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The use of mechanical circulatory support and passive ventricular constraint in patients with acute and chronic heart failure

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To

Eva, Axel & Erik

Abstract

Many patients are diagnosed as having chronic heart failure (CHF) and apart from the fact that daily activities are impaired, they are great consumers of health care, and the prognosis is poor. The distinction between acute heart failure (AHF) and CHF may be difficult and is more a question of time rather than severity. The "gold standard" treatment for end-stage heart failure is heart transplantation. Due to organ shortage this is reserved for selected patients only. Since the introduction of mechanical circulatory support (MCS) more and more patients with progressive CHF have been bridged-to-heart-transplantation. There are MCS systems available for both short- and long-term support. Newer concepts such as ventricular constraint to prevent ventricular remodelling are on the way. We have investigated short- (Impella™) and long-term (HeartMate™ I and II) MCS and ventricular constraint (CorCap™ CSD) as treatment concepts for all forms of heart failure, the aims being: bridge-to-decision, bridge-to-transplant and extended therapy, called "destination therapy" (DT).

Methods and results

In Paper I, the use of HM-I™ pulsatile MCS in bridge-to-transplantation patients in Sweden was retrospectively investigated regarding outcome and risk factors for mortality and morbidity. Fifty-nine patients were treated between 1993 and 2002. The dominating diagnosis was dilated cardiomyopathy in 61%. Median support time was 99.5 days. 18.6% died before transplantation. Four patients needed RV assist due to right ventricular failure. Haemorrhage was an issue. Six patients (10%) suffered a cerebrovascular thromboembolic lesion. 15% developed driveline infection. 45% of the MCS patients were discharged home while on pump treatment. Massive blood transfusion was a predictor for mortality and morbidity, $p<0.001$.

In Paper II the second generation long-term MCS, the continuous axial flow pump HM-II™, was prospectively evaluated for mortality and morbidity. Eleven patients, from 2005 until 2008, were consecutively included at our institution. One patient received the pump for DT. The median pump time was 155 days. Survival to transplantation was 81.8%. Ten patients could be discharged home before transplantation after a median time of 65 days.

Paper III investigated the Swedish experience and outcome of short-term axial flow MCS, the Impella™, in patients with AHF. Fifty patients were collected between 2003 and 2007 and divided into two groups: 1. *Surgical group* (n=33) with cardiogenic shock after cardiac surgery; and 2. *Non-surgical group* (n=17), patients with AHF due to acute coronary syndromes with cardiogenic shock (53%) and myocarditis (29%). The 1-year survival was 36% and 70%, respectively. 52% were reoperated because of bleeding. Predictors for survival at 30 days were preoperatively placed IABP ($p=0.01$), postoperatively cardiac output at 12 hours and Cardiac Power Output at 6 and 12 hours.

In Paper IV we evaluated the use and long term outcome of ventricular constraint CorCap™ CSD. Since 2003, 26 consecutive patients with chronic progressive heart failure were operated with CSD via sternotomy (n=25) or left mini-thoracotomy (n=1). Seven patients were operated with CorCap™ only. Nineteen patients had concomitant cardiac surgery. There were three early and three late deaths. The remaining cohort (n=18) was investigated in a cross-sectional study regarding QoL with SF-36. There was no difference in QoL measured with SF-36 after a mean 3-years follow up period, when compared to an age- and sex-matched control group from the general population. The one-year survival was 86%, and after three years 76%. Echocardiographic dimensions had improved significantly after three years.

Conclusion

In our unit, a non-transplanting medium-sized cardiothoracic department, short- and long-term MCS (Impella™ resp. HM™) in patients with acute or chronic HF have been used with good results. The use of ventricular constraint early in the course of the disease is a good adjunct to other treatment options in progressive chronic HF patients.

List of original papers

This thesis is based on the following papers, referred to in the text by their Roman numbers

I. Risk factor analysis of Swedish left ventricular assist device (LVAD) patients.
Granfeldt H, Koul B, Wiklund L, Peterzén B, Lönn U, Babic A, Ahn H.
Ann Thor Surg 2003;76:1993-99

II. A single center experience with the HeartMate-II™ left ventricular assist device (LVAD)
Granfeldt H, Peterzén B, Hübbert L, Jansson K, Ahn H.
Scand Cardiovasc J. 2009;43(6):360-365.

III. The experience with the Impella™ recovery axial-flow system for acute heart failure at three cardiothoracic centers in Sweden.
Granfeldt H, Hellgren L, Dellgren G, Myrdal G, Wassberg E, Kjellman U, Ahn H. *Scand Cardiovasc J. 2009;43(4):233-9*

IV. Long-term Quality of Life (QoL) in patients with progressive chronic heart failure after surgical ventricular restoration with passive ventricular constraint (CorCap CSD™). Comparison with a patient-matched reference group from the general population.
Granfeldt H, Holmberg E, Träff S, Jansson K, Ahn H. *Manuscript.*

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Abbreviations

ACE	Angiotensin Converting Enzyme
ARB	Angiotensin Receptor Blocker
ARF	Acute Renal Failure
ASA	Acetylsalicylic Acid
BiVAD	Biventricular Ventricular Assist Device
BNP	B-type Natriuretic Peptide
BSA	Body Surface Area
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CHF	Chronic Heart Failure
CO	Cardiac Output
CPB	Cardiopulmonary Bypass
CPO	Cardiac Power Output
CPR	Cardio-Pulmonary Resuscitation
CRP	C-reactive Proteine
CRT	Cardiac Resynchronization Therapy
CSD	Cardiac Support Device
CT	Computed Tomography
DCM	Dilated Cardiomyopathy
DT	Destination Therapy
ECMO	Extra-Corporeal Membrane Oxygenation
EF	Ejection Fraction
ESC	European Society of Cardiology
FDA	Food and Drug Administration
HF	Heart Failure
HM	HeartMate
HTx	Heart Transplantation
IABP	Intra-Aortic Balloon Pump
ICD	Implantable Cardiac Defibrillator
ICU	Intensive Care Unit
IHD	Ischemic Heart Disease
INR	International Normalised Ratio
ISHLT	International Society for Heart and Lung Transplantation
KNS	Coagulase Negative Staphylococcus
LD	Left Direct
LMWH	Low Molecular Weight Heparin
LOS	Low Output Syndrome
LP	Left Peripheral
LV	Left Ventricular
LVAD	Left Ventricular Assist Device
LVEDD	Left Ventricular End-Diastolic Dimension
LVEDDi	Left Ventricular End-Diastolic Dimension index
MCS	Mechanical Circulatory Support
$MCS_{(SF-36)}$	Mental Composite Summary
MLHF	Minnesota Living with Heart Failure
MRSA	Methicillin Resistant Staphylococcus Aureus
NYHA	New York Heart Association Class
PCI	Percutaneous Coronary Intervention

$PCS_{(SF-36)}$	Physical Composite Summary
QoL	Quality of Life
RD	Right Direct
RVAD	Right Ventricular Assist Device
RVF	Right Ventricular Failure
6-MWT	Six Minute Walk Test
SD	Standard Deviation
SF-36	Medical Outcomes Study Short Form General Health Survey
SvO_2	Mixed Venous Oxygen Saturation
SVR	Systemic Vascular Resistance
TAH	Total Artificial Heart
TEE	Trans-Esophageal Echocardiography
TEG	Thrombelastogram
VAD	Ventricular Assist Device
X-clamp	Aortic Cross Clamp

Introduction

Heart failure (HF) is a complex clinical syndrome characterised by haemodynamic abnormalities, neurohumoral and cytokine activation, fluid retention and reduced exercise capacity. Many patients are diagnosed with the disease and apart from impaired daily activitiy, they are great consumers of health-care, and the prognosis is poor. The distinction between acute and chronic HF may be difficult and is more an indicator of time rather than severity. Pharmacological treatment options have expanded, targeting on different pathways in the vicious circle of heart failure progression. Surgically, there are several treatment options for this category of patient. The "gold standard" for end-stage heart failure is still heart transplantation. Due to organ shortage this is available for selected patients only and the long-term morbidity and mortality remains high. Valve plasty or replacement and coronary artery revascularization are the most common surgical procedures performed to prevent further progression of the disease. Various techniques for ventricular restoration have been used for many years and new concepts are on the way. The development and use of mechanical circulatory support (MCS) devices have increased dramatically over the last decade as a form of therapy for both acute and chronic heart failure. The idea and the dream of a total artificial heart arose almost 50 years ago [1].

Our increased knowledge of HF pathophysiology plus technical advances in the field has resulted in the indications for MCS becoming wider and treatment duration longer. Different pump systems are available for short- (hours to days), intermediate- (days to weeks) and long-term use (months to years). Treatment concepts have been developed, bridge-to-recovery, bridge-to-bridge, bridge-to-transplant and bridge-to-destination. There is also the

possibility of a bridge-to-decision period during which cases may be further evaluated and ethical considerations made, so that correct treatment for the individual patient is provided. Destination therapy (DT) has gradually developed parallel to improvement in long-time reliability of the assist devices. Furthermore donor shortage now makes this a realistic option for an increasing number of patients. All kinds of severe HF have a treatment option regardless of cause. Cardiogenic shock, post-cardiotomy heart failure, and decompensated chronic heart failure can be treated by techniques ranging from bridge-to-decision to DT. As an adjunct in the management of chronic heart failure, ventricular constraint, in particular, has been introduced. There are results indicating that reverse remodelling can be achieved with such a device. This thesis describes the use and the strategy of MCS and ventricular constraint treatment in a non-transplanting University Hospital.

