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REVIEW

Novel devices

Biventricular pacing: current trends and future strategies

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The role of biventricular pacing is expanding beyond the New York Heart Association classes III and IV heart failure (HF) patient to include less symptomatic patients, earlier in the course of their disease process. This multisite pacing strategy has substantially altered the natural course of ventricular failure, exerting its physiological impact through favourable cardiac remodelling and improving the ejection fraction. This has in turn resulted in long-term clinical benefits such as improved quality of life and functional capacity with a concomitant reduction in hospitalization for HF and overall mortality. Despite the successes of cardiac resynchronization therapy (CRT) and the recent expansion of its role in the treatment of HF patients, there remain some inherent limitations to the technology and its delivery. A significant minority of patients continue to remain non-responsive to this pacing strategy. This review will highlight biventricular pacing in its present form, will elaborate on strategies to enhance response to CRT, and outline future trends and synergies towards maximizing the potential benefit of this therapeutic modality.

Keywords Biventricular pacing • Cardiac resynchronization therapy • Cardiomyopathy • Heart failure

Introduction

Biventricular pacing has become an accepted therapeutic modality for medically refractory congestive heart failure (CHF). This novel pacing strategy also known as cardiac resynchronization therapy (CRT) synchronizes ventricular contraction, which consequently results in improved pumping efficiency, enhanced left ventricular (LV) filling, and a reduction in the severity of the mitral regurgitation. Biventricular pacing has substantially altered the natural course of ventricular failure, exerting its physiological impact through favourable ventricular remodelling, with a reduction in LV volumes and improvement in ejection fraction (EF).[1] This in turn translates into long-term clinical benefits such as improved quality of life and functional capacity with a concomitant reduction in hospitalization for heart failure (HF) and overall mortality.[2,3] The standard indications for biventricular pacing which initially included patients with advanced HF and evidence of systolic dysfunction (EF $\leq$35%), with conduction tissue disease and marked cardiac symptoms [New York Heart Association (NYHA) classes III and IV] have now expanded to include even the mildly symptomatic patient (NYHA classes I and II).[4,5]

Despite this success of CRT and the recent expansion of its role in the treatment of patients with CHF, there remain many inherent limitations to the technology and its delivery. A significant minority of patients (~30%) continue to remain non-responsive to this pacing strategy.[1,2] This review will highlight biventricular pacing in its present form, will elaborate on strategies to enhance response to CRT, and outline future trends and synergies towards maximizing the potential benefit of CRT.

Physiology of cardiac resynchronization therapy

Electrical activation sequence and cardiac resynchronization therapy

The electrical activation sequence of the heart is an important determinant of co-ordinated cardiac contraction and relaxation, and overall cardiac function. Abnormalities in electrical activation such as in left bundle branch block (LBBB) in most cases may cause asynchronous and delayed contraction of the lateral wall,

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thereby diminishing the mechano-energetic efficiency of the heart, resulting in HF.[6]

It is important to note that often times it is the chicken-and-the-egg situation, where the cardiac conduction defects can either directly lead to HF or may occur secondarily as an integral part of the process of cardiac remodelling that accompanies advanced cardiomyopathies. Ventricular remodelling in HF is a progressive process that includes degenerative and maladaptive changes occurring at the tissue, cellular, and subcellular level.[7] These changes inclusive of myocyte hypertrophy, regional alteration in protein expression, necrosis, inflammation, and fibrosis affect the ventricular conduction system and in turn impulse generation and propagation.[8,9] Over and above changes in the conduction pattern, the extent of asynchrony can be significantly impacted by the changes in myocardial characteristics, such as the presence of scar, fibrosis, and ischaemia, all of which add to the complexity of the conduction pattern.

During CRT, the right ventricular (RV) and LV pacing leads (*Figure 1*) generate two ventricular activation wavefronts, which are initiated at the LV and RV pacing sites and move in opposite directions towards each other. The benefit of CRT lies in effective fusion of these two depolarization wavefronts, synchronizing the walls of the LV. The overall electrical activation can be further modulated by adjusting the atrioventricular and interventricular timings of the paced impulses.[10,11]

Mechanical dyssynchrony

The imprecision in the ability of a surface QRS to predict response is explained by the complexity and multiple levels of electrical and mechanical dyssynchrony in the myopathic heart. This dyssynchrony can exist at multiple levels and can be (i) interatrial, (ii) atrioventricular, (iii) interventricular, (iv) intraventricular, and (v) intramural (*Figure 2*).[10] Most studies have emphasized the importance of intraventricular dyssynchrony as the major contributing factor to progressive HF and a predictor of response to CRT. Echocardiographic measures have sought to fill this gap by improving our understanding of the anatomical and functional aspects of the cardiac substrate. M-mode, two dimensional echocardiography, three dimensional echocardiography, and tissue Doppler imaging (TDI) provide a better understanding of the level of baseline dyssynchrony, acute response, and evidence of favourable remodelling to CRT. Tissue Doppler imaging facilitates measuring dyssynchrony by evaluating the direction and velocity of the longitudinal movement of the myocardial wall within various segments.[11] The difference in time-to-peak velocities of various segments can be assessed, and in many single-centre studies, it has been shown to be a good predictor of response to CRT. However, with TDI, passive myocardial motion cannot be distinguished between active contractions as is the case when assessing a patient with ischaemic cardiomyopathy who might have segments of scar. Also, TDI is still predominantly a two-dimensional (2D) technique and the need for high frame rates required by this technique limits resolution and image quality.

