Università degli Studi di Padova

Facoltà di Medicina e Chirurgia

Scuola di Dottorato di Ricerca in Scienze Mediche, Cliniche e Sperimentali

Indirizzo: Scienze Cardiovascolari

Ciclo: XXIII

TESI DI DOTTORATO

Heart Transplantation and Mechanical Circulatory Support: A Synergy in the Era of Donor Organ Shortage

Direttore della Scuola: Ch.mo Prof. Gaetano Thiene

Coordinatore d'indirizzo: Ch.mo Prof. Gaetano Thiene

Supervisore: Ch.mo Prof. Gino Gerosa

Dottorando: Dott. Sandro Sponga

A Chiara e Luca

INDEX

SUMMARY

Introduction

During the past 30 years cardiac transplantation has become the gold standard for the treatment of patients with advanced heart failure. The progresses in this field permitted to consider the employement of marginal donors and recipients in an effort to enlarge the pool of patients who can benefit of heart transplant. Anyway this strategy may affect results at short and long term. Mechanical circulatory support may be useful to dalay the transplant in absence of a donor or to recovery temporary graft failure after heart transplant.

The aim of this thesis is to evaluate considering the experience of Quebec Heart and Lung Hospital:

1) the impact on mortality and hospitalization rate of the enlarged criteria for heart transplantation candidacy with inclusion of relative contraindications;
2) the results of LVAD as bridge to transplant;
3) the results of Ecmo to treat early graft failure.

Extended Selection Criteria for Heart Transplant Candidates, a Single Center 10-year Experience.

Aim of the study

The past 30 years of cardiac transplantation (CT) have led to better medical management of recipients. Many of the original contraindications such as age, diabetes, weight and renal failure are now considered to be relative. We sought to evaluate the impact of these relative contraindications on mortality and hospitalization rate after CT.

Methods/Results

From January 2000 to January 2010, we followed 142 transplanted patients for a total 254 person/year follow up time. Primary outcome was a composite of death from any cause and hospitalization for a CT related cause (heart failure, arrhythmia, graft rejection or infection). All prognostic factors of interest were the presence of insulin treated diabetes, age > 65, BMI > 30, transpulmonary gradients > 15 and creatinine clearance < 30 ml/min. Survival analysis was performed using Kaplan Meier cumulative Hazard function and multivariate analysis with Cox-Proportional Hazard models.

Of the 142 patients 49 had one of the considered factors at the time of listing, 38 had 2 and 10 had 3 or more. During follow-up there were 16 deaths in the group with risk factors and 7 in the group without risk factors.

Primary outcome occurred in 84 patients (61 hospitalizations and 23 deaths). Mean survival time was 657 days ± 879. Patients presenting 2 or more of the considered factors at listing time showed significantly higher rate of the primary outcome during the follow up (HR1.47, 1.02 - 2.28). These findings were amplified when the patients had 3 or more factors at listing time (HR 2.52, 1.2 - 5.29). The presence of a single relative controindication (Hazard Ratio, 95% CI) showed a non significant increase in the risk of developing the composite outcome. Age (1.43, 0.9 - 2.7), low creatinine clearance (1.14, 0.74 - 1.8), high BMI (1.53, 0.93 - 2.5), diabetes (1.4, 0.8 - 2.4), high transpulmonary gradient (1.4, 0.8 - 2.37).

Conclusions

Our data suggest that the presence of multiple co morbidities at baseline in CT candidates might be associated with worse clinical outcomes. This association seems to increase with the number of factors present at listing time. In our quest to increase

longevity and quality of life of our CT patients and considering scarcity of organ donors, these findings should be taken into account during the CT candidacy evaluation.

Bridge to transplantation with new axial assist devices

Aim of the study

Considering limited donor availability, the role of long term assist devices appears even more important. In the last years an increasing number of patients with unstable emodinamic conditions have been successfully bridged to a heart transplant with new axial left ventricular assist devices (LVAD). We describe our experience with Heart Mate II device as bridge to transplant.

Methods/Results

From 2008 to 2011, 19 consecutive patients received a HeartMate II LVAD (Thoratec Corporation, Pleasanton, CA) as bridge to transplant. The mean age was 50.1 ± 16.2 years, 78.9% patients were male, 31.6% of patients were affected by renal failure and 10.5% were treated with dyalisis before the operation. Left ventricular ejection fraction was 16.2 ± 6.1 % and cardiac index was 1.6±0.5 l/min/m2.

No patient died during the first 30 days but 3 patients died prior to hospital discharge (15,8%) because of MOF (n=1) and cerebral complications (n=2). Major adverse events included right ventricular failure (5.3%), LVAD driveline infections (5.3 %), mediastinitis (5.3%), and stroke (5.3%). The mean support was 227±175.6 days. Six patients underwent cardiac transplantation successfully after a mean support of 203.8±122.3 days.

Conclusions

The results of our experience show how BTT with HM II offers excellent outcomes when a donor is not avaible. Patient selection and improvement in anticoagulation management continue to be areas of focus to further improve outcomes reducing the risk of right ventricular failure and cerebral complications in patients undergoing LVAD implant.

Extra-corporeal membrane oxygenation temporary support to treat early graft failure after cardiac transplantation

Aim of the study

The imbalance in supply and demand of number of heart transplantation has led to the liberalization of donor acceptance criteria to enlarge the donor pool. This may result in an increased incidence of early graft failure (EGF) that is the most common cause of in-hospital mortality after cardiac transplantation. Extra-corporeal membrane oxygenation (ECMO) has been recently used as a therapeutic option for EGF.

We report here our experience of using ECMO in the setting of EGF.

Methods/Results

We retrospectively reviewed 13 patients with early graft failure unresponsive to ionotropic support at our institution between January 2007 and June 2011 treated with early (n=8) or delayed (n=5) ECMO. Eight patients (mean age 46.3 ± 19.5 years, male 75%) were weaned from cardiopulmonary bypass with peripheral arteriovenous ECMO. Five patients (mean age 38.4 ± 13.5 years, male 60%) treated with important ionotropic support for early graft dysfunction needed delayed ECMO support for acute hemodynamic collapse.

The 8 patients treated early were weaned after a mean support of 3.5 ± 1.3 days with full recovery of left ventricular function (ejection fraction 60 ± 12%). In this group the 30-day and 1-year survival was 87 % and 75 % respectively. The causes of mortality were respiratory failure in one patient (30-day) and septic shock (1 year) in the other.

All patients treated with delayed ECMO could not be weaned from mechanical support and died of multi organ failure.

Conclusions

In our experience ECMO support is a reliable therapeutic option for graft salvation in severe early graft failure if the support is initiated early. In this case complete recovery of cardiac function is frequent and usually occurs less than 4 days after ECMO installation with good survival. On the contrary delayed ECMO appears to be associated with poor outcome. This emphasizes the necessity to identify precociously the graft dysfunction and to treat it aggressively.

RIASSUNTO

Introduzione

Nel corso degli ultimi 30 anni il trapianto cardiaco è diventato il gold standard per il trattamento di pazienti con scompenso cardiaco. I miglioramenti terapeutici in questo campo hanno permesso di considerare anche l'impiego di donatori e riceventi marginali in uno sforzo di incrementare il numero di pazienti che possono beneficiare del trapianto cardiaco. L'utilizzo di queta strategia terapeutica può avere però una ripercussione sui risultati a breve ed a lungo termine. I devices per il supporto meccanico circolatorio vengono utilizzati sia per procrastinare il trapianto in assenza di un donatore sia in caso di early graft failure dopo il trapianto.
Lo scopo della tesi è valutare con particolare riferimento all'esperienza maturata al Heart and Lung Hospital di Quebec:

1) l'impatto sulla mortalità e sul tasso di reospedalizzazione dell'utilizzo di indicazioni meno restrittive con l'inclusione di controindicazioni relative al trapianto cardiaco
2) i risultati dell'assistanza con LVAD come ponte al trapianto;
3) i risultati dell' ECMO per il trattamento dell'Early Graft Failure

Indicazioni allargate per i candidati a trapianto cardiaco. Dieci anni di esperienza di un singolo centro.

Scopo dello studio

I progressi delle conoscenze sul trapianto cardiaco hanno portato ad una migliore gestione medica dei riceventi. Molte delle controindicazioni originarie come l'età, il diabete, l'obesità e l'insufficienza renale sono ormai considerati solamente relativi.

Abbiamo cercato di valutare l'impatto di queste controindicazioni relative su mortalità e tasso di reospedalizzazione dopo CT.

Metodi/Risultati

Dal gennaio 2000 al gennaio 2010, abbiamo seguito 142 pazienti trapiantati per un totale di 254 pazienti/anno di follow-up. L'outcome primario è stato definito come mortalità per qualsiasi causa o reospedalizzazione per una causa correlata al trapianto cardiaco (insufficienza cardiaca, aritmie, rigetto o infezioni). I fattori prognostici considerati erano diabete insulino-trattato, età> 65 anni, BMI> 30, gradiente transpolmonare> 15 e la clearance della creatinina <30 ml / min. La sopravvivenza è stata calcolata con il metodo della curva di di Kaplan Maier con l'analisi multivariata con i modelli di rischio proporzionale di Cox.

Dei 142 pazienti 49 presentavano un fattore di rischio, 38 pazienti ne presentavano 2 e 10 ne presentavano 3 o più. Durante il follow-up ci sono stati 16 decessi nel gruppo con almeno un fattore di rischio e 7 nel gruppo senza fattori di rischio. L' end-point primario si è verificato in 84 pazienti (61 ricoveri e 23 decessi). I pazienti che presentavano 2 o più fattori di rischio hanno mostrato un tasso significativamente più alto di end-point primario durante il follow-up (HR1.47, 1,02-2,28). I risultati si sono rilevati ulteriormente peggiori nei pazienti che avevano 3 o più controindicazioni relative (HR 2,52, 1.2 - 5.29). La presenza di una singola controindicazione relativa (Hazard Ratio, IC 95%) non ha mostrato un aumento non significativo del rischio di sviluppare l'outcome primario: età (1,43, 0.9 - 2.7), clearance della creatinina (1,14, 0,74-1,8), indice di massa corporea (1,53, 0,93 - 2,5), diabete (1,4, 0.8 - 2.4), gradiente transpolmonare (1,4, 0,8-2,37).

Conclusione

I nostri dati suggeriscono che la presenza di patologie concomitanti usualmente considerate controindicazioni relative nei candidati al CT potrebbe essere associata ad esiti clinici peggiori. Questa associazione sembra aumentare con il numero di fattori presenti. Per aumentare la longevità e la qualità della vita dei pazienti cardiotrapiantati e considerando la scarsità di donatori di organi, la candidatura di pazienti con controindicazioni al trapianto dovrebbe essere circoscritta a casi ben selezionati.

Bridge to transplant utilizzando assistenze assiali a flusso continuo

Scopo dello studio.

Data la scarsa disponibilità di donatori a fronte di un cresente numero di pazienti affetti da scompenso cardiaco, il ruolo delle assistenze ventricolari a lungo termine appare sempre più importante. Negli ultimi anni un numero crescente di pazienti con condizioni emodinamiche instabili sono stati assistiti con successo fino al trapianto grazie a questi devices.

Metodi/Risultati

Dal 2008 al 2011, 19 pazienti consecutivi sono stati trattati con l' HeartMate II LVAD (Thoratec Corporation, Pleasanton, CA) come ponte al trapianto al Heart and Lung Hospital di Quebec. L'età media dei pazienti era di 50,1 ± 16,2 anni, 78,9% dei pazienti erano di sesso maschile, 31,6% dei pazienti erano affetti da insufficienza renale e il 10,5% erano in trattamento dialitico prima dell'operazione. La frazione di eiezione ventricolare sinistra era 16,2 ± 6,1% e l'indice cardiaco 1,6 ± 0,5 ml/min/m2. Nessun paziente è morto nei primi 30 giorni, ma 3 pazienti sono morti prima della dimissione (15,8%) Le cause di mortalità sono state insufficienza multiorganica (n = 1)

e complicazione cerebrali (n = 2). Le principali complicanze sono state: insufficienza ventricolare destra (5,3%), infezione della drive line (5,3%), mediastinite (5,3%) e ictus (5.3). Il supporto medio è stato di 227 ± 175,6 giorni. Sei pazienti sono stati sottoposti a trapianto cardiaco con successo dopo una durata media di assistenza di 203,8 ± 122,3 giorni.

Conclusioni

Nella nostra esperienza il BTT con HM II, quando un donatore non è disponibile, offre risultati eccellenti. La selezione dei pazienti e il miglioramento della gestione anticoagulante continuano ad essere aspetti da studiare per migliorare ulteriormente i risultati riducendo il rischio di insufficienza ventricolare destra e di complicanze cerebrali.

L'utilizzo dell'ECMO per il trattamento della failure del graft precoce dopo trapianto cardiaco

Scopo dello studio

Lo squilibrio tra domanda e offerta del numero di trapianti di cuore ha portato ad una liberalizzazione dei criteri di accettazione dei donatori per aumentarne il pool di donatori. Ciò potrebbe determinare un aumento dell'incidenza di failure precoce che è la causa più comune di mortalità in ospedale dopo trapianto cardiaco. L'ECMO è stato recentemente utilizzato come opzione terapeutica per il trattamento della failure precoce dopo trapianto.

Descriviamo l'esperienza dell'Heart and Lung Hospital di Quebec nell' utilizzo ECMO per il trattamento dell'failure precoce dopo trapianto.

Metodi/Risultati

Abbiamo analizzato retrospettivamente 13 pazienti con failure precoce dopo trapianto non rispondente a supporto ionotropico massimale nel nostro istituto tra gennaio 2007 e giugno 2011 trattati con ECMO tempestivamente in sala operatoria (n = 8) o in un secondo momento in rianimazione (n = 5). Otto pazienti (età media 46,3 ± 19,5 anni, maschi 75%) sono stati svezzati dal bypass cardiopolmonare con ECMO periferico artero-venoso. Cinque pazienti (età media 38,4 ± 13,5 anni, maschi 60%) sono stati trattati con supporto ionotropico massimale per la failure precoce dopo trapianto gli stessi hanno necessitato in seguito un impianto emergente di un ECMO per un deterioramento delle condizioni emodinamiche.

Gli 8 pazienti trattati precocemente sono stati svezzati dopo un supporto medio di 3,5 ± 1,3 giorni, con il pieno recupero della funzione ventricolare sinistra (frazione di eiezione del 60 ± 12%). In questo gruppo la sopravvivenza a 30 giorni e ad 1 anno è stata rispettivamente del 87% e del 75%. Le cause di mortalità sono state insufficienza respiratoria in un paziente e shock settico in un altro.

In tutti i pazienti trattati con terapia farmacologica e in seguito con ECMO in terapia intensiva non è stato possibile lo svezzamento dal supporto meccanico e sono tutti morti di insufficienza multiorgano.

Conclusioni

Nella nostra esperienza l'ECMO si è rilavata un'opzione terapeutica efficace per il recupero del graft in caso di failure precoce dopo il trapianto solo nel caso il supporto sia iniziato precocemente. In questo caso il completo recupero della funzione ventricolare è frequente e di solito si verifica a meno di 4 giorni dopo l'installazione dell' ECMO garantendo una buona sopravvivenza. Al contrario quando l'impianto dell'

ECMO viene posticipato ed eseguito in emergenza è associato a prognosi sfavorevole. Questo enfatizza la necessità di individuare precocemente la failure dopo trapianto e di trattarla in modo aggressivo.

HEART FAILURE

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. With the exception of heart failure caused by reversible conditions, the other patients usually worsens with time. This progressive disease is associated with an overall annual mortality rate of 10%[1]. Moreover heart failure is a frequent cause of hospitalization in people older than 65. In developed countries, the mean age of patients with heart failure is 75 years and in patients 70 to 80 years old, heart failure occurs in 20-30 %.

In the United States the incidence of heart failure in the population older than 65 years is 10 per 1000 inhabitants [2]. Most of these patients are refractory to medical therapy and there are 260,000 deaths each year for heart failure. Despite advances in medical and surgical management, the 5-year mortality rate is around 50%.
The European Society of Cardiology reports that 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 and 78% of patients undergo two hospital admissions per year [3].

In Italy there is 1 million people suffering from congestive heart failure and there are more than 170,000 hospitalizations per year. In 30% of cases patients are over 65 years of age: ischemic heart disease is the main cause.

As a result of the costs of hospitalization, it is associated with high health expenditure; in 2004, the direct and indirect cost of heart failure has been estimated at 35 billion dollars, that is the 5% of the national health care budget.

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

Everywhere in the world the incidence is increasing. It is estimated that in the next years in USA there will be more than 400000 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 myocardial damage [3]. The incidence of congestive heart failure is one new case per 1000 inhabitants per year, but every year the percentage increases of 10%.

Medical therapy for heart failure is effective in one-third of patients but when optimal medical therapy and biventricular resynchronization are no longer successful, quality of live is poor, and prognosis is limited [3].

Prognosis in heart failure can be assessed in multiple ways including clinical prediction rules and cardiopulmonary exercise testing. Clinical prediction rules use a composite of clinical factors such as lab tests and blood pressure to estimate prognosis.

Many univariate predictors of poor prognosis have been identified, including NYHA functional class III or IV, reduced left ventricular ejection fraction (LVEF), and hyponatremia. However, because of substantial overlap, these factors are of limited use in a particular patient. This is not surprising, given the complexity of HF and the multiple neurohumoral, hemodynamic, and electrophysiological factors that may contribute to morbidity and mortality. In general, the peak VO2 (VO2max) appears to provide the most objective assessment of functional capacity in patients with HF and may be the best predictor of when to list an individual patient for cardiac transplantation [4, 5].

Peak VO2 is an independent predictor of survival. Patients with a value ≤10 ml/kg per min have lower survival and are usually considered for transplantation, moreover

patients with values between 10 and 14 ml/kg per min had an outcome that was slightly worse than patients with values between 14 and 18 ml/kg per min[6]. These patients in this intermediate range of peak VO2 should have several measurements of exercise capacity over a period of time. Some will improve on repeated testing, but those with persistent values of 10 to 12 ml/kg per min and poor exercise tolerance should generally be considered for transplantation. Repeated hospitalization and/or the requirement for increasing medical therapy are additional indicators of likely benefit from transplantation.

Several limitations must be considered when using peak VO2 to assist in the selection of patients for cardiac transplantation. VO2 is a continuous variable, and therefore, it is critical to interpret VO2 results in light of gender, age, level of physical conditioning, medical therapy, and other potential influences.

Although peak VO2 has often been the major factor used to guide the selection of heart transplant candidates, a single variable does not provide an optimal risk profile. As a result, several risk models have been developed that use factors identified in multivariable survival analysis to establish a risk score for prognosis in these patients [7-11]. One model that has been validated prospectively is the Heart Failure Survival Score (HFSS)[7]. This score was derived from a multivariable analysis of 268 ambulatory patients referred for consideration of cardiac transplantation from 1986 to 1991 and validated in 199 similar patients from 1993 to 1995. The predictors of survival in the HFSS include: presence or absence of coronary artery disease, resting heart rate, left ventricular ejection fraction, mean arterial blood pressure, presence or absence of an interventricular conduction delay on ECG, serum sodium, peak VO2 and pulmonary capillary wedge pressure

The HFSS stratifies patients into low, medium, and high risk categories, based upon a sum of the variables above multiplied by defined coefficients. Among the patients in the validation sample, one-year survival rates without transplant for these three strata were 88, 60, and 35 percent, respectively.

These newer studies confirmed the predictive value of peak VO2 and HFSS in the context of more modern therapies with neurohormonal blockade, including beta blockers[12, 13].However, in a contemporary patient population, a peak VO2 of 14.9 ml/min/kg may be average for well-medicated NYHA Class II-III patients. Therefore, a peak VO2 cut point lower than 14 mL/kg per min may be warranted as an indication for transplantation referral [13, 14].

An observational study of 715 patients with chronic HF evaluated the accuracy of HFSS and peak VO2 risk stratification in the era of ICD and CRT therapy. During an average follow-up of 2.6 years, 354 patients died or received an urgent cardiac transplant or left ventricular assist device. The HFSS provided more accurate risk stratification than the peak VO2. The HFSS discriminated between low-, medium- and high-risk groups in patients with and without devices. The study also found that a peak VO2 ≤10 ml/kg/min, rather than ≤14 ml/kg/min, is a useful threshold for identification of high-risk patients in the device era.

In contrast to the limitations of peak VO2 and the Heart Failure Survival Score, the Seattle Heart Failure Model has incorporated the impact of newer heart failure therapies on survival, including ICDs and CRT. The model was derived in 1125 heart failure patients and prospectively validated in five diverse cohorts [11]. The model provides an accurate estimate of one-, two-, and three-year survival with the use of easily obtained clinical, pharmacologic, device, and laboratory characteristics. It also allows the

operator to add in the estimated effect of interventions on an individual patient's prognosis.

These prognostic informations can be considered when making recommendations about transplantation and LVAD implantaiton.

HEART TRANSPLANTATION

Hystory of Heart Transplantation

Alexis Carrel performed the first heterotopic canine heart transplant with Charles Guthrie in 1905[15, 16]. Frank Mann in the 1930s proposed the concept of cardiac allograft rejection, which involved biologic incompatibility between donor and recipient manifested by an impressive leukocytic infiltration of the rejecting myocardium.

First sites of implantation were the neck and the inguinal regions. Vladimir Demikhov of the Soviet Union successfully implanted the first intrathoracic heterotopic heart allograft[17]. He later demonstrated that heart-lung and isolated lung transplantation also were technically feasible.

Norman Shumway and Richard Lower at Stanford University described the atrial cuff anastomotic technique in 1960 thanks to the use of moderate hypothermia, cardiopulmonary bypass, and an [17].

James Hardy in 1964 performed the first human cardiac transplant with a chimpanzee xenograft using a Shumway's technique but the primate heart was unable to maintain the recipient's circulatory load, and the patient succumbed some hours postoperatively[18].

South African Christiaan Barnard surprised the world when he performed the first human-to-human heart transplant on December 3, 1967 [19]. Over the next several years, poor early clinical results led to a moratorium on heart transplantation, with only the most dedicated centers continuing experimental and clinical work in the field. The pioneering efforts of Shumway and colleagues at Stanford eventually paved the way for the reemergence of cardiac transplantation in the late 1970s. Philip Caves in 1973 finally provided a reliable means for monitoring allograft rejection with the introduction

of transvenous endomyocardial biopsy [20]. The modern era of cardiac transplantation began with the introduction of cyclosporine-based immunosuppression in 1980. Following the institution of cyclosporine, survival rates improved significantly and cardiac transplantation became an accepted, widely used therapy. As an example, a review of 885 patients undergoing transplantation at Stanford found that the 5 and 10 year survival rates among patients treated with cyclosporine and OKT3 were 68 and 46 percent, respectively, compared to 41 and 24 percent with prior regimens [21]. The decrease in mortality was due to reductions in the 10 year incidence of death from rejection (5 versus 14 percent), infection (16 versus 50 percent), and graft coronary artery disease (9 versus 13 percent) [21]. Outcomes among transplant recipients have continued to improve over the past 30 years as a result of careful recipient and donor selection, advances in immunosuppression, and the prevention and treatment of infection. Major gains in survival have been largely limited to the first 6 to 12 months without improvement in the annual mortality rate after the first year.

Heart transplantation is now a widely accepted therapeutic option for end-stage cardiac failure. The 2009 report from the Registry of the International Society for Heart and Lung Transplantation (ISHLT) estimated that more than 5000 heart transplants are performed annually worldwide (including more than 2000 not reported). The majority of centers perform between 10 and 19 heart transplants per year. The most common age range for recipients is 50 to 59 years. The number of heart transplants reported to the Registry peaked in 1994 with lower numbers since then attributed both to decreased reporting of transplants, as well as decreased transplant volume in many countries. Decreased reporting is likely attributable to the fact that, although reporting to the Registry is legally mandated in the US, it is not in other countries, and many other

countries have established their own registries and no longer contribute their data. The number of transplant centers has also decreased from 243 in 1996 to 204 in 2007. The number of donor hearts is chronically much less than the number of potential recipients, some estimate by a factor of 10 [22].

Indication and Controinication to Heart Transplantation

Cardiac transplantation is reserved for a select group of patients with end-stage heart disease not amenable to optimal medical or surgical therapies. Prognosis for 1-year survival without transplantation should be less than 50%. Prediction of patient survival involves considerable subjective clinical judgment by the transplant committee because no reliable objective prognostic criteria are available currently. Low ejection fraction (<20%), reduced VO2,max (<14 mL/kg per minute), arrhythmias, high pulmonary capillary wedge pressure (>25 mm Hg), elevated plasma norepinephrine concentration (>600 pg/mL), reduced serum sodium concentration (<130 mEq/dL), and more recently, N-terminal probrain natriuretic peptide (>5000 pg/mL) all have been proposed as predictors of poor prognosis and potential indications for transplantation in patients receiving optimal medical therapy [23, 24]. Reduced left ventricular ejection fraction and low VO2 max are widely identified as the strongest independent predictors of survival.

Major society guidelines (2009 American College of Cardiology/American Heart Association (ACC/AHA) [5]; 2008 European Society of Cardiology (ESC) heart failure guidelines and the Canadian Cardiovascular Society consensus [25, 26]; 2006 Heart Failure Society of America (HFSA) guidelines [5])propose similar indications recommendations devided in absolute indications, relative indications and insufficient

indications. Absolute indications are considered: for hemodynamic compromise due to HF refractory cardiogenic shock, documented dependence on intravenous inotropic support to maintain adequate organ perfusion, peak VO2 less than 10 mL/kg per min with achievement of anaerobic metabolism, severe symptoms of ischemia that consistently limit routine activity and are not amenable to coronary artery bypass surgery or percutaneous coronary intervention, recurrent symptomatic ventricular arrhythmias refractory to all therapeutic modalities.

Relative indications are considered peak V02 of 11 to 14 mL/kg per minute (or 55 percent predicted) and major limitation of the patient's daily activities, recurrent unstable ischemia not amenable to other intervention, recurrent instability of fluid balance/renal function not due to patient noncompliance with medical regimen.

Insufficient indications: low left ventricular ejection fraction, history of functional class II or IV symptoms of HF, peak VO2 greater than 15 mL/kg per minute (or greater than 55 percent predicted) without other indications.

