

Mechanical circulatory support in advanced heart failure

Patient selection, treatment strategies and outcomes

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Cover illustration: The mechanical circulation by Tova Mårtensson

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In memory of my father

ABSTRACT

Background: Heart transplantation (HTx) remains the major treatment option for selected patients with end-stage heart failure. In hemodynamically unstable patients, or when there is a considerable risk of deterioration or death during the waiting time for transplantation, treatment with mechanical circulatory support (MCS) can be lifesaving. Durable MCS usually involves either a left ventricular assist device (LVAD) or a biventricular assist device (BiVAD) and can be either fully implantable or paracorporeal. Optimizing patient selection and the choice of pump strategy may lead to fewer complications and better patient outcomes.

Aims: (I) To investigate patients receiving a paracorporeal ‘EXCOR’ pump due to ineligibility for implantable MCS and to study their outcomes and pump-related complications. (II) To study adult patients receiving an EXCOR BiVAD as a bridge to transplantation and to compare them with contemporary LVAD recipients. (III) To investigate the effect of durable MCS treatment and consequent HTx on renal function. (IV) To compare post-transplantation outcomes between patients treated with or without durable MCS as a bridge to HTx.

Methods: Papers I–II are based on a local registry covering all patients who received durable MCS at Sahlgrenska University Hospital. Papers III–IV are based on the Transplant Registry at Sahlgrenska University Hospital. Data from these registries were analyzed retrospectively.

Results: (I) Treatment with paracorporeal ‘EXCOR’ pumps resulted in high survival in both children and adults. Safety was acceptable, but thromboembolism, mechanical pump problems and infections were the most significant complications. (II) Furthermore, survival was comparable between adult contemporary LVAD and BiVAD patients, although the latter were in a hemodynamically more compromised state at baseline. (III) Treatment with durable MCS led to an improvement in measured glomerular filtration rate (mGFR). After HTx, mGFR tended to decline again, but in some subgroups of patients a steady improvement in mGFR was seen. (IV) No differences were observed in graft survival, biopsy-proven rejections or renal function compared with HTx patients not bridged with MCS.

Conclusions: Durable MCS devices of different types can achieve good long-term outcomes as a bridge to transplantation. The results, especially in BiVAD patients, were similar to or better than those previously described. Treatment with durable MCS can be used to stabilize renal function before HTx and was not associated with worse post-HTx outcomes.

Keywords: Mechanical circulatory support, left ventricular assist device (LVAD), biventricular assist device (BiVAD), heart transplantation, advanced heart failure, cardiorenal syndrome, glomerular filtration rate

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LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by Roman numerals.

- I. Bartfay S-E, Dellgren G, Hallhagen S, Wåhlander H, Dahlberg P, Redfors B, Ekelund J, Karason K. Durable circulatory support with a paracorporeal device as an option for pediatric and adult heart failure patients
The Journal of Thoracic and Cardiovascular Surgery 2021 Apr;161(4):1453-1464.e4.
- II. Bartfay S-E, Dellgren G, Lidén H, Holmberg M, Gäbel J, Redfors B, Bech-Hanssen O, Karason K. Are biventricular assist devices underused as a bridge to heart transplantation in patients with a high risk of postimplant right ventricular failure?
The Journal of Thoracic and Cardiovascular Surgery 2017 Feb;153(2):360-367.e1
- III. Bartfay S-E, Kolsrud O, Wessman P, Dellgren G, Karason K. The trajectory of renal function following mechanical circulatory support and subsequent heart transplantation.
ESC Heart Failure 2022 Aug;9(4):2464-2473
- IV. Bartfay S-E, Bobbio E, Esmaily S, Bergh N, Holgersson J, Dellgren G, Bolzano E, Karason K. Heart transplantation in patients bridged with mechanical circulatory support: outcome comparison with matched medically managed controls.
In manuscript

SAMMANFATTNING PÅ SVENSKA

Bakgrund

Hjärtsvikt är ett stort folkhälsoproblem och den främsta orsaken till sjukhusvård hos personer över 65 år och uppskattas stå för 2–3% av den totala sjukvårdskostnaden i Sverige. Vid svår hjärtsvikt, som inte svarar på konventionell behandling, kan i utvalda fall hjärttransplantation bli aktuell. Då patienten riskerar att försämras kraftigt eller avlida i väntan på ett donatorshjärta kan behandling med mekanisk hjärtpump krävas som brygga till transplantation. Pumpar för långtidsanvändning finns av två huvudtyper: dels vänsterkammarpump (LVAD, left ventricular assist device), vilket innebär avlastning av vänster kammare, och dels biventrikulär pump (BiVAD, bi-ventricular assist device), som innebär avlastning av bägge hjärtkamrarna. Pumparna kan antingen vara helt inopererade, vilket är fallet med moderna LVAD-system, eller ha pumphusen utanför kroppen (parakorporeala pumpsystem). Behandling med mekanisk hjärtpump är kostsam, krävande för patienten och innebär betydande risker. Patientselektion för denna behandling är därför av stor betydelse. Likaså är det viktigt att välja rätt pumpsystem. Hur patienter ska väljas ut och vilket pumpsystem de ska få för att uppnå optimala resultat på kort och lång sikt är dock inte väl klarlagt. Vidare är effekten av mekanisk pumpbehandling på njurfunktion ofullständigt beskriven.

Det huvudsakliga syftet med detta doktorandprojekt var (I) att retrospektivt beskriva vår samlade erfarenhet av ett paracorporealt system (EXCOR®) till patientgrupper som inte lämpade sig för behandling med moderna LVAD-system, med avseende på utfall, säkerhet och komplikationer. (II) Att ytterligare studera vuxna patienter som fått behandling med BiVAD-EXCOR som brygga till transplantation och jämföra dem med samtida LVAD-patienter. (III) Att studera effekten av behandling med mekanisk hjärtpump och efterföljande hjärttransplantation på uppmätt njurfunktion (mGFR). (IV) Att jämföra överlevnad och andra utfall efter hjärttransplantation hos patienter som haft respektive inte haft mekanisk hjärtpump. Data hämtades från det lokala pumpregistret (delarbete I-II) respektive transplantationsregistret (delarbete III-IV) på Sahlgrenska Universitetssjukhuset.

Resultat

(I) Vi fann att behandling med ett paracorporealt pumpsystem (EXCOR) resulterade i hög överlevnad hos såväl barn som vuxna. Säkerheten var acceptabel, men med tromboembolism, mekaniska pumpproblem och infektioner som mest betydande komplikationer. (II) Vid jämförelse mellan vuxna LVAD- och BiVAD-patienter fann vi att överlevnaden var likvärdig. Med den strikta selektion som gjorts framstod BiVAD som en rimlig behandling vid mycket svår biventrikulär hjärtsvikt. (III) Behandling med mekanisk hjärtpump ledde till en förbättring av uppmätt njurfunktion (mGFR). Efter hjärttransplantation tenderade njurfunktionen att avta igen, men i vissa subgrupper av patienter sågs en stadigvarande förbättring av mGFR. (IV) Slutligen fann vi att överlevnaden efter hjärttransplantation var jämförbar hos patienter som haft respektive inte haft behandling med mekanisk hjärtpump före transplantationen. Inte heller kunde någon säkerställd skillnad mellan frekvensen av avstötningar eller mGFR ses.

Slutsatser

Mekaniska långtidspumpar kan erbjudas till de flesta patienter som behöver detta som en brygga fram till hjärttransplantation. Med den patientselektion som gjorts var överlevnaden hög och resultatet, framför allt i BiVAD-gruppen, i nivå med eller bättre än vad som tidigare beskrivits. Behandling med hjärtpump leder till förbättring av njurfunktionen. Överlevnad respektive förekomst av avstötningar efter hjärttransplantation är likvärdig med den hos patienter som klarat sig med konventionell medicinsk hjärtsviktsbehandling fram till transplantationen. Således utgjorde inte behandling med mekanisk hjärtpump en nackdel för den svårt sjuka gruppen som krävde detta.

CONTENTS

ABSTRACT	5
LIST OF ORIGINAL PAPERS	6
SAMMANFATTNING PÅ SVENSKA	7
ABBREVIATIONS	11
INTRODUCTION	13
Heart failure	13
Historical background and definitions of heart failure	13
Classification and treatment of heart failure	14
Advanced heart failure	14
The cardiorenal syndrome and chronic kidney disease	15
MCS	17
GFR in MCS patients	20
MCS as BTT - Treatment strategies	20
HTx	22
Complications after HTx	23
Survival after HTx	27
AIMS	29
PATIENTS AND METHODS	30
Patient populations	30
Data collection and registries	31
Methods and definitions	32
Ethics	32
Statistics	33
RESULTS	34
Main findings	34
Specific results of Papers I-IV	34
DISCUSSION	40
Durable MCS in patients less suitable for CF-LVADs	40
Renal function after durable MCS and HTx	42
Post-transplant outcomes in patients treated with or without durable MCS as a bridge to HTx	43
Strengths and limitations	44

CONCLUSIONS	46
FUTURE PERSPECTIVES	47
ACKNOWLEDGEMENTS	48
REFERENCES	50
APPENDIX: PAPERS I-IV	

ABBREVIATIONS

ACR	Acute cellular rejection
AdHF	Advanced heart failure
AMR	Antibody-mediated rejection
BiVAD	Biventricular assist device
BTT	Bridge to transplantation
CAV	Cardiac allograft vasculopathy
CF	Continuous flow
CKD	Chronic kidney disease
CNI	Calcineurin inhibitor
CS	Corticosteroids
DCM	Dilated cardiomyopathy
ECMO	Extracorporeal membrane oxygenation
EF	Ejection fraction
ESC	European Society of Cardiology
GFR	Glomerular filtration rate
HF	Heart failure
HLA	Human leukocyte antigen
HTx	Heart transplantation
ICU	Intensive care unit
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
ISHLT	International Society for Heart and Lung Transplantation
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
MCS	Mechanical circulatory support
MDRD	Modification of Diet in Renal Disease
MMF	Mycophenolate mofetil
mTOR	Mammalian target of rapamycin
NYHA	New York Heart Association
RHC	Right heart catheterization
ROC	Receiver operating characteristic
RV	Right ventricular
RVAD	Right ventricular assist device
TAH	Total artificial heart

INTRODUCTION

Heart failure

Heart failure (HF) is a major public health problem worldwide. In Sweden, its prevalence has been estimated to be $\approx 2\%$, which implies that $\approx 200,000$ people are affected (1). The condition is the commonest cause of hospital stay for patients aged >65 years and has been estimated to constitute 2–3% of total healthcare costs in Sweden (2).

Historical background and definitions of heart failure

Although descriptions of HF symptoms are found in ancient Greek and Roman texts, the pathophysiology behind the condition was poorly understood until Starling described and published his hemodynamic law in 1918 (3). This contributed to the understanding of the work of the healthy heart and to ideas about the hemodynamics of the failing heart. The first right heart catheterization (RHC) was performed by Werner Forssmann in 1929 (4) and this, as well as similar procedures performed in the following year, made it possible to directly measure right-sided pressures and cardiac output (CO). About 10 years later, André Cournand and Dickinson Richards performed more systematic measurements of central hemodynamics, including CO (5). For their discovery of RHC and their work on hemodynamic measurements, Cournand, Forssmann and Richards were awarded the Nobel Prize in Physiology and Medicine in 1956. After the introduction of the balloon-tipped Swan–Ganz catheter, more complete hemodynamic assessments, including measurement of pulmonary arterial wedge pressure (PAWP), which reflects left atrial pressure, could be made. Today, first-line assessment of cardiac function is done by echocardiography and other imaging methods, such as computed tomography and magnetic resonance imaging. However, in patients with advanced forms of HF, invasive hemodynamics still play an essential role (6).

One of the most frequently used definitions of HF was presented by Eugene Braunwald in 1967: “heart failure is a clinical syndrome characterized by well-known symptoms and physical signs... It is the pathological state in which an abnormality of myocardial function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues during ordinary activity” (7). That definition has subsequently undergone various iterations, reflecting advances in knowledge and the conceptualization of HF. The current definition according to the European Society of Cardiology (ESC) is as follows: “Heart failure is not a single pathological diagnosis, but a clinical syndrome consisting of cardinal symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema). It is due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate CO at rest and/or during exercise.” (6).

