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ORGAN REPLACEMENT THERAPY IN PEDIATRIC HEART FAILURE IN HUNGARY

PhD thesis

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Table of Contents

List of abbreviations

AKI	Acute Kidney Injury
ASD	Atrial Septal Defect
BHBiVAD	BerlinHeart Excor® Biventricular Assist Device
BHLVAD	BerlinHeart Excor® Left Ventricular Assist Device
BiVAD	Biventricular Assist Device
ccTGA	Congenitally Corrected Transposition of the Great Arteries
CDC	Complement-dependent Cytotoxicity
CHD	Congenital Heart Disease
CMP	Cardiomyopathy
CPB	Cardiopulmonary Bypass
DCM	Dilated Cardiomyopathy
ECMO	Extracorporeal Membrane Oxygenation
ET	Eurotransplant
FDA	Food and Drug Administration
GFR	Glomerular Filtration Rate
HLA	Human Leukocyte Antigen
HTX	Heart Transplantation
HVAD	Heartware™
HM3	HeartMate3™
IABP	Intra-aortic Balloon Pump
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
ISHLT	International Society for Heart and Lung Transplantation
IVIG	Intravenous Immunoglobulin

IV:	Intravenous
LVAD	Left Ventricular Assist Device
MCS	Mechanical Circulatory Support
MMF	Mycophenolate Mofetil
MRI	Magnetic Resonance Imaging
NS	Non-Significant
NYHA	New York Heart Association
PGF	Primary Graft Failure
PRA	Panel Reactive Antibody
SPSS	Statistical Package for Social Sciences
VAD	Ventricular Assist Device
VSD	Ventricular Septal Defect

1. Introduction

1.1. Heart failure: Definition and incidence

Heart failure is a condition in which the heart is unable to meet the metabolic demands of the cells. It can occur as a consequence of congenital and acquired heart diseases, which cause serious, life-threatening conditions by increasing the preload or afterload of the heart or by causing ventricular dysfunction (1). Based on published data, the incidence of the disease is approximately 0.9-7.4 cases per 100,000 children(2). The severity of the disease is confirmed by the fact that the 5-year transplant-free survival rate ranges between 54 and 65%(3, 4).

1.2. Diagnosis

In children, the underlying causes are usually congenital or developmental cardiac disorders; which contrasts with adults, where ischemic and valvular disease predominate. Consequently, their clinical presentation also shows a characteristic pattern distinct from adult patients.

Given that heart failure most commonly manifests during infancy, the modified Ross classification—one of the most widely applied scoring systems in this age group—provides a symptom-oriented framework for clinical assessment, as summarized in Table 1(5). The symptomatology of this age group is characterized by respiratory distress and feeding difficulties(6).

Table 1: Modified Ross heart failure classification for children

Modified Ross heart failure classification for children	
Class I.	Asymptomatic
Class II.	Mild tachypnea or diaphoresis with feeding in infants Dyspnea on exertion in older children
Class III.	Marked tachypnea or diaphoresis with feeding in infants Marked dyspnea on exertion Prolonged feeding times with growth failure
Class IV.	Symptoms such as tachypnea, retractions, grunting or diaphoresis at rest

In addition to medical history and typical symptoms, echocardiography plays a significant role in the diagnosis of the disease, as it can identify a significant proportion of congenital heart diseases and assess ventricular function. Cardiac magnetic resonance imaging has become an increasingly utilized non-invasive modality, allowing assessment of myocardial fibrosis and thereby contributing to prognostic evaluation.(7).

1.3. Treatment

Therapy is determined by the primary cause. If congenital heart disease is the underlying pathology, surgical or cardiological intervention may lead to short-term improvement or even complete resolution of symptoms. This is well applicable in cases of so-called simple defects, like septal defects, or valvular aortic stenosis. However, in the presence of complex congenital malformations, only palliative interventions (e.g., establishment of a single-ventricle circulation) may be possible, and significant residual lesions may persist even after corrective surgery, often necessitating repeated procedures over the long term. These anatomical and physiological abnormalities may predispose patients to recurrent heart failure due to repeated cardiopulmonary bypass procedures and increased circulatory stress.

If the triggering factor is ventricular dysfunction, the primary goal of treatment is to reduce congestion (in the systemic or pulmonary circulation).

In cases of systemic left ventricular failure, chronic therapy is based on neurohormonal blockade using agents that have proven effective in adults, including renin–angiotensin–aldosterone system inhibitors, β-blockers, and natriuretic peptides(8). However, a detailed analysis of these therapies is not the subject of this thesis.

1.3.1. Reversible pulmonary banding

First published in 2013 by Schranz et al.(9) and increasingly used in infants and young children, reversible pulmonary artery banding is an effective bridging procedure that can also be used as a curative treatment in some cases. The concept was derived from treatment strategies used to maintain left ventricular training in ccTGA that resulted in improved systemic right ventricular function. It is based on ventriculo-ventricular interaction(9). In addition, it can lead to cell proliferation and tissue repair through the

activation of signaling pathways(9). The basic condition for its use is preserved right ventricular function.

If signs of hypoperfusion determine the clinical picture, the use of inotropic drugs may be necessary as a temporary solution. If the above treatment strategies are unsuccessful, or in other indications to be detailed later, organ replacement therapy may be necessary as the only therapeutic solution.

1.3.2. Organ replacement:

1.3.2.1. The history

The first successful heart transplant was performed by Christiaan Barnard in 1967(10), although there had been earlier unsuccessful attempts using an organ from an animal. Unfortunately, the success of the initial attempts was substantially limited by the immature state of immunosuppressive treatment. A major breakthrough in the field of transplantation, not only of the heart but of all organs in general, came with the development of cyclosporine which provided new momentum to the field in the early 1980s(11). In Hungary, the first heart transplant was performed by professor Zoltán Szabó on January 3, 1992, while the first pediatric heart transplant at our institute was performed in 2007. Currently, the number of heart transplants performed in our country exceeds 800, of which 75 were pediatric heart transplants.

The shortage of donor organs raised the demand for mechanical circulatory support devices that could bridge patients with end-stage heart failure to heart transplantation. As early as the 1960s(12), even before the first successful transplant, reports appeared describing very short-term successes with experimental systems. The first successful long-term support was achieved by DeVries and his colleagues, who in 1982(13) were able to maintain circulatory assistance for 112 days using a pneumatically driven device, a technology that was later applied successfully in additional cases. The first FDA-approved long-term mechanical circulatory support device applied in childhood is the Berlin Heart Excor®(14), which operates on a pneumatic basis to provide pulsatile flow and can be used successfully from infancy to adulthood. Although it has only been available in the United States since 2011, it has been used successfully worldwide,

including in Hungary, prior to that. The first successful implantation in Hungary took place in 2008.

1.3.2.2. Indications of heart transplantation

The most common indication for heart transplantation in children, as in adults, is end-stage heart failure. This is most often caused by hereditary or acquired cardiomyopathies. Among genetic disorders, dilated cardiomyopathy represents the largest proportion. Although the hypertrophic form is not uncommon in childhood, it accounts for only a small fraction of transplant cases(15), whereas the restrictive type, despite being the rarest overall, remains a frequent indication for transplantation due to its early and often severe clinical presentation(16).

If the indication for transplantation is not a primary myocardial disorder, congenital heart defects constitute the next most common category. This patient group includes conditions that cannot be corrected by surgical or catheter-based interventions, as well as cases with residual abnormalities or secondary myocardial injury resulting from repeated bypass procedures. In rare instances, refractory arrhythmias or inoperable cardiac tumors may also serve as the etiological basis for transplantation.

Transplantation due to the two most common indications—congenital heart disease and cardiomyopathy—involves both preoperative and intraoperative differences that may affect the short- and long-term success of the procedure.

