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Mechanical circulatory support

in patients with severe heart failure

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Gothenburg 2010

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Severe heart failure has a poor prognosis. Mechanical circulatory support (MCS) is capable of assisting the circulation in selected patients to bridge them to heart transplantation or recovery of heart function. MCS is manufactured in short-term or long-term designs. Short-term MCS can be coupled to an oxygenator to supply oxygen to the blood, and in that case also assist the lungs. Short-term MCS is most often extra-corporeal, with the pump situated outside the patient's body and capable of assisting circulation for up to a few weeks. Long-term MCS is usually implantable, has batteries to run the pump, and allows the patient to be ambulatory. We have investigated different types of circulatory support and its influence on survival, possibility for recovery, and ameliorating effects on co-morbidities.

Methods and results

In the first paper we prospectively studied the possibility of avoiding the need for heart transplantation by allowing the hearts of transplant eligible patients to recover function during support with a long-term MCS. Eighteen patients were enrolled in the study and each had a battery driven long-term MCS implanted into the chest. They were then evaluated for the recovery of heart function. Three patients showed signs of recovery and had their long-term MCS explanted. Only one of these patients remained well. We conclude that this strategy is not applicable to heart transplant candidates in general.

In the second paper, we retrospectively investigated short-term MCS used for the emergency treatment of patients in refractory cardiogenic shock. Fifty-two patients with cardiogenic shock were included in the study and were split into two groups: those without previous surgery (n=19), and those treated after surgery (n=33). We noted a fairly good survival rate (63%) in the group without previous surgery. Patients that had undergone surgery fared less well, however, with a 33% survival rate. We believe that most patients would have succumbed to circulatory collapse, and from that perspective, the results are encouraging.

The third paper dealt with the problem of pulmonary hypertension (PH) in heart transplantation. Patients with PH treated with or without a long-term MCS implanted before heart transplantation were retrospectively reviewed regarding survival and reduction of PH. PH was effectively reduced, but no significant difference was seen in survival after heart transplantation.

The final paper is in manuscript. Here, we investigated the results of bridging patients in refractory cardiogenic shock to cardiac transplantation with short-term MCS. This strategy has been considered to result in inferior survival and is somewhat controversial. Twelve patients on short-term assist devices were accepted for transplantation, and transplanted without mortality. This is discussed and compared with the bridge-to-bridge concept where patients on short-term MCS are implanted with a long-term MCS, and then transplanted.

Conclusion

The results of treatment with mechanical circulatory support in patients with severe heart failure are encouraging. Mechanical circulatory support can be life saving but demands large resources and should be applied to carefully selected patients that could benefit from the treatment.

Cover by Boris Nilsson

Tillägnad min familj

Original papers

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I. Lidén H, Karason K, Bergh CH, Nilsson F, Koul B, Wiklund L.
The feasibility of left ventricular mechanical support as a bridge to cardiac recovery
Eur J Heart Fail. 2007 May;9(5):525-530.

II. Lidén H, Haraldsson Å, Ricksten SE, Kjellman U, Wiklund L.
Does pretransplant left ventricular assist device therapy improve results after heart transplantation in patients with elevated pulmonary vascular resistance?
Eur J Cardiothorac Surg. 2009 Jun;35(6):1029-34.

III. Lidén H, Wiklund L, Haraldsson Å, Berglin E, Hultman J, Dellgren G.
Temporary circulatory support with extra corporeal membrane oxygenation in adults with refractory cardiogenic shock
Scand Cardiovasc J. 2009 Aug;43(4):226-32

IV. Lidén H, Kolsrud O, Dellgren G, Haraldsson Å, Kjellman U, Wiklund L.
Results of short-term mechanical circulatory assist as a bridge to urgent cardiac transplantation
Manuscript

Contents

Abbreviations

AI	Aortic insufficiency
BiVAD	Bi-ventricular assist device
BMI	Body mass index
BSA	Body surface area
BTT	Bridge to transplant
BTB	Bridge to bridge
CI	Cardiac index
CO	Cardiac output
CPB	Cardiopulmonary bypass
CVP	Central venous pressure
ECMO	Extra corporeal membrane oxygenation
EF	Ejection fraction
GFR	Glomerular filtration rate
HLM	Heart-lung machine
Htx	Heart transplantation
IABP	Intra-aortic balloon pump
ICU	Intensive care unit
LVAD	Left ventricular assist device
LVEDD	Left ventricular end diastolic diameter
MAP	Mean arterial pressure
MCS	Mechanical circulatory support
NO	Nitric oxide
PH	Pulmonary hypertension
PVR	Pulmonary Vascular Resistance
PCWP	Pulmonary capillary wedge pressure
RRT	Renal replacement therapy
RVAD	Right ventricular assist device
SD	Standard deviation
SEM	Standard error of the mean
SVR	Systemic vascular resistance
TAH	Total artificial heart
TPG	Transpulmonary gradient
VAD	Ventricular assist device

1. Introduction

Assisting the failing heart with a pump is now an accepted treatment for selected patients with life threatening heart failure. Most of today's patients with long-term mechanical circulatory support are awaiting a heart transplant. An increasing number will depend on a heart pump for the remainder of their life, or until recovery of heart function.

The idea of supporting the human circulatory system has been documented since the early nineteenth century. When general surgery had a surge in the latter part of the same century, surgery on the heart was viewed as extremely hazardous. Christian Theodor Billroth, one of the giants of general surgery, even stated "Any surgeon who wishes to preserve the respect of his colleagues, would never attempt to suture the heart". Of Scandinavian interest is that the first recorded successful suturing of the heart was at Rikshospitalet, Oslo, by Axel Cappelen on the 4th of September 1895. He sutured a knife stab wound in a 24-year old man. With the exception of a few selected treatments, such as closed mitral commissurotomy, heart surgery was considered more or less impossible until the early 1950s. Several groups conducted experimental work, primarily on dogs, to develop the means to perform safe intra-cardiac surgery. Examples of ways explored to achieve this goal were deep hypothermia[1] and cross-circulation[2]. Walt Lillehei and John Lewis in Minneapolis used hypothermia in the world's first recorded successful open-heart surgery on September 2, 1952. Eventually, it was the efforts to temporarily replace the function of both the heart and lungs with a machine that was to conquer the world of open-heart surgery. The first clinical use of a heart-lung machine (HLM) was on April 5, 1951 when Clarence Dennis, also in Minneapolis, unsuccessfully tried to close a huge ostium primum defect in a 6-year old girl[3]. The first successful open heart surgery with a HLM was performed on May 6, 1953 when John Gibbon in Philadelphia closed an atrial septal defect in a 18-year old girl[4]. This landmark operation soon prompted other centres to engage in open-heart surgery with a HLM, and a new era had begun. During the first decade of open-heart surgery, severe heart failure during weaning from HLM, or the immediate post-operative period, was a major cause of morbidity and mortality. It was not until the late 1960s that myocardial protection was discovered to play a major role in this devastating complication[5]. A HLM could also support the circulation of patients who had not undergone surgery. In 1957, Jackson Stuckey in New York reported the use of a HLM in three patients with acute myocardial infarction (AMI) with cardiogenic shock. One of these three patients, who had a systolic arterial pressure of less than 70 mm Hg, was saved and could return to normal life[6]. Attempts at assisting the failing heart until recovery were made at several centres who were able to assist the heart for up to many hours during the post-operative course[7]. All systems relied on a roller pump or a HLM. With few exceptions, these attempts were unsuccessful. It was hypothesised that a longer period of post-operative support, up to several days, would improve the possibility of recovery and that a HLM or roller pump could not achieve this. The first successful ventricular assist device (VAD) implantation was carried out on August 8, 1966 by Michael E DeBakey[8]. This patient having had an unsuccessful predecessor in 1963[9]. The device had a pneumatically driven

displacement pump with either intra- or extracorporeal placement and ball valves for unidirectional flow. As heart transplantation became a reality after Christiaan Barnard performed the first[10] on December 3, 1967, the concept of bridge-to-transplantation (BTT) was realised. Denton Cooley and colleagues were able to bridge a patient to heart transplantation in 1978[11] with a left ventricular assist device (LVAD) for the first time. Another route to salvaging the patient's life was to completely excise the native heart and replace it with a total artificial heart (TAH). Drs. Willem Kolff and Tetsuzo Akutsu in Cleveland had, in 1957, been able to support a dog's circulation for 90 minutes with a TAH[12]. On April 4, 1969, the heart of 47-year-old Haskell Karp was taken out after an unsuccessful aneurysmectomy and replaced by a TAH in a staged procedure, aiming for transplantation. It supported his circulation for 64 hours until a donor heart became available and a transplantation was performed [13]. As reports of mechanical circulatory assist became more abundant, and in general provided positive experiences in clinical situations, the National Heart, Lung and Blood Institute (NHLBI) became interested. In 1977 the NHLBI issued a grant for the development of a LVAD. American government money had already been heavily invested in the development of the TAH as part of Lyndon B Johnson's goal of putting a man on the moon and placing an artificial heart in a man before 1970. Up until 2006, for example, the National Institute of Health invested more than 400 million US dollars in research grants. The new investment resulted in different types of devices, of which the Novacor and HeartMate became the best known. Both devices were intracorporeal and the Novacor was battery powered, while the HeartMate was pneumatically driven. They both proved to be efficient as patients waiting for a heart transplant could now be supported until transplantation if they deteriorated on the waiting list. Allowing the patient to be ambulatory and able to be discharged from hospital was one of the major leaps forward in the field[14]. Since then, many devices have emerged and there are dozens in clinical use and several others under development. Notable improvements have been made in making the devices smaller and less traumatic to the blood.