Despite very promising results in small-scale trials, when tested prospectively in two multicentre trials, echocardiographic methods have not convincingly predicted response to CRT. The PROSPECT[12] and RethinQ[13] trials were multicentre trials designed to assess the utility of dyssynchrony parameters in predicting response to CRT and, in the case of RethinQ, in patients with a narrow QRS. The PROSPECT trial was a non-randomized prospective observational trial, which enrolled 426 patients undergoing

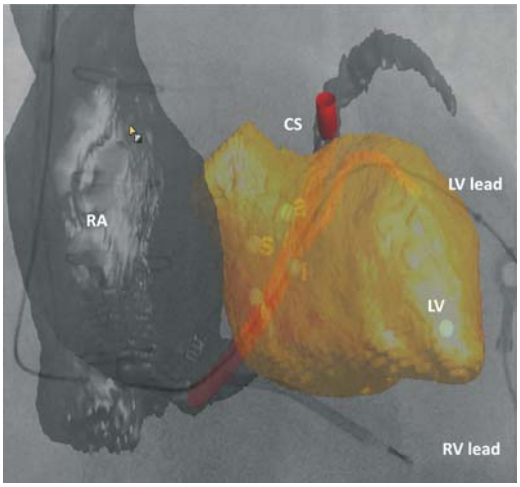

Figure 1 Computed tomography–fluoroscopy-integrated image. The figure shows an integrated image of a cardiac computed tomography with fluoroscopy. A reconstructed coronary sinus (CS) is seen with the left ventricular (LV) lead. The right ventricular (RV) lead is seen at the apex of the right ventricle. RA, right atrium (adapted from Truong *et al*).[36]

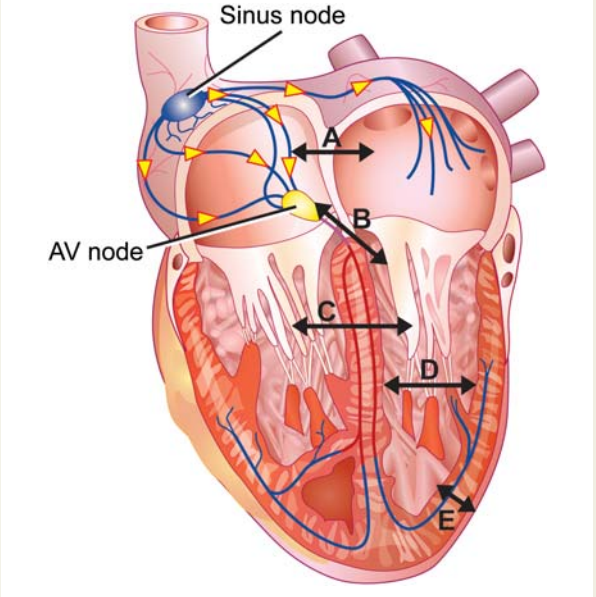

Figure 2 Levels of mechanical dyssynchrony. The figure shows the levels of dyssynchrony within the heart: (*A*) interatrial, (*B*) atrioventricular, (*C*) interventricular, (*D*) intraventricular, and (*E*) intramural mechanical dyssynchrony.

device placement according to the current selection criteria. Prior to implant, subjects underwent dyssynchrony assessment using various methods to assess intra- and interventricular dyssynchrony including M-mode and TDI. At 6 months, endpoints including a clinical composite score (all-cause mortality, HF hospitalization, NYHA class, and patient global assessment) and 15% reduction in LV end-systolic volume (LVESV) were assessed. Despite site training in acquisition methods and three blinded core-lab analyses, there was no single echocardiographic predictor of response to CRT. The RethinQ trial was a randomized multicentre trial designed to assess the utility of dyssynchrony parameters in predicting the response to CRT in patients with a narrow QRS. Two-hundred and fifty subjects with NYHA class III or IV HF, EF $\leq$35%, and a QRS duration of $<$130 ms were randomized to CRT or no CRT. Dyssynchrony was assessed by M-mode and TDI parameters. At 6 months, the two groups showed no difference in the endpoint of increase in peak oxygen consumption of at least 1.0 mL/kg of body weight/min. While these two studies showed no dyssynchrony parameter to be predictive of CRT, this comes in contrast to a myriad of smaller studies, which seemed to show some promise. This in part may be due to variability in study designs, weak and questionable endpoints, and in the methods used to obtain the data in these trials as well as variability and poor standardization among readers. There are currently trials (i.e. EchoCRT) underway to address these issues in patients with narrow QRS.[14]

Newer echocardiographic techniques using speckle tracking to measure radial strain seem to be evolving as better predictors of response. To date, these have been tested only in a non-randomized fashion in smaller studies.[15] Speckle tracking takes an advantage of interference in ultrasound beams which creates speckles in the 2D echo images (*Figure 3*). Software-assisted automatic tracking of changes in the distance between individual speckles throughout the cardiac cycle enables the direct measurement of strain. Strain is the change in length divided by the original length and can be measured along the longitudinal, circumferential, and radial axes. Also, of late, real-time 3D ultrasound, which allows for concurrent imaging of all the cardiac segments in a cardiac cycle, with new segmental wall volume methods may provide a enhanced appreciation of the extent of cardiac dyssynchrony during the same cardiac cycle.

Other techniques such as cardiac magnetic resonance (MR) and computed tomography (CT) offer the possibility of integrating measurements of dyssynchrony (*Figure 4*) with the presence of scar and coronary venous anatomy for LV lead placement. Small-scale studies have shown promising results. There remain no large-scale multicentre trials assessing these techniques.

Landmark cardiac resynchronization therapy trials

Severe heart failure

Several thousand patients with severe HF (NYHA classes III and IV) have now been studied via randomized controlled clinical trials, with an undisputed proof that CRT improves clinical outcome. Four trials which examined patients with moderate-to-severe HF with manifest conduction defects (i.e. wide QRS $\geq$120 ms) and a low LVEF ($\leq$35%) which helped solidify the role of CRT in this patient population are briefly discussed.

