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Journal of Atrial Fibrillation

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Optimizing CRT – Do We Need More Leads And Delivery Methods

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Abstract

Cardiac resynchronization therapy (CRT) is an established therapeutic option in symptomatic heart failure with reduced ejection fraction and evidence of left ventricular (LV) conduction delay (QRS width ≥120 ms), especially when typical left bundle branch block is present. The rationale behind CRT is restoration of aberrant LV electrical activation. As there is considerable heterogeneity of the LV electrical activation pattern among CRT candidates, an individualized approach with targeting of the LV lead in the region of latest electrical activation while avoiding scar tissue may enhance CRT response. Echocardiography, electro anatomic mapping, and cardiac magnetic resonance imaging with late gadolinium enhancement are helpful to guide such targeted LV lead placement. However, an important limitation remains the anatomy of the coronary sinus, which often does not allow concordant LV lead placement in the optimal region. Epicardial LV lead placement through minimal invasive surgery or endocardial LV lead placement through transseptal punction may overcome this limitation, obviously with an increased complication risk. Furthermore, recent pacing algorithms suggest superiority of LV-only versus biventricular pacing in patients with preserved atrio ventricular (AV) conduction and a typical LBBB pattern. Finally, pacing from only one LV site might not overcome the wide electrical dispersion often seen in patients with LV conduction delays. Therefore, multisite pacing has gained significant interest to improve CRT response. The use of multiple LV leads may potentially lead to more favorable reverse remodeling, improved functional capacity and quality of life in CRT candidates, but adverse events and a shorter battery span are more frequent because of the extra lead. The use of one multipolar LV lead increases the number of pacing configurations within the same coronary sinus side branch (within small distances from each other) without the use of an additional lead. Small observational studies suggest that more effective resynchronization can be achieved with this approach. Finally, there are many reasons for non effective CRT delivery in carefully selected patients with an adequately implanted device. Multidisciplinary, post implantation care inside a dedicated CRT clinic ensures optimal CRT delivery, improves response rate and should be considered standard of care.

Introduction

Cardiac resynchronization therapy (CRT) has evolved over the past two decades as an effective non pharmacological treatment option for selected patients with heart failure and reduced ejection fraction.[1, 2] CRT decreases hospital admissions and mortality, while improving exercise capacity and quality of live in heart failure with reduced ejection fraction patients with severe or mild functional disability.[3-6] However, a major prerequisite for a beneficial response to CRT is the presence of electrical dyssynchrony amenable to this therapy. Indeed, both QRS width (>150 ms) and the presence of a typical left bundle branch block (LBBB) on the surface electrocardiogram are important predictors of reverse left ventricular (LV) remodeling and favorable clinical outcome with CRT.[7] In absence of significant LV electrical dyssynchrony, biventricular pacing might even be harmful.[8] Consequently, optimal use of CRT depends on careful patient selection and subsequently effective correction of the underlying aberrant electrical activation pattern of the left ventricle. This review provides a contemporary view on how the use of multiple leads and delivery methods might contribute to achieve this.

Disclosures:
None.

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Defining Response To Cardiac Resynchronization Therapy

Depending on its precise definition, the rate of non response to CRT is often reported as ~30% in the literature. As new guidelines have progressively put a stronger emphasis on selecting patients with LBBB or very wide QRS complex (>150 ms), the current figure may already be significantly lower. In addition, there is considerable heterogeneity in how to define CRT response, with each definition suffering from important limitations. Hard clinical end points such as mortality and hospital readmissions are notoriously biased by the presence of non cardiac co morbid conditions in a typical CRT population.[9] In addition, reverse LV remodeling not always mimics functional improvement in CRT patients, and the latter is difficult to assess when CRT is used in less symptomatic patients.[10] While the former is probably the most specific marker of CRT response, generally proposed cut offs such as a ≥15% reduction in end systolic LV volume are somewhat arbitrarily and do not account for underlying disease progression.[11] Indeed, a small study in CRT patients hospitalized with advanced heart failure and progressive adverse LV remodeling has demonstrated persistent hemodynamic benefits with biventricular pacing programmed on versus off.[12] Nevertheless, a clear and robust correlation between LV reverse remodeling and improved outcomes has been demonstrated.[13] Alternatively, non response to CRT may reflect inadequate correction of electrical dyssynchrony, which should be prevented by careful pre implantation patient selection, targeted lead placement, and optimal device programming (Table 1). Indeed, it has been increasingly recognized that multiple factors may contribute to suboptimal CRT delivery, requiring a holistic approach with multidisciplinary cooperation between electrophysiology, heart failure and cardiac imaging specialists.[14] To ensure individualized patient care and optimal benefits from CRT, post implantation follow up should ideally take place inside dedicated CRT clinics providing such collaborative environment.[14,15] This multidisciplinary care approach has already shown to be associated with improved survival in CRT patients.[16,17]

