Cardiac resynchronization therapy: Dire need for targeted left ventricular lead placement and optimal device programming

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INTRODUCTION

Cardiac resynchronization therapy (CRT) is a well-established treatment strategy for patients with congestive heart failure (HF), as it has been associated with fewer hospitalizations and an improvement in left ventricular (LV) reverse remodeling, but most importantly with a prolonged survival. The recently updated guidelines recommend CRT in chronic HF patients with LV ejection fraction (LVEF) ≤ 35% who remain symptomatic in New York Heart Association (NYHA) functional class II, III and ambulatory IV, despite adequate medical treatment and who have left bundle branch block (LBBB) with QRS duration > 120 ms on electrocardiogram (ECG) or non-LBBB with QRS duration > 150 ms.[1] Irrespective of the proper patient selection according to guidelines,
Patients eligible for CRT therapy

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Figure 1 The factors that interact for the cardiac resynchronization response and improvement of heart failure symptoms. AV: Atrioventricular; CRT: Cardiac resynchronization; LV: Left ventricle; VV: Interventricular.

about one-third of them currently do not respond to CRT, and more than 40% do not show LV reverse remodeling[8]. The main reasons seem to be the presence of myocardial scar, the suboptimal LV lead position, and the inadequate CRT device programming (Figure 1). The standard approach to CRT implantation consists of simultaneous (or sequential) pacing of the right ventricle (RV) and the LV via an epicardial coronary sinus (CS) venous branch, commonly of lateral or posterolateral location[9]. Moreover, post-implant device programming is a first line approach to achieve the maximal benefit of biventricular pacing depending on the patients’ clinical characteristics. The purpose of this article is to review and evaluate the current data related to both optimal LV lead placement and device programming and their effects on CRT clinical outcomes.

LV LEAD PLACEMENT AND OUTCOMES

Optimization of CRT aims primarily to achieve biventricular pacing as much as possible, ideally 100%, and to reduce the rate of non-responders. This is commonly related to the implantation of the LV lead, its location with respect to the anatomical location of the LV, the presence of transmural scar tissue in the pacing site, its relationship with respect to the mechanical delay, and also the number of different LV pacing sites (Figure 2). Beyond LV lead position, optimal device programming is required to eliminate the atrioventricular (AV) and the interventricular (VV) dyssynchrony by configuring the respective delays. It is well known that patients with true LBBB pattern in the baseline ECG have more favorable clinical outcomes after CRT compared to those with non-LBBB morphology. Electrical conduction delays in the LV and RV produce LBBB and RBBB pattern, respectively[4-7]. Factors that may affect the efficacy of LV pacing may include the presence of transmural scar tissue and the degree of the mechanical contractile delay at the location where the LV lead is placed. It has been shown that the presence of LBBB leads to increased end-systolic volume and myocardial wall stress and decline of myocardial function[8,9]. Early clinical data showed that LV pacing at the most delayed activated site reduces mechanical dyssynchrony and improves LVEF and LV remodeling[10]. Over the last several years, with the use of modern echocardiographic techniques, such as tissue Doppler imaging, two dimensional strain and speckle tracking, a direct relationship between the improvement in NYHA class and the concordance of the placement of the LV lead tip in the maximally delayed activated LV site has been documented[10-11]. Posterolateral and free wall LV pacing has been correlated with LV reverse remodeling defined by an increase of the ejection fraction and a decrease of the end-diastolic diameter. Butter et al[12] examined the hemodynamic effects of different site LV pacing and they found that biventricular pacing, consisting of RV apex and LV free wall or anterior site pacing, was correlated with increased +dP/dtmax values of LV, suggesting that lateral and posterior branches are the optimal LV pacing sites. Van Campen et al[13] examined the effect of combined different pacing sites (RV apex or outflow tract and CS posterolateral or anterolateral) regarding the echocardiographic increase in cardiac index. They concluded that the CS posterolateral vein and RV apex configuration was the site with maximal increase in cardiac index in 29% of patients, the CS posterolateral and RV outflow tract (RVOT) combination produced the maximal increase in cardiac index in 21% of patients and CS anterolateral and RV apex in 19% of patients, respectively. This study suggested that the hemodynamic response and the increase in cardiac index varied between patients and moreover the changes were sustained over a 3-mo period[13]. Earlier, Gold et al[14] compared LV pacing from lateral and anterior sites and they reported no significant group differences in hemodynamic effects among different stimulation sites, although a larger hemodynamic effect with lateral wall stimulation was noted. A recently published study analyzed retrospectively
data from 457 recipients of CRT either with a pacemaker or with a defibrillator. Improvement in NYHA class was significantly greater in patients who underwent LV lead implantation in anterolateral and posterolateral sites with a tendency for greater improvement in LVEF in these regions compared to anterior wall. Long-term survival as estimated with the Kaplan-Meier method at 4 years varied by location (anterolateral: 72%, anterior: 48%, posterolateral: 62%, and posterior: 72% (P = 0.003)\(^{[13]}\).

