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

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). 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. 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.

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...
In the 1990s, with several trials conducted with advanced heart failure in sinus rhythm with a QRS duration ≥150 ms (I-B) and LBBB QRS morphology 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 HFmrEF 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.

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.

Current Clinical Practice in CRT Implantation

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, several methods have lost their popularity and value, the CRT score, which includes the comorbidities of the patients, echocardiogram (ECG) rhythm [sinus rhythm (SR) or atrial fibrillation (AF)], QRS width, bundle branch block pattern, and cardiomyopathy etiology, has been seen as useful.

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 atrio-ventricular 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
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 trans-septal 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 groups24 (Figures 2 and 3).

(a) His-Bundle Pacing (HBP):

Persistent HBP was first used by Deshmukh et al25 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 al26 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 al21 2017   | Single center Prospective Observation:     | 21 | 76               | Clinical: NYHA III to II QRSd: 180-129 ms LVEF (%): 27-41               |
| Sharma et al26 2018    | Multicenter Prospective Observation:       | 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 al28 2019  | Multicenter Prospective Randomized crossover trial | 41 | 76               | QRSd: 172-144 ms LVEF (%): 26-32                                       |
| Huang et al29 2019     | Single center Prospective Observation:     | 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 al26 2018:   | Multicenter Retrospective Observation:     | 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.
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 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. 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.

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.

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. 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. 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 Recommendations 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 (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.

**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,
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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