Update on Cardiac Resynchronisation Therapy for Heart Failure

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Abstract

Cardiac resynchronisation therapy (CRT) is well accepted therapy for the treatment of symptomatic systolic heart failure in defined patient subgroups. Large clinical trials over the past 20 years have shown that patients with a left ventricular (LV) systolic dysfunction and interventricular conduction delay benefit from this therapy. Recent advances in this field include the expansion indications for CRT to patients with mild heart failure and to those with a mildly depressed ejection fraction that require frequent right ventricular pacing. In addition, although CRT guidelines have included indications in atrial fibrillation, it is now clear that this is most effective when pacing is utilised nearly 100 % of the time, often requiring atrioventricular (AV) junction ablation. Strategies for optimising LV lead placement based on identifying late mechanical contraction or electrical delay are promising for maximising CRT response. Finally, the role of routine AV delay optimisation is no longer recommended based on the results of multicentre trials.

Keywords

Cardiac resynchronisation therapy, heart failure, pacing

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Interventricular conduction delay is common in patients with systolic heart failure (HF) and has been associated with a poor prognosis amongst these patients.[1] Abnormal ventricular depolarization results in prolonged ventricular activation time and increased myocardial tension thus increasing myocardial oxygen consumption and decreasing ventricular diastolic filling time. In addition, asynchronous ventricular contraction caused by conduction delay induces ventricular remodeling and has been shown to increase the duration of mitral regurgitation.[2,3] Cardiac resynchronisation therapy (CRT) has been investigated as a therapy to reverse the deleterious effects of conduction delay by improving electrical and mechanical synchrony.

The first attempt CRT was performed over thirty years ago by placing an epicardial lead on the left ventricular lateral wall in patients with a left bundle branch block undergoing aortic valve replacement.[4] Subsequently, Bakker, Gold and others assessed the role of epicaridal pacing in HF. Later, Daubert et al. reported the first case series of patients undergoing left ventricular pacing by transvenous lead placement into the coronary sinus.[5] During the early years of CRT, a haemodynamic benefit of improved interventricular synchrony was shown setting the stage for future study. Since that time, multiple large, randomised clinical trials have been performed and demonstrated that CRT improves mortality and clinical outcomes in severe HF patients who are symptomatic despite optimal medical therapy.[6–9]

Expanding Indications for Cardiac Resynchronisation Therapy In Heart Failure

The indications for CRT were recently updated in the European and American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)/Heart Rhythm Society (HRS) guidelines due in part to recent clinical trials on the subject.[1,10] Subsequently, the Resynchronization Reverses Remodeling in Systolic left Ventricular Dysfunction (REVERSE) and Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT) trials demonstrated that subjects with New York Heart Association (NYHA) class I or II HF had better outcomes with CRT.[11–13] The Resynchronization/Defibrillation for Ambulatory Heart Failure Trial (RAFT) extended these findings with a longer follow-up showing that CRT with implantable defibrillator (ICD) backup (CRT defibrillator [CRT-D]) prolongs survival compared with ICD alone, in NYHA class II subjects.[14] *Post hoc* analysis of the patients included in the MADIT-CRT and REVERSE trials revealed that the mildly symptomatic patients with only mild left ventricular systolic dysfunction also benefitted from CRT, suggesting that a larger population of patients may benefit from CRT.[15]

After the revision of the guidelines, the Biventricular Versus Right Ventricular Pacing in Heart Failure Patients With Atrioventricular Block (Block-HF) trial was published showing benefit of CRT in patients with an indication for pacing and a mildly depressed ejection fraction. The BLOCK-HF trial randomised 691 patients with an indication for pacemaker placement and an ejection fraction ≤50 % to biventricular (BiV) or right ventricular (RV) pacing. The primary endpoint was a composite of death from any cause, HF care requiring intravenous therapy or evidence of adverse cardiac remodeling as measured by an increase in left ventricular end-systolic volume index of ≥15 %. There were statistically improved outcomes with CRT for both the composite primary outcome as well as a secondary outcome of HF hospitalisation.[16,17] The Block-HF trial supports the previously published Dual Chamber and VVI Implantable Defibrillator

