Chapter

CRT Past, Present, and Future Directions: Toward Intelligent Responders Selection and Optimizing Pacing Modalities

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Abstract

Congestive heart failure (CHF) is a serious health problem affecting all nations of world. Its impact is increasing with increasing individual age. Ventricular dyssynchrony is well known to contribute to pathophysiological deterioration in more than one-third of CHF subjects. The therapeutic choices of CHF witnessed long decades of stagnant periods and a relative paucity of effective treatment. The discovery of the electrical therapy that is capable of reversing ventricular dyssynchrony, in the form of cardiac resynchronization therapy (CRT), is a true revolution in the timeline of CHF management. Despite the early enthusiasm associated with CRT implantations started in 2001, we know from the last two decades' experience that non-responders constitute to nearly 40% of all CRT patients. This chapter is devoted to reviewing the past, present and future of CRT with special attention on better intelligent detection of the electrical substrate responsive to CRT as well as optimizing the choice of CRT subjects using the latest knowledge in electrocardiographic and state-of-art imagining technologies. Novel future directions are discussed with new scientific philosophies capable of optimizing CRT. Promising new implants techniques such as endocardial pacing of the left ventricle, His bundle pacing as well as His-optimized cardiac resynchronization therapy are discussed.

Keywords: cardiac resynchronization therapy (CRT), congestive heart failure (CHF), electrical cardiac devices, left bundle branch block (LBBB), right bundle branch block (RBBB), future directions

1. Introduction

Congestive heart failure (CHF) is one of the most important epidemics in the current human species era affecting 1–2% of adults and around 10% of >70 years old in developed countries. The lifetime risk of developing heart failure is one in five after 40 years of age. In the United States, it costs around $39.2 billion in 2010. Sub group of CHF subjects with reduced ejection fraction and electrical dyssynchrony constitutes a true therapeutic challenge. Therapeutic strategies of this CHF sub group witnessed stagnant periods until electrical therapies were introduced to the world communities where cardiac resynchronization therapy (CRT) became available for clinical use first in 2001. Candidates for CRT are CHF subjects with

reduced left ventricular systolic function, QRS duration of >120 ms with left bundle branch (LBB) morphology, and functional classification with NYHA class III–IV. Accumulative knowledge in the last two decades has shown that more than one-third of patients are not responding with lack of echocardiographic reverse remodeling or no improvement in quality of life (QOL). Intelligent CRT subjects selection with multidisciplinary expertise and improved procedural skills and strategies, as well as optimizing post-implant care are the main targets to achieve the improved outcomes for the non-responders. Nowadays, a new CRT imaging techniques and innovative pacing strategies are top priorities for us in CHF electrical therapies arena. This chapter is a journey in the CRT timeline reviewing the past, discussing the current situation, and elaborating in future directions for better psychophysiological well-being of CRT subjects.

2. Applying electrical therapy as medicine to treat human disease

Utilizing electric current to treat human disease is an idea that fascinated humans since antiquity. The electrical discharges produced by torpedo fish were utilized as an efficient natural source for electric shock generation by Hippocrates (460–370 BC), Scribonius Largus, and Galen (129–210 AC). It was prescribed for neurological diseases like headache, arthritis gout pain, and prolapsed anus. In 46 AD Scribonius Largus in his compendium of medical treatments known as *Compositiones* described a novel treatment for headache, where, a living black torpedo is put on the place which is in pain, and results were very encouraging. The electric organ of the electric fish can produce amplitudes ranging from 10 to 860 V with a current of up to 1 A. In cardiac science, electrical stimulation was an attractive choice for incapacitating angina pain. An induction coil with sponge-tipped electrodes was used in 1853 to successfully treat abnormal heart rhythms and angina. Relief of angina pectoris by electrical stimulation of the carotid-sinus nerves was achieved repeatedly [1]. The introduction of coronary artery bypass shortly after this convert the electrical stimulation procedure to obsolete. The most fascinating and valuable incorporation of electric therapy in medicine was in the arena of treating rhythm disturbances, either in bradycardia or tachycardia management The first pacemaker was implanted in a person in 1958 and the first lithium battery was introduced in 1969. The deleterious hemodynamic effects of the left bundle branch block (LBBB) had been appreciated by many intelligent observers in the cardiac communities. About 30% of heart failure subjects with reduced ejection fraction with wide QRS interval in the electrocardiogram, tend to have worse clinical outcome [2, 3]. In addition, intraventricular conduction delay (IVCD) was observed as a pathological finding with multiple hemodynamic derangements, including reduced pulse pressure, impaired diastolic function, and mitral regurgitation of functional origin [4]. Early attempts to address this pathology which demonstrated favorable acute hemodynamics and medium-term functional improvements were observed using biventricular pacing [5, 6]. Multisite Stimulation in Cardiomyopathy (MUSTIC) Trial, published in 2001 was the first large trial demonstrating CRT benefits clinically, where three champers are paced, right atrium, right ventricle, and left ventricle. The first CRT device was implanted in the same year. In an attempt to improve the clinical outcome, 10 other prestigious trials were performed. Those 11 clinical trials constitute the determinants and guidelines dictator for CRT practice nowadays. **Table 1** illustrate the details of the inclusion criteria, comparison, and the significant findings of the most influential CRT trials [14]. Nowadays, the cardiac electrical devices communities are investigating methodologies and techniques to improve

CRT outcomes mainly in the non-responders group. The non-LBBB population is classically thought to be out of the selection criteria for CRT. In spite of that, we believe nowadays that 30–50% of these population will benefit from CRT. With this new knowledge, we should convert the necessity of LBBB criteria as lone evidence for ventricular dyssynchrony, an obsolete. In this chapter we are discussing with detail, an innovative diagnostic modalities to hunt the potential responders for CRT. Visionary insight for future speculations will conclude this CRT scientific journey.

