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ARRHYTHMIAS (J. BUNCH, SECTION EDITOR)

Characteristics that Predict Response After Cardiac Resynchronization Therapy

Anandaroop Lahiri[1] · Fahd K. Chahadi[1] · Anand N. Ganesan[1,2,3] · Andrew D. McGavigan[1,2]

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Abstract

Purpose of Review Cardiac resynchronization therapy (CRT) is an established modality for treating heart failure. However, one-third of patients do not respond and it is increasingly recognized that response is not binary and we should be aiming for "best response". This review looks at factors predicting response and remodelling and highlights areas where we may improve both the proportion of responders but also maximize response in an individual.

Recent Findings We review the clinical characteristics predicting response including structural and electrical remodelling and discuss areas of debate. We examine the evidence supporting the recently described move from anatomical-based placement of the left ventricular (LV) lead to an electrical approach with intra-operative electrical mapping and targeting of late activating regions of the LV. Finally, evidence for electrocardiographically guided post-implant programming, aiming for the narrowest paced QRS, is discussed. This includes the increasing use of atrioventricular and interventricular delay optimization and the use of newer algorithms and methods (Sync-AV, Adaptiv-CRT, Multipoint pacing, etc.) for achieving the best response.

Summary Recent data supports a tailored, individualized approach to patient selection, LV lead placement and programming to get the best response from CRT.

Keywords Cardiac resynchronization therapy · Response · Electrical delay

Introduction

Cardiac resynchronization therapy (CRT), with or without defibrillator capabilities, has been a major advance in the therapy of heart failure, and its use is reflected in all major guidelines [1–3]. However, there has been a consistent observation that about one-third of patients receiving CRT do not "respond" [4–6] and it is increasingly recognized that response is not binary and we should be aiming for "best response". This review examines clinical, procedural and post-procedural factors predicting response and remodelling and highlights areas where we may improve both the proportion of responders and maximize the response from CRT.

This article is part of the Topical Collection on *Arrhythmias*

✉ Andrew D. McGavigan
andrew.mcgavigan@sa.gov.au

Anandaroop Lahiri
anandaroop.lahiri@sa.gov.au

Fahd K. Chahadi
Fahd.Chahadi@sa.gov.au

Anand N. Ganesan
anand.ganesan@flinders.edu.au

[1] Department of Cardiology, Flinders Medical Centre, Flinders Drive, Bedford Park, SA 5042, Australia

[2] Faculty of Medicine, Flinders University, Bedford Park, South Australia, Australia

[3] South Australian Health and Medical Research Institute, Adelaide, South Australia, Australia

Definition of Response

Response to CRT has been variably described and lacks a consensus definition. Response can be driven by clinical endpoints (such as death or heart failure hospitalization), improvement in symptoms (New York Heart Association (NYHA) functional class, quality of life scores, six-minute walk test, etc.), or echocardiographic parameters (including left ventricular dimensions in diastole and systole and predefined absolute or relative increase in left ventricular ejection fraction (LVEF)) [5, 7–9]. Often, response is defined using a

mixture of clinical and/or echocardiographic findings; the most common being the Clinical Composite Score [8–10].

This makes cross-comparison of trials and registries challenging. For example, in the Predictors of Response to Cardiac Resynchronization Therapy (PROSPECT) trial, the response rate varied between 56 and 69%, purely dependent on the definition of the criteria for response to CRT [7]. Furthermore, the term "response", as arbitrarily defined in many studies, gives an impression that it is a categorical or binary variable. A "responder" may have achieved an improved LVEF and/or reduced internal dimensions and/or improved NYHA class, but this may be a sub-maximal response for that individual patient. We should be aiming to achieve the "best response" in every patient.

In our practice, we use a combination of symptomatic (NYHA class) and echocardiographic assessment (left ventricular dimensions and LVEF) as markers of response. This allows cross-comparison with the literature and the combination is useful as we find that clinical response occurs early, typically preceding positive echocardiographic remodelling by several months. Response using these variables is documented at every visit and changes in programming are performed to try and maximize response on a regular basis.