There are many controindication to heart transplantation.

The major hemodynamic factor excluding cardiac transplantation is a pulmonary vascular resistance (PVR) greater than 4 to 6 Wood units (320 to 480 dynes-sec/cm5). Patients with an elevated PVR or a transpulmonary gradient (mean pulmonary artery pressure minus mean pulmonary capillary wedge pressure) above 15 mmHg have an increased risk of right ventricular failure in the immediate postoperative period [27]. Fortunately, the pulmonary hypertension in most patients with HF is due to neurohumoral vasoconstriction, not structural changes in the pulmonary vasculature, such as calcification or intimal or medial hyperplasia. As a result, an elevated PVR can

be often reduced by using agents such as nitroprusside, dobutamine, inamrinone, milrinone, prostaglandin E1, prostacyclin, nesiritide and inhaled nitric oxide [27].

Patients whose PVR can be acutely reduced pharmacologically to below 4 Wood units (320 dynes-sec/cm5) are usually considered acceptable for transplantation. In one report, the three-month mortality rate was higher in patients whose PVR was above 2.5 Wood units compared to those with lower values (17.9 versus 6.9 percent) [27]. However, in patients with initially high PVR that was reduced by nitroprusside, the three-month mortality was only 3.8 percent compared to 41 and 28 percent, respectively, in those who were resistant to nitroprusside or who only responded at a dose that caused systemic hypotension.

Given the efficacy of bolus milrinone therapy [28], this intervention should be given initial consideration as a test for reversibility of pulmonary hypertension. A continuous infusion of milrinone, dobutamine, or prostaglandin E1 for several weeks has been used in some patients as a bridge to transplantation. A study of 68 patients found that prostaglandin E1 was more effective than prostacyclin or dobutamine for preventing a worsening of HF [29]. Intravenous B-type natriuretic peptide, has shown some efficacy in refractory pulmonary hypertension. Recently, ventricular assist devices (VADs) are playing an important role in heart transplantation candidates with pulmonary hypertension. A period of left ventricular assist device (LVAD) support may allow for a decrease of pulmonary artery pressure secondary to unloading of the left ventricle. Use of modestly larger donor hearts for recipients with severe pretransplantation pulmonary hypertension can provide additional right ventricular reserve Patients with irreversible pulmonary hypertension may be candidates for heterotopic heart or heart-lung transplantation. [30, 31].

Systemic diseases with poor prognosis and potential to recur in the transplanted heart or the potential to undergo exacerbation with immunosuppressive therapy are considered absolute contraindications for heart transplantation. Heart transplantation for amyloid remains controversial because amyloid deposits recur in the transplanted heart. Although case reports of long-term survival can be found in the literature, survival beyond 1 year tends to be reduced[31]. In some cases, patients now have combined heart and kidney or heart and liver transplant for amyloidosis [31].

Another absolute contraindications to transplantation are active malignancies of any kind. In fact these pathologies can be worsened by the immunosuppressive therapy given to prevent transplant rejection. Even without preexisting disease, the incidence of malignancy is increased following transplantation. Patients with a remote history of cured malignancy, many of whom develop their cardiomyopathy as a consequence of chemotherapy for the malignancy, are considered reasonable candidates for transplantation.

Heart transplantation in patients with clinically important chronic viral infection remains a subject of active debate. Individuals with chronic hepatitis B or hepatitis C infections who undergo heart transplantation have an increased frequency of liver disease [32]. However, it has been difficult to show that survival after heart transplantation is reduced in the presence of positive hepatitis B or C serology [33]. As a result, practices of individual centers differ. Evaluation of such patients usually includes assessment for the level of active viremia and often includes liver biopsy to assess for the presence of cirrhosis. Since the frequency of progressive liver disease appears to be more common with hepatitis B than with hepatitis C, many transplant programs will accept candidates who are anti-HCV antibody positive, but not those who

are HBsAg positive. HIV infection has been considered to be an absolute contraindication to heart transplantation, primarily because of concerns about the increased frequency of infectious and malignant complications and the previously poor survival of such patients. However, the advent of highly active antiretroviral therapy has changed the prognosis of HIV. As a result, the view has been expressed that HIV infection itself should not be sufficient reason to refuse transplantation [34]. At present, only a few case reports have described heart transplantation in this population. Active infection was a sound reason to delay transplantation before assist devices became more commonplace. Up to 48% of patients with implanted LVADs reportedly have evidence of infection. Interestingly, treatment for LVAD infection in these patients is to proceed with urgent transplantation[35].

Severe chronic bronchitis or obstructive pulmonary disease may predispose patients to pulmonary infections after heart transplantation. Patients who have a FEV1/FVC of less than 40 to 50% of predicted or an FEV1 of less than 50% of predicted despite optimal medical therapy are considered poor candidates for transplantation. Transplantation in patients with diabetes mellitus is only contraindicated in the presence of significant end-organ damage (e.g., diabetic nephropathy, retinopathy, or neuropathy)[36, 37]. Diabetic patients, compared to those without diabetes, had a nonsignificant trend toward decreased survival at one year (85 versus 91 percent) but comparable survival at five years (82 percent). Rates of infection severe enough to require hospitalization were higher among diabetic patients at 90 days (14 versus 3 percent) and four years (29 versus 15 percent). There were no differences in the incidence of rejection, transplant coronary disease, or renal dysfunction [38].

Among the relative contraindications to cardiac transplantation, age has historically been a major factor[39]. Many programs have routinely excluded patients over the age of 60 to 65, but most feel that physiologic age is more important than chronologic age.

A report based on UNOS data between 1999 and 2006 demonstrated that patients ≥60 years of age had more frequently comorbidities than younger patients and that their overall survival post-transplant was lower than in younger patients. Carefully selected patients over 60 years of age have a survival rate comparable to that in younger patients.

The 2006 ISHLT update on the listing criteria and management of cardiac transplantation candidates suggested that most patients 70 years of age or younger and carefully selected patients over age 70 can be considered for cardiac transplantation[40].

Advanced obstructive and/or restrictive lung disease is associated with a higher incidence of postoperative lung complications, including infection associated with immunosuppressive therapy. Objective exclusion criteria include a forced one-second expiratory volume (FEV1) of less than 1.0 liter, a forced vital capacity of less than 50 percent of predicted, or a forced expiratory volume-to-vital capacity ratio of less than 1.0.

In addition, recent pulmonary embolism with or without infarction should delay transplantation, because secondary infection in the affected lobe may occur postoperatively. Before putting the patient on the transplant list, most centers treat this disorder with systemic anticoagulants for six to eight weeks or until radiographic evidence of resolution is seen.

Impaired renal function as manifested by a stable plasma creatinine concentration above 2 mg/dL (177 μmol/L) or a creatinine clearance below 40 mL/min is a controindication to heart transplantation. The concern in this setting is the superimposed nephrotoxicity

of long-term cyclosporine therapy.Combined kidney-heart transplantation may be offered to those who require transplantation of both organs with expected outcomes that may be similar to those receiving a heart transplant alone.

A number of other conditions increase the rate of perioperative complications or interact [41] poorly with immunosuppressive agents: advanced peripheral vascular disease, morbid obesity, active peptic ulcer disease, cholelithiasis, and diverticulosis.

All cardiac transplant candidates should undergo a complete psychosocial evaluation during the initial screening process[40]. This may identify social and behavioral factors that cause difficulty during the waiting period, convalescence, and long-term postoperative management[42, 43]. The patient must understand that full cooperation and compliance are critical to the safe and effective use of immunosuppressive agents.

Marginal donors

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. 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 [40].

Continuing improvements in transplant outcomes have allowed increasingly high risk patients to be considered for transplantation. A growing body of evidence suggests that many patients who fail to meet prior“standard” criteria for transplantation may in fact

have outcomes comparable to those of standard list candidates [38, 44-47]. Nonetheless, at a time when a critical shortage of donors leaves many patients who meet standard criteria without a suitable organ, implementation of less restrictive recipient criteria without increasing the donor supply will likely only further exaggerate the donor organ shortage. Since the mid-1990s, alternate waiting list strategies have been promoted as a means to maximize the use of so-called "marginal donor hearts," and thereby offer the benefit of transplantation to a greater number of candidates. Under this strategy, patients who fail to meet standard criteria for transplantation are considered candidates for organs that would otherwise have been discarded. Paradoxically, this often has meant matching the highest risk patients with high-risk donors, a phenomenon that can often presage significant morbidity.

Survival analysis of Chen et al revealed no statistical difference in posttransplant survival when alternate list patients were compared with their standard list counterparts. In this study among measures of posttransplant morbidity, only mean ventilatory support time and number of sternal wound infections were significantly greater compared to the alternate list group; among the 12 patients receiving an organ from a hepatitis seropositive donor, only 1 seroconverted during the study period without signs or symptoms of liver disease. Even patients affected by amylodosis, severe diabetes mellitus and peripheral vascular disease, HIV positive obtained good results.

Differently Laks and colleagues[46] found significantly better 90-day survival among the standard group compared to hight risk group. From 1992 to 2000, the University of California at Los Angeles transplanted 260 donor hearts were classified as marginal because of abnormalities that included age over 55 years, ejection fraction ≤ 50% with inotropes, high-dose inotropes, CAD, mild LVH by echocardiography, hepatitis B and

C, and recent cardiac arrest[38].

Sixty-six of the 260 marginal donor hearts were used for alternate-list recipients, and the remainders were used for status I and II patients on the standard list. Although use of marginal donors in alternate recipients was associated with increased early mortality, the intermediate-term results have been favorable.

On the basis of this evidence, the use of an alternate list has the potential to increase the use of marginal donors when applied in large-volume centers, however, alternate recipient lists have not yet been widely implemented by transplant centers.

Some aspects of this approach remain controversial but general suggestion to implement donors may be done.

Medical and social advances have prompted that an increasing number of persons reach an advancedage with a good quality of life. Age, and specifically the age of 65 years, has classically been considered the upper age limit for a wide variety of medical procedures, including HTx. The establishment of this age limit is often arbitrary, and coincides with standard age to retire in Western countries. The establishment of a cutoff point for the performance of a HTx based on age is a difficult task. Various arguments have been used to establish an age limit for the performance of a HTx. These include the presence of a greater number of comorbidities, less functional reserve in the event of any contingency, greater negative impact of immunosuppressive drugs, and particularly, shortage of organs and lesser potential benefit derived from performance of a HTx. HTx would be a good short term option for many patients, even older ones, but the current consensus is to offer HTx to those patients who will most benefit from it in the medium to long term, which is the reason why older patients are usually excluded. The growing shortage of available organs and the emergence of ventricular assist devices (VAD) as

target therapy are important factors to consider. New VAD have been shown to provide an acceptable quality of life and survival. It is for this reason that some authors prefer to use VAD in older patients, reserving HTx for younger patients[39].

However, what most studies do seem to agree on is that older patients have fewer rejections, whereas they suffer more infections and develop more tumors.

Despite an increased risk associated with small donor size relative to the recipient, a normal-sized (70 kg) adult male donor is suitable for most recipients[48]. In the case of a small donor, size matching with body mass index or height is more accurate than weight matching.

HCV-positive or hepatitis B virus (core IgM-negative) positive donors may be appropriate in selected higher-risk recipients[46].

Mild left ventricular hypertrophy (wall thickness more than 13 mm by echocardiography) does not preclude transplantation, particularly with shorter ischemic times. Transplantation is inadvisable if both echocardiographic and ECG criteria for LVH are present. Pseudohypertrophy may be observed by echocardiography in the presence of left ventricular underfilling and should not preclude transplantation.

The presence of most valvular and congenital cardiac abnormalities is a contraindication to transplantation. In some cases, however, “bench” repair can be performed on a donor heart with mild or moderate mitral or tricuspid regurgitation or other mild valvular abnormalities, such as a normally functioning bicuspid aortic valve. Repair of a donor heart with a secundum-type atrial septal defect can also be performed.

Although cardiac-specific enzymes such as creatine kinase-MB and troponins are routinely obtained by some organ-procurement organizations, their role in donor evaluation remains unclear. There is some evidence that elevated cardiac enzymes are

associated with higher recipient inotropic requirements after transplantation[49] and higher rejection rates[50]. There is limited evidence of a relationship between elevated troponin levels and early graft failure[51, 52]. Normal levels of cardiac enzymes are reassuring in cases of donor ventricular dysfunction, because they provide evidence against recent myocardial damage. However, many cardiac donors have elevated cardiac enzymes without evidence of ventricular dysfunction by imaging or hemodynamic criteria.

For this reason, elevated cardiac enzymes, viewed in isolation from other donor factors, do not justify nonuse of a donor heart.

Recommendations for Extending Donor Empoyement

The assessment and management of donor left ventricular dysfunction offers the greatest potential to increase heart donor utilization. According to the 1995 UNOS database, 918 (42%) of 2199 unused donor hearts in the United States were declined because of poor ventricular function[53]. Strong evidence indicates, however, that younger hearts with left ventricular dysfunction can recover normal function over time in the donor and after transplantation into a recipient [54]. Although echocardiography is effective in screening for anatomic abnormalities of the heart, the use of a single echocardiogram to determine the physiological suitability of a donor is not supported by evidence. In addition, the accuracy of echocardiographic interpretation at donor hospitals may be suboptimal[55]. The Papworth Hospital transplant program in Great Britain increased its donor yield substantially by using a pulmonary artery catheter to guide the physiological assessment and management of ventricular dysfunction [56].

This approach has led to favorable recipient outcomes without the use of echocardiography.

Given that a single echocardiographic assessment may be inaccurate or may fail to predict long-term ventricular contractile function, failure to use a donor heart because of the initial ejection fraction alone is not justified. Hemodynamic and metabolic management should be performed before the organ is declined when donor left ventricular dysfunction is present. The goals of hemodynamic management are to achieve euvolemia, to adjust vasoconstrictors and vasodilators to maintain a normal afterload, and to optimize cardiac outputwithout relying on high doses of a agonists or other inotropes, which increase myocardial oxygen demand and deplete the myocardium of high-energy phosphates [57, 58]. Metabolic management includes maintenance of acid-base balance[59] and correction of the hormonal perturbations that occur after brain death and that impair circulatory function. There is evidence that treatment with insulin, corticosteroids [58, 59], riiodothyronine [60, 61] and arginine vasopressin improves ventricular performance, raises systolic blood pressure and reduces inotropic requirements.

Using a combined approach of hemodynamic and metabolic management, the Papworth program in Great Britain has shown that 92% of organs that fail to meet transplantation criteria on initial evaluation can be functionally resuscitated [56]. This has resulted in a 30% expansion of the Papworth donor pool[62].

.

Donor heart explantation

A median sternotomy is performed, and the pericardium is incised longitudinally. The heart is inspected and palpated for evidence of cardiac disease or injury. The superior and inferior venae cavae and the azygous vein are mobilized. Aorta is dissected from the pulmonary artery and isolated. The patient is administered 30,000 units of heparin intravenously. The azygous vein and superior vena cava are doubly ligated. The inferior vena cava is divided proximal to diaphfragm. Additional venting is achieved dividing the right superior pulmonary vein or cuttong the left atrial appendage is incised. After cross clamping the cardioplegia solution is infused and cold saline slush poured into the pericardium. The apex of the heart is elevated and pulmonary veins or left atrail cuff are divided. Than with a caudal traction the ascending aorta is transected proximal to the innominate artery, and the pulmonary arteries are divided distal to the bifurcation A long segment of the superior vena cava is transected.

Surgical thecnique of heart implantation

Following median sternotomy and vertical pericardiotomy, the patient is heparinized and prepared for cardiopulmonary bypass with bicaval venous cannulation and distal ascending aortic cannulation. The great vessels are transected above the semilunar commissures, whereas the atria are incised along the atrioventricular grooves, leaving cuffs for allograft implantation. Following cardiectomy, the proximal 1 to 2 cm of aorta and pulmonary artery are separated from one another.

In the donor heart the aorta is divided by the pulmonary artery. The left atrium is incised by connecting the pulmonary vein orifices, and excess atrial tissue is trimmed. Implantation begins from the left atrial suture beginning at the level of the left superior pulmonary vein in the recipient atrium and near the base of the atrial appendage in the donor atrium. The allograft is lowered into the recipient mediastinum. The suture is continued in a running fashion caudally and then medially to the inferior aspect of the interatrial septum. Some centers use continuous endocardial cooling of the allograft.

Once the left atrial anastomosis is complete, a curvilinear incision is made from the inferior vena caval orifice toward the right atrial appendage of the allograft. The right atrial anastomosis is performed in a running fashion similar to the left, with the initial anchor suture placed either at the most superior or inferior aspect of the interatrial septum so that the ends of the suture meet in the middle of the anterolateral wall.

The most commonly employed technique today is a bicaval anastomotic technique. With this technique, the recipient right atrium is excised completely, leaving a left atrial cuff and a generous cuff of the IVC and superior vena cava (SVC), respectively. In this case individual end-to-end anastomoses of the IVC and SVC are performed.

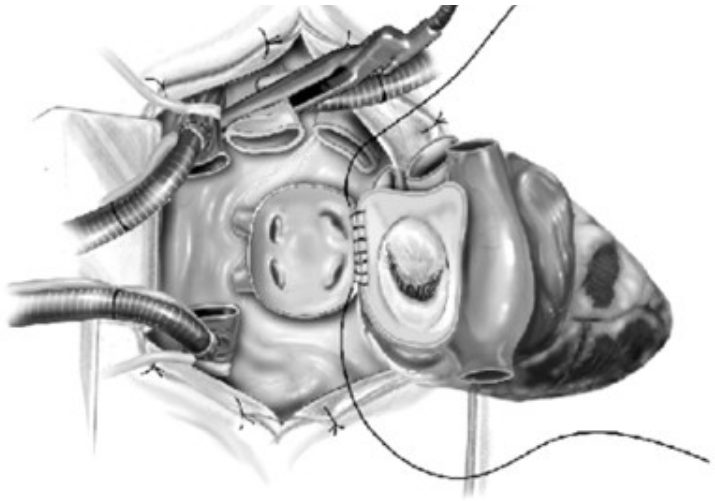
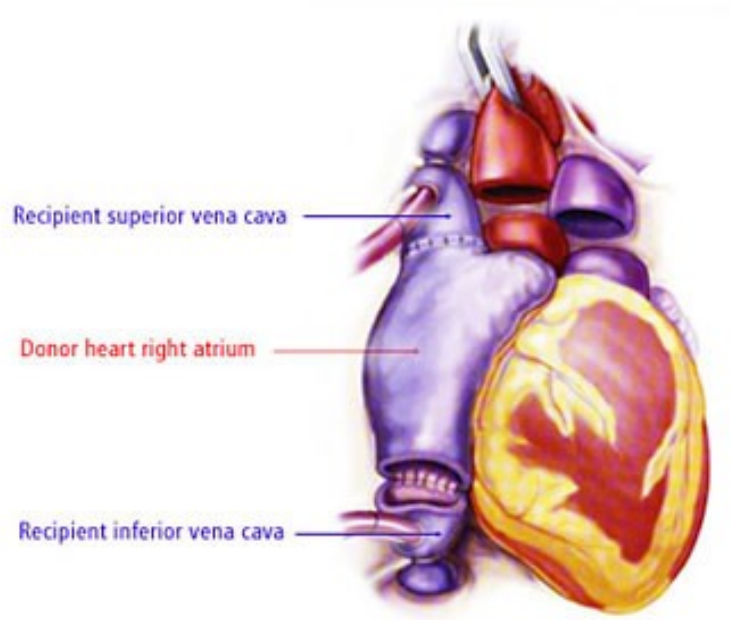


Figure 1: Heart transplantaiton. Surgical thecnique.

The end-to-end pulmonary artery anastomosis is next performed using a 4-0 Prolene suture beginning with the posterior wall from inside It is crucial to avoid kinking of the pulmonary artery Finally, the aortic anastomosis is performed using a technique similar to that for the pulmonary artery. Rewarming usually is begun prior to the aortic anastomosis. Routine deairing techniques then are employed. The aortic cross-clamp is removed. Following insertion of mediastinal and pleural tubes, the median sternotomy is closed in the standard fashion.

Figure 2: Heart transplantation. Surgical thecnique



Outcome of Heart Transplantation

Although no direct comparative trials have been or are likely to be performed, survival following heart transplantation remains favorable if compared with both the medical and device arms of the REMATCH trial. The superiority of heart transplantation is

more clearly evident in the medium- and high-risk patients with end-stage heart failure[63].

The most comprehensive information regarding patient survival after thoracic organ transplantation comes from data collected by the International Society for Heart and Lung Transplantation (ISHLT). The 2007 report included data from over 76,000 cardiac transplants performed since 1982 by more than 300 transplant programs and showed that there is an appreciable mortality in the first months. The reported operative (30-day) mortality for cardiac transplantation ranges from 5 to 10% [64]. Overall 1-year survival is up to 85%[65, 66]. The mortality during the first year is 1.4 times the mortality in the next four years combined[67].After the steep fall in survival during the first 6 months, survival decreases at a very linear rate (approximately 3.4% per year), even well beyond 15 years posttransplantation [66]. The half-life of patient survival has progressively improved from 8.9 years in 1982 to 1991 to 10.3 years in 1992 to 2001 to a projected half-life of approximately 11 years in 2002 to 2005. The major gains in survival are limited to the first 6 to 12 months, with the long-term attrition rate being unchanged. The improvement is probably larger than it appears, since the risk profile of recipients and the age of donors continues to increase.

The improvement in survival largely reflects improvements in immunosuppression and in the prevention and treatment of infection.

Recipient factors which influence prognosis are requirement for short-term extracorporeal mechanical circulatory support and congenital heart disease as the indication for transplantation (relative risk [RR] 3.38 and 2.13). Insulin-requiring diabetes prior to transplantation, or requiring dialysis or mechanical ventilation at the time of transplantation also increased the risk of mortality (RR 1.87, 1.83, 1.56,

respectively). Other identified risk factors were infection requiring IV drug therapy within 2 weeks prior to transplant (RR 1.28) and prior sternotomy (1.22). Even the use of a left ventricular assist device (LVAD) prior to transplantation but may be associated with a small decrease in long-term survival[68, 69]. There were also a number of continuous risk factors: recipient age, recipient weight (U-shaped curve, with better predictive power than body mass index), transplant center volume, increasing recipient pulmonary artery diastolic pressure, pulmonary vascular resistance, bilirubin, and creatinine.

Long donor heart ischemic time has an adverse impact on early prognosis [67]. Elevations in serum troponin I and T, which are markers of myocardial damage, predict the development of early graft failure and may be useful for heart donor selection. This was illustrated in a retrospective review of 118 brain dead donors who did not have renal insufficiency[52]. Elevated serum concentrations of troponin I (>1.6 μg/L) or troponin T (>0.1 μg/L) had a specificity of 94 and 99 percent, respectively, for predicting early graft failure; the odds ratio of developing graft failure was 43 and 57, respectively.

A female donor and donor history of hypertension were no longer significant risk factors as they were in earlier eras.

Risk factors for late mortality are less well defined. The most important risk factor is repeat transplantation (RR 3.86). Other risk factors are age HLA-DR and -B mismatches, preoperative diagnosis of coronary artery disease and male recipient of female donor, history of diabetes, drug-treated rejection prior to initial discharge and drug-treated infection prior to initial discharge. Hypertension, hyperlipidemia, diabetes mellitus, and renal dysfunction are all noted in a significant proportion of cardiac

transplant recipients and the incidence of these morbidities at each post transplant time-point have been increasing over time.

Causes of mortality differ in the time period at which they are most likely to occur, Graft failure and acute rejection occur early, allograft vasculopathy (with associated late graft failure) and malignancy later, and non-CMV infection at any time, but particularly between 31 days and one year.

Early cardiac failure still accounts for up to 4-20% of perioperative deaths of heart transplant recipients with a lack of objective standardized definition [70-72].

Many factors can interact in the genesis of EGF: increased pulmonary vascular resistances, myocardial dysfunction owing to donor instability, preservation injury, intrinsic organ donor dysfunction and acute rejection. Mechanical support with an intra-aortic balloon pump or ventricular assist device can be attempted in patients refractory to pharmacologic interventions, although this measure, as well as retransplantation, is associated with very high mortality[73].

Chronic left ventricular failure frequently is associated with elevated pulmonary vascular resistance, and the unprepared donor right ventricle may be unable to overcome this increased afterload. Although recipients are screened to ensure that those with irreversible pulmonary hypertension are not considered for transplantation, right-sided heart failure remains a leading cause of early mortality. Initial management involves employing pulmonary vasodilators such as inhaled nitric oxide, nitroglycerin, or sodium nitroprusside. Pulmonary hypertension that is refractory to these vasodilators sometimes responds to prostaglandin E1 (PGE1) or prostacyclin[73, 74].

Cardiac allograft rejection is the host response to cells recognized as nonself. Although about 85% of episodes can be reversed with corticosteroid therapy alone[75], rejection

is still a major cause of morbidity in cardiac transplant recipients[66, 76]. The vast majority of cases are mediated by the cellular limb of the immune response. Humoral-mediated rejection is less common. The highest risk factors are allografts from younger and female donors (irrespective of recipient sex)[77].Changes in immunosuppressive therapy have had a major impact on improving survival after heart transplantation, as evidenced by the decreasing number of deaths owing to rejection in recent years. Currently, the immunosuppression protocols for heart transplantation (so-called triple therapy) include a calcineurin inhibitor such as cyclosporine or tacrolimus, an antiproliferative agent such as azathioprine, mycophenolate mofetil, and corticosteroids such as prednisone or prednisolone.

Non-CMV infection represented the leading single cause of death from six months post-transplant through ten year follow-up [67]. However, the combination of allograft vasculopathy and late graft failure (most often due to allograft vasculopathy) accounted for more cumulative deaths than infections alone. Types of infection in these patients are diverse, including common, community-acquired bacterial and viral diseases and uncommon opportunistic infections of clinical significance only in immunocompromised hosts [52, 78]. The risk of infection in the heart transplant patient is determined by a semi-quantitative relationship between two factors: the epidemiologic exposures of the individual and the "net state of mmunosuppression," which is a measure of all of the factors that contribute to the individual's susceptibility (or resistance) to infection.