Having a foreign object acting as a pump inside the body and being in contact with the bloodstream creates several engineering challenges. The pump has to be durable, small, quiet, comfortable, easy to implant, and not too expensive. It is devastating for a patient to suffer from stroke, infection, device malfunction, native valve dysfunction or bleeding. Before having a device implanted the patient must be evaluated for suitability. This selection is crucial to the success of the therapy.

There are many ways to categorise MCS, examples include: intracorporeal vs. extracorporeal placement, pulsatile vs. continuous flow and short- vs. long-term use. We have chosen to divide our material into two groups: Short- and long-term MCS. As the most used long-term MCS is the left ventricular assist device (LVAD), the term LVAD is in some parts of the text used more frequently.

Short-term MCS

Indications. A patient with cardiogenic shock refractory to conventional therapy can be a candidate for short-term MCS if the individual is likely to 1) have a good chance of recovery (e.g. myocarditis, revascularised ongoing myocardial infarction, intoxication), 2) be a suitable candidate for heart transplantation or long-term MCS.

Operative technique. Peripheral cannulation. Groin cannulation is usually achieved by employing the Seldinger percutaneous technique with a separate cannula for distal perfusion. See Figure 1.

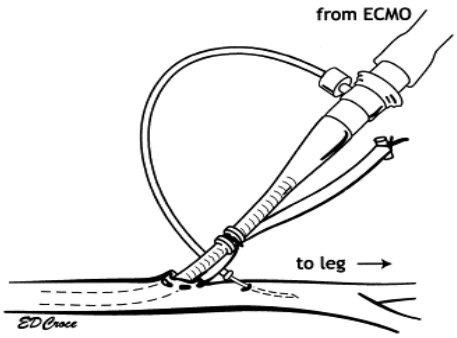

Figure 1. Schematic illustration of peripheral cannulation technique

Central cannulation. If the patient is unlikely to recover quickly it is sometimes preferable to assist the left, right or both ventricles separately. See figure 2. This way, the caregiver can monitor respiratory status. As most patients in shock have predominantly left ventricular failure it is possible to bridge the individual to either a heart transplant or a long-term assist device.

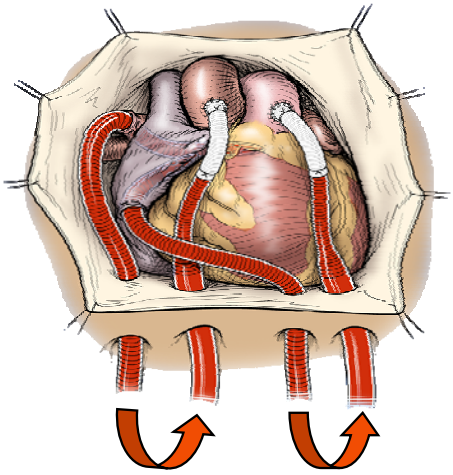

Figure 2. Schematic illustration of central cannulation technique

Weaning protocol. Many patients can be weaned from short-term support as their illness subsides. To check if the patient is ready to have the pump removed, a

meticulous scheme to assess native heart function is mandatory. As the pump speed is lowered, haemodynamic and ultrasonographic controls are made to investigate the potential recovery.

Anticoagulation protocol. Unfractionated heparin is most commonly used, with APTT (activated partial thromboplastin time) or TEG (thromboelastogram) analysis being used to monitor anticoagulation levels.

Complications. Bleeding problems or thrombus formations are not uncommon but can be managed by adjusting anticoagulation. Malperfusion of the lower extremity is avoided by introducing a separate cannula. If end-organ failure does not resolve it can be as a result of too late an institution of circulatory support.

Long-term MCS

Indications. The INTERMACS registry (Interagency Registry for Mechanically Assisted Circulatory Support) in the USA has defined six levels of decompensation in heart failure that lead to the implantation of a long-term MCS[15]. In short, a patient with chronic heart failure will usually decompensate. If this decompensation does not resolve or impairs end-organ function, a long-term MCS implantation is indicated. Most patients will be eligible for heart transplantation. An increasing number of patients will have the device as a permanent solution[16].

Operative technique. The most commonly used long-term MCS systems are implantable and require access to the heart and large vessels. Although some devices are possible to insert via thoracotomy or via the abdomen, most are implanted via sternotomy. When the patient is on bypass, the left ventricular apex is incised and the inlet to the pump secured. An intra-thoracic pocket is made, the drive-line cable is taken out through the skin and the outlet is sutured to the ascending aorta.

Anticoagulation protocol. Antiplatelet drugs and warfarin are the mainstay of anticoagulation treatment in long-term MCS. A TEG analysis is made to ensure that an adequate reduction of platelet aggregation is achieved. PT (prothrombin time) values are commonly aimed at 2-3 INR.

Complications. Bleeding in the perioperative period can be a major concern, particularly in the redo situation. Infections, like ventilator associated pneumonia or sepsis, are feared complications. Transient renal insufficiency is common, but usually resolves as haemodynamic stability is restituted. Device malfunction itself is rare with modern devices. Native valve dysfunction can appear late; months or even years after surgery and the reason is unknown. As the cardiac ailment reaches the right ventricle, right heart failure can develop. Arrhythmia can also be a problem. Driveline infections have been reduced with an increased knowledge of handling and dressing.

2. Aims of the study

1. To investigate if it is possible to achieve recovery of the heart in patients with advanced heart failure treated with a LVAD in order to avoid heart transplantation.

2. To investigate if pre-transplant LVAD therapy reduces elevated PVR in patients with advanced heart failure.

3. To investigate if pre-transplant LVAD therapy in patients with elevated PVR and advanced heart failure results in increased survival after heart transplantation.

4. To investigate if short-term MCS support in patients with refractory cardiogenic shock is beneficial.

5. To investigate if heart transplantation directly from short-term MCS is feasible with acceptable results.

3. Materials and methods

Paper I

Paper I studied eighteen consecutive patients receiving a LVAD as a bridge to transplantation. The study was performed between September 1997 and June 2002 at Sahlgrenska and Lund University Hospitals. The study population consisted of four women and 14 men with a mean age of 41 ± 3 (range 19-61) years. The causes of heart failure were: DCM (dilated cardiomyopathy) (n=9), myocarditis (n=5), ischaemic cardiomyopathy (n=3) and hypertrophic cardiomyopathy (n=1). Despite optimal medical treatment, all patients were in NYHA (New York Heart Association) functional class IV and had deteriorating renal and/or liver function. A pre-transplantation evaluation revealed no significant contraindications for heart transplantation (Htx) in any patient. After implantation, patients continued to receive optimal medical treatment for heart failure, including beta-blockers, ACE-inhibitors and spironolactone. During a four-month follow-up period, patients were repeatedly evaluated with echocardiography, blood samples and right heart catheterisation. If criteria for cardiac recovery were not fulfilled during this period, patients were activated on the Htx waiting list.

Paper II

In Paper II, the study population was derived from reviewing the medical records of all heart transplant recipients during the time period 1988 – 2007 (n=405), with or without PH (pulmonary hypertension) prior to transplant at Sahlgrenska University Hospital. Patients underwent routine right heart catheterisations, including thermodilution cardiac output measurement, and PH was defined as PVR (pulmonary vascular resistance) > 2.5 Wood units and (or) TPG (trans pulmonary gradient) > 12 mm Hg. Excluded from this analysis were patients undergoing a second heart transplantation (n=9), combined heart and kidney transplantation (n=9), children younger than 16 years (n=33) or patients who did not have pre-transplantation haemodynamic measurements available for analysis (n=48). The number of patients included in the study was 148 patients without and 158 patients with PH. Patients with PH were divided into two groups, one group included 147 patients with pre-transplant elevated PVR (> 2.5 WU) and one group included 11 patients who were pre-treated with a LVAD, for patient characteristics see Table 1. The patients with PH and without pre-treatment with a LVAD were then stratified into three subgroups: mild PH, 2.5 to 3.0 WU (n=41); moderate PH, 3.1 to 4.5 WU (n=56) and severe PH, ≥ 4.5 WU (n=50). Furthermore, historical controls were selected from the group of patients with PH in order to match patients pre-treated with a LVAD in a 2:1 fashion according to the following criteria: age ± 10 years, sex, era ± 10 years, underlying diagnosis, PVR within subgroup, body surface area (BSA) ± 0.2 m^2, body mass index (BMI) < or > 30, glomerular filtration rate (GFR) < or > 40 ml/min/1.72 m^2, diagnosed diabetes mellitus and properties specific for the donor: sex, age and BSA. For patient characteristics see Table 2.

Table 1. Preoperative data for patients with pulmonary hypertension pretreated with LVAD or not.

Variable		PH no LVAD	PH and LVAD
n		146	11
Age	years	49±11	46±10
Male		118 (81%)	10 (91%)
DCM		66 (45%)	6 (55%)
IHD		64 (44%)	4 (36%)
Miscellaneous		16 (11%)	1 (9%)
PCWP	mmHg	24±6	24±8
MPAP	mmHg	38±7	37±10
TPG	mmHg	13±5	15±5
CI	l/min/ m^2	1.7±0.4	1.5±0.4
PVR	WU	4.3±1.7	4.3±1.6
Donor age	years	34±13	41±13
Donor sex male		68%	82%
Ischaemic time	min	176±51	198±50

LVAD=left ventricular assist device; WU=wood units; PVR=pulmonary vascular resistance; BSA=body surface area; CI=cardiac index; PCWP= pulmonary capillary wedge pressure; MPAP=mean pulmonary artery pressure; GFR=glomerular filtration rate; IHD=ischemic heart disease.

