Heart failure (HF) is a complex syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the heart to function as a pump to support a physiological circulation. Medical therapy remains the mainstay of treatment for majority of patients with heart failure. Although medical therapy can improve the quality of life and the longevity of patients across the spectrum of heart failure symptoms, such therapy alone is insufficient in patients with advanced heart failure. Advanced heart failure may be defined as stage of heart failure, characterized by advanced structural heart disease and marked symptoms of heart failure at rest despite dietary modification, salt restriction and maximal medical therapy including ACE inhibitors, angiotensin II receptor blockers, digitalis, diuretics and beta blockers. These patients require frequent hospitalizations and the overall prognosis is poor.

Various devices have been used in heart failure patients who remain severely symptomatic despite adequate medical therapy including cardiac resynchronisation therapy (CRT), implantable cardioverter defibrillator (ICD), Combo device, ultrafiltration and continuous positive airway pressure (CPAP) ventilation (Table 1). Cardiac support or replacement with left ventricular assist devices (LVAD) and/or cardiac transplantation are often the only therapeutic alternatives in patients with advanced/end-stage heart failure. This review focuses on the recent advances in device and surgical therapy for advanced heart failure (Table 2).

**Table 1: Approaches in Refractory Heart Failure**

<table>
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<tr>
<th>Approach</th>
<th>Modalities</th>
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<tbody>
<tr>
<td>Optimize Compromised Heart Function</td>
<td>Optimal medical therapy, Cardiac Resynchronization therapy, ICD</td>
</tr>
<tr>
<td>Reverse remodeling</td>
<td>Drugs, CRT, Surgical or interventional mitral valve repair / annuloplasty, acorn device</td>
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<tr>
<td>Regenerate the Myocytes</td>
<td>Stem cells, myoblasts, stimulation of endogenous stem cells, gene therapy</td>
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<tr>
<td>Replace the Heart</td>
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<td>Treatment of comorbidities</td>
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<td>Treatment of Consequences</td>
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<td>Better delivery of care</td>
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Cardiac Resynchronization Therapy

Patients with systolic heart failure due to ischemia or dilated cardiomyopathy often show significant dyssynchrony between various walls of the left ventricle (intra-ventricular dyssynchrony), between right and left ventricle (inter-ventricular dyssynchrony) or between atria and ventricle (AV dyssynchrony). Most patients with intraventricular dyssynchrony display a left bundle branch block pattern on the surface ECG. This occurs in up to 25% of all heart failure patients and confers a higher risk of worsening heart failure and sudden cardiac death. In these patients, the left lateral wall is electrically activated after the septal contraction, which leads to contraction of the lateral wall during relaxation of the septum. This results in mechanical dysfunction leading on to an increase in the left ventricular volume, reduction of contractility, and worsening of mitral regurgitation. Resynchronization of the myocardial contraction can be done by pacing the right ventricle and left ventricle (through a lead in the coronary sinus) with the implantation of biventricular pacemakers. Many studies have shown the favorable effects of such cardiac resynchronization therapy (CRT) on symptoms, the quality of life, ventricular function, and blood pressure.

CRT not only improves the symptoms, but also significantly improves the prognosis in selected patients with heart failure. The use of CRT in the Care HF study showed a dramatic reduction of the combined endpoint of mortality and cardiovascular hospitalization by 37%. Significantly, there was a 36% improvement in overall survival. CRT minimizes regional left ventricular delay caused by prolonged ventricular conduction, reduces mitral regurgitation and left ventricular reverse remodeling, and normalizes neurohormonal factors. The observed benefits persist or even increase with longer follow-up. Interestingly, with better synchronization of the cardiac contraction there was a significant reduction in arrhythmias and sudden cardiac death.

The Care HF study consisted of patients in class III or IV symptoms despite standard pharmacologic therapy, with LVEF < 35% and a QRS interval of at least 120 msec. Patients with a QRS interval of 120 to 149 msec were required to meet two of three additional echocardiographic criteria for dyssynchrony: an aortic preejection delay of more than 140 msec, an interventricular mechanical delay of more than 40 msec, or delayed activation of the posterolateral left ventricular wall. Several small studies have suggested that CRT may be beneficial even in patients with narrow QRS and echocardiographic evidence of dyssynchrony. Recently, the effect of CRT was evaluated in a randomized controlled trial (RethinQ study) in patients with narrow QRS (< 120 msec). CRT did not improve peak oxygen consumption and heart
failure worsenings, thereby providing evidence that patients with heart failure and narrow QRS intervals may not benefit from CRT.\cite{9} Current guidelines support the use of CRT in patients with an ejection fraction of 35% or less, moderate or severe heart failure (New York Heart Association [NYHA] class III or IV), and a prolonged QRS interval ($\geq$ 120 msec).\cite{1-3}