Left Ventricular Lead Placement

Conventional Transvenous Approach

Because the rationale behind CRT is restoration of the underlying aberrant conduction pattern inside the left ventricle, adequate placement of the LV lead is crucially important to successful treatment. The current standard for LV lead placement is a transvenous approach with a single LV lead guided through a side branch of the coronary sinus. Acceptable lead positioning in the posterolateral region of the left ventricle is confirmed through classic sensing and capture parameters while avoiding phrenic nerve stimulation.[17] Apical LV lead placement is associated with worse CRT outcomes and should be avoided.[18] Procedural success with the transvenous approach is nowadays achieved in >90% of cases.[19-21] However, despite such good technical feasibility, it remains unsure whether conventional posterolateral lead placement is the best suitable option for every CRT patient. Even in patients with typical LBBB, considered to benefit most from CRT, studies have shown considerable variability in the ventricular electrical activation pattern.[22-24] Based on several mechanistic studies, the posterolateral region is generally considered to be the best pacing site in the majority of patients.[25] However, pacing that site clearly does not always lead to complete disappearance of dyssynchrony as the native conduction system can never be restored by one lead and the effects of right ventricular pacing also impact considerably on the electro mechanical delays. Several factors may contribute to electro mechanical heterogeneity such as variable conduction block, presence and burden of scar tissue and/or anatomical variances. As the primary goal of CRT remains to correct aberrant conduction patterns, such heterogeneity implies that with more targeted lead positioning, better response rates might be achieved.[26]

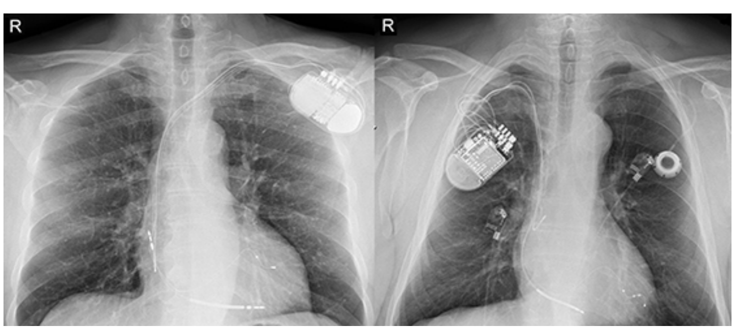

Figure 1: Antero posterior views of a chest x-ray in a cardiac resynchronization therapy patient with a conventional bipolar left ventricular lead (left) and another patient with a quadripolar lead (right)

Targeted Lead Positioning

Echocardiography Guided Approach

Echocardiography has rendered some disappointing results to improve patient selection for CRT.[11,20] However, it may help to decide the optimal position of the LV lead in individual patients. Two randomized controlled trials support this concept. The Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy (TARGET) study randomized 220 patients to conventional LV lead placement in an accessible posterolateral segment versus targeted lead placement in the region of latest contraction assessed by speckle tracking two dimensional radial strain imaging.[27] With targeted versus conventional lead positioning, more patients (70% versus 55%, respectively; p=0.031) fulfilled the predefined criterion for beneficial CRT response (≥15% reduction of the LV end systolic volume after 6 months). In addition, improvements in New York Heart Association (NYHA) functional class, 6 minutes walking distance, and Minnesota Living with Heart Failure Questionnaire score all significantly favored the targeted lead approach. Moreover, concordant lead positioning in the region of latest activation while avoiding scar was a strong independent predictor of death. Nevertheless, even with the targeted approach, this could only be achieved in 63% of patients, mainly because of anatomical limitations of the coronary sinus. Additionally, the time needed to identify the optimal region of LV lead placement increased the procedural time significantly, leading to an increased radiation dose. Remarkably similar results were reported by the Speckle Tracking Assisted Resynchronization Therapy for Electrode Region (STARTER) trial (n=187) with a comparable study design.[28] In the STARTER trial, after a mean follow up of 1.8±1.3 years, the primary composite end point of mortality or heart failure readmission was significantly reduced with 52% in the group with targeted LV lead placement (p=0.006). However, exact concordance of lead placement in the region of latest activation was only achieved in 30% of patients in the targeted approach group, with a substantial 15% of patients ending up with an LV lead in a remote region. In addition, it remains to be proven in larger trials that assessing dyssynchrony through speckle tracking two dimensional radial strain imaging is accurate, precise and reproducible.

