



ICE Guided CRT: Is there Evidence of Reverse Remodeling?

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Abstract

Cardiac resynchronization therapy (CRT) is an accepted treatment for patients with heart failure (HF), impaired left ventricular (LV) function, and a wide QRS complex. However, more than 30% of eligible patients fail to benefit from CRT. It is clearly necessary to define the characteristics of the best candidates for this therapy. To this end, surface ECG and echocardiography have been tested. Unfortunately, however, neither of these examinations has proved sufficiently able to identify the best patients. A tailored approach based on the evaluation of both electrical and mechanical delay to guide LV lead placement seems to be the most reasonable strategy in order to increase the efficacy of CRT therapy. The good preliminary data that have been published suggest that using intracardiac echocardiography to define the mechanical delay could be an interesting option. Moreover, at present it is the only option available that can enable intraprocedural evaluation of the mechanical activation sequence. Naturally, further randomized studies with larger populations should be performed in order to ascertain the real benefit of this approach and to evaluate whether it will outweigh the additional cost of this technology.

Introduction

Cardiac resynchronization therapy (CRT) is an accepted treatment for patients with heart failure (HF), impaired left ventricular (LV) function, and a wide QRS complex. The paradigm for CRT is based on the evidence that conduction disturbances, in particular left bundle branch block (LBBB), lead to LV dysfunction.¹ In 1983, it was first reported that simultaneous septal and LV free wall contraction was hemodynamically superior to dyssynchronous contraction and that the best hemodynamic effect arose from fusion between intrinsic LBBB conduction and the LV pacing stimulus.² In accordance with this concept, and on the basis of the benefit observed in early hemodynamic studies³⁻⁴ and the observation that delayed segments predominate at these sites, the conventional approach to resynchronization has involved directing the LV lead to the lateral and posterior walls.

In the last 20 years, several large randomized multicenter trials have shown the clinical benefits of CRT therapy on symptoms, exercise capacity, mortality and HF re-hospitalization.⁵⁻¹¹ In the CARE HF¹⁰ and REVERSE¹² studies, substantial improvements in LV size and function, LVEF, RV function, LA size and mitral

regurgitation severity were observed in patients treated with CRT in comparison with ICD only. These results provide consistent evidence of a substantial, progressive and sustained reverse remodeling effect conferred by CRT in the responder population.

The Dark Side: Non-Responder Population

However, more than 30% of eligible patients fail to benefit from CRT. The reasons for the high percentage of non-responders include inappropriate candidate selection, device programming and LV lead placement.¹³ In general, the response to CRT is greatest when biventricular pacing serves to synchronize left ventricular contraction as much as possible. The two criteria for pacing sites that are generally held to optimize CRT response are: (1) pacing at areas of live, non-scarred myocardium, and (2) pacing at the area of the most delayed mechanical contraction or electrical activation. Echocardiography and MRI reveal both the regions of latest mechanical activation and areas of scarred, non-contractile myocardium.¹⁴⁻¹⁵ By contrast, ECG excels in determining the regions of latest electrical activation; it also has some ability to distinguish areas of scarring, but is generally unable to guide lead placement.¹⁶⁻¹⁷

First Mission: Choose the Right Patient

It is clearly necessary to define the characteristics of the best candidates for this therapy. To this end, surface ECG and echocardiography have been tested. Unfortunately, however, neither of these examinations has proved sufficiently able to identify the best patients. Indeed, in candidate selection, electrocardiographic evidence of intraventricular conduction delay has been tested as a surrogate marker for mechanical interventricular and intraventricular dyssynchrony.^{6,18} In patients with severe CHF symptoms, LBBB morphology and QRS width > 150ms have been shown to predict

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a greater likelihood of CRT benefit. On the other hand, in patients with mild heart failure, non-LBBB morphology has been shown to predict minimal CRT benefit, and potentially even harm due to LV pacing. However, a significant proportion of CRT patients fail to respond symptomatically, and an even a larger proportion do not display objective evidence of benefit.^{7,10} Moreover, the utility of many echocardiographic measures of mechanical dyssynchrony that once held promise as predictors of response to CRT in single-center studies was tested by the PROSPECT (Predictors of Response to CRT) trial.¹⁹ Even after validation by blinded core laboratories, no echocardiographic measure of dyssynchrony could reliably predict the response to CRT. Negative evidence also comes from the recent Echo CRT study, which failed to show a benefit from CRT-D in patients with QRS duration <130 ms and dyssynchrony assessed echocardiographically.²⁰ These results seem to suggest that the battle to select patients has been lost, a conviction that is underlined by the simpler CRT indications reported in the latest guidelines.²¹ For this reason, research on LV lead placement has attracted considerable interest.

