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Multipoint left ventricular pacing improves response to cardiac resynchronization therapy with and without pressure-volume loop optimization: comparison of the long-term efficacy of two different programming strategies

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Abstract

Purpose Cardiac resynchronization therapy (CRT) with multipoint left ventricular (LV) pacing (MultiPoint™ Pacing [MPP]) improves long-term LV reverse remodeling, though questions persist about how to program LV pacing vectors and delays. We evaluated if an empirical method of programming MPP vectors and delays between pacing pulses improved CRT response similar to pressure-volume loop (PVL) optimized MPP programming.

Methods Patients undergoing CRT implant (Quadra Assura MP™ CRT-D and Quartet™ LV lead) received MPP with programmed settings optimized either by PVL measurements at implant (PVL-OPT group) or empirically determined by maximizing the spatial separation between the two cathodes and minimal delays between the three ventricular pacing pulses (MAX-SEP group). CRT response was prospectively defined as a reduction in end-systolic volume (ESV) of $\geq 15\%$ relative to baseline at 6 months as determined by a blinded observer.

Results Patient characteristics at baseline (NYHA II–III, ejection fraction [EF] $27 \pm 6\%$, QRS 151 ± 17 ms) were not significantly different between the PVL-OPT ($n = 27$) and MAX-SEP ($n = 26$) groups. During the follow-up period, there were no differences in the number of patients requiring reprogramming due to phrenic nerve stimulation or a high threshold for PVL-OPT vs. MAX-SEP (5/27 [19%] vs. 7/26 [27%], $p = 0.53$). After 6 months, ESV reduction, EF increase, and CRT response rate (RR) were similar for PVL-OPT vs. MAX-SEP (ESV -20 ± 11 vs. $-22 \pm 11\%$, $p = 0.59$; EF $+10 \pm 4$ vs. $+9 \pm 7\%$, $p = 0.53$; RR 20/27 [74%] vs. 21/26 [81%], $p = 0.74$), while fewer patients in the PVL-OPT group experienced NYHA class reduction ≥ 2 (4/27 [15%] vs.15/26 [58%], $p = 0.002$).

Conclusions Both evaluated methods of MPP programming resulted in similar CRT outcomes. Empirical MPP programming by maximum spatial separation of LV cathodes may be an effective, simple, and non-invasive alternative to pressure-volume optimization.

Keywords Heart failure · Cardiac resynchronization therapy · CRT response · Multipoint pacing

Abbreviations

AV	Atrioventricular
BiV	Biventricular
CONV	Conventional CRT
CRT	Cardiac resynchronization therapy
CS	Coronary sinus
CVA	Cerebrovascular accident
dP/dt	Rate of pressure change
EF	Ejection fraction
ESV	End-systolic volume
HF	Heart failure
IDE	Investigational device exemption
LV	Left ventricle
MPP	MultiPoint™ Pacing
NYHA	New York Heart Association
PV	Pressure-volume

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RV   Right ventricle
RA   Right atrium
TIA   Transient ischemic attack

1 Introduction

Cardiac resynchronization therapy (CRT) has become the standard treatment for patients with moderate to severe heart failure (HF), prolonged QRS duration, and reduced ejection fraction (EF) [1–5]. However, conventional therapy is partly limited by the inadequate response rate of 60–70% [6, 7]. Recently, multipoint left ventricular (LV) pacing from a quadripolar LV lead (MultiPoint™ Pacing [MPP], Abbott, Sylmar, CA) has been shown to provide acute benefit to LV electrical propagation [8, 9], mechanical synchrony [10–12], and hemodynamic response [13–15] and to improve mid- and long-term LV reverse remodeling and LV function [16–19]. However, the LV lead placement and selection of pacing vectors in many of these studies have been driven by invasive hemodynamic measurements despite questions about the connection between acute hemodynamic response and long-term response. Based on our previous acute hemodynamic measurements [13], we hypothesized that an MPP programming strategy based on maximizing the separation between the two LV cathodes to capture the greatest amount of LV tissue would be as effective as hemodynamically optimized MPP. In this study, we tested this hypothesis by evaluating 3- and 6-month outcomes between patients receiving MPP programming guided by hemodynamic optimization or MPP programmed empirically to maximize LV cathode separation.

2 Methods

2.1 Study population

The study prospectively enrolled consecutive patients meeting the inclusion and exclusion criteria at a single investigational center. The study protocol was approved by the local ethics committee and the investigation conformed to the principles outlined in the Declaration of Helsinki. Inclusion criteria were a CRT implant indication approved by ESC/EHRA guidelines [20] and the ability of the patient to provide informed consent. Exclusion criteria were permanent atrial fibrillation, New York Heart Association (NYHA) Class IV, myocardial infarction within 40 days prior to enrollment, CVA or TIA within 3 months prior to enrollment, cardiac surgery or coronary revascularization procedure within 3 months prior to enrollment or scheduled in the following 7 months, intravenous inotropic support in the last 30 days, age less than 18 years, and pregnancy. Two study groups were prospectively followed in this study: (1) patients with MPP programmed by

pressure-volume (PV) loop optimization (PVL-OPT group) and (2) MPP programmed by maximizing LV cathode separation (MAX-SEP group). Programming was guided by hemodynamic response in the PVL-OPT group and maximum cathodes separation in the MAX-SEP group, regardless of the presence or location of scar [13, 16]. Patient baseline characteristics are summarized in Table 1.

