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

PhD thesis

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List of Abbreviations

ACC: American College of Cardiology

ACR: acute cellular rejection

AHA: American Heart Association

AMR: antibody-mediated rejection

AV: arteriovenous

AVR: aortic valve replacement

BiVAD: biventricular assist device

BiVAD: biventricular assist device

BMI: body mass index

BTB: bridge-to-bridge

BTC: bridge-to-candidacy

BTD: bridge-to-decision

BTR: bridge-to-recovery

BTT: bridge-to-transplant

BTT: bridge-to-transplant

BUN: blood urea nitrogen

CABG: coronary artery bypass grafting

CBC: complete blood count

CCS: Canadian Cardiovascular Society

CDI: central diabetes insipidus

CI: cardiac index

CI: confidence interval

CPB: cardiopulmonary bypass

D1: type 1 deiodinase

D2: type 2 deiodinase

D3: type 3 deiodinase

DT: definitive therapy

ECG: electrocardiogram

EuroSCORE: European System for Cardiac Operative Risk Evaluation

fT3: free triiodthyronin

fT4: free thyroxine

HF: heart failure

HFmrEF: heart failure with mildly reduced rejection fraction

HFpEF: heart failure with preserved rejection fraction

HFrEF: heart failure with reduced rejection fraction

HRT: hormone replacement therapy

HTx: heart transplantation

IABP: intra-aortic balloon pump

ICU: intensive care unit

INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support

IQR: interquartile range

IS: Inotropic Score

ISHLT: International Society for Heart and Lung Transplantation

LOS: lengths of stay

LT4: levothyroxine

LV: left ventricle

LVAD: left ventricular assist device

LVEF: left ventricular ejection fraction

MELD: Model for End-Stage Liver Disease

MV: mechanical ventilation

MVR: mitral valve replacement

NTIS: non-thyroidal illness syndrome

NYHA: New York Heart Association

PASP: pulmonary artery systolic pressure

PCI: percutaneous coronary intervention

PCWP: pulmonary capillary wedge pressure

PGD: primary graft dysfunction

PRL: prolactin

PVAD: Parathoracic Ventricular Assist Device

R^2: correlation coefficient

RAP: right atrial pressure

RBC: red blood cell

rT3: reverse T3

RV: right ventricle

RVAD: right ventricular assist device

SD: standard deviation

T3: triiodthyronin

T4: thyroxine

TAH: total artificial heart

TH: thyroid hormone

TPG: transpulmonary gradient

TRH: thyrotropin-releasing hormone

TSH: thyroid stimulating hormone

TTE: testosterone

UNOS: United Organ for Network Sharing

VA-ECMO: veno-arterial extracorporeal membrane oxygenation

VIS: Vasoactive-Inotropic Score

1. Introduction

1.1. Heart failure

Owing to the escalating prevalence of cardiovascular diseases, particularly heart failure (HF), this upward tendency continues imposing a significant load on global public healthcare systems around the world (1). The diagnosed prevalence of HF is approximately 1-2% among the adult population in developed nations. Worldwide, more than 60 million individuals suffer from this condition (2). The escalating patient number can be attributed, on one hand, to the overall aging of the population, and on the other hand, to improved survival rates following myocardial injuries and cardiovascular diseases, as well as the widespread occurrence of metabolic comorbidities. HF exacts a substantial toll in terms of morbidity and mortality, significantly burdening healthcare resources. On average, HF patients are prescribed 4-6 medications targeted at HF, with a majority of them requiring hospitalization once or twice a year (3, 4).

Chronic HF is characterized as a multifaceted clinical syndrome, wherein there exists a restriction in exertion due to compromised ventricular filling and/or ejection of blood. The underlying mechanism of HF involves a substantial reduction in functional myocardial tissue subsequent to cardiac injury induced by diverse factors. Predominant contributors to HF encompass ischemic heart disease, hypertension, and diabetes mellitus. Additionally, significant triggers of HF involve hereditary cardiomyopathies, infections, toxins (such as cytotoxic drugs and alcohol), as well as structural anomalies (for example, valvular heart diseases) (5). These severely ill patients experience life-threatening clinical manifestations including inadequate organ perfusion, pulmonary congestion, pulmonary vascular disease, water retention, kidney hypoperfusion and cardiac cachexia (6).

The pathogenesis of HF involving hypertrophy and cardiac remodeling have undergone extensive investigations. These processes are developed in response to stress signals generated by the complex pathological conditions in order to sustain cardiac output and adequate tissue perfusion. Inflammatory cytokines and reactive oxygen species also take part in the pathomechanism. However, these compensatory responses eventually become maladaptive, leading to increased autonomic nervous system and unrestrained activation of the renin-angiotensin-aldosterone system. These alterations in neurohormonal activity and enhanced sympathetic function can deeply affect cardiac

structure and function. Left ventricular (LV) function is a crucial marker in assessment HF and stands as a pivotal focus of potential pathogenesis. The prevalence and progression of HF are in extensive association with cardiac remodeling that manifests as alterations in cardiac structure and function. Moreover, death of cardiomyocytes might play an important role in the cardiac remodeling as well (7-9).Nevertheless, even with appropriate treatment the long-term prognosis for heart failure remains discouraging. Therefore, there is an imperative need for novel and effective therapeutic strategies that can enhance the outcomes of HF.

Despite therapeutic approaches for HF continuously evolving, the clinical diagnoses and classifications of thy syndrome remain challenging. Several scoring systems have been created so far for risk assessment and for prognostic use as well. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) was created for accurate characterization of patients with HF considered for mechanical circulatory support (MCS) (10). New York Heart Association (NYHA) classification was created to assess the patients' functional capacity as an indicator of the severity of chronic HF with LV dysfunction (11). The latest update on ACC/AHA stages, published in 2022, renewed the terminology for stage A (at risk) and stage B (pre-HF), incorporating increased troponin concentration and elevated natriuretic peptide levels into the stage B definition to highlight the importance of biomarkers (12).

1.2. Therapeutic approach of chronic heart failure

The therapeutic approach to heart failure largely depends on the distinct phenotypes into which patients are divided with the INTERMACS classification providing a standardized system to categorize those with advanced heart failure based on their clinical status, symptoms, and the urgency for mechanical circulatory support (13).

Table 1. INTERMACS profiles

INTERMACS Profile	Classification	Clinical Description
1	Critical Cardiogenic Shock	Severe hemodynamic instability with critical organ dysfunction; requires immediate mechanical support.
2	Progressive Decline	Steady deterioration despite medical therapy; may require prompt mechanical support.
3	Stable but Inotrope Dependent	Clinically stable but dependent on intravenous inotropes to maintain cardiac output.
4	Resting Symptoms	Symptoms persist at rest despite optimal medical therapy; not in immediate shock.
5	Exertion Intolerant	Comfortable at rest but symptomatic with minimal physical activity.
6	Exertion Limited	Mild limitation with regular activity; may tolerate routine tasks but not exertion.
7	Advanced NYHA Class III	Clinically stable with significant limitations in exertion, typically managed medically.

INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support, NYHA Class: New York Heart Association Classification

As the severity of the HF increases the therapeutic solutions tend to move from pharmacological options to mechanical assist devices and end in heart transplantation as the only gold-standard therapeutic approach of end-stage HF. Pharmacological treatment is composed of angiotensin-converting enzyme inhibitors, angiotensin receptor II type 1 receptor blockers, beta-blockers, mineralocorticoid receptor antagonists, angiotensin receptor-neprilysin inhibitor, sodium-glucose co-transporter 2 inhibitors, diuretics, I_f-channel inhibitor, digoxin, combination of hydralazine and isosorbide dinitrate (12). Pharmacological treatment in itself not always means adequate therapy for managing HF.

1.2.1. Mechanical circulatory support

Mechanical circulatory support (MCS) devices stand as a strong pillar in the therapeutic approach of HF. Strategies for application of different type of MCS devices are presented in Table 2 (14).

Table 2. Different strategies for MCS implantation

Strategy	Definition	MCS devices
BTD and BTB	bridge therapy till patient stabilization or further therapy decision	IABP, VA-ECMO
BTC	bridge therapy in case of temporary contraindications	LVAD, BiVAD
BTT	bridge therapy till heart transplantation	LVAD, BiVAD, VA-ECMO
BTR	bridge therapy in case reversible HF	IABP, VA-ECMO, LVAD, RVAD, BiVAD
DT	definitive therapy for patient with contraindication of heart transplantation	LVAD

BTB: bridge-to-bridge, BTC: bridge-to-candidacy, BTD: bridge-to-decision, BiVAD: biventricular assist device, BTR: bridge-to-recovery, BTT: bridge-to-transplant, DT: definitive therapy, IABP: intra-aortic balloon pump, LVAD: left ventricular assist device, MCS: mechanical circulatory support, RVAD: right ventricular assist device, VA-ECMO: veno-arterial extracorporeal membrane oxygenation

The timeline of MCS modality usage provides a structured overview of various devices, highlighting their typical duration of application and clinical indications, which are crucial for optimizing patient management in different stages of heart failure (15-17). The timeline of MCS modality usage presented in Table3.

Table 3. Timeline of MCS modality usage

MCS Modality	Typical Duration of Use	Clinical Application
Intra-Aortic Balloon Pump	Hours to days	Temporary support in acute heart failure or cardiogenic shock.
Percutaneous LVAD (Impella)	Hours to weeks	Short-term support for high-risk PCI or cardiogenic shock.
Veno-Arterial ECMO	Days to weeks	Acute, temporary support for cardiogenic shock or cardiac arrest.
Centrifugal-Flow VAD	Weeks to months	Bridge to decision or recovery in acute heart failure.
Durable LVAD (e.g. HeartMate 3)	Months to years	Long-term support for advanced heart failure as bridge to transplant or destination therapy.

ECMO: veno-arterial extracorporeal membrane oxygenation, LVAD: left ventricular assist device, PCI: percutaneous coronary intervention, VAD: ventricular assist device

1.2.1.1 Left ventricular assist device (LVAD)

LVADs stand as the foremost choice among durable MCS devices. The initial generation of LVADs were pulsatile-flow devices delivering hemodynamic assistance to patients (18). Second generation of LVADs took the form of continuous-flow devices involving a solitary moving component with smaller pump dimensions and heightened mechanical reliability (19). Presently, continuous-flow LVADs contribute to roughly over 95% of all implantations, effectively supplanting other types of durable single-ventricular support (20). The third generation LVADs incorporate centrifugal-flow pumps, designed to be more compact and long-lasting. As LVADs have undergone size reduction therefore there has been a growing interest in techniques that involve

minimally invasive procedures and sternal-sparing approaches for implantation aimed to reduce postoperative adverse outcomes (21).

1.2.1.2 Biventricular assist device (BiVAD) and right ventricular assist device (RVAD)

Patients requiring BiVAD support have lower risk of survival until transplantation (22). The options for bridging patients with both left and right ventricular dysfunction to transplantation include BiVAD or total artificial heart (TAH). BiVAD involves an RVAD and an LVAD that work simultaneously, primarily for cases where LVAD patients develop right ventricular (RV) failure. Notably, no continuous flow, implantable centrifugal pump VAD available for RV support yet. However, a few pulsatile paracorporeal devices such as Parathoracic Ventricular Assist Device (PVAD) can offer support for RVAD and BiVAD scenarios (23). In some cases, off-label insertion of continuous flow LVAD in the right atrium or in RV can serve as a BiVAD (14). Despite these considerations the utilization of BiVAD support stays relatively uncommon, accounting for roughly 5% of patients with MCS devices (20).

