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Cardiac Resynchronization Therapy Optimization: A Comprehensive Approach

Asim Katbeh[a, b] Guy Van Camp[a] Emanuele Barbato[a, b] Maurizio Galderisi[b]
Bruno Trimarco[b] Jozef Bartunek[a] Marc Vanderheyden[a] Martin Penicka[a]

[a]Cardiovascular Center Aalst, OLV Clinic, Aalst, Belgium; [b]Department of Advanced Biomedical Sciences, University of Naples Federico II, Naples, Italy

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Abstract
Since the first report on biventricular pacing in 1994, cardiac resynchronization therapy (CRT) has become standard for patients with advanced heart failure (HF) and ventricular conduction delay. CRT improves myocardial function by resynchronizing myocardial contraction, which results in reverse left ventricular remodeling and improves symptoms and clinical outcomes. Despite the accelerated development of CRT device technology and its increased application in treating HF patients, almost one-third of these patients do not respond to the therapy or gain any clinical benefit from device implantation. Over the last decade, multiple cardiac imaging modalities have provided a deeper understanding of myocardial pathophysiology, thereby improving HF treatment management. However, the optimal strategy for improving the CRT response remains debatable. This article provides an updated overview of the electropathophysiology of myocardial dysfunction in ventricular conduction delay and the diagnostic approaches involving the use of multiple modalities.

Introduction

The selection of patients with heart failure (HF) and ventricular conduction delay who will benefit from cardiac resynchronization therapy (CRT) requires both an accurate assessment of myocardial structure and function and a clinical evaluation. According to recent guidelines, patients are considered candidates for CRT if they have HF symptoms of New York Heart Association (NYHA) class II–IV, left ventricular (LV) ejection fraction (LVEF) ≤35%, and a QRS duration >130 ms on ECG [1, 2]. Despite the selection criteria, 30–35% of patients are nonresponders with no symptomatic improvement or reverse LV remodeling [3, 4]. Some individuals even experience a clinical deterioration following device implantation [3, 4]. In addition, the parameters used to predict CRT response have not been significantly associated with an increase in the responder rate. Of note, left bundle branch block (LBBB) morphology, a QRS duration of ≥150 ms, and adequate coronary sinus anatomy have been most closely associated with a favorable CRT response [3, 4]; mitral valve regurgitation (MR), right ventricular (RV) dysfunction, and atrial fibrillation (AF) have been shown to have a negative impact on patient response [5–7]. However, all these conditions are highly and concomitantly prevalent in patients undergoing

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E-Mail karger@karger.com
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M. Penicka
Cardiovascular Center Aalst, OLV Clinic
Moorselbaan 164
BE–9300 Aalst (Belgium)
E-Mail martin.penicka@olvz-aalst.be

CRT, which makes their use challenging. Finally, CRT-device programing parameters that delay the progression of myocardial damage have largely remained unidentified.

During the past 2 decades, several echocardiography- or ECG-derived strategies to improve outcomes in CRT patients have been proposed [8, 9]. However, the exact cut-off values to predict the response and clinical outcome post-CRT are not yet established. Studies are ongoing to improve the role of imaging in predicting CRT response, including EuroCRT, a large European multicenter prospective observational study [10]. Furthermore, several CRT-device programming approaches for CRT optimization have emerged [11]. It has become clear that the development of appropriate strategies to improve CRT response will require answering a range of both clinical and technological questions. Novel bio-imaging markers associated with myocardial function restoration post-CRT are still to be identified and the available CRT technology needs further adjustment. This review provides an updated overview of the pathophysiology of myocardial dysfunction in ventricular conduction delay and the diagnostic approaches for CRT that involve multiple modalities.

