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TESI DI DOTTORATO

Implantable Ventricular Assist Devices in the Deutsches Herzzentrum Experience

Special Reference to Gender Differences

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SUMMARY

Background: Over the past 20 years the use of ventricular assist devices (VADs) in patients with chronic end-stage or acute heart failure has led to improved survival. There is very little literature about gender differences in mechanical assist devices implantation while different gender characteristics in heart failure exist. The aim of our study was to review the large experience of Deutsches Herzzentrum in mechanical assist devices implantation as bridge to recovery, bridge to transplant or destination therapy, specifically concerning gender differences.

Methods: We analyzed data from the database of Deutsches Herzzentrum Berlin, which contains the demographic, preoperative, postoperative, and long-term follow-up data of patients who have received mechanical circulatory support (MCS) devices between July 1987 and May 2009. We collected survival data of patients implanted only with long-term MCS with a left-ventricular or a bi-ventricular assist configuration. We excluded patients implanted with short-term devices, total artificial heart devices and isolated right ventricular assist devices. We analyzed differences between men and women.

Results: A total of 889 patients were implanted with long-term VADs: 492 left ventricular assist devices (LVAD) (55.3%) and 397 biventricular assist devices (BVAD) (44.7%). The mean age of the patients was 49.2 years (range 17 to 76 years) (mean age men 50.0 years \pm 12.4; mean age women 44.8 years \pm 13.7), 84.8% were male. Mean time of VAD was 4.48 (\pm 0.24) months with longer support (p 0.001) in men (4.7 months \pm 0.2) than in women (3.0 months \pm 0.5). Also in the two subgroups of LVAD and BVAD, mean support time was longer in men than in women (p < 0.001): 6.22

months \pm 0.41 in LVAD men and 4.2 months \pm 1.25 in LVAD women, 2.64 months \pm 0.26 in BVAD men and 2.38 months \pm 0.38 in BVAD women. Survival analysis showed that in patients needing mechanical circulatory support the 30 days survival is 88% and the p50 (= median survival) is 2.6 months. LVAD (p50 3.99 months) permit better survival than BVAD (p50 1.28 months) ($p < 0.0001$) and there is a trend (p 0.73) of worst survival in women (p50 1.38 months) than in men (p50 2.56 months), most of all in the first month after implant. In 55 patients (45 male) the device could be removed after myocardial recovery. In this subgroup of patients women had a survival near to significantly worse than men (p50 women 9.33 months vs. p50 men 77.42; p 0.08). A total of 260 patients were successfully bridged to heart transplantation (219 male). Also in this subgroup LVADs performed better than BVADs ($p < 0.0001$) and men better than women, even if not statistically significant.

Conclusion: VAD implantation is an effective therapy in patients with advanced heart failure, but early mortality is still high. LVADs perform much better, last longer and have lower mortality than BVADs. In percentage men are more often implanted with LVAD and have better survival with VAD than women.

RIASSUNTO

Introduzione: Negli ultimi 20 anni l'uso di dispositivi di assistenza ventricolare (VAD) in pazienti con insufficienza cardiaca cronica in fase terminale o acuta ha portato ad un miglioramento della sopravvivenza. La letteratura sulle differenze tra i due sessi nell'impianto di VAD è molto scarsa, mentre esistono delle diverse caratteristiche di sesso nell'insufficienza cardiaca. Lo scopo del nostro studio era quello di analizzare la grande esperienza del Deutsches Herzzentrum nella terapia con VAD come ponte al recovery del miocardio, come ponte al trapianto cardiaco o come destination therapy, specificamente riguardo alle differenze tra i due sessi.

Metodi: Abbiamo analizzato i dati provenienti dal database del Deutsches Herzzentrum di Berlino, che contiene le caratteristiche demografiche, preoperatorie, postoperatorie e il follow-up a lungo termine dei pazienti che hanno ricevuto dispositivi meccanici di assistenza circolatoria nel periodo compreso tra luglio 1987 e maggio 2009. Abbiamo raccolto i dati di sopravvivenza solo dei pazienti trattati con supporto meccanico di circolo (MCS) a lungo termine mediante un'assistenza ventricolare sinistra (LVAD) o un'assistenza biventricolare (BVAD). Abbiamo escluso i pazienti a cui erano stati impiantati dispositivi d'emergenza a breve termine, un cuore artificiale totale o un'assistenza ventricolare destra isolata. Abbiamo quindi analizzato le differenze tra uomini e donne.

Risultati: Un totale di 889 pazienti hanno ricevuto un VAD a lungo termine: 492 LVADs (55,3%) e 397 BVADs (44,7%). L'età media dei pazienti era di 49,2 anni (range 17-76 anni) (età media uomini 50,0 anni \pm 12,4; età media donne 44,8 anni \pm 13,7), l'84,8% erano maschi. Il tempo medio di assistenza ventricolare è stato di 4,48 (\pm 0,24)

mesi con supporto più lungo ($p < 0,001$) negli uomini ($4,7 \text{ mesi} \pm 0,2$) che nelle donne ($3,0 \text{ mesi} \pm 0,5$). Anche nei due sottogruppi di tempo in LVAD e BVAD, la durata media era più lunga negli uomini che nelle donne ($p < 0,001$): $0,41 \text{ mesi} \pm 6,22$ gli uomini con LVAD e $4,2 \text{ mesi} \pm 1,25$ le donne con LVAD; $2,64 \text{ mesi} \pm 0,26$ gli uomini con BVAD e $2,38 \text{ mesi} \pm 0,38$ le donne con BVAD. L'analisi di sopravvivenza ha dimostrato che nei pazienti che necessitano un MCS la sopravvivenza a 30 giorni è dell'88% e la p50 (= sopravvivenza mediana) è di 2,6 mesi. Gli LVADs (p50 3,99 mesi) consentono una migliore sopravvivenza rispetto ai BVADs (p50 1,28 mesi) ($p < 0,0001$) e vi è una tendenza ($p 0,73$) di peggiore sopravvivenza nelle donne (p50 1,38 mesi) che negli uomini (p50 2,56 mesi), soprattutto nel primo mese dopo l'impianto. In 55 pazienti (45 maschi) si è potuto rimuovere il dispositivo dopo avere ottenuto un accettabile recupero della funzione contrattile del miocardio. In questo sottogruppo di pazienti le donne hanno avuto una sopravvivenza significativamente peggiore rispetto agli uomini (p50 donne 9,33 mesi vs p50 uomini 77,42 mesi; $p 0,08$). Un totale di 260 pazienti (219 maschi) sono stati portati con successo al trapianto di cuore. Anche in questo sottogruppo gli LVADs hanno dato una sopravvivenza migliore rispetto ai BVADs ($p < 0,0001$) e gli uomini sono sopravvissuti più delle donne, anche se non in modo statisticamente significativo.

Conclusioni: l'impianto di VAD è una terapia efficace nei pazienti con insufficienza cardiaca avanzata, ma la mortalità peri-operatoria è ancora elevata. Gli LVADs hanno una migliore performance, durano più a lungo e danno una mortalità più bassa rispetto ai BVADs. In percentuale gli uomini vengono più spesso trattati con LVAD e hanno una migliore sopravvivenza in assistenza rispetto alle donne.

THE ISSUE OF HEART FAILURE

Heart failure is a leading cause of death in the developed countries. It is estimated that 22 million people suffer from congestive heart failure worldwide, with a prevalence of 2-5% in the population over 45 years of age. In 2001, the American Heart Association reports over 5 million US people affected and 500,000 new cases diagnosed every year. The incidence in the population older than 65 years is 10 per 1000 inhabitants ¹. Most of these patients are refractory to medical therapy and there are 260,000 deaths each year for heart failure in the United States. Despite advances in medical and surgical management, the 5-year mortality rate is around 50%. In 2004, the direct and indirect cost of heart failure has been estimated at 25.8 billion dollars, that is the 5% of the national health care budget. Consequently, over 12-15 million medical examinations and 6.5 million hospital admissions are required each year ²⁻⁶.

The European Society of Cardiology reports similar data. Europe has about 700 million people and of these at least 10 million are suffering from congestive heart failure. About half of patients with congestive heart failure die in 4 years and 300000 die for decompensation every year. 78% of all patients undergo two hospital admissions per year ⁷.

In Italy there is 1 million people suffering from congestive heart failure. In 30% of cases patients are over 65 years of age: ischemic heart disease is the main cause. In Italy there are more than 170,000 hospitalizations per year (Health Ministry). The incidence of congestive heart failure is one new case per 1000 inhabitants per year, but every year

the percentage increases of 10%. In Italy, the expenses for congestive heart failure are estimated to account of 1.4 % of total national health care budget.

The situation in Germany is similar and the expenses are even higher.

Everywhere in the world the incidence is increasing. It is estimated that in the next years in USA there will be more than 400 thousand new cases per year due to advancing age of the population and to the treatment of heart attack. In fact patients who survive to infarction after treatment with clot-busting drugs and catheters, develop more frequently than general population heart failure because of residual myocardial damage ⁷.

Medical therapy for heart failure is based on diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and beta blockers. Up to one-third of patients gain no symptomatic relief from (ACE) inhibitors and decompensation through dysrhythmias or pulmonary edema is the trigger for repeated hospitalizations. As these patients progress optimal medical therapy and biventricular resynchronization are no longer successful, quality of live is poor, and prognosis is limited ⁷. Cardiac surgery interventions have been performed for decades on patients with congestive heart failure secondary to ischemic disease, valvular disease, and ventricular aneurysm. However these interventions were generally considered high risk with regard to peri-operative morbidity and mortality and unpredictable in terms of chronic outcome ⁸. To date, cardiac transplantation has been the only treatment to provide consistent improvement in quality of life and survival, although extremely limited by donors, costs and long term morbidities. In 1999 only 2.184 patients in the United States underwent cardiac transplantation, representing less than half of patients on the waiting list. These were carefully selected patients predominantly under the age of 65 years. Seven hundred died while waiting for a donor and 676 were withdrawn from consideration because of

deteriorating end-organ function ⁷. In Europe heart transplantation is unable to satisfy all the requests either.

Most heart failure patients are not eligible to heart transplantation because of age limitations, concomitant diseases (diabetes, chronic obstructive airways disease, renal impairment or malignancy) or elevated pulmonary vascular resistance.

Furthermore, the effectiveness of heart transplantation should be reconsidered: more critically ill recipients and the use of the so-called “marginal donors” have limited improvement in outcomes after transplantation. Deng et al showed that listed patients with ischemic heart disease who did not receive a donor organ had 3 and 4 year survival rates similar to transplanted patients ⁹. The prediction of outcome for any individual patient without transplantation is complex: although the degree of left ventricular dysfunction is a prognostic indicator for mortality, many patients with markedly reduced left ventricular ejection fraction (LVEF) can survive for years with reasonable functional capacity ⁹.

In the meantime, the medical and non transplantation surgical treatment of these patients has improved. Revascularization of hibernating myocardium, surgical left ventricular remodelling, mitral valve repair, and ventricular assist devices are proving to be useful surgical tools in heart failure ⁷.

Early descriptions of mechanical support to human circulation are documented at least back to early nineteenth century but a real interest on support of circulation developed with the advent of open cardiac surgery in the 1950-60s. The inability to wean patients from cardiopulmonary bypass fuelled the interest in first mechanical supports as bridge to recovery. The first reports of successful support were with a roller pump by Spenser

in 1963, with pneumatically driver diaphragm pump by De Bakey in 1966 and with IABP by Kantrovitz in 1967.

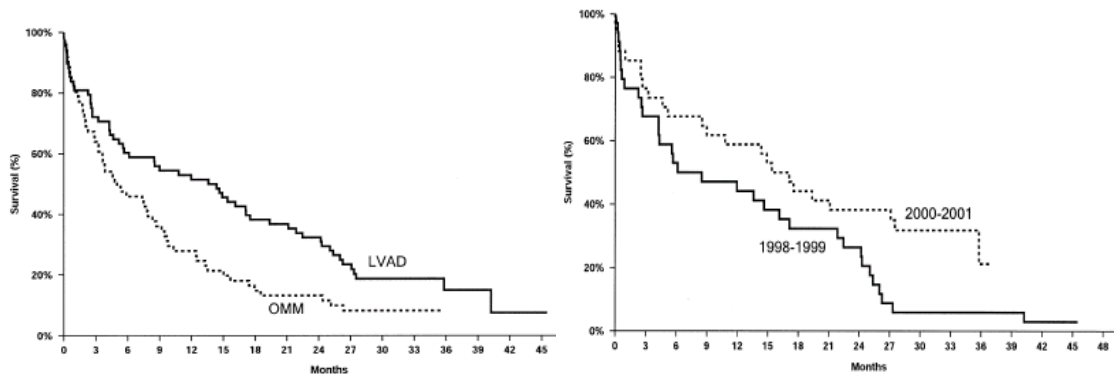
The second step was the development of different devices as bridge to transplant. The total artificial heart was used first as support until transplantation by Cooley in 1969 while the first case of bridging to transplantation with pneumatic assist device is due to Norman in 1978. Better results were obtained with Excor Berlin Heart, Novacor and HeartMate in 80-90s.

With the immutable limitation in the supply of suitable donor hearts a lot of patients with heart failure could not be offered the possibility of long survival and in the last 10-15 years were developed a second and third generation of pumps as Incor, DeBakey, Jarvik2000, HeartMateII.

These rotatory devices without mechanical or touching bearings can support circulation for long term and may be considered for destination therapy. The use of implantable second and third generation left ventricular assist devices (LVADs) in patients with end-stage heart failure as an alternative to heart transplantation, was first investigated in the landmark Randomized Evaluation of Mechanical Assistance in the Treatment of Congestive Heart Failure (REMATCH) trial. The study randomized 129 patients with New York Heart Association class IV heart failure who were ineligible for transplantation to either mechanical circulatory support or medical therapy. Patients supported with LVAD had significantly improved 1-year survival, from 25% to 52%, providing >2-fold survival benefit over maximal medical therapy. Survival during the first 12 months after LVAD implantation, however, was hindered by high postoperative mortality, raising concerns whether increased operative risk in many LVAD recipients

could minimize the potential benefit of this life-saving therapy and limit its expanded use¹⁰.