1.2.1.3 Intra-aortic balloon pump

Intra-aortic balloon pump (IABP) was the initial form of temporary MCS to be developed and remains the prevalent choice in clinical practice. IABP still continues to be one of the most frequently employed MCS device owing to its cost-effectiveness and straightforward insertion procedure (14). Lately, there has been a surge in notice regarding percutaneously inserted IABP devices through the axillary or subclavian arteries. This setup enables patients to engage in mobility and physical rehabilitation while awaiting transplantation. Studies indicate that end-stage HF patients with upper-extremity IABP devices achieve substantial success rates in transplantation with notable enhancements in ambulatory distances observed following axillary insertion (24, 25).

1.2.1.4 Veno-arterial extracorporeal membrane oxygenation (VA-ECMO)

VA-ECMO is typically inserted via peripheral cannulation where deoxygenated blood is withdrawn from the femoral or internal jugular vein and oxygenated blood is reintroduced into circulation via the femoral artery. It can also be inserted centrally, with cannulation directly into the heart or great vessels, depending on the clinical scenario. Contrasting other percutaneous MCS devices like IABP or peripheral VA-ECMO raises the afterload of the LV due to arterial blood return. This can result in

enhanced LV end-diastolic pressure and substantial dilation of the LV myocardium, potentially causing myocardial ischemia. Consequently, venting of the LV may be necessary with VA-ECMO to prevent further deterioration of LV function especially in patients in severe shock or with a low likelihood of recovery (14). Research has demonstrated that managing cardiogenic shock with a combination of VA-ECMO to alleviate the workload of LV has resulted in prolonged survival (26). Nonetheless, there is a certain matter of debate concerning whether the simultaneous utilization of IABP augments outcomes for bridge-to-transplantation (BTT) in patients being supported with VA-ECMO (27). Over the past decade, there has been a notable rise in the percentage of patients who are directly transitioned from ECMO to heart transplantation as a part of BTT (28). Nevertheless, despite the progress in LV unloading methods, using VA-ECMO as a strategy for BTT still exhibits higher rates of complications and elevated postoperative mortality in comparison to alternative temporary MCS devices (29).

1.2.2. Cardiac surgical procedures

1.2.2.1 Valve replacement procedures

Valve replacement procedures continue to be the most effective treatment for patients with substantial valve stenosis or regurgitation. The success of this procedure relies on a thorough preoperative evaluation of the patient and a deep knowledge of the anatomy of the coronary arteries. While specific surgical techniques might differ among surgeons, there are fundamental principles that remain consistent and contribute to achieving the best possible outcomes (30).

Cardiac surgical procedures are indicated for conditions involving coronary arteries and heart valves that can be improved through surgical interventions in HF patients. In cases of reduced systolic left ventricular function (LVEF <35%) and significant stenosis of the left main coronary artery or an equivalent branch, coronary artery bypass surgery has been proven to enhance survival, however, catheter-based procedures are also gaining ground. (31, 32).

1.2.2.2 Coronary artery bypass graft (CABG)

CABG stands as a surgical procedure involving the rerouting of atheromatous blockages in patients' coronary arteries using transplanted arterial or venous blood vessels aiming to restore normal circulation of the ischemic myocardium thereby revitalizing its

viability, function and lighten anginal symptoms. With nearly 400,000 CABG surgeries conducted annually, it is the most frequently performed major surgical intervention, however, surgical procedures have shifted due to the rise of alternative techniques like percutaneous coronary intervention (PCI) (33). Conventionally, CABG surgeries are divided into two categories: on-pump and off-pump based on the usage of a cardiopulmonary bypass (CPB) circuit and a temporarily arrested heart. The harvested bypass grafts are commonly the left or right internal mammary artery and the saphenous vein grafts (34). CABG has been shown to improve outcomes in heart failure patients with myocardial viability (35).

1.2.2.3 Heart transplantation

Patients who suffer from advanced HF and require both MCS and inotropic and/or vasopressor support often have a disappointing prognosis (36). Orthotopic HTx still remains the benchmark and gold standard therapeutic solution for end-stage HF (1). Nonetheless the landscape changed with the introduction of immunosuppressive therapies and improved insights into human anatomy and surgical methods causing HTx to gain traction in the 1990s. Notably, the International Society for Heart and Lung Transplantation (ISHLT) observed a peak in heart transplants between 1993 and 2004, and more recent data show a continued upward trend (37).

In Hungary, the first HTx was performed in 1992 by Professor Zoltán Szabó and his team at the Heart and Vascular Center of Semmelweis University, Budapest, Hungary. Over the past 28 years, significant progress has been made in the domestic heart transplantation program. The next major step in 2013 was our dual-stage integration into the Eurotransplant donor organ allocation system, established in 1969. Currently, our Center ranks as the second most active heart transplant center on the continent. The initiation of the MCS program in 2012 has further amplified our development (38-40).

Due to well-defined criteria and indications for HTx by collaborative efforts from institutions like the ACC, AHA and the European Society of Cardiology in coordination with the ISHLT, there's now greater clarity on who should be considered for HTx. Despite this progress, the number of individuals awaiting a suitable organ surpasses the available supply, underlining the persistent disparity (41, 42).

1.2.3. Complications after HTx

1.2.3.1 Mortality

In comparison to medical therapy, HTx has remarkable survival rates and enhances functional status among recipients. Nonetheless, the challenges posed by acute and chronic rejection coupled with the potential side effects of immunosuppressive treatments like infections or malignancies, and renal insufficiency, cardiac allograft vasculopathy act as barriers to achieving even more optimal outcomes. In recent times treatment involving MCS devices has exhibited promising outcomes thereby emerging as a potential contender to HTx, especially for specific patient cohorts. However, the long-term efficacy of this approach remains to be fully ascertained (43).

While center-specific data might vary, survival statistics derived from sources such as the ISHLT registry are commonly referenced to provide with post-transplant survival prospects. Among patients undergoing HTx 1-year survival rate stands at around 90% in North America, while it is roughly 80% in Europe and other global regions that contribute HTx data to the ISHLT (44). Impressively the median survival duration exceeds 12 years (45).

1.2.3.2 Rejection

Rejection continues to be a significant concern, as it remains one of the most frequently occurring complications after HTx. The noted decrease in cellular rejection rates over the past years attributed to advancements in targeted immunosuppression for T-cell mediated damage that has been accompanied by a corresponding increase in the identification of antibody-mediated rejection (AMR). Although the ISHLT consensus has made considerable expansion in standardizing the pathological diagnosis of AMR, gaps persist in fully comprehending the extent and severity of the associated damage (46, 47). Efforts to address these gaps have led to the use of endomyocardial assessments of specific pathogenesis-based transcripts through microarray gene analysis that has demonstrated its ability to accurately categorize acute rejection in addition to immune histology. Moreover, it exhibits a stronger correlation with the level of injury and the activity of the disease (48).

Mixed rejection episodes, characterized by the simultaneous occurrence of AMR alongside acute cellular rejection (ACR) have been documented. In a study focused on

adult HTx recipients mixed rejection was observed nearly 8% of cases with its occurrence being most the common within the first year postoperatively. This single center study also demonstrated a significant association between mixed rejection and elevated cardiovascular mortality rates with the risk escalating as the severity of the condition increased (49).

1.2.3.3 Primer Graft Dysfunction

Primary graft dysfunction (PGD) is a severe form of ventricular dysfunction that occurs in the immediate postoperative period when the graft is unable to meet the circulatory needs of the recipient resulting in low cardiac output and hypotension. PGD can involve either one or both ventricles, and it is often accompanied by inadequate filling pressures (50). A classification has been proposed by the ISHLT based on several aspects of the graft dysfunction. It is classified as PGD-LV if it affects the left ventricle or both ventricles, and as PGD-RV if it only affects the right ventricle (51). The severity of PGD-LV is classified as mild, moderate, or severe:

- Mild PGD-LV is defined as the need for low-dose inotropic support and presence of LVEF < 40%, or hemodynamic compromise with right atrial pressure (RAP) > 15 mmHg, cardiac index (CI) < 2.0 L/min/m2, pulmonary capillary wedge pressure (PCWP) > 20 mmHg,
- Moderate PGD-LV is defined as the need for high-dose inotropic support and presence of LVEF < 40%, or hemodynamic compromise with right atrial pressure (RAP) > 15 mmHg, cardiac index (CI) < 2.0 L/min/m2, pulmonary capillary wedge pressure (PCWP) > 20 mmHg, or the need for an IABP
- Severe PGD-LV is defined as the need for short-term MCS in the form of ECMO or VADs in any form (51)

A severity scale for PGD-RV does not exist. It is diagnosed based on the need for a RVAD or right heart catheter-measured hemodynamics consistent with isolated right-sided dysfunction. This hemodynamics includes RAP > 15 mmHg, CI < 2.0 L/min/m2, PCWP < 15 mmHg, pulmonary artery systolic pressure (PASP) < 50 mmHg, transpulmonary gradient (TPG) < 15 mmHg.

Despite the improvement in survival rates after HTx in the past decades, PGD still remains one of the most frequent principal causes of early mortality after HTx (52).

1.3. Neuroendocrine system and heart failure

HF is marked by a decrease in the heart's ability to function effectively leading to poor output, inadequate peripheral perfusion and potential disturbances in arterial pressure that triggers the activation of various compensatory paracrine and endocrine mechanisms aimed to maintain circulatory balance and proper arterial pressure. Consequently, the body abnormally amplifies the neuroendocrine response responsible for maintaining arterial pressure leading to the establishment of a detrimental cycle (53, 54). Beside general sympathetic nervous system and renin-angiotensin-aldosterone activation a various altered mechanisms come into play regarding the thyroid (55, 56).

1.3.1. Thyroid disorders

Thyroid hormones (TH) play a crucial role in regulating growth, metabolism and various vital functions including the cardiovascular system. The thyroid gland along with the anterior pituitary gland and the hypothalamus forms a self-regulating cycle known as the hypothalamic-pituitary-thyroid axis. The principal hormones, synthetized by the thyroid gland, are thyroxine (T4) and triiodothyronine (T3). Additionally, the thyroid gland produces another molecule known as reverse T3 (rT3), the exact role of which remains unclear. This dynamic system involves thyrotropin-releasing hormone (TRH) from the hypothalamus, thyroid-stimulating hormone (TSH) from the anterior pituitary gland and TH working in synchronized coordination to sustain effective feedback mechanisms and ensure homeostasis (57). Feedback mechanisms of the thyroid are shown in Figure 1.

T4, the principal hormone of the thyroid gland, functions as a prohormone as the biologically active hormone that binds to thyroid receptors is T3, primarily formed through the deiodination of T4. Deiodinases are crucial enzymes containing selenocysteine that possess the capability to eliminate iodide from iodothyronines. Type 1 deiodinase (D1) and type 2 deiodinase (D2) demonstrate 5′-deiodinase activity, facilitating the conversion of T4 into T3. In contrast, D1 and type 3 deiodinase (D3) demonstrate 5-deiodinase activity that results in the inactivation of both T4 and T3. Given that the expression of deiodinase enzymes is subject to developmental regulation

and cell-specific patterns, adjustments in local TH levels can be made to attain physiologically appropriate levels that is substantially distinct from systemic TH levels (58, 59).

