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Article type Review

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Journal name and URL Clinical Medicine: Cardiology
Accessible at http://la.press.com

Factors Influencing Response to Cardiac Resynchronization Therapy in Patients with Heart Failure

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KEYWORDS

Heart failure, Cardiac resynchronization Therapy

Heart failure (HF) currently affects over 5 million Americans, with approximately 500,000 new cases diagnosed each year. The rapid growth of HF has made it a disease of epidemic proportions that has tremendous clinical and financial impact on the US health care system. With 5-year mortality rates approaching 50%, this is the most common cause of hospitalization in patients older than 65 years and is the single most expensive diagnosis in the United States (1).

Cardiac resynchronization therapy (CRT) has rapidly become an integral treatment in patients with drug-refractory congestive heart failure (HF), but 18% to 52% of patients in randomized clinical trials do not respond to CRT (2,3). A number of tools and methods have been used to predict response to CRT, including clinical characteristics, electrocardiographic findings, hemodynamic response, echocardiographic features, multislice computed tomography and cardiac magnetic resonance imaging (4). The purpose of this article is to review the major factors influencing response to CRT and to propose standardized criteria for assessing response to CRT.

Etiology of heart failure: (Is the etiology of heart failure a major factor in the response to CRT?)

CHF patients with ischemic cardiomyopathy (IC) appear less likely to benefit from CRT than those with idiopathic dilated cardiomyopathy (IDC). Gasparini *et al*. (5) studed 158 patients in a single center, longitudinal, comparative investigation. Mean follow up period was 11.2 months. The left ventricular ejection fraction (LVEF) increased from 29 to 34% ($p<0.0001$), NYHA functional class III-IV decreased from 83% to 23% ($p=0.04$) in the coronary artery disease (CAD) group, and LVEF increased from 29 to 42% ($p<0.0001$), NYHA functional class III-IV decreased from 79% to 5% ($p=0.0001$) in the non-CAD group. Similarly, in the MIRACLE study (6) there was significantly greater LV remodeling and absolute gain in LVEF in the idiopathic dilated cardiomyopathy group compared to the ischemic group in the CRT patients at 6-12 months. The Cardiac Resynchronization in Heart Failure (CARE-HF) study (7) followed 813 patients for a mean of 29.4 months, and patients were randomized to CRT plus medical therapy or medical therapy alone. In subset analysis there was a trend for idiopathic dilated patients to fare better (hazard ratio for primary endpoint of death or cardiovascular hospitalization 0.51, 0.36–0.73) than the ischemic and other causes group (hazard ratio 0.68, 0.53–0.88). However, there was a study indicated that the underlying etiology of heart failure was not related to the response to CRT, 65% (26/40) responders in IDC group and 60% (24/40) in IC group (8). Studies demonstrated that sympathetic activation is a key component of the physiopathology of chronic congestive heart failure (CHF) (9, 10). The sympathetic overactivity is directly related to the severity of heart failure and is implicated in the poor prognosis of the disease (11).

Najem, et al (12) studied 23 patients with drug-refractory congestive heart failure. Blood pressure, heart rate, LVEF, and cardiac index did not differ between both groups at baseline, 16 patients responded to CRT after 15 ± 5 months, and 7 had not response to CRT after 12 ± 4 months. Muscle sympathetic nerve activity (MSNA) tended to be lower in the responders than in the nonresponders ($p=0.06$), and plasma norepinephrine levels did not differ. The study provides direct evidence that reversible sympathoinhibition is a marker of the clinical response to CRT. In the responder group, there were 9 patients with ischemic cardiomyopathy, 2 patients with valvular heart disease had previously surgery, and 5 patients with idiopathic cardiomyopathy. In the nonresponders, 3 patients

had ischemic heart disease and 4 patients had idiopathic cardiomyopathy (P = 0.40). In Najem's study, shows that sympathetic control may be as important as etiology of HF in determining response to CRT, etiology of heart failure was less important than reversibility of sympathoinhibition in determining response to CRT. However, non-coronary patients had a greater increase in LVEF and decrease NYHA failure class than patients with coronary artery disease after CRT in the larger clinical trials. In clinical practice, we can expect a more reliable response rate from patients with nonischemic cardiomyopathy than in patients with ischemic cardiomyopathy.

