Cardiac Resynchronization Therapy: The Remaining Challenges

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Introduction

Cardiac resynchronization therapy (CRT) has come a long way from its inception as a last-ditch attempt to salvage intractable heart failure (HF) in patients with demonstrated electrical dyssynchronies\(^1\)-\(^3\) to its current status as a routine mainstream therapy recommended for moderate and even mild HF.\(^4\) The increase in popularity of CRT is due to two main factors: large-scale randomized clinical trials demonstrating symptomatic, morbidity, and mortality benefits,\(^5\)-\(^11\) and better tools (catheters, leads and pulse generators) that facilitate therapy delivery. Despite the great advances which have been made, CRT still has several major remaining challenges. CRT requires left ventricular (LV) pacing, which is currently most commonly achieved by lead placement within a side branch of the coronary sinus (CS). This is not always successful and often suboptimal due to phrenic nerve stimulation, high LV capture threshold, or lead dislodgement.\(^12\) Even when CS lead placement is successful, \(\approx 30\%\) of CRT recipients do not “respond” by either clinical or echocardiographic parameters.\(^13\)-\(^15\) Different strategies have been used and explored to improve the clinical and echocardiographic response to CRT, including better patient selection, A-V and V-V delay adjustment, LV pacing site selection, multisite LV and RV pacing, and LV pacing configurations. Although originally developed for use in the presence of electrical dyssynchrony, CRT has been extended to patients with narrow QRS complexes but demonstrated mechanical dyssynchrony, with conflicting results. Finally, the effects of cardiac stimulation by electrical impulses may not be confined to the generation of activation wavefronts and extend to modulation of myocardial contractility. These topics will be reviewed in this article.

Patient selection

Patient selection for CRT is intimately intertwined with therapy optimization: Is non-response a fixed characteristic of the patient or a variable consequence of therapy delivery? In the early days of CRT, the scope for therapy optimization was limited and hence the emphasis was on patient selection. Improved technologies and increased clinical experience have shifted the research focus more towards therapy optimization.

The published guidelines base patient selection for CRT on four basic criteria: 1) New York Heart Association (NYHA) function class; 2) QRS duration and morphology; 3) LV ejection fraction (EF); and 4) optimal medical therapy. Of the four criteria, NYHA class and QRS duration and morphology have seen most refinements in the light of recent clinical trial data. The EF is a crude way of assessing the LV. “Optimal medical therapy” is not precisely defined and subjective.

New York Heart Association function class

CRT is now indicated for NYHA class II as well as NYHA class III–IV HF\(^4\) due to the morbidity, mortality and LV remodeling benefits from early intervention with CRT in NYHA class II patients demonstrated in randomized clinical trials.\(^9,10,16\)-\(^18\)
QRS duration and morphology

An increased QRS duration on the surface electrocardiogram (ECG) is the most commonly used criterion of electrical dyssynchrony, probably because it is simple, readily accessible and cheap. However, the QRS duration may vary in a patient (e.g. depending on the prevailing ventricular rate) and differ when assessed by a machine and a human observer. The QRA duration qualifying for CRT varies from ≥120 ms for NYHA class III–IV to ≥150 ms for NYHA class II, an inverse relationship between HF and electrical dyssynchrony severity. Patients with broader QRS complexes (>150 ms) benefited more from CRT than patients with less broad QRS complexes (120–150 ms) in randomized clinical trials, but a QRS complex duration of ≥150 ms alone does not guarantee clinical or echocardiographic response.

In the context of CRT, broad QRS complexes can be classified into four major patterns: left bundle branch block (LBBB), right bundle branch block (RBBB), non-specific intraventricular conduction delay (IVCD), and RV-only pacing. Patients with LBBB benefit most from CRT, whereas patients without LBBB (i.e. RBBB, IVCD, and RV-only pacing) benefit little if at all, in terms of morbidity, mortality, LV remodeling and ventricular arrhythmia reduction in randomized clinical trials. However, patients with RBBB and left intraventricular mechanical dyssynchrony may still benefit from CRT. Despite its impact on clinical response, QRS morphology classification is not a selection criterion for CRT in the latest guidelines. Patients with advanced HF (NYHA class III–IV) needing pacing are still recommended to receive CRT (level of evidence I–IIa).

