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Left ventricular scar and the acute hemodynamic effects of multivein and multipolar pacing in cardiac resynchronization

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ABSTRACT

Background: We sought to determine whether presence, amount and distribution of scar impacts the degree of acute hemodynamic response (AHR) with multisite pacing.
Multi-vein pacing (MVP) or multipolar pacing (MPP) with a multi-electrode left ventricular (LV) lead may offer benefits over conventional biventricular pacing in patients with myocardial scar.
Methods: In this multi-center study left bundle branch block patients underwent an hemodynamic pacing study measuring LV dP/dt_{max}. Patients had cardiac magnetic resonance scar imaging to assess the effect of scar presence, amount and distribution on AHR.
Results: 24 patients (QRS 171 ± 20 ms) completed the study (83% male). An ischemic etiology was present in 58% and the mean scar volume was 6.0 ± 7.0%. Overall discounting scar, MPP and MVP showed no significant AHR increase compared to an optimized "best BiV" (BestBiV) site. In a minority of patients (6/24) receiver-operator characteristic analysis of scar volume (cut off 8.48%) predicted a small AHR improvement with MPP (sensitivity 83%, specificity 94%) but not MVP. Patients with scar volume > 8.48% had a MPP-BestBiV of 3 ± 6.3% vs. −6.4 ± 7.7% for those below the cutoff. There was a significant correlation between the difference in AHR and scar volume for MPP-BestBiV ($R = 0.49$, $p = 0.02$) but not MVP-BestBiV($R = 0.111$, $p = 0.62$). The multielectrode lead positioned in scar predicted MPP AHR improvement ($p = 0.04$).
Conclusions: Multisite pacing with MPP and MVP shows no AHR benefit in all-comers compared to optimized BestBiV pacing. There was a minority of patients with significant scar volume in relation to the LV site that exhibited a small AHR improvement with MPP.
(Study identifier NCT01883141)

1. Background

Current cardiac resynchronization therapy (CRT) produces clinical improvement in approximately 70% of patients with systolic heart failure (HF) and a broad QRS [1]. Multiple studies have attempted to predict non-responders and to optimize CRT implantation [2,3]. Left ventricular (LV) scar adversely effects CRT acute response [4], chronic remodeling [5] clinical improvement and mortality [6]. Both total scar volume and scar location at the site of LV stimulation are associated with worse outcomes [6,7]. Cardiac magnetic resonance late gadolinium enhancement (CMR-LGE) can accurately quantify, categorize and assess

Abbreviations: HF, heart failure; CRT, cardiac resynchronization therapy; BiV, biventricular; MVP, multivein pacing; MPP, multipolar pacing; LV, left ventricular; AHR, acute hemodynamic response; CMR-LGE, cardiac magnetic resonance late gadolinium enhancement; LBBB, left bundle branch block; MEL, multielectrode lead; ECG, electrocardiogram; CMR, cardiac magnetic resonance; OR, odds ratio; CI, confidence interval.

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LV scar distribution and may improve CRT response by avoiding pacing within scarred myocardial segments [6].

Multisite left ventricular pacing is a promising technique, which may improve CRT response, particularly in patients with ischemic heart disease and LV scar. Such stimulation can be achieved either by introducing a second LV lead i.e. multivein pacing (MVP) [8–11] or pacing from multiple poles of a quadripolar lead i.e. multipolar pacing (MPP) [12,13]. Both techniques have demonstrated improvement in acute hemodynamic response (AHR) [10] and mid-term (3–12 months) remodeling parameters in small single center series [8,14]. Others have failed to show significant incremental benefit with multisite LV pacing compared to standard CRT [9,15,16] and some studies have suggested the additional benefit of multisite pacing may be limited to ischemic patients with myocardial scar [10,17].

The iSPOT study (Study identifier NCT01883141) was the first multicenter clinical trial designed to test AHR to both MVP and MPP within the same patients with left bundle branch block (LBBB) in a robust, reproducible protocol [16]. The results of the study showed no benefit of MPP compared to optimized BIV pacing in "all-comers" with LBBB. All patients in the study underwent pre-implantation CMR-LGE imaging to image myocardial scar burden and distribution.

We hypothesized that patients with a significant scar burden as percentage of the total LV and with significant scar per segment at the site of the implanted LV lead may stand to benefit from multisite techniques. We investigated the relationship between CMR-LGE derived scar volume and location with AHR between optimized conventional biventricular and multisite pacing (MPP and MVP).

2. Methods

The iSPOT study is a prospective non-randomized study at 7 hospitals in Europe and the Middle East (Israel) evaluating contractile function (AHR) using positive LV dP/dt_{max} between an optimized BiV and multisite pacing protocols in LBBB patients indicated for CRT. Patients were enrolled prospectively and served as their own control. The study was approved by local ethics committees and all patients gave written informed consent.

Patients recruited met inclusion criteria for CRT according to current ESC/AHA guidelines. All subjects were required to have LBBB and stable sinus rhythm. Patients had one baseline visit prior to the acute study including standard CMR-LGE techniques to assess scar volume and location.

