Biophysical Modeling to Determine the Optimization of Left Ventricular Pacing Site and AV/VV Delays in the Acute and Chronic Phase of Cardiac Resynchronization Therapy

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Device Optimization for Acute and Chronic CRT. Background: Cardiac anatomy and function adapt in response to chronic cardiac resynchronization therapy (CRT). The effects of these changes on the optimal left ventricle (LV) lead location and timing delay settings have yet to be fully explored.

Objective: To predict the effects of chronic CRT on the optimal LV lead location and device timing settings over time.

Methods: Biophysical computational cardiac models were generated for 3 patients, immediately post-implant (ACUTE) and after at least 6 months of CRT (CHRONIC). Optimal LV pacing area and device settings were predicted by pacing the ACUTE and CHRONIC models across the LV epicardium (49 sites each) with a range of 9 pacing settings and simulating the acute hemodynamic response (AHR) of the heart.

Results: There were statistically significant differences between the distribution of the AHR in the ACUTE and CHRONIC models (P < 0.0005 in all cases). The site delivering the maximal AHR shifted location between the ACUTE and CHRONIC models but provided a negligible improvement (<2%). The majority of the acute optimal LV pacing regions (76–100%) and device settings (76–91%) remained optimal chronically.

Conclusion: Optimization of the LV pacing location and device settings were important at the time of implant, with a reduced benefit over time, where the majority of the acute optimal LV pacing region and device settings remained optimal with chronic CRT. (J Cardiovasc Electrophysiol, Vol. 28, pp. 208-215, February 2017)

atrioventricular delay, cardiac resynchronization therapy, computer modeling/simulations, interventricular delay, left bundle branch block, left ventricular lead placement

Introduction

Cardiac resynchronization therapy (CRT) is an effective treatment for drug refractory patients with dysynchronous heart failure; however, 30% of patients fulfilling current CRT implant criteria do not respond.1 CRT nonresponse is multifactorial and reflects underlying patient substrate.

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The optimal AV/VVD settings and LV stimulation site have significant interindividual variation. This interindividual variability may be compounded by significant interindividual variation within a single patient over time due to changes in the cardiac anatomy and function caused by sustained CRT. Due to dynamic changes in cardiac physiology and anatomy, whether it be positive (in responders) or negative (in nonresponders), the optimal pacing location and device timings may change dynamically. Optimizing pacing location and timings as the heart remodels over time may therefore offer a strategy for maximizing CRT response.\textsuperscript{13,14} Dynamically optimizing timing delays during the course of CRT treatment remains controversial, with some studies showing improvement,\textsuperscript{15,16} while others finding no improvements in clinical outcome with optimization after 3–6 months of CRT.\textsuperscript{7,17} Recent advances in multisite LV stimulation from multipolar leads in a single vein or multivein pacing now offer the potential to noninvasively and dynamically optimize both the timing and location of pacing following device implantation to maximize patient response.\textsuperscript{18,19} However, determining the best way to alter the pacing location and device timings remains a significant challenge.

Biophysical models of a patient’s heart provide a framework for capturing patient physiology and pathology. Using models, the functional response of the heart can be simulated and thereby predict the optimal LV pacing location and the optimal AV/VVD timings. Modeling can be performed both to reflect the acute setting at implant and in the chronic setting following implantation after the heart has undergone LV reverse remodeling, with CRT associated changes in the geometry, electrophysiology,\textsuperscript{20,21} loading conditions, and cardiac mechanics.\textsuperscript{22,23}

We have previously modeled the acute effects of CRT in relation to the optimal LV pacing location and validated these findings with AHR from actual patients.\textsuperscript{24,25} The ability to create biophysical models to predict the optimal pacing site with chronic CRT following remodeling and the effects of AVD and VVD optimization is possible but has not previously been described, as this requires invasive data both at the time of implant and chronically following CRT, which is not routinely acquired in clinical practice. To perform this analysis, we used biophysical modeling in a small number of patients who had undergone invasive electrical and hemodynamic measures both at implant and after at least 6 months following CRT. We hypothesized that as the heart remodeled with chronic CRT, the optimal LV pacing location and AV/VVD combination and the benefits of optimizing these parameters would change over time.