Table 2. Demographics in patients pre-treated with LVAD prior to transplantation and matched controls.

		LVAD (n=11)	No LVAD (n=22)	p-value
PVR pre tx	WU	4.3 ± 1.6	4.5 ± 1.8	0.9
Recipient age	years	46± 10	50 ± 10	0.2
Recipient BSA	m^2	2.1 ± 0.2	2.0 ± 0.2	0.2
Ischaemia	min	198 ± 50	188 ± 57	0.6
Donor age	years	41 ± 13	39 ± 14	0.8
Donor BSA	m^2	2.0 ± 0.2	1.9 ± 0.2	0.5
CI	l/min/ m^2	1.5 ± 0.4	1.5 ± 0.3	0.6
PCWP	mmHg	24 ± 8	27 ± 6	0.1
MPAP	mmHg	37 ± 10	41 ± 6	0.2
GFR	ml/min/1.73 m^2	59 ± 20	63 ± 16	0.5

LVAD=left ventricular assist device; WU=wood units; PVR=pulmonary vascular resistance; BSA=body surface area; CI=cardiac index; PCWP=pulmonary capillary wedge pressure; MPAP= mean pulmonary artery pressure; GFR=glomerular filtration rate.

Paper III

The third study population consisted of patients receiving short-term MCS with veno-arterial ECMO (extracorporeal membrane oxygenation) during the years 2000-2007 (Table 3). Data were collected and reviewed from two institutions (the Sahlgrenska and Karolinska University Hospitals). Both these centres have programmes for VADs and heart transplantation. Our review was focused on patients with, primarily, acute heart failure. Excluded therefore were non-emergent patients (i.e. high-risk cardiac interventions such as percutaneous coronary intervention), patients with accidental deep hypothermia, and those with a primary pulmonary problem (i.e. lung transplantation, adult respiratory distress syndrome, etc). No patients receiving veno-venous ECMO were included in the study, and patients receiving a LVAD and/or a right ventricular assist device (RVAD) were also excluded. This was because interpretation of the results would have been even more difficult if acute heart failure was mixed with other diagnoses that can be treated with centrifugal circulatory support. Elderly patients were not considered for ECMO as heart transplantation was the final option in the case of failed recovery, but also due to the experience from the SHOCK study reporting dismal results in patients older than 75 years [17]. Post-cardiotomy shock was defined as any need of mechanical assist in a patient recently subjected to cardiac surgery. Veno-arterial ECMO support was initiated under the following circumstances: 1) acute refractory cardiogenic shock complicating acute myocardial infarction, 2) post-cardiotomy cardiogenic shock, 3) immediate post-transplant cardiac graft failure, 4) aortic aneurysm/acute aortic dissection, 5) myocarditis, 6) arrhythmia, 7) miscellaneous conditions. The ECMO was instituted either in the catheterisation laboratory or in the operating room.

	Post-cardiotomy	Non-cardiotomy	p-value*
Number	33 (63%)	19 (27%)	
Age (years±SD)	52.4 ± 12.7	45.3 ± 18.5	0.11
Males (n, %)	31 (94)	13 (68)	0.014
Reasons for ECMO support, (n, %)			
AMI	0	9 (47)	< 0.05
CABG (incl. ongoing AMI)	10 (30)	0	
Post htx	5 (15)	0	
AA/dissection	6 (18)	0	
Arrhythmia	0	4 (21)	
Myocarditis	0	2 (11)	
Miscellaneous	12 (36)	4 (21)	

Table 3. Patient characteristics in patients with cardiogenic shock after surgery (post-surgery) and in patients who did not undergo surgery (non-surgery). There were significantly more patients in the non-surgery group who had acute myocardial infarction compared to post-surgery patients, $p<0.05$.

Paper IV

The last paper included all consecutive adult or paediatric patients treated with short-term MCS devices *and* who underwent cardiac transplantation during support (n=12). The study was carried out between the years 2005 and 2009. For comparison, all consecutive adult or paediatric patients receiving a second or third generation LVAD as bridge-to-transplantation (BTT) during the study period were included in the LVAD group (n=18). Patients implanted with pulsatile devices (i.e. Berlin Excor, Syncardia TAH, HeartMate I) or patients with the intent of destination therapy were excluded. This retrospective review was focused on comparing early and intermediate outcomes in patients bridged with a short-term MCS device or a LVAD to cardiac transplantation, for patient characteristics see Table 4.

Table 4. Patients characteristics in patients treated with short-term MCS (n=12) and LVAD (n=18) until heart transplantation.

Patient characteristics	Short-term MCS	LVAD
Number of patients	12	18
Male sex, n (%)	10 (83)	16 (89)
Age, y	38 ± 19	47 ± 13
CPR, n	1	0
Intubated, n	7	2
Renal function		
Dialysis, n	3	0
Liver function		
ASAT (μkat/l)	6.1 ± 13	1.9 ± 4.8
ALAT (μkat/l)	5.9 ± 12	2.3 ± 5
PT (INR)	2.2 ± 1.2	1.3 ± 0.3
Blood pressure (mmHg)		
Systolic	85 ± 16	103 ± 12
Diastolic	60 ± 8	65 ± 10
Heart rate	115 ± 24	82 ± 15
Central venous pressure (mmHg)	20 ± 3	12 ± 6
Cardiac Index (l/min/m2)	1.4 ± 0.4	1.9 ± 0.8
PCWP (mmHg)	26 ± 9	24 ± 8

ASAT=aspartate aminotransferase, ALAT, ALAT=ala-Nine aminotransferas, INR=international normalized ratio, PCWP=pulmonary capillary wedge pressure, PT=prothrombin time.

Statistics

Paper I
All data are expressed as the mean ± standard error of the mean (SEM). Comparisons between values before implantation and during follow-up were performed with the Wilcoxon signed-rank test. A p-value of less than 0.05 was considered significant.

Paper II
The continuous variables are reported as mean ± standard deviation (SD). To test for statistical significance of differences between the groups LVAD treatment or not, the Mann-Whitney test was used, except for categorical data for which Fisher's exact test or chi-square was used. The correlation between PVR before the implantation of a pre-transplant LVAD and PVR during the time on support before transplantation was calculated according to Wilcoxon signed-ranked test. Patient survival was calculated according to the Kaplan-Meier method and the log-rank-test was used to test the two groups. A p-value of <0.05 was considered statistically significant.

Paper III
The continuous variables are reported as mean ± SD. Early mortality was defined as hospital mortality, which is all-cause death within any time interval after the mechanical assist operation during first hospital stay, or death within 30 days of surgery if the patient was discharged. Observed survival for patients was analysed using the life table technique and Kaplan-Meier estimates, and constructed with the computer program Statistica. The log-rank test was used to compare the two groups. The chi-square test was used to compare categorical variables. A p-value of < 0.05 was considered statistically significant.

Paper IV
The continuous variables are reported as mean ± SD. The chi-square test was used to compare groups. Patient survival was calculated according to the Kaplan-Meier method and the log-rank test was used to test the two groups. A p-value of < 0.05 was considered statistically significant.

4. Results

Paper I

All patients survived the surgical procedure. Four patients were re-operated for excessive bleeding. The mean LVAD support time was 201 ± 55 days (range 25 - 998 days). During LVAD support, all patients normalised their liver and renal function. Sixteen patients were discharged from hospital, whereas two remained hospitalised during support. One of these patients was transplanted after 20 days and the other was subjected to successful explantation after 83 days. Two patients died during LVAD support: one after 97 days due to a malignant ventricular arrhythmia (HeartMate VE®), and the other after 90 days due to a technical failure in the pump system (Jarvik 2000 VAD®).

Evaluation of heart function. Three patients did not undergo an evaluation of heart function during mechanical support. In one patient, Htx was performed before evaluation could take place, and another patient developed a significant inflow insufficiency with regurgitation of blood from the pump inhibiting rest of the heart. One patient fitted with a Jarvik 2000 was totally pump-dependent and showing no signs of recovery. The mean time for evaluation of the heart function (the evaluation when the final heart function decision was made) for the remaining 15 patients was 76 days (range, 42–122 days) after implantation of the LVAD.

Right heart catheterisation. The mean CI before implantation was 1.6 ± 0.1 L/min/m^2 and 1.9 ± 0.2 L/min/m^2 at the time of evaluation with the LVAD on. There were no statistical differences between patients with DCM and patients with other diagnoses. PCWP was 22 ± 1.5 mm Hg before implantation of the LVAD and 19 ± 2.3 mm Hg at evaluation and demonstrated no statistical significance between the two time periods.

Doppler echocardiography. There was a significant decrease ($p<0.005$) in LVEDD measured by Doppler echocardiography before implantation and at the time of evaluation with the pump on (75 ± 0.5 mm and 57 ± 0.6 mm, respectively). There was a significant increase in LVEF (left ventricular ejection fraction) from 15.5 ± 1.5% to 32 ± 5.7% with the pump on ($p<0.001$).

Blood analyses. There were no statistical differences in serum levels of MMP-2, MMP-9, IL-2, IL-6, TNF-α and NT-proBNP before implantation and at the final evaluation when the decision was made for Htx or explantation.