The MUSTIC study was among one of the first studies to examine the impact of CRT in 67 patients with severe HF, normal sinus rhythm, and a QRS duration of $>$150 ms. It was a single-blind randomized controlled cross-over study comparing the responses of patients to a period of inactive pacing with active pacing, of 3 months each. In the patients who completed both phases of the study, atrio-biventricular pacing significantly improved exercise tolerance, quality of life, and reduced hospitalizations for HF.[16] Subsequently, the Multicenter Insync Randomized Clinical Evaluation (MIRACLE) Trial randomized 453 patients with NYHA classes III and IV to CRT with optimal pharmacological therapy vs. optimal pharmacological therapy alone.[1] The other inclusion criteria were an LVEF of $\leq$35% and a QRS of $\geq$130 ms. A significant improvement in symptomatic (NYHA class and quality-of-life score) and functional improvement (6 min walk distance) was observed. These improvements were accompanied by enhanced ventricular remodelling and a 40% risk

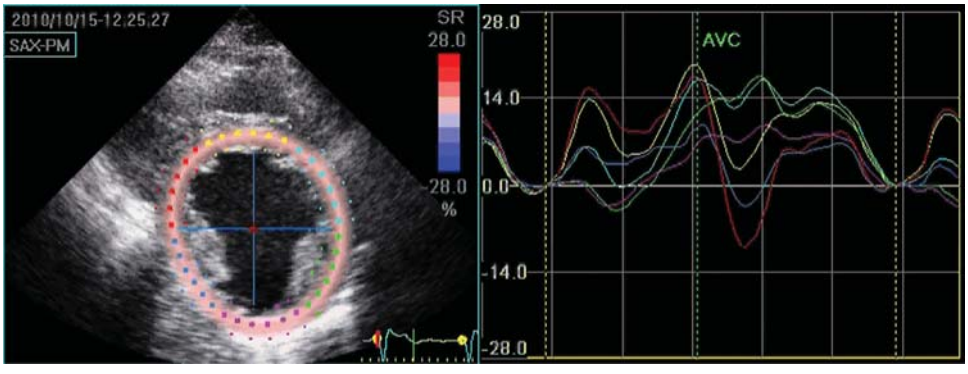

Figure 3 Speckle-tracking strain imaging. On the left panel two-dimensional strain images are shown. The right panel shows the segmental time–strain curves for the left ventricle. The time differences in the peak systolic strain between segments can be assessed.

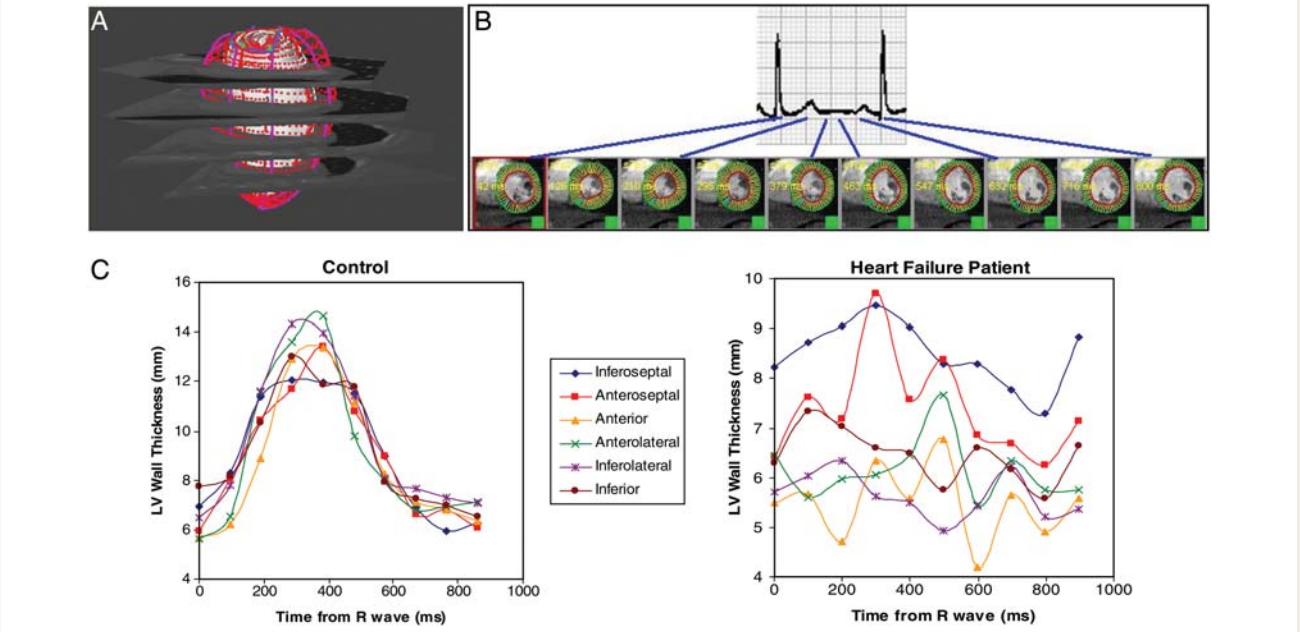

Figure 4 Computed tomography and mechanical dyssynchrony. The figure shows a computed tomographic image for sectioning the heart for mechanical dyssynchrony. Time-to-peak-thickness plots for the different segments shown for the normal and heart failure patients. Marked increase in mechanical dyssynchrony seen in the heart failure patient.[36]

