EFFECT OF HORMONAL IMBALANCES IN THE PERIOPERATIVE PERIOD OF CARDIAC SURGICAL PROCEDURES

PhD thesis

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1. Introduction

The diagnosed prevalence of heart failure (HF) is approximately 1-2% among the adult population in developed nations. Orthotopic heart transplantation (HTx) still stand as one of the gold standard and final therapeutic approaches for end-stage heart failure, where enhanced organ allocation strategies are needed. Despite recent progress, the number of individuals awaiting a suitable organ surpasses the available supply, underlining the persistent disparity.

Cardiac surgical procedures result in major stress and can cause disturbances in the physiological regulation of homeostasis. 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.

Nonthyroidal illness syndrome (NTIS) is widely known terms for thyroid hormone alterations during critical care that is usually hallmarked by low serum levels of free triiodothyronine (fT3) and low or normal serum levels of free thyroxine (fT4) accompanied by an impaired response of the hypothalamic-pituitary-thyroid (HPT) axis represented by low or normal serum levels of thyroid-stimulating hormone (TSH). The magnitude of changes in thyroid functions usually corresponds with the severity and criticality of NTIS and increases the probability of adverse outcomes of the patients' critical condition.

Other hormones, such as testosterone, have a modest impact on cardiac function by presenting androgen receptors in cardiac myocytes. Prolactin (PRL) potentially has a hypertensive impact via a positive chronotropic effect in animal studies

All these factors combined might contribute to improving proper patient care.

2. Objectives

In our studies we aimed to investigate the hormonal trends, imbalances and their effects on adverse outcomes in the perioperative period of cardiac surgical procedures.

In Study I. heart transplanted patients was enrolled whose perioperative data was analyzed retrospectively. The aim of this study was to investigate the role of endocrine support and supplementation as a major part of donor management during HTx. Our aim was to determine:

I/1. the role of donor thyroid hormone and methylprednisolone supplementation in PGD

I/2. the role of donor thyroid hormone and methylprednisolone supplementation in postoperative survival

I/3. the associations between CDI and PGD

In Study II. patients who underwent elective cardiac surgical procedures were involved whose data was analyzed prospectively. The objective of current research was to describe hormonal patterns and trends including TSH, T3, T4, PRL, TTE in the perioperative period cardiac surgical procedures. Moreover, we aimed to uncover connections between hormonal changes and their possible cofactors. Our aim was to determine:

II/1. the changes between preoperative and postoperative hormonal values within 24h

II/2. the cofactors of postoperative thyroid hormone values

In Study III. heart transplanted patients were enrolled whose perioperative data was analyzed prospectively. The objective of this investigation was to expose deeper associations between thyroid status and adverse outcomes after HTx. Our aim was to determine:

III/1. the tendency of thyroid hormones in the perioperative period

III/2. the role of donor thyroid hormone replacement in postoperative survival
III/3. the role of recipient thyroid hormone replacement in postoperative survival
III/4. the associations between different type of MCS and deiodinase enzyme levels
III/5. the role of D2 in postoperative graft survival

3. Methods

In current researches patients who underwent cardiac surgical procedures at the Heart and Vascular Center of Semmelweis University, Budapest, Hungary between 2012 and 2020 were enrolled. All study was reviewed and ethically approved by the regional Institutional Review Board and Regional Ethics Committee (IRB:65/2017; (TUKEB No. 35287-2/2018/EKU; ETT TUKEB 7891/ 2012/EKU (119/PI/12.) and IV/10161-1/2020/EKU, respectively). All research was performed in accordance with the guiding principles and latest directives of the Declaration of Helsinki, with the Hungarian National Blood Transfusion Service and with the Eurotransplant standards for organ sharing. Written informed consent was obtained from every patient.

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, European System for Cardiac Risk Evaluation (EuroSCORE) II, Canadian Cardiovascular Society (CCS) grading, preoperative blood test (complete blood count (CBC), renal and liver function, hormone panels) and types of cardiac surgical procedures, were collected for all patients. In addition, the standard Model for End-Stage Liver Disease (MELD) score and MELD XI and MELD albumin scores were calculated to assess the probability of liver and kidney function deficiency prior to the operation. Postoperative

variables, such as 30-day and all-cause mortality, lengths of ICU stay, lengths of in-hospital stay, lengths of mechanical ventilation, 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 obtained.

Donor and recipient variables of heart transplanted patients were retrieved from the National and Eurotransplant donor data report form (according to the location of the heart donation) and from electronic medical records. Due to the relatively small sample size of our studies, the United Network for Organ Sharing (UNOS) score was calculated for donors, recipients and overall. The donor-specific UNOS score includes donor age, total ischaemic time, sex mismatch and donor diabetes mellitus. The recipient-specific UNOS score considered the following: age, body mass index, mean pulmonary artery pressure, total bilirubin, creatinine, previous transplant, previous cancer, and pre-transplant mechanical ventilation or mechanical circulatory support.