1.3.2.3. Transplantation challenges in congenital heart disease

Various anatomical variations and even complex heterotaxias can complicate the surgical feasibility of the procedure. Difficulties may arise if the patient has undergone significant, and in some cases multiple chest surgeries, resulting complex adhesions and residual abnormalities that must be addressed during the procedure. In addition, systemic-pulmonary collaterals developing due to chronic cyanosis may increase the risk of bleeding and result in significant shunt volumes, making adequate perfusion challenging(17). Blood products used in previous interventions, homograft materials, and allosensitization during perfusion can greatly reduce the availability of suitable donor organs and, through activation of the immune system, the survival of the graft(18).

Addressing all of these challenges can significantly prolong both the surgical preparation phase and the time required for successful implantation. Comprehensive, preoperative multidisciplinary planning is essential to minimize cold ischemic time. In cases of complex congenital heart disease (CHD), mechanical circulatory support (MCS) also poses serious challenges for the surgeon. These have a negative impact on surgical and waiting list mortality. Although CHD patients generally have higher surgical risks and more complicated postoperative recovery, they can achieve similar long-term outcomes to patients with cardiomyopathy (CMP). One study even showed that their ten-year survival rate is better than that of the latter(19). In the case of patients undergoing transplantation due to cardiomyopathy, timing is one of the key issues in childhood. The time spent on the waiting list can vary quite significantly, especially in the low-weight group of patients. Accordingly, correct timing is a major challenge for healthcare professionals. Efforts should be made to minimize the use of mechanical circulatory support, as this can pose a significant risk not only from a surgical but also from an immunological point of view.

1.3.2.4. Mechanical circulatory support in children

In Hungary, parallel with the pediatric heart transplant program, the introduction of mechanical circulatory support devices has led to a significant reduction in waiting list mortality(20). It is possible to use short- and long-term circulatory support devices that can temporarily replace the lost organ function. These devices can be classified according to whether they support both ventricles, only the right ventricle, or the left ventricle(21). Depending on whether the devices are capable of providing pulsatile or continuous flow(22), and whether they are located intra- or extracorporeally, they can be further divided into subgroups.

Continuous flow devices are capable of providing home care for patients, which is a significant advantage especially for children. Unfortunately, for infants and toddlers, only pulsatile devices are currently available. For both implantable and external devices, the substantial thrombogenic surface necessitates the use of vitamin K antagonists and, depending on the device, even combination antiplatelet therapy(23). Anticoagulation protocols have undergone several modifications as clinical experience has accumulated, resulting in a reduced incidence of complications. In addition, a significant risk of

infection must be considered with both types of devices(24). The occurrence of possible complications can be grouped into three main problems: infection, thromboembolic(25) complications, and bleeding. Providing mechanical support for patients under one year of age remains particularly challenging, as this group is exposed to an even higher risk(26), which, according to the above study, is an independent risk factor for survival, because adequate anticoagulation in this age group is particularly difficult. Using these devices, on the other hand, patients can undergo heart transplantation in more favorable hemodynamic state, with adequate organ perfusion and improved nutritional status, thereby clearly improving short-term outcomes. However, implantation of these devices involves thoracotomy, which carries an increased surgical risk during subsequent transplantation, significantly increasing the risk of bleeding-related complications and the duration of the transplant procedure. The perioperative factors described above may influence the length of hospital stay, which in turn may increase the risk of infection following heart transplantation.

2. Objectives

The objective of this work was to analyze and interpret the clinical outcomes of organ replacement therapies in Hungarian pediatric patients with heart failure.

We present a comprehensive analysis of organ replacement therapies performed in Hungary in pediatric patients with heart failure.

We conducted a comparative assessment of transplantation outcomes across distinct etiological categories, specifically congenital heart disease and cardiomyopathy.

In addition, we provided a detailed evaluation of cases managed with mechanical circulatory support, with particular emphasis on differences in clinical performance and patient outcomes between pulsatile and continuous devices.

Finally, we interpreted our institutional results within the broader context of international experience and published evidence.

3. Methods

This study provides a retrospective assessment of the outcomes achieved Gottsegen National Cardiovascular Center, Pediatric Heart Center. Given that both pediatric heart transplantation and long-term mechanical circulatory support are available exclusively at our institution, we were able to provide nationally representative data on organ replacement therapies utilized in the management of pediatric heart failure.

Data on all heart transplants and long-term circulatory support performed since the initiation of the pediatric heart transplant program in 2007 were collected retrospectively.

We conducted two different studies.

Children undergoing heart transplantation were analyzed separately, and in addition, children receiving long-term mechanical circulatory support were included in a second study

There is partial overlap between the patient populations included in the two analyses; however, it is important to emphasize that not all individuals receiving long-term mechanical circulatory support was placed on the active transplant waiting list. In several instances, the clinical indication for circulatory support did not necessitate activation on the list.

3.1. The heart transplant study

Heart transplantation (HTX) as a treatment modality has been available at our center since 2007. In the first fifteen years (up to 31 December 2022), a total of 62 pediatric heart transplants were performed. All transplanted children under 18 years of age were included in this study, with the guardians of each patient providing written informed consent. Currently, only ABO-compatible heart transplants are permitted in Hungary, and due to legal regulations, only donation after brain death is accepted. As a result, all transplants in our series were ABO-compatible and from brain-dead donors.

The primary indication for transplantation was myocardial disease, either genetically inherited or acquired, in 42 patients cardiomyopathy group, (CMP), while the remaining 20 patients underwent transplantation for congenital heart disease (CHD group). Within the CHD group, nine patients had univentricular physiology and were at various stages

of palliative surgical reconstruction. Congenitally corrected transposition of the great arteries (ccTGA) represented the second most common anatomical diagnosis in this group, affecting four patients (20% of CHD cases). Among patients with ccTGA, one individual had previously undergone anatomical correction, whereas in the remaining cases, Ebstein-like malformations of the tricuspid valve may have contributed to the early onset of heart failure despite optimal medical therapy. In patients transplanted for valvular heart disease or tetralogy of Fallot, the development of heart failure may be attributed to multiple and prolonged cardiopulmonary bypass (CPB) procedures during prior reconstructive surgeries. Follow-up data were complete for all 62 patients enrolled in the program.

The requirement for cardiac surgery prior to transplantation was evaluated, with only major surgical interventions being considered, including ventricular assist device (VAD) implantation. Procedures related to the implantation or replacement of arrhythmia management devices were not classified as major surgeries.

Exposure to blood products, cryopreserved homografts, xenografts, and other foreign materials used during cardiac surgery with potential immunomodulatory effects was reviewed. Blood products were not analyzed in detail by type; instead, only the total number of administered products was recorded. Pre-transplant immunization status was assessed using standard panel reactive antibody (PRA) screening with the complement-dependent cytotoxicity (CDC) method, applying a cut-off value of 10%(27).

Clinical parameters analyzed included the need for mechanical circulatory support (MCS) and its duration, preoperative hemoglobin levels, renal function before and after transplantation, donor ischemic time, total cardiopulmonary bypass duration, and overall operative time. Post-transplantation outcomes included duration of mechanical ventilation, as well as early (0–30 days), intermediate (1–12 months), and late (beyond 1 year) mortality.

3.1.1. Immunosuppression, Protocol Biopsy and Rejection Therapy

Maintenance immunosuppressive therapy consisted of tacrolimus, mycophenolate mofetil (MMF), and corticosteroids, with steroids discontinued at six months following transplantation. All patients received induction therapy with basiliximab. Target trough levels for tacrolimus were 10–12 ng/mL during the first three months, 8–10 ng/mL during

the subsequent nine months, and 6–9 ng/mL thereafter. Mycophenolate mofetil was initiated at a dose of 300 mg/m² twice daily and increased to the maximum tolerated dose or up to 600 mg/m², without the use of predefined target serum levels.