Second Mission: Choose the Right Vein

The standard technique of CRT implantation has remained substantially unchanged since it was first described in the 1990s.²² A posterolateral position with acceptable pacing parameters and no diaphragmatic stimulation is usually considered a good angiographic result. However, several studies have reported a correlation between LV lead position and CRT outcome and mortality.²³⁻²⁵ Derval and colleagues showed that the pacing site is the primary determinant of the hemodynamic response to LV pacing in patients with non-ischemic, dilated cardiomyopathy,²⁶ pacing at the best LV site being associated acutely with fewer non-responders. In another study, Duckett et al. reported that the acute hemodynamic response seemed to predict reverse remodeling both in ischemic and dilated cardiomyopathy.²⁷ In a smaller but significant group of patients, Spragg and colleagues assessed the greatest percentage rise in LV-dP/dtmax in a target other than the posterolateral and lateral veins. They reported that, in their institutional experience, 8 of 11 patients who underwent intraoperative hemodynamic measurements while being paced at various endocardial surfaces were found to have an optimal pacing site that was not at locations traditionally used for LV pacing.²⁸

These data confirm the idea that even when the LV lead is deployed in a “good” fluoroscopic position, the response is variable. Thus, a concept has evolved according to which targeting segments of latest LV “activation” improves response. The ways of defining the optimal LV segment to pace are different.

Pacing at the Site of Latest Mechanical Activation

Dyssynchrony imaging, which plays a small role in patient selection, may be useful in LV lead deployment. In a prospective study, Ypenburg et al. found that pacing at the site of latest mechanical activation, as determined by speckle-tracking radial strain analysis, resulted in a superior echocardiographic response after 6 months of CRT and better prognosis during long-term follow-up.²⁹ In the TARGET randomized study, the authors showed that a targeted approach to LV lead placement based on the definition of the latest segment activated, as identified by speckle-tracking echocardiography, resulted in significant benefit in terms of LV reverse remodeling, clinical status and the long-term endpoint

of combined death and heart failure-related hospitalization, in comparison with a standard approach.³⁰ The main limitation of that study was that speckle-tracking echocardiography could not be performed in all the patients. Secondly, despite targeting, the constraints of coronary venous anatomy appear to have restricted concordance to only two thirds of patients, and in 8% of all patients the LV lead was still placed at areas of scarring. Several data have suggested that the viability of the paced LV segment can influence the outcome of CRT. In this regard, pacing areas of scarring is associated with a worse response^{31,32} than pacing viable myocardium. Increasing scar transmural³¹ and scar density¹⁴ also portend a worse response. Another recent randomized study evaluated the impact of echocardiography-guided left ventricular lead placement with the aid of speckle-tracking echocardiography at the site of latest mechanical activation on the rate of freedom from appropriate CRT-D therapy for ventricular arrhythmias. The authors reported a higher percentage of CRT response in the echo-guided LV lead placement group (72% vs 48%, $p = 0.006$) with a consequent improved therapy-free survival rate.³³ When the trans-thoracic echocardiography approach is used, the best LV lead site is identified and implantation is performed at different times; it is therefore impossible to adjust the lead position if placement is suboptimal.