There are various underlying causes of HF, of which ischemic heart disease, hypertension, valve disease, cardiomyopathies and arrhythmias are the commonest. The diagnostic work-up in HF is presented in the current ESC guidelines (6), where cor-

nerstones are the presence of symptoms and signs, elevated N-terminal pro B-type natriuretic peptide (NT-proBNP) and/or abnormal echocardiographic findings.

Classification and treatment of heart failure

HF can be subdivided in several ways: into acute and chronic HF, based on the underlying etiology; related to symptomatology according to New York Heart Association (NYHA) classes I–IV (8); or based on left ventricular ejection fraction (LVEF). Here, we will focus on classification of HF related to LVEF according to the ESC guidelines (6) (Table 1). EF is the stroke volume (the end-diastolic volume minus the end-systolic volume) divided by the end-diastolic volume and can be expressed either as a decimal fraction or a percentage. For HF with reduced EF (HFrEF) and HF with mildly reduced EF, specific medical therapy, including angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor neprilysin inhibitors (ARNI), beta-blockers, sodium glucose cotransporter-2 (SGLT-2) inhibitors and mineral receptor antagonists (MRA), is recommended. In HF with preserved EF (HFpEF), however, only symptomatic therapy and treatment of underlying diseases is suggested, although SGLT-2 inhibitors have shown positive results in recent trials (9).

Table 1. Definition of heart failure based on LVEF according to the 2021 ESC guidelines

Type of heart failure	HFrEF	HFmrEF	HFpEF
LVEF	≤ 40%	41-49%	≥ 50%
Other criteria	Symptoms ± signs	Symptoms ± signs	Symptoms ± signs
	-	-	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides

LVEF = left ventricular ejection fraction, ESC = European society of Cardiology, HFrEF = heart failure with reduced ejection fraction, HFmrEF = heart failure with mildly reduced ejection fraction, HFpEF = heart failure with preserved ejection fraction

Modern conventional HF treatment including the optimal medical therapy described above and, if certain criteria are fulfilled, cardiac resynchronization therapy (CRT) and/or an implantable cardioverter-defibrillator (ICD), has improved prognosis, particularly for patients with HFrEF, during the past decades (6, 10). However, in individuals with more advanced forms of HF, for whom these therapies have become insufficient, the prognosis remains poor.

Advanced heart failure

Advanced heart failure (AdHF) constitutes ≈5–10% of the total HF population and has attracted attention in recent years, as reflected in current guidelines and by a position statement from the ESC (11). Indications that a patient suffers from AdHF include: 1) severe and persistent symptoms of HF (NYHA functional classes IIIB–IV); 2) severe cardiac dysfunction defined by imaging, biomarkers (NT-proBNP) and/or

hemodynamics; 3) episodes of worsening HF requiring high-dose diuretics and/or inotropes, or malignant arrhythmias causing hospitalization; and 4) severe impairment of exercise capacity measured by objective methods. “Severe cardiac dysfunction” often refers to patients with severely reduced LVEF, although pronounced restrictive physiology or severe right ventricular (RV) failure can also satisfy this criterion. In addition to the above, extracardiac organ dysfunction due to HF and/or secondary pulmonary hypertension may be present but is not required to fulfill the criteria for AdHF.

In patients with AdHF, diagnostic work-up should be carried out in timely fashion and, in selected patients, treatments such as mechanical circulatory support (MCS) and/or heart transplantation (HTx) should be considered (12). In patients who are not eligible for advanced treatment options, the best medical and, in cases of end-stage HF, palliative treatment should be given.

In order to better classify AdHF patients, and especially those suitable for durable MCS, the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles have been developed (13). This classification of severely ill patients in advanced NYHA classes III and IV describes clinical parameters and characteristics consistent with a need for advanced therapies (Table 2). The profiles have also been useful in risk assessment of ambulatory patients in whom such therapies can be considered (14).

Table 2. INTERMACS profiles of advanced heart failure

Profile	Patient characteristics	Inotrope use
1	Critical cardiogenic shock despite escalating support	x
2	Progressive decline despite inotropes	x
3	Clinically stable but inotrope dependent	x
4	Recurrent, not refractory, advanced heart failure	
5	Exertion intolerant but comfortable at rest	
6	Exertion limited; able to perform mild activity, but fatigued within a few minutes of exertion	
7	Advanced NYHA Class III	

INTERMACS = Interagency Registry of Mechanically Assisted Circulatory Support

The cardiorenal syndrome and chronic kidney disease

Patients with severe HF also often have impaired renal function, a combination which has been characterized as ‘cardiorenal syndrome’. The cause of this syndrome is multifactorial but to a large degree is related to the deleterious hemodynamic changes present in severe HF, including decreased CO, hypotension and venous congestion, all of which lead to renal hypoperfusion and decreased glomerular filtration (15). Severe impairment of renal function constitutes a potential obstacle to HTx in patients who are otherwise eligible for it. According to the International Society for Heart and Lung Transplantation (ISHLT) the presence of irreversible renal dysfunction, identified as a

glomerular filtration rate (GFR) of <30 mL/min/1.73 m², is a relative contraindication to HTx (12).

Inotropes can be considered as treatment for patients with decompensated and/or AdHF in cases where the perfusion of vital organs, such as the kidneys, is severely affected. Inotropes that have been most frequently used at our center are dobutamine, milrinone and levosimendan. All of these agents increase CO but, in a study comparing dobutamine with levosimendan, the levosimendan-induced elevation of CO not only increased renal blood flow but also, and in contrast to dobutamine, enhanced GFR (16). The treatment effect of inotropes is transient, however, and their use has not been shown to improve long-term prognosis.

Assessment of GFR: GFR describes the amount of blood plasma filtered by the renal glomeruli per time unit (17). In daily clinical practice, GFR is normally estimated by means of creatinine-based calculations such as the Cockcroft–Gault, Modification of Diet in Renal Disease (MDRD) and CKD-Epidemiology Collaboration (EPI) equations. An overview of the MDRD and CKD-EPI equations is shown in Table 3. However, these equations have not been thoroughly validated in patients with AdHF or those who have undergone HTx and several factors, especially low muscle mass, may limit their accuracy in these populations. GFR can also be measured directly (and to a high degree of accuracy) through the clearance of exogenous filtration markers such as inulin, iohexol or ⁵¹Cr-ethylenediaminetetraacetic acid (EDTA) (18). These direct measurements are in general more expensive and time consuming to perform than estimated GFR (eGFR), which has limited their general use in HF populations. Nevertheless, they are used routinely during HTx work-up and follow-up at the two Swedish heart transplant centers (19, 20).

Table 3. The MDRD and CKD-EPI formulas for estimation of GFR

eGFR
MDRD:
GFR = 175 × (creatinine/ 88.4) ^{-1.154} × (age) ^{-0.203} (if female: × 0.742) (if african-american: × 1.212)
CKD-EPI:
Female, creatinine ≤62: GFR= 144 × [crea/(0.7 × 88.4)] ^{-0.329} × (0.993) ^{age}
Female, creatinine >62: GFR= 144 × [crea/(0.7 × 88.4)] ^{-1.209} × (0.993) ^{age}
Male, creatinine ≤80: GFR= 141 × [crea/(0.9 × 88.4)] ^{-0.411} × (0.993) ^{age}
Male, creatinine >80: GFR= 141 × [crea/(0.9 × 88.4)] ^{-1.209} × (0.993) ^{age}

eGFR = estimated Glomerular Filtration Rate, MDRD = Modification of Diet in Renal Disease, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration.
Creatinine levels are expressed in μmol/L

Chronic kidney disease (CKD) was originally defined by the Kidney Disease Outcomes Quality Initiative (KDOQI) as “kidney damage or a GFR below 60 ml/min/1.73 m² for three months or more”. The five different CKD stages described by the KDOQI in 2002 are shown in Table 4 (21). Although these stages have since been somewhat refined, the basic principles of the original grading system remain (22). Many patients with reduced cardiac function also have CKD.

Table 4. The 2002 KDOQI working formulation on grading of CKD

Stage	Description	GFR (ml/ min x 1.73 m ²)
1	Kidney damage with normal GFR	> 90
2	Kidney damage with mildly decreased GFR	60-89
3	Moderately decreased GFR	30-59
4	Severely decreased GFR	15-29
5	Kidney failure	< 15 (or dialysis)

KDOQI = Kidney Disease Outcomes Quality Initiative, CKD = chronic kidney disease, GFR = glomerular filtration rate

In retrospective analyses, it has been shown that impaired renal function is associated with increased risk of death in HF patients (23). Thus, determining whether HF patients have irreversible CKD or acute renal impairment due to HF (or both) is important when considering options for AdHF treatments, since the latter condition may be reversible whereas the former is probably not.

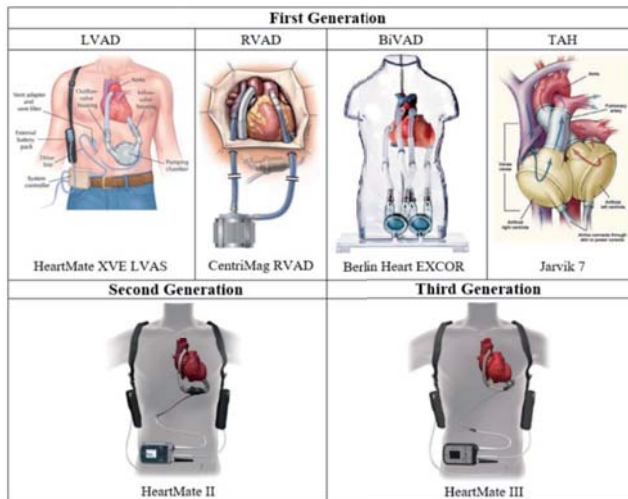
MCS

In patients with hemodynamic instability, or when there is a considerable risk of circulatory deterioration or death during the waiting time for transplantation, treatment with MCS can be lifesaving. MCS can be either short or long term. Short-term MCS (of which the most commonly utilized form is extracorporeal membrane oxygenation [ECMO]) is used exclusively in the intensive care unit (ICU) for a limited period of time. Here we will focus on long-term MCS.

Treatment with a mechanical pump to assist the failing heart for a longer period of time is now an accepted therapy in selected cases (24). Durable ventricular assist devices (VADs) can support either the left ventricle (left ventricular assist device [LVAD]), the right ventricle (right ventricular assist device [RVAD]) or both ventricles (biventricular assist device [BiVAD]). These devices can be implanted either intracorporeally, in the thorax or abdomen, which is the case with most modern LVAD systems, or paracorporeally, i.e. located outside the body. Severe biventricular failure can also be addressed by the implantation of a total artificial heart (TAH) after completely excising the native heart. An overview of common MCS types is shown in Figure 1.

Speculations about the feasibility of supporting the human circulatory system have existed since the early nineteenth century, and achieved practical expression with the introduction of the heart–lung machine in the early 1950s (25). The first successful VAD implantation was carried out in 1966 by Michael DeBakey (26). He used a device consisting of a pneumatically driven displacement pump and valves that enabled unidirectional pulsatile flow. This technique is still used in today’s paracorporeal devices, such as the ‘Berlin Heart EXCOR[®]’, which is primarily used in children with small bodies, and as a BiVAD in adults with severe biventricular failure.

The development of a TAH received generous economic support from the United States (US) government during the mid-to-late 1960s, in part because President Lyndon B. Johnson had goals to “put a man on the moon” and “place an artificial heart in a human” before the year 1970.

