

10 *New Avenues in Management of Congestive*

Heart Failure—Understanding the Modalities and Mechanisms

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Abstract: Heart failure is a major public health problem, especially in the urban and industrialized parts of India where the burden of ischemic heart disease is increasing in mammoth proportions. Risk factor modification is the first line in the treatment of heart failure. Control of systolic and diastolic blood pressure, cessation of smoking, control of lipid levels, avoidance of alcohol abuse and illicit drug use, control of thyroid overactivity, dietary modification and graded physical activity are important preventive measures. Diuretics are useful in the acute management of congestive heart failure till the fluid levels in the body are controlled. There is some evidence that use of diuretics might be detrimental in patients with heart failure due to reduction in GFR and alterations in myocardial architecture. Digoxin formed a large part of the treatment of heart failure in yesteryears. But now its only strongest indication is for use in patients with congestive heart failure with atrial fibrillation. ACE I are the cornerstone in the management of heart failure. ARB are the next in line of treatment. Long term use of ACE I and ARB have been shown to be beneficial in terms of mortality and morbidity reduction. Beta-blockers have a definite role in the management of chronic congestive heart failure. Acute congestive heart failure is treated with nitroglycerine, nitroprusside and nesiritide infusion but milrinone, an ino-dilator has a minimal role in the treatment. The current years have seen the emergence of electrophysiological interventions such as ICD placement and CRT for the management. Mechanical assist devices have also been designed for managing heart failure in the chronic setting as against the previous indication as a bridge between heart failure and heart transplant.

INTRODUCTION

The past four decades have seen a dramatic change in the way heart failure is treated. This progress has been contributed by our advances in the understanding of the pathology of heart failure and the discovery of newer drugs and electrophysiological modalities of treatment. *The developments in the treatment of heart failure are so much that the modalities used 30 years back are now obsolete. For example, those days the treatment for heart failure was norepinephrine infusion to improve the cardiac output, whereas today we use beta-blockers, the exact opposite! Digoxin formed the cornerstone of management with its positive inotropic action, whereas today the focus is towards balanced vasodilatation and digoxin is not used to the extent it was used before. Yet another major progress is the understanding of the concept of diastolic heart failure, which has changed the way the cardiologist treats the patient with*

heart failure. Today the armamentarium that is employed to tackle this problem comprises of newer diagnostic tests such as Brain Natriuretic Peptide (BNP) assay, new medications such as Angiotensin Converting Enzyme Inhibitors (ACE I), Angiotensin Receptor Blockers (ARB), aldosterone antagonists, the combination of isosorbide dinitrate and hydralazine, beta-blockers, phosphodiesterase inhibitors and nesiritide, electrophysiological modalities such as cardiac resynchronization therapy (CRT) and implantable cardioverter defibrillator (ICD) and, finally, ventricular assist devices (VAD). This article will provide a brief overview of the use of these newer therapies in the management of congestive heart failure.

PATHOPHYSIOLOGY OF HEART FAILURE—CURRENT CONCEPTS

Congestive heart failure is the result of maladaptation of the cardiac myocytes to increased cardiac wall stress, which occurs due to primary myocyte injury as in ischemic heart disease or secondary to various factors leading to hyperdynamic circulatory states such as valvular heart disease, anemia, etc. There is a hyperadrenergic state due to cardiac compensatory mechanisms, which in turn leads to increased heart rate, increased force of contraction, increased oxygen demand, and a vicious cycle of worsening of the cardiac failure. In addition, there is activation of the Renin-angiotensin-aldosterone system (RAAS) leading to salt and water retention and increased myocardial workload worsening the heart failure. The angiotensin II is also said to be responsible for myocardial remodeling, a process by which there is myocardial hypertrophy, myocyte loss due to apoptosis and interstitial fibrosis. This leads to a state of increased myocardial volume but diminished function. Other humoral mechanisms worsening this state are also described namely, natriuretic peptides, endothelin, adenosine, tumor necrosis factor alpha (TNF alpha), etc.¹ The other important concept in heart failure is the distinction between systolic and diastolic heart failure. It is reported that almost 30-40% of all congestive heart failure is due to systolic failure, about 30-40% is diastolic and about 20 to 30% is a combination of both.

It is important to recognize that heart failure is a clinical syndrome arising from diverse causes. Not all patients with the condition have poorly contracting ventricles and a low ejection fraction. The causes of heart failure could range from hypertension, diabetes, coronary artery disease, cardiomyopathies to valvular heart disease and arrhythmias.