Although the above data support the superiority of the lateral vs non-lateral LV lead placement sites, results from some of the major CRT trials perhaps report different outcomes. Thus, in the COMPANION trial, LV leads were located anteriorly (26%), posteriorly (10%) and the majority laterally (64%). Mortality rates in patients who received CRT with defibrillator were indifferent to LV lead position. Also, all functional outcomes, including 6-min walk distance, quality of life parameters and functional class, improved with CRT regardless of LV lead location\(^{[10]}\). The REVERSE study indicated that a lateral LV wall pacing was beneficial concerning reverse LV remodelling and the composite of time to death or first HF hospitalization, while the position of the RV lead tip was indifferent\(^{[17]}\). The PROSPECT study evaluated different LV pacing sites in three different groups of patients with evidence for CRT using a fluoroscopy-based clockwise principle: group A, “optimal” (between 3 and 5 o’clock and longitudinal basal/mid-position), group B, “non-optimal” (between 12 and 2 o’clock and longitudinal mid-apical anterior position) and group C (all other positions). No relation was found between the groups and CRT outcome or all-cause mortality. However, further sub-analyses, when groups A and C were combined vs B, suggested that the LV pacing site may impact outcomes in non-ischemic patients, those with LBBB, and when LV lead is located in an apical position\(^{[19]}\). In MADIT-CRT trial, the LV lead location was classified with the use of coronary venograms and X-rays along the short and long axis into an anterior, lateral, or posterior region and basal, mid ventricular, or apical region, respectively. During the follow-up period, the primary end point (HF hospitalization or death) was similar for leads in the region and basal, mid ventricular, or apical region, respectively. The MIRACLE study evaluated different LV pacing sites in three different groups of patients with evidence for CRT using a fluoroscopy-based clockwise principle: group A, “optimal” (between 3 and 5 o’clock and longitudinal basal/mid-position), group B, “non-optimal” (between 12 and 2 o’clock and longitudinal mid-apical anterior position) and group C (all other positions). No relation was found between the groups and CRT outcome or all-cause mortality. However, further sub-analyses, when groups A and C were combined vs B, suggested that the LV pacing site may impact outcomes in non-ischemic patients, those with LBBB, and when LV lead is located in an apical position\(^{[19]}\). In MADIT-CRT trial, the LV lead location was classified with the use of coronary venograms and X-rays along the short and long axis into an anterior, lateral, or posterior region and basal, mid ventricular, or apical region, respectively. During the follow-up period, the primary end point (HF hospitalization or death) was similar for leads in the region and basal, mid ventricular, or apical region, respectively. The MIRACLE study revealed that CRT was more beneficial, with respect to LVEF and reverse remodeling, in patients with non-ischemic HF and less severe mitral regurgitation. To assess the transmurality of LV scar tissue, cardiac magnetic resonance imaging (MRI) with delay enhancement is currently the preferred imaging method of choice. Bleeker et al\(^{[25]}\) used contrast enhanced MRI to define LV scar burden and reported that those who failed to respond to CRT were more likely to have transmural scar in the posterolateral region of the LV. It is noteworthy that from 14 patients who had scar in the posterolateral wall, 11 had significant dyssynchrony as assessed by tissue doppler imaging (TDI) but a clinical benefit from CRT was only seen in 2 of these 11 patients.

