Cardiac Resynchronization Therapy
State-of-the-Art of Current Applications, Guidelines, Ongoing Trials, and Areas of Controversy

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More than 2 decades of research has established the role of cardiac resynchronization therapy (CRT) in medically refractory, mild to severe systolic heart failure (HF) with abnormal QRS duration and morphology. CRT confers a mortality benefit, reduces HF hospitalizations, and improves functional outcome in this population, but not all patients consistently demonstrate a positive CRT response. The reported nonresponder rate ranges between 20% and 40%, depending on the response criteria used.1 Efforts to improve response to CRT have focused on methods to optimize the correction of electrical and mechanical dyssynchrony (the primary target of CRT) and on improving patient selection and optimizing post-implant care. The present article reviews the state-of-the-art of CRT and discusses developments on potential promises and areas of controversy.

Update of Clinical Trials
Although CRT became common clinical practice >10 years ago, the last 2–3 years have shown a series of large clinical trials that clearly outlined the categories of patients that benefit from CRT. First of all, 3 landmark studies—REsynchro- nization reVersed Remodeling in Systolic left vEntricular dysfunction (REVERSE);2 Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT)3 and Resynchronization for Ambulatory Heart Failure Trial (RAFT)4—have been performed to investigate the effectiveness of CRT in HF patients with a wide QRS complex and mild symptoms (New York Heart Association [NYHA] class I–II), in which patients have been randomized to CRT-ON and CRT-OFF. The main findings were that REVERSE showed significant reverse remodeling, MADIT-CRT showed less hospitalization, and RAFT also showed significant reduction in mortality in the CRT arm. The CRT benefit shown in these studies is consistent with those from older studies performed in patients with more severe HF symptoms. Figure 1 displays that the increase in left ventricular (LV) ejection fraction (EF) by CRT is independent of baseline EF.

This evidence is in line with the finding of increased pump function even in canine hearts with isolated left bundle-branch block (LBBB)7 and the beneficial effects of biventricular pacing as compared with right ventricular (RV) pacing in patients with normal ejection fraction.6,8,9

Another very large group of patients recently successfully treated with CRT is represented by those requiring pacemaker implantation as a result of atrioventricular (AV) block, regardless of LVEF: Biventricular pacing for atrioventricular block to prevent cardiac desynchronization (BIOPACE)10 and Biventricular versus RV Pacing in patients with Left Ventricular dysfunction and atrioventricular Block (BLOCK-HF).9 The BLOCK-HF study is by far the largest (691 patients) randomized study in this field. The results show that biventricular pacing significantly reduces a combined end point of mortality, HF-related urgent care and increase in LV end systolic volume, by 26% compared with RV pacing.9 This change was mainly driven by the reduction in LV end systolic volume. This trial built on evidence from trials, like Dual Chamber and VVI Implantable Defibrillator (DAVID)11 and MoDe Selection Trial (MOST),12 showing that RV pacing worsens long-term ventricular function and outcome. However, this improvement was at the cost of a higher number of adverse events (83 versus 30 patients), mostly represented by LV lead issues. A similar high complication rate has been observed in RAFT, indicating that a proper risk and benefit analysis is crucial, especially in patients with limited symptoms.4

Permanent atrial fibrillation (AF) is present in 25% to 30% of CRT candidates, but there is little evidence from randomized studies that CRT is effective in AF. The recently published RAFT study13 included more patients with permanent AF than all other published studies combined. RAFT failed, however, to demonstrate a clear improvement in any clinical or surrogate outcome by CRT in patients with permanent AF, despite a trend for reduction of HF hospitalizations. This poor outcome might be attributed to suboptimal delivery of CRT, because only one third of patients received >95% ventricular pacing.13 To increase the percentage of pacing in AF, ablation of the atrioventricular junction is applied and increases CRT response.14 Prospective evidence for this idea may be provided from the Cardiac Resynchronization Therapy and AV Nodal Ablation Trial in Atrial Fibrillation Patients study.

