Cardiac Resynchronization Therapy – New Approach of treatment for CHF

Satish Khadse

Heart failure is the inability of the heart to pump blood resulting into a complex set of symptoms – fatigue, shortness of breath, orthopnea & congestion that are related to inadequate perfusion of tissue during exertion & often leads to the retention of fluids.

-Cohn JN, NEJM 1996

ABSTRACT

Heart failure affects 5 million patients each year. Both prevalence & incidence of HF increases with age. Specially, the incidence for 1000 population of new and recurrent HF event for white American men is 21.5 for 65 to 74, 43.3 for age 75 to 84 & 73.1 for the age of 85 and older. Infact in patients older than 65 at least 20% of hospital admission are attributed to HF.

Despite advance in pharmacological therapy, the prognosis of patients who have NYHA cl. III & IV remains poor & this has lead to the development of innovative strategies for better management of this common clinical problem. Cardiac Resynchronization therapy known alternatively as biventricular pacing, is simultaneous pacing of right & left ventricle, an approach that can improve symptoms & outcome in some patients, who have HF. In addition to aggressive medical therapy, use of implantable device like Biventricular pacing & Implantable Cardioverter Defibrillator (ICD) has become mainstay. Clinical data indicate a decrease in mortality & considerable improvement in symptoms with both types of devices. In this article author review the role of CRT in management of HF.

INTRODUCTION AND DEFINITION

Though the exact Indian figures for CHF are not available it seems to be increasing due to increase in life span. The prevalence of chronic heart failure is steadily rising. In Europe it is estimated between 0.4 & 2.0% of the general population. The prevalence of CHF rapidly increases with age: in the Echo-Cardiographic Heart of England Screening (ECHOES) study, definite diagnosis of CHF was made in 0.2% of the patients aged 45-54yrs. but in, 15.2% of aged 85 yrs & above. In persons 65yrs of age or older, heart failure – also named the "New Epidemic of Cardiovascular disease" CHF is single most frequent cause of hospitalization. Mortality is high, death rate of patients with the principal diagnosis of CHF, reaches 45.5%, 76.5%, & 87.6% after 1, 5 and 10 years respectively. In Framingham study, CHF had mortality 4 – 8 times more than that of general population of same age group.

As a complex syndrome, CHF results in dyspnoea, orthopnea & Fatigue, this limits exercise capacity with water & salt retention, which may induce pulmonary and peripheral oedema. These clinical symptoms basically reflect the major patho-physiologic features of CHF i.e. decreased effective circulating volumes with subsequent sodium and water retention.

Address for correspondence

Professor & HOD, *Cardiology,*
MD, DM (Cardiology)
J.N.Medical college, Sawangi (Meghe)

Heart failure is diagnosed in a patient whenever he/ she has symptoms or signs of either low cardiac output or pulmonary venous hypertension or systemic venous hypertension or any combination thereof due to either systolic or diastolic dysfunction of the ventricles. Classical definition of CHF based on cardiac output and filling pressures derived from the physiology laboratory; but have limited practical utility. Hence, there has been a move towards more practical clinically useful definition of CHF. One of such definition adopted by European Society of Cardiology is more useful for clinical practice:

· Subjective – Symptoms of CHF.

· Objective – Evidence of important cardiac dysfunction.

· Retrospective – Response to appropriate therapy for CHF.

Most of the studies have concentrated on the diagnosis, treatment & prognosis of CHF due to impaired LV systolic function (LV Contractibility), so called LV systolic dysfunction. All systolic CHF are accompanied by diastolic dysfunction (Abnormality of relaxation).