Does QRS duration predict response to CRT?

The primary criteria of candidate for cardiac resynchronization therapy was: left bundle branch block –QRS >120 msec, New York Heart Association [NYHA] class III–IV, and left ventricular ejection fraction <35%). Despite patient selection in accord with the traditional selection criteria, 20% to 35% of patients failed to benefit from CRT (13,14,15,16). A possible explanation of failure to respond to CRT is that QRS duration alone is not a robust indicator of cardiac dyssynchrony. One study examined 67 patients with QRS duration > 120 msec (form of LBBB or IVCD) and 45 patients with QRS duration ≤ 120 msec using tissue Doppler imaging, it was shown that systolic dyssychrony was present 43% of heart failure patients with narrow QRS and in 64% with wide QRS complexes (17). In this study, about 1/3 of heart failure patients with LBBB or ICVD ECG pattens did not exhibit significant mechanical dyssynchrony. Bleeker et al reported the severe intraventricular dyssynchrony (defined as septal-to-lateral delay > 60 ms) in 27% of heart failure patients with narrow QRS (<120ms), in 60% of patients with a QRS duration 120-150ms and in 70% of patients with QRS ≥ 150ms (13). In a single center 123 patients study (14), 56 patients had a QRS duration <120 ms (Group 1), 33 patients had a QRS duration between 120 and 150 ms (Group 2), and 34 patients had a QRS duration ≥150 ms (Group 3). Intraventricular dyssynchrony was present in 36% of Group 1, in 58% of Group 2, and in 79% of Group 3 (P < 0.0001). A greater proportion of patients with interventricular dyssynchrony was observed in Group 3 or Group 2 compared to patients with normal QRS duration (32% in Group 1 vs. 51.5% in Group 2

vs. 76.5% in Group 3, P < 0.0001). Linear regression demonstrated a weak relation between QRS and intraventricular dyssynchrony, and a significant relation between QRS duration and interventricular mechanical delay- that is, the difference between left and right ventricular preejection intervals. The lack of interventricular dyssynchrony in many patients with standard CRT indication by QRS duration may provide us insight into the nonresponders rates. Cardiac interventricular dyssynchrony absence at baseline would be expected to limit the potential of cardiac resynchronization therapeutic benefits. One study indicated that QRS duration is more related to interventricular than intraventricular mechanical dyssynchrony: in 30 patients, intra-VD was defined as the longest delay between the opposing walls, and inter-VD was defined as the delay between the right ventricular free wall and the LV lateral wall. Baseline group mean QRS duration (150± 30ms) corrected with inter-VD ($r=0.56$, $p<0.01$) more strongly than the intra-VD ($r=0.44$, $p<0.05$) (18). Chalil et al measured LV dyssynchrony with a cardiovascular magnetic resonance tissue synchronization index (CMR-TSI), in relation to QRS duration in 66 HF patients and 20 age matched controls, CMR-TSI was higher in patients with HF and a QRS < 120 ms (79.5 [31.2ms], $p=0.0003$) and those with a QRS ≥ 120 ms (105.9 [55.8] ms, $p<0.0001$) than in controls (21.2 [8.1] ms). At the same study, CMR-TSI was assessed in relation to death or unplanted hospitalization in 77 patients with HF and a QRS ≥ 120 ms undergoing CRT. Over a mean follow up of 763 days, at a cut-off of CMR-TSI ≥ 110 ms predicted cardiovascular death with a sensitivity of 93% and a specificity of 67% ($p<0.0001$). Myocardiol dyssnchrony assessed by CMR-TSI is a powerful independent predictor of mortality and morbidity following CRT (19)

