

An Overview of Current Cardiac Resynchronization Therapy

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Cardiac resynchronization therapy (CRT) is currently an established device therapy for heart failure (HF) patients. Existing knowledge of implantation techniques, advances in device-based technologies and clinical trial experience have all significantly impacted this evolving therapy in recent years. This review article will address the updated CRT guidelines, and potentially new indications for CRT such as patients with mild HF symptoms and prolonged QRS duration; it also highlights new approaches for placement of the left ventricular (LV) lead, multi-site LV pacing, and the role of automatic device optimization in CRT.

Key Words: Cardiac resynchronization therapy • Guideline • Heart failure • Optimization

INTRODUCTION

Cardiac resynchronization therapy (CRT) has become an effective treatment modality in patients with drug-refractory advanced congestive heart failure (HF).¹ CRT is indicated for patients with severe left ventricular (LV) systolic dysfunction, medically-refractory HF symptoms and intraventricular conduction delay.^{1,2} In HF patients, CRT with Comparison of Medical Therapy, Pacing and Defibrillation in Chronic Heart Failure (COMPANION)³ or Cardiac Resynchronization-Heart Failure (CARE-HF)⁴ without an implantable cardiac defibrillator (ICD) all reduce HF hospitalizations and prolong survival compared to optimal medical therapy alone. Moreover, CRT

improves patient symptoms and enhances quality of life, increases exercise tolerance, and reduces LV dilatation.^{5,6}

Recent studies also suggest that CRT results in decreased neurohormonal and proinflammatory biomarkers.⁷ Additionally, the positive impact of markers on matrix remodeling may be associated with LV reverse remodeling that occurs with CRT.⁷ This review article will address the updated CRT guideline for patient selection, new approaches for placement of the left ventricular (LV) lead, multisite LV pacing, and the role of automatic optimization by the device.

PATIENT SELECTION FOR CRT

Improved cardiac mechanical synchrony, especially within the LV, is thought to be a key element of the overall benefit derived from CRT.⁷ The ability of any single echocardiographic dyssynchrony assessment to predict benefit from CRT remains unproven.⁸ Presently, there is a greater reliance on the use of QRS duration and morphology as substitutes for mechanical dyssynchrony. There have been multiple studies, including the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT)⁹ and the Resynchronization in Ambulatory Heart Failure Trial

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(RAFT),¹⁰ which found that QRS morphology and QRS duration appear to be useful in predicting benefit from CRT. QRS duration is correlated with mechanical dyssynchrony, and CRT has been shown efficacious only in patients with prolonged QRS durations.¹¹ Markedly prolonged QRS durations are associated with greater benefit from CRT than those shorter durations. In patients with mild HF symptoms, both the MADIT-CRT⁹ and Resynchronization Reverses Remodeling in Systolic Left Ventricular dysfunction (REVERSE)¹² studies demonstrated an apparently reduced HF morbidity with CRT, and it should be noted that the patient population in both studies were largely New York Heart Association functional class (NYHA Fc) II patients. NYHA Fc I patients accounted for 18% of the REVERSE population and 15% of the MADIT-CRT population. No definite outcome advantages in NYHA Fc I patients were appreciated in these trials.

GUIDELINES OF CRT IN 2012¹

The most extensive experience with resynchronization derives from patients with NYHA Fc III symptoms of HF and LVEF ≤ 35%. Patients with NYHA Fc IV symptoms of HF have accounted for only 10% of all patients in clinical trials of resynchronization therapy.¹³ Although there were some patients with more severe acute decompensation benefits from resynchronization therapy in the case report, CRT is not used as a “rescue therapy” for such patients. However, patients with ambulatory NYHA Fc IV symptoms who derive functional benefit from CRT may return to a better functional status and a reduced chance of sudden cardiac death.

The clinical effects of long-term CRT have been evaluated in a large number of randomized multi-center trials with crossover or parallel treatment assignment,^{4-6,14-18} using CRT pacemakers (CRT-P) or CRT-implantable cardioverter defibrillator (ICD) devices (CRT-D).

The 2012 DBT (device-based therapy) Focused Update Recommendations proposes several changes in recommendations for CRT, compared with the 2008 document.¹ They are summarized in Figure 1.

