The impact of perioperative liver dysfunction and perioperative thyroid hormone support on survival following heart transplantation

PhD thesis

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1. INTRODUCTION

1.1 The end-stage heart failure and heart transplantation

The incidence of end-stage heart failure is rapidly groiwing the aging population. The cardiovascular death comprises one third of the overall mortality, and the incidence is growing. Since heart transplantation is still the only definitive treatment, careful donor management and allocation, as well as close follow-up of the recipients is essential. Due to worldwide donor shortage, the wait list mortality rate is high.

1.1.1. Factors influencing the outcome of heart transplantations

Besides the well-known, general preoperative factors, as age and co-morbidities, several specific factors have lower or higher impact on post-heart transplant outcome.
High impact factors are the indication of transplantation, the need for preoperative organ support, and the immunologic sensitisation. Besides these recipient characteristics, some donor parameters have also high influence on outcome. The most important ones are the donor age, size and age mismatch.
Causes of mortality following heart transplantation differ in the early and late postoperative period. In the first month, the most frequent cause is graft failure followed by multiorgan failure and infection. At the end of the first year, infections become the leading cause, while the frequency of the above metioned ones are decreasing. Fatal rejections and immunological graft failure are specific for the later years, as well as malignancies and allograft vasculopathy.

1.1.2. Donor identification and management

The identification of potential donors, donor management, organ function assessment and preservation are key points of the transplantational process. During brain dead donation, which is the only method of deceased donation allowed by Hungarian laws, donor management ensures the preservation of organ function by maintaining stable donor homeostasis with thorough intensive care and respiration therapy. Furthermore, the

eligibility for transplantation and organ function should be assessed by several examinations and tests.

Severe brain injury is always followed by a systemic inflammatory response before brain death. Thereafter, an autonomic storm accompany the brain-stem coning followed by gradual arrest of the central sympathetic andrenergic regulation. This phase is characterised by cardiovascular instability, hypothermia, endocrine disturbances, mainly diabetes insipitus, low metabolic rate and carbon-dioxid production. Close monitoring, prevention and correction of the above symptoms play critical role in the organ preservation.

1.1.3. Risk assessment of the recipient-donor pairs

The United Network for Organ Sharing (UNOS) scoring system established a new approach of risk assessment. It estimates the common risk of recipient-donor pairs at a later stage of the transplantational pathway. The score incorporates the recipint's age, body mass index, mean pulmonary arterial pressure as a measure of pulmonary hypertension. Assessing the preoperative organ dysfunction, it takes into account the serum creatinine and total bilirubin leves, as well as the need for mechanical circulatory and respiratory support. Besides these factors, history of malignant disease is also a part of the risk assessment. According to the score, the recipients are devided into very low, low, medium, high and very high risk groups.

Regarding the donor, it considers age, history of diabetes, sex mismatch and the ischaemic time of the organ. According to the above factors, they are devided into low, medium and high risk groups.

The sum of the two above, recipient and donor scores gives the total score describing the risk of the given transplantation. This total score is a good predictor of the one- and five-years survival. The authors, Trivedi et al. concluded that the recipient factors have higher impact on survival than the features of the donor.

1.2. The relationship between heart failure and liver dysfunction

Primarily cardio-renal interplay was investigated among the phenomenons of the multi-organ dysfunction in heart failure. The multiple relationship between the heart and the liver reached increasing attention in the last few years. According to the latest result, these interactions have prognostic role in survival of patients with heart failure.

1.2.1. Mechanisms and features of cardiac hepatopathy

The forward and backward components of heart failure cause different changes in the liver. The forward failure in acute states cause ischaemic injury, characterised by hypoxic hepatic cell necrosis and cirrhosis. Rapid increase of transaminases and lactate dehydrogenase levels can be measured. Low levels of coagulation factors and albumin show the impairment of the synthetic activity. The chronic heart failure is characterised by congestion, causing disruption of endothelial cells and tight juctions that separates the extravascular space from the bile canaliculus. Therefore serum bilirubin, alkaline phosphatase and gamma-glutamyl-transferase levels increase. Liver dysfunction has prognostic impact on survival even in chronic heart failure. In end-stage heart failure, more or less combined features can be seen.

