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Review Article

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The Past, Present and Future of Cardiac Resynchronization Therapy

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ABSTRACT

Cardiac resynchronization therapy (CRT) has revolutionized the care of the patients with heart failure with reduced ejection fraction and electrical dyssynchrony. The current guidelines for patient selection include measurement of left ventricular systolic function, QRS duration and morphology, and functional classification. Despite consistent and increasing evidence supporting CRT use in appropriate patients, CRT has been underutilized. Notwithstanding the heterogeneous definitions of non-response, more than one-third of patients demonstrate a lack of echocardiographic reverse remodeling or poor clinical outcome following CRT. Since the causes of this non-response are multifactorial, it will require multidisciplinary efforts to overcome including optimal patient selection, procedural strategies, as well as optimizing post-implant care in patients undergoing CRT. The innovations of novel pacing approaches combined with advanced imaging technologies may eventually offer a personalized CRT system uniquely tailored to each patient's dyssynchrony signature.

Keywords: Heart failure; Cardiac resynchronization therapy; Current status; Future innovations

INTRODUCTION

Heart failure (HF) continues to manifest increasing prevalence, significant morbidity, high mortality and rapidly expanding cost.[1-7] Cardiac resynchronization therapy (CRT) has revolutionized the care of the patients with HF with reduced ejection fraction (HFrEF) and electrical dyssynchrony.[8-12] In the short-term, proper resynchronization therapy leads to improvement in left ventricular (LV) systolic function, reduction in mitral regurgitation and optimization of ventricular filling. Over a longer period, CRT facilitates LV reverse remodeling, as well as significant improvements in quality of life, functional capacity and survival.[12-16] However, despite overall success of CRT in improving morbidity and mortality in selected patients with HF, a significant minority continues to demonstrate suboptimal response to CRT. This review summarizes the brief history of CRT development including landmark clinical trials, the current status of CRT usage, optimizing strategies to improve outcome and future innovations in CRT.

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Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

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HISTORY OF CARDIAC RESYNCHRONIZATION THERAPY

The thought that pacing therapies could be helpful for treatment of HF well pre-dated the development of techniques for LV pacing and CRT. It's important to note that the deleterious effects of RV apical pacing only became fully appreciated with the report of the Dual Chamber and VVI Implantable Defibrillator trial[17] in 2002. Before that time, there was hope that dual chamber pacing techniques would improve HF outcomes.

Earlier attempts to treat HF with pacing focused on efforts to improve atrioventricular (AV) mechanics through dual chamber pacing with short AV intervals. Noting the adverse hemodynamic consequences of single chamber ventricular pacing, dual chamber pacing algorithms were developed that mimicked the natural AV interval with changing heart rates. Small pilot studies in the early 1990's seemed to show potential benefit of standard dual chamber pacing.[18-20] However, when subjected to a randomized controlled trial, dual chamber pacing with a short AV delay does not improve hemodynamic and clinical status or ejection fraction (EF) measured on the day after pacemaker implantation in patients with chronic HF.[21] In a larger MOde Selection trial, dual chamber pacing does not improve stroke-free survival, as compared with ventricular pacing. However, dual chamber pacing reduces the risk of atrial fibrillation (AF), reduces signs and symptoms of HF, and slightly improves the quality of life.[22]

The deleterious effects of left bundle branch block (LBBB) had been appreciated well before the advent of CRT. About 30% of patients with HFrEF have been shown to have wide QRS intervals, and this subgroup appears to have worse clinical outcomes.[22][23] Intraventricular conduction delay (IVCD) is associated with a wide array of hemodynamic arrangements including reduced pulse pressure, impaired diastolic function and functional mitral regurgitation.[24] Early attempts to address this pathology using biventricular pacing demonstrated favorable acute hemodynamics and medium term functional improvements.[25][26] In 1996, Cazeau et al.[27] reported a series of 8 advanced HF patients with widened QRS intervals. All received atrial triggered biventricular pacers. Four died in the perioperative period, but of the 4 who survived, HF class improved form IV to II. HF worsened when pacing was deactivated. These and other favorable early experiences set the stage for further technological development and larger trials of CRT.