Protocol endomyocardial biopsies were performed in patients weighing more than 15 kg at 2–4 weeks after transplantation, followed by scheduled biopsies at 3, 6, and 12 months. Diagnostic biopsies were systematically undertaken in cases of suspected rejection, including elevated donor-specific antibody levels, impaired ventricular function, or electrocardiographic abnormalities.

Clinically relevant rejection was defined as International Society for Heart and Lung Transplantation (ISHLT) grade 2 R cellular rejection on histology or immunohistochemically confirmed antibody-mediated (humoral) rejection(28). The grading system is presented in Table 2 and 3. (28)

Table 2. ISHLT acute cellular rejection grading

Grade 0	No rejection
Grade 1 R, mild	Interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage (grade 1A, 1B, and 2 in the 1990 system)
Grade 2 R, moderate	2 or more foci of infiltrates with associated myocyte damage (grade 3A in 1990 system)
Grade 3 R, severe	Diffuse infiltrate with multifocal myocyte damage, with or without edema, hemorrhage, or vasculitis (grade 3B and 4 in the 1990 system)

Table 3: Antibody- mediated rejection grading

Grade 0	Negative histologic and immunopathologic findings
Grade 1	Presence of positive histologic and immunopathologic findings
Grade 2	Presence of both histologic and immunopathologic findings
Grade 3	Presence of severe histologic plus immunopathologic findings

In cases where histological abnormalities were detected during protocol biopsies without associated functional impairment, treatment was guided by the type of rejection. Cellular rejection was managed with intravenous methylprednisolone pulses (10 mg/kg administered three times on alternate days), whereas humoral rejection was treated with rituximab (375 mg/m² body surface area, administered twice at one-week intervals) and a single dose of intravenous immunoglobulin (IVIG) at 1 g/kg.

When histological findings were accompanied by clinical or echocardiographic signs of rejection, initial steroid therapy was supplemented according to the underlying rejection mechanism. Antithymocyte globulin (ATG) at a dose of 1.5 mg/kg was administered in cases of cellular rejection, while plasmapheresis was considered in addition to rituximab and IVIG for the treatment of humoral rejection.

Immunopathologic findings for acute antibody-mediated rejection include positive immunofluorescent staining for C4d, C3d, and anti-HLA-DR or immunoperoxidase staining for C4d and CD68 (or C3d).

3.2. The MCS study

In this retrospective study, we analyzed data from patients who underwent implantation of ventricular mechanical circulatory support (MCS) devices between 2008 and 2025. All patients who received medium- or long-term support devices during this period were

included. A total of 27 durable ventricular assist devices were implanted. Patients were followed for an average duration of 42.9 ± 38.9 months, starting from device implantation and continuing until device removal, patient death, or transfer to adult care. Patients were categorized into two groups according to the type of hemodynamic support: pulsatile-flow versus continuous-flow devices. Anthropometric characteristics were recorded, and each patient's clinical condition at the time of implantation was assessed using the internationally accepted INTERMACS classification(29), a simplified overview of which is presented in Table 4 below.

3.2.1. Preoperative evaluation

To evaluate tissue perfusion, renal function was assessed prior to implantation(30, 31). Glomerular filtration rate (GFR) was calculated using the bedside Schwartz formula(32), with impaired renal function defined as a GFR < 60 mL/min/1.73 m². To assess oxygen-carrying capacity, we analyzed preoperative hemoglobin levels. As an objective perioperative parameter, we recorded the number of days of mechanical ventilation, counting each initiated 24-hour period as a full day.

3.2.2. Clinical Outcomes

Patients were classified into three outcome categories based on the result of MCS therapy:

1. Successful bridge to transplantation
2. Death during MCS support
3. Successful weaning from mechanical support (bridge-to-recovery)

Among patients who subsequently underwent heart transplantation, we assessed the immunological impact of MCS by determining the proportion of sensitized patients and the number of post-transplant rejection episodes. Significant rejection was defined as ISHLT grade 2–3R cellular rejection (moderate or severe by histology) or rejection with hemodynamic consequence(28).

Table 4: INTERMACS stages (33)

Profile	Description
Profile 1	**Critical cardiogenic shock:** Patients are in life-threatening shock with critical hypoperfusion, often on high-dose intravenous (IV) pressors/inotropes, and require immediate intervention (hours).
Profile 2	**Progressive decline on inotropic support:** Patients are dependent on IV inotropic support and continue to deteriorate despite escalating doses or temporary MCS (e.g., IABP), but are not in critical shock.
Profile 3	**Stable but inotrope dependent**: Patients appear clinically stable on *stable*, mid-level doses of IV inotropes but cannot be weaned off the medication without symptomatic hypotension or organ dysfunction. They can be in the hospital or occasionally at home.
Profile 4	**Resting symptoms on oral therapy ("Frequent Flyer"):** Patients have recurrent advanced heart failure symptoms (e.g., orthopnea, dyspnea) at rest at home despite optimal oral therapy and frequent hospitalizations (the "frequent flyer" modifier).
Profile 5	**Exertion intolerant (Housebound)**: Patients are comfortable at rest but severely limited by minimal physical activity and largely housebound, without overt fluid overload at rest.
Profile 6	**Exertion limited**: Patients are similar to Profile 5 but slightly more active, able to perform minor activities outside the home (e.g., going to a restaurant) before fatigue sets in. They have no evidence of fluid overload at rest.
Profile 7	**Advanced NYHA Class III symptoms**: Patients are clinically stable with a reasonable level of comfortable activity but have severe, objective limitations with more than mild exertion, corresponding to advanced NYHA Class III symptoms.

IV: intravenous; IABP: inta-aortic balloon pump; NYHA: New York Heart Association

3.3. Statistics:

All analyses were performed using Statistical Package for Social Sciences (SPSS) software (SPSS, Chicago, IL, USA). Data are expressed as mean ± SD, median and [range], or numbers and percentages as appropriate. To assess for normality, all data were first analyzed using the Kolmogorov–Smirnov test. Categorical variables were compared using the Chi-square test or Fisher's exact test; continuous variables were compared using the Student's t-test and Mann–Whitney U test where appropriate. For the comparison of numerical (continuous/scaled) data from three or more independent groups, the analysis of variance (ANOVA) method was used. Between-group survival after transplantation was compared using the Kaplan–Meier survival analysis, and Cox-regression. All p-values were two-tailed, and $p < 0.05$ was considered statistically significant

3.4. Ethics:

All studies were conducted in accordance with the guidelines of the Declaration of Helsinki, with the approval of the Scientific and Research Ethics Committee of the Health Sciences Council (BM/22988-3/2024, 3/10/2024; OOI/Ált08018-1/2025).

4. Results

4.1. The heart transplant study

4.1.1. Demographic Data:

The median age at transplantation was 11 years in both (CHD and CMP) groups (range: 2.9 months–17.5 years). There were no significant differences between the two groups in terms of patient body size. The only significant difference was observed in gender distribution. There was a moderate female predominance in the group with cardiomyopathy, while there was a significant male predominance in the group with congenital heart disease (p = 0.018). Detailed anthropometric data are presented in Table 5.