1.2.2. The Model for End-Stage Liver Disease (MELD) score and its modified versions

The MELD score was originally developed for the risk assessment of liver transplant and transjugular intrahepatic portosystemic shunt (TIPS) candidates. It incorporates the total serum bilirubin, the international normalized ratio (INR) and creatinine levels, as the measures of synthetic and metabolic activity of the liver and concomitant renal failure, Therefore, it's an appropriate multisystemic risk assessment tool.
It was applied in the risk assessment of end-stage heart failure patients awaiting for heart transplantation or mechanical circulatory support soon. The scoring system showed also good prognostic performance in this population. Since the high proportion of anticoagulated patients in this population, MELD-XI (MELD excluding INR) and modified MELD score were introduced. The MELD-XI does not consider the synthetic

activity of the liver, while the modified MELD score (modMELD) substitutes INR with serum albumin levels.

1.3. The relationship between thyroid dysfunction and heart transplantation

Heart transplantation candidates have end-stage heart failure. The prevalence of thyroid dysfunction and the question of hormonal support is well known and intensively studied in this population as well as in other groups of critically ill patients.

1.3.1. Low T_3 syndrome in critically ill

Low thyroid hormone levels in critically ill patients have been reported by several authors. However, the latest results indicate, that these changes are adaptive and protective in the acute phase of the critical illness, switching the metabolism into a lower, starvational mode. Neither early parenteral nutrition, nor hormone therapy is recommended in that phase. Hormonal changes may be caused by excessive release of inflammatory mediators. Along with the decreased levels of the most effective T_3, increased, than decreased levels of T_4 and high reverse T_3 levels can be seen.

On the contrary, the cronic critical illness is characterised by different hormonal changes. At that point, even T_4 is decreased, the production of central stimulating hormones, as TSH and TRH are also reduced, resembling to central hypothyroidism. In case of chronic malnutrition, these changes appear already in the acute phase of the critical illness. The most important pathophysiologic processes in the background are the alteration of the hypothalamic feedback set-piont by the increased type 2 deiodinase activity and subsequent reduction in the TRH release. The reasons are still unexplained, the role of increased endogenous hypothalamic dopamine and cortisol levels or the adverse effect of dopamine or corisole therapy have been addressed. The above changes seem to be maladaptive: decreased serum levels of T_4 were independent predictor of mortality and extended intensive care and mechanical ventillation.

1.3.2. Changes in the levels and effects of thyroid hormones in heart failure

Likewise in cronic critical illness, patients with advanced heart failure also show low T_3 levels related to higher mortality. Thyroid hormone treatment was appeared to be beneficial in these states, no adverse reactions, as arrithmia or ischemic episodes were observed.

Novitzky et al. detected beneficial effect of thyroid hormone treatment following ischemic myocardial injury in several animal studies.

Significant decrease in T_3 levels were observed even following cardiac surgery. It was previously considered as a post-bypass effect, but further studies found no difference between the hormonal changes following on-pump and off-pump procedures. Postoperative hormonal therapy was widely investigated, but in spite of significantly better haemodynamics and reduced need for vasoactive treatment, no difference was observed in terms of mortality and length of ICU stay.

1.3.3. Thyroid hormone therapy of the donors

As a part of misregulation in brain-dead donors, dysregulated function of the hypothalamic-pituitary axis is also present. Thyroid hormone deficiency may be a reason of the cardiovascular instability in donors. Conflicting results have been reported regarding the efficacy of thyroid hormone support. Routine thyroid hormone treatment is not recommendend by the European and the American donor management guidelines, but it can be useful in unstable, cardiac donors.

2. AIMS

Our research group is attended to the assessment of non-cardiac risk factors in cardiac surgery and heart transplantation. The scope of the present thesis is the impact of perioperative liver dysfunction and perioperative thyroid hormone support on survival following heart transplantation.

