Optimization of left ventricular pacing site plus multipoint pacing improves remodeling and clinical response to cardiac resynchronization therapy at 1 year

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BACKGROUND Approximately one-third of the patients with heart failure (HF) treated with cardiac resynchronization therapy (CRT) fail to respond. Positioning the left ventricular (LV) pacing lead in the area of the latest electrical delay may improve the response to CRT. Multipoint pacing (MPP) of the LV has been shown to improve the acute hemodynamic response.

OBJECTIVE The purpose of this study was to test the hypothesis that patients treated with MPP in whom LV pacing location is optimized have better long-term clinical outcomes than do patients treated with conventional CRT.

METHODS We evaluated the echocardiographic and clinical response of 110 patients with HF treated for nearly 1 year with either conventional CRT (standard [STD] group, n = 54, 49%), CRT with hemodynamic and electrical optimization of the LV pacing site (optimized [OPT] group, n = 36, 33%), or OPT combined with MPP (OPT + MPP group, n = 20, 18%). Responders were classified in terms of reduction in end-systolic volume index ≥15%, reduction in New York Heart Association (NYHA) class ≥1, and Packer score variation (NYHA response with no HF-related hospitalization events or death).

RESULTS In STD, OPT, and OPT + MPP groups, 56%, 72%, and 90% of patients, respectively, were end-systolic volume index responders ($P = .004$) and 67%, 78%, and 95% were NYHA class responders ($P = .012$); 59%, 67%, and 90% of patients exhibited a 1-year Packer score of 0 ($P = .018$). These trends remained significant after adjustment for confounding factors by multivariate logistic analysis.

CONCLUSION Combining MPP with optimal positioning of the LV lead on the basis of electrical delay and hemodynamics enhances reverse remodeling and improves clinical outcomes beyond the effect due to conventional CRT.

KEYWORDS Heart failure; Cardiac resynchronization therapy; Multipoint pacing; Hemodynamic response; Left ventricular pacing; Electrical delay

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Introduction

Cardiac resynchronization therapy (CRT) involves electrical stimulation of the left ventricle (LV) of patients with heart failure (HF). Commonly applied through a tributary of the coronary sinus, it attempts to restore ventricular synchrony and improve hemodynamics. CRT has been shown to reduce HF-related morbidity and mortality and to improve quality of life.[1–3] However, in approximately one-third of the patients with HF, CRT fails to improve clinical parameters, and in up to 50% of the treated patients it does not reverse LV remodeling (decrease in LV end-systolic volume [ESV]).[4,5]

Efforts to address CRT nonresponse have included optimizing the LV pacing site. While attempts have been made to identify superior LV pacing sites on the basis of anatomy alone, but consistent correlations with CRT response have not emerged across patient populations.[6] Addressing electrical dyssynchrony directly by pacing at the latest activated LV site, however, seems promising. Previous studies,[7,8] including ours,[9] have demonstrated a correlation between the intrinsic electrical delay of an LV

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pacing site and subsequent improvement in hemodynamics and reduction in electrical dyssynchrony. Specifically, positive correlations have emerged between Q-LV (LV lead electrical delay) and both LV dP/dt_{max} (maximum rate of increase in LV pressure) and QRS narrowing.[9] Moreover, pacing at sites with longer Q-LV is linked to better long-term outcome.[7,10,11]

The recently introduced quadripolar leads simplify pacing site selection by allowing the LV pacing site along a target vein to be remotely programmed without lead repositioning. Additional acute hemodynamic improvement has been achieved with the introduction of multipoint pacing (MPP) of the LV,[12–17] whereby multiple LV sites along the single quadripolar lead are stimulated in order to capture a broader region of excitable myocardium.[18] It has been demonstrated that MPP elicits a greater hemodynamic improvement than does conventional CRT (pacing single sites at the right ventricular [RV] and the LV lead) in terms of LV dP/dt_{max},[12,13] pressure-volume loop metrics,[14] LV radial strain,[15] LV outflow tract velocity-time integral,[16] and impedance cardiography.[17]

However, little information is available on the long-term benefits of MPP and there is conflicting evidence as to whether the acute hemodynamic response to CRT predicts long-term clinical outcome.[19,20] We therefore aimed to investigate the long-term effects of optimized LV lead placement, both alone and in combination with MPP. To this end, we analyzed the 1-year follow-up data on patients treated in our hospital and compared echocardiographic and clinical improvements in 3 patient groups: those undergoing conventional CRT, those with optimized lead placement (lead at the longest Q-LV), and those in whom optimized lead placement was combined with MPP.

