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Overview of Current Strategies Aiming at Improving Response to Cardiac Resynchronization Therapy

ABSTRACT

Cardiac resynchronization therapy is a treatment modality developed in the early 2000s that targets the mechanical and electrical dyssynchrony in heart failure with reduced ejection fraction patients. Appropriate patient selection conditions specified in the guidelines include measurement of left ventricular systolic dysfunction, QRS width, and assessment of functional classification. Despite consistent and increasing evidence supporting the use of cardiac resynchronization therapy in eligible patients, proportion of patients with the device is still not at the desired level. In addition, studies conducted in recent years have shown that the cardiac resynchronization therapy response of patients is quite heterogeneous and in echocardiographic follow-up, it was observed that reverse remodeling was not at the supposed level in approximately one-third of the patients. In order to change this result, which is due to many reasons, solutions such as using assistive imaging methods, providing optimal patient selection, trying different pacing techniques and post-procedural programming strategies (AV-delay and VV-delay optimization) have been the subject of debate. In this article, we aim to review the mechanisms that have been revealed regarding the differences in cardiac resynchronization therapy response and new pacing techniques—especially conduction system pacing—that may be preferred to resolve poor cardiac resynchronization therapy response.

Keywords: Cardiac resynchronization therapy, cardiomyopathy, congestive heart failure, left ventricular dysfunction, pacemaker

INVITED REVIEW

INTRODUCTION

Heart failure continues to be an important cause of mortality and morbidity with its increasing frequency. Cardiac resynchronization therapy (CRT) has been a critical weapon in terms of leading to revolutionary improvement in patients with heart failure with reduced ejection fraction (HfrEF).[1] Resynchronization therapy provides an opportunity to reduce mitral regurgitation, optimize ventricular filling, and improve left ventricular systolic function in the early period, as well as a significant improvement in the quality of life and survival of patients through reverse remodeling in the long term.[2] However, in a substantial group of patients (about 30%), the CRT response has been shown to be suboptimal. This review summarizes the historical evolution of CRT use, landmark clinical trials of CRT, the current status of CRT use, and in particular current strategies and future innovations that can be developed to improve CRT response.

Historical Development of the Cardiac Resynchronization Therapy

In the 1990s, cardiac dyssynchrony was thought to be a poor prognostic factor in heart failure patients. In this regard, dual-chamber pacing was used primarily by targeting the optimization of the AV interval in order to ensure cardiac resynchronization. Although a decrease in the incidence of new-onset atrial fibrillation and improvement in quality of life were observed with this application, the expected improvement in non-stroke mortality and left ventricular ejection fraction could not be achieved.[3]

In the following years, the view that intraventricular conduction defect (IVCD) was the main problem causing ventricular dyssynchrony gained importance. It has been shown that patients with wide QRS, especially HFrEF with Left Bundle Branch

Yakup Yunus Yamantürk
Başar Candemir
Emir Baskovski
Kerim Esenboğa

Department of Cardiology, Faculty of Medicine, Ankara University, Ankara, Turkey

Corresponding author:
Başar Candemir
basarcandemir@yahoo.com

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Table 1. Classes I and II-A Indication of CRT Reported in 2021 ESC Cardiac Pacing and Cardiac Resynchronization Therapy Guideline

Class I	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.
Class II-A	CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration 130-149 ms and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.
	CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 ms and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.
	In patients with symptomatic AF and an uncontrolled heart rate who are candidates for AVJ ablation (irrespective of QRS duration), CRT rather than standard RV pacing should be considered in patients with HFmrEF.
	In patients with sarcoidosis and indication for permanent pacing who have LVEF <50%, implantation of a CRT-D should be considered.

AV, atrioventricular; CRT, cardiac resynchronization therapy; ESC, European Society of Cardiology; GDMT, guideline-directed medical therapy; HF, heart failure; HFmrEF= heart failure with mildly reduced ejection fraction; 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.