Auricchio et al. demonstrated that only the wide QRS duration patients (>150 ms) showed significant improvements in peak oxygen consumption , oxygen consumption at anaerobic threshold, distance walked in 6 minutes, and quality of life scores after 3 months of biventricular pacing, whereas the narrow QRS group did not have any improvements in those endpoints (20). Beshai et al (21) recent reported a multicenter study that in the CRT group, a QRS ≥ 120 ms in 17 patients and a QRS < 120 ms in 59 patients. In control group, a QRS ≥ 120 ms in 25 patients and a QRS < 120 ms in 55 patients, CRT did not improve peak oxygen consumption ($p=0.45$) at 6 months in patients

with moderate-to-severe HF and narrow QRS (< 120 ms) intervals, but a significant improvements in patient with QRS ≥ 120 (p=0.02). Patients with advanced HF and a wide QRS complex routinely with CRT have a favorable long-term outcome (22). A study from The Cleveland Clinic showed same results that no any significant clinical benefit of CRT in 29 patients with a QRS ≤ 150 ms (23). In a QRS duration to predict response to CRT study (24), 61 heart failure patients with QRS > 120 ms with LBBB. After 6 months of CRT, 45 (74%) patients were responders and 16 (26%) nonresponders. A significant decreased QRS duration was observed (from 179 ± 30 ms to 159 ± 25 ms) in the responders and no reduction in the nonresponders (171 ± 32 ms at baseline versus 168 ± 19 ms, NS). There was no significant difference in QRS duration at baseline between the responders and nonresponders (179 ± 30 ms vs 171 ± 32 ms, NS). Alonso et al. had similar results (25); the wide QRS duration patients (>150 ms) showed significant improvements after initiation of CRT, and this reduction in QRS duration was maintained at 6 months follow-up in responders but not in nonresponders. However, in a 38 patients with dilated cardiomyopathy study, they were divided into two groups based on QRS > 120 ms or ≤120 ms, all patients had significant improvements after CRT, including NYHA class, 6 minutes walking distance, and indices of left ventricular modeling (26). There may have different results in patients with narrow (QRS< 120 ms) duration between singecenter and multicenter studies.

According most of studies, patients with LBBB and wide QRS duration are good candidates for CRT, even though there were about 25 % of patients may be failed to get improvement.

How importance is the site of left ventricular lead?

CRT by placement of LV pacing lead resynchronizes the electromechanical activation sequence of the LV. Precise placement of LV lead at the targeted free wall region appears to be important for maximal benefit of CRT. An acute study, stimulated at multiple left ventricular sites with temporary transvenous pacing leads positioned via the coronary sinus showed significant differences in the percent increase in pulse pressure and left ventricular

+ dP/dt for different sites. The LV lead at the mid-lateral region compared with other sites resulted in the largest gain in hemodynamic status including max % of pulse pressure change (23%) and +dp/dt (34%)(27).

A study including sixty-one patients were evaluated by echocardiography before and 4 ± 2 months after CRT and grouped by the LV lead placement: lateral 33 (54%), posterolateral 15 (25%), or anterolateral 13(21%). Lateral LV lead placement was associated with significantly smaller LV volumes compared with the posterolateral lead placement ($p < 0.01$). Diastolic dyssynchrony improved with lateral lead placement compared with anterolateral lead site ($p<0.05$), resulted in greater reverse LV remodeling (28). A study used novel real-time three dimensional echocardiography technique to define sites of latest LV mechanical activation, 46 HF patients were divided into 2 groups according to concordance between the pacing sites to the sites of the latest mechanical activation: concordant (group 1, n=28) and discordant (group2, n=18), the site of latest activation was lateral in 14 (30%), postero-lateral in 14 (30%), and antero-lateral in 5(12%). The lead placement was lateral in 27 (59%), postero-lateral in 13 (27%), posterior in 3 (7%) and antero-lateral in 3 (7%). At 6 months after CRT, 30 patients had > 15% reduction in the LV end-systolic volume "responders", of which 19 (63%) were in group1. All of patients in Group1 had greater improvement in six-minutes walk distance (41% vs 25%), greater reduction in LV end-diastolic volume (29% vs 11%), end-systolic volume (39% vs 14%) and improvement in LVEF (60% vs 33%) than group 2 (all $p<0.01$).(29).