Electro Anatomic Mapping

Another approach to visualize even more precise the LV electrical activation pattern is electro anatomic mapping. Catheter based 3D non fluoroscopic contact and non contact mapping techniques allow in vivo reconstruction of the cardiac anatomy whilst assessing the electrical activation sequence with high spatial resolution.[29,30] In patients with typical LBBB versus non specific intra ventricular conduction disturbance, such electro anatomic mapping shows more pronounced ventricular electrical uncoupling (the difference between right ventricular and LV activation time) and a longer total LV activation time, i.e., more inter ventricular and intra ventricular dyssynchrony.[31] Intriguingly, in a small study including 33 CRT candidates, it was demonstrated that these electro anatomic features predicted clinical CRT response better than QRS duration or LBBB presence itself.[31] Therefore, electro anatomic mapping is especially promising to identify patients who might benefit from CRT, but have surface electrocardiogram characteristics known to be associated with worse CRT response. Indeed, benefits with CRT are less consistently observed in patients with a preimplantation QRS width <150 ms or non LBBB pattern, but still a substantial proportion of this group may improve with CRT.[32,33] Alternatively, electro anatomic mapping can be used during LV lead placement to search for the region of latest electrical activation. In a sub study, including 426/846 patients from the SmartDelay determined AV Optimization: A Comparison of AV Optimization Methods Used in Cardiac Resynchronization Therapy (SMART-AV) trial, it was observed that patients with a longer QLV time, defined as the time from onset of the QRS complex on the surface electrocardiogram to the peak of the LV electrogram, had more pronounced reverse LV remodeling and a larger improvement in quality of life at 6 months after implantation, which remained so after correction for QRS width and presence of typical LBBB.[34] In addition, pacing the left ventricle at the site with maximal QLV delay is associated with acute hemodynamic improvements.[35] A recent study in 25 consecutive CRT patients has shown that electro anatomic mapping of the coronary sinus system is feasible during implantation, with concordant lead placement possible in 18 out of 25 patients.[36] Importantly, the conventionally targeted inferolateral vein was the vein with maximal QLV delay in only 3 patients, clearly supporting the use of electro anatomic mapping over relying on the anatomy alone. Major device companies are already using this knowledge to superimpose information on the fluoroscopy images. Nevertheless, further studies are required to determine the precise role of electro anatomic mapping in CRT optimization.

Table 1: Determinants of CRT response

	Important features
Pre-implantation patient selection	
Gender	women
Presence of electrical dyssynchrony	Typical LBBB
	QRS width >150 ms
	Electro-anatomic mapping
Absence of extensive scar, especially in the posterolateral region	Cardiac MRI
Avoid “rescue CRT” in very advanced heart failure	Early implantation strategy
Procedural characteristics	
Left ventricular lead in region with latest electrical activation	Coronary sinus anatomy
	Avoid apical position
	Electro-anatomic mapping
Avoid lead placement next to scar region	Cardiac MRI
Avoid phrenic nerve stimulation	Multipolar left ventricular leads
Optimal correction of electrical dyssynchrony	Multiple/multipolar leads
Post-implantation care	
Optimal heart failure treatment	Pharmacological therapy
	Treatment of co morbid conditions
Adequate CRT delivery	Biventricular pacing >95%
Stroke	Rate control/AV node ablation in AF
Ischemic	Ablation of frequent ectopic beats
Hemorragic	Left ventricular lead dislodgement
Optimal programming	AV optimization
	VV optimization
	Advanced pacing algorithms