Methods

Study design

This investigation was a retrospective single-center study involving nonparallel cohorts. The study protocol was approved by the local ethics committee and adhered to the principles outlined in the Declaration of Helsinki. All patients enrolled in the study were indicated for CRT in accordance with the European Society of Cardiology/European Heart Rhythm Association guidelines[21] and provided written informed consent to use their clinical data.

The following baseline demographic characteristics, comorbidities, and HF status metrics were recorded before CRT implantation: age, sex, New York Heart Association (NYHA) class, LV ejection fraction, end-diastolic volume index (EDVi), end-systolic volume index (ESVi), QRS duration, and history of ischemic cardiomyopathy, left bundle branch block, percutaneous coronary intervention (PCI), coronary artery bypass graft, valvular disease, acute myocardial infarction, diabetes, hypertension, atrial fibrillation, and renal failure (glomerular filtration rate <30 mL/min). EDVi and ESVi were calculated as the ratio of EDV and ESV to body surface area, respectively. Echocardiographic parameters and inter- and intraobserver variability in our center have already been described.[22]

QRS morphology was classified according to American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society guidelines.[23] Because all these measurements had been taken as part of standard clinical care in our center and before the study groups were formed, the researchers performing the analyses were blinded to the group to which a patient belonged.

In accordance with our standard implantation procedure, the RV lead was implanted in the mid-septum and the atrial lead was implanted in the right atrial appendage. A previously described telescopic approach[24] was used for cannulation of the coronary sinus and subcannulation of all suitable collateral veins; this approach allows continuous selective navigation with angiographic visualization. All veins that were actually cannulated and then targeted with the LV pacing lead were defined as available veins. We did not collect data on veins that were visualized but not cannulated. LV pacing sites were anatomically classified by using a system previously established by Singh et al.[25] Briefly, on segmenting the left anterior oblique (short-axis) fluoroscopic view, the pacing site was classified as anterior, anterolateral, lateral, posterolateral, or posterior; on segmenting the right anterior oblique (long-axis) fluoroscopic view, the pacing site was classified as basal, mid, or apical.

After nearly 1 year of follow-up, patients were reevaluated to determine the chronic response to resynchronization therapy; ESVi, NYHA class, and Packer score[26] were compared with the preimplantation baseline values. "ESVi responders" were those with a reduction in ESVi of $\geq$15%[27]; "NYHA responders" were those with a reduction in NYHA class of $\geq$1; and "Packer responders" were those exhibiting a Packer score of 0, indicating a reduction in NYHA class with no HF-related hospitalization events or death in the year before the follow-up examination.

Cohort description

Three groups of patients were compared.

The conventional CRT group was composed of 54 consecutive patients with HF with conventional CRT devices equipped with bipolar LV leads without any optimization (standard [STD] group). The STD group received CRT treatment between January 2011 and March 2012. According to our practice,[24] coronary sinus angiography was performed to visualize a target vein in the LV free wall, preferably in the lateral or posterolateral region. The target vein was chosen according to the angle, bifurcation, and caliber of the vessel; the anatomical position along the LV free wall (for lead stability); and the electrical parameters (pacing threshold and phrenic nerve stimulation).