The Pacing Therapies for Congestive HF trial[28] investigated pacing in patients with advanced HF. Patients enrolled had 2 pulse generators implanted then were randomized to either univentricular (LV or RV lead) or biventricular pacing. Of the 25 patients who were ultimately analyzed, biventricular pacing was associated with reduction in LV dimensions and increased EF.

In 2001, results of the Multicenter InSync Randomized Clinical Evaluation trial,[13] the largest multicenter prospective randomized clinical trial to date were presented. It enrolled 453 patients with QRS >130 ms, LVEF <35% (mean 22%), LV end diastolic diameter (LVEDD) >55 mm, and New York Heart Association (NYHA) III-IV HF (with 6-minute walk test [6MWT] ≤450 m). In this trial, CRT improved functional class, increased 6MWT and peak VO_2, and improved quality of life. This improvement was seen in 67% of CRT patients versus 39% of controls. That same year, MUltisite STimulation in cardiomyopathy[29] was published showing similar positive results, among 67 randomized patients with reduced LVEF (mean 23%), NYHA III HF, LVEDD >60 mm, and QRS >150 ms. Soon thereafter, Cardiac Resynchronization-HF[14] and Comparison of Medical Therapy, Pacing, and Defibrillation

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in HF[30] trials showed reductions in the primary composite end-point (all-cause mortality or hospitalization for major adverse cardiovascular event) for CRT compared to standard medical therapy alone. A high quality meta-analysis confirmed approximately a 30% reduction in both hospitalization and mortality for CRT.[31]

THE CURRENT PRACTICE OF CARDIAC RESYNCHRONIZATION THERAPY

Patient selection

In the current era, guidelines for utilization of CRT have been generated by multiple groups, each synthesizing their interpretation of the aforementioned landmark trials, coupled with expert opinion. These guidelines include those from the combined writing group of American Heart Association/the American College of Cardiology/Heart Rhythm Society, the Heart Failure Society of America, and the European Society of Cardiology. While there are a few distinctions between the guidelines, the vast majority of recommendations put forth are concordant.[5-7][32] Current class I indications of CRT are summarized in **Table 1**.

Generally accepted class I indications are restricted to the symptomatic patients with LVEF ≤35%, NYHA II-IV, with a QRS duration ≥130 ms despite guideline-directed medical treatment (GDMT).[8] In the past few years, these guidelines have been updated in such a way as to better categorize patients according to their likelihood of benefiting from CRT including CRT upgrade. The most recent guidelines are account for the observations that the greatest benefits are consistently seen in those with a QRS duration >150 ms and a LBBB pattern.[33-35] Echocardiographic methods of detecting mechanical dyssynchrony, on the other hand, have not been able to identify any superior predictors for a favorable response to CRT.[36] Therefore, criteria for patient selection for CRT remain: measurement of LV systolic function (LVEF), QRS duration, and morphology and function class (NYHA class II-IV).

In Korea, CRT had been underutilized because of cultural resistance, low HF awareness of physicians, and restrictive insurance coverage.[2] Nonetheless, CRT has increased steadily, doubling in use over the past 5 years as shown in **Figure 1**. Outcomes of these early implants in Korea are consistent with published literature. Over a median follow-up period of 17.5 months, Korean patients implanted between October 2005 to May 2013[37] showed significant improvements in NYHA class (3.1±0.5 to 1.7±0.4), QRS duration (169.1 to 146.9 ms), LV

Table 1. Current class I indications of CRT in patients with HF

	Recommendations
ACC/AHA (2013)	CRT is indicated of patients who have LVEF ≤35%, sinus rhythm, LBBB with a QRS ≥150 ms, and NYHA class III or ambulatory IV (I-A) or II (I-B) symptoms on GDMT.
ESC (2016)	CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 ms (I-A) or 130–149 ms (I-B) and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality. CRT rather than RV pacing is recommended for patients with HFrEF regardless of NYHA class who have an indication for ventricular pacing and high degree AV block in order to reduce morbidity. This includes patients with AF (I-A).

