Surgical Management of Heart Failure

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Introduction

Heart failure (HF) is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. The cardinal manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention. Despite widespread use of evidence-based therapies the morbidity and mortality of heart failure are still high. It remains the most common hospital discharge diagnosis for patients older than 65 years (1). There are several reasons that may explain why the prevalence of heart failure is increasing: aging of the population, the success in prolonging survival in coronary patients, and the success in postponing coronary events by effective prevention in those patients at high risk or patients who have already survived a first event (secondary prevention). At present time, cardiac transplantation remains the gold standard of cardiac replacement therapy. However, the supply of donor hearts is limited and therefore is not an option for many patients because of age and other comorbid conditions. Alternative forms of cardiac replacement therapy are ventricular assist devices implantation and total artificial heart. The others are cell therapy, xenotransplantation and gene therapy which are still in experimental stage.

Heart failure is often a long-term (chronic) condition, but it can sometimes develop suddenly. It can be caused by many different heart problems. The condition may affect only the right side or the left side of the heart. These are called right-sided HF or left-sided HF. More often, both sides of the heart are involved.

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The most common cause of HF is coronary artery disease (2). Others are congenital heart disease, valvular cardiomyopathy, myocarditis, long-standing arrhythmias amyloidosis, emphysema thyrotoxicosis, sarcoidosis, severe anemia and hemochromatosis.

Heart failure is either due to left ventricular systolic dysfunction which is caused by impaired left ventricular contraction and usually characterized by a reduced left ventricular ejection fraction, or with preserved ejection fraction which is usually associated with impaired left ventricular relaxation, rather than left ventricular contraction, and characterized by a normal or preserved left ventricular ejection fraction (3,4).

For both patients and their carers, HF can be a financial burden and have adverse effects on their quality of life. Healthcare professionals are expected to take it fully into account when exercising their clinical judgment. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer. Treatment and care should take into account patients' needs and preferences. People with chronic heart failure (CHF) should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. Good communication between healthcare professionals and patients is essential. It should be supported by evidence-based written information tailored to the patient's needs.

■ When a diagnosis of HF has been made, assess severity, etiology, precipitating factors, type of cardiac dysfunction and correctable causes. All patients with CHF require monitoring. This monitoring should include a clinical assessment of functional capacity, fluid status, cardiac rhythm, cognitive status and nutritional status, a review of medication, including need for changes and possible side-effects, serum urea, electrolytes, creatinine. More detailed monitoring will be required if the

patient has significant comorbidity or if their condition has deteriorated since the previous review.

Classification

There are four stages of HF (5):

- Stage A identifies the patient who is at high risk for developing HF but has no structural disorder of the heart;

- Stage B refers to a patient with a structural disorder of the heart but who has never developed symptoms of HF;

- Stage C denotes the patient with past or current symptoms of HF associated with underlying structural heart disease; and

- Stage D designates the patient with end-stage disease who requires specialized treatment strategies such as mechanical circulatory support, continuous inotropic infusions, cardiac transplantation, or hospice care.

Only the latter two stages, of course, qualify for the traditional clinical diagnosis of HF for diagnostic or coding purposes.

Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS)

This classification (6) is an elaboration of NYHA IV which further guides level of severity. It helps in the management of the patient in a more defined way.

Profile 1: Critical cardiogenic shock

Patients with life-threatening hypotension despite rapidly escalating inotropic support, critical organ hypoperfusion, often confirmed by worsening acidosis and/or lactate levels. "*Crash and burn.*"

Profile 2: Progressive decline

Patient with declining function despite intravenous inotropic support, may be manifest by worsening renal function, nutritional depletion, inability to restore volume balance "Sliding on inotropes." Also describes declining status in patients unable to tolerate inotropic therapy.

Profile 3: Stable but inotrope dependent

Patient with stable blood pressure, organ function, nutrition, and symptoms on continuous intravenous inotropic support (or a temporary circulatory support device or both), but demonstrating repeated failure to wean from support due to recurrent symptomatic hypotension or renal dysfunction "*Dependent stability.*"

Profile 4: Resting symptoms

Patient can be stabilized close to normal volume status but experiences daily symptoms of congestion at rest or during activities of daily living. Doses of diuretics generally fluctuate at very high levels. More intensive management and surveillance strategies should be considered, which may in some cases reveal poor compliance that would compromise outcomes with any therapy. Some patients may shuttle between 4 and 5.

Profile 5: Exertion intolerant

Comfortable at rest and with ADL but unable to engage in any other activity, living predominantly within the house. Patients are comfortable at rest without congestive symptoms, but may have underlying refractory elevated volume status, often with renal dysfunction. If underlying nutritional status and organ function are marginal, patient may be more at risk than INTERMACS 4, and require definitive intervention.

Profile 6: Exertion limited

Patient without evidence of fluid overload is comfortable at rest, and with activities of daily living and minor activities outside the home but fatigues after the first few minutes of any meaningful activity. attribution to cardiac limitation requires careful measurement of peak oxygen consumption, in some cases with hemodynamic monitoring to confirm severity of cardiac impairment. "*Walking wounded.*"

Profile 7: Advanced NYHA III

A place holder for more precise specification in future, this level includes patients who are without current or recent episodes of unstable fluid balance, living comfortably with meaningful activity limited to mild physical exertion.