AF, atrial fibrillation; AV, atrio ventricular; CRT, cardiac resynchronization therapy; LBBB, left bundle branch block; MRI, magnetic resonance imaging, VV, ventriculo-ventricular

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance (CMR) imaging with the use of late gadolinium enhancement has evolved as the preferred method to visualize scar tissue along the myocardium. Understandably, presence of scar tissue negatively affects response to CRT, which might explain why patients with ischemic cardiomyopathy consistently experience fewer benefits with CRT compared to their non ischemic counterparts.[37] Several studies confirm that extensive myocardial scarring found on either echocardiography or CMR imaging predicts poor response to CRT.[38-41] This is especially true for scarring in the posterolateral region, the conventional position of LV lead placement. In one prospective study (n=559) with CRT patients randomized to conventional versus CMR imaging guided LV lead placement, patients in the latter group had a 6 times higher risk of cardiovascular death after median follow up of 1.8 years if the LV lead was placed inside a scar region.[42] In patients with conventional LV lead placement, this risk was 51% higher compared to patients where scar could be avoided, although this result did not reach statistical significance (p=0.073). Importantly, if the LV lead was placed inside a scar region, the risk of death due to progressive pump failure as well as the risk of sudden cardiac death were significantly increased. While less viable myocardium surely impacts on the amount of LV reverse remodeling that is possible, pacing into a scar region may also elicit a pro arrhythmogenic substrate.[43]

Surgical Epicardial Left Ventricular Lead Placement

Initially, surgical epicardial LV lead placement was predominantly used as a backup technique to overcome limitations of an inaccessible coronary sinus or unfavorable anatomy of the latter. Studies comparing conventional transvenous LV lead placement with the surgical epicardial approach have generally rendered similar results.[44-46] Yet, as operator experience with CRT and implantation materials both have improved, the use of surgical LV lead placement has been decreasing over time.[21] However, with the emerge of minimal invasive surgical techniques, the benefits of allowing targeted LV lead placement, a reduced risk of lead dislodgment, and less problems with phrenic nerve stimulation, have placed surgical LV lead placement in the spotlight again. An additional advantage is that radiation exposure can completely be avoided and there is no need for intravenous contrast. Downsides of the surgical LV lead approach are the necessity of general anesthesia, invasiveness of the procedure, higher procedural related costs, and higher pacing thresholds reducing the battery life-span.[44] Different minimal invasive procedures exist for the placement of an epicardial LV lead, with the choice often depending on availability and experience of the operator. Mini thoracotomy, video assisted thoracoscopy and robotic surgery are used nowadays and clinical experience with these techniques is improving.[45-51] Still, due to higher costs and insufficient evidence of long term superiority, surgical epicardial lead placement is currently indicated only when conventional transvenous lead placement fails and should be performed in centers with significant expertise. Whether targeted LV lead placement through minimal invasive surgery in combination with multimodality imaging and electro-anatomic mapping might be a superior approach is currently under research.

Endocardial Left Ventricular Lead Placement

A potential alternative to conventional transvenous or surgical epicardial LV lead placement is to perform a transseptal punction with endocardial LV lead placement. Different studies have shown that this approach is feasible in experienced hands, although technically more challenging, while long term efficacy and safety remain unsure.[52-55] In particular, the incidence of major stroke at 6 months has been reported up to 10%.[56] Based upon the understanding of the normal cardiac depolarization sequence, it was postulated that endocardial compared to epicardial pacing is more physiological. Indeed, impulse conduction is faster with endocardial pacing.[57] Moreover, observational studies in humans have suggested that endocardial pacing is associated with an improved acute hemodynamic response, measured as peak rate increase of LV pressure (dP/dt(max)).[58, 59] In addition, a promising advantage of endocardial LV pacing is that it allows an easy targeting of the site with the best acute hemodynamic response or latest electrical activation.[60,61] One prospective study (n=35) has shown improved CRT response rates with endocardial LV lead placement.[60] Remarkably, the LV lateral wall and coronary sinus region were rarely the best sites for endocardial pacing. In spite of these potential benefits, a major concern regarding endocardial LV lead placement is the increased risk for thrombo-embolic events warranting therapeutic anticoagulation, with lead infection, endocarditis and mitral valve regurgitation other major attention points that however did not occur more frequent in one small study with 6 months of follow up.[56] Therefore, it is most likely that with leadless pacing in the future, endocardial LV pacing will gain more attention.