Some studies have reported conflicting results in the effects of LV lead site on hemodynamics and clinical outcomes after CRT. In a 233 patients with ischemic and dilated cardiomyopathy heart failure study (30), 167 patients implanted LV leads in the lateral and posterolateral branches of coronary vein as group1, another 66 patients in the anterior and anterolateral branches, as group 2. After a mean follow up of 546 days, functional capacity improved from an average of NYHA 3.1 to 2.3 in group1 ($p<0.01$), and 3.1 to 2.7 in group 2, ($p<0.01$), LVEF increased from 19±8% to 27±16% in group 1 ($p=0.008$), but no more improve in group 2 (18±8% to 20±10%, p NS). This improvement does not appear to influence mortality, there were 30 deaths in group 1

(17.9%) and 9 in group 2 (13.6%) (p=NS) (30). An another report, a total of 38 patients with ischemic cardiomyopathy study concluded LV lead proximity to an akinetic segment do not impact acute hemodynamic or 12 month clinical response to CRT (31). Murph RT et al. studied the relation between LV lead position and the area of maximal delay to peak velocity by tissue synchronization imaging in 54 patients with advanced heart failure, and found pacing at the site of maximal mechanical delay was associated with reverse remodeling, but delay in peak myocardial velocity in the anteroseptal area is associated with a failure to respond to CRT (32).

Dekker et al. studied 11 patients who failed the initial attempt at coronary sinus LV lead placement and underwent surgical lead implantation. Acute hemodynamic measurements were obtained intraoperatively at multiple LV pacing sites. The study indicated that to optimize cardiac resynchronization therapy with epicardial leads, mapping to determine the best pace site is a prerequisite, but the best hemodynamic region was varied among patients (33).

The best LV lead site for CRT is usually the lateral wall but may vary among the patients with heart failure. The LV lead location and the effects on ventricular dyssynchrony have not been extensively studied and may be of importance to provide additional insights regarding the response in LVEF and LV remodeling after CRT.

Does myocardial scar tissue affect response to CRT in patients with ischemic cardiomyopathy (ICM)?

The success of CRT requires local electrical capture with relatively rapid and homogeneous impulse transmission and excitation-contraction coupling. Placement of a pacing lead through the coronary vein at or near the location of myocardial scar may limit efficacy of CRT. In a 40 patient CRT study including 14 (35%) with a transmural posterolateral scar and 26 (65%) without scar tissue, 21 patients (81%) of the entire group

were clinical responders, but there were significant differences between those with and without large scars. LVEF improved significantly (from24±7% to 32±10%; $p<0.05$). In the patients with posterolateral transmural scar group, only 2 cases were responders at the 6-month follow-up ($p<0.05$ versus patients without scar tissue) (34). Another study indicated that only patients with severe baseline LV dyssynchrony and without scar tissue (n=22) had an excellent response rate (95%), a significant reduction in LV dyssynchrony (from 105±31 to 30±28 ms; $p<0.05$) and an excellent improvement in both clinic and echocardiographic parameters at the 6-month flower-up. Patients with severe baseline LV dyssynchrony and a posterolateral transmural scar tissue (n=11) had a response rate of 18% (35).

In a recent gadolinium enhancement cardiovascular magnetic resonance (RGE-CMR) study (36), including 62 patients with HF due to coronary heart disease, scar volume is expressed as a % of left ventricular myocardial volume. Patients were followed up for 741(75-1602) days. 33 patients demonstrated the present of a posterolateral scar, and responder rate of 47%, whereas 100% of patients without transmural posterolateral scar were responders ($p<0.001$). 14/33 (42%) patients with a posterolateral scar died, compared to only 2/29 (7%) in non-scar group ($p<0.0014$). In patients with a posterolateral scar, pacing over non-scar left ventricular free wall was associated with a lower mortality and morbidity (all $p<0.05$) and with a better response to CRT (responder rate: 94% vs 56%, $p=0.0112$) than pacing over the scar. Adelstein et al. (37) used 201 TI obtained rest and redistribution images and 99m Tc sestamibi as the radioisotope obtained stress images, and using a 17 –segment polar map scoring system (38). Scar was defined as all segments with abnormal uptake after redistribution or abnormal uptake at rest (0=normal, 1= possibly abnormal, 2 = mildly abnormal, 3 = moderately abnormal or 4 = without uptake radiotracer). The total score of scarred segments was called the summed perfusion score, yielding a number between 0 (i.e, no scar) and 68 (i.e, 17 segments × maximum score of 4). The mean perfusion score was significantly lower (18.8 ± 11.3 vs 33.7 ± 11.1; $p = .00003$) in responders versus nonresponders. Despite similar baseline values, the post-CRT LV end-diastolic diameter (5.71 ± 0.98 vs 6.55 ± 0.79 cm; $p =0.003$) and LV end-systolic diameter (4.68 ± 1.01 vs 5.74 ± 1.02 cm; p =