The ESC guidelines do not specify NYHA functional class, rather they state that the guidelines refer to symptomatic patients with HF.
ACC = American College of Cardiology; AF = atrial fibrillation; AHA = American Heart Association; AV = atrioventricular; CRT = cardiac resynchronization therapy; ESC = European Society of Cardiology; GDMT = guideline-directed medical therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; OMT = optimal medical therapy; RV = right ventricular.

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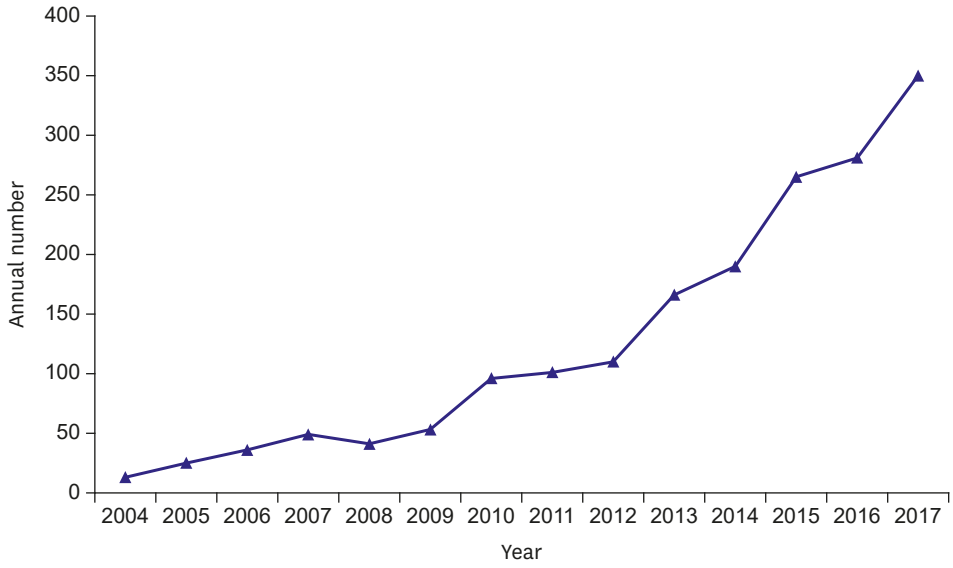

Figure 1. Temporal trends of cardiac resynchronization therapy in Korea.

end-diastolic (255.0 to 220.1 mL) and end-systolic (194.4 to 159.4 mL) volumes, as well as LVEF (22.5% to 31.1%).[33] The overall survival free of HF hospitalizations was 90.1% (95% CI, 0.81–0.99) at 1 year and 69.4% (95% CI, 0.47–0.91) at 3 years. More recently, a single center prospective study of 120 patients from January 2010 to June 2017 showed 67.8% of CRT response rate at 1 year, defined by the reduction of LV end-systolic volume >15%.[38] Nonetheless, CRT in Korea remains grossly underutilized. Even in the Western nations, CRT uptake remains relatively low.[39] Furthermore, there appears to be treatment disparities based on gender and race. Use of CRT remains more common among white than black HF patients; women are less likely than men to receive CRT despite greater likelihood of benefit.[40] Although age is not a contraindication to CRT, elderly patients are underrepresented in studies of CRT as well as in clinical practice.[41] In the Swedish HF Registry, both IVCD and LBBB were more common with increasing age, but CRT was underutilized in the elderly.[41]

Despite consistent evidence supporting CRT use in appropriate HF patients, CRT remains relatively underutilized around the world to varying degrees.[42] Perhaps clinical benefit of CRT is underappreciated and physicians are concerned that the benefits do not outweigh the risks of CRT in HF patients with multiple comorbidities or in advanced HF patients. Lacks of physician experience and skill for proper lead placement may also be contributing in some instances. Current guidelines that further stratify recommendations based on HF etiology/severity, QRS duration/morphology may have shifted the expectation of physicians to focus primarily on class I indicated patient. A better understanding of the factors impacting CRT utilization will help to increase appropriate CRT implantation and improve outcomes of eligible HF patients.[42]