### Methods

Data were acquired from 3 patients with standard indications for CRT, who had undergone both acute and chronic invasive hemodynamic pacing studies as part of dedicated research protocols.\textsuperscript{26} Patients were male, aged 64 ± 6 years with ischemic heart disease, 2-dimensional (2D) ejection fraction was 20 ± 12%, and all patients had left bundle branch block on the surface electrocardiogram (ECG) with a mean QRS duration (QRSd) of 151 ± 25 ms, with New York Heart Association (NYHA) class III symptoms at the time of implant. In all cases, the LV lead was placed in the lateral or postero-lateral branches of the coronary sinus vein using a multipolar LV lead (Quartet St. Jude Medical), while the right ventricle (RV) lead was placed in the RV apex.

For each patient, the CRT clinical response (NYHA class, Minnesota Living with Heart Failure Questionnaire score, and 6-minute walk distance) and the LV reverse remodeling response (percentage change in 2D cardiac echo LV systolic volume [ESV]) were recorded within 3 months prior to implant and after at least 6 months of CRT for the 3 patients, which is summarized in Table 1. In contrast to the improvement in the LV response for cases 1 and 2, an improvement in the clinical measures was reported for cases 2 and 3 (Table 1). In a previous work by Yu et al.,\textsuperscript{27} it was found that though there was a tendency for an improvement in the clinical response to be correlated with long-term survival, this was not statistically significant.\textsuperscript{27} A decrease of ≥10% LV ESV was found to be a strong predictor of the long-term survival and lower heart failure events for patients\textsuperscript{27} and has been used to classify the 3 patient cases into responders (cases 1 and 2) and nonresponders (case 3) in this study.

All patients provided written informed consent for both procedures that were approved by the local research ethics committee. Patients underwent an acute hemodynamic pacing study at the time of CRT implant with a pressure wire (Radi wire, Radi Medical Systems, Uppsala, Sweden) placed into the LV cavity to measure the maximal change in pressure over time (dP/dt\textsubscript{max}) with atrial and biventricular (BiV) pacing. The relative improvement of dP/dt\textsubscript{max} between atrial and BiV pacing was used to calculate the AHR of the patient to pacing (Table 2):

\[
AHR = \frac{\text{max} \frac{dP}{dt}_\text{BiV} - \text{max} \frac{dP}{dt}_\text{atrial}}{\text{max} \frac{dP}{dt}_\text{atrial}}
\]

All patients underwent magnetic resonance imaging (MRI) within 3 months prior to device implantation as a

### Table 1

| Case  | Time   | ESV Change | NYHA Class | HF Score | 6-Minute Walk Distance | Responder? |
|-------|--------|------------|------------|----------|------------------------|------------|
| Case 1| ACUTE  | −67%       | III        | 45       | Unchanged              | Y          |
|       | CHRONIC|            | III        | 55       |                        |            |
| Case 2| ACUTE  | −11%       | III        | 36       | 280 m                  | Y          |
|       | CHRONIC|            | I          | 26       | 370 m                  | Y          |
| Case 3| ACUTE  | +36%       | III        | 64       | 505 m                  | N          |
|       | CHRONIC|            | I          | 4        | 546 m                  |            |
The Clinical Functional Response of the Patient to Baseline (AAI) and Biventricular (DDD-BiV) Pacing was Recorded at Time of Implant (ACUTE) and After at Least 6 Months of Sustained Pacing (CHRONIC)

| Case | Time    | Clinical AHR | Simulated AHR |
|------|---------|--------------|---------------|
| Case 1 | ACUTE  | 34.2%        | 30.1%         |
|       | CHRONIC| 18.9%        | 18.1%         |
| Case 2 | ACUTE  | 17.8%        | 16.1%         |
|       | CHRONIC| 19.2%        | 19.7%         |
| Case 3 | ACUTE  | 0.3%         | 6.1%          |
|       | CHRONIC| 23.0%        | 20.5%         |

The pacing lead locations were mapped onto personalized biophysically based models of the heart for 3 patients. The heart models were used to simulate AAI and DDD-Biv pacing at the ACUTE and CHRONIC points. The acute hemodynamic response (AHR) of the heart to pacing was calculated as the relative change in the maximal change in left ventricular pressure over time between DDD-BiV and AAI pacing. The simulated AHR shows good agreement with the clinical AHR at both the ACUTE and CHRONIC time points.