The non-thyroidal illness syndrome (NTIS) pertains to alterations in serum TH levels witnessed in critically ill patients even when there is no primary dysfunction in the hypothalamic–pituitary–thyroid axis. Patients affected by NTIS often exhibit reduced T3 levels, elevated rT3 levels and TSH levels that are abnormally within the normal range. The mechanisms driving these changes in pituitary–thyroid function are not yet fully comprehended, but they are likely the result of various factors acting in combination. The initial phase of this syndrome appears to stem from modifications primarily in peripheral TH metabolism. The alterations in thyroid hormone levels are in connection with the lengths and severity of the illness. Comprehensive data collected from critically sick patients have illustrated that the extent of decrease in TH levels corresponds with patient mortality. Additionally, serum rT3, free T4 (fT4) levels and the T3/rT3 ratio have been identified as independent prognostic markers for mortality. Notably, low free T3 (fT3) levels are also independently associated with both short- and long-term mortality in patients diagnosed with conditions such as HF, myocardial infarction or acute stroke (60, 61).

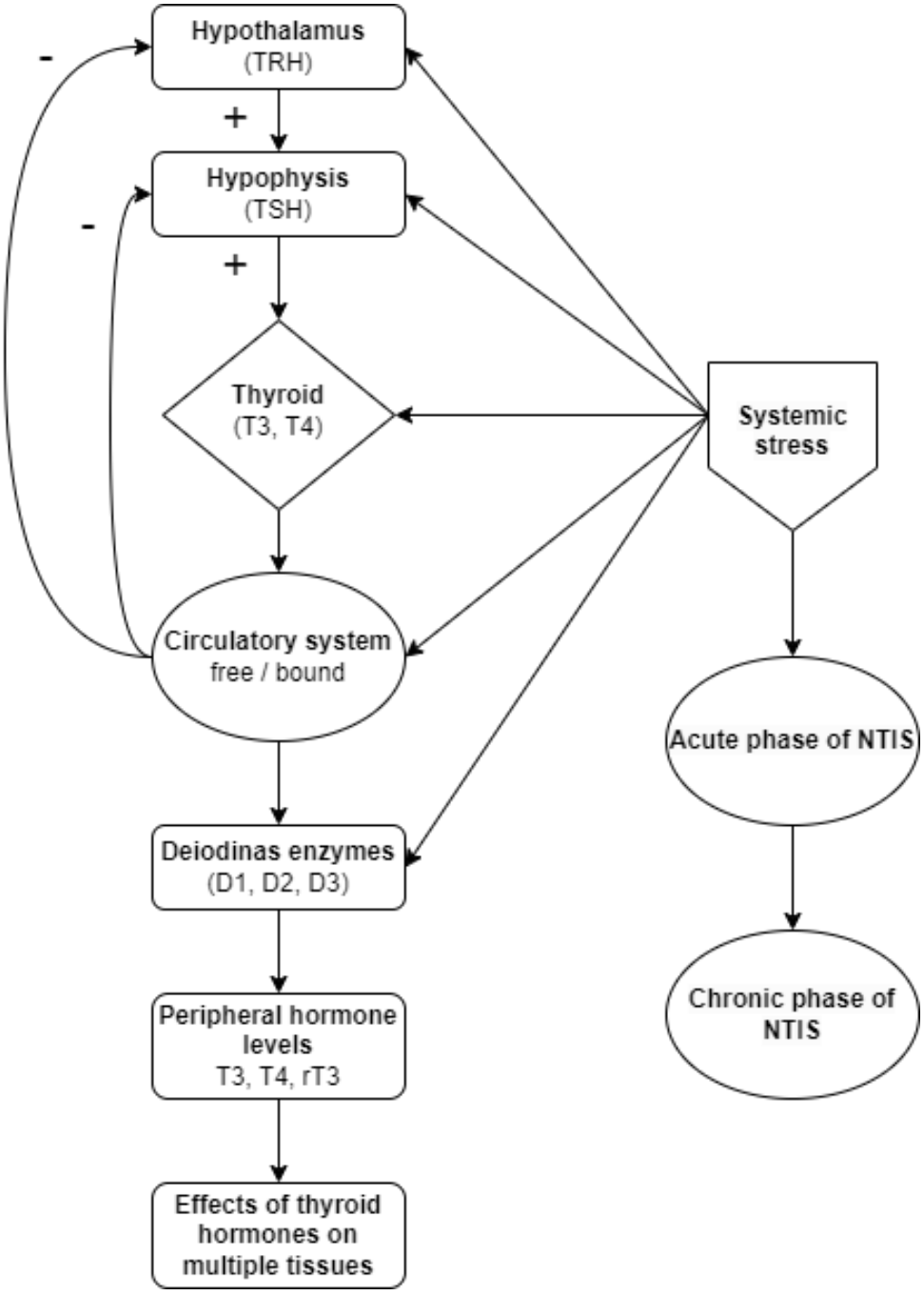

Figure 1. The hypothalamic–pituitary–thyroid axis. D1: type 1 deiodinase, D2: type 2 deiodinase, D3: type 3 deiodinase, NTIS: non-thyroidal illness syndrome, rT3: reverse T3, TRH: thyrotropin-releasing hormone, TSH: thyroid stimulating hormone, T3: triiodthyronin, T4: thyroxine

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.

2.1. Study I.

In current study 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.

We aimed to research:

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 central diabetes insipidus (CDI) and PGD

2.2. Study II.

This research prospectively analyzed data from patients undergoing elective cardiac surgery to examine perioperative hormonal patterns (TSH, T3, T4, prolactin (PRL), testosterone (TTE)) and explore associations between hormonal changes and potential cofactors.

We aimed to research:

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

II/2. the cofactors of postoperative thyroid hormone values

2.3. Study III.

In this study 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.

We aimed to research:

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

3.1. Methods of Study I.

3.1.1. Study design and setting

In current retrospective, single-center research patients who underwent HTx at the Heart and Vascular Center of Semmelweis University, Budapest, Hungary between January 2012 and September 2018 were enrolled. The study was reviewed and ethically approved by the regional Institutional Review Board (IRB; 65/2017). The 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.

3.1.2. Donor management and protocols

"In Hungary, organ donation is controlled by the National Blood Transfusion Service. Guidelines for donor management are based on international references last updated in 2018. Once the diagnosis of brain death has been made, this service coordinates with the Eurotransplant International Foundation the further action necessary for successful transplant.

The following monitoring strategy should be implemented in the donor reporting ICU: ECG, pulse oximetry, invasive arterial blood pressure and central venous pressure monitoring, core temperature monitoring, and urine output monitoring. The current guideline recommends defining exact hemodynamic targets and various homeostatic targets, which should be maintained. The most common complications are severe hypotension and CDI. After excluding the obvious causes for hypotension, the first vasopressor of choice is norepinephrine up to 0.5 µg/kg/min. Dobutamine or epinephrine are considerable for further hypotension.

The definition of diabetes insipidus is based on increased urine output (>2.5 ml/kg/hour), hypernatremia (>145 mmol/L), increased serum osmolality (>305 mmol/kg) and decreased urine specific gravity (<1.005 g/ml) (62). Adequate fluid replacement (dextrose 2.5% with electrolytes) should be used for symptomatic treatment of diabetes insipidus. For specific therapy, desmopressin should be used (0.5-1 µg iv., every 6-12 hours) until the goal urine output (1-1.5 ml/kg/h) is reached. Alternatively, continuous administration of vasopressin should be considered. The guidelines

recommend administering corticosteroids (hydrocortisone 100 mg iv. loading and 200 mg/day iv.) after brain death; otherwise, the routine administration of thyroid hormones according to the Hungarian protocol is not recommended; it is only an option for hemodynamically unstable donors. (63)"

"Donor and recipient variables were retrieved from the National and Eurotransplant donor data report form (according to the location of the heart donation) and from electronic medical records. The following data on donors were collected and analysed: age, sex, height, weight, body mass index, cause of brain death, overall length of stay (LOS), donor management time at the intensive care unit (ICU), diabetes mellitus, hypertension, smoking, drug abuse, active malignant tumour, serum sodium, potassium, chloride, glucose concentration, urine specific gravity, blood urea nitrogen (BUN), blood group, urine output (ml/kg/h), administration of inotropic and vasoactive medication (norepinephrine, epinephrine, dopamine), administration of diuretic medication (furosemide, mannitol, spironolactone), HRT (hydrocortisone, methylprednisolone, thyroxine, desmopressin, vasopressin), presence of CDI, ejection fraction of the heart and interventricular septum thickness in end-diastole (IVSd). Patients who received more than one dose of hydrocortisone or methylprednisolone were considered treated. The expected osmolality of the serum was calculated using the following formula: 2 x (sodium + potassium) + BUN + glucose; all parameters are in mmol/L. Demographic characteristics, body mass index, recent pre-transplant hemodynamic measurements (right heart catheterization using Swan Ganz catheter), preoperative laboratory tests (total bilirubin, creatinine), previous transplant, previous malignant disease, and pre-transplant mechanical ventilation or mechanical circulatory support were retrieved from the recipients.

Due to the relatively small sample size of our study, 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 (64). The total score is the sum of donor- and recipient-specific

scores, and this score was used in the multivariable Cox regression analyses for adjustment. (63)"

3.1.3. Outcomes of Study I.

PGD defined as per the 2017 consensus criteria of ISHLT was our primary outcome (65). 2-year mortality was our secondary outcome.

3.2. Methods of Study II.

3.2.1. Study 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. (66)"

3.2.2. Investigated population

"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. (66),,

3.2.3. 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 (67), European System for Cardiac Risk Evaluation (EuroSCORE) II (68), Canadian Cardiovascular Society (CCS) grading (69), preoperative blood test (complete blood count (CBC), renal and liver function, hormone panels) and types of cardiac surgical procedures, were collected (70). In addition, the standard Model for End-Stage Liver Disease (MELD)

score (71) and MELD XI (72) and MELD albumin (73) 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:

MELD = 5.11 x ln(INR) + 3.78 x ln(Total Bilirubin) + 9.57 x ln(Creatinine) + 6.43 (71)

MELD XI = 5.11 x ln(Total Bilirubin) + 11.76 x ln(Creatinine) + 9.44 (72)

MELD albumin = 11.2 x ln(1) + 3.78 x ln(Total Bilirubin) + 9.57 x ln(Creatinine) + 6.43 (Albumin ≥ 4.1 g/dl) (73)

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/min (74). Formulas for calculating IS and VIS are presented below:

IS = dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 x epinephrine dose (μg/kg/min)

VIS = IS + 10 x PDE inhibitor (milrinone or olprinone) dose (μg/kg/min) + 100 x norepinephrine dose (μg/kg/min) + 10000 x vasopressin dose (U/kg/min) (74)

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 (75). 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 (76, 77).
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, for the post-CPB period hemoglobin <8.5 g/dL were defined as institutional trigger criteria (78).