Name	Population (n)	Inclusion	Endpoint	Results
MUSTIC SR	58	III, EF < 35%, QRS ≥ 150	6MWT, QoL, pVO2, hospitalization	CRT-P improved : 6MWT, QOL, pVO2; reduced hospitalization
MIRACLE [7]	228-CRT 25-control	III-IV, EF <35%, QRS ≥130	NYHA class, QoL, pVO2	CRT-P improved: NYHA, pVO2, 6MWT
MIRACLE-ICD	186	II, EF < 35%, QRS ≥ 130	6MWT,QoL, hospitalization	CRT-D improved all from baseline (not ICD)
COMPANION [8]	ICM NICM 1,520	III-IV, EF < 35%, QRS > 120	All-cause mortality or hospitalization	CRT-P/CRT-D; reduced endpoints HR 0.80 (CRT vs medical)
CARE-HR [9]	ICM NICM 813	III-IV, EF < 35%, QRS > 120	All-cause mortality or hospitalization	CRT-P/CRT-D; reduced endpoints HR 0.63
MUSTIC AF	59	III, EF < 35%, QRS ≥200 (paced QRS)	6MWT, QoL, pVO2, hospitalization	CRT-P improved : 6MWT, QOL, pVO2, hospitalization
CONTAK-CD			All-cause death + HF hospitalization, pVO2, 6MWT, NYHA class, QoL, LVEDD, LVEF	CRT-D improved: pVO2, 6MWT; reduced LVEDD and increased LVEF
RAFT [10]	1798	II, III, EF <30%, QRS ≥120	Death from any cause or hospitalization for HF	The addition of CRT to an ICD reduced rates of death and hospitalization for HT
REVERSE [11]	610	I-II, EF <40%, QRS ≥ 120	(i) % worsened by clinical composite endpoint, (ii) LVESVi, (iii) HF hospitalization, (iv) all-cause death	Primary endpoint NS; CRT-P/CRT-D reduced (ii) and (iii) hospitalization but not (iv)
MADIT-CRT [12]	ICM NICM 1820	I-II, EF <30%, QRS ≥ 130	(i) HF event or death, (ii) All-cause death, (iii) LVESV	CRT-D reduced (i) and (iii) but not (ii)
MIRACLE-ICD II [13]	186	II, EF <35%, QRS ≥ 130	VE/CO2, pVO2, NYHA, QOL, 6MWT, LV volumes, LVEF	CRT-D improved: NYHA, VE/CO2; volumes, LVEF

Table 1.
Major clinical trials.

3. The dilemma of intelligent resynchronization therapy subjects selection

The philosophy of resynchronizing the electrical stimulation of both ventricles developed into more mature practice, nowadays. The current CRT guidelines are the product of knowledge of the aforementioned clinical trials (**Table 1**) in addition to the accumulation of personal and institutional expert opinions. The most important organizations contributing most importantly to today's guidelines are: American Heart Association, the American College of Cardiology, Heart Rhythm Society, the Heart Failure Society of America, and the European Society of Cardiology. American criteria to define LBBB as defined by AHA/ACC/HRS are as follows:

- QRS >_120
- Notch-, slurred R in I, aVL, V5, and V6
- Occasional RS pattern in V5–V6
- Absent q in I, V5–V6, and aVL
- R peak time >60 ms in V5 and V6
- Normal R-peak time in V1–V3
- No negative concordance
- Usually discordant ST-T segments

The vast majority of recommendations of those organizations are concordant to each other making class I indications clear for CRT specialists to implement. 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) [15]. 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 LBBB pattern [16–18]. On the other hand, echocardiographic evaluation looking for mechanical dyssynchrony results of the Predictors of Response to CRT (PROSPECT) Trial published in 2008 did not show superiority for CRT outcome for any of the predictors [19]. Accumulation of data in the last two decades demonstrated clearly that the CRT success in electrical resynchrony, mechanical remodeling, and quality of life improvement is not always directly linked to the current selection criteria. Response to CRT seems to be more complex than we thought earlier. Currently, 30–40% of our subjects are non-responders. We recommend extension criteria for CRT subjects selection considering the old criteria of QRS duration >130 ms, LV dysfunction (<35%), and NYHA class II-IV as a guideline with more extensive clinical, pathological, imaging and programming variables to be considered. Critical variables such as global scar burden, scar location, lead position, programmed AV and VV interval, mitral regurgitation, and irreversibly advanced heart failure cases are imperative considerations to improve the outcome [20] Despite the traditional dogma that normal QRS duration is a contraindication for CRT, recent challenging groups suggest that QRS complex <130 ms might benefit from CRT. This response as they describe it, is personalized but having QRS complex <130 ms should not be a reason to withhold the option of CRT in systolic heart failure if no other effective treatment is available [21]. Despite the claim that CRT is under-utilized worldwide, we suggest more wise selections

with the advanced criteria for more intelligent selection. Our top priority should be the perfection of patients' choices to optimize benefits from CRT. Adjunction of defibrillator therapy with CRT as primary prevention of SCD is indicated in most CRT patients. For this reason, current guidelines advocate an implant of a CRT-D in eligible patients [9, 12]. Most of the systems we are implanting nowadays are CRT-D. This addition of defibrillator stress more for the need of more intelligent and comprehensive criteria for subjects selection. It is imperative to treat any primary disease before thinking of introducing the choice of CRT. Reversible heart diseases such as myocardial ischemia, arrhythmia (tachycardia-induced cardiomyopathy), or primary valvular heart disease must be treated. When AF is a risk factor, catheter ablation of AF is superior to AV node ablation combined with biventricular pacing. This superiority is increasing with the dramatic improvement in our skills and technology, especially with pulmonary veins cryoablation technique. In the subgroup of patients who received prior pacemaker or ICD with worsening heart functions, an upgrade plan for CRT-D seems appropriate. The majority of patients we are implanting, died without experiencing an appropriate ICD shock. A selection system that is capable of predicting survival in patients who received a CRT-D as primary prevention of SCD, identify a subgroup with a significantly poor prognosis despite a CRT-D, as well as being able to discriminate between patients with a low or high risk for mortality, is highly needed. The predictive HF meta-score is constructed of independent mortality predictors identified in a meta-analysis. Three continuous variables constitute this comprehensive evaluation score. In addition to age, LVEF and eGFR, New York Heart Association (NYHA) functional class; 11 dichotomous variables which give the score true discriminative strength including: male gender, African-American race, diabetes, chronic obstructive pulmonary disease, peripheral vascular disease, ischemic cardiomyopathy, HF admission within 1 year before implantation, past or present atrial fibrillation, wide QRS (≥120 ms), secondary prevention indication, and history of ICD shocks (appropriate and inappropriate) [22]. The authors of this meta-analysis found the HF meta-score, a good predictor for survival and useful to detect a subgroup with a significantly poor prognosis despite a CRT-D. In addition, accumulated medical literature in the last few years pin point other conduction system disorders in addition to the major well-known indication of the LBBB as potential indications for CRT. Those indications were based on evidence derived from sub-analyses from the landmark trials and will be discussed in the next section.