Class I

CRT is indicated for patients who have LVEF ≤

35%, sinus rhythm, left bundle branch block (LBBB) with a QRS duration ≥ 150 ms, and NYHA Fc II, III, or ambulatory Fc IV symptoms on guideline-directed medical therapy (GDMT). (Level of Evidence: A for NYHA Fc III-IV;^{4,10,19} Level of Evidence: B for NYHA Fc II^{9,10})

Class IIa

1. CRT can be useful for patients who have LVEF ≤ 35%, sinus rhythm, LBBB with a QRS duration 120 to 149 ms, and NYHA Fc II, III, or ambulatory Fc IV symptoms on GDMT.^{4,10,14} (Level of Evidence: B)
2. CRT can be useful for patients who have LVEF ≤ 35%, sinus rhythm, a non-LBBB pattern with a QRS duration ≥ 150 ms, and NYHA Fc III/ambulatory Fc IV symptoms on GDMT.^{10,14} (Level of Evidence: A)
3. CRT can be useful in patients with atrial fibrillation and LVEF ≤ 35% on GDMT if: (a) The patient requires ventricular pacing or otherwise meets CRT criteria and (b) AV nodal ablation or pharmacologic rate control will allow near 100% ventricular pacing with CRT.^{20,21} (Level of Evidence: B)
4. CRT can be useful for patients on GDMT who have LVEF ≤ 35% and are undergoing new or replacement device placement with anticipated requirement for significant (> 40%) ventricular pacing.^{22,23} (Level of Evidence: C)

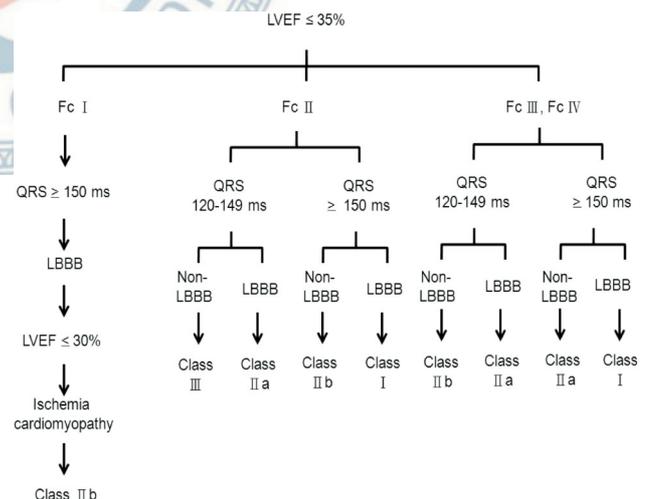


Figure 1. The algorithm of summary of 2012 AHA/ACC/HRS CRT indications. AHA, American Heart Association; ACC, American College of Cardiology; CRT, Cardiac Resynchronization Therapy; Fc, function class; HRS, Heart Rhythm Society; LBBB, complete left bundle branch block; LVEF, Left ventricular ejection fraction.

Class IIb

1. CRT may be considered for patients who have LVEF \leq 30%, ischemic etiology of heart failure, sinus rhythm, LBBB with a QRS duration \geq 150 ms, and NYHA Fc I symptoms on GDMT.^{9,10} (Level of Evidence: C)
2. CRT may be considered for patients who have LVEF \leq 35%, sinus rhythm, a non-LBBB pattern with QRS duration 120 to 149 ms, and NYHA Fc III/ambulatory Fc IV on GDMT.^{10,24} (Level of Evidence: B)
3. CRT may be considered for patients who have LVEF \leq 35%, sinus rhythm, a non-LBBB pattern with a QRS duration \geq 150 ms, and NYHA Fc II symptoms on GDMT.^{9,10} (Level of Evidence: B)

Class III: No benefit

1. CRT is not recommended for patients with NYHA Fc I or II symptoms and non-LBBB pattern with QRS duration $<$ 150 ms.^{9,10} (Level of Evidence: B)
2. CRT is not indicated for patients whose comorbidities limit survival with good functional capacity to less than 1 year.¹ (Level of Evidence: C)