Analyses of multiple data bases have shown that malignancies (both lymphoma and solid tumors) are more common in heart compared with renal transplant recipients probably due to the overall need for more intense immunosuppression.

Allograft vasculopathy is a unique, rapidly progressive form of atherosclerosis in transplant recipients. Long-term survival of cardiac transplant recipients is limited severely by the development of this complication that is reported in approximately 40 to 50% of patients by 5 years after transplantation [67]. Allograft vasculopathy is characterized by intimal proliferation is concentric rather than eccentric, and the lesions are diffuse, involving both distal and proximal portions of the coronary tree. Calcification is uncommon, and the elastic lamina remains intact.

Quality of Life after Transplantation

Ninty % of patients has no limitation of activity at one and five years [67]. However, despite generally excellent functional capacity following cardiac transplantation, less than 30 % of patients return to full-time work; less than 10 % resume only part-time work and about 40 % remain unemployed. In the United States, this discrepancy may be in part related to the link between employability and insurability.

Mortality in wayting list

Controlled trials of patients with stable NYHA class III to IV have demonstrated mortality benefit from medical management including angiotensin converting enzyme (ACE) inhibitor therapy, beta-blocker (eg, carvedilol, metoprolol succinate, and bisoprolol) therapy, and aldosterone antagonist therapy, and, for African Americans, combination hydralazine/nitrate therapy. Subsequent to these observations, randomized trials of patients with NYHA class III to IV showed improved survival with two device therapies: implantable cardioverter-defibrillator (ICD) for primary prevention of sudden cardiac death and cardiac resynchronization therapy in patients with a wide QRS, often

in a combined device with an ICD. Survival on the waiting list significantly improved between the era 1990 to 1994 and the era 2000 to 2005. Predictors of death within two months from listing of status 1 candidates included status 1A, mechanical ventilation, inotropic and intra-aortic balloon pump support, pulmonary capillary wedge >20 mmHg and serum creatinine >1.5 mg/dl, failed cardiac transplant, valvular cardiomyopathy, age >60 years, Cauccasian ethnicity, weight ≤70 kg, as well as lack of ICD on the day of listing. One-year survival for status 1 candidates improved from 49.5 to 69.0 %; for status 2 candidates it improved from 81.8 to 89.4 %.

The one-year survival of status 2 candidates approached outcomes with heart transplantation. Thus, the one-year mortality in patients with advanced failure treated medically has fallen dramatically with improvements in medical and device therapy[40]. Pulsatile LVAD in patient with heart failure demonstrated results significavelly superior to medical therapy but in post Rematch era results did not improove. New axial LVAD support in the last years increased the quality of life of these patients and obtained a survival similar to heart transplant.

History of Mechanical Circulatory Support

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.

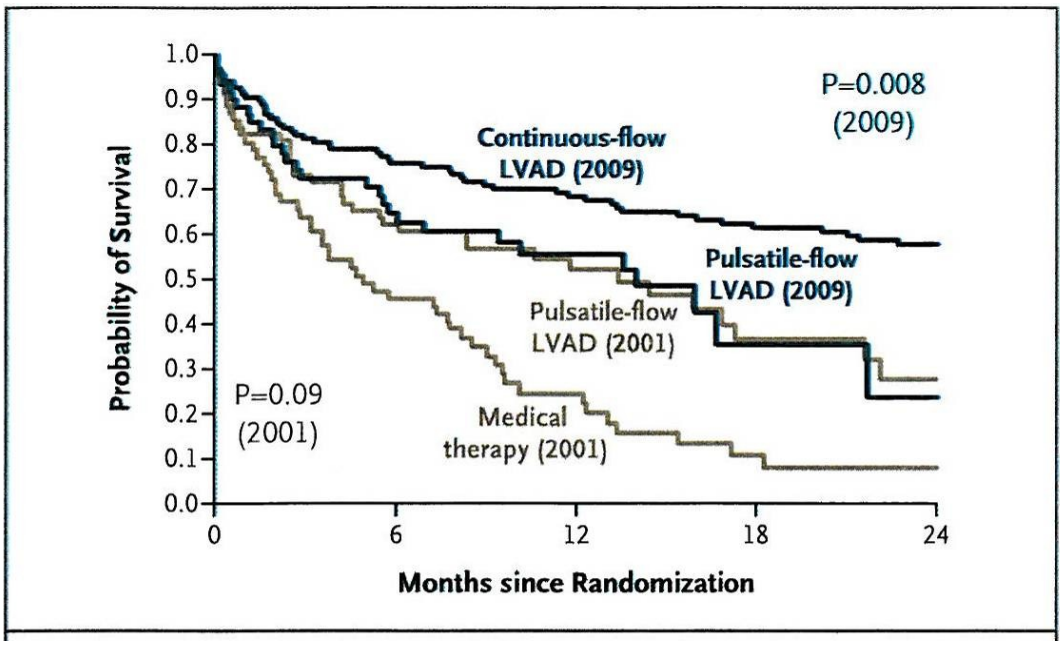
The second step was the development of different devices as bridge to transplant. The total artificial heart was used first as support until transplantation by Cooley in 1969 while the first case of bridging to transplantation with pneumatic assist device is due to Norman in 1978. Better results were 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 a second and third generation of pumps as Incor, DeBakey, Jarvik2000, HeartMateII were developed.

These rotatory devices without mechanical or touching bearings can support circulation for long term and may be considered for destination therapy, in patients non eligible for heart transplantation. 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 use. After the approval of axial flow LVAD by the FDA we assisted to an impressive reduction of morbidity and mortality [79].

Figure 3: Kaplan-Maier survival curves for patient receiving medical therapy or LVAD in REMATCH study in pre e post-REMATCH trial and after the introduction of axial flow LVAD.



SHORT-TERM CARDIAC SUPPORT

Indications to Short Term Mechanical Circulatory Support

Patients in cardiogenic shock require early aggressive therapy. Despite inotropic drugs, intubation, and control of cardiac rhythm, some patients remain hemodynamically unstable, are refractory to medical therapy, and require some type of mechanical circulatory support [80, 81].

Hemodinamic criteria used as indication for temporary circulatory support include a cardiac index of less than 2.2 L/min/m^2, systolic blood pressure of less than 90 mm Hg, mean pulmonary capillary wedge pressure or central venous pressure of greater than 20 mm Hg, and concomitant use of high doses of at least two inotropic agents[82]. These situations may be associated clinically with arrhythmias, pulmonary edema, and oliguria.

Circulatory support with either mechanical assist devices remains the only means of survival in this very sick group of patients who often have extreme hemodynamic instability, coagulopathy, and multiple end-organ dysfunction suchas significant renal and liver failure.

The need for circulatory support in the postcardiotomy period has been estimated to be in the range of 0.2 to 0.6% [83]. In addition, cardiogenic shock occurs in 2.4 to 12% of patients with acute myocardial infarction[84] with a mortality as high as 75% [85].

The complex and lengthy operation for placement of a permanent VAD further increases the morbidity and mortality associated with this condition. Further, outcomes of permanent LVAD implantation in patients with multisystem organ failure (MSOF) with prior cardiac arrest or severe hemodynamic instability are extremely poor [86]

Additionally, transplant candidacy is uncertain with the combination of MOF, uncertain neurologic status, and uncertain social support (due to lack of time to adequately perform such an evaluation). Therefore, there is clearly a role for temporary circulatory support in this population as a bridge to decision. This support must be easy to place, rapidly stabilize the patient's hemodynamics, be transported easily with the patient, and allow time to address the patient's MOF and neurologic status.

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

Short Term Devices

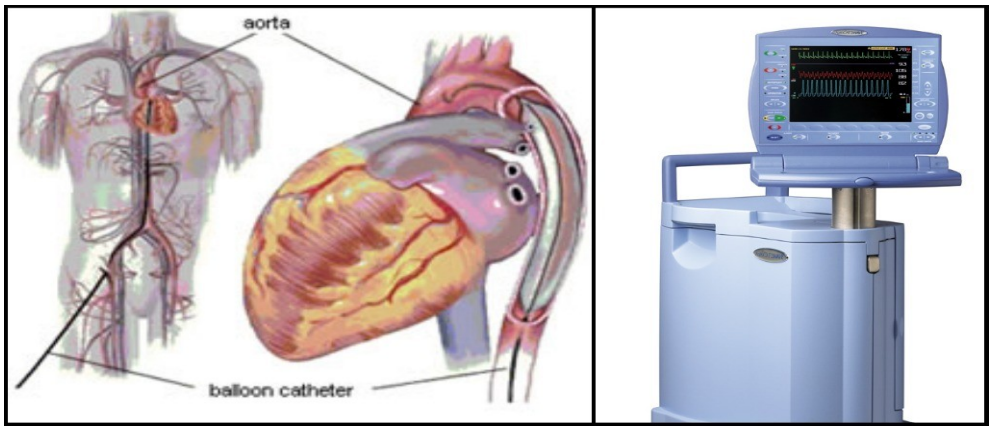
Counterpulsation devices

The Intra-aortic balloon pump (IABP) is a mechanical device that increases myocardial oxygen perfusion while at the same time increasing cardiac output. Increasing cardiac output increases coronary blood flow and therefore myocardial oxygen delivery. It consists of a cylindrical polyethylene balloon that sits in the aorta, approximately 2 centimeters from the left subclavian artery and counterpulsates. That is, it actively deflates in systole, increasing forward blood flow by reducing afterload. It actively inflates in diastole, increasing blood flow to the coronary arteries. These actions combine to decrease myocardial oxygen demand and increase myocardial oxygen supply.

The 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 4).

Figure 4: Intraaortic Balloon Pump.

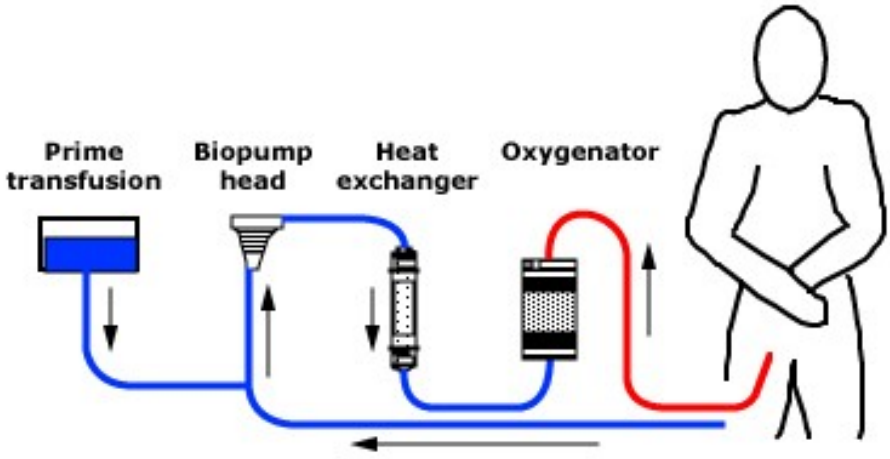


Cardiopulmonary support (CPS) provides full cardiopulmonary support (including hemodynamic support and oxygenation of venous blood) analogous to that provided by bypass during cardiac surgery. Blood from the venous catheter is pumped through a heat exchanger and oxygenator, and then returned to the systemic arterial circulation via the arterial cannula. CPS requires continuous, highly technical support.

The CPS may be used in case of acute hemodynamic deterioration such as cardiogenic shock and cardiopulmonary arrest, and fulminant myocarditis presenting with cardiogenic shock [87]. CPS is contraindicated in case of the significant aortic regurgitation, severe peripheral artery disease, bleeding diathesis, recent CVA or head trauma and 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 % of patients, with almost one-half requiring surgical treatment. Recent revisions in technique have decreased the major complication rate to only 1.4 % [88].

Figure 5: 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.



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 6: 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.

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.

A particularly useful niche for the device is for donor heart dysfunction following transplantation.

Figure 7: Abiomed 5000™ circulatory support system

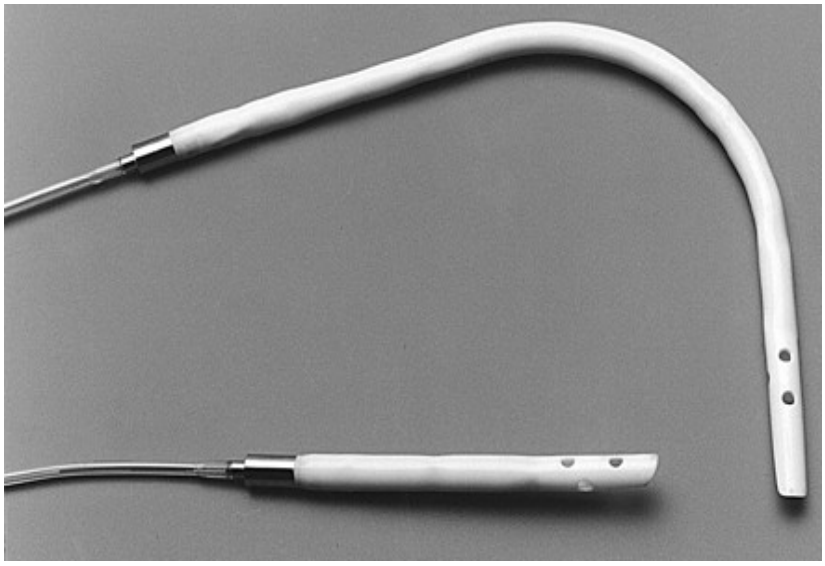
Berlin Heart EXCOR is a paracorporeal mechanical, pulsatile system for short- to long-term support of left or/and right ventricular pumping function. Since the beginning it has had and has still a great success all over the world, because it is the only paracorporeal system available also in the paediatric configuration.

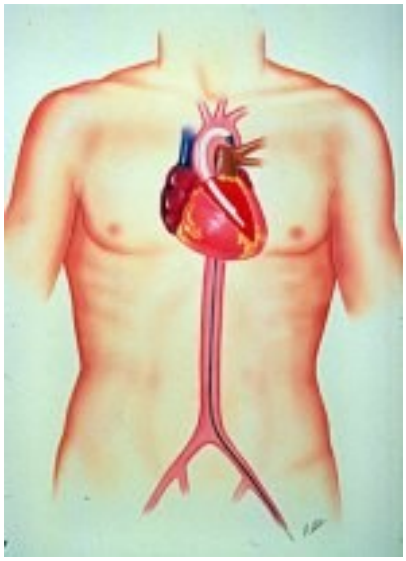
Figure 8 Berlin Heart EXCOR

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. A good and simple example is the Hemopmp system.

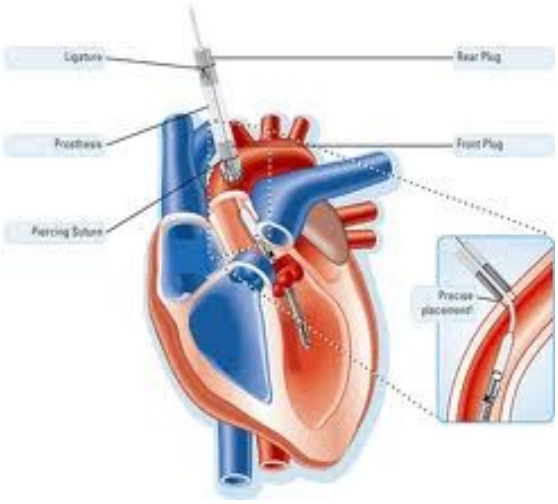
Figure 9: The Hemopump system.





The Hemopump system has a centrifugal screw pump at the proximal portion of the soft 14F cannula that draws blood from the left ventricle and ejects it into the central aorta just beyond the pump. Clinical use of the Hemopump in patients began at the Texas Heart Institute in April 1988 as a short-term treatment (hours to days) for cardiogenic shock. This catheter-mounted, intra-aortic axial flow pump is about the size of the eraser on an ordinary pencil. It was inserted through a small incision in the femoral or external iliac artery, advanced to the aorta, and positioned across the aortic valve. A screw element rotated 17,000 to 25,000 times per minute. Power was provided through a percutaneous drive-line connected to an external electromechanical console. The console produced flows of up to 3.5 liters per minute and assumed up to 80% of the left ventricle's workload.

Figure 10: Impella microaxial flow device



The Impella 2.5 is a percutanously placed microaxial support device that pumps blood from the ventricle nto the ascending aorta and can deliver up to 2.5 L/min of flow augmentation [89]. It is inserted via a 13-French catheter into the femoral artery and positioned across the aortic valve, with outflow in the ascending aorta, under fluoroscopic guidance. Once placed across the aortic valve, the catheter is connected to a portable external console for monitoring pump speed and invasive pressure measurements, which help to verify pump function and positioning. The console has nine gradations n speed from 2000 to 50,000 rpm. At maximum rpm, the pump can provide a flow of 2.5 L/min. After insertion, the patients should be placed on a heparin drip to maintain a partial thromboplastin time (PTT) of 50 to 56 seconds [86, 89, 90].

The Impella 2.5 has been used as a percutaneous LVAD successfully during high-risk coronary angioplasty and for patients with cardiogenic shock caused by myocardial infarction[91, 92]. In this subset of patients, Seyfarth et al. found that when compared to treatment with traditional IABP, the Impella 2.5 device provided superior hemodynamic

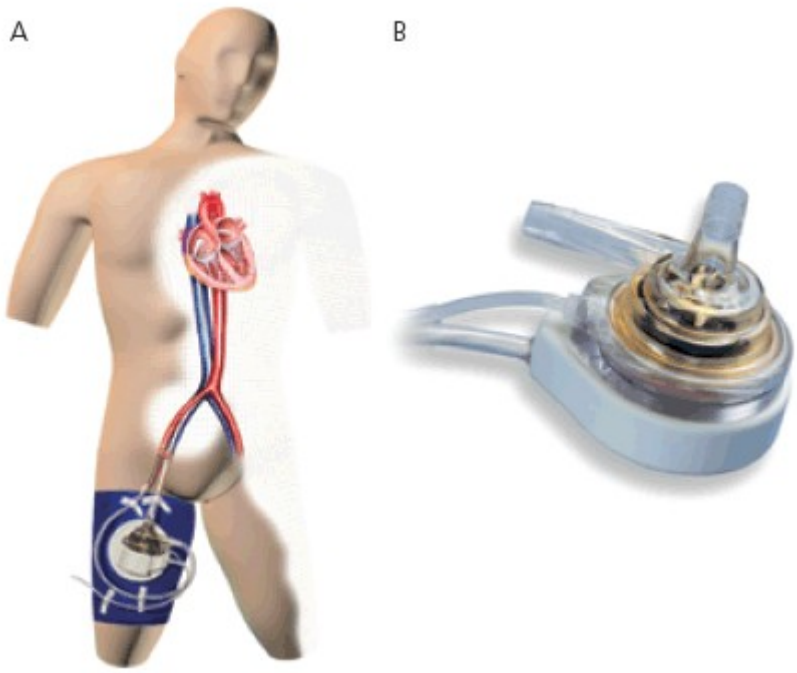
support and was both feasible and safe. This study did not, however, find a significant difference in 30-day mortality between the two groups [91]. Abiomed also makes the Impella 5.0 percutanous device that can produce flows of up to 5 L/min. In contrast to the Impella 2.5, the Impella 5.0 device requires a surgical cutdown for access and placement into the femoral artery[93]. This device has been used via the femoral artery to successfully treat acute heart failure due to acute cardiac allograft rejection [93].

Abiomed also manufactures the surgically implanted Impella LD (Abiomed Inc.). It is inserted retrograde through a 10-mm vascular graft that is sewn to the ascending aorta, then through the aortic valve and positioned using TEE and pressure measurements. The tail of the graft with the device line inside is brought out through the apex of the sternotomy incision with the sternum left open with skin closure or a synthetic patch. Siegenthaler et al. used the Impella LD for circulatory support in patients with postcardiotomy heart failure. The device functioned similarly to the percutaneous approach and flows were found to be 3.5 to 5.0 L/min. Once weaned, the device was removed and the graft was ligated flush with the ascending aorta or oversewn and the sternum was closed. The study found that mortality was significantly reduced in patients with the Impella LD device if their heart was able to pump 1 L/min or more above the device flow. The Impella 5.0 can produce flows of up to 5.0 L/min, and was recently approved by the FDA in April 2009 for providing temporary circulatory support;.

Some disadvantages of the Impella and all percutaneous devices are limited availability, short duration for support, possibility for cannulae dislodgement, lower extremity ischemia, and the difficulty for transport to a tertiary care facility.[94, 95].

Tandem Heart: The TandemHeart (Tandem Heart™)is a left atrial-to-femoral artery bypass system comprising a transseptal cannula, arterial cannulae, and a centrifugal blood pump. The pump can deliver flow rates up to 4.0 L/min at a maximum speed of 7500 rpm.

Figure 11: Tandem Heart.

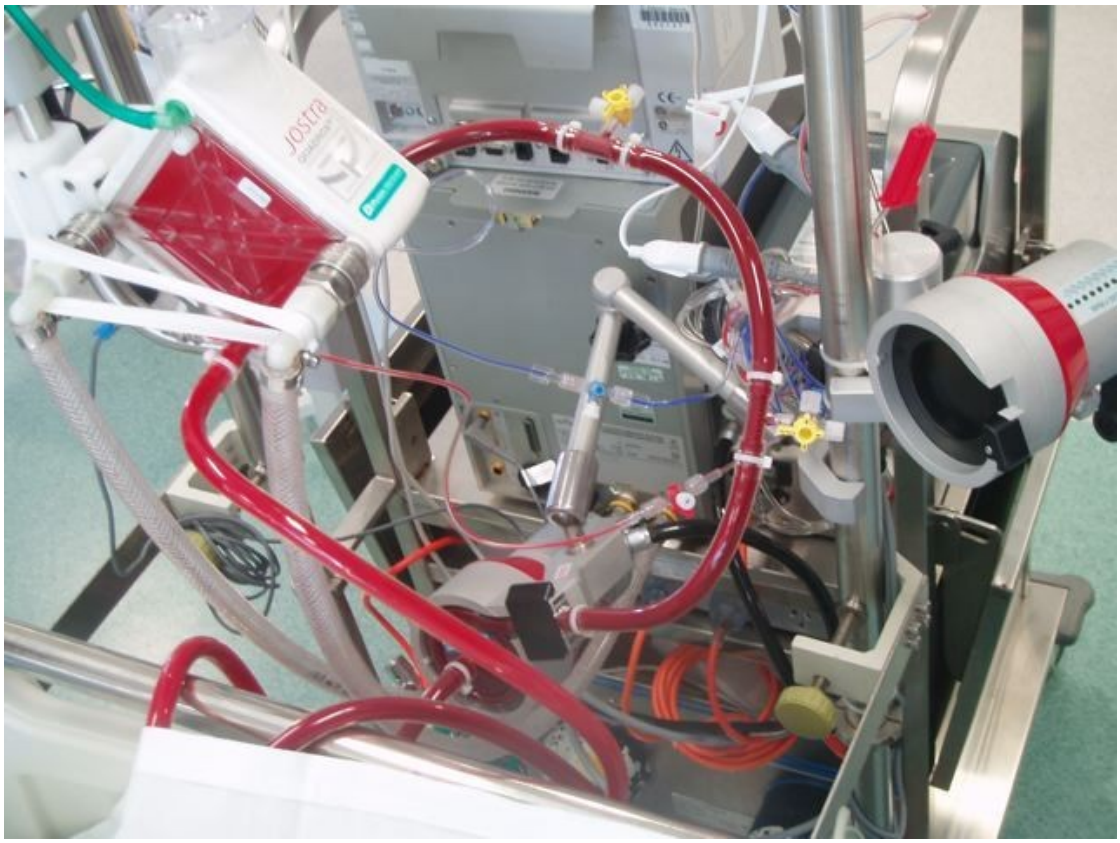


Extracorporeal Membrane Oxigenation (ECMO)

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 12: Extracorporeal membrane oxygenation



ECMO has been used for the treatment of cardiogenicshock in adult patients for several decades.

The main difference between other VAD devices andECMO is incorporation of an oxygenator into the circuit[96, 97]. It is used when a patient has both heart failure and inability to adequately oxygenate the blood.

The basic ECMO circuit is composed of inflow and outflow cannula, a blood pump, and an in-line oxygenator. The technique for cannulation depends on the indicationfor placement. In patients with postcardiotomy failure, cannulation is typically via the ascending aorta and right atrium, which were used for CPB. Another site for cannulation is the femoral artery for arterial outflow and the femoral vein for inflow. Other large vessels like the subclavian artery and internal jugular vein can be used for arterial and venous access respectively[96, 98]. The patient can be placed on ECMO at the bedside via percutaneous femoral access, or a femoral cutdown. Often, ECMO circuits are heparin coated; however, the patient still requires full anticoagulation with heparin to maintain an ACT of 160 to 180 seconds. While on ECMO a patient's coagulation parameters, platelets, and hemoglobin are monitored closely because of platelet destruction and hemolysis secondary to trauma in the circuit and oxygenator. Platelets are typically kept at greater than 100,000 109/L and hemoglobin greater than 10 g/100mL [96, 98]. Although the pump provides adequate oxygenation, the patient is ventilated normally to prevent pulmonary atelectasis. Blood flow onECMOdepends on the pump used; however, it is at least at 2.5 L/min−1·m−2 for full circulatory support. Patients are weaned from support as soon as pulmonary and cardiac functions are adequate. Bleeding is a major complication associated with ECMO support due to platelet destruction and need for high levels of anticoagulation. Unfortunately, the stringent adherence to anticoagulation is necessary to prevent clot formation that can embolize or disturb the pump flow in the circuit components. Frequent checks of coagulation profile and platelet count with appropriate administration of blood products can help to prevent this complication. Another major complication is distal leg ischemia seen with peripheral cannulation [96, 98].

Results of Short Term Support

There are currently many options to treat patients presenting with acute refractory cardiogenic shock. These patients have historically been treated with IABP. ECMO is suitable for cardiopulmonary support, it does not always unload the ventricles to the degree possible with a VAD, requires stringent anticoagulation and has high rate of device-related complications [96-98]. Temporary ventricular assist devices provide adequatecirculatory support while allowing MOF to recover and neurologic status to be adequately assessed. While questions remain as to the ideal device, the optimal duration of temporary support, and the timing to bridge to a long-term device.