Block (LBBB), have poor clinical outcomes. The biventricular pacing (BVP) trial performed by Cazeau et al in 8 patients with wide QRS diagnosed with advanced heart failure in 1996 was remarkable because of the prognostic improvement it provided in uncomplicated cases due to the procedure.[4] Then, in the 2000s, with several trials conducted with larger patient groups, CRT solidified its place as an indispensable treatment modality in suitable patient groups with HFrEF diagnosis.[5-7] Although the latest current guidelines show the LVEF limit as 35% for patients benefiting from CRT, there have also been studies suggesting that this threshold can be 40% in the presence of wide QRS (>130 ms).[8]

Current Clinical Practice in CRT Implantation

In current clinical practice, guidelines for the use of CRT appear as a synthesis of the comments of landmark trials and the views of experts in the field. These guidelines include those from the joint writing group of the American Heart Association/American College of Cardiology/Heart Rhythm Society, the American Heart Failure Association, and the European Society of Cardiology.[9] While there are a few distinctions between guidelines, the majority of recommendations are consistent. Current class I and class II-A indications for CRT are summarized in Table 1.

HIGHLIGHTS

- Cardiac resynchronization therapy (CRT) is an indispensable treatment modality in patients with heart failure with reduced ejection fraction with wide QRS and in patients with systolic dysfunction who need permanent pacing.
- A substantial proportion (approximately 30%) of patients receiving resynchronization therapy do not demonstrate a significant response during follow-up.
- Non-responders of CRT should be detected and evaluated for alternative pacing methods.
- Conduction system pacing, left ventricular endocardial pacing, and multipoint pacing stand as permanent pacing methods that can be preferred in routine clinical practice in the near future for patients who do not benefit from conventional biventricular pacing if their adequacy is proven in randomized controlled studies with large patient groups.

The generally accepted indication group for CRT consists of patients with wide QRS (>130 ms), LVEF ≤35%, and symptomatic heart failure (NYHA class II-IV) despite optimal medical therapy. Also, the CRT option should be kept in mind in patients with LVEF <50, in case of need for ventricular pacing or in patients with decreased ejection fraction under right ventricular (RV) pacing. Most of the patients who benefited maximally from CRT had QRS width >150 ms and LBBB morphology. It has been reported that CRT has limited benefit in patient groups with IVCD in non-LBBB morphology. In detailed studies on this, it has been suggested that this is due to the fact that radial dyssynchrony in patients with isolated Right Bundle Branch Block is not impaired in the case of moderate QRS width (<150 ms).[10] In addition, in a subgroup comparison analysis, it was noted that patients with left fascicular hemiblock in addition to RBBB had better CRT responses than HF patients with isolated RBBB.[11] Therefore, it is recommended to review different lead positions and pacing strategies in HF patients with RBBB.

In recent years, scoring systems created by including both the information provided by imaging methods and the clinical characteristics of the patients have been used to see the CRT response. Among these, while the mechanical dyssynchrony measurements determined by the echocardiographic method have lost their popularity and value, the CRT score, which includes the comorbidities of the patients, electrocardiogram (ECG) rhythm [sinus rhythm (SR) or atrial fibrillation (AF)], QRS width, bundle branch block pattern, and cardiomyopathy etiology, has been seen as useful.[12]

The Optimization of Cardiac Resynchronization Therapy

In the analyses performed on CRT patients, which have become widespread in the last 20 years, a group of non-responders ranging from 30% to 40% has been revealed. In the studies revealing this, there is no consensus on the definition of non-responders. It is recommended to demonstrate not only the poor clinical response but also the absence of echocardiographic reverse remodeling.

It would be beneficial to implement a multi-pronged strategy in tackling under-response. Routine approach items that can be applied to prevent CRT unresponsiveness can be listed as correct determination of the patient group to be treated, procedural strategies during lead implantation, and improvements that can be applied in device control after CRT implantation. In addition to these, alternative methods to conventional BVP have been discussed in recent years. There are small nonrandomized studies with exciting results claiming that especially conduction system pacing and fusion pacing strategies may be superior to conventional BVP in appropriate patient groups.