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THE OPTIMIZATION OF CARDIAC RESYNCHRONIZATION THERAPY

Non-responder to cardiac resynchronization therapy

Despite 20 years of clinical development, a consensus definition of response and non-response to CRT has not been reached.[10] **Figure 2** shows the comparison of CRT response according to follow-up duration, criteria for primary endpoint and number of enrolled patients. The non-response rates were generally lowest when functional measures were used as endpoints. Notwithstanding the heterogeneous definitions of nonresponse, approximately one-third of patients will demonstrate a lack of echocardiographic reverse remodeling or poor clinical outcome following CRT. Since the underlying causes of suboptimal response are generally multifactorial, it will require a multi-faceted effort to overcome them. This includes optimal patient selection, procedural strategies at the time of lead implantation, as well as optimizing post-implant care in patients undergoing CRT.[10][12]

Optimal patient selection

First of all, treatment with CRT must be preceded by addressing any reversible cause of HF, such as ischemia, arrhythmia (tachycardia-induced cardiomyopathy), or primary valvular disease.[10] In addition to patient selection criteria in current guidelines including LVEF, functional class, QRS morphology and duration, there are several other baseline clinical features that may influence the response to CRT. In unselected patient populations, 25% of CRT recipients are in permanent AF.[10] These patients are older and suffer from more advanced HF and higher prevalence of comorbidities than patients who are in sinus rhythm. Catheter ablation of AF with HFrEF demonstrated improvement of LV function in

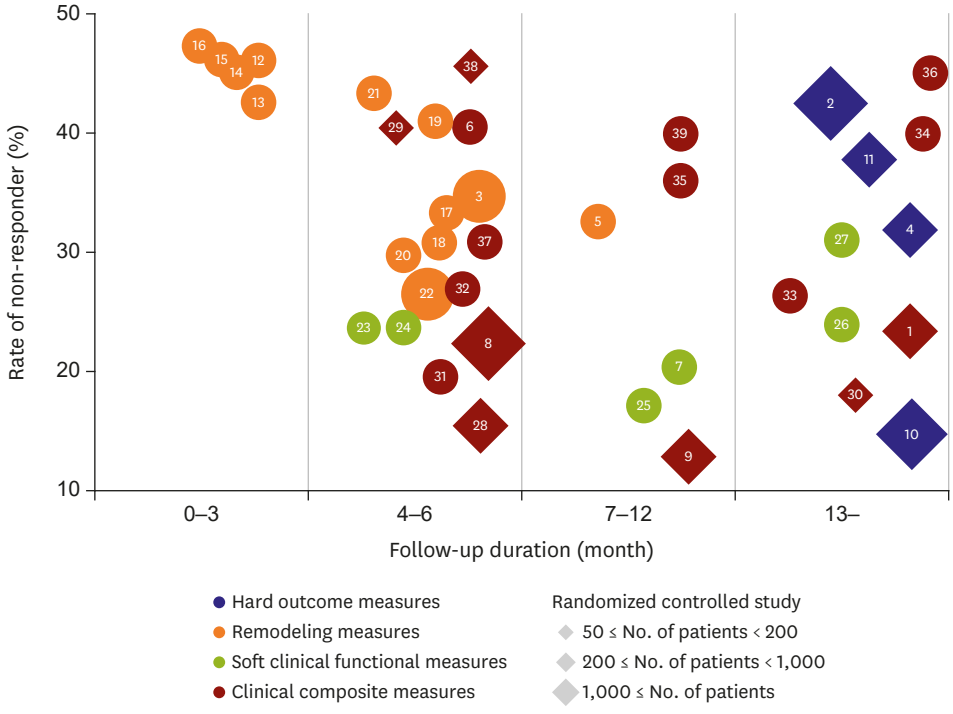

Figure 2. Comparison of CRT response according to follow-up duration, criteria for primary endpoint and number of enrolled patients.
The studies cited in **Figure 2** are listed in **Appendix 1**.
CRT = cardiac resynchronization therapy.