Heart Failure

The definition of HF is a combination of symptoms and signs together with objective evidence of structural or functional abnormalities of the heart.

Heart failure definition according to ESC guidelines,

- *Symptoms* of HF; like breathlessness, fatigue, ankle swelling and
- *Signs* of HF; tachycardia, tachypnoea, raised jugular venous pressure and
- Objective *structural changes* of the heart; cardiomegaly, ECG-changes

A useful classification in the European Society of Cardiology (ESC) Guidelines [2] is based on the nature of the clinical presentation and divided into

- New onset HF
- Transient HF
- Chronic HF

Despite the aetiology of chronic heart failure (CHF) the long-term prognosis is poor, 40% of patients hospitalised for CHF are dead or readmitted within one year [2, 3]. Epidemiological studies shows 51% and 35% survival after 2 and 5 years, respectively, from the initial diagnosis [4]. The prevalence in Sweden is 2-3% and increases with age. Almost 6-10% of patients over the age of 65 years have this disorder. The most common cause is coronary artery disease (CAD) in more than 70% of cases.

Cardiogenic shock appears in 7-10 % of myocardial infarctions and is associated with 70- 80% mortality [5, 6]. The era of early revascularization led to a decline and in 2005 Babaev et al. reported 47% in-hospital mortality for cardiogenic shock [7]. The patients that survive the initially HF have a fairly

good two-years survival of 80% [8]. Survival after cardiac arrest in hospital is 25% and with increasing cardiac support systems such as IABP and extracorporeal membrane oxygenation (ECMO) survival rates have increased to 40% [9]. Acute heart failure (AHF) can resolve or progress to CHF depending of the initial cause. Postcardiotomy HF occurs in 2-5% of all cardiac operations [10]. Early mortality is high, but has declined with the use of MCS [11].

Critical to the understanding of HF are observations that the progression of the disease is related to progressive alterations in structure and function of the heart. Progressive left ventricular (LV) hypertrophy, enlargement, and cavity distortion over time is termed "ventricular remodelling". This condition is related to deterioration of LV performance and is associated with an increase in mortality and morbidity [12]. Classification can be made based on structural abnormality or symptoms related to functional capacity [2].

Stage A; No structural changes	NYHA I; No physical limitation
Stage B; Structural changes without symptoms	NYHA II; Slight limitation
Stage C; Symptomatic heart failure	NYHA III; Marked limitation
Stage D; Advanced structural changes and marked symptoms	NYHA IV; Symptoms at rest

There is a distinction between systolic and diastolic HF. Diastolic dysfunction is characterised by HF with preserved left ventricular function in terms of ejection fraction (EF), such as aortic stenosis or untreated hypertension. This is a matter of debate [13].

Cardiac remodelling

CHF is increasing in incidence and prevalence, is expensive to treat, and is associated with substantial morbidity and mortality [14]. The understanding of the pathophysiology in the development of HF, and its management has also increased. The disease process long precedes the development of clinical symptoms and structural changes in the left ventricle is the key issue [15]. The heart size increases, changes shape and becomes more spherical and performance is altered, Fig 1. The process involves myocytes, interstitium, collagen structure and probably vasculature.

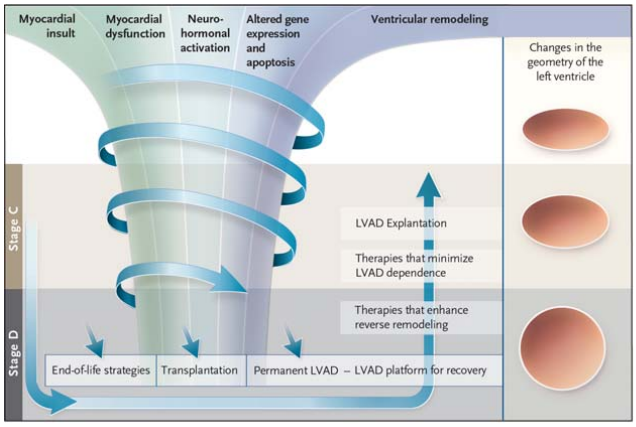


Figure 1; Pathophysiological mechanisms of and treatment options for End-Stage Heart Failure. Renlund, Kfoury. NEJM 2006. With courtesy from Dr Kfoury.

The classical process of ventricular remodelling is elicited by a myocardial infarction. Pressure and volume overload adequate to initiate the process, regardless of physiologic mechanism, is a prerequisite. Hormonal stimulation has been identified as a key contributor to the progressive left ventricular structural remodelling process that accounts for symptoms and mortality in heart failure, a growth-mediated response [16].

The role of the neurohumoral systems (sympathetic nervous system, renin-angiotensin-aldosteronesystem, endothelin and others) has led to the development of several pharmacological inhibitors with favourable effect on the clinical syndrome. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARB), ß-adrenoreceptor inhibitors and aldosterone inhibitors have all been shown to exert a favourable effect of the disease and probably on the course of structural remodelling of the left ventricle.

The impaired function of the ventricle is the fundamental cause of the symptoms, whether mediated directly by left ventricular haemodynamics or indirectly by mechanical changes on ventilation, renal sodium retention, or neurohormonal activation. Diuretics used to reduce filling pressure are effective in reversing symptoms, as are vasodilators and inotropes to improve left ventricular ejection fraction and reduce filling pressure. Symptom relief is not necessarily effective in reversing or slowing the progressive structural remodelling process. Reversion of the heart toward more normal shape and function is called reverse remodelling [17] and is the goal of treatment with ventricular constraint devices such as the CorCap CSD.

Remodelling may be an adaptive process like ventricular dilatation as compensatory response to volume overload in valve insufficiency with regurgitation in order to maintain a sufficient cardiac stroke volume. In conditions like myocardial infarction, non-ischaemic forms of myocarditis, and cardiomyopathy, structural changes are maladaptive from the beginning. There is a relationship between impaired left ventricular function (ejection fraction (EF), left ventricular end-diastolic dimension (LVEDD)) and poor prognosis [18]. Natriuretic peptide levels, especially B-type natriuretic peptide

(BNP) strongly correlates with left ventricular remodelling and prognosis [19]. They can be used as a complement to clinical assessment in the management of heart failure [20, 21].

Pharmacological treatment;

Objectives in the treatment are to relieve symptoms and signs, improve Quality of Life (QoL) and prevent the occurrence and/or progression of myocardial damage in order to slow the process of ventricular remodelling and reduce mortality. New pharmacological treatment have been developed during the last two decades including ACE-inhibitors, ARBs, beta-blockers (Class I, Level A) and spironolactone (Class I, Level B), which all interact in the process of ventricular remodelling [15, 22].

Angiotensin-Converting-Enzyme (ACE)-inhibitors (Class I, Level A) are strongly recommended in patients with CHF, regardless of symptoms and an EF<40%. It improves the ventricular function, patients QoL, reduces hospital readmissions and improve survival [23].

ß-*Blockers* (Class I, Level A) are also strongly recommended with the same indications and treatment results as for the ACE-inhibitors [24].

Aldosterone antagonists (Class I, Level B) are recommended for severe HF with EF<35%. Hospital readmissions are reduced and survival improved when added to existing therapy [25].

Angiotensin receptor blockers (ARB) (Class I, Level A) are used when patients still are symptomatic despite ACE-inhibitors and ß-blocker treatment [26].

There are several other pharmacological medications used in the HF treatment, but the levels of evidence are lower. Complementary drugs include *Hydralazine* (Class IIa, Level B), *Digoxin* (Class I, Level C) and *diuretics* (Class I, Level B). These have a more symptomatic profile and do not affect survival.

Experimental studies suggest that *gene transfer* may be effective in the process of ventricular remodelling, but the clinical implication still remains to be seen. The use of embryonic and adult stem cells in the treatment of ventricular remodelling is interesting. The process called plasticity or transdifferentiation shows great potential, though there is a long way left to clinical application. The development of stem cell therapy, after animal testing, stands in front of clinical studies in randomized trials [27].

Surgical treatment;

There are several treatment options for this category of patients. The presence of surgically correctable conditions causing HF constitutes an indication for surgical correction.

Coronary artery disease *(CAD)* is the most common cause of HF [28]. In myocardial infarction early reduction of wall stress and restoration of blood flow to the infarcted area can minimize myocyte damage, limit infarct size and remodelling [29], and improve function [30]. Two revascularisation modalities are available, percutaneous angioplasty/stenting (PCI) and coronary artery bypass grafting (CABG). The choice is depending on time frame, availability, indications, co-morbidity and the extent of coronary atherosclerosis. Hibernating myocardium represents dysfunctional tissue distal to a severe stenosis where the metabolic function is markedly down-regulated.