- The impact of preoperative liver dysfunction was widely investigated, therefore, we assessed the perioperative changes of hepatic function and its effect on posttransplant mortality.
- Related to this question, we assessed the applicability of preoperative and post-dischaege MELD scores in mortality risk assessment.

Other focus of the study is the usefullness of thyroid hormone treatment of the recipients and the donors in heart transplantation.

- We examined the relationship between perioperative hormone support of the recipient and long term survival following heart transplantation.
- We aslo assessed the effect of thyroid hormone support of the donors on the survival of recipients.

3. METHODS

3.1. Population

For the study of hepatic dysfunction, we analyzed the data of patients who underwent orthotopic heart transplantation (OHTX) between 30th January 2012 and 19th October 2016. For the retrospective analysis, we used a single-center database from the Heart and Vascular Center, Semmelweis University, Budapest. For the analysis of the effect of thyroid hormone therapy, we also used retrospective method with an extended study period until 31st December 2017. Our patients were older than 18 years, other exclusions were not made.

3.2. Recipient data

The demographic data, coexisting diseases and medication of the recipients were analysed in both study.

We recorded and analyzed the perioperative laboratory values, blood group, serologic results, the latest hemodynamic measurements and echocardiographic measurements during the 1st, 2nd, 3rd postoperative days, as well as the need for preoperative mechanical ventilation and circulatory support.

Perioperative course and postoperative complications during OHTX hospitalization were recorded, including respiratory failure (mechanical ventilation longer than 72 hours), renal failure requiring hemodialysis, bleeding, the number of blood products required during hospitalization, infections, primary graft failure, ventricular assist device placement, cerebrovascular accident and in-hospital death.

3.2.1. Liver function tests and MELD scores

We recorded and analyzed the last preoperative, 1st-, 2nd-, 3rd-, and 4th-7th-postoperative day maximum bilirubin and transaminase values. After discharge, the same laboratory markers were recorded and the pre-transplant and post-discharge MELD, MELD-Na, MELD-XI and modMELD scores were also calculated.

Liver enzyme levels were expressed as raw values in U/l, in quartiles, and as the multiplier of the sex-specific top-normal level. The difference between the maximal postoperative and the preoperative levels were also calculated.

3.2.2.. Data regarding the thyroid hormone therapy

The patients' medical history was reviewed with specific regard to thyroid dysfunction, thyroid medication and amiodarone use. Patients on preoperative steroid medication use were also identified. We recorded the preioperative thyroid hormone results, but few data was available for further analysis, since these tests are not part of the routine peritransplantational care. Further analyses were made regarding the history of thyroid dysfunction and thyroid homone treatment.

3.3. Donor specific data

We retrieved the available donor specific data from the national transplantational registry and from the clinical database. The following data were registered and analysed age, sex, height, body mass index, inotropic medication, serum sodium levels and history of diabetes. We also incorporated the steroid, l-thyroine and desmopressin support during the donor management and the graft ischaemic time in the analysis.

3.4. United Network for Organ Sharing (UNOS) score

Our multivariate models were adjusted for UNOS scores, the risk groups were also analysed.

3.5. End-points of the studies

Long-term, all-cause mortality was the primary end- point of both studies. The Hungarian National Death Register for vital status was accessed on the 15th November 2016 for the study evaluating the effects of perioperative liver failure and on the 27th April, 2018 for the analysis of perioperative thyroid hormone suppont, respectively.

3.6. Statistical methods

Statistical analyses were performed using the SPSS 22.0 software (SPSS, Inc., Chicago, IL, USA). For continuous variables, the median and the interquartile range are presented. Categorical variables are described as a number and a percent. Two-sided, non-parametric tests were used.

In survival analyses using quartiles, liver enzyme levels <25th percentile were used as references. Logistic regression, Kaplan-Meyer method and Cox regression analyses were performed to evaluate the power of the percentiles for each liver enzyme with all-cause mortality. Survival among the groups was compared using the Log Rank test.