4. Understanding the pathophysiological mechanism for becoming a CRT responder

The presence of intrinsic LV electrical dyssynchrony is considered to be the traditional electrical substrate of CRT. Mechanical inefficiency is the result of inefficient electrical-mechanical coupling ending up with triggering two main important outcomes: first is a hemodynamic disturbance in the form of reduced stroke volume and second structural deformation in the form of a cardiac remodeling process. Biventricular pacing, delivered by a CRT device, by correcting the dyssynchrony can improve both hemodynamic and structural derangements [23]. Studying ventricular activation time (known also as intrinsicoid deflection) and variability in activation sequence and passive conduction properties of normal hearts must be perceived very well for accurate comparison and assessment of ventricular dyssynchrony or other activation disorders [24]. Building on this important consideration, we in pacing communities must remind ourselves always of the fact that biventricular pacing is never physiological. Biventricular pacing induces a stage of dyssynchronous electrical activation, remarkably observed at the level of the LV [25].

But with significant baseline electrical dyssynchrony, biventricular activation can be of benefit. Worsening of ventricular synchrony is expected in cases of little or no electrical dyssynchrony resulting in iatrogenic electrical dyssynchrony [25]. Being able to distinguish between patients that may or may not benefit from CRT, is based on a proper understanding of the true deviation from the normal activation pattern of ventricles and proper establishment of the presence of sufficient baseline electrical dyssynchrony.

Research projects supporting this important understanding in biventricular pacing science are multicenter randomized LESSER-EARTH (cardiac resynchronization therapy in patients with heart failure and a QRS complex <120 ms: the evaluation of resynchronization therapy for heart failure) in addition to ECHO-CRT (echocardiography in cardiac resynchronization therapy) trials. Premature termination of patients with narrow QRS duration was elected due to safety concerns [26, 27].

4.1 LBBB is deficient criteria to diagnose CRT responders

Incorporating LBBB as ECG criteria to anticipate responders to CRT is proved to be deficient criteria in at least one-third of patients [28]. In the current CRT literature, there are multiple 'criteria to define LBBB. Present examples are the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS), the European Society of Cardiology (ESC), and Strauss. Clinical outcomes in terms of remodeling reversal, hospitalization for heart failure, survival rates differ between those classifications, as well as clinical outcomes after CRT. In addition, interpretation of slurring and notching differs according to the format and filtering of the ECG. Positioning of the lateral leads is also an important contributing factor. In addition, interpersonal differences in reading ECG impact the LBBB diagnosis [29]. Significant interobserver, and to a lesser extent, intraobserver variability in the classification of LBBB by the use of the various definitions have been documented. Despite applying specific LBBB criteria, 1 in every 5 or 6 ECG will be classified differently by a different observer. If the same observer is tested, 1 in 10 ECG will be classified differently [30]. This conceivably means that a significant proportion of the scientific publications on CRT is niether mentioned nor nonspecific. It is astonishing to know that QRS morphology was not associated with response to CRT with regard to morbidity and mortality in five randomized key CRT trials constituting meta-analysis of data from 3782 patients (CAREHF [Cardiac Resynchronization in Heart Failure], RAFT [Resynchronization/Defibrillation for Ambulatory Heart Failure Trial], MIRACLE [Multicenter InSync Randomized Clinical Evaluation], MIRACLEICD [Multicenter InSync Randomized Clinical Evaluation—Implantable Cardioverter-Defibrillator], REVERSE [Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction]) [31, 32]. *It is clear at this point that what we are looking to treat with CRT is the dominance of leftward electrical delay, not LBBB.* Subjects classified as having LBBB or non-LBBB may or may not have leftward electrical delay [25].

4.2 How to detect dominant left ward electrical delay (LED)

One of the best diagnostic modalities to diagnose electrical-mechanical coupling mismatch is endocardial electrical activation mapping where 3-dimensional electroanatomical reconstruction contact or noncontact mapping can be evaluated with extreme accuracy. Utilizing this unique diagnostic tool declare that in most patients with LBBB there is a dominant leftward electrical delay [33–35]. The ECG imaging

or body surface mapping can display electrical activation sequences noninvasively. This predominant leftward electrical conduction delay is a critical component of the electrical substrate, which is amenable for CRT with expected electrical and mechanical derangements recovery.

4.3 The electrical substrate in Intraventricular conduction delay and CRT

A heterogenous and complex ventricular activation pattern, different from bundle branch pattern, is associated with IVCD. This is thought to be due to electrical disease in combination with the myocardial disease [35, 36]. Subjects with IVCD are known to have LV activation time shorter than LBBB subjects. In addition the latest activation time in IVCD is variable. In IVCD subjects electrical delay is not as advanced but there is evidence of underlying myocardial disease. This results in a less favorable response of CRT in IVCD subjects [33, 35, 37]. Ventricular activation studies displayed electrical conduction disturbance in IVCD similar to LBBB in 20–52% of IVCD subjects [33, 35, 37]. This group of patients has the potential of gaining the best advantage from CRT [3]. In patients with typical LBBB, change to atypical LBBB might be indicative of scar formation after myocardial infarction that may benefit from CRT. National Cardiovascular Data Registry Implantable Cardioverter-Defibrillator (NCDR ICD) registry studied 11,505 CRT patients with non-LBBB, demonstrated that CRT implantation appeared to be associated with better outcomes than did implantable cardioverter-defibrillator (ICD) therapy alone in IVCD patients with a QRS duration of > or =150 ms, but not in patients with QRS duration < 150 ms or RBBB [38].