The fiber architecture was set to vary from apex to base and transmurally using a previously described, rule-based method derived from cadaveric and canine data. The electrical activation of the heart was simulated using the Cardiac Arrhythmia Research Package. The electrical activation of the heart was simulated by pacing the heart at the intrinsic or paced activation sites and fitting the conductivity parameters to the QRSd determined from 12-lead ECG. The geometry of the LV endocardium in the model at the CHRONIC stage was derived from 3D cardiac echo images, while the EnSite system maps the LV endocardial surface separately (Fig. 1). The model simulations of the electrical activation were qualitatively compared against the clinical measurements, as currently there is no standard method for mapping between the LV endocardial

Figure 1. Top row: Clinical measurements of the LV endocardium electrical activation were taken using an ENSITIE balloon catheter for case 2 with (A) atrial pacing and (B) biventricular (BiV) pacing. Middle row: The model parameters were fitted to the electrical activation of the heart with (A) atrial or (B) BiV pacing. (C) The models were then used to simulate the electrical activation of the heart at a range of LV epicardium sites. Bottom row: The simulated activation wave on the LV endocardium was projected onto the 17-segment AHA map for the different scenarios.
surfaces derived from medical images and the Esite system. To quantitatively validate the model, we predicted activation times for additional protocols (RV or LV only pacing) and it was found that the electrical conductivity parameters led to an error between the model predicted and clinical QRSd of 7.1 ± 3.1 ms (see Supplementary Table S2).

The passive and active mechanics parameters and the pressure boundary condition model parameters were fitted based on the pressure-volume curve (PV loop). The volume transients at the ACUTE and CHRONIC time points were acquired from semiautomatic tracking of the LV endocardial surface using TomTec software (www.tomtec.de) with ECG gated cine MR and 3D cardiac echo images, respectively. The volume transients were normalized with regard to the end diastolic volume of the LV. Volume transients were registered to the invasive pressure measurements using simultaneously recorded ECG to generate PV loops at ACUTE and CHRONIC time points, as described previously.

A 3-element Windkessel model was used to represent the systemic blood flow and pressure out of the ventricles. The Windkessel and passive mechanic parameters in each model were fitted to the PV loops for each patient at ACUTE and CHRONIC time points. The active contraction of the heart was represented using a length-dependent model. The active parameters were fitted to both the PV loops and the AHR of the heart with atrial and BiV pacing for the ACUTE and CHRONIC models for the 3 cases (Fig. 2). The function of the heart, as reproduced with the AHR for the ACUTE and CHRONIC studies, shows a good agreement between the measured and modeled AHR (Table 2). Epicardial and endocardial wall motion contours are overlaid in the cine MRI to validate the simulated motion of the heart throughout the modeled phases of the heart cycle as shown in Figure 3.

Quantification of the Size of the Optimal Pacing Region

Pacing sites across the LV free wall were simulated using the models to determine the relative roles of LV pacing location and timing settings on AHR with chronic CRT over time. Actual LV coronary sinus pacing is limited to sites accessible via the coronary branch anatomy, whereas in computer models activation can be simulated at all points across the myocardium. In each ACUTE and CHRONIC model, 49 simulations were run, where the LV pacing site was varied to span the LV epicardium (Fig. 1). Each LV pacing site was activated along with the RV lead pacing site and the intrinsic activation sites, for 9 AV/VVD permutations. The AHR was evaluated across the LV epicardium and interpolated to provide a continuous estimate of AHR at all locations. The optimal pacing region was defined as the area within 70% of the global maximal AHR as proposed previously by Helm et al. and was plotted on the AHA model.