Figure 1



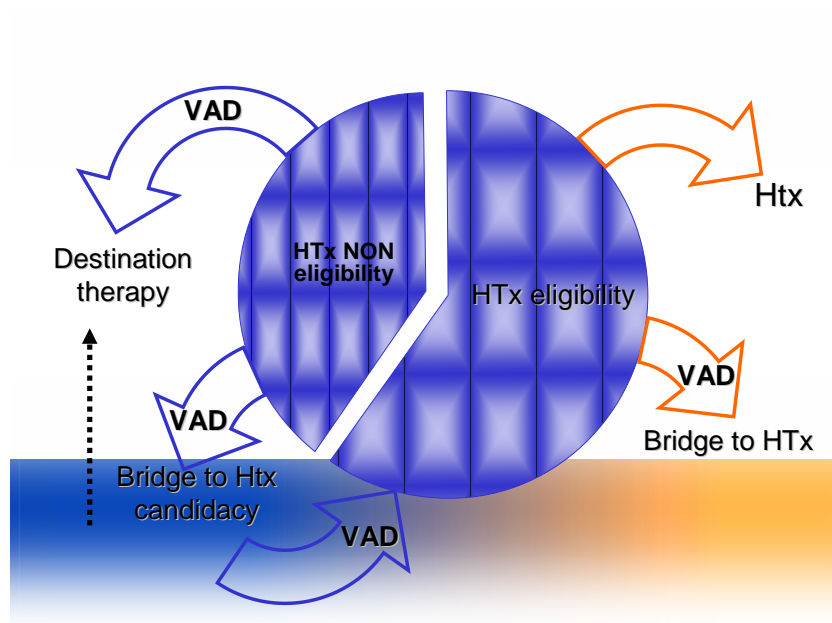
Kaplan-Meier survival curves for patient receiving medical therapy or LVAD in REMATCH study and comparison between survival in pre e post -REMATCH trial.

More than three hundred patients underwent LVAD implantation as an alternative to heart transplantation, or destination therapy (DT), since the completion of the landmark REMATCH trial, which first demonstrated the superiority of mechanical circulatory support over medical therapy for end-stage heart failure in patients who were not eligible for heart transplantation¹¹. Survival rates at 1 and 2 years in REMATCH trial were of 56% and 33% (Figure 1). New second and third generation LVADs have even improved the results. The study of Slaughter et al., called the REMATCH II study, shows that implantation of a continuous-flow left ventricular assist device, as compared with a pulsatile-flow device, significantly improved the probability of survival free of stroke and reoperation for device repair or replacement at 2 years in patients with

advanced heart failure in whom current therapy had failed and who were ineligible for transplantation¹². In addition, the actuarial survival over a 2-year period of support by a left ventricular assist device was significantly better with the continuous-flow device than with the pulsatile-flow device in a population of patients whose 2-year survival rate while receiving medical therapy has been shown to be approximately 10%^{11, 13}. The continuous-flow left ventricular assist device was also associated with significant reductions in the frequency of adverse events and the rate of repeat hospitalization, as well as with an improved quality of life and functional capacity. The survival rate at 2 years among the patients with a pulsatile-flow left ventricular assist device was similar to that among patients with a left ventricular assist device in the REMATCH I trial¹¹, whereas the survival rate among the REMATCH II trial patients with a continuous-flow device was more than twice the rate among the REMATCH I patients⁸. In addition, as many as 17% of DT recipients were able to undergo heart transplantation after their relative contraindications improved on mechanical support. The vast majority of deaths occurred within the first 3 months after LVAD surgery. Sepsis, right heart failure and multi organ failure were the main causes of postoperative death and were the main contributors to the relatively high in-hospital mortality (26.8%) after device implantation. For patients with hemodynamic deterioration not due to post-cardiotomy shock, a “two-track” paradigm has evolved in which patients are assigned to either “bridge to transplant” or “destination therapy” based on their perceived transplant candidacy at the time of implantation. This dichotomy, in which clinicians are required to assign patients to “bridge to transplant” or “destination therapy” before device implantation, is inconsistent with the realities of clinical care of patients with advanced heart failure. In fact prolonged device support is associated with the reversal of

molecular and clinical aspects of the end stage heart failure state. The molecular changes (neurohormonal and cytokine profile and cellular phenotype) often are accompanied by substantial improvement in renal function, resolution of pulmonary hypertension, and improvement in overall functional status ¹⁴. In this way it is clear that VAD support may convert some patients with contraindications to transplant into appropriate transplant candidates. The data from Deng et al. clearly demonstrate that many patients initially implanted as “destination therapy” because of renal dysfunction or pulmonary hypertension may subsequently become acceptable transplant candidates after prolonged device support and rehabilitation. Alternatively, some patients initially implanted as a “bridge to transplant” may subsequently experience either recovery of ventricular function or complications during VAD support (such as a disabling stroke) that may make them inappropriate or ineligible for transplant. The boundary between devices for a bridge and for permanent destination is increasingly blurred and it may be most appropriate to consider a broader plan of selection for long term support ¹⁴ (Figure 2).

Figure 2



INDICATIONS FOR VENTRICULAR ASSIST DEVICE IMPLANTATION

The tremendous impact of patient selection on the outcomes of LVAD surgery has been recognized since the first devices were used.

Despite several modifications, improved safety and reliability of the new device, and growing overall experience with mechanical support, the 1-year outcomes of LVAD therapy continued to be hindered by high rates of serious postoperative complications. The vast majority of hospital mortality occurs within the first 3 months after LVAD surgery. Because these complications were unrelated to device malfunction, this finding suggests that selection of candidates and timing of LVAD implantation are the most likely determinants of the operative success¹⁵.

There are no absolute hemodynamic criteria to meet in order to implant one left ventricular assist devices therefore appropriate judgment is required to select the proper patients and timing of device intervention.

Typically the three most important data are considered cardiac index < 2.0 L/min/m², systolic blood pressure < 90 mmHg, pulmonary capillary wedge pressure > 20 mmHg¹⁵.

Also non hemodynamic data are important, the criteria used to recruit the patients of REMATCH trial included: (1) New York Heart Association class IV symptoms for at least 60 days despite maximized oral therapy or requirement of inotropic support as outlined by the American Heart Association/American College of Cardiology guidelines for heart failure treatment, (2) left ventricular ejection fraction (LVEF) $\leq 25\%$, (3) peak oxygen consumption < 12 ml kg⁻¹ min⁻¹ or documented inability to wean intravenous inotropic therapy and (4) contraindications to heart transplantation because of either age

>65 years or comorbidities such as insulin-dependent diabetes mellitus with end-organ damage or chronic renal failure ¹¹.

Other reports suggest to consider the evidence of cardiac decompensation manifested by a evidence of poor tissue perfusion, reflected by oliguria, rising serum creatinine and liver transaminases, acidosis, mental status changes and cool extremities, despite the use of optimal pharmacologic therapy, are guidelines to necessity of mechanical support. Clinical situations in which assist devices implantation is indicated may also include subtle, progressive organ dysfunction despite inotropic therapy in a patient with chronically low cardiac output awaiting heart transplantation, even though hemodynamic parameters may not have significantly changed. Patients with refractory ventricular arrhythmias or life-threatening coronary anatomy with unstable angina not amenable to revascularization and who are at risk of imminent death (hours, days, or weeks) may be considered for mechanical support without necessarily meeting hemodynamic criteria.

The patient's history and overall clinical setting are considered in the decision process to initiate mechanical support. Increasing degrees of chronic organ dysfunction also represent additional risk factors for death. The presence of irreversible respiratory, renal or hepatic failure is a contraindication to device implantation. Neurologic dysfunction with significant cognitive deficits and the presence of sepsis are additional contraindications ¹¹.

Chronic pulmonary disease associated with significantly impaired pulmonary reserve and systemic oxygenation can contribute to peri-operative hypoxia and pulmonary vasoconstriction resulting in right-sided circulatory failure. Patients with severe chronic pulmonary disease usually present elevated pulmonary vascular resistance (> 4 Wood

units) that are not reversible represent a contraindication to heart transplantation and so mechanical support remains the only possibility even if lower results can be expected. However moderate increase of pulmonary pressure when tricuspid regurgitation is not severe is an index of conserved right ventricular function and so can be considered a positive prognostic factor concerning right failure after the implantation of left ventricular assist devices implantation. Additionally, in some instances, left ventricular assist devices have been effective in reducing pulmonary vascular resistance in patients previously found to have elevations in their pulmonary vascular resistance not readily responsive to inotropic or vasodilator therapy.

Acute renal failure requiring dialysis is a relative contraindication to initiating MCS. In the setting of cardiogenic shock with acute renal failure, establishing normal hemodynamic with MCS may solve the renal failure in a relatively short period of time. Thus, the degree and duration of cardiogenic shock, along with the patient's baseline renal function, must be considered in estimating the probability of recovery of renal function. Similarly improvement in hepatic congestion and recovery of synthetic functions of the liver can occur with institution of MCS. The presence of portal hypertension or liver cirrhosis is an absolute contraindication to initiating MCS and liver biopsy may be indicated to definitively rule out significant parenchymal fibrosis.

Numerous studies investigating the adverse prognostic factors influencing outcomes of MCS recipients have consistently demonstrated that progressive degrees of organ dysfunction are associated with poor outcome. These observations led to the development of risk stratification models. Although no one variable may predict survival, nearly every composite risk score describing clinical status and severity of multi organ impairment, including classic risk scores used in critically ill patients such

as the APACHE (Acute Physiology and Chronic Health Evaluation) score, closely correlated with outcomes of LVAD surgery ¹⁶.

Specifically, the need for mechanical ventilation, oliguria (urine output less than 30 cc/h), preoperative right-sided circulatory failure manifest as an elevated central venous pressure greater than 16 mmHg, liver dysfunction as measured by a prothrombin time greater than 16 s and increasing serum creatinine and bilirubin levels are adverse prognostic risk factors for survival following initiation of MCS. In addition to organ dysfunction, other patient factors or clinical settings that have been associated with adverse outcomes include small body size, anaemia, poor nutritional status with low serum albumin, acute myocardial infarction, prior sternotomy, post-cardiotomy setting, advancing age, probable infection evidenced by leukocytosis and declining platelets count ¹⁷.

TIMING FOR VENTRICULAR ASSIST DEVICE IMPLANTATION

Timing of MCS implantation is crucial to patient outcome. Usually in centres without a lot of experience the implantation of the devices occurs too late and best results are obtained. Early initiation of extracorporeal MCS, based on hemodynamic parameters and degree of intra-operative inotropic support, demonstrates improved rates of survival and more quickly hospital discharge. Most of all concerning univentricular assistance the indication should be precocious and LVAD should be considered one option for the treatment of heart failure and not the last hope when the patient is too ill for every other treatment. As the severity of illness and organ dysfunction increases, patients are more likely to require biventricular support. Patients requiring biventricular support have a decreased survival ¹⁷.

An episode of cardiac arrest prior to the initiation of MCS significantly reduces intra-operative survival (47% versus 7%) ¹¹.

Selection of the appropriate MCS device is also critical to successful outcome and is dependent on a number of factors. These factors include the etiology of the circulatory failure, the duration of expected support, whether biventricular or univentricular support is required, whether combined cardiac and pulmonary failure is present, the size of the patient, the intended use for the device. Consideration of all these factors help to define the end point of therapy, which may include bridge to recovery, bridge to heart transplantation, bridge to bridge and destination therapy ¹⁷.

A lot of ischemic morphological or valvular cardiac abnormalities can have important adverse consequences in patients being considered for assist devices implantation and may require correction in order to initiate successful MCS.

The presence of even mild-moderate aortic insufficiency can have a significant impact on the left ventricular distension and subendocardial ischemia after that left ventricular pressure will be significantly reduced by emptying of the left ventricular cavity by the device and the aortic root pressure will be elevated above baseline because of device flow. Blood pumped into the aortic root by the device will flow backward across the incompetent aortic valve, thereby decreasing net forward flow and compromising organ perfusion.

Mitral stenosis can impair left ventricular filling.

Severe tricuspid regurgitation can significantly impair the forward flow of blood on the right side, particularly in situations of high pulmonary vascular resistance. Furthermore, severe tricuspid regurgitation contributes to elevated central venous pressure, hepatic congestion, and renal dysfunction. Severe tricuspid regurgitation may be present preoperatively in the setting of volume overload and biventricular failure or may develop following institution of LVAD support as a consequence of right ventricular dilation from leftward shift of the interventricular septum. If severe tricuspid regurgitation is present during the initiation of LVAD support, tricuspid valve repair should be performed to improve right-sided circulatory function.

Atrial or ventricular septal defect should be closed at the time of implantation of left ventricular assistance to prevent right-to-left shunting. In fact during left ventricular assistance left atrial pressure is reduced, a shunting of deoxygenated blood from the right atrium into the left can occur, resulting in significant systemic hypoxemia.

Patients who have significant obstructive coronary artery disease may continue to experience angina after the implantation of mechanical assistance. Then ischemia of the right ventricle may be of hemodynamic significance during institution of LVAD

support. Right ventricular ischemia causing myocardial stunning or infarction that occurs during or soon after implantation of a LVAD can elicit right-sided circulatory failure, resulting in decreased flow to the LVAD. In selected situations it may be important to perform a coronary artery bypass to the right coronary artery or left anterior descending coronary artery systems to optimize right-heart function in the peri-operative period.

Arrhythmias are common in patients with ischemic heart disease or idiopathic cardiomyopathies and represent an important problem in the immediate postoperative period and some patients have persistence of the arrhythmia also after mechanical support, due to their underlying pathology (e.g.: giant-cell myocarditis). Although these arrhythmias can solve after cardiac support as the hemodynamic condition improves generally severe ventricular arrhythmias have been thought to be a contraindication to left ventricular support. However, recent experience reveals that in the late postoperative period the hemodynamic consequences of ventricular fibrillation could be sustained by a ventricular assist devices and an adequate flow is guaranteed. In fact in the absence of pulmonary hypertension and elevated pulmonary vascular resistance left ventricular assistance physiology is analogous to a Fontan circulation ¹¹. Atrial fibrillation and flutter hinder right ventricular filling and can reveal and make clinically evident a latent right ventricular dysfunction but it's reasonably well tolerated in recipients of ventricular assist devices ¹⁸.