Pathophysiology of Myocardial Dysfunction in LV Conduction Delay

Mechanical contractility is a consequence of electrical activation of the heart. Hence, early detection of abnormal electrical-mechanical patterns is important. LV systolic function is inversely correlated with electrical width and vector of the QRS complex on ECG. However, in clinical practice, electrical reverse remodeling is not always accompanied by mechanical reverse remodeling. Accordingly, CRT optimization focused on achieving the shortest-paced QRS duration has yielded mixed echocardiographic and clinical results [12]. The major determinants of myocardial performance and cardiac output are preload, myocardial contractility, and afterload [13, 14]. In the dyssynchrony pattern, the systolic stretching leaves the septum in a hibernation state characterized by switching metabolism from free fatty acids to glucose as the preferred substrate; consequently, the septum no longer contributes to LV systolic function and stroke volume [15]. The systolic stretching caused by LV free-wall shortening impairs the work performed by the septal segment and the septum absorbs energy. In LBBB, the abnormal early activation may result in a partial or complete loss of septum contribution. These changes in myocardial function can eventually lead to alterations in adrenergic density as well as the deterioration of the resting function, inotropic reserve, and function recovery [16]. In HF patients with ventricular conduction delay, impaired LV function has been considered a reversible process which can be improved by restoring the myocardial function using CRT, but the most favorable effects are observed in patients with significant myocardial viability and contractile reserve. Such patients have the potential to improve after CRT therapy [15, 17].

Patterns of Motion and Deformation

In patients with LBBB, the apex exhibits a pre-ejection rocking motion, due to active septal contraction unopposed by the absence of activation of LV lateral wall contraction. Many researchers suggested using visual markers of cardiac motion including apical rocking and septal flash as indicators for dyssynchrony [18, 19]. However, dyssynchrony is often subtle, and so it cannot be quantified by visual assessment alone. Quantitative tools should be used to complement the visual description of myocardial deformation [18–20].

Since 2002, cardiac motion dyssynchrony has traditionally been described by parameters such as a septal-to-posterior wall motion delay ≥130 ms measured by M-mode echocardiography [21]. More recently, myocardial deformation has been assessed by imaging tools such as color-coded or pulsed tissue Doppler imaging, with dyssynchrony indicated by an opposing wall delay of ≥65 ms and a time to onset systolic velocity of ≥100 ms. However, these indicators have many technical limitations [21].

Speckle-tracking echocardiography (STE) imaging applied to routine echocardiography can provide higher accuracy to predict reverse LV remodeling post-CRT, as defined by an acute improvement of LVEF or LV end-systolic volume [22]. An acute increase in magnitude, together with more extensive synchronization of LV longitudinal strain, has been associated with improved functional capacity and NYHA class post-CRT [23]. This finding supports the use of STE to assess global longitudinal and radial strains to predict the extent of reverse LV remodeling following CRT (Fig. 1). Furthermore, regional strain patterns, particularly of septal strain, may help in assessing myocardial deformation in dyssynchronous HF, although the extent of acute change that predicts the clinical outcome remains unknown [24, 25].