Left ventricular assessment

In a simplistic model, CRT improves clinical outcomes by reducing electrical and hence mechanical dyssynchrony within the heart. Mechanical dyssynchrony should thus predispose to or may even be a prerequisite for response to CRT, and many imaging modalities have been used to assess its presence and extent. Even though there are different forms of mechanical dyssynchrony involving all the heart chambers (interatrial, atrioventricular, interventricular, LV intraventricular, and intramural), investigation has focused on the LV as it is the major pumping chamber of the heart. LVEF is a measure of global rather than regional LV systolic function and does not predict response to CRT. Structural abnormalities within the LV myocardium (scarring, fibrosis, infarction) can cause systolic and diastolic dysfunction and affect response to CRT.

Echocardiography is the most popular imaging modality for investigating the heart for CRT. The methods which have been used for this purpose include M-mode, Doppler, pulsed-wave and color-coded tissue Doppler, longitudinal and radial strain and strain rate, speckle (two-dimensional-derived strain) tracking, and real-time three-dimensional mode. Numerous indices based on these methods have been devised, with different cut-off values for separating responders from non-responders, but none has emerged as clearly superior. When 12 echocardiographic conventional and tissue Doppler parameters were tested in a multicenter clinical trial, they showed only modest interobserver concordance and predictive power for response to CRT.

Cardiac magnetic resonance imaging (MRI) can assess cardiac dimensions, velocities in all orientations strain rate (through tagging), and tissue viability (through gadolinium contrast uptake), making it extremely suitable for evaluation of mechanical dyssynchrony and myocardial scarring. Apart from mechanical dyssynchrony, the site and extent (burden) of myocardial scarring may also determine response to CRT. However, MRI may not be safely performed in the presence of foreign metal objects, including cardiovascular implantable electronic devices (CIEDs), in the body. This used to mean that patients considered for CRT could only be assessed with MRI before but not after device implantation. MRI-compatible pacemakers are now commercially available, and it is only a matter of time before MRI-compatible technologies are extended to CRT devices. However, MRI compatibility may be restricted to certain magnetic field strengths (e.g. 1.5 tesla) for the scanner. MRI-compatible CIEDs still cast significant artifacts in the MR image.

Figure 1: Magnetic resonance imaging (MRI) of the heart in the presence of a MRI-compatible pacemaker. (a) Significant artifacts over the pacemaker pulse generator in the left pectoral region, and (b) minimal artifacts over the pacing leads within the heart.
depending on the physical sizes and ferromagnetic contents of the components (Figure 1).

Radionuclide angiography, and ECG-gated single photon emission computed tomography (SPECT) myocardial perfusion imaging have also been explored for use in assessing LV dyssynchrony.

**A-V and V-V delays adjustment**

The A-V and V-V delays are programmable parameters in a CRT device and provide a possible means of non-invasively improving response to CRT through their adjustment. Two major approaches are currently used to guide their adjustment: echocardiography and intracardiac electrograms (IEGMs). Echocardiography-directed adjustment can be by many different methods (e.g. the Ritter’s formula, the iterative technique), but LV outflow tract velocity–time integral (VTI) (a surrogate measure of stroke measure) maximization is probably the most popular in practice. IEGM-directed adjustment is by proprietary algorithms developed by different CIED manufacturers recommending values for the A-V and V-V delays on the basis of the intracardiac atrial, RV and LV signals.