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experienced centers.[43] Catheter ablation of AF is superior to AV node ablation combined with biventricular pacing in terms of 6MWT, LVEF, and HF symptoms.[44] Catheter ablation of AF in patients with HF and preexisting implantable cardioverter defibrillator (ICD) showed improvement of mortality and HF hospitalization, improvement of LVEF, and freedom from AF.[45][46] However, if a patient with HF and symptomatic AF is not a candidate for AF ablation or has failed ablation, AV junction ablation followed by CRT is a best treatment option.[5-7] For patients with AV block requiring pacemaker placement, CRT is generally recommended for patients with NYHA functional class I, II, or III HF who have LVEF ≤50% and AV block (with AF or sinus rhythm) who are expected to require a high percentage of ventricular pacing based on Biventricular versus RV Pacing in HF Patients with AV Block trial.[47] Upgrade to a CRT device in patients already implanted with a conventional pacemaker of ICD is another important indication. Patients with HFrEF who have received a conventional pacemaker or an ICD and subsequently develop worsening HF despite GDMT and who have a high proportion of RV pacing may be considered for upgrade to CRT.[5][48] Several other factors have been shown to influence the efficacy of CRT, including medical comorbidities (chronic kidney disease), hemodynamic abnormalities (pre-capillary pulmonary hypertension), and abnormalities of LV substrate (non-revascularized coronary artery disease, myocardial scar).[12] Because of the heterogeneity of benefit conferred by treatment as a function of patient factors, the lack of compelling data in some patient populations, and the frequency of comorbidities in patients with HF, decision making around CRT is often complex. Ultimately, the decision to pursue the therapy should be informed by best estimates of both benefits and risks in the context of shared decision making, based on selecting a reasonable therapy that is aligned with the patient's values, goals, and preferences.[49] Because CRT is associated with risk, both acutely during implantation and chronically, the risk-benefit ratio of CRT implant must be considered in each individual patient, particularly in those with less robust indications.

Procedural strategies

The standard lead configuration of CRT systems consists of 1 lead implanted inside the right ventricle and another placed over the LV-free wall via a tributary of the coronary sinus (CS).[10] Suboptimal stimulation due to a poor LV lead position, insufficient ventricular resynchronization, loss of LV capture, LV pacing latency, as well as other factors, is a common cause of non-response. It was originally hypothesized that LV leads should optimally be placed at sites of latest ventricular activation during intrinsic conduction. The lateral or posterolateral LV wall was the site of latest activation in a majority of patients and LV apex is usually the worst location. However, the response to CRT is often variable even when the LV lead is placed in this optimal anatomic position, reflecting the complex interaction of myocardial substrate, heterogeneity of ventricular wave front activation (even within similar QRS duration or bundle branch morphology), as well as RV pacing-induced shifts in LV activation.[12]

Strategies to overcome potential limitations in lead targeting include the use of multisite pacing, surgical implantation of epicardial leads, and endocardial pacing.[12] Multisite pacing has been proposed with a view to obtain a more rapid and homogeneous LV activation.[10] Multisite pacing using 2 LV leads was tested in a randomized study of patients who had not responded to standard biventricular stimulation. Unfortunately, no clinical or echocardiographic benefits were found, and a high complication rate, particularly infection, was observed.[50] Multipoint pacing is new way to deliver multisite pacing through a unique quadripolar LV lead and a dedicated algorithm enabling LV stimulation from 2 separate dipoles located in the same CS tributary. In short-term hemodynamic studies, LV dP/dt was greater than that with standard biventricular stimulation.[51] Based on the results of a small

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randomized study, which observed a significant decrease in the rate of non-responders with multipoint stimulation,[52] and with the post-hoc analysis of potential efficacy in phase I trial,[53] a phase II large randomized trial based on LV reverse remodeling in non-responders to CRT is under investigation.[54]