The second CRT group was composed of 36 patients with HF with CRT devices equipped with either bipolar or quadripolar LV leads, the sites of which were optimized on the basis of LV dP/dt_{max} and Q-LV (optimized [OPT] group). OPT group patients underwent implantation between

April 2012 and June 2013. All the veins of the coronary sinus were subcannulated using an angiographic telescopic approach to selectively visualize all suitable collateral veins, as described in our previous study.[9] At each pacing site, classified in accordance with the criterion used by Singh et al,[25] QRS duration and electrical delay (Q-LV) were measured using a BARD LabSystem Pro EP V2.4a recording system (C.R. Bard Inc, Lowell, MA). The *Q-LV interval* was defined as the interval from the onset of the intrinsic QRS on the surface electrocardiogram to the first large positive or negative peak of the LV electrogram, recorded in bipolar configuration. Measurements of LV dP/dt_{max} were taken with a Certus Pressure Wire and PhysioMon software (St. Jude Medical Systems AB, Uppsala, Sweden). The LV lead was left at the pacing site corresponding to the greatest increase in LV dP/dt_{max} (also corresponding to the latest activated site, as previously reported[9]).

The third group was composed of 20 patients. After the same acute optimization procedure described for the OPT group, these patients received CRT devices equipped with quadripolar LV pacing leads capable of delivering MPP therapy (Quadra Assura MP CRT-D with the Quartet lead, St. Jude Medical, Sylmar, CA) (OPT + MPP group). OPT + MPP group patients underwent implantation between July 2013 and October 2014.

In all patients, CRT devices were programmed with a fixed atrioventricular delay of 130 ms. In STD and OPT groups, simultaneous interventricular RV-LV pacing was programmed. CRT devices in the OPT + MPP group were programmed with 5 ms (minimum value available) intraventricular LV1-LV2 pacing and 5 ms (minimum value available) interventricular LV2-RV pacing. The first vector (LV1) was selected according to the last electrically activated site.

Statistical analysis

To compare characteristics between patient groups (STD, OPT, and OPT + MPP) at the baseline and follow-up examination, the Pearson χ^2 test was used for categorical parameters, while 1-way analysis of variance was used for continuous parameters. The Bonferroni post hoc method was used for descriptors with different distribution between patient groups.

The χ^2 test was used for the intergroup comparison of the proportions of the responses considered (ESVi, NYHA class, and Packer score); values are presented with their 95% confidence intervals (Wilson's calculation method).[28] A linear-by-linear association test for trend was also carried out.

Potential confounders (male sex, age, left bundle branch block, atrial fibrillation, CRT with defibrillator, ischemic cardiomyopathy, acute myocardial infarction, percutaneous coronary intervention-coronary artery bypass grafting (PCI-CABG), valvulopathy, hypertension, glomerular filtration rate <30 mL/min, diabetes, oral anticoagulation therapy, antiarrhythmic therapy, basal ESVi, and basal NYHA class) were selected using the Wald's forward stepwise method and were included as covariates in 3 multivariate logistic regression models, together with the type of pacing implemented (with STD pacing as reference) and the response considered (ESVi or NYHA class or Packer score) as dependent variables. Interactions between the factors included were tested. Adjusted odds ratios (ORs) for each factor and their 95% confidence intervals, correct classification proportions, and χ^2 statistics for the final models were calculated. In the logistic regression models, a probability level to enter the models was fixed at $P<.10$.

All calculations were performed using SPSS version 22.0 (IBM Corp, Armonk, NY).

Results

Study population

Preimplantation baseline patient demographic characteristics, comorbidities, and HF metrics in all 3 groups were similar overall, except for age, which was significantly higher in the OPT group (Bonferroni test for post hoc comparison: OPT vs STD, $P = .01$; OPT vs OPT + MPP, $P = .005$) (Table 1).

The anatomical distribution of LV leads in each group is illustrated in Figure 1. No significant differences were found between the 3 groups. LV leads were predominantly placed in mid-to-apical sites along veins in the lateral LV wall, but there were more posterolateral lead placements in the STD group.