Delays adjustment by echocardiography can be very time-consuming and operator dependent. Delays adjustment by IEGM methods depends critically on the validity of the algorithms used, which were derived empirically from observed clinical data without any underlying physiological bases. The A-V and V-V delays “optimal” by whatever criteria vary with the prevailing atrial rate (such as with exercise) and over time, which means delays adjustment should be repeated periodically. This largely precludes the use of invasive hemodynamic measurement (e.g. LV dP/dt) for this purpose. In contrast, intracardiac impedance may provide a new approach to delays adjustment, with the potential of being incorporated into future generations of CIEDs as an automated feature. “Optimal” values by different methods do not always agree. Improvement of the surrogate measures used for guiding delays adjustment may not translate into enhanced echocardiographic or clinical response to CRT. Patients with atrial fibrillation cannot be programmed to have the LV paced ahead of the RV unless intrinsic conduction through the atrioventricular node is suppressed by a high lower rate setting on the device, drugs, or ablation.

**Left ventricular pacing site selection**

The “optimal” site for LV pacing can be chosen on several theoretical bases: latest electrical activation; avoidance of slow electrical conduction areas; latest mechanical activation; avoidance of myocardial scars; and maximum or minimum hemodynamic parameters (e.g. cardiac output; stroke work, LV dP/dt, LVEF).

With conventional transvenous epicardial CS lead placement, selection of the LV pacing site is heavily constrained by the CS venous anatomy. A lead may not be placed at a desired site because of lack of a suitable side branch, high LV capture threshold, repeat lead dislodgement, or phrenic nerve stimulation. In practice, some degree of CS lead placement site selection is still possible. The longest local LV electrical delay (compared to the surface QRS complex) or maximum hemodynamic enhancement (e.g. on pressure–volume loop analyses) can be assessed intraoperatively and are more suitable for this purpose than correlating the CS venous anatomy revealed intraoperatively by retrograde venography, or preoperatively by multislice computed tomography with a desired pacing site identified preoperatively by echocardiography or cardiac MRI, which can be at best only approximate.

Surgical epicardial LV lead placement offers more choices on the pacing site than transvenous epicardial CS lead placement, but is inevitably more invasive and hence used mainly as a second-line option. Correlating the lead placement site intraoperatively with a desired site identified preoperatively with an imaging modality will still be difficult, but invasive intraoperative hemodynamic assessment can be used to guide lead placement. Implanting a pacing lead on a moving target that is the epicardial surface of a beating heart can be technically challenging if the pericardial sac is opened or the desired site is on the posterior surface. Epicardial fat may obscure the underlying cardiac anatomy. Surgically placed epicardial pacing leads have a much higher failure rate than transvenously placed leads, and extraction and replacement will require repeat open chest surgery.

Endocardial LV lead placement has emerged as an alternative technique for achieving LV pacing in CRT. Endocardial LV lead placement can be achieved transvenously through a transseptal puncture or surgically through a LV apical puncture from the epicardial surface. The transseptal approach is less invasive than the transapical approach. Even when the transapical puncture is performed percutaneously under echocardiographic guidance, hemostasis around the puncture site and fixation of the lead to the epicardial surface still require open chest surgical access. Regardless of the approach, endocardial LV lead placement carries the risk of systemic thromboembolism (including stroke) and the need for long-term oral anticoagulation. The transseptal approach requires the endocardial LV lead crossing the mitral valve, with the potential of causing valvular stenosis, regurgitation, leaflet perforation, chordal rupture, or infective endocarditis. However, the pacing lead can theoretically be placed anywhere on the endocardial surface of the LV cavity, opening up the opportunity of “optimization” as guided by hemodynamic parameters. Endocardial LV pacing is more physiological and hemodynamically effective, and should be less pro-arrhythmic, than epicardial LV pacing.

**Multisite left and right ventricular pacing**

Multisite (≥3) ventricular pacing has been explored as a means of enhancing response to CRT. The combinations...
which have been tried include (2 RV sites + 1 LV site) and (1 RV site + ≥2 LV sites).