DIFFERENT TYPES OF DEVICE

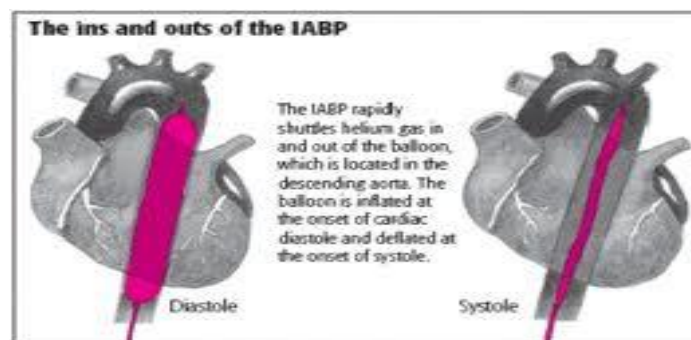
1) CARDIOPULMONARY ASSIST DEVICE

Circulatory assist devices were initially designed to support patients in hemodynamic collapse, but are now used for a wide range of clinical conditions ranging from prophylactic insertion for invasive procedures to cardiogenic shock or cardiopulmonary arrest. There are three major types of percutaneous device (as well as surgically-implanted LVAD):

- Counterpulsation devices (intra-aortic balloon pump and noninvasive counterpulsation)
- Cardiopulmonary assist devices (Cardiopulmonary support or CPS)
- Left ventricular assist devices (eg: Impella)

The intraaortic balloon (IABP) is the most commonly used mechanical support device. It has a long clinical record of success, is simple, is inserted easily and rapidly, is the least expensive of all the devices, and does not require constant monitoring by technical support personnel (Figure 3).

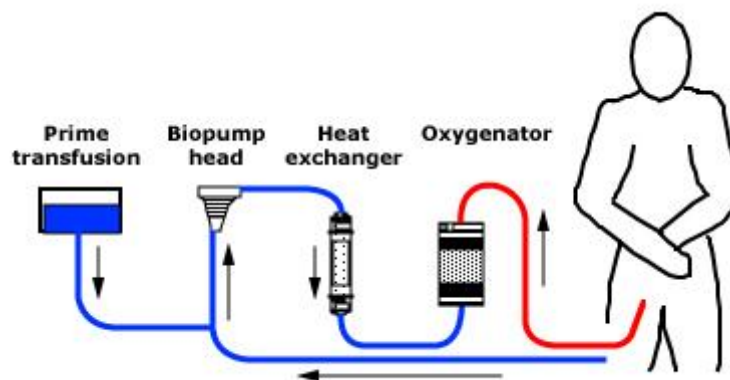
Figure 3: Intraaortic Balloon Pump



Percutaneous cardiopulmonary support (CPS) provides full cardiopulmonary support (including hemodynamic support and oxygenation of venous blood) analogous to that provided by bypass during cardiac surgery. The Bard CPS involves placement in the central arterial and venous circulation of large bore catheters that allow positioning of cannulae in the aorta and right atrium. Blood from the venous catheter is pumped through a heat exchanger and oxygenator, and then returned to the systemic arterial circulation via the arterial cannula. CPS requires continuous, highly technical support (Figure 4).

Figure 4

Cardiopulmonary bypass support system



Schematic representation of the cardiopulmonary bypass support system showing active aspiration of venous blood by a vortex pump with subsequent passage of blood through the heat exchanger to the membrane oxygenator and then back to the patient.

The CPS may be used in the following circumstances:

- Acute hemodynamic deterioration such as cardiogenic shock and cardiopulmonary arrest
- High-risk percutaneous transluminal coronary angioplasty (PTCA)

- Fulminant myocarditis presenting with cardiogenic shock ¹⁹.

CPS is contraindicated in the following clinical conditions:

- Significant aortic regurgitation
- Severe peripheral artery disease
- Bleeding diathesis
- Recent CVA or head trauma
- Uncontrolled sepsis

Local vascular (arterial or venous) or neurologic complications are most common because the cannulae are large. These complications initially occurred in approximately 12 percent of patients, with almost one-half requiring surgical treatment. Recent revisions in technique have decreased the major complication rate to only 1.4 percent ²⁰. However, the reported experience comes from a small number of centers; these improvements may not be widely applicable at less experienced centers.

2) SHORT-TERM VADs

There are many short-term ventricular assist devices (VADs) available and they are classified according to the pump mechanism.

Centrifugal pumps — Centrifugal pumps are an extension of cardiopulmonary bypass. They use rotating cones or impellers to generate energy that is recovered in the form of pressure flow work. There are presently three centrifugal pumps available, the Bio-Medicus (Bio-Medicus Inc, Minneapolis, MN), the Sarns (Sarns/3M Ann Arbor, MI) and the Levitronix Centrimag® (Levitronix LLC, Waltham, MA) (Figure 5). All of them have the capability of supporting patients who cannot be weaned from cardiopulmonary bypass or who are waiting cardiac transplantation. The pumps are versatile and can be used as a right ventricular assist device (RVAD), left ventricular assist device (LVAD) or biventricular (BiVAD) support.

Figure 5

Levitronix Centrimag® centrifugal pump



Insertion of centrifugal pumps generally requires a sternotomy. The right and or left atrium can be cannulated by using simple purse string sutures. The aorta and/or the pulmonary artery are cannulated by using standard cardiopulmonary bypass aorta cannulae placed through a purse string suture. These devices can also be placed percutaneously in the catheterization laboratory.

Centrifugal pumps have several important limitations:

- Flow is non-pulsatile which can be reflected in poor end-organ function, specifically renal dysfunction.
- The devices are traumatic to blood, causing a significant amount of hemolysis and a generalized inflammatory response. Patients with centrifugal pumps should be maintained on continuous intravenous heparin which is begun as soon as the initial bleeding subsides and continued until device removal. The activated partial thromboplastin time is maintained between 150 and 200 seconds but can be reduced if flows are maintained and if bleeding increases.
- Patients are unable to ambulate or exercise with the device in place.

In summary, centrifugal pumps are quite effective for short-term support during cardiopulmonary bypass. However, long-term use of these devices poses serious problems; the success rate when used for patients who cannot be weaned from cardiopulmonary bypass is only 10 percent.

Extracorporeal pump — The Abiomed biventricular system (BVS 5000) and the more recent AB5000 version (Figure 6) were designed as alternatives to centrifugal pumps for short-term support. The pump is an extracorporeal device which has an atrial chamber that is filled by gravity drainage. Blood from the atrial chamber flows across

polyurethane valves to a ventricular chamber where it is pneumatically pumped back to the patient. The reported total duration of support with this system has varied from one to forty-two days. Simplicity and ease of use are the primary advantages of this device. Outflow is through a coated graft into the pulmonary artery or the aorta. As a result, this device can be used in LVAD, RVAD, or BVAD configurations. The devices are more expensive than centrifugal pumps, but can be maintained with minimal personnel. The extracorporeal pump has a low incidence of hemolysis. However heparinization is essential since clots can form along the polyurethane valve surface, on the outflow cannula, or at the tip of the atrial cannula where it enters the left atrium.

The extracorporeal pump is associated with a 30 percent success rate if it is used in a postcardiotomy situation to wean from cardiopulmonary bypass after intraaortic balloon pump insertion. If the native heart does not recover, a long-term device can be used as a bridge to transplantation. A particularly useful niche for the device is for donor heart dysfunction following transplantation.

Figure 6

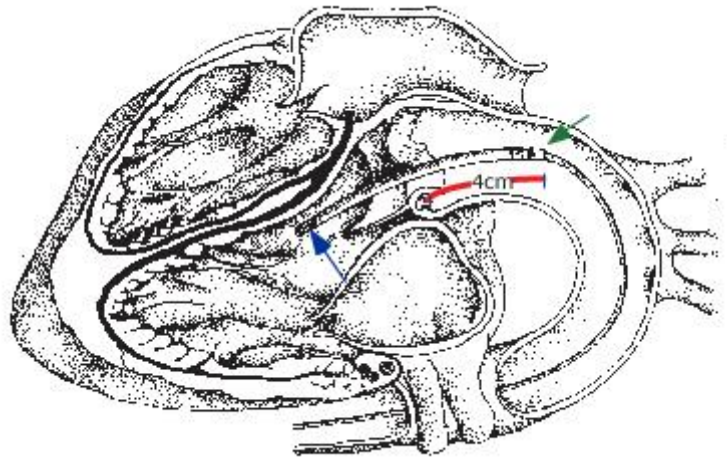
Abiomed 5000™ circulatory support system



Axial flow pumps — The axial flow pump works on the principle of an Archimedes screw. The inflow is placed retrograde across the aortic valve into the left ventricle; a pump revolving at high speeds draws blood out of the left ventricle and ejected into the ascending aorta beyond the end of the pump. Thus, there is active drainage, but with non-pulsatile flow and a low level of hemolysis (Figure 7).

Figure 7

Axial flow pump

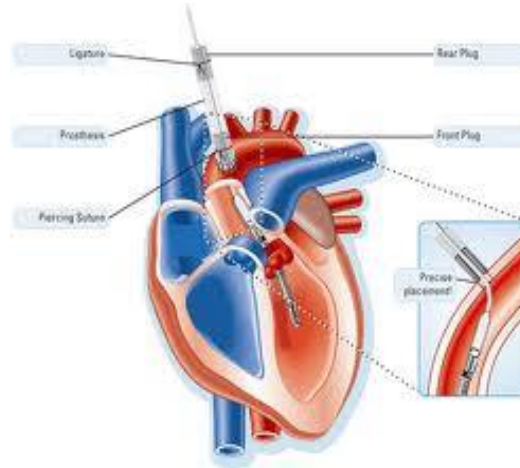


The Hemopump system has a centrifugal screw pump at the proximal portion of the soft 14F cannula (long arrow) that draws blood from the left ventricle and ejects it into the central aorta just beyond the pump (short arrow). Note the smaller 9F sheath and the coupling drive extending from the 14F cannula to the external drive, which is maintained outside the body. This arrangement produces much less vascular compromise than the cardiopulmonary support system, which requires a large catheter in both the femoral artery and femoral vein.

A device that uses this principle is the Impella microaxial flow device, which is a miniature impeller pump located within a catheter. Impella was designed for either surgical placement via a graft in the ascending aorta (Figure 8) or for percutaneous placement via the femoral artery^{21,22}.

Figure 8

Impella microaxial flow device: surgical placement

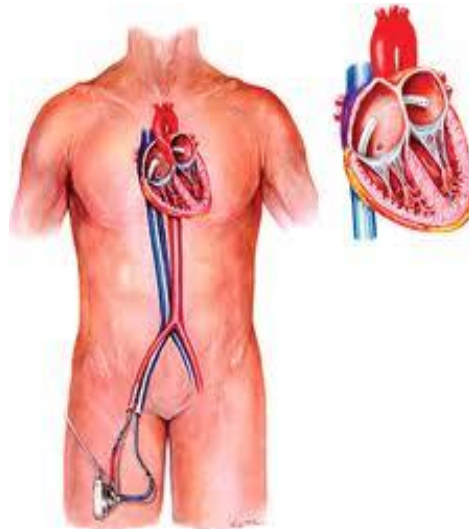


Percutaneous left atrial-to-femoral-arterial VAD — A percutaneous left atrial-to-femoral arterial VAD (Tandem Heart™), with a venous catheter inserted into the left atrium by trans-septal puncture and an arterial cannula inserted into the iliac artery for the return of blood, can be positioned within 30 minutes (Figure 9). The role of this device for short-term stabilization until recovery of jeopardized myocardium or as a bridge to definite surgical treatment was evaluated in 18 patients with cardiogenic shock due to a myocardial infarction²³. After a mean of four days of assistance, cardiac index improved from 1.7 to 2.4 L/min/m² and there was a significant increase in mean blood pressure and reduction in pulmonary artery, pulmonary capillary wedge, and central venous pressures. A subsequent randomized trial compared this device to an intraaortic balloon pump in 41 patients with cardiogenic shock after an acute myocardial infarction²⁴. Although hemodynamic and metabolic parameters were more effectively reversed

with the LVAD, complications such as severe bleeding and acute limb ischemia were more common and there was no difference in mortality.

Figure 9

Tandem Heart™



COMPLICATIONS:

A common and potentially fatal complication of the LVAD is infection. The rate of infection was examined in a retrospective review of 76 patients who underwent LVAD implantation as a bridge to cardiac transplantation ²⁵. LVAD-related infection was diagnosed in 38 patients (50 percent); 29 bloodstream infections (including 5 cases of endocarditis) and 17 local infections. Among the patients with infection, continuous antimicrobial treatment before, during, and after transplantation was associated with fewer relapses than was a limited course of antibiotics (2 of 23 compared to 7 of 12 with

a limited antibiotic course). Infection did not preclude successful transplantation. A second smaller study had similar results ²⁶.

Several factors may contribute to the susceptibility to infection. In addition to the presence of a foreign body, the LVAD may impair T cell function ²⁷.

Other complications include:

- 1) Mechanical irritation of the left ventricle produces ventricular arrhythmias in over 25 percent of patients.

- 2) Left ventricular thrombus and thromboembolic complications occur in 10 to 16 percent; risk factors for the development of thrombus include myocardial infarction before device implantation, left atrial cannulation, and post-implantation bleeding ²⁸.

- 3) Thrombocytopenia is seen in 7 percent.

- 4) Some degree of hemolysis occurs in most patients, but is generally not severe enough to be a significant problem.

3) EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO)

Extracorporeal membrane oxygenation (ECMO) removes carbon dioxide from and adds oxygen to venous blood via an artificial membrane lung (Figure 10). The pulmonary circulation is bypassed, and oxygenated blood returns to the patient via an arterial or venous route. With veno-venous bypass, ECMO is effective primarily as a therapeutic option for patients with severe respiratory failure. With veno-arterial bypass, an extracorporeal pump is employed to support systemic perfusion, thus providing a hemodynamic support option in patients with cardiac failure.

Figure 10

Extracorporeal membrane oxygenation



These devices can be used to provide continuous extracorporeal oxygenation and carbon dioxide removal for several weeks.

Indications for the ECMO are severe acute respiratory failure or cardiac failure. The use of ECMO for cardiac failure has been less extensively studied than ECMO for severe acute respiratory failure. Observational studies and case series have reported survival rates of 20 to 43 percent among patients who received veno-arterial (VA) ECMO for cardiac arrest, severe cardiogenic shock, or failure to wean from cardiopulmonary bypass following cardiac surgery ²⁹⁻³⁴. VA ECMO has also been used as a bridge to cardiac transplantation or placement of a ventricular assist device.

ECMO is a temporary life support for patients with potentially reversible severe acute respiratory failure or cardiac failure ³⁵. Examples of clinical situations that may prompt us to begin ECMO include the following:

- Hypoxemic respiratory failure with a ratio of arterial oxygen tension to fraction of inspired oxygen (PaO₂/FiO₂) of <100 mmHg despite optimization of the ventilator settings, including the tidal volume, positive end-expiratory pressure (PEEP), and inspiratory to expiratory (I:E) ratio
- Hypercapnic respiratory failure with an arterial pH less than 7.20
- Refractory cardiogenic shock
- Cardiac arrest
- Failure to wean from cardiopulmonary bypass after cardiac surgery
- As a bridge to either cardiac transplantation or placement of a ventricular assist device.