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(CAAN-AF). This study is powered to detect a reduction in the combination of all-cause mortality and HF events.

Finally, a series of recent trials have provided convincing evidence that the application of CRT in patients with narrow QRS complex and mechanical dyssynchrony is not beneficial or even may lead to excess in mortality, thus contraindicated. Initially, several single center studies have observed that CRT is effective in patients with QRS duration <120 or <130 ms in combination with mechanical dyssynchrony. However, the 4 randomized studies in this field have consistently been neutral or negative. The RethinQ study randomized 172 patients to CRT or no CRT. Primary outcome (the number of patients showing a sizeable increase in peak oxygen uptake) was not different between groups. The CRT group also did not show significant reverse remodeling. However, peak oxygen consumption increased in CRT patients with a QRS interval of 120 to 130 ms, suggesting that mechanical dyssynchrony might help in corroborating existence of the electrical substrate, as mentioned above (Figure 2).

Evaluation of Screening Techniques for Electrically-Normal, Mechanically Dyssynchronous HF Patients Receiving CRT (ESTEEM-CRT) was a multi-center, single-arm study in 68 patients. First the acute hemodynamic effects of CRT were determined, which were negligible (improvement in LV dP/dt max, 2±2%). After 6 and 12 months CRT the NYHA class and quality of life scores were improved but exercise capacity and LV volumes were unchanged. In the Evaluation of Resynchronization Therapy for Heart Failure (LESSER-EARTH) study, CRT was applied in any heart failure patient with narrow QRS complex and an ejection fraction <35%; moreover there was no prerequisite for LV dyssynchrony. This study was prematurely interrupted after randomization of 85 patients as a result of futility and safety concerns. Biventricular pacing was associated with a prolongation of the QRS complex, no change in echocardiographic parameters, a significant reduction in the 6-minute walk distance, and a nonsignificant trend toward an increase in heart failure-related hospitalization.

With these results in mind, the results from the most recent Echocardiography Guided Cardiac Resynchronization Therapy (Echo-CRT) study are not surprising. Echo-CRT trial randomized 809 patients to CRT on and off. Importantly, in this study several shortcoming of previous trials have been carefully managed; among the others mechanical dysynchrony was assessed by a single core lab, and more modern measures of mechanical dyssynchrony (primarily speckle-tracking strain) were used than in RethinQ and ESTEEM (M-mode echocardiography and Doppler imaging). Strikingly, EchoCRT was prematurely stopped because of a lack of

![Figure 1. Change in left ventricular ejection fraction after cardiac resynchronization therapy (CRT) in patients with different functional heart failure classes. Compared with before CRT (blue bars), left ventricular ejection fraction increased significantly in all studies after 3–6 months (red bars) and even more during longer follow-up (green bars; derived from Auricchio and Prinzen with permission). The larger bars on the right indicate data from a study comparing right ventricular (RV) and biventricular (BiV) pacing in pacemaker-dependent patients with mild HF symptoms. The lines indicate the individual response. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation. BL indicates baseline; and NYHA, New York Heart Association.](http://circ.ahajournals.org/)

![Figure 2. Top, Percentage of patients with an increase in peak oxygen consumption >1 ml/kg body weight in the RethinQ trial. Significant improvement only in patients with QRS duration >120 ms. Reproduced from Beshai et al with permission. Bottom, Percentage of patients reaching end points in the EchoCRT trial. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation. HFH indicates heart failure hospitalization.](http://circ.ahajournals.org/)
**Table. Overview of Clinical Practice Recommendations to CRT in Different Patient Categories Issued by the Heart Failure Society of America (HFSA), Jointly by American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society (ACCF/AHA/HRS), and the European Society of Cardiology (ESC) in Collaboration With the European Heart Rhythm Association (EHRA)**

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benefit on hospitalization. Moreover, final analysis showed a significantly increased all-cause and cardiovascular mortality in the CRT arm (Figure 2).