Table 5: Anthropometric data of Hungarian pediatric heart transplantation

	CMP	CHD	Total	p:
Median age at the time of HTX (years (range))	11.5 (0.2–16.9)	11.1 (0.5–17.5)	11.5 (0.21–7.5)	0.761
Male/Female	18/24	15/5	33/29	**0.018**
Body weight (kg)	38.4 ± 26.3	35.4 ± 21.9	37.5 ± 24.8	0.638
Height (cm)	132 ± 39.0	132 ± 38.4	132 ± 38.5	0.945
Body mass index (kg/m^2)	18.5 ± 5.9	17.8 ± 3.6	18.3 ± 5.2	0.759
Body surface area (m^2)	1.16 ± 0.57	1.11 ± 0.52	1.15 ± 0.55	0.582

HTX: heart transplantation

4.1.2. Diagnosis:

The detailed diagnoses of the two patient groups are presented in Table 6. As noted in the introduction, the CHD group is dominated by various stages of univentricular palliation. More than three-quarters of the patients in the CMP group have dilated cardiomyopathy.

Table 6: Primary diagnosis of heart transplanted children

Diagnosis			
CHD	Number of Patients	CMP	Number of Patients
Univentricular heart, Norwood stage 1 palliation	1	Dilated CMP	33
Tricuspid atresia after pulmonary arterial banding	1	Restrictive CMP	3
Univentricular heart, Norwood stage 2 (Glenn) procedure	3	Noncompact CMP	5
Univentricular heart, Norwood stage 3 (total cavopulmonary connection)	4	Arrhythmogenic CMP	1
Tetralogy of Fallot	2		
Transposition of great arteries	1		
Congenitally corrected transposition of great arteries (CCTGA)	4		
Combined valvular aortic disease	2		
Valvular pulmonary stenosis	2		

CHD: congenital heart disease
CMP: cardiomyopathy

4.1.3. Waitlist

During the study period, waiting list duration was analyzed according to weight categories in order to obtain objective, quantifiable information. Based on this sub analysis, it can be concluded that although no statistically significant differences were observed among the three predefined weight groups, the mean waiting time for patients weighing more than 50 kg was approximately half of that observed in patients with lower body weight

Hungary became a full member of Eurotransplant in 2012. The impact of this accession on waiting times was evaluated, including subgroup analyses stratified by body weight. Based on these analyses, no statistically significant differences were detected in any of the weight-based subgroups; however, a reduction of more than 40% in waiting time was observed in the two higher weight categories. Detailed results are presented in Table 7

Table 7. Waiting times of successful pediatric heart transplants

	0-10 kg	10-50 kg	+50 kg	Total	
Before ET (days)	46.4 ± 52,2	168 ± 157	73 ± 95.5	113.1 ± 130.9	
Post ET (days)	189.2 ± 142.8	100.4 ± 189.6	39.3 ± 61.44	91.2 ± 161.1	
p:	0.137	0.31	0.545	0.585	
Total	109.9 ± 121.1	118.3 ± 181.7	47.7 ± 69.4	97.9 ± 151.7	p: 0.303

ET: Eurotransplant

4.1.4. Follow-Up:

Patients were followed until their 18th birthday or death. No patients were lost during follow-up. The median follow-up in the CMP group was 45.5 (0–177) months, while slightly less 40 months (0.2–117.5) in the CHD group (p = NS).

4.1.5. Laboratory findings:

Preoperative renal function showed notable differences between the two study groups CHD vs. CMP). The mean creatinine clearance calculated using the bedside Schwartz formula (32) was significantly lower in the CHD group (74.3 ± 20.5 vs. 90.3 ± 21.7 mL/min/m², **p = 0.008**). Chronic renal insufficiency (creatinine clearance < 60 mL/min/m²) was also more common among CHD patients (6/20 — one case with missing data — vs. 2/41, **p = 0.012**).

When comparing heart transplanted patients with and without ventricular assist device (VAD) support (regardless of underlying diagnosis), those with VAD therapy demonstrated superior pre-transplant renal function (GFR: 80.6 ± 28.5 vs. 96.5 ± 18.1 mL/min/m², **p = 0.04**).

Hemoglobin concentration, as a key indicator of oxygen transport capacity, was also evaluated. CHD patients presented with higher mean hemoglobin levels (132.2 ± 34.2 g/L vs. 114.0 ± 17.1 g/L, p = 0.07), although neither group exhibited clinically significant anemia on average.

4.1.6. Pre-Transplantation Surgical History (Including MCS)

In the CMP group, 19 patients underwent major surgery prior to transplantation. Nearly 40% (16/42) received mechanical circulatory support devices, and one infant underwent pulmonary artery banding according to the Giessen protocol as an intermediary palliation(9).

Two other patients in the CMP group had previous cardiac surgeries (ASD and VSD closure, respectively), but these were unrelated to the underlying cause leading to transplantation, which was genetically proven to be familial dilated cardiomyopathy (DCM) in both cases.

The need for MCS in the CHD group was much lower, 10% (2/20), than in the CMP group.

For two patients in the CHD group, transplantation was the first major cardiac procedure. In the remaining 18 patients, 44 cardiac surgical procedures were performed prior to transplantation; thus, CHD patients underwent HTX after significantly more multiple

major cardiac surgeries (defined as palliative/reconstructive operations or assist-device implantation) per patient (2.5 [0–5]) compared to CMP patients (0.5 [0–2], **p < 0. 01**), without significant allosensitization.

4.1.7. Usage of Foreign Materials:

Data on pre-transplant, perioperative blood consumption were available for 57 patients (17/40). Comparing red blood cell usage in the two groups showed a marked difference (13 ± 17 vs. 5.9 ± 11.3, p = 0.1), but it was not statistically significant. Platelet usage, however, was significantly higher in the CHD group (2.9 ± 4.6 vs. 0.6 ± 1.5, **p = 0.006**). Surgical descriptions were available for 60 patients. Non-biological materials were used in 17/9 cases. Homografts, or homograft products, were used only in the CHD group in six cases; in two other cases, xenografts were also applied during surgery.

4.1.8. Pre-transplantation Sensitization

All but one patient listed for transplantation had available panel reactive antibodies (PRA) levels in the medical files. Unfortunately, the highly sensitive Luminex single antigen test has only been available in our country since 2017, so we had to use the CDC test for nearly all our patients. Despite the large amount of blood transfusions used in both groups prior to transplantation, allosensitization was only observed in three patients (CHD/CMP: 2/1). One of these was a retransplantation after a PGF (primary graft failure) and four other major heart operations with homografts and xenografts (PRA: 21%), and one after three surgeries in which a homograft was also implanted and also required MCS (PRA: 100%).

The one in the CMP group needed long-lasting MCS (PRA: 59%).

Mean PRA was not significantly different in the two groups (7.68 (0–100%) compared to 3.14 (0–59%); p = 0.27)

4.1.9. Perioperative Data:

Perioperative outcomes are summarized in Table 8.

None of the patients required permanent pacemaker implantation, although temporary pacing was necessary in 11 cases during the early postoperative period, primarily due to reduced atrial activity.

Diaphragmatic paralysis occurred in four patients (three CHD and one CMP), two of which were related to interventions undertaken before transplantation. In one case, postoperative mechanical circulatory support (BiVAD) was required due to primary graft dysfunction. Additionally, three patients underwent dialysis treatment after transplantation.

To assess surgical complexity, total operative time and cardiopulmonary bypass (CPB) duration were analyzed. As anticipated, CMP patients experienced significantly shorter bypass times and overall operative times and required shorter durations of invasive mechanical ventilation.

The incidence of acute kidney injury (AKI), categorized according to KDIGO criteria (34), did not differ significantly between the two groups.