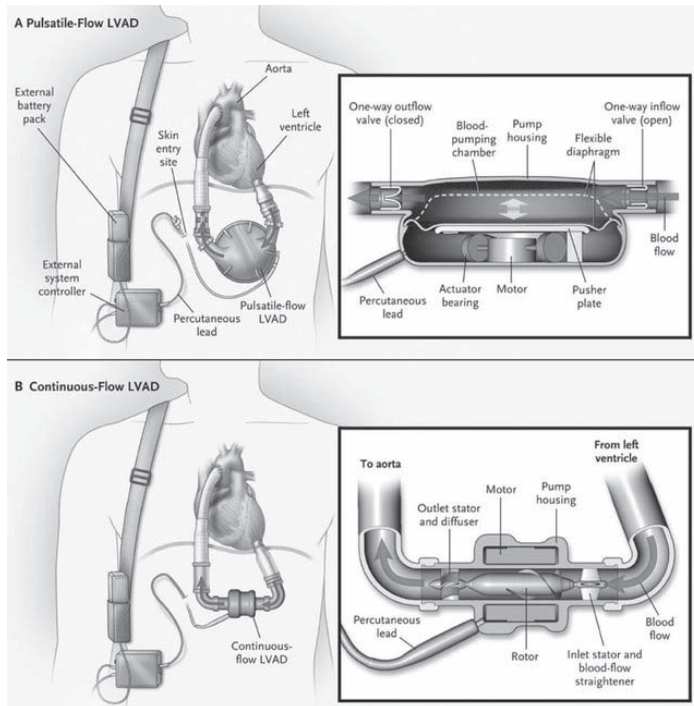


MCS = mechanical circulatory support, LVAD = left ventricular assist device, RVAD = right ventricular assist device, BiVAD = biventricular assist device, TAH = total artificial heart. Reproduced from *Bioengineering* 2019, 6, 18; doi:10.3390/bioengineering6010018, distributed under the terms and conditions of the Creative Commons Attribution license

Figure 1. First, second and third generation MCS systems. CentriMag RVAD represents short term MCS and the other systems long-term MCS.

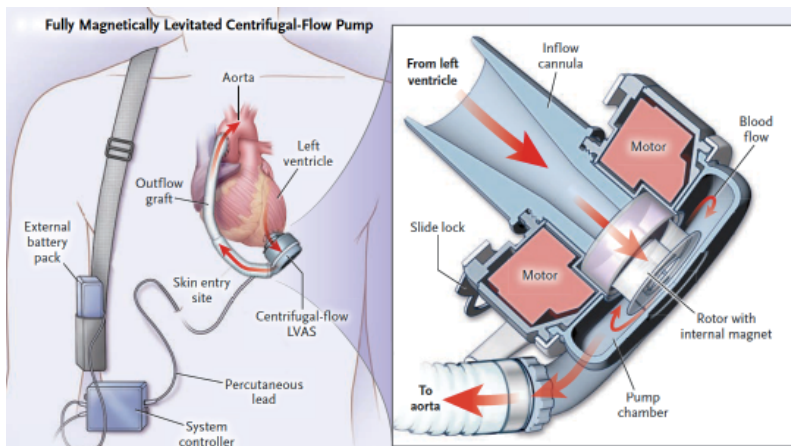
HTx was still associated with high waiting-list mortality long after it became an established surgical reality, prompting the evolution of the concept of bridge to transplantation (BTT) to sustain waiting-listed patients. In 1969, the heart of a middle-aged man with severe ischemic heart disease was explanted after an aneurysmectomy with unsuccessful ventriculoplasty and replaced by a TAH in a staged procedure, aiming for HTx. This TAH supported the circulation for 64 hours while a donor heart was obtained and HTx could be performed, but the patient died due to *Pseudomonas pneumonia* 32 hours after the transplant procedure (27). Positive reports on the use of MCS continued during the 1970s, however, and, in 1978, Denton Cooley and colleagues were then, for the first time, able to bridge a patient to HTx using an abdominally placed LVAD (28).

Subsequently, different types of devices were developed, including the Heart Mate and the Novacor (29, 30), which became the best-known devices during the 1980s and 1990s. Both devices were positioned using an intracorporeal approach which enabled patients to be mobilized and, in some cases, even allowed outpatient care during the HTx waiting time. Subsequently, the devices have undergone considerable technical development. A modern device provides continuous flow, which has allowed for miniaturization, improved operational reliability and led to fewer complications. The second-generation pumps, such as the Heart Mate II, use axial flow generated by a rotating screw (31) and, in the third-generation pumps (such as Heartware and the Heart Mate 3), the blood flow is generated by a magnetically driven rotating disk that has no mechanical bearings (Figures 2 and 3). These innovations have successfully been used in LVADs, but are still not approved for biventricular assistance, although case series on the use of two implanted Heartware (32) or Heart Mate 3 devices have been published (33, 34).



LVAD = left ventricular assist device. Reproduced from Neth Heart J. 2012 Apr; 20(4):167-175, doi: 10.1007/s12471-011-0211-4, distributed under the terms and conditions of the Creative Commons Attribution license

Figure 2. Panel A shows a pulsatile first generation LVAD with a diaphragm and uni-directional artificial heart valves. Panel B shows a continuous flow second generation LVAD with a valveless axial pump.



LVAD = left ventricular assist device, LVAS = left ventricular assist system. Reproduced with permission from N Engl J Med. 2017 Feb 2;376(5):440-450. doi: 10.1056, Mehra et al (ref 39). Copyright Massachusetts Medical Society.

Figure 3. Continuous flow third generation magnetically levitated LVAD.

Despite these advances, MCS is a demanding treatment for both the patient and health professionals and is not without risks. The choice of MCS type is of great importance as risks, outcomes and the patient's quality of life may differ between different pump systems. Whatever model is used, MCS is consistently costly.

Rigorous assessment of patient eligibility for MCS is thus a crucial consideration. The principles for MCS selection in order to obtain optimal results are still not well defined, however, and differ considerably between centers and countries. For example, whereas LVADs for long-term use, i.e. 'destination therapy', is an accepted treatment pathway in the US, it is still the subject of a clinical study in Sweden (35).

The commonest complications during MCS treatment are infections, thromboembolism and bleeding (36, 37). The frequency of such complications, and whether they differ between different durable MCS systems used as BTT in the Swedish healthcare system, have not been properly investigated. A recent registry report from the ISHLT Mechanically Assisted Circulatory Support Registry suggests a lower frequency of complications in centrifugal-flow third-generation LVADs compared to the older second-generation axial-flow models (38). In particular, it has also been shown that the third-generation LVAD Heart Mate 3 seems to be associated with considerably lower thromboembolic risk than previous devices (39, 40) and that, in general, long-term outcomes are good. Even so, the prognosis in patients with INTERMACS profile 1, especially those bridged with ECMO to durable LVAD, is markedly worse than that of patients with higher INTERMACS profiles (38).

GFR in MCS patients

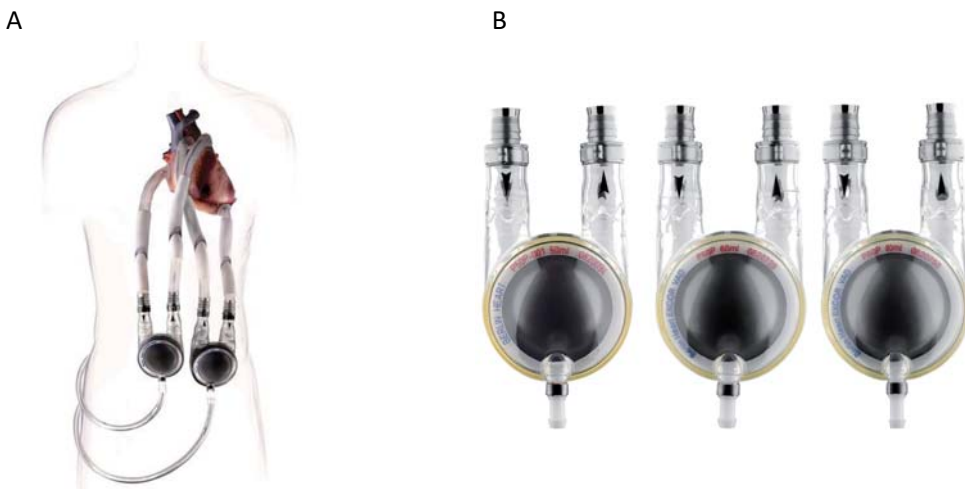
Implantation of durable MCS restores the circulation at rest in the form of continuous flow and not pulsatile flow as accomplished with the normal native heart. The degree to which MCS may improve renal function, as described by GFR, is not fully known. Despite the risk of acute kidney injury during and after the procedure, implantation of a MCS device may facilitate renal function through increased CO and reduced venous congestion. Previous studies have investigated the effect of MCS on eGFR alone (41-43), but the accuracy of eGFR in these patients can be questioned. How treatment with MCS as BTT affects measured GFR is not clear. It is also a matter of debate whether newer continuous flow (CF) devices may affect kidney function differently to older pulsatile systems (44, 45). Many factors can influence the trajectory of renal function during MCS treatment. Worsening right heart failure causes venous congestion and has a negative impact on GFR. Infections per se and any antibiotic treatment given may affect renal function in the long run. Hence, more information is needed about the effects of MCS on GFR.

MCS as BTT - Treatment strategies

Treatment with the modern, implantable LVAD systems that generate a continuous blood flow is the easiest and safest way to bridge patients to HTx (46, 47). However, this requires adequate RV function. RV failure during LVAD therapy disrupts the function of the system and causes increased morbidity and mortality (48-51). One way to overcome this problem is to assist both heart chambers, but the results with bi-

ventricular support have generally been worse than those with LV support alone (52). Postoperative conversion from an LVAD to a BiVAD configuration is associated with poorer outcomes than a strategy involving planned ‘de novo’ BiVAD implantation (53). Direct comparisons between uni- and biventricular support in patients with a high risk of post-implantation RV failure are scarce. Potential confounding influences also hamper assessment: it can be difficult to interpret whether differences in survival between LVAD and BiVAD patients are due to the treatment strategy itself or the fact that the patients receiving biventricular support are sicker, often with multiorgan failure.

For patients who, after thorough evaluation, have been considered to be in need of a BiVAD, Sahlgrenska University Hospital, like some other European centers (54), has used a paracorporeal pump of the type ‘Berlin Heart EXCOR’ (Figure 4). Candidates considered suitable for such therapy include patients with acute severe HF in immediate need of intensive care, a group for whom treatment options have previously been very limited. The EXCOR system can also be used in patients who are less suitable for conventional continuous-flow LVAD systems, such as infants and children with small bodies (55-63), as well as adults with complex congenital heart disease. The configuration of two implantable CF devices as a ‘BiVAD’ has not yet been used in our institution.



BiVAD = biventricular assist device. Reproduced with permission from Berlin Heart GmbH

Figure 4. Berlin Heart EXCOR® ventricular assist device. Panel A shows the system used as a BiVAD. Panel B shows the pneumatically driven pumphouses in three different sizes (50, 60 and 80 ml) with the membranes and valves

As focus on and awareness of AdHF has increased in recent years, we have observed that adult patients with severe HF may be referred for evaluation earlier in their disease course. Hopefully, these patients can then be managed and considered for advanced treatment options prior to the development of severe RV failure. This, along with the use of the new third-generation CF-LVADs, has already reduced the need for BiVAD implantations.

HTx

The first HTx was carried out in Cape Town, South Africa in 1967 by Christian Barnard and colleagues (64). The donor heart, which came from a trauma victim with severe cerebral injuries, was prepared using the technique developed by Norman Shumway at Stanford University, California. The initial recovery of the transplant recipient, who had suffered from severe HF on the basis of ischemic heart disease, was excellent, but the patient's condition deteriorated after 2 weeks. This clinical worsening was mistakenly interpreted as rejection and intensified immunosuppressive treatment was given. In fact, the patient was suffering from pneumonia and died of sepsis 18 days after HTx.

In the year following Barnard's pioneering surgery, 120 heart transplants were done globally with a 1-year survival rate of only 20%, which led to the procedure gaining a bad reputation and being questioned (65). Shumway, who many had expected to be the first to attempt human HTx, performed the procedure for the first time in January 1968 (66). It was not until the early 1980s, when cyclosporine was established as an immunosuppressive agent, that results improved considerably (67, 68). About one decade earlier, the technique of percutaneous endomyocardial biopsy had been adopted, facilitating the detection of graft rejection (69).

Owing to the availability of effective immunosuppressants, and the ability to detect acute rejections at an early stage, HTx emerged as a treatment for end-stage HF. The first HTx in Sweden was performed on 22 June 1984 at Sahlgrenska University Hospital in Gothenburg, but it was not until 1988 - when Swedish law was changed to permit braindead donors - that the HTx program gained momentum. Today, HTx is a well-established treatment for selected patients with AdHF: at Sahlgrenska, 30–40 procedures are performed annually, with excellent long-term results (70).