0.001) were significantly smaller in responders compared with nonresponders. There was a significant correction between transmural scar and a lack of response to CRT and a negative impact upon CRT response rates as the proportion of overall scar rises and as dense scar becomes more anatomically extensive.(38).

CRT may be inefficacious once a threshold of global scar, particularly transmural scar, is crossed in patients with prior myocardial infarction. In addition, in those patients referred for CRT, sites with significant scar burden should be avoided as a final resting location for LV lead placement to gain the maximum of benefits. It is still unclear whether underling dyssynchrony may be ameliorated when there is significant scar tissue at or near the site of maximum dyssynchrony. Auricchio et al. studied LV activation sequences in 24 patients with HF and LBBB QRS morphology using 3D contact and noncontact mapping during intrinsic rhythm and asynchronous pacing. About 1/3 patients with LBBB QRS morphology had normal transseptal activation time and a slightly prolonged or near normal LV endocardial activation time. A "U-shaped" activation wave front was present in 23 patients because of a line of block that was located anteriorly (n=12), laterally (n=8) and inferiorly (n=3). Patients with a lateral line of block had significantly shorter QRS ($p<0.003$), transseptal durations ($p<0.001$) and a longer distance from the left breakthrough site to line of block ($p<0.03$). Two thirds of the patients with idiopathic cardiomyopathy, thus lacking the presence of ischemic myocardial scar associated with morphology based conduction delay and block, and presented the same patterns as patients with coronary artery disease. (39). In patients with ischaemic cardiomyopathy, a higher number of viable segments at baseline was associated with a higher probability of response, a higher total scar score was associated with a lower probability of response. In an included 51 patients with ischaemic heart failure study, all patients underwent gated SPEC before CRT implantation to determine the extent of scar tissue and viable myocardium. Clinical and echocardiographic parameters were assessed at baseline and after 6 month of CRT. The results demonstrated that the responses were directly related to CRT and the extent of viable myocardium and scar tissue (40)

The LV pacing lead in the transmural scar tissue area may prohibit response. Both LV dyssynchrony and the extent of scar tissue are of value in the prediction of response to CRT.

Is the optimization of the AV interval crucial to obtain the best CRT results?

Correct programming of a CRT device can maintain biventricular pacing all the times. The atrial ventricular (AV) delay is optimized to maximize left atrial contribution to left ventricular filling. This requires an optimal AV interval to prevent a period of diastasis of the mitral valve with resultant mitral regurgitation but not as short as to truncate left atrial contribution to ventricular filling (41). Methods for optimizing the AV delay in CRT patients were adopted from those developed for dual-chamber pacemaker (42). A major component of the AV delay is the time required for interatrial conduction time (IACT) from the RA to LA. Some simplified methods for AV optimization of CRT devices based on derived formulas (43, 44, 45), but most formulas still require the use of transmitral Doppler echo to determine the LA electromechanical delay (44). A recent study that the only requirements were implantation of the RA lead prior to coronary sinus lead implantation and use of a simple non-deflectable quardipolar EP catheter in the distal coronary sinus, demonstrated the paced IACT has a strong correction with the echo derived optimal paced delay (46). They demonstrated that even the LV pacing lead alone could hypothetically be used as it is being guided through the inferiolateral coronary sinus and this measurement could be performed without need for an EP recording system by connecting the outputs from the EP catheter to the pacing analyzer's input during RA pacing (46). The association of the IACT with the paced AV delay seems to be a reasonable way to program the paced AV delay in an attempt to reduce the numbers of nonresponders after CRT (47). AV and VV delay were measured by Acoustic cardiography based on third heart sound (S3), electromechanical activation time and LV systolic time, the AV delay setting that produces the lowest S3 value along with the shortest electromechanical activation time and longest systolic time. The AV delay in 22 patients with implanted CRT devices was independently optimized using echo (Doppler transmitral flow) and acoustic cardiography were compared, the mean value for

