Introduction
The incidence of heart failure continues to grow commensurate with aging of the general population. The incidence of heart failure more than doubles with each decade after the age of 45 years. Medications for heart failure have evolved from diuretics to digoxin to vasodilators, ACEIs, ARBs & beta-blockers. However, despite these advances, the quality of life in patients with advanced heart failure remains poor with frequent hospitalizations and a high morbidity and mortality. The treatment of heart failure leaves much to be desired. Researchers and clinicians have now started looking beyond drug therapy for the treatment of this condition.

Pathophysiology

Myocardial insult
(Myocardial ischaemia, valvular, etc.)

Myocardial dysfunction
(systolic, diastolic)

Increased preload / Reduced systemic perfusion

Activation of neurohormonal cytokine and mechanical stretch signals
(RAS, beta-adrenergic, endothelin, TNF alpha, IL-1 beta)

Altered gene expression
(alpha-MyHC, beta-MyHC, SR Ca\(^{2+}\) ATPase)

Growth and remodelling
Apoptosis

Toxicity, Ischaemia, energy depletion
Necrosis

Cell death
Clinical Stages of Heart Failure

Stage A: Identifies the patient who is at high risk for developing heart failure 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 heart failure.

Stage C: Denotes the patient with past or current symptoms of heart failure associated with underlying structural heart disease.

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

Patients with refractory heart failure may be defined as those with advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy and who require specialized interventions. This is similar to stage D of heart failure. It includes patients who:

1. Are frequently hospitalized for heart failure or cannot be safely discharged from the hospital.
2. Are awaiting heart transplantation.
3. Are at home receiving continuous intravenous support for symptom relief or are being supported with a mechanical circulatory assist device.

Clinical Stages & Prognosis

<table>
<thead>
<tr>
<th>Stage</th>
<th>NYHA Class</th>
<th>Annual Mortality %</th>
<th>Annual Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>I - II</td>
<td>2 - 5</td>
<td>&lt;0.25</td>
</tr>
<tr>
<td>B</td>
<td>II - III</td>
<td>5 - 15</td>
<td>0.25 - 0.75</td>
</tr>
<tr>
<td>C</td>
<td>III - IV</td>
<td>15 - 25</td>
<td>0.75 - 2</td>
</tr>
<tr>
<td>D</td>
<td>IV</td>
<td>&gt;25</td>
<td>&gt;2</td>
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Approach to a Patient with CHF

Asymptomatic LV dysfunction LVEF < 40%

\[ \downarrow \text{ ACEI} \]

Symptomatic NYHA class II

\[ \downarrow \text{ ACEI/ARBs} \]

Thiazides, Spironolactone

? Digoxin

Symptomatic NYHA Class III

\[ \downarrow \text{ + Loop Diuretics} \]

Refractory CHF

\[ \downarrow \text{ I.V. inotropes + specialized therapy} \]

Secondary Prevention

Lifestyle modification

Lifestyle modification

Treatment of Heart Failure - Beyond Drug Therapy
Management of Refractory Heart Failure

- Elimination of precipitating causes
- Maximize and optimize medical therapy
- Cardiac resynchronization therapy
- Intermittent inotropic support
- Cardiac revascularisation and other cardiac surgeries
- LV assist devices and Total artificial heart
- Cardiac transplant
- Immunomodulatory Agents
- Gene Therapy

I. Cardiac Resynchronization Therapy for Heart Failure (CRT)

In 1990, Hochleitner et al first implanted a dual chamber pacemaker with a short AV delay. In 1992 Brecker et al reported symptomatic relief in 12 patients with dilated cardiomyopathy. However, results with dual chamber pacing were inconsistent until 1996, when Cazeau et al showed that biventricular pacing unlike dual chamber improved NYHA functional class.

Mechanics of Resynchronization Therapy

In a patient with CHF, cardiac asynchrony occurs at 3 levels.

i. atrioventricular
ii. intra-ventricular
iii. inter-ventricular

Prolongation of the PR interval & widening of the QRS complex are present in 20-50% of patients with CHF. Both these are independent predictors of mortality and are consistently found in patients with NYHA class IV symptoms. Patients with a QRS complex >200 ms has a five times greater mortality risk than those with a narrow <90 ms QRS duration.

Prolongation of the PR interval has several detrimental consequences.

i. decrease in ventricular filling time.
ii. diastolic atrioventricular (AV) valve regurgitation
iii. decreased pulse pressure and cardiac output.

Prolonged PR intervals is more detrimental during physical activity when an increase in heart rate will shorten an already reduced ventricular filling. Altered ventricular activation secondary to LBBB results in delayed LV contraction with consequent decline in LV ejection fraction and cardiac output.