Published reports suggest that weaning can be accomplished in approximately 45 to 60% of patients; however, survival overall is less than 30%, with only 50% of weaned patients discharged alive from the hospital. Risk factors associated with increased mortality have included age greater than 60 years, emergency operations, reoperations, renal insufficiency, and pre-existing LVD. In all series, sepsis, multisystem organ failure, and neurologic complications stand out as the causes of death.

The overall survival rate in reported series over the last decade has undergone a significant improvement at transplant centers where appropriate candidates are bridged to transplantation after a period of support. In the Cleveland Clinic experience, 72% survived after bridge to transplantation with 92% 1-year survival. Korfer and colleagues[99] supported 68 patients with the ABIOMED BVS 5000, 32 patients were weaned and 13 were transplanted with an overall survival of 47%.

Complications tend to increase with increasing length of support. Therefore, in general, these devices are used for less than 2 weeks, but longer durations have been reported.

During the acute phase, bleeding remains a significant problem, occurring at suture lines and cannulation sites and often a diffuse coagulopathy.

Golding had reported severe bleeding in 87% of patients supported with centrifugal pumps, with a mean transfusion requirement of 53 units of blood[100]. More recently, the Cleveland Clinic reported a median transfusion requirement of 14 units using ECMO[101].

Despite the development of heparin-coated systems thrombin deposition in centrifugal pumps remains a constant. Golding reported thromboembolism in 12.7% of 91 patients supported with a centrifugal pump. Similarly, thromboembolic incidences of 8 and 13% have been reported for the Thoratec and ABIOMED devices, respectively.

LONG-TERM CARDIAC SUPPORT

Indications to Long Term Mechanical Circulatory Support

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 success [102].

There are no absolute hemodynamic criteria to meet in order to implant one LVAD, 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 mmHg [102].

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) ≤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 [103].

Other reports suggest to consider the evidence of cardiac decompensation. 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 [103].

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 LVADs. Additionally, in some instances, LVADs 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 mechanical circulatory support (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 [104].

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 [105].

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 bed 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 [105].

An episode of cardiac arrest prior to the initiation of MCS significantly reduces intra-operative survival (7% versus 47%) [103].

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 [105].

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 with 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 LVAD to prevent right-to-left shunting. In fact during left ventricular assistence 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 VAD 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 [103]. 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 VADs [106].

Long Term Devices

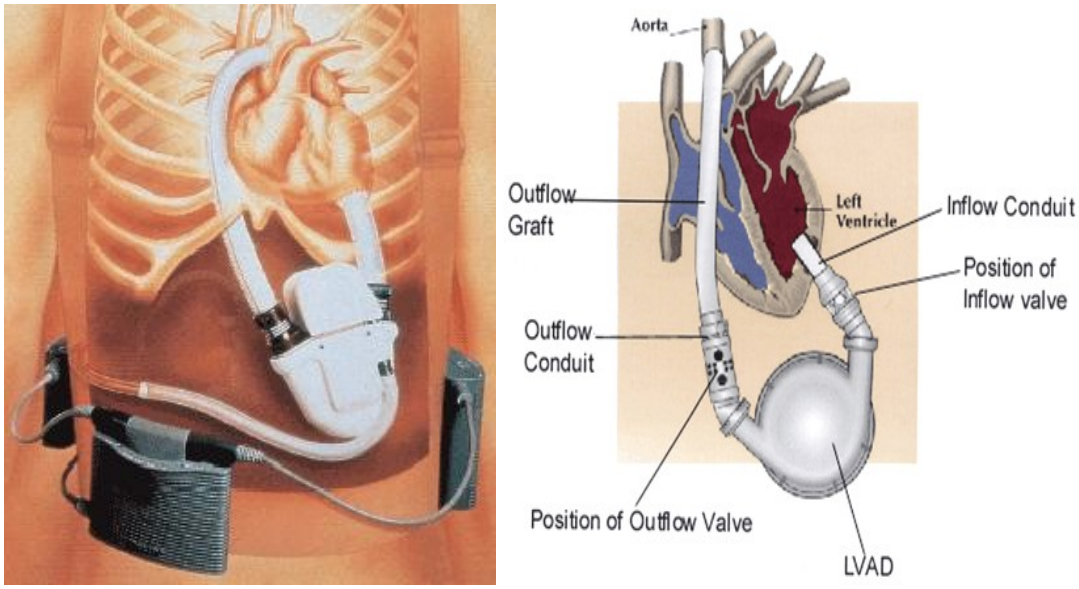
The most widely used device approved by the Food and Drug Administration (FDA) is the Thoratec Paracorporeal Ventricular Assist Device (PVAD). It is a paracorporeal system, in which the pump is located outside the body. It is versatile allowing for RVAD, LVAD, or BVAD configuration (Figure 11). The atria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

Figure 13: The Thoratec ventricular assist system in the biventricular support configuration

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. Despite the advances in the design of the Thoratec PVAD, 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 [107].

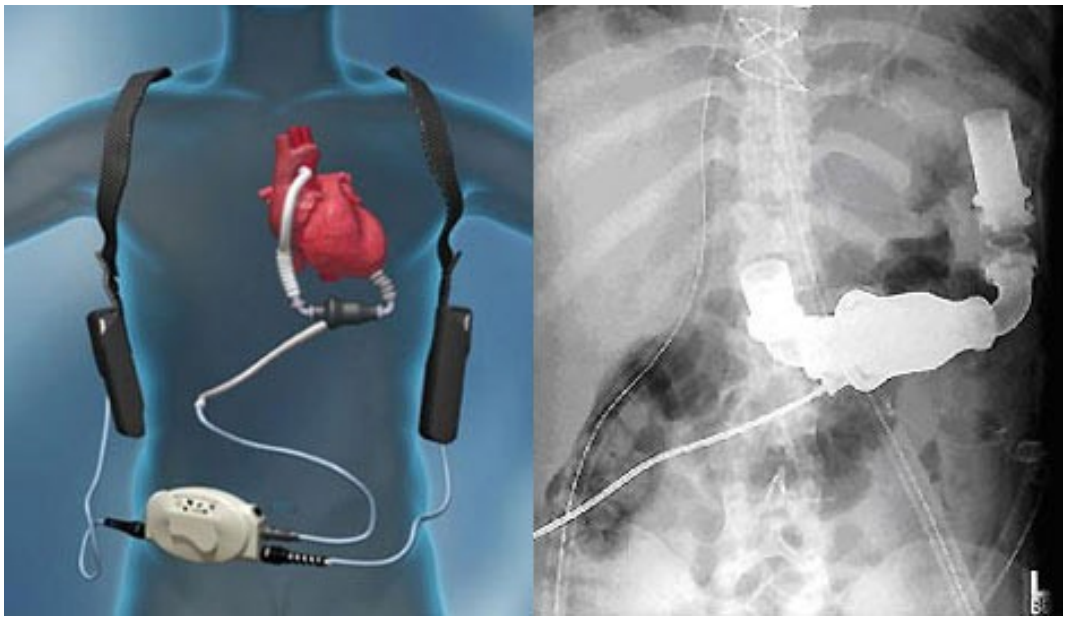
The Novacor VAD in an intracorporeal device who works with a magnetic actuator . The electromagnet activates a pusher plate designed to collapse a bladder which along with two bioprosthetic valves propels blood in one direction, from the left ventricular apex to the ascending aorta. As with other LVADs,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

Figure 14: The Novacor and Heart Mate left ventricular assist system



The Heartmate 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 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 [108, 109]. These clinical benefits, together with the physical recovery that is possible in the ambulatory patient, reduce the perioperative risk to patients undergoing transplantation. 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

Figure 15: The Heartmate II LVAS pump.



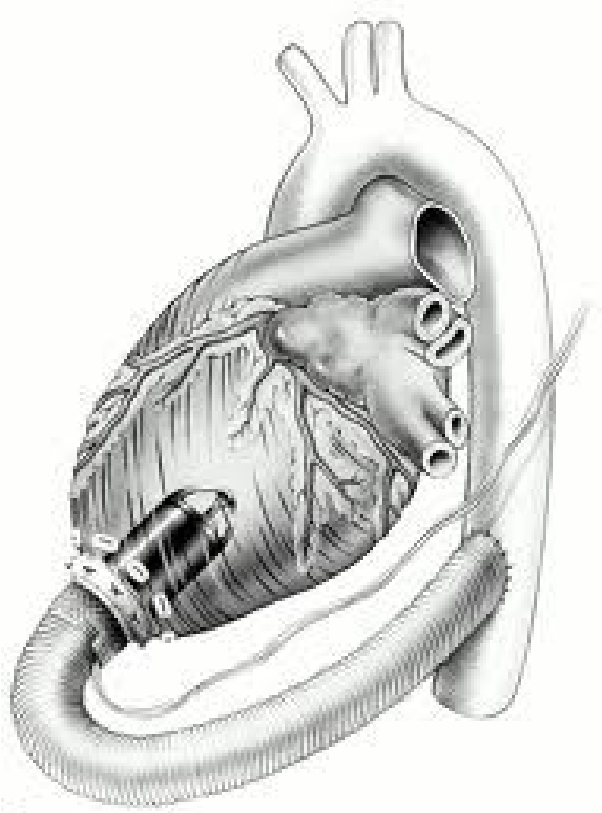
Axial-flow impeller pumps, with their potential for small size, low noise, and absence of a compliance chamber, have been developed for clinical use. They provide continuous rather than pulsatile flow and are totally implantable.

The HeartMate (FDA approved as destination therapy in 2010) is a continuous flow device consisting of an internal axial flow blood pump with a percutaneous lead that connects the pump to an external system driver and power source. The redesigned HeartMate II has a left ventricular apical inflow cannula with a sintered titanium blood-contacting surface. The bladed impeller spins on a bearing and is powered by an electromagnetic motor. No compliance chamber or valves are necessary, and a single driveline exits the right lower quadrant of the abdomen. The inlet cannula is placed in the ventricular appendage, and the pump is placed either intraperitoneally or extraperitoneally. The outflow cannula is connected to a Dacron graft, which is then anastomosed to the ascending. The external controller and batteries resemble those of the original HeartMate as well. The pump is designed to spin at 6,000 to 15,000 rpm and to deliver as much as 10 L/min of cardiac output. A computerized algorithm is used to continuously estimate flow from the device.

.

The Jarvik 2000 pump is a compact intracardiac continuous axial flow impeller pump that is silent, easily implantable and unobtrusive [110] (Figure 16). 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.

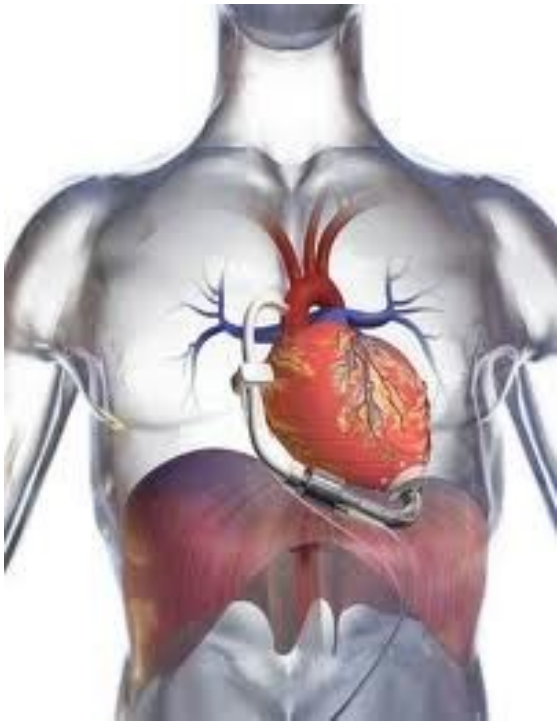
Figure 16: Jarvik 2000.



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 [111].

Figure 17 The DeBakey LVAD

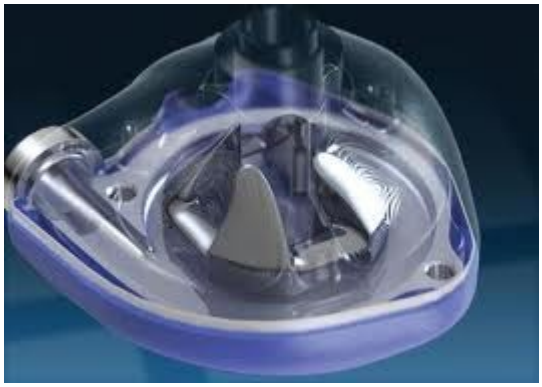


The DeBakey VAD Child (HeartAssist 5 Pediatric VAD) is FDA approved under the Humanitarian Device Exemption program as a bridge to transplantation in children between 5 and 16 years old [112]. The HeartAssist 5 device is EC certified but is not FDA approved in adults.

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. 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 18: 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. The pump is designed to draw blood from the left ventricle and propel it through an outflow graft connected to the patient's ascending aorta. The device is capable of generating up to 10 liters of blood flow per minute. With a displaced volume of only 50cc, the device pump is designed to be implanted in the pericardial space, directly adjacent to the heart. Implantation above the diaphragm is expected to lead to relatively short surgery time and quick recovery. The HVAD pump has only one moving part, the impeller, which spins at rates between 2,400 and 3,200 revolutions per minute. The impeller is

suspended within the pump housing through a combination of passive magnets and hydrodynamic thrust bearings. This hydrodynamic suspension is achieved by a gentle incline on the upper surfaces of the impeller blades. When the impeller spins, blood flows across these inclined surfaces, creating a "cushion" between the impeller and the pump housing. There are no mechanical bearings or any points of contact between the impeller and the pump housing.

Device reliability is enhanced through the use of dual motor stators with independent drive circuitry, allowing a seamless transition between dual and single stator mode if required. The pump's inflow cannula is integrated with the device, ensuring proximity between the heart and the pump itself. This proximity is expected to facilitate ease of implant and to help ensure optimal blood flow characteristics. The use of a wide-bladed impeller and clear flow paths through the system are expected to help minimize risk of pump induced hemolysis (damage to blood cells) or thrombus (blood clotting).

Figure 19: The Heartware left ventricular assist system

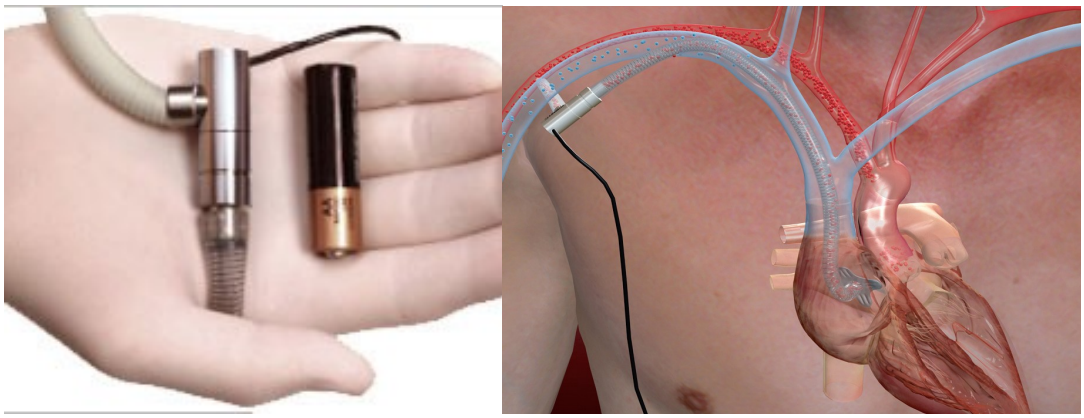
The Terumo Duraheart most important and peculiar characteristics are a closed straight blade impeller which helps minimize turbulence by promoting gentle and consistent flow patterns, a wide stable spacing between the impeller and chamber wall which helps minimize pump-induced hemolysis by providing ample room for smooth unimpeded flow and a proper washout. 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 20: 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. 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 [113].

Figure 21: CircuLite Synergy Pocket Micropump

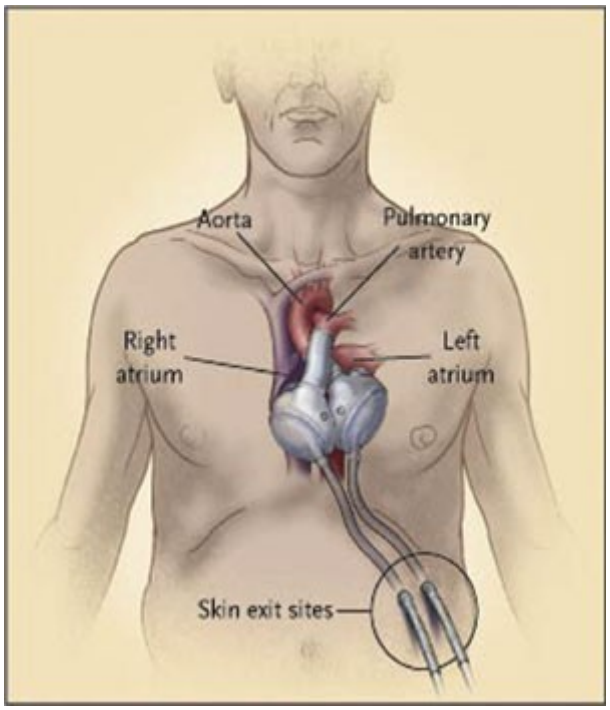


Total artificial Heart

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: The CardioWest total artificial heart



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 batteries [5, 26, 114].

Abiomed TAH is a thotal artificial heart totally implantable. 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

Results of long term support

In 2002, the International Society for Heart and Lung Transplantation (ISHLT) began the ISHLT Mechanical Circulatory Support Device database. This voluntary database has collected information on mechanical circulatory support from 60 centers globally[115]. Nowadays more than three hundred patients underwent LVAD implantation as an alternative to heart transplantation, or destination therapy (DT) with a doubled number of implantation in the last year that is reaching the number of heart transplantation per year in the US.

The vast majority of patients underwent isolated LVAD placement, overall survival was 70-80% at 1 year and 60-70% at 2 years.

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 transplantation [103]. 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 transplantation [116]. 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% [103, 117]. 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 trial [103], 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 patients [118]. 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 [119]. 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 [119].

Transplant after LVAD therapy presents some pequliarity that has to be underlined. LVAD implantation was performed as a bridge to transplantation in 18 % of IHLTS Registry patients [120]. In these patients humoral sensitization (panel-reactive antibody [PRA] screen >10 percent) was significantly increased but without effect on the rate of rejection after transplant. The interaction between prosthetic device surfaces and circulating blood elements has systemic immunologic effects in patients undergoing device implantation. Itescu and John have described aberrant T-cell activation and heightened T-cell proliferation, as well as increased apoptotic cell death, and simultaneous defects in T-cell proliferation in response to T-cell–receptor activation. In addition, T cells in LVAD patients demonstrated increased susceptibility to activation-induced cell death. Another aspect of immunologic disturbance that is seen is B-cell hyperreactivity. Alterations in circulating cytokines and cellular milieu are postulated to be responsible for polyclonal B-cell activation. Patients undergoing LVAD placement have a higher frequency of circulating antiphospholipid and anti–human leukocyte

antigen antibodies. The overall clinical effect of these changes is not clear but might increase the risk of infections and rejection.

LVAD use was associated with a small but significant reduction in survival at one year (82.3 versus 87.1 percent) and two years (77.8 versus 83.0 percent). A similar mortality difference was seen when only status 1A patients were analyzed, suggesting that the difference was not due to LVAD use being performed in sicker patients. LVAD use was not associated with increased risk of five year mortality[120].

Increase in mortality was most prominent when transplantation was performed either within the first two weeks or after six months post LVAD placement. This may reflect at least in part the early deaths of unstable patients and the eventual development of device-related complications, respectively

Morgan and associates recently reported the bridging-to-transplantation experience at Columbia Presbyterian Hospital.[121]. This series of 243 patients spanned a period of 12 years and included three versions of the Thoratec Heartmate device (pneumatic, dual-lead vented electrical, and single-lead vented electrical). Over this time period, improvements were seen in rates of successful bridge to transplantation and in 1-, 3-, and 5-year survival following transplant. The authors attribute this improvement to a combination of factors, including advances in device design, patient selection, surgical technique, and perioperative patient management.

Concerning morbidity 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 [122]. LVAD-related infection was diagnosed in 38 patients (50 %); 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 [123].

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 [124].

Other complications include: mechanical irritation of the left ventricle produces ventricular arrhythmias in over 25 percent of patients, left ventricular thrombosis 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 [125], thrombocytopenia is seen in 7 percent, some degree of hemolysis occurs in most patients, but is generally not severe enough to be a significant problem.

Extended Selection Criterias for Heart Transplant Candidates, a Single Center 10 Years Experience.

Aim of the study

The past 30 years of cardiac transplantation (CT) have led to better medical management of recipients.

Adherence to fairly rigid criteria for recipient selection has been considered a prerequisite for a successful outcome after heart transplantation. However, increasing experience and improved results of CT have led to a less strict observation of such criteria in an effort to extend the benefits of this operation also to patients previously judged to be marginal or unacceptable candidates [126]. Shortage of donor organs apparently militates against this attitude since the goal of reaching the highest possible rate of success is best achieved by careful recipient selection and its imperative to allocate organs to patients with the greatest need and the greatest chance to derive the maximum benefit [127]. In an effort to reasonably enlarge the pool of candidate, adequate risk assessment at the time of candidacy evaluation, based on classical criteria but also on extended criteria seemed a reasonable approach. Many of the original contraindications such as age, diabetes, weight and renal failure are now considered to be relative and very few are to be considered absolute excluding criteria to heart transplantation.

Advanced age has been traditionally considered a contraindication for CT because of the reported adverse effect of increased age on long-term survival. However, as the field of transplantation continues to evolve, the criteria regarding recipient's upper age limit have been expanded and selected patients 70 years of age and older can now

successfully be transplanted with similar morbidity, mortality and intermediate-term survival [44].

Diabetes mellitus causes many concerns when considering a patient for CT: wound healing after surgery, hyperglycemia with steroid use, complications such as nephropathy and neuropathy which may affect later long-term survival and quality of life. Anyway many studies have found that survival of recipients with and without diabetes, if not complicated, were comparable [127].

The International Society for Heart and Lung Transplantation (ISHLT) guidelines published in 2006 stated that candidates should achieve a BMI <30 Kg/m^2 or a percent ideal body weight <140% before listing for CT. Recently it has been demonstrated that obesity type I (BMI of 30-35) is not associated with significantly higher morbidity and mortality [128].

Renal failure has always been a contraindication for heart transplantation overall because calcineurin inhibitors are nephrotoxic and can worsen a previous renal insufficiency bringing the patient to dialysis more frequently and in a shorter time. However pretransplant light renal dysfunction alone is not associated with an increased development of chronic renal dysfunction after CT [129].

The aim of our study was to evaluate the impact of these relative contraindications on mortality and hospitalization rate after CT especially when multiple comorbidity are present at baseline.

Methods

Patient Population

We prospectively followed all the patients who underwent cardiac transplantation between January 2000 and January 2010 in Québec Heart and Lung Institute, Québec, QC, Canada for a total 254 person/year follow up time. No patients were excluded and no patients underwent re-transplantation. A total of 142 patients were included in the analysis. Our Institutional Review Board approved this study.

Measurement

Primary outcome was a composite of death from any cause and hospitalization for a CT related cause: heart failure, arrhythmias, graft rejection or infection. Prognostic factors of interest were the presence of: insulin treated diabetes, age > 65 years old, BMI > 30 Kg/m^2, transpulmonary gradient > 15 mmHg and creatinine clearance < 30 ml/min.

Data Collection

Patients data was collected through extensive chart review. Outcomes adjudication and follow up were also made through chart review. Data collected on donors included demographics, anthropometry, laboratory data, hemodynamic data, ischemic time, cause of death and cytomegalovirus serology. Right heart catheterization was performed using the standard procedure of inserting a Swan-Ganz thermodilution catheter percutaneously, positioned in the pulmonary artery. Supine central hemodynamic measurements were obtained and, for patients with baseline PVR >3 Wood Units (WU) and/or transpulmonary gradient >15 mmHg, reversibility was assessed by milrinone challenge, which was used in an incremental fashion to a maximum dose of 0.5 μg/Kg/minute.

The pulmonary hypertension variables assessed included mean PAP (= pulmonary artery pressure), PVR (= pulmonary vascular resistances) and TPG (= transpulmonary gradient).

Statistical Analysis

Continuous variables are presented as mean ± SD; discrete variables are presented as frequency distribution. Means were compared using 2-sample independent and paired t test, and categorical variables were compared using conventional x^2 testing. All time-to-event distributions were estimated with the Kaplan Meier methods. All reported time-to-event comparisons were made with the log rank test. Multivariate analysis of prognostic factors were made with Cox-Proportional Hazard models and expresses as Hazard Ratios.

Results

Table 1 summarize baseline characteristics including demographics, anthropometry, details of pulmonary hemodynamic and other known prognostic factors in CT according to the presence of two or more risk factors. In the total cohort, mean age at the time of transplantation was 51 ± 14 years. Seventy-six percent were male. Their mean weight was 75,3 ± 18,4 and BMI was 26 ± 5. Sixty-two patients (43,7%) had an ischemic cardiomyopathy as etiology of the heart failure. Twenty-four (17%) were active smokers at the time of transplantation, 6 (4,2%) had insulin dependent diabetes and 3 (2,1%) had a severe vasculopathy. Mean peak VO2 was 13,4 ± 4 ml/Kg/min. Forty-six (32,4%) were treated with milrinone infusion and 29 (20,4%) had a ventricular assist device at the time of CT. Mean donor age was 36 ± 14 years. One-hundred-six donors were male (74,6%). Average donor ischemic time was 164 ± 44 minutes. Regarding combination of risk factors at baseline, 49 had 1 of the considered factors at the time of listing, 38 had 2 and 10 had 3 ore more. During the follow-up there were 16 deaths in the group with risk factors and 7 in the group without risk factors.

