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Body surface activation mapping of electrical dyssynchrony in cardiac resynchronization therapy patients: Potential for optimization☆,☆☆

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ABSTRACT

Background: Electrical synchronization is likely improved by cardiac resynchronization therapy (CRT), but is difficult to quantify with 12-lead ECG. We aimed to quantify changes in electrical synchrony and potential for optimization with CRT using a body-surface activation mapping (BSAM) system.
Methods: Standard deviation of activation times (SDAT) was calculated in 94 patients using BSAM at baseline CRT (CRT_{bl}), native, and different CRT configurations.
Results: SDAT decreased 20% from native to CRT_{bl} ($p < 0.01$) and an additional 26% ($p < 0.01$) at optimal CRT (CRT_{opt}), the minimal SDAT setting. Patients with LBBB and patients with QRS duration ≥150 ms had higher native SDAT and greater decrease with CRT_{bl} ($p < 0.01$); however, the improvement from CRT_{bl} to CRT_{opt} was similar in all four groups (range: 24–28%). CRT_{opt} was achieved with biventricular pacing in 52% and LV-only pacing in 44%. We propose that improved wavefront fusion demonstrated by BSAMs contributed substantially to the improved electrical synchrony.
Conclusion: Optimization potential is similar regardless of pre-CRT QRS morphology or duration. BSAM could possibly improve CRT response by individualizing device programming to minimize electrical dyssynchrony.

Cardiac resynchronization therapy (CRT) improves quality of life, exercise capacity, left ventricular size and function as well as hospitalization rate and mortality in select patients with heart failure (HF) [1,2]. However, minimal or suboptimal response to CRT continues to be a problem, with ~25–30% of patients considered non-responders to therapy [3]. CRT is thought to treat HF by correcting electrical and/or mechanical dyssynchrony. Thus, reasons for non-response to CRT include: 1) lack of native dyssynchrony, or 2) inadequate correction of the underlying dyssynchrony. The only readily clinically available method for measuring electrical dyssynchrony is 12-lead ECG QRS duration (QRS_d), and changes in QRS_d have not correlated well with response to CRT [4]. Numerous studies have focused on pre-CRT patient characteristics that predict response to CRT [4–7]. Other studies have assessed causes of uncorrected dyssynchrony including presence of myocardial scar [8], poor left ventricular (LV) lead location [9], and sub-optimal device programming [10]. However, a major factor hindering further advances in this field is the lack of a practical, sensitive tool for measuring electrical or mechanical dyssynchrony at different time-points (pre-CRT, during implant, post-CRT) and at multiple programmed device settings.

We developed a novel non-invasive body-surface activation mapping (BSAM) technology for generating isochronal activation maps based on 53 body surface electrodes that can be used in the clinical setting to quickly and reproducibly measure electrical dyssynchrony at multiple CRT settings [11]. We have previously demonstrated that improvements in electrical dyssynchrony as measured by this BSAM technique correlate with improved acute hemodynamic response [12] and 6-month LV remodeling response [11]. In the present study, we utilize this technology post-CRT in the outpatient clinic to study the acute impact of different CRT device timings including different atrio-ventricular

Abbreviations: AV, atrio-ventricular; BiV, biventricular; BSAM, body surface activation mapping; CHB, complete heart block; CRT, cardiac resynchronization therapy; EF, ejection fraction; HF, heart failure; IVCD, interventricular conduction delay; LBBB, left bundle branch block; LV, left ventricle; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association; RBBB, right bundle branch block; RV, right ventricle; SDAT, standard deviation of activation times; VV, ventricular-ventricular.

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(AV) and ventricular-ventricular (VV) delays on electrical dyssynchrony with the goal of demonstrating the potential of this approach to individually optimize CRT device programming.

Methods

Patient population

We studied 94 HF patients at least 4 months post-CRT who were clinically stable. All patients had EF ≤ 40%, QRS_d ≥ 120 ms, and were NYHA class II – ambulatory class IV HF on optimal medical therapy prior to CRT. Patients were previously managed per our standard post-CRT protocol which included assessment of AV synchrony early post-CRT using mitral inflow patterns at different AV delays and programming AV delay using the iterative method. Patients with CRT implants after April 2014 (n = 48) also underwent 12-lead ECG-guided CRT optimization with the goal of programming to minimize QRS_d and maximize electrical wavefront fusion [13,14].

This study was approved by an Institutional Review Board and all patients gave informed consent.

12-lead ECG and ECG Belt

Native (CRT off) ECGs were analyzed for rhythm, PR and QRS intervals, and QRS morphology. QRS_d was defined as the widest complex on 12-lead ECG. LBBB, right bundle branch block (RBBB), and interventricular conduction delay (IVCD) were defined using standard definitions as previously described [11]. A 53-electrode ECG belt was used for BSAM. Details of this system have been previously described [11,12]. Briefly, the ECG belt measures body-surface unipolar ECGs and generates activation maps using 17 anterior and 36 posterior electrodes placed on the upper torso. Isochronal maps of electrical activation are created based on body surface activation time at each electrode (time of steepest negative slope of the unipolar QRS complex) as previously described [15]. The earliest activation of any electrode is defined as time zero and activation times at other electrodes are referenced to this time origin. Software then calculates the standard deviation of the 53 individual activation times (SDAT) as a measure of electrical dyssynchrony. Data for electrodes not making contact with the skin were removed from the dyssynchrony calculation and no mathematical interpolation was used.