Heart transplant recipients require lifelong immunosuppression to prevent rejection of the donor heart (graft). The immunosuppressive therapy typically consists of three types: induction, maintenance and rejection treatment. Induction treatment is normally given peri- and postoperatively with the aim of reducing the doses of standard drugs given as maintenance immunosuppression after HTx. *Induction* is often given in the form of antibody therapy. At Sahlgrenska University Hospital, T-lymphocyte-depleting antithymocyte globulins (ATG/ thymoglobuline) are used.

Maintenance immunosuppression is normally a combination of three different groups of agents: calcineurin inhibitors ([CNIs]; cyclosporine or tacrolimus), antimetabolites (azathioprine or mycophenolate mofetil [MMF]) and corticosteroids (CS). CS can be tapered during the first year after HTx and, in many cases, are discontinued prior to the first annual post-transplantation clinical assessment. In addition to the above, mammalian target of rapamycin (mTOR) inhibitors (everolimus or sirolimus) can be used as an alternative or complementary drug to decrease the development of vasculopathy and reduce the nephrotoxicity of CNIs (71). However, mTORs probably do not have the same immunosuppressive potency as CNIs and may therefore be associated with increased incidence of acute cellular graft rejections when applied as mainstay immunosuppressive therapy (72).

During the last 10–15 years, cyclosporine has mostly been replaced by tacrolimus, and azathioprine by MMF (73, 74). As the favorable effects of mTOR inhibitors have been shown in several randomized trials (72), including the SCHEDULE trial and its sub-studies (75, 76), a protocol involving CNI-free everolimus treatment or low-dose CNI in combination with intermediate-dose everolimus has been introduced at our center. This practice may reduce the worst early nephrotoxicity of CNIs, without increasing the risk of rejections. Clinical experience with this treatment strategy has been positive.

Rejection treatment is normally given as high-dose CS or, in selected cases, as ATG or other antibodies. Treatment against antibody-mediated rejection (AMR) often requires plasmapheresis and antibody treatment.

Complications after HTx

The commonest complications after HTx are infections, rejections, cardiac allograft vasculopathy (CAV), chronic kidney disease (CKD) and malignancies. Infectious agents that are of special concern in HTx recipients include cytomegalovirus, *Pneumocystis jirovecii*, *Toxoplasma gondii* and - especially in the early postoperative period - various fungi. Special prophylaxis is therefore recommended by the ISHLT (77). COVID-19 affects solid-organ transplant recipients more severely than immunocompetent patients and has led to increased morbidity and mortality (78, 79).

As regards malignancies, recent studies from our center show a six-fold increase in cancer rates among HTx recipients compared with a matched cohort from the general population (80). The commonest malignancies were skin cancer and non-Hodgkin's lymphoma.

Attention will now be focused on rejections, CKD and CAV.

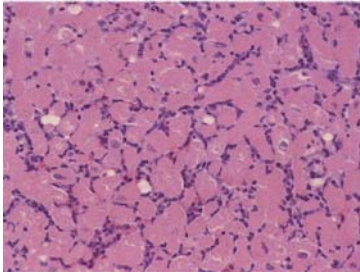
Rejections

Rejections can be divided in several ways, but classically they fall into the following three categories: hyperacute rejection, acute cellular rejection (ACR) and AMR (77).

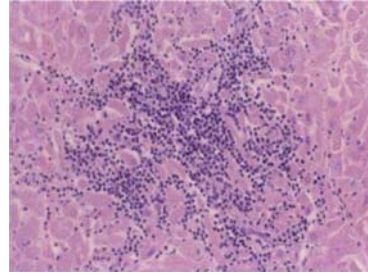
Hyperacute rejections normally occur within hours after the transplant procedure and are typically thought to be caused by preformed antibodies against the donor blood group or human leukocyte antigens (HLAs). These rejections are rare nowadays owing to the structured principles of HLA antibody and crossmatch testing prior to listing and HTx.

ACR are more common than hyperacute rejections and are diagnosed by endomyocardial biopsies. In ACR, the inflammatory response mainly consists of T-lymphocytes creating cellular infiltration of the myocardium and necrosis of the myocytes. Eventually this can lead to graft failure. The grading of ACR (0–3R) is assessed histopathologically and shown in Table 5a (81). The difference between ACR grades 1R and 2R is shown in Figure 5. First-line treatment of ACR grade ≥ 2 is high-dose CS for 3 days, with the addition of ATG in severe or therapy-resistant cases.

A



B



ACR = acute cellular rejection. Pictures reprinted from “Revision of the 1990 Working Formulation for the Standardization of Nomenclature in the Diagnosis of Heart Rejection”, *J Heart Lung Transplant*. 2005 Nov;24(11):1710-20. doi: 10.1016/j.healun.2005.03.019. Epub 2005 Jun 20, Stewart et al (ref 81), with permission from Elsevier.

Figure 5. Light microscopy with hematoxylin and eosin stain of endomyocardial biopsy from a heart transplant recipient. Panel A shows ACR grade 1 R: Diffuse mononuclear cell infiltrate with an interstitial pattern without associated myocyte damage. Panel B shows ACR grade 2 R: Damaging mononuclear cell infiltrate with myocyte damage and architectural distortion.

Table 5a. 2004 ISHLT Standardized Cardiac Biopsy Grading in Acute Cellular Rejection

2004		1990	
Grade 0 R ^a	No rejection	Grade 0	No rejection
Grade 1 R, mild	Interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage	Grade 1, mild A—Focal B—Diffuse	Focal perivascular and/or interstitial infiltrate without myocyte damage Diffuse infiltrate without myocyte damage
Grade 2 R, moderate	Two or more foci of infiltrate with associated myocyte damage	Grade 2 moderate (focal)	One focus of infiltrate with associated myocyte damage
Grade 3 R, severe	Diffuse infiltrate with multifocal myocyte damage ± edema, ± hemorrhage ± vasculitis	Grade 3, moderate A—Focal B—Diffuse Grade 4, severe	Multifocal infiltrate with myocyte damage Diffuse infiltrate with myocyte damage Diffuse, polymorphous infiltrate with extensive myocyte damage ± edema, ± hemorrhage + vasculitis

^aWhere “R” denotes revised grade to avoid confusion with 1990 scheme.

ISHLT = International Society for Heart and Lung Transplantation, ACR = acute cellular rejection. Reprinted from “Revision of the 1990 Working Formulation for the Standardization of Nomenclature in the Diagnosis of Heart Rejection”, *J Heart Lung Transplant*. 2005 Nov;24(11):1710-20. doi:10.1016/j.healun.2005.03.019. Epub 2005 Jun 20, Stewart et al (ref 81) with permission from Elsevier.

AMR is caused by recipient antibodies directed against the endothelium of the transplanted heart. Antibodies reactive with donor HLA are termed donor-specific antibodies (DSA). DSA binding to the graft can cause tissue injury, mainly by activation of the complement cascade (82). Grading of AMR according to the ISHLT is shown in Table 5b (83). Current AMR treatment is largely based on consensus, with rather weak evidence. It is generally focused on reducing the amount of circulating antibodies with plasmapheresis and different monoclonal antibodies directed against recipient immune cells and the complement system (77).

Table 5b. The 2013 ISHLT Working Formulation for Pathologic Diagnosis of Cardiac Antibody-Mediated Rejection

pAMR 0	Negative for pathologic AMR	Histologic and immunopathologic studies are both negative.
pAMR 1 (H+)	Histopathologic AMR alone	Histologic findings are present and immunopathologic findings are negative.
pAMR 1 (I+)	Immunopathologic AMR alone	Histologic findings are negative and immunopathologic findings are positive (CD68+ and/or C4d+).
pAMR 2	Pathologic AMR	Histologic and immunopathologic findings are both present.
pAMR 3	Severe pathologic AMR	Interstitial hemorrhage, capillary fragmentation, mixed inflammatory infiltrates, endothelial cell pyknosis, and/or karyorrhexis, and marked edema and immunopathologic findings are present. These cases may be associated with profound hemodynamic dysfunction and poor clinical outcomes.

AMR, antibody-mediated rejection.

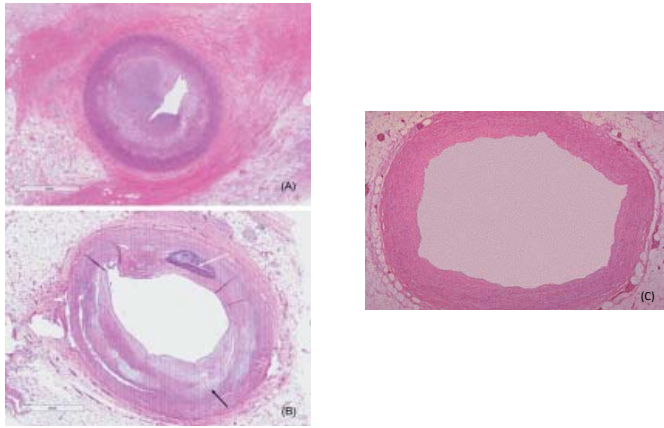
Reprinted from “The 2013 International Society for Heart and Lung Transplantation Working Formulation for the standardization of nomenclature in the pathologic diagnosis of antibody-mediated rejection in heart transplantation” *J Heart Lung Transplant.* 2013 Dec;32(12):1147-62. doi: 10.1016/j.healun.2013.08.011, Berry et al (ref 83), with permission from Elsevier.

Renal function and CKD after HTx

Impaired renal function is a well-described short- and long-term complication after heart and other organ transplantation. CKD can be present before HTx - as a result of pre-existing renal disease and/or the cardiorenal syndrome - or arise after the transplantation. CKD after HTx may develop as a consequence of CNI-related nephrotoxicity. Broad research has been undertaken into immunosuppressive drugs that preserve renal function. Regimens that add an mTOR inhibitor and minimize the CNI agent have been shown to spare kidney function and prevent the development of CKD (72, 76, 84). Kidney function seems to be better with CNI-free regimens than with protocols that include CNIs, but the number of biopsy-proven treated rejections has been somewhat higher early post-transplantation, albeit this has not been shown to significantly affect cardiac function (85). As well as immunosuppressive agents, post-transplant comorbidities such as diabetes and hypertension contribute to the development of CKD. Furthermore, the transplant procedure itself can be associated with acute kidney injury. In patients transplanted at our center, pre-transplantation mGFR was not predictive of mortality or end-stage renal disease after HTx. On the other hand, mGFR declined by 12% during the first year after HTx and those who developed end-stage renal disease had a worse prognosis (86). Therefore, optimized immunosuppression and optimal general care early after HTx may be advantageous in preventing CKD.

CAV

CAV is an accelerated form of coronary artery disease, and both immunologic and non-immunologic mechanisms are believed to contribute (87). Typically, CAV develops over the course of years after HTx. The primary cause is probably inflammatory activity driven by cellular and AMR processes that causes a chronic fibroproliferative intimal hyperplasia along the length of coronary vessels. This differs from normal atherosclerosis, which is non-circumferential, focal and commonest in the proximal epicardial vessels (88) (Figure 6). Inflammation in CAV may also be triggered by donor arrest, allograft ischemia and ischemia - reperfusion injury at the time of HTx. Traditional risk factors for atherosclerosis are likewise thought to be associated with the development of CAV (89). These include hypertension, hyperlipidemia, diabetes and obesity.



Reproduced with permission from Wiley (Clinical Transplantation 2020;34:e13794, DOI: 10.1111/ctr.13794, Lee et al, ref 89) and from Springer Nature (Cardiotoxicity; Leonard, Wazer 2019).

Figure 6. Light microscopy with hematoxylin and eosin stain of coronary artery in (A) cardiac allograft vasculopathy (CAV) with concentric intimal hyperplasia and near obliteration of lumen, and (B) atherosclerotic disease with eccentric calcified (white arrow) lipid (black arrow) plaque. As comparison a section of a normal coronary artery is shown (C).