Table I: New York Heart Association Classification

Class I	No Symptoms with ordinary physical activity
Class II	Symptoms with ordinary activity (Slight limitation of activity)
Class III	Symptoms with less than ordinary activity (Marked limitation of activity)
Class IV	Symptoms with any activity or at rest

Symptoms & Signs of Heart failure

Following are the Symptoms & Signs with physical findings:

Dyspnoea	:	Jugular venous distension
Orthopnea	:	Gallop rhythm
PND	:	Pulmonary rales or wheezes
Cough	:	Hepatomegaly
Nocturia	:	Ascities
Anorexia	:	Peripheral Oedema

Causes of Heart Failure:

- Hypertensive Heart disease

Cardiomyopathy	Idiopathic (Most Common Cause for DCM)
	Ischemia
	Dilated
	Restrictive
	Inflamatory:
	· Autoimmune
	· Infectious
	Peripartum
	Tachycardia induced
Valvular Hear diseases	
Congenital Heart Disease	
Pericardial disease	
Drugs & toxins	Alchohol
	Cocaine
	Anthracyclines
Endocrine disorders	

Diagnostic aims in CHF are summarized as below:

1) To ascertain that patient has CHF.
2) To ascertain etiology (Ischemia, Valvular Heart Disease etc.).
3) To ascertain the features which will determine therapy (e.g. diuretric for water retention, ACE for LV systolic dysfunction).
4) To identify features that predict mortality & morbidity.
5) To identify co-existing disease that may alter management (e.g. renal disease, DM).
6) To predict patients at risk of developing CHF.

While evaluation patients following points to be considered in details and should be included in the management:

1) Symptoms & Signs – NYHA class.
2) Prior Hospitalization & diagnosis.

3) ECG – 12 leads.

4) Chest X- Ray .

5) Pulmonary function tests.

6) Echocardiography.

7) Coronary Angiography.

8) More advanced diagnostic techniques e.g. Nuclear Angiography.

9) Neuro Endocrine Assessments.

10) Precipitating Factors.

Factors adversely affecting prognosis in Heart failure:

1) Diabetes Mellitus

2) Hypertension.

3) Use of tobacco.

4) ECG abnormalities: LV hypertrophy.

5) Ejection Fraction < 25%.

6) Exercise capacity (peak VO2 < 14 ml / Kg / min.).

7) Haemo-dynamics (PCWP more than 18mm Hg).

8) Race (1.5 – 2 times higher in mortality among African American).

9) Age older than 65 years.

10) Male sex.

11) Serum sodium levels less than <135 mmol / L.

12) Arrhythmias (LV Conduction delay; NSVT).

13) Neuro Hormonal Plasma levels (Norepinephrine > 400 ng/ml).

Management:

Aims of therapy:

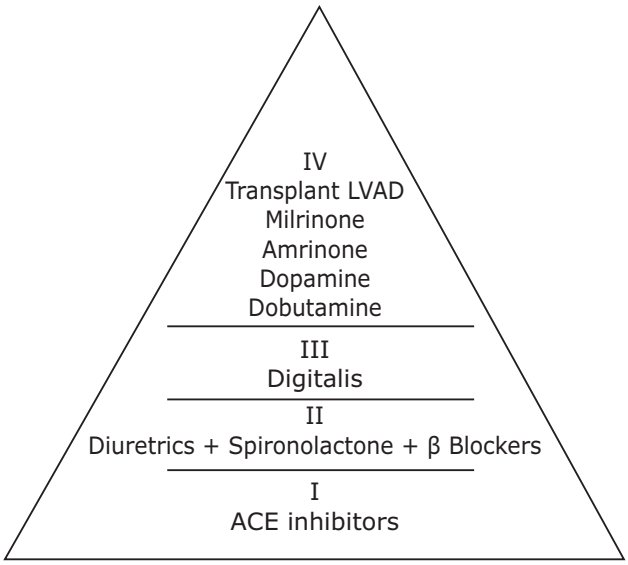
1) Improvement in quality of life (Decrease in symptoms and increase in exercise tolerance)

2) Improvement in quantity of life

(Improved survival)

Institution or increase in the dosages of any drug can be justified if at least one f the above aim is achieved.

Algorithm for management of Heart Failure:



New therapeutic options on Horizon

New Drugs

- Vasopeptidase Inhibitors.
- Antianaemia Regimens.
- Immunomodulators.
- TGF – α Antagonists.
- MMP inhibitors.
- GRK Antagonists.
- B- ARK inhibitors.
- MAP – Kinase inhibitors.
- Nitirc Oxide Modulators.
- Xanthinoxidase Inhibitors.
- Adenosine antagonisits.
- Atrial natriuretic peptide.
- Aquaporin protein therapies.