Modifiers for profiles

TCS - Temporary Circulatory Support can modify only patients in hospital (other devices would be INTERMACS devices) includes IABP, ECMO, TandemHeart, Levitronix, BVS5000 or AB5000, Impella.

A - Arrhythmia - can modify any profile. Recurrent ventricular tachyarrhythmias that have recently contributed substantially to clinical compromise. This includes frequent ICD shock or requirement for external defibrillator, usually more than twice weekly.

FF - Frequent Flyer - can modify only outpatients, designating a patient requiring frequent emergency visits or hospitalizations for diuretics, ultrafiltration, or temporary intravenous vasoactive therapy.

Treatment

Modalities of treatment starting from conservative medical management to transplantation in the ascending order are as follow:

- Drugs

- Cardiac resynchronization therapy

- Mechanical circulatory support

- Cardiac transplantation

Drugs

Many patients with advanced HF have symptoms that are related to the retention of salt and water and thus will respond favorably to interventions designed to restore sodium balance. Hence, a critical step in the successful management of end-stage HF is the recognition and meticulous control of fluid retention. Controlled trials suggest that patients with advanced heart failure respond favorably to treatment with both ACE inhibitors and β-blockers in a manner similar to those with mild to moderate disease (7,8). Others are diuretics, calcium channel blockers, digoxin (9), amiodarone, aspirin and anticoagulants.

Ionotopes

Intravenous inotropic agents (such as dobutamine, milrinone or enoximone) should only be considered for the short-term treatment of acute decompensation of CHF. This will require specialist advice. Dobutamine and milirinone are the common ionotropes being prescribed as home therapy (infusion pumps) as an interim measure to stabilize till definitive intervention is considered.

Cardiac resynchronization therapy (CRT)

It reduces symptoms and improves left ventricular function in CHF patients with left ventricular systolic dysfunction and prolonged QRS duration. Recent studies have demonstrated a reduction in mortality associated with CRT. When combined with an implantable cardioverter defibrillator (ICD), reduction in mortality is likely to happen further (10). Cardiac resynchronization therapy is well tolerated and free from compliance issues and therefore should be considered for all suitable patients. It has now become a part of standard therapy for patients with severe symptomatic CHF and intraventricular dyssynchrony (11).

Mechanical circulatory support

Thousands of patients underwent LVAD implantation as an alternative to heart transplantation, or destination therapy, since the completion of the landmark REMATCH trial, which first demonstrated the superiority of mechanical circulatory support over medical therapy for end-stage HF in patients who were not eligible for heart transplantation (12). Survival rates at 1 and 2 years in REMATCH trial were of 56% and 33% (Fig. 1).
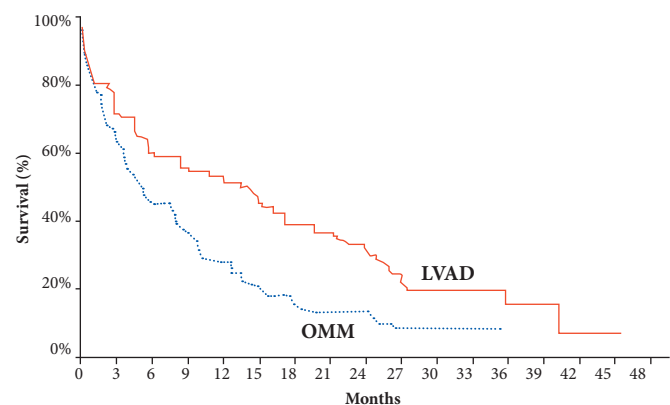

Figure 1. Kaplan–Maier survival curve comparing medical therapy versus LVAD in REMATCH study.

Indications

- Post cardiotomy failure

- Acute myocardial infarction who have undergone such significant myocardial damage that recovery is unlikely

- Acute decompensation of chronic failure

- Acute myocarditis

- CHF in transplantation candidates

- Intractable ventricular arrhythmias not responding to cardiac defibrillator and aggressive pharmacological regimens

- High-risk reparative cardiac operation

Terminology and Classification of MCS Devices

Ventricle supported

- Left ventricular assist device

- Right ventricular assist device

- Biventricular assist device

- Total artificial heart

Anatomical position

- Extracorporeal pump

- Intracorporeal pump

- Paracorporeal pump

- Orthotopic TAH

Pump mechanism

- Pulsatile, volume displacement

- Pneumatic or electrical actuation

- Continuous-flow rotary pump

- Axial design

- Bearing-supported rotor

- Magnetic suspension

- Centrifugal design

- Passive or active magnetic levitation

- Hydrodynamic (fluid forces)

Intended use

Duration of support

- Short-term MCS

- Patient remains within hospital, for example, intraaortic balloon pump, Tandem heart, Centrimag, Impella, Abiomed BVS 5000

- Long-term, "durable" MCS

- Patient discharged to home – "hands free" untethered mobility, for example, Thoratec HeartMate I1 MicroMed DeBakey HeartAssist 5 Jarvik 2000 Berlin HeartIncor, HeartWareHVAD, DuraHeart

Indications

- Bridge to recovery

- Bridge to transplant

- Destination therapy

Intraaortic balloon pump, TandemHeart pVAD, Abiomed Impella 2.5 LP provide partial circulatory support (15–30%). Other short- and long-term devices provide full circulatory support.

Abiomed AB/BVS 5000: This is a Pulsatile pump with pneumatic actuation. Operative placement requires sternotomy. It provides full circulatory support and commonly used for bridge to recovery. It can be used for left, right or biventricular support.