It was only possible to turn off the LVAD in four patients and three of these cases are described in detail below and some data are presented in figure 3 and 4.

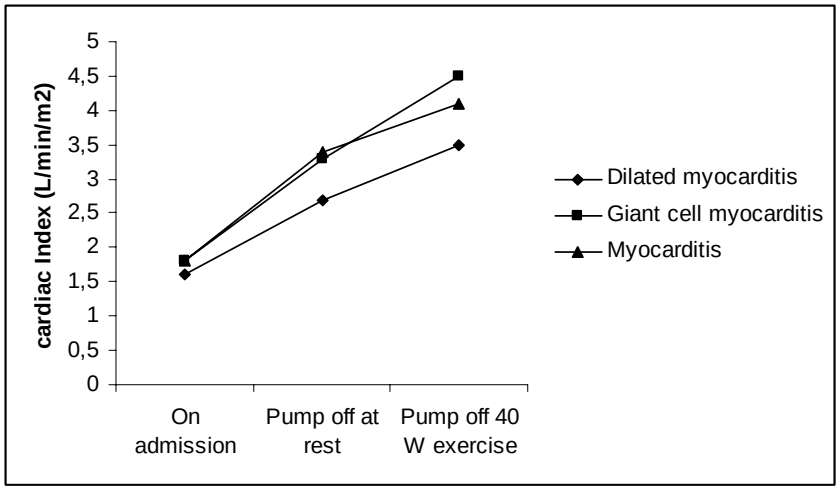

Figure 3. Three patients, one with dilated cardiomyopathy (DCM), one with giant cell myocarditis and one with myocarditis show increased CI at the time of evaluation. Supine exercise of 40 W workload resulted in further increase in cardiac index.

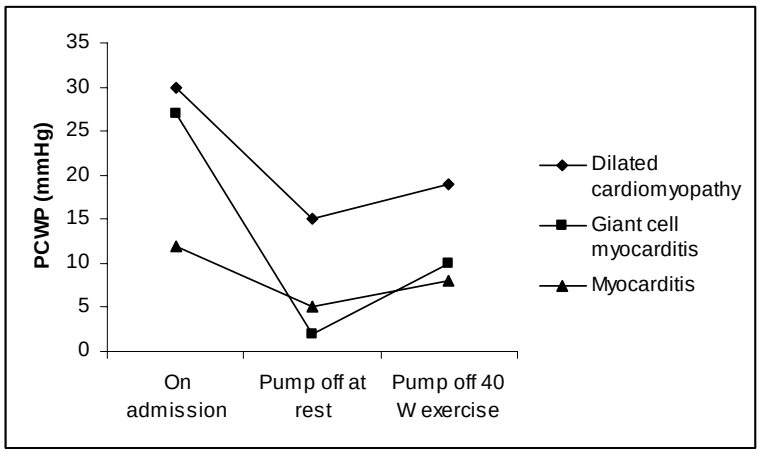

Figure 4. Three patients, one with dilated cardiomyopathy (DCM), one with giant cell myocarditis and one with myocarditis show decreased PCWP at the time of evaluation. Supine exercise of 40 W workload did not result in significant increase in filling pressure.

1. A 29-year old man presented with acute decompensation due to DCM and was on mechanical ventilation and maximal inotropic support. A HeartMate VE was implanted. Haemodynamic evaluation after two months revealed a dramatic improvement in CI (3.3 L/min/m^2) and a LVEF of 45% with a low PCWP (Figure 2 a-b). The stroke volume was 63 ml. During supine exercise of 40 W workload, CI was 3.5 L/min/m^2, PCWP 19 mm Hg and the stroke volume was 64 ml. The patient had borderline haemodynamic data for weaning but after discussion it was decided that the device should be explanted. Three days after a successful explantation the patient developed cardiogenic shock and a bi-ventricular Abiomed BVS 5000 was implanted

as an urgent procedure. After another ten days on temporary support the patient underwent a successful Htx.

2. A 22-year old male presented with acute giant cell myocarditis and circulatory collapse. He received a HeartMate VE and displayed improvement of heart function during the follow-up period. After 65 days of support, CI had risen to 3.3 L/min/m^2 at rest and increased to 4.5 L/min/m^2 during 40 W supine exercises. Further measurements showed a decrease in PCWP to 10 mm Hg and normalisation of stroke volume to 65 ml (Figure 2 a-b). The patient fulfilled the criteria for weaning. However, despite treatment with immunosuppressive medication, the patient developed a relapse of giant cell myocarditis resulting in Fontan circulation. The patient therefore underwent successful Htx.

3. A 19-year old, previously healthy woman, developed neurological signs of multiple sclerosis and shortly thereafter heart failure due to acute myocarditis [10]. The patient required mechanical ventilation and a HeartMate VE was implanted in an emergency situation. The early post-operative period was uneventful, except for repeated periods of septicemia. During evaluation, the heart function showed significant recovery. Resting CI, which was found to be 1.8 L/min/m^2 at admission, had risen to 3.4 L/min/m^2 (pump off) and LVEF > 50% two months after the implantation of the device. During supine exercise with a 40 W workload, the CI measured 4 L/min/m^2 and PCWP 20 mm Hg (Figure 2 a-b). The patient fulfilled the criteria for weaning and the device was successfully explanted. Still after eight years of follow-up the heart function remains normal with the patient on treatment with beta-blockade and ACE-inhibitors.

A fourth patient fitted with a Jarvik 2000 showed signs of recovery but refused weaning and remained on the pump for 998 days until a successful Htx was performed.

Paper II

Pre-treatment with LVAD. The mean age for patients with PH without a LVAD prior to transplant was 49 ±11 years and 46 ±10 years in the LVAD group. Thirty-two percent were female in the non-LVAD group and 18% in the LVAD group. There were no statistical differences between the groups regarding pre-operative data as diagnoses, haemodynamic measurements, data on the donors and ischaemic time, Table 1. PVR measured at the time of pre-transplant evaluation was 4.3 ± 1.7 WU in patients who were transplanted without pre-treatment with a LVAD. In patients who were treated with a LVAD, the PVR measured before the implantation of the LVAD was 4.3 ± 1.6 WU. PVR was significantly reduced to 2.0 ± 0.6 WU after implantation but before transplantation, $p < 0.05$ (Figure 5). Duration of LVAD treatment was 239 (24-1002) days. One patient, not pre-treated with a LVAD, developed acute right heart failure after transplantation requiring mechanical support whereas three LVAD treated patients required bi-ventricular mechanical support, none attributable to acute RV failure. One patient developed an acute humoral rejection, another had an immediate,

massive myocardial infarction and a third patient suffered from primary graft failure, all three cases proving fatal.

LVAD treatment vs. matched controls. There were no statistical differences between patients pre-treated with a LVAD and matched controls regarding: transplant era ± 10 years, underlying diagnosis, PVR within subgroup, sex, age ± 10 years, BSA, BMI, GFR, diagnosed diabetes mellitus and properties specific for the donor: sex, age and BSA. The need for post-operative RRT (renal replacement therapy) was 27% in patients not treated with a LVAD and 64% in patients treated with a LVAD prior to transplantation (p=0.04). The stay in ICU was 11 days (2-84) in patients without pre-treatment with a LVAD compared with 8 days (1-30 days) in patients treated with a LVAD (p=0.56). The total length of hospital stay was comparable between the two groups. See table 5.

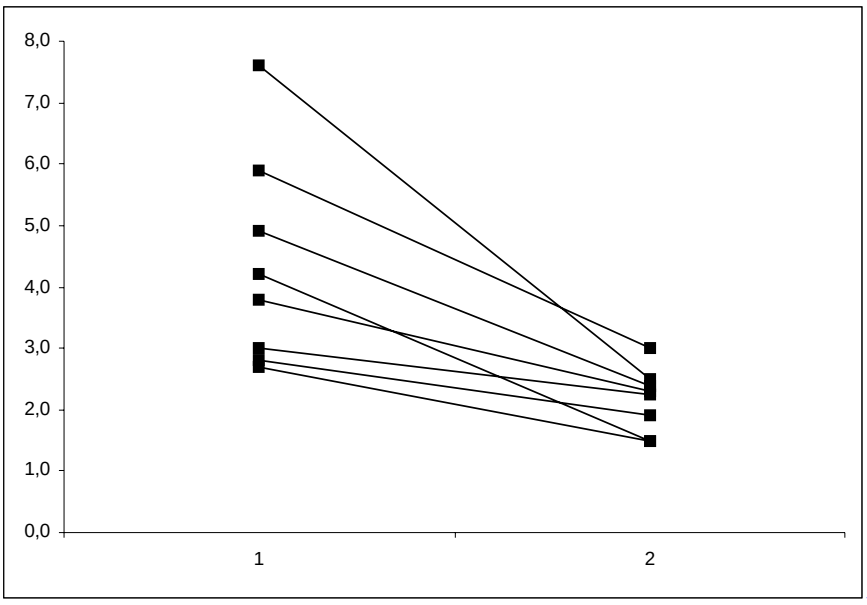

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Figure 5. Pulmonary vascular resistance (Wood units) measured before the implantation of a LVAD (1) and during support before transplantation (2). There was a significant reduction in pulmonary vascular resistance in patients supported with a LVAD, p <0.01.