Improvement in function and reduced mortality can be achieved with revascularisation [30-32]. Detection of viability and the potential for regained function in hibernating myocardium is important before revascularisation is carried out [33] (Class IIa, Level C). Recently a score system, the SYNTAX-score [34], based on the angiographic pattern of coronary stenosis, have been suggested as a help in deciding whether to perform PCI or CABG.

Valvular heart disease, i.e significant aortic stenosis (Class I, Level C)/ regurgitation (Class I, Level B), mitral valve regurgitation (Class I, Level C) and tricuspid insufficiency (Class III, Level C) should be handled according to the ESC Guidelines for Valvular Heart Disease [35]. Preoperative optimisation is important to reduce the perioperative risk for morbidity and mortality and acute surgery should be avoided.

Cardiac Resynchronization Therapy *(CRT).* Patients with CHF frequently develop electrical abnormalities leading to mechanical abnormalities. CRT is recommended to reduce mortality and morbidity [36-38] in patients with low EF and QRS width >120 ms on the electrocardiogram, and with symptoms despite optimal medical treatment (Class I, Level A) [39]. A broad QRS complex is associated with poor long-term survival [40]. There is also reason to combine the CRT with an internal defibrillator (CRT-D) due to the risk of sudden cardiac death (Class I, Level A) [41]. CRT is an adjunct to pharmacological medication in many patients with CHF to reduce mortality. Therapy development is heading at preventive implantation to reduce heart failure events [42].

Heart transplantation; The gold standard in patients with end-stage CHF is heart transplantation (Class I, Level C) [43]. Due to organ shortage, this option is only for a limited number of patients and the waiting time for an adequate organ can be long. World-wide about 3.300 transplants are performed annually. Ten-year survival is approximately 50% [44] but is continually improving. There is a significant risk of morbidity due to long-term immunosupression therapy with hypertension, aggressive CAD and development of malignant disease. Non-CMV infections, graft failure and rejection are the dominant cause of mortality in the first year [45]. Newer pharmacological treatments reduce the risk for rejection. The dominant primary indication for transplantation has shifted towards non-coronary cardiomyopathy. In a recent audit of the ISHLT register 29% of transplant candidates were on some form of mechanical support preoperatively, an increase from previous estimates [45]. There has been an improvement in early post-transplant survival in MCS patients, but no significant difference long-term mortality. In recent years fewer recipients have been hospitalized prior to surgery due to outpatient treatment with MCS. The disappointing long-term survival is explained by the fact that recent recipients have more risk factors than before.

Mechanical assist devices (Class IIa, Level C) have been used since the end of the Eighties and they are mostly used for bridging treatment in critically ill patients waiting for transplantation [46, 47]. Reversing multi-organ failure, allows patients to rehabilitate and gain strength, increasing their survival while awaiting transplantation. Improved tissue microcirculation [48] allows end-organ function to recover. Achieving a time frame, > 30 days, prior to transplantation also improves post-transplant survival [49], at least with the

first generation of MCS devices. The use of left ventricular assist devices (LVAD) has shown signs of reverse remodelling [50-52] including regression in myocardial fibrosis, reduction in apoptosis and myocytolysis, and improved myocyte function [53]. With time there is a decrease in the neurohumoral activation [54].

A milestone in the development and progress of the use of MCS was the REMATCH-study [55], reporting better survival after one year for LVAD patients compared to a control group of patients receiving optimal pharmacological therapy for advanced HF and not eligible for heart transplantation. Newer pump generations are smaller and have improved long-term reliability. This has made DT a more feasible alternative [56], where transplantation can be postponed or even avoided altogether [57, 58]. Survival at one year has improved with the second generation LVAD [46]. Some patients can be bridged to recovery [59], but the rate is low.

There are several pump systems, both for acute and chronic HF, giving new possibilities for MCS to work as bridge-to-bridge, bridge-to-destination and also bridge-to-recovery. The systems can be used for unloading the left ventricle (LVAD), right ventricle (RVAD) or both ventricles (BiVAD) of the heart. There is also the totally artificial heart device (TAH), where the entire heart is replaced. Patient selection is demanding and based on a multi-professional team-work [60]. There are difficulties in conducting randomised studies in this group of very sick patients where pharmacological treatment has failed. Morbidity such as bleeding [61], infections, thrombo-embolic events and right ventricular failure, are demanding issues during MCS support [62]. Deplacement pumps were the first generation of flow pumps, the axial flow pumps were the second generation, and the third generation includes small

centrifugal assist devices. There are several other available pumps systems on the market. First generation pump systems; HM-I, Berlin Heart, CardioWest (TAH), second generation; HM-II, DeBakey, Jarvik 2000, Incor, and the third generation; DuraHeart, HeartWare. The TAH is under constant development and has so far been used as bridge-to-transplant.

Surgical restoration of the left ventricle in order to reshape the heart to improve pump function has been done [63, 64]. There are several methods of ventricular surgery to reduce wall stress and decrease ventricular size according to the law of LaPlace. The Dor-procedure [65], and ventricular constraint are examples [66]. There has been an ongoing debate since the STICH-trial was published 2009 [67].

A novel option for CHF patients is the concept of passive ventricular constraint, the Acorn Cardiac Support Device (CSD). The theory behind this is to slow down the process of ventricular remodelling by wrapping a net around the ventricles of the heart, named reverse remodelling. According to the law of LaPlace, wall stress decreases when there is a mechanical restriction outside the wall. This stimulates reverse remodelling leading to improved function of the heart [68]. Animal studies shows decreased echocardiographic dimensions [69] and signs of reverse remodelling at the cellular level [70]. Initial clinical evaluation indicates smaller dimensions and better performance of the heart with improved QoL [71]. It is even more convincing when combining reverse remodelling with mitral valve surgery [72]. Long-term follow-up shows sustained improvement regarding echocardiographic dimensions and cardiac function after five years [73, 74].

Acute heart failure (New onset heart failure)

This can be defined as an acute onset of HF symptoms necessitating rapid treatment measures [2]. The clinical presentation can be divided into acute decompensated HF and acute vascular failure (hypertensive, pulmonary oedema, cardiogenic shock, high output failure) [75]. The underlying mechanism can be described like an afterload mismatch with elevated systemic vascular resistance (SVR) in combination with impaired systolic performance [76], a combination of a cardiac and a vascular pathway. Cotter et al suggests that fluid accumulation, ischaemia, and arrhythmias play a minor role for the initiation of AHF, but other mechanisms such as neurohormonal activation, decrease in vascular plasticity, and fluid redistribution are more important. There are several aetiologies like IHD including acute coronary syndrome, acute myocardial infarctions, and also decompensation of CHF, valvular disease, myopathy, myocarditis and also other non-cardiac conditions such as septicaemia. Acute coronary syndrome is the cause in 42% of patients admitted for AHF for the first time [77]. In a French study, of patients admitted to the ICU because of AHF, 61% were diagnosed with IHD and 29% presented with cardiogenic shock. Early mortality (30 days) was 43% and after one year 62% [78]. The authors also report that patients presenting with cardiogenic shock had a 58% early mortality, but during the time period from 30 days to one year there was no difference in mortality between shock and non-shock patients. The immediate goal with these patients is to stabilise the haemodynamic situation for optimal tissue oxygenation and relief of symptoms.

Various forms of inotropic support are used (Class IIb, Level B) in deteriorating patients with cardiogenic shock. In patients with acute coronary

syndromes early revascularisation is mandatory [32]. The use of IABP or MCS (ECMO, LVAD) as adjuvant therapy may be necessary. The IABP is the most widespread cardiac support device in use. It reduces afterload and increase coronary perfusion by increasing mean arterial pressure during diastole. The cardiac work-load is decreased and the oxygen demand lower [79]. It is mostly used in patients with cardiogenic shock [80], but also in coronary syndromes and after cardiac surgery. Evidence for the prevention of remodelling is lacking. The IABP has [81] been in clinical use for many years, but its use has been less than expected [82]. Only 20- 30% of patients with cardiogenic shock world-wide are treated with IABP, possibly due to lack of large randomised trials, even though its use is recommended in the European Society of Cardiology guidelines (Class I, Level C) for myocardial infarction [83]. Since it is relatively cheap and easy to use it is widely spread around the world. The idea behind the Impella™ LVAD axial flow pump originates from the Hemopump™ [84], used in the 1990^{ties} as short-term MCS [85].

A clinical programme, involving cardiologists, anesthesiologists and cardiovascular surgeons, for new onset heart failure is important, because time matters [86]. It is also important to have a referral network based on the use of implantable MCS [87]. This should also include patients after cardiac surgery with postoperative cardiogenic shock. The subject of cardiac metabolism in heart failure is interesting. Impaired metabolic flexibility in the heart may reduce the contractile function [88]. Substrate selection, glucose control and improving mitochondrial function are targets for improving contractility. A metabolic strategy has been shown to reduce mortality and the use of inotropic agents in ischaemic patients with reduced left ventricular function and new onset heart failure after coronary artery bypass grafting [89].