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. (66)"

3.2.4. Outcomes of Study II.

"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. (66)"

3.3. Methods of Study III.

3.3.1. Study design and setting

"This prospective, single-center cohort study was performed on patients who underwent HTx at the Heart and Vascular Center of Semmelweis University, Budapest, Hungary, and provided written informed consent. The present study was approved by the Regional Ethics Committee of Semmelweis University in Budapest [ETT TUKEB 7891/ 2012/EKU (119/PI/12.) and IV/10161-1/2020/EKU]. Written informed consent was obtained from every patient. (79)"

3.3.2. Population and sampling

"Classification of end-stage HF was categorized as per the ACC/AHA guidelines, while functional classification was defined as per the New York Heart Association (NYHA) classification. We included patients between 18 and 80 years who underwent heart transplant at the Heart and Vascular Center of Semmelweis University and the Department of Anesthesiology and Intensive Therapy of Semmelweis University, Budapest, Hungary, between February 2013 and November 2020. Exclusion criteria were pregnancy, exposure to iodine-containing contrast material, lack of written informed consent, and missing relevant data. (79)"

"Oversight of organ donation in Hungary falls under the purview of the National Blood

Transfusion Service. The protocols governing donor management draw upon international standards. The determination of brain death was made by a team of experts in accordance with the accepted medical standards. Following the confirmation of brain death, the National Blood Transfusion Service collaborates with the Eurotransplant International Foundation to orchestrate the subsequent steps crucial for a successful transplant. At the time of the determination of brain death, LT4 was administered as a part of a decision made by a team of experts. One hundred micrograms of LT4 was administered enterally every 24 hours during donor management. Once T4 therapy was initiated, it was administered regularly until explantation. (79)"

3.3.3. Sample collection, RNA isolation, and gene expression

"Well-characterized, deidentified human myocardial tissue samples were obtained from the Transplantation Biobank of the Heart and Vascular Center of Semmelweis University, Budapest, Hungary. The procedure of sample procurement was reviewed and approved by the institutional and national ethics committee (ETT TUKEB 7891/2012/EKU (119/PI/12.) and IV/10161-1/2020/EKU). Informed consent was obtained from each patient in line with the Declaration of Helsinki prior to sample collection. Myocardial left ventricular (LV) samples from end-stage HF patients were collected during HTx from the diseased hearts of the recipients immediately after explantation. (79)"

"Myocardial LV tissue samples (~25 mg) were homogenized in Buffer RLT (Qiagen, Netherlands) using a Bertin Precellys 24 Tissue Homogenizer with a Bertin Cryolys cooling system (Bertin Technologies, France) to ensure adequate and constant cooling (~0 °C) of samples throughout the procedure. Then, total RNA was isolated using an RNeasy Fibrous Tissue Kit (Qiagen) according to the manufacturer's protocol. The RNA concentration was measured photometrically at 260 nm, while RNA purity was ensured by obtaining 260/280 nm and 260/230 nm optical density ratios of ~2.0. Reverse transcription of RNA to complementary cDNA was conducted with a QuantiTect Reverse Transcription Kit (Qiagen) by using 1 μg of RNA from each sample and random primers, as per the protocol. (79)"

"Gene expression of deiodinases was measured from cDNA of heart bioptate samples acquired from Transplantation Biobank of the Heart and Vascular Center of

Semmelweis University, Budapest, Hungary. Briefly, total RNA from the bioptates was isolated with a Qiagen RNeasy Fibrous Tissue Mini Kit (Cat. No. 74704) including repeated steps of DNase treatments during and after the isolation procedure, as instructed. One microgram of total RNA was reverse transcribed with a QuantiTect Rev. Transcription Kit (Cat. No. 205313) according to the manufacturer's instructions. Qubit ssDNA assay kit (Thermo Fisher Scientific Cat. No. Q10212) was used to measure the cDNA content of the samples according to the manufacturer's instructions. This allowed to use the same known amount of cDNA and 10 ng cDNA was used for each reaction. To enhance the detection of deiodinase expression, reactions of Dio2 and Dio3 were assembled with 30 ng of cDNA. Gene expression of Dio2, Dio3, Hcn2 and Myh7 was determined with TaqMan qPCR (Applied Biosystems ViiA 7). PCR efficiency of premade TaqMan assays is 1 by design. Beyond using the same amount of cDNA, Hprt1 expression was also determined as an extra control that was stable with low variability under the study conditions and it was used as a reference gene. Gene expression is given as dCt, one increase in dCt translates as decrease in gene expression by 50 %. (79)"

3.3.4. Outcomes Study III.

"Our primary outcome was long-term mortality, specifically defined as mortality within 2 years. Secondary outcomes included short-term and midterm mortality, assessed at 30 days and 1 year, respectively. Mortality rates were last assessed on June 6, 2023.

Acute allograft rejection after HTx was defined as an adverse event that requires enhanced immunosuppression with an International Society of Heart and Lung Transplantation (ISHLT) grade ≥ 2R endomyocardial biopsy result or hemodynamic compromise with noncellular reactions. (80, 81)

According to institutional protocols, echocardiography and endomyocardial biopsy were performed weekly in the first month after HTx was performed as well as after 3, 6, 9, and 12 months as a part of routine surveillance for allograft function. The decision to implant an MCS device was always made by a team of experts, including a cardiac surgeon, a cardiologist, and a cardiac anesthesiologist, based on international protocols and guidelines. (79)"

3.4. Hormone levels and assays

"Serum concentrations of TSH (normal range [NR]: 0.350-4.940 µIU/mL), free triiodothyronine (fT3) (NR: 2.63-5.70 pmol/L), free thyroxine (fT4) (NR: 9.00-23.20 pmol/L), PRL (NR: male: <330 µIU/mL; nonpregnant female: <500 µIU/mL) and total testosterone (NR: male: 1.8-25.0 ng/mL; female: 1.8-15.0 ng/mL) 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 hours after the first sample was taken. (66)"

"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. (66)"

Normal ranges for serum hormone levels are shown in Table 4.

Table 4. Normal ranges of serum hormone levels

	Low	Normal	High
TSH (µU/mL)	<0.35	0.35-4.94	>4.94
T3 (pmol/L)	<2.63	2.63-5.70	>5.70
T4 (pmol/L)	<9.00	9.00-23.20	>23.20
PRL (µU/mL)			
male	<53.0	53.0-330.0	>330.0
female	<40.0	40.0-500.0	>500.0
TTE (ng/mL)			
male	<1.8	1.8-25.0	>25.0
female	<1.8	1.8-15.0	>15.0

PRL: prolactin, TSH: thyroid stimulating hormone, TTE: testosterone, T3: triiodthyronin, T4: thyroxine

3.5. Statistical analysis

De-identified data were collected and systematized in a final analysis set. Categorical data are presented as numbers (n) and percentages (%). Kolmogorov-Smirnov and

Shapiro-Wilk statistical tests were applied in order to determine the distribution of continuous data. Normally distributed data are presented as means and standard deviations (SD) whereas skewed data with non-normal distribution are presented with as medians and interquartile ranges (IQR 25-75). Chi-square test was used to analysis categorical data while Fisher's exact test was applied in case of the frequency of categorical variables were less, than 5. Mann-Whitney U test was used to compare continuous data between two independent groups. Paired sample t-test was performed to analyze the connection between preoperative and postoperative hormonal values. Univariate Cox regression analysis was performed to explore primary cofactors of mortality. Univariate Cox regression tests with a significance level of $p < 0.20$ were involved in the multivariate Cox regression model. To conduct multivariate Cox model backward elimination and enter method were used to adjust the model for further variables. Kaplan-Meier analysis completed with Mantel-Cox log-rank test was applied to compare survival distributions. Kaplan-Meier survival curves with patients at risk numbers are presented as visual interpretations. Follow-up time was determined from the day of the operation till decease or the last query. Linear regression analysis was performed to uncover possible predictors that are in connection with hormonal values. F test and cubic spline interpolation was used to explore the linearity of continuous data. None of the values were deviated from linearity therefore linear forms were presented for all variables. Enter mode was used during conducting linear regression and results are presented as beta and R^2 (correlation coefficient). Logistic regression analysis was applied to assess possible cofactors of endpoints. Univariate logistic regression with a significance level of $p < 0.05$ entered the multivariate logistic regression where further adjustment was performed. C-index (receiver operating characteristic curve) was evaluated to assess appropriateness of inclusion. Hosmer-Lemeshow goodness-of-fit test was calculated for the final model. R_2 using the Nagelkerke method was calculated also for logistic regression and Cox models to quantify the variation accountable to the investigated parameters. To account for multiple testing, the Bonferroni method was applied to adjust the p value. Confidence intervals (CI) were 95% for all tests. All statistical tests were two-sided and significance level of $p < 0.05$ was considered statistically significant. IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp were applied to perform all statistical tests and

analyses. Figures and visual presentations of statistical results were carried out using GraphPad Prism version 8.0.1 for Windows, GraphPad Software, Boston, Massachusetts USA.

4. Results

4.1. Results of Study I.

4.1.1. Demographic data and baseline characteristics

"A total of 303 brain-dead donors were considered for inclusion. Of these, 297 were included in the final analyses. The median follow-up time was 1475 days (IQR25-75: 952-1983 days), and the median survival time was 1076 days (IQR25-75: 543-1768 days). Of the 297 donor hearts, 226 (76.1%) were transplanted in Hungary, the rest were obtained from other member countries of Eurotransplant. (63)"

"The median age of the donors was 41 years, and of those, 26.3% (n=78) were female. The median age of the recipients was 54 years, and of those, 25.9% (n=77) were female. The basic characteristics of donors, recipients and transplants are listed in Table 5. Donor hearts from patients who developed PGD had a significantly higher total ischaemic time. Hearts from donors who developed CDI during the period of donor treatment were more likely to have PGD after HTx. In contrast, treatment with methylprednisolone (n=61, 25.3%) and thyroxine (n= 92, 92.9%) was more frequent in donors in cases without PGD. Patients with developed PGD were more likely to have a higher recipient UNOS score and more likely to receive a heart from a donor with a higher UNOS score. For the other aspects measured, there were no significant differences between patients with and without PGD. PGD was more common in recipients who received a graft from a donor with diabetes mellitus (without PGD n=18, 7.5% vs with PGD n=9, 16.1%; p=0.044) (63)."