echocardiography-based recommendation was 168±53 ms and for the acoustic cardiography-based was 175± 50 ms, which is not significantly different. The correlation coefficient is r=0.90 ($p<0.001$)(48). In 1990, Hochleitner first reported improvement in cardiac function in 16 patients with idiopathic dilated cardiomyopathy treated with dual-chamber pacemakers programmed with AV delay of 100 ms (49). Some studies with echo after CRT have noted that 40% of patients undergoing optimal AV delay assessment have final programmed AV intervals of > 140 ms (50). A randomized prospective trial, echocardiography-guided AV delay optimization using the aortic Doppler VTI improves clinical outcomes at 3 months compared to an empiric AV delay program of 120 ms. This study indicated that the optimal AV delay varied widely from patients to patients. Immediately after CRT initiation with AV delay programming, VTI improved by 4.0 ± 1.7 cm vs 1.8 ± 3.6 cm (P <0.02), and ejection fraction (EF) increased by 7.8 ± 6.2% vs 3.4 ± 4.4% (P <0.02) in optimal AV delay group vs empiric AV delay group, respectively. After 3 months, NYHA classification improved by 1.0 ± 0.5 vs 0.4 ± 0.6 class points (P < 0.01), and QOL score improved by 23 ± 13 versus 13 ± 11 points (P < 0.03) for optimal AV delay group vs empiric AV delay group, respectively (51).

After implant bi-pacing leads, to adjust and get optimal AV delay time for each patient is very important for getting best benefit from CRT.

What about V-V timing and its role in ventricular performance?

As known, about 30 % of patients implanted with CRT devices do not realize any benefit from therapy. These so-called “nonresponders” are the focus of new technologies that aim to optimize the therapy to each individual patient. One of the ways may be accomplished by adjustment of the ventricle to ventricle (V-V) or atria to ventricle (A-V) timing delays programmed into devices in order to optimize ventricular function. There are studies suggest that optimal both A-V and V-V interval improves response rates and cardiac function, as well as New York Heart Association (NYHA) class and 6 minutes walking distance. About A-V delay has been discussed above, the studies related to V-V delay are limited. An observational study including 20 patients, using tissue tracking and

3-dimensional echocardiography to optimize individual programming of the interventricular (V-V) delay, the optimum sequential CRT immediately increased LVEF from 22.4±6% to 29.7±5% ($p<0.01$), on 3 months after CRT further improved LVEF from 33.6±6% to 38.6± 7.2%, $p<0.01$), suggested that sequential biventricular stimulation significantly improves long-term LV function when compared with simultaneous CRT (52). However, a single blind randomized trial, including 121 recipients of a device for CRT with cardioverter/defibrillator capabilities (CRT-D) randomly assigned in a 1:3 ratio to simultaneous (n = 30) versus optimized (OPT) (n = 91) biventricular pacing. V-V delay was optimized by echocardiography. The optimization of the V-V delay conferred no additional benefit compared with simultaneous biventricular stimulation after 6 month (53). The benefits of optimal V-V delay in CRT are not clear and need more studies.

Most methods are echo–based for A-V and V-V optimization. These include tissue Doppler imaging, aortic valve velocity time integral optimization and M-mode echocardiography with septal or posterior wall times. These methods are timing consumer, in some cases may take 1-2 hours, which are not easy in practice. Efforts to facilitate time optimization have yield new technologies, such as intracardiac electrogram (54). This technique offers physicians the option of automatic programming. After all the timing cycles are measured and the mathematical calculation is completed, the program displays the optimal numbers for A-V and V- V delay. This is done via an automatic algorithm. The technology takes little time to perform (about 1-2 minutes), and it can be done easily and reproducibly at the bedside or in the office (55).