Table 8. Perioperative data of heart transplantation

	CMP	CHD	p
Ischemic time (min)	181 ± 54	208 ± 48	0.056
CPB time (min)	219 ± 127	295 ± 141	**0.049**
Operative time (min)	375 ± 162	468 ± 156	**0.037**
Ventilation (days)*	3 ± 1.9	7 ± 6.9	**0.021**
AKI stage 0 (n/percent)	22/52%	7/35%	0.25
AKI Stage 1 (n/percent)	6/14%	3/15%	
AKI Stage 2 (n/percent)	2/5%	3/15%	
AKI Stage 3 (n/percent)	12/29%	7/35%	
Postoperative transient pacemaker	4	7	

Nervus phrenicus paresis	1	3	

CBP: cardiopulmonary bypass; AKI: acute kidney injury

4.1.10. Rejection and Graft Failure:

Thirteen rejection episodes required active treatment: four in CHD patients (20%) and nine in the CMP cohort (21%).

Throughout the follow-up period, 12 grafts were lost in 11 patients. No issues related to treatment adherence were identified as contributory factors. One graft was lost in a patient transplanted with a positive crossmatch, who nonetheless experienced four years of improved quality of life before developing chronic humoral rejection with no further therapeutic options available. Another graft was lost due to therapy-resistant humoral rejection, and this patient subsequently underwent a successful retransplantation.

Two additional graft failures were attributed to cellular rejection. Two perioperative deaths occurred due to primary graft failure; one of these patients was bridged with ECMO to early retransplantation, though without success.

There was no significant difference in graft loss between the CHD and CMP groups

Table 9: Causes of graft loss

	PGF	Rejection	Infection	Tumor	Other	Early 0–30 days	Intermediate 31–365 days	Late + 365 days	Total
CMP N = 42	1	2	1	1	1	1	1	5	6
CHD N = 20	1	2	1	1	1	1	3	2	6

PGF: primary graft failure; CMP: cardiomyopathy; CHD: congenital heart disease

Overall graft survival during follow-up was 83%, with a rate of 70% in the CHD group and 85% in the CMP group (p = NS). Based on our data, the estimated 1-year graft survival was 80% (95% CI: 64.3–99.6%) for CHD patients and 95.2% (95% CI: 89.0–100%) for those in the CMP group. The estimated 5-year survival was 80% (95% CI: 64.3–99.6%) in the CHD group compared to 87.4% (95% CI: 75.8–100%) in the CMP group.

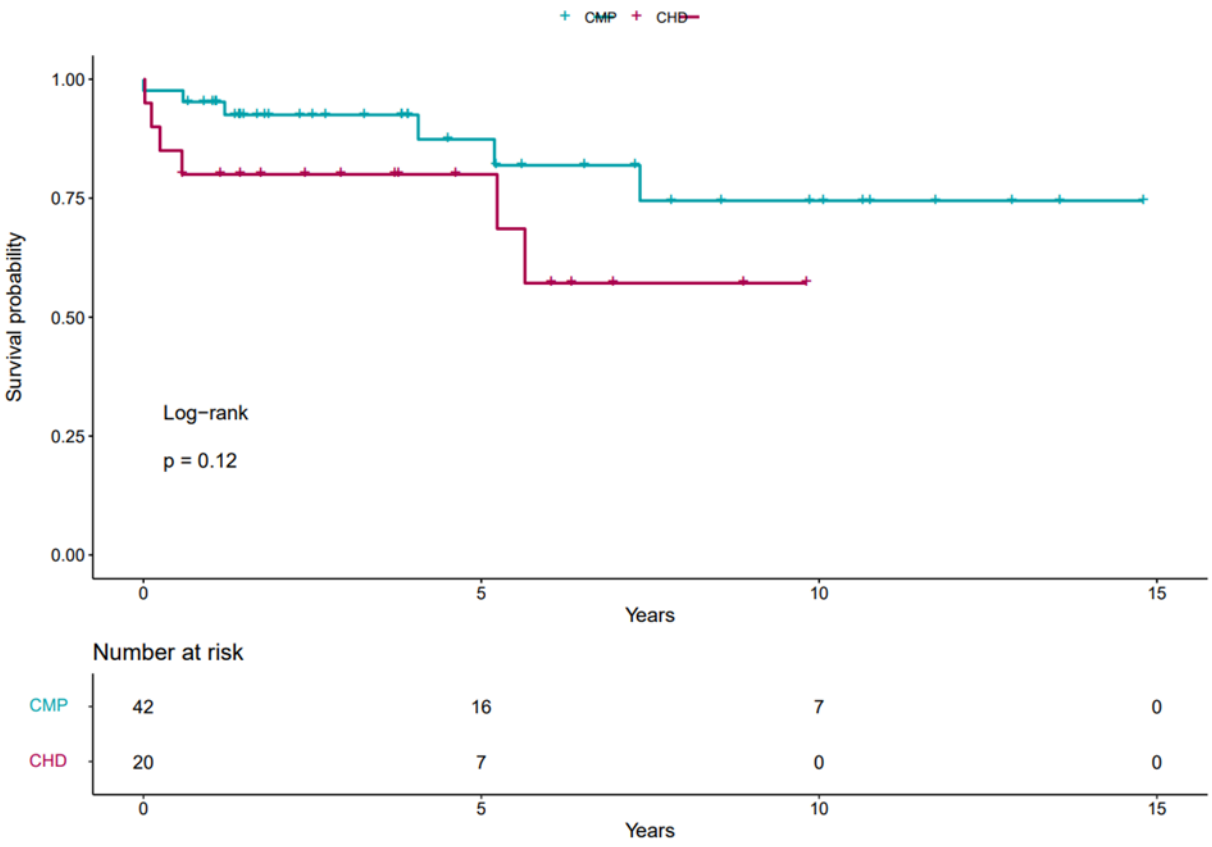

Figure 1: Survivor curve of pediatric heart transplantation

Cox regression analysis did not reveal a statistically significant association between heart failure etiology and post-transplant mortality, with congenital heart disease (CHD) yielding a hazard ratio of 2.1 (p = 0.2). In the multivariate model, preoperative surgical history, impaired renal function, and prolonged postoperative mechanical ventilation were not independently associated with an increased risk of mortality following transplantation.

4.1.11. Neurological Outcome

Significant disability was observed after transplantation in five children due to embolic stroke. All required MCS, with the complication occurring during MCS in all but one case. There were no other notable neurological complications during and after the transplantation.

4.2. The MCS study:

4.2.1. Historical overview

At the beginning of the program, only a single device was available, the BerlinHeart Excor®, a paracorporeal system that provides organ perfusion through a pneumatic mechanism. In the early phase, biventricular support was utilized; however, due to the higher rate of complications, we gradually transitioned—whenever feasible—to isolated left ventricular support. Subsequently, continuous-flow, fully implantable devices (HeartWare™ and HeartMate 3™) became available for larger children (above 20 and 40 kilograms).

4.2.2. Anthropometrics, duration of support and follow-up

The median age of patients at the time of implantation was 9.14 ± 5.86 years. The sex distribution was 40/60%, indicating a slight predominance of females. The mean body weight was 36.6 kg (range: 4–98 kg), while mean height was 130 cm (58–180 cm).

The mean duration of circulatory support was 217 days, with the shortest period being 20 days and the longest nearly 800 days (798).

During this period, pulsatile-flow and continuous-flow devices were used in similar proportions. The annual distribution of implantations and device types is shown in Figure 2.

