Cardiac Resynchronisation Therapy in Heart Failure

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ABSTRACT

Cardiac resynchronization therapy (CRT) represents one of the recent advances in heart failure (HF) management. It implies an attempt to establish left ventricular synchronous contraction in order to improve left ventricular hemodynamics; thereby improving functional class, and quality of life. CRT has come a long way from an incidental treatment modality to an accepted and indicated treatment strategy for patients suffering from severe and chronic heart failure. With its ever increasing use, it is important that we become conversant with its role in the management of heart failure. This article aims to review the evidence for CRT, how CRT benefits patients of heart failure and reveals the indications of CRT implantation in HF patients.

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1. Introduction

Heart failure (HF) is the final common end result of all forms of cardiac injury. Better and evidence-based management of patients, presenting with acute cardiac insult, has led to an increased burden of HF, as more and more patients with cardiac injury survive for longer duration of time, and add up to the pool of HF. Further addition to this epidemic pool is made by an increasing incidence of diabetes, hypertension, obesity and increased lifespan. Fortunately, management strategies for HF has also been continuously evolving starting from basic measures like lifestyle, modification to newer drug therapies and advanced interventions; like device therapy that has significantly contributed to the improved outlook for such patients. CRT represents one such device intervention indicated in patients with NYHA, Class III or ambulatory Class IV HF symptoms. It is not only reduces symptoms and incidence of hospital admission, but also significantly improves quality of life, functional status, exercise capacity, and left ventricular hemodynamics (1-4), that ultimately translates into a mortality benefit (1, 5).

2. Intra-Ventricular Conduction Delay and Left Ventricular Dysfunction

Left ventricular dysfunction in HF is associated with IVCD (Intra-ventricular conduction delay) in 15 to 30 percent (6-8) of cases, which usually manifests as bundle-branch block of LBBB morphology type (3, 4). In LBBB, the left ventricle is depolarized. Later than, right ventricle and activation of the anterior septum precedes inferior septal activation, the inferior and lateral aspects of the
left ventricle are the last regions to get depolarized (9, 10). Therefore, when depolarization spreads through LV, the septum and anterior LV are the first-to-contract while the lateral wall contraction is delayed. This results in pre-stretch of the lateral wall, delaying intracavitary pressure rise and mitral valve closure. Later on, when LV lateral free wall contracts the septum, and anterior LV is not synchronous, a corresponding stretch of the anteroseptal region is caused; thereby, aortic valve ejection is decreased. Dysynchronous contraction creates mechanical inefficiency, with blood in heart partially getting pumped out of aorta and partially lying in the two dynamic intracavitary sinks (the stretched lateral wall in early systole, and the anteroseptal region in late systole). The delayed contraction of the posterolateral LV wall and lateral papillary muscle promotes functional mitral regurgitation, by preventing the proper coaptation of the valve leaflets. Also, abnormal septal depolarization causes increasing in LV end-systolic diameter and decreasing in regional ejection fraction, decreasing cardiac output, mean arterial pressure, and dp/dt (9, 11, 12). Delayed and prolonged depolarization in LBBB is associated with significantly later aortic valve closure and mitral opening, and delayed diastolic filling with concordant decrease in the duration of LV filling (9).

3. Pathology

Pathological changes are myriad ranging from a globally impaired ventricular function to an abnormally increased fiber strain, with concordant increase in metabolic activity, and tissue hypertrophy (13-15). Electrophysiological properties of these myocardial fibers are also deranged and reduced tissue refractoriness and conduction velocity is commonly found (16).

4. Mechanism of CRT Benefit

The exact mechanisms of CRT benefit are not known, but electrical synchronization can reduce the LBBB inducing, mechanical interventricular dysynchrony between the right and left ventricle and intraventricular dysynchrony within left ventricle. The beneficial effects of mechanical LV resynchronization appear to be independent of electrical synchrony.

5. Acute Effect

Mechanical benefits appear instantaneously after CRT implantation and include improving in dp/dtmax, aortic systolic pressure, and cardiac output (CO) (17). The PCWP declines and systolic pressure improves principally from an enhanced mechanical efficiency of LV (18-20). Elimination of early systolic lateral free wall stretch increases CO, while late-systolic synchronous anteroseptal LV wall contraction causes an attendant decline in end systolic stress.

6. Chronic Effects

Chronic benefit includes reverse remodeling (21-25), improved LV function and decreased myocardial oxygen consumption (26). Long term bi-ventricular pacing is associated with a significant reduction in mitral regurgitation jet area (4, 27), left ventricular mass, left ventricular end-systolic and end-diastolic dimensions of all indicative reverse remodeling (28-30). MIRACLE and Vigor-CHF have reported approximately 10 % of reductions in both end-systolic and end-diastolic volumes with 6-month CRT treatments (29, 30). The effect on chamber volume persists, even after cessation of CRT pacing suggested a remodeling effect rather than an active effect of CRT.