Hemodynamic and mechanical changes due to LBBB.

i. Decreased septal contribution to global LVEF
ii. Prolonged LV contraction, ejection and relaxation
iii. No increase in LVEF with exercise.
iv. RV contraction precedes LV by 85 ms
v. Late LV sites continues to depolarize in early diastole.
vi. Septum displaced towards LV during RV contraction.
vii. Delayed aortic / mitral opening and closure.
viii. Worsening mitral regurgitation.
### Potential Mechanisms of CRT

<table>
<thead>
<tr>
<th>Shortened AV delay</th>
<th>Biventricular pacing</th>
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</thead>
<tbody>
<tr>
<td>i. Decreased diastolic AV valve regurgitation</td>
<td>i. Improves interventricular synchrony</td>
</tr>
<tr>
<td>ii. Improved filling time</td>
<td>ii. Synchronizes septal and LV free wall contraction</td>
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<tr>
<td>- Improved ventricular preload</td>
<td></td>
</tr>
<tr>
<td>- Decreased pulmonary venous pressure</td>
<td></td>
</tr>
<tr>
<td>iii. Increase pulse pressure</td>
<td>iii. Decreases mitral regurgitation</td>
</tr>
<tr>
<td></td>
<td>- may remodel LV geometry</td>
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### Patient Selection and Clinical Trials

Several studies of CRT for the treatment of advanced CHF have been published. Selection criteria include:

1. Dilated cardiomyopathy
2. LVEF < 35%.
4. PR interval ≥ 150 ms (some studies)
5. NYHA class II or more
6. Symptoms despite adequate treatment

The improvement after biventricular pacing is proportional to the QRS duration. Longer the duration, more the benefit. Studies are also underway in patients with RBBB as the conduction abnormality with encouraging initial results.

### Heart Failure and Sudden Death

The incidence of sudden death increases from 5-10% in patients in NYHA class II to close to 60% in patients in NYHA class IV. This is roughly 6-9 times the rate of SCD in the general population. ICDs combined with biventricular pacing have shown to improve the prognosis in such patients.

### CRT - The Indian Scenario

There are many centres in India that now perform CRTs. However, it must be remembered that not all patients respond to this therapy. Non-responders cannot be identified prospectively. Close to 25% of patients may be non-responders. There is also a steep learning curve. The other limitation is the cost involved. A biventricular pacemaker may cost Rs.3.5 lacs onwards while a combined biventricular + ICD is Rs.9 lacs and beyond.

#### 2. Role of Continuous/Intermittent Inotropic Support (Dobutamine, Milrinone)

**a. Potential beneficial effects**

1. Increase in alpha - myosin heavy chain levels.
2. Induction of beta - receptor up-regulation (short term pulsed therapy)
3. Improved mitochondrial morphology and biochemical energetics.
4. Enhanced peripheral endothelial function.

**b. Potential deleterious effects.**

1. Enhanced arrhythmogenicity and direct cardiotoxicity through increased levels of cAMP.
2. Increased release of calcium from intracellular stores.
iv. Increased oxygen cost of contractility
v. Increased mortality

3. LV Assist Device and Total Artificial Heart

In 1966, DeBakey first implanted an extracorporeal LVAD while Cooley in 1969, first implanted the Total Artificial Heart. Yet, over the intervening four decades, the technology is still confined to a select few centers in the world.

These mechanical circulatory assist devices may be used as:

i. A bridge to myocardial recovery
ii. A bridge to another bridge
iii. A bridge to transplantation
iv. Lifetime use (destination therapy)

These devices may be divided into 2 major classes of design

i. Fluid dynamic - rotary pumps (continuous ow, axial and centrifugal pumps)
ii. Displacement type (pulsatile ow)

The advantages of axial ow blood pumps are:

a. Fully implantable
b. No atmospheric vent
c. Small
d. Silent
e. Valveless
f. Can be made pulsatile

The systolic and diastolic phases of the LVAD should be synchronized with the systolic and diastolic phases of the native heart. This timing is very difficult and often impossible to achieve. However, optimal circumstances require that ventricular systole occur during LVAD diastole which results in a maximal filling of device and unloading of the LV. This is the “in-phase”. In contrast, “out-phase” describes a state whereby ventricular systole occurs during LVAD systole. Thus, the two pumps are in direct competition.

4. Coronary Revascularisation and Other Surgical Approaches

A major and important surgical approach to ischemic cardiomyopathies is reperfusion of the ischemic myocardium by coronary artery bypass surgery or percutaneous transluminal coronary angioplasty. This is based on the concept that transiently ischemic myocardium (stunned) and myocardium with reduced blood ow (hibernating) myocardium have reduced contractility which may return to normal with restoration of adequate coronary blood ow. Revascularisation also helps prevent recurrent infarction in ischemic areas.