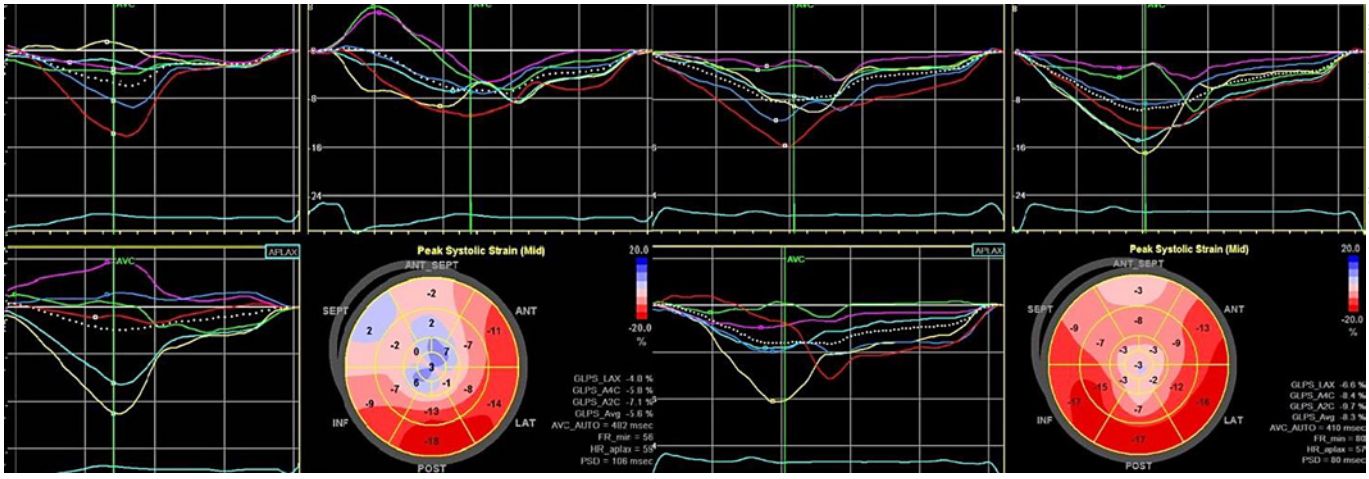

Fig. 1. Speckle-tracking echocardiography showing global longitudinal strain of the left ventricle in a patient with heart failure treated by cardiac resynchronization therapy (CRT). Left, before implanting CRT; right, echocardiography-based CRT optimization at 3 months.

Tissue tracking by using cine cardiac magnetic resonance (cine-CMR) has shown promising results, with recent studies reporting comparable results for radial dyssynchrony between cine-CMR and STE [26]; CMR can also be used to identify and evaluate mechanical dyssynchrony in patients with LBBB [27]. However, CMR has technical limitations in HF patients with LBBB, and further evaluation is needed before it can be clinically implemented [27]. Other limitations are high costs and limited availability.

Myocardial Viability and Fibrosis

CRT response may be reduced by diminished myocardial viability associated with extensive LV scarring [28]. Moreover, CRT electrodes should not be placed in segments with scar tissue which can be easily identified on CMR [29, 30]. Patients with ischemic LV dysfunction and LBBB may have various amounts of focal myocardial fibrosis including in the interventricular septum. In contrast, patients with nonischemic cardiomyopathy may have a high level of diffuse fibrosis in the septum. A detailed description of regional myocardial fibrosis in dyssynchrony is needed (Fig. 2).

Advanced imaging methods, such as CMR, allow quantitative assessment of focal and diffuse myocardial fibrosis, but they do have limitations. CMR with late gadolinium enhancement, in particular, shows wide variation in quantifying focal fibrosis and cannot detect diffuse fibrosis [31, 32]. Other CMR approaches, such as T1 mapping and extracellular volume mapping, are affected by specific CMR techniques and magnetic field strength; they lack reference ranges, and there is a significant overlap of T1 mapping values of healthy and disease states [31, 32].

Using innovative imaging tools in this field is key to understanding the disease of the myocardial muscle, in terms of cellular and tissue abnormalities. Nuclear imaging, including positron emission tomography (PET), demonstrates reduced myocardial perfusion, glucose uptake, and oxidative metabolism in the septum of LBBB patients [33]. CRT partially normalizes these changes; therefore, measuring these radionuclide parameters may offer an improved approach for selecting CRT candidates [33]. Similarly, single-photon emission computed tomography (CT) supplies information about perfusion and is complementary to PET, which reflects metabolism. Radiation dose and the limited availability of PET may hamper routine clinical use. The advantages and limitations of different imaging techniques are summarized in Table 1.

Concomitant Cardiac Conditions

RV dysfunction is associated with a poor prognosis for HF patients [34]. Its role in CRT candidates is controversial. Impaired RV function pre-CRT, similar to HF, is associated with worse survival post-CRT [35], but a study has shown that CRT may improve RV function and prognosis in patients with RV dysfunction [36]. A previous