Factors contributing to long-term mortality following OHTX were examined using Cox regression analysis. Clinically relevant variables were investigated in series of univariable models, and variables with $P<0.2$ were selected and entered the multivariable models to identify multivariable predictors of long-term mortality. The final models were adjusted for the most relevant variables based on the above tests and literature data. A $p<0.05$ was considered statistically significant in all tests.

4. RESULTS

4.1. The impact of liver dysfunction

Between the 1st of January 2012 and the 15th of October 2016, 209 patients underwent orthotopic heart transplantation and their median age was 53 years (IQR {interquartile range}: 44-58.5 years). During the follow-up, 55 patients (26.3%) died and the 30-day mortality was 30 patients (14.4%). The mean survival was 3.61 years (95 % C.I=3.3-3.9 years).

4.1.1. Analysis of the preoperative recipient risk factors

No significant differences were found between survivors and non-survivors in terms of age, demographic parameters, etiology of heart failure, haemodynamic measures and concomitant illnesses. Those who died were more frequently women (22.4% vs. 36.1% in survivors and non-survivors, respectively, p=0.029) and patients with mechanical cardiac support before HTX (6.5% vs. 23.6%, in survivors and non-survivors, respectively, p=0,001). Pre-transplant laboratory values and MELD scores did not differ significantly between patients who died and those who survived except for preoperative albumin (median= 44.24, IQR= 38.53-47.4 vs. median= 39.9, IQR= 33.8-75 for survivors and non-survivors, respectively, p=0.004) and modMELD levels (median= 9.47, IQR= 7.47-12.89 vs. median= 11.59, IQR= 7.94-16.93 for survivors and non-survivors, respectively, p=0.043).

4.1.2. Comparison of postoperative laboratory results and complications between groups of survivors and non-survivors

In the post-transplantation period, non-survivors more frequently had primary graft failure (6.5% vs. 30.9% in survivors and non-survivors, respectively, p<0.001) and needed postoperative mechanical circulatory support (9.1% vs. 49.7%, p=0.001), dialysis (20.1% vs. 43.6%, p=0.001) and mechanical ventilation longer than 72 hours (40% vs. 80%, p=0.001).

In assessing the echocardiographic findings in the early postoperative phase, no significant difference was found between long-term survivors and non-survivors. Only the left ventricular posterior wall thickness at end-diastole on the 3rd postoperative day was higher in survivors compared to non-survivors (median of survivors: 12 mm, IQR 11-13 mm vs. median of non-survivors: 11 mm, IQR 9-12.3 mm, p= 0.025).

In the first post-transplantation week, transaminase values and bilirubin were significantly higher in patients who died compared to those who survived. The difference in transaminanse levels were significant from the 2nd postoperative day, but bilirubin level showed significant difference only from the 3rd postoperative day.

Among post-discharge values, INR, MELD-Na and modMELD scores were significantly higher in non-survivors compared to survivors, excluding patients who died in the hospital. Interestingly, transaminase and bilirubin levels did not differ between the two groups.

4.1.3. Uni- and multivariate analyses of risk factors for long-term mortality

Preoperative hepatobiliary markers showed independent relationship with long-term mortality. In assessing different MELD scores preoperatively, only modMELD was significantly associated with mortality in the univariate Cox regression analysis (P=0.012; HR=1.06; 95%CI=1.014-1.114).

Assessing the postoperative hepatobiliary markers, the highest quartiles of maximal AST, ALT and bilirubin levels were significantly associated with long-term mortality.

The multivariate Cox regression analysis, adjusted for age, sex, and the need for postoperative MCS and extended mechanical ventilation, revealed that preoperative modMELD score and higher maximum AST and ALT levels on PODs 4-7 (in quartiles) were independently associated with higher mortality. The differences between the baseline and the greatest bilirubin and AST levels were also independently associated with mortality. By expressing the transaminase values as the multiplier of the sex-specific top normal value, maximum AST and ALT levels were independently related to worse survival. (Table 1.)