Pacing at the Site of Latest Electrical Activation

Another approach to identifying the right vein to pace is based on the evaluation of local eCG delay. The measurements of the QLV interval in each of the CS tributaries is the most used method to define the area of most delayed ventricular electrical activation. The QLV interval is defined as the time that elapses between the beginning of the QRS complex on surface ECG and the onset of the sensed electrogram at the LV lead. Placement of the CS lead at the site of the longest QLV interval is correlated with improved hemodynamics, including higher maximum dP/dT.³⁴ Moreover, a substudy of the SMART-AV trial showed that the length of the QLV interval was associated to a better outcome of CRT in patients with greater electrical dyssynchrony.³⁵ Similar results were observed also in the MADIT trial.²⁴

This approach has the advantages of requiring minimal additional procedural time and it does not require the implementation of additional tests as echocardiography or cardiac MRI.

Another strategy was described in 2012 by Del Greco and colleagues, who demonstrated the ability of an electroanatomic navigation system (NavX system) to guide CRT-ICD implantation. The authors concluded that this approach was feasible and safe and reduced X-ray exposure both for patients and physicians. A further benefit was that the system provided more detailed information and accuracy during CS lead placement, in terms of both 3D visualization of anatomy and ventricular activation time, which optimize the pacing site choice.³⁶

Currently, several additional studies are underway to correlate the QLV interval, as measured at the CS lead, and the clinical and echocardiographic response to CRT.

Intracardiac Echocardiography

In an early study conducted on dogs, Jiang et al. reported the feasibility and ability of intracardiac echocardiography in visualizing the left ventricle from the right ventricle and monitoring LV function.³⁷ Some years later, Saksena and colleagues proposed a clinical technique using intraoperative ICE to guide LV lead

positioning and CRT device optimization. In their study, ICE was used in 23 patients to assess baseline LV function and LVEF in the B-mode and/or M-mode view and to evaluate the stroke volume indirectly by means of aortic flow spectra from Doppler analysis. The final LV position was selected according to the greatest changes in LVEF and/or aortic flow parameters measured in each possible vein during CRT stimulation.³⁸ The same approach was also used for AV and VV optimization. Intracardiac echocardiographic visualization of LV function was achieved in all the patients. On using this approach, the authors reported a significant improvement in LVEF compared with the baseline evaluation (24±9% to 43±13%) and only one patient experienced worsening of heart failure during a follow-up of 11±5 months. On the other hand, ICE evaluation prolonged the procedure time by 45 minutes. The main limitations of that study were the small patient population and the inability to confirm the real benefit of ICE, owing to the study design.

In another study, Bai et al. proposed using ICE coupled with vector velocity imaging to evaluate LV dyssynchrony and to guide LV lead placement at the time of CRT implantation. Starting from a manual endocardial perimeter tracing of each B-mode LV image, the vector velocity imaging software creates 6-segment radial/longitudinal strain curves that enable LV dyssynchrony to be detected.³⁹ This analysis was performed in the basal condition, during LV only or during CRT pacing in at least 2 veins in the first 50 patients. These data were compared with those from the following 54 patients, in whom standard CRT implantation was performed. Reverse remodeling was observed in both groups, but the percentage of responders in the ICE group was significantly higher than in the standard group (82% vs 63%). In the ICE group, all the responders displayed optimal visual resynchronization on vector velocity imaging. The authors concluded that ICE-VVI analysis could be easily and safely performed during CRT implantation, and that its use was associated with a better outcome on CRT therapy during follow-up. Moreover, ICE guidance enables the final LV lead position to be chosen from among all candidate veins by means of “real-time” synchrony analysis. Alternatively, if optimal resynchronization cannot be achieved in the procedure, the patient may not be a suitable candidate for transvenous CRT.

Conclusions

Cardiac resynchronization therapy is the most powerful weapon to reduce morbidity and mortality in patients with symptomatic severe heart failure and ECG evidence of interventricular conduction delay. A tailored approach based on the evaluation of both electrical and mechanical delay to guide LV lead placement seems to be the most reasonable strategy in order to increase the efficacy of CRT therapy. The good preliminary data that have been published suggest that using intracardiac echocardiography to define the mechanical delay could be an interesting option. Moreover, at present it is the only option available that can enable intraprocedural evaluation of the mechanical activation sequence. Naturally, further randomized studies with larger populations should be performed in order to ascertain the real benefit of this approach and to evaluate whether it will outweigh the additional cost of this technology.

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