Clinical Characteristics Predicting Response

Multiple factors have been suggested as predictors of a positive response to CRT, including female sex, non-ischaemic cardiomyopathy, absence of scar on cardiac magnetic resonance (CMR), ejection fraction and ECG duration and morphology [11–15, 16•, 17, 18]. Fornwalt and colleagues [19] examined 15 clinical and echocardiographic parameters associated with response and applied them to the 426 patients enrolled in the PROSPECT trial [7]. Using these parameters, prediction of response varied between 32 and 91%. Utilizing κ-values for agreement between parameters, they found overall agreement to be poor, especially between echocardiographic and clinical parameters.

Of the various clinical variables associated with response, gender and the underlying substrate appear to be the most important and reproducible. There has been a consistent demonstration of superior benefit from CRT in females compared with males [11, 12]. Furthermore, the benefit of CRT appears to be less reliant on QRS duration [12], raising the question as to whether women should have a different QRS width cut-off for qualifying for CRT as opposed to men [11]. With respect to substrate, multiple authors have shown improved response to CRT in patients with non-ischemic cardiomyopathy (NICM) compared with those with ischemic cardiomyopathy (ICM) [13, 14]. This is driven by a higher increment in LVEF [13], better functional status [13] and possibly improved survival [14]. Furthermore, NICM is associated with improved electrical remodelling [20] and higher chance of "super-response" with increased rates of normalization of LVEF [21].

ECG Characteristics Predicting Response

QRS duration and morphology remain the biggest independent predictor of response to CRT, which is reflected in international guidelines [1–3]. This is not surprising, given that CRT aims to electrically resynchronize the heart and a broad QRS duration (> 150 ms) associated with left bundle branch block (LBBB) indicates electrical delay in the LV and therefore electrical dyssynchrony.

The benefit of CRT in right bundle branch block (RBBB), intraventricular conduction defect (IVCD) and more modest QRS durations (130–149 ms) is less clear and has lower classes of recommendation in guidelines [1–3]. However, this is a large group of patients and may still benefit from targeted LV lead placement, especially when one considers LV electrical delay in the absence of LBBB. Poole et al. (2016) [16•] examined the pattern and local timings of LV activation in patients with various patterns of conduction system disease (Fig. 1). As expected, in patients with LBBB, the latest activating LV segments are the lateral basal LV and the adjoining regions—the traditional target for LV lead implantation. In contrast, in those with RBBB, latest activation occurs in areas of the RV free wall. Although there can be relative delays between LV segments, the absolute delay is lower than in those with LBBB, indicating a lesser degree of dyssynchrony, reducing the potential benefit of CRT. However, a sub-group of patients with RBBB have associated distal conduction disease in the left system (left anterior fascicular and left posterior fascicular block). In such patients, there were areas in the LV that had both relative and absolute late activation compared with similar segments in patients with pure RBBB. In this group, targeted implantation of an LV lead at the latest activated LV site may significantly improve dyssynchrony and derive benefit from CRT. In those with IVCD, there were variable areas of late activation within the LV, often not in the traditional basal or lateral areas, again raising the possibility of targeted LV lead placement.

In contrast, CRT confers no benefit (and may be harmful) in patients with narrow QRS duration (< 130 ms) [17, 22] even in the presence of echocardiographic dyssynchrony [17] and is therefore *not* recommended in this group.

Implantation Characteristics

The key step of a CRT procedure is the placement of the LV lead in a tributary of the coronary sinus (CS). The greatest benefit is derived from a LV lead which is able to optimally resynchronize the ventricle. Therefore, the primary objective