Table 5. Donors and recipients' characteristics

	Without PGD (n=241)		**With PGD (n=56)**		**p**
	n	**%**	**n**	**%**	
	median	**(IQR 25-75)**	**median**	**(IQR 25-75)**	
Donor characteristics					
Age (years)	41.0	(33.0-49.0)	40.0	(26.3-50.3)	0.552
BMI	26.1	(23.6-27.8)	26.3	(24.3-30.7)	0.122
UNOS risk group					<0.001
low risk (0)	133	55.2	18	32.1	
intermediate risk (1,2)	84	34.9	22	39.3	
high risk (>2)	24	10.0	16	28.6	
Cause of brain death					0.241
subarachnoid haemorrhage	56	23.2	18	32.1	
intracerebral haemorrhage	67	27.8	8	14.3	
epidural or subdural haemorrhage	31	12.9	6	10.7	
trauma	56	23.2	15	26.8	
hypoxia	31	12.9	9	16.1	
Cardiac arrest during donor care	34	14.1	9	16.1	0.707
Total duration of donor care (h)	73	(41-121)	67	(43-115)	0.619
Simultaneous donor treatment					
norepinephrine	202	83.8	49	87.5	0.493

norepinephrine dose (μg/kg/min)	0.08	(0.04-0.14)	0.07	(0.03-0.10)	0.109
desmopressin	158	65.6	33	58.9	0.351
vasopressin	21	8.7	2	3.6	0.271
methylprednisolone	61	25.3	6	10.7	0.019
cortisol	61	25.3	13	23.2	0.744
thyroxine	92	38.2	7	12.5	<0.001
Laboratory values					
sodium (mmol/L)	149.0	(144.0-154.5)	149.5	(145.0-154.0)	0.861
potassium (mmol/L)	4.10	(3.79-4.30)	4.01	(3.71-4.40)	0.788
glucose (mmol/L)	7.74	(6.35-9.40)	8.00	(6.83-8.98)	0.948
BUN (mmol/L)	4.50	(2.95-6.25)	4.50	(2.93-5.50)	0.749
expected serum osmolality (mOsm/kg)	320.9	(310.0-331.3)	320.3	(311.4-328.7)	0.685
urine output (ml/kg/h)	2.40	(1.48-4.04)	2.59	(1.43-4.22)	0.662
Central diabetes insipidus	45	18.7	18	32.1	0.026
Ejection fraction (%)	60	(58-66)	61	(60-68)	0.341
IVSd (mm)	11	(9-12)	10	(9-12)	0.313
Transplant characteristics					
Gender mismatch	40	16.6	7	12.5	0.449
Total ischemic time (min)	190.0	(155.5-225.0)	249.5	(206.5-266.8)	<0.001
Recipient characteristics					
Age (years)	53.0	(44.0-59.0)	55.0	(47.5-59.0)	0.265
UNOS risk group					0.012

very low risk (0)	58	24.1	7	12.5	
low risk (1)	70	29.0	11	19.6	
intermediate risk (2)	50	20.7	10	17.9	
high risk (3, 4)	47	19.5	21	37.5	
very high risk (>4)	16	6.6	7	12.5	
Preoperative thyroxine treatment	30	12.8	9	16.1	0.470

PGD: primary graft dysfunction; IQR 25-75: interquartile range 25-75; BMI: body mass index; UNOS: United Network for Organ Sharing; BUN: blood urea nitrogen; IVSd: interventricular septum thickness at the end-diastole.

4.1.2. Outcome data

"PGD appeared in 56 patients (18.9%), of whom 43 (76.8% of the PGD cases) required MCS treatment. Of the patients with PGD, 29 (51.8%) died in the first 30 postoperative days, and a further 8 patients died in the first two years after HTx. The 30-day and 2-year mortality rates were 10.8% (n=32) and 21.5% (n=64), respectively. During a median follow-up of more than 49 months, 77 (25.9%) patients died. (63)"

4.1.3. Associations regarding donor management

"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. (63)"

"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. (63)"

"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. (63)"

Results are presented in Table 6 and Table 7.

Table 6. Univariate and multivariate Cox regression analysis

	Univariate PGD (n=56)	**Multivariate**
	OR (95% CI); p	**OR (95% CI); p**
desmopressin	0.77 (0.46-1.33); 0.354	
vasopressin	0.47 (0.11-1.93); 0.293	
vasopressin and desmopressin	0.72 (0.42-1.23); 0.231	
methylprednisolone	0.43 (0.19-1.01); 0.052	0.38 (0.16-0.90); 0.027
cortisol	1.06 (0.54-1.87); 0.985	
thyroxine	0.34 (0.15-0.76); 0.009	0.38 (0.17-0.86); 0.020
central diabetes insipidus	1.67 (0.95-2.93); 0.073	
thyroxine and methylprednisolone	0.09 (0.01-0.68); 0.019	0.10 (0.01-0.73); 0.023

PGD: primary graft failure; OR: odds ratio; 95% CI: 95% confidence interval. Table was adapted without modifications from: Nagy Á, Szécsi B et al. Transplantation Proceedings 2021

Table 7. Univariate and multivariate Cox regression analysis

	Univariate 2-year mortality (n=64)	**Multivariate**
	OR (95% CI); p	**OR (95% CI); p**
desmopressin	0.98 (0.59-1.63); 0.924	
vasopressin	0.76 (0.28-2.10); 0.598	
vasopressin and desmopressin	0.88 (0.52-1.47); 0.615	
methylprednisolone	0.70 (0.36-1.33); 0.272	
cortisol	0.76 (0.41-1.40); 0.376	
thyroxine	0.52 (0.29-0.94); 0.030	0.53 (0.29-0.96); 0.036
central diabetes insipidus	1.16 (0.65-2.06); 0.622	
thyroxine and methylprednisolone	0.53 (0.24-1.17); 0.114	

OR: odds ratio; 95% CI: 95% confidence interval. Table was adapted without modifications from: Nagy Á, Szécsi B et al. Transplantation Proceedings 2021

"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. (63)"

Results are shown in Figure 2.

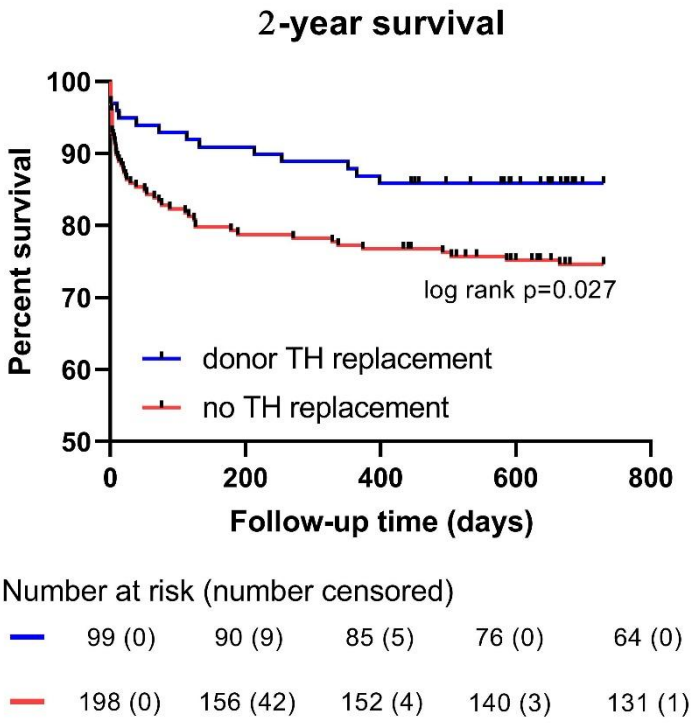

Figure 2. Kaplan–Meier curves comparing the 2-year survival of recipients with a heart from a thyroxine-treated donor or not from a thyroxine-treated donor. Figure was adapted without modifications from: Nagy Á, Szécsi B et al. Transplantation Proceedings 2021

4.2. Results of Study II.

4.2.1. 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. (66)"

Results are presented in Table 8.

Table 8. 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 Gender - female	40 9	81.6 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 hour*		
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)	141.0	130.5-149.0	108.0	96.5-113.0	<0.001
WBC (G/l)	7.2	5.7-8.8	11.5	9.1-13.8	<0.001
Thrombocyte (G/l)	210.0	181.5-250.0	153.0	125.0-196.0	<0.001
Lymphocyte (G/l)	1.72	1.35-2.24	0.7	0.6-	<0.001

				0.85	
GFR (ml/min)	81.6	63.6-88.2	76.9	59.4-94.5	0.756
Creatinine (μmol/l)	87.0	73.0-101.5	87.0	73.0-106.5	0.816
BUN (mmol/l)	6.3	5.4-7.8	5.4	4.5-6.3	0.001
Sodium (mmol/l)	140.0	137.0-141.0	138.0	136.0-140.0	0.021
Potassium (mmol/l)	4.4	4.0-4.7	4.4	4.3-4.8	0.058
Total protein (g/l)	68.4	64.7-71.5	48.0	45.3-50.6	<0.001
Albumin (g/l)	45.5	43.1-48.2	31.7	30.2-33.3	<0.001
Total bilirubin (μmol/l)	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)	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			
Peripheral vascular disease	5	10.2			
Arthritis	10	20.4			

AV: 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. Table was adapted without modifications from: Szécsi B et al. Physiology International 2023

4.2.2. Perioperative data

"MV was required during all surgeries. The median CPB time was 180 minutes (IQR 25-75: 170-210 minutes), and the median aorta cross-clamp was 58 minutes (IQR 25-75: 0-73.5 minutes). 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 hours (IQR 25-75: 0-14.5 hours) and 23 hours (IQR 25-75: 10.6-52 hours), respectively. Seven patients (14.3%) spent more than 72 hours in the ICU, and 4 patients (8.2%) needed more than 24 hours on a MV device. Five patients (10.2%) died in the first postoperative year. The most 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. (66)"

Results are presented in Table 9.

Table 9. Intra- and postoperative data

	N **Median**	**%** **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)	3572	2824-4350
Fluid output (ml)	2000	1455-2422
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 was adapted without modifications from: Szécsi B et al. Physiology International 2023

4.2.3. Perioperative hormonal changes

"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]) (Figure 3). (66)"

Total testosterone levels decreased significantly in men within the first 24 hours after surgery (from mean 4.17 ng/mL [SD±1.57] to mean 1.73 ng/mL [SD±1.35] [p<0.001]); however, this was not observed in women (from mean 1.00 ng/mL [SD±2.32] to mean 0.85 ng/mL [SD±1.49] [p=0.618]). (66)

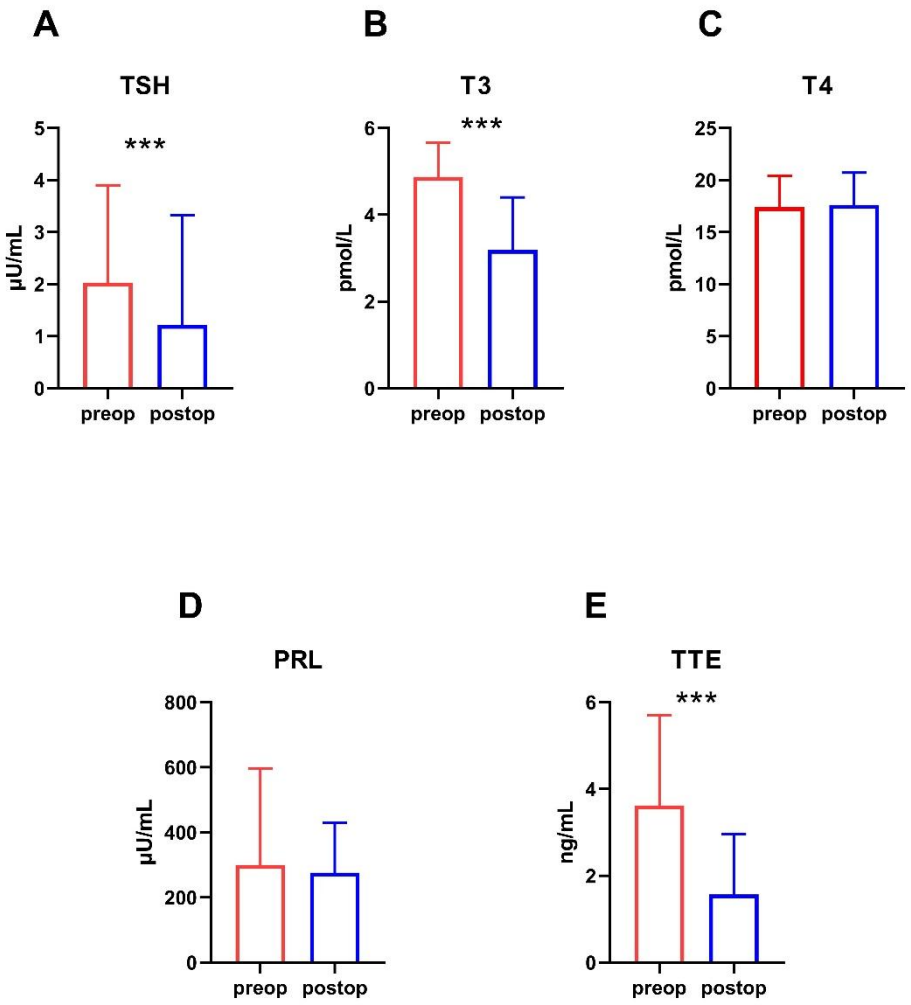

Figure 3. Comparison between preoperative and postoperative hormone levels. TSH: thyroid stimulating hormone, fT3: free triiodothyronine, fT4: free thyroxine, PRL: prolactin, TTE: testosterone, preop: preoperative, postop: postoperative, ***: $p < 0.001$. Figure was adapted without modifications from: Szécsi B et al. Physiology International 2023