reduction in the composite endpoint of death and HF hospitalization with CRT. Another landmark study, the Cardiac Resynchronization on Morbidity and Mortality in Heart Failure (CARE-HF), in 813 NYHA III and IV patients showed the superiority of CRT over optimal medical management.[3] There was a 37% relative risk reduction in the composite endpoint of hospitalization for a cardiovascular event and overall mortality. Interestingly, the inclusion criteria for this study was a little more stringent, and besides an LVEF of $<35\%$, it required patients to have a wider QRS, i.e. a width of ≥ 150 ms or a QRS of 120–149 ms with the additional presence of echocardiography-defined mechanical dyssynchrony. The Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial was the largest study conducted in this subgroup of HF patients.[2] A total of 1520 patients with NYHA III or IV, LVEF $<35\%$, and QRS >120 ms were randomized to optimal medical therapy (OPT) alone vs. biventricular pacing (CRT-P) + OPT or biventricular pacing with defibrillator (CRT-D) + OPT. CRT-P and CRT-D were shown to significantly reduce hospitalization for HF, with an additional mortality benefit in the CRT-D arm. The trial was, however, not designed and powered to compare CRT-P vs. CRT-D, thereby leaving the crucial question regarding the choice of the appropriate kind of device unanswered.

Mild-to-moderate heart failure

Early investigative work from the Cardiac Resynchronization Therapy for the Treatment of Heart Failure in Patients with Intraventricular Conduction Delay and Malignant Ventricular Tachyarrhythmias (CONTAK-CD) and Effects of Cardiac Resynchronization on Disease Progression in Patients with Left Ventricular Systolic Dysfunction (MIRACLE ICD-II) along with a substudy form CARE-HF showed that CRT may extend its benefits to the less severe HF patient groups.[17–19] Evidence of favourable reverse remodelling was observed in both studies in patient subgroups with NYHA class II symptom class. These hypothesis-generating results were subsequently tested in the REVERSE-HF[5], MADIT-CRT,[4] and RAFT study[20] (*Figure 5*).

The REVERSE-HF study examined 610 patients with an LVEF of $<40\%$, a QRS duration of ≥ 120, and NYHA classes I and II HF, randomized to CRT on or off. In this study, there were geographical differences in the extent of follow-up with patients in Europe being followed up for 2 years, as opposed to those in North America for a year. The primary endpoint in this study was the percentage of patients that worsened clinical composite score (which included an HF hospitalization, a cross-over to the other arm of the study or worsening of their NYHA class, QOL score). The prespecified secondary endpoint was the change in the LVESV. At the 12-month mark, there was no significant difference in the primary endpoint (proportion of patients with worsened outcome, although significant reduction in the LVESV was observed in the CRT-on group. At the 24-month mark in the European cohort, 19% of the CRT-on group vs. 34% of the CRT-off group had a worsened clinical composite response ($P = 0.01$). A striking reduction in the LVESV was observed in the CRT-on group (27.5 ± 31.8 mL/m^2) vs. 2.7 ± 25.8 mL/m^2 in the CRT-off group.

The MADIT-CRT trial enrolled 1820 patients over 110 centres in Europe and North America, all of whom were followed up for a mean of 2.4 years. Subjects were required to have an LVEF of $<30\%$ and a QRS duration of >130 ms and NYHA class I or II HF status. Patients were randomized to either an implantable

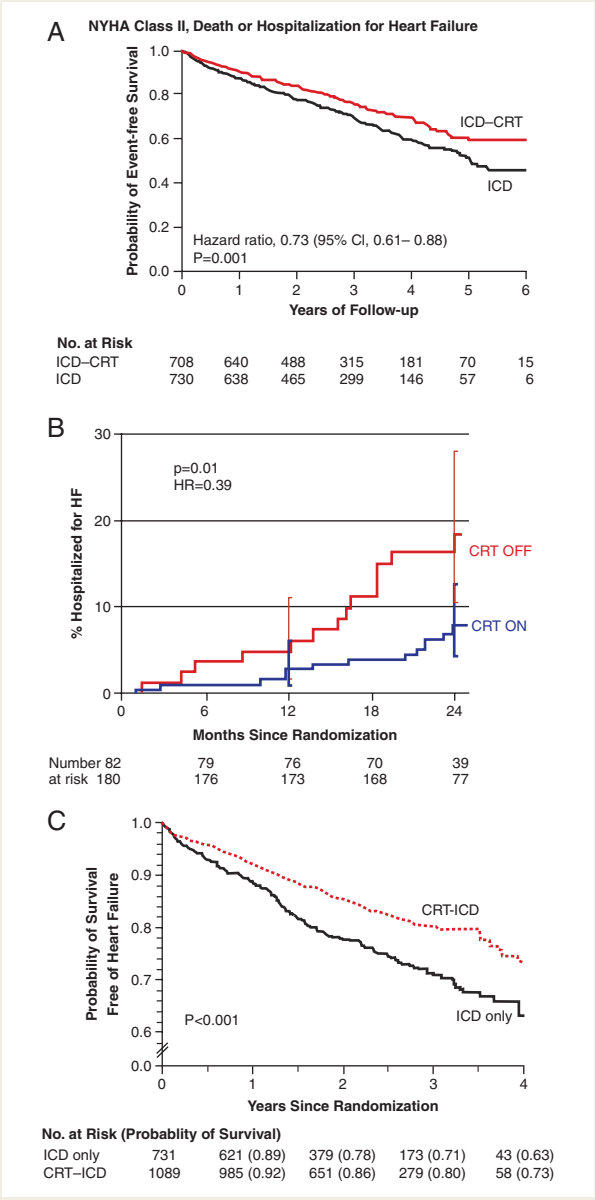

Figure 5 Impact of CRT-D in the mildly symptomatic. (*A*) The data from the RAFT study, depicting the benefit of CRT-D, via reduced mortality and heart failure hospitalization in the patients with New York Heart Association class II. (*B*) The impact of CRT-on in reducing the hospitalizations for heart failure in the REVERSE-HF study and (*C*) the improved survival free of heart failure hospitalization in the MADIT-CRT population.