Figure 2. Abiomed BVS 5000 (extracorporeal).

TandemHeart pVAD (percutaneous left atrial-to-femoral-arterial VAD): It is a continuous-flow centrifugal pump which provides partial support; average flow is usually 3.5–4.0 L/min at 7500 RPM. The cannulae are placed percutaneously under fluoroscopy. The 21 french (F) left atrial drainage cannula through transseptal approach and 15–17 F femoral artery cannula are used. The role of this device is for short-term stabilization as a bridge to recovery or as a bridge to definite surgical treatment.
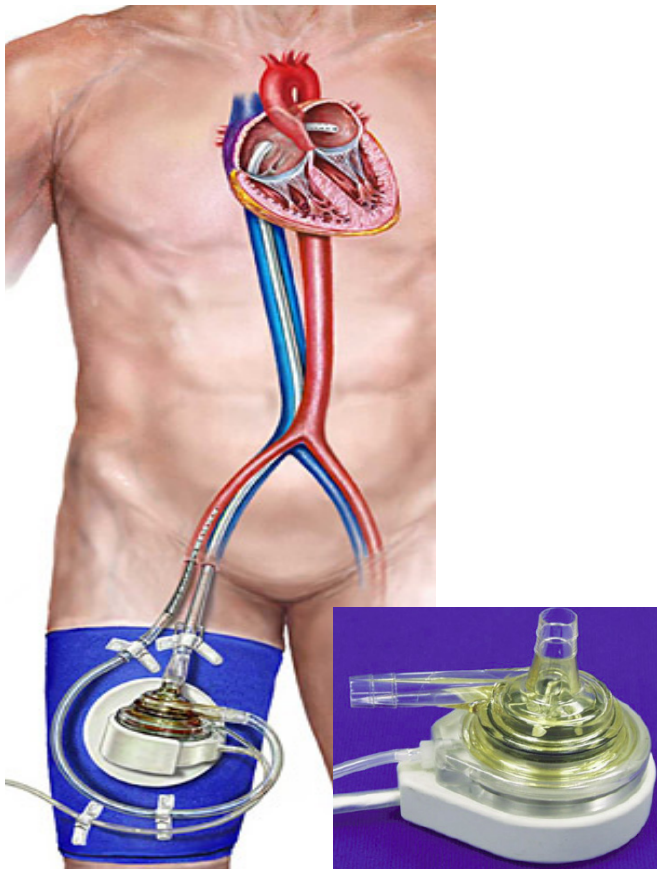
Figure 3. Tandem Heart pVAD.

Impella: It is a microaxial flow device, which is a miniature impeller pump located within a catheter. Impella was designed for either surgical placement via a graft in the ascending aorta (5.0 LD) or for percutaneous placement (2.5 L) via the femoral artery (13,14). It provides partial to full support (Fig. 4 and 5).
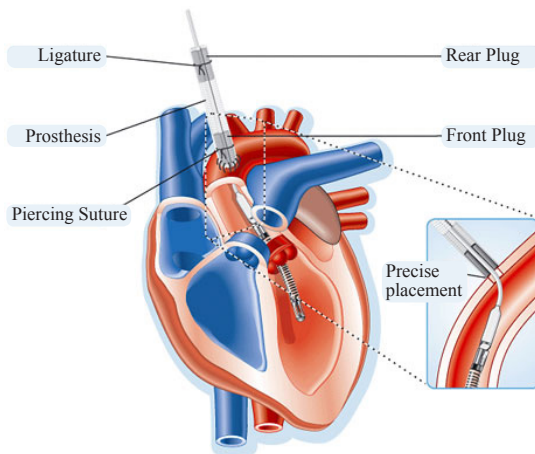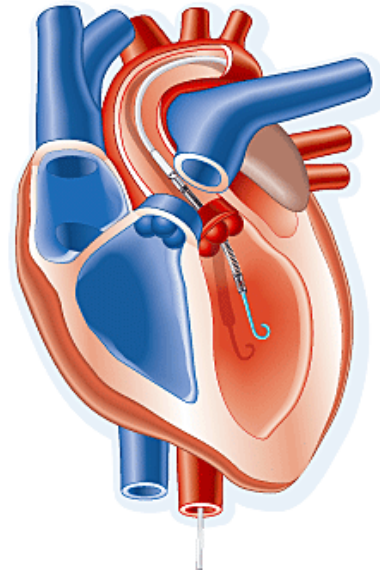

Figure 4. Surgical placement of Impella device.

Figure 5. Percutaneous placement of Impella device.

Paracorporeal Devices:

■　Pneumatic actuation pump

■　Indications

－　Bridge to recovery

－　Bridge to transplantation

■　It permits patient discharge to home but require tethering to portable drive console. Not "hands free"

■　Left, right, or biventricular support options (Fig. 6–8)

■　Pediatric applications: Berlin Heart Excor Pediatric

Figure 6. Thoratec IVAD.

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Figure 7. Berlin Excor.