When the underlying aetiology for CHF is valvar dysfunction valve repair or replacement is advisable. Valve repair is preferred as it obviates the need for long term use of anticoagulants and its attendant complications.

Other approaches to the dilated heart include:

i. Removing a segment of left ventricular wall ‘Battista operation’ to reduce LV volume and thus wall stress. The surgical risk is immense and specific benefits have not been established.
ii. LV reconstruction (Dor type) for post infarct LV dysfunction: purse string suture is placed to exclude the non functional portion of the left ventricle
iii. LV aneurysmectomy
iv. Dynamic cardiomyoplasty which uses latissimus dorsi muscle as a wrap around the heart
with a pacemaker implanted to condition the muscle into a slow, fatigue resistant pump.

v. Acorn wrap elastic mesh sheet is wrapped around the right and left ventricle. This helps in LV remodelling and is shown to down regulate stretch mediated SR Ca\(^{2+}\) ATPase indicative of early reverse remodeling.

5. Cardiac Transplantation

This has come a long way since it was first successfully done in humans in December 1967 by Dr. Christian Bernard at Cape Town, South Africa. Heart transplantation is now an accepted mode of treatment for end stage CHF.

The criteria for cardiac transplantation are

1. End stage heart disease with poor (6-12 month) prognosis and refractory to aggressive tailored medical or any other surgical treatment.
2. NYHA functional class III or IV.
3. Age ≤ 60-65 years
4. Pulmonary vascular resistance <3RU or <2.5RU after intravenous nitroprusside
5. Strong self motivation and psychological support
6. Absence of malignancy
   - active infection
   - active peptic ulcerative disease
   - advanced IDDM with end organ damage
   - kidney and liver dysfunction beyond that expected from severe CHF
   - advanced peripheral vascular disease.
   - collagen vascular disease

Transplantation significantly increases survival, exercise capacity, and quality of life compared to conventional treatment. Recent results in patients on triple immunosuppressive therapy have shown 5 year survival of about 70 to 80 percent, and a return to full or part time work after 1 year in about two thirds of the patients.

Besides a shortage of donor hearts, the main problem in heart transplantation is rejection of the allograft which is responsible for a considerable percentage of deaths in the first post operative year. The long term outcome is limited predominantly by the consequences of immunosuppression (infection, hypertension, renal failure, malignancy, accelerated progression of atherosclerotic vascular disease) and by transplant coronary artery disease.

Experimental work is underway looking at xenotransplantation of myocardial cells and entire organs (pig hearts) as potential heart failure treatment. The humoral response of the recipient against the graft remains a preeminent hurdle.

6. Gene Therapy

In experimental studies gene therapy has been shown to improve failing human cardiac myocyte function by transfection of the myocytes invitro with an adenovirus expressing the sarcoplasmic reticulum Ca\(^{2+}\) ATPase, SERCA 2a. Transfection increased Ca\(^{2+}\) ATPase activity by 80 percent. The enhanced function of the myocytes was associated with corresponding improvement in kinetics of calcium transient. The isolated myocyte results confirm previous invitro studies by Meyer and associates that indicated that adenoviral transfection of SERCA 2a can improve contraction and relaxation.

7. Immunomodulatory Agents and Miscellaneous Therapies

Intravenous gamma globulin has been tried in patients with dilated cardiomyopathy. Similarly, pentoxiphylline has been tried to suppress TNF-alpha production. Etanercept is a recombinant
human TNF-alpha receptor fusion protein that specifically blocks the effect of TNF-alpha. This drug is approved for use in Rheumatoid arthritis and has shown encouraging results in the treatment of CHF.

Enhanced external counterpulsation is a noninvasive therapy consisting of gated diastolic sequential leg compression, producing hemodynamic effects similar to those of an intra aortic balloon pump. This procedure improves exercise capacity and LV failure in patients who are already receiving medical therapy.

Immuno absorption procedures have been directed against Beta 1 adrenergic receptor antibodies, with clinical improvements found in patients with heart failure.

Conclusion
The treatment of heart failure has come a long way beyond pharmacotherapy. The need for mechanical strategies was dictated by the relentless progressive course and the high rates of morbidity and mortality associated with advanced heart failure. Cardiac resynchronization therapy in the form of biventricular pacing offers a ray of hope for such patients. However, not all patients of heart failure are candidates for CRT. Similarly, there are a significant number of non-responders who cannot be identified prospectively. Cost is another limiting factor. The use of LV assist device is limited to a few centres world-wide primarily as a bridge to cardiac transplant. LV assist device as a destination therapy for lifetime is an exciting prospect. Certainly, the last word in the treatment of heart failure is yet to be written !!.

References