Description of mechanical assist systems in use

HeartMate I™ (HM-I); Fig 2. (Thoratec Inc., Pleasanton, Ca, USA) This first

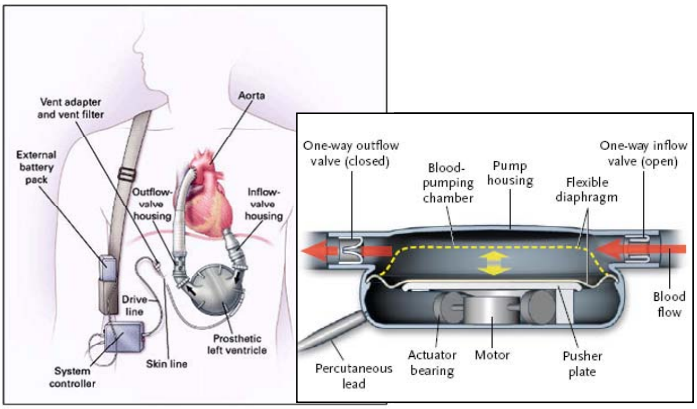


Figure 2; Schematic components of the Left Ventricular Assist Device, HM-I. Rose et al. NEJM 2001. With permission from NEJM.

generation of implantable mechanical assist devices. It has a housing of 83 mL, containing a pusher-plate membrane that was initially driven with compressed air and later, with electricity. Power is supplied via a cable through the wall of the abdomen which is connected to an external drive console or long-life batteries. The pump is positioned pre- or intra-peritoneally via a sternotomy combined with a laparotomy. The pump inlet cannula is connected to the left ventricle via the ventricular apex. There are two biological valves in the pump, causing the flow to be unidirectional. An outflow graft connects the pump outflow to the ascending aorta. The pump can work in auto-mode, where the pump rate adjusts automatically according to the amount of venous return, or in fixed-rate where the rate is fixed. The capacity could be up to ten litres per minute. The interior of the pump housing is made of sintered titanium and the membrane is made of polyurethane.

These raw surfaces reduce the need for anticoagulation due to the development of a pseudointima. It is intended for long-term use.

HeartMate II™ (HM-II); Fig 3. (Thoratec Inc., Pleasanton, Ca, USA). The second generation of implantable mechanical assist devices. These are axial-flow pumps with an impeller that rotates at high speed. The HM-II have the same flow capacity as HM-I, depending on afterload. The pump is connected to the left ventricle via the left ventricular apex and to the ascending aorta as with the HM-I. The pump has no valves inside. The impeller has ceramic bearings to minimize friction. Due to its small size it is positioned inside the pericardial sac above the diaphragm. The surface in the pump housing necessitates full anticoagulation. The cable is tunneled through the wall of the abdomen and is connected to an external drive console or long-life batteries. It is intended for long-term use.

Figure 3; Schematic components of the Left Ventricular Assist Device, HM-II. With permission from Thoratec Inc.

Impella™; Fig 4. (Abiomed, Inc, Danvers, Mass, USA.). An axial flow pump for acute heart failure. This catheter-assist is intended for short-time use. It is CE-marked for up to ten days of use. It consists of an impeller rotating up to 12.000 revolutions per minute in a short tube, the flow capacity depending on type of pump. This is introduced via the aortic valve into the left ventricle where blood will be sucked out and delivered in the ascending aorta. The

electromagnetic motor is placed in the pump, near the impeller. A power cable is connected to a drive console bedside. There is a monitor on the pump housing that can measure the pressure gradient between the ventricle and the

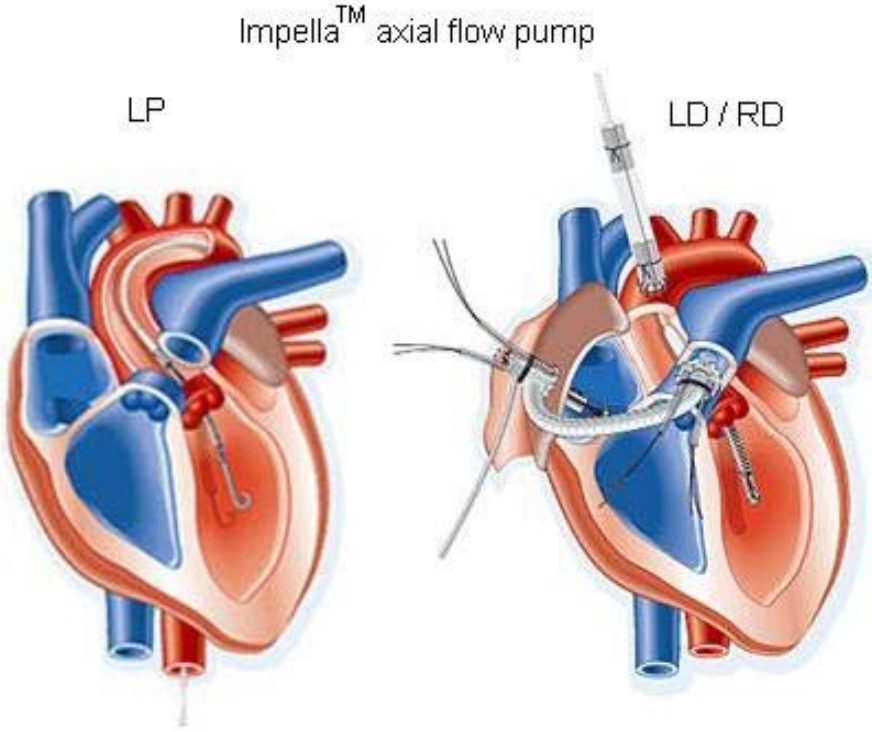


Figure 4, Different Impella™ pumps. LP; left peripheral, LD; left direct, RD; right direct
With permission from Abiomed Inc.

ascending aorta, indicating correct placement. There are three different types, Left Direct (*LD*) *5.0* placed via the ascending aorta through a synthetic graft. It provides flows up to 5 litres per minute. Sternotomy is required for implantation and removal. Left Peripheral (*LP*) *5.0* and *2.5*, the same principle as the LD but access via the femoral artery. It is positioned in the left ventricle with the aid of fluoroscopy or echocardiography. There is one pump for right ventricular failure, *RV*, which unloads the right ventricle when connected

between the right atrium and the pulmonary artery. This pump, however, has been withdrawn by the manufacturer and is no longer commercially available.

CorCap Cardiac Support Device™ *(CSD)*; Fig 5. (Acorn Cardiovascular, Inc, St. Paul, MN). A synthetic net, to surgically be wrapped around both ventricles of the heart, providing diastolic support and reducing wall stress. It is made of polyurethane weave with a bidirectional stretch to promote the ellipsoid shape of the heart. The first generation necessitates sternotomy and is sewn with interrupted sutures to the AV-groove and adjusted to fit the size of the ventricles. The sternotomy access is easy when in combination with valve- or bypass-surgery. The second generation has a delivery tool to be used with a left mini-thoracotomy, where the net in a parachute manner can be placed around the ventricles. The size of the net is determined from preoperative CT-scans.

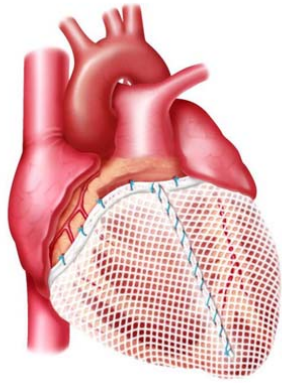


Figure 5; CorCap CSD.
With permission from Acorn Inc.

Intra-aortic ballon pump *(IABP);* A catheter-based balloon, placed in the descending aorta via the femoral artery, Fig 6. During diastole, the balloon inflates and thereby displacing blood from the descending aorta and then deflates immediately before systole, creating a void in the aorta, and thereby producing its haemo-dynamic effect. Inflation causes a rise in the aortic

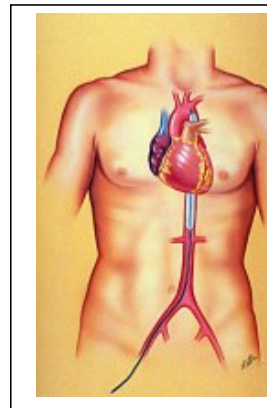


Figure 6; Intra-aortic balloon Pump, IABP. With courtesy Texas Heart Institute.

pressure causing an increase in the coronary pressure gradient and therefore increases coronary flow. Aortic counter-pulsation also causes a drop in systolic blood pressure due to balloon deflation just prior to systole. The increase in diastolic pressure is typically greater than the decrease in systolic pressure, resulting in an increase in mean arterial pressure. Helium is used in the balloon.