4. Results

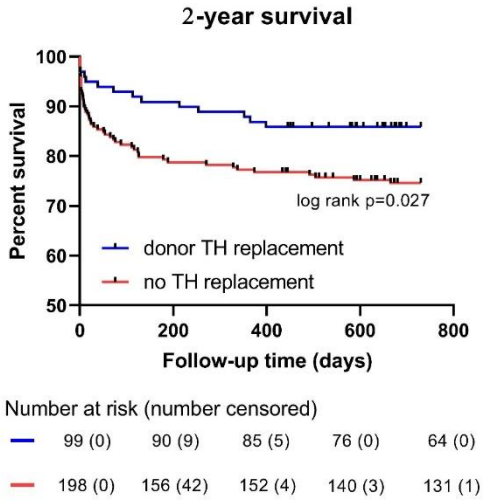
4.1 Results of Study I.

CDI developed in 63 (21.2%) donors, 43 (68.3% of the CDI cases, 14.5% of the entire cohort) of whom received desmopressin or vasopressin treatment during the management period. Without CDI, 159 (67.9%) donors were treated with desmopressin or vasopressin. Desmopressin and vasopressin treatment were not associated with PGD or 30-day and 2-year mortality in our univariate analyses. CDI also showed no trend-like association with PGD in our univariate analyses.

Methylprednisolone was negatively associated with the development of PGD. After adjustment for UNOS summary score, methylprednisolone treatment was independently associated with lower occurrence of PGD (OR: 0.38; 95% CI: 0.16-0.90; p=0.027). Univariate analysis showed that hydrocortisone treatment was not related to the study outcome.

Donor thyroxine supplementation was independently associated with a lower odd for PGD (OR: 0.38; 95% CI: 0.17-0.86; p=0.020) and 2-year-survival (OR: 0.53; 95% CI: 0.29-0.96; p=0.036) after adjustment for UNOS recipient score and for the most important donor characteristics, such as: age, diabetes mellitus, gender mismatch and total ischemic time. Kaplan-Meier curves for PGD with or without thyroxine supplementation are shown in Figure 2. The administration of combined thyroxine and methylprednisolone showed a significant reduction in PGD compared to no thyroxine (chi-square: 12.00; p=0.001) and thyroxine use alone (chi-square: 7.61; p=0.006). In our multivariate analysis, combined thyroxine and methylprednisolone supplementation was independently associated with lower risk of PGD (OR: 0.10; 95% CI: 0.01-

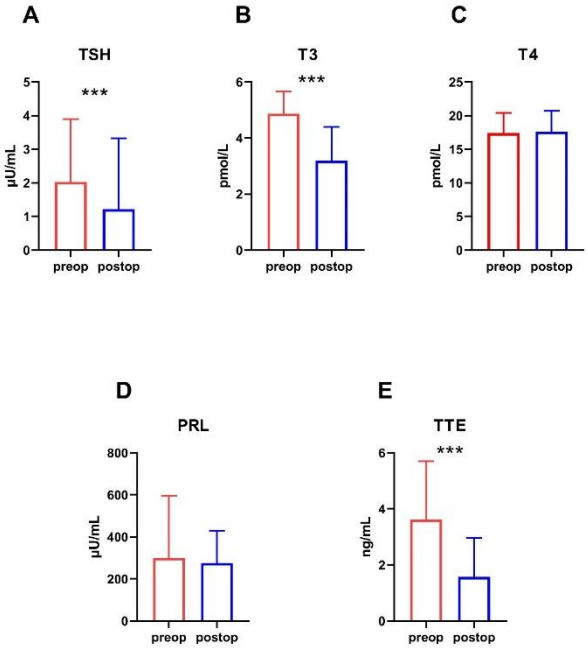
0.73; p=0.023), but there was no significant benefit in terms of survival.



Kaplan–Meier curves comparing the 2-year survival of recipients with a heart from a thyroxine-treated donor or not from a thyroxine-treated donor.

4.2 Results of Study II.

Preoperative and postoperative blood samples were obtained within 24 hours to evaluate the hormonal changes. Significant decreases in TSH, T3 and serum testosterone levels were observed in the first 24 hours, 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 (SD±0.79) preoperatively to mean 3.19 pmol/L (SD±1.21) postoperatively ($p<0.001$). Total testosterone decreased in the first 24 hours after the surgery (from mean 3.62 ng/mL [SD±2.08] to mean 1.57 ng/mL [SD±1.40] [$p<0.001$]).



Comparison between preoperative and postoperative hormone levels.