2.2 Device implant and patient cohorts

Patients were implanted with a CRT device (Unify Quadra MP™ or Quadra Assura MP™, Abbott, Sylmar, CA) with the ability to deliver MPP (i.e., two LV pacing pulses [LV1 and LV2] and right ventricular [RV] pacing pulse with programmable delays between pacing pulses [LV1-LV2 and LV-RV delays]). Conventional RV and right atrial (RA) leads were placed according to standard practice. The quadripolar LV lead (Quartet™ LV lead, Abbott, Sylmar, CA) with electrodes named D1, M2, M3, and P4 (distal to proximal) was targeted to a lateral, posterolateral, or anterolateral branch of the CS. The distal electrode was targeted to an apical or mid-ventricular position, allowing for greater lead stability. Initial patient enrolled underwent PV loop measurements (PVL-OPT group) to optimize the LV pacing electrode configuration; the subsequent group, prospectively enrolled, had MPP settings programmed by maximizing LV cathode separation (MAX-SEP group).

2.3 Hemodynamic measurements

Patients in the PVL-OPT group underwent acute hemodynamic measurements during CRT device implant to optimize LV1 and LV2 pacing vectors, LV1-LV2 delay, and LV2-RV delay according to our previously published protocol [13]. Briefly, after final placement of all leads, patients underwent hemodynamic testing with a PV loop system (Inca, CD Leycom, Zoetermeer, The Netherlands) during a pacing protocol including at least seven MPP configurations with different LV vector combinations and delays between pacing pulses at a fixed atrioventricular (AV) delay of 100 ms to ensure consistent ventricular capture. A PV loop catheter was inserted, via arterial femoral access, into the LV chamber and placed in the apex. Sixty second recordings were collected during each test pacing intervention with return to baseline (RV pacing) following each test pacing intervention. Hemodynamic parameters were averaged over 16 consecutive beats and expressed as the relative percent change to measurements during adjacent baseline recordings to account for any drift and isolate the cardiac effect of pacing [21]. All hemodynamic measurements were repeated twice for each pacing intervention. Patients in the MAX-SEP group did not undergo any hemodynamic measurements.

Table 1 Baseline characteristics of patients enrolled and retrospective supplemental patient data for MAX-SEP and PVL-OPT arm who completed a 6-month follow-up

Parameter	All patients ($N = 53$)	MAX-SEP ($N = 26$)	PVL-OPT ($N = 27$)	p value
Gender, male (%)	45 (85%)	23 (88%)	22 (81%)	0.69
Age (years)	68 ± 11	69 ± 13	67 ± 9	0.42
Height (cm)	171 ± 8	170 ± 9	172 ± 8	0.50
Weight (kg)	81 ± 19	84 ± 19	85 ± 23	0.87
LBBB	28 (52%)	16 (62%)	12 (44%)	0.22
RBBB	2 (4%)	1 (4%)	1 (4%)	1.0
Non-permanent AF history	47 (89%)	23 (88%)	24 (89%)	0.96
Ischemic etiology	32/53	16/26	16/27	0.91
NYHA Class	51/53 Class III	24/26 Class III	27/27 Class III	–
	2/53 Class II	2/26 Class II	0/27 Class II	
QRSd (ms)	151 ± 17	156 ± 18	150 ± 13	0.20
EDV (mL)	240 ± 67	249 ± 77	231 ± 56	0.32
EDV_i (mL/m^2)	124 ± 34	116 ± 27	132 ± 38	0.09
ESV (mL)	176 ± 60	183 ± 69	168 ± 50	0.36
ESV_i (mL/m^2)	91 ± 30	85 ± 25	97 ± 33	0.15
EF (%)	27 ± 6	27 ± 6	28 ± 7	0.97

2.4 Selection of LV pacing vectors

Before leaving the hospital, patients in the PVL-OPT group were programmed to the MPP configuration that produced the largest increase in dP/dt$_{Max}$ relative to baseline during the intraoperative PV loop measurements.

Patients in the MAX-SEP group were programmed to LV1 and LV2 vectors with the maximum separation between cathodes along the LV lead body and the minimum delay between LV1-LV2 and LV2-RV pacing pulses allowed by the device. Maximum cathode separation was achieved by selecting an LV1 vector with the most distal available cathode and an LV2 vector with the most proximal available cathode. A pacing vector was considered available if the capture threshold was ≤ 5 V, and phrenic nerve stimulation (PNS) was not present. When multiple anodes were available for the target cathode, the anode was selected to minimize the pacing capture threshold and avoid PNS. Anodes used in the LV stimulation were 39% RV coil, 16% P4, and 45% M2. P4 was not selected in all cases due to high capture thresholds and PNS in a few patients.

Adjustments to device programming during the observation period, defined from the time of implant to subject's 6-month follow-up visit, necessitated by changes in LV capture threshold or new onset of PNS were addressed by reprogramming to the configuration that either produced the next largest increase in dP/dt$_{Max}$ in the PVL-OPT group or kept the largest separation between the remaining available cathodes in the MAX-SEP group. LV pacing vectors programmed are summarized in Table 2 for the MAX-SEP and PVL-OPT group.

2.5 Echocardiographic measurements and clinical exam

Patients underwent echocardiographic and clinical evaluation prior to implant (BASELINE) and at 3 and 6 months after implant. LV end-systolic (ESV), end-diastolic volume, and the EF were measured by an observer blinded to the patients' pacing configuration with a transthoracic echocardiography system (iE33, Philips, Amsterdam, The Netherlands). Patients were considered as responders to CRT at the 6-month follow-up visit if they experienced a reduction in ESV of $\geq 15\%$ relative to BASELINE [22–24]. A subgroup analysis of echocardiographic and clinical changes was conducted based on patient heart disease etiology (ischemic or non-ischemic). Etiology was based on patient medical history (previous MI or LV dysfunction associated with coronary artery disease).

