Inverse Electrocardiographic Imaging to Assess Electrical Dyssynchrony in Cardiac Resynchronization Therapy Patients

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Abstract

Electrical dyssynchrony is postulated to be one of the main factors contributing to non-response of patients to cardiac resynchronization therapy (CRT). We applied inverse epicardial imaging computed from patient-specific geometry and body-surface potential recordings to assess global and regional electrical dyssynchrony. Patients were imaged pre- and post-device implantation, without and with pacing function (P-OFF and P-ON). The reconstructed maps of activation in the dyssynchronous pre-CRT rhythm agree with published contact mapping activation maps with earliest activation starting on the RV free wall and slowly spreading to the LV in a U-shaped pattern. The new ΔQRSi metric captures global pre-CRT dyssynchrony showing negative values (-0.32±0.10) with minimal variability beats (coefficient of variation 10±3.6%) while post-CRT pacing indicates positive values (0.18±0.11). The imaging method is well-suited to study electrical dyssynchrony and potentially guide CRT lead placement.

1. Introduction

Heart failure is a major public health problem in the United States, with 5 million people affected and an increasing number of hospitalizations and death attributed to this disease [1]. Biventricular (biV) pacing delivered during cardiac resynchronization therapy (CRT) has emerged as a meaningful non-pharmacological therapy for patients with symptomatic heart failure and contractile dyssynchrony. CRT has been shown in a number of larger randomized clinical trials to improve clinical status as well as slow down or reverse left-ventricular (LV) remodelling that occurs as a result of the progression of heart failure in selected patients [2,3,4,5]. However, the non-response rate among patients who receive CRT devices remains high - in the 30-40% range. A number of factors have been hypothesized to contribute to the non-response to the therapy including mechanical dyssynchrony, electrical dyssynchrony, scar location/size and LV pacing lead location. We present non-invasive imaging and analysis methods based on inverse electrocardiographic imaging [6] to evaluate electrical function of the heart with application to assessing patient response to CRT and pre-planning of CRT lead implantation.

2. Methods

2.1. Body surface potential mapping

Electrocardiographic body surface potential mapping (BSPM) records electrocardiograms (ECG) on the torso at multiple locations in order to capture the complete time-varying electrical activity of the heart. Eighteen strips of disposable radiolucent Ag/AgCl surface electrodes were placed in a specific arrangement at 120 torso locations and connected via cables to 128-channel acquisition system (Active Two, BioSemi, Amsterdam, Netherlands) to record body potentials during various electrophysiological conditions (sinus rhythm and device biventricular pacing). The acquisition system provides band-pass filtering, signal amplification, multiplexing and digitization of all channels simultaneously at 2048 Hz with 24-bit resolution. The acquisition system is optically isolated from the subject outputs and connects to a laptop computer running a custom research program (MAPPER, Dalhousie University, Halifax, Canada) for visual display and data storage. The raw data files were recorded for 15 seconds and then stored for subsequent analysis. Custom written MATLAB computational routines were used to process the acquired BSPM data. The data was digitally filtered (low-pass 100 Hz, high-pass 0.25 Hz and notch 60 Hz) in two directions to produce zero-phase shift. Faulty leads due to poor skin-electrode contact, motion artifact or inaccessibility of the torso area were estimated using a least-squares interpolation method. Dynamic beat-averaging was performed to improve signal-to-noise ratio and obtain a high fidelity averaged beat.

2.2. Inverse epicardial imaging procedure

Potential distributions on the epicardial surface of the heart were estimated non-invasively using electrical BSPM measurements. The potential distribution in the conductive torso was modelled using Laplace's equation assuming a homogeneous torso. Subject-specific discretized geometries of the heart's epicardial ventricles and body surface were related with respect to electrical potentials (V_B and V_H) using a linear forward transformation (A) [7] according to (1)

$$V_B = A\, V_H \qquad (1)$$

The inverse problem which reconstructing epicardial potential electrograms (EGM) is ill-posed and small errors in the input BSPM measurements, inevitable in practical settings, generate unbound error in the solution. Inverse epicardial potential (V_H) were calculated using zero order Tikhonov regularization [8] with the regularization parameter (t) determined by the L-curve method [9] according to the minimization problem in (2)

$$\min \{\| A\, V_H - V_B \|^2 + t\, \| V_H \|^2\} \qquad (2)$$

The inverse solution is obtained by selecting the regularization parameter (t) such that a trade-off is achieved between accuracy (residual error in 2) and stability (solution semi-norm). Epicardial potentials at each time instant were computed for the whole duration of the heart beat and displayed on the heart geometry for analysis. Algorithms for computation of the forward transfer matrix and inversion procedure were developed and tested in MATLAB^{TM} computing package. Electrode labeling, heart geometry segmentation and discretization were performed using commercial software (Amira^{TM} 4.1, Mercury Computer Systems, Chelmsford, MA).