AV/VVD Optimization Simulation

The modeling framework focuses on the ventricles and does not explicitly represent the atria. The AVD is the time delay between when atrial pacing occurs to when the ventricles are paced. The intrinsic electrical activation of the heart from the atria passes through the atrio-ventricular node, where it then travels via the fast conducting Purkinje network to activate the ventricles. The effect of changing AVD was approximated by changing the timing of the intrinsic activation that is set by atrial pacing, and the delay to the ventricle pacing leads. A short AVD where the ventricle leads are activated early is modeled by the absence of any intrinsic activation. A fused AVD is modeled by simultaneous activation of the ventricle leads and intrinsic activation, while a long AVD delay is modeled by ventricle lead activation 40 ms after the intrinsic activation. Three VVDs were modeled with –20, 0, and +20 ms with positive values for early RV pacing. This gives 9 AV/VVD permutations.

The ACUTE and CHRONIC models were paced across the LV free wall (49 sites) with 9 different AV/VVD combinations giving 441 simulations per model (2,646 simulations in total). In contrast to a sequential optimization, where the LV pacing location, AVD, and then VVD timing delays are successively optimized, the exhaustive search method that we have taken calculates the global maximal AHR for each case for the ACUTE and CHRONIC models across all locations and timing combinations.
Figure 3. The motion of the cardiac models during the cardiac cycle was validated against cine MR images. For a high quality, full color version of this figure, please see Journal of Cardiovascular Electrophysiology’s website: www.wileyonlinelibrary.com/journal/jce

Statistics

For each case, ACUTE and CHRONIC models were used to simulate pacing at 9 device settings and 49 locations across the LV free wall to predict the AHR. Values are reported as the mean ± standard deviation. Post-hoc comparisons of the 441 simulations of the AHR between the ACUTE and CHRONIC time points were made using paired t-tests for each patient case. P < 0.05 was considered statistically significant.

Results

Biophysically based models of the heart were generated for the 3 patient cases at both the ACUTE and CHRONIC time points. Simulations of pacing at 49 different sites across the LV epicardium with 9 different AV/VVD device settings were used to predict the AHR of the heart to pacing at the ACUTE and CHRONIC time points.

Difference Between ACUTE and CHRONIC Models

To determine if the optimal LV pacing location and the AV/VVD settings change with chronic CRT, in each patient case, a paired t-test was used to compare the AHR distribution over the LV free wall between the ACUTE and CHRONIC models. The mean ± SD for the AHR across the LV free wall for the 9 timing variations for the ACUTE and CHRONIC models was: case 1: 32.9 ± 18.2% and 18.0 ± 7.7%; case 2: 4.4 ± 5.7% and 5.9 ± 7.9%; and case 3: 2.1 ± 1.7% and 5.7 ± 5.8%, respectively, with P < 0.0005 in all cases.

Figure 4. The area where any 1 of the 9 combinations of AV/VVD timings would give an optimal response is shown (ACUTE: gray with solid outline; CHRONIC: brown with dashed outline). Areas of no overlap between the optimal regions for CHRONIC and ACUTE models are shown as striped. Regions in the CHRONIC models where all 9 of the AV/VVD combinations would give an optimal response are shown as yellow (dotted outline) for cases 1 and 3. There were no such regions in the ACUTE model and the CHRONIC model for case 2. The locations of the multipolar LV lead (blue), RV lead (red), and scar (green) are shown for all cases. The location of the maximal response for any of the 9 AV/VVD timings is shown as stars (ACUTE: gray; CHRONIC: brown). For a high quality, full color version of this figure, please see Journal of Cardiovascular Electrophysiology’s website: www.wileyonlinelibrary.com/journal/jce
Figure 5. The LV free wall was paced and the AHR was simulated at 49 locations with 9 AV/VVD settings in the ACUTE and CHRONIC time points for each case. The optimal LV pacing regions were defined as the LV sites within 70% of the global maximal AHR. The percentages of the 49 sites on the LV free wall that gives an optimal response for pacing with 1–9 of the simulated AV/VVD timing settings for the ACUTE and CHRONIC models are shown for the 3 cases. For a high quality, full color version of this figure, please see Journal of Cardiovascular Electrophysiology’s website: www.wileyonlinelibrary.com/journal/jce