Multisite Pacing

As the electrical and myocardial substrate of patients receiving CRT shows significant heterogeneity, the concept of multisite pacing to optimize resynchronization has sparked significant interest lately. A recent study has confirmed that patients not responding well to conventional LV lead placement may benefit in particular from multisite pacing.[62] Two major strategies exist to deliver multisite pacing, including the use of multiple leads or alternatively a single multipolar lead.

Multiple Leads

Dual Right Ventricular Leads

One small study (n=21) has explored the use of CRT with 2 right ventricular leads (apical and outflow tract) in addition to a conventionally placed transvenous LV lead.[63] The authors reported an improved correction of mechanical dyssynchrony assessed by tissue Doppler echocardiography and a larger increase in cardiac output with this pacing configuration. Another study (n=20) has reported a significant increase in 6 minutes walking distance with dual right ventricular leads in the apex and high septum compared to conventional CRT.[64] However, dual right ventricular lead placement has not been evaluated in adequately powered long term clinical trials. A particularly interesting approach might be to target the extra right ventricular lead to allow direct His bundle pacing. This has been shown to be technically feasible in most CRT candidates and may result in a narrower QRS width.[65] In a cross over study of conventional CRT versus direct His bundle pacing, QRS narrowing with the latter was observed in 72% of patients and those had similar remodeling and clinical response as compared to with conventional CRT.[66]

Dual Left Ventricular Leads

Table 2 summarizes the data from currently available controlled CRT studies with multiple LV leads. Pacing the left ventricle with two separate leads was first tested in a cohort of 14 patients undergoing CRT implantation.[67] This study indicated that the acute hemodynamic response (measured as dP/dt(max), aortic pulse pressure and end diastolic pressure) was superior in patients undergoing dual site pacing. However another study did not corroborate this finding after AV optimization was performed, while a third suggested benefits predominantly in patients with extensive posterolateral scar.[68, 69] The feasibility of placing two instead of one lead inside the coronary sinus system looks acceptable, 85-95% in experienced hands, and currently available evidence from small studies may indicate some benefits with this approach.[64, 70-73] One study randomized 54 CRT candidates with LBBB in sinus rhythm to single versus dual LV lead placement.[72] The implantation procedure took more time in the dual LV lead group, but fluoroscopy exposure and complication rates were non significantly different. After 3 months, pacing the left ventricle with two separate leads was associated with

Table 2: Prospective, controlled cardiac resynchronization therapy studies with multiple left ventricular lead

First author, year	n*	Study population	Lead configuration	Benefits of multisite pacing
Pappone, 2000 (67)	14	NYHA III/IV, sinus rhythm, LBBB, QRS >150 ms	Two coronary sinus leads (posterior base & lateral wall)	Increased peak dP/dt, higher aortic pulse pressure, shorter QRS duration
Leclercq, 2008 (71)	40	NYHA III/IV, permanent AF, LVEF ≤35%	Two coronary sinus leads (widest distance)	Higher LVEF
Padeletti, 2008 (68)	12	NYHA III/IV, LVEF ≤35%, QRS ≥120 ms	Two coronary sinus leads (lateral/posterolateral & anterior/anterolateral)	None
Lenarczyk, 2009 (72)	27	NYHA III/IV, LVEF ≤35%, QRS ≥120 ms	Two coronary sinus leads (widest distance)	Lower NYHA, increased VO2max & 6MWD, higher LVEF, less dyssynchrony, more responders
Ginks, 2012 (69)	22	Conventional CRT criteria	Two coronary sinus leads (widest distance)	Increased peak dP/dt
Rogers, 2012 (64)	43	NYHA II/III/IV, LVEF ≤35%, QRS ≥150 ms	Two coronary sinus leads (widest distance)	Increased 6MWD, MLWHF score and LVEF
Lenarczyk, 2012 (73)	48	NYHA III/IV, sinus rhythm, LVEF ≤35%, dyssynchrony on echocardiography	Two coronary sinus leads (widest distance)	Lower NYHA
Ogano, 2013 (75)	22	NYHA III/IV, LVEF ≤35%, QRS ≥120 ms	Two coronary sinus leads (best hemodynamic response)	Less ventricular arrhythmia