	LVAD (n=11)	No LVAD (n=22)	p-value
Post tx RRT	7/11 (64%)	6/22 (27%)	0.04
Days in ICU post tx	8 ± 9 (1-30)	11 ± 18 (2-84)	0.7
In-hospital mortality	4/11 (36%)	2/22 (9%)	0.8
Total length of stay (days)	30± 21	43± 44	0.7
Post tx mechanical support	3/11 (27%)	1/22 (5%)	0.1

Table 5. Outcome in patients pre-treated with LVAD prior to transplantation and matched controls.

All-cause mortality. In patients with PH, there was no significant difference between mild, moderate and severe PH in 10-year actuarial survival (p=0.12). The 5-year survival was 88%, 63% and 78%, respectively.

Matched LVAD vs. non-LVAD patients. Thirty-day survival for patients in the matched non-LVAD group was 91% compared with 82% in patients in the LVAD group. Four-year survival in patients without prior LVAD treatment was 82% and 64% in patients who were treated with a LVAD prior to transplantation (p=0.12) (Figure 6).

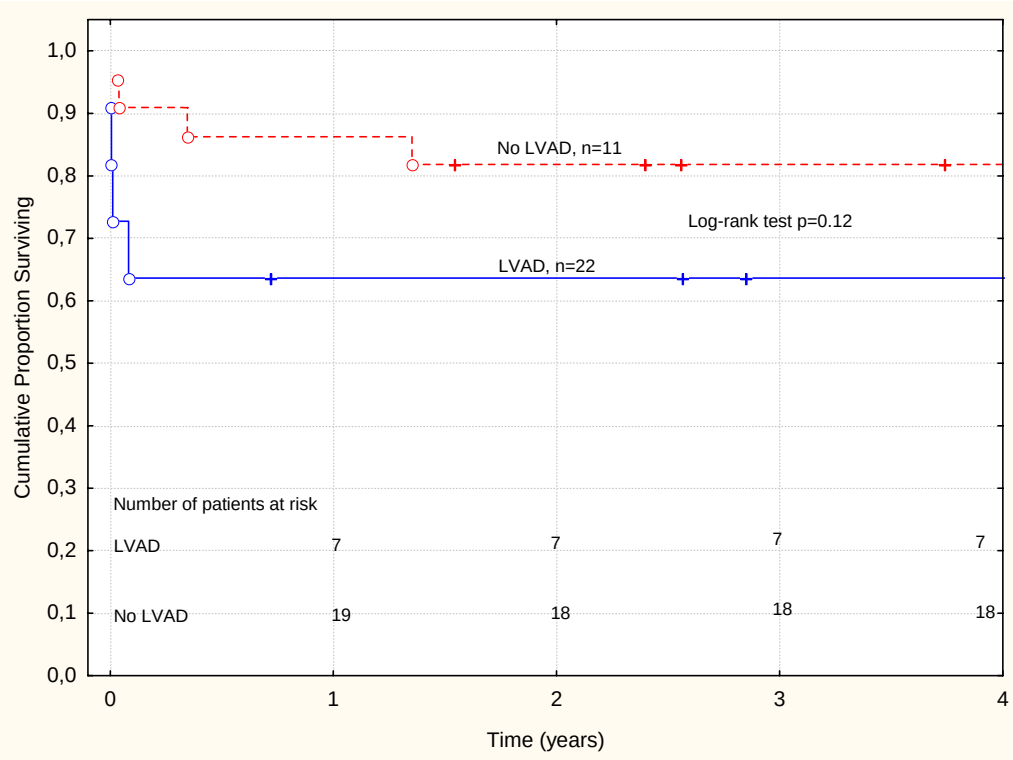

Figure 6. Survival in patients with pulmonary hypertension transplanted directly (n=22) and patients who were supported with a LVAD prior to transplantation (n=11) according to Kaplan-Meier. There were no statistically significant differences between groups (p=0.12).

Table 6. Outcome in post- cardiotomy and non- cardiotomy patients. There were significantly more patients in the non- cardiotomy group who underwent pre-ECMO CPR compared to patients in the post-cardiotomy group, p< 0.05.

	Post-cardiotomy	Non-cardiotomy	p-value
Discharged alive (n, %)	15 (45)	12 (63)	n.s.
Time on ECMO (days ± SD)	5.5 ± 4.9	11.6 ± 17.7	0.068
Pre-ECMO IABP (n, %)	14 (42)	4 (21)	n.s.
Pre-ECMO CPR (n, %)	6 (18)	9 (47)	0.025
ICU stay (Days ± SD)	12.8 (1-82)	16.8 (0-58)	n.s.
Post-operative dialysis (n, %)	16 (48)	9 (50)	n.s.
RBC (no, range)	23.3 (0-109)	17.3 (0-55)	n.s.
Re-operation for bleeding (n, %)	18 (55)	9 (50)	n.s.

Paper III

Fifteen patients (29%) had their assist device inserted during ongoing CPR (cardiopulmonary resuscitation). There were significantly more patients with ongoing CPR at ECMO institution in the non-cardiotomy group (p=0.025). Eighteen patients (35%) had IABP prior to implantation of the centrifugal pump. Survival was 47% in the group of patients with on-going CPR and 49% in the group not in need of CPR. There was no significant difference in early mortality between patients with CPR compared with patients with no CPR at ECMO institution (Table 6).

Mean time on ECMO support for all patients was eight (range 0 - 80) days. Mean time on support for the post-cardiotomy group was 5.5 days (1-26 days) and for the non-cardiotomy group 11.6 days (1-80 days). Two patients had two or more episodes of treatment, which were added in the analysis. Twenty-six patients (50%) could be weaned from circulatory support. The use of pre-ECMO IABP did not influence outcome, weaning rate or mortality. Surviving patients were on ECMO for an average of 9.9 days (2-80 days) and non-survivors 5.7 days (1-14 days) (p=0.2).

Total (all cause) mortality for all patients was 56% at a mean follow-up time of 2.7 years. Early mortality was 48%. Early survival in post-cardiotomy patients and non-cardiotomy patients was 4% and 63%, respectively (p=0.2). There was a tendency towards higher long-term survival for patients in the non-cardiotomy group, 63%, when compared with the post-cardiotomy group, 33% (p=0.07). The cause of death is shown in Table 7. There were no statistical differences regarding survival in patients younger or older than 55 years (p=0.47) or cannulation site (p=0.5). There was a statistically significant better survival for women (p=0.03).

	Post-cardiotomy	Non-cardiotomy
No or poor cardiac function	6	1
Multiorgan failure	8	3
Severe brain damage	1	3
Retroperitoneal bleeding	1	0
Fungal sepsis	1	0
Vasoplegia	1	0
Unknown	1	0

Table 7. The cause of death in post-cardiotomy and non-cardiotomy patients treated with extracorporeal membrane oxygenation (ECMO).

In the beginning of our series, two patients with femoral cut-down cannulation developed severe ischaemia of the lower limb, resulting in amputation. One survived. Two patients had severe pulmonary complications that prolonged ECMO treatment but did not result in patient death. Mechanical assist was deliberately terminated in two patients in whom brain death was diagnosed. The ECMO device in two post-cardiotomy patients was converted to a long-term left ventricular assist device as a bridge-to-heart transplantation and another two patients underwent heart transplantation.

Paper IV

Most patients in both groups were men, 10/12 (83%) in the short-term MCS device group and 16/18 (89%) in the LVAD group. Patients bridged with a short-term MCS device and a LVAD had a mean age of 38 and 47 years, respectively. Seven (58%) of the patients in the short-term MCS group were on a ventilator at the time of implantation of the support compared with two (11%) in the LVAD group. Three patients in the short-term assist device group had renal insufficiency requiring dialysis as compared to none in the LVAD group. Two patients in the LVAD group had a short-term assist device before LVAD implantation. All LVAD implantations were done electively and all of the short-term assist device implants were done emergently. Fourteen of the patients in the LVAD group underwent Htx. One patient died on the waiting list due to cerebral hemorrhage. Three patients are currently active on the waiting list. Three patients in the LVAD group died early post-operatively due to cerebral hypoxia, pulmonary embolism and hyper-acute rejection. Eleven patients are alive and well after transplantation. In the short-term MCS device group, all patients survived the early post-transplant period and could leave hospital. One patient died from an unknown cause nine months after transplantation. Early mortality after cardiac transplantation in the LVAD and MCS groups was 3/20 (15%) and 0/14 patients, respectively. All patients were completely followed-up in this retrospective study.

Perioperative results. In the short-term MCS group, five patients were re-operated for bleeding. Mean time on short-term MCS before transplantation was 11.3 (2-30) days. The mean post-transplant ICU stay was 15.1 days for the MCS group. In the LVAD

group, mean post-implant and post-transplant ICU stay was 6.5 (2-45) and 12.5 (2-40) days, respectively. The length of stay on the ward post-transplant was 31.8 (1-63) days in patients with short-term MCS. In the LVAD group, length of stay on the ward was 22.3 (0-36) post-implant and 18.5 (0-35) days post-transplant, respectively. See table 8 and figure 7.

Table 8. Patients characteristics in patients treated with short-term MCS (n=12) and LVAD (n=18) until heart transplantation.