(DAVID) and Left Ventricular-Based Cardiac Stimulation Post AV Nodal Ablation Evaluation (PAVE) trials suggesting that frequency of right ventricular pacing leads to adverse clinical outcomes and adverse ventricular remodeling.[18,19]

Despite the Block-HF trial, concern has been raised about the composite endpoint being driven mostly by adverse ventricular remodeling rather than 'harder' clinical outcomes, and that the control arm also received a LV lead that was programmed not to pace thus neutralising procedural complications.[20] These concerns were further heightened by the recent preliminary report of the Biventricular Pacing for Atrioventricular Block to Prevent Cardiac Desynchronization (BIOPACE) trial. The BIOPACE trial was designed to randomise subjects with an indication for permanent ventricular pacing, but no guideline indication for CRT pacing, to standard right ventricular pacing device verses BiV device. Primary endpoints include the combination of time-to-death or first HF admission and secondary endpoints include quality of life, six-minute hall walk and echocardiographic signs of adverse remodeling.[21] Preliminary results presented at the ESC Congress 2014 were notable for a non-significant 13 % reduction in the primary endpoint with CRT.[22] The inconsistent results from this and other studies may reflect some of the challenges of designing trials for implantable devices. Many of these design issues are evident comparing the REVERSE study, which had an implanted, double-blind design and MADIT-CRT, which was unblinded with one arm receiving CRT-D devices and the other arm ICD. The challenges of performing a device-based trial in HF have been discussed elsewhere.[23]

Cardiac Resynchronisation Therapy in Atrial Fibrillation

Despite the abundant data on CRT among patients in sinus rhythm, this therapy in patients with atrial fibrillation (AF) has been less well studied. AF was excluded from most of the clinical trials. In RAFT, which included the largest number of AF patients randomised to CRT, the outcomes of CRT in AF were non-significant, which may be due to the relatively low BiV pacing percentage in this cohort.[24] The PAVE trial showed benefit of CRT in patients with a depressed left ventricular ejection fraction undergoing atrioventricular junction (AVJ) ablation secondary to refractory, symptomatic atrial fibrillation.[1,19] CRT is also recommended in permanent AF patients that have symptomatic HF with a severely depressed ejection fraction and significant interventricular conduction delay.[1]

Currently, AVJ ablation is recommended after the inability to achieve complete BiV pacing.[1] Recent studies have indicated that a very high pacing percentage is required to achieve full CRT benefit. One large cohort of patients followed by remote telemetry monitoring suggested over 98 % of conducted beats must be paced beats in order to confer all of the mortality benefits of CRT, and that AF limited the percentage of paced beats.[25] The RAFT randomised to CRT without ablation, required patients to be aggressively rate controlled before trial enrolment, with a resting heart rate <60 and a heart rate of <90 after six-minute walk, but still only achieved greater than 95 % BiV pacing in one-third of patients.[24] Initial registry and meta-analysis data shows similar outcomes for patients that undergo AVJ ablation to the sinus rhythm group, but worse outcomes for patients in AF who are treated with medical rate control.[26–28] Randomised controlled trials are needed to identify the optimal timing of AVJ ablation in the permanent AF population, but the emerging consensus is that more aggressive use of this technique is needed in CRT.

Cardiac Resynchronisation Therapy Non-Responders

Despite the overall benefit demonstrated by CRT, a clinical non-response is noted in approximately one-third of patients throughout the literature, although this estimate varies based on the clinical outcome used to define response.[29,30] CRT is an expensive and invasive therapy thus significant interest in understanding, predicting and reducing non-responders has been evaluated. The reason for the clinical non-response is complicated and likely multifactorial in most patients with irreversibly advanced HF, myocardial scar, lead placement, lack of clinically significant dyssynchrony and lack of AV and VV optimisation all thought to play a role in certain cases.[31] The remainder of this review will highlight some of the proposed methods to decrease the CRT non-response rate.