cardioverter defibrillator (ICD) or a CRT-D device. Nearly two-thirds of the MADIT-CRT population had a QRS of >150 ms and 80% of the patients were classified as NYHA II. Significant differences were observed, with 17.2% of the patients in the CRT-D vs. 25.3% of the ICD-only group experiencing a combined endpoint of death and HF hospitalization ($P < 0.001$). Reverse remodelling was observed to track clinical outcome, with the LVESV decreasing by 57 mL in the CRT-D arm vs. 18 mL in the ICD-only arm ($P < 0.001$). There was a 41% reduction in risk for hospitalization for HF in the MADIT-CRT group, as opposed to 53% reduction in time to first hospitalization for HF in the REVERSE study. Interestingly, women had a reduced incidence of HF hospitalization and total mortality with enhanced reverse remodelling in comparison to men.[21]

The more recently published RAFT trial studied 1798 patients with NYHA classes II and III HF for a 40-month period. The primary outcome of death and/or HF hospitalization occurred in 33.2% of the subgroup of patients with CRT-Ds vs. 40.3% in the ICD group. When substratified by severity of HF, a 27% relative risk reduction in the primary endpoint was observed in the NYHA class II group of patients. Despite the overall benefit of CRT, importantly, an increased incidence of early adverse events was noted in this group. Interestingly, CRT had an independent beneficial impact on both mortality and HF hospitalization in the NYHA class II subgroup.[20] It is noteworthy that in all the three aforementioned studies, an enhanced response to biventricular pacing was observed in patients with a wider QRS (>150 ms) and in those with an LBBB morphology.

Maximizing response to resynchronization therapy

Notwithstanding these obvious benefits, there continue to be more than a few unsettled questions, with the most central one being that up to one-third of patients treated with CRT do not derive any noticeable gain. On account of the high prevalence, morbidity, and mortality from CHF and the considerable cost to society both from CHF as an ailment and from CRT as a remedy, one cannot underestimate the significance of maximizing the response of all patients to CRT. Selecting the right patient and understanding inter-patient differences can predict variability in response; using patient-specific approaches to implant the LV lead, with careful device programming and post-implant follow-up, can enhance the successful delivery and response to CRT.

QRS morphology, electrical activation, and beyond

After meeting the criteria of a compromised LV function and OPT, patient selection is still driven by the presence of a wide QRS on the surface EKG. Ascribing the QRS duration as the 'holy grail' for patient selection and prediction of response seems over-simplistic. The value of the surface QRS signal is further reduced by the fact that there are patients with a wide QRS duration who have minimal mechanical dyssynchrony while there are those with a narrow QRS and significant mechanical dyssynchrony.[22] Additionally, an extra large QRS duration may be reflective of a very advanced cardiomyopathy, where the very best CRT option may not reverse the natural process of the disease. Other approaches examining the 'baseline' and 'CRT-induced changes' in the QRS axis, morphology, and duration from the surface EKG have not been able to forecast the electrical activation pattern of the ventricles, but may have some ability to predict response.[23,24]

A recent work has suggested that there may be considerable variability in the clinical response between patients with LBBB

and non-LBBB morphology. Typically, LBBB is linked with an electrical activation sequence that courses the apex with delayed activation of the lateral and posterolateral portion of the LV.[10] Since this electrical activity spread is accompanied by delayed mechanical activation in the same territory, targeting the lateral wall for LV pacing seems intuitive. Notably, even in the classic LBBB, there remains a high level of heterogeneity in the LV activation pattern, accompanied by a wide variance in the line of functional block. A recent work has suggested that within patients with non-LBBB morphology, a non-specific intraventricular conduction defect subset has a poorer outcome, while those with right bundle branch block (RBBB) fare the worst.[25–27] Right bundle branch block patients may not do as well as the LBBB patient since these patients may not have a dyssynchrony pattern suitable for CRT.[28] Moreover, patients with an RBBB usually have concomitant RV dysfunction, elevated pulmonary artery pressures, and more extensive conduction disease. Although only a quarter of the patients with RBBB may have LV conduction delays comparable to LBBB, nearly 50% have some delay, which may be amenable to resynchronization.[29] The reduced response to CRT in the non-LBBB patient group can be explained by the current lack of change in the lead implantation approach, despite the altered depolarization wavefront characteristics in this group. In the RBBB patient, it is uncertain whether an LV lead is really mandatory to synchronize the heart or an adequately timed pacing impulse from an RV lead may be adequate.

Beyond the QRS duration, there are several other clinical determinants that may impact ventricular remodelling and clinical outcome. It is important to recognize that the presence of RV dysfunction, pulmonary hypertension, high scar burden, and markedly enlarged hearts could all impact clinical response to CRT.[30,31] Additionally, co-existent co-morbidities such as end-stage renal disease, anaemia, severe non-revascularizable coronary artery disease, etc. can influence the response to CRT.[32] Although most studies have shown that patients with both ischaemic and non-ischaemic aetiology of their cardiomyopathy benefit from CRT, a trend towards greater response has been observed in the non-ischemic subset. [4,33,34]

Imaging to enhance patient-specific approaches

Imaging is an integral part of the care of the CRT patient. Imaging is needed in all three phases, i.e. pre-procedurally (for patient selection and planning for the implant procedure), intra-procedurally (device implantation), and post-procedurally (follow-up and optimization). Unfortunately, no single imaging modality can transcend all these three aspects of care delivered. Since most of the imaging modalities provide complementary information regarding cardiac structure (e.g. fluoroscopy and CT for coronary venous anatomy) and function (e.g. echocardiography for mechanical dyssynchrony), combining some of these technologies may help facilitate patient selection and procedural planning.[35] Pre-procedural evaluation of mechanical dyssynchrony and intra-procedural integration with venous mapping may be a useful strategy (*Figure 6*), but still needs to be made more practical and robust, and tested prospectively. Conceptually, targeted pacing sounds very appealing since data from small retrospective studies have shown that pacing over the site with maximal discordance and avoiding a region of scar may result in a better outcome. Although echocardiography would seem a natural fit, the use of intra-procedural echo to demonstrate the most delayed segment to guide LV lead placement is cumbersome and technically challenging.