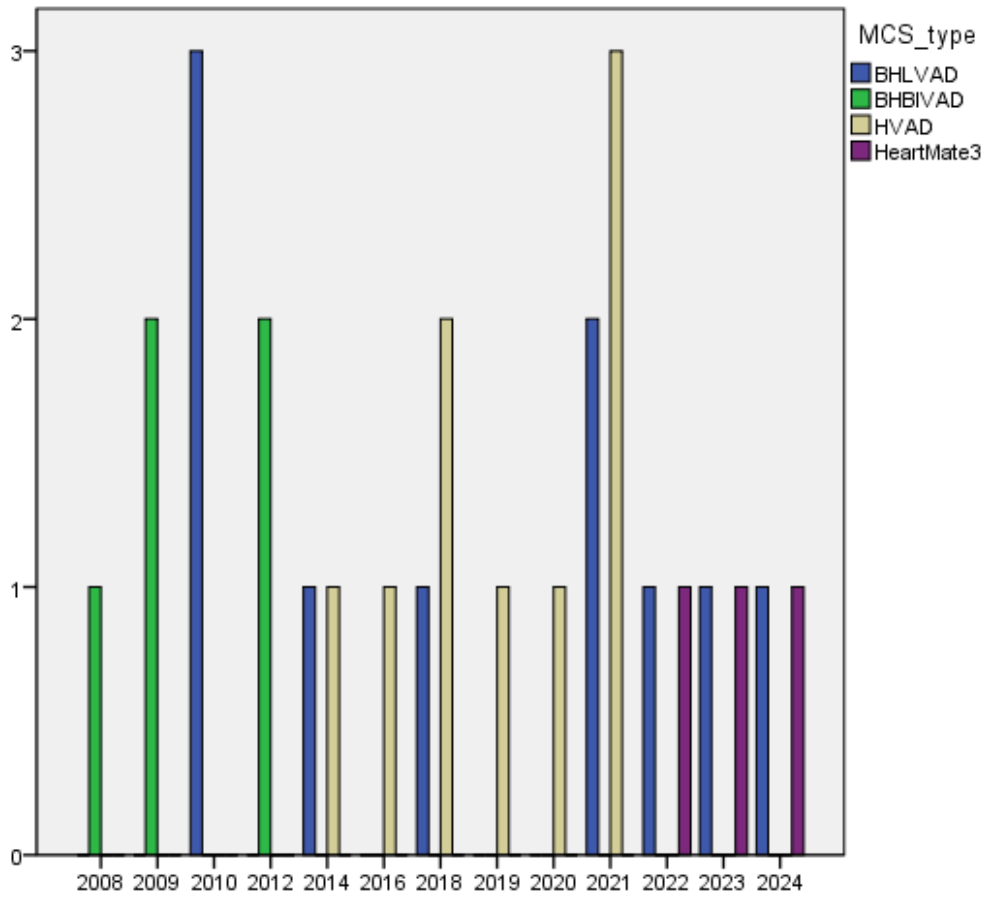

Figure 2: MCS implantation/year

BHBiVAD: BerlinHeart Excor® biventricular assist device; BHLVAD: BerlinHeart Excor® left ventricular assist device; HVAD: Heartware™; HM3: HeartMate3™;

The proportion of biventricular support was higher in the early phase; however, after 2012, almost exclusively left ventricular assist devices were used. In total, 22 patients (81.5%) received isolated LV support, which closely mirrors international data (81%)(35). Five patients (18.5%) received biventricular support, all with the BerlinHeart Excor® device.

4.2.3. Preoperative data

Patients' primary diagnoses and device types are summarized in Table 10.

Table 10: Primary diagnosis of different mechanical circulatory supports

	pulsatile paracorporal		Continuous flow centrifugal		
	BHLVAD	BHBiVAD	HVAD	HM3	Total
DCM	8	3	3	2	16
CHD	1	2	0	0	3
Myocarditis	1	0	4	0	5
RCM, NCCM	0	0	1	1	2
Toxic	0	0	1	0	1
Total	10	5	9	3	27

BHBiVAD: BerlinHeart Excor® biventricular assist device; BHLVAD: BerlinHeart Excor® left ventricular assist device, CHD: congenital heart disease; DCM: dilatative cardiomyopathy; HVAD: Heartware™; HM3: HeartMate3™; NCCM: non-compact cardiomyopathy; RCM: restrictive cardiomyopathy

A total of 74% of patients were implanted at INTERMACS level 2, indicating that the patient could not be stabilized even with combined or escalating inotropic therapy. Circulatory status was well reflected by the markedly elevated NT-proBNP values measured in 70% of patients. In the remaining cases, the test was either not technically available, or BNP measurements (the previously used assay) were recorded in the documentation. There was no significant difference in NT-proBNP levels between patients supported with pulsatile-flow versus continuous-flow devices. In four patients (15%), device implantation occurred under even more critical circumstances, essentially as immediate life-saving intervention.

Elective implantation was performed in two patients, where the indication was secondary pulmonary hypertension resulting from left ventricular failure. These patients did not receive intravenous inotropes prior to implantation.

When comparing pulsatile-flow and continuous-flow devices, we found that patients supported with pulsatile devices were significantly smaller both in age and anthropometric measures than those receiving continuous-flow devices.

Detailed data are provided in Table 11. Based on the table, a significant difference in the duration of support is also evident.

Table 11: anthropometric data, preoperative results and post-transplant rejections of MCS

MCS type	Pulsatile paracorporal (n=15)	Continuous flow centrifugal (n=12)	p
Weight (kg)	21±16.7	56±21.2	< **0.001**
Height (cm)	108±32	157±13.9	< **0.001**
Age at the time of implant (year)	5.3±4.9	13.9±2.5	< **0.001**
Treatment time (days)	141±90	312±212	**0.009**
Follow-up time (months)	48.5±48.5	35.9±22.1	0.414
Preop GFR	81,1±26.4	66.5±32.3	0.214
Preop NTproBNP (pg/ml)	17490±11738 (n=8)	9552±9216 (n=11)	0.116
Preop hemoglobin (g/l)	110.8±16.6	125±24	0.08
Ventilator days	19.9±32	5.9±6.2	0.166
INTERMACS	1.93±0.45	2.5±1.67	0.278
Preop. azoteamia	3/15	4/12	0.68
Posttransplant rejection	3/15	1/12	0.605

MCS: mechanical circulatory support; GFR: glomerular filtration rate

Patients with continuous-flow devices required longer support (312 days on average; **p = 0.009**).

The mean duration of mechanical ventilation tended to be shorter among patients with implantable continuous-flow devices than in those with the more invasive paracorporal systems, but this difference did not reach statistical significance (19.9 vs. 5.9 days; p = 0.166).

No significant anemia was observed in either group prior to implantation, and the group averages did not differ substantially.

4.2.4. Clinical Outcomes

More than 70% of patients in both groups underwent successful transplantation (66% vs. 83%).

However, 26% of patients in the pulsatile-flow group were lost due to severe complications, whereas no device-associated mortality occurred in the continuous-flow group. At the time of writing, no patient remained on device support.

In each group, one patient was successfully weaned from support after prolonged cardiac recovery following fulminant myocarditis; however, after the removal of the pulsatile device, the patient—despite good cardiac status—died due to severe neurological complications. Regarding complications, the advantage of continuous-flow devices is also evident: complication-free support occurred in 8 out of 12 cases in this group, compared to only 40% in the pulsatile group. This is consistent with international data showing a twofold higher cerebrovascular complication rate in the pulsatile-flow group.

Exact complication numbers are shown in Table 12.

Table 12. Complications during mechanical circulatory support

	Pulsatile paracorporal		Continuous flow centrifugal		
Complication	9/15 (60%)		4/12 (33%)		p: 0,25
	BHLVAD n=8	BHBiVAD n=5	HVAD n=9	HM3 n=3	Total n=27
No complication	5	1	6	2	14
Thromboembolism	2	1	0	1	4
Bleeding	0	1	1	0	2
Infection	0	0	1	0	1
Thromboembolism and bleeding	1	1	0	0	2
All three	1	1	1	0	3
Other	1	0	0	0	1
Total	10	5	9	3	27

BHBiVAD: BerlinHeart Excor® biventricular assist device; BHLVAD: BerlinHeart Excor® left ventricular assist device; HVAD: Heartware™; HM3: HeartMate3™;

Based on eGFR, 26% of patients had eGFR values below 60 prior to implantation.