* Number of patients who actually underwent multisite pacing
6MWD, 6 minutes walking distance; AF, atrial fibrillation; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MLWHF, Minnesota living with heart failure; NYHA, New York Heart Association functional class; QoL, Quality of Life; VO2max, maximal aerobic capacity

a significantly larger decrease in NYHA functional class, increase in maximal aerobic capacity and improvement in 6 minutes walking distance, while a higher LV ejection fraction and less dyssynchrony were observed on echocardiography. In the single versus dual LV lead group, more patients qualified as CRT responders. The same group of researchers is performing the Triple Site Versus Standard Cardiac Resynchronization therapy (TRUST CRT) trial, which has finished recruiting, randomizing patients to conventional CRT (n=50) versus dual LV pacing (n=48).[74] The final results of the main trial have not been published yet, but an intermediate report after one year showed an improved NYHA functional class in favor of dual LV pacing,[73] However, placement of an additional LV lead did result in longer procedural time, additional fluoroscopic exposure and less favorable electrical characteristics (i.e., higher pacing thresholds) negatively affecting battery longevity. Another small crossover study in 23 CRT patients with dual LV leads was also able to demonstrate improvements in functional capacity and reverse remodeling when a triventricular versus conventional biventricular pacing mode was programmed.[64] In addition, an intriguing finding of one small study (n=58) is that triventricular pacing might be associated with a lower risk of ventricular arrhythmia when compared to conventional biventricular pacing.[75] In this study, patients were not randomized towards single versus dual LV lead placement, but instead the optimal approach was chosen based on the acute hemodynamic response observed during implantation. For this reason it is difficult to interpret the results, as the need for triventricular pacing to improve hemodynamics may indicate more advanced cardiac disease and consequently a higher risk of ventricular arrhythmia. Still, it might be worthwhile to look at incidence of ventricular arrhythmia in prospectively collected data of currently available randomized/cross over studies of biventricular versus triventricular pacing. Finally, one particular study of dual LV lead placement has specifically focused on patients with atrial fibrillation. The Triple Resynchronization in Paced Heart Failure Patients (TRIP-HF) study included 40 patients with LBBB and permanent atrial fibrillation requiring cardiac pacing for slow ventricular rate.[71] The study showed no significant differences in functional capacity or quality of life with triventricular versus biventricular pacing, although more pronounced reverse remodeling was observed in the former group. In conclusion, CRT with multiple LV lead placement still remains to be considered an experimental therapy with more evidence from long term randomized trials needed to assess whether potential benefits of more pronounced reverse LV remodeling and improvements in functional capacity may outweigh the more complex implantation procedure and higher risks associated with the placement of an extra lead.

Table 3: Studies comparing conventional biventricular pacing with multisite pacing through a quadripolar lead

First author, year	n	Comparison	Study findings
Thibault, 2013 (88)	19	Distal electrode versus 4 multisite pacing configurations	Invasive dP/dt better with multisite pacing in 72% (mostly through combined proximal and distal electrode stimulation)
Rinaldi, 2013 (89, 91)	41/40	Distal electrode versus 8 multisite pacing configurations	1. Dyssynchrony by tissue Doppler echocardiography reduced in 63% with multisite pacing 2. Radial strain >20% higher in 63% with multisite pacing
Pappone, 2014 (90)	44	Distal/proximal electrode versus 7 multisite pacing configurations	Acute improvement in hemodynamic parameters and significant decrease in NYHA with more pronounced reverse remodeling after 3 months in multisite pacing group