Table 6. ISHLT nomenclature for cardiac allograft vasculopathy (CAV). Reproduced with permission from Wiley (Clinical Transplantation 2020;34:e13794, DOI: 10.1111/ctr.13794, Lee et al, ref 89)

CAV grade	Angiographic features	Allograft dysfunction
0 (not significant)	No detectable angiographic lesion	Absent
1 (mild)	Angiographic left main < 50% or primary vessel with maximum lesion < 70 or branch stenosis < 70%	Absent
2 (moderate)	Angiographic left main < 50% or single primary vessel ≥ 70% or isolated branch stenosis in 2 systems ≥ 70%	Absent
3 (severe)	Angiographic left main ≥ 50% or 2 primary vessels ≥ 70% or isolated branch stenosis in all 3 systems ≥ 70% or evidence of allograft dysfunction	Left ventricular ejection fraction ≤ 45% with CAV grading 1 or 2 disease or evidence of restrictive physiology ^a

^aRestrictive physiology defined as symptomatic heart failure with corresponding findings on echocardiography (E to A velocity > 2, isovolumetric relaxation time < 60 ms, deceleration time < 150 ms) and/or invasive hemodynamics (right atrial pressure > 12 mm Hg, pulmonary capillary wedge pressure > 25 mm Hg, cardiac index < 2L/min/m²).

As described by the ISHLT, the prevalence of CAV in post-HTx patients at 1, 5 and 10 years was 8%, 29% and 47%, respectively (90).

CAV is normally diagnosed by coronary angiography and can be described in better detail by intravascular imaging methods such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) (87). The ISHLT working formulation defines the grading of CAV (91) (Table 6). Treatment is firstly focused on management of traditional cardiovascular risk factors and secondly on optimized immunosuppression. mTOR inhibitors have been shown to be effective for preventing the development and progression of CAV (72, 92). In cases of significant stenoses, revascularization via percutaneous coronary intervention is recommended but the risk of re-stenosis is high. Cardiac re-transplantation may be considered in carefully selected cases with advanced CAV.

Survival after HTx

Survival after HTx has improved owing to better pre-, peri- and postoperative care, advancements in immunosuppression and refined techniques for detection of early rejection (93). The outcomes at our institution since the initiation of the HTx program in the mid-1980s have been well in line with the best results published, as well as with those reported from all Scandinavian centers (94). Data from Sahlgrenska University Hospital have shown an ongoing improvement in outcome after HTx (Figure 7A) (70). Transplant procedures after BTT with MCS, in children, as re-transplantations and with concomitant kidney transplantation have been performed with good results. The inferior prognosis of patients bridged with MCS compared with non-MCS HTx recipients (Figure 7B) seems to be driven by patients with short-term devices (Figure 7C). After 2008, direct transplantation from short-term MCS was therefore avoided and, as mentioned previously, a renal-sparing immunosuppressive protocol has been used with greater frequency, which may have influenced the beneficial outcome. However, as patients live longer after HTx an increased prevalence of long-term side effects can be anticipated. Whether survival, rejections and the evolution of renal function among patients bridged with MCS differ from those who were medically managed before HTx in the recent era is not clear. In general, the evidence regarding the effects of MCS on post-transplantation survival is somewhat conflicting. Some studies indicate a negative effect on outcomes (46, 95, 96), while others show no differences on long-term endpoints such as survival (97-99). Differences in patient demographics between studies is likely to be one factor contributing to these disparate results.

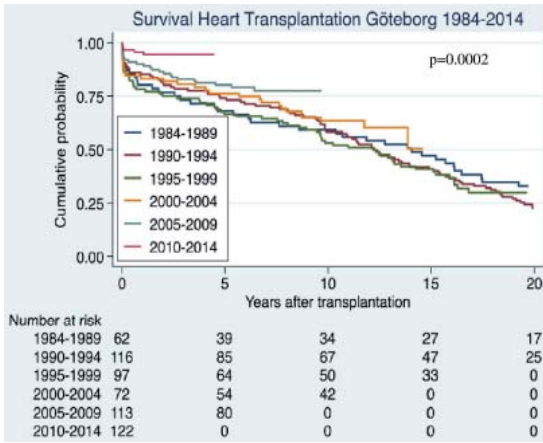
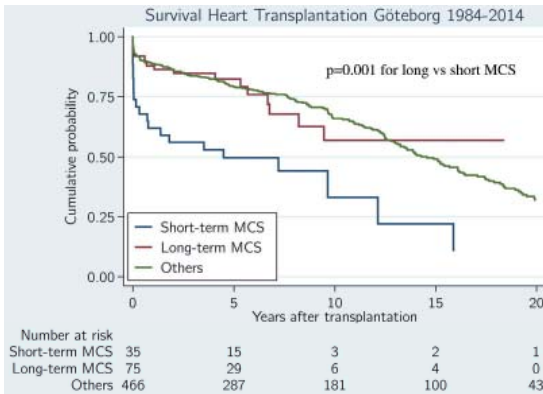
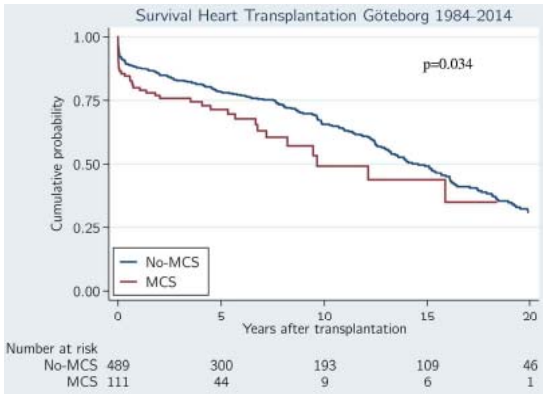


Figure 7. Survival after HTx in patients transplanted at Sahlgrenska University Hospital 1984-2014.

Panel A shows actual survival grouped according to transplant era.

Panel B shows actual survival for patients bridged to HTx with MCS versus non-bridged patients.

Panel C shows actual survival for patients bridged with short-term MCS versus long-term MCS and non-bridged patients.



HTx = heart transplantation, MCS = mechanical circulatory support. Reproduced from *Int J Cardiol.* 2017 Mar 15;231:188-194. doi:10.1016/j.ijcard.2016.12.186 (ref 70) with permission from Elsevier.

AIMS

The general aim of this thesis is to increase knowledge in the field of durable MCS and HTx as treatments for AdHF and to further investigate the effect of such treatments on renal function described as mGFR. Since the treatment strategy was changed from 2008 onwards, a current evaluation of the outcomes of durable MCS and HTx is an important issue to investigate. The results may offer optimization of patient selection and choice of pump strategy, which in turn could lead to fewer complications and better patient outcomes.

The specific aims are as follows:

- To characterize patients receiving paracorporeal ‘EXCOR’ pumps owing to their ineligibility for implantable durable MCS devices and to study their pre-implantation profiles, outcomes and pump-related complications.
- To explore the characteristics and outcomes of adult patients receiving a BiVAD as a BTT measure and to compare them with contemporary LVAD recipients.
- To study the effect of durable MCS treatment and consequent HTx on renal function.
- To compare post-transplantation outcomes between patients treated with or without durable MCS as a bridge to HTx.

PATIENTS AND METHODS

Patient populations

Paper I included 50 patients (21 children and 29 adults) who received ‘EXCOR’ pumps between April 2008 and December 2018. The indications for use of this device differ between children and adults. At our pediatric heart center, the ‘EXCOR’ has been used as the primary system for long-term MCS in patients with small bodies and the long-term MCS strategy may involve either BTT or bridge to myocardial recovery. In adolescents and adults, the system has been used as a BTT in selected patients considered less eligible for CF-LVAD. This includes patients with complex congenital heart disease and those in need of biventricular support.

Paper II included 41 of the 43 adult patients who received durable MCS as a BTT between February 2010 and April 2014. Twenty of them were treated with a paracorporeal pulsatile BiVAD (Berlin Heart EXCOR) and 21 received a CF second-generation LVAD (Heart Mate II).

The decision-making process regarding whether to implant an LVAD or a BiVAD in both these patient cohorts was based on the evaluation of clinical, echocardiographic and hemodynamic parameters to assess the risk of postoperative RV failure. All patients were discussed at a multidisciplinary transplantation board, where the final decision was made. Notably, we did not systematically use risk scores or standardized criteria at that time. However, the following risk factors were considered and favored BiVAD implantation: hemodynamic signs of increased RV filling pressure and/or low RV stroke work index, multi-organ failure, low INTERMACS profile, need for short-term circulatory support, echocardiographic signs of poor RV function and severe tricuspid regurgitation.

In these two studies (Papers I and II), complications and outcomes were calculated and compared retrospectively.

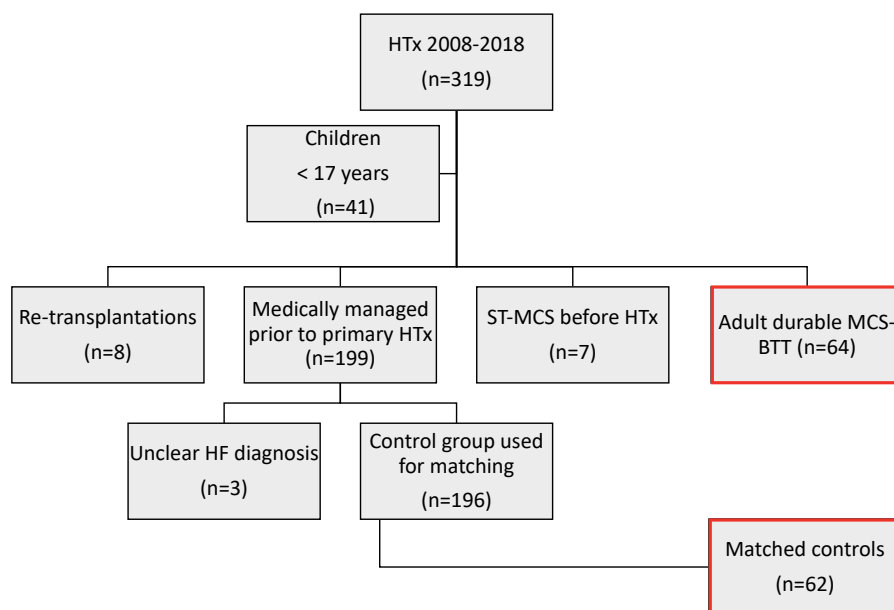
Paper III included 88 patients who were treated with durable MCS and underwent subsequent HTx between 1996 and 2018. Among the included patients, 41 had pulsatile pumps and 47 had CF pumps. GFR was measured at three time-points: 1) during HF evaluation; 2) 3–6 months after MCS implantation; and 3) at 1-year follow-up after HTx. At the same three time-points, the CKD stage was classified based on the level of GFR estimated by the MDRD equation.

Paper IV included 126 patients who had undergone HTx between 2008 and 2018. Sixty-four patients had been bridged with MCS and 62 controls were obtained from a group of 196 patients medically managed before HTx during this time era by direct matching of age group (± 10 years), sex, HF diagnosis (dilated cardiomyopathy [DCM], ischemic heart disease or other) and transplantation year (± 5 years). A flow chart displaying patient selection for the study is shown in Figure 8.

Data collection and registries

Papers I–II are based on a local registry covering all patients who have received a durable MCS at Sahlgrenska University Hospital. The information provided includes all baseline data such as age, gender, HF diagnosis, BMI, laboratory values, blood pressure level, hemodynamics from RHC, use of inotropes, need for ventilator and short-term MCS, as well as implantation and transplantation dates. Papers III–IV are based on the Transplant Registry at Sahlgrenska University Hospital, which provides similar baseline information as well as intraoperative data from the time of HTx, donor characteristics and follow-up information from annual post-HTx clinical assessments. In addition, complementary information was collected through a retrospective review of clinical records. Death dates were always verified by electronic patient records linked to the national population registry. All patients in the time period studied were consecutive and considered for inclusion in the respective studies. In paper IV the medically managed control group was obtained by direct matching with the MCS patients.

Papers I, II and IV studied patients undergoing MCS implantation and/or HTx after 2008, when direct transplantation from short-term MCS was phased out. No patients were lost to follow-up.



HTx= heart transplantation, MCS = mechanical circulatory support, BTT = bridge-to-transplantation, ST = short term, HF = heart failure

Figure 8. Study outline of Paper IV. The MCS-BTT and matched control groups are marked with red frames.

Methods and definitions

INTERMACS profiles were obtained from the patients' clinical records. Where these were lacking, the patients were classified retrospectively based on the clinical and hemodynamic information provided.