Primary outcome occurred in 84 (59%) patients (61 hospitalizations and 23 deaths). Patients presenting 2 or more of the considered factors at listing time showed significantly higher rate of the primary outcome during the follow-up (HR 1.47, 1.02-2.28). These findings were amplified when the patients had 3 or more factors at listing time (HR 2.52, 1.2-5.29). Prognostic factor evaluated (Hazard Ratio, 95% CI) showed alone a non significant increase in the risk of developing the composite outcome. Age (1.43, 0.9-2.7), low creatinine clearance (1.14, 0.74-1.8), BMI > 30 Kg/m² (1.53, 0.93-2.5), insulin treated diabetes (1.4, 0.8-2.4), TPG > 15 mmHg (1.4, 0.8-2.37).

Discussion

Presence of multiple co morbidities at baseline in CT candidates might be associated with worse clinical outcome and this association seems to increase with the number of factors present at listing time.

Anyway in our study the presence in the transplant recipients of only one prognostic risk factor didn't demonstrate a significant increase in the risk of death from any cause and hospitalization for a CT related cause.

We have chosen to investigate the most important pre-transplant prognostic risk factors: age > 65 year old, BMI > 30 Kg/m², presence of insulin treated diabetes, TPG > 15 mmHg and creatinine clearance < 30 ml/min.

No consensus exists regarding maximum age for heart transplantation (HTx) candidacy. Older recipients have been traditionally denied transplantation because of the critical shortage of donor organs and because of the assumption that selection for heart transplantation should be based on patient potential for maximum benefit in terms of functional recovery and length of survival. It has been argued that older patients have a

post-operative period characterized by higher infection rate, higher incidence of malignant disease, greater functional impairment, increased postoperative hospital stay and associated costs and poorer survival [130-134]. However, the definition of advanced age for HTx among those reports is poorly defined, having been reported as more than 55 years [130], 60 years [131, 132] and 65 years of age [134]. These results are supported by data from the Registry of the ISHLT that shows a significant decrease in survival at 1 and 5 years with increasing recipient age, especially in those over 65 years. Age remains a predictor of transplantation mortality in a multivariate analysis even when adjusted for other comorbidity factors. Further, the vast majority of risk factors known to affect the 1-year mortality, advanced age included, persist at 5-year point [135]. On the basis of these data, it is easy to understand the natural reluctance of most heart transplant centers to consider elderly patients as potential candidates [44]. However, several studies have shown that HTx in older patients (defined as older than 55 to 65 years of age) can be performed successfully with acceptable morbidity and mortality and excellent long-term survival, comparable with those of younger patients. These reports, as our study, have concluded that the recipient's age is not a significant risk factor alone for mortality and that advanced age, although its definition is not uniform, should not be considered a major contraindication for HTx [136-142].Anyway highly selective criteria should be applied, identifying risks and benefits individually for each patient.

Obesity traditionally has been identified as a relative contraindication to HTx. However it has not been found to be an evidence-based risk factor for mortality after HTx. Obesity increases the risk for hypertension, diabetes and cardiovascular disease. Serum cholesterol, low-density lipoprotein and triglyceride concentrations are elevated

significantly after transplantation in most patients and the developing of obesity may only aggravate the dyslipidemia [143]. Kocher et al [144] evaluated the effect of obesity on outcome after HTx already in 1999. They found that post-operative survival was slightly but insignificantly decreased in patients with a BMI > 27 kg/m² ($p = 0.018$). Grady et al [145] in the same year evaluated obesity, indexed by percent ideal body weight, as a risk factor for mortality and morbidity in HTx in a single-center study. They concluded that percent ideal body weight was an independent predictor of survival after HTx ($p = 0.046$) but they found no significant differences among the different weight groups in acute rejection, infection and allograft arteriopathy. To further assess the role of obesity and post-transplant mortality, the CRTD later evaluated 4515 patients [145] analyzing both BMI and percent ideal body weight. They found that survival was influenced by pre-HTx percent ideal body weight but not BMI and the risk of death was significantly greater in men. In contrast a recent study of the ISHLT Registry suggested that recipient weight was not a risk factor for 5-year survival [146]. A more recent study by Russo et al [128] found that BMI has a significant impact on mortality, perioperative morbidity, post-transplant cardiovascular comorbidities and long-term complications of transplantation. Recipients with BMIs in both the low and high extremes experienced the worst outcomes. Compared with normal weight candidates, underweight patients suffered significantly diminished survival at 2 months and in overall survival while overweight and light obesity recipients had nearly identical survival on the waiting list than normal weight patients. These findings have important implications not only for heart transplant recipients, but all end-stage heart failure patients. First, they support observations that malnutrition is a marker of more severe heart failure and a risk of worsening prognosis [147]. Second, they further highlight the need to more completely

assess and monitor nutritional status, using associated biomarkers and clinical markers. The best risk-adjusted survival occurred in a BMI range from 22 to 28 Kg/m², a range straddling the normal and overweight groups. In our study we found that even a BMI > 30 kg/m² was not a significant prognostic factor, if present alone.

Complicated diabetes mellitus (DM) causes many concerns when considering a patient for HTx. These include wound healing after surgery, hyperglycemia with steroid use and complications such as nephropathy and neuropathy, which may affect long-term survival and quality of life after HTx [127]. At large centers, approximately 10% or more of HTx recipients have a history of DM and 13% of those patients use insulin at the time of HTx [148]. Mancini et al [148] studied 374 HTx recipients, of which 76 had DM, from the time of transplantation to 5 years post-HTx between 1995 and 1999. They found that survival of recipients with and without DM were comparable. Czerny et al [149], in contrast with the findings of Mancini et al, found that the 5-year survival of HTx recipients who had DM was significantly lower (58.6% vs 70.3%). Concurrent use of insulin had no effect on survival and the rates of infection and acute rejection did not differ from those of HTx recipients who did not have DM. Recipients with DM showed a trend toward increased rates of graft coronary arteries disease. In our study patients with insulin dependent diabetes had not a decreased survival if they had no other concomitant risk factors, anyway they have a tendency to develop more allograft vasculopathy and in a shorter time.

Elevated pulmonary vascular resistance (PVR) or transpulmonary gradient (TPG) is a risk factor for mortality in the early and late stages following HTx. The high risk of right ventricular failure exists because the grafted heart is unable to adapt to significant pulmonary hypertension (PHT) [27, 150-154]. The degree of PHT as an absolute

contraindication for orthotopic transplantation is unknown. However, there is a consensus that the risk of death after HTx is increased if the PVR are greater than 2.5 Wood-Units and/or the TPG is greater than 12 mmHg [155, 156]. Thus, it is extremely important to determine preoperatively whether or not PHT can be reversed. Several pharmacologic agents including nitroprusside, nitric oxide, urapidil, milrinone and prostaglandins have been used in the assessment of reversibility [29, 150, 153, 154, 157-162]. If reduction to normal PVR and TPG is possible, HTx can be performed successfully without increased risk of acute right ventricular failure. Klotz et al in their study found instead that patients with non-reducible PHT had a significant higher mortality, despite adequate therapy [163]. The ISHLT data indicate that PVR correlates in a linear fashion with mortality after HTx [164]. However, patients with increased PVR show a prompt decrease in PVR immediately after HTx if they had some degree of reversibility in response to pharmacologic agents or inhaled nitric oxide before surgery or after transplantation. In addition VADs play a role in successful transplants in patients with previously elevated PVR and/or TPG [165]. Curiously in our study we did not find a significant increase in the risk of death from any cause and hospitalization for a CT related cause in patients with no reversible TPG > 15 mmHg if this was the only present risk factor, but it became significant if another or 2 other risk factors were affecting the same patient.

Chronic renal dysfunction is a major complication of cardiac transplantation that is mainly attributed to therapy with calcineurin inhibitors [166]. Already impaired pre-transplant renal function, with creatinine clearance < 30 ml/min, is recognized as a major risk factor for hemodialysis need and mortality post HTx. Anyway data in the literature are controversial. Drakos et al [129], in their study, found that the pre-

transplant renal function, as expressed by the serum creatinine, was not associated with increased post-transplant development of chronic renal dysfunction. Many other studies [167-172] failed to show any correlation between pre-transplant renal insufficiency and the decline in renal function after transplantation. On the contrary, Sehgal et al [173] found that patients with renal insufficiency before HTx and those with a more pronounced depression of renal function at 6 months after transplant had a high risk for progressive kidney failure after HTx. In our study creatinine clearance < 30 ml/min alone was not a significant risk factor for our composite outcome.

Anyway our data suggests that patients presenting 2 or more of these considered risk factors at listing time showed significantly higher rate of death for any cause and hospitalization for an Htx related cause during the follow up.

This association seems to increase with the number of risk factors present at listing time.

So, considering the scarcity of organ donors and looking to increase longevity and quality of life of our Htx patients, we should carefully consider all these risk factors during the HTx candidacy evaluation.

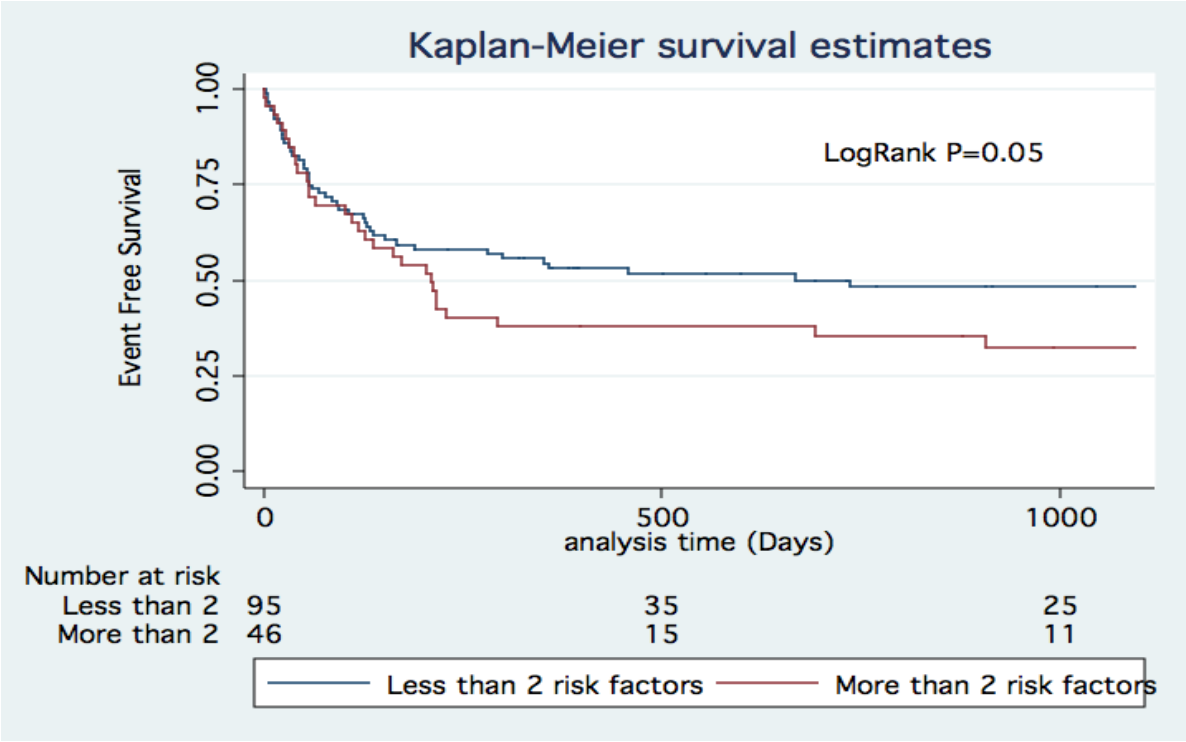
Table 1: baseline data of heart transplant candidates

Baseline Characteristics	N=142
Gender (male)	108 (76%)
Age at transplant (years)	51 ± 14
Weight (Kg)	75,3 ± 18,4
Body mass index	26 ± 5
Creatinine (µmol/L)	118,4 ± 44,3
Creat. Cl. (ml/min)	1,08 ± 0,42
Peak VO2 (ml/Kg/min)	13,4 ± 4
Pre-CT insulin dependent diabetes	6 (4,2%)
Glycosylated Hemoglobin (±SD)	0,067 ± 0,006
Smokers	24 (17%)
Severe vasculopathy %	3 (2,1%)

Table 2: Risk factors for composite end-point

	Hazard Ratios (95%CI)	
	Univariate	**Multivariate**
Age more than 65	1.43 (0.9 - 1.47)	1.52 (0.77 - 3.0)
Transpulmonary gradients >15 mm Hg	1.4 (0.8 - 1.37)	1.02 (0.58 - 1.8)
Creatinine clearance < 30 ml /min	1.14 (0.74 - 1.8)	1.14 (0.77 - 1.69)
Presence of insulin treated diabetes	1.4 (0.8 - 2.4)	1.17 (0.66 - 2.07)
BMI > 30	1.53 (0.93- 1.5)	1.25 (0.75 - 2.07)
Prensence of 2 or more risk factors	**1.47 (1.02 - 2.28)**	NA
Presence of 3 or more risk factors	**2.52 (1.2 - 5.29)**	NA

Figure 24: Survival in patients < 2 risk factors and ≥ 2 risk factors


Kaplan-Meier survival estimates
LogRank P=0.05
Event Free Survival
0.00
0.25
0.50
0.75
1.00
0
500
1000
analysis time (Days)
Number at risk
Less than 2 95 35 25
More than 2 46 15 11
Less than 2 risk factors
More than 2 risk factors

Aim of the study

When the limited donor availability (2000 donors yearly in US), and drug-related morbidity (eg, hypertension, renal dysfunction) are considered, the role of longterm assist devices appears even more important [116, 174]. In the last years an increasing number of patients with unstable emodinamic conditions are being successfully bridged to a heart transplant with new axial left ventricular assist device (LVAD). Old devices provide excellent hemodynamic support and improve patient survival rates, but do have significant constraints, including the need for extensive surgical dissection, requirement for the patient to have a large body habitus, need for a large-diameter percutaneous lead, audible pump operation and reduced durability. Over the last few years, tremendous progress has been made with the use of the newer LVADs such as HeartMate II LVAD (HM II). These continuous-flow rotary pumps have demonstrated enhanced durability and provide improved quality of life for extended periods of support. We describe our experience with Heart Mate II as bridge to transplant [116, 174].

Methods

From January 2000 to June 2011 67 patients were treated with assist devices as bridge to transplant at the Quebec Heart and Lung Hospital. Between 2000 through 2008 we used Thoratec paracorporeal device (Thoratec Corporation, Pleasanton, CA) and from June 2008 to June 2011, 19 consecutive patients received the HeartMate II LVAD (Thoratec Corporation, Pleasanton, CA) as bridge to transplant.

HeartMate II LVAD

The HM II is a continuous flow device consisting of an internal axial flow blood pump with a percutaneous lead that connects the pump to an external system driver and power source. The redesigned HM II has a left ventricular apical inflow cannula with a sintered titanium blood-contacting surface. The bladed impeller spins on a bearing and is powered by an electromagnetic motor. No compliance chamber or valves are necessary and a single driveline exits the right lower quadrant of the abdomen. The inlet cannula is placed in the ventricular appendage, and the pump is placed either intraperitoneally or extraperitoneally. The outflow cannula is connected to a Dacron graft, which is then anastomosed to the ascending aorta. The external controller and batteries resemble those of the original HeartMate as well. The pump is designed to spin at 6,000 to 15,000 rpm and to deliver as much as 10 L/min of cardiac output. A computerized algorithm is used to continuously estimate flow from the device.

Patient and Device Management

Pulsatility index is mantained greater than 3.5 to 4.0. We optimize the rpm (revolutions per minute) speed, using both hemodynamic and echocardiographic parameters, at the time of LVAD placament in the operating room, during the postoperative period and if clinical events (new symptoms or suction events) warrant further adjustment. In the operating room, the presence of a transesophageal echocardiogram and continuous pulmonary artery catheter monitoring helps us to optimize pump speed in order to achieve left ventricular decompression without septal shift toward the left ventricle or evidence of progressive right ventricular dilation. Goals for central venous pressure are typically 10 to 15 mm Hg, pulmonary artery systolic pressure less than 45 mm Hg, and cardiac index greater than 2.2 L /min/ m2.

Data Collection

We collected baseline and follow-up data, including patient characteristics, blood chemistry analyses, hematologic findings, neurologic status and concomitant medication use. After patients were discharged from the hospital, they returned to our center for follow-up, device review and clinical assessment. We recorded hospital readmission and patient adverse events throughout the study period as they occurred, using standardized definitions.

Anticoagulation Therapy

We used antiplatelet therapy with aspirin in the first 24 houres if there was no active bleeding and warfarin therapy starting on postoperative day 2 or 3, titrating the dose to an international normalized ratio of 1.5 to 2.

Statistical Analysis

We prospectively collected and retrospectively analyzed all data. Continuous data are presented as the mean standard deviation. Categoric data are presented as a percentage. Continuous data were compared with analysis of variance or the t test as indicated. The Chi 2 or the Fisher exact test was used for categoric variables. Results were considered statistically significant for a p value less than 0.05. All analyses were done with SPSS 12.0 software.

Results

Patient Characteristics

The last 19 patients of 67 patients treated with BTT therapy underwent HeartMate II placement. The mean age of patients treated with HMII was 50.1 ± 16.2 years (range, 14 to 75 years). Seventy-eight (78.9%) patients were male. The etiology of heart failure

was ischemic in 47.4%, idiopathic in 31.6%, and other etiologies in 21% (including myocarditis, congenital heart disease, and postcardiotomy shock). Most part of patients (63.2%) were treated with elective priority.

The major commorbidities are summarized in Table 1. Many patients (31.6%) were affected by renal failure and 2 patients (10.5%) were treated with dyalisis before the operation.

Hemodynamic data as baseline and organ biochemistry data are presented in Table 1. Left ventricular ejection fraction was depressed (LVEF 16.2 ± 6.1 %) as well as cardiac index (1.6±0.5 l/min/m2) with an increased pulmonary pressure (SPAP 49.2±6.1)

Survival

No patient died in the first 30-days. After the initial 1-month postoperative period, 3 patients died prior to hospital discharge (overall in-hospital mortality was 15,8%) one because of MOF (5.3%), another because of stroke (5.3%), and and the last because of intracranial bleed after an accidental fall(5.3%).

Major adverse events patients included right ventricular failure requiring right ventricular assist device support with ECMO before and paracorporeal Thoratec later in 1 patient (5.3%), LVAD driveline infections in 1 patient (5.3 %), mediastinitis in 1 patient (5.3%), stroke in 1 patient (5.3).

The overall mean duration of HeartMate II support was 227±175.6 days. Three patients (15.8%) had sign of “high power”due to partial pump thrombosis but no patient required a device replacement. One patient (5.3%) needed to use the backup controller because of a malfunction. One patient (5.3%) developed relevant hemolisis requiring hospitalization, because of ventricular function recovery the patient was explanted and 1 patient (5.3%) developed gastrointestinal bleeding requiring multiple transfusions.

The 30-day, 6-month, 12-month and 18-month survival were respectively 100%, 74.3%, 74.3%, 74.3%. Six of the 19 BTT patients underwent cardiac transplantation successfully after a mean duration to transplant period of 203.8±122.3 days.

Comment

Recently, several multicenter studies have shown significantly improved outcomes with the HeartMate II LVAD as BTT [116, 174]. Our experience supports the application of this device in patients with end-stage heart failure [175-177]. The results from this study support the efficacy, reliability, and utility of this device in a "real world" post-FDA approval BTT patient population. In fact we reported a survival of 100% at 30 days and of 74.3% at 6, 12 and 18 months. However our study also highlights some of the adverse events such as MOF, gastrointestinal bleeding, driveline infections and neurologic events that continue to limit further success of this therapy.

Durability and reliability of LVAD design is, perhaps, one of the most significant features for continued extended use of mechanical circulatory support devices.

Previous studies have demonstrated limited durability and reliability of the pulsatile HeartMate XVE LVAD, with nearly 50% of patients experiencing device exchange due to infection or mechanical malfunction at 18 months [178] while very few device replacements were required for device thrombosis, malfunction, and infection with HMII device. No mechanical failures of the device pumping mechanism needing pump exchange were observed in our serie as many other experiences [116, 174, 176]. An out patient needed controller exchange. He changed by himself the controller with his back up whithout problems. The absence of mechanical failures of the pumping mechanism is significant advantage, in fact the remarkable durability of the HeartMate II LVAD

can allow for improved donor selection as opposed to the pulsatile pump era, in which decreasingm durability beyond the 1-year mark increased the urgency for transplantation and a subsequent potential for suboptimal donor selection.

While the increased incidence of gastrointestinal bleeding in patients with continuous-flow devices has been well recognized, only recently has the loss of the high molecular weight von Willebrand factor multimers been documented to occur in 100% of these patients [179]. However, this abnormal finding (namely, acquired von Willebrand syndrome) cannot alone predict the risk of bleeding in these patients.

The role of routine follow-up of von Willebrand factor levels and subsequent adjustment of either warfarin or antiplatelet therapy needs to be evaluated more closely to see if this can favorably impact gastrointestinal bleeding. In our serie 1 patient developed a severe upper gastro-intestinal bleeding secondary to diffuse angiodysplasia refractory to conventional therapy. He required 2 to 4 red blood cell units per week for 23 weeks for a total of 60 red blood cell units.

One reasonable approach reported to treat this complication is to reduce the pump speed to allow near to total return of pulsatile blood pressure and to reduce shear stress [180]. However, we did not notice any bleeding reduction with this measure nor with conventional endoscopic cauterization, erythropoietin and somatostatin treatments.

Some authors suggest that bleeding occurs solely when a patient has loss of large von Willebrand multimers and a prolonged INR induced by oral anticoagulant therapy. For these reasons a therapy with aspirin alone is frequently proposed [180]. Other reports suggest to cease all anticoagulation and antiaggregation agents, with no clinically reported VAD thrombosis [180]. In this patient mantainig aspirin treatment with the interruption of warfarin gave no benefit.

After having documented the lack of large von Willebrand multimers, suggesting a defective platelet function, we switched from aspirin (81 mg daily) to warfarin therapy (target INR between 1.5 and 2.0). Three days after the anticoagulant regimen change the patient stopped bleeding and required no more transfusion

In such circumstances, we believe that if one anticoagulant has to be mantained it is more rationale to stop the aspirin and maintain the warfarin. In fact, even if von Willebrand participates at different levels in the haemostaic process, its key role is represented by promotion of adhesion and aggregation of platelets at the vascular site injury, activities that are compromized in both inherited and acquired von Willebrand disease.

We experienced a low rate of drive line infection in fact only 1 patient developed this complication. Other single-center studies have reported a 20% incidence of LVAD-related infections using HM II device [177]. However the incidence of driveline infections is clearly reduced when compared with pulsatile flow devices with a nearelimination of pump pocket infections. Clearly, infections contribute to readmissions to increase mortality and cost. While the presence of a driveline as a "foreign body" will always be associated with the risk of an adverse host-environment interaction, strategies to limit the morbidity of an infection are paramount until a totally implantable LVAD is available.

One of our patient experienced severe right ventricular failure needing support with ECMO before and with a thoratec pneumatic device later. Because the LVAD does not replace the patient's own heart, the ability of the right ventricle to provide sufficient output to fill the LVAD is the major determinant of correct LVAD functioning and the patient's survival. Right ventricular dysfunction has been identified in 25% to 40% of

patients treated with an LVAD [177]. Twenty to thirty percent of patients either died or required right ventricular assistance for right ventricular failure refractory to drug therapy. The therapy to treat right ventricular failure is not yet well defined and it doen't exist a long term device tosupport right ventricle. In our experience the combination of a pneumatic device on rhe right side and an axial device on left one is a fasable option.

The incidence of perioperative bleeding was relatively high 26.3 % but not surprisingly thinking to the severity of the disease and the expected development of coagulopathies. In present clinical practice this problem has been apparently reduced but persists as a frequent complication that develop in 40-50 % of patients [102, 177]

Cerebral tromboembolism and bleeding even in our experience are a frequent cause of death in fact cerebral complications were the cause of death of 2 of our 3 dead patients. In one of the 2 patients the cause was a cerebral ischemia, in the other one was an accidental fall in a patient in stable conditions.

It has been suggested that moving toward LVAD implantation in earlier stages of heart failure such as class III is feasible[181]. While the operative mortality of LVAD implantation is similar to other high-risk cardiac surgical procedures, the incidence of adverse events may limit the decision to implant a LVAD in a less sick heart failure patient population.

In conclusion, the results from our experience show how BTT with HM II offers excellent outcomes when a donor is not avaible. Patient selection and improvement in anticoagulation management continue to be areas of focus to further improve outcomes reducing the risk of right ventricular failure and cerebral complications in patients undergoing LVAD implantaition.

Table 3: Baseline data of patients candidate to LVAD.

Variable	%
Male	78.9
Age (years)	50.1±16.2
Euro Score	25.2±10.1
NYHA 3/4	73.7
NYHA 4/4	26.3
Elective Priority	63.2
Preoperative AF	47.4
Previous AMI	47.4
Periferal vascular disease	10.5
Cerebrovascular disease	15.8
Previous strokes	5.3
Diabetes	31.6
BMI	28.3±5.7
Systemic hypertension	31.6
Dyslipidemy	57.9
COPD	15.8
Renal failure	31.6
Dialysis	10.5
Creatine (mg/dl)	122.3±46.3
Clairance Cretinine(ml/min)	75.4±33.8
White blood cells/ul	9.1±3.4
Hématocrite/ul	35±4.9
Platelettes/ul	194.1±74.5
LVEF	16.2±6.1
Systolic PAP(mmHg)	49.2±13.4
Diastolic PAP (mmHg)	34±6.1
Cardiac index (l/min/m2)	1.6±0.5

Table 4: Results of LVAD.

Variable	%
30 days mortality	0
In hospital mortality	15.8
Mean support (days)	227.5±175.6
Stroke	5.3
Sepsis	5.3
Mediastinitis	5.3
Drive line infections	5.3
Pneumonie	21.1
Postoperative AF	31.6
Renal failure	31.6

Dialysis	26.3
Bleeding	26.3
Intubation >48H	42.1

EXTRA-CORPOREAL MEMBRANE OXYGENATOR TEMPORARY SUPPORT TO TREAT EARLY GRAFT FAILURE AFTER CARDIAC TRANSPLANTATION

Aim of the study

Heart transplantation is a well-established treatment for intractable end-stage heart failure but the imbalance in supply and demand has led to the liberalization of donor acceptance criteria to enlarge the donor pool. This may result in an increased incidence of early graft failure (EGF)[182] .