Benefits of LV Lead Location Optimization

Figure 4 shows the optimal area and maximal AHR site for LV pacing for the ACUTE and CHRONIC models. Across all 3 cases, the majority of the optimal region from the ACUTE model remained within the CHRONIC optimal region. In case 2, the optimal pacing region in the ACUTE model laid entirely within that of the CHRONIC model. For cases 1 and 3, the optimal pacing area shifted, predicting that if the pacing lead was within the ACUTE optimal region, then it had an 82% and 76% probability, respectively, of remaining optimal after chronic CRT. The best single site for pacing the LV shifted in all cases after sustained pacing (Fig. 4); however, altering the pacing site from the maximal ACUTE to the maximal CHRONIC pacing location only improved the AHR by <2% for all cases (case 1: 0.4%, case 2: 1.3%, and case 3: 1.2%).

Benefits of Timing Delay Optimization

Figure 5 shows the percentage of the 49 evaluated pacing locations that achieve an optimal response for different numbers of combinations of AV/VVD timings. In all 3 case studies, the predicted number of AV/VVD/pacing locations that delivered optimal AHR increased between the ACUTE and CHRONIC CRT models (20–26% for case 1; 3–10% for case 2; and 8–18% for case 3). The majority of optimal AV/VVD settings in the ACUTE models are predicted to remain optimal chronically (case 1: 88%, case 2: 91%, and case 3: 76%) at the same LV pacing site.

Discussion

ACUTE and CHRONIC biophysical models were generated for 3 case studies to predict the relative importance of LV lead location and AV/VVD optimization in the acute response of the heart immediately post-implant and after sustained CRT treatment.

Our results are the first to model both acute and chronic response to CRT in humans and show that:

(1) The model replicates measured hemodynamic and electrical indices for both the ACUTE and CHRONIC time points.

(2) Lead optimization and AV/VVD optimization at the time of implant were important in improving acute and chronic response.

(3) The models predicted that the benefits of AV/VVD and lead location optimization decreased over time with sustained pacing, i.e., with chronic CRT, there was less incremental benefit seen with AV/VVD or lead position optimization.

Benefits of Optimizing the LV Lead Location Over Time

Acute optimization of the LV lead location is a recognized strategy for maximizing CRT response. Optimizing the pacing location acutely using multisite pacing has shown improved AHR; however, the ability to dynamically optimize pacing location post-implant with these new lead technologies has yet to be evaluated. At both acute and chronic time points, our models predicted distinct pacing regions that gave optimal AHR that covered most of the LV lateral free wall, consistent with acute animal studies, clinical studies, and clinical guidelines for CRT. Our models predicted that the majority (76–100%) of the ACUTE optimal pacing locations remain optimal in the CHRONIC case. The maximal AHR site shifted for all 3 cases as the heart remodeled (Fig. 4) supporting postimplant lead location optimization; however, the predicted improvement in AHR achieved by moving from the best ACUTE to the best CHRONIC pacing location in the CHRONIC model was small (<2%). The model indicates that it is more important to optimize the LV lead location at the time of implant, that this location is likely to be in the LV lateral wall, and that in the majority of locations this site will remain optimal as the heart remodels.

Benefits of Optimizing the AV/VVD Over Time

Studies have shown the acute benefits of optimizing the AV/VVD and our model simulations also reflected this, where optimizing the AV/VVD settings could improve the AHR (dependent on the default settings) at the ACUTE time point (Fig. 5). The slope and the area under the curve for the ACUTE traces in Figure 5 reflect how beneficial optimizing between the simulated AV/VVD combinations would be. The greater the slope of the curve and the smaller the area under the curve is, the less overlap there is between the optimal areas of LV pacing for any of the 9 simulated combinations.
In the chronic setting, we find that as the heart remodels, the number of timing combinations that deliver an optimal response increases (shown as a rightward shift of all curves in Fig. 5), consistent with previous studies that have not found a consistent benefit of dynamic A/V VD optimization.\(^1\)\(^7\)\(^17\) In addition, our models predicted that an optimal A/V VD/LV pacing site will likely remain optimal after sustained pacing indicating that it is more important to optimize for the A/V VD at the time of implant.