New Targets:

- Gene / Protein Therapy.
- Angiogenesis Therapy.
- Stem cell Therapy.
- CAM Kinase inhibitors.

Non Pharmacological Interventions:

- Resynchronization Therapy – Implantable Defibrillators.
- Ultra-filtration.
- CPAP therapy.
- Assist devices.

This review article will focus on the available guidelines and major clinical trial results to help practicing clinicians on appropriate use of Cardiac Resynchronization Therapy (CRT) with heart failure patients as a result of systolic dysfunction with NYHA class III and IV and optimal medical therapy.

Historically, CRT as a concept for heart failure dates back in 1990, Hocheleitner et .al. reported clinical improvement in dual chamber pacemaker implanted patients, allowing cardiac ionotropic therapy withdrawal; with short AV delay. Follow-up study of same group showed continued clinical improvement in patients who survived.

In 1992 Brecker et al reported symptomatic and Echocardio Graphic improvements with physiologic pacing in 12 cardio-myopathy patients, without conventional pacing indications. At a programmed short AV interval, breathlessness, cardiac output, exercise duration (Six minute walk >30 m)and maximum oxygen consumption improved compared with a long, either programmed or spontaneous AV delay.

Nishimura et all found that in severe LV Dysfunction AV sequential pacing resulted in minimizing pre-systolic AV Valve regurgitation; (Specifically in patients with PR interval more than 200 msec) significant improvement in cardiac output, LV – end diastolic pressure, diastolic filling time and diastolic mitral valve regurgitation.

In 1926 Wiggers described ventricular asynchrony with ventricular dysfunction; confirmed by Harrison in 1965, with Kineto-cardiogram.

Grines et al showed that RV – LV asynchrony leads to delayed LV contraction with subsequent decline of LVEF and abnormal inter-ventricular septal motion.Finally Xiao et

all revealed that a prolonged QRS duration was associated with reduced peak dP / dT, prolonged overall duration of the pressure Pulse, and time to peak dP/ dT. If QRS Duration could be reduced, cardiac function will improve and this can be achieved with certain specific pacing configurations.

Mechanism of Resynchronization Therapy

Cardiac resynchronization therapy implies potential improvement at many different levels, in any given patient

With CHF, Cardiac asynchrony may occur in different degrees at firstly, an AV level, secondly at an inter-ventricular level, thirdly at intra-ventricular level.

Artrio – Ventricular synchrony reduces the mitral diastolic regurgitation. Inter-ventricular asynchrony is due to electromechanical inter-ventricular delay. Consequences of this includes –

a) LV isovolumetric contraction and relaxation time prolongation

b) Worsening of mitral regurgitation

c) Shortening of LV filling time, leading to diminished cardiac output.

Restoration of inter-ventricular synchrony shows improvement in all above factors. Intra-ventricular asynchrony means overlap of systole and diastole, and therapeutic aim is to abolish this overlap by intra ventricular synchrony. Thus, inter & intra ventricular asynchrony leads adversely to affect the

pumping efficiency. Clinical manifestation of this is:

a) Wide QRS complexes on ECG typically LBBB (Left Bundle Branch Block)

b) Paradoxical Septal wall motion and late LV lateral wall contraction on Echocardio

– graphy

c) Dilatation of heart

Ultimate effect of ventricular dysfunction causes adverse Hemodynamic consequences with:

1) Delayed activation of the postero – lateral Left ventricular wall.
2) Reduced forward flow of blood due to low ventricular filling time.
3) Mitral Regurgitation.

Over 30% of moderate to severe heart failure patients have a wide QRS. Prevalence of conduction defects increases with severity of heart failure. LBBB predicts a 36% greater risk of one year mortality regardless of the severity of heart failure and treatment regime. Wider the QRS, the greater is the risk of mortality.

Relative risk of the widest QRS group (>200 ms) is 5 times higher than the narrowest (<90 ms). In cardiac resynchronization Left ventricle is paced with lead in postero lateral cardiac vein or sometimes in anterior cardiac vein. Right ventricle is paced with RV lead and right atrium with lead in right appendage.