We collected data from echocardiography images looking for the akinetic/dyskinetic regions. In particular, an anterior/anteroseptal akinetic/dyskinetc region was present in 18.5%, 16.6%, and 10% of patients in STD, OPT, and OPT + MPP groups, respectively. A posterior akinetic/dyskinetic region was present in 11.1%, 25%, and 20% of patients in STD, OPT, and OPT + MPP groups, respectively. A lateral akinetic/dyskinetic region was present in 7.4%, 13.8%, and 10% of patients in STD, OPT, and OPT + MPP groups, respectively. No significant differences in the distribution of akinetic/dyskinetic areas were found in the 3 groups. A total of 3.0 ± 0.8 and 3.1 ± 0.6 veins per patient were cannulated in OPT and OPT + MPP groups, respectively, while the mean number of veins not suitable for cannulation was 0.26 ± 0.35 and 0.27 ± 0.43 veins per patient (small size or extreme tortuosity) in OPT and OPT + MPP groups, respectively.

In OPT and OPT + MPP groups, the lead was placed at the longest Q-LV site, with the exception of 1 case (a patient of the OPT group), in whom the lead was slightly pulled back to a mid position owing to the high phrenic nerve stimulation pacing threshold in the lateral-apical position. At this site, the Q-LV and the increase in LV dP/dt_{max} were the second highest values of the sets.

Chronic CRT response

Follow-up evaluations of the response to CRT were performed in STD, OPT, and OPT + MPP groups approximately 300 days

Table 1 Baseline patient characteristics.

	STD (n = 54, 49%)	OPT (n = 36, 33%)	OPT + MPP (n = 20, 18%)	p
Age (years, mean±SD)	69.7 ± 10.4	76.1 ± 6.5	67.4 ± 12.5	0.002
Male Gender (%)	37 (68.5)	24 (66.7)	16 (80.0)	0.549
LBBB (%)	33 (61.1)	22 (61.1)	13 (65.0)	0.95
AF (%)	15 (27.8)	13 (36.1)	8 (40.0)	0.530
ICMP (%)	27 (50.0)	20 (55.6)	11 (55.0)	0.853
AMI (%)	18 (33.3)	17 (47.2)	6 (30.0)	0.311
PCI-CABG (%)	18 (33.3)	14 (38.9)	7 (35.0)	0.863
Valvulopathy (%)	9 (16.7)	8 (22.2)	2 (10.0)	0.143
Hypertension (%)	43 (79.6)	32 (88.9)	15 (75.0)	0.366
Creatinine (ml, mean±SD)	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	0.826
GFR < 30.0 (mL/min)	8 (14.8)	3 (8.3)	1 (5.0)	0.404
Diabetes (%)	19 (35.2)	8 (22.2)	5 (25.0)	0.376
Insulin therapy (%)	7 (13.0)	5 (13.9)	1 (5.0)	0.575
OAT (%)	17 (31.5)	16 (44.4)	9 (45.0)	0.364
Primary prevention (%)	10 (18.5)	5 (13.9)	1 (5.0)	0.339
Optimized medical therapy (%)	39 (72.2)	29 (80.6)	16 (80.0)	0.603
LVEF (%, mean±SD)	30.4 ± 6.3	31.1 ± 6.3	27.2 ± 4.3	0.054
ESVi (ml/m^2, mean ± SD)	76.6 ± 25.4	70.7 ± 27.7	72.9 ± 28.2	0.572
NYHA class (%)				
I	1 (1.9)	0	0	0.700
II	11 (20.4)	5 (13.9)	3 (15.0)	
III	37 (68.5)	30 (83.3)	16 (80.0)	
IV	5 (9.3)	1 (2.8)	1 (5.0)	

AF = atrial fibrillation; AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CRT = cardiac resynchronization therapy; ESVi = end-systolic volume index; GFR = glomerular filtration rate; ICMP = ischemic cardiomyopathy; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MPP = MultiPoint Pacing; NYHA = New York Heart Association; OAT = oral anticoagulant therapy; OPT = CRT with optimized left ventricular site; PCI = percutaneous coronary intervention; SD = standard deviation; STD = standard.

postimplantation. Characteristics at the end of follow-up (ESVi, NYHA class, NYHA class variation, and number of events including all-cause death or HF hospitalization) are summarized in Table 2.

The response rates in terms of ESVi, NYHA class, and Packer score are listed in Table 3 and presented in Figure 2.