2.3. Inverse electrical activation maps and dyssynchrony index ΔQRSi

Activation times were computed from inverse electrograms from the point of steepest downward slope as is conventional in contact unipolar mapping. A 5-point finite difference method was used to estimate first derivatives. In order to characterize global electrical dyssynchrony, the normalized QRS integral (ΔQRSi) metric was developed and tested. ΔQRSi is the inter-ventricular difference between *average* right ventricular (RV) and left ventricular (LV) *regional integral* of the QRS complex over the first one-third of the QRS duration normalized to the range ±1 by the absolute maximum QRS integral according to:

$$\text{Regional QRSi} = \frac{\int_0^{QRSd/3} \Phi(t)\,dt}{\max \int_0^{QRSd/3} \Phi(t)\,dt}$$

$$\Delta\text{QRSi} = \sum_{i \in RV} QRSi - \sum_{i \in LV} QRSi$$

A second electrical dyssynchrony index (Esyn) previously reported by Jia et al. [10] was computed for comparison purposes. Esyn quantifies the inter-ventricular *average activation times* between the RV and LV.

2.4. Patients

Patients were recruited from the Electrophysiology clinic at Johns Hopkins Hospital undergoing CRT implantation. Ethics approval was obtained from the Institutional review board and patients underwent informed consent. BSPM and magnetic resonance (MR) imaging was obtained at two time points: prior to device implantation and 9-months post-implant. During the follow up imaging session, both BSPM and MR imaging were obtained while the pacing function of device was disabled (P-off) and during clinically-optimized biventricular pacing (P-on). Results are represented as mean±standard deviation. Student t-test was used to compare group means at 0.05 level of significance.

3. Results

3.1. Electrical dyssynchrony pre-CRT and inter-beat variability

Figure 1 shows an example of activation times computed from a case with heart failure (HF) and left-bundle branch block (LBBB) on both the three- and two-dimensional displays. The three-dimensional ventricular geometry was mapped to the clinically used two-dimensional bulls-eye plots to facilitate beat-to-beat as well as subject-to-subject comparisons. The activation pattern reconstructed on the epicardial surface is consistent with LBBB conduction starting on the RV free wall and spreading in a "U-shaped" pattern in two directions anteriorly and inferiorly to the LV. The latest region to activate is basal and mid-wall inferior LV wall. The value of the normalized dyssynchrony index (ΔQRSi) for this case is -0.44 indicating inter-ventricular conduction delay (QRS duration of 104 ms).
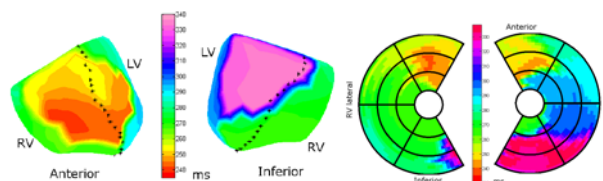

Figure 1. Reconstructed activation times prior to CRT. Left: Earliest activation starts on the RV spreading slowly to the LV. Right: Epicardial activation times projected on 2D bulls-eye plots of the epicardial RV and LV regions (Esyn = -40 ms. ΔQRSi = -0.44).

The activation maps computed from a number of consecutive beats in the same case are shown in Figure 2. The reconstructed epicardial maps show great consistency in the sequence of activation over multiple beats. ΔQRSi and Esyn computed over multiple beats also show minor variability (-0.46±0.027 and -38±3.9 ms, respectively).
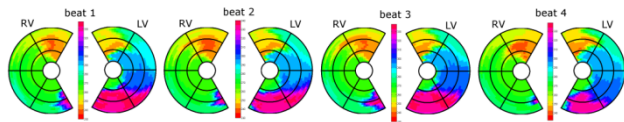

Figure 2. Inter-beat changes in regional activation maps.

The performance of the dyssynchrony (dyssync) metrics ΔQRSi and Esyn with respect to beat-to-beat variation was compared over multiple (>6) beats in 7 patients. In the non-pacing group (pre and pacing off), both metrics indicated large RV to LV conduction delay (negative values) with minimal coefficient of variation (COV taken as standard deviation/mean) as shown in Figure 3. However, in the pacing group, the ΔQRSi shows much less variation as compared to Esyn. This effect can be attributed to abrupt changes that accompany the second device pacing stimulation which sometimes causes the steepest slope criteria of Esyn to incorrectly define the activation time as compared to the smoother property of the integral in ΔQRSi.
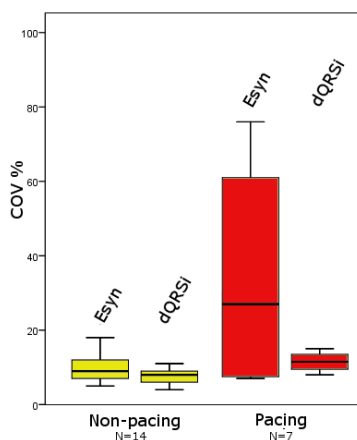

Figure 3. Beat-to-beat average coefficient of variation of the dyssynchrony metrics in the non-pacing (yellow) and pacing (red) groups.