Surgical complications (Papers I and II): Specific data were obtained through a systematic review of patient charts. Dates of complications were also registered. In case of the same complication developed more than once, all dates were registered in order of appearance.

Echocardiographic data regarding RV function and the degree of RV failure (Paper II) were obtained by a blinded retrospective review of the echocardiography studies by an experienced echocardiography specialist.

GFR (Papers III and IV) was measured by the ^{51}Cr -EDTA or iohexol clearance methods. These methods were considered to be interchangeable (100). CKD stage (Paper III) was classified based on the estimated level of GFR (21).

HLA antibodies: The presence and levels of panel-reactive HLA antibodies in patients listed for HTx (Paper IV) were determined by flow cytometry (FC) analysis or, more recently, by using the Luminex bead-based LABScreen™ mixed assay. For specificity determination, LABScreen single-antigen assays were used in more recent cases. Patients with HLA antibodies had a complement-dependent cytotoxicity crossmatch performed prior to HTx, whereas those without antibodies normally had a FC crossmatch.

Immunosuppression after HTx (Papers III and IV) consisted of induction therapy (ATG) and maintenance treatment with a CNI (cyclosporine or tacrolimus), an anti-metabolite (azathioprine or MMF) and a CS (prednisolone). CNI trough levels were measured and adjusted according to our local treatment protocol. CS were normally tapered during the first year after HTx. Selected patients were also treated with everolimus instead of CNIs (76) or, more commonly, with everolimus and CNI with lower target trough levels.

Rejections: After HTx, patients underwent 11–13 endomyocardial biopsies and acute rejections were classified according to the ISHLT revised guidelines (81) (Paper IV). Rejections \geq ISHLT grade 2R were treated with high-dose methylprednisolone.

CAV was assessed by coronary angiography with the addition of IVUS or OCT when necessary according to the ISHLT working formulation (91).

Ethics

All studies were approved by the Regional Ethical Review Board in Gothenburg (*Regionala etikprövningsnämnden i Göteborg*; diary number Dnr 728-12). Furthermore, the specific research questions in this thesis are described in amendment Dnr 2020-04281 approved by the Swedish Ethical Review Board (*Etikprövningsmyndigheten*).

Statistics

For descriptive statistics in Papers I–IV, data were presented as means and standard deviations, medians and interquartile ranges or numbers and percentages. Depending on the type of data, parametric or non-parametric tests were used for comparisons between groups at different time-points. For baseline comparisons, an unpaired t-test (Papers I–IV), the Mann–Whitney U-test (Papers I, III and IV) or the Kolmogorov–Smirnov asymptotic test (Paper II) were used. For comparisons of categorical variables, we used Fisher’s exact test (Papers I–IV) or the chi-square test (Paper IV). Time-to-event analyses are shown using Kaplan–Meier curves and comparisons between groups were done using the log-rank or Wilcoxon tests. P-values <0.05 were considered statistically significant.

A further description of analyses used in the specific papers is as follows:

Paper I: Although the two groups (children and adults) were apparently different, statistical comparisons between them at baseline and during follow-up were performed. The cumulative incidence of HTx or weaning from device was estimated using a Fine–Gray competing-risk regression model (101). In these analyses, deaths were treated as competing events. Kaplan–Meier curves for overall survival and survival free from major stroke are shown. The later analysis uses a combined endpoint of time to stroke or time to death. Alive patients without stroke were censored with cut-off after a maximum of 8 years. Comparisons of the following subgroups were also performed: children versus adults; males versus females; univentricular support versus BiVAD treatment; DCM etiology versus other HF etiologies; and cardiogenic shock (INTERMACS profile 1) versus INTERMACS profiles >1.

Paper II: Comparisons between the two groups (BiVAD and LVAD) were performed at baseline and after implantation of MCS. Kaplan–Meier curves were used to estimate survival and time on device between the BiVAD and LVAD groups and the difference between groups was evaluated with the long-rank test. Two risk scores for RV failure were retrospectively calculated and receiver operating characteristic (ROC) curves are shown for these risk scores. Areas under the curve (AUCs) were compared using the chi-square test.

Paper III: All patients with at least one measurement of GFR were included in the analysis of renal function over time. The assessment of within-patient change in mGFR and eGFR used a paired t-test with Bonferroni–Holm-adjusted p-values. Mean mGFR levels over time were explored by analyzing repeated measurements with a mixed model including age category, MCS type, period of implantation and visit (baseline, post-MCS or post-HTx). Least-square means were presented with nominal 95% confidence intervals and p-values. We studied both the total study population (unadjusted and adjusted) as well as predefined subgroups: pulsatile and CF pumps, three different age groups and three periods of implantation. By using this mixed model, we were able to adjust for the other parameters and to study the effects of pulsatility, age group and implantation period.

Paper IV: Comparisons between the MCS group and the medically managed matched controls were performed at baseline and at different time-points during follow-up. Time-to-event analyses regarding graft survival and rejections used Kaplan–Meier estimates and comparisons between groups were performed using the log-rank test.

RESULTS

In Paper I, we investigated the outcomes of all patients treated with the paracorporeal EXCOR device at our institution. In Paper II, we compared the results for adult EXCOR BiVAD patients with those for contemporary LVAD patients. Paper III studied the effect of durable MCS, followed by HTx, on mGFR. Finally, in Paper IV we compared the post-HTx outcomes in patients bridged to HTx with MCS (MCS-BTT patients) with that in patients who were medically managed before HTx.

Main findings

Survival: Although the indications for use of the paracorporeal EXCOR device were different in children and adults, survival was high and did not differ significantly between these groups (Paper I). In selected adult patients, use of this paracorporeal device as a BiVAD also resulted in high survival, which was comparable to that of the contemporary LVAD patients (Paper II). Compared with matched controls who were medically managed before HTx, MCS-BTT patients showed similar high graft survival (Paper IV).

Complications: The most frequent MCS-related complications occurring during the entire treatment period were strokes, pump thromboses and infections treated with antibiotics (Papers I and II). None of these complications differed significantly between children and adults (Paper I). When comparing complications between adult BiVAD and LVAD patients, they tended to be slightly higher in the BiVAD group. However, a significant difference was only seen for minor stroke (Paper II).

After HTx, the probability of rejections as well as the proportion of patients with CAV grade ≥ 1 was comparable between the MCS-BTT patients and the group who were medically managed prior to HTx (Paper IV).

Renal function: mGFR increased after treatment with durable MCS. For the whole group, no further improvement was seen at 1 year after HTx, but in certain subgroups the trajectory of renal function seemed to improve (Paper III).

At 1, 3 and 5 years after HTx, there was no difference in mGFR between MCS-BTT patients and those who were medically managed before HTx (Paper IV).

Specific results of Papers I–IV

Paper I: The study outline and main results are shown in Figure 9. The vast majority of both children and adults were in a serious hemodynamic condition, with high frequencies of inotropic use and low INTERMACS profiles. Short-term MCS as a bridge to long-term MCS with the EXCOR device was also quite common. In children, the device was used as an LVAD in 71% of cases, whereas in adults it was used as a BiVAD in 97% of cases. The proportion of all study patients surviving on device until HTx or weaning was 90% (Figure 9). Regaining of myocardial function, which allowed for weaning of the device, was more common in children than adults (38%

HF less suitable for CF-LVAD

- Small body size
- Congenital heart disease
- Severe biventricular failure (n=50)

Paracorporeal Pulsatile pump

- LVAD/ RVAD
- BIVAD



All patients followed

Overall survival analyzed

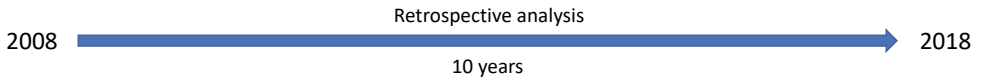
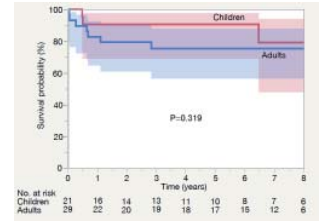
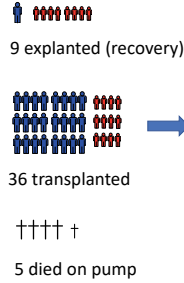
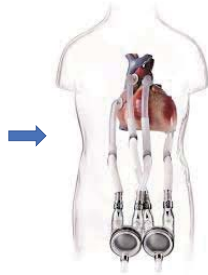


Figure 9. Study outline and main results of Paper I. Reproduced with permission from Elsevier.

versus 3%; $p < 0.01$). Children were listed for HTx quite soon after the implantation of MCS, but in adults a period of at least 3 months elapsed before they were activated on the waiting list. This was done to allow for rehabilitation, wound healing and end-organ recovery. As a result, the time to transplant or weaning was shorter in children than adults (median 85 versus 125 days; $p = 0.03$; Figure 10).

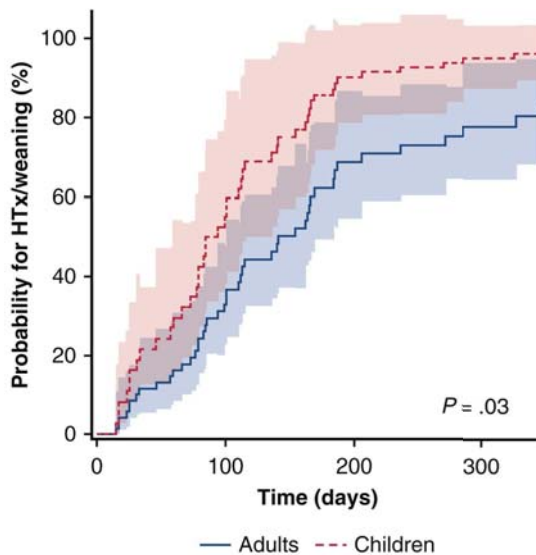


Figure 10. Time on EXCOR to heart transplantation (HTx) (n=36) or weaning (n=9) in children versus adults. Shaded areas represent 95% confidence intervals. Reproduced and modified from Paper I with permission from Elsevier.

The commonest postoperative complications were re-operations due to bleeding and infections (mediastinitis, pneumonia and 'hospital-acquired bacteremia'). Among pump-related complications that occurred during the entire treatment period, the most frequent were strokes, pump thromboses requiring intervention and cannula infections treated with antibiotics. None of these complications differed significantly between children and adults. Stroke with residual neurologic impairment was, in our opinion, the most serious complication and occurred in 12% of all patients.

The overall survival probability in children was 90% at both 1 and 5 years. In adults, survival was 82% at 1 year and 75% at 5 years ($p=0.30$) (Figure 9). The combined endpoint (survival free from major stroke) also showed no differences between children and adults. Because strokes were the primary reason for death in both groups, the combined endpoint was largely unchanged as compared to deaths alone, although the events occurred somewhat earlier. Patients with DCM as HF etiology had better survival free from stroke than those with HF of other etiologies ($p=0.01$).

Paper II: BiVAD patients were younger, more often female and did not have AdHF of ischemic origin. As expected, they were also in a hemodynamically more compromised situation, with poorer RV function, higher right atrial pressure, lower cardiac index and a higher central venous pressure/PAWP ratio.

The overall survival probability in BiVAD recipients was 85% at 1 year and 79% at 2 years. For LVAD recipients it was 86% at both 1 and 2 years. There was no difference between groups ($p=0.66$) (Figure 11). The median time on device until transplantation or weaning was shorter in the BiVAD group than the LVAD group (154 versus 302 days; $p<0.01$). This was not unexpected since BiVAD patients were prioritized on the waiting list. Complications, expressed as episodes per 100 patient-months, tended to be somewhat higher in the BiVAD group, but a statistically significant difference was seen only for minor stroke.

ROC curves for two RV failure risk failure scores - the 'Matthews score' (102) and the 'Fitzpatrick score' (103) - were generated and the AUCs compared. The AUC for the first risk score was 0.72 and that for the second was 0.92, with a strong trend towards significance between the two ($p=0.05$).

This study suggested that use of the paracorporeal BiVAD in carefully selected patients was likely to reduce hospital stay and improve survival by avoiding the negative consequences of severe post-implantation RV failure. Thus, under the circumstances prevailing at our center, the approach used seems reasonable.