Table 2 Programmed MPP LV vector combination throughout the study observation period for both MAX-SEP and PVL-OPT groups

Cathode combination		MAX-SEP ($N = 26$)	PVL-OPT ($N = 27$)	Cathode separation (mm)
LV1	LV2			
D1	P4	13	9	47
D1	M3	5	6	30
D1	M2	7	3	20
M2	P4	1	3	27
M2	M3	0	2	10
M3	P4	0	2	17
M3	M2	0	1	10
M3	D1	0	1	30

2.6 Statistical analysis

Categorical and continuous variables were expressed as absolute and relative frequencies or as mean ± SD. Comparisons between PVL-OPT and MAX-SEP groups were made with unpaired t tests for continuous variables and binomial variables with Fisher test, as appropriate. A p value < 0.05 was considered significant. All continuous variables are expressed as mean ± standard deviation. Statistical analyses were conducted using SPSS (SPSS v22, Chicago, IL, USA).

3 Results

3.1 Study population, enrollment, and follow-up

Sixty consecutive patients were prospectively enrolled and successfully received a MPP-enabled CRT device with quadripolar LV lead. Patient baseline characteristics (44% vs. 62% LBBB [$p = 0.22$], 26% vs. 38% AF history [$p = 0.34$] in the PVL-OPT and MAX-SEP group) and pharmacological treatment (89% vs. 88% [$p = 0.96$] beta blockers, 48% vs. 46% ACE inhibitors [$p = 0.89$], 93% vs. 81% diuretics [$p = 0.21$] in the PVL-OPT and MAX-SEP group) were similar among the two study groups. Among them, the first 30 patients underwent acute hemodynamic optimization using PV loop (PVL-OPT group), whereas the following 30 patients received optimization according to the widest LV cathodes separation (MAX-SEP group). LV lead location was comparable among the two groups (15% vs. 8% antero-lateral, 66% vs. 46% lateral, and 19% vs. 46% postero-lateral in the PVL-OPT and MAX-SEP group, $p = 0.08$). Each implanting physician placed the RV lead according to preference (38% in the apex and 62% on the septum). During the 6-month observation period, 1 patient in the MAX-SEP group died, 1 was withdrawn due to MPP unavailability (2 LV pacing electrodes could not be programmed without PNS, patient programmed to conventional bi-ventricular pacing from a single LV site), 2 patients were lost to follow-up with no additional echocardiographic clinical information available (Fig. 1), leaving 26 patients with complete follow-up data. In the PVL-OPT group, 1 subject died and 2 were lost to follow-up, resulting in 27 patients with complete data. Overall, 2 patients died for non-cardiac causes, whereas those lost to follow-up were alive throughout the course of the study (assessed by phone interview) yet could not perform the study visit during the required window. The mean total follow-up period was 183 ± 11 days in the PVL-OPT and 182 ± 22 days in the MAX-SEP group ($p = 0.75$). Baseline patient characteristics for those patients that completed the 6-month follow-up visit were not significantly different between the two groups for any of the parameters considered (Table 1).

All patients were implanted due to symptomatic heart failure. Among ischemic patients, 63% had suffered a previous MI. LV lead was positioned trying to avoid any scar region, as assessed by high capture thresholds and echo guidance. Unfortunately, in four patients, LV lead corresponded to scar region (three in PVL-OPT vs. one MAX-SEP). Scar region cannot be avoided because of difficult vein anatomy in two points, PNS 2. None of them was a CRT responder.

Fig. 1 Enrollment and follow-up in PVL-OPT and MAX-SEP groups. After a baseline examination and CRT implant, patients received either PVL-OPT or MAX-SEP programming parameters and followed-up after 6 months
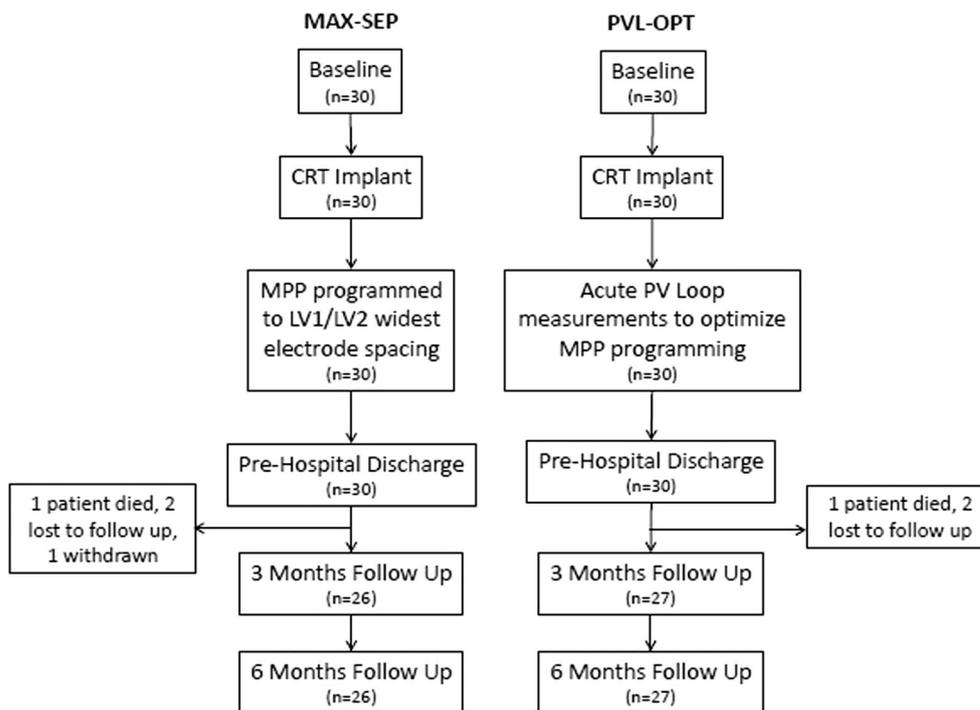
3.2 Device programming