Improved Patient Selection for Cardiac Resynchronisation Therapy (Electrocardiography and Beyond)

Subgroup analyses from multiple studies have shown that the greatest response to CRT is noted with QRS prolongation and left bundle branch block (LBBB). Patients with LBBB and QRS duration >150 ms receive the most benefit from therapy and have a Class I indication in the current guidelines, whereas patients with a non-LBBB and QRS duration of 120–150 ms receive only a Class IIB in severe HF and are not indicated in mild HF.[1] Given the expense of large randomised clinical trials and the number of trials that have already addressed these issues in the past, it is unlikely that a trial will be designed with enough power to further tease out the clinical and electrocardiography (ECG) factors that are the best predictors in HF patients in sinus rhythm that do not require RV pacing. Recently a large individual patient meta-analysis of the Cardiac Resynchronization in Heart Failure (CARE-HF), Multicenter InSync Randomized Clinical Evaluation (MIRACLE), REVERSE, MIRACLE ICD and RAFT studies was performed to evaluate the further predictors for CRT response. In this large cohort, QRS duration but not QRS morphology (i.e. LBBB) predicted survival or HF hospitalisations. In addition, CRT response rates did not differ based on ejection fraction including the groups of patients with a left ventricular ejection fraction over 35 %, males and females appeared to respond similarly to CRT, and there were no differences in response rates in patients with a diagnosis of ischaemic or non-ischaemic cardiomyopathy.[8,9,14,24,32]

There was much early enthusiasm for the use of echocardiography to identify mechanical dyssynchrony to predict CRT response. However, subsequent prospective multicentre trials failed to support this strategy. The Predictors of Response to CRT (PROSPECT) trial assessed several echocardiographic parameters (including several tissue Doppler parameters and M-mode parameters) to predict CRT response rate, and none of these parameters were found to have clinically useful value.[29] More recently, the Echocardiography Guided Cardiac Resynchronization Therapy (EchoCRT) trial was a randomised trial designed to determine if mechanical dyssnchrony as identified by tissue Doppler or colour tracking radial stain predicted CRT response in patients with a QRS duration <130 ms and NYHA class III or IV HF. All patients were implanted with CRT devices with the control group having CRT turned off. The trial was stopped early by the safety monitoring board due to futility with a trend towards increased mortality at the time of trial stoppage.[33] These trials further reinforced the importance of QRS duration as a predictor of CRT response.

Left Ventricular Lead Position

The traditional strategy for left ventricular lead placement was based on early haemodynamic studies indicating that the best acute response was achieved with lateral wall positions. Such strict anatomic criteria have not been validated in multicentre studies. Specifically, *post hoc* analysis of the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) study showed no significant impact of lead position on outcomes including mortality and HF hospitalisations.[34] Subsequently, apical lead position was shown to be associated with increased risk of HF death or hospitalisation in a *post hoc* analysis of the MADIT-CRT, but this and other studies indicated significant heterogeneity in the ideal left ventricular pacing site to achieve optimal haemodynamic and clinical response.[35–37] Furthermore, LV pacing on the site of transmural scar has been associated with an adverse haemodynamic response and scar burden has been associated with poor clinical response to CRT.[38–41]