Outcome	Short-term MCS	LVAD
n	12	18
Time on assist, d	11.3 ± 9.6	154 ± 114
ICU stay, d (post-implant/post-Htx)	15.1	19 (6.5+12.5)
Ward stay, d (post-implant/post-Htx)	29.6	40.8 (22.3+18.5)
CVL, n, (pre-/post-Htx)	1	3 (2+1)
Death, n, (pre-/post-Htx)	0	4 (1+3)

ICU=intensive care unit, CVL=cardiovascular lesions, Htx=heart transplantation

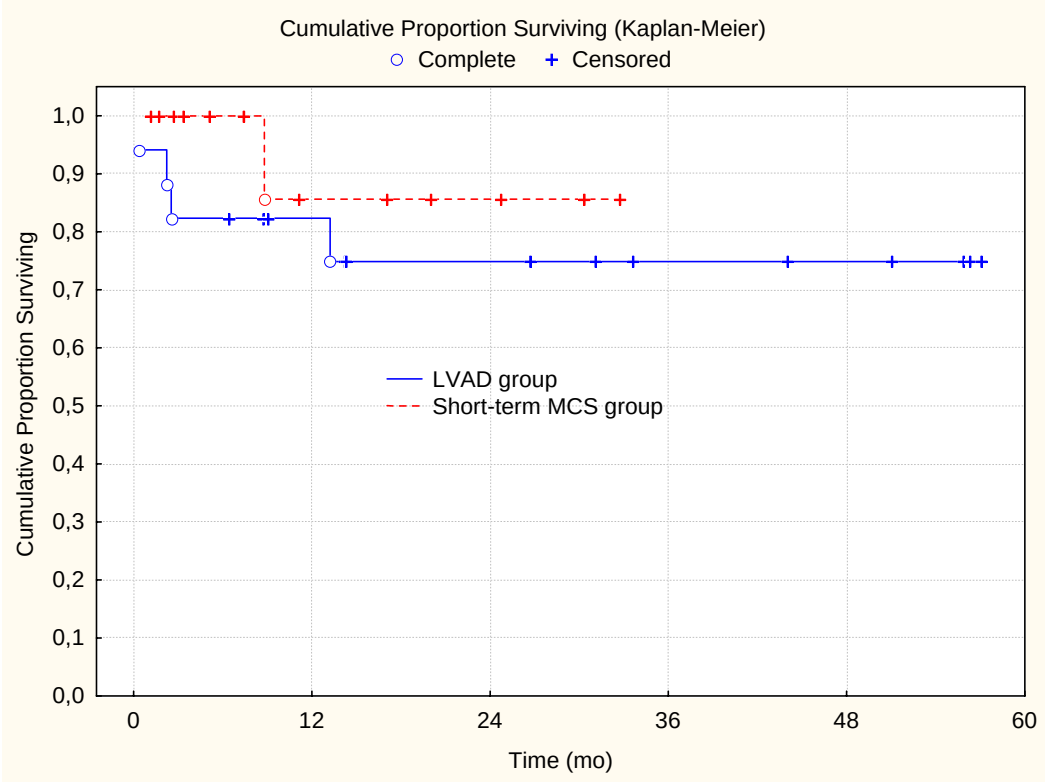

Figure 7. Kaplan-Meier survival curve in patients who were supported to heart transplantation with short-term mechanical support (n=12) and with left ventricular assist device (n=18) and patients at risk.

Economic calculations. Our cost calculations according to the hospital's "cost-per-patient" budgetary system showed that costs for the LVAD and MCS groups were

similar with about 3.2 million SEK (Swedish kronor) per patient in total. In the LVAD group, implantation amounted to 1.6 million SEK and transplant also 1.6 million SEK. In the short-term MCS group, the assist and transplantation occurred during the same stay and amounted to an average of 3.2 million SEK per patient.

5. Discussion

Paper I

Haemodynamic unloading with LVADs in chronic end-stage heart failure is associated with reverse remodelling including favourable changes on a structural, cellular and molecular level [18-20]. In addition, reports have emerged showing improvement of myocardial function sufficient enough to allow explantation of the supporting device. Consequently, treatment with LVADs has been proposed to be a feasible approach to bridge selected patients with end-stage heart failure to myocardial recovery and, thereby, reduce the need for heart transplantation.

In the present study, the occurrence of significant cardiac recovery during LVAD support was low. Despite optimal medical heart failure therapy during mechanical unloading, none of the patients with chronic end-stage heart failure could be subjected to successful weaning from the device. One patient, who suffered from dilated cardiomyopathy, fulfilled pre-defined criteria for myocardial recovery and underwent explantation, but suffered a relapse a few days later and required re-institution of mechanical support. The only patient who could be successfully weaned from the device was a young female, who presented with acute cardiogenic shock due to fulminant myocarditis.

Sustained cardiac recovery following mechanical support in patients with dilated cardiomyopathy has been described in two publications from the German Heart Institute in Berlin [21 22]. In 1995, Muller et al. reported functional improvement in five (29%) out of 17 patients enabling device explantation, and in 2005, Dandel et al. reported successful weaning in 32 (24%) out of 131 patients, who after explantation displayed a 78% 5-year survival[22]. All patients received medical heart failure treatment during unloading. A heart failure history of less than five years, LVEDD < 5 cm and off-pump LVEF > 45% were predictive of stable recovery.

In contrast to the findings of the Berlin group, our results do not support the concept of LVADs as a bridge to recovery in patients with chronic end-stage heart failure. Differences in post-implant treatment cannot explain the discrepancy, since all of our LVAD patients received medical heart failure therapy similar to that given in the German studies. On the other hand, it is possible that the patient population referred to mechanical support may have differed between centres. In the present study population, every possible effort was made to treat patients with maximally tolerated neurohormonal inhibition before a decision on mechanical support was made, which may have lead to a selection of pump recipients with a larger degree of irreversible myocardial damage.

Among the multiple changes that occur within the myocardium after prolonged mechanical support, not all appear to be favourable. An observed decrease in myocyte area after LVAD implantation has raised concerns over a possible risk of myocardial atrophy[23]. Furthermore, LVAD treatment has been shown to be associated with increased myocardial fibrosis resulting in augmented chamber stiffness. These findings suggest that cell death with replacement fibrosis continues to take place during mechanical support. The observations of the present study are more in line with the findings of Mancini et al., who in a retrospective study identified only five (5%)

successful explantations among 111 LVAD recipients[24]. Likewise, our experience is in accordance with the study by Helman et al. who reported that heart failure reoccurred shortly following explantation in two patients, a phenomenon they termed recurrent remodelling[25]. Thus, in our opinion, patients with long-term end-stage heart failure, resistant to adequate medical therapy, are unlikely to display significant recovery following treatment with a LVAD.

The LVAD Working Group Recovery Study was established in response to the contrasting reports of functional recovery during LVAD support. In this study, patients were assessed both prospectively and monthly with echocardiography during LVAD support. Despite observed improvements in cardiac function, none of the patients with chronic heart failure demonstrated sufficient cardiac restoration to be weaned from LVAD support.

The possible application of novel pharmacological therapy to facilitate cardiac recovery during mechanical support is of interest. The Harefield group has, in addition to customary neurohormonal blockade, treated LVAD patients with the β_2 agonist clenbuterol, which has been shown to induce physiological hypertrophy in the myocardium[20]. It has been suggested that such treatment might improve contractile function by changing calcium metabolism at a cellular level. Another potential approach would be to develop strategies to modulate the regenerative potential of the heart. Such interventions would require implantation of cardiac stem cells and promotion of their differentiation into myocytes and coronary vessels, an exciting future challenge.

The role of mechanical circulatory support as a bridge to recovery has not been defined. The success rate of such treatment is likely to depend on the degree of irreversible myocardial damage at the time of implantation. It is plausible that patients with reversible causes of heart failure, such as acute myocarditis, myocardial ischaemia or therapy-resistant arrhythmia will show sustained recovery following mechanical unloading and, possibly, also patients with heart failure of short duration showing signs of ongoing myocardial inflammation. On the other hand, patients with heart failure of a longer duration, not responding to adequate medical treatment or resynchronisation therapy, are unlikely to display cardiac recovery following mechanical circulatory support. Whether novel pharmacological therapy during mechanical unloading may facilitate cardiac healing and/or regeneration remains to be established.

Paper II

This retrospective, single-centre study describes the effect of unloading the left ventricle with a mechanical assist device on elevated PVR in heart transplant candidates, prior to orthotopic heart transplantation. Furthermore, we report the outcome after heart transplantation in recipients with elevated PVR managed according to standard clinical practice to the time of transplant as compared with patients subjected to pre-transplant LVAD treatment. The PVR in the group of patients treated with a LVAD decreased significantly from elevated level at implant to a normal range at the time of transplant. Outcome after heart transplantation was comparable with that of matched, pulmonary hypertensive control patients.

Furthermore, the study revealed no difference in survival between patients regardless of the severity of the elevated PVR. Our study demonstrates that mechanical circulatory support effectively reduces an elevated resistance in the pulmonary vasculature, in agreement with other reports[26 27]. It has also been shown that long-term post-transplant survival is comparable to patients with normal PVR[27]. Surprisingly, the cohort of patients in the present study, elevated PVR, treated with a LVAD or not, had no impact on post-transplant mortality and morbidity. It is also striking that there were no differences attributable to the severity of PH. There could be several explanations for the observations in this study. First, the decision to implant a LVAD was not entirely dependent on the severity of PH in all the studied patients though all had elevated PVR. Candidates with PH may present with rapid deterioration in organ function and the implantation of a LVAD becomes a high-risk procedure with a resultant complicated post-operative course. In this study, we have not presented data concerning morbidity at implant but since there were no differences in peri- or post-transplant morbidity and mortality compared to patients with PH not subjected to LVAD treatment, even more or less emergent implants did not affect transplant prognosis. However, the significantly higher number of patients in the LVAD group requiring RRT (renal replacement therapy) in the immediate post-operative period might reflect a somewhat more technically complicated transplant operation. Given the fact that these patients are chronically anticoagulated with combinations of several, long-acting, potent drugs and are subjected to a re-operation, it is surprising that this study did not reveal differences with respect to stay in the ICU or total length of stay. The chosen matching criteria in the selection of the control population may have been unable to reveal differences between the groups. Another obvious limitation of the study is the modest number of patients treated with LVAD, a fact that may have affected the investigators ability to recognise important associations owing to insufficient power, and thereby masking a positive effect of LVAD treatment of patients with PH.