The distance along the lead body between LV1 and LV2 cathodes was 35.7 ± 12.0 mm in the MAX-SEP group and 31.0 ± 13.1 mm in the PVL-OPT group ($p = 0.18$). Patients in the PVL-OPT group were programmed with a mean LV1-LV2 delay of 23 ± 16 ms and mean LV2-RV delay of 12 ± 13 ms. Patients in the MAX-SEP group were programmed with a mean LV1-LV2 delay of 6 ± 2 ms and mean LV2-RV delay of 6 ± 2 ms. Electrical conduction delay from RV activation to activation at each LV electrode during intrinsic rhythm showed no statistically significant differences between the MAX-SEP and PVL-OPT groups (D1: 87 ± 35 ms vs. 77 ± 43 ms, $p = 0.46$; M2: 88 ± 33 ms vs. 89 ± 52 ms, $p = 0.92$; M3: 87 ± 33 ms vs. 90 ± 31 ms, $p = 0.75$; P4: 92 ± 48 ms vs. 94 ± 43 ms, $p = 0.78$). Programmed LV1 and LV2 cathode conduction delays (RV sensed to LV electrode) were also non-significant between the two groups (LV1: 88 ± 38 ms vs. 79 ± 46 ms, $p = 0.60$ and LV2: 90 ± 32 ms vs. 89 ± 47 ms, $p = 0.90$, in the MAX-SEP and PLV-OPT, respectively). AV delays were programmed at the discretion of the physician (110–140 ms).

During the observation period, two patients (2/26, 8%) in the MAX-SEP group experienced a rise in capture threshold at one of the two LV sites that required programming to a different MPP configuration. Five patients (5/26, 19%) in the MAX-SEP group experienced phrenic nerve stimulation with one LV vector in the assigned configuration, which was resolved by reprogramming to a different MPP configuration. Similarly, in the PVL-OPT group, five patients required device reprogramming, three (3/27, 11%) due to PNS and two (2/27, 7%) due to high thresholds.

3.3 Echocardiographic, clinical findings and CRT response at 6-month follow-up

Echocardiographic and clinical parameters after 6 months are shown in Fig. 2a–c. Relative to BASELINE, ESV reduction and EF increase were similar between the PVL-OPT and MAX-SEP groups (ESV: $-20 \pm 11\%$ vs. $-22 \pm 11\%$, $p = 0.59$, Fig. 2a; EF: $+10 \pm 4\%$ vs. $+9 \pm 7\%$, $p = 0.53$, Fig. 2b). Overall, 47 patient experienced NYHA class reduction (22/27 [81%] PVL-OPT vs. 25/26 [96%] MAX-SEP group, $p = 0.19$, Fig. 2c). Using the response definition of ESV decrease $\geq 15\%$ relative to BASELINE, 20/27 (74%) patients in the PVL-OPT group vs. 21/26 (81%) patients in the MAX-SEP group were classified as CRT responders ($p = 0.74$), resulting in a total of 41/53 (77%) patients responding to MPP in the study. QRS duration at follow-up reduced by $21.8 \pm 13.1\%$ and $15.0 \pm 11.3\%$ ($p = 0.20$) with respect to baseline in the MAX-SEP (117 ± 19 ms) and PVL-OPT (128 ± 17 ms) groups, respectively. Out of 12 non-responder patients, a mean 1.2 ± 0.5

(range 1–3) HF re-admissions occurred in 7 individuals after CRT implantation.

3.4 Dependence of echocardiographic response on etiology

Ischemic patients in the PVL-OPT group ($N = 16$) and MAX-SEP group ($N = 15$) experienced similar ESV reduction ($-23 \pm 9\%$ vs. $-20 \pm 11\%$, $p = 0.43$) and absolute EF increase ($+10 \pm 7\%$ vs. $+11 \pm 5\%$, $p = 0.68$) at 6 months relative to BASELINE, Table 3. Non-ischemic patients in both groups (PVL-OPT: $N = 11$, MAX-SEP: $N = 10$) also experienced similar ESV reduction ($-20 \pm 14\%$ vs. $-21 \pm 11\%$, $p = 0.95$) and EF increase ($+8 \pm 6\%$ vs. $+9 \pm 4\%$, $p = 0.60$). CRT response rate at 6 months was not significantly different for non-ischemic patients in the PVL-OPT group vs. MAX-SEP group (8/11 [73%] vs. 7/10 [70%], $p = 0.48$) or for ischemic patients (12/16 [75%] vs. 14/16 [87%], $p = 0.33$).