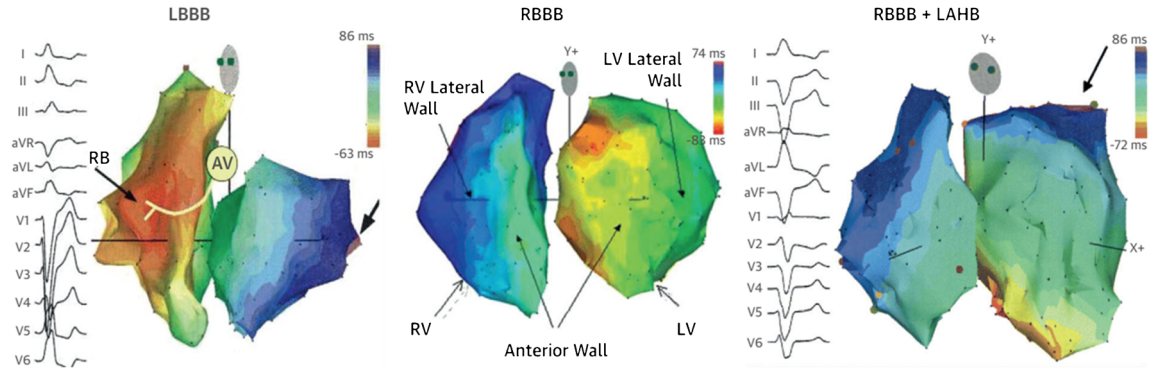

Fig. 1 Activation patterns using 3-dimensional electroanatomic mapping comparing right bundle branch block (RBBB), left bundle branch block (LBBB) and RBBB + left anterior hemiblock (LAHB). Earliest activation displayed in red, latest in blue. In LBBB (left panel), latest activation is seen in the lateral LV. In RBBB (middle panel), the RV free wall has latest activation with the LV lateral wall activated mid cycle. In RBBB and LAHB (right panel), although latest activation remains in the RV free wall, basal lateral LV is also activated late, towards the end of the QRS. Figure adapted with permission from Poole et al. [16•]

is to consider the best possible lead position rather than to use a branch that is just procedurally easy or quick to target. We believe delineation of all available CS branches is important and use sequential balloon occlusion venography with long cine times to outline all tributaries of the CS, as well as collaterals. Collaterals may be important for advanced techniques including snaring. Suitable veins can then be targeted anatomically or electrically.

Anatomical Considerations

Anatomically, the principal considerations are lateral versus a non-lateral and basal versus apical position. As previously discussed, typical LBBB usually produces latest activation in the basal lateral LV [16•]. CS tributaries in this area have been traditionally targeted for LV lead placement. A snapshot of real-world practice comes from a meta-analysis from Gamble and colleagues [23] who identified a total of 164 studies (including randomized trials and cases series) that yielded 29,503 patients. The final LV lead position was reported in 7695 LV leads (26%). Nearly three-quarters had a LV lead position in the lateral or postero-lateral position (43% lateral and 30% postero-lateral), and > 80% in the non-apical position (62% mid-ventricular, 22% basal and 15% apical).

Implanters are therefore preferentially targeting lateral and non-apical sites and early data supported this concept. Butter et al. [24] studied acute haemodynamic response with respect to the placement of the LV lead at anterior versus lateral free wall sites of the LV in 30 patients included in the PATH-CHF II trial. The lateral free wall LV sites yielded better acute haemodynamic parameters—LV dp/dt(max) and pulse pressures—compared with anterior sites. However, data on improved long-term outcome is lacking, with the MADIT CRT Study [25] showing no significant relationship of LV lead position (anterior, lateral and posterior) to outcome. However, the same study demonstrated significantly better outcomes in patients with basal placement compared with apical placement of LV leads [25]. However, this was recently challenged by Leyva and colleagues [26] who found in a retrospective study that an apical position was significantly better than a non-apical position for cardiac survival, the difference being driven by reduced pump failure and sudden cardiac death.

The data on LV lead position is conflicting with only retrospective analyses of trials with heterogeneous lead positions to guide us. At best, targeting anatomical placement gives some guidance but cannot solely be relied on to produce best outcomes.

Electrical Considerations

The central concept of CRT is correction of electromechanical dyssynchrony via electrical resynchronization. As such, consideration of the electrical timings of LV lead placement provides an intriguing target to maximize response to CRT (Fig. 2).