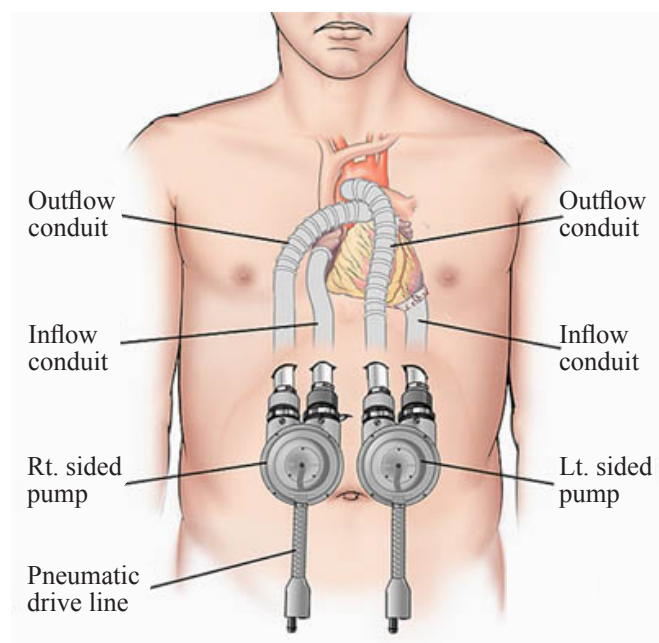**Figure 9.** Levitronix Centrimag® centrifugal pump.

Figure 8. The thoratec ventricular assist system in the biventricular support configuration.

Centrifugal pumps: Centrifugal pumps are an extension of cardiopulmonary bypass. They use rotating cones or impellers to generate energy that is recovered in the form of pressure flow work. There are presently three centrifugal pumps available: the Bio-Medicus (Bio-Medicus Inc, Minneapolis, MN), the Sarns (Sarns/3M Ann Arbor, MI) and the Levitronix Centrimag® (Levitronix LLC, Waltham, MA) (Fig. 9). 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.

CentriMag or other short-term devices are frequently used mainly for the following reasons:

■ Left ventricular failure post cardiotomy or transplant graft failure

■ Right ventricular failure post cardiotomy

■ Right ventricular failure post LVAD insertion

■ Myocarditis

■ Post infarction shock

■ As ECMO support

■ Bridge to a decision, whether it be to attempt recovery, long-term LVAD, or transplant

Extracorporeal Membrane Oxygenation (ECMO): This is mainly used when pulmonary support is required with or without systemic support. It removes carbon dioxide from and adds oxygen to venous blood via an artificial membrane lung. 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. ECMO is a temporary life support for patients with potentially reversible severe acute respiratory failure or cardiac failure (15).
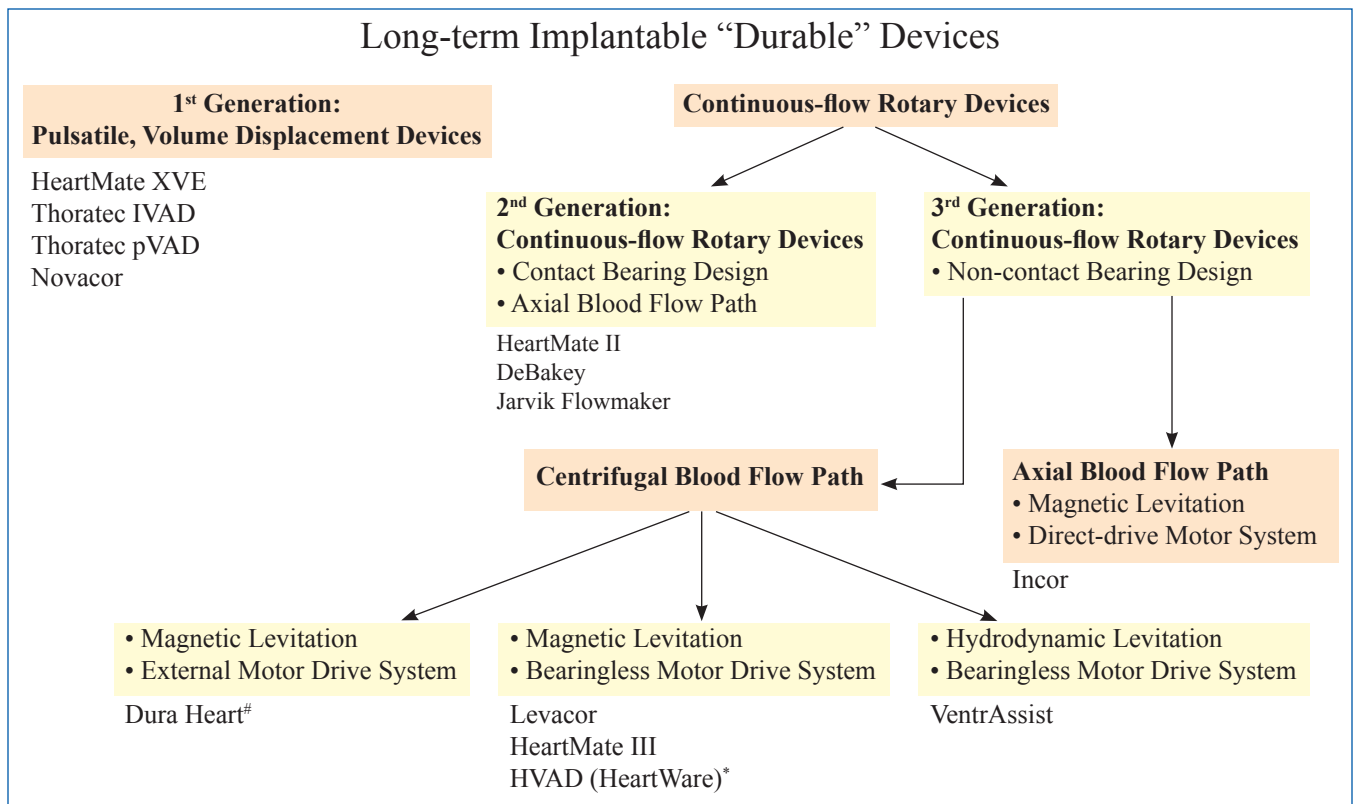
Figure 10. Classification of long-term implantable devices.