EGF represents the most common cause of in-hospital mortality after cardiac transplantation [182]. Causes of EGF include severe acute or hyperacute rejection with cardiogenic shock, pulmonary hypertension with right ventricular failure, and primary graft failure. Possible treatments for EGF unresponsive to full inotropic support are mechanical support and re-transplantation. Extra-corporeal membrane oxygenation (ECMO) has been recently used as a therapeutic option for EGF [183, 184]. We report here our experience of using ECMO in the setting of EGF.

Methods

From January 2003 to June 2011, 133 heart transplantations were performed at the Institut Universitaire de Cardiologie et Pneumologie de Québec. The present study is based on 13 patients who developed severe EGF after cardiac transplant, leading to severe cardiogenic shock unresponsive to inotropic support and treated with early ECMO (EE) or delayed ECMO (DE).

EGF was defined as a significant graft dysfunction in the early post-transplant period with hemodynamic instability despite full inotropic support independently from its

cause: acute or hyperacute rejection, technical errors, right ventricular failure, pulmonary hypertension, primary graft failure [185].

The extra-corporeal system consisted in polyvinyl chloride tubing, a membrane oxygenator (Quadrox Bioline, Jostra- Maquet, Orleans, France), a centrifugal pump (Biomedicus) and either percutaneous arterial and venous femoral cannulas or central right atrial and aortic cannulas (Biomedicus Carmeda, Medtronic, Boulogne-Billancourt, France). Femoral ECMO was used with 5-Fr cannula inserted distally into the femoral artery to prevent possible leg ischemia. Peripheral cannulation was converted in central one in case of insufficient venous drainage. Anticoagulation with unfractioned heparin was started 6 hours after the end of the operation to achieve an activated cephalin time of 180 sec.

When a pulsatile arterial waveform was maintained for at least 24 h and the echocardiographic evaluation demonstrated systolic heart function recovery and pulmonary blood oxygenation was not compromised, an ECMO-weaning trial was undertaken by progressively increasing activated cephalin time to 300 sec and reducing pump flow to <1 L/min (respecting the minimum rotational speed to prevent retrograde flow). Inotropes were started, ventilation was optimized and the patients were evaluated with trans-oesophageal echocardiography and every 15 minutes with blood gas analysis and Swan Ganz catheter measures.

In this setting, if left ventricular ejection fraction was >35 %, cardiac index >2.2 L/min and there was no acidosis ECMO was removed.

All clinical, echocardiographic, procedural and post-procedural data were prospectively gathered.

Qualitative variables were expressed as percentages and quantitative variables as mean

(standard deviation) or median (interquartile range). Univariate and multivariate analysis were performed in transplanted patient to identify possible risk factors for EGF.

Results

Preoperative data of ECMO patients.

Eight of the 13 patients treated with ECMO (EE group) were weaned from cardiopulmonary bypass with ECMO for severe graft failure refractory to inotropic support while 5 patients (treated with important inotropic support for early graft dysfunction needed delayed ECMO support for acute hemodynamic collapse (DE group).

The main cause of EGF was PGF in both groups (n=6 in EE group, n=3 in DE group). Alternative causes of EGF were donor recipient weight mismatch with consequent pulmonary artery kinking (n=2 in EE group and n=1 in DE group) and right ventricular failure in 1 patient of DE group. One patient with pulmonary artery kinking in EE group was treated with pulmonary plasty with reduction of transpulmonary gradient.

There was no significant difference in the 2 groups: mean age was 46.3 ± 19.5 years in EE group vs 38.4 ± 13.5 years in DE group (p=0.45), Logistic Euroscore were 7.9 ± 5.8 vs 9.1 ± 8.6, patients with previous operation were 6 (75%) vs 2 (40%) (p=0.29), systolic pulmonary pressure was 51.5±6.1 mmHg vs 40.0±13.7, (p=0.189), ischemic time was similar 192.4±22.0 vs 160.3±58.2 (p=0.217). All other preoperative data are shown in table 2.

ECMO data

EE patients were treated with peripheral cannulation with femoral recirculation. One of them was converted to central cannulation with left ventricular venting because of

insufficient venous drainage. In DE group 2 patients were treated with central ECMO with a vent drainage of the left ventricle and 3 with peripheral ECMO.

Mean speed rotation was 3133 ± 311 rpm in EE group vs DE group 3043 ± 150 p=0.56 to obtain a men support of 2.1 ± 01 vs 2.2 ± 0.1 l/min/m2 p=0.30. The anticoagulation level was similar ACT of 175 ± 7.6 vs 186 ± 13.4 (p=0.08).

All patients received inhaled nitric oxide and 1 patient in EE group received IABP to unload left ventricle.

In EE group all patients were weaned after a mean support of 3.5 ± 1.3 days with full recovery of left ventricular function (ejection fraction 59.6 ± 12%). While in DE group no patient recovered and no patient could be weaned from ECMO (p<0.01).

Survival and complications

In EE group the 30-day and 1-year survival was 7/8 patients (87.5 %) and 6/8 patients (75 %) respectively while no patient survived in DE group p<0.01 and p=0.02. In EE group the causes of mortality were respiratory failure (29th post operative day) in one patient and septic shock in the other (2 months after the operation). All patients in DE group died for multi organ failure. No patient was re-transplanted.

Concerning complications, acute renal failure was a serious problem needing ultrafiltration in 5 patients (62.5%) in EE group and in 4 patients (80%) in DE group (p=1). Repeated transfusions were required in all patients while surgical bleeding needing revision occurred in 4 patients in EE group (50%) and in 3 patients in DE group (60%) p=1. Even after ECMO weaning pulmonary infections were frequent in EE group (7 patients 87.5%) while only 1 patient (20%) developed an infection in DE group (p=0.03). Postoperative data are shown in table 3

Risk factors of EGF

The recipients and donor pre-transplant characteristics are listed in Table 1.

Patients who developed EGF were younger that other transplanted patients (42.7±17.7 vs 50.9±13.3 p=0.037), more frequently affected by hypertrophic cardiomyopathy (23.1% vs 5%, p=0.037) with higher left ventricular ejection fraction (40.2± 16.9 vs 22.1±12.7, p<0.001), better renal function (clearance 100.3±66.2 vs 65.7±28.4, p =0.001), lower Euroscore (8.3±6.7% vs 16.5±13.0, p=0.001) and longer cardiopulmonary bypass (153.7±61 min vs 111.3±43, p=0.001) and longer ischemic time (189±42 min vs 164±41, p=0.034).

At multivariate analysis the only predictor factor of EGF was the hypertrophic aetiology with an OR of 5.7 (1.33-24, p=0.019).

Discussion

EGF is a major cause of death in the perioperative period after cardiac transplantation. In our series, the incidence of severe EGF was 9.8% (13 of 133 patients). The incidence of EGF reported in the literature varied the incidence of EGF between 4% and 24% with a lack of objective standardized definition [72, 183, 186, 187].

Many factors can interact in the genesis of EGF: increased pulmonary vascular resistances, preservation injury or even intrinsic organ donor dysfunction. In previous publication ischemic time, donor age and pre-transplant VAD have been identified as factors [70-72, 186]. In our experience patients who developed EGF were statistically significant younger, more frequently affected by hypertrophic cardiomiopathy with higher left ventricular ejection fraction, better renal function, lower Euroscore and longer cardiopulmonary bypass and longer ischemic time. At multivariate analysis the

only predictor factor of EGF was the hypertropic aetiology with an OR of 5.7. Be believe that many other variable shown at univariated analysis are linked to the aetiology in fact patients affected by hypertropic myocardiomyopathy have a good left ventricular ejection fraction and are usually younger with consequent better general conditions. In EGF group the cardiopulmonary bypass time was longer because patients could not be weaned from extracorporeal circulation: the additive time is presumably the time to bridge to ECMO.

As EGF physiopathology is poorly understood, the treatment also remains unclear. Medical therapy alone is associated with a uniformly dismal survival [188] and also results of re-transplantation in the early postoperative period [189, 190] are poor.

Mechanical circulatory support until the transplanted heart recovers or the patient undergoes retransplantation offers the only chance of survival. However, compared with the use of mechanical circulatory support in postcardiotomy and bridge-to-transplantation patients, the results of mechanical support following heart transplantation are markedly worse.

Minev et al [71] reported a 80% mortality in subgroup with primary graft failure because of patients disastrous conditions. Other series report similar results [186].

On the other hand, Petrofski et al [191] reported 71% survival to discharge in their group of seven patients affected by EGF treated with Abiomed BVS5000 assist device (Abiomed,Inc, USA).

Mechanical circulatory support for cardiac allograft failure consists of sporadic case reports, often describing the use of a variety of devices in a small patient population with a complete spectrum of indications [192].

Even if Hooper et al [192] reported a case of EGF using only a LVAD in addition to

inotropic support to augment right ventricular function, it is intuitive to treat such a biventricular failure condition with ECMO, BVAD or TAH.

Kavarana et al [71] noted that 70% of patient with EGF needs biventricular support because of biventricular failure. Ventricular interdependence after transplant has been implicated in the development of RVF after LVF [193].

We have decided to use ECMO because it can provide a biventricular circulatory support with minimal surgical trauma, avoiding end-organ damage and allowing both ventricles to rest and recover. It can be rapidly installed in the transplanted heart and be removed without need of cardiopulmonary bypass.

Permanent VADs often require ventricular cannulation, making explantation more difficult. Such long-term support is limited by higher cost and it is usually not necessary, in fact the weaned patients recovered in the first 24-48 hours. According to our data, the duration of support in the majority of survivors in Chou study was less than 6 days [70].

Weaning and survival rates with ECMO improved in the last years thanks to new oxygenators and pumps technologies : D'Alessandro described a weaning rate of 68% and a survival of 50%, Chou a weaning rate of 84% and a survival of 53%, and Taghavi a weaning rate of 77% and a survival of 54% [70, 193, 194]. The last group treated with ECMO right ventricular failure (a different and less disastrous scenario).

In our series, 13 patients received mechanical support post-operatively for EGF. All patients treated with EE were weaned off mechanical support while no patient treated with DE was weaned. Total 30 days survival was of 53% with a difference depending of the time of the implantation: 87% in EE group and 0% in DE group. It is intuitive that better results can be obtained when ECMO is implanted in a stable condition than in a

catastrophic emergency situation. Previous papers did not define exactly the time of the implantation and so it is difficult to compare them with our results.

A recent series of Listijono et al [195] considered 19 patients treated with ECMO post transplant. All of them were treated before return to ICU and 8 of them with prophylactic implantation in a setting of preceding donor cardiac dysfunction, underlining the importance of an early employing of the assistance. They obtained a 30 day survival of 82% despite the employment of marginal donors.

It is important to remember that these patients remain very fragile even after weaning and pulmonary and infective complications should be prevented and monitored as suggested in most of reports [194, 196]. We also reported a patient who died for sepsis 2 months after weaning.

After the first 3 months we reported no additional mortality according with D'Alessandro data which suggest that EGF patients weaned from ECMO have the same life expectancy as the other transplanted patients [194].

ECMO support can be obtained with peripheral or central cannulation. In our series when possible we used peripheral femoral vein and artery cannulation with additional cannula for distal femoral perfusion.

Peripheral approach is minimally invasive and quickly available even at the bedside; removal of the ECMO is performed without re-opening the chest, which could reduce the risk of infection that represent a major problem for mechanical assist device in immunosuppressed cardiac transplant patients.

When the thorax was reopened in emergency situations for tamponade we installed a central ECMO but we believe that in all other situations peripheral ECMO should be preferred.

We did not experience any late complication of the femoral cannulation, as reported by Zimpfer [196], and only 1 patient needed central conversion for insufficient venous drainage with good result.

A limitation of our study is that it is a retrospective analysis. Fortunately EGF is rare and, despite our extensive experience, the sample size was small, limiting the analysis.

In conclusion in view of the poor results observed in early re-transplantation and the uniformly dismal outlook with medical therapy, we advocate the aggressive use of ECMO for EGF because it permits an acceptable survival. In our experience ECMO support is a reliable therapeutic option for graft salvation in severe early graft failure if the support is initiated early. In this case complete recovery of cardiac function is frequent and usually occurs less than 4 days after ECMO installation with good survival. On the contrary delayed ECMO appears to be associated with poor outcome. This emphasizes the necessity to identify precociously the graft dysfunction and to treat it aggressively.

Table 5: Recipient and donor pretransplant data.

Univariated analysis

	Early Graft Failure N=13	Non Early Graft Failure N=180	p. value
Female	4 (30.8%)	38 (21.1%)	0.48
Sex mismatch	4 (30.8%)	43 (23.9%)	0.52
Age recipient	42.7±17.7	50.9±13.3	0.03
Age donor	31.3±11.0	36.3±14.1	0.22
Hypertrophic etiology	3 (23.1%)	9 (5.0%)	0.03
Congenital etiology	2 (15.4%)	5 (2.8%)	0.07
Previous VAD	1 (7.7%)	22 (12.2%)	1.00
Diabetis	1 (7.7%)	27 (15.0%)	0.70
Weight (kg)	72.0±17.2	74.5±16.9	0.60

Weight < 60 kg	2 (15.4%)	35 (19.4%)	1.00
Pulmonary vascular resistences	1.7 ± 0.9 (1.5)	2.2 ± 1.1 (2.0)	0.15
Mean pulmonary artery pressure	26.2 ± 7.6	28.8 ± 9.3	0.34
Transpulmonary gradient	7.1 ± 2.7	8.8 ± 4.9	0.24
Dialysis	0	3 (1.9%)	1.00
Creatinine	98.5±39.9	128.0±45.9	0.02
Clearance (MDRD)	100.3±66.2	64.7±28.4	<0.01
Left ventricular ejection fraction	40.2±16.9	22.1±12.7	<0.01
Logistic Euroscore	8.3±6.7	16.5±13.0	0.03
Cardiopulmonary bypass time	153.7±61.0	111.3±43.0	<0.01
Clamping time	133.8±64.1	138.0±63.8	0.82
Ischemic time	189.7±42.5	164.4±41.3	0.03

Table 6: baseline data of ECMO patients

	OR N=8	>24h N=5	P. value
Female	2 (25.0%)	2 (40.0%)	1.00
Age	46.3±19.5	38.4±13.5	0.45
Redo	6 (75.0%)	2 (40.0%)	0.29
Previous Stroke	1 (12.5%)	1 (20.0%)	1.00
Diabetis	0	1 (20.0%)	0.38
IMC	26.9±6.1	24.8±3.8	0.51
Creatinine	98.4±48.5	98.6±25.5	0.99
Clairance MDRD	109.1±82.0	86.2±31.4	0.57
Left ventricular ejection fraction (median)	44.1±13.0 (45)	34.6±21.6 (28)	0.36
PAP_Diastolic	15.5 ±4.9	19.5±0.7	0.37
PAP_Systolic	51.5±6.1	40.0±13.7	0.19
Logistic Euroscore (%)	7.9±5.8	9.1±8.6	0.75
Cardiopulmonary time	164.3±65.3	136.8±55.9	0.45
Clamping time	137.1±67.7	128.4±65.3	0.82
Ischemic time	192.4±22.0	160.3±58.2	0.22

Table 7: postoperative data

	OR N=8	>24h N=5	P. value
Pump speed	3133.8±311. 5	3043.6±150.7	0.56

Cardiac index	2.1±0.1	2.2±0.1	<0.01
Days of support	3.5±1.3	5.0±2.1	0.14
Central cannulation	1 (12.5%)	0	0.36
Central cannulation + Vent	0	2 (40.0%)	
Femoral cannulation	7(87.0%)	2 (60.0%)	
Stroke	0	0	----
Sepsis	2 (25.0%)	0	0.49
Pulmonary infection	7 (87.5%)	1 (20.0%)	0.03
Dialysis	5 (62.5%)	4 (80.0%)	1.00
Surgical bleeding	4 (50.0%)	3 (60.0%)	1.00
Intubation > 48h	8 (100%)	5 (100%)	1.00
ICU stay	15.5±11.3	6.5±4.5	0.12
Hospital stay	52.1±73.9	6.6±4.3	0.2047
Red cells blood transfusions	21.5±11.5	42.4±34.0	0.1307
Platelettes transfusions	40.3±31.7	70.4±62.7	0.2960
Plasma transfusions	13.1±10.6	35.6±25.4	0.0456
Left ventricular ejection fraction post ECMO	59.6±12.0	30.6±20.7	0.0079
30 days mortality	0 (0%)	5 (100%)	0.0210

REFERENCES:

[1] American Heart Association. 2001 Heart and Stroke Statistical Update., 2002.

[2] Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Staiger C, Holcslaw TL, Amann-Zalan I, DeMets DL. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation 2002;106:2194-2199.

[3] Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, Francis GS, Ganiats TG, Goldstein S, Gregoratos G, Jessup ML, Noble RJ, Packer M, Silver MA, Stevenson LW, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Jacobs AK, Hiratzka LF, Russell RO, Smith SC, Jr. ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure): Developed in Collaboration With the International Society for Heart and Lung Transplantation; Endorsed by the Heart Failure Society of America. Circulation 2001;104:2996-3007.

[4] Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, Mark DB, McCallister BD, Mooss AN, O'Reilly MG, Winters WL, Jr., Antman EM, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Russell RO, Smith SC, Jr. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force

on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). Circulation 2002;106:1883-1892.

[5] Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009;119:e391-479.

[6] Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH, Jr., Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation 1991;83:778-786.

[7] Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. Circulation 1997;95:2660-2667.

[8] Alla F, Briancon S, Juilliere Y, Mertes PM, Villemot JP, Zannad F. Differential clinical prognostic classifications in dilated and ischemic advanced heart failure: the EPICAL study. Am Heart J 2000;139:895-904.

[9] Hansen A, Haass M, Zugck C, Krueger C, Unnebrink K, Zimmermann R, Kuebler W, Kuecherer H. Prognostic value of Doppler echocardiographic mitral inflow patterns: implications for risk stratification in patients with chronic congestive heart failure. J Am Coll Cardiol 2001;37:1049-1055.

[10] Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. JAMA 2003;290:2581-2587.

[11] Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, Anand I, Maggioni A, Burton P, Sullivan MD, Pitt B, Poole-Wilson PA, Mann DL, Packer M. The Seattle Heart Failure Model: prediction of survival in heart failure. Circulation 2006;113:1424-1433.

[12] Butler J, Khadim G, Paul KM, Davis SF, Kronenberg MW, Chomsky DB, Pierson RN, 3rd, Wilson JR. Selection of patients for heart transplantation in the current era of heart failure therapy. J Am Coll Cardiol 2004;43:787-793.

[13] O'Neill JO, Young JB, Pothier CE, Lauer MS. Peak oxygen consumption as a predictor of death in patients with heart failure receiving beta-blockers. Circulation 2005;111:2313-2318.

[14] Gardner RS, McDonagh TA, MacDonald M, Dargie HJ, Murday AJ, Petrie MC. Who needs a heart transplant? Eur Heart J 2006;27:770-772.

[15] Carrel A. Heterotransplantation of Blood Vessels Preserved in Cold Storage. J Exp Med 1907;9:226-228.

[16] Carrel A, Guthrie CC. Functions of a Transplanted Kidney. Science 1905;22:473.

[17] Lower RR, Shumway NE. Studies on orthotopic homotransplantation of the canine heart. Surg Forum 1960;11:18-19.

[18] Hardy JD, Kurrus FD, Chavez CM, Neely WA, Eraslan S, Turner MD, Fabian LW, Labecki TD. Heart Transplantation in Man. Developmental Studies and Report of a Case. JAMA 1964;188:1132-1140.

[19] Barnard CN. The operation. A human cardiac transplant: an interim report of a successful operation performed at Groote Schuur Hospital, Cape Town. S Afr Med J 1967;41:1271-1274.

[20] Caves PK, Stinson EB, Billingham M, Shumway NE. Percutaneous transvenous endomyocardial biopsy in human heart recipients. Experience with a new technique. Ann Thorac Surg 1973;16:325-336.

[21] Robbins RC, Barlow CW, Oyer PE, Hunt SA, Miller JL, Reitz BA, Stinson EB, Shumway NE. Thirty years of cardiac transplantation at Stanford university. J Thorac Cardiovasc Surg 1999;117:939-951.

[22] Edwards LB, Keck BM. Thoracic organ transplantation in the US. Clin Transpl 2002:29-40.

[23] Cohn JN, Johnson GR, Shabetai R, Loeb H, Tristani F, Rector T, Smith R, Fletcher R. Ejection fraction, peak exercise oxygen consumption, cardiothoracic ratio, ventricular arrhythmias, and plasma norepinephrine as determinants of prognosis in heart failure. The V-HeFT VA Cooperative Studies Group. Circulation 1993;87:VI5-16.

[24] Mudge GH, Goldstein S, Addonizio LJ, Caplan A, Mancini D, Levine TB, Ritsch ME, Jr., Stevenson LW. 24th Bethesda conference: Cardiac transplantation. Task Force 3: Recipient guidelines/prioritization. J Am Coll Cardiol 1993;22:21-31.

[25] Arnold JM, Liu P, Demers C, Dorian P, Giannetti N, Haddad H, Heckman GA, Howlett JG, Ignaszewski A, Johnstone DE, Jong P, McKelvie RS, Moe GW, Parker JD, Rao V, Ross HJ, Sequeira EJ, Svendsen AM, Teo K, Tsuyuki RT, White M. Canadian Cardiovascular Society consensus conference recommendations on heart failure 2006: diagnosis and management. Can J Cardiol 2006;22:23-45.

[26] Dickstein K. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: application of natriuretic peptides. Reply. Eur Heart J 2008.

[27] Costard-Jackle A, Fowler MB. Influence of preoperative pulmonary artery pressure on mortality after heart transplantation: testing of potential reversibility of pulmonary hypertension with nitroprusside is useful in defining a high risk group. J Am Coll Cardiol 1992;19:48-54.

[28] Givertz MM, Hare JM, Loh E, Gauthier DF, Colucci WS. Effect of bolus milrinone on hemodynamic variables and pulmonary vascular resistance in patients with severe left ventricular dysfunction: a rapid test for reversibility of pulmonary hypertension. J Am Coll Cardiol 1996;28:1775-1780.

[29] Stanek B, Sturm B, Frey B, Hulsmann M, Bojic A, Berger R, Rodler S, Locker G, Grimm M, Laufer G, Pacher R. Bridging to heart transplantation: prostaglandin E1 versus prostacyclin versus dobutamine. J Heart Lung Transplant 1999;18:358-366.

[30] Salzberg SP, Lachat ML, von Harbou K, Zund G, Turina MI. Normalization of high pulmonary vascular resistance with LVAD support in heart transplantation candidates. Eur J Cardiothorac Surg 2005;27:222-225.

[31] Pelosi F, Jr., Capehart J, Roberts WC. Effectiveness of cardiac transplantation for primary (AL) cardiac amyloidosis. Am J Cardiol 1997;79:532-535.

[32] Hosenpud JD, Pamidi SR, Fiol BS, Cinquegrani MP, Keck BM. Outcomes in patients who are hepatitis B surface antigen-positive before transplantation: an analysis and study using the joint ISHLT/UNOS thoracic registry. J Heart Lung Transplant 2000;19:781-785.

[33] Castella M, Tenderich G, Koerner MM, Arusoglu L, El-Banayosy A, Schulz U, Schulze B, Schulte-Eistrup S, Wolff C, Minami K, Koerfer R. Outcome of heart

transplantation in patients previously infected with hepatitis C virus. J Heart Lung Transplant 2001;20:595-598.

[34] Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. N Engl J Med 2002;347:284-287.

[35] Morgan JA, Park Y, Oz MC, Naka Y. Device related infections while on left ventricular assist device support do not adversely impact bridging to transplant or posttransplant survival. ASAIO J 2003;49:748-750.

[36] Boyle A, Colvin-Adams M. Recipient selection and management. Semin Thorac Cardiovasc Surg 2004;16:358-363.

[37] Costanzo MR, Augustine S, Bourge R, Bristow M, O'Connell JB, Driscoll D, Rose E. Selection and treatment of candidates for heart transplantation. A statement for health professionals from the Committee on Heart Failure and Cardiac Transplantation of the Council on Clinical Cardiology, American Heart Association. Circulation 1995;92:3593-3612.

[38] Marelli D, Laks H, Patel B, Kermani R, Marmureanu A, Patel J, Kobashigawa J. Heart transplantation in patients with diabetes mellitus in the current era. J Heart Lung Transplant 2003;22:1091-1097.

[39] Steinman TI, Becker BN, Frost AE, Olthoff KM, Smart FW, Suki WN, Wilkinson AH. Guidelines for the referral and management of patients eligible for solid organ transplantation. Transplantation 2001;71:1189-1204.

[40] Mehra MR, Kobashigawa J, Starling R, Russell S, Uber PA, Parameshwar J, Mohacsi P, Augustine S, Aaronson K, Barr M. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates--2006. J Heart Lung Transplant 2006;25:1024-1042.

[41] Young JN, Yazbeck J, Esposito G, Mankad P, Townsend E, Yacoub M. The influence of acute preoperative pulmonary infarction on the results of heart transplantation. J Heart Transplant 1986;5:20-22.

[42] Mai FM, McKenzie FN, Kostuk WJ. Psychiatric aspects of heart transplantation: preoperative evaluation and postoperative sequelae. Br Med J (Clin Res Ed) 1986;292:311-313.

[43] Rovelli M, Palmeri D, Vossler E, Bartus S, Hull D, Schweizer R. Noncompliance in organ transplant recipients. Transplant Proc 1989;21:833-834.

[44] Blanche C, Blanche DA, Kearney B, Sandhu M, Czer LS, Kamlot A, Hickey A, Trento A. Heart transplantation in patients seventy years of age and older: A comparative analysis of outcome. J Thorac Cardiovasc Surg 2001;121:532-541.

[45] Everett JE, Djalilian AR, Kubo SH, Kroshus TJ, Shumway SJ. Heart transplantation for patients over age 60. Clin Transplant 1996;10:478-481.

[46] Laks H, Marelli D. The alternate recipient list for heart transplantation: a model for expansion of the donor pool. Adv Card Surg 1999;11:233-244.