**Implantable Defibrillator (ICD)**

The most common cause of death in patients with advanced heart failure is progressive pump failure and the proportion of sudden cardiac death is less. Hence, ICDs are more effective in less advanced heart failure, because sudden cardiac death is the main cause of death in less severe heart failure. Even after an appropriate shock, patients with advanced heart failure may die from electromechanical dissociation.\cite{10} Such theoretical considerations were proven in the large SCD-HEFT trial.\cite{11} Among patients with NYHA class II heart failure, there was a 46 per cent relative reduction in the risk of death with ICD therapy as compared to amiodarone. The absolute reduction in mortality among patients in NYHA class II was 11.9 per cent at five years. However, in patients with advanced heart failure there was no apparent reduction in the risk of death with ICD therapy.\cite{11}

Although ICDs are less effective in end-stage HF, CRT and ICD may be combined as CRT may improve function status, making patients eligible also for ICD therapy. In the COMPANION trial,\cite{12} either CRT alone or CRT with ICD (combo device) reduced the rate of death from any cause or hospitalization for any cause by approximately 20 per cent as compared with the group that received optimal pharmacologic therapy alone. The addition of a defibrillator to CRT did not appreciably affect the combined outcomes of death or hospitalization for any cause. However, there was a 36% reduction in the mortality. Hence, whether to institute only CRT or Combo device should be individualized and guided by cost, likely survival, and sickness status.\cite{10}

**Percutaneous and Surgical Interventions**

Among the percutaneous and surgical therapies available for advanced heart failure, heart transplantation remains the most effective and proven therapy. The other interventions aim to either repair or reshape the heart, or replace the heart function.

**Coronary Revascularization Procedures**

Coronary artery disease is common in patients with advanced heart failure, with some studies suggesting a prevalence of 50%-70\%.$^{13}$ Coronary revascularization with coronary artery bypass surgery or percutaneous coronary intervention as appropriate should be considered in patients with heart failure and suitable coronary anatomy presenting with significant angina, or acute coronary syndrome.$^{1-3}$ However, this approach has not yet been prospectively tested. Revascularization is also indicated in patients who show evidence of myocardial viability or the presence of inducible ischemia in areas of significant obstructive coronary disease. There are a variety of imaging technics to detect non-contractile but viable myocardium including nuclear imaging, stress echocardiography and magnetic resonance imaging. A few ongoing clinical trials (including STICH trial) are prospectively evaluating the benefit of routine coronary revascularization in patients with heart failure and obstructive coronary artery disease.

**Stem Cell Therapy**

Myocardial regeneration with either percutaneously or surgically delivered stem cell is promising. Both surgical and non surgical intracoronary stem cell injection is undergoing evaluation at AIIMS and other centers, and the initial results are promising. Improvement in ventricular function and symptoms are shown with autologous bone marrow stem cell injection. Mesenchymal cell injections have also been found to be beneficial. Experimental studies using embryonal cells have shown ability to grow into sacs or rings, which develop the properties of
cardiac muscle.\textsuperscript{14,15}

**Mitral Valve Interventions**

In patients with heart failure, mitral regurgitation occurs commonly due to annular dilation with incomplete coaptation of the mitral leaflets and apical displacement of one or both papillary muscles causing restricted leaflet motion.\textsuperscript{16} Mitral valve annuloplasty in dilated and ischemic cardiomyopathy is shown to be safe with low mortality (2\%) and morbidity.\textsuperscript{17} Small studies have shown improvement in symptoms, ejection fraction, quality of life and reduction in hospitalizations.\textsuperscript{16} However, there is no clear survival advantage when compared with propensity-matched patients not undergoing mitral valve annuloplasty.\textsuperscript{18} Considering the high recurrence rate with ring annuloplasty, some centers advocate mitral valve replacement rather than repair in functional and ischemic cardiomyopathy. However, the impact of mitral valve repair/replacement on quality of life and clinical outcomes has also not clearly been demonstrated.\textsuperscript{16,19}

Percutaneous mitral and/or tricuspid valve repair may provide some benefit in suitable patients with advanced heart failure and the various devices are in early stages of development.\textsuperscript{19} The devices aim to reproduce the various technics that are used during surgery. The coronary sinus is anatomically very near the mitral annulus. By placing a series of progressively stiffer rods or ‘cinching’ devices in the coronary sinus can move the posterior mitral apparatus forward, thereby reducing the mitral annulus and regurgitation. The other devices aim to remodel the posterior mitral annulus by a transventricular or transatrial approach while still others intend to decrease the septal lateral diameter by either a transventricular or transatrial bridge and tether system.

