Chapter 26

Advances in Management of Heart Failure and What can We Do in India?

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INTRODUCTION
Heart failure is a common cardiovascular disease with high morbidity and mortality. In India, it affects the younger age group unlike the western countries where heart failure is predominantly the disease of the elderly. Important risk factors include coronary artery disease, hypertension, diabetes mellitus, valvular heart disease and cardiomyopathies.1,3,4

Unlike in patients with systolic heart failure where several therapies have been shown to improve survival, clinical trial results in diastolic heart failure have been disappointing and therapy in these patients is restricted to symptom improvement and risk factor control.5

The diagnosis of heart failure is mainly clinical but various investigations help us to understand the underlying cause and assessment of severity of heart failure.6–18

Symptoms of heart failure are exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, sensitivity of these symptoms is 23–66%, specificity 50–80%.1 Patients may also present with pedal edema and abdominal distention.

Signs of heart failure are also nonspecific. Basal crepitations, edema, raised jugular venous pressure and hepatic enlargement are diagnostic of the condition. There is an inconsistent relationship of the symptoms and signs of heart failure to hemodynamic parameters like left ventricular end-diastolic pressure, cardiac index and ventricular function.1,6,7,15,17,18

This century has seen rapid advances in the management of heart failure.

MANAGEMENT STRATEGIES
Positive inotropic agents are used for the treatment of acute decompensated heart failure. Although role of long-term positive inotropic therapy for heart failure is controversial short-term therapy with positive inotropes is likely to benefit patients with acute decompensated heart failure.

Levosimendan
It is a positive inotropic agent that has a dual mechanism of action.

Mechanism of Action
• Sensitizes troponin C to calcium dependent on calcium concentration, increases the effects of calcium during systole.
• During diastole, sensitization is reduced and it does not hamper diastolic relaxation.

This is an advantage of levosimendan over other inotropic agents that cause diastolic calcium overload.

Some studies indicate that levosimendan may enhance myocardial relaxation and diastolic function.

It also opens adenosine triphosphate (ATP)—dependent potassium channels in muscle and blood vessels causing vasodilatation which reduces preload, and afterload, which in turn increases coronary and other organ blood flow. This mechanism is also the cause for the cardio protective effect by levosimendan by inhibition of mitochondrial apoptotic pathway.

Levosimendan in therapeutic doses does not increase epinephrine/norepinephrine levels and leads to marked reduction in B-type natriuretic peptide (BNP) levels.

It has a half-life of 1 hour through one of the metabolites (OR-1896) is metabolically active and it reaches its maximum concentration 2 days after a 24 hours levosimendan infusion.

However, several recent studies showed some adverse effects of levosimendan.

REVIVE study showed that ventricular tachycardia and atrial fibrillation were more in patient given levosimendan than dobutamine.

SURVIVE study did not show any statistically significant mortality reduction in patients with heart failure, although mortality in those treated with levosimendan was less.

Dosage Advised
• Initiating dose: Bolus 12 µg/kg
• Maintenance dose: 0.1–0.2 µg/kg/min

Our Experience
We find majority of our patients with heart failure develop profound hypotension with bolus dose of intravenous (IV) levosimendan. Our practice usually is to start on the maintenance dose of 0.2 µg/kg/min for 48 hours. Patients develop profound diuresis and become symptomatically better.

Milrinone (an Inodilator)
A phosphodiesterase III inhibitor—inhibits breakdown of cAMP, so the concentration of cAMP increases, and it enhances myocardial contraction. It may act synergistically with beta-adrenergics to achieve a greater increase in cardiac output. It is also more effective than dobutamine in increasing cardiac output. When used with beta-blocker it produces a greater decrease in left ventricular filling pressures with a greater risk of hypotension.

Dosage Advised
• Bolus dose 50 µg/kg/min
• Infusion 0.1–0.75 µg/kg/min
Our Experience

Bolus dose of milrinone is not tolerated by majority of heart failure patients, as they develop severe hypotension. We usually start infusion IV milrinone 0.2 µg/kg/min, together with IV dopamine 2.5–5 µg/kg/min, and continue the infusion for 24–48 hours.

Dobutamine

It is the most commonly used inotropic agent in acute heart failure, stimulates beta-1 and beta-2 receptors, with little effect on alpha-1 receptors.

It is usually given as continuous infusion for 48 hours.

Dosage Advised

- Dose—initially 1–2 µg/kg/min
- There is little benefit in increasing the dose more than 10 µg/kg/min

If maintained on chronic infusions more than 72 hours, patient may develop tachyphylaxis and may require stopping of the infusion, or decreasing the dose of the drug.