The normalisation of PVR with LVAD treatment in this group of patients with PH may have important implications. Patients with non-reversible PH, not eligible for heart transplantation due to an unacceptably high risk of fatal RV failure and a poor long-term outcome may be converted to candidates with the same transplant prognosis as patients with normal PVR. On the other hand, the data analysis in this study did not reveal any impact of elevated PVR on long-term survival post-transplant, regardless of classified severity, which is quite inconsistent with other reports. Furthermore, in our institution there is the practice of using moderately larger donor hearts for those with significant pre-transplant PH, but data analysis in this study revealed that this strategy has not been possible to apply.

Our definition of PH was dependent on a calculated value, PVR, assessed in a setting where medical therapy was not being actively adjusted. Baseline measurements and calculated PVR reflect the patient's true clinical state at a given time, understanding that the haemodynamic state can easily fluctuate with and without medication adjustment. At our institution, once the candidate has been accepted for transplantation, medical management of the patient's clinical condition is continued in a sometimes more multidisciplinary manner which may, theoretically, optimise the

patient resulting in reclassification of mildly elevated PVR into the normal range due to pharmacological adjustments. However, associated with time on the waiting list, re-evaluation of patients with right heart catheterisation is not always necessary and improvements with respect to an elevated PVR might pass undetected. On the other hand, given the fact that there is a prevailing shortage of donor organs, time awaiting transplant might obliterate initial improvement. In this study, the analysed data were those obtained closest to the time of heart transplantation. Nevertheless, more than 50% of included patients had PH and the stratifying with regard to its severity resulted in more than 60% being classified with moderate to severe PH (35% and 30%, respectively). Thus concluding that included patients were those with more advanced heart failure than other studies[28], which is consistent with previous reports from this institution[29]. Given this perspective, the impact of elevated PVR on transplant prognosis may need to be revisited. This, however, has to be studied further.
It has been stated that RV dysfunction after cardiac transplantation is primarily related to status of the donor heart[30]. The donor RV is exposed to factors associated with brain death and organ preservation detrimental to its mechanical performance well before facing an increased afterload in the recipient. This single-centre experience has been subjected to evolving new techniques and strategies for almost 20 years, including a change in preservation solution and cardioplegia that may have affected the outcome. Heart transplantation in patients with fixed, severe PH is contraindicated but sometimes it is difficult to determine the degree of reversibility in PVR. Therefore, a final option to evaluate reversibility could be LVAD therapy and, in case of irreversible PH, heart transplantation is contraindicated.
In conclusion, treatment with a LVAD prior to transplantation reduces elevated PVR in heart transplant recipients, and there was no statistically significant difference in short-term or long-term survival between patients with PH managed according to standard clinical practice or pre-treated with a LVAD. LVAD therapy for elevated PVR in heart transplant candidates emerges as an option but further studies are required and the cut-off value in PVR for LVAD therapy remains to be established. Furthermore, there was no correlation in long-term survival and the severity of PH.

Paper III

This retrospective, two-centre study, describes the effect of treatment with veno-arterial ECMO in patients in refractory cardiogenic shock. An important finding in this study was the surprisingly high survival rate, despite an expected poor prognosis. In addition, initiation of ECMO in the moribund post-cardiotomy patients resulted in a higher survival than expected from clinical experience[31-33]. The number of long-term survivals is, to our knowledge the highest reported to date. There could be several reasons for these good results. One could be the selection of patients receiving ECMO. Recently, Chen et al. presented relatively poor survival rates of critically sick patients with AMI and refractory cardiogenic shock where ECMO was initiated during CPR[34]. On the other hand, almost half of the patients with ongoing CPR in our cohort of patients survived. Our study period is also more recent than the one described by Chen et al., gaining advantage by the rapid developments in pump technology and the properties of cannulas etc, which also could explain the improved outcome.

Acute myocardial infarction and cardiogenic shock is seen in approximately 10% of cases admitted to the emergency room and is hence a fairly common situation. Without aggressive treatment, cardiogenic shock results in high mortality[35]. The survival in patients needing a post-cardiotomy assist device, such as a LVAD or ECMO has previously been reported to be dismal and nearly always inferior to survival after cardiogenic shock of non-cardiotomy aetiology[31-34]. Our study is well in accordance with these findings and shows that short-term circulatory assist can result in approximately 50% survival of patients who would otherwise have succumbed. Most publications, however, include patients with a wide variety of diagnoses, and elective and emergent patients are mixed together with those with primary pulmonary problems. The reports also contain different approaches to support the failing heart, i.e. LVAD, RVAD and ECMO.

Another important finding was that if the patient survived the early post-operative period long-term survival was excellent. This further supports an aggressive treatment of patients with cardiogenic shock in non-cardiotomy patients and stresses the need and importance of having an organisation trained for the quick initiation of circulatory support. An increased survival was also noted for female sex. This could in part be explained by the fact that there were only two females in the post-cardiotomy group. The time from refractory cardiogenic shock to initiation of ECMO is very important and has been shown to be a risk factor for mortality[34 36]. The risk for severe neurological damage increases in a time-dependent manner during CPR and therefore it is important to start the ECMO as soon as possible. After diagnosing severe brain damage in several patients who came to our hospital under CPR we now only consider ECMO in patients with in-hospital-witnessed cardiac arrest.

There are several therapeutic options for the rescue of critically ill patients depending on the clinical situation. Patients with AMI complicated with cardiogenic shock are treated conventionally with vasopressors and IABP support followed by angioplasty or CABG (coronary artery bypass grafting) depending on the clinical situation and the decision of the cardiologist and the surgeon. This regimen has improved survival in critically sick patients but mortality is still significant[37]. Therefore, the timing of when to initiate ECMO in patients with refractory cardiogenic shock is difficult to determine and remains debateable. There are no controlled studies supporting a specific time of when to initiate ECMO and our policy has been to use it in patients refractory to the therapeutic algorithm described above. It is unknown if earlier initiation of ECMO would improve survival and it has to be considered that ECMO itself is also associated with complications, sometimes lethal, due to bleeding, infections, but also technical failures. Therefore, randomised studies aimed at the clarification of these issues would be of the utmost importance. However, there are ethical problems associated with randomisation in a salvage therapy context. Before the era described in this report, our strategy was to selectively support the failing ventricle, often ending up with bi-ventricular support. There are several reasons why we changed our routine in favour of veno-arterial ECMO as a circulatory support. One is the rapid development regarding the pump technology and the durability of the oxygenators. In an emergent situation it is easy to insert an ECMO system without first trying to distinguish between uni- or

bi-ventricular failure. Femoral percutaneous cannulation offers an easy approach that is preferable to sternotomy in patients with cardiogenic shock. Central cannulation was more common in post-cardiotomy patients because of the already opened sternum and easy conversion from cardiopulmonary bypass CPB to ECMO. There are some advantages with central cannulation compared with peripheral cannulation. Peripheral cannulation may cause retrograde perfusion and conflicting flows, forcing the heart to pump against retrograde flow, which theoretically could inhibit heart recovery. It is therefore important to closely investigate recovery of the heart and initiate the weaning procedure at an optimal time.
The duration of ECMO in our patients was longer when compared with those described in other studies[33 34 36-40]. It was most obvious in the non-cardiotomy group; a finding also reported by other study groups[36]. Our strategy was to provide sufficient time for the heart to recover from myocardial injury. The shorter duration on ECMO support in post-cardiotomy patients was due to the lack of recovery in this very sick patient group. When there was no or very poor heart function after 4-5 days, the ECMO-treatment was electively terminated.

It has been proposed that a LVAD would be an appropriate treatment option for patients in acute cardiogenic shock[39]. The results reported in the literature are however not promising and it seems a better option to use temporary mechanical circulatory support in an emergency situation for stabilisation of the circulation, also allowing time for further evaluation of the total patient situation. In our experience, some patients on temporary mechanical support have been diagnosed with a more or less severe neurological damage, making a LVAD implantation and/or transplantation contraindicated. Patients who were declared brain-dead became organ donors. On the other hand, with improved LVAD technology the use of a LVAD may become a primary therapeutic option in selective post-cardiotomy patients who can not be weaned off CPB.

The use of IABP has been shown to be a predictor for better survival in patients with refractory cardiogenic shock[41]. Based on the hypothesis of the beneficial effect of additional pulsatile flow, reduction of afterload, and better coronary flow our policy is to use IABP routinely in patients undergoing ECMO[38]. However, only 35% of the patients in our material had IABP prior to implantation of mechanical support which, consequently, was a deviation from our protocol. The decision to go directly for ECMO without previous IABP was based on the individual surgeon's preference, often when IABP was assessed not to be effective enough due to very poor or no circulation at all. Our hypothesis needs to be proven in a randomised prospective study which, however, would be difficult to perform for ethical reasons.