4.2.4. Cofactors of thyroid hormones

"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 10). (66)"

Table 10. The results of univariate and multivariate regression analysis of postoperative thyroid parameters

		Univariate linear regression			Multivariate linear regression		
Dependent variable	**Independent variable**	**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. Table was adapted without modifications from: Szécsi B et al. Physiology International 2023

"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). (66)"

Results are sown in Table 11.

Table 11. Uni and multivariable results for MELD scores and pre/postoperative hormonal values

		Univariable linear regression			Multivariable linear regression		
Dependent variable	**Independent variable**	**Beta**	**CI (95%)**	**p value**	**Beta**	**CI (95%)**	**p value**
TSH pre	MELD albumin	-0.199	(-0.383) - (-0.015)	0.036			
	MELD	0.176	0.002-0.351	0.048			
fT4 pre	MELD XI	0.434	0.030-0.837	0.036			
	EuroSCORE	0.370	0.170-0.570	0.001			
fT4 post	EuroSCORE	0.322	0.103-0.540	0.005			
	MELD albumin	0.634	0.127-1.140	0.016	0.656	0.174-1.138	0.010
testosterone pre	MELD	0.301	(-0.001) - 0.603	0.050			
	MELD XI	0.320	0.033-0.606	0.030			

R^2 adj. for fT4 post = 0.247 including age, gender, EuroSCORE, fluid balance and operation time; R^2 adj. for fT4 post = 0.340 including MELD albumin score, 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. Table was adapted without modifications from: Szécsi B et al. Physiology International 2023

4.3. Results of Study III.

4.3.1. Demographic data and baseline characteristics

"A total of 387 patients' data were evaluated for eligibility for the present study and 283 were included in the final analysis. A total of 104 patients were excluded due to missing thyroid values. (79)"

"The recipients' median age was 54 years [interquartile range (IQR) 25–75: 45–59 years], and 71 female patients (25.1%) were included. The donors' median age was 42 years (IQR 25–75: 32–50 years), of whom 70 were female (24.7%). Dilated cardiomyopathy (n = 187, 66.1%) and ischemic-dilated cardiomyopathy (n = 61, 21.6%) were the most common indications for HTx. The median follow-up time was 57.6 months (IQR 25–75: 29.5–81.7 months). The median Index for Mortality Prediction After Cardiac Transplantation (IMPACT) score was 4 (IQR 25–75: 2–10). (79)"

"Thirty-five patients (12.4%) were diagnosed with overt hypothyroidism, while 6 patients (2.1%) were diagnosed with subclinical hypothyroidism, and 19 patients (6.7%) were diagnosed with hyperthyroidism before HTx. Of the donors, 107 patients (37.8%) were given LT4 replacement during donor management. Thirty-two recipients (11.3%) took LT4 supplementation preoperatively, whereas 55 patients (19.4%) received LT4 replacement postoperatively. Seventy-eight patients (27.6%) were on amiodarone treatment. (79)"

4.3.2. Changes in TH levels

"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). (79)"

These results are shown in Table 12.

Table 12. Thyroid-related characteristics of patients

Variables	n/N median	% IQR 25-75	p
Hypothyroidism	41/283	14.5	
Hyperthyroidism	19/283	6.7	
Levothyroxine replacement preop (donor)	107/283	37.8	
Levothyroxine replacement preop (recipient)	32/283	11.3	
Levothyroxine replacement postop	55/283	19.4	
Amiodarone treatment	78/283	27.6	
TSH preop (μU/ml)	1.45	0.80-3.81	0.009
TSH postop (μU/ml)	1.30	0.39-2.92	
fT3 preop (pmol/l)	3.12	2.49-3.79	<0.001
fT3 postop (pmol/l)	2.38	2.03-2.98	
fT4 preop (pmol/l)	14.14	11.63-15.96	<0.001
fT4 postop (pmol/l)	11.81	10.81-14.11	

fT3, free triiodothyronine; fT4, free thyroxine; IQR, interquartile range; postop, postoperative; preop, preoperative; TSH, thyrotropin. Table was adapted without modifications from: Szécsi B et al. Thyroid 2024

"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). (79)"

4.3.3. Thyroid function and mortality

"During the postoperative period of HTx, 42 patients (14.8%, n/n = 42/283) died within 30 days, 64 patients (22.6%, n/n = 64/283) died within 1 year, and 67 patients (23.7%,

n/n = 67/283) died within 2 years. Kaplan–Meier curves show better survival with LT4 treatment in 30 days and in 2 years' time, as shown in Figure 4. (79)"

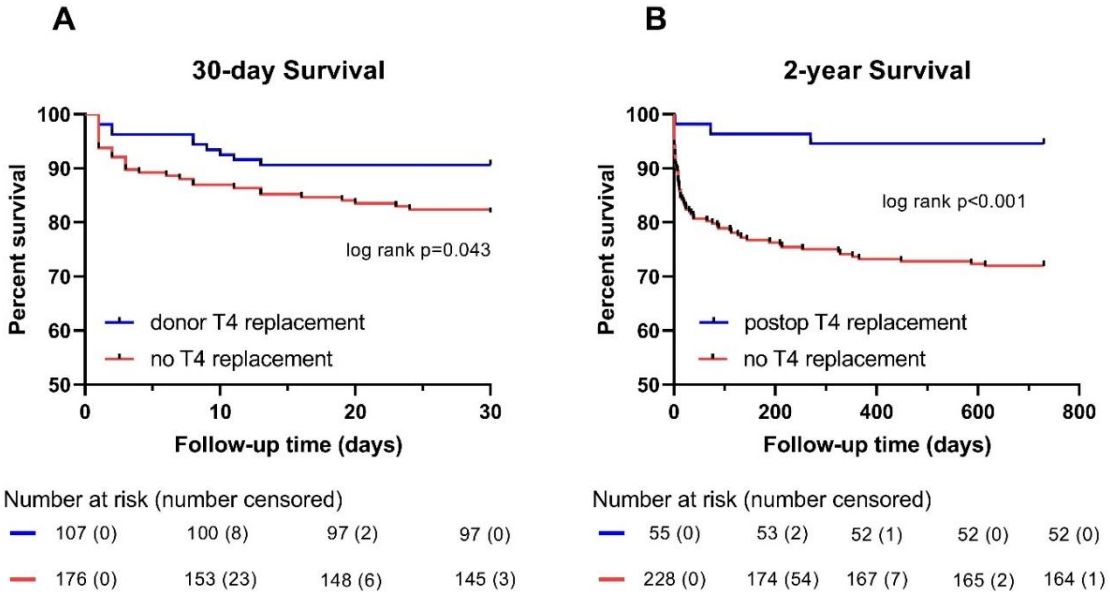

Figure 4. Kaplan–Meier curves for 30-day (A) and 2-year (B) survival between donor/recipient thyroxine replacement and no thyroxine replacement in the perioperative period heart transplantation. postop: postoperative, T4: levothyroxine. Figure was adapted without modifications from: Szécsi B et al. Thyroid 2024

"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). (79)"

Results are shown in Table 13 and Figure 5.

Table 13. Univariate Analyses and a Multivariable Cox Regression Model Examining Associations with 2-Year Mortality After Heart Transplantation

Variables	Univariate Analyses			Multivariable Model		
	Hazard Ratio	**95% CI**	**p**	**Hazard Ratio**	**95% CI**	**p**
IMPACT score	1.124	1.09-1.16	<0.001	1.130	1.10-1.16	<0.001
Hypothyroidism	0.558	0.24-1.29	0.173	2.051	0.77-5.46	0.150
Hyperthyroidism	1.174	0.47-2.92	0.730			
Levothyroxine replacement preoperatively (donor)	0.603	0.36-1.03	0.062	0.736	0.43-1.26	0.263
Levothyroxine replacement preoperatively (recipient)	0.619	0.25-1.54	0.302			
Levothyroxine replacement postoperatively	0.170	0.05-0.54	0.003	0.100	0.03-0.39	0.001
Amiodarone treatment	1.622	0.99-2.66	0.056	1.665	0.99-2.74	0.054
Dio2	0.986	0.86-1.14	0.848			
Dio3	1.003	0.92-1.10	0.952			

A total of 275 patients were included in the multivariable analysis, Harrell's C- index = 0.83, Nagelkerke R_2 = 0.39. CI, confidence interval; Dio2, type 2 deiodinase mRNA; Dio3, type 3 deiodinase mRNA; IMPACT, Index for mortality prediction after cardiac transplantation. Table was adapted without modifications from: Szécsi B et al. Thyroid 2024

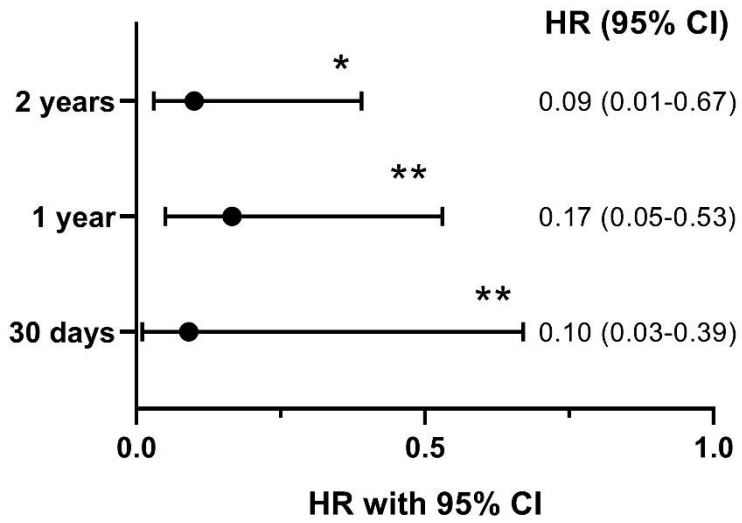

Figure 5. The association of postoperatively administered thyroxine and mortality assessed in multivariable Cox regression models at different time points. CI: confidence interval, HR: hazard ratio, *: $p < 0.02$, **: $p < 0.002$. Figure was adapted without modifications from: Szécsi B et al. Thyroid 2024

4.3.4. Thyroid function and MCS

"Preoperatively, 68 patients (24.0%) required extracorporeal membrane oxygenation (ECMO), 49 patients (17.3%) were treated with left ventricular assist device (LVAD), 41 patients (14.5%) required right ventricular assist device (RVAD), and 21 patients (7.4%) were treated with biventricular assist device (BiVAD) as a part of bridge to transplant solution. Furthermore, 69 patients (24.4%) required ECMO postoperatively. DIO2 and DIO3 expression levels were analyzed among the patients who required any type of MCS. (79)"

Results are shown in Figure 6.