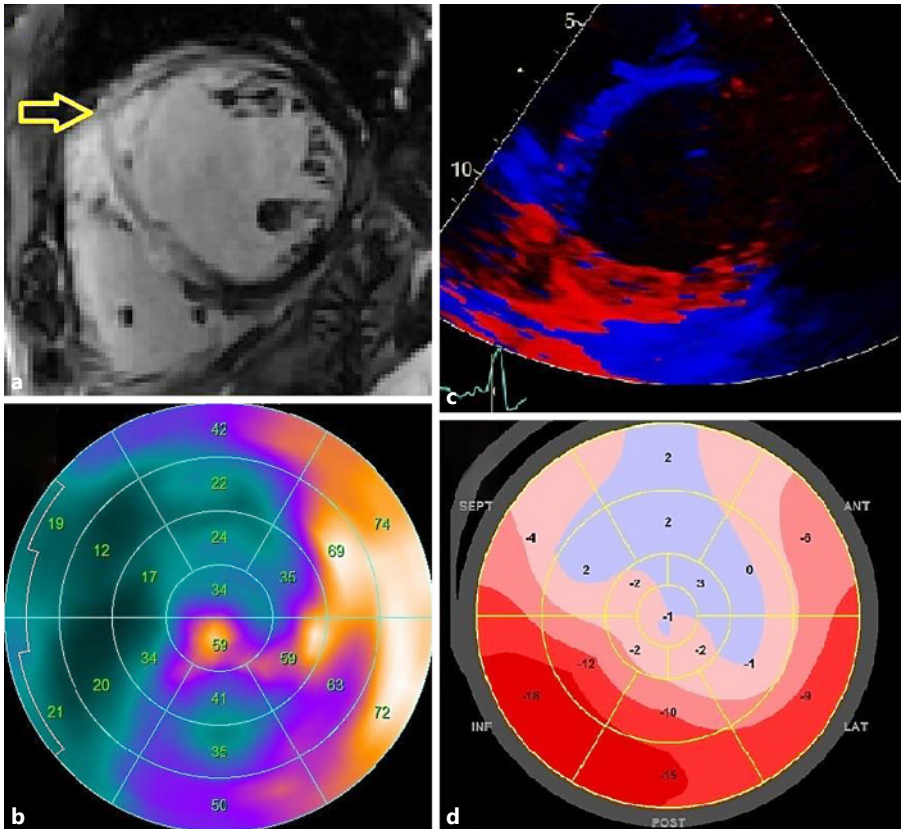

Fig. 2. Examples of resting global longitudinal strain (GLS) of the left ventricle compared with the extent of hypoperfusion and the distribution of myocardial fibrosis in a patient with complete left bundle branch block and significantly reduced biventricular function. **a** Late gadolinium enhancement on cardiac magnetic resonance imaging demonstrating a dense septal scar in the left ventricular septal wall. **b** Scintigraphy image of a very large area of severe myocardial hypoperfusion and extensive transmural infarction in the septum. **c**, **d** Tissue Doppler image of myocardial dyssynchrony with a reduced magnitude of 2D GLS measured by speckle-tracing echocardiography.

Table 1. Cardiovascular imaging modalities and their advantages and limitations for the selection of cardiac resynchronization therapy candidates and optimizing therapy

	Advantages	Limitations
Echocardiography	Widely used; safe after CRT implantation	Relative subjectivity in quantifying myocardial dynamics
Tissue tracking with STE	Non-Doppler angle-independent evaluation of myocardial deformation evaluation; good reproducibility	Tracking affected by out-of-plane cardiac motion; intervendor variability
CMR mapping	More objective quantification of myocardial systolic dynamics; LGE and T1 mapping are promising methods for detecting focal and diffuse myocardial fibrosis, respectively	High cost and limited availability; adverse reaction to gadolinium; relative complexity of acquisition
Tissue tracking with CMR	Imaging possible in any plane; complete myocardium visualization	Technical limitations in HF patients with LBBB; time-consuming
PET and SPECT	Complementary assessment of CRT candidate with ischemic cardiomyopathy	Not widely used
X-ray fluoroscopy	Guides the position of the CRT leads by contrast injection through the right heart cavity and coronary sinus	Limited used for guiding the CRT leads during the procedure
MSCT	Visualization of cardiac veins; evaluation of structural remodeling in patients with inadequate echocardiographic images and CMR contraindications	High radiation dose

CRT, cardiac resynchronization therapy; STE, speckle-tracking echocardiography; CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; HF, heart failure; LBBB, left bundle branch block; PET, positron emission tomography; SPECT, single-photon emission computed tomography; MDCT, multidetector computed tomography.

meta-analysis revealed that echocardiographic parameters of RV function do not predict CRT response-related changes in LVEF [37]. In contrast, a recent study reported that RV systolic dysfunction before CRT implantation could identify patients that might not benefit from CRT [38], and a prospective study concluded that CRT induces RV reverse remodeling and improves RV function with improved interventricular dependence [39]. Furthermore, a higher baseline RV-pulmonary artery (PA) coupling is associated with improved LV reverse remodeling and independently associated with a better prognosis [40]. Of note, the response to CRT was strongly associated with RV-PA coupling in both studies [39, 40]. However, using the RV-to-PA ratio as a potential guide for CRT in patients with diseases in whom RV failure predominates needs further investigation [39, 40].