Cardiac resynchronization is thus achieved with mimicking natural electrical activation of the heart (right atrium, left atrium followed by synchronized right and left ventricular contraction) resulting in improved cardiac hemodynamic through energetic and efficient cardiac function.

CRT can result in reverse cardiac remodeling with improvement in cardiac structure and function. The benefits are dependent upon the delivery of synchronized ventricular pacing. Through advanced pacemaker technology CRT also detects and treats brady-arrythmias, atrial arrhythmias and detects and treats ventricular arrhythmias as if combined with ICD.

MECHANISM OF CRT (on last page)

Indications for Cardiac Resynchronisation Therapy

- Moderate to severe Heart Failure
  NYHA Class III or IV
- Ventricular Dysynchrony
  QRS>/+= 130 ms
- LV dilatation
  LVEDD> 56 mm
- Impaired LV ejection fraction
  EF< 35%

Together with medical therapy and cardiac recynchronisation therapy provides a new option to one in every three heart failure patients (those with QRS> 130 ms and EF< 35%) offering:

(a) Fewer hospitalisation

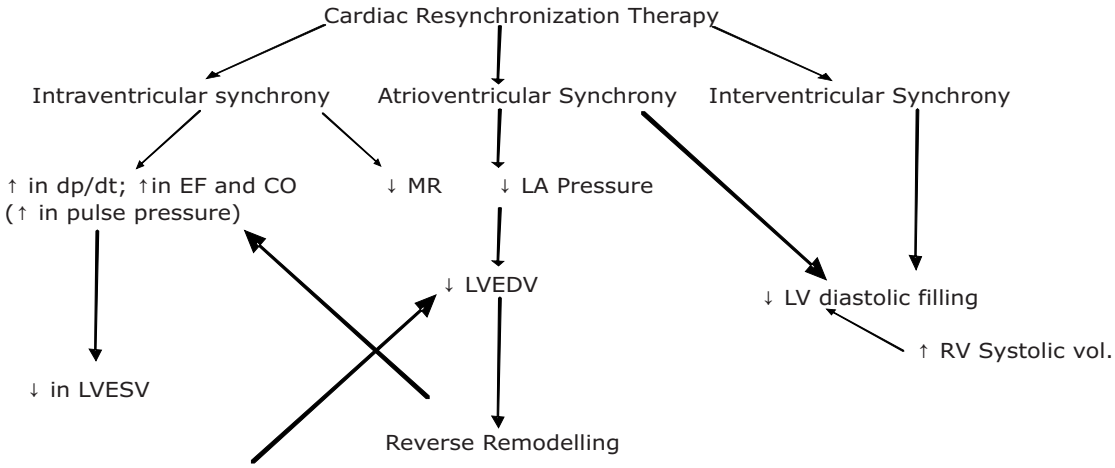
(b) Enhanced exercise capacity

(c) Improved quality of life

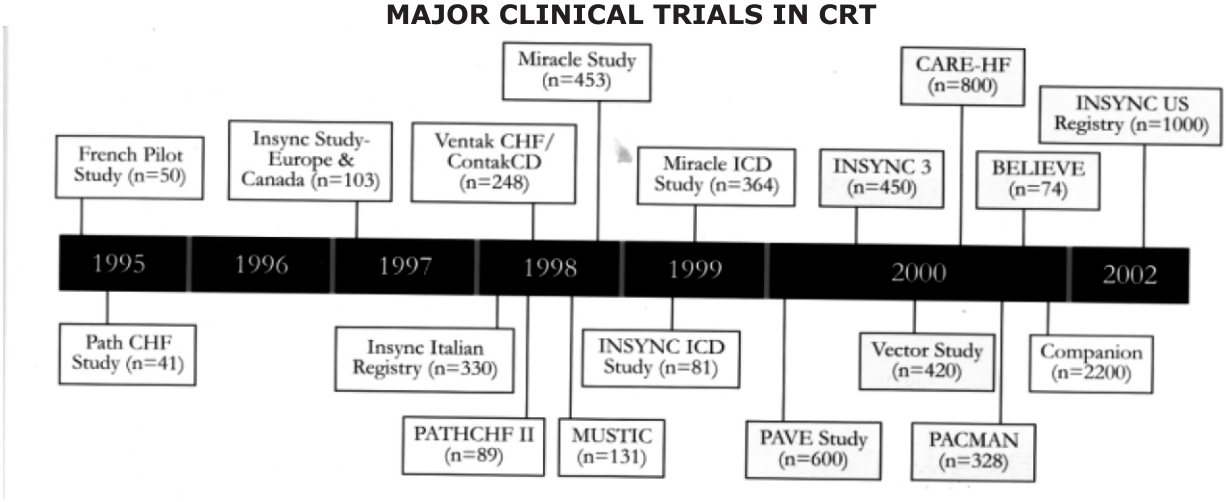
Biventricular pacing with Defibrillator capability