The numerical difference between groups was not statistically significant (81.1 vs. 66.5 mL/min/1.73 m²; p = 0.214).

When dividing patients into preserved and impaired renal function groups, the difference remained non-significant (3/15 vs. 4/12; p = 0.66).

Importantly, none of the surviving patients required chronic renal replacement therapy.

Among the 20 transplanted patients, only two exhibited significant sensitizations accompanied by elevated panel-reactive antibody levels.

Both were supported with paracorporeal devices and both had undergone previous congenital heart surgery involving considerable blood product exposure.

No relevant sensitization occurred in the remaining patients.

Regarding postoperative rejection rates, no substantial differences were observed between the two groups (1/12 vs. 3/15).

5. Discussion

Our finding provides a more comprehensive picture of the therapies used in Hungary for end-stage heart failure in children.

The factors triggering end-stage circulatory failure in children differ from those in adult patients. In contrast to the most common etiological factor in adult organ replacement therapy, ischemic heart disease, the leading cause in children is non-ischemic dilated cardiomyopathy, followed by congenital heart disease. Similar to the international experiences (37), such patients are increasingly included among the indications for pediatric heart transplantation in Hungary. Among them, children who have undergone single-ventricle palliation represent an increasingly large proportion. Postoperative outcomes are influenced by a number of factors, but graft survival after successful heart transplantation also has limitations, so timely listing plays a key role. Such preoperative factors may include adequate oxygen transport capacity(38), the presence of target organ damage(39), and the degree of preoperative immunization (18). The latter is thought to be mainly due to the use of homografts and blood products, as well as the need for mechanical circulatory support prior to transplantation. In our cohort, we were unable to demonstrate a significant negative effect of any of these factors on graft survival. It is important to note, however, that no patients with severe damage requiring renal replacement therapy were included in the study. Although the preoperative hemoglobin concentration was significantly higher in the CHD group, presumably due to the compensatory polycythemia of the cyanotic patients, this was not a factor that significantly influenced the prognosis. Severe postoperative renal failure might affect the outcome. Although this study didn't prove that renal failure leads to a worse prognosis, the groups are small and the data aren't statistically significant.

In terms of surgical risk, a very significant factor, in addition to the complex anatomy, is the presence of previous thoracic surgical manipulations and the formation of a significant collateral network caused by prolonged cyanosis. However, these pose not only surgical but also immunological risks. More than half of the 62 transplant patients underwent major cardiac surgery (VAD or palliative/reconstructive surgery) prior to transplantation. Nevertheless, we were unable to detect increased sensitization. It is important to note, however, that our tests were performed using complement-dependent cytotoxicity testing,

as newer flow cytometry-based cross-reactivity testing has only been available in Hungary since 2017.

On the other hand, the number of previous surgeries significantly increased both the cardiopulmonary bypass and the total surgical time. This was mainly due to longer bleeding control and, especially in the CHD group, frequent additional surgical manipulations.

Thirty percent of patients who later underwent transplantation and nearly 40% of patients who underwent transplantation due to myocardial disease required mechanical circulatory support for some indication. These indications can be divided into three main categories: bridge-to-recovery, bridge-to-transplantation, and bridge-to-decision. This therapy is not applicable as a destination therapy in children. The cases in our own database are also from this group of indications, so their number exceeds that of treatments purely prior to transplantation.

The vast majority of patients undergo surgery in a progressively deteriorating condition (INTERMACS stage 2) even with combined inotropic therapy. From a prognostic point of view, it can be said that renal impairment can negatively affect the outcome. This was observed in a quarter of patients. The effectiveness of the therapy is supported by the fact that none of the survivors required chronic renal replacement therapy. This may be partly due to the absence of comorbidities, which are rare in childhood compared to adult cases.

Adult studies have shown that anemia can be a factor influencing the prognosis of heart failure (38). No significant anemia was observed in our analysis of the study population.

When comparing systems with different flow kinetics, we observed significant differences. The above classification differs not only in terms of mechanics, but also in that continuous flow devices are placed intracorporeally, while pulsatile devices are placed paracorporally.

For lower body weights (<20 kg), the BerlinHeart Excor® device is currently the device with the most extensive global experience, but its use carries a higher risk (35). The implantation rate of paracorporeal pulsatile pumps is around 40% worldwide (35), compared to which our own data show a slightly higher rate, which may be due to the fact that only this device was available at the onset of the program. Literature data support that low body weight is an independent risk factor for MCS (26). Based on the literature,

treatment is associated with a complication rate of around 50%(40). The higher complication rate compared to the published data can be explained by the low number of cases, the learning curve, and the use of anticoagulation protocols that were applied in the past but have since undergone significant revision. Of the available implantable devices (axial versus centrifugal LVAD), we used centrifugal magnetic pumps (Heartware™, HeartMate3™, HeartMate3™) and applied them successfully.

In the comparison of pulsatile and continuous-flow mechanical circulatory support systems, both our institutional experience and international reports suggest that continuous-flow devices are associated with a lower risk of complications. International studies have also described a reduced requirement for intensive care unit treatment in patients supported with continuous-flow systems (35).

Comparing the time of ventilatory support our analysis showed that the use of paracorporeal devices was associated with a trend toward longer ventilation times; however, this difference did not reach statistical significance, likely due to the limited sample size.

An important advantage of continuous-flow devices, which is difficult to quantify using clinical parameters but highly relevant from a psychosocial perspective, is that patients can be discharged home while receiving this therapy. In both modalities, a high proportion of patients were successfully bridged to transplantation. According to international registry data (40), the success rate—defined as support until weaning or transplantation—is approximately 80%, whereas this rate was 85% in our patient cohort.

In cases of surgically successful transplantation, the length of intensive care is a decisive factor in recovery. This is significantly influenced by the need for ventilation. In the 62 patients analyzed, this proved to be 4.3 ± 4.5 days on average. Our CHD patients spent significantly longer on ventilation, which can be explained by longer operative times, related to the increased number of previous cardiac operations and additional surgical procedures during the HTX.

No significant differences were observed between the transplant etiology groups with respect to early mortality within 30 days. Early postoperative mortality was primarily attributable to primary graft failure and its related complications. In contrast, the previously described surgical technical difficulties, prolonged cardiopulmonary bypass

time, and extended duration of mechanical ventilation did not constitute risk factors for early mortality in the CHD group(36).

Mortality occurring beyond 30 days post-transplant was mainly associated with infection, rejection, and malignancy. Although long-term survival appeared slightly inferior in the CHD group, this trend did not reach statistical significance.

The 5-year and 10-year survival rates of the combined cardiomyopathy and congenital heart disease (CM/CHD) cohort were marginally lower than those reported in recent ISHLT registry data(37). This difference may be related to the relatively low transplant volume of the center and the limited number of cases included in the analysis.

While a longer postoperative recovery period can be anticipated in patients with congenital heart disease, this was not associated with a statistically significant increase in mortality, but rather reflected a non-significant trend. The degree of pre-transplant sensitization did not differ between the groups, which may explain the absence of differences in the frequency and severity of rejection episodes. Nevertheless, longer follow-up and larger patient cohorts are required to adequately assess potential differences in the incidence of transplant-related conditions between the two groups.

In summary, the most important message of these studies is that both advanced therapies—MCS as a temporary solution until transplantation and HTX itself—are effective and viable for pediatric patients in Hungary and, despite the unique challenges posed by congenital anatomical features and the small size of the patients, produce results that meet international reference values.