ECMO may not be initiated if anticoagulation is contraindicated (e.g.: bleeding, recent surgery, recent intracranial injury), if the cause of the respiratory or cardiac failure is

irreversible, or if the patient is not a potential candidate for an implantable ventricular assist device.

Bleeding is a frequent complication and can be life threatening. It is due to both the necessary continuous unfractionated heparin infusion and platelet dysfunction. The latter results from contact and sheer stress associated activation. Meticulous surgical technique, maintaining platelet counts greater than 100,000/mm³, and maintaining the target ACT appear to reduce the likelihood of bleeding. Thromboembolism due to thrombus formation within the extracorporeal circuit is an infrequent complication that can be devastating. Its impact is greater with VA ECMO than VV ECMO because infusion is into the systemic circulation. Heparin infusion that achieves its target ACT and vigilant observation of the circuit for signs of clot formation successfully prevents thromboembolism in most patients. A variety of complications can occur during cannulation, including vessel perforation with hemorrhage, arterial dissection, distal ischemia, and incorrect location (e.g.: venous cannula within the artery). A skilled and experienced surgeon is important to avoid or address such complications³⁶.

4) INTERMEDIATE AND LONG-TERM CARDIAC SUPPORT

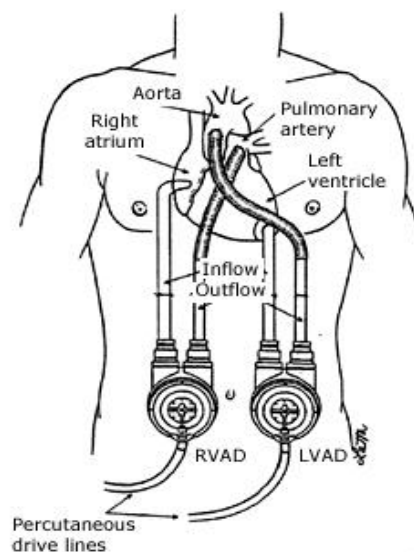
- Bridge to transplantation

Intermediate term devices can be thought of as the true "bridges" to transplantation³⁷. They are intended to be removed during transplantation and are not designed for chronic, permanent support.

The most widely used Food and Drug Administration (FDA) approved device is the Thoratec Paracorporeal Ventricular Assist Device (PVAD) which has supported patients for up to 3.3 years. It is a paracorporeal system, in which the pump is located outside the body. It is versatile, allowing for right ventricular assist device (RVAD), left ventricular assist device (LVAD), or biventricular assist device (BVAD) configuration (Figure 11). The atria are cannulated with outflow grafts sewn into the arteries; the left ventricular apex can also be cannulated allowing for better drainage.

Figure 11

The Thoratec ventricular assist system in the biventricular support configuration



RVAD: right ventricular assist device; LVAD: left ventricular assist device.

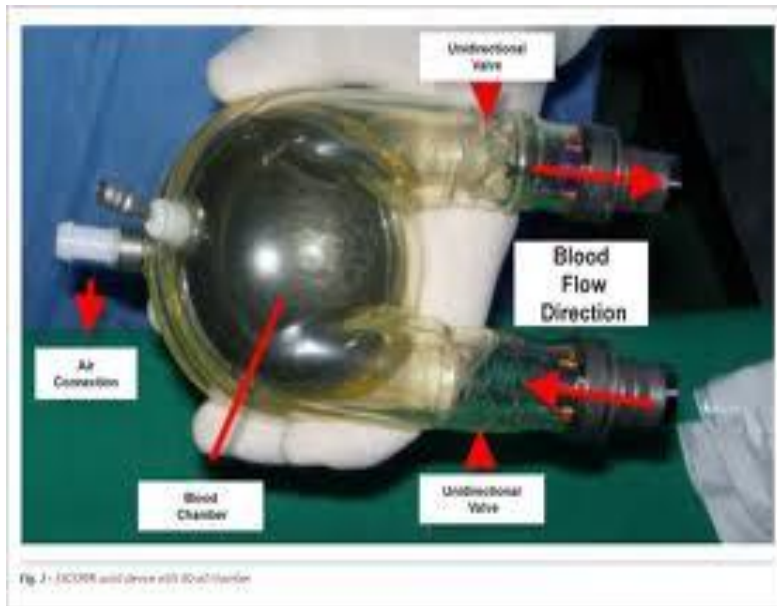
The device uses suction drainage with pulsatile flow. As a result, it can cause traumatic hemolysis and the need for blood transfusions. However, the pulsatile flow permits recovery of end organs and, with the new portable drive, the patients can be discharged home and are allowed some mobility. Heparinization is essential. The device can be used as a bridge to transplantation (with an approximately 60 percent success rate) or, on a more temporary basis, to buy time for recovery from viral myocarditis, postpartum myocarditis, or severe rejection in transplanted hearts ³⁸. Despite the advances in the design of the Paracorporeal Thoratec Ventricular Assist Device, there is a significant complication rate. In one study of 111 patients, significant bleeding occurred in 31 percent, device-related infections occurred in 18% and 8% had a device related thromboembolism ³⁹.

Abiomed AB 5000, already shown before, and Berlin Heart EXCOR (Figure 12) are other similar paracorporeal systems.

Figure 12

Berlin Heart EXCOR®





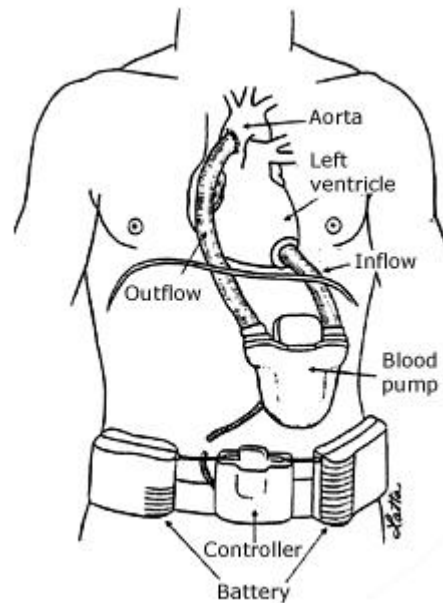
Long-term devices were designed in the United States as replacement therapy for patients with HF. Work on these devices started in the late 1960s and the designs that are now available were developed several decades ago. However, it has taken over 40 years of rigorous laboratory and clinical evaluation to bring these devices into clinical use.

The three major FDA approved devices are the WorldHeart Novacor and Thoratec HeartMate XVE and HeartMate II. Other devices similar to HeartMate II are Berlin-Heart INCOR and Jarvik 2000.

The Novacor VAD works with a magnetic actuator (Figure 13). The electromagnet activates a pusher plate designed to collapse a bladder which along with two bioprosthetic valves propels blood in one direction, from the left ventricular apex to the ascending aorta. As with other left ventricular assist devices, a competent native aortic valve is essential for its use.

Figure 13

The Novacor wearable left ventricular assist system

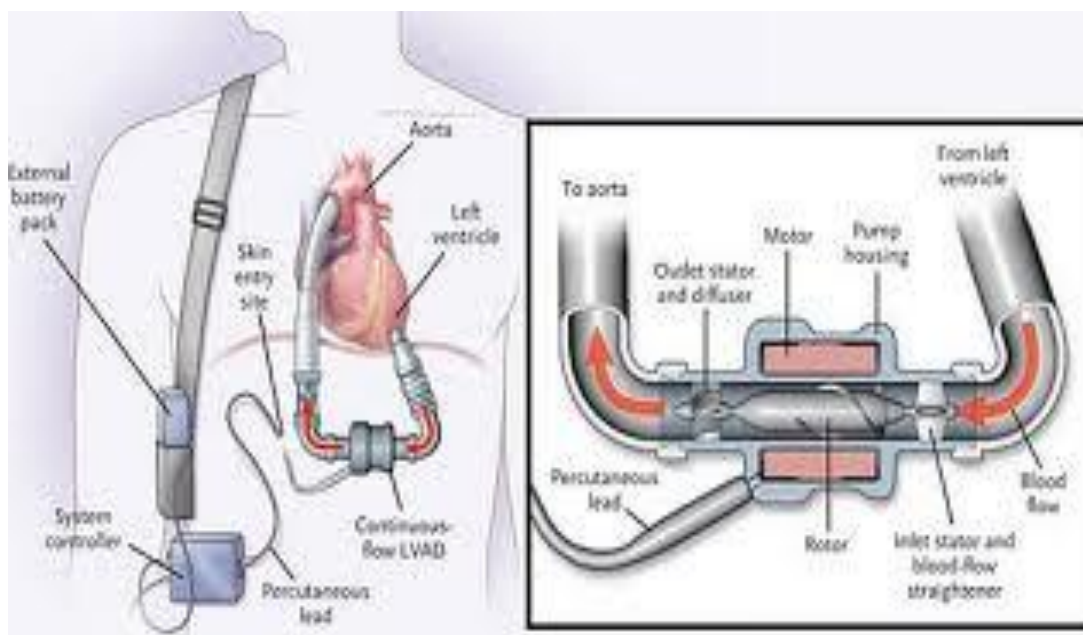


The Heartmate was the most used implantable pump in the USA during 2008. It is FDA approved for use both as a bridge to transplantation and as destination therapy. It is an intracorporeal device, it is available only in a LVAD configuration and is connected to the LV by an apical cannula which delivers inflow of blood from the LV with pulsatile ejection into the ascending aorta. The Heartmate LVAD (Figure 14) is unique in that it uses a counterintuitive approach to surface design in which the surface of the device is textured rather than smooth. This results in the formation of a protein coat which becomes non-thrombogenic over time. As a result, anticoagulation with warfarin is not required for this device and the thromboembolic rate is below 3 percent. Other benefits with the Heartmate include improvement in renal function and reduction in pulmonary

hypertension prior to transplantation^{40, 41}. These clinical benefits, together with the physical recovery that is possible in the ambulatory patient, reduce the perioperative risk to patients undergoing transplantation.

Figure 14

The Heartmate II LVAS pump



- Destination therapy

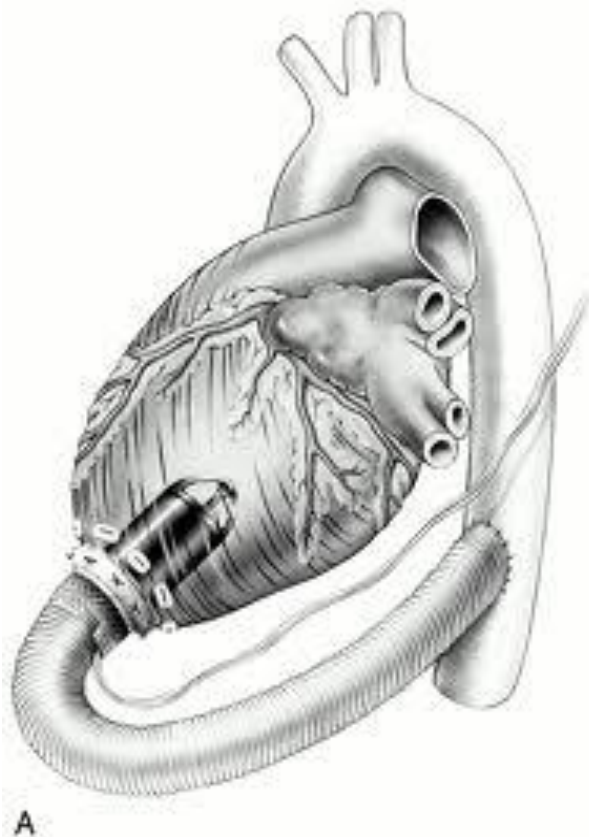
Axial-flow impeller pumps, with their potential for small size, low noise, and absence of a compliance chamber, have been developed for clinical use. They provide continuous rather than pulsatile flow and are totally implantable.

The HeartMate II was FDA approved as destination therapy in 2010.

The Jarvik 2000 pump is a compact intracardiac axial flow impeller pump that is silent, easily implantable and unobtrusive⁴² (Figure 15). The device is practically encapsulated by the native myocardium, reducing the risk of infection around the device. It has no inflow graft, no valves, and produces a high-flow stream of blood that continuously washes the tiny bearing; these factors reduce the risk of thrombus formation and hemolysis.

Figure 15

Jarvik 2000 pump



The reliability and ease of removal of this device suggest that it may be useful as a bridge to myocardial recovery or transplantation or for long-term support. A power cable is tunneled either to the right upper quadrant (for patients being bridged to transplant) or to the base of the skull (for destination therapy). The cable is attached to an external power source, a rechargeable lithium-ion battery that can be worn on the patient's waist.

The DeBakey pump was the first axial-flow impeller pump to be implanted clinically as a bridge to transplant ⁴³ (Figure 16).

Figure 16

The DeBakey LVAD



The DeBakey VAD Child (HeartAssist 5 Pediatric VAD) is FDA approved under the Humanitarian Device Exemption program as a bridge to transplantation in children

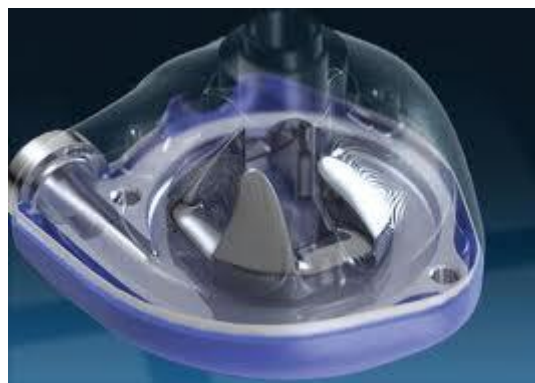
between 5 and 16 years old ⁴⁴. The HeartAssist 5 device is EC certified but is not FDA approved in adults.

Magnetically levitated centrifugal pumps are currently undergoing clinical trials for the treatment of heart failure. They have several advantages over the axial flow pumps: 1) they are energetically more efficient 2) they have lower tolerances so manufacturing is easier and they are less prone to thrombosis 3) they are potential very durable (>10 year life-span). The three main devices in this category are the Ventracor VentrAssist LVAD, the Heartware LVAD and RVAD and the Terumo Duraheart.