Study protocol

Device interrogation was performed to evaluate each patient's underlying AV conduction. ECG belt data was first collected at different AV delays with both biventricular and LV-only pacing, beginning with a programmed AV delay 50% of PR interval and increasing in 20 ms increments until ventricular sensing occurred. If patients were in atrial fibrillation or complete heart block AV delays were not evaluated. Next, ECG belt data was acquired at different VV offsets with AV delay at the baseline value. This was most often assessed at VV simultaneous and with LV pre-excitation of 20, 40, and 60 ms, although in some patients (e.g. patients with RBBB) RV pre-excitation of 20 ms was studied. The baseline programmed setting (pacing mode, AV delay, VV offset) was then evaluated with different LV pacing vectors in the patients with quadripolar LV leads. Data obtained pacing from different quadripolar leads was not reported here as many patients did not have quadripolar leads in place. Patients were also studied with RV-only pacing and with CRT programmed off (native condition). If the patient had a Medtronic device with adaptive-CRT algorithm turned on (n = 25), then algorithm-based programmed parameters at the time of study were considered the CRT_{bl} setting. Activation maps were acquired at an average of 9 ± 3 settings in order to determine the optimal setting with the lowest SDAT, called CRT_{opt}.

Statistical analysis

All continuous variables were expressed as mean ± standard deviation, and categorical variables as count (percentage), unless otherwise noted. Comparisons of continuous variables between groups and within groups were performed using unpaired and paired Student's *t*-tests as appropriate. STATA/MP software version 14.2 (StataCorp, College Station, TX) was used for data analysis and a two-sided p-value <0.05 was considered statistically significant.

Results

Patient population

There were 94 patients in the study as described in Table 1. Mean EF was 25.7 ± 7% and QRS_d was 159 ± 23 ms prior to CRT. QRS morphology was LBBB in 62% of patients. RV-paced patients (n = 14) had underlying CHB and were thus 100% RV-paced. Patients were on good medical therapy and were studied 1.9 ± 2.7 years after CRT implant. At CRT_{bl}, 77 (82%) of patients were programmed to BiV pacing and 17 (18%) to LV-only pacing. Mean AV delay was 129 ± 33 ms (range 60–220 ms). Of the 77 patients BiV-paced at baseline, 48 (62%) had simultaneous LV and RV pacing, 26 (34%) had LV pre-excitation (32 ± 14 ms) and 3 (4%) had RV pre-excitation (23 ± 8 ms).

Reproducibility of SDAT and relationship between ΔSDAT and ΔQRS duration

Beat-to-beat reproducibility of SDAT was assessed by comparing 195 paired SDAT measurements from 65 different conditions (native and paced) in 23 patients. The correlation coefficient r was 0.99 with the line of fit running through 0 with a slope near 1. Fig. 1 shows this data in a Bland-Altman plot demonstrating a mean difference between two beats of 0 ms and a 95% confidence interval of ±2.5 ms. We have previously shown that reproducibility of SDAT measurements obtained about 30 min apart at the same device settings are also reproducible with a 95% confidence interval of about ±6 ms [11].

We assessed the relationship between % ΔSDAT and % ΔQRS duration in order to determine if the information on electrical dyssynchrony obtained with the ECG belt differed from that obtained with 12-lead ECG. In 45 patients who had 12-lead ECGs acquired at native rhythm

Table 1
Demographic and clinical characteristics of patients (n = 94).

Characteristic	Value
Age at 1st CRT (years)	69 ± 11
Male gender n (%)	64 (68%)
Pre-CRT EF (%)	25.7 ± 7
Pre-CRT QRS duration (ms)	159 ± 23
Pre-CRT QRS morphology	
LBBB n (%)	58 (62%)
RBBB n (%)	6 (6%)
IVCD n (%)	16 (17%)
RV paced n (%)	14 (15%)
Pre-CRT NYHA III classification n (%)	72 (77%)
Pre-CRT ischemic etiology n (%)	47 (50%)
Pre-CRT COPD n (%)	12 (13%)
Pre-CRT chronic AF n (%)	11 (12%)
Pre-CRT diabetes n (%)	29 (31%)
Pre-CRT CKD (creatinine ≥1.5 mg/dL) n (%)	17 (18%)
Pre-CRT beta-blocker use n (%)	88 (94%)
Pre-CRT ACE-I or ARB use n (%)	75 (80%)

CRT = cardiac resynchronization therapy; EF = ejection fraction; LBBB = left bundle branch block; RBBB right bundle branch block; IVCD = interventricular conduction delay; RV = right ventricular; NYHA = New York Heart Association; COPD = chronic obstructive pulmonary disease; AF = atrial fibrillation; CKD = chronic kidney disease; ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker.

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