The (2 RV sites + 1 LV site) combination has two leads in the RV (at the apex and in the outflow tract) and one lead in the CS, and has been shown to be beneficial in some patients, especially with enlarged LV diastolic volume.

The (1 RV site + ≥2 LV sites) combination has one lead in the RV and one or two leads in the CS. The two LV pacing sites can be radially separated (2 CS leads into 2 separate side branches – usually one posterior-lateral and one anterior-lateral) or longitudinally separated (the different poles of a quadripolar lead in one CS side branch). The (1 RV lead + 2 CS leads in 2 different side branches) combination did not demonstrate consistent benefits in previous clinical studies, but a larger scale study is ongoing. The (1 RV lead + 2 pacing sites on 1 quadripolar CS lead) combination may offer some minor extra hemodynamic benefits in patients with posterior-lateral LV scar compared with conventional (1 RV lead + 1 pacing site on 1 CS lead) combination in an electromechanical biophysical model of the human heart, but generally speaking does not produce as significant hemodynamic changes as two radially separated LV pacing sites. On the other hand, there are data suggesting that LV only pacing with one lead may not be inferior to conventional RV + LV pacing.

Left ventricular pacing configurations

Experimentally, the myocardium can be electrically activated either during (make) or after (break) a cathodal (negative) or an anodal (positive) impulse delivered from a single electrode. The impulse generates a “dog-bone” shape area of identical polarity across the direction of myocardial fibers in the immediate vicinity of the physical electrode, and two areas of opposite polarity within the concavities of the dog-bone shape along the direction of the myocardial fibers further away from the physical electrode. These areas of identical and opposite polarities are larger than the physical size of the actual electrode and give rise to “virtual electrodes” (Figure 3). For “make” stimulation, the virtual cathode initiates wavefront activation whereas the virtual anode impedes wavefront propagation. For “break” stimulation, the virtual anode initiates wavefront activation whereas the virtual cathode impedes wavefront propagation. The higher the impulse amplitude, the larger the sizes of these virtual electrodes, and the further away from the physical electrode electrical activation starts. Activation wavefronts propagate faster along than across the direction of myocardial fibers. Based on these principles, anodal “make” stimulation will be more effective than conventional cathodal “make” stimulation in initiating wider and faster myocardial activation – there will be two simultaneous activation wavefronts starting further away from the
physical electrodes and propagating faster along the direction of myocardial fibers. Cathodal “break” stimulation theoretically generates an activation pattern similar to that of anodal “make” stimulation, but “break” stimulation is not useful in practice as the impulse has to be delivered at a time when the myocardium is refractory (to avoid “make” stimulation) and generally requires a higher current density, with the potential of myocardial damage and localized hydrolysis around the physical electrode. Interestingly, apart from a higher pacing output and faster myocardial conduction velocities, anodal pacing was also associated with increased myocardial contractility compared to cathodal pacing in animal studies.\textsuperscript{127,128}

Clinically, increasing the output of LV cathodal pacing shortens the QRS duration and LV–RV interventricular delay, but this might be due to RV anodal capture in some cases.\textsuperscript{129,130} Deliberate anodal pacing increased the LV outflow tract VTI by around 15% compared with cathodal pacing, regardless of whether it was LV only, unipolar (indifferent electrode at the skin), or extended bipolar (indifferent electrode at the RV coil).\textsuperscript{131} Gradual increases in the LV pacing output from a true bipolar CS lead attached to a CRT device caused abrupt changes in the QRS morphology, shortening of the QRS duration and LV–RV interventricular delay, and lengthening of the QTc and JTc, possibly as a result of reaching the anodal capture threshold.\textsuperscript{132} These effects were more marked for CS leads with longer tip-ring electrode spacing, and less likely to occur for leads with a bigger ring electrode area (and lower anodal current density).