The most significant changes in the present document compared to the 2008 DBT Guideline are the expansion of the Class I recommendation for CRT to include patients with LBBB, QRS duration \geq 150 ms, and NYHA Fc II and the addition of a Class IIb recommendation for patients with LVEF \leq 30%, ischemic etiology of HF, sinus rhythm, LBBB with a QRS duration \geq 150 ms, and NYHA Fc I symptoms. These recommendations are based on 4 studies in which CRT was evaluated in patients with minimal or mild symptoms of HF in the setting of low LVEF. These include MADIT-CRT,⁹ RAFT,¹⁰ REVERSE,¹² and MIRACLE ICD II.¹⁷

For mortality rate, the trials showing benefit in NYHA Fc III and IV patients typically included those with LVEF \leq 35%. For patients with NYHA Fc II, trials showing mortality rate benefit included those with LVEF \leq 30%. A mortality rate benefit with CRT has not been shown for patients who are NYHA Fc I.^{9,12}

In terms of demonstrating improvement in cardiac function (e.g., significant reduction in LV size and improvement in ejection fraction), trials have included patients with LVEF \leq 35% who are NYHA Fc III and IV. For patients with LVEF \leq 40%, trials demonstrating improvement in heart function have included those who are NYHA Fc I and II.^{9,17,25}

ISSUES IN THE IMPLANTATION

CRT requires LV lead placement in left heart through coronary sinus (CS) in the treatment of medically refractory HF. LV lead placement is technically difficult with successful rates reported between 53% to 98% and implantation time ranging from 90 minutes to 5 hours.^{26,27} The anatomic variability of the cardiac veins limits the feasibility of LV lead placement. The engagement of the CS ostium played an important role for CS venography and LV lead placement. Before CS venography was performed, it was important to locate the CS ostium. Left anterior oblique (LAO) view would provide the information of CS anatomy. However, the fluoroscopic tube may interfere with the operators at the left side while performing LAO view over 40°. We analyzed a novel procedure using a single plane, LAO 20° and caudal 20° with RV lead inserted first, which could lay out the tricuspid annulus (TA) and help to find the CS ostia (Figure 2). After engagement of CS by the EP catheters, local electrograms would be analyzed to find their characteristics (Figure 3).²⁸

Guided by RV lead curve

According to the CS venography, most of the CS ostia were closely below the TA which could be laid out by the bulge of RV lead curve (62/70, 89%). But the CS ostia were located above the TA in some cases (8/70, 11%) with larger LV size. The CS ostia could be primarily predictable by the TA guide upon the RV lead. The distribution of CS ostia in the study could be circled within a radius of 3.75 cm, with the tip of TV bulge as the center point (Figure 2).²⁸

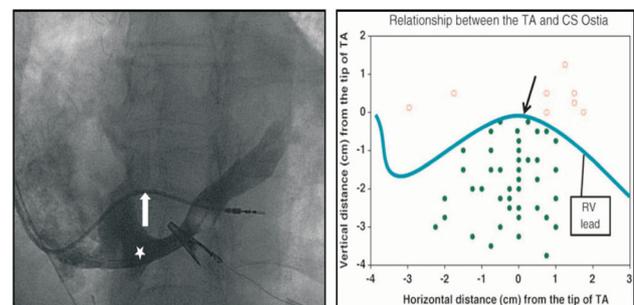


Figure 2. Left panel showed the CS (coronary sinus) ostium (white star) below the tricuspid annulus (TA) (white arrow) shaped by the RV lead. Right panel showed the distribution of the CS ostium by scatter plots. The scatter plots include 62 patients (blue dots) with CS ostia under the TA and 8 patients (red dots) with CS ostia over the TA.

Roles of local electrograms of CS by the EP catheter

The local electrograms of CS could provide good information to confirm if the catheter is in the CS or RV. Only ventricular signals would be found if the catheters were in the RV. As the catheter enters the CS, both atrial and ventricular signals typically would be found during sinus rhythm or atrial fibrillation (Figure 3).

THE OPTIMAL LV& RV PACING SITE

The proximity of the LV pacing site to the region of latest activation in the LV may be essential to the patient benefit derived from CRT.²⁹ A detailed analysis of lead position and outcome among 799 patients in MADIT-CRT⁹ found similar outcomes in patients with anterior, lateral, or posterior LV lead positions. However, an apical LV lead location was independently associated with a 1.7-fold higher risk of heart failure or death compared to a non-apical pacing site ($p = 0.02$). Furthermore, placing an LV lead in an area free of significant scar is mandatory.³⁰ Non-apical RV pacing site showed greater improvement in LVEF compared with apical RV pacing site.³¹ In particular, RV septal pacing compared to apical pacing resulted in a shorter electrical activation delay and consequently less-mechanical dyssynchrony.³¹ The use of an optimal LV site becomes a critical issue when

branches of cardiac vein are inaccessible. There has been interest in LV endocardial pacing as a method which is theoretically advantageous to CS epicardial lead positioning for CRT.³² However, preliminary concerns were raised about the potential for thromboembolic events in patients with hardware placed in the systemic circulation.