Paper III: DCM was the commonest cause of HF in the study group. Mean mGFR increased significantly after MCS implantation (mean change $+8.3$ mL/min/1.73 m²; $p<0.001$). At the first annual clinical assessment after HTx the mean GFR had again tended to decrease, although the reduction was not statistically significant (Figure 12).

Patients treated with pulsatile compared with CF pumps differed somewhat at baseline. The patients with pulsatile devices were younger, more often female, had

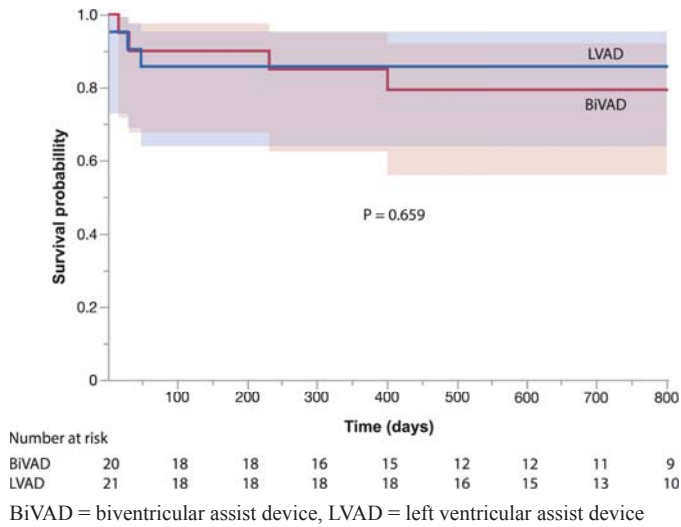


Figure 11. Survival in BIVAD and LVAD recipients. Shaded areas represent 95% confidence intervals. Reproduced from Paper II with permission from Elsevier.

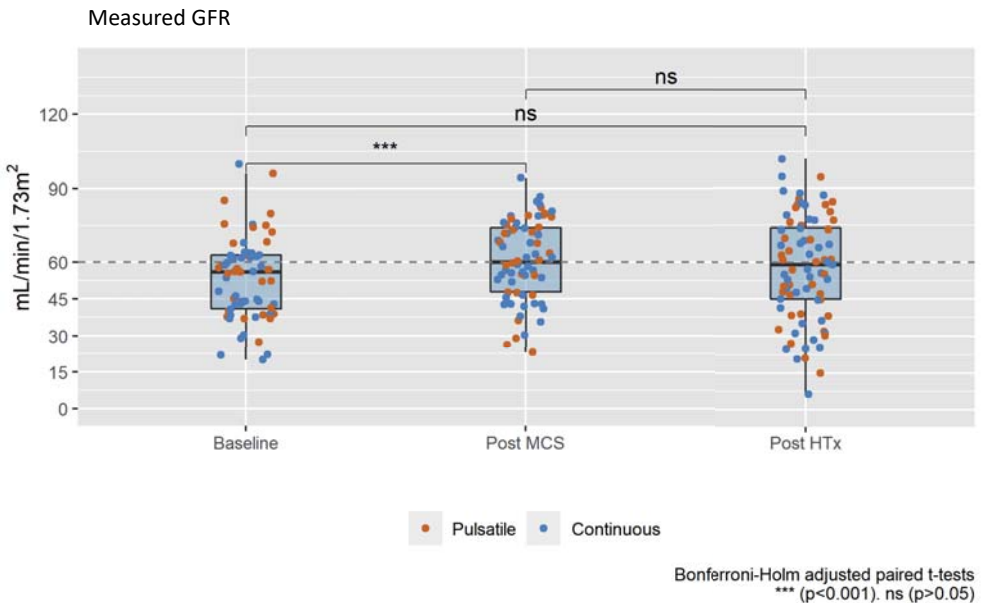


Figure 12. mGFR at baseline, after implantation of MCS, and at 1-year follow-up after HTx. Filled circles indicate individual measurements and colors type of MCS. Median, Q1 and Q3 are displayed in boxes. mGFR, measured glomerular filtration rate; MCS, mechanical circulatory support; HTx, heart transplantation.

lower hemoglobin levels and were less likely to have hypertension. Of the 41 pulsatile pumps used, 27 were used as BiVADs, which perhaps may explain some of the baseline differences. No significant difference in mGFR was seen between pulsatile and CF pumps after adjustment for age and period of implantation.

mGFR in subjects aged 35–49 years increased following MCS implantation and subsequent HTx (+8.4 mL/min/1.73 m²; p=0.04) after adjustment for device type and period of implantation. No significant changes were seen, however, for the other two age groups.

Patients from the implantation period 1996–2004 displayed a steady decrease in mGFR (–18 mL/min/1.73 m²; p=0.01), whereas those from the more recent implantation period (2012–2018) showed an increase in mGFR (difference from baseline to post-HTx +7.6 mL/min/1.73 m²; p=0.04) after adjustment for age and type of device (Figure 13). Perioperative events such as organ ischemic time, reoperation for bleeding, need for continuous renal replacement therapy after HTx, days in the ICU and days in hospital (post HTx) were comparable between implantation periods.

Based on eGFR, the proportion of patients in CKD stage 1–2 compared with stage 3–4 increased from 50% at baseline to 79% post-MCS (p=0.008). After HTx, it was reduced to 56% (p=0.02).

Paper IV: As expected after matching, there were no differences between MCS-BTT and medically managed patients regarding age, gender and diagnosis. Furthermore, baseline creatinine, mGFR, donor age, donor heart ischemia time, time in the ICU and time in hospital after HTx were similar between groups. Allosensitization before HTx was more frequent in the MCS group and MCS-BTT patients spent longer on the waiting list.

Overall graft survival probability after a maximal follow-up of 10 years was 84% in the MCS-BTT patients and 90% in the medically managed group (p=0.32). During the first year post-HTx, 19 MCS-BTT patients and 18 in the control group were treated for rejection (\geq ISHLT grade 2R). There were no significant differences regarding freedom from treated rejection and freedom from any rejection (p=0.94 and p=0.98, respectively). Neither were there any differences in mGFR at 1, 3 and 5 years after HTx. NT-proBNP level, LVEF and the proportion of patients with CAV grade \geq 1 were also comparable between the two groups.

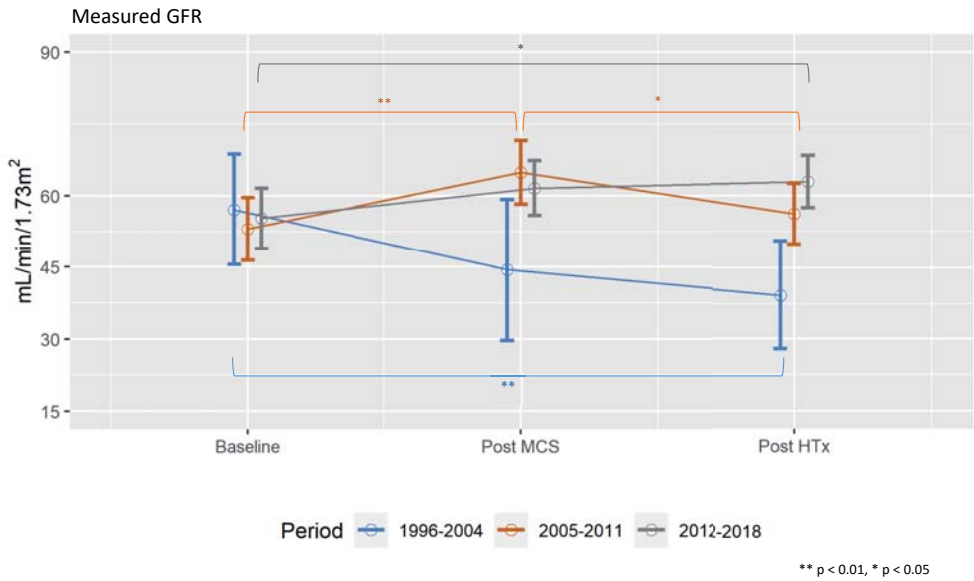


Figure 13. Adjusted mean measured GFR at baseline, after implantation of MCS, and at 1-year follow-up after HTx by periods of implantation. Error bars presenting 95% confidence intervals and brackets show significant changes. GFR, glomerular filtration rate; MCS, mechanical circulatory support; HTx, heart transplantation. Reproduced and modified from Paper III under the terms of the Creative Commons Attribution-NonCommercial License.

DISCUSSION

Durable MCS in patients less suitable for CF-LVADs

Treatment with a long-term CF-LVAD is, as previously mentioned, the most well-established way to bridge HF patients in need of mechanical hemodynamic support to HTx (46, 47). However, in certain groups of patients, this may not be possible or is associated with considerable risks. These categories include smaller children, patients with congenital heart disease and adults/adolescents with severe biventricular failure. In Paper I we show the results of treatment with the EXCOR device in those groups.

In *children* with smaller bodies, survival and complication rates are in line with - or better - than those described in previous studies (55-59, 104-106). This also includes the incidence of stroke (105). For the pediatric population, alternatives to the EXCOR system are limited. The recovery rate of $\approx 30\%$ is higher than that in the North American experience (106). We had a stated goal to avoid extended treatment with short-term MCS. In cases where patients did not show signs of recovery after 7–10 days, treatment with short-term MCS was replaced by the EXCOR device. Our findings also suggest that the chance of myocardial recovery during MCS treatment is related to age, disease duration and the etiology of HF. Patients with shorter disease duration and reversible causes of HF, such as myocarditis or tachyarrhythmia, had a greater potential to regain their heart function. In Paper I, pump explantation was possible in eight children. Of those, seven had either myocarditis, tachycardia-induced cardiomyopathy or persistent severe HF after cardiac surgery. In adults, myocardial recovery was less frequent and occurred in only one case, Figure 9.

Patients with *congenital heart disease (CHD)* constitute a growing population of adolescents and adults. These patients have an increased risk of HF and show excess mortality (107). Therefore there is a need for AdHF therapies in this population. Previous reports show that MCS is used less frequently in CHD patients than in other HTx candidates (108). Published results of treatment with long-term MCS in this patient group are scarce, although recent data have suggested promising outcomes with the Heart Mate 3 device in selected patients (109). However, implantation of a CF-LVAD can be technically difficult, partly due to anatomical aberrations that make device placement problematic and partly due to failing function of the venous heart chamber. In our study (Paper I), a total of six patients (four children and two adults) with complex CHD received the EXCOR system. Both the 1- and 5-year survival probability of these patients was 83%, which is high given the degree of complexity of their cardiac malformations and the severity of HF.

How *severe biventricular HF* should be treated when there is a need for MCS in adults and adolescents eligible for HTx is a matter of debate. Early RV failure - normally occurring within 14 days after implantation - develops in $\approx 20\text{--}30\%$ of all LVAD patients (110) and is associated with significantly increased mortality (48, 50, 111). Strategies to facilitate RV recovery after LVAD implantation include use of inotropes, specific pulmonary vasodilators (112, 113) and temporary RV assists (51, 114, 115). However, patients in need of such measures spend longer time in the ICU (111) and

show impaired 1-year survival, ranging from 70% to $\leq 50\%$ (116). In one retrospective case series, a majority (51%) of patients treated with temporary RVADs could not be weaned, and this subgroup had an even worse prognosis with a 6-month survival rate of only 13% (51). An additional problem with RV failure after LVAD implantation is that it can contribute to organ failure to the extent that the results after HTx are negatively affected (117). At the same time, there are data suggesting that preplanned BiVAD implantation in patients at high risk of post-implantation RV failure may be better than subsequent conversion from LVAD to BiVAD (53). This is also supported by our findings. Patients with cardiogenic shock (INTERMACS profile 1) can be particularly difficult to evaluate with respect to RV function and *per se* have an increased risk of postoperative RV failure. Two recent publications have shown reasonable results with a paracorporeal pulsatile BiVAD as bridge to HTx in patients with an INTERMACS profile of 1–2 (118, 119).