Pulsatile Volume Displacement Pump (First Generation Pumps): Out of first-generation pumps Heart Mate XVE is the most commonly used device. It was the first device used for REMATCH trial which showed benefit of device placement over medical therapy. This device is also approved by FDA for the destination therapy. Nowadays this is being used less frequently because of cumbersome size, limited durability and availability of smaller and more durable pumps.
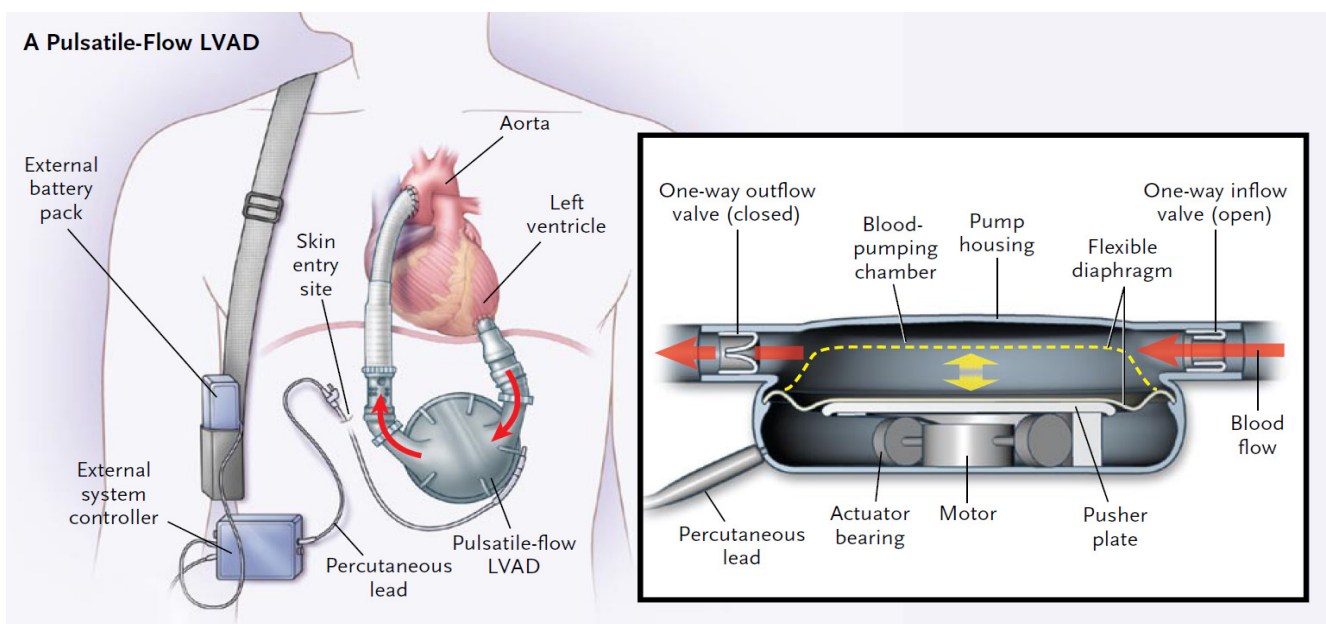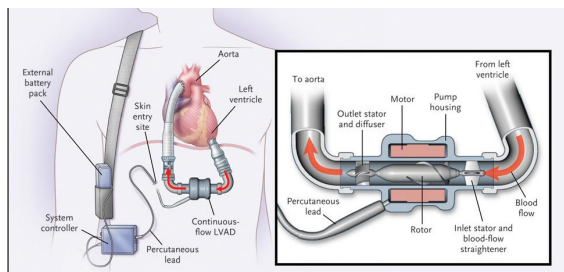

Figure 11. Heart Mate XVE.

Advantages
- No heart valves
- No flexible diaphragm
- No large housing to accommodate pump "stroke volume"
- Fewer moving parts
- Potential for biventricular application

Disadvantages
- Minimal pulse
- Significant AI if pump malfunction occurs
- Operated in fixed mode speed may limit cardiac output
- Afterload dependent

Figure 12. HeartMate II.

Continuous-flow Rotary Pumps (Second- and third-Generation Pumps): The second-generation pump most commonly used is Heart Mate II axial flow pump. The third-generation pumps are magnetically levitated centrifugal blood flow pumps with no contact bearing design.

Heart Mate II is a second-generation axial flow pump most commonly implanted device. Its durability, reliability and promising results opened the avenue for mechanical support. Its potential for small size, low noise and absence of a compliance chamber have been developed for clinical use. It provides continuous rather than pulsatile flow and are totally implantable.

Magnetically levitated centrifugal pumps. These are currently undergoing clinical trials for the treatment of heart failure. They have several advantages over the axial flow pumps: (i) they are energetically more efficient; (ii) they have lower tolerances so manufacturing is easier and they are less prone to thrombosis; (iii) they are potentially 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.