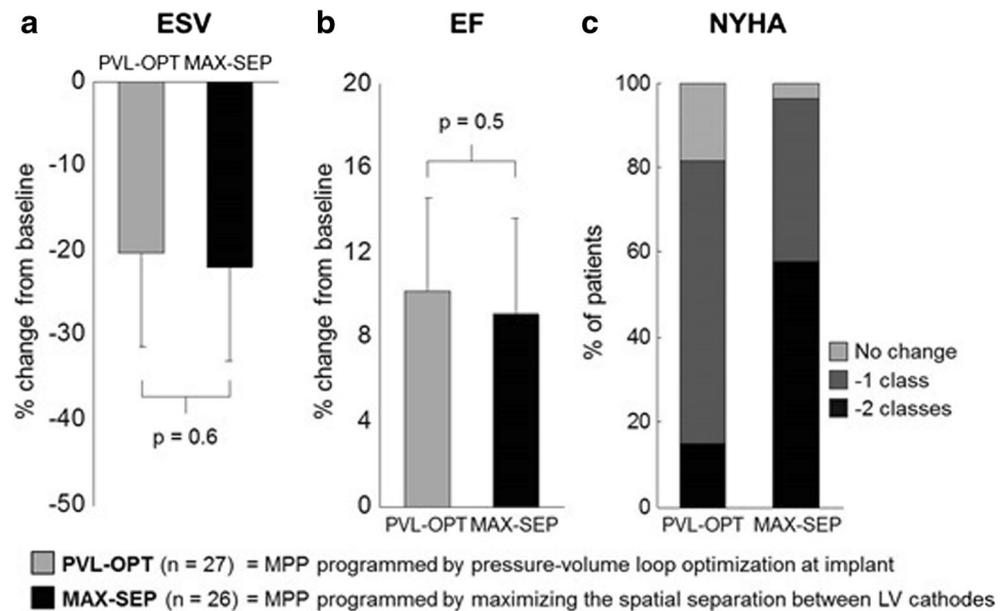## 3.5 Progression of echocardiographic parameters

The progression of ESV and EF throughout the study duration is shown in Fig. 3. For both echocardiographic parameters, the majority of improvement occurred from baseline to 3 months (ΔEF: $+9 \pm 5\%$ [PVL-OPT], $+7 \pm 7\%$ [MAX-SEP]; ΔESV: -28 ± 25 mL [PVL-OPT], -34 ± 35 mL [MAX-SEP]) with incremental additional improvement from 3 to 6 months (ΔEF: $+1 \pm 4\%$ [PVL-OPT], $+2 \pm 6\%$ [PVL-OPT]; ΔESV: -5 ± 20 mL [PVL-OPT], -5 ± 17 mL [MAX-SEP]).

4 Discussion

To the best of our knowledge, this is the first prospective study evaluating the role of an empirical optimization method based on the wider distance among LV cathodes as compared to the acute hemodynamic assessment.

A number of recent studies have evaluated the benefits of multipoint LV pacing to acute electrical [8, 9], mechanical [10, 11], and hemodynamic [13–15] response and long-term changes to LV remodeling and function [17–19]. While the addition of a second LV pacing pulse may benefit patients, questions have persisted about how to best program MPP. Previous studies examining acute hemodynamic response with pressure-volume loop measurements suggested an approach based on selecting cathodes with the widest separation along the lead body with minimum delay between ventricular pacing pulses [13, 14]. In this study, we report the results of a prospective evaluation of long-term response in patients assigned to receive MPP programmed based on maximum separation (MAX-SEP group) compared to an initially enrolled cohort of patients receiving PV loop optimization (PVL-OPT group). We found that patients in the two groups

Fig. 2 Change in echocardiographic and clinical parameters from BASELINE to 6-month follow-up. After 6 months, patients in the PVL-OPT and MAX-SEP groups had similar improvements in ESV and EF

PVL-OPT (n = 27) = MPP programmed by pressure-volume loop optimization at implant
MAX-SEP (n = 26) = MPP programmed by maximizing the spatial separation between LV cathodes

experienced a similar reduction in ESV, increase in EF, and CRT response rate at 6 months follow-up. One might speculate that 6 months may not be enough to appreciate outcome differences; however, the structural and functional changes associated with CRT can occur as early as 3 months post-implant and typically progress until 6 months of therapy [25]. Beyond 6 months, a plateau is generally reached with limited additional changes [26].

The study was not powered to properly resolve differences in subgroups. During implant, we have tried to avoid LV lead placement on potential scar regions, as indicated by echocardiography. This may provide some information on the positive results in ischemic patients. In addition, statistical analysis performed on such small study patients (7/10 [70%] vs. 14/16 [87%]) prevent to draw substantial conclusions regarding this issue.

This study supports the principle of programming MPP to allow initial depolarization of a broad area of LV tissue by separating two LV cathodes along the lead body as wide as possible. The empirical group (MAX-SEP) was purposely programmed to the LV cathodes that offered the widest lead

spacing possible with adequate capture threshold and no PNS. This resulted in an LV lead electrode spacing greater than the PVL-OPT group yet not statistically significant (35.7 ± 12.0 vs. 31.0 ± 13.1, $p = 0.18$). Of note, PVL-OPT had the best acute hemodynamic response with the maximum LV1-LV2 cathode spacing, supporting the hypothesis that wider anatomical spacing between the stimulating electrodes determines a better acute response. Reprogramming rates among the two groups were also similar throughout the study follow-up period. For these reasons, we believe that a non-invasive programming approach based on the widest separation among the cathodes may represent a first attempt in CRT MPP optimization.

Our previous hemodynamic study of 44 patients showed that in 71% of patients the greatest increase in LV dP/dt_{Max} occurred during an MPP setting with maximized separation of LV cathodes [13]. Other studies have supported the approach of maximum cathode separation for MPP programming as well. Thibault et al. showed that multipoint LV pacing with the most distal and most proximal LV electrodes as cathodes as significantly improved dP/dt_{Max} relative to standard BiV pacing with the distal electrode alone [14]. A retrospective analysis of the MPP IDE study found that patients randomized to MPP and programmed with LV cathode spacing ≥ 30 mm and minimum LV1-LV2 delay had a response rate of 87%, significantly higher than patients with other MPP programmed settings [27]. While these previous investigations have suggested the benefit of LV cathode separation, the current study is the first prospective, long-term demonstration of the benefit of programming MPP by this principle. The ongoing, international, multicenter MORE-CRT MPP study [28, 29], scheduled for completion on May 2019, may be able to provide further insight into the impact of MPP on non-responders to standard CRT.