The TARGET trial is the first randomized study that was designed to assess the impact of targeted LV lead placement, using baseline echocardiographic speckle-tracking 2-dimensional radial strain imaging vs conventional approach, on clinical CRT outcomes. After 6 mo, patients who underwent the echocardiography-guided implantation had a greater extent of LV reverse remodelling, better clinical response as well as lower HF hospitalization, although there was no difference in all-cause mortality. Multivariate analysis suggested that the greatest benefit was demonstrated in patients with a concordant LV lead at sites free of scar, whereas in patients with either an LV located remote to the latest site of contraction or in scar area, the response was significantly lower\(^{[23]}\). More recently, results from the STARTER study, which randomized patients on echo-guided transvenous LV lead placement, determining the site of latest time to peak radial strain by speckle tracking echocardiography, vs a conventional fluoroscopy approach confirmed the superiority of the echocardiography-guided approach. Using intention-to-treat analysis, patients in the echocardiography group had a significant more favorable event-free survival (fewer HF hospitalizations or deaths) and furthermore, LV lead placement concordance with the site of latest mechanical activation was achieved significantly higher in these patients compared to others\(^{[20]}\). The impact of LV lead position on LV dyssynchrony in CRT recipients was evaluated also by two-dimensional speckle tracking radial strain echocardiography in the study of Kristiansen et al\(^{[28]}\). Mechanical dysynchrony was assessed by anteroseptal-to-posterior delay and interventricular mechanical delay and the LV lead was targeted to the latest activated LV segment (concordant). At 6-mo follow up, superior LV reverse remodeling, as defined by ≥ 15% LV end-systolic volume reduction, was observed to be significantly higher in patients with concordant compared to those with discordant LV leads. Moreover, mechanical resynchronization responders 6 mo after CRT were significantly more in this group and the concordant LV lead was the only independent predictor of LV reverse remodeling\(^{[28]}\). Gated single photon emission computed tomography (SPECT) has also been used to identify the scar region in CRT recipients. Ypenburg et al\(^{[29]}\) assessed the importance of transmural scar quantified by gated SPECT in the LV pacing target region and reported that transmural scar in the region of the LV pacing lead (as determined by chest X-ray) was negatively related to subsequent LV reverse remodelling although patients with transmural scar at the LV tip pacing site exhibited less LV dyssynchrony.

IMPACT OF MYOCARDIAL SCAR BURDEN AND IMAGING ON CRT RESPONSE

The extent of myocardial scar has been inversely related to clinical response in patients undergoing a CRT device implantation. Although there are data supporting that there is no difference between patients with ischemic and non-ischemic cardiomyopathy concerning CRT response, plenty of studies have shown significant differences in the efficacy of CRT depending on the etiology of cardiomyopathy\(^{[26,21]}\). The MIRACLE study revealed that CRT was more beneficial, with respect to LVEF and reverse remodeling, in patients with non-ischemic HF and less severe mitral regurgitation. To assess the transmurality of LV scar tissue, cardiac magnetic resonance imaging (MRI) with delay enhancement is currently the preferred imaging method of choice. Bleeker et al\(^{[25]}\) used contrast enhanced MRI to define LV scar burden and reported that those who failed to respond to CRT were more likely to have transmural scar in the posterolateral region of the LV. It is noteworthy that from 14 patients who had scar in the posterolateral wall, 11 had significant dyssynchrony as assessed by tissue doppler imaging (TDI) but a clinical benefit from CRT was only seen in 2 of these 11 patients.

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The optimal CRT device programming is crucial in the post implantation period in order to achieve the maximum percentage of biventricular pacing. Optimization of both AV and VV timing intervals have been suggested as potential methods to improve response rates and even increase the magnitude of symptomatic improvement in these patients. Nevertheless, data from multicenter trials in CRT recipients suggest that AV and VV optimization has limited efficacy on clinical outcomes and echocardiographic parameters, compared with a fixed 100-120 ms AV delay and simultaneous biventricular pacing\textsuperscript{[32-36]}. The combination of the optimal LV lead implantation site and optimal device programming is considered the gold standard for the best response in CRT recipients. However, the optimization of AV and VV delays in patients with non-optimal LV pacing site could partly ameliorate the hemodynamic effect\textsuperscript{[37]}. Several methods have been proposed to optimize the AV and VV delays and have been classified into two main groups: echocardiography-based and non-echocardiography-based methods (Table 1).

### LV LEAD MULTISITE AND ENDOCARDIAL PACING

Transvenous LV lead implantation \textit{via} CS cannulation is the currently adopted technique for CRT device implantation procedures. During the recent years, a new technique has been described, consisting of true multisite pacing with a second LV lead placed in a second branch of the CS, especially in patients with large LV dimensions in order to reduce the mechanical dyssynchrony. Leclercq \textit{et al}\textsuperscript{[27]} reported that triple site pacing was correlated with significantly better LV reverse remodeling, in terms of higher LVEF, and smaller LV end-systolic volume and diameter after 9-mo follow up. The recently published results of the TRUST CRT (“Triple Site Versus Standard Cardiac Resynchronization Therapy”) study indicated that after 12 mo of follow up significantly fewer patients with triple site CRT were in NYHA functional class \textit{III} or \textit{IV} compared to those with conventional CRT. Moreover, the incidence of serious, CRT-related adverse events was similar in triple-site and conventional group\textsuperscript{[28]}. Endocardial LV pacing theoretically offers greater options for pacing to patients in whom the CS system is inaccessible. There is always a need for lifelong anticoagulation therapy and the available clinical data although they are positive regarding efficacy and safety, they are still limited\textsuperscript{[29,30]}. LV endocardial pacing was compared to a single epicardial pacing site in the study of Padeletti \textit{et al}\textsuperscript{[31]} and the investigators reported no significant differences between endocardial and epicardial pacing configurations in terms of LV systolic or diastolic function measurements. Nevertheless, the optimal LV endocardial site producing the best LV function improvement was consistently better than the chosen epicardial pacing location.