An AHR study was performed from femoral arterial and venous access sites. An LV catheter (Micro-Cath™, Millar, TX) measured LV dP/dt_{max} using a trans-aortic approach. An occlusive coronary sinus venogram was obtained to identify the target vessels for LV stimulation. To perform MPP either a quadripolar LV pacing lead or a decapolar catheter was deployed via the femoral vein targeting a posterolateral vein. For MVP two coronary veins (one anterior and one posterior) were cannulated with LV leads (Fig. 1). The LV lead positions in an anterior to posterior orientation were determined by the implanting physician from fluoroscopy in the left anterior oblique projection; the basal to apical position was determined using the right anterior oblique fluoroscopy parameterized by the LV length from the cardiac magnetic resonance images. Following the acute procedure the patients either had immediate CRT or CRT implantation occurred at a later date dependent on operator preference.

The following LV pacing configurations were evaluated:

1. Biventricular pacing with LV pacing from the distal electrode of the multielectrode lead (MEL-dis)
2. Biventricular pacing with LV pacing from the mid electrode (MEL-mid)
3. Biventricular pacing with LV pacing from the proximal electrode (MEL-prox)
4. MPP with LV pacing simultaneously from all three electrodes of the MEL.
5. Biventricular pacing with LV pacing from or via the anterior vein lead
6. Biventricular pacing with LV pacing from or via the posterior vein lead
7. MVP with LV pacing from anterior and posterior leads.

All measurements were compared to baseline atrial pacing at 100 bpm. For all configurations a ventricular-ventricular delay of zero was used. Each configuration was performed with 5 different atrio-ventricular delays: the patient specific optimal atrio-ventricular delay derived from the CardioSync™ algorithm, as well as at ±20 ms and ±40 ms. Each pacing configuration and atrio-ventricular delay was repeated a minimum of 4 times to reduce variance and increase signal to noise ratio. Each pacing configuration was performed for ≥20 beats, and interspersed with baseline AAI pacing (Fig. 1). The mean change in dP/dt_{max} from AAI pacing was the primary outcome.

Scar volume and location was calculated using CMR[42] (Circle Cardiovascular Imaging Inc., Calgary, Canada) from CMR-LGE short axis stacks by segmenting endocardial and epicardial borders and applying a user-defined high pass signal filter to highlight scarred regions. Scar volume was calculated as percentage of total myocardial mass and per segment. A scar volume ≥ 10% per American Heart Association segment was used as a threshold for the lead in or adjacent to scar analysis. Adjacent to scar was lead placement in any segment surrounding a scarred segment and lead placement distant to scar was where it was neither in nor adjacent to scar. Scar volume using CMR-LGE was assessed at a single core lab blinded to the AHR results.

All the study participants and implanters were blinded to analysis of AHR data, which was performed offline (RC). The techniques used to analyze the AHR data have previously been described [16]. The best improvement in mean AHR with BiV pacing (BestBiV) was subtracted from the mean AHR to MPP to test for improvement with the MPP protocol (MPP-BestBiV); this was repeated for the MVP protocol (MVP-BestBiV). Further analyses were undertaken where the best BiV AHR from the MEL was subtracted from the mean MPP AHR (MPP-BestBiV(MEL)) and where the best BiV from either the anterior or posterior leads was subtracted from the mean MVP AHR (MVP-BestBiV(MVL)) in order to directly test the potential AHR advantage with the advanced pacing techniques from BestBiV using only the leads used within these protocols.

Statistical analysis was performed on PASW Statistics 21 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov one-sample test was used to ensure variables were normally distributed. Continuous variables were expressed as mean ± SD. Group comparisons were performed using an independent-samples *t*-test for normally distributed data, and the Mann-Whitney *U* test if non-parametric. Nominal variables were expressed as absolute count and percentages and compared with Fisher's exact test. Scar volume was assessed using receiver-operator characteristic analysis for additional benefit with multi-site pacing. Values of $p < 0.05$ were considered statistically significant.

3. Results

A total of 31 patients were enrolled in 7 separate cardiac centers. Seven patients were excluded due to difficulties in completing the protocol [16]. The characteristics of the remaining 24 patients with full datasets are shown in Table 1. All patients had CMR-LGE available. Fourteen patients had ≥10% scar in one or more segments, 10 patients had no detectable scar. The total scar volume for the entire cohort was 6.0 ± 7.0%. The total scar volume in patients with scar was 9.5 ± 7.3%.

The MEL was placed in the posterolateral (50%), anterolateral (4%) or lateral vein (46%). MVP was not possible in 1 patient; in the remaining 23 patients the "anterior" lead was positioned in an anterior vein in 91% and an anterolateral vein in 9% with the "posterior" lead in a posterior vein in 48%, a posterolateral vein in 39% and a lateral vein for the remaining 13%. The right ventricular electrode was placed in the right ventricular apex (63.3%) and right ventricular septum (36.7%).