4.4 The electrical substrate responsive to CRT in RBBB

In right bundle branch block (RBBB) subjects the RV is activated slowly after LV activation. This fact explains convincingly the failure of CRT in RBBB subjects. As a matter of fact conventional CRT induces, rather than resolves, electrical dyssynchrony in RBBB subjects. Preclinical research and computer simulations evaluating the hemodynamic consequences of RBBB failing heart document this state of dyssynchrony in this subset of patients [39, 40]. There was no significant difference in total and regional LV endocardial activation times between RBBB and LBBB patients [34]. This fact is not a contradiction to the fact of dyssynchrony induced by CRT in RBBB. The conclusive statement here is that: RBBB subjects who have concomitantly sufficiently significant coexisting LV conduction delay, CRT will result in hemodynamic improvement [39]. *This is a new era of biventricular pacing where RBBB in the ECG may constitute an indication for CRT.* In the 1960s Rosenbaum et al. intelligently mentioned a new RBBB pattern that he called "RBBB masking LBBB," characterized by a broad slurred R wave in leads I and aVL, together with a left axis deviation [41]. In addition, Tzogias et al. in 2014 found that atypical RBBB(RBBB pattern in lead V1 and absent significant S-wave in the lateral leads I and aVL) might be explained as coexisting left bundle branch delay (bilateral bundle-branch delay) and might suggest possible CRT responders within a group of patients with RBBB [42]. Left hemiblock in the presence of RBBB is another indicator alarming for leftward conduction delay and supporting the decision for biventricular pacing with CRT in RBBB subjects, although heterogeneity of trials data are evident. The heterogeneity of positive outcomes in this group of patients can be explained by the fact that left hemiblock might be a primary conduction system disease with associated dyssynchrony, or by infarction of the proximal left anterior descending coronary artery, where dyssynchrony is absent [43].

4.5 Contribution of CRT to atrioventricular dyssynchrony

Ventricular resynchronization was thought to be the sole target of CRT. Atrioventricular conduction delay represented by prolonged PR interval in the ECG was found to be a potential target for CRT [44]. Consequences of inefficient atrioventricular coupling are elevated LV end-diastolic pressure, diastolic mitral regurgitation, and reduced stroke work. Atrioventricular conduction disturbances are frequent findings in the heart failure population with an increased rate of hospitalization, atrial fibrillation, and mortalities [45]. CRT was found to be associated with worsened outcomes in prolonged PR intervals compared to normal patients in several nonrandomized trials [46, 47]. In contrast, subanalyses in two of the MADIT-CRT trial, investigating CRT effects on patients with non-LBBB and long PR interval, document reduction in the risk of all-cause mortality as well as heart failure hospitalization [48–50]. *In conclusion, our directions now considering differences in methodology, design, and outcome measures in different studies, obviate drawing solid conclusion to decide for atrioventricular dyssynchrony as electrical substrate responsive to CRT.*

5. Response prediction of new echocardiographic mechanical dyssynchrony markers

5.1 Eye balling and time-based mechanical dyssynchrony markers

Accumulation of resynchronization trials knowledge demonstrated clearly that an important proportion of the CRT population is not responding. All-cause mortality combined including heart failure hospitalization, NYHA class, and patient global assessment were used in a heart failure clinical composite score (CCS) in Multicenter InSync Randomized Clinical Evaluation (MIRACLE) and was not able to show improvement in 34% of patients [7, 51]. A special new concern group in today's trials are the non-LBBB subjects. The use of echocardiographic markers before 2008 for this important group was not able to show additive benefit of the use of echocardiographic markers to predict CRT in important landmark trials like PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy), ECHO-CRT, and others [26]. Iatrogenic electropathy has been reported as a possible deleterious effect of biventricular pacing [52]. *New echocardiographic parameters to evaluate ventricular dyssynchrony were made available to provide proper measurement tool for resynchronization therapy* [53, 54]. Two parameters are in clinical use nowadays: first is simple eyeballing to assess the degree of dyssynchrony. The second is more technical demanding based on strain study called strain-based speckle tracking echocardiography (STE). Mechanical dyssynchrony is present when an interventricular mechanical delay of > or = 40 ms and a septal-to-posterior radial peak strain delay of > or = 130 ms assessed with STE-strain curves.

Incorporation of echocardiographic mechanical parameters to evaluate ventricular dyssynchrony contribute significantly to the improvement of the prognostic value of guideline-based patient selection for CRT [54, 55]. Reduction of all-cause mortality was associated with incorporation of the apical rocking and/or septal flash at baseline evaluation for CRT [56, 57]. Incorporation of mechanical dyssynchrony parameters as a selection criterion for CRT was associated with a significant reduction in LV end-systolic pressure in comparison to the old criteria based on QRS duration and morphology alone [55]. Despite those early promising outcome studies, not all non-LBBB with mechanical dyssynchrony have improved outcomes.

Here it is wise to remember that absence of response, especially in the time dyssynchrony-based studies, might be related to a non-electrical disease that is not responding to CRT like myocardial hypocontractility and scaring, which are very frequent pathologies in the heart failure population. Future randomized control trials must consider those important discriminative factors.

5.2 Septal rebound stretch analysis for the prediction of volumetric response to cardiac resynchronization therapy

Utilizing detection of specific wall motion patterns to serve as markers for CRT response is the most recent advance in the investigation toward optimal response prediction for CRT [54, 58–60]. It is promising as a superior ventricular dyssynchrony measure tool compared to timing-based measures. Early septal contraction and delayed lateral wall activation give rise to myocardial stretching of the opposing wall during systole [54, 59, 61, 62]. This stretching is paradoxical systolic LV motion that is not contributing to LV ejection and, will result in waste of energy. This myocardial stretch and the resulting waste of energy can be converted to myocardial shortening when we perform biventricular pacing [58, 63, 64]. Systolic rebound stretch of the septum (SRSsept) refers to the amount of systolic stretching of the septum after initial systolic shortening (**Figure 1**). It is considered as a good indicator to reflect the potential for recovery of LV function with CRT and might be one of the best response indicators for resynchronization therapy [53, 58, 66]. Salden et al. and after their pioneering publication in the strategies to improve the selection of patients without typical LBBB for cardiac resynchronization therapy [67] and in a recent publication, published the first results from the multicenter study that investigated the association of baseline echocardiographic SRSsept with the volumetric response after CRT. They found that SRSsept is independently associated with favorable changes in LVESV post CRT. In addition, they found that for the prediction of volumetric response, assessment of SRSsept implies additional predictive information compared to visual assessment of apical rock alone. For assessment of subjects without strict LBBB criteria, SRSsept is an excellent echocardiographic discriminator to predict response to CRT [65]. We and others recommend incorporation of echocardiographic SRSspet for future prospective validation studies for CRT subjects evaluation.