Non-invasive methods, such as echocardiography, to identify the site of latest ventricular activation and avoid significant myocardial scar have become the focus of recent randomised trials. The Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy (TARGET) trial randomised 220 consecutive CRT patients to standard based LV lead placement or echocardiogram derived radial strain based LV lead placement. In the echocardiography group the LV lead was placed at the site of latest ventricular activation without evidence of significant myocardial scarring defined by decreased amplitude of contraction. There was a significant increase in the primary endpoint of positive left ventricular remodeling by echocardiogram as well as a decrease in a combined clinical endpoint of death and hospitalisation.[42] Long-term follow-up of the TARGET study data at a mean of 39 months has suggested decreased mortality and improved LV remodeling.[43] These results have been reinforced by the recently published Speckle Tracking Assisted Resynchronization Therapy for Electrode Region (STARTER) study.[44] The Empiric Versus Imaging Guided Left Ventricular Lead Placement in Cardiac Resynchronization Therapy (ImagingCRT) trial should be complete in the near future and will further evaluate echocardiogram speckle tracking combined with cardiac and single photon emission computed tomography-computed tomography (SPECT CT) to guide lead implant site.[45]

In addition to late mechanical contraction to guide lead placement, there are accumulating data to show that electrical delay at the site of LV pacing is a strong predictor of CRT response. The most commonly used measure is the QLV interval, which is the time from the onset of the QRS complex to the peak of the local electrogram at the LV electrode. The QLV is a strong predictor of acute haemodynamic response, both with BiV and LV only pacing.[46] In addition, QLV is a strong independent predictor of echocardiographic remodeling response as well as quality of life improvement with QLV.[47] An analysis of the RV–LV interval, another measure of electrical delay, from the Pacing Evaluation-Atrial Support Study in Cardiac Resynchronization Therapy (PEGASUS CRT) trial showed that this was an independent measure of HF events.[48]

Device Optimisation

AV delay programming has been shown to have haemodynamic effects in left ventricular pacing but its use is controversial and routine optimisation is not recommended in the current guidelines based on recent trial results.[1,49] Despite this fact, almost all trials studying CRT in HF used an echocardiographic method to attempt to improve AV synchrony.[50]

The method of left ventriculoventricular (VV) optimisation has also been controversial. VV optimisation was somewhat limited in the past as early devices allowed only simultaneous BiV pacing. Current devices are much more complex and diverse allowing individualised programming of the VV intervals and proprietary device algorithms are designed to optimise VV synchrony making programming more complex. Unfortunately, manual VV optimisation is time-consuming and requires an understanding of both interventricular (left ventricular relative to right ventricular contraction) and the intraventricular (septa-to-posterior delay of the LV) dyssnchrony.[50] Methods to measure dyssnchrony have included time-consuming echocardiographic measures as well as left ventricular outflow tract (LVOT) velocity time integral (VTI) measurement at different device settings for optimisation.

More recent large clinical trials such as the SmartDelay determined AV Optimization: A Comparison of AV Optimization Methods Used in Cardiac Resynchronization Therapy (SMART-AV) trial and Frequent Optimization Study using the QuickOpt Method (Freedom) trial used device algorithms for AV and VV optimisation and did not show benefit in clinical endpoints resulting in the current guidelines recommending against routine AV or VV optimisation.[1,51,52] The SMART-AV trial randomised CRT patients to a fixed AV delay, echocardiographic mitral inflow based AV delay, or an automated device algorithm based AV delay and found no difference in clinical outcomes or left ventricular end-systolic volume at six months.[51] A substudy of the SMART-AV trial using the QLV interval at the LV pacing site showed that the SmartDelay method improved remodeling at six months among patients with long QLV intervals and the LV pacing site.[53] The recently published ADAPTIVE trial randomised patients with a normal intrinsic AV interval to left ventricular fusing pacing verses echocardiography optimised BiV pacing and demonstrated non-inferiority in the left ventricular pacing cohort. Higher percent left ventricular pacing was associated with improved clinical outcomes.[54] Using AV and VV optimisation in non-responders to CRT and in specific patient populations needs further review.

Conclusion

Over the last twenty years the use of CRT has expanded and evolved considerably. The indications for CRT implant now include subjects with mild HF as well as those with mild LV dysfunction and frequent RV pacing. New techniques help to identify optimal sites for LV pacing. Finally, the role of AV optimisation is less clear with routine optimisation discouraged. ■

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