

## 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 a hemodynamic pacing study measuring LV dP/dt<sub>max</sub>. 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.

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**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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### 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

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  $\pm 20$  ms and  $\pm 40$  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  $\geq 20$  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<sup>42</sup> (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  $\geq 10\%$  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.

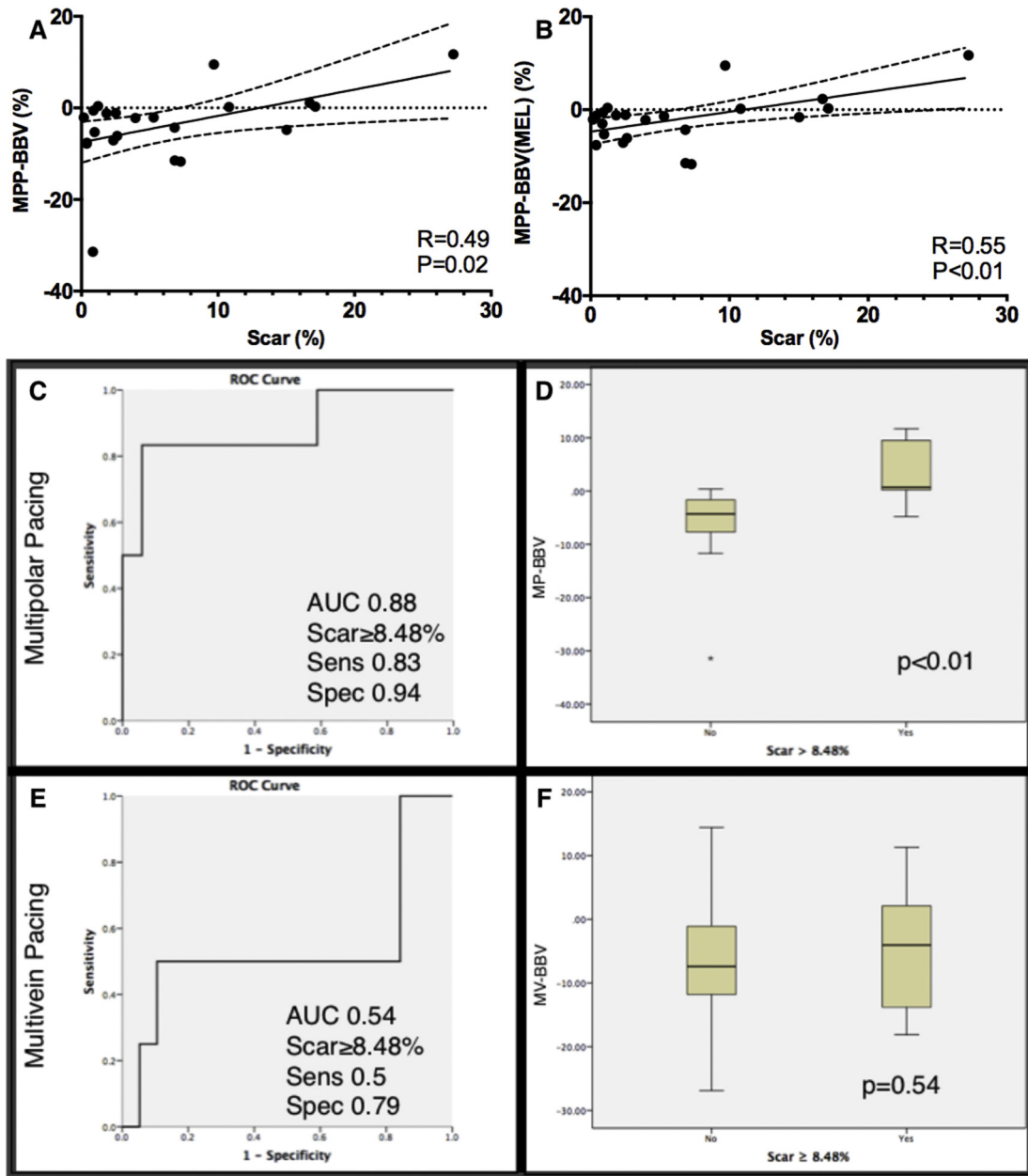
All the study participants and implanters were blinded to analysis of AHR data, which was performed offline (RC). The techniques used to analyze the AHR data have previously been described [16]. The best improvement in mean AHR with BiV pacing (BestBiV) was subtracted from the mean AHR to MPP to test 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  $\pm$  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  $\geq 10\%$  scar in one or more segments, 10 patients had no detectable scar. The total scar volume for the entire cohort was  $6.0 \pm 7.0\%$ . The total scar volume in patients with scar was  $9.5 \pm 7.3\%$ .