Optimal Patient Selection

First, prior to treatment with CRT, any reversible cause of HF such as ischemia, arrhythmia (cardiomyopathy caused by tachycardia), or primary valve disease should be elucidated. In addition to patient selection criteria in current guidelines, including LVEF, functional class, QRS morphology and duration, there are several other key clinical features that may affect response to CRT. It has been shown that CRT response is lower in patients diagnosed with AF. Due to loss of atrioventricular synchrony and uncontrolled ventricular rates, these patients exhibit insufficient BVP, more ICD shocks from ventricular tachycardia, more inappropriate shock, inadequate symptomatic recovery, recurrent hospitalizations, and increased mortality.[13] In addition, AF can lead to fusion and pseudofusion beats in patients with CRT. This situation may lead to the interpretation that the patients are non-responder despite the high left ventricular (LV) pacing rate, if the electrogram recordings are not carefully examined in the device control. In order to prevent all these, patients with CRT should be carefully evaluated in terms of rate control, rhythm control with antiarrhythmic drugs and/or catheter ablation, and, if necessary, Atrio-ventricular junction ablation in the presence of AF.[14] Apart from AF, several other factors have been shown to affect the efficacy of CRT, including medical comorbidities (chronic kidney disease, chronic obstructive pulmonary disease), hemodynamic abnormalities (pre-capillary pulmonary hypertension), and LV substrate abnormalities (non-revascularized coronary artery disease, myocardial scarring).

Another important CRT indication group that should not be forgotten is the patients who need permanent pacing and have LVEF <50, regardless of NYHA class and QRS width, and patients with decreased ejection fraction and hemodynamic deterioration under RV pacing.

Procedural Strategies

The CRT standard lead configuration system consists of 2 leads, 1 fixed within the RV and the other advanced to the appropriate coronary sinus branch that offers the ability to pace the LV-free wall. Loss of capture or delay in activation due to indirect stimulation of the LV can be a major source of problems in a group of non-responder patients. In terms of optimizing resynchronization, the consensus currently in routine practice is to target the point of maximum ventricular delay, which is usually achieved by targeting the LV lateral or posterolateral wall.[15] However, despite anatomical optimization, serious treatment response differences can be observed even in patients with similar bundle branch block morphology due to the complex interaction of myocardial substrate and heterogeneity of ventricular wave front activation.

In recent years, alternative ventricular pacing techniques, which can be summarized as LV multipoint pacing (MPP), endocardial pacing, surgically epicardial pacing, and conduction system pacing, have been focused on in order to solve the limitations and efficiency problems of conventional BVP (Figure 1).

Alternative Pacing Techniques

1-Multipoint Pacing

This method emerged with the idea that pacing from more discrete points and/or from a larger vector (multisite and