Table 1: Multivariate Cox-regression analysis. *Each model was adjusted for UNOS score, sex, need for postoperative mechanical circulatory support and extended ventilation. Abbreciations: HR: hazard ratio, CI: confidence interval, AST: aspartate transaminase, ALT: alanine transaminase, max.: maximum, POD: postoperative day, modMELD: modified Model for End-stage Liver Disease.*

Variables	HR (95% CI)	p	Variables	HR (95% CI)	p
Models using maximum postoperative AST and ALT quartiles					
modMELD	1.05 (1.00-1.10)	0.051	modMELD	1.06 (1.01-1.12)	**0.025**
Max. AST POD 4-7.		**0.009**	Max. ALT POD 4-7		**<0.001**
1st quartile	reference		1st quartile	reference	
2nd quartile	0.85 (0.32-2.26)	0.744	2nd quartile	0.86 (0.31-2.38)	0.767
3rd quartile	0.73 (0.27-1.97)	0.537	3rd quartile	0.56 (0.21-1.46)	0.231
4th quartile	2.47 (1.12-5.45)	**0.025**	4th quartile	2.87 (1.35-6.10)	**0.006**
Models using bilirubin, AST and ALT elevation from baseline to maximum of POD 4-7					
modMELD	1.06 (1.01-1.11)	**0.029**	modMELD	1.06 (1.01-1.12)	**0.016**
Rise of bilirubin (µmol/l)	1.01 (1.002-1.02)	**0.014**	Rise of bilirubin (µmol/l)	1.01 (1.003-1.02)	**0.008**
Rise of AST (U/l)	1.000 (1.000-1.001)	**<0.001**	Rise of ALT (U/l)	1.001 (1.000-1.001)	**0.007**

Among the post-discharge parameters, modMELD scores (HR= 1,17, 95%CI= 1,09-1,27; p <0,001) and AST was significantly associated with post-discharge mortality (HR= 1,002, 95%CI= 1,001-1,003; p <0,001 as a continuous variable; HR= 1,07, 95%CI= 1,05-1,10; p <0,001, expressed as the multiplier of the sex-specific normal value, respectively).

The post-discharge models were also adjusted for age, sex, and the need for postoperative MCS and extended mechanical ventilation.

4.2 The impact of thyroid hormone therapy

During the extended study period, 266 patients underwent OHTX at our institution. Their mean age was 53 years (IQR: 44-58.5 years), 156 (74.6%) of them were male. The mean survival was 4.59 years (95% CI =4.26-4.92 years), 70 patients (26.3%) died during the follow-up period. The most frequent causes of death were graft failure in 17 cases (24.7% of death), multiorgan failure in 15 cases (21.4%) and infection in 13 cases (18.6%).
In the study population 48 patients (18.1%) received l-thyroxin substitution in the perioperative period, of these in 30 (11.3%) cases l-thyroxin substitution was initiated preoperatively. History of hypothyroidism was present in 34 cases, whereas hyperthyroidism in 12 cases. The frequency of amiodarone use (n=65, 24.4 %) showed no significant difference between patients with or without thyroid disease (30.4% vs. 23.2% for normal thyroid function vs. thyroid dysfunction, respectively; p=0.298).

4.2.1. Comparison of patients with or without perioperative l-thyroxin substitution

There were significant differences observed in demographic characteristics and cardiac output between recipients with and without l-thyroxin substitution. Half of the patients receiving l-thyroxin perioperatively were male, whereas the proportion of males were significantly higher in the other group and in the whole population.
Those, who received no thyroid hormone supplementation were higher, had higher weight, body mass index and body surface area. There were no difference in the etiology of heart failure and co-morbidities. Among the haemodynamic parameters, only cardiac output was significantly higher in the non-substituted group.
There were no difference in postoperative adverse outcome between the two groups.