Post-implant care

Care of the patient following implantation of CRT includes GDMT and optimization of device programming as well as early recognition of patients at risk for nonresponse.[12] The most important settings to achieve optimal CRT are the pacing mode, the lower and upper rate limits, the capture output, the stimulation vectors configuration, and the AV and interventricular (VV) intervals. Echocardiography based routine optimization of the AV and VV delay in CRT recipients is not warranted. The current guidelines recommend a fixed 100–120 ms AV delay without a VV interval.[55] However, in subgroups of patients, especially in the presence of a long interatrial delay, the intervals should be optimized after the implant. Further echocardiography based optimization procedures may be advised in case of non-response to CRT.[10] Ideally, the device should be able to evaluate the optimal setting automatically.[56] Therefore, in an attempt to simplify CRT optimization, the CRT manufacturing companies have developed several intracardiac automated electrogram-based algorithms including adaptive CRT algorithm (Medtronic, Dublin, Ireland) and SyncAV algorithm (Abbott, Chicago, IL, USA).

GDMT includes the optimization of pharmacological therapy, education, exercise training, and monitoring. Multidisciplinary program may assist in the optimization of medical therapy, adherence, and patient education. Such a multidisciplinary approach was associated with improved clinical outcomes in a retrospective report.[57] The doses of drugs recommended in the professional practice guidelines are often limited by hypotension and renal dysfunction. CRT, however, may support the systemic blood pressure and heart rate, enabling an increase in the doses of β-adrenergic blockers with less risk of profound bradycardia or hypotension.[10]

Role of imaging in cardiac resynchronization therapy

The finding that mechanical resynchronization paralleled a benefit from CRT formed the basis for dyssynchrony assessment in patient selection.[11] Many echocardiographic measures of mechanical dyssynchrony once held promise as predictors of response to CRT in single-center studies. Their utility was then tested by the Predictors of Response to CRT trial.[36] Even after validation by blinded core laboratories, no echocardiographic measure of dyssynchrony could reliably predict the response to CRT. Negative evidence also comes from the recent EchoCRT study, which failed to show a benefit from CRT-defibrillator in patients with QRS duration ≤130 ms and pre-implant dyssynchrony assessed echocardiographically.[58] Accordingly, none of the clinical guidelines support echocardiographic measures of dyssynchrony for patient selection. However, mechanical dyssynchrony can also be measured using cardiac magnetic resonance (CMR). CMR can provide high-resolution strain images to assess dyssynchrony with reduced inter-observer variability.[59] The myocardial tagging technique is the most commonly used, but the recently developed cine displacement encoding with stimulated echoes methodology provides accurate assessment of myocardial displacement and circumferential strain with higher resolution.[59] However, the techniques for assessing dyssynchrony with CMR still remain mostly for research purposes, and large, prospective, multicenter trials of clinically feasible external validation have not been undertaken to evaluate their performance. Cardiac computed tomography also can

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provide strain, scar assessment, and coronary venous anatomy information for pre-CRT implantation planning.

Although dyssynchrony imaging may not have a role in patient selection, it may be useful in LV lead deployment. CMR can be used to guide LV leads away from scars. Based on late gadolinium enhancement detected by CMR which can directly visualize myocardial scar, the patients who received LV lead placement away from myocardial scar showed better clinical outcome.[60] In the targeted LV lead placement to guide cardiac resynchronization therapy study, 220 patients were randomly assigned into 2 groups with or without targeted LV lead deployment using speckle-tracking 2-dimensional radial strain measured by transthoracic echocardiogram. Targeted LV lead placement group showed a higher portion of CRT responder and lower rate of combined endpoint compared with the control group.[61] Combination of multi-modality imaging including nuclear imaging and radial strain demonstrated a higher response rate compared with the control group.[62]