NYHA, New York Heart Association functional class

Multipolar Leads

A way to mimic multisite pacing with its potential benefits but without the need of placing an extra lead is to use an LV lead with multiple electrodes positioned on the same lead (Figure 1). Multipolar leads were initially designed and tested to overcome phrenic nerve stimulation as a result of high LV pacing thresholds. The first use of a quadripolar LV lead was reported in 2010.[76] Subsequent studies have indicated that multipolar leads allow electronic repositioning, representing a change in pacing configuration with a different electrical vector but without physical repositioning of the LV lead. In this way, a pacing configuration without phrenic nerve stimulation and with acceptable LV pacing thresholds can generally be achieved.[77] Several studies have indicated that the use of multipolar leads is safe with implant success rates, a lead dislodgement risk and pacing thresholds similar to unipolar leads.[78-83] Using quadripolar versus bipolar LV leads result in substantially more pacing configurations (up to 17 versus 6, respectively), increasing the chance that a favorable configuration can be found.[84-86] One study in 16 CRT patients with quadripolar LV lead showed that the difference in acute hemodynamic response as dP/dt(max) change differed as much as 10% between the best and worst pacing configuration.[87] Up till now, only three small studies have compared the acute CRT response in patients with a conventional pacing configuration versus multisite pacing from a quadripolar lead (Table 3).[88-92] All have shown that with the optimal multisite pacing configuration, acute hemodynamic effects of CRT can be improved. One study subsequently randomized patients to a conventional pacing configuration versus multisite pacing and demonstrated that after 3 months the improvement in NYHA functional class and reverse remodeling favored the multisite pacing group.[92] Two large multicenter randomized double blind clinical trials are currently enrolling patients and will be adequately powered to detect the possible superiority of multipolar leads to increase CRT response. The MultiPoint Pacing IDE Study (NCT01786993) has planned to enroll up to 506 patients in the United States of America, comparing safety and clinical response with a bipolar versus quadripolar lead in CRT patients. The More Response on Cardiac Resynchronization Therapy With MultiPoint Pacing (MORE-CRT MPP) trial (NCT02006069) has estimated to enroll 1256 patients, all implanted with a quadripolar LV lead, and will assess the percentage of cross over from conventional to multisite pacing because of CRT non response. One needs to recognize though that pacing still occurs in the same coronary sinus side-branch and that a favorable hemodynamic response over a classic bipolar lead might be related to more proximal pacing within the same side branch more than a true multisite pacing.

Cardiac Resynchronization Post Implantation Follow Up

Even with careful selection of patients who demonstrate LV electrical dyssynchrony and implantation of an LV lead in the optimal position, there are many other reasons for CRT non response.[14] A lot of these can be addressed by good heart failure management and treatment of co morbid conditions, which explains why intensive collaboration between electrophysiology and heart failure specialists is needed. However, persistent electrical dyssynchrony because of suboptimal device programming, loss of biventricular pacing or arrhythmia is not at all uncommon in CRT patients.[14] Even minor reductions in biventricular pacing delivery are known to be associated with poor CRT response.[93] Therefore, AV node ablation in case of atrial fibrillation and focal ablation in case of frequent ventricular ectopy should be considered when insufficient biventricular pacing delivery is observed despite adequate pharmacological therapy.[17] Finally, suboptimal programming of the AV delay is a frequent reason contributing to poor CRT response.[14] Therefore, a quick assessment of the transmitral inflow pattern, ensuring a nicely separated E and A wave is helpful during the evaluation of every CRT patient.[94] However, data from the SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy (SMART-AV) study suggest that routine AV optimization in all patients including good responders is not warranted as it does not lead to better outcomes.[95] Gathering all experience and knowledge to achieve such patient centered follow up care inside a dedicated CRT clinic has proven to improve clinical outcomes.[15, 16]

Conclusion

CRT has been established as an important non pharmacological therapeutic option in heart failure with reduced ejection fraction. However, a beneficial CRT response can only be expected in properly selected patients who demonstrate electrical dyssynchrony and subsequently have effective correction of the latter with biventricular pacing. As the electrical activation pattern of the left ventricle may differ markedly between individual patients, targeted LV lead placement in the region of latest electrical activation while avoiding scar tissue may improve CRT response. Yet, conventional transvenous LV lead placement is limited by the coronary sinus anatomy. While epicardial LV lead placement through minimal invasive surgery or endocardial LV lead placement through transseptal punction may overcome this limitation, each technique has its own downsides. Recently, multisite pacing through multiple LV leads or even more through one multipolar LV lead has gained significant interest. Small observational studies suggest that more effective resynchronization can be achieved with multisite pacing, but large randomized clinical trials should confirm these promising results. Finally, many reasons for non effective CRT delivery exist, even in carefully selected patients with an adequately implanted device. Multidisciplinary, post implantation care inside a dedicated CRT clinic ensures optimal CRT delivery and should be considered standard of care.

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