In patients with heart failure the myocardial conduction system is vulnerable to the same pathophysiological processes that occur in the myocytes and interstitium, with altered conduction properties observed in response to ischemia, inflammation, fibrosis, and aging. Supraventricular arrhythmias, particularly atrial fibrillation, are often the precipitating events that herald the onset of either systolic or diastolic heart failure.¹

STAGING OF HEART FAILURE

Patients with stage A are at high risk for heart failure but do not have structural heart disease or symptoms of heart failure. This group includes patients with hypertension, diabetes, coronary artery disease, previous exposure to cardiotoxic drugs, or a family history of cardiomyopathy. Patients with stage B heart failure have structural heart disease but have no symptoms of heart failure. This group includes patients with left ventricular hypertrophy, previous myocardial infarction, left ventricular systolic dysfunction, or valvular heart disease, all of whom would be considered to have New York Heart Association (NYHA) class I symptoms. Patients with stage C heart failure have known structural heart disease and current or previous symptoms of heart failure. Their symptoms may be classified as NYHA class I, II, III, or IV. Patients with stage D heart failure have refractory symptoms of heart failure at rest despite maximal medical therapy, are hospitalized, and require specialized interventions or hospice care. All such patients would be considered to have NYHA class IV symptoms. This classification is from the American College of Cardiology/American Heart Association Guidelines of the year 2002.² This staging is helpful in stratifying the patients for treatment purposes.

BRAIN NATRIURETIC PEPTIDE—THE NEW DIAGNOSTIC TOOL

The cardiac ventricle is the major source of Brain Natriuretic Peptide (BNP) (the name is a misnomer). The release of BNP is directly proportional to the stretch exerted on the wall of the failing ventricle and the intramural pressure in the ventricle. The normal levels of BNP in different age groups are as shown in Table 10.1.

Table 10.1: The normal serum BNP levels in different age groups

<i>Age Group</i>	<i>Serum BNP Levels in pg/ml</i>
55-64	26.2 ± 1.8
65-74	31.0 ± 2.4
>74	63.7 ± 6

The assay of BNP levels is a very sensitive marker of heart failure. It correlates very well with the NYHA class. BNP levels of more than 100 pg/ml have a sensitivity of more than 98% and specificity of more than 95% in the diagnosis of heart failure. The BNP levels also correlate well with the clinical outcome of these patients.³ In the Breathing Not Properly (BNP) study the serum BNP and pro-BNP levels were shown to be 90% sensitive and 76% specific for the diagnosis of heart failure as a cause for breathlessness.⁴ Thus, assay of serum BNP has now emerged as an indispensable tool in the emergency room to differentiate the cause for acute breathlessness.

BETA BLOCKERS—OLD DRUG WITH A NEW INDICATION

Beta blockers are old and very popular drugs for use in ischemic heart disease and hypertension. They are used in heart failure for the past decade or so after the CIBIS II, MERIT-HF and the BEST trials were reported.⁵⁻⁸ It is counterintuitive that the beta-blockers being negative inotropic and negative chronotropic can lead to improvement in heart failure. In clinical practice not only do they improve symptoms, exercise tolerance and cardiac hemodynamics, they also cause the gene defects in the cardiac myocytes to revert. They have also been shown to reduce mortality. Several molecular mechanisms have been proposed for their beneficial effects. There are certain definite indications for use of beta-blockers in heart failure. These indications are shown in Table 10.2.

Table 10.2: Indications for the use of beta-blockers in heart failure

<i>Stage of heart failure</i>	<i>Indication for beta blocker</i>
Stage A	To treat hypertension
Stage B	Beta-blockers should be used in all patients with a recent or remote history of MI
Stage C	Beta-blockers are recommended for all stable patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated
Stage D	No specific indication

There are certain cardinal principles for use of beta-blockers in heart failure. These are:

- Start low and Go slow.
- Start Beta-blockers as add on to preexisting ACE I, ARB or digoxin therapy in a stable patient, preferably not NYHA Class III or Class IV.
- Do not withdraw abruptly.
- Use carvedilol, metoprolol or bisoprolol, as their effect, dose and side effects are well studied in heart failure.
- Monitor closely and supervise carefully.