Lone imaging modalities like CT and MR imaging (MRI) have the capability to provide both anatomical and functional information, thereby obviating the requirement for image integration approaches.[36] Multidetector CT can provide important information pertinent to the coronary venous anatomy, LV contractile function, and mechanical dyssynchrony, as well as integrated information regarding the relation of the venous branch with the segment of dyssynchrony and/or scar.[18,33] Magnetic resonance imaging is enthusiastically being researched in its ability to more accurately compute dyssynchrony and better select patients.[37] At present, an effort at the MRI level is also focused on the development of novel methods to characterize myocardial fibre architecture and ultrastructure, as well as 3D imaging of myocardial strain. Magnetic resonance imaging, however, remains a logistically exigent proposition in this ailing patient population, many of whom may have pre-existing implanted devices.

Pacing strategies: can we do better?

Biventricular pacing improves LV synchrony via stimulation of the late-activated regions of the LV. The conventional approach to LV lead placement is transvenous, with the lead finally positioned in one of the tributaries of the coronary sinus (CS). Once the vascular access is obtained, the CS is cannulated with a guiding sheath and the pacing lead is advanced through this to a second- or third-order branch of the CS. There is still controversy regarding the best lead positioning strategy and the choice between an optimal anatomical position, targeting either the segment with maximal mechanical dyssynchrony or a region with maximal electrical delay is still up for debate. The current trends continue to remain simplistic and indicate that the LV lead be placed at an optimal anatomic pacing site (usually defined as the lateral and posterolateral LV wall).[38] However, the lack of a favourable clinical response in nearly a third of the patients receiving CRT suggests limitations in this approach to pacing site selection. The complex interaction between the unpredictable LV activation pattern, the often random selection of the final pacing site (dictated by the presence of a suitable venous branch), and RV pacing-induced shifts in the electrical and mechanical activation pattern of the LV could be a potential explanation for the high percentage of non-responders to CRT (even in those with anatomically optimal LV lead positions). Little is known about the segmental impact of LV lead location within select substrates. A recent work has shown that apical LV lead placement is associated with worse CRT outcomes and preferential positioning of LV leads in the basal/mid-ventricle segments may improve outcomes.[39] These results were recently substantiated in a substudy analysis of the MADIT-CRT study.[40]

Small retrospective studies have shown that pacing over the site with maximal dyssynchrony may enhance reverse remodelling and consequently improve clinical outcomes. In all of these studies, the assessment of the lead–segment relation was a retrospective

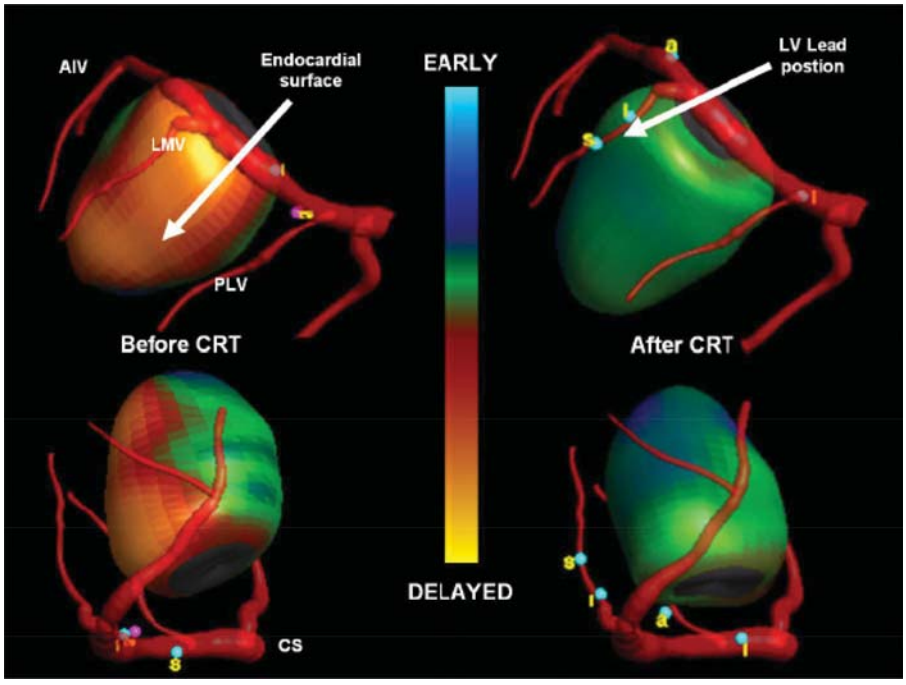

Figure 6 Image integration of the coronary venous anatomy with the segment of mechanical dyssynchrony. The image shows the integrated image of the reconstructed coronary veins and the mechanical dyssynchrony pattern using tissue Doppler imaging with three-dimensional echocardiography. There is a complete change in the dyssynchrony pattern (reduced) after cardiac resynchronization therapy with the left ventricular lead located along the lateral wall, mid-ventricular position (adapted from Tournoux *et al.*[35]).