Patients with congenital heart disease (CHD) may benefit from CRT. A recent German registry revealed that CRT can be used as an adjunct in the HF treatment of selected CHD patients [41]. A retrospective review on 20 patients with congenitally corrected transposition of the great arteries reported that CRT implantation is feasible, and that the long-term outcome is favorable but linked to systematic morphologic RV dysfunction in some patients [42]. Since most of the studies available are retrospective in nature, the impact of CRT on long-term prognosis in this population is still unknown [43, 44].

Several studies have shown that CRT improves secondary MR [45, 46]. A less favorable effect on MR has been reported in ischemic LV dysfunction with extensive scarring. Larger residual MR (an effective orifice area ≥ 0.20 cm^2) following CRT has been associated with increased mortality and HF hospitalizations [47]. A recent study on 277 HF patients observed that MR severity at 6 months decreased in 48 (42%), remained stable in 42 (37%), and worsened in 24 (21%). Four-year adverse event rates were strongly predicted by the presence of at least moderate MR after, but not before, CRT [48]. On the other hand, a prospective study on 198 patients demonstrated that significant secondary MR after CRT is associated with higher morbidity and mortality, i.e., MR despite CRT provides important prognostic information beyond LV reverse remodeling [49].

Patients with AF before and after CRT represent a challenging cohort with insufficient data to guide clinical decision-making. CRT is recommended in patients with AF and ≤35 LVEF who meet the CRT criteria and in whom atrioventricular (AV) node ablation or pharmacological rate control allow approximately 100% ventricular pacing with CRT [50]. Although CRT improves some risk factors for AF, such as atrial size and LV systolic function, it does not reduce AF recurrence [50]. It is of note that, in HF with AF, pulmonary vein isolation may result in a better control of symptoms at short-term follow-up compared than CRT plus AV node ablation [51]. However, because the long-term effects remain unknown, pulmonary vein isolation should be only performed in selected individuals, taking into account patients' preference [51]. Further data on these patients are needed for developing a standardized approach.

Noncardiac Comorbidities

Many noncardiac comorbidities, e.g., diabetes, hypertension, dyslipidemia, obesity, respiratory insufficiency, and renal dysfunction, negatively affect myocardial contractility. CRT response is associated with the stabilization or improvement of renal function, which, in turn, is associated with lower mortality [52, 53]. A meta-analysis suggested that diabetic patients with advanced HF who received CRT exhibited higher total mortality than nondiabetic patients [54]. However, the increased mortality might have been attributable to insulin administration [54]. In the same context, another retrospective analysis showed that coexisting chronic obstructive pulmonary disease was an independent predictor of a nonresponse to CRT [55]. Cardiac disease but also noncardiac concomitant diseases should be taken into consideration when selecting patients for CRT [56].

Blood Biomarkers

Blood biomarkers, such as N-terminal pro-B-type natriuretic peptide (NT-proBNP), troponin T, galectin-3, and plasma miRNA-21, reflect myocardium status in HF patients. A reduction in the levels of these markers is mostly associated with a favorable CRT response [57]. The BIOCRT study revealed that NT-proBNP levels were 20% higher in the coronary sinus than in the peripheral veins [58]. It suggested that the coronary sinus sampling of HF biomarkers is more accurate than the peripheral venous blood sampling for predicting CRT outcomes. This study also reported that elevated galectin-3 levels during CRT device implantation are associated with the absence of MR improvement after CRT [59]. Thus, high circulating levels of these markers at the coronary sinus or peripheral veins may predict the CRT response and could therefore be used to document therapy success.