Q-LV

The interval from the beginning of the surface QRS to the sensed LV epicardial electrogram gives the Q-LV (Fig. 2a). A long Q-LV interval indicates late local activation, and may be a useful feature to guide CS lead placement.

One of earliest studies looking at targeting LV leads to electrical "lateness" [27] examined 71 patients undergoing resynchronization therapy for standard indications. Intraoperatively, they measured left ventricular lead electrical delay (LVLED)—the Q-LV interval expressed as a percentage of the QRS duration—and examined acute

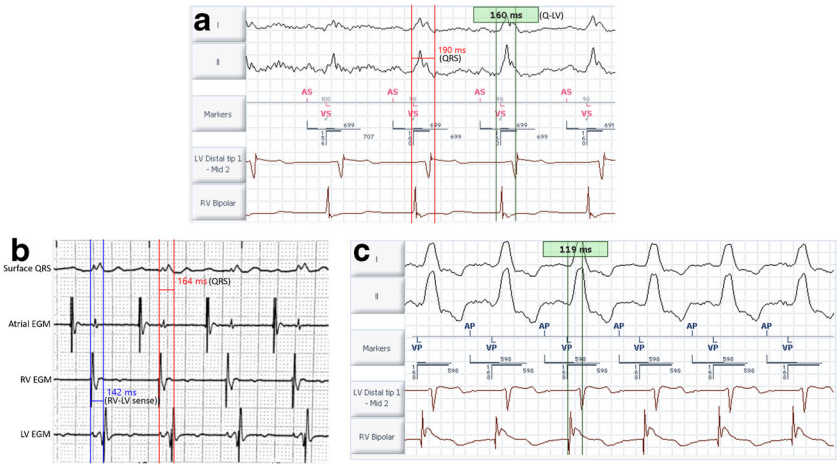

Fig. 2 Examples of electrical parameters tested. The timing callipers measure intervals from either the beginning of the QRS or the RV electrogram to the point of the maximum deflection (positive or negative) on the LV electrogram for the sake of consistency and reproducibility. **a** Device recording during intrinsic conduction showing five channels, from top to bottom—ECG lead I, ECG lead II, marker channel, LV channel and RV channel. The surface QRS duration is 190 ms (marked with a red calliper) and the Q-LV duration is 160 ms (marked with a black calliper). **b** Device recording during intrinsic conduction showing four channels, from top to bottom—ECG lead I, atrial channel, RV channel and LV channel. The surface QRS duration is 164 ms (marked with a red calliper) and the duration between the sensed RV electrogram and the sensed LV electrogram is 142 ms (marked with a blue calliper, RV-LV sense). **c** Device recording during sequential atrial and RV pacing showing five channels, from top to bottom—ECG lead I, ECG lead II, marker channel, LV channel and RV channel. The duration from the RV-paced electrogram to the LV-sensed electrogram is 119 ms (marked with a black calliper, RVp-LVs)

haemodynamic response using echocardiographic derived delta dp/dt change. They reported significant correlation of LVLED with delta dp/dt. Additionally, at 12-month follow-up, reduced LVLED (< 50% of the QRS) was associated with significantly higher combined endpoint of heart failure hospitalization and/or all-cause mortality (HR 2.7, 95% confidence interval 1.17–6.68, $P = 0.032$). Subsequent investigators have confirmed these findings, with high predictive values of a prolonged Q-LV for positive remodelling [28–31•].

Van Everdingen and colleagues [30] examined mean Q-LV timings in 51 patients at various branches of the CS and found that the segment with the average most prolonged Q-LV timings was the lateral segment. However, while this was true of the whole group, there was heterogeneity within the group, with the absolute latest site in individual patients being spread between the antero-lateral, posterior and postero-lateral segments. Furthermore, there was heterogeneity in the longitudinal direction no clear cut "best site" between apical and non-apical segments.