Statistics;

In Paper I all continuous variables had normal distribution. Statistical analysis was performed with analysis of variance (parametric tests) and discriminant analysis using SPSS software (v 10.1.0; SPSS Inc, Chicago, IL). Descriptive data are expressed as median and range. In the variance analyses mean ±standard deviation was used. For the non-parametric ordinal data a χ^2-test was used. A p value < 0.05 was considered statistically significant. In Papers II, III and IV the samples were analysed using the software STATISTICA (StatSoft, Inc. 2004, version 7, Tulsa, Ok, USA). The data was analysed using the non-parametric Mann-Whitney U-test for group comparison and Wilcoxon matched pair tests for longitudinal comparison. $p < 0.05$ was considered significant.

Aims

- to investigate the outcome and risk factors for mortality and morbidity in patients treated with mechanical circulatory support for long-term use in patients accepted for heart transplantation. (Paper I)

- to study the morbidity and mortality in patients treated with the axial flow pump, HeartMate-II™ as bridge-to-transplantation and destination therapy. (Paper II)

- to investigate the use and outcome in patients with acute heart failure treated with Impella™ axial flow pump as short-term assist. (Paper III)

- to study the use and long-term outcome, especially regarding Quality of Life in patients operated with ventricular constraint CorCap-CSD™, in patients with chronic heart failure, compared to a reference group from the general population. (Paper IV)

Methods

Paper I

All Swedish patients (n=59) on the waiting list for heart transplantation, since 1993 until May 2002, and treated with long-term assist device as bridge-to-

Table 1, Demographics

	Paper I (n=59) (median, range)	Paper II (n=11) (median, range)	Paper IV (n=26) (mean, SD)
Sex (male)	46	7	26
Age (y)	49 (14 to 69)	45 (28 to58)	60.3 ±11.7
BSA (m^2)	1.93 (1.42 to 2.65)		2.0 ±0.2
Higgins score	9 (3 to 15)		
EuroScore, standard	10 (5 to 17)	10 (8 to 15)	
Dilated cardiomyopathy	36 (61%)	5	8
Ischemic cardiomyopathy	11 (18.6%)	5	7
Myocarditis	7 (11.9%)	0	
Cytotoxic etiology	0	1	
Concomitant valve surgery			10
Postcardiotomy heart failure	3 (5.1%)		
Hypertrophic cardiomyopathy	1 (1.7%)		
Unspecified heart failure	1 (1.7%)		1
Previous heart surgery	22 (37%)	2	0
Diabetes mellitus	6 (10.1%)		5
Stroke	4 (6.7%)		2
Active infection	11 (18.6%)		
Myocardial infarction	12 (20.3%)	5	8
Preoperative ICU stay	46 (77.9%)		
Preoperative inotropic support	48 (81.4%)		
Preoperative mechanical assist	9 (15.2%)	2	

Abbreviations, BSA, body surface area; ICU, intensive care unit.

transplantation due to deteriorating heart failure, were retrospectively investigated. Demographics are depicted in Table 1. Dominating diagnoses were dilated cardiomyopathy (61%) and ischaemic heart disease (18.6%). Nine (15.2%) patients had a mechanical assist device before the LVAD implant. Pre-, per- and postoperative variables were recorded from the LVAD implant to heart transplantation. The variables were evaluated regarding mortality and morbidity prior to transplantation and risk factors for mortality, right ventricular failure and infection.

Paper II

Patients receiving the second generation of long-term mechanical assist devices with axial flow at our department were consecutively included. Eleven patients from October 2005 until May 2008 with ischaemic cardiomyopathy (n=5), dilated cardiomyopathy (n=5) and cytotoxic aethiology (n=1) were treated with HeartMate-II due to deteriorating heart failure. They were prospectively studied using a protocol. Demographics are depicted in Table 1. In ten patients the HM-II was implanted electively and in one patient acutely due to rapid irreversible deterioration of the disease despite maximal pharmacologic treatment. Two patients had a temporary left ventricular (LV) assist (Impella™) before implantation of the HM-II, one due to cardiogenic shock in association with myocardial infarction and one with deteriorating dilated cardiomyopathy (CMP). In ten of the patients the indication for implantation was bridge-to-heart transplantation. One patient with recent malignancy and cytotoxic CMP received the pump as bridge-to-recovery or ‘‘destination’’ therapy.

Paper III

Data on all Swedish patients treated with the Impella axial flow pump for acute heart failure between 2003 and 2007 were retrospectively collected from those Swedish cardiothoracic centres using the device. Fifty patients were divided into two groups, the Surgical group (n=33) which involved patients with acute heart failure after cardiac surgery, and the Non-surgical group (n=17) where patients suffered from acute heart failure due to cardiological conditions. Demographics are shown in Table 2. The main treatment intension was bridge-to-recovery. In the surgical group 55% of the patients had a severely reduced (EF<20%) left ventricular function preoperatively. Prior to surgery, eight patients (25%) were on intra-aortic balloon counter pulsation (IABP), one (3%) was supported with a LVAD, 11 patients (33%) were on inotropic support and seven patients (21%) were mechanically ventilated. Fifteen of 19 failure-to-wean patients (79%) received the Impella prior to weaning from the CPB. The remaining 14 patients developed their postoperative cardiac failure in the ICU. Transoesophageal echocardiography (TEE) was used to verify correct positioning of the pump in the LV. The patients were considered to be responding to the therapy when the haemodynamics were stable, with improved cardiac output (CO) and lowering of the filling pressures and/or demonstration of an increased mixed venous oxygen saturation (SvO_2). Our definition of therapy response also required a combination of improved echocardiographic movement, small to moderate doses of inotropic support and an acceptable diuresis. The weaning procedure started when all parameters were stable for at least 24 hours.

Table 2, Demographics (Paper III)

	Surgical group (n=33) (n)	Non-surgical group(n=17) (n)
Age, years (mean, range)	58.1 (27 to 84)	47.5 (36 to 63)
Male	24 (73%)	11 (79%)
BSA, m^2 (mean, range)	1.9 (1.5 to 2.7)	1.9 (1.1 to 2.1)
Previous cardiac surgery	7 (21%)	0 (0%)
Myocardial infarction	14 (42%)	6 (43%)
Stroke	1 (3%)	0 (0%)
Diabetes Mellitus	7 (21%)	2 (14%)
Atrial fibrillation	11 (33%)	1 (7%)
Impaired kidney function	4 (12%)	2 (14%)
CPB-time, min (mean, range)	249 (57 to 452)	
X-clamp time, min (mean, range)	100 (0 to 236)	
NYHA (mean)	3.6	3.8
EuroScore standard (mean, range)	9.1 (2 to 18)	10.1 (3 to 17)
Indication for treatment		
Postcardiotomy LOS	19 (58%)	
Cardiogenic shock	10 (30%)	9 (53%)
Myocarditis	1 (3%)	5 (29%)
Prophylactic use		3 (18%)
Other	3 (9%)	
Treatment aim		
Bridge to recovery	22 (67%)	15 (88%)
Bridge to other LVAD	8 (24%)	2 (12%)
Bridge to HTx	3 (9%)	

Abbreviations: BSA, Body Surface Area; CPB-time, cardiopulmonary bypass time; LOS, low output syndrome; LVAD, left ventricular assist device; NYHA, New York Heart Association class; HTx, Heart transplantation; X-clamp time, aortic cross-clamp time.

Paper IV

From 2003 onwards, 26 consecutive patients with chronic progressive heart failure and optimal pharmacological treatment met the inclusion criteria for passive ventricular constraint and were operated with CorCap CSD via sternotomy (n=25) and left thoracotomy (n=1). Demographics are depicted in Table 1. Seven patients were operated with CorCap-only, with (n=3) or without (n=4) epicardial leads for cardiac resynchronisation therapy (CRT). Nineteen patients were scheduled for concomitant cardiac surgery. They were prospectively followed each year for five years postoperatively regarding mortality, echocardiographic findings, execise tests (6MWT, ergometry) and QoL (MLHF). There were three early and three late deaths during the follow-up period. Two patients, operated within the last month were not included in the follow-up because they were still in the postoperative phase. The remaining cohort (n=18) was investigated in a cross-sectional study regarding QoL using the Medical Outcomes Study Short Form General Health Survey (SF-36) questionnaire. An exact age and sex-matched reference group (n=140) was randomly selected from the Swedish SF-36 general population reference group database (n=8.930).