Mortality in biventricular pacing patients remains high despite improvement in acute hemodynamics and mid term symptom progress. Followup of 153 patients paced with biventricular configuration for 10-15 months revealed a 20%-30% death rate of which 33% tp 47% was sudden death. Obviously, arrhythmia secondary to LV dysfunction and associated heart failure is of paramount concern and given the proven efficiency of ICD therapy in preventing sudden death in heart failure appears most attractive.

MECHANISM OF CRT



MAJOR CLINICAL TRIALS IN CRT



The following studies provided evidence of the positive effects of cardiac resynchronization therapy.

Clinical Study	QoL	NYHA Class	Exercise Capacity	Cardiac Function/ Structure	Heart Failure Hospitalization
MIRACLE[1] (n=453)	+	+	+	+	+
MIRACLE ICD[2] (n=364)	+	+	+	+	+
MUSTIC[3] (n=131)	+	+	+	↔	↔
InSync[4] (Europe) (n=103)	+	+	+	+	
InSync ICD[5] (Europe) (n=84)	+	+	+	+	
PATH-CHF[6] (n=41)	+	+	+	+	+

References:

1) Braunwald E. Shattuck lecture- Cardiovascular medicine at the turn of the millennium . N Engl J. Medicine 1997, 337:1360-9

2) MacIntyre K; Capwell S. et all. Evidence of improving prognosis in heart failure: Circulation 2000, 102:1126-31

3) Karin Miller, G. Gamber, F. Jaquet, B.Hess; The European Journal of Heart Failure 5 (2003) 793-801

4) Cleland JGF, Erdmann E: Ferrari R. Guidelines for the diagnosis of heart failure. Euro Heart Journal 1995:16:741-51

5) Manual of cardiovascular Medicine S. Marso;B. Graffin, Eric J.Topol Page 100-101 (Edi 2000)

6) Manual of cardiovascular Medicine S. Marso;B. Graffin, Eric J.Topol Page 100-101 (Edi 2000)

7) Handbook of Optimising Heart Failure Management edited by B. Stanek 2004-page no 2

8) Cardiology Update 2009- Advances in management of heart failure 2009-Sandeep Shah, VK Bahl Page 315-322

9) Hochleitner M; Horingagal H, Frederich L. et all. Usefulness of physiologic dual chamber in drug resistant idiopathic dilated cardiomyopathy- Am. J. Cardiology 66:198-202, 1990

10) Breaker SJ, XIAO et all. Effect of dual chamber pacing with short Av delay in DCM Lancet 340:1308-1312, 1992

11) Nishimura RA, Holmes et all- Mechanism of hemodynamic improvement by dual chamber pacing for severe Lv Dysfunction: J am Coll Cardiol 25:281-288, 1995

12) Wiggers C. Are ventricular changes important in the dynamics of left ventricular contraction? Am.J.Physiol 74:12-30,1926

13) Harrison T: Some unanswered questions concerning enlargement and failure of heart Am Heart J 69:100-115,1965

14) Grines et al- Functional abnormalities in isolated LBBB- The effect of interventricular asynchrony. Circulation 79: 845-853,1989.

15) Breaker SJ, XIAO et all. Effect of dual chamber pacing with short Av delay in DCM Lancet 340:1308-1312, 1992