### OPTIMIZATION OF CRT DEVICE PROGRAMMING

The optimal CRT device programming is crucial in the post implantation period in order to achieve the maximum percentage of biventricular pacing. Optimization of both AV and VV timing intervals have been suggested as potential methods to improve response rates and even increase the magnitude of symptomatic improvement in these patients. Nevertheless, data from multicenter trials in CRT recipients suggest that AV and VV optimization has limited efficacy on clinical outcomes and echocardiographic parameters, compared with a fixed 100-120 ms AV delay and simultaneous biventricular pacing\textsuperscript{[32-36]}. The combination of the optimal LV lead implantation site and optimal device programming is considered the gold standard for the best response in CRT recipients. However, the optimization of AV and VV delays in patients with non-optimal LV pacing site could partly ameliorate the hemodynamic effect\textsuperscript{[37]}. Several methods have been proposed to optimize the AV and VV delays and have been classified into two main groups: echocardiography-based and non-echocardiography-based methods (Table 1).

### Echocardiography-based methods

The goal of AV optimization is to ensure that LV contraction does not occur before complete filling, whereas with VV optimization the goal is to minimize LV mechanical dyssynchrony. AV optimization is achieved using the Ritter method which aims at maximizing the LV filling during diastole by allowing for mitral valve closure to occur after a complete atrial systole. The interval between QRS onset and closure of mitral valve is measured by programming short and long AV intervals. It is noteworthy that the Doppler A wave is truncated with short AV delay programming and the opposite happens with very long AV delay which can cause fusion of the E and A waves and mitral valve diastolic regurgitation. The optimal AV delay is calculated as the long AV delay less the difference of the time intervals of the QRS onset to mitral valve closure at short and long AV intervals\textsuperscript{[38]}.

AV optimization is also performed with the estimation of the maximal stroke volume measuring the aortic velocity-time integral (VTI) with multiple AV intervals\textsuperscript{[39]}. Similarly, the same measurements could be performed using diastolic mitral inflows including E and A waves. The measurement of the maximum mitral inflow VTI has been shown to correlate better with the maximal LV dp/dT values\textsuperscript{[39]}. In patients with mitral regurgitation, LV dp/dT can also be measured by the continuous Doppler curve of mitral regurgitation jet and determines better functional class and LVEF at 6-mo follow-up relative to an empiric AV delay program\textsuperscript{[40]}. New echocardiographic techniques, such as three dimensional echocardiography, are also used for CRT optimization leading to improvement of LVEF, stroke volume and myocardial performance index\textsuperscript{[41]}. AV delay optimization has been shown to have chronic beneficial hemodynamic effects, when it was performed 31 ± 8 wk after CRT device implantation and at a follow up period of 43 ± 5 d later. A slight significant increase in LVEF and 6-min walk time was reported and a significant decrease in N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) values\textsuperscript{[42]}.

### Table 1. Echocardiographic and non-echocardiographic methods for atrioventricular and interventricular optimization

<table>
<thead>
<tr>
<th>AV optimization</th>
<th>VV optimization</th>
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<tr>
<td>Echocardiography-based methods</td>
<td>Aortic VTI</td>
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<tr>
<td>Aortic and mitral VTI (velocity time integral)</td>
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<tr>
<td>Device integrated methods</td>
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<td>Smart Delay™</td>
<td>AdaptiveCRT™</td>
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<td>AdaptiveCRT™</td>
<td>Peak Endocardial Acceleration sensor SonR®</td>
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<td>Peak Endocardial Acceleration sensor SonR®</td>
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<tr>
<td>Other methods</td>
<td>Acoustic cardiology</td>
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<td>Finger plethysmography</td>
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Concerning VV optimization, the commonly used method is to calculate the maximal aortic VTI usually with pulse wave Doppler, which is considered to be a representative index of stroke volume. The time interval between LV and RV activation could be adjusted (commonly LV activation is usually preferred to precede) in the available CRT devices. TDI is also used to identify LV areas displaying delayed longitudinal contraction in order to achieve the optimum interventricular delay programming. There is no ideal method for AV and VV optimization as the results from clinical studies are controversial. A direct comparison of different echocardiographic measurements for VV interval optimization showed that aortic VTI and VV dysynchrony were the most feasible (100% and 93% of feasibility, respectively). On the contrary, Zuber et al. reported the superiority of acoustic cardiography derived electromechanical activation time compared to aortic VTI for AV and VV delay optimization.