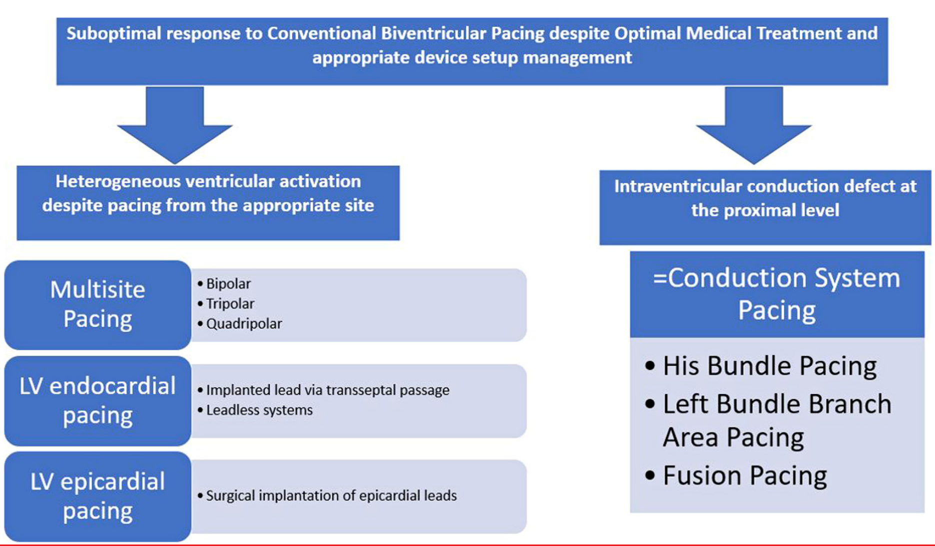

Figure 1. Alternative pacing techniques can be applied in the case of suboptimal CRT response.

multipoint pacing) could improve left ventricular resynchronization, especially in patient groups with heterogeneous ventricular activation patterns.

Different studies and meta-analyses have shown that MPP offers a more effective resynchronization therapy than conventional BVP.[16] Although the battery longevity is significantly shortened in patients undergoing MPP, this problem becomes more negligible compared to the benefit when the pacing capture threshold of the LV vector, which provides maximum possible anatomical separation, is ≤4.0 V.[17]

2-Left Ventricular Endocardial Pacing

The method of stimulating the LV over the appropriate branches of the coronary sinus in conventional BVP practice has limitations due to the non-physiological activation pattern it creates in the LV, lead stability, the occasional high threshold requirement, and the risk of phrenic nerve capture. Extremely satisfactory results have been demonstrated in terms of LV systolic performance in studies on LV endocardial pacing, which is an option to overcome these problems.[18]

However, the risk of systemic embolization due to a transseptal lead implanted in the left ventricular endocardium appears to be a major barrier to the routine use of LV endocardial pacing.[19] It is thought that this risk can be eliminated in appropriate patient groups who routinely use oral anticoagulants for other reasons. Besides, the frequency of these complications may decrease with leadless pacing technologies, which are predicted to become widespread in the future.[20]

3- Left Ventricular Epicardial Pacing

Surgical LV epicardial pacing seems to be a good alternative to conventional BVP in patients who do not have a suitable CS branch.[21] However, there are conflicting results in studies on its superiority in terms of threshold stability and mortality rates.[22] For this reason, lead placement over the CS is the first choice in routine practice in case of anatomical suitability.

4-Conduction System Pacing (CSP)

Conduction system pacing is a pacing technique that aims to implant permanent pacing leads at different points of the cardiac conduction system, including the left bundle branch and His bundle. Experiments have shown that CSP is an important alternative in solving the residual dyssynchrony problem created by conventional BVP between the 2 ventricles and in the interventricular septum (Table 2).[23] In addition, considering that IVCD is not limited to the distal area and may include the proximal conduction system in patients with poor conventional CRT response, it is thought that CSP can be used as the first choice in appropriate patient groups[24] (Figures 2 and 3).

(a) His-Bundle Pacing (HBP): Persistent HBP was first used by Deshmukh et al[25] to maintain interventricular synchrony after AVJ ablation in patients with AF-induced cardiomyopathy. Later, interest in HBP started to increase due to the good results in patients requiring ventricular pacing or CRT.

In a prospective and multicenter study conducted by Sharma et al[26] in 2018 with 106 patients, HBP was tested as a rescue strategy in patients with failed left ventricular lead or non-response to BVP (group I), or as a primary strategy in