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%).



**Fig. 1.** Scatter diagrams of A) MPP-BBV AHR (x axis) vs. Scar burden (%) and B) MPP-BBV AHR from only multielectrode (MEL) electrodes vs. Scar burden (%) with lines of fit and 95% CIs. C) ROC curve for any improvement with multipolar pacing (MPP) over best BiV pacing. D) Box and whisker plot for difference between MPP and best BiV AHR in the presence or absence of significant scar. E) ROC curve for any improvement with multivein pacing over (MVP) best BiV pacing. F) Box and whisker plot for difference between MVP and best BiV AHR in the presence or absence of significant scar.

**Table 1**  
Demographic data of the cohort.

Patient demographics		Total subjects (N = 24)
Gender	Male	20 (83%)
	Female	4 (17%)
Age (years)		61.5 ± 13.4
LVEF (%)		24.6 ± 6.4
NYHA class	II	9 (38%)
	III	15 (62%)
Etiology	Ischemic	14 (58%)
	Non-Ischemic	10 (42%)
QRS duration (ms)		171.4 ± 21.0
Mean scar burden (%)		6.0 ± 7.0

Values are total numbers (percentage) and mean ± standard deviation. LVEF – left ventricular ejection fraction, NYHA – New York Heart Association.

Overall AHR in the MPP cohort was  $31.4 \pm 16.3\%$ . The majority of patients (75%) did not improve with MPP (i.e.  $\text{MPP-BestBiV} \leq 0\%$ , mean  $-6.7 \pm 7.5\%$ ). Only a minority of patients ( $N = 6, 25\%$ ) improved with MPP (i.e.  $\text{MPP-BestBiV} > 0\%$ ). The additional increase AHR in these patients was  $3.9 \pm 5.3\%$  (range 0.2–11.7%).

There was a significant correlation between scar volume and  $\text{MPP-BestBiV}$  ( $R = 0.49, p = 0.02$ ); undertaking this analysis with  $\text{MPP-BestBiV(MEL)}$  improved this correlation ( $R = 0.55, p < 0.01$ , Fig. 1) altering the BestBiV in 6 patients. Receiver-operator characteristic analysis of scar volume for any improvement in  $\text{MPP-BestBiV}$  generated an area under the curve (AUC) of 0.88. Scar volume of 8.48% had a sensitivity of 83% and specificity of 94%. Patients with a scar volume greater than this value had an  $\text{MPP-BestBiV}$  of  $3 \pm 6.3\%$  vs.  $-6.4 \pm 7.7\%$  for those with a scar volume below the cutoff ( $p < 0.01$ , Fig. 1).

BiV pacing from the multielectrode lead was tested against MPP when the LV pacing site was within or outside scar; there was no significant

difference for each electrode (Table 2). In order to test if proximity of scar was influential this analysis was repeated for whether the LV electrode was in or adjacent to scar vs. distant to scar (Table 2). The presence of any LV pacing electrode within scar was compared against a positive improvement to MPP. For the MPP protocol 57% of patients with LV pacing within scar improved as opposed to 12% where LV pacing was outside scar ( $p = 0.04$ ). If the electrodes were assessed to be in or adjacent to scar this was 50% vs. 7% ( $p = 0.05$ ) (Table 3).

Overall AHR improvement with MVP was  $30.8 \pm 16.5\%$ . The majority of patients (83%) did not improve with MVP (i.e. MVP-BestBiV  $\leq 0\%$ , mean  $-26.9 \pm 7.6\%$ ). Only a minority of patients ( $N = 4$ , 17%) improved with MVP (i.e. MVP-BestBiV  $> 0\%$ ). The additional increase AHR in these patients was  $8.3 \pm 5.6\%$  (range 2.1–14.4%).

There was no significant correlation between MVP-BestBiV and scar volume ( $R = 0.111$ ,  $p = 0.62$ ); repeating this analysis only using the BestBiV AHR from the multivein leads (i.e. the anterior and posterior leads only) did not improve this correlation ( $R = -0.134$ ,  $p = 0.542$ ).

Receiver operator characteristic analysis of scar volume for any improvement in MVP-BestBiV generated an AUC of 0.539. The scar volume of 8.48% had a sensitivity of 50% and specificity of 79%. There was no difference in MVP-BestBiV between those with or without significant scar ( $-4.4 \pm 10.9\%$  vs  $-7.4 \pm 10.0\%$   $p = 0.54$ , Fig. 1). There was no significant difference in MVP-BiV for individual pacing protocols where the LV electrode was within or in/adjacent to scar compared to outside scar (Table 2).