Malperfusion of the leg resulting in ischaemia may occur with cannulation of the femoral artery[42]. It is therefore of the utmost importance to follow the circulation in the cannulated leg. Insufficient circulation due to cannulation was not seen in patients who had been percutaneously cannulated, which seems to be a way of limiting distal malperfusion. The currently preferred method is to place a separate cannula distally in

the femoral artery before placing the femoral artery cannula percutaneously, thereby securing the peripheral circulation of the leg.

Paper IV

Cardiac transplantation directly from ECMO or short-term assist devices has historically been considered a last resort as outcomes have been considered to be inferior to the more traditional alternative with bridge-to-bridge with a LVAD to heart transplantation (Htx)[43]. In our study population with patients in circulatory shock rescued with a short-term assist device, all twelve were successfully bridged to Htx. These good results are in contrast with the present common opinion that Htx directly from ECMO or short-term assist devices is not to be recommended and that patients should instead should be bridged with a LVAD to Htx. The recommendations are in concurrence with the ISHLT (international society of heart and lung transplantation) registry which shows that pre-transplant need of short-term mechanical assist significantly increases 1-year mortality by an odds ratio of more than three [44]. Although this needs to be taken into account, we believe that these data are based on patients bridged with older systems in an earlier era and does not reflect the current situation. In the present study, only a small cohort of patients (about 10%) who underwent Htx at our institution during the time period chosen were included, but they represent the most critically ill individuals. These patients with circulatory collapse have close to 100% mortality without rescue with a short-term assist device. As mentioned, the most common concept in patients awaiting Htx with circulatory collapse is the bridge-to-bridge concept [45]. However, from the patient's perspective, the risks of significant morbidity and mortality associated with the implantation of a LVAD or total artificial heart (TAH) in individuals on a short-term assist device needs to be acknowledged. In our small case series, risks in terms of mortality seem higher for patients transplanted from a LVAD compared with short-term MCS, despite the fact that the latter were the sickest patients imaginable. It may even be the case that there is a survival benefit for patients being transplanted directly from MCS, since they do not need to undergo additional surgical procedures.

As technical and care giving improvements have been made, short-term MCS is perhaps no longer a contraindication to an urgent cardiac transplantation. Both others and ourselves have gained better understanding of who is a good candidate for cardiac transplantation from a short-term assist device. We now believe that bridging patients with short-term assist devices does not at all preclude these patients from an excellent outcome. However, the support time on a short-term assist device is a predictor for outcome and the availability of a donor heart is crucial. The time on support is also dependent on the patient's condition; the patient has to be transplantable at the time of an available donor. This is not only demanding for the team taking care of the patient but also for the patient's relatives. A long waiting time is also costly; therefore, the size of the centre is important. A larger centre performs more transplantations and receives more donor offers than a smaller centre.

In this report, we compare two different subsets of patients that perhaps cannot be compared or handled equally in an algorithm. Patients bridged to Htx with a LVAD are more stable and sometimes the indication is to relieve a contraindication to Htx, such as kidney failure or high pulmonary vascular resistance. But in the majority of LVAD patients, the indication is life-threatening deterioration of heart failure. In the majority of MCS patients bridged to heart transplantation, however, the indication is life-threatening deterioration of the acute heart failure often presented as cardiogenic shock. A more suitable comparison would be patients with bridge-to-bridge, but very few patients have been converted from short-term MCS to VADs, making a comparison difficult in our centre. It is possible though to use INTERMACS data for comparison. In the most recent report from the registry [46], INTERMACS level 1 patients reach about 70% three month survival but the majority are still not transplanted and a further 5-10% will probably expire in the immediate post-transplant period.

Even if we believe that excellent outcomes from transplanting patients from MCS are possible we recognise that a major problem with this approach is that many donor organisations do not have algorithms for these procedures. To manage direct cardiac transplantation from MCS requires a better balance between available donors and recipients than that seen in most of the donor systems. In some donor organisations, patients with end-stage heart failure never receive a cardiac transplant without first having a long-term LVAD. Severely diseased patients will therefore need to be treated according to the bridge-to-bridge concept in order to obtain a LVAD, and finally a cardiac transplantation, and will suffer from several high risk procedures from which not all will survive. Our results suggest that young patients suffering from acute cardiogenic shock that recover from multiorgan failure on MCS should be transplanted directly without passing by other systems or procedures. To achieve this, we will require new rules and regulations in many donor organisations.

Regarding costs for treating these patients, it is possible to estimate that a bridge-to-bridge concept to cardiac transplantation would increase costs by approximately 1.6 million SEK. This is to be compared with other reports of costs associated with this kind of treatement[47].

In conclusion, it is both possible and cost-effective to bridge severely ill heart failure patients with short-term MCS to cardiac transplantation with good outcomes.

6. Conclusions

1. It was not possible to achieve sustained recovery of the heart in patients supported with LVAD.

2. LVAD therapy reduced elevated PVR effectively.

3. LVAD therapy in patients with elevated PVR did not seem to offer significant benefits with respect to survival.

4. Short-term MCS seemed to improve survival in patients with refractory cardiogenic shock, especially in patients without prior surgery.

5. Heart transplantation directly from short-term MCS is feasible with good results.

7. Study limitations

The follow-up was 100% complete and reliable regarding survival in all papers, however, since three of the studies were retrospective there is always a risk of underestimating clinical events such as complications and other outcome data. There is also a limitation on the number of variables, such as pre-operative haemodynamic and laboratory values that could be retrieved from the medical records.
Managing protocols were evolving during the study period and there was no developed algorithm that was followed in advance, rather we came up with practical solutions for different patients. These solutions are now being developed as an algorithm but need to be tested further.
As the study populations are small, the risk for type II errors is present. The patients are very heterogeneous and have varying diagnoses, with the common denominator of having severe heart failure. Age varies substantially and there are no control groups. These limitations are inherent in these kinds of studies as MCS is a relatively uncommon treatment.

8. Acknowledgements

I wish to express my appreciation and gratitude to:

My supervisor, **Lars Wiklund**, Head of department and associate professor, for his never failing enthusiasm and impressive writing talent.

My co-supervisor, **Åsa Haraldsson,** for good support.

My co-writers

My friends at work.

My parents.

And most of all, my family.

The study was supported by grants from the Gothenburg Medical Society, Sahlgrenska University Hospital, and the Medical Faculty at Göteborg University (LUA).

9. Sammanfattning på svenska

Hjärtsvikt är ett allvarligt tillstånd som i sin mest avancerade form är livshotande. Hjärtpumpar kan hjälpa patienter att överleva fram till återhämtning av hjärtfunktion eller hjärttransplantation. Dessa stödpumpar för hjärtat finns att tillgå i många former för både korttids och långtidsbruk. Vi har undersökt olika typer av hjärtpumpar och deras möjligheter att förbättra patienters tillstånd och överlevnad.

Metoder och resultat

I det första delarbetet har vi prospektivt studerat möjligheten att undvika behovet av hjärttransplantation genom att se om utvalda patienter kan återfå tillräcklig hjärtfunktion med stöd av en inopererad hjärtpump för långtidsbruk. Arton patienter inkluderades. Patienterna utvärderades med avseende på återhämtning av hjärtfunktion. Tre patienter visade tecken på återhämtning och fick hjärtpumpen borttagen. Endast en av dessa patienter förblev välmående. Vi drog slutsatsen att denna strategi inte lämpar sig för alla patienter med hjärtpump för långtidsbruk.

Det andra delarbetet studerar patienter som akut fått livshotande hjärtsvikt. Patienterna fick behandling med en hjärtpump för korttidsbruk som inkluderar en apparat som syresätter blodet. Femtiotvå patienter ingick i studien. Patienterna delades in i två grupper. Patienter utan tidigare operation (19 patienter) och patienter som nyligen genomgått kirurgi (33 patienter). Vi noterade en relativt god överlevnad på 63 % i gruppen utan tidigare operation. Patienter som hade opererats klarade sig sämre med 33 % överlevande. Vi tror att de flesta patienter skulle ha avlidit utan behandlingen, och i det perspektivet är resultaten uppmuntrande.

Delarbete tre behandlade problemet med högt blodtryck i lungkretsloppet hos patienter aktuella för hjärttransplantation. Det är beskrivet att behandling med hjärtpump för långtidsbruk kan avhjälpa detta tillstånd som anses försämra resultaten vid hjärttransplantation. Patienter med högt blodtryck i lungkretsloppet behandlades med eller utan hjärtpump för långtidsbruk innan hjärttransplantation och undersöktes för att se om blodtrycket i lungkretsloppet minskade. Det höga blodtrycket i lungkretsloppet sänktes effektivt, men ingen signifikant skillnad sågs i överlevnad efter hjärttransplantation.

I det sista delarbetet undersökte vi hur patienter vars hjärtfunktion inte återhämtade sig med hjärtpump för korttidsbruk klarade att bli hjärttransplanterade. Denna strategi med hjärttransplantation direkt från hjärtpump för korttidsbruk är något kontroversiell då det historiskt ansetts att den medför sämre överlevnad. Tolv patienter som hjärttransplanterats direkt från hjärtpump för korttidsbruk granskades. Ingen patient avled i samband med transplantation och samtliga kunde skrivas ut till hemmet.

Slutsats

Behandling med hjärtpumpar kan många gånger vara livräddande för patienter med livshotande hjärtsvikt. Det är en resurskrävande metod som bör erbjudas särskilt utvalda patienter som kan ha nytta av behandlingen.

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Figures 1 and 2 were taken from an educational material used at our clinic.