Table 2. Study Summary for HBP and CRT

Study	Design and Follow-Up	n	Success Rate (%)	Outcomes
Ajijola et al[51] 2017	Single center Prospective Observational -12 months	21	76	**Clinical:** NYHA III to II **QRSd:** 180-129 ms **LVEF (%):** 27-41
Sharma et al[26] 2018	Multicenter Prospective Observational -14 months	106	90	**Clinical:** NYHA 2.8-1.8 **QRSd:** 157-118 ms **LVEF (%):** 30-44 for BVP failure group, 25-40 for primary HBP group
Upadhyay et al[28] 2019	Multicenter Prospective Randomized crossover trial -12 months	41	76	**QRSd:** 172-144 ms **LVEF (%):** 26-32
Huang et al[29] 2019	Single center Prospective Observational -37 months	74	76	**Clinical:** NYHA 2.8-1.0 **QRSd:** 171-113 ms *in selective HBP group: 173-105 ms *in non-selective HBP group: 161-140 ms **LVEF (%):** 31-57
Sharma et al[26] 2018: Permanent HBP in RBBB	Multicenter Retrospective Observational -15 months	39	95	**Clinical:** NYHA 2.8-2.0 **QRSd:** 158- 127 ms **LVEF (%):** 31- 39 26- 34 = HBP appears to be a suitable treatment alternative for patients with RBBB and depressed LVEF.

HBP, His-bundle pacing; CRT, cardiac resynchronization therapy; RBBB, right bundle branch block; LVEF, left ventricular ejection fraction.

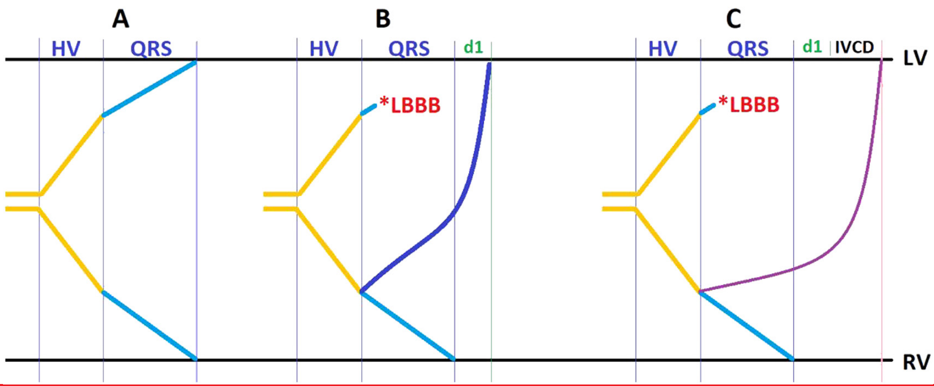

Figure 2. (A) Normal conduction. (B) LBBB without distal IVCD. (C) LBBB with distal IVCD. d1, delay 1, IVCD, intraventricular conduction defect; LBBB, left bundle branch block.

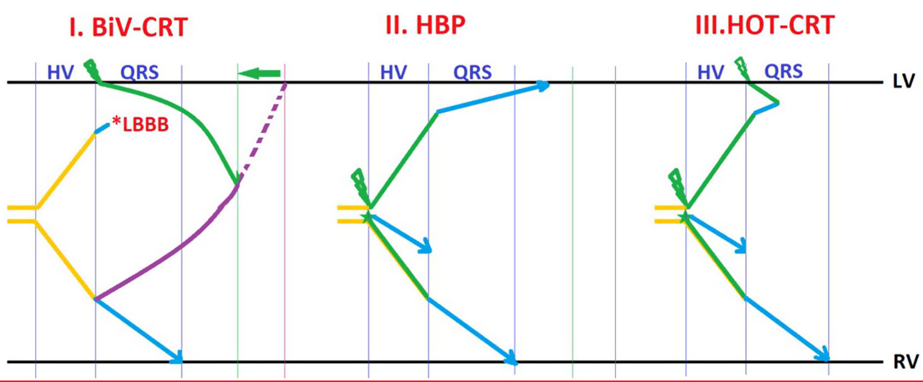

Figure 3. Schematic summary of the effects of CRT techniques on QRS width and IVCD. BiV, biventricular; HBP, His-bundle pacing; HOT-CRT, His-optimized CRT; CRT, cardiac resynchronization therapy; IVCD, intraventricular conduction defect.

patients with AV block, BBB, or high ventricular pacing burden as an alternative to BVP (group II) in patients with indications for CRT.[26,27] At the end of the follow-up period, HBP was found to be significantly beneficial ($P = .0001$) in both groups in reducing QRS width, increasing LVEF, and improving NYHA functional class, and it was seen to be an important alternative among CRT options. Again, in a study by Sharma et al[26] in patients with heart failure and RBBB for whom RV pacing was not appropriate, HBP appears to be a suitable treatment alternative for patients with RBBB and depressed LVEF.[27] In the first trial by Upadhyay et al[28] comparing HBP and BVP with the randomized method, HBP proved to be a good alternative in terms of feasibility and safety.