In terms of a ≥15% reduction in ESVi relative to preimplantation baseline values, 55.6% (30 of 54) of patients in the STD group, 72.2% (26 of 36) in the OPT group, and 90.0% (18 of 20) in the MPP + OPT group were considered as responders.

In terms of a reduction in NYHA class, 66.7% (36 of 54) of patients in the STD group, 77.8% (28 of 36) in the OPT group, and 95% (19 of 20) in the MPP + OPT group were considered responders. The NYHA class improvement in each group is shown in Figure 3.

Interestingly, 35% (7 of 20) of patients in the MPP + OPT group showed an NYHA class downgrade of 2 or more classes as compared with only 20.4% (11 of 54) of patients in the STD group and 11.1% (4 of 36) of patients in the OPT group. Similarly, more patients in the MPP + OPT group than in the STD and OPT groups were Packer score

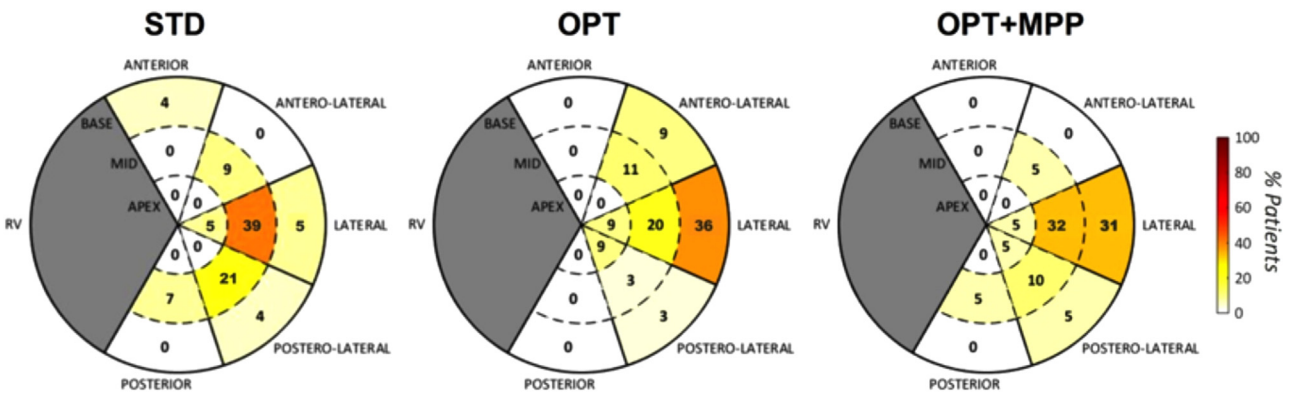

Figure 1 Anatomical distribution of LV leads. Distribution of lead location among the 15 LV wall segments, shown as the percentage of patients in each group. LV = left ventricular; MPP = multipoint pacing; OPT = optimized; RV = right ventricle; STD = standard.

Table 2 Patient characteristics at 1-year follow-up.

	STD (n = 54)	OPT (n = 36)	OPT + MPP (n = 20)	P
Follow-up (days, mean ± SD)	317.7 ± 99.8	300.6 ± 96.9	281.3 ± 97.5	0.349
ESVi (ml/m^2, mean ± SD)	61.4 ± 26.8	53.3 ± 25.1	59.1 ± 27.1	0.357
NYHA class (%)				
I	12 (22.2)	6 (16.7)	14 (25.0)	0.182
II	33 (61.1)	25 (69.4)	37 (66.1)	
III	9 (16.7)	4 (11.1)	4 (7.1)	
IV	0 (0)	1 (2.8)	1 (1.8)	
NYHA class delta (%)				
0	18 (33.3)	8 (22.2)	1 (5.0)	0.046
-I	25 (46.3)	24 (66.7)	12 (60.0)	
-II	9 (16.7)	4 (11.1)	7 (35.0)	
-III	2 (3.7)	0	0	
Events (%)[†]	5 (9.3)	7 (19.4)	1 (5.0)	0.198

CRT = cardiac resynchronization therapy; ESVi = end-systolic volume index; LV = left ventricle; MPP = MultiPoint Pacing; NYHA = New York Heart Association; OPT = CRT with optimized LV site; SD = standard deviation; STD = standard CRT.