The choice of beta-blockers as mentioned above is between carvedilol, metoprolol and bisoprolol. Among these carvedilol has been shown to have a slight edge over metoprolol for use in heart failure. The COMET study showed that carvedilol lowered the relative risk of cardiovascular death more than metoprolol (35% in the metoprolol group vs 29% in the carvedilol group).⁹

PHOSPHODIESTERASE III INHIBITORS— THE RISE AND FALL

The prototype of the phosphodiesterase inhibitor is milrinone. They are also referred to as “inodilators.” They cause positive inotropy without increasing the heart rate or blood pressure. They also cause vasodilatation thus leading to afterload reduction. Theoretically, PDE III inhibitors form a very powerful and ideal drug for combating heart failure. This led to their rapidly rising popularity.^{10,11} But clinically they did not live up to their theoretical promises.¹² There is no benefit of these agents on long-term use without potentially serious hazards. Hence, their transient popularity started to fade.

NESIRITIDE—PROMISING NEW OPTION

Nesiritide is human recombinant BNP with properties of natriuresis, diuresis and more importantly balanced vasodilatation. It is very useful in the setting of acute heart failure. In the Vasodilatation in the Management of Acute Congestive Heart Failure (VMAC) study nesiritide was compared with nitroglycerine and placebo in the setting of acute heart failure.¹³ There were significant improvements in both the reduction of PCWP and dyspnea with nesiritide as compared to placebo and nitroglycerin. Abnormal renal function developed in some of the study patients on nesiritide and there was an increased 30-day mortality in the nesiritide group. The study did not demonstrate a benefit of nesiritide over nitroglycerine in terms of mortality rates or readmission rates. In another study compared with dobutamine, nesiritide was required for a shorter period and gave a lower 6-month mortality. With these findings now nesiritide is indicated for patients with acute congestive heart failure with dyspnea at rest or minimal activity. The increase in serum creatinine that is observed with nesiritide might be directly proportional to the starting dose of the drug and in the currently approved dose it is not observed and has no bearing on 30-day mortality.¹⁴

EPLERENONE FOR POST INFARCT HEART FAILURE

Eplerenone is a synthetic derivative of spironolactone without its antiandrogenic effects and well tolerated. Therefore, the side effects of gynecomastia, impotence and oligomenorrhea seen with the use of spironolactone are lesser with eplerenone, except risk of hyperkalemia. In the EPHESUS trial, in patients with post infarction heart failure, eplerenone was added to optimal medical management including ACE-I, diuretic and beta-blocker and it significantly reduced mortality and morbidity.¹⁵

THE ISOSORBIDE DINITRATE AND HYDRALAZINE COMBINATION

In the 1980's treatment of heart failure was in its primitive state. In the V-HeFT I trial, the combination of Isosorbide Dinitrate with Hydralazine was compared with placebo in men with impaired cardiac function and reduced exercise tolerance. Although the results showed no significant difference in mortality between the 2 treatment groups, there was a trend favoring the combination.¹⁶ This was the beginning of the interest in this combination. A second mortality study, V-HeFT II, this time comparing the ISDN-hydralazine combination *vs* an ACE-I, enalapril, in men with impaired cardiac function and reduced exercise tolerance revealed that the ISDN-hydralazine combination was inferior to enalapril overall.¹⁷ A subsequent retrospective analysis of the results of the V-HeFT trials, revealed that the trend toward efficacy in V-HeFT I was attributable to a positive

effect in the black enrollees, and the apparent lack of efficacy in V-HeFT II was due entirely to the response in the white enrollees. Following this, a study, the A-HeFT, evaluated the effects of ISDN plus hydralazine at a total daily dose of up to 120 mg ISDN and 225 mg hydralazine compared with placebo in 1050 self-identified black patients with NYHA functional class II-IV HF. The trial was terminated early because of a significantly lower mortality rate in patients randomized to ISDN-hydralazine (6.2%) compared with placebo (10.2%) and a 39% reduction in the risk of first hospitalization for HF.¹⁸

ROLE OF IMPLANTABLE CARDIOVERTER DEFIBRILLATOR (ICD)

Implantable Cardioverter Defibrillator (ICD) devices have become popular in the treatment of congestive heart failure. The ICDs have been shown to reduce sudden death in patients with or without ischemic heart disease. The definite indications for the use of ICD in congestive heart failure are as tabulated in Table 10.3.