Huang et al's[29] study in 2019 revealed that HBP is more beneficial especially in HF patients with typical LBBB, which is a remarkable finding on whether ECG features can guide the pacing strategy.

However, in addition to all these promising studies, difficulties in the implantation technique and problems in atrial oversensing and ventricular capture threshold stability, which may cause problems in the clinical follow-up of patients, hinder the widespread use of HBP.[30-32] Unfortunately, Electrogram (EGM) recordings in patients with HBP are insufficient in detecting transitions between the NS-HBP, S-HBP, BBB recruitment, and RV septal capture when making threshold adjustments during device controls. Therefore, His-capture threshold tests should be performed under 12-channel ECG guidance.[33]

(b) Left Bundle Branch Area Pacing (LBBAP): The fact that the His bundle area is quite narrow in studies on HBP and that LBBB correction can be made at lower thresholds as a result of pacing from the distal His bundle has caused electrophysiologists to concentrate more on LBB pacing. LBBAP, which is shaped by these opinions, is a pacing technique that has been tried in the last few years and the conduction system is stimulated from a more distal area than HBP. LBBAP, which does not have the problem of R wave instability and the requirement for a high capture threshold in HBP, is thought to be an important resynchronization treatment option, especially in HF patients with QRS in LBBB morphology.

In a multicenter, retrospective, observational study conducted by Vijayaraman et al[34] in 2021 with 325 patients, it was seen that LBBAP is a viable and important alternative to CRT in patients with ischemic and non-ischemic cardiomyopathy.[34,35]

In the near future, like LBBAP, LV septal pacing may be an important alternative to HBP and BVP in the presence of intrahissian disease and proximal BB disease.[36]

(c) Fusion Pacing: His-Optimized CRT (HOT-CRT) and Left Bundle Branch-Optimized CRT (LOT-CRT): Conduction system pacing has shown the contribution of eliminating proximal conduction delays in HF patients. In recent years, fusion pacing strategies have become the subject of popular interest in order to maximize this contribution in the presence of IVCD in some patients in both the distal and proximal areas.

Large studies with HOT-CRT in 2019 and 2021 showed the most severe contraction in QRS duration when compared to BVP, MPP, and HBP. In these studies, the superiority of HOT-CRT in terms of providing a shorter right ventricular activation time compared to other resynchronization techniques is remarkable, and in this respect, it is a candidate to be the ideal resynchronization method in patients with RBBB.[37,38] For patients with LBBB, it may be reasonable to prefer LOT-CRT, which is a fusion pacing method such as HOT-CRT. As a result of the trials conducted by the international LBBAP collaborative study group, it has been reported that LOT-CRT is a pacing technique that should be tried in patients who did not respond to BVP or whose response was insufficient due to the greater electrical resynchronization provided by LOT-CRT.[39]

In conclusion, although all of the conduction system pacing methods seem to be as good or even superior alternatives to BVP, the development or presence of septal fibrosis in patient follow-ups is a question of interest.[40]

