for the majority of the patients while nearly a third of the patients were presented with low T3 level. Serum T4 levels often remain in the normal range at early stage, although it might fall in chronic exposure or in severe cases [28]. As the severity and lengths of NTIS increasing the more the hormonal values become altered [28]. Due to the development of surgical techniques and more advanced intensive care therapy our study population managed to present less altered thyroid values than classical NTIS but the trend remained the same. Thyroid hormone replacement therapy has been investigated in the past, however, results are still controversially discussed [29]. Our results support the fact that NTIS may occur in the early postoperative phase of heart surgery and is associated with the lengths of stay in the ICU, prolonged MV and a higher VIS score.

The hypertensive impact of PRL via a positive chronotropic effect was shown in a study in an animal population [11]. PRL is also reported to participate in peripartum cardiomyopathy [30]. PRL is also a stress hormone that often increases when psychological or physical stress occurs via a stress-induced neuroendocrine that results in PRL release [31]. These effects might increase during chronic stress due to PRL receptor upregulation in the heart [32]. The CPB-associated systemic inflammatory response via labyrinthian cascade mechanisms induced by ischemia–reperfusion injury and CPB surface-related contact activation might increase proinflammatory processes [33]. Due to the significant progress that has been made regarding CPB technique and guide management since it was first utilized, PRL was not presented as a stress hormone in our study population. We found that PRL was associated with 1-year mortality, but the analysis lacked sufficient power. Serum PRL level was not in association with dobutamine administration, as dopamine receptors are not affected by dobutamine that implies a lack of change in serum PRL [34].

Due to androgen receptors in cardiac myocytes, serum testosterone levels might be associated with coronary heart disease [10]. The link among serum total testosterone and dihydrotestosterone levels and higher MELD scores is more highly evident in cirrhotic patients [35]. We have found correlation between MELD score and preoperative testosterone within the normal range. Despite the robust epidemiological association between low serum testosterone and an increased risk of cardiovascular events, testosterone replacement therapy remains controversially discussed and presents with a neutral overall effect [36]. In addition, the appropriate dosage of postoperatively administered testosterone remains unclear given that lower or higher serum testosterone levels than the normal range might be associated with an increased risk for cardiovascular mortality and morbidity [37]. Low hemoglobin exhibits a positive association with low serum testosterone levels in all age groups of male patients [38]. Our study population confirms this finding given that the change in hemoglobin levels was associated with a decrease in serum testosterone levels. Bioavailable testosterone level is calculated with the use of total testosterone, sex hormone binding globulin and albumin [39]. During our analysis total testosterone level was used to perform statistical analysis, so the decrease of serum albumin level might contribute to the change of serum total testosterone. An impaired endocrine response was reported in male patients after cardiothoracic surgery who presented with a rapid decrease in serum testosterone levels in the postoperative period. A study reported that testosterone levels became undetectable in the postoperative period in the ICU; however, this phenomenon was not detected in female patients [40]. Our results confirm this phenomenon, as a decline in serum testosterone levels was more pronounced in male patients.

The MELD score was originally created to predict the survival of patients undergoing elective surgical treatment for portal hypertension [41]. However, standard and modified MELD scores were investigated regarding cardiac surgical procedures. MELD XI was associated with unsatisfactory results in heart transplant patients [42]. In addition, the MELD albumin score might increase risk stratification for all-cause mortality in the acute heart failure population [18]. The standard MELD score also correlated with thyroid hormone levels within the normal range. TSH, T3, and T4 levels and the fT3/fT4 ratio were all significantly inversely connected with the MELD score [43]. In our study population, thyroid hormone levels were associated with standard and modified MELD scores as well within the normal range.

Plasma dilution caused by CPB is a well-known phenomenon and is often associated with postoperative morbidity and an increased need for transfusions [44]. Low levels of coagulation factors, hemoglobin and plasma proteins are all present after CPB and after a large amount of fluid administration due to fluid shift [44]. Low levels of thyroid hormones were reported 24 h after weaning from CPB [45]. All these hemodynamic and homeostatic changes might contribute to decreased levels of hemoglobin and albumin.

### Limitations

Current research was conducted as a single-center study and was limited mainly by its small sample size. Significant predictors seemed to have sufficient power after using post hoc power analysis based on the current sample size; however, Cox regression analysis was performed with poor power. A notable bias in the last phase of patient enrollment was noted due to the SARS-CoV-2 (COVID-19) pandemic. The number of female patients was also low in this study.

## CONCLUSIONS

We found that postoperative serum T3 levels might represent a reliable tool to assess the presence of possible NTIS after cardiac surgical procedures, as this parameter may indicate the severity of stress caused by the operation. The changes in serum TSH and T4 levels are insignificantly associated with postoperative adverse events, so measuring these parameters routinely comes with negligible benefit.

A decrease in serum testosterone levels may be more highly apparent in male patients as a sign of an impaired endocrine response; furthermore, serum testosterone levels might be associated with preoperative standards and modified MELD scores as a sign of hepatic dysfunction. PRL acts as a stress hormone but only in female patients.

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## SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1556/2060.2023.00219.

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