Some implantable sensor technologies under development that may be able to continuously assess and automatically reoptimize the V–V timing. All of new techniques are needed to be valid in clinic trial.

The heart rate is changing during daily life, the optimal V-V and A-V delays should be change with activity, therefore a technology that allows V-V and A-V delays change with heart rate may certainly be beneficial.

May assessment of baseline mitral regurgitation help predict responsiveness to CRT?

Functional mitral regurgitation in dilated cardiomyopathy results from an imbalance between the closing and the tethering forces that act on the mitral valve leaflets (56). LV dyssynchrony including the posterior mitral leaflet is an important determinant of the MR in CRT, the study showed that the baseline presence of severe (regurgitant orifice area (ROA) $\geq$0.20 cm^2**)** mitral regurgitation was associated with a lack of response in reverse remodelling (defined as reduction $\geq$10% in LVESV) after biventricular pacing. Those patients who had no, or just mild mitral regurgitation responded significantly to CRT (57). The study evaluated the effect of reverse remodelling in 20 patients with dilated cardiomyopathy before and 6 months after undergoing CRT according to the presence or absence of severe FMR. Of the 20 patients, 9 had marked mitral regurgitation (ROA 0.40 $\pm$ 0.12 cm^2), 6 mild (ROA 0.15 $\pm$ 0.02 cm^2), and 5 had trivial or no mitral regurgitation. CRT reduced the presence of mitral regurgitation by 33.3% and induced reverse remodelling in 60% of the patients. The presence of a ROA <0.20 cm^2 prior to implantation was associated with a significant reduction in LVESV (–41.7 $\pm$ 21%, $P <$ 0.0001). This association remained if reverse remodelling after CRT was considered to be a reduction of at least 10% in LVESV (100% of the patients, $P < 0.001$). Using this cut-off point, the presence of a ROA $\geq$ 0.20 cm^2 in this study was associated with 100% sensitivity and 90% specificity for the prediction of lack of reverse remodeling (57). In a study included 143 patients, at the 6 month of follow up, 94 of 115 (85%) responded patients were ROA < 0.20 cm^2. Patients with severe mitral regurgitation at baseline had less chance of improving with CRT. Furthermore, responders had a shorter LV end-diastolic diameter than nonresponders. Both parameters may be markers of more advanced cardiac disease and poorer prognosis (58). A multicenters study reported that independent predictors of lack of response to CRT were IHD (OR =2.9, 95% CI 1.2-7; p=0.023), severe MR (jet area > 40%) (OR=3.5, 95%CI 1.3-9; p = 0.014) and LVEDD $\geq$ 75mm (OR =3.1, 95%CI 1.1-8, p=0.026) (59). In the MIRACLE multicenter trial (6), severity of MR decreased significantly at 3 months (-2.1 cm^2 vs 0.1 cm^2 jet area; p<0.01)

and at 6 months (-2.5 cm^2 vs 0.5 cm^2 jet area; $p<0.001$) in CRT-ON group (172 patients) and no changes in MR in the control group (151 CRT-OFF patients). The changes in NYHA class, in QOLS were associated with changes in MR and interventricular mechanical delay. An acute effects study (58) indicated that CRT was associated with a significant reduction in mitral regurgitation severity. Effective ROA decreased from 25 ± 19 mm^2 (OFF) to 13 ± 8 mm^2 (CRT) ($p<0.01$). The change in EROA was directly related to the increase in LVSP (LV+dP/dt max) ($r=-0.83$, $p<0.0001$). During CRT, transmitral pressure gradients (TMP) increased more rapidly and a higher maximal TMP was observed (73± 24 mm Hg (OFF) vs 85± 26 mm Hg(CRT) $p<0.01$)(60). It appears that an increase in TMP, mediated by a rise in LV+dP/dt max due to more coordinated LV contraction, may facilitate effective mitral valve closure. Reduction in exercise-induced MR and LV dyssynchrony in parallel to reverse LV remodelling translates into improved LV function and cardiopulmonary performance (61).