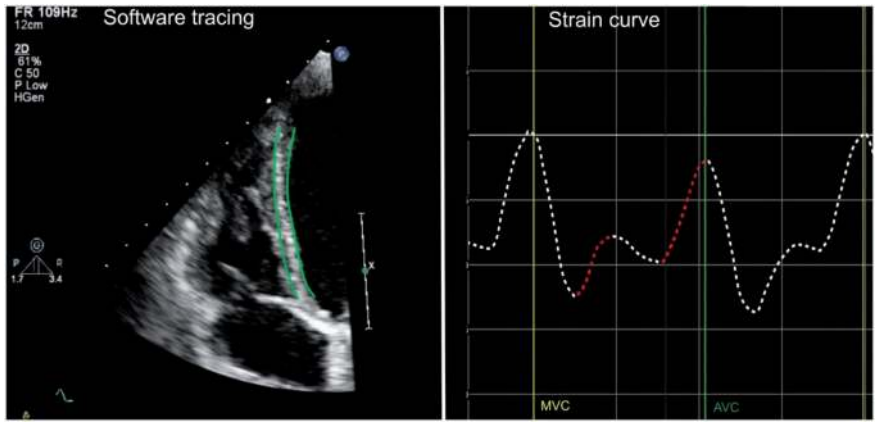

Figure 1.
Septal single wall image acquisition of systolic rebound stretch of the septum (SRSsept)-in red-defined as septal stretching after initial shortening. Speckle tracking echocardiography software was used to deduce strain curves of the focused LV septal wall image. MVC, mitral valve closing; AVC, aortic valve closing [65].

6. Cardiac resynchronization therapy guided by cardiovascular magnetic resonance

Cardiovascular magnetic resonance (CMR) is well known for its unprecedented image quality for cardiac structures as well as for functional assessment of cardiac functions. In addition, it has been introduced to CRT communities as a unique diagnostic tool in differentiating between the various causes of LV dysfunction. CMR is well known to be an excellent evaluating tool for critical factors in the potential response to CRT like a myocardial scar, the total amount of scar (scar burden), and scar location and its relationship to the pacing stimulus. The intricate arrangements of human heart myocardial fibers are a complex anisotropic fiber structure showing longitudinal, circumferential, and oblique layers that form a mechanical link between remote areas of the myocardium [68–71]. Electrically heterogeneous conduction from endocardium to mid-myocardium and epicardium is also a feature of the human heart [72]. Conduction disturbances, superimposing in this inherent anatomical, functional, and electrical heterogeneity of the myocardium is expected to yield multiple areas of dyssynchrony [72, 73]. This finding raises the possibility that deploying an LV lead over a single site of late wall motion may not correct global cardiac dyssynchrony. By the same token, multiple LV leads may be preferable to one LV lead in some patients (**Figure 2**) [74].

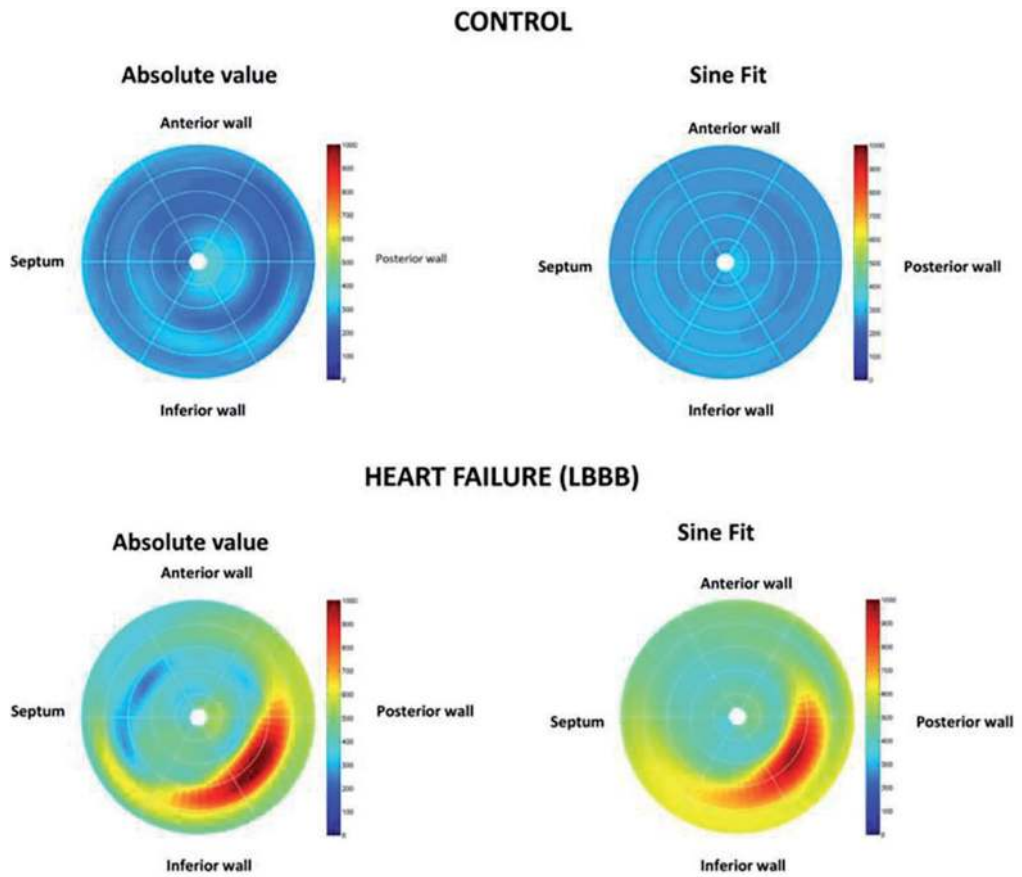

Figure 2.
CMR radial wall mapping illustrating inward wall motion with colors ranging from blue to green and to red. Bull's eye with a homogenous red color throughout denotes complete synchrony, where the bull eye with homogenous blue color denotes complete synchrony. Heterogenous color coding denotes dyssynchrony of radial motion where blue is representing early (global systolic phase) activation and red representing late (global diastolic phase) inward radial wall motion (from Foley et al. [74, 75]).