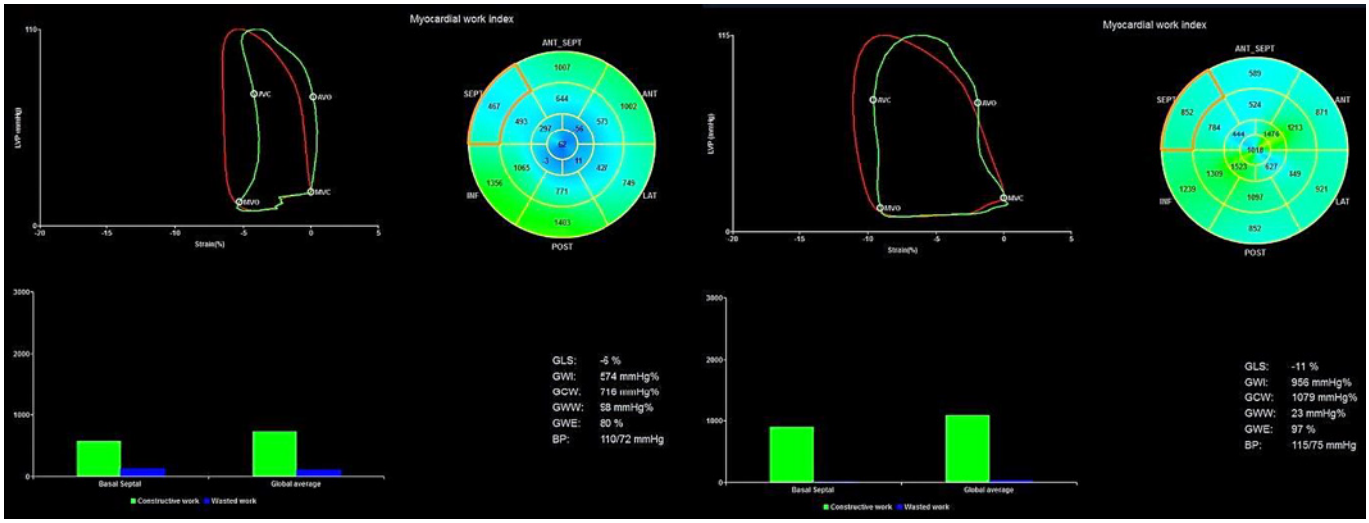

Fig. 3. Regional and global myocardial work in a heart failure patient responded to cardiac resynchronization therapy (CRT). Left, before implanting CRT; regional work was inhomogeneous in the septal segments. Right, after 12 months; CRT increases the global myocardial work and this inhomogeneity disappeared.

AV and Ventriculoventricular Time Interval

Prolonged PR intervals may impair AV mechanical coupling and the restoration of AV mechanical coupling with CRT may improve survival [60]. Following CRT implantation, AV interval optimization is of crucial importance to allow the completion of the atrial contribution to diastolic filling, resulting in the most favorable preload before ventricular contraction [61]. Several approaches have been used to optimize AV time interval. The CRT device's AV interval time setting has been considered the cornerstone for restoring myocardial contractility and performance. Doppler echocardiography-derived AV optimization has been associated with an improvement in both LV systolic function and presystolic MR. In brief, AV delay is programmed so that the end of atrial contraction is timed to coincide with the onset of ventricular contraction [62]. Because AV dyssynchrony is common and modifiable, Doppler echocardiography-guided AV optimization after CRT is warranted, particularly in nonresponders with a fused or truncated LV filling pattern [63]. The clinical efficacy of AV optimization has yet to be established.

The ventriculoventricular (VV) interval optimization, which is affected by LV and RV function, is rarely performed because it is time-consuming and without proven clinical benefit [64]. The methods used for VV optimization may be suboptimal to achieve adequate inter- and intraventricular resynchronization. However, it is still necessary to demonstrate its clinical relevance, and VV interval modification may be proposed to reduce the persistent asynchrony in nonresponders [65]. In summary, in clinical practice, CRT system parameters are often set empirically, using a shortened AV interval (90–120 ms) and simultaneous biventricular (BiV) pacing, with no further optimization during follow-up.