3.2. Follow-up analysis and dyssynchrony metrics

At the 9-month follow up time point, BSPM maps were collected while the pacing function is turned off in a group of 7 patients and inverse activation maps were computed as before. Figure 4 shows an example of the

2D activation maps during the three heart rhythms (native rhythm, pacing off and pacing on) in case 4. The sequence of activation during P-off shows overall similar activation to pre-CRT which could be indicating lack of reverse remodeling. Activation starts on the RV free wall and spreads in a U-shaped pattern to the infero-lateral LV where activation ends. Two lines of slow conduction are seen on the antero-lateral margin and infero-septal groove contributing to the majority of the RV to LV conduction delay in this case. During the pacing on condition, there are two areas of early activation on the apical RV and infero-lateral basal LV corresponding to the biventricular pacing sites. Interestingly, the area of latest LV activation is shifted to the LV anterior apical region which contributes little to blood ejection during contraction.
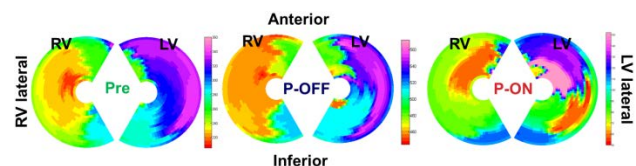

Figure 4. Reconstructed electrical activation during pre-, pacing-off and pacing-on rhythms.

Pooled analysis of the ΔQRSi metric shows negative values for both the pre-CRT (-0.32±0.10) and pacing off (-0.29±0.19) groups. The index for all cases shifts to positive values (0.18±0.11) during pacing indicating earlier and faster electrical activation of the LV. A cut off of 0.05 clearly separates the pacing from the non-pacing groups (p<0.001, see figure 5).
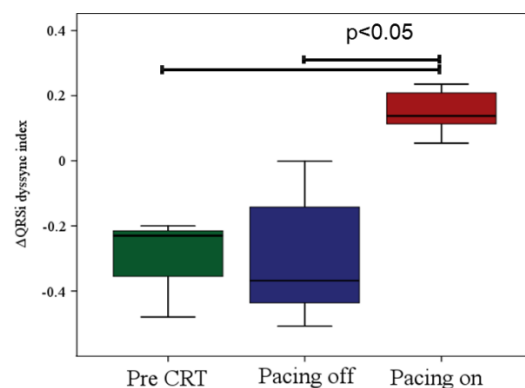

Figure 5. Electrical dyssynchrony index ΔQRSi computed at 2 time points: pre- (green, N=7) and post- implant during pacing off (blue) and pacing on (red, N=7).

4. Discussion

Inverse electrocardiographic imaging provides a useful and unique approach to non-invasively evaluate the

electrical function of the heart in heart failure patients eligible for cardiac resynchronization therapy. The reconstructed regional activation maps capture the abnormal wave conduction due to left-bundle branch block. The sequence of activation in the dyssynchronous heart qualitatively agrees with activation maps in contact mapping of Auricchio et al. [11] with earliest activation starting on the RV free wall and slowly spreading to the LV rather than conducting normally through the Purkinje network to both ventricles simultaneously. Late regions to activate were mainly found on the lateral wall with variation from patient to patient of the region of latest electrical activation. This capability to determine the most delayed region to activate would greatly assist in guiding the placement of the epicardial pacing lead of the CRT device prior to the implantation surgery thereby personalizing the delivery of therapy. The ability to image how pacing modifies the sequence of activation and specifically area of latest activation could be a reasonable way to evaluate optimal pacing location.

The proposed global dyssynchrony index (ΔQRSi) is capable of quantifying the electrical changes that accompany CRT therapy with minimal variation over multiple consecutive beats. It was generally observed that respiration can contribute to 10-20% to the COV of ΔQRSi thus it is highly recommended to obtain all BSPM recordings during breath hold. A clear threshold can be defined to separate the paced from the non-paced rhythms. The performance of the index would still need to be compared to quantitative functional reverse remodeling parameters such as left-ventricular end systolic volume to establish correlation to CRT response.

The rationale behind using the QRS integral stems from the fact that as the depolarization wave breaks through the epicardial wall and starts travelling away, the local electrogram exhibits an early negative (Q-wave) deflection while epicardial regions that activate later exhibit a positive followed by a negative deflection (RS-wave). By taking the integral of regional inverse electrograms over the first one third of the QRS interval, the extent and timing of depolarization is captured such that an early steep Q-wave will indicate earlier and faster activation relative to an RS wave which will have a positive QRS integral. While the point of steepest slope has been commonly used to define the activation time and has been used in this study to plot regional activation maps, it is prone to instability in the mathematical regularization procedure (as shown in figure 3 using COV) hence the choice to develop the QRS integral-based global dyssynchrony metric.

5.   Conclusion

The non-invasive regional imaging method is capable of reconstructing abnormal LBBB conduction morphology and the global dyssynchrony metric can detect significant differences between the native rhythm pre-CRT and the biventricular pacing rhythm post CRT with minimal variation over multiple consecutive beats and thus holds promise to understanding electrical mechanisms of dyssynchrony and guiding LV lead placement.

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