With its unique discriminative and diagnostic accuracy, CMR has become the gold standard for the in vivo assessment of myocardial scarring. The cutoff point for scar burden, where more is associated with poor response to CRT, is different between different investigators but in general, we consider scar burden less than 15–33% is a potentially good indicator for better response to CRT [76, 77]. Another delicate feature of CMR contribution to CRT management is that CMR can be a fine assessment tool for diagnosing the substrate of heart failure. It is well known that myocardial infarctions can be silent in about one-third of patients and coronary angiography study can be normal after myocardial infarction. In addition, wall motion abnormalities are not equivalent to myocardial ischemia. Unparalleled anatomical imaging, combined with late gadolinium enhancement (LGE)-CMR findings, makes CMR an ideal radiation-free diagnostic tool for the actual heart failure substrate. Scarring in the subendocardial or transmural distribution along arterial territories is typical for infarcted myocardium. Lack of localized myocardial scarring is characteristic of non-ischemic cardiomyopathy or less often, by mid-wall LGE, characterized fibrosis. Myocarditis, sarcoidosis, and arrhythmogenic right ventricular cardiomyopathy are characterized by the patchy distribution of LGE. Amyloidosis and Anderson-Fabry diseases are characterized by diffuse LGE.

7. Cardiac resynchronization therapy guided by computed tomography

Although CMR is an excellent diagnostic tool for evaluating CRT response evaluation, the frequent presence of pacemakers in this group of patients renders its use limited especially in countries where MRI-compatible devices are not available. Non-response to CRT might be caused by factors other than dyssynchrony of electrical activation. Important hidden factors that must gain attention for non-responders are myocardial scar, myocardia hypocontractility, and suboptimal left ventricular (LV) lead location. All of these factors can be investigated with computed tomography (CT). Late iodine enhancement computed tomography (LIE-CT) was found to be an important elegant diagnostic modality in this regard. Théo Pezel et al. investigated CT dyssynchrony measurements for which the LV short-axis images from the multiphase reformatted reconstructions were used [78]. CT dyssynchrony indices used in their investigation were: global and segmental time to maximal wall thickness, global and segmental time to maximal inward wall motion, and time to minimum systolic volume. The dyssynchrony they measured were not the baseline dyssynchrony but the persistent dyssynchrony despite biventricular stimulation. LV lead malpositioning is a serious potentially avoidable reason for non-responders group. Pre-determination of LV lead positioning might be approached by invasive angiogram during implantation and CT coronary angiography. Short axis of the heart is used to determine LV lead final position as anterior, anterolateral, lateral, inferolateral, or inferior. In the long axis of the heart searched positions are basal, mid, or apical. Théo Pezel et al. evaluated concordance of the lead location to regional LV mechanical contraction, where they calculated the mean times to maximal wall thickness and maximal wall motion of each segment using an 8-segment model. Identification of the segment of the myocardium with the latest mean times to either maximal wall thickness or wall motion was determined. Greater global dyssynchrony, as measured by the time to maximal wall thickness, time to peak inward wall motion, and time-to-minimum systolic volume was found between non-responders. Greater segmental dyssynchrony between the anterior and inferior segments, between the inferoseptal and anterolateral segments, and between the anteroseptal and inferolateral segments was found between non-responders. In addition, in the non-responders, the LV

lead location was less often concordant with the region of maximal wall thickness (9% vs. 72%, p = .001) [78].

In addition, CT was found to be an appropriate diagnostic tool to follow up the association of LV wall thickness and the ability to reverse LV remodeling and mitral regurgitation improvement after CRT [79].

8. Future directions to optimize cardiac resynchronization therapy

CRT is well known since its inception to be a promising electrical therapeutic device to treat CHF. After more than two decades in clinical use, we know that around 30–40% of CRT subjects do not exhibit any detectable clinical or echocardiographic benefit. As a matter of fact, some of them are deteriorating after resynchronization. For this reason, most of the discussion in this chapter and selected recent literature is devoted to non-responders toward optimizing resynchronization therapy [80, 81]. The special diagnostic tools mentioned earlier in this chapter are to refine our CRT subjects selection especially the subgroup without conspicuous LBBB criteria. Those special diagnostic tools can be still considered as future direction that has been started and in the way for mature applicable understandings in the field of CRT science. *Promising new directions can be classified as new diagnostic tools and new basic knowledge with deeper investigation in the biomechanics of cardiac electromechanical coupling and spatial orientation of the ventricular muscles, as well as ‚new advances in implant and resynchronization site.*

8.1 Vectorcardiography guided cardiac resynchronization therapy

Vectorcardiography (VCG) was developed by E. Frank in the mid-1950s. The magnitude and direction of the electrical forces that are generated by the heart are recorded in 3-dimensional information format by means of a continuous series of vectors that form curving lines around a central point. The area under the 3-dimensional QRS complex (QRS area) is reflecting the electrical forces during depolarization and the area under the 3-dimensional T-wave (T area) is reflecting the electrical forces during repolarization. Volumetric response and survival after CRT were thought to be predicted strongly by the QRS area, but also T area and the sum of QRS and T areas (QRST area) [82, 83]. QRS area was also found repeatedly to be superior to QRS duration and morphology as a predictor of CRT response [28, 82, 84, 85]. One retrospective multicenter study displayed that this was true for a cohort of patients that received CRT and also for patients without a Class I indication for CRT according to American guideline recommendations [56] (QRS duration 120–149 ms or non-LBBB) [28]. Only the QRS area in these patients, was significantly associated with all-cause mortality. Reviewing volumetric CRT response, demonstrated that both QRS area and LBBB morphology were associated with an LV end-systolic volume reduction of = or >15 [28]. The advantage of the QRS area is that it is an objective measure and observer-independent parameter, whereas the definition for LBBB is subjective measure and operator-dependent. Variability in the QRS area is less than QRS duration as it is determined by QRS complex amplitude, not the beginning and end of the QRS complex [28]. VCG is not yet commercially available in clinical practice, but the QRS area is a promising non-invasive diagnostic evaluation tool for identifying possible CRT responders.