Table 3 Echocardiographic parameters at 6-month follow-up in non-ischemic and ischemic patients relative to baseline characteristics

Parameter	MAX-SEP	PVL-OPT	p value
Non-ischemic	$N = 10$	$N = 11$	
ΔESV (%)	-21 ± 11	-20 ± 14	0.95
Follow-up–baseline EF	$+9 \pm 4$	$+8 \pm 6$	0.60
Ischemic	$N = 16$	$N = 16$	
ΔESV (%)	-20 ± 11	-23 ± 9	0.43
Follow-up–baseline EF	$+11 \pm 5$	$+10 \pm 7$	0.68

Fig. 3 Progression of echo parameters throughout the study duration. Mean ESV and EF are shown for patients in both the PVL-OPT and MAX-SEP groups at baseline (EF: $p = 0.97$, ESV: $p = 0.36$), 3-month visit (EF: $p = 0.46$, ESV: $p = 0.54$), and 6-month visit (EF: $p = 0.64$, ESV: $p = 0.62$)
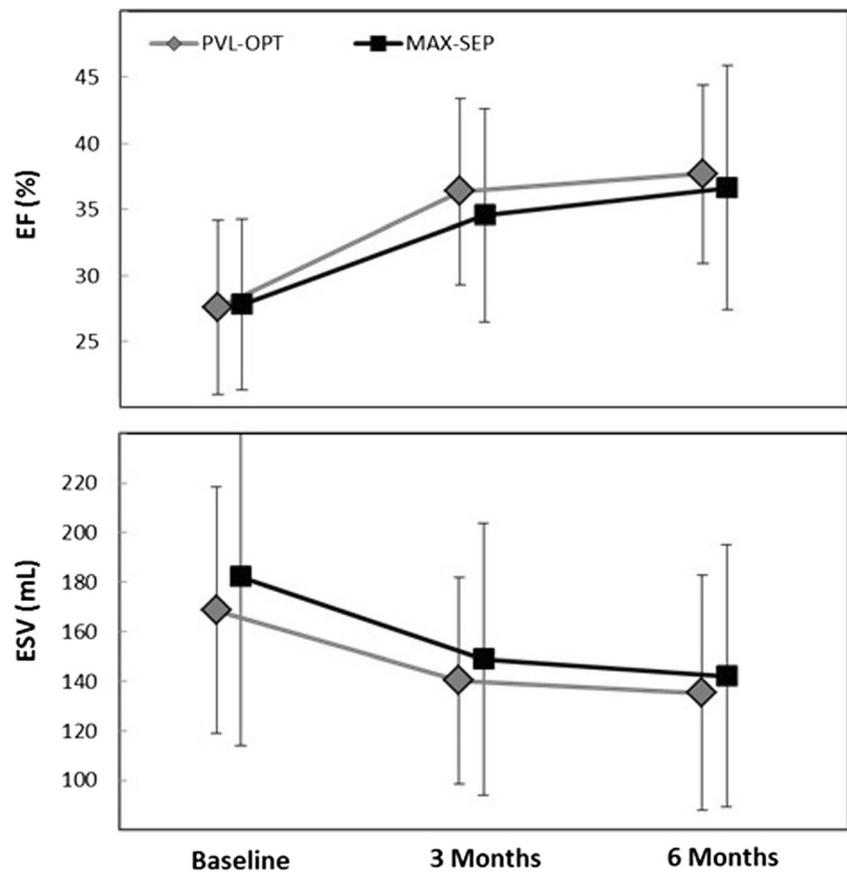
Hemodynamic optimization of MPP sites and ventricular pacing delays by dP/dt_{Max} did not lead to a better long-term response in the current study compared to an empirical programming method. While one study suggested improvement in $dP/dt_{Max} \geq 10\%$ with pacing is predictive of CRT response [30], others have found no relationship between dP/dt_{Max} improvement and LV reverse remodeling [31, 32]. In the current study, both methods of programming led to MPP configurations with average LV1-LV2 spacing ≥ 30 mm. In the PVL-OPT group, the vectors recommended by hemodynamic optimization were often the same as those that would have been selected according to the widest spacing method (21/27 [78%] patients). Invasive measurements in the PVL-OPT group showed that optimum dP/dt_{Max} resulted in LV cathode selection with wide cathode spacing. The similarity in LV1-LV2 spacing among the two study groups suggests a relation between the amount of myocardium initially captured and ventricular hemodynamic response, leading to a better patient outcome. The discrete optimization at the time of implantation should not be considered sufficient, as continuous/repeated evaluations during the follow-up and re-optimization may further improve the clinical response rate, particularly in case of non-responders [33].