This argues for the case that there are potentially good sites for LV leads in terms of timing delay at positions that are not "traditionally ideal" by anatomical standards. This may be especially true in those with non-LBBB morphology. Kandala et al. [32] studied 144 patients receiving CRT—82 patients with LBBB and 62 patients with non-LBBB morphology. They reported that Q-LV correlated with paced QRS duration significantly in both LBBB and non-LBBB groups ($r = 0.52$, $P < 0.0001$). Importantly, LVLED was significantly higher for the LBBB group as opposed to the non-LBBB group (73 ± 25% vs. 61 ± 21%, $P = 0.002$), indicating a larger "electrical window" for resynchronization in patients with LBBB as opposed to non-LBBB, and may also indicate one of the reasons for a lack of comparable reverse remodelling in non-LBBB patients. In terms of clinical end-points such as heart failure hospitalization and composite outcomes (comprising heart failure hospitalization, left ventricular assist device implantation, cardiac transplantation and all-cause mortality), although those with LBBB and LVLED ≥ 50% had the best outcome, LVLED predicted response regardless of left or right bundle branch morphologies.

These findings introduce the idea of individualization of LV lead placement based on direct electrical measurement, rather than relying purely on anatomical parameters, but need to be validated in prospective randomized controlled trials.

RV to LV Timings

Q-LV is a measure of delayed activation of the LV, but CRT needs to resynchronize the heart and consideration of the relative timings of the septum to the lateral wall is critical. This can be determined by examining the timing delay between the RV lead electrogram (often placed on the septal aspect of the RV) and the LV lead electrogram. Gold et al. [33•] studied 1342 patients having CRT for standard indications and examined the timing delay of the sensed LV electrogram with respect to the sensed RV electrogram during intrinsic conduction (the interventricular delay) (Fig. 2b). They dichotomized the cohort into two groups above or below the median value of RV-LV timing (67 ms). They demonstrated an improved

outcome with better heart failure–free survival at 12 months in the group with intrinsic RV-LV timing > 67 ms, compared with the ones with a shorter interval. Similar results have been reported by the same group [34] where longer RV-LV timings predicted significantly better CRT outcomes and have been reproduced by other authors [28, 35••].

Sensed RV-LV timings during intrinsic conduction are a reflection of His-Purkinje and intramyocardial conduction delay but examination of intramyocardial conduction delay between leads during RV pacing may be more useful in predicting response to biventricular pacing. This may be especially pertinent in the group of patients with both intrinsic AV nodal and distal conduction system (BOCK HF group) [36]. Oddone et al. [37] studied 97 patients undergoing CRT and measured the timing interval between the RV-paced electrogram and the sensed CS electrogram (Fig. 2c) and quantified this as a percentage of the total QRS width which they termed as the RLD index. They found that the sites with the longest RLD were found in the basal and mid-lateral segments and were correlated inversely and significantly with biventricular paced ECG QRS width, which can be considered a surrogate for clinical outcome. RLD index was not altered by the presence of intrinsic AV nodal disease. Other authors have demonstrated similar positive results for RV-paced to LV-sensed timings predicting outcome [38, 39], and a larger prospective trial is recruiting (OPSITE 2) [37].

Workflow in our Lab

The RV lead in our lab is typically placed in the mid to low septum. The steps for implantation of the LV lead (after the RV and RA leads) are as follows:

1 CS venogram delineating all the branches—high and low, with long cine times to look at collaterals and proximal tributaries.
2 Electrical mapping of the CS tributaries—a 014-in. coronary wire is passed through the CS and inner sheaths to cannulate a previously identified tributary and a unipolar signal is obtained by connecting cathode to the wire and anode to the skin. The duration from the onset of the surface QRS to the first rapid change in deflection of the unipolar electrogram is obtained from the wire at a sweep speed of 100 mm/s, giving the Q-LV. This is repeated for all identified tributaries and the longest two chosen for placement of CS lead.
3 RV-LV timings—a quadripolar lead is passed to the tributary with longest Q-LV and tested for sensing, pacing and diaphragmatic capture. Assuming adequate pacing parameters, Q-LV is reconfirmed using all four poles as cathodes, followed by measurement of both sensed RV to sensed LV timings and paced RV to sensed LV signal (using all four cathodes). This is repeated in the other branch identified on initial Q-LV screening, unless there are concerns over ability to recannulate the vein. Final placement is determined based on pacing parameters and combination of all timing intervals.
4 Post-implant—the CS poles are checked again for the longest Q-LV, longest sensed RV to sensed LV times and longest paced RV to sensed LV times. Assuming satisfactory pacing parameters, the bipole with the longest time is chosen for pacing. Subsequently, multiple ECGs are performed with different LV offsets and different AV delays—the settings that yield the narrowest QRS are chosen and programmed.