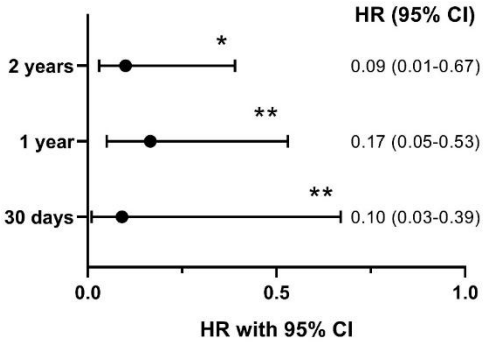
Variables were adjusted for age, sex, EuroSCORE, fluid balance and operation time in the multivariable model. ICU hours ($p<0.001$), MV hours ($p<0.001$) and VIS ($p= 0.008$) were independently associated with the postoperative level of fT3. ICU hours ($p= 0.028$) and MELD albumin score ($p= 0.010$) were independently associated with postoperative level of fT4.
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 ($p= 0.016$).

4.3 Results of Study III.

In the perioperative period after HTx, significant decreases were observed in the levels of serum TSH, fT3, and fT4. The serum TSH level declined significantly from a median value of 1.45 lU/mL (IQR 25–75: 0.80-3.81 lU/mL) preoperatively to a median value of 1.30 lU/mL (IQR 25–75: 0.39- 2.92 lU/mL) postoperatively ($p = 0.009$). The serum fT3 level was reduced from 3.12 pmol/l (IQR 25–75: 2.49-3.79 pmol/l) preoperatively to a median of 2.38 pmol/l (IQR 25– 75: 2.03-2.98 pmol/l) postoperatively ($p < 0.001$). The serum fT4 level exhibited a significant decrease from a median of 14.14 pmol/l (IQR 25–75: 11.63-15.96 pmol/l) preoperatively to a median of 11.81 pmol/l (IQR 25–75: 10.81-14.11 pmol/l) postoperatively ($p < 0.001$). Recipients on LT4 replacement had significantly lower TSH levels after the administration of T4 (3.78 lU/ml vs. 1.96 lU/ml; $p < 0.001$). There was no significant difference in pre- and postoperative fT3 levels in patients who received LT4 (2.84 pmol/l vs. 2.42 pmol/l; $p = 0.152$).

Univariate Cox regression models showed significantly better survival for the postoperative 30-day period in cases where donors received LT4 replacement ($p = 0.049$). Postoperatively administered LT4 replacement therapy was associated with better survival in the first 30 days, 1 year, and 2 years ($p = 0.019$, $p = 0.004$, and $p = 0.003$, respectively). After adjustment of the multivariable model for thyroid status (hypothyroidism, hyperthyroidism, LT4 replacement treatment, amiodarone treatment, and Dio mRNA levels), in addition to the IMPACT score ($p < 0.001$), postoperatively administered LT4 was associated with greater survival at the 30-day survival ($p = 0.018$). A multivariable Cox regression analysis showed a statistically significant association between postoperatively

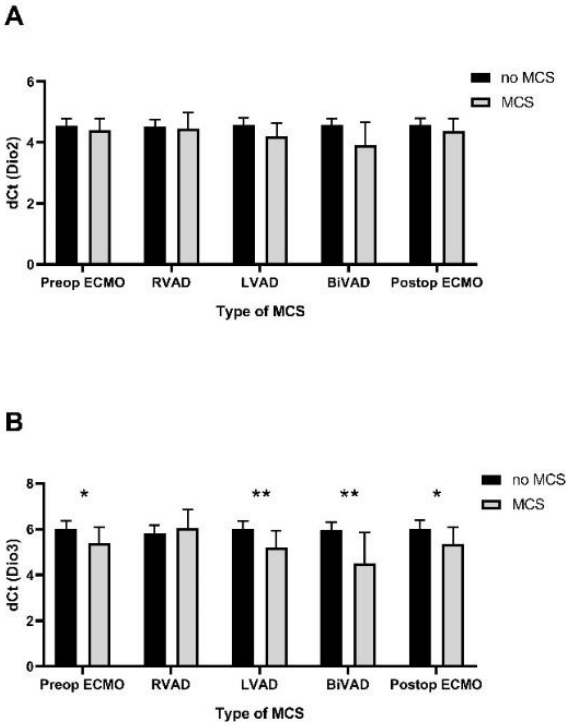
administered LT4 and 1-year survival (p = 0.002) LT4 treatment initiated in the postoperative period was associated with significantly better survival at 2 years (p = 0.001).



The association of postoperatively administered thyroxine and mortality assessed in multivariable Cox regression models at different time points.