7. Where to Pace; Bi–Ventricular or LV, Anterior or Free Wall?

Though electrical synchrony and isovolumic relaxation rate is better with Bi-Ventricular CRT, (31-33) the mechanical effects are nearly the same with both types of CRT lead placement. Both modes increase dp/dtmax, CO, and stroke volume to almost similar extent and independent of electrical effects (34). Butter et al. compared the acute effects of LV pacing site (anterior vs. free wall) on net change in global systolic function. He found that LV free wall pacing consistently resulted in greater increases in dp/dtmax and aortic pulse pressure than did anterior pacing (35). Accordingly, CS pacing leads are typically placed in midlateral wall positions, frequently over a guidewire directed into the selected tributary. In a study by Gasparini et al. the effects of differential pacing sites were evaluated in CRT treated patients, the results were not in favor of lateral wall pacing. Separated from the stimulation site, the clinical and echocardiographic parameters were significantly improved in the most of the patients (36). Thereby, the pacing of an alternate site when leading a lateral wall placement is not technically feasible.

8. Major Trial Evidence for CRT

MUSTIC: This trial was divided into two groups based on their basic rhythms (2, 37). Group one (MUSTIC SR) included 67 patients with NYHA class III heart failure, QRS duration > 150 ms with stable sinus rhythm and no conventional indications for pacemaker therapy (2). The patients were randomly assigned to BiV pacing, or no BiV pacing for three months after which the pacing modes were switched. Significant improvement was seen with exercise tolerance, quality of life, peak oxygen consumption, with a two-thirds reduction in rate of hospital admission. The benefits with BiV pacing compared to baseline were maintained at 12 months (37). Group two MUSTIC – AF included 59 patients with heart failure and chronic AF (atrial fibrillation) with a wide QRS complex that required a permanent pacemaker, because of a slow ventricular rate. These patients were randomly assigned to either single site RV pacing or BiV pacing for three
months and later the pacing modes were switched (37). Benefits were similar to the MUSTIC – SR group, though fewer patients eventually completed this study arm.

9. MIRACLE
First Randomized double blind trial evaluated the morbidity benefits of CRT on patients with NYHA Class III and IV symptoms and LV dysfunction (LVEF < 35% and a QRS duration > 130 ms). Compared with the control group, patients randomized to cardiac resynchronization demonstrated a significant improvement in quality of life score, 6-minute walk distance, NYHA functional class, treadmill exercise time, peak O2 consumption and LVEF (29). The benefits shown by this trial lead FDA to approve CRT as a treatment modality for CHF.

10. CARE-HF
Open labeled RCT evaluated mortality benefit in patients on optimized medical therapy (OMT) with CRT vs. OMT alone (38). Enrolled patients were in NYHA class III or IV systolic heart failure and had evidence of ventricular dyssynchrony (QRS duration > 150 ms, or QRS duration between 120 - 150 ms plus echocardiographic evidence of dyssynchrony). At a mean of 29-month follow up CRT reduced both the primary-end point and the secondary-end point of all-cause death by approximately 36 %, and the survival curves continued to separate thereafter.

11. PATH CHF
Patients with CRT (Bi-V or LV) had significant improvement on peak O2 consumption, 6-min walk test and NYHA class (39).

12. CRT With ICD: Trials
COMPANION Study (40): Open-labeled randomize-controlled trial that enrolled 1,520 patients in a 1:2:2 fashion to OMT, CRT, and CRT-D therapy. The criteria for inclusion had in addition to NYHA Class III or IV and QRS > 150 ms an episode of hospitalization for HF in the year preceding to randomization. The primary-end point was the composite of death or hospitalization from any cause; secondary-end points included death from any cause. The trial was prematurely discontinued in Nov 2002, due to the significant benefit seen in the device group. Compared with control patients (group 1), the primary-end point was significantly reduced in device group in comparison to the medical controls (18.6 % in CRT and by 19.3 % in CRT-D group, \( P < 0.015 \) and 0.005, respectively). All-cause mortality was reduced significantly only in CRT-D group (43 % reduction, \( P = 0.002 \)) when compared to the controls, the CRT group showed a strong trend towards mortality benefit that did not reach statistical significance (reduction by 24 %, \( P = 0.12 \)). The study was underpowered to compare mortality benefit between the device groups. The result of this trial paved the way for the use of CRT-D in above subset of patients.