Table 10.3: Indications for the use of ICDs in patients with heart failure

<i>Stage of heart failure</i>	<i>Indication for ICD use</i>
Stage A	<ul style="list-style-type: none"> No indication
Stage B	<ul style="list-style-type: none"> Ischemic cardiomyopathy – Post MI-LVEF ≤ 30% - NYHA I Nonischemic cardiomyopathy and an LVEF ≤ 30%-NYHA I
Stage C	<ul style="list-style-type: none"> Current or prior symptoms of HF and reduced LVEF-history of cardiac arrest, VF, or hemodynamically destabilizing VT Ischemic heart disease – post-MI-LVEF ≤ 30% – NYHA II, III Nonischemic cardiomyopathy-LVEF ≤ 30% – NYHA II, III LVEF 30-35% of any origin – NYHA II, III
Stage D	<ul style="list-style-type: none"> Refractory end-stage HF

In the Multicenter Automatic Defibrillator Implantation Trials (MADIT) it was shown that ICDs significantly enhance survival in patients with a history of myocardial infarction and depressed left ventricular ejection fraction when compared with optimal medical therapy.¹⁹ On the other hand, findings from the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT)²⁰ and the Coronary Artery Bypass Graft Patch (CABG-Patch)²¹ trial did not find statistically significant benefits of ICDs on survival in patients with recent ischemic events or revascularisation.

A recent review of 7 prospective, randomized, controlled primary- and secondary-prevention trials determined that ICD or Cardiac Resynchronization Therapy plus defibrillator significantly lowered all-cause mortality in 2146 patients with nonischemic cardiomyopathy.²² The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) included patients with LVEF ≤ 35% secondary to ischemic or nonischemic disease. Use of a single-lead, shock-only (i.e., no pacing for bradycardia) ICD resulted in a decrease in all-cause mortality of 23% compared with placebo.²³ The Antiarrhythmic Versus Implantable Defibrillator (AVID) study demonstrated significant survival benefits in favor of ICD over class III antiarrhythmic agents (chiefly amiodarone). The survival benefits from ICDs compared with antiarrhythmic drugs were most pronounced in patients with LVEF of 20 to 34%, and virtually absent in those with LVEF ≥ 35%.²⁴

CARDIAC RESYNCHRONIZATION THERAPY (CRT) – THE EXPANDING ROLE OF ELECTROPHYSIOLOGY

Heart failure is a progressive disease and the mechanisms the heart uses to make up for the deficient pumping can change the architecture of the heart and cause ventricular dyssynchrony, which occurs when the right and left ventricles fail to contract with physiologic timing.²⁵ This

usually occurs when there are delays in the regional electrical depolarization of the ventricle, and these intraventricular conduction delays lead to dyssynchronous LV contraction. This cardiac dyssynchrony occurs in 15-30% of all heart failure, especially the ones with dilated cardiomyopathy, and causes reduced systolic function. Several large, randomized, controlled trials have demonstrated the efficacy of CRT in slowing this progressive process through ventricular reverse remodeling, resulting in improved symptoms and reduced mortality. Biventricular pacing of the heart synchronizes the activation of the intraventricular septum and left ventricular free wall and thus improves cardiac function.²⁵

In the Comparison of Medical Therapy, Pacing, and Defibrillation Heart Failure (COMPANION) trial all patients who received a CRT device had a significantly reduced risk of death or hospitalization from any cause. However, those who received a CRT device with a defibrillator (CRT-D) fared better than those who received a device with CRT pacing capabilities only (CRT-P). After 16 months of follow-up, the CRT-D group demonstrated a 40% reduction in the risk of death or hospitalization from heart failure and a 36% reduction in the risk of death from any cause. Those who received CRT-P trended toward a reduction in all-cause mortality, but this was not statistically significant.²⁶

The Cardiac Resynchronization-Heart Failure (CARE-HF) trial compared CRT-P to drug therapy alone and followed patients for a longer period of time than COMPANION. After a mean follow-up of 29.4 months, patients receiving CRT-P demonstrated a highly significant reduction in all-cause mortality, with a relative risk reduction of 37% in the primary endpoint of death and cardiovascular hospitalization and a reduction of 36% in all-cause mortality, compared with control.²⁷

Several issues regarding use of CRT in patients with heart failure remain to be answered including the role of CRT-P vs. CRT-D, the most effective way to measure ventricular dyssynchrony, whether the best and worst responders to CRT can be identified prior to implantation, and the cost effectiveness of CRT in managing heart failure.