Results

Paper I;

Fifty-nine patients (46 men) listed for heart transplantation, with a median age of 49 years (range, 14 to 69 years) received a LVAD as bridge to transplantation during the observation period. They were supported for a median time of 99.5 days (range, 1 to 873 days), Table 4. Forty-five patients underwent heart transplantation. Mortality prior to transplantation was 11 patients (18.6%). Three patients (5.1%) were weaned from the device. One of them received HTx after 13 days as a result of progressive heart failure. Eighteen (30.5%) of the patients had additional surgery; 3 patients underwent coronary artery bypass grafting; 9 patients had aortic valve replacements; 2 patients atrial septal defect repairs; 1 patient had mitral valvuloplasty; 1 patient had a pericardial patch sutured over a preexisting mechanical aortic prosthesis; and 2 had removal of a pacemaker. Four patients were treated with an RV assist device because of RV failure. The ICU-stay postoperative was in median of 12 days (range, 1 to 25 days) after surgery. Twenty patients (34%) were reoperated within 24 hours due to bleeding. In 5 patients (8.5%), the LVAD had to be replaced because of mechanical failure. In total, 5 patients had inflow valve incompetence and valve endocarditis. Nine of 59 patients (15.2%) had an infection at the cable exit site or LVAD pocket. A total of 26 patients (44%) had some form of infection in the postoperative period (septicaemia, pneumonia, or device-related). Strong predictors were elevated filling pressures of the right heart and elevated C-reactive protein (CRP). One hospital had a lower frequency of cable infections due to different fixation technique of the driveline. Eleven patients (19%) were diagnosed with RV failure. High cardiac index, high postoperative central venous pressure, long

operation time, low baseline mean arterial pressure, and high baseline C-reactive protein were predictors. Minor technical problems included sensor dysfunction with the pneumatic Heart-Mate LVAD in 3 patients. Controller malfunction with the electrical HeartMate occurred in 7 patients, primarily in early cases. Six patients (10%) experienced a cerebrovascular thromboembolic lesion. Post-transplantation follow-up of all patients in January 2003 showed 11 late deaths (24%), after a median time of 100 days (range, 0 to 1.092 days). Seventeen of 38 (45%) of the vented electrical Heart-Mate pump patients were discharged home while on pump treatment. The patient treated for 873 days was treated as an ambulatory patient for 441 days before HTx.

Table 3, Risk factors for mortality, RV-failure and infection (ANOVA) HM-I patients.

Mortality	p
Blood transfusions	<0.001
Plasma transfusions	<0.001
Ventilator time	<0.001
S-Creatinine (end)	<0.001
RV-failure	
CRP preoperatively	0.001
CVP postoperatively	0.002
Infection	
Pcw (end)	<0.001
CRP (end)	0.001
Implanting hospital (χ^2-test)	<0.001

Abbreviations; RV; right ventricular, HM; HeartMate, CRP; C-reactive proteine, CVP; central venous pressure, pcw; pulmonary capillary wedge pressure.

Paper II;

Eight patients were transplanted after a median pump time of 155 days (range, 65 to 316 days), Table 4. One has been on a device since November 2006. The cumulative pump time is 6.45 years. One patient died intraoperatively because of severe biventricular heart failure in combination with extreme vasoplegia. The patient was implanted with a right ventricular (RV) assist (BioMedicus™), but despite this, an adequate systemic circulation was not achieved. One patient died after 274 days because of a cerebrovascular embolus. At autopsy a thrombus formation was found in the inlet cannula of the pump. One patient suffered from a minor stroke and the antithrombotic treatment was complemented with clopidogrel. However, the symptoms disappeared after two days. Ten patients could be discharged home awaiting transplantation after a median time of 65 days (range, 40 to 105 days).

Table 4, Postoperative results, HM-I (n=59) and HM-II (n=11)

	HM-I	HM-II
Transplanted, n=	45 (80 %)	8 (80 %)
Pump time to Tx, (median, range)	99.5 days (1 to 873)	155 days (65 to 316)
Ongoing, n=	0	1
Ongoing time, days	n.a	748
Total pump time, years	n.a	6.45
Mortality 30 days,	n.a	1
Mortality before Tx	11 (18.6 %)	2 (18.2 %)
Discharged home before Tx,	17/38 VE (45 %)	10 (91%)
Hospital time, days (median, range)	n.a	65 (40 to 105)
Readmissions before Tx,	n.a	4
Readmission hospital stay, days (median, range)	n.a	3 (3 to 44)
Bridge to transplant,	56	10
Destination therapy,	0	1
Weaned from device	3 (5.1 %)	0

Abbreviations: Tx, Heart transplant, VE; vented electrical.

Nine of them were on the waiting list for heart transplantation.
Four patients were re-admitted to the hospital with a median hospital stay of 3 days (range, 3 to 44 Days). Ten patients were given a LVAD for bridge-to-transplant and one for destination therapy. Three patients had transient right ventricular failure, responding to pharmacological therapy, when weaning from CPB. Four patients were reoperated due to bleeding, two patients during the first 24 hours and two patients later in the postoperative period. The median postoperative blood loss the first postoperative day was 1 228 mL (range, 360 to 5 600 mL). The median time on ventilator was 11 days (range, 0.5 to 27 days) postoperatively. One patient required temporary dialysis.
All patients received low molecular weight heparin (LMWH) initially and acetylsalicylic acid (ASA) from the first postoperative day. Warfarin was started and administered individually depending on the early postoperative course. The LMWH was discontinued when international normalised ratio (INR) reached therapeutic level. Almost all patients recieved triple therapy with ASA, clopidogrel and warfarin. Dosage was adjusted regarding the response to the thrombelastogram (TEG). Two patients had late minor haemorrhagic events with gastrointestinal bleeding. Six patients were diagnosed with cable infections according to wound cultures and treated successfully with intravenous antibiotics. No surgical revision was performed. Two patients also developed septicaemia caused by KNS, Candida albicans and methicillin-resistant staphylococci (MRSA). This complication was treated successfully with antibiotics without sequele or signs of pump endocarditis. Two patients experienced ventricular arrhythmias necessitating pharmacological treatment and in one case electro-conversion. One patient suffered from increasing abdominal pain prior to planned discharge. He was

operated on for gangrenous cholecystitis and made an uneventful postoperative course.
Cardiac output, filling pressures and mixed venous oxygen saturation improved significantly when comparing preoperative and postoperative values.
All patients (n=8) that were transplanted are still alive (December 2008) with a good life quality. No mechanical errors were recorded. There was one pump-stop, probably due to battery change error caused by the patient.

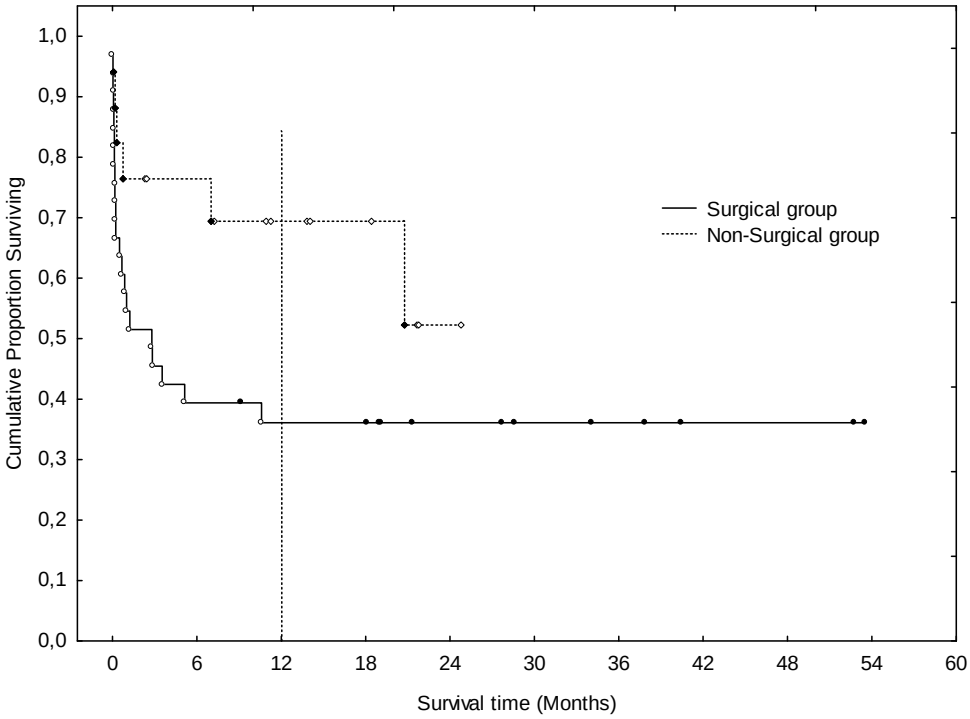
Paper III;

Early mortality in the surgical and non-surgical groups was 45% and 23%, respectively, see figure 7. Complications included infection, 36% and right ventricular failure, 28%.
Surgical group; Cardiac output and cardiac power output postoperatively were significantly higher among survivors than non-survivors. The 30-day mortality was 45% (15/33 patients). Nine of these 15 patients died within one week of their operation. The most common cause of death was multiorgan failure. The 1-year mortality was 64% (21/33). Patients who received Impella RD for right ventricular failure had a 30-day mortality of 75% (6/8), and the one-year mortality for these patients was 87% (7/8). In all, the Impella device was used for a mean of 3.8 days (range, 0.1 to 9 days). The RD was used for a mean of 4.1 days (range, 0.1 to 8 days) and LD/LP for a mean of 3.9 days (range, 0.1 to 9 days). Seventeen patients (52%) were reoperated within 24 hours because of excessive bleeding. Nine patients (27%) were reoperated late in the postoperative period because of bleeding (n=3), sternal infection (n=4), late sternal closure (n=1) and one for a reason unknown. Device failure was

recorded in one case at 3 days. Ten patients (30%) had septicaemia and 13 patients (39%) required dialysis. Fourteen patients (42%) had transient and pharmacologically treated right ventricular failure, and four of the patients treated with Impella LVAD had transient right ventricular (RV) failure necessitating RV-assist systems. Survival after 30 days was significantly better for patients with preoperatively placed IABP (p=0.01). Cardiac output (CO) at 12 hours and Cardiac Power Output (CPO) at 6 and 12 hours were also significantly higher among survivors. Improved survival postoperatively was indicated by low filling pressures and high mixed venous oxygen saturation (SvO_2) after the first 12 hours, but these observations did not reach statistical significance. At one-year follow-up the mortality was 64% (21/33). The survivors had significantly higher SvO_2 (12 hours) and higher CPO at 12 hours. The preoperative use of IABP was a marker of improved survival (p=0.01).