Post-implant Characteristics

Post-implantation programming of the device has two major objectives, to convert non-responders to responders and to maximize response in all patients. Traditionally, the non-responder group has been the principal focus, but the recognition that response is not a binary variable has pushed many investigators to seek maximal response in all.

It is critical to ensure high degrees of biventricular pacing [40] and in patients with AF, one should consider AV nodal ablation [41]. There are several avenues open for programming to try and maximize response, predominantly modification of atrioventricular and interventricular timing delay with or without the use of proprietary algorithms such as Sync-AV, Adaptiv-CRT or SonR and the use of multipoint pacing. There is increasing interest in the use of paced ECG duration to guide programming (Fig. 3).

Early trails such as PATH-CHF and PATH-CHF II [42, 43] showed significant changes in LV dp/dt max with different AV delays and small studies of AV delay optimization using echo parameters showed a small benefit in clinical outcome [6, 44]. However, the larger prospective SMART-AV and FREEDOM studies [45, 46] failed to show any significant difference in the outcome of optimization of AV intervals compared with nominal settings. This may in part be explained by the dynamic nature of the intrinsic AV intervals, dependent on heart rate, autonomic tone and other factors, where "best" AV delays may vary significantly over time. This could be potentially overcome by automated algorithms to assess intrinsic AV times and proprietary algorithms for programming AV delays.

Sync-AV (Abbott Medical, USA) is one such algorithm of dynamic AV optimization using fixed reduction of sensed AV delay. Verma and colleagues [47•] have

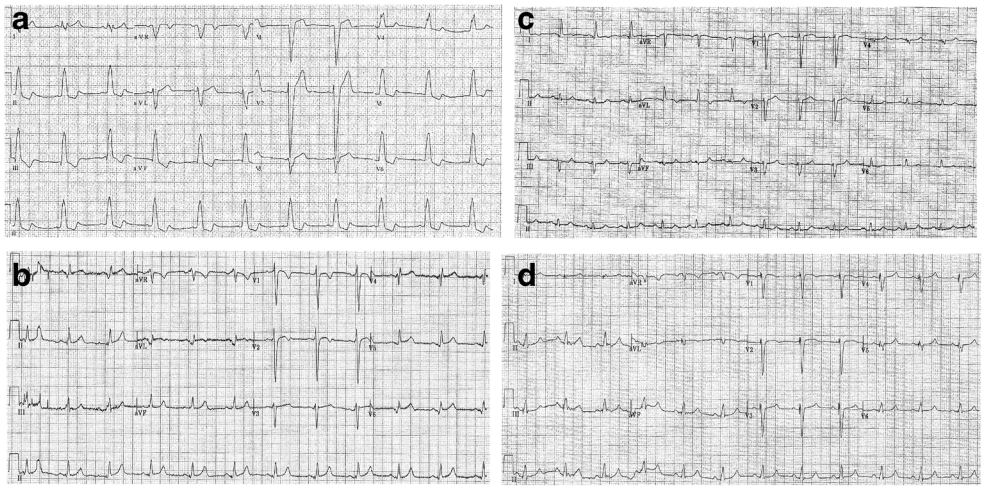

Fig. 3 Examples of ECG morphologies from same patient. **a** Intrinsic ECG, sinus rhythm, LBBB, QRS width 170 ms. **b** Atrial sensed, biventricular paced rhythm, sync AV mode (optimal sync AV delay), with simultaneous LV and RV pacing, paced QRS width 130 ms. **c** Atrial sensed, biventricular paced rhythm, sync AV mode (optimal sync AV delay), with LV ahead of RV by 20 ms, paced QRS width 120 ms. **d** Atrial sensed, biventricular paced rhythm, sync AV mode (optimal sync AV delay), with LV ahead of RV by 40 ms, paced QRS width 110 ms