**CRT Nonresponder**

In this study, response/nonresponse was classified based on an improvement of the LV response (≥10% decrease in the LV ESV\(^27\)). Case 3 was classed as a nonresponder based on the LV response deteriorating (LV ESV +36%). This is in keeping with the poor AHR acutely measured (0.3%) and predicted by the model (6.1%). However, after sustained pacing, the measured AHR increased (from 0.3% ACUTE to 23.0% CHRONIC) (Table 2). An increase in the AHR in the nonresponder seems counter-intuitive; however, if we consider that if the LV response of the heart continues to deteriorate for case 3, then there is greater capacity for improvement with BiV pacing. In addition, we have shown that the models predicted that the site of maximal AHR shifts after sustained pacing (Fig. 4). The predicted maximal AHR site in the ACUTE model was further from the LV pacing lead than in the CHRONIC model (ACUTE: 33 mm; CHRONIC model: 15 mm). The improvement in the proximity of the LV pacing lead to the ideal pacing site, in combination with the increased capacity of response to pacing, could contribute to the observed increase of the AHR for this case.

**Limitations**

In this study, we have only used 3 clinical case studies at 2 time points to generate our results; thus, the conclusions drawn need to be taken in this context. The extensive clinical data required to build and validate biophysical models of patient’s hearts limit the expansion of this framework to large groups. We have chosen instead to run an in-depth study for these 3 patients, where 2,646 simulations of different pacing locations and timing delays were run to explore the relative importance of LV lead and A/V VD optimization over time.

The range of AVD and VVD tested was limited to only 3 settings each, giving 9 combinations of device timing settings to be run over 49 different sites per model (441 simulations), to remain computationally tractable. Instead of optimizing for AVD at increments of 20 ms over a wide range of AVD values as performed clinically,\(^9\)\(^15\) we chose to represent 3 scenarios for the AVD: a short AVD, a fused AVD, and a long AVD. The VVD was set to be −20, 0, and 20 ms, as previous work found that the optimal VVD lies between ±20 ms.\(^31\)

The model accounted for scar at the time of implant, but we assumed the location, degree, and properties of the scar at the ACUTE time remained constant in the CHRONIC model. Nor did we account for phrenic nerve stimulation. Changes in either of these conditions at a local pacing site could require the pacing location to be altered post-implant, which could be enabled by multisite pacing lead technologies.

In this study, we optimized the LV pacing location and the A/V VD settings using the AHR as a measure of the function of the heart. However, the link between the AHR and LV reverse remodeling remains controversial, with some studies finding no link,\(^34\) while others have found a positive correlation between AHR and clinical outcome.\(^35\) Other measures of acute improvement such as diastolic parameters and pressure volume loop have also been proposed; however, they have yet to be linked to long-term clinical response.\(^1\)\(^2\)\(^2\)

**Clinical Relevance**

The heart anatomy and physiology dynamically remodels in response to CRT. We have generated biophysical patient-specific models to predict how these changes affect the optimal CRT lead pacing location and device timings. We find that there is diminished benefit in postimplant optimization of the pacing location or timings as the heart reverse remodels with the majority of settings remaining optimal as the heart responds to CRT. This emphasizes the importance of ensuring good lead position and optimized device settings at the time of implant.

**Conclusion**

In this study, patient-specific biophysical models were used as a framework to predict the optimal LV pacing location and the effects of A/V VD optimization immediately post-implant and after at least 6 months of CRT for 3 case studies. The models predict that although the optimal pacing region can shift, the majority of the optimal pacing sites remain in the LV lateral wall. The models predict that optimization of lead position and A/V VD optimization are more beneficial at the time of implant than after sustained CRT pacing.

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Supporting Information

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