MULTISITE LEFT VENTRICULAR PACING

Currently, only one LV lead is implanted during CRT to achieve resynchronization of the ventricle(s). However, in HF patients with enlarged LV and prolonged ventricular conduction delay, multi-site pacing with a second LV lead placed in a location distant from the first may further shorten LV conduction time and therefore further reduce mechanical dyssynchrony.^{33,34} The potential superiority of placing two LV leads as opposed to a single LV lead was suggested by a study which was compared with a historical cohort of conventional CRT implantation. Another small randomized study compared the two pacing strategies in patients with atrial fibrillation. These two studies observed a greater improvement of LVEF for patients implanted with two LV leads.^{33,34} There are two ongoing randomized, single-center clinical trials that examined the role of dual-site LV leads when compared with a single LV lead. The two ongoing trials include “The Dual Site Left Ventricular

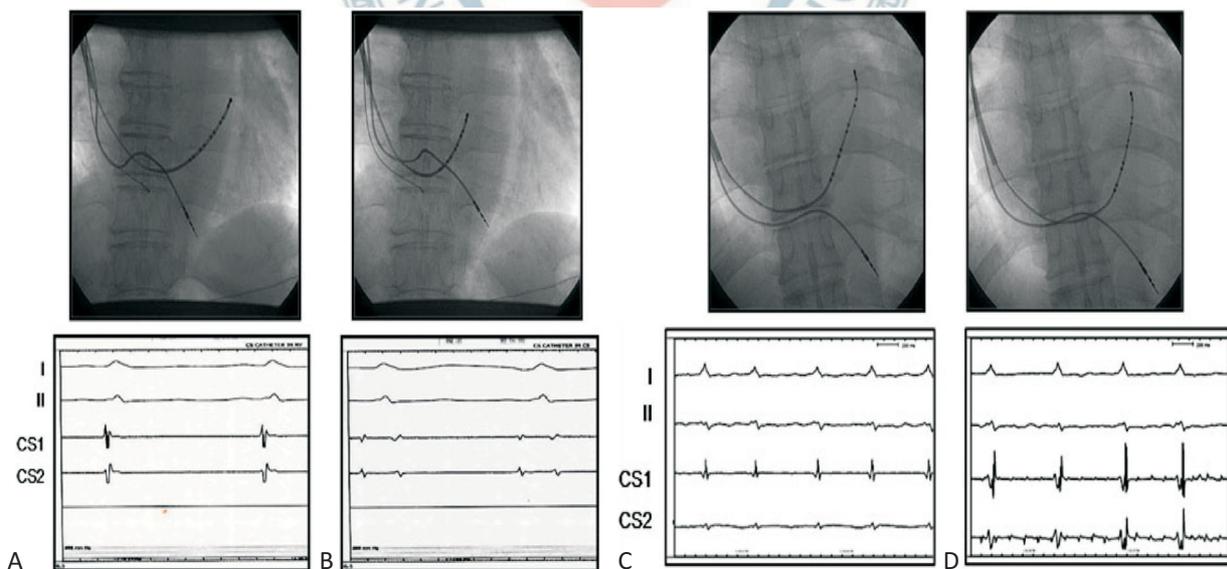


Figure 3. The relations between the position of CS (coronary sinus) catheter and local electrograms in the distal two bipolar electrodes (CS1, CS2). (A) CS catheter in right ventricular outflow tract (RVOT) with only right ventricular (RV) potential in the local electrograms. (B) CS catheter in the CS with both atrial and ventricular potentials. (C) CS catheter in RVOT showed only RV potential even under atrial fibrillation (AF). (D) CS catheter in CS with AF and ventricular potentials.

Pacing (DIVA) study” and the “Triple-Site Versus Standard Cardiac Resynchronization Therapy’ (TRUST-CRT) study”.