[†]Events: number of events in the follow-up period (all-cause death or hospitalization due to HF worsening).

responders. In the MPP + OPT group, 90% (18 of 20) of patients experienced a reduction in NYHA class with no 1-year HF-related hospitalization or death (Packer score 0) as compared with 59.3% (32 of 54) of patients in the STD group and 66.7% (24 of 36) of patients in the OPT group.

We collected data on pacing history during follow-up, and in particular pacing percentage, premature ventricular contraction, and atrial fibrillation burden did not significantly differ between groups. Moreover, the compliance with drug therapy between groups did not vary significantly.

Multivariate analysis

Each of the responses considered, ESVi, NYHA class, and Packer score, was included as a dependent variable in 3 distinct multivariate logistic regression models.

As shown in Table 4, OPT + MPP was a strong predictor of ESVi response vs STD pacing (OR 9.53; $P = .007$), whereas no difference was found between OPT and STD pacing (OR 2.16; $P = .118$). Two other factors were significantly associated with ESVi response: the favorable presence of hypertension (OR 3.03; $P = .048$) and the unfavorable effect of PCI-coronary artery bypass graft (OR 0.33; $P = .016$).

With regard to NYHA response, OPT + MPP displayed a strong independent effect vs STD pacing (OR 9.59; $P = .044$), whereas no difference was found between OPT and STD pacing (OR 1.38; $P = .568$). Two other factors were significantly associated with NYHA response: the baseline NYHA class (OR 8.83; $P = .001$; in that we most frequently observed a decrease in NYHA class in the more severe cases) and the unfavorable effect of the presence of severe renal insufficiency (OR 0.18; $P = .024$).

An independent effect on Packer's response was exerted by OPT + MPP vs STD pacing (OR 7.95; $P = .064$), whereas no difference was found between OPT and STD pacing (OR 1.20; $P = .742$). Two other factors were significantly associated with Packer's response: the baseline NYHA class (OR 9.64; $P = .001$) and the unfavorable strong effect of the presence of severe renal insufficiency (OR 0.01; $P = .001$).

No significant interactions were found between factors included in the models.

Discussion

Our retrospective single-center study is the first to demonstrate that the combination of OPT and MPP improves long-term outcome of CRT to levels of around 90%. In the STD group, the percentage of responders (56% volumetric responders and 67% NYHA class responders) was well within the range indicated in a large number of studies, which reported a lack of clinical response in approximately 30% of patients and a lack of structural remodeling response in

Table 3 CRT Response Rates.

	STD (54) (%; 95% CI)	OPT (36) (%; 95% CI)	OPT + MPP (20) (%; 95% CI)	P
ESVi response	30 (55.6%; 42.4-68.0)	26 (72.2%; 56.0-84.2)	18 (90%; 69.9-97.2)	$X^2 = 0.015$[†] $LT = 0.004$
NYHA response	36 (66.7%; 53.4-77.8)	28 (77.8%; 61.9-88.3)	19 (95.0%; 76.4-99.1)	$X^2 = 0.039$[†] $LT = 0.012$
PACKER's response	32 (59.3%; 46.0-71.3)	24 (66.7%; 50.3-79.8)	18 (90.0%; 69.9-97.2)	$X^2 = 0.043$[†] $LT = 0.018$

CI= confidence intervals; CRT = cardiac resynchronization therapy; ESVi = end-systolic volume index; LT= Linear trend; MPP = multipoint pacing; NYHA = New York Heart Association; OPT = optimized; STD = standard.

[†]X^2= Pearson chi-square.