The overall CRT response rate by ESV decrease $\geq 15\%$ in this study at 6 months with MPP (77%) is in line with the previous publications showing 3 and 12 months MPP response rates of 77% [16] and 76% [17], respectively, and higher than the response rate observed with conventional CRT at 12 months (57%) or at 6 months (57%) using the same definition [30]. Furthermore, it adds to recent reports from other groups of long-term results with MPP. Zanon et al. reported 1 year follow-up results from 110 patients undergoing CRT implant [19]. Patients receiving MPP with electrical and hemodynamic optimization of the LV pacing sites had a response rate of 90% according to ESV index decrease $\geq 15\%$, compared to 72% with similarly optimized conventional CRT and 56% with conventional CRT without optimization. The IRON-MPP registry compared response at 6 months in 232 patients at 76 Italian centers programmed to MPP "ON" or "OFF" at the discretion of the treating physician [18]. A significantly greater proportion of patients with MPP "ON" were improved according to clinical composite score compared to patients with MPP "OFF" (56% vs. 38%), and MPP activation was an independent predictor of EF increase $\geq 5\%$. Finally, as occurred in our cohort, the overall clinical CRT response rate did not differ among the groups, thus supporting the concept that a non-invasive programming strategy might be equivalent over a more invasive technique. However, further multicenter randomized trials are necessary to confirm this promising experience.

5 Limitations

This study represents a single-center experience with a relatively limited sample size. Sequential enrollment, the small sample size, and lack of randomization may represent a limitation potentially preventing to appreciate significant differences among the study groups, and more robust comparisons between groups with propensity score matching could not be performed due to the limited number of patients available. Nevertheless, these findings may suggest that the use of invasive systems in optimizing such devices may be avoided, although future, larger randomized multicenter studies are needed to confirm these promising findings.

LV lead location was not optimized in each individual patient, and although the region with longest LV delays (qLV) are relevant for optimal LV lead location, it was not considered as standard practice in the study protocol. LV stimulating anode, AV delays, and RV lead location were also not standardized per study protocol and were left at the discretion of the implant physician, which may also influence the results. Patients with poor prognosis were excluded, thus potentially overestimating CRT response rate.

Another possible limitation was the patient characterization for etiology, which was solely based on medical history. In ischemic patients, no scar assessment using advanced imaging techniques (e.g., MRI) was performed, thus potentially affecting CRT outcome. We tended to avoid scar regions; however, considering the lack of advanced imaging, we cannot exclude that in a certain percentage of patients, potentially non-responders, LV lead position corresponded to a scar area. Therefore, comparison of anatomic separation and programming based on electrical delay among patients with and without scars could not be performed in this study and will be a matter of future research.

Inter- and intra-observer variability is a known limitation of echocardiographic measurements. In this study, a single, blinded operator conducted all echocardiographic exams and performed all analysis to minimize this possible limitation. The role of acute hemodynamic optimization regarding long-term CRT response is still under debate. PV loop analysis has been used in this study to optimize MPP programming in one study arm. We acknowledge that this strategy is not a common clinical practice in all CRT devices implanting centers; its clinical benefit in the long term has been proven in single-center experiences and not in multicenter randomized trials. However, from our recent study, the use of PV loop optimization has led to an increase in CRT response in MPP patients compared to conventional biventricular pacing [17]. According to the abovementioned reasons, we have decided to compare a simpler and non-invasive approach to a more complex and invasive one, which finally resulted in similar CRT outcomes.

6 Conclusions

CRT with MultiPoint LV pacing improved LV reverse remodeling and LV function and response rate at 6 months was in line with previous long-term MPP investigation and higher than typically observed with conventional CRT.

An empirical MPP programming optimization by maximizing spatial separation of LV cathodes seems to offer similar CRT response rate as compared to acute hemodynamic optimization using PV loop. These findings might offer an effective and simple method for programming CRT-MPP devices; however, randomized multicentre studies are needed to finally confirm these promising results.

Compliance with ethical standards

Conflict of interest LMcS, KR, IC, and JM are employed by Abbott. All other authors have nothing to disclose.

Ethical approval The study protocol was approved, and all procedures were performed in accordance with the local ethics committee.

Informed consent All patients provided written informed consent before the procedure(s).

References

1. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, de Marco T, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med. 2004;350:2140–50.
2. Cleland JGF, Daubert J-C, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med. 2005;352:1539–49.
3. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med. 2009;361:1329–38.
4. Tang ASL, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med. 2010;363:2385–95.
5. Goldenberg I, Kutyifa V, Klein HU, Cannom DS, Brown MW, Dan A, et al. Survival with cardiac-resynchronization therapy in mild heart failure. N Engl J Med. 2014;370:1694–701.
6. Fornwalt BK, Sprague WW, BeDell P, Suever JD, Gerritse B, Merlino JD, et al. Agreement is poor among current criteria used to define response to cardiac resynchronization therapy. Circulation. 2010;121:1985–91.
7. Birnie DH, Tang AS. The problem of non-response to cardiac resynchronization therapy. Curr Opin Cardiol. 2006;21:20–6.
8. Menardi E, Ballari GP, Goletto C, Rossetti G. Characterization of ventricular activation pattern and acute hemodynamics during multipoint left ventricular pacing. Heart Rhythm. 2015;12:1762–9.
9. Shetty AK, Sohal M, Chen Z, Ginks MR, Bostock J, Amraoui S, et al. A comparison of left ventricular endocardial, multisite, and multipolar epicardial cardiac resynchronization: an acute haemodynamic and electroanatomical study. Europace. 2014;16:873–9.

10. Rinaldi CA, Kranig W, Leclercq C, Kacet S, Betts T, Bordachar P, et al. Acute effects of multisite left ventricular pacing on mechanical dyssynchrony in patients receiving cardiac resynchronization therapy. J Card Fail. 2013;19:731–8.

11. Rinaldi CA, Leclercq C, Kranig W, Kacet S, Betts T, Bordachar P, et al. Improvement in acute contractility and hemodynamics with multipoint pacing via a left ventricular quadripolar pacing lead. J Interv Card Electrophysiol. 2014;40:75–80.