Therefore, together these randomized trials consistently argue against the application of CRT in patients with narrow QRS complex, even if mechanical dyssynchrony is present. Moreover, these results illustrate that if CRT has no benefit, it may even harm some patients. This view is clearly expressed in the 2013 European Society of Cardiology guidelines, which are currently not recommending the use of CRT in patients with QRS duration of <120 ms.23

Overview of Current Guidelines and Recommendations

The main results of the abovementioned large trials have prompted the international scientific societies to update their clinical recommendations to CRT. Common to all clinical practice guidelines on CRT is the recommendation of careful evaluation of underlying causes of chronic HF, the assessment of the general health status, the investigation of major comorbidities, the appropriate use of optimal dosage of HF medications, and the estimation of a reasonable life expectancy. The recommendations of the 3 major international scientific societies are shown in the Table. The table highlights the similarities in the recommendations to CRT but also the divergences in the recommendations, partially related to different levels of evidence for grading the recommendation. Undoubtedly the lack of uniformity about the subgroups of patients indicated, less recommended, or contraindicated to CRT poses significant difficulty in the implementation process of the clinical practice guidelines. Although part of the inconsistency may be attributable to the fact that between the publication of the guidelines of each scientific society major randomized, controlled trials have been published and consequently included in the guidelines, unavoidably inconsistency may lead to disparity of treatment of U.S. and European patients. A joint revision process of clinical evidence leading to recommendation is therefore highly desired.

The opinion of the experts converges in the following: (1) LBBB as key underlying conduction disturbance (see also Figure 3); (2) a wide QRS complex (>150 ms) as predictor of CRT benefit; (3) RV pacing-induced LBBB as substrate for poor mechanical function and adverse remodeling.4,26–28 A QRS morphology consistent with LBBB appears to reflect an electrical substrate that is strongly amenable to CRT, independent of NYHA functional class and cause. CRT was particularly effective when LBBB was associated with female sex, relatively normal left atrial size, and body mass index; this phenotype (also termed super responder) showed a near normalization of ventricular volumes and \( \approx 2\% \) yearly event rate after CRT implantation.29

Imaging to Improve CRT Success

Over the last decade, interest has grown for imaging methods to better characterize patients undergoing CRT to better assess the patients' electrical substrate, regional mechanical function, and location and extent of scar. Such knowledge may lead to improve selection of patients for CRT and to guide LV lead placement. However, the use of imaging tests may increase costs and may not reduce complications.

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placement. This targeted approach may further (1) enhance the response to CRT in those patients who respond to CRT and (2) reduce the proportion of patients not benefiting from CRT.

Electrical Imaging

Along with the increasing evidence that an electrical substrate can predict CRT response, electrical mapping techniques are gaining interest. Several studies using invasive electrical mapping techniques found evidence that in LBBB the electrical activation of the LV follows a U-shaped path, starting at the septum and turning around the apex and subsequently toward the inferior wall of the LV. This activation pattern coincides with a functional line of block that is oriented from the base toward the apex of the LV. Location and length of the lines of block are variable but related to the site and time of LV breakthrough (Figure 4).

Noninvasive, ECG-based, electrical imaging methods may further increase the clinical use of electrical mapping. These methods calculate the inverse solution from body surface potential mapping, in combination with patient specific heart–torto anatomy, derived from an ECG-gated CT-scan where also all >100 electrodes are visible. In this way electroanatomic maps are created depicting epicardial potentials, electrograms, and activation and repolarization sequences. The first studies have shown that this technique can be used to assess the sequence of electrical activation during intrinsic rhythm and during pacing from different sites and using different AV and interventricular (VV) intervals and that it may contribute to better patient selection.