The Ventracor VentrAssist LVAD is a cardiac assist system primarily designed as a permanent alternative to heart transplants for patients suffering heart failure (Figure 17). It is a blood pump that connects to the left ventricle of the diseased heart to help the ailing heart's pumping function. It can also be used as a bridge to heart transplant and possibly as a bridge to recovery, where it may allow a deteriorating heart an opportunity to recuperate. The Ventracor VentrAssist LVAD has only one moving part, a hydrodynamically suspended impeller. It weighs just 298 grams and measures 60mm in diameter.

Figure 17

Ventracor VentrAssist LVAD



The Heartware device is very small and fits in the pericardial space. It is approved in Europe and it is undergoing a clinical trial as a bridge to transplantation in the US (Figure 18).

Figure 18

The Heartware left ventricular assist system



The Terumo Duraheart most important and peculiar characteristics are: a closed straight blade impeller which helps minimize turbulence by promoting gentle and consistent flow patterns, a wide stable spacing between the impeller and chamber wall which helps minimize pump-induced hemolysis by providing ample room for smooth unimpeded flow and a proper washout (Figure 19). Consistent primary and secondary flow patterns are designed to improve washout and reduce the potential for stasis and, ultimately, pump thrombus. His sensitivity to patient heart rate, preload and afterload provides

immediate physiologic-responsive flow and low shut-off pressure minimizes the risk of ventricular suction.

Figure 19

The Terumo Duraheart left ventricular assist device



A new but still experimental miniaturized ventricular assist device is the Synergy Pocket Micropump produced by the CircuLite company (Figures 20-21). It has been described as “the world’s smallest heart pump” to provide partial circulatory support. Similar in size to an AA battery, the Synergy pumps up to three liters of blood per minute; in comparison, full support VADs provide 5-6 liters/min. The Synergy contains a proprietary rotor, which is magnetically and hydrodynamically stabilized and levitated. This allows the motor to be sealed, eliminating blood contact in the motor and reducing the potential for thrombus formation. In addition, the pump features a washout channel that ensures that blood flow does not stagnate within the device, further

minimizing the risk of thrombosis. The Synergy is powered by a rechargeable dual battery pack, worn externally. The whole system weighs around three pounds, which not only makes it the smallest, but also the lightest, device of its kind in the world. The Synergy system is designed to be implanted subcutaneously via a mini-thoracotomy. Here, the inflow cannula is surgically placed into the left atrium. The outflow graft is then attached to the subclavian artery using surgical anastomosis and the pump is placed in the pacemaker “pocket”. The whole procedure, performed off-pump, takes around 90 minutes. Patients who have been implanted with the device so far have shown “rapid” recovery: according to the company, the length of stay at the ICU is around three days with the patients being discharged after 14 days or so ⁴⁵.

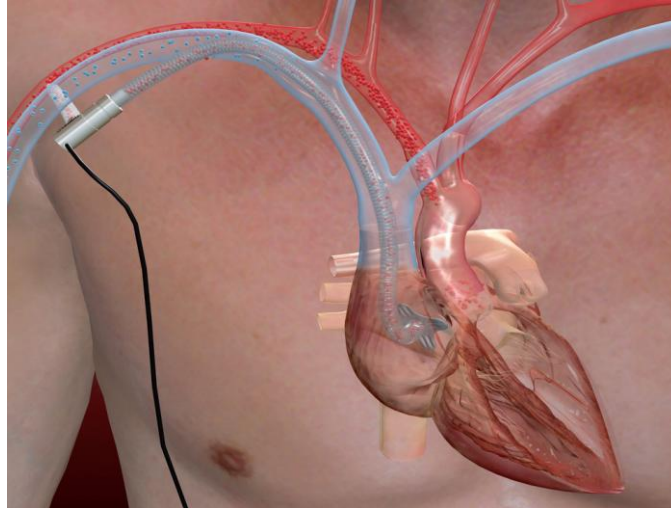
Figure 20

CircuLite Synergy Pocket Micropump



Figure 21

CircuLite Synergy Pocket Micropump



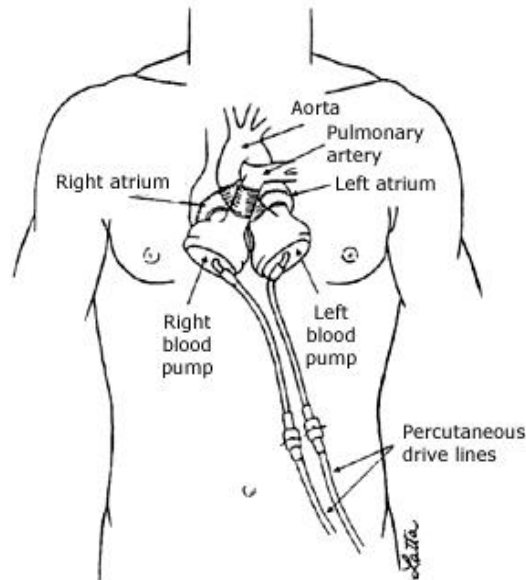
THE TOTAL ARTIFICIAL HEART

A total artificial heart (TAH) is a device that is inserted orthotopically, in the location of the native heart; this procedure is accompanied by removal of the patient's own ventricles. Several experimental TAH devices have been developed, but use has never been widespread, primarily because of complications including thromboembolism, infection and bleeding.

The CardioWest device is a pneumatic TAH that has been used as bridge to transplantation and as destination therapy (Figure 22).

Figure 22

The CardioWest total artificial heart



In one study, 81 patients with severe HF underwent implantation of this device; they were compared to 35 matched retrospective controls⁴⁶. Patients supported with the CardioWest TAH, compared to controls, had a significantly higher rate of survival to transplantation (79 versus 46 percent) and of overall survival at one year (70 versus 31 percent). Complications were frequent in the device group, including bleeding, infection, renal dysfunction, respiratory dysfunction, hepatic dysfunction, and neurologic events. However, these complications were determined to have influenced outcome in only a minority of patients.

There are several factors that limit the ability of currently available mechanical circulatory support devices to serve as permanent heart replacement (destination) therapy. These include mechanical deterioration of the device, the requirement for external drive lines and air vents, with the associated risk of infection and the limited life of currently available batteries⁴⁷⁻⁴⁹.

The device that has the greatest potential of being completely implantable is the Abiomed TAH (Figure 23). Its use involves total excision of the patient's heart and provides both right and left ventricular pump function. Instead of using air or mechanical energy to drive the pumping mechanism, it uses a low viscosity oil which is shunted via a rotary pump between the right and left ventricles. Because of this decompression shunt, a compliance chamber is not required and the device is placed in its entirety within the mediastinum. An electrical wire is implanted around the abdomen and acts as a conduction cable through which the battery energy can be provided transcutaneously.

The Abiomed TAH is currently undergoing clinical trials which will determine whether the device can enhance the survival of patients with severe heart failure. The cost of these devices is likely to be quite high, but may not be very different from the cost of heart transplantation, which involves both the initial cost of the surgery and that of chronic maintenance therapy and immunosuppression.

Figure 23

The Abiomed total artificial heart



GENDER DIFFERENCES IN HEART FAILURE

There is only little literature about gender differences in mechanical assist devices implantation but we know very well different gender characteristics in heart failure (HF).

A review of HF survival trials conducted over the last 30 years using various sources, however, clearly demonstrates the inadequate representation of women⁵⁰⁻⁷⁶. In the “real world” more than half of all HF patients are women, compared with half of that number in clinical trials (23%)⁷⁶. Before accepting the premise that HF therapies proven beneficial in men exert similar beneficial effects in women, we should closely examine the similarities and differences between men and women with HF.

The incidence of HF increases with age in both men and women and is higher in men at all ages^{77, 78}. The prevalence of HF also increases with age and is higher in men than in women until the age of 80 years and above when women have a slightly higher prevalence with just over 12% of women and just under 12% of men having a diagnosis of HF^{77, 78}.

At all ages, women with HF have a higher prevalence of preserved systolic function in both outpatient and hospitalized cohorts^{79, 80}. Age-adjusted studies demonstrate that women with HF have a better prognosis than their male counterparts⁷⁶.

A number of explanations for differences in systolic function and mortality have been suggested. These include intrinsic sex-related differences in cell function⁸¹ as well as differences in sex hormones⁸²⁻⁸⁴, risk factors and etiology of HF⁸⁵.

Risk factors for HF are similar in men and women but women have a higher prevalence of hypertension and diabetes and a lower prevalence of ischemia as an etiology for HF

⁸⁵. Differences in risk factors combined with sex differences in remodelling, already described, probably account for at least some of the higher prevalence of preserved systolic function in women.

It should be mentioned that significant sex-related differences in clinical and laboratory characteristics have been described ^{2, 86-93}. Women tend to have worse New York Heart Association (NYHA) functional class, a larger cardiothoracic ratio and a lower serum norepinephrine. They have a higher rate of systolic blood pressure and left ventricular ejection fraction (LVEF), a higher prevalence of left bundle branch block and a lower prevalence of atrial fibrillation. These differences would be expected to have an impact on outcome.

The Coronary Artery Surgery Study (CASS) demonstrated that female subjects were more symptomatic and used more diuretics, despite similar left ventricular end-diastolic pressure, higher LVEF and less three-vessel coronary disease ⁹⁴. Furthermore, several studies have shown women to have more advanced NYHA class. The reasons underlying the increased symptoms of women are unknown.

VADs can be used, as we have already told, to support either the left or right ventricles or both and may be used either as “bridge to transplantation” or as “destination therapy” ⁹⁵. Although women have been underrepresented in studies of VADs, presumably primarily due to smaller body size, sex does not appear to be a predictor of operative risk ¹³. Many women, however, are unable to have a VAD implanted because of small body size. A new and smaller type of VAD is likely to be useful in women who would have previously been ineligible because of small body size ¹³.

Cardiac transplantation can be successfully performed in women with survival rates equivalent to those in men ⁹⁶.

As heart transplantation recipient, women need a donor within 30% of their weight. A larger donor is indicated for the recipient with high pulmonary vascular resistance. Female recipients of cardiac transplantation have been reported to have an increased mortality when compared with male recipients ⁹⁷.

Various immunologically related conditions, such as systemic lupus erythematosus and rheumatoid arthritis, are found in increased prevalence among women. Further, there is experimental evidence to suggest that fundamental immune responses, such as antibody production and rejection of allogenic grafts, are potentiated in females. Thus, it is not surprising that studies have shown that female cardiac allograft recipients have a higher risk of cardiac rejection and the subsequent need for increased immunosuppression ⁹⁸. How this affects survival in female patients remains to be seen.

An increased risk of sensitization may be seen in multiparous females, especially when associated with placement of a LVAD. Patients who are highly sensitized can be pretreated with intravenous immunoglobulin (IVIg) in preparation for heart transplantation ⁹⁹.

The type of VAD a woman receives is based on size of patient, degree of heart failure and whether or not she is a transplant candidate.

Small body size is associated with increased operative mortality ¹⁰⁰.

Right ventricular dysfunction after LVAD insertion does not appear to be related to gender ¹⁰¹.

In the future, women may receive more devices as destination therapy is more frequently applied in older patients and as devices are designed for use in smaller patients.

AIM OF THE STUDY

The aim of our study was to review the large and long experience of Deutsches Herzzentrum Berlin (DHZB) in mechanical assist device therapy, specifically concerning the differences between men and women.

We have excluded all the patients under the age of 16 year old to have a homogenous adult population, which is basically different from a paediatric population.

We have decided to concentrate in left ventricular assist device (LVAD) and biventricular assist device (BVAD) support, not considering right ventricular assist device (RVAD) alone, total artificial heart and short-term devices, to have a more homogenous and reliable analysis.

We wanted to see the different characteristics between men and women before and after VADs implantation and we asked to ourselves why patients treated with VADs are in the great majority men.

We aimed to discover which kind of VAD gives the best results in each type of patient and which is more used for each sex.

Finally with our study we wanted to examine the differences in survival between men and women, concerning only VAD support, VAD followed by heart transplantation and VAD followed by weaning from the device for myocardial recovery.

METHODS AND STATISTICAL ANALYSIS

We collected data from the database of Deutsches Herzzentrum Berlin (DHZB), which contains the demographic, preoperative, postoperative and long-term follow-up data of patients who have received mechanical circulatory support devices between July 1987 and May 2009. We analyzed data only of the patients implanted with long-term mechanical circulatory support (MCS) with a left ventricular or a biventricular assist configuration. We excluded patients implanted with short-term devices, total artificial heart devices and isolated right ventricular assist devices. We analyzed differences between men and women.

We made a general survival analysis for the two sexes and then we measured the ventricular assist device (VAD) support time and the survival during support to the moment of VAD explantation. Later we considered patients who were successfully bridged to heart transplantation (HTx) (n = 260) and we analyzed gender differences in length of assistance and survival before and after HTx and the differences between bridging with LVAD and with BVAD. Finally we examined patients whose device could be explanted after recovery of the myocardial function (n= 55) and we analyzed gender differences in length of assistance and survival during support time and after VAD explantation and, also in this subgroup, we checked the differences between bridging with LVAD and with BVAD.

Demographic characteristics of the population and cardiopathy etiologies are shown in Tables 1 and 2.

Types and number of VAD used at the DHZB are shown in Tables 3 and 4.

VAD explantation indications are shown in Table 5.

STATISTICAL ANALYSIS

Qualitative data are presented as percentages and quantitative data as mean \pm SD or median (25% - 75% interquartile range, [IQR]). Differences in proportions were tested with the χ^2 test or Fisher's exact test, and continuous variables were compared with the Student t test or the Wilcoxon test. The survival function was obtained from the Nelson-Aalen estimator of the cumulative hazard rate. The Cox regression model was performed to obtain hazard risk with 95% confidence intervals. The adequacy of the proportional hazards assumption was checked using first the graphical representation of the logarithm cumulative hazard rates versus time to assess the parallelism and the constant separation among the different values of nominal variables. Second, an artificially time-dependent covariate was added to the univariate model to test the proportionality assumption. For all variables in the final models, the proportional hazards assumptions were not rejected as local tests linked to the time-dependent covariates were not significant and scatter plots were roughly constant over time. Time to death curves and time to event were compared using the log-rank test. The results were considered significant with p-values ≤ 0.05 . The data were analyzed using the statistical package program SAS v9.2 (SAS Institute Inc., Cary, NC).

RESULTS:

Between July 1987 and May 2009 in Deutsches Herzzentrum Berlin (DHZB), a total of 889 patients were implanted with 889 long-term ventricular assist device (VAD): 492 left ventricular assist devices (55.3%) (441 men and 51 women) and 397 biventricular assist devices (44.7%) (313 men and 84 women). We excluded short term devices, as Biomedicus centrifugal pump, Levitronix Centrimag centrifugal pump and extracorporeal membrane oxygenation (ECMO), because of their very high perioperative mortality and their characteristic of emergency implantation. We excluded also total artificial heart and right ventricular assist devices (RVAD) to have a more homogenous population.