**Device integrated methods/automated algorithms**

Automatic CRT optimization algorithms, based on intracardiac electrograms (IEGMs), have been developed to calculate the optimal AV and VV delays and consequently to improve the clinical outcomes. The Smart AV Delay™ (Boston Scientific Corporation, Minneapolis, MN, United States) algorithm estimates the sensed and paced AV intervals and the duration of native VV conduction time from the IEGMs and can only be used in patients with QRS duration ≥ 120 milliseconds, normal AV conduction, and intrinsic sensed or paced AV intervals from 100 milliseconds to 400 milliseconds. The algorithm aims at maximal resynchronization which is thought to occur when there is optimal fusion between intrinsic conduction through the interventricular septum and the paced activation of the late activated region of LV. The QuickOpt™ (St. Jude Medical, St. Paul, MN, United States) algorithm is based on the duration of intrinsic atrial depolarization, as measured from the right atrial electrogram duration, and determines the optimal sensed AV delay and ensures that ventricular pacing occurs after atrial depolarization and mechanical contraction are complete. The paced AV delay is always set as the optimal sensed AV delay plus 50 milliseconds. The QuickOpt™ software also includes calculation of optimal VV timing, measuring the interval for maximal intrinsic activation between the LV and RV leads and taking into account the VV conduction delay during both LV and RV pacing. The AdaptiveCRT™ (Medtronic, Minneapolis, MN, United States) algorithm uses electrograms to calculate the AV delay to optimize fusion of the LV-pacing-derived wavefront with that from intrinsic conduction. The algorithm provided mostly synchronized LV pacing and demonstrated better clinical outcomes compared to echocardiography-optimized biventricular pacing. The Peak Endocardial Acceleration sensor (SonR®, Sorin CRM SAS, Clamart, France) is embedded in the RV or atrial pacing electrode and determines the optimal AV and VV delays based on the peaks of endocardial acceleration. Its effectiveness was evaluated in the multicenter CLEAR study which showed a significant improvement in subjective NYHA functional class, with the SonR® algorithm compared with usual practice.

**CLINICAL TRIALS RESULTS**

**CONCERNING AV AND VV OPTIMIZATION**

The Frequent Optimization Study Using the QuickOpt Method (FREEDOM) trial concluded that optimization using QuickOpt did not significantly influence outcome as defined by the HF clinical composite score. Additionally, the SMART-AV trial using Smart Delay™ algorithm reported that a fixed AV delay of 120 milliseconds was not inferior to the optimal AV delay, as derived from echocardiography or Smart Delay™ algorithm. Long term outcomes of VV interval optimization were investigated in the InSync III, RHYTHM II ICD and DECREASE-HF trials. The InSync III trial demonstrated that the optimal VV interval ranges between RV and LV pre-excitation of 40 milliseconds, respectively with a higher prevalence of LV pre-excitation although the sequential CRT optimization improved only the 6 min walking distance. Similarly, data from the RHYTHM II ICD study demonstrated no clinical benefit after 3-6 mo of follow-up by the optimized sequential CRT over the simultaneous biventricular pacing. Furthermore, the DECREASE-HF trial, which enrolled patients with QRS duration > 150 milliseconds and symptomatic HF, examined the potential benefits comparing simultaneous VV optimized biventricular pacing. Furthermore, at 6-mo follow-up, no significant differences between these two pacing modes (simultaneous VV optimized biventricular pacing) were reported regarding the reduction in LV size and the improvement of LVEF.

**CONCLUSION**

CRT is an important treatment approach in selected patients with HF. The maximum desired results are achieved with the proper patient selection according to proposed indications, and with careful pre-implant and post-implant management. Although initial studies of different LV anatomic pacing sites suggested benefit of posterior or lateral sites, subsequent data has yielded conflicting results. Based on the current data, LV lead placement to sites of latest LV mechanical activation, as defined by speckle tracking echocardiography, remains a better method to improve the clinical results. Multisite and endocardial LV pacing are promising methods, but additional data are required. On the other hand, the role and efficacy of AV and VV optimization in improving clinical outcomes in CRT, albeit promising, remains unclear and there is no clearly superior technique or algorithm. It remains to investigate whether AV and VV interval optimization may improve the long-term survival.
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