HeartWare HVAD. This is a third-generation centrifugal pump. It weighs 145 g and pumps 4–5 L of blood per minute. This does not require pocket formation unlike other devices.

CircuLite: CircuLite's circulatory support systems are designed with unique attributes, which include the following:

- World's smallest implantable blood pump (the size of a AA battery and weighing 25 g)

- First superficially implanted micro-pump, designed to be placed without cardiopulmonary bypass or sternotomy

- Small percutaneous lead

- Designed to supplement native cardiac output

- Designed for long-term support

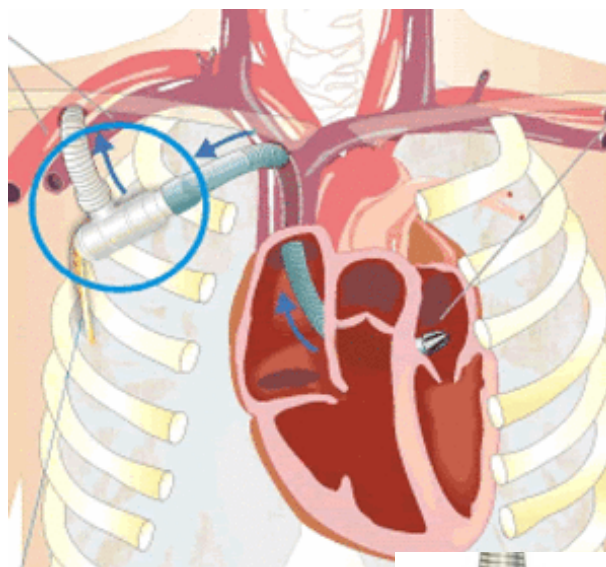- Magnetically and hydrodynamically stabilized rotor design

Figure 13. HeartWare pump.

Figue 14.
Circilite device and its placement.

■ Lightweight, rechargeable dual battery pack system (average power 6–8 hours)

With the immutable limitation in the supply of suitable donor hearts a lot of patients with heart failure could not be offered the possibility of long survival and in the last 10–15 years were developed a second- and third-generation of pumps. Those patients who do not qualify for transplantation of long-term devices are used for them as a destination therapy. In addition, destination recipients can undergo heart transplantation after their relative contraindications improve on mechanical support. The vast majority of deaths occur within the first 3 months after LVAD surgery. Sepsis, right heart failure and multiorgan failure are the main causes of postoperative death and are the main contributors to the relatively high in-hospital mortality after device implantation.

Total Artificial Heart

SynCardia total artificial heart

The SynCardia total artificial heart (TAH) is a pulsatile, biventricular, pneumatically driven, orthotopic TAH that replaces some of the recipient atrial tissue, all four cardiac valves, both ventricles, and the proximal portions of the aorta and pulmonary arteries (16).

Each ventricle has a polyurethane diaphragm that separates blood from air. Medtronic-Hall mechanical valves in the atrioventricular and the semilunar positions (27 mm inflow and 25 mm outflow) provide unidirectional blood flow. Maximum stroke volume is 70 ml, and maximum cardiac output is 9.5 L/min. Total weight is 160 g with a volume displacement of 400 ml. A pneumatic driveline is connected to each ventricle, which is tunneled through the chest wall and connected to an external console.

AbioCor total artificial heart

The AbioCor TAH is a fully implantable, biventricular, orthotopic, pulsatile electrohydraulic TAH that is driven by a battery-powered motor. The motor powers an internal centrifugal pump, which hydraulically moves a membrane sac responsible for the pumping action. The AbioCor TAH replaces recipient atrial tissue, all four cardiac valves, both ventricles, and the proximal portions of the aorta and artery. The pump and valves are made from titanium and proprietary polyurethane. A miniaturized internal electronics package monitors the

pumping speed (17).

An internally implantable battery is continuously recharged from an external power source by a process called transcutaneous energy transmission (TET), which obviates the need for percutaneous power or pneumatic drive lines. An external battery pack with a TET coil provides 2–4 hours of use, while the internal battery allows 30 minutes of tether-free operation. The AbioCor TAH weighs 1090 g and has a volume displacement of 800 ml, making it significantly larger and heavier than the SynCardia TAH.
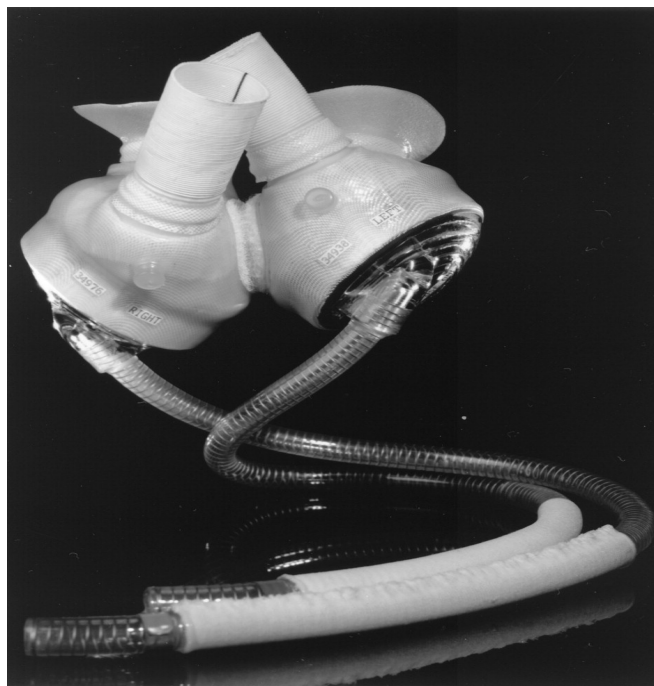

Figure 15. Total artificial heart.