[47] Morgan JA, John R, Weinberg AD, Remoli R, Kherani AR, Vigilance DW, Schanzer BM, Bisleri G, Mancini DM, Oz MC, Edwards NM. Long-term results of cardiac transplantation in patients 65 years of age and older: a comparative analysis. Ann Thorac Surg 2003;76:1982-1987.

[48] Young JB, Naftel DC, Bourge RC, Kirklin JK, Clemson BS, Porter CB, Rodeheffer RJ, Kenzora JL. Matching the heart donor and heart transplant recipient. Clues for successful expansion of the donor pool: a multivariable, multiinstitutional report. The Cardiac Transplant Research Database Group. J Heart Lung Transplant 1994;13:353-364; discussion 364-355.

[49] Anderson JR, Hossein-Nia M, Brown P, Holt DW, Murday A. Donor cardiac troponin-T predicts subsequent inotrope requirements following cardiac transplantation. Transplantation 1994;58:1056-1057.

[50] Vijay P, Scavo VA, Morelock RJ, Sharp TG, Brown JW. Donor cardiac troponin T: a marker to predict heart transplant rejection. Ann Thorac Surg 1998;66:1934-1939.

[51] Grant JW, Canter CE, Spray TL, Landt Y, Saffitz JE, Ladenson JH, Jaffe AS. Elevated donor cardiac troponin I. A marker of acute graft failure in infant heart recipients. Circulation 1994;90:2618-2621.

[52] Potapov EV, Ivanitskaia EA, Loebe M, Mockel M, Muller C, Sodian R, Meyer R, Hetzer R. Value of cardiac troponin I and T for selection of heart donors and as predictors of early graft failure. Transplantation 2001;71:1394-1400.

[53] Rayburn BK, Burton TM, Wannenburg T, Pennington DG, Oaks TE. Are efforts at expanding the donor pool misdirected? J Heart Lung Transplant 1998;17:998-1003.

[54] Milano A, Livi U, Casula R, Bortolotti U, Gambino A, Zenati M, Valente M, Angelini A, Thiene G, Casarotto D. Influence of marginal donors on early results after heart transplantation. Transplant Proc 1993;25:3158-3159.

[55] Ladowski JS, Kormos RL, Uretsky BF, Griffith BP, Armitage JM, Hardesty RL. Heart transplantation in diabetic recipients. Transplantation 1990;49:303-305.

[56] Wheeldon DR, Potter CD, Oduro A, Wallwork J, Large SR. Transforming the "unacceptable" donor: outcomes from the adoption of a standardized donor management technique. J Heart Lung Transplant 1995;14:734-742.

[57] Powner DJ, Darby JM. Management of variations in blood pressure during care of organ donors. Prog Transplant 2000;10:25-30; quiz 31-22.

[58] Van Bakel AB. The cardiac transplant donor: identification, assessment, and management. Am J Med Sci 1997;314:153-163.

[59] Novitzky D, Cooper DK, Reichart B. Hemodynamic and metabolic responses to hormonal therapy in brain-dead potential organ donors. Transplantation 1987;43:852-854.

[60] Jeevanandam V. Triiodothyronine: spectrum of use in heart transplantation. Thyroid 1997;7:139-145.

[61] Novitzky D, Cooper DK, Chaffin JS, Greer AE, DeBault LE, Zuhdi N. Improved cardiac allograft function following triiodothyronine therapy to both donor and recipient. Transplantation 1990;49:311-316.

[62] Wheeldon DR, Potter CD, Jonas M, Wallwork J, Large SR. Using "unsuitable" hearts for transplantation. Eur J Cardiothorac Surg 1994;8:7-9; discussion 10-11.

[63] Lim E, Ali Z, Ali A, Motalleb-Zadeh R, Jackson C, Ong SL, Halstead J, Sharples L, Parameshwar J, Wallwork J, Large SR. Comparison of survival by allocation to medical therapy, surgery, or heart transplantation for ischemic advanced heart failure. J Heart Lung Transplant 2005;24:983-989.

[64] Luckraz H, Goddard M, Charman SC, Wallwork J, Parameshwar J, Large SR. Early mortality after cardiac transplantation: should we do better? J Heart Lung Transplant 2005;24:401-405.

[65] Kirklin JK, Naftel DC, Bourge RC, McGiffin DC, Hill JA, Rodeheffer RJ, Jaski BE, Hauptman PJ, Weston M, White-Williams C. Evolving trends in risk profiles and causes of death after heart transplantation: a ten-year multi-institutional study. J Thorac Cardiovasc Surg 2003;125:881-890.

[66] Taylor DO, Edwards LB, Boucek MM, Trulock EP, Deng MC, Keck BM, Hertz MI. Registry of the International Society for Heart and Lung Transplantation: twenty-second official adult heart transplant report--2005. J Heart Lung Transplant 2005;24:945-955.

[67] Taylor DO, Stehlik J, Edwards LB, Aurora P, Christie JD, Dobbels F, Kirk R, Kucheryavaya AY, Rahmel AO, Hertz MI. Registry of the International Society for Heart and Lung Transplantation: Twenty-sixth Official Adult Heart Transplant Report-2009. J Heart Lung Transplant 2009;28:1007-1022.

[68] Drakos SG, Kfoury AG, Long JW, Stringham JC, Gilbert EM, Moore SA, Campbell BK, Nelson KE, Horne BD, Renlund DG. Effect of mechanical circulatory support on outcomes after heart transplantation. J Heart Lung Transplant 2006;25:22-28.

[69] Joyce DL, Southard RE, Torre-Amione G, Noon GP, Land GA, Loebe M. Impact of left ventricular assist device (LVAD)-mediated humoral sensitization on post-transplant outcomes. J Heart Lung Transplant 2005;24:2054-2059.

[70] Chou NK, Chen YS, Chi NH, Hsu RB, Ko WJ, Yu HY, Lin FY, Wang SS. Extracorporeal membrane oxygenation hybrid with various ventricular assist devices as double bridge to heart transplantation. Transplant Proc 2006;38:2127-2129.

[71] Kavarana MN, Sinha P, Naka Y, Oz MC, Edwards NM. Mechanical support for the failing cardiac allograft: a single-center experience. J Heart Lung Transplant 2003;22:542-547.

[72] Marasco SF, Esmore DS, Negri J, Rowland M, Newcomb A, Rosenfeldt FL, Bailey M, Richardson M. Early institution of mechanical support improves outcomes in primary cardiac allograft failure. J Heart Lung Transplant 2005;24:2037-2042.

[73] Hauptman PJ, Aranki S, Mudge GH, Jr., Couper GS, Loh E. Early cardiac allograft failure after orthotopic heart transplantation. Am Heart J 1994;127:179-186.

[74] Potapov EV, Sodian R, Loebe M, Drews T, Dreysse S, Hetzer R. Revascularization of the occluded right coronary artery during left ventricular assist device implantation. J Heart Lung Transplant 2001;20:918-922.

[75] Miller LW. Treatment of cardiac allograft rejection with intravenous corticosteroids. J Heart Transplant 1990;9:283-287.

[76] Sharples LD, Caine N, Mullins P, Scott JP, Solis E, English TA, Large SR, Schofield PM, Wallwork J. Risk factor analysis for the major hazards following heart transplantation--rejection, infection, and coronary occlusive disease. Transplantation 1991;52:244-252.

[77] Kobashigawa JA, Kirklin JK, Naftel DC, Bourge RC, Ventura HO, Mohanty PK, Cintron GB, Bhat G. Pretransplantation risk factors for acute rejection after heart transplantation: a multiinstitutional study. The Transplant Cardiologists Research Database Group. J Heart Lung Transplant 1993;12:355-366.

[78] Montoya JG, Giraldo LF, Efron B, Stinson EB, Gamberg P, Hunt S, Giannetti N, Miller J, Remington JS. Infectious complications among 620 consecutive heart transplant patients at Stanford University Medical Center. Clin Infect Dis 2001;33:629-640.

[79] Vitali E, Colombo T, Bruschi G, Garatti A, Russo C, Lanfranconi M, Frigerio M. Different clinical scenarios for circulatory mechanical support in acute and chronic heart failure. Am J Cardiol 2005;96:34L-41L.

[80] Mehta SM, Aufiero TX, Pae WE, Jr., Miller CA, Pierce WS. Results of mechanical ventricular assistance for the treatment of post cardiotomy cardiogenic shock. ASAIO J 1996;42:211-218.

[81] Pae WE, Jr., Miller CA, Matthews Y, Pierce WS. Ventricular assist devices for postcardiotomy cardiogenic shock. A combined registry experience. J Thorac Cardiovasc Surg 1992;104:541-552; discussion 552-543.

[82] Samuels LE, Kaufman MS, Thomas MP, Holmes EC, Brockman SK, Wechsler AS. Pharmacological criteria for ventricular assist device insertion following postcardiotomy shock: experience with the Abiomed BVS system. J Card Surg 1999;14:288-293.

[83] Torchiana DF, Hirsch G, Buckley MJ, Hahn C, Allyn JW, Akins CW, Drake JF, Newell JB, Austen WG. Intraaortic balloon pumping for cardiac support: trends in practice and outcome, 1968 to 1995. J Thorac Cardiovasc Surg 1997;113:758-764; discussion 764-759.

[84] Goldberg RJ, Gore JM, Alpert JS, Osganian V, de Groot J, Bade J, Chen Z, Frid D, Dalen JE. Cardiogenic shock after acute myocardial infarction. Incidence and mortality from a community-wide perspective, 1975 to 1988. N Engl J Med 1991;325:1117-1122.

[85] Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, Buller CE, Jacobs AK, Slater JN, Col J, McKinlay SM, LeJemtel TH. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. N Engl J Med 1999;341:625-634.

[86] Desai NR, Bhatt DL. Evaluating percutaneous support for cardiogenic shock: data shock and sticker shock. Eur Heart J 2009;30:2073-2075.

[87] Kato S, Morimoto S, Hiramitsu S, Nomura M, Ito T, Hishida H. Use of percutaneous cardiopulmonary support of patients with fulminant myocarditis and cardiogenic shock for improving prognosis. Am J Cardiol 1999;83:623-625, A610.

[88] Vogel RA, Shawl F, Tommaso C, O'Neill W, Overlie P, O'Toole J, Vandormael M, Topol E, Tabari KK, Vogel J, et al. Initial report of the National Registry of Elective Cardiopulmonary Bypass Supported Coronary Angioplasty. J Am Coll Cardiol 1990;15:23-29.

[89] Raess DH, Weber DM. Impella 2.5. J Cardiovasc Transl Res 2009;2:168-172.

[90] Valgimigli M, Steendijk P, Sianos G, Onderwater E, Serruys PW. Left ventricular unloading and concomitant total cardiac output increase by the use of percutaneous Impella Recover LP 2.5 assist device during high-risk coronary intervention. Catheter Cardiovasc Interv 2005;65:263-267.

[91] Seyfarth M, Sibbing D, Bauer I, Frohlich G, Bott-Flugel L, Byrne R, Dirschinger J, Kastrati A, Schomig A. A randomized clinical trial to evaluate the safety and efficacy of a percutaneous left ventricular assist device versus intra-aortic balloon pumping for treatment of cardiogenic shock caused by myocardial infarction. J Am Coll Cardiol 2008;52:1584-1588.

[92] Thomopoulou S, Manginas A, Cokkinos DV. Initial experience with the Impella Recover LP 2.5 micro-axial pump in patients undergoing high-risk coronary angioplasty. Hellenic J Cardiol 2008;49:382-387.

[93] Samoukovic G, Al-Atassi T, Rosu C, Giannetti N, Cecere R. Successful treatment of heart failure due to acute transplant rejection with the Impella LP 5.0. Ann Thorac Surg 2009;88:271-273.

[94] Siegenthaler MP, Brehm K, Strecker T, Hanke T, Notzold A, Olschewski M, Weyand M, Sievers H, Beyersdorf F. The Impella Recover microaxial left ventricular assist device reduces mortality for postcardiotomy failure: a three-center experience. J Thorac Cardiovasc Surg 2004;127:812-822.

[95] Jurmann MJ, Siniawski H, Erb M, Drews T, Hetzer R. Initial experience with miniature axial flow ventricular assist devices for postcardiotomy heart failure. Ann Thorac Surg 2004;77:1642-1647.

[96] Doll N, Kiaii B, Borger M, Bucerius J, Kramer K, Schmitt DV, Walther T, Mohr FW. Five-year results of 219 consecutive patients treated with extracorporeal membrane oxygenation for refractory postoperative cardiogenic shock. Ann Thorac Surg 2004;77:151-157; discussion 157.

[97] Magovern GJ, Jr., Simpson KA. Extracorporeal membrane oxygenation for adult cardiac support: the Allegheny experience. Ann Thorac Surg 1999;68:655-661.

[98] Risnes I, Wagner K, Nome T, Sundet K, Jensen J, Hynas IA, Ueland T, Pedersen T, Svennevig JL. Cerebral outcome in adult patients treated with extracorporeal membrane oxygenation. Ann Thorac Surg 2006;81:1401-1406.

[99] Korfer R, El-Banayosy A, Arusoglu L, Minami K, Korner MM, Kizner L, Fey O, Schutt U, Morshuis M, Posival H. Single-center experience with the thoratec ventricular assist device. J Thorac Cardiovasc Surg 2000;119:596-600.

[100] Curtis JJ, Walls JT, Schmaltz RA, Demmy TL, Wagner-Mann CC, McKenney CA. Use of centrifugal pumps for postcardiotomy ventricular failure: technique and anticoagulation. Ann Thorac Surg 1996;61:296-300; discussion 311-293.

[101] Smedira NG, Moazami N, Golding CM, McCarthy PM, Apperson-Hansen C, Blackstone EH, Cosgrove DM, 3rd. Clinical experience with 202 adults receiving extracorporeal membrane oxygenation for cardiac failure: survival at five years. J Thorac Cardiovasc Surg 2001;122:92-102.

[102] Frazier OH, Delgado RM. Mechanical circulatory support for advanced heart failure: where does it stand in 2003? Circulation 2003;108:3064-3068.

[103] Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, Long JW, Ascheim DD, Tierney AR, Levitan RG, Watson JT, Meier P, Ronan NS, Shapiro PA, Lazar RM, Miller LW, Gupta L, Frazier OH, Desvigne-Nickens P, Oz MC, Poirier VL. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med 2001;345:1435-1443.

[104] Gracin N, Johnson MR, Spokas D, Allen J, Bartlett L, Piccione W, Parrillo JE, Costanzo MR, Calvin JE. The use of APACHE II scores to select candidates for left ventricular assist device placement. Acute Physiology and Chronic Health Evaluation. J Heart Lung Transplant 1998;17:1017-1023.

[105] Deng MC, Loebe M, El-Banayosy A, Gronda E, Jansen PG, Vigano M, Wieselthaler GM, Reichart B, Vitali E, Pavie A, Mesana T, Loisance DY, Wheeldon DR, Portner PM. Mechanical circulatory support for advanced heart failure: effect of patient selection on outcome. Circulation 2001;103:231-237.

[106] Farrar DJ, Compton PG, Hershon JJ, Fonger JD, Hill JD. Right heart interaction with the mechanically assisted left heart. World J Surg 1985;9:89-102.

[107] McBride LR, Naunheim KS, Fiore AC, Moroney DA, Swartz MT. Clinical experience with 111 thoratec ventricular assist devices. Ann Thorac Surg 1999;67:1233-1238; discussion 1238-1239.

[108] Aaronson KD, Eppinger MJ, Dyke DB, Wright S, Pagani FD. Left ventricular assist device therapy improves utilization of donor hearts. J Am Coll Cardiol 2002;39:1247-1254.

[109] Bank AJ, Mir SH, Nguyen DQ, Bolman RM, 3rd, Shumway SJ, Miller LW, Kaiser DR, Ormaza SM, Park SJ. Effects of left ventricular assist devices on outcomes in patients undergoing heart transplantation. Ann Thorac Surg 2000;69:1369-1374; discussion 1375.

[110] Westaby S, Katsumata T, Houel R, Evans R, Pigott D, Frazier OH, Jarvik R. Jarvik 2000 heart: potential for bridge to myocyte recovery. Circulation 1998;98:1568-1574.

[111] Wieselthaler GM, Schima H, Hiesmayr M, Pacher R, Laufer G, Noon GP, DeBakey M, Wolner E. First clinical experience with the DeBakey VAD continuous-axial-flow pump for bridge to transplantation. Circulation 2000;101:356-359.

[112] Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, Dunkman WB, Jacobs W, Francis GS, Flohr KH, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. N Engl J Med 1986;314:1547-1552.

[113] Meyns B, Klotz S, Simon A, Droogne W, Rega F, Griffith B, Dowling R, Zucker MJ, Burkhoff D. Proof of concept: hemodynamic response to long-term partial ventricular support with the synergy pocket micro-pump. J Am Coll Cardiol 2009;54:79-86.

[114] Heart Failure Society Of A. HFSA 2006 Comprehensive Heart Failure Practice Guideline. J Card Fail 2006;12:e1-2.

[115] Livi U, Luciani GB, Boffa GM, Faggian G, Bortolotti U, Thiene G, Mazzucco A. Clinical results of steroid-free induction immunosuppression after heart transplantation. Ann Thorac Surg 1993;55:1160-1165.

[116] Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, Sun B, Tatooles AJ, Delgado RM, 3rd, Long JW, Wozniak TC, Ghumman W, Farrar DJ, Frazier OH. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med 2009;361:2241-2251.

[117] Lietz K, Long JW, Kfoury AG, Slaughter MS, Silver MA, Milano CA, Rogers JG, Naka Y, Mancini D, Miller LW. Outcomes of left ventricular assist device implantation as destination therapy in the post-REMATCH era: implications for patient selection. Circulation 2007;116:497-505.

[118] Westaby S. Non-transplant surgery for heart failure. Heart 2000;83:603-610.

[119] Deng MC, Young JB, Stevenson LW, Oz MC, Rose EA, Hunt SA, Kirklin JK, Kobashigawa J, Miller L, Saltzberg M, Konstam M, Portner PM, Kormos R. Destination mechanical circulatory support: proposal for clinical standards. J Heart Lung Transplant 2003;22:365-369.

[120] Taylor DO, Edwards LB, Boucek MM, Trulock EP, Aurora P, Christie J, Dobbels F, Rahmel AO, Keck BM, Hertz MI. Registry of the International Society for Heart and Lung Transplantation: twenty-fourth official adult heart transplant report--2007. J Heart Lung Transplant 2007;26:769-781.

[121] Morgan JA, Weinberg AD, Hollingsworth KW, Flannery MR, Oz MC, Naka Y. Effect of gender on bridging to transplantation and posttransplantation survival in

patients with left ventricular assist devices. J Thorac Cardiovasc Surg 2004;127:1193-1195.

[122] Simon D, Fischer S, Grossman A, Downer C, Hota B, Heroux A, Trenholme G. Left ventricular assist device-related infection: treatment and outcome. Clin Infect Dis 2005;40:1108-1115.

[123] Herrmann M, Weyand M, Greshake B, von Eiff C, Proctor RA, Scheld HH, Peters G. Left ventricular assist device infection is associated with increased mortality but is not a contraindication to transplantation. Circulation 1997;95:814-817.

[124] Deng MC, Erren M, Tjan TD, Tamminga N, Werntze B, Zimmermann P, Weyand M, Hammel D, Schmidt C, Scheld HH. Left ventricular assist system support is associated with persistent inflammation and temporary immunosuppression. Thorac Cardiovasc Surg 1999;47 Suppl 2:326-331.

[125] Reilly MP, Wiegers SE, Cucchiara AJ, O'Hara ML, Plappert TJ, Loh E, Acker MA, St John Sutton M. Frequency, risk factors, and clinical outcomes of left ventricular assist device-associated ventricular thrombus. Am J Cardiol 2000;86:1156-1159, A1110.

[126] Livi U, Milano A, Bortolotti U, Casula R, Zenati M, Casarotto D. Results of heart transplantation by extending recipient selection criteria. J Cardiovasc Surg (Torino) 1994;35:377-382.

[127] Cimato TR, Jessup M. Recipient selection in cardiac transplantation: contraindications and risk factors for mortality. J Heart Lung Transplant 2002;21:1161-1173.

[128] Russo MJ, Hong KN, Davies RR, Chen JM, Mancini DM, Oz MC, Rose EA, Gelijns A, Naka Y. The effect of body mass index on survival following heart transplantation: do outcomes support consensus guidelines? Ann Surg;251:144-152.

[129] Drakos SG, Kfoury AG, Gilbert EM, Long JW, Stringham JC, Hammond EH, Jones KW, Bull DA, Hagan ME, Folsom JW, Horne BD, Renlund DG. Multivariate predictors of heart transplantation outcomes in the era of chronic mechanical circulatory support. Ann Thorac Surg 2007;83:62-67.

[130] Borkon AM, Muehlebach GF, Jones PG, Bresnahan DR, Jr., Genton RE, Gorton ME, Long ND, Magalski A, Porter CB, Reed WA, Rowe SK. An analysis of the effect of age on survival after heart transplant. J Heart Lung Transplant 1999;18:668-674.

[131] Bourge RC, Naftel DC, Costanzo-Nordin MR, Kirklin JK, Young JB, Kubo SH, Olivari MT, Kasper EK. Pretransplantation risk factors for death after heart transplantation: a multiinstitutional study. The Transplant Cardiologists Research Database Group. J Heart Lung Transplant 1993;12:549-562.

[132] Bull DA, Karwande SV, Hawkins JA, Neumayer LA, Taylor DO, Jones KW, Renlund DG, Putnam CW. Long-term results of cardiac transplantation in patients older than sixty years. UTAH Cardiac Transplant Program. J Thorac Cardiovasc Surg 1996;111:423-427; discussion 427-428.

[133] Fabbri A, Sharples LD, Mullins P, Caine N, Large S, Wallwork J. Heart transplantation in patients over 54 years of age with triple-drug therapy immunosuppression. J Heart Lung Transplant 1992;11:929-932.

[134] Heroux AL, Costanzo-Nordin MR, O'Sullivan JE, Kao WG, Liao Y, Mullen GM, Johnson MR. Heart transplantation as a treatment option for end-stage heart

disease in patients older than 65 years of age. J Heart Lung Transplant 1993;12:573-578; discussion 578-579.

[135] Hosenpud JD, Bennett LE, Keck BM, Fiol B, Boucek MM, Novick RJ. The Registry of the International Society for Heart and Lung Transplantation: sixteenth official report--1999. J Heart Lung Transplant 1999;18:611-626.

[136] Baron O, Trochu JN, Treilhaud M, al Habash O, Remadi JP, Petit T, Duveau D, Despins P, Michaud JL. Cardiac transplantation in patients over 60 years of age. Transplant Proc 1999;31:75-78.

[137] Crespo-Leiro MG, Paniagua MJ, Rodriguez JA, Hermida LF, Fojon S, Vazquez N, Muniz J, Cuenca JJ, Juffe-Stein A, Castro-Beiras A. Morbidity and mortality among heart transplant patients older and younger than 65 years. Transplant Proc 1999;31:2537-2538.

[138] Frazier OH, Macris MP, Duncan JM, Van Buren CT, Cooley DA. Cardiac transplantation in patients over 60 years of age. Ann Thorac Surg 1988;45:129-132.

[139] Hosenpud JD, Pantely GA, Norman DJ, Cobanoglu AM, Hovaguimian H, Starr A. A critical analysis of morbidity and mortality as it relates to recipient age following cardiac transplantation. Clin Transplant 1990;4:51-54.

[140] McCarthy JF, McCarthy PM, Massad MG, Cook DJ, Smedira NG, Kasirajan V, Goormastic M, Hoercher K, Young JB. Risk factors for death after heart transplantation: does a single-center experience correlate with multicenter registries? Ann Thorac Surg 1998;65:1574-1578; discussion 1578-1579.

[141] Miller LW, Vitale-Noedel N, Pennington G, McBride L, Kanter KR. Heart transplantation in patients over age fifty-five years. J Heart Transplant 1988;7:254-257.

[142] Olivari MT, Antolick A, Kaye MP, Jamieson SW, Ring WS. Heart transplantation in elderly patients. J Heart Transplant 1988;7:258-264.

[143] Grady KL, Costanzo-Nordin MR, Herold LS, Sriniavasan S, Pifarre R. Obesity and hyperlipidemia after heart transplantation. J Heart Lung Transplant 1991;10:449-454.

[144] Kocher AA, Ankersmit J, Khazen C, Ofner P, Zuckermann A, Grimm M, Schlechta B, Ehrlich M, Wolner E, Laufer G. Effect of obesity on outcome after cardiac transplantation. Transplant Proc 1999;31:3187-3189.

[145] Grady KL, White-Williams C, Naftel D, Costanzo MR, Pitts D, Rayburn B, VanBakel A, Jaski B, Bourge R, Kirklin J. Are preoperative obesity and cachexia risk factors for post heart transplant morbidity and mortality: a multi-institutional study of preoperative weight-height indices. Cardiac Transplant Research Database (CTRD) Group. J Heart Lung Transplant 1999;18:750-763.

[146] Taylor DO, Edwards LB, Boucek MM, Trulock EP, Keck BM, Hertz MI. The Registry of the International Society for Heart and Lung Transplantation: twenty-first official adult heart transplant report--2004. J Heart Lung Transplant 2004;23:796-803.

[147] Louis A, Cleland JG, Crabbe S, Ford S, Thackray S, Houghton T, Clark A. Clinical Trials Update: CAPRICORN, COPERNICUS, MIRACLE, STAF, RITZ-2, RECOVER and RENAISSANCE and cachexia and cholesterol in heart failure. Highlights of the Scientific Sessions of the American College of Cardiology, 2001. Eur J Heart Fail 2001;3:381-387.

[148] Mancini D, Beniaminovitz A, Edwards N, Chen J, Maybaum S. Survival of diabetic patients following cardiac transplant. J Heart Lung Transplant 2001;20:168.

[149] Czerny M, Sahin V, Zuckermann A, Zimpfer D, Kilo J, Baumer H, Wolner E, Grimm M. Diabetes affects long-term survival after heart transplantation. J Heart Lung Transplant 2001;20:245.

[150] Chen JM, Levin HR, Michler RE, Prusmack CJ, Rose EA, Aaronson KD. Reevaluating the significance of pulmonary hypertension before cardiac transplantation: determination of optimal thresholds and quantification of the effect of reversibility on perioperative mortality. J Thorac Cardiovasc Surg 1997;114:627-634.