FUTURE INNOVATIONS IN CARDIAC RESYNCHRONIZATION THERAPY

Expansion of patient selection

The optimal selection of patients for CRT remains challenging particularly for patients with non-LBBB morphology.[12] More careful pre-procedural identification of dyssynchrony or intra-procedural targeting of electrical delay may helpful for better patient selection in non-LBBB candidates. This strategy is recently evaluated in the Electrical Delay for Non-LBBB Patients study.[63] In this study, investigators compared the effects of targeting the region of increased electrical delay (Q-LV approach) for LV lead location to a standard of care (SOC) anatomical implant approach in non-LBBB patients. The comparison was assessed on the Clinical Composite Score (CCS) after 12 months of follow-up. A total of 190 subjects were available for data analysis at 12 months of follow-up (128 Q-LV arm; 62 SOC arm). There were no significant differences between the 2 interventional arms in quality of life or LVEF. However, CRT in non-LBBB patients was associated with a marked clinical improvement as evidenced by the CCS and favorable reverse remodeling in both groups. The expansion of CRT to nonstandard population also remains an area of active investigation.[12] For example, the MADIT-Chemotherapy Induced Cardiomyopathy (NCT02164721) trial will assess the efficacy of CRT therapy in patients with chemotherapy-induced cardiomyopathy. As more pertinent data accumulate, CRT may also become eligible in patients with relatively preserved LVEF and significant pacing.

Endocardial left ventricular pacing

Given the potential challenges of trans-venous LV lead implantation including limitations of CS anatomy, high LV pacing threshold and/or phrenic nerve capture, there has been considerable interest in the role of an endocardial LV lead strategy in patients eligible for CRT.[9][64][65] Pacing the LV endocardium reflects a more rapid and physiological activation of the left ventricle as compared to standard epicardial LV pacing, and previous studies have identified greater acute hemodynamic improvements with endocardial versus conventional LV pacing.[66] The Alternate Site Cardiac Resynchronization study demonstrated both safety and efficacy of LV endocardial pacing patients who either demonstrated CRT non-response or in whom LV lead placement was not technically possible.[67] LV endocardial pacing in this study was associated with clinical and echocardiographic improvement in two-thirds of

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patients. It should be noted that anticoagulation was required in this study given permanent LV endocardial leads, and that thromboembolic events were detected in some patients in this study despite anticoagulation. The wireless stimulation endocardially for CRT (EBR Systems, Sunnyvale, CA, USA) system employs a pacing system using a small leadless ultrasound-responsive electrode placed onto the LV endocardial surface.[64] In the recent Safety and Performance of Electrodes implanted in the Left Ventricle study, 35 patients who had failed conventional CRT underwent successful implant in 97% of cases.[68] At 6 months, approximately two-thirds of patients demonstrated LV reverse remodeling (improved LVEF ≥5%) and 85% of patients demonstrated an improvement in CCS. The Stimulation of the LV Endocardium for CRT in Non-Responders and Previously Untreatable Patients study (NCT02922036) will be the first randomized comparison of an endocardial LV pacing strategy in CRT non-responders or those in whom a standard trans-venous LV lead implantation was not feasible.

His bundle pacing

His bundle pacing (HBP) represents a theoretically ideal site for ventricular pacing as it retains activation of the intrinsic electrical conduction system.[9][69-72] Several limited case series have suggested that HBP may lead to resynchronization in CRT-eligible patients with LBBB.[73] For example, in a recent series of 21 patients eligible for CRT, HBP was successfully implanted in 16 patients with evidence of electrical resynchronization (i.e., narrowing of QRS duration) in 76% and LV reverse remodeling overall (improved LVEF and decreased LV dimensions), although not all studies of HBP have demonstrated this high rate of QRS narrowing in LBBB patients.[9] The ongoing HBP versus CS Pacing for CRT (NCT02700425) will be the first randomized comparison of HBP versus standard CS LV lead implantation in CRT-eligible patients. HBP is clearly an attractive alternative to patients who are non-responders to conventional CRT or have a history of previously failed CS lead placement, right/LBBB cardiomyopathy, or pacing-induced cardiomyopathy.[72]

CONCLUSION

CRT has revolutionized the care of HFrEF patients with electrical dyssynchrony. Performance improving strategies to enhance implantation rates in those meeting current guidelines and consensus efforts toward defining non-response to CRT are necessary steps towards optimal use. Multidisciplinary efforts to overcome non-response include optimal patient selection, procedural strategies, as well as optimizing post-implant care in patients undergoing CRT. The innovations of novel pacing approaches combined with advanced imaging technologies may eventually offer a personalized CRT system uniquely tailored to each patient's dyssynchrony signature.

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