Nowadays TAH is being used more frequently and patients can be sent home with portable driver. The main advantage of TAH is that it provides biventricular support in orthotopic position.

Cardiac Transplantation

Cardiac transplantation represents the most effective long-term treatment strategy for advanced heart failure; however, the supply of donor hearts is limited. It has been a gold standard treatment for end-stage HF.

Indications

■ Cardiogenic shock requiring mechanical assistance.

- Refractory heart failure with continuous inotropic infusion.

- NYHA functional class 3 and 4 with a poor 12-month prognosis.

- Progressive symptoms with maximal therapy.

- Severe symptomatic hypertrophic or restrictive cardiomyopathy.

- Medically refractory angina with unsuitable anatomy for revascularization.

- Life-threatening ventricular arrhythmias despite aggressive medical and device interventions.

- Cardiac tumors with low likelihood of metastasis.

- Hypoplastic left heart and complex congenital heart disease

- Patients should receive maximal medical therapy before being considered for transplantation. They should also be considered for alternative surgical therapies including CABG, valve repair/replacement, cardiac septalplasty, etc.

- VO2 has been used as a reproducible way to evaluate potential transplant candidates and their long-term risk. Generally a peak VO2 >14 ml/kg/min has been considered "too well" for transplant as transplantation has not been shown to improve survival over conventional medical therapy. Peak VO2 10–14 ml/kg/min had some survival benefit, and peak VO2 <10 had the greatest survival benefit.

Contraindications

Absolute contraindications

- Systemic illness with a life expectancy <2 years despite heart transplant, including

- Active or recent solid organ or blood malignancy within 5 years (e.g., leukemia, low-grade neoplasms of prostate with persistently elevated prostate-specific antigen)

- AIDS with frequent opportunistic infections

- Systemic lupus erythematosus, sarcoid or amyloidosis that has multisystem involvement and is still active

- Irreversible renal or hepatic dysfunction in patients considered for only heart transplantation

- Significant obstructive pulmonary disease (FEV1 <1 L/min)

- Fixed pulmonary hypertension

- Pulmonary artery systolic pressure >60 mmHg

- Mean transpulmonary gradient >15 mmHg

- Pulmonary vascular resistance >6 Wood units

Relative contraindications

- Age >72 years

- Any active infection (with exception of device-related infection in VAD recipients)

- Active peptic ulcer disease

- Severe diabetes mellitus with end-organ damage (neuropathy, nephropathy or retinopathy)

- Severe peripheral vascular or cerebrovascular disease

- Peripheral vascular disease not amenable to surgical or percutaneous therapy

- Symptomatic carotid stenosis

- Ankle brachial index <0.7

- Uncorrected abdominal aortic aneurysm >6 cm

- Morbid obesity (body mass index >35 kg/m^2) or cachexia (body mass index <18 kg/m^2)

- Creatinine >2.5 mg/dL or creatinine clearance <25 ml/min*

- Bilirubin >2.5 mg/dL, serum transaminases >3×, INR >1.5 off warfarin

- Severe pulmonary dysfunction with FEV1<40% normal

- Recent pulmonary infarction within 6–8 weeks

- Difficult-to-control hypertension

- Irreversible neurological or neuromuscular disorder

- Active mental illness or psychosocial instability

- Drug, tobacco or alcohol abuse within 6 months

- Heparin-induced thrombocytopenia within 100 days

Surgical techniques

Cardiac transplantation can be done in an orthotopic or heterotopic fashion (18,19). The gold standard technique is biatrial approach but nowadays bicaval approach is practiced more often. Recepient's cardiectomy is done and donor heart is implantated starting from left atrium

Figure 16. Bicaval technique of transplantation.

aorta, pulmonary artery inferior vena cava and then superior vena cava in bicaval approach or right atrium to recepient's right atrium in biatrial approach. Total transplantation is done when disparity is more between recipient's and donor left atrial size (20).

Immunosuppresion

The followings are commonly used drugs other than steroids for immunosuppression. Here are the key sites of their action and their side effects.

- *Cyclosporine* acts on cyclophilin receptors and main side-effects are hypertension, seizures, hyperlipidemia, renal insufficiency, microangiopathic hemolytic anemia, gingival hyperplasia and increase in hair growth.

- *Tacrolimus* acts on FKBP-12 receptors and its side-effects are hypertension, seizures, hyperlipidemia, renal insufficiency, microangiopathic hemolytic anemia, hyperglycemia and hair loss.

- *Azathioprine* acts through purine synthesis inhibition and its side-effects are leukopenia, thrombocytopenia, anemia pancreatitis and myelodysplastic syndrome.

- *Mycophenolic acid* inhibits inosine monophosphatase dehydrogenase (IMDPG) and its adverse effects are nausea, diarrhea, anorexia, weight loss leukopenia, thrombocytopenia, anemia and hyperkalemia

- *Sirolimus/everolimus* inhibit "target of rapamycin" (m-TOR) via FKBP-12 and the side-effects are delayed wound healing, hepatic vein thrombosis, interstitial pneumonitis, lymphocele, anemia, hypertriglyceridemia, renal insufficiency and proteinuria.