Our Experience

We usually start patients diagnosed for the first time with heart failure on IV dobutamine for 48 hours and switch over to IV levosimendan for 48 hours if there is no satisfactory clinical improvement in these patients.

PHARMACOGENETICS

Pharmacogenetics attempts to define common gene polymorphism, or a set of polymorphisms that underlie variability in drug action. Given the tremendous heterogeneity that exists in heart failure patients, it is likely that genetic variation plays a significant role in determining drug metabolism, disposition and functional activity in heart failure patients. Thus, even though drugs deemed beneficial in a clinical trials, there is no guarantee that an individual patient will benefit from treatment. For example (e.g.) beta-blockers have been shown consistently to reduce the risk of death in heart failure patients by approximately 35%; however, clinical trials have also shown that beta-blockers will need to be discontinued in 8–25% of heart failure patients because of significant side effects including worsening of heart failure. 14

Recent advances in the field of pharmacogenetics support that a careful analysis of the underlying gene polymorphism within a given patient may enable clinicians to develop personalized therapeutic regimens for heart failure patients. Given the wealth of data emerging from the Human Genetic Project and Human Haplotype mapping program (HapMap) it will soon be possible to analyze complex phenotypes in relation to drug responsiveness in individual heart failure patient to better predict outcome.

METABOLIC MODULATORS

Partial inhibitors of fatty acid oxidation are:
- Perhexilene
- Oxenifene

Perhexilene: It is a potent prophylactic antianginal agent that has been shown to inhibit myocardial utilization of long chain fatty acids and to inhibit the myocardial enzyme carnitine palmityltransferase I (CPT-I).

Both perhexilene and oxenifene attenuate the increases in diastolic tension during ischemia, without significant effects on developed tension or on cardiac function during reperfusions and hence protects against diastolic dysfunction during ischemia. 9,10

CARDIAC RESYNCHRONIZATION THERAPY

Indicated in patients in heart failure with left ventricular ejection fraction less than or equal to 35% normal sinus rhythm in New York Heart Association (NYHA) III-IV despite recommended optimal medical therapy, who have ventricular dysynchrony, unless contraindicated. Heart failure guidelines support the case of cardiac resynchronization therapy (CRT) and implantable cardioverter defibrillators (ICD) combined devices in patient who have indications for implantation of both these devices.

Recently focus has also turned to narrow QRS patients with echocardiographic evidence of mechanical dyssynchrony, atrial fibrillation, and patients with indications for chronic right ventricular pacing. Long-term outcomes from device optimization and the potential effect on the nonresponder rate are the focus of the response of CRT optimization with V-V timing in heart failure patient (RESPONSE-HF) trial.

Extracorporeal Membrane Oxygenation in Heart Failure

Extracorporeal membrane oxygenation (ECMO) can take on the functions of heart/lung, till a limited time, until the patient recovers from the initial cause of heart failure or may be used as a “bridge” to heart transplant, when ECMO, can continue to support until a heart becomes available, for transplantation.

Gene therapy improvement in gene transfer vectors and gene transfer methodology has enabled recombinant genes to be expressed at robust levels in cardiac myocytes. Key pathogenic genes can be “silenced” by advances in RNA interferences that are activated in the failing heart. 11,12

IMPLANTABLE CARDIOVERTER DEFIBRILLATOR

Patients with heart failure and left ventricular systolic dysfunction are at increased risk of sudden cardiac death, at a rate of six to nine times that seen in general population. A randomized controlled trial of beta-blockade in heart failure demonstrated that patient with NYHA class II or III symptoms die most frequently as a result of sudden cardiac death. 12 Given this high incidence of sudden cardiac death in heart failure, ICDs are indicated as primary prophylaxis for sudden cardiac death in patients with either ischemic or nonischemic group of patients with severe left ventricular dysfunction. In the postmyocardial infarction group, it should be considered at least 40 days postmyocardial infarction, with left ventricular ejection fraction less than 35% with functional NYHA class II-IV while receiving optimal medical therapy and have reasonable expectation of survival. 9