Mechanical Dyssynchrony Versus Mechanical Discoordination

Conventionally, mechanical dyssynchrony is defined as an increased time delay between the peak of shortening or tissue velocity between the various LV wall regions, most commonly LV lateral and septal wall. Comparison between the various studies is, however, hampered by differences in the used dyssynchrony indices and equipment. Accuracy, feasibility, and physiological relevance of mechanical dyssynchrony measurements should be considered. Myocardial velocities, measured with tissue Doppler imaging, are increasingly recognized as unreliable, because velocity does not imply active myocardial shortening and because misalignment of the ultrasound beam with the myocardial wall provides erroneous information. Also, the multiple shortening peaks, especially in the septum of LBBB hearts, may create a definition problem between investigators quantifying dyssynchrony. In this regard it is relevant that analysis of all echocardiograms by a core lab did result in a significant prediction of the likelihood of death, transplantation, or LVAD implantation by CRT. However, even time-to-peak shortening delays, calculated from strains measured with the gold-standard MRI tagging technique, were not predictive of CRT response. This may be explained by results from a study that combined computer modeling and patient data. In the computer model the time-to-peak shortening delays do not linearly relate to true dyssynchrony, but provide only 3 clusters of values (Figure 5).
Similar clustering of time-to-peak data was observed in CRT patients. All these issues may explain why the use of mechanical dyssynchrony in CRT is still controversial (see below).

As an alternative to mechanical dyssynchrony (time-to-peak delays) several investigators propose the use of measures of mechanical discoordination. Examples of such indices are the CURE index, internal stretch fraction, systolic dyssynchrony index, and septal rebound stretch. So far these indices have only been tested in single-center studies. In direct comparisons, discoordination markers had an area under the curve (AUC) for response that were approximately 0.1 unit higher than dyssynchrony indices. Although promising, these indices of mechanical discoordination have to be validated in prospective multicentre studies yet.

**Scar-Imaging**

Scar negatively influences the clinical and functional improvement of CRT because its presence indicates a reduced amount of viable myocardium which may be amenable to CRT. Indeed, scar size is predictive of CRT response. Pacing in a scarred region may also provide inadequate resynchronization due to the slow conduction in that region. This may explain why a posterior-lateral scar is a strong predictor of nonresponse. Together with a possible arrhythmogenic effect, this may explain why studies using cardiac MRI show that pacing in scarred myocardium is associated with an ≈5-fold worse outcome, in terms of pump failure and sudden cardiac death, compared with pacing in nonscarred myocardium (Figure 6). Also midwall fibrosis, observed in a small subgroup of CRT recipients with dilated cardiomyopathy, is a strong predictor of morbidity and mortality. An animal study showed, however, that the presence of scarred infarction does not preclude hemodynamic response to CRT but that finding the best LV lead placement outside the scarred region and timing of LV stimulation requires more attention. These observations indicate the importance of appropriate scar imaging to guide LV lead placement.

**Improving CRT Delivery**

The site of pacing is a major determinant of the benefit of CRT. In nonischemic LBBB animal hearts a significant improvement in hemodynamic effect is achieved by positioning the LV pacing lead in almost 80% of the LV free wall. Recent trial data partially seem to confirm these preclinical data, but averaged data from large populations may conceal differences between individuals. Indeed, the location of the optimal LV pacing site strongly differs between patients. Therefore, testing the effect of LV pacing at various sites might be warranted. Alternatively, the region of latest activation may be determined, based on measurement of the interval between Q-wave and LV electrograms depolarization (Q-LV time; Figure 7) or of the latest contraction.