PHRENIC NERVE STIMULATION (PNS)

PNS prevalence ranges from 20 to 37% of patients when a posterolateral LV lead placement is utilized.^{35,36} False-negatives are common during implantation, when sensitivity is approximately 60-80%. Symptoms may dictate repositioning the LV lead, creating a risk of lead dislodgement, decreased CRT efficacy, or high LV threshold. CRT turn-off occurred in 2% of patients because of refractory PNS. Several strategies have been used to manage PNS: whereas lead repositioning was the only option available in the early CRT experience, the use of bipolar/multipolar leads combined with cathode programmability enabling several pacing configurations has made possible the targeting of optimal LV pacing sites in nearly all patients.^{37,38} Despite technological improvements, PNS is sporadically reported by 6-8% of patients at follow-up, suggesting that there is still an unmet need to address this problem.

OPTIMIZATION OF CRT

AV optimization

Achieving the optimal outcome from CRT may be dependent on proper programming of the appropriate atrioventricular delay (AVD). In fact, suboptimal AV delay programming may result in as much as a 10-15% decline in cardiac output. However, the large-scale randomized clinical trials to date establishing the overall efficacy of CRT have differed widely in their approach to AV optimization.^{39,40}

Ritter’s method was used in the MIRACLE (Multi-center InSync Randomized Clinical Evaluation) study, the iterative method was used in the CARE-HF study, and a device-based algorithm was used in the COMPANION study.^{39,40}

Currently available pacemakers offer programmable AVD, as well as rate-adaptive AVD programming and rate-response features. The most commonly utilized method for pacemaker optimization is echocar-

diographic Doppler assessment of LV diastolic filling and LV ejection. Several studies from single centers have shown improved cardiac output by tailored echo Doppler-guided CRT AVD optimization. One single, blind, randomized trial that investigated the impact of AVD optimization based on the aortic velocity time integral (VTI) showed improvement in NYHA Fc in optimized versus control patients.⁴⁰ Similar to AVD optimization, data from small, single-center studies demonstrated that sequential bi-ventricular pacing after AVD optimization may substantially further improve LV stroke volume.⁴¹

VV optimization

Optimization of the atrioventricular delay (AVD) and interventricular delay (VVD) may result in an improvement of cardiac functions after CRT.⁴² However, the internal survey by Gras et al. showed that at the time of CRT implant, nearly 58% of the investigators did not optimize the CRT devices.⁴³ The main reasons are that the traditional methods of optimization are time-consuming and costly. The intra-cardiac electrograms (IEGM)-based method⁴⁴ and surface ECG-guided method⁴² had been shown to produce hemodynamic performance similar to that obtained by echo-guided aortic VTI maximization. These two simple methods showed the same efficacy in the VVD optimization.⁴⁵

THE INTRACARDIAC ELECTROGRAM (IEGM) METHOD

The IEGM-based VVD algorithm is based on the hypothesis that at the optimal VVD, two paced depolarization wavefronts activated at the RV and LV leads will meet near the interventricular septum. The VVD algorithm has two components: the time of peak intrinsic activation on the LV lead (R_{LV}) and the RV lead (R_{RV}) [$\Delta = R_{LV} - R_{RV}$] [Figure 4(A)]. The correction term ε is the difference in the interventricular conduction delay (IVCD) between two ventricular paced propagation waveform time delays. $IVCD_{LR}$ is the interventricular conduction delay when the LV lead is paced and the delay is sensed at the RV lead [Figure 4(B)]. $IVCD_{RL}$ is the interventricular conduction delay when the RV lead is paced and the delay is sensed at the LV lead [Figure

4(C)]. Each chamber is paced with a short AVD to ensure no fusion occurs. The correction term equation is $\varepsilon = IVCD_{LR} - IVCD_{RL}$. The IEGM optimal VVD = $0.5(\Delta + \varepsilon)$ and if VVD > 0, the LV is activated first and if VVD < 0, the RV is activated first. The predicted optimal VVDs were linearly correlated with echocardiographic aortic VTI.⁴⁴