While the electromechanical benefits of LV anodal capture are worth exploring, the costs of a higher pacing output (and hence reduced battery longevity) and the pro-arrhythmic effects of a longer QTc need to be borne in mind. It is unclear whether LV anodal capture from the endocardial surface will be substantially different from the epicardial surface. RV anodal capture has been associated with non-response to CRT, but that could be the reflection of a suboptimal LV placement site necessitating the use of a the RV coil or ring electrode as part of the LV pacing circuit.\textsuperscript{133}

**Patients with narrow QRS complexes**

LV mechanical systolic and diastolic dyssynchrony by tissue Doppler imaging was found in 51% and 46% respectively of HF patients with narrow QRS complexes, compared with 73% and 69% respectively of HF patients with wide QRS complexes, in one study.\textsuperscript{134} This and other similar studies\textsuperscript{135,136} spurred interest in extending the indications of CRT to HF patients with narrow QRS complexes (and hence no evidence of electrical dyssynchrony ) but evidence of mechanical dyssynchrony on echocardiography. While some observational studies showed benefits of CRT in such patients,\textsuperscript{137–140} this was not supported by randomized clinical trials.\textsuperscript{141} At the moment, the role of CRT in patients with narrow QRS complexes but mechanical dyssynchrony is unclear. Mechanical dyssynchrony in the absence of electrical dyssynchrony implies intramural not electrical dyssynchrony. Biventricular pacing is not so much “resynchronizing” the electrical activation heart as “pre-exciting” areas of the myocardium with long electromechanical activation delays. LV pacing site selection by intraoperative hemodynamic measurement may improve the response to CRT in HF patients with mechanical dyssynchrony and narrow QRS complexes.\textsuperscript{142}

**Effects of cardiac stimulation by electrical impulses**

Originally, CRT or biventricular pacing was developed to reverse electrical dyssynchrony, which presumably caused mechanical dyssynchrony, and hence reduced cardiac efficiency and hence failure. Biventricular pacing in HF patients with narrow QRS complexes and mechanical dyssynchrony is mechanical resynchronization through deliberate electrical dyssynchronization. However, the effects of cardiac stimulation with an electric impulse may not be confined to the production of one or more activation wavefronts propagating through the myocardium. Anodal stimulation increases myocardial contractility and conduction compared with cathodal pacing,\textsuperscript{127,128} suggesting an electrical impulse may affect myocardial contractility in ways independent of its electrical activation. Non-excitatory electrical impulses delivered to the myocardium during its refractory period can improve its contractility, a concept called cardiac contractility modulation (CCM).\textsuperscript{143} The inotropic effects on CMM have been demonstrated in HF patients,\textsuperscript{144–146} and are associated with LV remodeling and systolic improvement unrelated to LV diastolic function or mechanical dyssynchrony\textsuperscript{147} without increases in myocardial oxygen consumption or metabolic demands.\textsuperscript{148,149} However, the high electrical stimulus output (around 5.8–7.7-V output at 20-ms pulse width) required to achieve CCM means the responsible pulse generator needs to be recharged with energy frequently through induction, which forms a major barrier to the widespread utilization of the treatment. Although there was no excess hospitalization or mortality, long-term CCM did not improve the ventilatory anaerobic threshold in a large-scale clinical study except in a retrospectively identified subgroup.\textsuperscript{150–152}

**Conclusions**

CRT straddles three different cardiac subspecialties: HF, electrophysiology, and imaging, which adds to the complexity of its study and refinement. Even though CRT is an established clinical treatment, there are still many aspects around it which have not been completely elucidated and are under active investigation. Better coordination of research efforts into larger scale, multicenter randomized prospective clinical studies will help clarify the conflicting data around many of these issues and more effectively guide clinical practice. The non-excitatory physiologic effects of electrical stimulation of the heart may be used to enhance myocardial contractility, extending the scope of cardiac stimulation (in...
contradistinction to just resynchronization) therapy even further to include patients with failing myocardium but neither electrical nor mechanical dyssynchrony.

References


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