8.2 Improving our understanding of the biomechanics of cardiac electromechanical coupling and the contribution of spatial orientation of the ventricular muscle band to cardiac pumping functions

Perceiving heart pumping functions as a simple contraction of the bullet-shaped left ventricle is thought nowadays as a misunderstanding which contributes significantly to delaying the successful progress of electrical device treatment for heart failure. The process of contraction and myocardial stretch need more investigation at the cellular, as well as, at gross myocardial fibers orientation level. At the cellular level, electrical activation will trigger mechanical contraction via an intracellular calcium-dependent process known as excitation-contraction coupling. Disturbance of the process of cardiac myocyte intracellular calcium handling is a common feature of heart failure. At the organ scale, pump dysfunction is the end result of mechanical alterations secondary to electrical dyssynchrony in heart failure subjects. A reverse coupling between cardiac mechanics and electrophysiology is also well established. It is commonly referred to as *cardiac mechanoelectric feedback* and is thought to be an important contributor to the increased risk of arrhythmia during pathological conditions that alter regional cardiac wall mechanics, including heart failure. The roles of stretch-activated ion channels and mechanisms that are independent of ionic currents need more investigation. We in the CRT community, are in high demand for new multicellular tissue-scale model systems and experiments to obtain a better understanding of how interactions between electrophysiological and mechanical processes at the cell scale affect ventricular electromechanical interactions at the organ scale in the normal and diseased heart [86]. At a gross level, many observations demand serious investigations considering proper understanding of the mechanics of heart pumping and the true contribution of the spatial orientation of the ventricular muscle band to cardiac pumping functions. Without this knowledge, our understanding and interpretation of ventricular activation and dyssynchrony will be deficient. The existence of right and left ventricles as a continuous muscle band has been proposed [87–90]. The muscle band is organized in special spatial orientation as a helix formed by basal and apical loops. Both ventricular contraction and relaxation controlling the ejection and the filling of ventricles are thought to be affected by this unique arrangement [91, 92]. A deeper investigation of this spatial fibers orientation and the contribution of its activation sequence to cardiac pumping functions in health and disease will improve our therapeutic measures for proper resynchronization of dyssynchronized ventricles. Sengupta PP et al, elaborated in this direction and describe LV as a complex structure in which myofibers are arranged in the form of a left-handed helix in the subepicardium and of a right-handed helix in the subendocardium, while the mid-wall is consisting of circumferential fibers. This type of fibers arrangement allows for myocardial deformation in multiple planes and explains the complexity of the ventricular dyssynchrony process (**Figure 3**) [94]. During LV systole, there is apical counterclockwise rotation and basal clockwise rotation around the LV long axis. During LV diastole, there is Untwisting of the subendocardial layers that occurs during diastole and contribute to diastolic suctioning. Simultaneously, the LV shortens in systole and lengthens in diastole. At this level of understanding, we are confident that the extent of LV mechanical dysfunction is never a matter of one direction of motion or deformation. Future research for resynchronization therapy must consider this basic understanding.

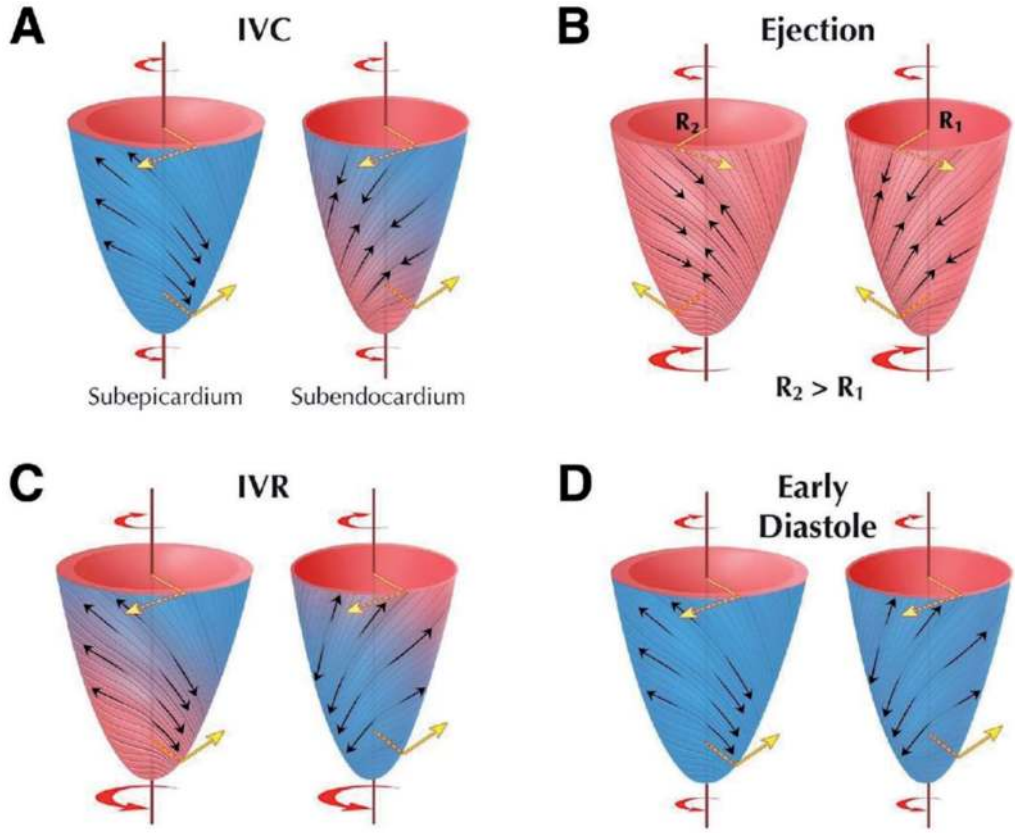

Figure 3.
Twist mechanics of the left ventricle. A period of left ventricular isovolumic contraction (IVC) follows electrical and mechanical activation in the apical subendocardial region, during which (A), the subendocardial myofibers (right-handed helix) shorten with stretching of the subepicardial myofibres (left-handed helix) resulting in clockwise rotation of the apex and counterclockwise rotation of the base. Simultaneous shortening of the subendocardial and subepicardial layers is occurring during ejection (B). The larger arm of the moment of the subepicardial fibers dominates the direction of twist, causing counterclockwise and clockwise rotation of the apex and base, respectively. During isovolumic relaxation (IVR) (C). Subepicardial fibers lengthen from base to apex and subendocardial fibers lengthen from apex to base. In diastole, there is relaxation in both layers, with minimum untwisting (D). Illustration is from Sengupta PP [93].