5.1. Limitations

The findings of the present studies should be interpreted in light of several important limitations. First, both analyses are based on a relatively small patient population and originate from a single-center experience. Although this cohort represents a considerable case volume in the context of pediatric heart transplantation and mechanical circulatory support, the limited sample size restricts statistical power and may have precluded the detection of smaller but clinically relevant differences between subgroups. Consequently, causal inferences cannot be drawn, and several observed associations should be regarded as exploratory rather than definitive

Second, the retrospective design of both studies inherently limits data completeness and uniformity. Certain clinical and laboratory parameters—such as detailed immunological profiling using modern single-antigen bead assays or consistently available preoperative biomarkers—were not obtainable for all patients. In particular, assessment of allosensitization relied predominantly on complement-dependent cytotoxicity assays, as more sensitive techniques were not routinely available throughout the entire study period. This limitation may have led to an underestimation of subclinical sensitization and donor-specific antibody formation

Third, temporal heterogeneity represents a relevant limitation. Over the extended study periods, significant advancements occurred in surgical techniques, perioperative management, immunosuppressive strategies, anticoagulation protocols, and device technology. Especially in the mechanical circulatory support cohort, both paracorporeal pulsatile systems and newer continuous-flow implantable devices were used during different eras, each associated with distinct complication profiles. These evolving practices could not be fully adjusted for in the analyses and may have influenced outcomes independently of patient-related factors

Another important limitation relates to follow-up duration and continuity of care. Due to national regulations, pediatric patients are transferred to adult care after reaching 18 years of age, which restricts long-term follow-up, particularly for patients transplanted during adolescence. As a result, late complications—including chronic rejection, malignancy, and long-term end-organ dysfunction—may be underrepresented. Integration of adult

follow-up data would be essential for a more comprehensive assessment of long-term outcomes.

Finally, the rarity and heterogeneity of pediatric end-stage heart failure necessitate cautious interpretation of subgroup analyses. Differences in underlying diagnosis, body size, disease trajectory, and timing of intervention introduce confounding factors that cannot be fully controlled in single-center observational studies. Multicenter collaborations and prospective registries are therefore required to validate these findings, refine risk stratification, and optimize therapeutic strategies for both pediatric heart transplantation and mechanical circulatory support

6. Conclusions

The aim of this dissertation was to comprehensively evaluate the Hungarian experience with organ replacement therapies in pediatric end-stage heart failure, with particular emphasis on heart transplantation and mechanical circulatory support, and on the impact of underlying etiology and device characteristics on outcomes. Based on the presented results, the following main conclusions can be drawn:

Pediatric heart transplantation in Hungary is an effective and safe therapeutic option, providing short- and mid-term survival outcomes that are comparable to international registry data. Despite the relatively low patient number and the single-center nature of the program, overall graft survival and patient outcomes meet accepted international standards, confirming the advanced level of development and robust reliability of the national pediatric heart transplant program.

The underlying etiology of heart failure did not emerge as an independent predictor of post-transplant survival in our study cohort. Although children transplanted for congenital heart disease (CHD) present with more complex anatomical conditions, a higher number of previous cardiac surgeries, and a more demanding perioperative course, these factors did not translate into a statistically significant disadvantage in graft survival or overall mortality when compared with patients transplanted for cardiomyopathy (CMP). Multivariate and Cox regression analyses confirmed that etiology alone was not an independent predictor of mortality.

Postoperative recovery was more prolonged in patients with congenital heart disease, as reflected by longer cardiopulmonary bypass times, operative durations, and ventilation requirements. These findings are attributable to surgical complexity rather than inferior graft function. Importantly, these perioperative challenges did not increase early (0–30 day) mortality, indicating that they primarily influence resource utilization and recovery rather than ultimate survival.

Mechanical circulatory support plays a pivotal role in the successful management of pediatric end-stage heart failure. The availability and appropriate use of MCS significantly reduced waiting list mortality and allowed transplantation to be performed under more favorable hemodynamic and metabolic conditions. In the majority of cases,

MCS served as an effective bridge to transplantation, while in selected patients it enabled myocardial recovery.

Continuous-flow ventricular assist devices demonstrate a more favorable complication profile than pulsatile paracorporal systems. Although their use is limited to larger children, continuous-flow devices were associated with fewer device-related complications, shorter ventilatory support requirements, and improved quality of life, including the possibility of outpatient management. Pulsatile devices remain indispensable in small children and infants; however, their use is associated with a higher complication burden and requires intensive monitoring and multidisciplinary expertise.

None of the investigated pre-transplant factors emerged as independent predictors of post-transplant mortality. Prior surgical history, moderate renal dysfunction, and prolonged postoperative ventilation did not show a significant association with mortality in multivariate analyses. These findings suggest that, with careful patient selection and optimized perioperative management, even higher-risk pediatric patients can achieve favorable transplant outcomes.

The degree of pre-transplant sensitization and the incidence of clinically relevant rejection did not differ significantly between etiological groups. This likely reflects standardized immunosuppressive protocols and careful donor–recipient matching. Nevertheless, long-term immunological surveillance remains essential, particularly as more sensitive diagnostic techniques become routinely available.

In conclusion, our results demonstrate that advanced organ replacement therapies—mechanical circulatory support as a bridging strategy and heart transplantation as definitive treatment—are both feasible and highly effective for children with end-stage heart failure in Hungary. The additional challenges posed by congenital heart disease primarily affect perioperative management rather than long-term survival. Continued technological progress, standardized protocols, and multicenter collaboration will be essential to further reduce complications, optimize timing of intervention, and improve long-term outcomes for this vulnerable patient population.

7. Summary

Pediatric heart failure is a rare but life-threatening condition with etiological characteristics that differ substantially from those observed in adults. In childhood, end-stage heart failure most commonly arises from non-ischemic dilated cardiomyopathy and complex congenital heart disease. In such cases, advanced organ replacement therapies, including heart transplantation (HTX) and mechanical circulatory support (MCS), represent the only definitive treatment options. As these therapies are performed exclusively at our national center, this study provides a comprehensive overview of pediatric organ replacement therapy in Hungary.

Two retrospective analyses were conducted. The heart transplantation cohort included all pediatric patients (<18 years) who underwent HTX between 2007 and 2022 (n=62). Patients were categorized according to underlying diagnosis as cardiomyopathy (CMP, n=42) or congenital heart disease (CHD, n=20). Perioperative variables, rejection episodes, and graft survival were analyzed using appropriate statistical methods, including Kaplan–Meier survival analysis and Cox regression modeling. Overall graft survival during follow-up was 83%. One-year survival was 95.2% in the CMP group and 80% in the CHD group, while five-year survival reached 87.4% and 80%, respectively. Although CHD patients required longer cardiopulmonary bypass and operative times and experienced prolonged mechanical ventilation, no statistically significant difference in long-term mortality was demonstrated between the two groups.

The second study evaluated pediatric patients receiving durable ventricular MCS between 2008 and 2025 (n=27). Patients were divided according to device type into pulsatile paracorporeal and continuous-flow implantable systems. Successful bridge-to-transplantation or recovery was achieved in more than 70% of cases. Continuous-flow devices were associated with lower complication rates and no device-related mortality, whereas pulsatile systems showed higher rates of thromboembolic and bleeding events.

In conclusion, advanced organ replacement therapies in Hungarian pediatric patients provide outcomes comparable to international reference data. Despite increased surgical complexity in congenital heart disease and small children, heart transplantation remains an effective long-term treatment strategy. Mechanical circulatory support significantly

reduces waiting list mortality and improves pre-transplant clinical status, with continuous-flow systems demonstrating a more favorable safety profile.

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9. Bibliography of the candidate's publications

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