In patients in whom the initial CRT response was poor, adding another LV lead in combination with RV pacing (triventricular pacing) showed promising improvements. Stronger effects have been observed by using LV endocardial pacing, especially in preclinical studies. In small clinical studies the benefit was less consistent when the endocardial site opposing the CS lead was studied, but other endocardial sites usually provided better hemodynamic effects. LV endocardial pacing is currently applied using a transseptal septal puncture and advancing the lead through the mitral valve onto the LV endocardial wall in patients with no other options. Wider application of LV endocardial pacing awaits novel design of pacing leads or lead delivery systems.
Another factor in the equation of CRT benefit is programming of the AV and VV interval of the CRT device. Many small studies have demonstrated significant, especially acute hemodynamic, effects of CRT optimization (reviewed by Houthuizen et al\textsuperscript{63}). However, recent multicentre trials failed to provide support for the idea that either echocardiographic or algorithm-based optimization is of long-term benefit as compared with using default settings.\textsuperscript{64–66} The only multicentre study showing some, subjective, benefit compared default device settings with those advised by an endocardial accelerometer.\textsuperscript{67}

One of the problems in echocardiographic or hemodynamic optimization is that the effect of CRT is of similar size as the variability in the measured parameter, thus creating a poor signal-to-noise ratio.\textsuperscript{68} Another problem may be that the acute hemodynamic response poorly predicts long-term volumetric changes.\textsuperscript{69} Further studies are required to more precisely delineate how to optimize programming of CRT devices.

**Nonresponder Management**

There is considerable confusion about the definition of nonresponse and whether a patient is a true nonresponder or not. These terms oversimplify the extremely complex HF disease process. Happily, it is progressively recognized that suboptimal response to CRT is multifactorial. Beside better patient selection and delivery techniques, a multidisciplinary post-implantation approach can improve outcome of CRT. Mullens et al\textsuperscript{70} were the first to describe potential reasons for non-response during follow-up and showed that a protocol-driven treatment can improve reverse remodeling (Figure 8).\textsuperscript{71}

Recently, a large retrospective study showed a 38% relative risk reduction for HF hospitalization, cardiac transplant, or mortality by using systematic multidisciplinary follow-up.\textsuperscript{72}

Essential in the evaluation of nonresponders is the analysis of the ECG of the underlying rhythm, identifying the presence of typical LBBB or a QRS duration >150ms\textsuperscript{3,4} (Figure 8). In patients with an underlying narrow QRS complex, RBBB or intraventricular conduction delay it might be questioned whether CRT is effective at all (see above). CRT is most effective if >95% of heartbeats are resynchronized. Although this can be evaluated using device counters, the latter do not provide reliable information on the effective delivery of biventricular pacing. Both arrhythmias...
cause irregular heartbeats that escape from resynchronization. Importantly, in AF the pacing devices overestimate the effective percentage of biventricular pacing attributable to (pseudo-) fusion. Ablation of the AV-node or of the premature ventricular contractions may be considered to acquire the optimal percentage of biventricular pacing.

There is an important role for optimization for AV and VV intervals, because it was shown that careful optimization of device settings could induce CRT response in 50% of the initial nonresponders. Pharmacological HF treatment may be uptitrated after CRT implantation because the improved hemodynamic status after implantation often provides space to increase HF medication doses. In addition, the patient should be educated to comply to medication and to diet, such as salt and fluid intake restriction. Also, structured exercise training programs have been shown to be of additional benefit for CRT patients and referral should be considered.

Finally, significant functional mitral regurgitation is another cause of clinical nonresponse to CRT, and valve insufficiency reduction with MitraClip treatment substantially improves HF symptoms and reverses ventricular remodelling. This benefit should be weighed against the peri- and postprocedural morbidity and mortality risk of the MitraClip procedure in this population with advanced HF.

In conclusion, it seems timely to integrate delivery of multidisciplinary HF care with CRT management using a protocol-based multidisciplinary approach, as has recently demonstrated by Altman et al.

**Controversial Applications**

**Mechanical Dyssynchrony in Patients With Wide QRS Complex**

There is still considerable discussion as to whether mechanical dyssynchrony has (reviewed in 77) or does not have (reviewed in 78) added value on top of ECG analysis in predicting CRT response in patients with a wide QRS complex (QRS>120 ms). The 2 multicenter studies on this topic could not identify an echocardiographic marker of mechanical dyssynchrony that contributes to prediction of CRT response. The editorial comment to the PROSPECT study addresses the considerably larger number of small single-center studies that are positive than those that are negative in this area, suggesting a significant publication bias.