13. MIRACLE-ICD
Prospective randomized controlled trial that enrolled 369 patients with NYHA class 3 or 4 HF, LVEF < 35%, and a wide QRS interval (> 130 milliseconds), to either the active treatment arm with CRT (CRT on, ICD on; \( n = 187 \)), or to the control group (CRT off, ICD on; \( n = 182 \)) and followed for 6 months for a composite endpoint of mortality, hospitalization and symptomatic improvement (41). At six months, patients assigned to CRT therapy had a greater improvement in median quality-of-life score, functional class and exercise capacity than the control group, but there were no differences in the six-minute walk test or arrhythmic events. Therefore, the combination of CRT with ICD was considered to be safe and effective in patients requiring both devices.

14. Current Indications
According to the recent updated guidelines of the American Heart Association, implantation of CRT is a class I recommendation in patients with EF < 35 %, class III or ambulatory class IV heart failure; despite maximal medical therapy, QRS more than 120 ms, and who are in sinus rhythm (Level of evidence A) (42, 43). In addition, CRT is considered reasonable (Class IIa) for patients with LVEF ≤ 35 percent with NYHA functional class III, or ambulatory class IV symptoms who are receiving OMT and who have frequent dependence on ventricular pacing or are in atrial fibrillation (42). Consideration for CRT implantation (Class IIb) may be given to patients with LVEF ≤ 35 percent with NYHA functional class I or II symptoms, who are receiving optimal recommended medical therapy and who are undergoing implantation of a permanent pacemaker and / or ICD with anticipated frequent ventricular pacing (42). The appropriateness of CRT for patients in marked dyssynchrony and class I or II HF, patients with HF and sustained RV apical pacing, and patients with end-stage CHF are recognized as unresolved issues (43).

15. Implantation Technique
The CRT device is implanted by venous approach, using fluoroscopic guidance to place pacing lead through the cephalic, axillary, or subclavian veins into the right atrium, right ventricle, and a tributary of the (coronary sinus). CS venography using an occlusive balloon tipped catheter is done at the time of LV lead implantation, in order to select the most appropriate lateral vein for LV pacing (44). Whether to approach the vein from right or left side depends on the operator’s practice and the layout of the laboratory; however, if the CRT device is implanted includes cardio version / defibrillation functions, the left side is preferred, since the average defibrillation energy requirements are lower from the left side due to better electrical vectors. Following LV leads to the placement of the position which is confirmed by fluoroscopy in left anterior oblique view. LV leads in base to mid-posterolateral position with maximum LV-RV lead separation indicates
a good position. The pacing and sensing parameters are checked and diaphragmatic stimulation ruled out by high voltage pacing. Pacing thresholds are acceptable if they are less than 3V at 0.5 milliseconds. Finally, the CRT device is connected to the leads and site closed.

16. Programming for Optimization

Usually in CRT device the RV lead is bipolar with distal stimulating cathode and a proximal non-stimulating anode, while the LV lead has a distal stimulating uninipolar cathode. Modification of the AV and VV delay is required for optimal cardiac synchrony during sequential atrioventricular pacing. This can be done by:

- Aortic VTI (velocity time integral) method: Aortic VTI is directly proportional to the stroke volume and AV delay is so timed, so that VTI is maximum.

- Mitral inflow method: Shortest AV delay that allows for separation of E and A wave with the end of A wave coinciding with the closure of mitral valve.

- Left Ventricular dP/dt method: AV delay is optimized for a maximum rate of pressure change in left ventricle.

Aurrichio et al., however, demonstrated that comparable mechanical benefits are achieved across a moderate range of AV delays (19). Thus, while some patients with particularly long intrinsic delays require customization, most will gain a similar CRT effect by using a nominal delay of around 120 ms.

With the use of newer CRT devices optimal VV delay, customisation is also required. This is done by selecting the V-V delay that maximizes the VTI across the aortic valve. Sogard et al reported that LV ejection fraction improves by about 8% by V-V delay optimization with LV dyssynchrony, showing an improvement after implantation (45). In the recent nSync III Marquis trial, though the primary endpoint of clinical composite response at 6 months did not significantly differ between CRT-D and CRT-D+V-V groups (P < 0.001), the investigators noted a small trend toward improvement in patients with CRT-D + V-V patients (46).

17. Pitfalls and Complications of CRT Therapy

CRT implantation is a technically challenging procedure. Most studies have found failure rate of 8-12% (47, 48), majority being due to failed LV lead implantation (6% according to MacAllister55). Mortality during the procedure averages 0.4-1 percent (49, 50) and device-related complications, during the first 6 months included lead malfunction or dislodgement (8.5%), device infection (6.7%), arrhythmia attributable to CRT (2%), and site infection (1.4%) (5, 48). The complication rates are generally higher when implantation is done by a non-electrophysiologist (51).

18. Conclusion

CRT represents one of the recent additions to the growing armamentarium of HF therapy and with an increasing body of evidence, showing mortality advantages in patients with CRT devices. It may be not far off that this therapy finds an ever growing indication for use and compete with drug therapy; as the primary modality of treating incipient or manifest heart failure.

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