The development of the VAD program at the DHZB along the course of the years is illustrated in Figure 24 and the increasing number of LVADs implanted in the last years is shown in Figure 25.

Figure 24

Number of VADs implanted at the DHZB by year

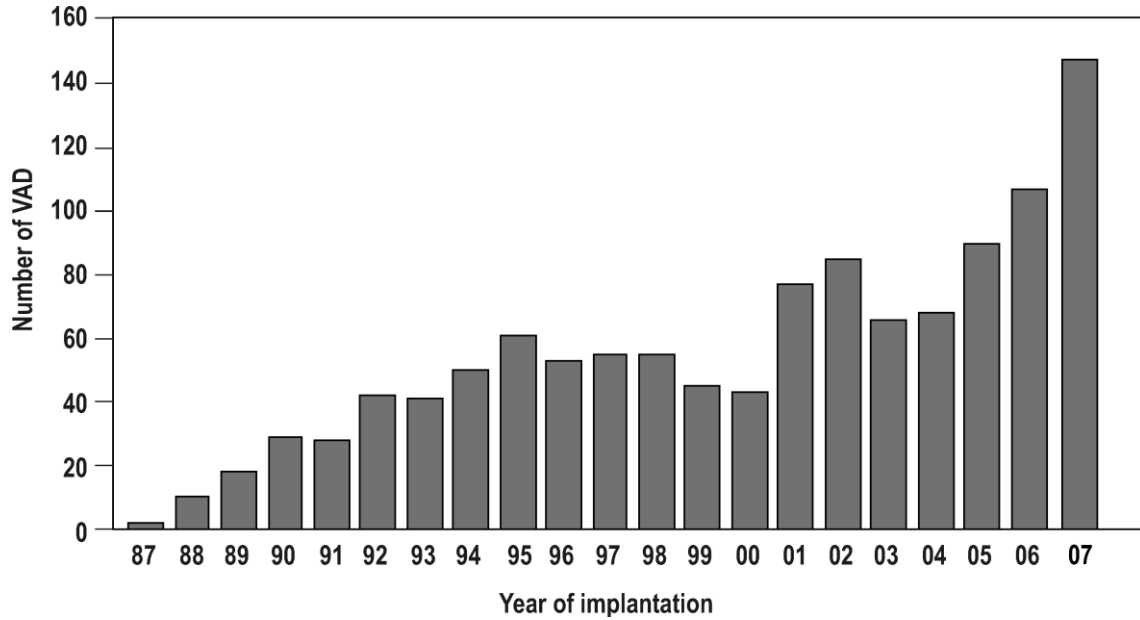
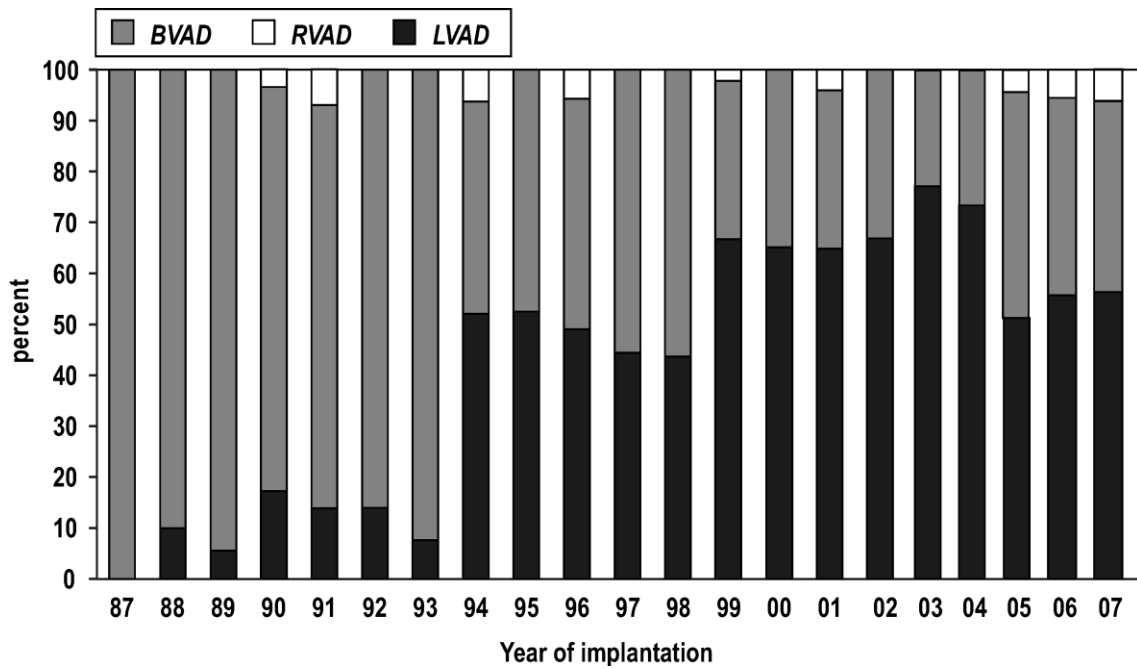


Figure 25

Increasing number of left ventricular assist devices implanted over the years



The mean age of the patients was 49.2 years (range 17 to 76 years) (mean age men 50.0 years \pm 12.4; mean age women 44.8 years \pm 13.7), 84.8% were male. The cardiopathy etiologies were: dilated cardiomyopathy in 448 patients (51.2%) of which 389 were male (86.8%), ischemic cardiomyopathy in 315 patients (36%) of which 283 were male (89.8%), myocarditis in 35 patients (4%) of which 18 were male (51.4%), valvular disease in 30 patients (3.4%) of which 20 were male (66.6%), restrictive cardiomyopathy in 14 patients (1.6%) of which 5 were male (35.7%), post-cardiotomy in 10 patients (1.1%) of which 8 were male (80%), congenital disease in 4 male patients (0.4%), post-transplant acute allograft failure in 3 patients (0.3%) of which 2 were male (66.6%) and other etiologies in 18 patients (2%) of which 15 were male (83.3%). The etiology was unknown in 12 patients. The distribution of the various etiologies between men and women was significantly different ($p < 0.0001$).

The different types of device used were: Berlin Heart Excor in 518 patients (58.3%) of which 417 were male (80.5%), Berlin Heart Incor in 149 patients (16.8%) of which 133 were male (89.3%), Novacor in 110 patients (12.4%) of which 103 were male (93.6%), Micromed DeBakey in 41 patients (4.6%) of which 36 were male (87.8%), Thoratec Heart Mate II in 25 patients (2.8%) of which 20 were male (80%), Heartmate I in 23 patients (2.6%) of which 22 were male (95.6%), Terumo DuraHeart in 10 patients (1.1%) all male, Lion Heart in 6 patients (0.7%) all male, Jarvik 2000 in 5 patients (0.5%) all male and VentrAssist in 2 patients (0.2%) both male. Only 34 women (25%) were treated with total implantable devices and 26 (19.25%) with second generation non-pulsatile devices. On the contrary 337 men (44.69%) were treated with total implantable devices and 212 (28.19%) with second generation non-pulsatile devices.

The distribution between men and women among the various devices was significantly different ($p < 0.0001$).

The reasons for device removal were: death in 554 patients (62.3%) of which 470 were male (84.8%), heart transplantation (HTx) in 246 patients (27.7%) of which 206 were male (83.7%), recovery of myocardial function in 55 patients (6.2%) of which 45 were male (81.8%), VAD-related technical problem in 24 patients (2.7%) of which 23 were male (95.8%), pump thrombosis in 5 patients (0.6%) all male, VAD-type switch in 4 patients (0.4%) all male and VAD infection in 1 male patient (0.1%). The distribution between men and women among the reasons for device removal was not different ($p = 0.49$).

Tables 1 and 2 show demographic characteristics of the population and cardiopathy etiologies.

Tables 3 and 4 show the different types of VAD implanted.

Table 5 shows the indications to VAD explantation.

Table 1

Assist Configuration	Total N (%)	Male N (%)	Female N (%)	Age (Mean \pm SD)
BVAD	397 (45%)	313 (42%)	84 (11%)	45,4 \pm 12,4
LVAD	492 (55%)	441 (58%)	51 (7%)	52,2 \pm 12,2
Total	889	754	135	49,2 \pm 12,8

Table 2

Etiology (p < 0.0001)	Patients	Male	Female
Idiopathic Cardiomyopathy	448 (50,4%)	389 (51,6%)	59 (7,8%)
Ischemic Cardiomyopathy	315 (35,4%)	283 (37,5%)	32 (4,2%)
Miocarditis	35 (3,9%)	18 (2,4%)	17 (2,3%)
Valvular Disease	30 (3,4%)	20 (2,7%)	10 (1,3%)
Restrictive Cardiomyopathy	14 (1,6%)	5 (0,7%)	9 (1,2%)
Post-cardiotomy	10 (1,1%)	8 (1,1%)	2 (0,3%)
Congenital Heart Disease	4 (0,4%)	4 (0,5%)	0
Acute HTx Failure	3 (0,3%)	1 (0,1%)	2 (0,3%)
Other	30 (3,4%)	26 (3,4%)	4 (0,5%)
Total	889 (100%)	754 (84,8%)	135 (15,2%)

Table 3

Assist Model	Number	Configuration	Type of Flow	Placement
Berlin Heart	518	LVAD/BVAD	Pulsatile	Extracorporeal
Incor	149	LVAD	Axial	Implantable
Novacor LVAS	110	LVAD	Pulsatile	Implantable
MicroMedDeBakey	41	LVAD	Axial	Implantable
HeartMate II	25	LVAD	Axial	Implantable
TCI (HeartMate I)	23	LVAD/BVAD	Pulsatile	Implantable
DuraHeart	10	LVAD	Centrifugal	Implantable
LionHeart	6	LVAD	Axial	Implantable
Jarvik2000	5	LVAD	Axial	Implantable
Ventrassist	2	LVAD	Centrifugal	Implantable
Total	889			

Table 4

Device (p < 0.0001)	Patients	Male	Female
Berlin Heart -Excor	518 (58,3%)	417 (55,3%)	101 (13,4%)
Berlin Heart-Incor	149 (16,8%)	133 (17,6%)	16 (2,1%)
Novacor	110 (12,4%)	103 (13,7%)	7 (0,9%)
MicroMed De Bakey	41 (4,6%)	36 (4,8%)	5 (0,7%)
HeartMate II	25 (2,8%)	20 (2,7%)	5 (0,7%)
HeartMate I (TCI)	23 (2,6%)	22 (2,9%)	1 (0,1%)
DuraHeart	10 (1,1%)	10 (1,3%)	0
LionHeart	6 (0,7%)	6 (0,8%)	0
Jarvik2000	5 (0,6%)	5 (0,7%)	0
VentrAssist	2 (0,2%)	2 (0,3%)	0
Total	889 (100%)	754 (84,8%)	135 (15,2%)

Table 5

Indication to Explant (p = 0.49)	Patients	Male	Female
Death	554 (62,3%)	470 (62,3%)	84 (11,1%)
Heart Transplantation	246 (27,7%)	206 (27,3%)	40 (5,3%)
Recovery	41 (4,6%)	32 (4,2%)	9 (1,2%)
VAD-related problems	24 (2,7%)	23 (3,1%)	1 (0,1%)
Failed Recovery	14 (1,6%)	13 (1,7%)	1 (0,1%)
Thrombosis	5 (0,6%)	5 (0,7%)	0
VAD-replacement	4 (0,4%)	4 (0,5%)	0
Infection	1 (0,1%)	1 (0,1%)	0
Total	889 (100%)	754 (84,8%)	135 (15,2%)

VAD SUPPORT TIME

Mean time of ventricular assist device was 4.48 (\pm 0.24) months. Support was significantly longer (p 0.01) in men (4.7 months \pm 0.2) than in women (3.0 months \pm 0.5) and significantly longer ($p < 0.0001$) in LVAD (6.01 \pm 0.39) than in BVAD (2.59 \pm 0.22). In both the subgroups of men and women, mean support time was longer with left than with biventricular assist device ($p < 0.0001$): in men LVAD 6.22 months \pm 0.41 vs. BVAD 2.64 months \pm 0.26, in women LVAD 4.2 months \pm 1.25 vs. BVAD 2.38 months \pm 0.38.

GENERAL SURVIVAL

Survival analysis showed that in patients needing mechanical circulatory support, independently if they were transplanted or they had recovered, the 30 days survival was 88% and the p50 was 2.6 months. Left ventricular assist devices (p50 3.99 months) permitted better survival than biventricular assist devices (p50 1.28 months) ($p < 0.0001$) (Figure 26) and there was a trend (p 0.73) of worst survival in women (p50 1.38 months) than in men (p50 2.56 months), overall in the first month after implant (Figure 27).