Rather than counting and weighing the number of positive and negative studies, we prefer to discuss mechanical dyssynchrony from a more mechanistic point of view. In patients with wide QRS complex mechanical dyssynchrony may be used to exclude the presence of nonviable myocardium that might limit CRT response in patients with clear electrical substrate (like LBBB) or to corroborate the presence of an electrical substrate in patients with intermediate QRS duration or morphology. With regard to the latter, retrospective analysis in the PROSPECT and the RethinQ study show that mechanical dyssynchrony predicts a good CRT response in patients with QRS duration 120–130 ms. Further prospective studies are required to demonstrate this unequivocally.
Patients With RBBB
Post hoc analysis of the REVERSE, MADIT-CRT, and RAFT trials has shown that subgroups with non-LBBB QRS morphology do not derive significant benefit from CRT.24 (Figure 3). Although in patients with diffuse intraventricular conduction disturbance a nonsignificant trend toward higher HF event rate and deaths was observed, in patients with RBBB there was no significant benefit of CRT. However, some investigators suggest that subgroups of RBBB patients may respond significantly to CRT. A recent single-center analysis showed that RBBB patients who demonstrated evidence of LV mechanical dyssynchrony by speckle-tracking radial strain or interventricular mechanical delay did benefit from CRT.83 This finding seems supported by data showing that a long Q-LV time predicts a good CRT response, even for patients with RBBB (Figure 7).54 These data emphasize the importance of accurate tailoring pacing therapy (LV site providing long Q-LV, and timing of pacing) in RBBB patients to achieve the best possible resynchronization.

To address the subgroup of RBBB patients, the Pacing Affects Cardiovascular Endpoints in Patients With Right Bundle-Branch Block (PACE-RBBB) trial will investigate whether resynchronization by univentricular RV pacing improves myocardial performance and symptoms and reverses remodeling. The study will include a relatively small number of 75 patients and may be completed in 2013.

Transcatheter Aortic Valve Implantation–Induced LBBB
Finally, if CRT works in essentially all hearts with LBBB, one may wonder whether CRT is effective in a newly developing population of patients: those who acquired LBBB during a Transcatheter Aortic Valve Implantation procedure, currently ≤30% of all Transcatheter Aortic Valve Implantation patients. This LBBB leads to a decrease in LVEF and increases all-cause and cardiovascular mortality.86 These patients do not qualify for CRT according to current guidelines, because their EF is usually >35%, but considering the detrimental effect of desynchronization in these patients it seems plausible that CRT is able to reverse it.

Conclusion
CRT has made a dramatic impact on the treatment of most patients with HF and an abnormal QRS duration. However, clinicians continue to be faced with the fact that some patients, selected using conventional criteria, do not appear to benefit clinically from CRT. This overview highlights the importance of assessing disease substrate as electrical and mechanical substrate, a narrow QRS complex clearly being a contraindication for the use of CRT. In patients with wide QRS complex the response to CRT relates to multiple factors, including duration and morphology of the QRS complex, mechanical dyssynchrony or discoordination, scar location, global scar burden, lead position, programmed AV and VV interval, mitral regurgitation, and irreversibly advanced HF. The interplay of these factors remains complex, and current research and clinical developments make this an exciting time with ongoing discoveries contributing to our further understanding of the pathophysiology of dysynchronous HF and response to CRT. Some studies already indicate the importance of combining the various aforementioned factors to predict the extent of CRT response, including super-response.29 Thus, appreciation of these factors may aid in better anticipation of patient response and better counseling of patients. Advances in research will eventually lead to a treatment algorithm that leads to optimal CRT response.

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