[151] Erickson KW, Costanzo-Nordin MR, O'Sullivan EJ, Johnson MR, Zucker MJ, Pifarre R, Lawless CE, Robinson JA, Scanlon PJ. Influence of preoperative transpulmonary gradient on late mortality after orthotopic heart transplantation. J Heart Transplant 1990;9:526-537.

[152] Espinoza C, Manito N, Roca J, Castells E, Mauri J, Ribas M, Claret G. Reversibility of pulmonary hypertension in patients evaluated for orthotopic heart transplantation: importance in the postoperative morbidity and mortality. Transplant Proc 1999;31:2503-2504.

[153] Murali S, Kormos RL, Uretsky BF, Schechter D, Reddy PS, Denys BG, Armitage JM, Hardesty RL, Griffith BP. Preoperative pulmonary hemodynamics and early mortality after orthotopic cardiac transplantation: the Pittsburgh experience. Am Heart J 1993;126:896-904.

[154] Murali S, Uretsky BF, Armitage JM, Tokarczyk TR, Betschart AR, Kormos RL, Stein KL, Reddy PS, Hardesty RL, Griffith BP. Utility of prostaglandin E1 in the pretransplantation evaluation of heart failure patients with significant pulmonary hypertension. J Heart Lung Transplant 1992;11:716-723.

[155] Delgado JF, Gomez-Sanchez MA, Saenz de la Calzada C, Sanchez V, Escribano P, Hernandez-Afonso J, Tello R, Gomez de la Camara A, Rodriguez E, Rufilanchas JJ. Impact of mild pulmonary hypertension on mortality and pulmonary artery pressure profile after heart transplantation. J Heart Lung Transplant 2001;20:942-948.

[156] Deng MC, Gradaus R, Hammel D, Weyand M, Gunther F, Kerber S, Haverkamp W, Roeder N, Breithardt G, Scheld HH. Heart transplant candidates at high risk can be identified at the time of initial evaluation. Transpl Int 1996;9:38-45.

[157] Pamboukian SV, Carere RG, Webb JG, Cook RC, D'Yachkova Y, Abel JG, Ignaszewski AP. The use of milrinone in pre-transplant assessment of patients with congestive heart failure and pulmonary hypertension. J Heart Lung Transplant 1999;18:367-371.

[158] Pascual JM, Fiorelli AI, Bellotti GM, Stolf NA, Jatene AD. Prostacyclin in the management of pulmonary hypertension after heart transplantation. J Heart Transplant 1990;9:644-651.

[159] Simonsen S, Molstad P, Geiran O, Froysaker T. Heart transplantation in patients with severe pulmonary hypertension and increased pulmonary vascular resistance. Scand J Thorac Cardiovasc Surg 1990;24:161-164.

[160] Trautnitz M, Pehlivanli S, Behr J, Schwaiblmair M, Uberfuhr P, Meiser B, von Scheidt W. [Pharmacological testing of the reversibility of increased pulmonary vascular resistance before heart transplantation with prostaglandin I2 (prostacyclin)]. Z Kardiol 1999;88:133-140.

[161] Weiss CI, Park JV, Bolman RM. Prostaglandin E1 for treatment of elevated pulmonary vascular resistance in patients undergoing cardiac transplantation. Transplant Proc 1989;21:2555-2556.

[162] Zink M, Gombotz H, Wasler A, Grasser B, Rehak P, Metzler H. Urapidil reduces elevated pulmonary vascular resistance in patients before heart transplantation. J Heart Lung Transplant 2002;21:347-353.

[163] Klotz S, Deng MC, Hanafy D, Schmid C, Stypmann J, Schmidt C, Hammel D, Scheld HH. Reversible pulmonary hypertension in heart transplant candidates--pretransplant evaluation and outcome after orthotopic heart transplantation. Eur J Heart Fail 2003;5:645-653.

[164] Hosenpud JD, Bennett LE, Keck BM, Boucek MM, Novick RJ. The Registry of the International Society for Heart and Lung Transplantation: seventeenth official report-2000. J Heart Lung Transplant 2000;19:909-931.

[165] Adamson RM, Dembitsky WP, Jaski BE, Daily PO, Moreno R, Kim JC, Sono J, Akasaka T, Hoagland PM, Gordon JB. Left ventricular assist device support of medically unresponsive pulmonary hypertension and aortic insufficiency. ASAIO J 1997;43:365-369.

[166] Herlitz H, Lindelow B. Renal failure following cardiac transplantation. Nephrol Dial Transplant 2000;15:311-314.

[167] Gonwa TA, Mai ML, Pilcher J, Johnson C, Pierson S, Capehart JE, Alivizatos PA. Stability of long-term renal function in heart transplant patients treated with induction therapy and low-dose cyclosporine. J Heart Lung Transplant 1992;11:926-928.

[168] Goral S, Ynares C, Shyr Y, Yeoh TK, Johnson HK. Long-term renal function in heart transplant recipients receiving cyclosporine therapy. J Heart Lung Transplant 1997;16:1106-1112.

[169] Greenberg A, Thompson ME, Griffith BJ, Hardesty RL, Kormos RL, el-Shahawy MA, Janosky JE, Puschett JB. Cyclosporine nephrotoxicity in cardiac allograft patients--a seven-year follow-up. Transplantation 1990;50:589-593.

[170] Lindelow B, Bergh CH, Herlitz H, Waagstein F. Predictors and evolution of renal function during 9 years following heart transplantation. J Am Soc Nephrol 2000;11:951-957.

[171] Tinawi M, Miller L, Bastani B. Renal function in cardiac transplant recipients: retrospective analysis of 133 consecutive patients in a single center. Clin Transplant 1997;11:1-8.

[172] Zietse R, Balk AH, vd Dorpel MA, Meeter K, Bos E, Weimar W. Time course of the decline in renal function in cyclosporine-treated heart transplant recipients. Am J Nephrol 1994;14:1-5.

[173] Sehgal V, Radhakrishnan J, Appel GB, Valeri A, Cohen DJ. Progressive renal insufficiency following cardiac transplantation: cyclosporine, lipids, and hypertension. Am J Kidney Dis 1995;26:193-201.

[174] Pagani FD, Miller LW, Russell SD, Aaronson KD, John R, Boyle AJ, Conte JV, Bogaev RC, MacGillivray TE, Naka Y, Mancini D, Massey HT, Chen L, Klodell CT, Aranda JM, Moazami N, Ewald GA, Farrar DJ, Frazier OH. Extended mechanical circulatory support with a continuous-flow rotary left ventricular assist device. J Am Coll Cardiol 2009;54:312-321.

[175] Frazier OH, Gemmato C, Myers TJ, Gregoric ID, Radovancevic B, Loyalka P, Kar B. Initial clinical experience with the HeartMate II axial-flow left ventricular assist device. Tex Heart Inst J 2007;34:275-281.

[176] John R, Kamdar F, Liao K, Colvin-Adams M, Boyle A, Joyce L. Improved survival and decreasing incidence of adverse events with the HeartMate II left ventricular assist device as bridge-to-transplant therapy. Ann Thorac Surg 2008;86:1227-1234; discussion 1234-1225.

[177] Struber M, Sander K, Lahpor J, Ahn H, Litzler PY, Drakos SG, Musumeci F, Schlensak C, Friedrich I, Gustafsson R, Oertel F, Leprince P. HeartMate II left ventricular assist device; early European experience. Eur J Cardiothorac Surg 2008;34:289-294.

[178] Pagani FD, Long JW, Dembitsky WP, Joyce LD, Miller LW. Improved mechanical reliability of the HeartMate XVE left ventricular assist system. Ann Thorac Surg 2006;82:1413-1418.

[179] Crow S, John R, Boyle A, Shumway S, Liao K, Colvin-Adams M, Toninato C, Missov E, Pritzker M, Martin C, Garry D, Thomas W, Joyce L. Gastrointestinal bleeding rates in recipients of nonpulsatile and pulsatile left ventricular assist devices. J Thorac Cardiovasc Surg 2009;137:208-215.

[180] Uriel N, Pak SW, Jorde UP, Jude B, Susen S, Vincentelli A, Ennezat PV, Cappleman S, Naka Y, Mancini D. Acquired von Willebrand syndrome after continuous-flow mechanical device support contributes to a high prevalence of bleeding during long-term support and at the time of transplantation. J Am Coll Cardiol;56:1207-1213.

[181] John R, Kamdar F, Eckman P, Colvin-Adams M, Boyle A, Shumway S, Joyce L, Liao K. Lessons learned from experience with over 100 consecutive HeartMate II left ventricular assist devices. Ann Thorac Surg;92:1593-1599; discussion 1599-1600.

[182] Sweeney MS, Lammermeier DE, Frazier OH, Burnett CM, Haupt HM, Duncan JM. Extension of donor criteria in cardiac transplantation: surgical risk versus supply-side economics. Ann Thorac Surg 1990;50:7-10; discussion 10-11.

[183] Kannel WB, Belanger AJ. Epidemiology of heart failure. Am Heart J 1991;121:951-957.

[184] Ko WJ, Lin CY, Chen RJ, Wang SS, Lin FY, Chen YS. Extracorporeal membrane oxygenation support for adult postcardiotomy cardiogenic shock. Ann Thorac Surg 2002;73:538-545.

[185] Icenogle TB, Williams RJ, Smith RG, Cleavinger M, Vasu MA, Rhenman B, Copeland JG. Extracorporeal pulsatile biventricular support after cardiac transplantation. Ann Thorac Surg 1989;47:614-616.

[186] Lima B, Rajagopal K, Petersen RP, Shah AS, Soule B, Felker GM, Rogers JG, Lodge AJ, Milano CA. Marginal cardiac allografts do not have increased primary graft dysfunction in alternate list transplantation. Circulation 2006;114:I27-32.

[187] Kavarana MN, Pessin-Minsley MS, Urtecho J, Catanese KA, Flannery M, Oz MC, Naka Y. Right ventricular dysfunction and organ failure in left ventricular assist device recipients: a continuing problem. Ann Thorac Surg 2002;73:745-750.

[188] Segovia J, Pulpon LA, Sanmartin M, Tejero C, Serrano S, Burgos R, Castedo E, Ugarte J. Primary graft failure in heart transplantation: a multivariate analysis. Transplant Proc 1998;30:1932.

[189] John R, Chen JM, Weinberg A, Oz MC, Mancini D, Itescu S, Galantowicz ME, Smith CR, Rose EA, Edwards NM. Long-term survival after cardiac retransplantation: a twenty-year single-center experience. J Thorac Cardiovasc Surg 1999;117:543-555.

[190] Miniati DN, Robbins RC. Mechanical support for acutely failed heart or lung grafts. J Card Surg 2000;15:129-135.

[191] Petrofski JA, Patel VS, Russell SD, Milano CA. BVS5000 support after cardiac transplantation. J Thorac Cardiovasc Surg 2003;126:442-447.

[192] Hooper TL, Odom NJ, Fetherston GJ, Waterhouse P, Hilton CJ, Dark JH. Successful use of left ventricular assist device for primary graft failure after heart transplantation. J Heart Transplant 1988;7:385-387.

[193] Taghavi S, Zuckermann A, Ankersmit J, Wieselthaler G, Rajek A, Laufer G, Wolner E, Grimm M. Extracorporeal membrane oxygenation is superior to right ventricular assist device for acute right ventricular failure after heart transplantation. Ann Thorac Surg 2004;78:1644-1649.

[194] D'Alessandro C, Aubert S, Golmard JL, Praschker BL, Luyt CE, Pavie A, Gandjbakhch I, Leprince P. Extra-corporeal membrane oxygenation temporary support for early graft failure after cardiac transplantation. Eur J Cardiothorac Surg;37:343-349.

[195] Listijono DR, Watson A, Pye R, Keogh AM, Kotlyar E, Spratt P, Granger E, Dhital K, Jansz P, Macdonald PS, Hayward CS. Usefulness of extracorporeal membrane oxygenation for early cardiac allograft dysfunction. J Heart Lung Transplant;30:783-789.

[196] Zimpfer D, Heinisch B, Czerny M, Hoelzenbein T, Taghavi S, Wolner E, Grimm M. Late vascular complications after extracorporeal membrane oxygenation support. Ann Thorac Surg 2006;81:892-895.

APPENDIX:

RESEARCH ACTIVITY DURING PhD:

Publications

Performance of the pulmonary autograft in four infants after the Ross procedure. VL Vida, M Rubino, T Bottio, S Sponga, O Milanesi, G Stellin. Pediatr Cardiol. 2005 Nov-Dec;26(6):797-800

Grp94 Overexpression Counteracts Ischemia-Induced Activation of Caspase-12 and Protects Cells After Transplantation in the Infarcted Myocardium. M. Vitadello, E. Tarricone, M. Crocco, F. Zigrino, S. Sponga, G. Gerosa, L. Gorza. Circulation. 2006;114:II_295.

Systemic sclerosis and aortic valve stenosis: therapeutic implications in two cases of aortic valve replacement. S Sponga, C Basso, A Ruffatti, G Gerosa. J Cardiovasc Med 2009;10(7):560-2.

Reconstruction of two independent neo-atria after resection of recurrent leiomyosarcoma. S Sponga, A Rizzi, P Gerometta, G Rocco, V Arena. Ann Thorac Surg. 2009;88(1):1-2.

Mitral valve repair after papillary muscle rupture through beating heart adjustment of artificial chordae length. S Sponga, P Tartara P, E Vitali , V Arena. Ann Thorac Surg. 2010; 90(2):32-3.

A case of inefficient defibrillation during thoracotomy. S Sponga, G Mascioli, P Voisine, E Vitali. J Card Surg, 2011;26:338-9

Transapical Aortic Valve Implantation Compared to Conventional Aortic Valve Replacement in High-Risk Patients with Severe Aortic Stenosis and Previous Coronary Artery Bypass Grafting. S Sponga, J Rodes Cabau, D Doyle, R De Larochelliere, R Bagur, E Dumont. Circulation.2010;122:A18287.

Von Willebrand factor abnormalities in aortic valve stenosis: pathophysiology and impact on bleeding. A Casonato, S Sponga, E Pontara, MG Cattini, C Basso, G Thiene, G Cella, V Daidone, G Gerosa G, A Pagnan. Thromb Haemost 2011;106:58-66.

Reversible circumflex coronary artery occlusion during mitral annuloplasty with Viacor system. S Sponga, F Bertrand, F Philippon, A St Pierre, F Dagenais, E Charbonneau, R Bagur, M Senechal. JACC 2012;59:288.

Preoperative treatment with levosimendan in candidates for mechanical circulatory support. S Sponga, E Ivanitskaia-Kühn, , EV Potapov, T Krabatsch, R Hetzer HB Lehmkuhl. ASAIO 2012;58:6-11.

Unexpected Porcelain Aorta After Sternotomy For Aortic Valve Replacement and Coronary Artery Bypass Surgery: Aortic Balloon Valvuloplasty as a Bail Out Procedure, S Sponga, E Dumont, J Rodes-Cabau, F Dagenais, D Doyle. Can J Card 2011;27:868.

Impact of residual regurgitation after aortic valve replacement. S Sponga, J Perron, F Dagenais, S Mohammadi, R Baillot, D Doyle, P Voisine. Eur J Cardiothorac Surg 2011 In press.

Severe upper gastro-intestinal bleeding in heartmate ii induced by acquired von willebrand deficiency: anticoagulation management. S sponga, C Nalli, S Casonato, E Charbonneau. Ann Thorac Surg 2011. In press.

Role of an aggressive rhythm control strategy on sinus rhythm maintenance following intra-operative radiofrequency ablation of atrial fibrillation in patients undergoing surgical correction of valvular disease S Sponga, L Leoni, G Buja, C Nalli, G Gerosa. J Caldiol 2011. Pending of minor revisions.

Intraoperative radiofrequency ablation combined to congenital heart defect repair. S Sponga, J Sarrazin, M Padalino, L Leoni, C Nalli, G Buja, D Corrado, O Milanesi, G Stellin. J Caldiol 2011. Pending of minor revisions.

Transcatheter Aortic Valve Implantation in Patients with Severe Aortic Stenosis and Calcified Ascending Aorta Sandro Sponga, Josep Rodes Cabau, Daniel Doyle, Robert De Larochelliere, Rodrigo Bagur, Eric Dumont. Under revision J Thorc Surg

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 Ann Thorac Surg

Fifteen Year Follow-Up After Aortic Root Replacement with Stentless Biological Valve Conduits: Homograft versus Freestyle. S Sponga, F Dagenais, J Perron, , P Voisine, V. Tchana-sato, D Doyle, S Mohammadi. Under revision Circulation (Surgical supplements)

Eighteen Year Clinical and Echocardiographic Follow up of the Freestyle Stentless Bioprostheses. V. Tchana-sato, F Dagenais, J Perron, , P Voisine, S Sponga, D Doyle, S Mohammadi. Under revision Circulation (Surgical supplements)

Congress presentations

Intraoperative radiofrequency ablation of atrial tachyarrhytmias. M A Padalino, S Sponga, L Leoni, M Rubino, V L Vida , G Stellin. I Congresso Italiano di Cardiochirurgia Pediatrica. Taormina 22-27/9/2004

Combined congenital heart disease repair and intraoperative radiofrequency ablation of atrial tachyarrhytmias. M A Padalino, L Leoni, G Buja, M Rubino, M Ornella, S Sponga, V L Vida , G Stellin. XII Congresso Italino di Chirugia Cardiaca. Bologna 6-9/11/2004

Overexpression of the glucose regulated protein GRP94 enhances survival of myogenic H9c2 cells transferred into the infarcted myocardium. L.Gorza, M.Vitadello, M.Crocco, S.Gomirato, F.Zigrino, S.Sponga and G.Gerosa. "First Biannial Meeting of the Association for European Cardiovascular Pathology". Praglia 21-23/11/2004

Increased levels of the glucose regulated protein Grp94 ameliorate survival of myogenic H9c2 cells transplanted into the infarcted myocardium. L Gorza, M. Vitadello, M. Crocco, E. Tarricone, F. Zigrino, S. Sponga, G.Gerosa. "European Society of Cardiology.Heart failure 2005". Lisbona 11-13/6/2005.

Survival of transplanted cells in the infarcted myocardium is enhanced by overexpression of the glucose-regulated protein GRP94. L. Gorza, M. Vitadello,

M.Crocco, S.Gomirato, F.Zigrino, S.Sponga and G.Gerosa. Molecular biology of cardiac disease and regeneration. Stemboad Springs, Colorado. 3-8/4/2005

Intraoperative radiofrequency ablation in combination to repair of congenital heart defects. S.Sponga, M.A.Padalino, L. Leoni, G.Buja, O.Milanesi, G.Stellin. Congresso Italiano di Cardiochirurgia Pediatrica. Genova 2-5/10/2005.

Grp94 Overexpression Counteracts Ischemia-Induced Activation of Caspase-12 and Protects Cells After Transplantation in the Infarcted Myocardium. M. Vitadello, E. Tarricone, M. Crocco, F. Zigrino, S. Sponga, G. Gerosa, L. Gorza. Circulation. 2006;114:II_295.

The importance of a strict follow up and of electrical cardioversion in patients who underwent radiofrequency ablation. S. Sponga, L. Leoni, L.Testolin, G.BuJa, G.Gerosa. XIII Catalan Congress. Barcelona 20-22/04/2007

Hemorrhage is not common in severe aortic stenosis, despite the frequency of von Willembrand factor abnormalities. S. Sponga, E. Pontata, MG.Cattini, F.Sartorello, C.Basso, A.Pagnan, G.Gerosa, A.Casonato. XIII Catalan Congress. Barcelona 20-22/04/2007.

Long-term mechanical circulatory support. S.Sponga, T.Drews, M.Jurmann, Y.Weng, R Hetzer. XIII Catalan Congress. Barcelona 20-22/04/2007

Intraoperative radiofrequency ablation in combination to repair of congenital heart defects. S.Sponga, M.A.Padalino, L. leoni, G.Buja, O.Milanesi, G.Stellin. XIII Catalan Congress. Barcelona 20-22/04/2007

Induction of GRP94 expression increases short-term viability of transplanted cells. M. Vitadello, E. Tarricone, M. Crocco, F. Zigrino, S. Sponga, G. Gerosa, L. Gorza, V incontro dell´ Istituto di neuroscienze, Cagliari 3-5/06/2007

La forma end stage dal trapianto alla destination therapy. S Sponga, E Vitali. Presente e futuro della cardiopatia ischemica, Caserta 12-13/06/2008

Evaluación hemodinámica y clínica de pacientes portadores de prótesis biológicas aórticas Perimount Magna. Laura Vidal Bonet, José Ignacio Sáez de Ibarra Sánchez, Carlos Fernández Palomeque, Fernando Enríquez Palma, Rubén Fernández Tarrio, Sandro Sponga, Ramón Barril Baixeras, José Oriol Bonnin Gubianas, Madrid 9-11/10/2008

Reconstruction of two indipendent atrial neo-cavities after mediastinal mass resection. S. Sponga, A Rizzi, P.Gerometta, V.Arena. Congresso Italiano di Chirurgia Toracica, Forlì 15-18/10/2008

Cardiac damnage during aortic arch surgery S. Sponga, G. Cagnoni, P.Gerometta, V.Arena Congresso Italiano di Cardiochirurgia. Roma 08-11/11/2008

Bridge to transplant and destination therapy. S. Sponga, E Vitali. European School for Cardio-Thoracic Surgery. Bergamo 10-15/11/2008

Effect of inotropic support with levosimendan in patients scheduled for LVAD implantation. E Ivanitskaia-Kühn, HB Lehmkuhl, EV Potapov, T Krabatsch, S Sponga, A Stepanenko, R Hetzer. 38th Annual Meeting of the German Society for Thoracic and Cardiovascular Surgery. Stuttgard 15-18/02/2009

Transapical Aortic Valve Implantation Compared to Conventional Aortic Valve Replacement in High-Risk Patients with Severe Aortic Stenosis and Previous Coronary

Artery Bypass Grafting. S Sponga, J Rodes Cabau, D Doyle, R De Larochelliere, R Bagur, E Dumont. CCS Congress, Montreal 23-26/10/2010

Transapical Aortic Valve Implantation Compared to Conventional Aortic Valve Replacement in High-Risk Patients with Severe Aortic Stenosis and Previous Coronary Artery Bypass Grafting. S Sponga, J Rodes Cabau, D Doyle, R De Larochelliere, R Bagur, E Dumont. AHA congress, Chicago 13-17/11/2010

Preoperative treatment with levosimendan in candidates for mechanical circulatory support. S Sponga, E Ivanitskaia-Kühn, EV Potapov, T Krabatsch, R Hetzer HB Lehmkuhl. ISHLTS congress. San Diego 13-16/04/2011

Impact of residual regurgitation after aortic valve replacement S Sponga, J Perron, F Dagenais, S Mohammadi, R Baillot, D Doyle, P Voisine. European Congress fo Cardiac Surgery. Lisbon 1-5/10/2011

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. Canadian Congress of Cardiology. Vancouver 22-26/10/2011

Residual regurgitation after aortic valve replacement increases mortality. S Sponga, J Perron, F Dagenais, S Mohammadi, R Baillot, D Doyle, P Voisine. Canadian Congress of Cardiology. Vancouver 22-26/10/2011

Transcatheter Aortic Valve Implantation in Patients with Severe Aortic Stenosis and Calcified Ascending Aorta Sandro Sponga, Josep Rodes Cabau, Daniel Doyle, Robert De Larochelliere, Rodrigo Bagur, Eric Dumont. Canadian Congress of Cardiology. Vancouver 22-26/10/2011

Impact of paravalvular leak. S Sponga, J Perron, F Dagenais, S Mohammadi, R Baillot, D Doyle, P Voisine. American Heart Association Congress. Orlando 13-15/11/2011

Fifteen Year Follow-Up After Aortic Root Replacement with Stentless Biological Valve Conduits: Homograft versus Freestyle. S Sponga, F Dagenais, J Perron, , P Voisine, V. Tchana-sato, D Doyle, S Mohammadi. American Heart Association Congress. Orlando 13-15/11/2011

Eighteen Year Clinical and Echocardiographic Follow up of the Freestyle Stentless Bioprostheses. V. Tchana-sato, F Dagenais, J Perron, , P Voisine, S Sponga, D Doyle, S Mohammadi. American Heart Association Congress. Orlando 13-15/11/2011

Preoperative treatment with levosimendan in candidates for mechanical circulatory support. S Sponga, E Ivanitskaia-Kühn, , EV Potapov, T Krabatsch, R Hetzer HB Lehmkuhl. Congresso Italiano di Cardiologia. Roma 10-12/12/2011.

Transcatheter Aortic Valve Implantation in Patients with Severe Aortic Stenosis and Calcified Ascending Aorta Sandro Sponga, Josep Rodes Cabau, Daniel Doyle, Robert De Larochelliere, Rodrigo Bagur, Eric Dumont. Congresso Italiano di Cardiologia. Roma 10-12/12/2011.

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. Congresso Italiano di Cardiologia. Roma 10-12/12/2011.

Residual regurgitation after aortic valve replacement increases mortality. S Sponga, J Perron, F Dagenais, S Mohammadi, R Baillot, D Doyle, P Voisine. Canadian Congress of Cardiology. Congresso Italiano di Cardiologia. Roma 10-12/12/2011.

Transcatheter Aortic Valve Implantation in Patients with Severe Aortic Stenosis and Calcified Ascending Aorta Sandro Sponga, Josep Rodes Cabau, Daniel Doyle, Robert De Larochelliere, Rodrigo Bagur, Eric Dumont. Congresso Italiano di Cardiologia. Roma 10-12/12/2011.

Impact of paravalvular leak. S Sponga, J Perron, F Dagenais, S Mohammadi, R Baillot, D Doyle, P Voisine. Congresso Italiano di Cardiologia. Roma 10-12/12/2011.

Awards

Leonardo da Vinci European Young Investigator Award 2011.

Other

Coinvestigator in SWISS TRIAL (international trial on immunosuppression in heart transplantation) and EXELL TRIAL (international trial to evaluate PTCA vs CABG in left main coronary artery disease).