Mechanical Work

To assess myocardial reverse remodeling which directly affects the cardiac output following CRT, previously, studies used simple visual patterns such as apical rocking and septal flash to predict CRT responders [19, 20, 66]. Furthermore, it was reported that the correction of mechanical dyssynchrony versus the volumetric response was associated with long-term survival [67]. Recently, the calculation of the systolic dyssynchrony index (SDI) via real-time 3D echocardiography showed a superiority in the assessment of LV performance following CRT [68]. In contrast to a previous small study which reported that CRT optimization of interventricular delay by using SDI (vs. QRS width) assessment did not reveal any significant difference in terms of volumetric and clinical response at the 12-month follow-up [69], recent large studies have demonstrated that a more pronounced reduction in SDI immediately after CRT is independently associated with a superior long-term outcome [70], and that SDI derived

Table 2. Echocardiography-based cardiac resynchronization therapy candidate selection criteria and response optimization

Method	Useful markers and parameters	Comments
M-mode	Septal-to-posterior wall motion delay of ≥130 ms	Limited assessment in clinical practice
B-mode	LVEF improvement and ≥15% ESV reduction relative to baseline	Standard parameters for predicting CRT response
Color-coded tissue Doppler imaging	Opposing wall delay of ≥65 ms	Many technical limitations
Pulsed tissue Doppler imaging	Delay in time-to-onset systolic velocity of ≥100 ms	Many limitations
Standard views based on LV mechanical description	Apical rocking and septal flash introduced to describe myocardial dyssynchrony	Relatively subjective
STE-derived strain	STE-derived regional strain and global strain measurement to determine LV reverse remodeling	Non-Doppler; angle-independent; underutilized
Area tracking using 3D STE	Area strain dyssynchrony index may enable a more objective quantification of myocardial systolic dynamics	Good image quality required for 3D STE; debatable STE standardization
Assessment of wasted myocardial work	Pressure-strain loops describe strain dispersion due to load change	Further investigation required

CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; ESV, end-systolic volume; LV, left ventricular; STE, speckle-tracking echocardiography.

by 3D speckle-area tracking shows a good correlation with the reduction of end-systolic volume post-CRT [71]. However, there is no consensus regarding the feasibility of using SDI to optimize the CRT.

Recently, noninvasive methods of calculating myocardial work have been applied in research into CRT response. Recent studies focused on mechanical dyssynchrony by taking into account the wasted and constructive myocardial work by means of strain analyses and hemodynamic data [72, 73]. The assessment of regional distribution to myocardial work based on different hemodynamics patterns can be used to determine the impact of elevated load on myocardial performance in HF patients that qualify for CRT [74]. These myocardial work indices derived from pressure-strain loops may provide comparable beneficial effects to serial evaluation of LV function (Fig. 3). At present, it is reasonable to consider these indices as semiquantitative novel tools to aid in guiding CRT, but caution is needed until this is validated in larger prospective studies. Echocardiography-based CRT candidate selection criteria and response optimization are summarized in Table 2.

The assessment of BiV performance by echocardiography stress test should be interpreted to identify pathways and targets, so that we can address different phase patterns of ventricular remodeling and determine the degree of residual dyssynchrony, particularly in nonresponders [75]. On the other hand, cardiopulmonary exercise testing (CPET) might be helpful to assess the exercise capacity of HF patients with diseases of heart muscle and other significant diseases underestimated by rest evaluation [76]. Contemporary trends suggest that combined CPET imaging stress test can be implemented in clinical practice to assess BiV dysfunction in different HF phenotypes not detectable with rest evaluation [77].

Lead Placement

Optimal LV lead placement is crucial for a favorable CRT response. Accumulated evidence suggested that mechanical resynchronization is the primary mechanism underlying CRT response. Accordingly, in the absence of scarring, the optimal LV lead position is generally lateral or posterolateral because this is often the latest segment to contract in the presence of LBBB [78]. In contrast, apical pacing and pacing in a densely scarred region should be avoided when tailoring the therapy and to prevent adverse events [78, 79]. A multimodality complementary approach is ideal to establish the optimal CRT lead placement precisely. Multidetector CT can be used for preoperative mapping of the cardiac veins to assess

the availability of suitable veins in potential target segments prior to CRT implantation [80]. The CRT outcome can be predicted by analyzing the 3D coronary sinus lead-tip trajectory and optimizing its placement based on advanced imaging methods [81]. Clearly, the introduction of a LV quadripolar lead provides multiple ways to pace the ventricle, and thus more options to avoid negative workload of the LV segments and achieve CRT optimization [82].