4.2.2. The impact of recipient parameters on postoperative survival

There were no significant association between the demographc data (except for height), co-morbidities and haemodynamic parameters of recipients and long-term mortality in univariate models. However, there was a strong association between the recipient specific (HR= 1.18, 95% CI= 1.04-1.33, p= 0.009) and total UNOS scores (HR= 1.12, 95% CI= 1.02-1.23, p= 0.017), preoperative recipient l-thyroxin substitution (HR=0.22; 95% CI= 0.05-0.91; p=0.037) and long-term mortality as indicated by the results of the univariable Cox-regression analyses. In addition, there was also an association between a need for preoperative mechanical ventilation (HR= 3.10, 95% CI= 2.01-4.76, p<0.001) and mechanical circulatory support (HR= 2.94, 95% CI= 1.70-5.10, p<0.001), and long-term mortality.

Those, who received l-thyroxine preoperatively showed significantly longer survival compared to the non-supplemented (p=0.022), or postoperatively supplemeted (p=0.043) patients.

4.2.3. The impact of donor l-thyroxine support on recipient survival

Assessing the donor parameters and ischaemic time, only donor height (HR= 0.97, 95% CI= 0.94-1.00, p=0.020) and l-thyroxine substitution (HR= 0.41, 95% CI= 0.18-0.94, p=0.035) showed significant, namely negative association with long-term mortality in univariate models.

L-thyroxine substitution was administered in 52 (19.5 %) donors. The long-term survival of recipients who received a heart from a donor with l-thyroxin substitution was significantly better compared to recipients who received a heart from a donor without l-thyroxin substitution. (p= 0.028).

4.2.4. Assessment of the impact of recipient and donor parameters on long-term mortality in multivariate models

According to the multivariable Cox-regression analyses adjusted on UNOS score due to relatively small population, preoperatively initiated donor and recipient l-thyroxin substitution was associated with a significantly lower hazard for long-term mortality.

However, the postoperatively initiated supplementation showed no benefit in survival. (Table 2.)

Table 2: The assessment of l-thyroxine supplementation and long-term mortality using multivariate models. *Abbreviations: HR: hazard ratio, CI: confidence interval, UNOS: United Network for organ Sharing, preop.: preoperatively, postop.: postoperatively*

Multivariate Cox-regression analysis for long term mortality			
	HR	**95% CI**	**p**
Total UNOS score	1.09	0.98-1.20	0.101
Recipient l-thyroxine substitution			0.130
No supplementation	reference		
Preop. initiated	**0.24**	**0.06-0.98**	**0.047**
Postop. initiated	1.14	0.46-2.85	0.780
Donor l-thyroxin supplementation	**0.31**	**0.11-0.87**	**0.025**

5. CONCLUSIONS

5.1. The impact of perioperative hepatic dysfunction on long-term mortality

- According to the above results, the preoperative modMELD score is an independent risk factor of long-term mortality.

The preoperatively elevated modMELD score is a sort of measure of multiorgan-dysfunction associated with end-stage heart failure. It assesses the renal failure by kreatinine levels, the conjugative, excretional and synthetic hepatic function, by the incorporation of bilirubine and albumin levels. Interestingly, the haemodynamic parameters showed no impact on survival. It points to the fact that not the haemodynamic failure itself lead to worse outcome instead, the concomitant organ dysfunctions should be closely followed. There is usually a significant progression in systolic cardiac function following heart transplantation, but the reversibility of consecutive organ dysfunction is not always feasible by normal blood flow.

Our results supports the applicability of MELD score or its modified versions in the pre-transplantational risk stratification, urgency evaluation and allocation. Since high proportion of the patients receives anticoagulation medication, the application of MELD excluding INR, or modfified verision, incorporating albumin level instead of INR is more appropriate.

- Based on our results, postoperative hepatic dysfunction is an independent risk factor for long term mortality following heart transplantation.

The transaminase and bilirubin levels reached their maximum between the 4^{th} and 7^{th} postoperative days. The reason of the slower and less pronounced bilirubine elevation may be its almost two weeks half time.

However, the time between the baseline and peak levels was enough to measure significant differences.