Figure 26

VAD Differences in Survival: p50 (= median survival) BVAD 1.28 months, p50 LVAD 3.99 months, $p < 0.0001$

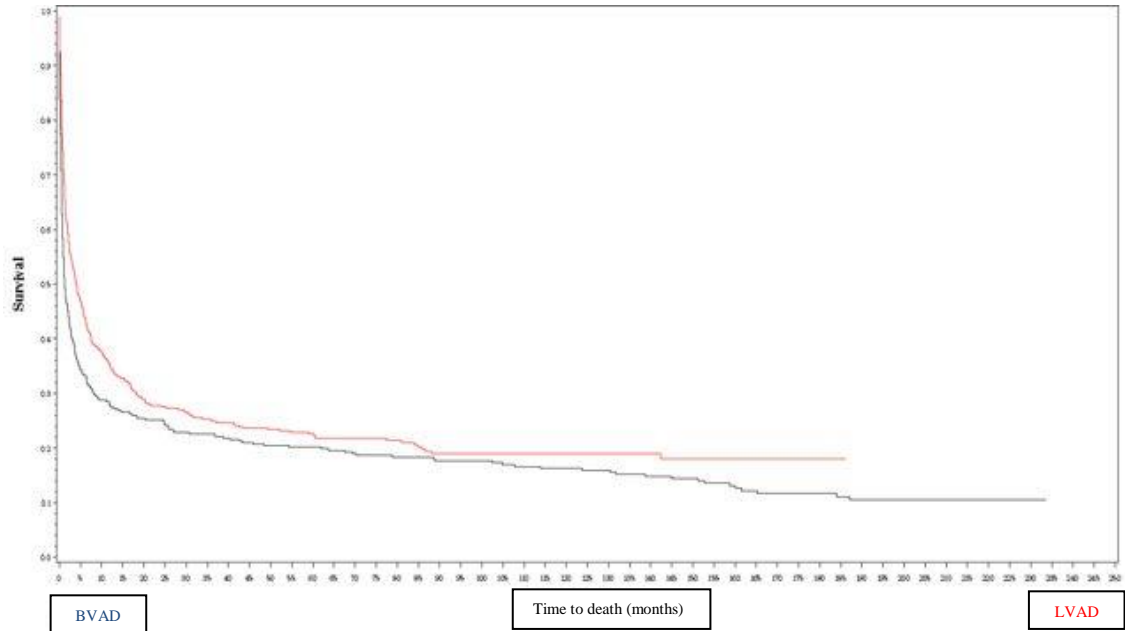
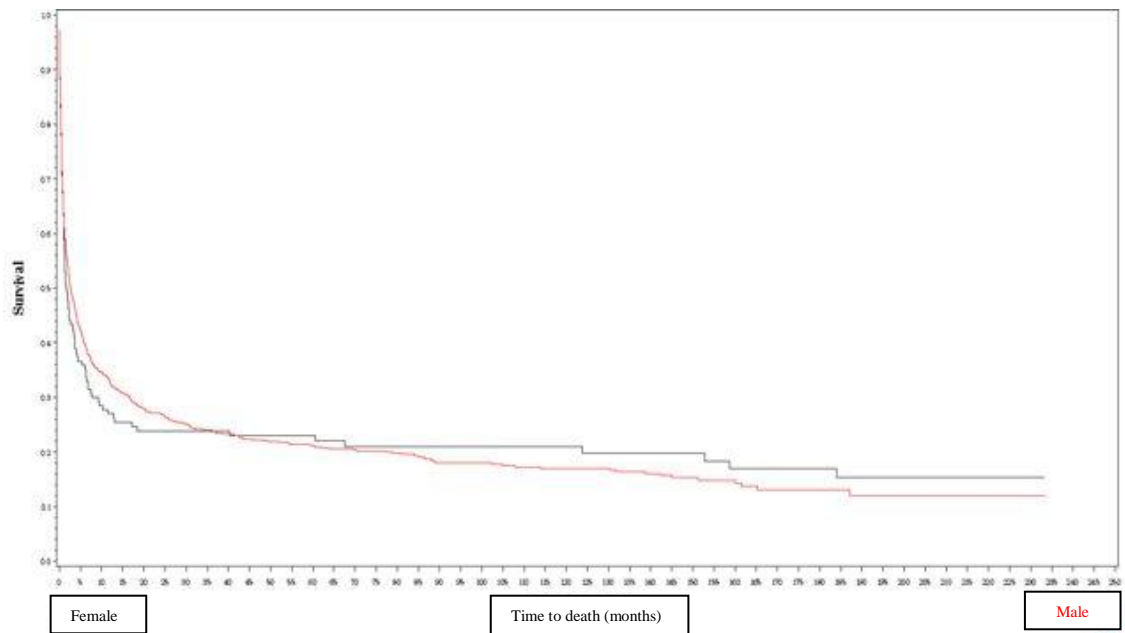


Figure 27

Gender Differences in Survival: p50 (= median survival) female 1.38 months, p50 men 2.56 months, $p = 0.73$



SURVIVAL IN VAD

While patients were on mechanical circulatory support the 30 days survival was 88% and the p50 was 2.6 months. Left ventricular assist devices (p50 4.39 months) gave better survival than biventricular assist devices (p50 1.28 months) ($p < 0.0001$) (Figure 28) and men (p50 2.92 months) had better survival than women (p50 1.83 months) ($p = 0.05$) (Figure 29). In LVAD men (p50 5.18 months) had a significantly better survival than women (p50 1.83 months) ($p < 0.0001$) whereas in BVAD the gender survival was not different (p50 men 1.08 months vs. p50 women 1.84 months) ($p = 0.9$) (Figure 30).

Figure 28

VAD Differences in Survival during support: p50 (= median survival) BVAD 1.28 months, p50 LVAD 4.39 months, $p < 0.0001$

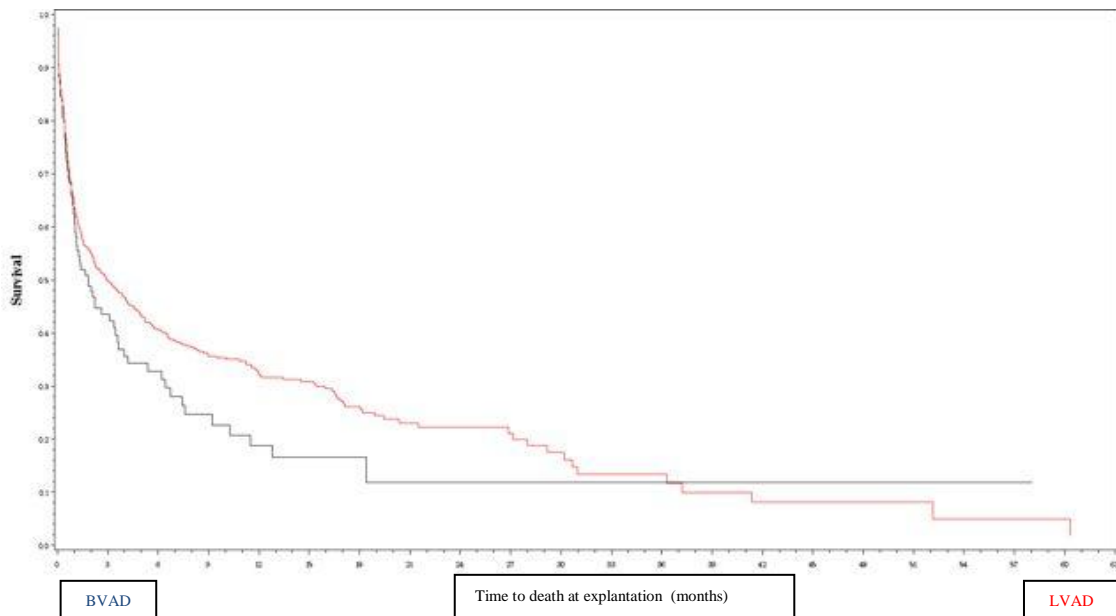


Figure 29

Gender Differences in Survival during VAD support: p50 (= median survival) female 1.83 months, p50 male 2.92 months, p = 0.05

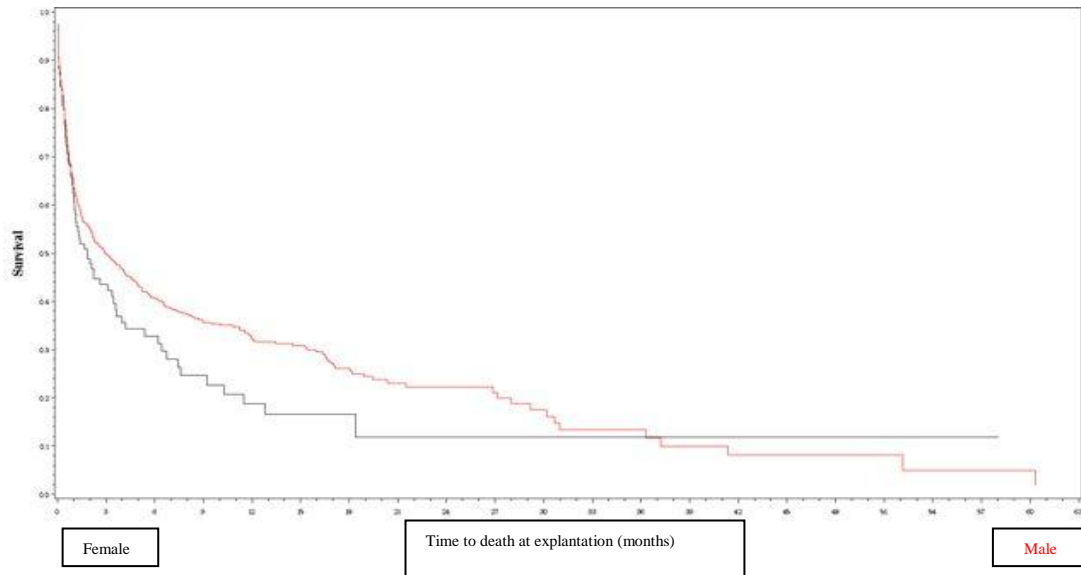
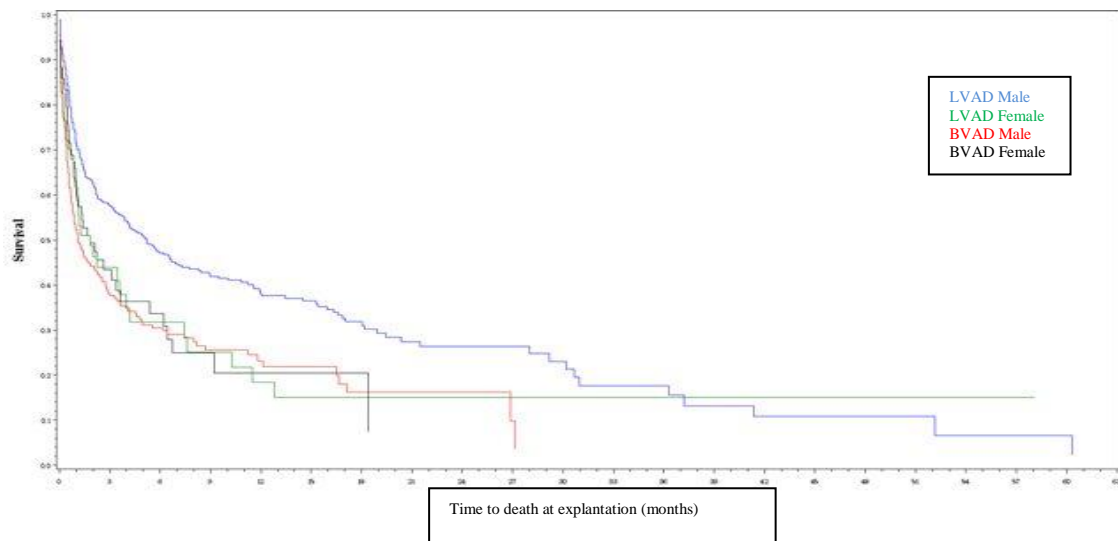


Figure 30

Gender Differences in Survival during LVAD and BVAD support: in LVAD p50 (= median survival) female 1.83 months, p50 male 5.18 months, p < 0.0001 whereas in BVAD p50 female 1.84 months, p50 male 1.08 months, p = 0.9



RECOVERY GROUP

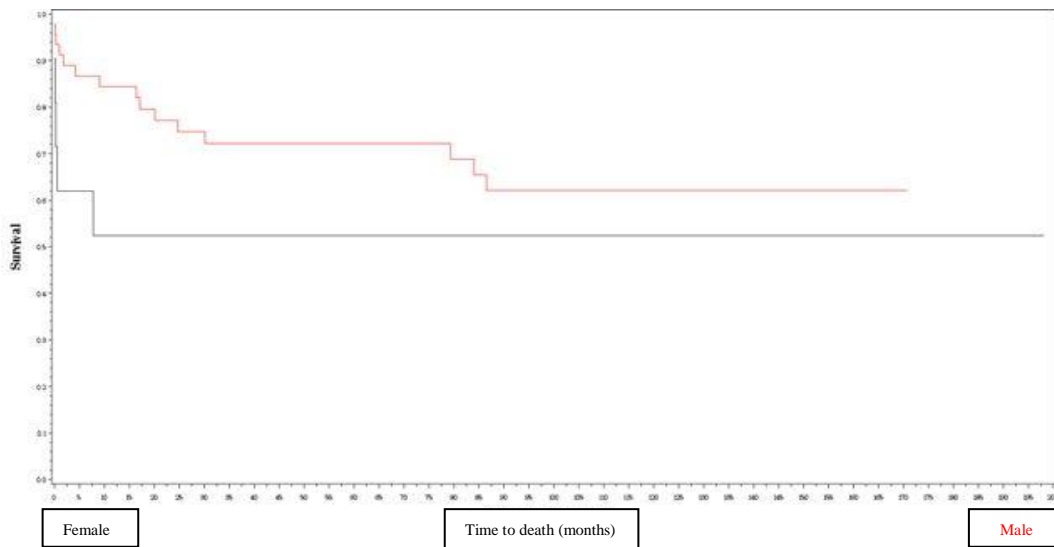
In 55 patients (45 male) the device could be explanted after myocardial recovery. In this subgroup survival p50 was 76.78 months. For these patients survival in women was near to significantly (p 0.08) worse than in men (p50 women 9.33 months vs. p50 men 77.42 months) (Figure 31). Total survival in patients who had a BVAD as bridge to recovery (n=7) was not different (p 0.28) than in patients (n=48) who had a LVAD (p50 BVAD 48.46 months vs. p50 LVAD 53.39 months).

The length of assistance with VAD before recovery was significantly different in men (mean 5.0 months, median 3.3 months, interval 0.9-26.1 months) and in women (mean 1.3 months, median 1.1 months, interval 0-3.4 months) (p<0.0001).

The post-recovery 30 days survival, after VAD explantation, was 85% and the p50 was 86.6 months. This survival was not significantly different in men (p50 86.61 months) and in women (p50 79.76 months) (p 0.07).

Figure 31

Gender Differences in Survival in Recovery Group: p50 (= median survival) female 9.33 months, p50 male 77.42 months, p = 0.08



TRANSPLANTATION GROUP

A total of 260 patients were successfully bridged to heart transplantation (219 male). In this subgroup survival p50 was 107.75 months. In these patients there were no gender differences in survival (p50 men 102.53 months vs. p50 women 158.72 months; p 0.9).

Total survival in patients who had a LVAD as bridge to transplant (n=142) was significantly better (p<0.0001) than in patients (n=8) who had a BVAD (p50 LVAD 142.32 months vs. p50 BVAD 67.59 months).

The length of assistance with VAD before heart transplantation was significantly different in men (mean 9.2 months, median 6.0 months, interval 0-86.0 months) and in women (mean 4.6 months, median 2.2 months, interval 0.1-19.8 months) (p<0.0001).

The post-transplantation 30 days survival, after heart transplant surgery, was 79% and the p50 was 104.91 months. This survival was similar in men (p50 88.33 months) and in women (p50 152.58 months) (p 0.9).