12. Osca J, Alonso P, Cano O, et al. The use of multisite left ventricular pacing via quadripolar lead improves acute haemodynamics and mechanical dyssynchrony assessed by radial strain speckle tracking: initial results. Europace. 2015:1–8.

13. Pappone C, Ćalović Ž, Vicedomini G, Cuko A, McSpadden LC, Ryu K, et al. Multipoint left ventricular pacing improves acute hemodynamic response assessed with pressure-volume loops in cardiac resynchronization therapy patients. Heart Rhythm. 2014;11:394–401.

14. Thibault B, Dubuc M, Khairy P, Guerra PG, Macle L, Rivard L, et al. Acute haemodynamic comparison of multisite and biventricular pacing with a quadripolar left ventricular lead. Europace. 2013;15:984–91.

15. Zanon F, Baracca E, Pastore G, Marcantoni L, Fraccaro C, Lanza D, et al. Multipoint pacing by a left ventricular quadripolar lead improves the acute hemodynamic response to CRT compared with conventional biventricular pacing at any site. Heart Rhythm. 2015;12:975–81.

16. Pappone C, Ph D, Cuko A, et al. Multipoint left ventricular pacing in a single coronary sinus branch improves mid-term echocardiographic and clinical response to cardiac resynchronization therapy. J Cardiovasc Electrophysiol. 2014:1–6.

17. Pappone C, Calovic Z, Vicedomini G, et al. Improving cardiac resynchronization therapy response with multipoint left ventricular pacing: twelve-month follow-up study. Heart Rhythm. 2015;12: 1250–8.

18. Forleo GB, Santini L, Giammaria M, et al. Multipoint pacing via a quadripolar left-ventricular lead: preliminary results from the Italian registry on multipoint left-ventricular pacing in cardiac resynchronization therapy (IRON-MPP). Europace 2016; euw094.

19. Zanon F, Marcantoni L, Baracca E, Pastore G, Lanza D, Fraccaro C, et al. Optimization of left ventricular pacing site plus multipoint pacing improves remodeling and clinical response to cardiac resynchronization therapy at 1 year. Heart Rhythm. 2016;13: 1644–51.

20. Dickstein K, Vardas PE, Auricchio A, et al. 2010 Focused Update of ESC Guidelines on device therapy in heart failure: an update of the 2008 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC guidelines for cardiac and resynchronization therapy. Eur Heart J. 2010;31:2677–87.

21. Thibault B, Dubuc M, Karst E, Andrade J, Dyrda K, Guerra PG, et al. Design of an acute dP/dt hemodynamic measurement protocol to isolate cardiac effect of pacing. J Card Fail. 2014;20:365–72.

22. Bleeker GB, Bax JJ, Fung JW-H, van der Wall EE, Zhang Q, Schalij MJ, et al. Clinical versus echocardiographic parameters to assess response to cardiac resynchronization therapy. Am J Cardiol. 2006;97:260–3.

23. Yu C-M, Chan Y-S, Zhang Q, Yip GWK, Chan CK, Kum LCC, et al. Benefits of cardiac resynchronization therapy for heart failure patients with narrow QRS complexes and coexisting systolic asynchrony by echocardiography. J Am Coll Cardiol. 2006;48:2251–7.

24. Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, et al. Results of the Predictors of Response to CRT (PROSPECT) trial. Circulation. 2008;117:2608–16.

25. St MG, Sutton J, Plappert T, et al. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. Circulation. 2003;107:1985–90.

26. Verhaert D, Grimm RA, Puntawangkoon C, Wolski K, de S, Wilkoff BL, et al. Long-term reverse remodeling with cardiac resynchronization therapy results of extended echocardiographic follow-up. J Am Coll Cardiol. 2010;55:1788–95.

27. Niazi I, Baker J II, Corbisiero R, et al. Safety and efficacy of MultiPoint pacing in cardiac resynchronization therapy: the MultiPoint Pacing (MPP) IDE Study. JACC Clin Electropysiol. 2017;13:1510–8.

28. ClinicalTrials.gov. MOre REsponse on Cardiac Resynchronization Therapy with MultiPoint Pacing (MORE-CRT MPP).

29. Leclercq C, Burri H, Curni A, et al. Six-month biventricular CRT response with quadripolar CRT system in more response on Cardiac Resynchronization Therapy with MultiPoint Pacing (MORE-CRT MPP) trial. EP Europace. 2017;19:87–8.

30. Duckett SG, Ginks M, Shetty AK, Bostock J, Gill JS, Hamid S, et al. Invasive acute hemodynamic response to guide left ventricular lead implantation predicts chronic remodeling in patients undergoing cardiac resynchronization therapy. J Am Coll Cardiol. 2011;58: 1128–36.

31. Bogaard MD, Houthuizen P, Fa B, et al. Baseline left ventricular dP/dtmax rather than the acute improvement in dP/dtmax predicts clinical outcome in patients with cardiac resynchronization therapy. Eur J Heart Fail. 2011;13:1126–32.

32. Stellbrink C, Oa B, Franke A, et al. Impact of cardiac resynchronization therapy using hemodynamically optimized pacing on left ventricular remodeling in patients with congestive heart failure and ventricular conduction disturbances. J Am Coll Cardiol. 2001;38:1957–65.

33. Filippatos G, Birnie D, Gold MR, Gerritse B, Hersi A, Jacobs S, et al. Rationale and design of the AdaptResponse trial: a prospective randomized study of cardiac resynchronization therapy with preferential adaptive left ventricular-only pacing. Eur J Heart Fail. 2017;19:950–7.