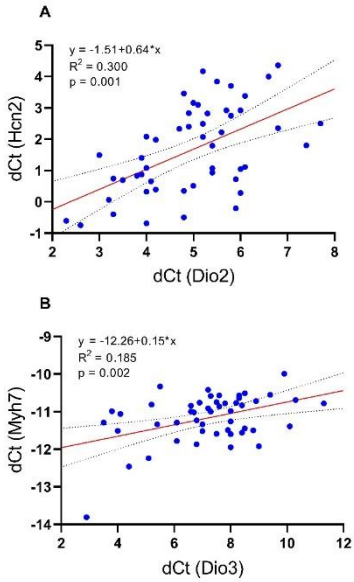
There was no statistically significant difference in DIO2 expression between patients requiring MCS and patients who did not. However, a statistically significant difference was observed in DIO3 mRNA levels among these patient groups (p =0.022). Preoperatively, DIO3 mRNA was significantly increased among those patients who were treated with ECMO compared with those who were not (n/n = 68/283, p = 0.026). Patients with preoperative LVAD implantation had significantly higher Dio3 expression than those patients who did not (n/n = 49/283, p = 0.008). Patients with BiVAD insertion had significantly higher DIO3 expression than those patients who did not require BiVAD implantation (n/n = 21/283, p = 0.013). Dio3 mRNA levels in patients with postoperative ECMO treatment were significantly elevated compared with those who were not treated with ECMO (n/n = 69/283, p = 0.042). In the

case of RVAD insertion, a statistically significant difference was not observed regarding Dio3 expression (n/n=41/283, p=0.834).



Deiodinase enzyme type 2 (A) and deiodinase enzyme type 3 (B) mRNA levels according to type of MCS received.

To evaluate local TH action in the heart, we also assessed the expression of the Hcn2 gene, positively regulated by TH, and the Myh7 gene, which is negatively regulated by TH. Hcn2 and Myh7 mRNA levels were measured in a subpopulation of 52 participants selected from those not requiring any MCS and cases where postoperative ECMO was applied. We found no significant difference in the expression of either marker gene between the on-ECMO and off-ECMO groups (Hcn2: 1.55 vs. 1.76, p= 0.519; Myh7: -11.26 vs.-11.15, p = 0.056, respectively). Neither marker showed a significant linear correlation with preoperative or postoperative serum hormone levels. Weak linear correlations were found between Hcn2 versus Dio2 (R_2=0.30, p = 0.001), and between Myh7 versus Dio3 (R_2=0.19, p=0.002).



Pearson correlation between Hcn2 vs. Dio2 and between Myh7 vs. Dio3.

Exploratory univariate logistic regression analyses were applied to assess possible associations between thyroid related factors and 30-day acute allograft rejection. Moreover, the Hosmer–Lemeshow goodness-of-fit test had a nonsignificant p value of 0.807, indicating that our final multivariable regression model suitably fits the data presented. The final model was adjusted for age, female sex, T4 administration for donors, and LT4 replacement for recipients pre- and postoperatively. Final multivariable logistic regression analysis demonstrated a significant association between Dio2 expression and acute allograft rejection after HTx (odds ratio: 0.667; confidence interval: 0.517-1.861; p = 0.002). DIO3 expression was not associated with rejection after HTx (p = 0.344) (Hosmer–Lemeshow goodness-of-fit test p = 0.807).

5. Conclusions

Monitoring TH during cardiac surgery could improve treatment, reduce complications, and boost survival. Administration of thyroxine along with methylprednisolone may reduce the risk of PGD; however, thyroxine alone is particularly important due to its positive effect on long-term survival.

Our results indicates that postoperative serum T3 levels could be a reliable marker for assessing NTIS following cardiac surgery, as they may reflect the level of stress induced by the surgery. On the other hand, variations in serum TSH and T4 levels show minimal correlation with postoperative adverse events, making regular measurement of these parameters less useful. Additionally, our study highlights a significant drop in serum testosterone levels, which appears to be more pronounced in male patients, indicating a disrupted endocrine response. This decrease in testosterone may also be associated with preoperative conditions and altered MELD scores, hinting at underlying hepatic dysfunction. Furthermore, PRL acts as a stress hormone, but this effect is observed exclusively in female patients, underscoring the gender-specific responses to surgical stress.

In conclusion, central parameters of TH function, such as TSH, fT3, and fT4, decreased post-HTx compared to preoperative levels, indicating the development of NTIS. Levothyroxine replacement therapy for both donors and recipients may provide advantages post-HTx, correlating with improved survival. The expression of Dio3 mRNA was influenced by different MCS devices. Additionally, higher expression of Dio2 in the heart, which may be mitigated by levothyroxine replacement, is linked to acute allograft rejection, a common complication post-HTx. These findings collectively emphasize the importance of tailored TH management in improving postoperative outcomes and long-term survival in cardiac surgery patients.

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