VENTRICULAR ASSIST DEVICES—MECHANICAL SUPPORT

In 1966, the first successful use of a left ventricular assist device was reported after a double valve operation. DeBakey used an assist device that was implanted in an extracorporeal location between the left atrium and the axillary artery, marking the first use of an extracorporeal temporary device support system. Till the beginning of this century the ventricular assist devices were being used as a bridge between end stage heart failure and heart transplant. This was changed by the landmark study, Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial. It was the first trial to specifically compare the survival of patients receiving the ventricular assist device with those treated with optimal medical therapy. The rates of survival at one year were 52% in the device group and 25% in the medical therapy group, and the rates at two years were 23% and 8%, respectively. The results of these trials will open the doors for the use of these assist devices for treatment of patients with chronic congestive heart failure.²⁸ In a study conducted recently on 15 patients with severe heart failure secondary to nonischemic cardiomyopathy, who underwent implantation of left ventricular assist devices and were treated with lisinopril, carvedilol, spironolactone, and losartan to enhance reverse remodeling, it was found that sustained reversal of the heart failure could be achieved.²⁹

CONCLUSION

The current milieu of heart failure management has advanced much. It is prudent on the part of the clinician to make a judgment as to which one to use when and provide optimal care for the patient.

REFERENCES

1. Mariell Jessup, Susan Brozena. Heart Failure. *N Engl J Med* 2003;348: 2007-18.
2. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Evaluation and Management of Chronic Heart Failure in the Adult. Feb 2002.
3. Cheng V, Kazanagra R, Garcia A, et al. A rapid bedside test for B-type peptide predicts treatment outcomes in patients admitted for decompensated heart failure: A pilot study. *J Am Coll Cardiol* 2001;37(2):386-91.
4. McCullough PA, Nowak RM, McCord J, et al. B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: Analysis from Breathing Not Properly (BNP) Multinational Study. *Circulation* 2002;106(4): 416-22.
5. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med* 1996;334:1349-55.
6. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS II): a randomised trial. *Lancet* 1999;353:9-13.
7. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;353:2001-7.
8. Domanski MJ. Beta-blocker Evaluation of Survival Trial (BEST). *J Am Coll Cardiol* 2000;35: Suppl A:202A-203A.
9. Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): Randomised controlled trial. *Lancet* 2003;362:7-13.
10. DiBianco R, et al. A comparison of oral milrinone, digoxin and their combination in the treatment of patients with chronic heart failure. *N Engl J Med* 1989;320: 677-83.
11. Cuffee MS, et al. Short term intravenous Milrinone for acute exacerbation of chronic congestive heart failure. *JAMA* 2002;287:1541-7.
12. Felker G.M, et al. Heart failure etiology and response to milrinone in decompensated heart failure: Results from the OPTIME-CHF study. *J Am Coll Cardiol* 2003;41:997-1003.
13. Publication Committee for VMAC Investigators. Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. *JAMA* 2002;287:1531-40. [Erratum, *JAMA* 2002;288:577.
14. Teerlink JR, Massie BM. Nesiritide and worsening of renal function: The emperor's new clothes? *Circulation* 2005;111:1459-61.
15. Pitt B, et al. Eplerenone, a selective aldosterone blocker in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003; 348:1309-21.
16. Cohn JN, Archibald DG, Ziesche S, 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;314:1547-52.
17. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine–Isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991;325: 303-10.
18. Taylor AL, Ziesche S, Yancy C, et al. For the African-American Heart Failure Trial Investigators: Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 2004;351:2049-57.
19. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med* 1996;335:1933-40.
20. Hohnloser SH, Kuck KH, Dorian P. On behalf of the DINAMIT Investigators. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med* 2004;351:2481-8.
21. Bigger JT Jr. For the Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. *N Engl J Med* 1997;337:1569-75.
22. Desai AS, Fang JC, Maisel WH, Baughman KL. Implantable defibrillators for the prevention of mortality in patients with nonischemic cardiomyopathy: A meta-analysis of randomized controlled trials. *JAMA* 2004;292:2874-9.
23. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352: 225-37.
24. AVID Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. *N Engl J Med* 1997;337:1576-83.
25. Trautmann SI, Kloss M, Auricchio A. Cardiac resynchronization therapy. *Curr Cardiol Rep* 2002;4:371-8.
26. Bistow MR, Saxon LA, Boehmer J, et al. For the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350:2140-50.
27. Cleland JGF, Daubert JC, Erdmann E, et al. For the Cardiac Resynchronization –Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352:1539-49.
28. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, Long JW, Ascheim DD, Tierney AR, Levitan RG, Watson JT, Meier P, “Long-term use of a left ventricular assist device for end-stage heart failure.” *N Engl J Med* 2001;345:1,435-1,443.
29. Berks EJ, Tansley PD, Hardy J, et al. Left Ventricular Assist Device and drug therapy for the reversal of heart failure. *N Engl J Med* 2006;355:1873-84.