As per current guidelines isolated mitral valve repair or replacement for severe mitral regurgitation secondary to ventricular dilatation in the presence of severe LV systolic dysfunction is not generally recommended.\textsuperscript{1–3}

**Cardiac Reshaping Surgeries**

In patients with dilated cardiomyopathy, partial left ventriculectomy (Batista procedure) was a very popular technic some years ago. Despite a sound theoretical basis, Batista procedure is no longer used since the long term results are disappointing.\textsuperscript{20} In patients with ischemic heart disease with dyskinetic regions of left ventricle, such ventricle reshaping procedures may be of benefit. Aneurysmectomy and endoventricular circular patch plasty (Dor procedure) is a promising technique.\textsuperscript{21–23} The Assessment of a Cardiac Support Device in Patients with Heart Failure (ACORN) trial evaluated an innovative passive cardiac restraint device in patients with end-stage HF that suggested modest improvement in ventricular remodeling but no benefit in mortality.\textsuperscript{24}

**LV Assist Devices**

LV assist devices (LVADs) improve survival and quality of life in patients ineligible for a heart transplant. LVADs also serve as a “bridge” to transplant and ventricular recovery. Recently LVADs are being used more as end-stage or “destination-therapy”.\textsuperscript{23,25} In a prospective, multicenter study, 129 end-stage HF patients, ineligible for heart transplantation, were randomized to receive either an LVAD or optimal medical therapy. After 1 year, a 48\% reduction in death and improved quality of life were shown with LVAD group as compared to medical therapy group.\textsuperscript{26} Several new ventricular assist devices are currently undergoing Phase III trials and are eagerly awaited.

Current indications for LVADs include patients awaiting heart transplantation who have become refractory to all means of medical circulatory support as a bridge to transplant. Permanent mechanical assistance using an implantable assist device may be considered in highly selected patients with severe HF refractory to conventional therapy who are not candidates for heart transplantation, particularly those who cannot be weaned from intravenous inotropic support at an experienced HF center.\textsuperscript{1–3}

Percutaneous implantable devices are useful for
short-term stabilization in patients with advanced HF. Intaortic balloon counterpulsation has been used for many years, but it can only be used for short term and the effects are modest at best. Other percutaneous devices like the TandemHeart percutaneous LVAD and the Impella Recover LP 2.5 System may provide rapid and better circulatory support. The Impella Recover device provides 3 to 4 L/min flow. It is shown to improve survival in patients with low-output syndrome following postcardiotomy. At present the use of these devices is limited to patients undergoing PCI or surgery with advanced decompensated cardiac status.

**Heart Transplantation**

Cardiac transplantation remains the most effective treatment to improve the prognosis of patients with truly refractory heart failure. The absolute indications for heart transplant include refractory cardiogenic shock, dependency on intravenous inotropic drugs, and persistent NYHA class IV symptoms with oxygen consumption less than 10 mL/kg/min. The relative and absolute contraindications are listed in Table 3. Improvements in patient selection, surgical techniques, organ preservation, and postoperative management have increased survival rates over the decades and reduced complications after heart transplantation. Current survival rates are 83% at 1 and 72% at 5 years, with 50% of patients surviving 9.8 years. However, limited availability of donor is the most important limitation.

**Other Interventions**

**Ultrafiltration**

Safe removal of excess fluid is one of the most demanding challenges in the management of severe congestive heart failure, particularly in patients refractory to diuretic therapy. Intermittent outpatient ultrafiltration using peritoneal dialysis or hemofiltration could be a useful adjunct in selected patients with advanced heart failure. The use of peritoneal dialysis for refractory heart failure has been advocated for many years and the fluid removal rates achieved by peritoneal dialysis are comparable with those obtained by extracorporeal technics. Peritoneal dialysis is shown to reduce hospitalization rates and improve the functional capacity.

In the UNLOAD trial, 200 patients with acute decompensated heart failure with volume overload were randomized to veno-venous ultrafiltration and ravenous diuretic therapy. Ultrafiltration was shown to produce greater fluid and weight loss during index hospitalization. Further, it reduced rehospitalization rates at 90-days. Larger studies are needed to establish the effect of ultrafiltration on long term outcomes and mortality of heart failure. At present, ultrafiltration should be reserved for patients at high risk of complications with diuretic therapy who need extensive fluid removal.
CPAP
A significant number of patients with advanced heart failure have obstructive sleep apnea. Continuous positive airway pressure (CPAP) is an effective treatment for sleep apnea. Hence, CPAP has been evaluated as a therapy in advanced HF patients with sleep apnea. Small prospective controlled trials have shown that CPAP improves LV EF, reduce urinary norepinephrine levels, and improve cardiac output. In a recent trial, a 3 month treatment with CPAP is shown to increase LVEF when compared to sham-CPAP. However, the beneficial effect was not marked in patients with LVEF < 30% and in patients with predominantly Cheyne-Stokes events.35,36

References