recently examined the effect of various programming modes including the use of Sync-AV on paced QRS duration in 73 patients and found significantly narrower QRS duration with Sync-AV programmed on. However, to date, no prospective data on outcome is available using this algorithm. Adaptive CRT (Medtronic, USA) is another proprietary algorithm dynamically altering AV delays to produce LV pacing synchronized with intrinsic activation to produce fusion with intrinsic conduction, also effecting VV timings. This produces narrower QRS duration and is superior to echocardiographically optimized biventricular pacing with reduced risk of death or heart failure hospitalization [48]. Finally, SonR (Sorin, Italy) is a proprietary algorithm with automatic optimization of AV and VV delays based on a Peak Endocardial Acceleration signal system. The CLEAR study demonstrated with improvement in composite clinical endpoint using SonR, largely driven by improved symptomatic status [49]. The larger RESPOND-CRT trial [50] demonstrated non-inferiority to echo optimization, with a 35% risk reduction in heart failure hospitalization.

Both Sync-AV and adaptive CRT produce shorter paced QRS duration which has been shown to be a good predictor of clinical response [5, 51, 52] and recent data shows correlation with long-term mortality [53]. Programming to shortest QRS duration has recently been examined prospectively by Trucco and colleagues [54] where 180 patients with LBBB undergoing CRT implant were randomized to fusion optimized intervals (FOI) or nominal settings. In the FOI group, atrioventricular and interventricular delays were optimized using the narrowest QRS using fusion and intrinsic conduction. They reported significantly shorter paced QRS duration in the FOI group with improved LV reverse remodelling (74% vs. 53%, $P = 0.026$).

Multipoint pacing is associated with shorter paced QRS duration [55] and is associated with improved acute haemodynamic response compared with conventional biventricular pacing [56, 57]. Smaller studies have suggested some benefit over conventional CRT [55, 58] with the larger MPP trial [59] showing non-inferiority overall, but increased rates of response in those in whom multipoint pacing was programmed appropriately (> 30 mm inter-electrode spacing and near-simultaneous activation). The use of multipoint pacing is being addressed in currently enrolling trials.

Workflow in our Clinic

There is no consensus in the manner, timing or frequency of post-implant programming. However, post hoc analysis of the CLEAR study [60] demonstrated improved outcome of more intense follow-up in the 1st year post-implant with respect to the composite endpoint of freedom from death or heart failure hospitalizations and improved symptomatic status (85% vs. 61%, $P < 0.001$), largely driven by a reduction in heart failure hospitalizations. We optimize immediately post-implant and review the patient at 2–4 weeks to test baseline lead function as well as to look at the wound site. Patients are reviewed at 3 months and 6 months post-implant then 3–6 monthly thereafter in a dedicated CRT clinic.

At all visits, the following steps are undertaken:

1. Documentation of symptoms (NYHA class) left ventricular dimensions and LVEF.
2. Standard testing examining %pacing, arrhythmia burden, lead and battery parameters.
3. Baseline 12-lead ECG in current settings and with pacing turned off (intrinsic conduction). The goal of programming is to achieve the narrowest QRS, as this has been shown in the past to be a good predictor of clinical response [5, 51, 53]. With each adjustment in settings, we repeat a 12-lead ECG to assess the QRS width.
4. Choosing the LV pacing pole: If the patient has intrinsic rhythm, Q-LV and RV-LV timings are measured at all four poles and the pole with the longest interval is selected, provided acceptable pacing parameters. In patients who have no or weak intrinsic AV nodal conduction, the pole with the longest RV-paced to LV-sensed timing is used. In the case of high threshold or diaphragmatic pacing, the pole with the next best timings is selected.
5. AV delays: After determining the appropriate LV polarity, sequential 12 lead ECGs are performed for various AV delays in an effort to further narrow the QRS width. In devices where they are available, we programme dynamic AV delays and use proprietary algorithms as appropriate (Sync-AV, Adaptiv-CRT, SmartDelay, etc.). It is our preference to ensure 100% atrial sensing or pacing to ensure homogeneity of AV delays and programme the device accordingly.
6. VV delays: Using the best AV delay, we programme various VV timings and offsets, starting with simultaneous LV and RV timings increasing and decreasing LV offset in increments of 10 ms—recording QRS duration on 12-lead ECG at each point.
7. Recheck of AV delay: Once best VV timing has been confirmed, step 4 is repeated to check no significant change following VV optimization.
8. Multipoint pacing (MPP): There is no strong evidence for MPP. However, the MultiPoint Pacing Trial [59] has shown non-inferiority and safety and a suggestion of improved outcome. As such, we reserve trial of MPP for non-responders or those whose response has been minor.

Nonresponse/Poor Response

The above steps recognize that response is not a binary variable, and the aim is maximal response to CRT in any individual patient. However, there will be a small group of people who will not respond or only poorly respond to CRT despite careful implantation and follow-up. In such patients, the following points should be considered.

1. Re-evaluate the 12-lead ECG with intrinsic conduction (if present): Occasionally, the intrinsic QRS may be narrower than the best-paced QRS, in which case the patient may be better with CRT programmed OFF.
2. Re-evaluate medical therapy: Ensure the patient is on appropriate maximal medical therapy. Close liaison with heart failure physicians is mandatory in this group.
3. Re-evaluate substrate: Was the patient really expected to improve? In some situations, CRT may have been performed on hearts that are extremely scarred where there is no scope of positive remodelling. Such patients would not obviously be expected to improve—these patients probably need consideration of assist device/transplant.
4. Re-evaluate venous anatomy: Review of original CS venogram films can be performed to look for alternative branches which could be targeted as a new site of LV endocardial pacing. If no suitable tributaries, consider the need for an epicardial LV lead.
5. "Non-progressor": Heart failure is a progressive disease with the expectation of continued reduction in pump function. The concept of the "non-progressor" has recently been raised [61], where although LV chamber parameters do not improve, they remain constant over time, with CRT arresting the expected worsening of LV function over time. While this is an intriguing concept, we would caution its importance in routine practice.
6. Echo optimization: Although imaging with cardiac MRI and echocardiography is important to define the nature of the substrate and serial assessment of LV internal dimensions and ejection fraction by echocardiography is critical to assess efficacy of CRT programming, the evidence for its routine use in CRT optimization is lacking [62, 63]. We find it cumbersome and non-reproducible and use it in very limited cases of non-responders where electrical reprogramming has failed.

Conclusions

Our goal is to maximize the response to CRT both to improve symptoms and achieve positive electrical and structural remodelling. This involves choosing the right patient, implanting the LV lead in the best position and ensuring correct programming. Clinical characteristics such as sex and underlying substrate are important, but the 12-lead ECG remains the most powerful pre-implant characteristic predicting response to CRT. More work is required to try and identify a subset of patients who are unlikely to benefit from CRT, to allow better targeting of therapy. With respect to implantation, intra-operative electrical mapping represents a paradigm shift for LV lead placement, introducing the concept of individualized therapy. This has recently extended to programming,

with increasing recognition of the importance of paced QRS duration and the use of algorithms to improve AV and VV timings on a dynamic basis. The era of "one size fits all" is behind us and future clinical trials need to focus on principles of programming with therapy tailored to the individual.

Compliance with Ethical Standards

Conflict of Interest Andrew D McGavigan reports conflict of interest as declared in the disclosure form. Anandaroop Lahiri, Fahd K Chahadi and Anand N Ganesan declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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