Gene Therapy

Despite the progress achieved in conventional treatment modalities, heart failure remains a major cause of mortality and morbidity. The identification of novel signaling pathways has provided a solid scientific rationale which has stimulated preclinical development of gene-based therapies for heart failure (21). Advances in somatic gene transfer technologies have been crucial to the advent of the first human clinical trials which are currently in progress. As these and other trials of gene transfer based therapies are initiated, these approaches have generated excitement and hope for novel treatments for cardiovascular disease. Recent advances in understanding of the molecular basis of these calcium cycling abnormalities, together with the evolution of increasingly efficient gene transfer technology, have placed heart failure within reach of gene-based therapy. Furthermore, the recent successful completion of a phase 2 trial targeting the sarcoplasmic reticulum calcium pump (SERCA2a) ushers in a new era for gene therapy for the treatment of heart failure.

End-of-Life Care

With the increasing life expectancy, disease volume has increased. Despite the improvements in the treatment many patients come in the terminal stage of heart failure when aggressive therapy will not change the course and conservative management seems more appropriate (22). Effective communication then becomes fundamental between patients and clinicians. Although the opportunity to discuss these issues should be available at all stages of care. The palliative needs of patients and carers should be identified, assessed and managed at the earliest opportunity. Patients with heart failure and their carers should have access to professionals with palliative care skills within the heart failure team. Talking to the patients, managing pain, nausea and distress, and the many facets of good terminal care are the attention they deserve.

References

1. Kannel WB. Epidemiology and prevention of cardiac failure: Framingham Study insights. *Eur Heart J*. 1987;(8 Suppl F)23–6.

2. B.Gheorghiade M, Bonow RO. Chronic heart failure in the United States: a manifestation of coronary artery disease. *Circulation*. 1998;97:282–9.

3. Davie AP, Francis CM, Caruana L, Sutherland GR, McMurray JJ. The prevalence of left ventricular diastolic filling abnormalities in patients with suspected heart failure. *Eur Heart J*. 1997;18:981–4.

4. G .Litwin SE, Grossman W. Diastolic dysfunction as a cause of heart failure. *J Am Coll Cardiol*. 1993;22:49A–55A.

5. 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, Gregoratos G, Jacobs AK, Hiratzka LF, Russell RO, Smith SC Jr; 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); International Society for Heart and Lung Transplantation; Heart Failure Society of America.. 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). *Circulation*. 2001; 104:2996–3007.

6. Stevenson LW, Pagani FD, Young JB, Jessup M, Miller L, Kormos RL, Naftel DC, Ulisney K, Desvigne-Nickens P, Kirklin JK. INTERMACS Profiles of Advanced Heart Failure: The Current Picture. *J Heart Lung Transplant*. 2009;28:535-41.

7. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med*. 1987;316:1429–35.

8. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Roecker EB, Schultz MK, DeMets DL; Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001;344:1651–8.

9. Consensus recommendations for the management of chronic heart failure. On behalf of the membership of the advisory council to improve outcomes nationwide in heart failure. *Am J Cardiol*. 1999;83:1A–38A.

10. Yao G, Freemantle N, Calvert MJ, Bryan S, Daubert JC, Cleland JG. The long-term cost-effectiveness of cardiac resynchronization therapy with or without an implantable cardioverter-defibrillator. *Eur Heart J*. 2007;28:42-51.

11. Fei LüH Cardiac Resynchronization Therapy Handbook of Cardiac Anatomy, Physiology, and Devices 2009, pp 475-497.

12. 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;345:1435-43.

13. 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;127:812-22.

14. 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;77:1642-7.

15. ELSO guidelines for ECMO centers, 2007.

16. Marvin J Slepian The SynCardia Temporary Total Artificial Heart—Evolving Clinical Role and Future. *US Cardiology*. 2011;8:39-46.

17. Copeland JG, Arabia FA, Tsau PH, Nolan PE, McClellan D, Smith RG. Total artificial hearts: bridge to transplantation. *Cardiol Clin*. 2003;21:101-13.

18. Yacoub M, Mankad P, Ledingham S. Donor procurement and surgical techniques for cardiac transplantation. *Semin Thorac Cardiovasc Surg*. 1990;2:153-61.

19. Blanche C, Valenza M, Aleksic I, Czer LS, Trento A. Technical considerations of a new technique for orthotopic heart transplantation. *J Cardiovasc Surg*. 1994;35:283-7.

20. Couetil JP, Mihaileanu S, Lavergne T, et al: Total excision of the recipient atria (TERA) in orthotopic heart transplantation (OHT) as a new clinical procedure: technical consideration and early results. *J Heart Lung Transplant* 1991;10:101.

21. Njeim MT, Hajjar RJ. Gene therapy for heart failure. *Arch Cardiovasc Dis*. 2010;103:477-85.

22. Goodlin SJ, Hauptman PJ, Arnold R, Grady K, Hershberger RE, Kutner J, Masoudi F, Spertus J, Dracup K, Cleary JF, Medak R, Crispell K, Piña I, Stuart B, Whitney C, Rector T, Teno J, Renlund DG. Palliative and supportive care in advanced heart failure. *J Card Fail*. 2004;10:200-9.