FMR is characteristically dynamic during exercise. The magnitude of exercise-induced changes in MR severity was not related to the degree of MR at rest (62). The increase in MR severity during exercise identified a subgroup of patients at high risk of cardiac events (63). The effects of CRT on both dynamic MR and LV dyssynchrony differ in the early and late stage of pacing. In the early stage (1 week after pacing), exercise-induced LV dyssynchrony persists with no significant reduction in dynamic MR, but in the 3 months late, a progressive reduction in resting MR and in LV volumes occurred without additional improvement in LV synchronicity at rest. Synchronicity was maintained during exercise, the magnitude of exercise-induced MR was significantly attenuated. The exercise capacity improved more in patients with smaller changes in MR severity during exercise (63,64). Therefore, both baseline MR and the magnitude of changes of MR by exercise played a role in response to CRT. Assessment of baseline MR and LV dyssynchrony may help predict responsiveness to CRT.

Factors Influencing Cardiac Resynchronization Therapy Summarized from References are Shown in table 1 and Predictors of Failure to Response to CRT are Shown in table 2.

Conclusions

It has been demonstrated that cardiac resynchronization therapy (CRT) improves clinical status, cardiac functions, quality of life, exercise capacity and prognosis of patients with drug-refractory heart failure. However, 20% to 30% cases still classified as nonresponders right now. Recent studies indicated that the patients with dilated cardiomyopathy, QRS duration > 150 ms, severe cardiac dysfunction (NYHA functional class III-IV), maximum myocardial dyssynchrony, implantation of left ventricular lead in mid- lateral wall region, optimizing AV and V-V delay as well as no or smaller resting mitral regurgitation (regurgitant orifice area (ROA) < 0.20 cm^2) would have better benefits. However, the maximal benefit of CRT is varies severely from patient to patient, a number of questions in the CRT community should be investigated in future trials.

Table 1. Factors Influencing Cardiac Resynchronization Therapy Summarized from References

Authors (year)	Patient no	Follow-up	Conditions	Responders
Molhoek SG (2004)	40	6-month	IDC	65%
Bleeker GB (2006)	40	6-month	IC without scar tissue	81%
Chalil S (2007)	29	Mean 741 days	IC without scar tissue	100%
Haghjoo M (2007)	56		QRS (ms) < 120	36%
Haghjoo M (2007)	33		QRS (ms) 120-150	58%
Haghjoo M (2007)	34		QRS (ms) > 150	79%
Rossillo A (2004)	167	Mean 546 days	LV Lead in the lateral and	Significant improvement in

			posterolateral area	cardiac function
Burkhardt JD (2007)	53	6 month	Simultaneous BiV pacing	Maximum dP/dt increase 18%, LVFT(ms)=404±102. VTI (mm)=122±31
Burkhardt JD (2007)	53	6 month	Optimized V-V BiV pacing	Maximum dP/dt increase 26%, LVFT(ms)=472±110. VTI (mm)=154±42
Diaz-Infante E (2005)	115	6 month	MR (ROA cm^2< 0.20)	85%

IDC= Idiopathic dilated cardiomyopathy; IC= Ischemic cardiomyopathy;
LV= Left ventricular; BiV= Biventricular; MR= Mitral regurgitation; ROA= Regurgitant orifice area;
LVFT= Left ventricular filling time; VTI= velocity time integral.

Table 2. Predictor of Non-response to CRT

Authors (year)	Patient no	Follow-up	Predictors	Nonresponders
Bleeker GB (2006)	40	6-month	IC with scar tissue	85.7%
Rossillo A (2004)	66	mean 546 days	Lead in the anterior and antero-lateral area	No significant improvement in cardiac function
Dekker AL (2004)	11		Lead in the mid-posterior area	Poor response.
Cbrera-Bueno F (2007)	20	6 month	MR (ROA cm^2>0.20)	Sensitivity100%, Specificity 90%

IC= Ischemic cardiomyopathy; MR= Mitral regurgitation; ROA= Regurgitant orifice area.

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