assumption without true image integration.[41] This approach currently is also limited by the constraints of the venous anatomy. Since CRT is a form of electrical therapy for disorderly electrical activation of the heart, it makes sense to attempt to target the region with the maximal electrical delay.[38] More than a few invasive and non-invasive imaging methods have been proposed to identify the region of the LV with the latest electrical activation. Although 3D non-contact LV endocardial mapping provides exact characterization of the LV activation sequence, it remains impractical to perform this at the time of LV lead placement. A more practical strategy is the intra-procedural use of intracardiac electrograms to measure the LV lead electrical delay (LVLED) to help individualize lead placement. The electrical delay is calculated as the time between the onset of the QRS on the surface ECG and the sensed signal on the LV lead. This delay is corrected for the baseline QRS (recorded simultaneously) by expressing it as a percentage of the baseline QRS duration.[42] Pacing the heart in regions with a greater LVLED has been shown to be associated with improved acute haemodynamic response and clinical outcome. A good venous angiogram is an important part of the implantation procedure, as a detailed venous map helps delineate the different options available. Coupled with improving technology (i.e. smaller leads and multiple electrodes) will enable the implanting physician to target specific 'non-scarred' regions, in either optimal anatomical locations or within segments with marked electrical or mechanical delay. Recent efforts to electrically map the venous system for scar and extent of electrical delay can be performed using newer electro-anatomical imaging methods (*Figure 7*).

Although the location of the RV pacing lead is always relegated to a second-order status, it is noteworthy that this can have an effect on the LV depolarization wavefront and consequently on resynchronization. A previous work has demonstrated that shifting the RV pacing lead can change the LV activation sequence as well as the mechanics of the LV.[43] There is some evidence to suggest that the RV–LV relation can in turn affect clinical outcome. However, based on variability of the substrate, LV lead location, LV size, and the presence and absence of scar, it is quite likely that one uniform position of the RV lead across the board is unlikely to have the same effect. In fact, there is a dire need to develop patient-specific approaches, which need to be evaluated prospectively.

Given the limitations of the conventional transvenous route, several alternative pacing approaches have been proposed. Newer targeted approaches via the endocardial and epicardial approach have the potential to change the playing field.[44,45] Endocardial biventricular pacing has shown promising results with superior clinical and LV haemodynamic improvements when compared with epicardial biventricular pacing.[46] Endocardial pacing may provide a more physiological electrical activation since electrical activation originates in the endocardium and spreads towards the epicardium.[47] Several techniques have been proposed, namely transaortic, transseptal via the interatrial or interventricular septum, and transapical. Transseptal approaches from the shoulder may pave the way to integrate the endocardial LV lead implantation approach with the conventional pectoral device implant (*Figure 8*). Recent studies reported that an individually based approach with

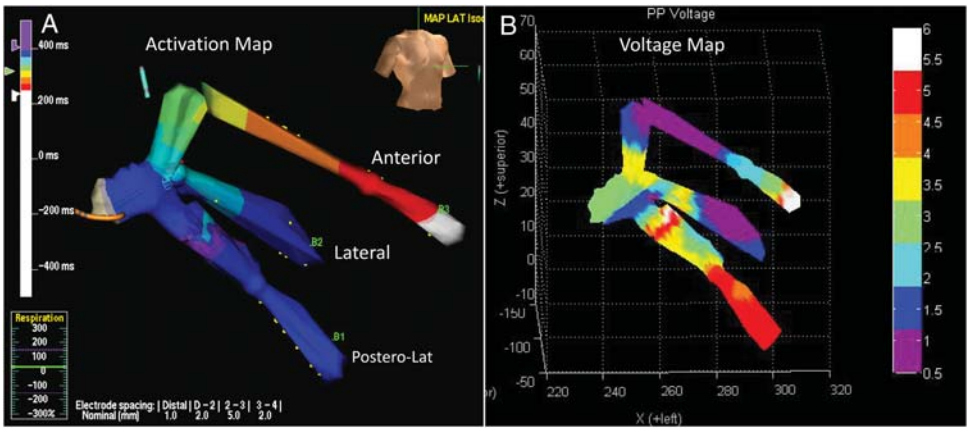

Figure 7 Electrical activation and voltage mapping within the coronary sinus. The figure shows an activation map delineating the extent of delay within the three branches of the coronary sinus (using the NaVx system). The most delayed activation can be seen in the lateral and posterolateral branches. Also, voltage mapping shows the presence of scar in the posterolateral segment, suggesting that the best location for the left ventricular lead is in the lateral mid-ventricular region (adapted from Ryu *et al.*[58]).

systematic testing revealed a variety of optimal LV pacing locations that were quite different from the conventional CS pacing, lateral wall pacing, and the echo-guided approaches. This study showed that when it comes to optimizing the lead location, there is considerable inter-individual variability.[42] This research provided evidence that the best LV pacing site is not only specific to the individual, but also that it is difficult to define a priori. However, several safety issues such as thrombo-embolism or infection of the endocardial pacing lead requiring extraction will need to be contended with.[48] A recent preliminary work has also shown that multisite ventricular stimulation using two separate LV leads positioned in the coronary venous system may improve clinical and echocardiographic outcomes.[49] Further studies are, however, warranted to confirm the superiority and safety of either multisite or endocardial pacing over conventional strategies.

In up to 8–10% of the patients undergoing biventricular pacemaker implantation, LV lead placement is not possible for a variety of reasons, namely inability to cannulate the CS, absence of suitable branches, lack of lead stability, phrenic nerve capture, etc. Surgical LV epicardial lead placement is an option in these patients. Several surgical techniques have been proposed and could include left anterior or lateral mini-thoracotomy, video-assisted thoracoscopy approach, and robotically enhanced systems.[44] Notably, newer non-surgical percutaneous strategies from the sub-xyphoid approach for the implanting physician are being developed. The most pertinent issues to this approach that still need to be addressed are lead fixation strategies as well as mechanisms to ensure that the epicardial lead does not inadvertently lacerate or become adherent to the coronary arterial tree.