The distribution of scar was similar between the AHR improvers to MPP and MVP, with the scar burden predominantly being located posterolaterally and apically.

The QRS duration of those patients where MPP improved AHR was  $167 \pm 15$  ms vs.  $176 \pm 21$  ms for those who did not ( $p = 0.33$ ). Where MVP augmented AHR the QRS duration was  $182 \pm 11$  ms vs.  $174 \pm 18$  ms ( $p = 0.39$ ).

#### 4. Discussion

This the first multicenter study to assess AHR to multisite CRT delivered via multivein and multipolar pacing in the same patient cohort and using cardiac magnetic resonance to characterize the effect of myocardial scar on both.

The key findings are that within our cohort of LBBB patients:

- 1) The majority of patients fulfilling CRT criteria with LBBB failed to show incremental AHR with multisite (multipolar or multivein) pacing versus hemodynamically optimized BiV pacing.
- 2) Total LV scar volume may impact on improvement from MPP; patients with scar on MRI were likely to have incremental hemodynamic benefit with MPP.

- 3) The presence of scar at or adjacent to the MEL increased the likelihood of MPP response.
- 4) Scar volume and distribution had no impact on the likelihood of improvement from MVP.

The results of the main iSPOT study showed that multisite pacing offered no significant improvement in AHR in LBBB patients compared to optimized standard CRT. The current results would suggest that in a small sub-group of patients with significant myocardial scar there may be incremental benefit [16]. In this analysis only 25% of patients gained additional benefit from MPP and 17% with MVP. These improvement rates are considerably less than other published data [12,13]. The AHR benefit was minimal with a mean additional AHR amongst those who improved of  $3.9 \pm 5.3\%$  for MPP. This degree of additional benefit is in keeping with previous AHR studies [12,15] and also within biophysical models of multisite pacing [18]. The lower positive response to multisite pacing is likely to be driven by the inclusion criteria as all patients had LBBB (mean QRS duration  $171.4 \pm 21.0$  ms). This is in keeping with a recent publication by Sohal et al. demonstrating a beneficial effect of multisite pacing in only 7 of 16 patients, notably patients with strict LBBB had no additional benefit [17]. The low response to multisite pacing in this study is important as the study used rigorous methodology to ensure that standard BiV stimulation was optimized with programming of the atrio-ventricular delay and by repeated measures of AHR [16]. The failure of multisite pacing to enhance AHR over optimized conventional CRT is in agreement with Padeletti et al. [9] who demonstrated little added benefit when atrio-ventricular delays were optimized in 12 patients, 7 of whom were ischemic. The current findings also agree with a recent canine study which demonstrated in a LBBB model that additional pacing sites (up to 7) did not improve AHR if the initial site was optimal [19].

This is the first study to report the impact of LV scar volume on AHR with both MVP and MPP in the same patients. Of interest is the positive effects seen in the presence of scar with MPP but not the MVP group. This is in keeping with the findings of Pappone et al. [13] in 44 patients where “multipoint” pacing in the 45% with ischemic cardiomyopathy was as effective as in non-ischemic patients, despite a poorer response to conventional BiV pacing. The difference in the two modalities may be explained when considering the incremental benefit that each adds to best BiV. The MEL is targeted to the posterolateral wall, which is generally considered to be the optimal position in LBBB. The BestBiV is most likely to be as close to the posterolateral wall where scar is either absent, or has the lowest impact on activation. The addition of a second pacing point in a distant vein, which is more likely to be in scar if total scar volume is greater, is unlikely to add benefit. However, the addition of a second posterolateral pacing point in the presence of scar has a greater chance of adding incremental benefit on top of the best BiV pacing

**Table 2**

Multipolar pacing and multivein pacing improvement dependent on spatial relationship of left ventricular lead and scar.