Non-surgical group; 30-day mortality in this group was 23% (4/17). Excluding the three patients with LP 2.5 used prophylactically, the 30-day mortality for non-surgical patients with an Impella placed for acute cardiac failure was 21% (3/14). One of the 30-days survivors died during the first year after the treatment. Five of these patients have not yet reached one-year follow-up. The patients in the non-surgical group were significantly younger than the surgical patients. No RV-failure was recorded. Three patients (18%) required dialysis. In this group of patients the left Impella was used for a mean time of 7.3 days (range, 2 to 14 days). One patient was bridged-to-ECMO after one day and did not survive. One patient was bridged-to-HM-II after 8 days and later had a cardiac transplant.

Figure 7, Cumulative survival Impella patients



Patients at risk

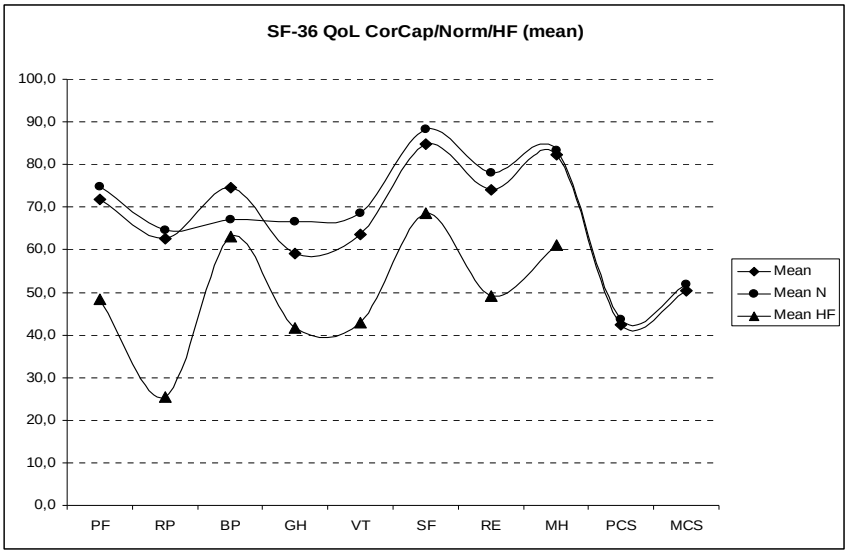
Surgical	33	11	7
Non-surgical	17	7	

Paper IV;

The mean follow-up time for the CSD group after cardiac surgery is 3.9 years (range, 0.9 to 7 years). The one-year survival for CSD patients was 86% and after three years 76%. There were three early deaths, two patients with septicaemia after 6 and 50 days, and one sudden cardiac death after 14 days. There were three late deaths, two after 2 years (cardiac arrest and multiorgan

failure), and one after almost five years in progressive heart failure. The comparison of QoL measured by the SF-36 between CSD patients and the control group is similar regarding all eight dimensions and the two summary parameters $PCS_{(SF-36)}$ and $MCS_{(SF-36)}$, Fig 8. Echocardiographic dimensions (LVEDD, EF) and QoL (MLHF) improved significantly after one and three years postoperatively for the CSD patients.

Figure 8,



SF-36 eight dimensions and summary composite for mental and physical health. Mean; CSD-group. Mean N; SF-36 general population reference group. Mean HF; Heart failure patients according to Juenger (Heart 2002). PCS and MCS were not calculated in this reference.
Abbreviations; PF, physical function; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social function; RE, role emotional; MH, mental health; PCS, physical component summary; MCS, mental component summary.

Discussion

Patients with heart failure are a large group with poor prognosis and they consume much healthcare. Heart transplantation is still the "gold standard" for terminal chronic heart failure. Long-term survival has improved, 10-year survival in the ISHLT-register is about 50% [44]. The problem is that a number of patients on the waiting list die before a suitable donor organ becomes available [90]. Mechanical circulatory support (MCS) as a bridge-to-transplant allows the patient to survive, rehabilitate and gain more strength before the transplantation. Early post-transplant survival is better in patients treated with MCS, even if long-term benefits have been difficult to prove [45]. Different sorts of MCS for short and long-term use enable bridging from severe heart failure of any aetiology to recovery, or time to make a decision on implantation of another more powerful device before transplantation. Increasing numbers of patients worldwide is also treated with MCS as an alternative to cardiac transplantation, i.e. destination therapy [91]. New devices such as ventricular constraint, aiming to prevent CHF deterioration of and possibly enabling reverse remodelling are interesting alternative approaches.

The evaluation of patients with severe CHF is demanding especially when considering implantation of MCS as bridge to transplant. A critically ill patient must improve considerably after MCS if multiorgan failure is to recover. High morbidity and mortality rates are not acceptable for ethical and economical reasons. Studies report higher mortality and morbidity in critically ill patients and the optimal patient planned for a long-term device should be reasonable stable [92], an INTERMACS level 3 for instance [60], see Appendix. The identification of risk factors for mortality and morbidity with the help of score

systems is important in the issue of patient selection [93, 94]. Our good results with the use of HM-I™ in CHF showing 94% survival to transplantation, became the cornerstone in our continued interest and ability to handle these sick patients using a multidisciplinary approach.

Over the years we have developed a programme that includes the use of short- and long-term MCS for indications ranging from bridge-to-decision in emergency situations to bridge-to-transplantation, and we have even adopted the concept of "destination therapy" (DT). The use of ventricular constraint fits this strategy as an adjunct to conventional surgery in selected patients with enlarged severely depressed hearts. Our department is a medium sized cardiothoracic centre without transplantation facilities. Based on the size of our cathment area, we have chosen to limit the number of pump models used in the clinical practice. The IABP and the Impella for short-term support and the HeartMate-II for intermediate and long-term support, cover patients with acute onset heart failure, regardless of cause, to progressively deteriorating heart failure in patients on the waiting list for heart transplantation. Even with comparably low numbers of MCS patients over the years we have achieved outcomes that compare well with others [11, 46, 95]. Participation in an international network and fruitful national cooperation are key factors for our success.

The assist devices for short-term use have been refined since the introduction of the first clinically useful axial flow pump, the Hemopump, in the eighties [96]. Our experience with the Impella™ in the treatment of cardiogenic shock has been favourable due to its minimally invasive and user-friendly characteristics.

Even if the survival rates have improved with time, cardiogenic shock is still a disease with high mortality and morbidity, especially after cardiac surgery [11]. In patients with deteriorating cardiogenic shock our first option is the IABP, followed by the Impella™ if the clinical situation remains unstable. The time factor for insertion is very important. Early optimized hemodynamics (CPO [97], SvO_2) are important for long-term survival, which helps us in the postoperative decision-making regarding these patients. This is in accordance with the prognosis after AHF [76].

The concept of long-term devices used as bridge-to-transplantation has swung towards "destination therapy" due to donor shortage and an aging group of patients. Increased mechanical durability, newer technical solutions and lessons learned in patient selection, timing, pathophysiology and perioperative strategies are important factors in this development. There are patients treated with MCS who have survived for over seven years [98]. The current INTERMACS database includes 15% DT patients [91]. In our clinical setting, treatment times have increased with the second generation MCS, the axial flow pumps. One of our HM-II™ patients, who was implanted in November 2006, is still ongoing with the device. We have had no mechanical failures and no pump endocarditis with the current axial flow pumps. MCS replacement, when required, is associated with acceptably low operative mortality rates and good intermediate-term survival [99]. In a recent study [100], patients treated with MCS for more than one year could spend most of their time outside the hospital with a reasonable QoL and physical function. This is our experience as well. The HM-II™ was recently granted FDA approval for "destination therapy".

High-volume centres with great experience are able to conduct large studies and develop guidelines. Clinical trial networks concerning acute heart failure have been discussed [86] and are important. A multidisciplinary approach is essential. With the development of pump reliability and frictionless bearings, the trend is directed towards long-term device treatment in older patients, and destination therapy. The use of continuous axial flow pumps (second generation) has led to better survival, lower stroke rate, and fewer reoperation because of mechanical failure, compared to pulsatile pumps after two years [101].