We adopted a similar strategy with preplanned BiVADs at our center and, in Paper I, showed that patients with biventricular failure had a high survival rate with the EXCOR device as well as a good long-term survival probability. The results of Paper II also support the use of BiVAD as a bridge to HTx in selected patients with a high risk of postoperative RV failure. Survival in the BiVAD group was higher here than previously reported and comparable to that of the contemporary LVAD patients, despite the fact that those who received BiVAD were in poorer health regarding their hemodynamic state and INTERMACS profile. Fairly short waiting times to HTx and the ability to prioritize BiVAD patients on the waiting list may have contributed to these outcomes. The frequency of adverse events was comparable between the two groups, and the majority of patients in both groups could be discharged while waiting for HTx. However, the rates of pump thrombosis and stroke in our paracorporeal BiVAD group were considerably higher than those described with some of the modern third-generation LVADs (39, 40). It is hard to tell whether the patient populations in these different studies are entirely comparable, which limits the resilience of any conclusions that may be drawn from comparing these studies.

The use of ‘double’ third-generation CF devices as a ‘BiVAD’ may seem a more modern option than the strategy used by us, but it is complicated and still not approved for biventricular use. A smaller multicenter study describing biventricular support with two Heart Mate 3 devices showed worse survival compared to Paper II (120). In a recent small single-center study, 1-year survival was high, but only one of 12 patients was classified as INTERMACS 1 (34). Therefore, one may argue that the ‘old-fashioned’ paracorporeal pulsatile BiVAD still has a role in the treatment of critically ill patients with severe biventricular failure (121).

The use of *RV failure risk scores* for predicting the risk of postoperative RV failure in LVAD patients is also under debate. Several scores have been proposed (48, 102, 103, 122) but these have generally failed to predict the need for RV support after implantation of an LVAD when validated in another patient population (123). Even the most recent ‘EUROMACS right HF risk score’ (122) showed limited discrimination when externally validated (124, 125). In Paper II, the ‘Fitzpatrick score’ (103) proved useful in predicting severe RV failure resulting in BiVAD support, compared to those

handled with an LVAD alone. The area under the ROC curve was 0.92, which could support the usefulness of this risk model as an aid to determining treatment strategy in our population, although its value in more recent and larger studies has been questioned (123, 126). At our center, no risk scores were used in pre-operative clinical practice at the time of the study, but it can of course not be ruled out that the decision-making process was influenced by the awareness of some of the parameters included in those scores.

Renal function after durable MCS and HTx

The extent to which durable MCS can improve renal function measured as GFR is not fully known. Patients with AdHF often suffer from the cardiorenal syndrome, which in itself is associated with increased morbidity and mortality (15, 23). Correct assessment of renal function can be crucial in determining patients' eligibility for HTx. Previous studies have shown that treatment with long-term MCS can improve renal function, in the form of reduced creatinine levels or improved eGFR (43, 127-130), but that eGFR then tends to gradually fall again while on MCS treatment (131). One explanation for this may be a reduction in muscle mass early after surgery that causes creatinine levels to decline, which in turn leads to overestimation of GFR. Conversely, an increase in muscle mass during the following months after device implantation (as patients recover their health and become more active) may cause higher creatinine levels and a decrease in eGFR without any actual changes in renal function actually occurring. An overestimation of eGFR is presumably a problem when used in the broader AdHF population as well. In Paper III, which studied mGFR, considered the gold standard for estimating renal function, we saw a significant increase in mGFR after MCS implantation. Since we only had one measurement during ongoing MCS treatment, we could not study longitudinal changes of mGFR before HTx. However, we had measured renal function at 1 year after HTx and found that mGFR tended to decrease again, although not significantly.

There has been ongoing discussion concerning whether newer CF devices may affect renal function more negatively than older pulsatile systems (44, 45). In our study, no differences were seen between these device types. This is reassuring as the vast majority of new VAD implants today are CF.

Middle-aged patients (35–49 years) showed an increase in mGFR after MCS and subsequent HTx, as did patients managed during the latest era (2012–2018). By contrast, patients treated during the earlier era (1996–2004) showed a continuous decrease in mGFR. We speculate that the better renal function observed in the recent era can be related to several factors, such as improved donor management and peri-/ postoperative care.

The tendency towards declining mGFR levels in the total study group after HTx in Paper III was not unexpected. In a previous study from our group, we found an average reduction in mGFR of 12% in the first year after HTx compared with the preoperative value (86). The reduction then seemed to continue over time. Based on iohexol clearance (i.e. mGFR), a publication from Lund University Hospital (20) described the cumulative incidence of patients in CKD stage ≥ 4 as 25% and 41% at 5 and 10 years

after HTx, respectively. This is clearly higher than described in previous studies using eGFR (132, 133). We conjecture that this difference may be due to overestimation of GFR by the MDRD formula used. The presence of CKD (eGFR <60 mL/min/1.73 m²) at 1-year post-HTx (134) or a drop in mGFR of >25% during the first year after HTx (86) has been associated with worse survival. The large reduction in GFR observed early after HTx is likely an adverse effect of the quite high doses of CNIs given. Certainly, the introduction of mTOR inhibitors and early reduction or withdrawal of CNIs has proved to be useful (76, 84, 85). Unfortunately, the effect of mTOR inhibitors per se could not be studied in Paper III due to the limited number of patients. However, in Paper IV, in which about one-third of patients were treated with everolimus, this decline in mGFR after HTx was not seen. We hypothesize that the increased use of everolimus, along with advanced perioperative care, may have contributed to the improved trajectory of renal function over time.

Post-transplant outcomes in patients treated with or without durable MCS as a bridge to HTx

When more patients are bridged with MCS to HTx it is instructive to investigate how this influences short- and long-term outcomes. More specifically, we wanted to explore the effect of the altered bridging strategy that was initiated in 2007–2008. After that time, direct transplantation from short-term MCS was, as far as possible, avoided at our center and most transplant candidates in need of MCS were instead bridged with durable devices.

Several previous studies have shown the negative effects of short-term MCS on post-HTx survival (70, 135, 136). Our results in Paper IV, namely a cumulative graft survival (and a slightly higher patient survival) of 84% after a maximum of 10 years in the MCS group, are better than those previously reported from our center and from the ISHLT registry (70, 136). We can speculate that this, in part, may be a consequence of the altered bridging strategy.

Evidence about the effect of long-term MCS on post-HTx survival is contradictory (46, 95-99, 137). Comparisons with patients who are managed medically until HTx can be difficult to conduct owing to differences between patient groups. (Normally, MCS patients are hemodynamically more severely compromised before device implantation and need prolonged rehabilitation after the device procedure.) At our center, we therefore usually wait at least 3 months until they are listed for HTx or reactivated on the transplant waiting list. Even though treatment with durable MCS allows for end-organ recovery (Paper III), some studies have shown that these patients are at increased risk of early post-transplantation mortality (95, 96, 99). In some cases, significantly worse long-term outcomes in MCS-bridged patients are also seen (95). While previous studies have included all patients (95, 98, 99, 138) or used propensity score-matched cohorts (96), we performed direct matching of non-bridged patients with the MCS-BTT cohort based on sex, diagnosis, age and year of transplantation. We aspired to make our groups as similar as possible and no differences in other baseline variables were identified after matching. Our MCS group included both LVAD and BiVAD patients, who may differ in some respects. However, as shown in Paper II, long-term outcomes with these two device types have been similar at our center.

After HTx, we observed no significant difference in long-term graft survival between MCS-BTT patients and medically managed matched controls (Paper IV).

Allosensitization - the formation of circulating HLA antibodies - in general is considered to negatively affect survival after HTx (139). As MCS implantation has been recognized as an independent risk factor for formation of HLA antibodies (140), the question arises whether MCS-related allosensitization is also associated with worse post HTx-outcomes. The mechanisms behind this are not completely understood and results from previous studies are somewhat conflicting (138, 141, 142). In Paper IV we showed that, despite a higher degree of pre-HTx allosensitization in MCS patients, ACRs did not differ between groups. This is true for both the incidence (time-to-event analysis) and the total number of rejections. Unfortunately, no analyses of 'isolated' AMR could be made due to small numbers of cases in our population and no conclusions could be drawn regarding this aspect. We have until now not been able to retrieve detailed information about specific cross-match testing in the individual allosensitized patients. This may be studied in the future.

Regarding other parameters such as mGFR, the frequency of CAV, NT-proBNP and LVEF, no inter-groups differences were seen at follow-up in Paper IV.

The tendency towards greater use of everolimus in the medically managed patients may be of some interest. At year 5 this difference was significant, but the proportion of missing data was also larger. We can speculate that these medically managed patients are in a hemodynamically less optimal situation than the MCS patients at the time of HTx and therefore may develop more renal problems post-HTx. This could lead to greater use of a renal-sparing immunosuppressive regimen. Conversely, MCS patients can have more problems with wound healing, resulting in a more restrictive use of everolimus early post-HTx.

We conclude that, with the current bridging strategy, short- and long-term outcomes after HTx in either MCS-BTT or medically managed patients are good and comparable between groups.

Strengths and limitations

The major strengths of Papers I–IV are their complete follow-up and reliability regarding the documentation of survival and other major events. No patients were lost to follow-up and patients were followed thoroughly for a long time. The fact that the studies were conducted at a single center streamlined data collection and may have helped to minimize data losses/omissions. Paper I contains one of the larger populations to date treated with the EXCOR device. Paper II describes a direct comparison between long-term survival in BiVAD and contemporary LVAD patients. In Paper III, the availability of mGFR is a key point and provides important evidence. Key features of Paper IV include the matching of patients in both groups and the accrual of detailed information about ACRs.

Many of the limitations of this research are inherent in the clinical circumstances of our patients: MCS is a relatively uncommon treatment for severely ill patients.

The retrospective nature of the studies places limitations on the standard of evidence we can extract from the results. The variables available in the registries were sometimes not complete and the complementary search and data collection from medical records, while rigorous, may have underestimated clinical events. In addition, there were limits on the number and details of peri- and postoperative values that could be retrieved retrospectively from medical records. The relatively small patient populations constrain the statistical power of these studies, which means that interpretations of outcomes need to be cautious.

The fact that the studies were performed at a single center may limit the generalizability of the results. Published long-term results with BiVADs are scarce and the diverse approaches used at different centers unfortunately makes a multicenter approach very difficult.

CONCLUSIONS

The following conclusions can be drawn:

- In patients less eligible for CF-LVADs, use of the paracorporeal ‘EXCOR’ device as a bridge to HTx or recovery resulted in excellent survival.
- The main complications of this treatment were thromboembolism, mechanical problems and infections requiring close surveillance and intensive clinical monitoring.
- In selected patients with a high risk of RV failure, BiVAD, planned in advance, can be a feasible strategy to improve survival with a complication rate similar to that of second-generation CF-LVAD patients.
- mGFR improved after treatment with long-term MCS but tended to decrease again after HTx. In certain subgroups, there was however a continuous increase in GFR after MCS and subsequent HTx.
- Graft survival in patients bridged to HTx with MCS was similar to that seen in matched controls who were managed medically before HTx. The numbers of rejections were also closely comparable in these groups.

FUTURE PERSPECTIVES

MCS devices have undergone considerable technical development in recent years. During the course of this project, third-generation LVADs, which are associated with a lower frequency of complications than earlier devices, have been introduced. Nevertheless, the majority of patients studied in this work had first-generation paracorporeal or second-generation CF devices.

In recent years, we have noted a trend for adult patients with AdHF to be referred for evaluation earlier in their disease course and before the development of severe right HF. As a result of this, and the increasing use of third-generation LVADs, the choice between an LVAD or a BiVAD is likely to be shifted in favor of LVAD implantation. This may reduce the need for BiVAD implants at our center. In patients less eligible for CF-LVADs, however, and/or with very low INTERMACS profiles, there will be a need for alternative devices and configurations. It would be desirable to investigate more systematically the effects and safety of third-generation CF devices used as BiVADs.

The proportion of patients bridged to HTx with MCS is increasing and that trend may continue. Furthermore, as survival after HTx has improved over recent decades, concerns related to long-term complications will probably attract further attention. This includes more individualized immunosuppressive regimens aiming to minimize doses of, particularly, CNIs, without increasing the number and severity of rejections. Other nephroprotective agents, such as SGLT-2 inhibitors, may also have a role post-HTx, although this has still to be fully elucidated.

If a workable technical solution for wireless power transmission in MCS can be developed then the complications of MCS use could be further reduced and quality of life increased. This could lead to further improvements in organ function and survival in the future.

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