Post-implant care: maximizing the patient–doctor–device potential

Contemporary post-device implant care is lacking on many fronts, namely: optimization of the AV and VV intervals, consideration of device diagnostic information, utilization of such data to risk stratify

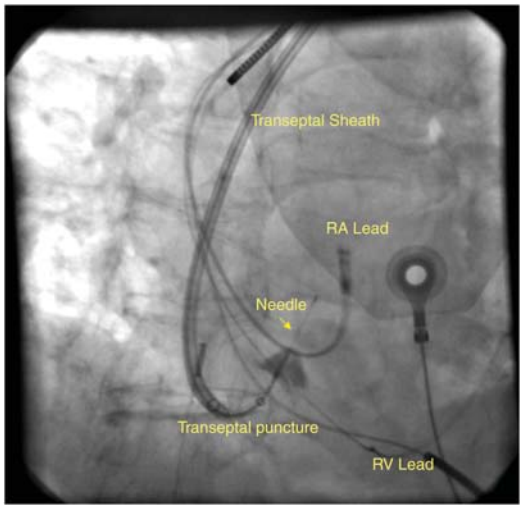

Figure 8 Shoulder approach for transseptal endocardial left ventricular lead placement. The figure shows a transseptal puncture from the shoulder with the right atrial and right ventricular lead in place.

patients as well as titrate medications, and more importantly, early identification and treatment of non-responders.

There are considerable data to suggest that adjusting and optimizing the AV interval can result in haemodynamic benefits; however, there is a paucity of information on the impact of this optimization on the electrical activation pattern. The highest improvement in systolic function is achieved with a short AV interval that allows a complete capture of the ventricles by the two pacing-induced activation wavefronts.[50] The exact value of this AV delay that improves synchrony is variable, being patient-specific. Recently, Mullens *et al.*[32] showed that a substantial

percentage of non-responders to biventricular pacing may actually benefit from AV interval optimization. Whether AV optimization is necessary for every patient at the time of their device implantation is controversial, although it does seems intuitive that patients would need these intervals optimized due to the large extent of variability in the position of the atrial, RV, and LV lead, in conjunction with significant inter-patient differences in substrate and scar distribution. So far, the jury is still out, even though the FREEDOM and SMART-AV study suggested that 'out of the box' settings may work just fine.[51,52] Both studies had significant limitations in their design, patient population evaluated, pre-study assumptions, and power calculations.

Another factor that influences ventricular activation during biventricular pacing is the interventricular (VV) timing. The modern CRT devices have the possibility of programming the VV pacing interval, allowing LV–RV simultaneous or sequential pacing with different degrees of LV or RV pre-excitation. These adjustments together with AV interval adjustments can produce a multitude of patterns of ventricular depolarization by offering, in patients with ventricular conduction defects and intact AV conduction, a certain degree of control over the three fronts of activation originating from the right bundle branch, the RV, and the LV pacing leads. Although in most patients, simultaneous RV–LV pacing produces good haemodynamic results, pre-exciting the LV before RV pacing seems to further optimize synchrony and increase LV systolic function in a subset of patients.[53] Importantly, other randomized studies have not shown any significant clinical benefit from programming the VV timings.[54,55]

Cardiac resynchronization therapy devices record and provide detailed information pertinent to patient activity, heart rate, autonomic activity, and transthoracic impedance; and in the near future, they will also provide real-time haemodynamic data.[56,57] The recent advent of remote monitoring of these devices has enabled the real-time automatic transmission of ambulatory information regarding the heart rate, physical activity, development of incipient pulmonary oedema (transthoracic impedance measure), etc. via the Internet. Also, ongoing work to enhance sensor technology has enabled over-the-web transmission of other important parameters such as blood pressure, weight, oxygen saturations, etc. Web-based monitoring of these patients and their devices provides the option for the different subspecialists to share patient data and provide a more personalized form of medicine. Sensor strategies will continue to evolve and in addition to facilitating risk stratification and predicting risk of acute decompensation will enable early, automated therapeutic interventions and improve clinical outcomes.

A multidisciplinary approach in treating and following these patients seems to be the wave of the future. Most often, non-responsive patients usually come to attention via an HF exacerbation or a hospitalization, and one of the goals of an integrated multidisciplinary approach is to detect problems early, with proactive modification of the drug regimen or device settings to prevent acute disease decompensation. Having all the disciplines (electrophysiology and HF and imaging subspecialists) work together can facilitate better patient selection, CRT device optimization, and careful titration of medical therapy in the post-implantation period. Despite the perception that a multispeciality model would translate into better patient care, the impact of such integrated services still needs to be prospectively assessed.

Conclusion

Biventricular pacing is now recognized as a safe and efficient therapeutic strategy for medically refractory CHF. Implantable CRT devices via synchronized pacing from the RV and LV can enhance the contractility of the failing heart and thereby alter the natural history of the disease process. Although biventricular pacing has had a large impact on the field of HF, its complete potential has not yet been realized. Over the next few years, our understanding of ventricular mechanical dyssynchrony along with substrate- and pacing site-specific response will improve, enabling wider applicability of innovative forms of pacing of the ventricle(s) in the narrow and wide QRS population of HF patients. A greater uniformity in defining response to CRT and early identification of and treatment of non-responders will improve its overall applicability and consequently its cost-effectiveness.

Conflict of interest: D.G. received Consultancy fees from Medtronic, St Jude Medical, Biotronik and J.S. received Research grants from St. Jude Medical, Medtronic Inc., Boston Scientific Corp., and Biotronik. He is a Advisory Board/Steering Committee/Consultant in Boston Scientific Corp., St. Jude Medical, Medtronic, CardioInsight Inc., Thoratec Inc., and Biosense Webster. He also received Honoraria/Speaker fees from Medtronic Inc., Biotronik, Guidant Corp., St. Jude Medical and Sorin Group.

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