Post-procedural Programming Strategies

In BVP, ventricular activation occurs by the fusion of 3 vectors formed by the patient's intrinsic ventricular conduction and electrical stimulation of the CS lead and the RV lead. The timing of this fusion activation and its morphology in the 12-channel ECG can be changed by adjustments made via AV delay and VV delay during device interrogation. It is believed that with these adjustments, the efficiency of resynchronization can be increased. In studies using different algorithms based on echocardiography and ECG, it has been reported that shortening the AV delay provides QRS narrowing and an increase in the average aortic velocity time integral (aVTI), especially in patients with left bundle branch block. In studies using automatic algorithms of devices (QuickOpt, SmartDelay, AdaptivCRT), echocardiography and ECG-based different algorithms, shortening of AV delay and RV-synchronized LV Results have been reported that pacing provides QRS narrowing and an increase in the average aVTI, especially in patients with left bundle branch block.[41-44] However, in studies testing these algorithms, the low number of patients and the question of their adaptability to the patient population with CRT-D, whose heart structure and valvular disease severity and type are not homogeneous, prevent us from making a strong recommendation with AV-delay and VV-delay optimization. It is also known that keeping the AV delay time short may cause adverse effects on the ventricular filling pattern.[45] Nevertheless, it can be seen as a post-procedural strategy that can be evaluated in the group with low CRT response.

In addition, checking the optimal configuration of the stimulation vector and reviewing the suitability of the patient's medical treatment are routinely critical for correct patient management in the post-procedural period.

Additional Reccommendations and Future Technologies in CRT

Studies on whether advanced imaging methods such as MRI and PET-CT and ventricular potential mapping will be useful in determining the appropriate CRT technique for the patient are increasing[46-49] (Figure 4). Also, it is predicted that the increasingly widespread leadless pacemaker technology will open different horizons in resynchronization optimization. In the future, important animal studies can be conducted in terms of treatments that can regulate the contraction of myocardial cells with stimuli other than electricity.[50]

CONCLUSION

In the CRT technique, which was mainly developed to treat HF patients with electrical dyssynchrony, we suggest the application of current techniques that may be beneficial in light of current guideline recommendations. Conduction system pacing, especially LBBAP, HOT-CRT, and LOT-CRT,

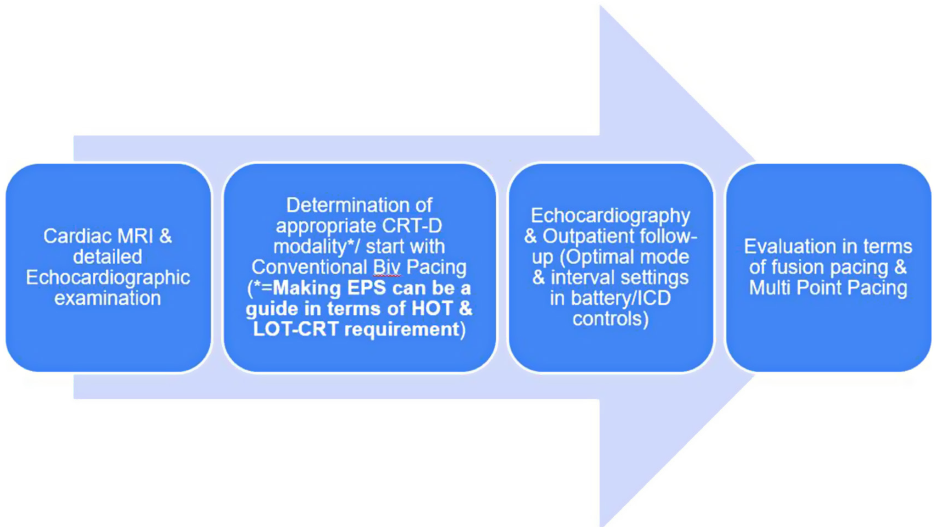

Figure 4. Optimal CRT-D management in current clinical practice. BiV, biventricular, CRT, cardiac resynchronization therapy; HOT & LOT-CRT, His-Optimized CRT and left bundle branch-optimized CRT.

stands out as candidate alternatives to be a suitable solution for patients with poor response to conventional BVP after its benefits have been supported by randomized controlled studies in the near future. It should be noted that after device implantation, correct management of patients in terms of optimal drug therapy, close follow-up in terms of echocardiographic controls, and device setting controls are of great importance (Figure 4).

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