	In scar	Outside Scar	p-Value	In or adjacent to scar	Distant from scar	p-Value
<i>MPP</i>						
Distal	$2.8 \pm 5.6$	$0.8 \pm 8.4$	0.6	$2.4 \pm 5.0$	$0.7 \pm 9.0$	0.63
Mid	$4.8 \pm 7.2$	$2.1 \pm 7.6$	0.45	$4.4 \pm 6.4$	$1.7 \pm 8.1$	0.42
Proximal	$4.9 \pm 8.3$	$1.0 \pm 3.9$	0.13	$4.1 \pm 7.4$	$0.6 \pm 3.3$	0.18
<i>MVP</i>						
Distal	$-2.4 \pm 12.1$	$1.4 \pm 20.7$	1.0	$-2.0 \pm 10.2$	$1.7 \pm 22.4$	0.67
Mid	$0.03 \pm 9.7$	$1.1 \pm 14.5$	0.61	$-1.4 \pm 8.4$	$2.3 \pm 15.8$	0.92
Proximal	$3.0 \pm 6.6$	$-0.6 \pm 16.0$	0.60	$-1.7 \pm 9.3$	$1.6 \pm 16.7$	0.59
Anterior lead	$1.7 \pm 2.5$	$10.1 \pm 12.5$	0.08	$6.5 \pm 7.6$	$10.0 \pm 14.0$	0.73
Posterior lead	$-0.4 \pm 8.4$	$1.8 \pm 5.2$	0.46	$-0.5 \pm 7.3$	$2.4 \pm 5.2$	0.30

Top panel - difference in AHR with multipolar pacing and BiV pacing from the multielectrode lead dichotomized by LV pacing site in scar and in or adjacent to scar.

Bottom panel - difference in AHR with multivein pacing and BiV pacing from the multielectrode lead and multivein leads dichotomized by LV pacing site in scar and in or adjacent to scar. Values are mean  $\pm$  SD (%).

**Table 3**  
Bivariate comparisons of spatial relationship of scar and left ventricular lead with multipolar or multivein pacing improvement.

	Lead(s) outside scar	Lead(s) in scar	p-Value	Lead(s) distant from scar	Lead(s) in or adjacent to scar	p-Value
No multipolar improvement	15 (88%)	3 (43%)	p = 0.04	13 (93%)	5 (50%)	p = 0.05
Multipolar improvement	2 (12%) OR 10, 95% CI 1.2–81.8	4 (57%)		1 (7%) OR 13, 95% CI 1.2–140.7	5 (50%)	
No Multivein Improvement	13 (87%)	6 (75%)	p = 0.59	9 (82%)	10 (83%)	p = 1.0
Multivein Improvement	2 (13%) OR 2.2, 95% CI 0.2–19.3	2 (25%)		2 (18%) OR 0.9, 95% CI 0.1–7.8	2 (17%)	

Values are N (% of patients within each scar group). OR – odds ratio, CI – confidence interval.

point due to modification of the activation wavefront. The finding that MVP does not seem to confer benefit is in keeping with Behar et al. who recently demonstrated poor long-term results, especially concerning device longevity, with this strategy [20].

MPP benefit from within scar was previously predicted by Niederer et al. in a biophysical model with minimal  $dP/dt_{max}$  improvement in the absence of scar but a 4.4% improvement with dense scar modelled in the posterolateral wall [18]. This degree of AHR improvement is strikingly similar to that seen in this study. The potential mechanism of benefit may be that the scarred region has viable but slow conduction and multisite pacing may pre-excite the region bringing forward the contraction in the cardiac cycle. Two areas activated close to one another may increase the volume of activation thereby coordinating the activation to a greater extent. This is in keeping with a recent study by Umar et al. who deliberately deployed a MEL straddling LV free wall scar and compared AHR of MPP with conventional CRT in 16 patients [21]. In this study 8 patients acutely responded to CRT, with the optimal settings being MPP in 5 and apical LV lead placement of conventional CRT in 3.

## 5. Study limitations

The main study limitation is low sample size, albeit relatively large for studies which are similarly invasive. The predictive scar value of 8.48% is both derived and tested within the same cohort and a prospective study is needed to corroborate this result. All patients fulfilled stringent criteria for LBBB and are therefore likely to respond well to BiV pacing; assessing for AHR beyond this is challenging. A further study investigating these findings amongst right bundle branch block and interventricular conduction delay patients is indicated. Finally, it is uncertain that invasive  $dP/dt_{max}$  improvement confers long term prognostic benefit, however it is currently the foremost acute response metric available.

## 6. Conclusions

In conclusion multisite pacing with MPP and MVP shows no AHR benefit in all-comers compared to optimized BestBiV pacing. However, there was a minority of patients (25%) with significant scar volume, especially at the LV pacing site, that exhibited a small AHR improvement ( $3.9 \pm 5.3\%$ ) with MPP. There is a significant correlation between left ventricular scar volume and improvement with multipolar LV pacing from a single multipolar lead, however anterior-posterior multivein pacing does not confer the same benefit in patients with scar.

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