8.3 Endocardial left ventricular pacing

Challenges of transvenous LV lead implantation including limitations of coronary sinus (CS) anatomy, high LV pacing threshold, and/or phrenic nerve capture, have led to serious efforts to look for better alternatives [94]. As compared to standard epicardial LV pacing, pacing the LV endocardium reflects a more rapid and physiological activation of the left ventricle. Shetty AK et al have identified greater acute hemodynamic improvements with endocardial versus conventional LV pacing [95]. Subjects who demonstrated CRT non-response or known to have LV lead technical difficulties were evaluated in the alternate site cardiac resynchronization study. Endocardial LV lead placement was found to be safe and reported clinical and echocardiographic improvement in two-third of subjects [96]. An important drawback of this new trend of an implant is the need for anticoagulation and the reported few cases of thromboembolic events despite anticoagulation. The endocardial wireless stimulation for CRT (EBR Systems, Sunnyvale, CA, USA) incorporates a pacing system using a small ultrasound-responsive leadless electrode placed onto the LV endocardial surface [97]. The safety and performance of electrodes implanted in the left ventricle study is coming up with encouraging results. A total of 35 patients who had failed conventional CRT implant, underwent successful

implant in 97% of the sample [93]. At 6 months, approximately two-thirds of patients demonstrated LV reverse remodeling with improved LVEF ≥5%. LV endocardial pacing seems to be a revolution creator in CRT practice in the present and future.

8.4 His bundle pacing and His-optimized cardiac resynchronization therapy for electrical resynchronization in heart failure

In 1977, Narula et al. reported that the QRS complex may be normalized by pacing the distal His bundle in patients with LBBB [98]. Permanent pacing of the His bundle region to achieve ventricular resynchronizing has been described, with clear clinical advantages over traditional RV apical pacing [99–102]. Medtronic has announced US Food and Drug Administration (FDA) clearance and commercial launch for the SelectSite C304-HIS deflectable catheter system for use in procedures involving His bundle pacing (HBP). The physiologic benefit of permanent His bundle pacing (HBP) is theresult of synchronous electrical and mechanical activation with stimulation of both ventricles through the intrinsic His-Purkinje system. The anatomic site of the conduction disorder seen with BBB is frequently located proximally within the bundle of His, with longitudinal dissociation of the conducting fibers [103, 104]. Overall, it has been reported that approximately three quarters of BBB patients were found to respond with QRS narrowing using HB pacing [103]. Using epicardial electrocardiography (ECG), imaging Arnold et al, demonstrated that HB pacing was superior to biventricular pacing for restoring LV synchrony in selected patients with LBBB [105]. In the presence of distal BBB or the co-existence of IVCD, QRS may not normalize. In patients without complete LBBB correction, Vijayaramanet P et al demonstrated that His-optimized CRT (HOT-CRT) with synchronized LV pacing resulted in significant QRS duration narrowing [106, 107]. In patients with atrioventricular (AV) block in whom fusion with intrinsic His-Purkinje conduction cannot be achieved, HOT-CRT may provide the new therapeutic option. However, it is wise to remember that QRS duration reflects total ventricular activation time which is not always equivalent to a perfect marker of LV synchrony. HOT-CRT was found to be a novel approach to further optimize electrical resynchronization by combining the concept of fused adaptive LV pacing with HBP.

9. Conclusion

CHF is one of the most important epidemics in the current human species era affecting 1–2% of adults and around 10% of >70 years old in developed countries. In addition to its psychophysiological and social burden, the economic impact of CHF on the world nations is Gargantum. Treatment options for CHF witnessed relative stagnation until 2001, where the first electrical device in the form of biventricular pacing to resynchronize the failing desynchronized ventricles, was implanted in 2001. In spite of the early excitement for this type of therapy most international landmark trials reported 30–40% of non-responders. Factors contributing to this large proportion of non-responders are related to scar burden and scar localization to the vicinity of the LV pacing stimulus, hypocontractility, and the degree of pre-implant mechanical dyssynchrony. It was surprising to medical communities to discover that a significant proportion of CHF without LBBB responds to CRT. This chapter is a scientific journey to understand the pathophysiological mechanism to optimize the selection of CRT responders. We confirm that LBBB is deficient criteria for selecting CHF patients for CRT. A spectrum of ventricular

conduction disorders that might benefit from CRT, as derived from landmark trials were discussed including IVCD and RBBB. New techniques to detect dominant left ward electrical delay (LED) including endocardial 3-dimensional electroanatomical mapping and ECG imaging or body surface mapping to display electrical activation sequences as well as the elaboration of the best electrical substrate to optimize response to CRT in IVCD, RBBB, and atrioventricular delay are discussed. Determination of pre-implant degree of dyssynchrony is critical as pacing is known to induce more dyssynchrony for mild cases at the baseline with clinical and hemodynamic compromise. For this reason, special attention in this chapter was devoted to new echocardiographic mechanical dyssynchrony markers like eyeballing, septal flash, and time-based mechanical dyssynchrony markers. Systolic septal rebound stretch (SRSsept) was found to be an excellent echocardiographic discriminator to predict response to CRT. Cardiovascular Magnetic Resonance (CMR) was found to be an ideal radiation-free diagnostic tool for the diagnosis of the actual heart failure substrate and accordingly to optimize CRT responders selection. CRM is known to be the gold standard for scar diagnosis but is also considered to be an excellent diagnostic tool for fibrosis, myocarditis, sarcoidosis, arrhythmogenic right ventricular cardiomyopathy, amyloidosis, and Anderson-Fabry disease. Computed tomography is also an excellent tool to diagnose myocardial scar as well as for coronary venous system reconstruction images for optimal LV lead positioning. An innovative future direction for the best outcome of CRT is discussed. The non-invasive nature of vectorcardiography (VCG) with its strong prediction capabilities for volumetric as well as survival indicators after CRT, makes VCG an attractive adjunct diagnostic tool to optimize CRT responders selection. Improving our understanding of the biomechanics of cardiac electromechanical coupling and the contribution of the spatial orientation of the ventricular muscle band to cardiac pumping functions is creating a new visionary approach toward understanding the extent of LV mechanical dysfunction and perfective lead positioning in CRT subjects. New LV lead positions like pacing the LV endocardium reflect a more rapid and physiological activation of the left ventricle with excellent early results. Permanent pacing of the His bundle region to achieve ventricular resynchronizing has been described, with clear clinical advantages over biventricular pacing. Progressive narrowing in QRS duration was documented with HB pacing compared to conventional CRT with the best narrowing was gained with His-optimized cardiac resynchronization therapy (HOT-CRT). This multi-disciplinary approach to optimize CRT response is promising for a better future of resynchronization therapy aiming toward the best possible quality of life for this important group of CHF subjects in the next decades.

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