The perioperative hepatobiliary markers showed significant relationship with long-term mortality independently of primary graft failure and echocardiographic right heart function measures. These findings support the above conclusion that the presence of organ dysfunctions are more sensitive markers of prognosis than measures of cardiac function itself. Close monitoring of organ functions are strongly recommended in this population.

In our study, the discriminative power of the model comprising postoperative peak AST levels and compications as well as preoperative risk stratification scores as UNOS and modMELD was excellent for long-term mortality.

However, the cardio-hepatic interaction should be examined from the other side as well. It has also been reported that the liver cirrhosis alters hemodynamic parameters, results in arterial vasodilatation and hypervolaemia, which means a critical overload for a heart with impaired reserve. Futhermore, there are tight metabolic and hormonal relations between the two organs. Therefore, it is quite straightforward that hepatic dysfunction may be independently associated with worse survival, even if it is secondary to heart failure.

5.2. The impact of recipient and donor parameters on long-term mortality following heart transplantation

- According to our results, donor and recipient l-thyroxin substitution was associated with a significantly lower hazard for long-term mortality following heart transplantation.

The presence of thyroid dysfunction before heart transplantation might be similar to that of thyroid dysfunction observed in prolonged illness. On the other hand, an end stage heart failure is encountered not only with severe organ dysfunction, but with endocrine dysregulation. Therefore, patient undergoing OHTX with so-called non-thyroidal illness might be already in the prolonged, maladaptive and not in the early, adaptive phase of the critical illness.

Our result, that the preoperatively initiated l-thyroxine support of heart transplant candidates has strong, protective effect on long-term mortality, means that exogenous l-thyroxine support is beneficial in that phase. Based on the above results, close monitoring and on-demand preoperative thyroid hormone supplementation are recommended, so that these patients might be pre-conditioned, normal endocrine function supports the performance of the transplanted organ, and normal receptor sensitivity may help the adaptation of the circulatory system. To our knowledge, no previous data of recipient thyroid hormone substitution has been published.

On the other hand, the impact of endocrine dysfunction and its treatment as part of the donor management after brain death has not been satisfactorily addressed. Routine l-thyroxin supplementation of the donors is not recommended, but according to the current European and American donor management guidelines it should be considered in case of hemodynamic instability or in potential cardiac donors with reduced ejection fraction.

Our finding, that donor l-thyroxin medication is a strong protective factor against recipient mortality supports the necessity of thyroid supplementation.

Nevertheless, it should be emphasized that the power of present results themselves are not sufficient. Further prospective, multi-center studies shoud deal with the above issues to draw causative and therapeutic conclusions. Therefore, some prospective studies are already started by our study group.

6. PUBLICATIONS

6.1. Publications related to the doctoral work

1. Holndonner-Kirst E, Nagy A, Czobor NR, Fazekas L, Dohan O, Kertai MD, Lex DJ, Sax B, Hartyanszky I, Merkely B, Gál J, Székely A. (2019) The impact of l-thyroxine treatment of donors and recipients on postoperative outcomes after heart transplantation. J Cardiothorac Vasc Anesth. 33(6):1629-35.

2. Holndonner-Kirst E, Nagy A, Czobor NR, Fazekas L, Lex DJ, Sax B, Hartyanszky I, Merkely B, Gál J, Székely A. (2018) Higher transaminase levels int he postoperative period after orthotopic heart transplantation are associated with worse survival. J Cardiothorac Vasc Anesth. 32(4):1711-18.

3. Nagy A, Holndonner-Kirst E, Eke Cs, Kertai MD, Fazekas L, Benke K, Pólos M, Szabolcs Z, Hartyánszky I, Gál J, Merkely B, Székely A. (2020) Model for End-Stage Liver Disease Scores in Veno-Arterial Extracorporeal Membrane Oxygenation. Int J Artif Organs, 2020 Febr 25. Published Online Ahead of Print

6.2. Other publications

1. Czobor NR, Lehot JJ, Holndonner-Kirst E, Tully PJ, Gál J, Székely A. (2019) Frailty in patients undergoing vascular surgery: a narrative review of current evidence. Ther Clin Risk Manag. 15: 1217-32.