Maximal electric separation-guided placement of the RV defibrillation lead during CRT should be considered. The results of recent studies clearly show the benefits, in terms of reverse LV remodeling and clinical response, that can be obtained with optimization of the RV lead pacing position; the placement of the RV lead guided by maximal electric separation compared with standard apical placement not only improves cardiac function but can also reduce the risk of ventricular arrhythmia [83, 84]. For CRT therapy, multipoint pacing, guided by noninvasive hemodynamics, shows a positive LV structural remodeling [85]. However, many limitations in LV lead implantation, due to anatomical or other constraints, need to be considered. At present, permanent His-bundle pacing is a feasible alternative for patients in whom BiV pacing provided no clinical response. His-bundle pacing allows for the recruitment of BBB disease and ventricular activation in a more physiological fashion, specifically in patients with right BBB and those with AV block [86].

Emerging Optimization Strategy

A timely upgrade to BiV- or His-bundle-pacing devices needs to be considered in patients with CRT. A single-center registry involving 304 patients demonstrated that daily remote monitoring can be useful to identify the percentage of BiV pacing, and that a higher percentage improves the long-term prognosis after CRT [87]. Moreover, a recent study including 201 candidates reported that a higher percentage of BiV pacing (>98% at 6 months after CRT) is essential for patients to become superresponders [88]. However, the real clinical value of BiV-pacing percentage still needs to be validated in multicenter prospective studies.

Sensor-derived approaches are rapidly developing in modern cardiology. In CRT patients, the SonR sensor, which is embedded in the right atrial lead and picks up the intensity of the first heart sound as a surrogate for cardiac contractility, has been used to optimize CRT settings [89]. It provides the opportunity for continuous reading of myocardial contractility during rest and exercise. This allows continuous adaptation of the AV and VV interval setting of the CRT device according to the instantaneous needs of the patient [89]. A comparative study demonstrated that automatic optimization with the SonR sensor is as effective as echo-guided optimization, allowing the primary efficacy end point to be met with a 35% significant reduction in HF hospitalization rates during long-term follow-up [90].

Advanced Computer Modeling

Advanced computer modeling combined with machine learning may provide mechanistic insights into CRT efficacy. It may help to solve complex problems involving big data by identifying interaction patterns among multiple variables in potential CRT candidates [91, 92]. The application of neural networks and deep learning in cardiovascular medicine plays a crucial role in imaging accusation, reconstruction, quantification, and analysis [93]. A combined deep-learning and deformable-model approach is a promising tool for fully automatic segmentation of the myocardium in CMR [94].

Thanks to recent advances in addictive manufacturing technologies, computational modeling and 3D printing have become powerful tools to describe the heart structure and the properties of myocardial tissue [95]. The encouraging results highlight clinical perspectives on the use of computer-aided design models to monitor myocardial structural changes following CRT and ultimately shape a favorable remodeling response to CRT [96, 97]. Certainly, the integration of imaging and nonimaging information based on computer-aided diagnosis will allow us to determine not only the effect of CRT on myocardial performance in the different phenotypes of cardiomyopathy, but also the long-term impact of CRT on the different symptomatic classes of HF patients [98].

Conclusion

CRT has shown significant clinical benefits for patients with HF refractory to medical therapy. Despite the great advances in CRT technology over the past decade, a further improvement of device settings, lead placement, and imaging tools is needed to improve the efficacy of CRT. However, programming devices to optimize the delivery of CRT remains challenging, and there are still no parameters that are routinely indicated to predict CRT

response or guide CRT optimization. At present, multivariate computational models are promising tools used in the assessment of electromechanical dyssynchrony, and the latent strength of these methods to optimize CRT has shown great promise. Future advances will hopefully facilitate the identification of new bio-imaging markers and technical approaches to increase the responder rate. The promising results of pilot studies to date need to be validated in a multicenter, prospective setting.

Disclosure Statement

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