Complications during Mechanical Circulatory Support (MCS)

Right ventricular failure (RVF) is a major risk factor when using mechanical assist devices. The definition of RVF is difficult. The need for right ventricular assist device or inotropic support >14 days, inhaled nitric oxide > 48 hours, and discharged home with inotropic support are rather rough criteria used by Matthews et al [94]. The frequency of patients with mild RVF after MCS implantation is probably greater than believed, but these are disguised by early aggressive treatment with inotropes and/or inhalation of pulmonary vasodilators. The cause is multifactorial and related to anatomical and peri-operative factors [93]. The authors reported higher mortality and morbidity pre-transplant for these patients because of disturbances in volume and pressure distribution across both systemic and pulmonary circulation. RVF also predicts mortality after subsequent transplantation [92]. Massive blood transfusions have a relationship to right ventricular failure, but also infections, pulmonary insufficiency, allosensitisation and viral transmission [102]. In our early experience with the HM-I (paper I) we also found massive transfusion to be a risk factor for mortality as well. With the use of echocardiography in the

operating room and ICU, the diagnosis of RV-failure and treatment response can be monitored.

Hemorrhage is a very important issue for mortality and morbidity using any kind of assist device [61] and is the most common postoperative complication after LVAD implantation, occurring in up to 60%. In our series with HM-I and HM-II the re-operation rate for bleeding was lower, 34% and 36%, respectively, but the rate using the Impella, especially in the failure-to-wean situation, was quite high, 52%. Significant haemorrhage intra- and postoperatively was the major cause of emergency reoperation and reflects the complexity of the procedure on patients undergoing extensive surgery, including disturbed coagulation, activated cascade systems with the use of cardiopulmonary bypass, and the effects of the pump surfaces. Postoperative bleeding necessitating re-operation was more common in the early days of LVAD experience at our centre. Coming over the learning curve and increased experience with LVAD implantation has led to a reduction in rate. Our anticoagulation routines have changed over the years, especially for the failure-to-wean short-time assists. In patients with long term assist devices, the coagulation status was followed in an increasing number of cases using the thrombelastogram (TEG). The TEG is a valuable tool when differentiating responders from non-responders to antiplatelet therapy in the postoperative period, in order to avoid thromboembolic and bleeding complications [103].

Thromboembolic events are complications with severe consequences and responsible for the majority of mortality [92]. There is a balance between bleeding and embolus. Efforts are being made to control this matter and the trend with non-pulsatile devices is to reduce the amount of anticoagulation [104]. Flow patterns are important, such as the direction of the inflow cannula

in the left ventricle where turbulent flow should be avoided. There is a debate over whether there should be flow over the aortic valve or not, and if so, how much? Should a previously implanted aortic valve prosthesis be closed or not? Reports have described fusion of native valves with time [105], as well as thrombus formation close to the artificial aortic valve [106]. Our intention has been to have some flow over the aortic ostium, evaluated with intermittent echocardiography. We have seen no signs of aortic valve fusion. The important thing is that the ventricle is unloaded. A change in flow patterns into the pump may be a sign of thrombus formation. A sudden increase in pump energy consumption indicates the same.

Infection, especially driveline infection, is still the Achilles heel of implanted pump systems connected to a power supply through the skin. Zierer et al reported 23% driveline infections with the first generation LVAD [107]. The REMATCH-study reported even more, 28% [55]. The appearances of driveline and/or ascending pump pocket infections are probably a matter of time, regardless of care taken. The cumulative hazard for developing infection after one year of pump treatment is 94% according to Zierer et al. Proper immobilisation of the driveline and exit care is essential. Newer pump systems have a smoother and more flexible driveline that has decreased the development of driveline infections [58, 108]. This has also been our experience. We also find it important to let dedicated patients take responsibility for their local wound care at home, and patient education is essential. The axial flow pumps do not twist in their action like the electric HM-I, avoiding local irritation of the driveline. There may also be a learning curve on how to handle these problems. Driveline infections will not disappear until the entire system is totally implanted. Even though the long-

term prognosis after transplantation is not affected by infections [107], destination therapy patients will suffer troublesome long-term morbidity. The Jarvik 2000 has an interesting solution with a skull-pedestal-based power line, in an attempt to avoid driveline infections thus promoting long-term treatment [98]. Local or systemic antibiotic treatment of local driveline infections is necessary to avoid further migration of the infection, and aggressive surgical revision must be applied when necessary. Long-term antibiotic treatment may be necessary because bacteria are difficult to eradicate. Bacteria adhere to foreign material and recurrent infections are common. Systemic infections are more serious and life-threatening. Early extubation and mobilisation in the intensive care unit are important factors to avoid this. Antibiotic treatment immediately prior to transplantation due to systemic infection is a risk factor for mortality post-transplant [45], and surgery should be postponed when possible. With more flexible drivelines and extended treatment duration, the problem with driveline fractures becomes a reality [58].

Acute renal failure (ARF) is also common in patients operated with LVAD. ARF patients have a higher risk for complications and have a worse outcome regarding mortality while awaiting transplantation [109]. In our material the occurrence was low using the HM-devices, and in patients in acute cardiogenic shock treated with Impella the rate was 39%.

Ventricular constraint (CSD)

The use of ventricular constraint has been questioned because of difficulties in evaluating its real contribution to reverse remodelling. The study performed in our department using the CorCap™ (Acorn, Inc) shows significantly smaller ventricular dimensions (LVEDD), higher contractility (EF) and

improved QoL (MLHF) compared to preoperative values. The problem is, however, that there was no control group for comparison. The mortality in the group was what would have been expected when comparing with the logarithmic EuroScore [110, 111]. Interestingly there was no difference in QoL measured with SF-36 after more than a 3-year mean follow-up period, compared to an age- and sex-matched control group from the general population. The groups are small and a study on larger cohorts could possibly dispute this. Valve surgery and/or coronary artery revascularisation plays a large part in the prevention or postponement of further deterioration of heart failure. The 3-year follow-up in the Acorn-study [112] showed no difference in mortality between the treatment and control group. Improved echocardiographic dimensions, however, remained after five years in the CSD-only group [73]. These authors did not study QoL, brain natriuretic peptide or functional status. CSD combined with mitral valve surgery have shown significant improvement that remains at three years [72]. An explanation for this may be that CSD-induced reverse remodelling prevents the recurrence of ischaemic [113] and non-ischaemic mitral regurgitation [114]. The discussion introduced by Di Salvo et al, about a multi-option approach for mitral regurgitation, applies for chronic heart failure as well. New knowledge that improves selection of the ideal patient group will come. Our experience with CorCap CSD™ is promising and supports the findings from the Acorn study, in the aspect to be used as an additional therapeutic option in the early phase of severe heart failure, together with medication, CRT-D and eventually cardiac surgery. It is not reasonable to believe that the process of remodelling will be entirely prevented by ventricular constraint. The new approach via a lateral mini-thoracotomy is promising, avoiding median sternotomy and

possibly the use of CPB. A European multicentre study on the mini-thoracotomy technique, in which our department is participating, is under way.

Appendix

INTERMACS profile of advanced heart failure,

	Profile	*Time frame for intervention*
1	Critical cardiogenic shock "crash and burn"	within hours
2	Progressive decline "sliding on inotropes"	days
3	Stable but inotrope-dependant "dependent stability"	elective, weeks
4	Resting symptoms	weeks to few months
5	Exertion intolerant	months
6	Exertion limited "Walking wounded"	variable, months
7	Advanced NYHA III	not currently indicated

Modifiers for Profiles,

Temporary circulatory support
Arrhythmias
"Frequent flyer"

ISHLT classification of patients with advanced heart failure allowing optimal selection of patients for the current options of medical and pacing therapies, cardiac transplantation and mechanical circulatory support.
INTERMACS; Interagency Registry of Mechanically Assisted Circulatory Support, ISHLT; International Society for Heart and Lung Transplantation. Copied from [60].

Conclusion

We conclude that transfusions per- and postoperatively is a risk factor for mortality. Risk factors for right ventricular failure and postoperative infections are difficult to define in a retrospective study of HM-I™ MCS in patients on the waiting list for heart transplantation. About 80% of the patients could be bridged to transplantation with an incidence of mortality and morbidity that correlates well with international reports.

The second generation MCS including the axial flow pump, HM-II™, has acceptable low morbidity and mortality rates. It works well as bridge-to-transplantation and for extended long-term support in patients not eligible for heart transplantation. The rates of device-related infection and mechanical failure are lower than for HM-I ™.

Treatment of acute heart failure with short-term devices such as the Impella™ axial flow pump offers a good treatment option in selected patients, even though mortality and morbidity is high. Long-term survival was better for the group of "non-surgical patients".

Ventricular constraint, using the CorCap CSD™, in patients with progressive CHF, shows similar QoL (SF-36) after more than 3 years, compared to a general population reference group. Reduction in echocardiographic dimensions of the left ventricle is sustained with time.

In our department, a non-transplanting medium-sized cardiothoracic unit, short- and long-term MCS with Impella™ and HM™ in patients with acute or chronic HF, have been used with good results. In our hands the use of ventricular constraint is a good adjunct in the treatment of progressive chronic HF patients, early on in the course of the disease.

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