Surface ECG method

Time from the pacing spike to the beginning of the earliest fast deflection of the QRS complex in the precordial leads was measured, first stimulating the epicardial LV lateral wall (T1) and then during RV pacing (T2) [Figure 4(D, E)]. This measure was assumed as a surrogate marker of the time needed for the stimulus deployed from the cathode of each pacing lead to spread rapidly through the ventricular tissue. This time

may include the latency capture phenomenon of the ventricular myocardium (both healthy and diseased) and the propagation time to access the specific conduction system. In case of LV pacing, in which the lead was located in the epicardial position, the intramyocardial delay of conduction produces a slurred initial part of the QRS complex that is called pseudo-delta wave. Therefore, T1 was measured from the pacing spike to the end of the pseudo-delta wave [Figure 4(D)]. The difference between T1 and T2 was considered the time delay necessary to depolarize the LV simultaneously from the lateral wall and septum.⁴²

Optimization of the VVD may result in an improvement of cardiac functions after CRT. The IEGM-based method and surface ECG-guided method had been shown to produce hemodynamic performance similar to that obtained by echo-guided aortic VTI maximization.^{42,44}

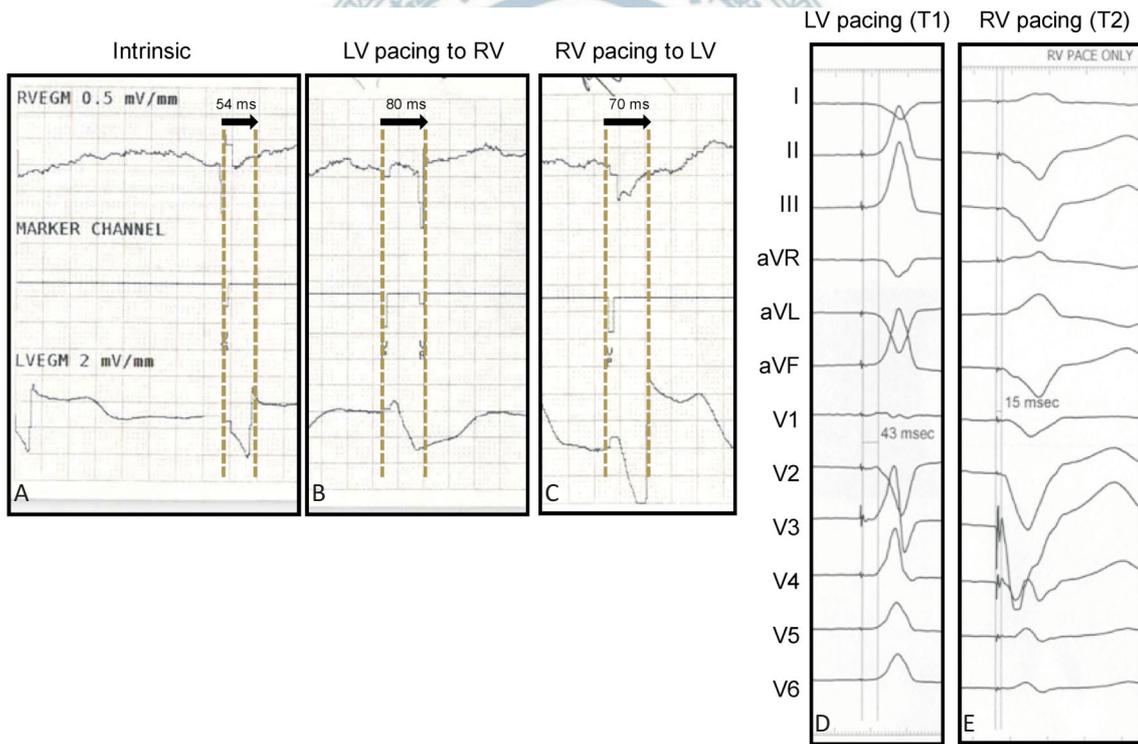


Figure 4. A CRT case received VV delay (VVD) optimization by either the intracardiac electrogram or surface ECG method. The IEGM-based VVD algorithm: the VVD algorithm has two components – the time of peak intrinsic activation on the LV lead (R_{LV}) and the RV lead (R_{RV}) [$\Delta = R_{LV} - R_{RV} = 54$ ms] (A). The correction term ε is the difference in the interventricular conduction delay (IVCD) between two ventricular paced propagation waveform time delays. $IVCD_{LR} = 80$ ms: the interventricular conduction delay when the LV lead is paced and the delay peak is sensed at the RV lead (B). $IVCD_{RL} = 70$ ms: the interventricular conduction delay when the RV lead is paced and the delay peak is sensed at the LV lead (C). The correction term equation is $\varepsilon = IVCD_{LR} - IVCD_{RL} = 10$ ms. The optimal VVD by the IEGM method = $0.5(\Delta + \varepsilon) = 0.5(54 + 10) = 32$ ms and the LV is activated first 32 ms. Surface ECG method: time from the pacing spike to the beginning of the earliest fast deflection of the QRS complex in the precordial leads was measured, first stimulating the epicardial LV lateral wall (T1 = 43 ms) (D) and then during RV pacing (T2 = 15 ms) (E). The difference between T1 and T2 was 28 ms and the LV is activated first at 28 ms.

AUTOMATIC OPTIMIZATION OF CRT BY DEVICE

It is time consuming to do CRT optimization by conventional echocardiography. Consequently, automatic CRT optimization has been developed to improve the clinical outcome. CRT with automatically optimized AV and VV delays, based on a Peak Endocardial Acceleration signal system, showed significant increase of one-year response rate (76% vs. 62% in the control group).