MYOCARDIAL REPAIR AND REGENERATION

Stem cells: Clearly the use of stem and progenitor cells for cardiac repair is currently not at a stage for routine clinical practice. Despite a wealth of experimental and clinical data supporting feasibility, safety and even early clinical efficacy in patients with acute myocardial infarction, progression to widespread clinical application of progenitor cell administration to promote functional cardiac regeneration must be balanced against inherent risk of testing a novel therapy. Such interventions should proceed in controlled trials with utmost scientific and ethical standards. Presently, our center is a part of Indian Council of Medical Research (ICMR) trial on stem cell therapy for severe ventricular dysfunction. Till date approximately 70 patients have undergone bone marrow mononuclear cell coronary stem cell installation in our center.
ASSIST DEVICES
A mechanical circulatory support pump may be positioned extracorporeally (outside) the body or intracorporeally (contained within the body). It may be a biventricular assist device (BIVAD), right ventricular assist device (RVAD), or more commonly left ventricular assist device (LVAD). Further these devices are stratified into pulsatile and nonpulsatile assist devices. The first generation mechanical circulatory devices used volume displacement to invoke pulsatility (HeartMate XVE®), the newer second generation pumps are continuous flow axial pumps (HeartMate II®) (Figures 1A and B). Pulsatile volume displacement pumps are large in profile, preload dependent and associated with decreased durability. Continuous flow pumps are smaller capable of similar degrees of pumping support (10 L/min) more durable and functionally dependent on both preload and afterload.

Third generation mechanical circulatory support devices represent the emerging future of this technology. These devices are uniformly continuous flow devices but may be axial or centrifugal.

TOTAL ARTIFICIAL HEART
This complete cardiac replacement system is designed to provide biventricular support. The SynCardia CardioWest device is the only total artificial heart approved by US Food and Drug Administration (FDA) for bridge to transplantation (Figure 2). The current device does not allow discharge to the ambulatory setting. This device consists of two pneumatically driven pumps with tilting disk valves and short outflow grafts that replace both native ventricles and the proximal segment of aorta and pulmonary artery and all four of the associated valves.

SURGICAL MANAGEMENT OF HEART FAILURE
- Coronary artery bypass surgery may be of value in patients with severe left ventricular dysfunction with significant ischemia.
- Aortic/mitral valve surgery in patients with left ventricular dysfunction may be useful to prevent left ventricular remodeling and decrease in left ventricular ejection fraction.
- Left ventricular reconstruction to exclude the scarred area of left ventricle to restore elliptical ventricular chamber to diminish remote valve stress, to reduce end-systolic volume, to diminish mitral insufficiency and eliminate residual ischemia.
- Passive cardiac support devices to inhibit or reverse left ventricular remodeling. CorCap cardiac support device, is a fabric mesh sock that is Surgically implanted around the heart to provide circumferential diastolic support and to reduce left ventricular wall stress, thereby leading to reverse cardiac remodeling. This device not currently approved by FDA.13

HEART TRANSPLANTATION
The final therapy for end-stage heart failure is not responding to conventional therapies. Advancements in immunosuppressive therapy regimes and infection control help patients with autologous heart transplantation live longer fulfilling lives.

WHAT CAN WE DO IN INDIA?
Management can be categorized as follows:
- Prevention of heart failure
- Treatment of heart failure

Primary Prevention
We have to identify the risk factors for the development of heart failure and their prevention with an aim to reduce the incidence and burden of heart failure. Hypertension, diabetes mellitus, coronary artery diseases and rheumatic heart diseases are the most important risk factors. Physical activity, dietary control and lifestyle modification can drastically bring down some of these modifiable risk factors and reduce the load of heart failure.

Secondary Prevention
Heart failure can be controlled by screening through population-based approach. This approach can yield greater reduction in congestive heart failure. Screening for hypertensive individuals more than 30 years of age and at interval of every 3–5 years, screening for diabetic individuals, and screening of individuals 45 years of age and above who have other risk factors is necessary. Cholesterol screening (lipid profile) can be performed in individuals, 45 years of age and above, having risk factors for coronary artery disease and screening school children for identification of rheumatic heart diseases, as this is the age group frequently affected. Health education and health promotion strategies are quite important in the success of these programs.
**Community-based Intervention for Prevention of Congestive Heart Failure**

Most major large scale community-based cardiovascular disease intervention projects use population approach or a combination of both high-risk and population approach. They all carry out comprehensive activities involving innovative media campaigns, local media, community participation, and co-operation with local and national sectors in policy making. The heart failure prevention strategy must include an educational approach as well as environmental and policy approach. These community-based strategies must focus on diet, ban on smoking, physical activity, blood pressure reduction, diabetic control and cholesterol monitoring.

Thus, the thrust should be in primary prevention.

For patients in heart failure requiring advanced therapy, the Government should subsidize the cost of treatment, and in deserving cases give heart failure grants for treatment of these unfortunate patients.

Advanced research should be encouraged to manufacture low-cost drugs and devices.

**REFERENCES**