DISCUSSION

In our study one of the most relevant find we had is that women are undertreated with ventricular assist device therapy in comparison to men, that they are implanted more often with older devices, most of all paracorporeal devices, and that their survival with mechanical circulatory support is lower.

Treatment of heart failure has undergone revolutionary changes in the past 30 years. Sex related differences in clinical, laboratory characteristics and prognosis are well documented, but less is known about gender differences in therapies. In fact most information regarding therapies has been obtained from studies conducted primary in men. In the real world more than half of all the heart failure patients are women but the vast majority of trials has been done predominantly in men (77%)¹⁰². Current guidelines do not recommend differences in therapy for heart failure by sex^{49, 103}, however not all therapies have been adequately demonstrated to be as beneficial in women as in men⁷⁸. Even less it's known about gender differences in ventricular assist devices. In our experience women were treated less frequently with ventricular assist devices than men, in fact in a total of 889 patients only 15.2% were women and their time on support was significantly shorter (men 4.7 months vs. women 3.0 months). Also in INTERMACS registry, in a total of 1420 implants between 2006 and 2009, only 22% were women¹⁴. In Jeffrey et al. article too only 19.1% of 119 patients, bridged to heart transplantation with ventricular assist device, were female but there was no difference in the mean support time (51.5 days in men vs. 46 days in women)¹⁰⁴.

DEVICE SELECTION

In the past 22 years a number of different VADs were used in DHZB (Fig. 8). Recently, almost two thirds of implantations were LVADs (Fig. 9). The philosophy of LVAD support received a boost with the use of the first implantable LVADs: in November 1993 the Novacor LVAS and in May 1994 the HeartMate I. Further, the number of LVAD implantations has risen due to many developments including the introduction of inhaled nitric oxide in 1996 ¹⁰⁵, the implantation of the LVAD through lateral thoracotomy in patients with previous sternotomy since 1997 ^{106, 107}, the introduction of a large apical cannula for the Berlin Heart system which allows better unloading of the left ventricle, the use of miniaturized axial flow pumps since 1998 with the development of the novel magnetically suspended axial flow LVAD Incor ¹⁰⁶ and the improvements in preventing postoperative right heart failure ^{17, 108}. Implantable wearable electrical LVADs give patients greater mobility and quality of life, while implantation of a BVAD requires more extensive surgery, the blood is exposed to a greater area of foreign surface, and the drive units are larger, restricting the patient's ability to walk around freely. It's interesting to know that in our experience in 492 patients treated with left ventricular assist devices only 51 were women (10%). Furthermore only 34 of all women (25%) were treated with total implantable devices and only 26 (19.25%) with second generation non-pulsatile devices. On the contrary 337 men (44.69%) were treated with total implantable devices and 212 (28.19%) with second generation non-pulsatile devices.

In the INTERMACS registry, in the group of patients treated with more advanced LVAD, women are less represented (21%) ¹⁰⁹. The use of older and less sophisticated

devices in women can partially explain their significantly lower survival in VAD demonstrated in our study (p50 men 2.92 months vs. p50 women 1.83 months). The older devices have a bigger incidence of VAD-related problems because of the presence of valves, bearings, friction, abdominal pocket, etc. The use of older devices in women may explain their shorter assist length. Besides, Berlin Heart Excor was the most implanted device in women and the presence of big cannulas (2 in case of a LVAD only, 4 in case of a BVAD) and the housing outside the body surface expose women to a relevant higher risk of infection. The major difference in the axial pumps is the presence of a unique and smaller driveline which, moreover, is not subject to all the vibrations related to the external pulsatile devices. Of course this technical improvement was studied and created also to reduce the infection risk.

LVAD is only able to support the left ventricle; consequently impending right heart failure has been a major concern in these patients. We don't think that in our study women were more implanted with biventricular devices for a higher incidence of right ventricular failure but because they arrived too late to the time of VAD implantation, with worse general and cardiac conditions than men, as described for other types of heart failure therapies ¹¹⁰. Confirming our theory other papers have demonstrated that right ventricular dysfunction after LVAD insertion does not appear to be related to gender ¹⁰¹.

Other groups suggested that the type of VAD a woman receives is based on size of the patient, degree of heart failure, and whether or not she is a transplant candidate ¹⁰⁰. In fact some devices as Novacor LVAD and Thoratec VE HeartMate LVAD require a body surface area greater than 1.5 m² and CardioWest total artificial heart needs a body surface area even greater than 1.6 m² ¹¹¹. This explains while in a population of 127

patients treated with Cardio West as bridge to transplant only 19 (15%) were women ¹¹¹. Anyway small body size was associated with increased operative mortality ¹⁰⁰. There are other technical challenges in women, in fact they are shorter than men and with not much length to their aortas ¹⁰⁰. Circulatory arrest has even been used to deal with a lack of aorta when removing the VAD and performing the heart transplant. Smaller women have had difficulty with the abdominal placement of the pump. Previous left upper quadrant surgery or a long narrow rib cage can also contribute to difficulties intra-operatively, as well as to postoperative pain.

The use of old devices has an impact also in the quality of life (noise, carry on portability, limited social life, psychological and behavioral problems, difficulty to be evidently “different” from the others, etc). Quality of life issues are being evaluated after heart transplantation and/or VAD insertion in women. Fifty women who were status-post heart transplantation filled out a Herth Hope Index, Multiple Affect Adjective Checklist and SF-12 ¹¹². The study revealed that they had moderately low hope and relatively high anxiety, depression and hostility. Hope was found to be an independent predictor of mood and quality of life. A certain patient, who had had redo sternotomy and heart transplantation a few years earlier, would say: “I’m in pretty good shape for the shape I’m in.” A positive attitude works, but providing false hope is not a kindness to the patient or her family. Interestingly, in a study on the change in the quality of life after LVAD implementation to after heart transplantation, only 1 patient was a woman (out of 40) ¹¹³. Another review of lifestyle and quality of life in long-term survivors of cardiac transplant included only 8 women among 93 patients (8.6%). The investigators did realize that their study findings could not be applied to women because of their underrepresentation ¹¹⁴.

TRANSPLANTATION

In candidates for HTx with rapid deterioration of cardiac function, implantation of a long-term VAD should be considered. Most of these patients present with acute cardiogenic shock and signs of multi organ failure. Emergency implantation of a BVAD or TAH is required to support the circulation and keep the patient alive. Patients with optimized treatment of heart failure presenting with marginal, but stable, hemodynamic conditions under intravenous (IV) catecholamines are immobilized and may suffer rapid decompensation with acute multi organ failure or sudden death due to arrhythmia. In these patients early implantation of a VAD is a better option than IV catecholamines in order to keep them in a marginal condition until HTx ⁴⁰. Moreover, implantation in stable patients mostly allows the use of an implantable LVAD even in the case of pulmonary hypertension ¹¹⁵, with subsequently better survival and better quality of life. The survival rates after HTx in patients with and without previous VAD implantation are, in DHZB experience similar ¹¹⁶. Aaronson et al. even showed a superior survival rate for patients bridged with VADs ⁴⁰. This might be explained by normalized organ function following improved hemodynamic status ^{17, 117, 118}. Different studies have demonstrated sex differences in survival after various cardiac surgery procedures, with superior survival for male over female patients ¹¹⁹. This might be due to a lower threshold to diagnose and aggressively treat heart disease in male patients, resulting in female patients presenting with more advanced pathology and systemic manifestations ¹²⁰. In our study a total of 260 patients were successfully bridged to heart transplantation, of them only 41 were women (15.7%). Surprisingly the length of assistance with VAD before HTx was significantly longer in men than in women (men

9.2 months vs. women 4.6 months). There were no gender differences in survival (p50 men 102.53 months vs. p50 women 158.72 months) but survival in patients who had a LVAD as bridge to transplant was significantly better than in patients who had a BVAD (p50 LVAD 142.32 months vs. p50 BVAD 67.59 months). In Morgan et al. study, LVAD implantation scores were significantly higher for female patients than for male patients. Median support time was similar between the groups. However, when comparing male and female patients with similar LVAD implantation scores, there was no significant difference in survival (p not significant) ¹⁰⁴. In the study of Potapov et al. male patients demonstrated superior survival while receiving mechanical assistance, a higher rate of successful bridging to transplantation and improved survival after transplantation. Also in this study LVAD pre-implantation scores were significantly higher for female patients, indicating that female patients presented in a more advanced state of heart failure. This is consistent with studies that have demonstrated a significant delay in the preliminary suspicion, performance of diagnostic studies, and therapeutic intervention for women with heart failure ^{99, 121}. The multivariate analysis supported the notion that higher LVAD scores in female patients and not sex in and of itself accounted for inequities in outcome between male and female patients. In multiparous females waiting for HTx we can see also an increased risk of sensitization, especially when associated with placement of a ventricular assist device. Patients who are highly sensitized can be pretreated with intravenous immunoglobulin (IVIg) in preparation for heart transplantation ⁹⁹.

MYOCARDIAL RECOVERY

Recovery of myocardial function on VAD support in patients with dilated cardiomyopathy remains a fascinating phenomenon¹²². In our experience, since 1995, the previously implanted VAD could be removed in 55 patients and in 41 of them myocardial function remained stable for maximal follow-up of over 10 years. In DHZB all patients with dilated cardiomyopathy implanted with VADs are routinely evaluated by echocardiography for recovery of myocardial function¹²³. As yet no preoperative biochemical or histological predictors for this phenomenon are known¹²⁴⁻¹²⁷. However, patients presenting myocardial recovery showed a shorter history of the disease⁷⁸. The indication for explantation is improvement of left ventricular ejection fraction to over 45%, decrease of left ventricular end-diastolic diameter to 55 mm or less and improvement of the systolic wall motion of the left ventricle to over 8 cm/s measured during pump stop. After device removal, all patients continue to receive heart failure medication including ACE inhibitors, beta blockers, aldactone, vitamins and antioxidants and, if necessary, diuretics and digitalis¹²⁸. In selected patients, administration of clenbuterol may enhance myocardial recovery as advocated by Yacoub and associates¹²⁹. This treatment and the intra-operative application of stem cells are currently under clinical investigation in DHZB. Routine follow-up including echocardiographic studies should be performed after device removal. If necessary, the patients presenting deterioration of myocardial function should be referred for HTx^{128, 130}. To our knowledge there are no studies about gender differences in VAD implantation as bridge to recovery. In our experience only 10 patients of the 55 who could be explanted after myocardial recovery were women (18%) and their survival was

near to significantly worse than in men (p50 women 9.33 months vs. p50 men 77.42 months). Surprisingly survival in patients who had a BVAD as bridge to recovery was not different than survival in patients who had a LVAD (p50 BVAD 48.46 months vs. p50 LVAD 53.39 months), maybe because patients choice in case of VAD implantation with a view to recovery is more selective and patients have less comorbidities. The length of assistance with VAD before recovery was significantly longer in men (mean 5.0 months) than in women (mean 1.3 months), suggesting that recovery of myocardial function is faster and more effective in women. Further larger studies are needed to verify this new finding.

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APPENDIX:

RESEARCH ACTIVITY DURING PhD:

SUCCESSFUL IMMUNOGLOBULIN TREATMENT FOR FULMINANT MYOCARDITIS. Nalli C, Bernier M, Couture C, Bergeron S, Cantin B, Leblanc MH, Proulx G, Sénéchal M. Accepted for publication in the American Journal of Case Reports.

HEARTMATE II INDUCED ACQUIRED VON WILLEBRAND DEFICIENCY CAUSING A SEVERE UPPER GASTRO-INTESTINAL BLEEDING. Chiara Nalli, Sandro Sponga, Mario Sénéchal, Bernard Cantin, Daniel Doyle, Eric Charbonneau. Under revision.

RISK FACTORS FOR VASOPLEGIA SYNDROME FOLLOWING CARDIAC TRANSPLANTATION. Nalli C, Charbonneau E, Leblanc MH, Bernier M, Bergeron S, Cantin B, Proulx G, Sénéchal M. Under revision.
EXTENDED SELECTION CRITERIAS FOR HEART TRANSPLANT CANDIDATES, A SINGLE CENTER 10 YEARS EXPERIENCE. Chiara Nalli, Mario Sénéchal, Bernard Cantin, Marie-Hélène Leblanc, Sébastien Bergeron, Guy Proulx, Christine Bourgault, Eric Charbonneau, Daniel Doyle, Francois Dagenais, Eric Dumont, Pierre Voisine, Mathieu Bernier. Under revision.

EXTRA-CORPOREAL MEMBRANE OXYGENATION SUPPORT FOR EARLY GRAFT FAILURE AFTER HEART TRANSPLANTATION. Sandro Sponga, Mario Sénéchal, Chiara Nalli, Bernard Cantin, Pierre Voisine, François Dagenais, Eric Dumont, Marie-Hélène Leblanc, Daniel Doyle, Eric Charbonneau. Under revision.

USE OF SILDENAFIL IN PATIENTS WITH SEVERE SYSTOLIC DYSFUNCTION AND PULMONARY HYPERTENSION: CAN WE DO BETTER? Leblanc MH, Bernier M, Nalli C, Bergeron S, Bourgault C, Cantin B, Proulx G, Sénéchal M. Under revision.

CONGRESS PRESENTATIONS 2010:

Heart Transplantation Canadian Congress 25-27 February 2010, Québec (Canada):

SUCCESSFUL IMMUNOGLOBULIN TREATMENT FOR FULMINANT MYOCARDITIS. Nalli C, Bernier M, Couture C, Bergeron S, Cantin B, Leblanc MH, Proulx G, Sénéchal M.

Canadian Congress of Cardiology 23-27 October 2010, Montreal (Canada):

EXTENDED SELECTION CRITERIAS FOR HEART TRANSPLANT CANDIDATES, A SINGLE CENTER 8 YEARS EXPERIENCE. Chiara Nalli, Mario Sénéchal, Bernard Cantin, Marie-Hélène Leblanc, Sébastien Bergeron, Guy Proulx, Christine Bourgault, Eric Charbonneau, Daniel Doyle, Francois Dagenais, Eric Dumont, Pierre Voisine, Mathieu Bernier.

American Heart Association Congress 13-17 November 2010, Chicago (USA):

EXTENDED SELECTION CRITERIAS FOR HEART TRANSPLANT CANDIDATES, A SINGLE CENTER 10 YEARS EXPERIENCE. Chiara Nalli, Mario Sénéchal, Bernard Cantin, Marie-Hélène Leblanc, Sébastien Bergeron, Guy Proulx, Christine Bourgault, Eric Charbonneau, Daniel Doyle, Francois Dagenais, Eric Dumont, Pierre Voisine, Mathieu Bernier.