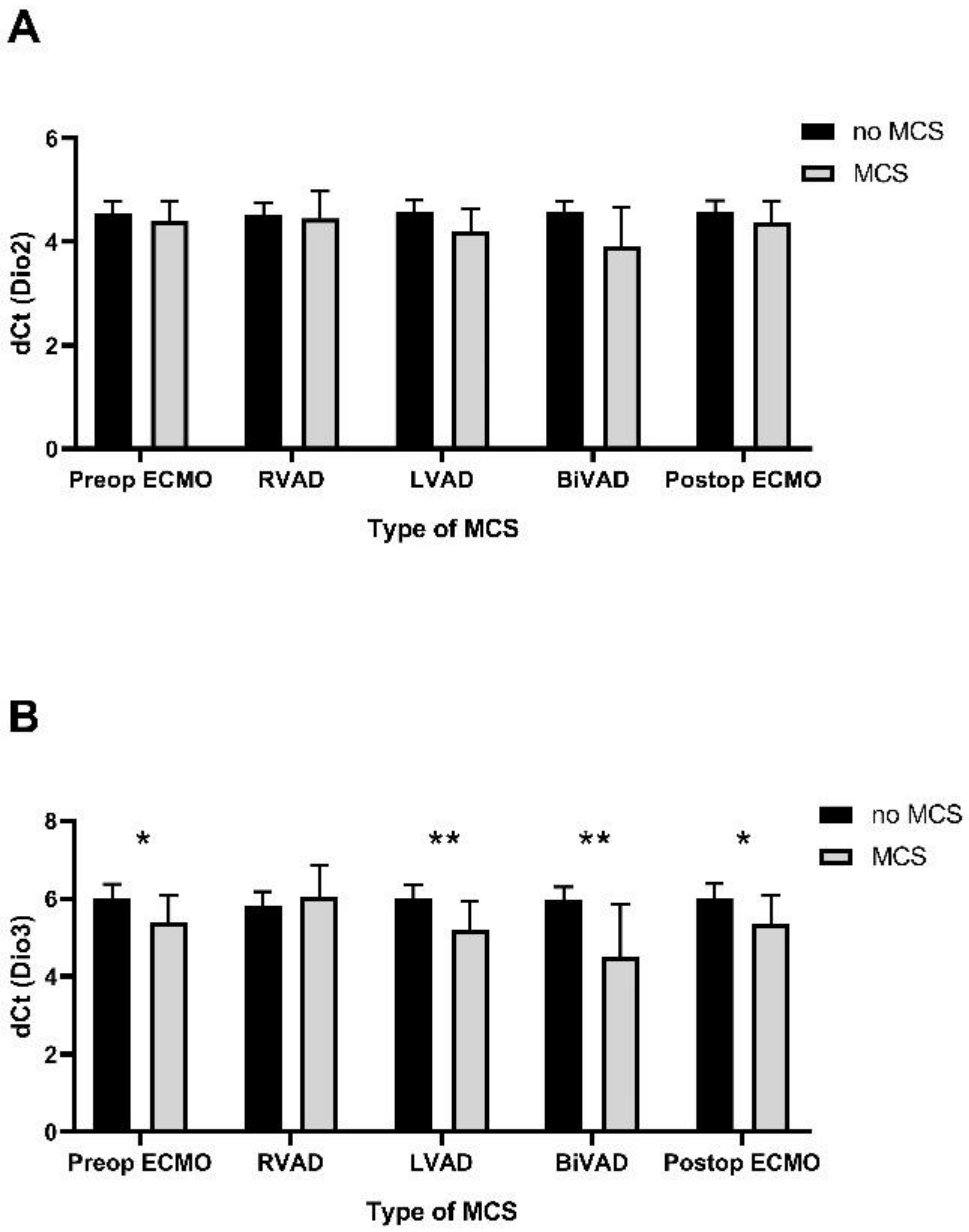

Figure 6. Deiodinase enzyme type 2 (A) and deiodinase enzyme type 3 (B) mRNA levels according to type of MCS received. BiVAD: biventricular assist device, dCt: delta cycle threshold, Dio2: type 2 deiodinase mRNA, Dio3: type 3 deiodinase mRNA, ECMO: extracorporeal membrane oxygenation, LVAD: left ventricular assist device, MCS: mechanical circulatory support, postop: postoperative, preop: preoperative, RVAD: right ventricular assist device; *: $p < 0.05$, **: $p < 0.015$. Figures show mean with confidence interval. Gene expression is given as dCt, one increase in dCt translates

as decrease in gene expression by 50%. Figure was adapted without modifications from: Szécsi B et al. Thyroid 2024

"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). 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). (79)"

Results are shown in Table 14 and Figure 7.

Table 14. Pearson correlation between *Hcn2* and *Myh7* vs. serum thyroid parameters

Variables	Hcn2		Myh7	
	R^2	p	R^2	p
TSH preop	0.028	0.421	0.239	0.162
TSH postop	0.112	0.220	0.052	0.360
fT3 preop	0.174	0.232	0.195	0.206
fT3 postop	0.082	0.294	0.068	0.316
fT4 preop	0.074	0.379	0.095	0.346
fT4 postop	0.027	0.428	0.234	0.053

fT3: free triiodothyronine, fT4: free thyroxine, *Hcn2*: hyperpolarization activated cyclic nucleotide gated potassium channel 2, *Myh7:* myosin heavy chain 7, R^2: correlation coefficient, TSH: thyroid-stimulating hormone. Table was adapted without modifications from: Szécsi B et al. Thyroid 2024

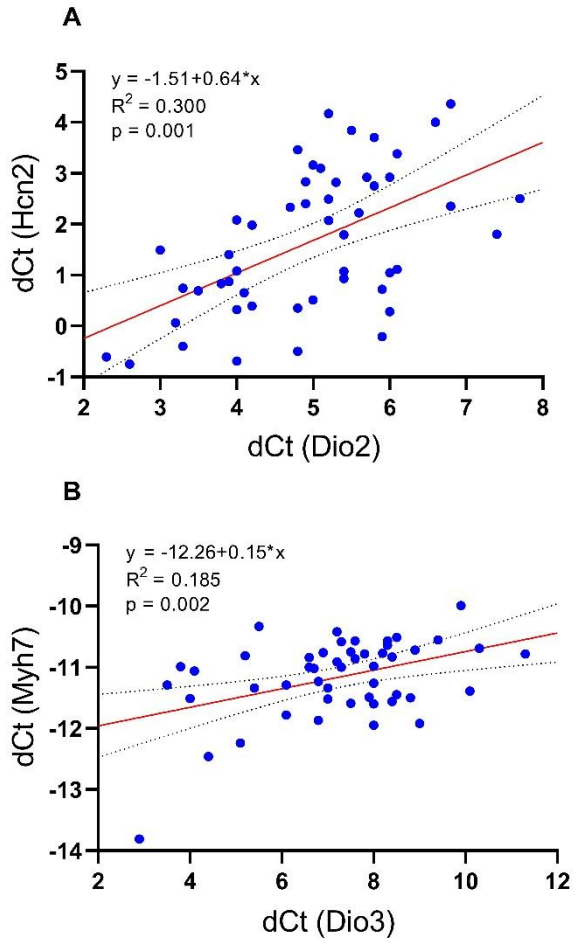

Figure 7. Pearson correlation between *Hcn2 vs. Dio2* and between *Myh7 vs. Dio3.* dCt: delta cycle threshold, *Dio2*: type 2 deiodinase mRNA, *Dio3*: type 3 deiodinase mRNA, *Hcn2*: hyperpolarization activated cyclic nucleotide gated potassium channel 2, *Myh7:* myosin heavy chain 7 Gene expression is reported as dCt, one increase in dCt translates as decrease in gene expression by 50 %. Figure was adapted without modifications from: Szécsi B et al. Thyroid 2024

4.3.5. Thyroid function and graft survival

'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). (79)"

Results are shown in Table 15.

Table 15. Multivariable Logistic Regression Model Examining Potential Associations with Possible 30-Day Acute Allograft Rejection (ISHLT Grade ≥ 2R) After Heart Transplantation

Variables	Odds Ratio	95% Confidence Interval		p
		lower	upper	
age	0.987	0.952	1.023	0.476
female sex	1.003	0.729	1.381	0.985
Levothyroxine replacement preop (donor)	1.002	0.426	2.356	0.997
Levothyroxine replacement preoperatively (recipient)	1.302	0.199	8.522	0.783
Levothyroxine replacement postoperatively	0.725	0.162	3.251	0.675
Dio2	0.668	0.517	0.862	0.002

A total of 271 patients were included in the multivariable analysis, Harrell's C- index = 0.69, Nagelkerke R_2 = 0.21. Dio2, type 2 deiodinase mRNA; ISHLT, International Society for Heart and Lung Transplantation. Table was adapted without modifications from: Szécsi B et al. Thyroid 2024

5. Discussion

Our results underline the importance of hormonal imbalances in the perioperative period of cardiac surgical procedures. Although the estimation of hormonal effects on postoperative outcomes is highly controversial, we found that thyroid hormones, in particular, play a significant role in adverse events following cardiac surgical procedures.

Our findings underscore the significance of thyroxine treatment in enhancing both short- and long-term outcomes while reducing the incidence of PGD. Methylprednisolone supplementation similarly shows a correlation with a reduced PGD risk, and the combination of thyroxine and methylprednisolone independently decreases the likelihood of PGD. Notably, thyroxine supplementation does not increase the need for inotropic support, MCS, rejection, or retransplantation. Treatments involving desmopressin and vasopressin are not linked to PGD onset or survival outcomes, and no association is found between CDI-related antidiuretic hormone deficiency and PGD or mortality.