³⁹ Some novel device algorithms showed promising results in comparison with conventional echocardiography. An algorithm employed in St. Jude Medical CRT devices (QuickOpt) claimed to optimize these settings automatically and showed superior haemodynamic outcome. For the clinical outcome, the Frequent Optimization Study Using the QuickOpt Method (FREEDOM) trial demonstrated that frequent optimization using QuickOpt did not significantly influence outcome as defined by the HF clinical composite score.⁴⁶ The SmartDelay determined AV optimization: a comparison to other AV delay methods used in cardiac resynchronization therapy (SMART-AV) trial showed electrogram optimization algorithm (Boston Scientific). However, the SMART-AV trial showed neither SmartDelay nor echocardiography was superior to a fixed AV delay of 120 milliseconds.⁴⁷ The routine use of AV optimization techniques assessed in this trial is not warranted. Another novel adaptive CRT algorithm was developed by Medtronic Corp. for CRT pacing that provides automatic dynamic optimization of AVD and VVD. The adaptive CRT trial showed that this adaptive CRT algorithm is safe and at least as effective as biventricular pacing with comprehensive echocardiographic optimization.⁴⁸

CARDIAC RESYNCHRONIZATION THERAPY WITH DEFIBRILLATOR (CRT-D) FOR HF

According to American guidelines, patients should receive CRT, with or without an ICD, who have LVEF \leq 35%, sinus rhythm and NYHA Fc II to IV symptoms, despite recommended optimal medical therapy, and who have cardiac dyssynchrony, which is currently defined as a wide QRS duration. The use of an ICD in combination with CRT should be based on the known indications for

ICD therapy.¹ In particular, they state that the survival advantage of CRT-D versus CRT-P has not been adequately addressed.

Although there is evidence showing a benefit in both CRT-D and CRT-P patients with NYHA Fc III and IV symptoms, for NYHA Fc I and II patients, all of the trials tested only CRT-D and not CRT-P; as such, any recommendations for these classes of patients can be made only for CRT-D.^{9,10,12} Although it is probable that combined therapy is the best option for reducing mortality (0.75 probability in present analysis) it has not been demonstrated to be associated with a mortality rate different from that with either CRT or ICD therapy.^{3,14,49} Therefore, when the following question is posed: "in patients with HF and a wide QRS complex, should we implant a CRT-D or a CRT-P?", such a question could be definitively answered by prospective, randomized and controlled studies, designed to evaluate the superiority of CRT-D over CRT-P. However, CRT-D could be reimbursed by the National Health Insurance in Taiwan on the co-existence of VT or VF in the CRT candidates.

CONCLUSIONS

CRT benefit is thought to depend on mechanical resynchronization of cardiac electrical and mechanical activity. The modality of CRT has been clearly proven to enhance quality of life, reduce hospitalization for heart failure, and improve survival in specific selected patients in whom the likelihood of benefit was greatest (e.g., patients with LBBB conduction and QRS duration \geq 150 ms). In addition, CRT guided by the RV lead would enhance the engagement of the CS ostia. Quick optimization by either simple method or automatic device algorithms could save time and achieve a similar efficiency with conventional echocardiography.

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