Multiple studies have highlighted decreased serum levels of anterior pituitary hormones, such as cortisol and thyroid hormones, in brain-dead organ donors (82, 83). The efficacy of HRT remains a contentious topic, with studies often focusing on donor organ procurement and recipient survival. Plurad et al.'s retrospective analysis of 10,431 potential donors from the Organ Procurement and Transplantation Network found that vasopressin supplementation is independently associated with higher organ recovery rates (84). Pinsard et al.'s CORTICOME study, involving 259 patients (80% heart donors), indicated that low-dose glucocorticoid administration significantly reduced vasopressor use without improving graft function (85). Novitzky et al. reported that thyroid hormone supplementation increased the number of organs available for transplantation without adversely affecting post-transplant survival (86). Mi et al.'s multiple comparison modeling identified the optimal HRT combination as thyroid hormone, glucocorticoid, insulin, and vasopressin (87). Sorabella et al. found no improvement in 1-year survival with donor thyroxine treatment in their UNOS registry analysis of 15,428 individuals (88). Dhar et al. noted no significant cardiac recovery improvement with thyroxine treatment in their single-center randomized controlled trial (89). Rosendale et al.'s retrospective analysis of 4,543 organ donors showed improved

short-term graft function with HRT, including thyroid hormone, glucocorticoid, and vasopressin (90). However, a double-blind, randomized controlled trial revealed no improved hemodynamics in donors receiving any HRT (91). Our results suggest that thyroxine and methylprednisolone treatment in donors reduces PGD risk without affecting survival, potentially due to altered deiodinase enzyme activity.

Corticosteroid and thyroid hormone replacement are generally recommended only in specific cases, such as impaired hemodynamics, and not routinely for potential organ donors. Recipient outcomes did not significantly differ regarding CDI between thyroxine-treated and non-thyroxine-treated donors in our patient group. Most studies and guidelines support vasopressin supplementation for CDI (62, 92). Diabetes insipidus, associated with severe dehydration, hypernatremia, and polyuria, leads to hemodynamic instability. However, our hypothesis that severe CDI could indicate thyroxine or cortisol deficiency was not supported by our data. CDI management has been aggressive over the past decade, as emphasized in guidelines (62).

We found that TSH, T3, and testosterone levels significantly decreased within 24 hours post-cardiac surgery involving CPB. Prolonged inotropic support and extended MV were linked to notably lower postoperative T4 levels. Postoperative T3 levels inversely correlated with longer ICU stays, extended MV, and higher VIS. Both preoperative and postoperative testosterone levels, but not their changes, independently correlated with higher MELD scores. Postoperative testosterone levels and Δtestosterone were connected to ICU stays exceeding 72 hours. Additionally, ΔT4 independently associated with 1-year mortality post-cardiac procedures.

Reductions in serum T3 levels, with stable T4 and slightly elevated or normal TSH levels, indicate NTIS, which might be induced by a CPB-related stress response (93, 94). NTIS is linked to multi-organ failure in critically ill patients, though the exact pathophysiological mechanism remains unclear; proinflammatory cytokines and oxidative stress may disrupt deiodinase enzyme function (61, 95, 96). Advances in surgical techniques and intensive care have led to less altered thyroid values in our population compared to classical NTIS, though the trend remained. Our findings suggest that NTIS can occur early after heart surgery, associated with extended ICU stays, prolonged MV, and higher VIS scores.

PRL's hypertensive effects through a positive chronotropic effect were demonstrated in an animal study [11].

PRL is implicated in peripartum cardiomyopathy and often increases during stress-induced neuroendocrine responses, while CPB-induced systemic inflammatory response can enhance proinflammatory processes (97-99). Despite advancements, PRL was not identified as a stress hormone in our population. We found an association between PRL and 1-year mortality, though analysis lacked power.

Serum testosterone levels, influenced by androgen receptors in cardiac myocytes, may be linked to coronary heart disease (100). Higher MELD scores correlate with serum testosterone and dihydrotestosterone levels in cirrhotic patients (101). We found a correlation between MELD score and preoperative testosterone within normal ranges. Though low serum testosterone is linked to higher cardiovascular event risk, testosterone replacement therapy remains debated (102). Optimal postoperative testosterone dosage is unclear, as levels outside the normal range may increase cardiovascular risks (103). The reduction in serum albumin may contribute to the observed changes in total testosterone. Male patients exhibit a rapid decrease in serum testosterone post-cardiothoracic surgery, a phenomenon not seen in females (104). Our findings confirmed a more pronounced decline in male patients.

The MELD score, originally designed to predict survival in patients undergoing elective surgery for portal hypertension, has been examined in cardiac surgery contexts, with MELD XI associated with poor outcomes in heart transplant patients, and the MELD albumin score potentially improving risk stratification for all-cause mortality in acute heart failure patients (73, 105, 106). Standard MELD scores correlated with normal-range thyroid hormone levels. TSH, T3, T4, and the fT3/fT4 ratio were significantly inversely related to MELD score. Our findings showed that thyroid hormone levels correlated with both standard and modified MELD scores within normal ranges.

Plasma dilution from CPB is well-known and linked to postoperative morbidity and increased transfusion needs, with low levels of coagulation factors, hemoglobin, and plasma proteins commonly observed post-CPB due to fluid shifts (107). Reduced thyroid hormone levels were reported 24 hours post-CPB (108). These hemodynamic and homeostatic changes contribute to decreased hemoglobin and albumin levels.

We extensively analyzed the relationship between thyroid status and survival, along with other potential adverse outcomes. We observed significant reductions in serum TSH, fT3, and fT4 levels during HTx compared to preoperative values as well. Donor levothyroxine replacement was linked to improved 30-day survival, and in recipients, it was associated with better survival at 1- and 2-years post-HTx. To explore local TH activity, we measured mRNA expression of two key TH metabolizing enzymes, Dio2 and Dio3, to understand the heart's strategy for TH activation (D2) and inactivation (D3) pre- and post-operation. Dio2 levels were not linked to MCS device usage, but Dio3 mRNA significantly increased in patients treated with LVAD, BiVAD, and ECMO, pre- and postoperatively, compared to those without MCS. In addition, Dio2 expression was found to be independently associated with acute allograft rejection after HTx.

The influence of hypoxia on Dio3 expression in relevant cells has been documented (109). Dio3 is positively regulated by T3, serving as a crucial regulator of intracellular T3, thus affecting local TH action (110). Hypoxia upregulates Dio3 through a hypoxia-inducible factor (HIF)-dependent pathway (111). Increases in D3 activity and mRNA levels in response to hypoxia suggest Dio3 as a direct transcriptional target of HIF-1 (111, 112). Endogenous D3 activity reduces T3-dependent oxygen consumption in neuronal and hepatocyte cell lines, indicating hypoxia-induced D3 might help lower metabolic rates in hypoxic tissues (111) [27].

We hypothesized that local hypoxia in certain patients necessitated MCS despite compensatory mechanisms reducing T3 availability. Higher Dio3 expression, and consequently lower TH availability, might indicate severe HF, affecting recovery and subsequent circulatory support. To explore this hypothesis, we assessed local TH action in a subsample of participants. Hcn2, positively regulated by TH, and Myh7, negatively regulated, showed weak linear correlation with Dio3 (113). However, no evidence suggested that MCS affected these markers' expression. Additionally, the markers showed no correlation with serum parameters or each other, suggesting either poor reflection of circulating TH levels or less representative cardiac TH action. It is important to note that endogenous markers are regulated not only by TH but also by various other mechanisms, including medications; therefore, conclusions drawn from these markers should be made with caution (114-116). Despite this, changes in Dio3

expression likely reflect an attenuated effect on cardiac TH action, with the heart possibly maintaining stable local T3 availability as a compensatory mechanism for NTIS.

Interestingly, Dio2 expression was independently associated with acute allograft rejection post-HTx, suggesting enhanced cardiac TH activation and increased local T3 availability. However, it is puzzling how increased T3 availability in NTIS patients could be detrimental. Such a conclusion is challenging to make based on mRNA levels alone, as D2 enzyme activity is robustly regulated posttranslationally (110). Although weak linear correlation was found between Hcn2 and Dio2 expression, we cannot exclude the possibility that the observed increase in Dio2 expression translates partially into actual T3 generation.

Extended NTIS may trigger various tissue-specific adaptations, involving enhanced D2-mediated TH activation and suppressed D3-mediated inactivation (117). Recent studies show that central and peripheral deiodination and consequent tissue TH action can vary among different NTIS forms in mice (94, 118). These aspects of NTIS underscore the importance of measuring local TH action tissue-specifically.

Our results offer new insights into the tissue-specific characteristics of cardiac TH economy post-HTx, a perspective previously lacking in human studies. Levothyroxine replacement therapy, crucial for managing hemodynamically unstable potential organ donors, revitalizes suboptimal donor hearts, enhances recipient myocardial aerobic metabolism, reduces the need for inotropic and vasopressor agents, and prevents cardiovascular collapse (119, 120). Further studies revealed that levothyroxine replacement post-brain death might increase organ procurement rates and salvage potentially transplantable organs (95). Administering levothyroxine before declaring brain death in potential donors has also been considered (121). A recent study involving over 23,000 heart transplant recipients, using the ISHLT registry, highlighted an independent association between donor T4 administration and increased early graft loss risk, defined as death or retransplantation (122). Another study by the same author noted that donor T4 therapy negatively impacts primary graft dysfunction via the withdrawal effect (123). A recent multicenter trial found no benefit in intravenously administered T4 for hemodynamically unstable heart donors concerning the number of hearts transplanted. However, the T4 group had more cases of tachycardia and severe

hypertension, possibly linked to the higher T4 dose in their protocol. Yet, 30-day graft survival was slightly higher in the T4 group than the saline group, aligning with our results (124). Reliable data on recipient TH usage are still missing; however, a retrospective study highlighted the association between decreased mortality and levothyroxine replacement therapy for both donors and recipients (125). A recent rodent study showed that hypothyroidism before a cardiac event and hyperthyroidism afterward might be optimal conditions (126). The benefits or harms of levothyroxine replacement therapy in the perioperative period of HTx remain debatable, necessitating further studies for conclusive results. Nonetheless, our data suggest that both pre- and postoperative T4 supplementation benefits survival.

6. Conclusion

Our findings propose that monitoring TH status during the perioperative period of cardiac surgical procedures could enable appropriate TH treatment, reduce complications, and enhance both short- and long-term survival. The 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.

7. Summary

Current thesis aimed to explore the hormonal trends, imbalances and their effects on adverse outcomes in the perioperative period of cardiac surgical procedures.

The objective of this thesis was to describe hormonal patterns and trends including TSH, T3, T4, PRL, TTE in the perioperative period of cardiac surgeries. In addition, we investigate the role of endocrine support and supplementation as a major part of donor management during HTx. Furthermore, the research aimed to expose deeper associations between thyroid status and adverse outcomes after HTx.

Our findings suggest that postoperative serum T3 levels may serve as a reliable indicator for evaluating NTIS after cardiac surgery. In contrast, changes in serum TSH and T4 levels demonstrate minimal correlation with postoperative adverse events, rendering the routine measurement of these parameters less useful. TH treatment can reduce complications and improve both short- and long-term survival. Administering thyroxine alongside methylprednisolone may decrease the risk of PGD. Central TH parameters, including 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 offer post-HTx benefits, correlating with improved survival rates. The expression of Dio3 mRNA was influenced by different MCS devices. Additionally, higher Dio2 expression in the heart, which may be reduced by levothyroxine replacement, is associated with acute allograft rejection, a common complication following HTx. A significant decrease in serum testosterone levels may be more pronounced in male patients, indicating a disrupted endocrine response. Additionally, serum testosterone levels may be linked to preoperative conditions and altered MELD scores, suggesting hepatic dysfunction. PRL acts as a stress hormone, but this effect is observed only in female patients.

Our findings indicate that monitoring TH status during the perioperative period of cardiac surgery could facilitate appropriate TH treatment, reduce complications, and improve both short- and long-term survival outcomes.

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