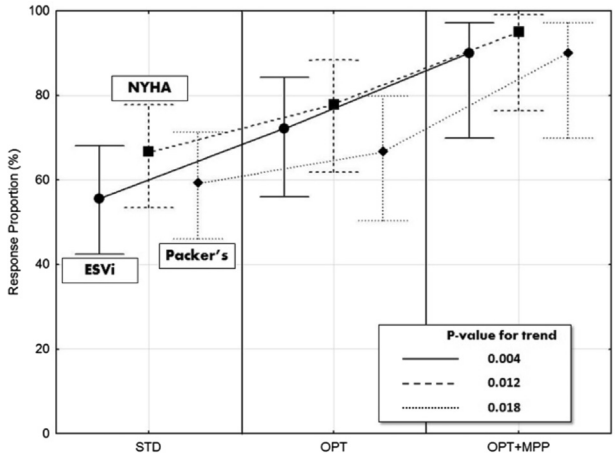

Figure 2 ΔESVi, ΔNYHA, and Packer's response rates. Response indicates ΔESVi ≥15%, ΔNYHA class >0, or Packer score 0 at follow-up relative to preimplantation baseline values. The vertical segments represent the 95% confidence intervals of the estimated proportions. ESVi = end-systolic volume index; MPP = multipoint pacing; NYHA = New York Heart Association; OPT = optimized; STD = standard.

40%–50%.[4,5] Although optimization of LV lead positioning tended to improve this response, the increase was not significant in this relatively small population. However, implementing MPP at optimized LV pacing sites resulted in an adjunctive effect, with an increase in response rates to 90% for ESVi, 95% for NYHA class improvement, and 90% for Packer score.

These data extend earlier observations that OPT and MPP acutely improve both the electrical and the hemodynamic response. Our group linked electrical delay with acute hemodynamic evaluation[9] and found a significant correlation between increased LV dP/dt_{max} and Q-LV in 32 patients. In that study, the correlation was observed in every vein, with an average of 6.4 ± 2.3 pacing sites in each patient.

Recent research has characterized the acute hemodynamic advantages of MPP over conventional biventricular pacing by using a variety of systolic and diastolic metrics.[13–15] Our previous study revealed an acute, intrapatient, hemodynamic superiority of MPP over conventional CRT across multiple veins and LV pacing sites in 90% (26 of 29) of patients.[12]

With regard to long-term outcome, optimal positioning of the LV pacing lead, based on the latest electrical delay, has shown a strong and independent association with reverse remodeling and quality of life[8,11] and with reduced hospitalization and improved survival.[7,10] In the present study, the difference between STD and OPT was not significant; this was probably due to the much smaller sample size than that used in the aforementioned studies.

However, the combination of OPT and MPP did significantly improve long-term CRT response.

In the present study, the mode of MPP applied was dual bipolar pacing (combining bipolar pacing of the 2 proximal and 2 distal electrodes on the lead). No attempts were made to optimize atrioventricular, interventricular, or intraventricular delay. While several studies have shown the acute hemodynamic benefit of optimizing these delays, evidence that such optimization improves long-term response is scarce.[29,30]

Other MPP-focused studies have reported that the intraventricular LV-LV delay between the 2 MPP LV pacing vectors may also impact on acute hemodynamics.[14]

Pappone et al[31] compared the 1-year responses of 44 patients randomized (in a 1:1 ratio) to either MPP or conventional CRT after acute hemodynamic optimization of not only the LV pacing site but also the interventricular RV-LV delay and, in patients treated with MPP, the intraventricular LV-LV delay. Optimal LV pacing sites were chosen from among the electrodes of a quadripolar lead at a fixed position. Pacing vectors were optimized individually on the basis of LV dP/dt_{max} measurements. One-year response rates were reported in terms of a 15% reduction in ESV (76% MPP vs 57% conventional CRT) and improvement in NYHA class (90% MPP vs 84% conventional CRT). The effect size in their study seems smaller than that in our study, supporting the importance of optimizing the lead positioning by exploring different options rather than only a single vein.

Interestingly, in the present study, the distribution of LV lead location was similar across all 3 groups, regardless of whether the position was guided by the electrical delay and, despite potential minor changes in the implantation practice over time, ultimately there were no significant differences in the distribution of the location of the LV lead between the groups. In other words, the pacing site that provided optimal hemodynamics was patient-specific and not associated with

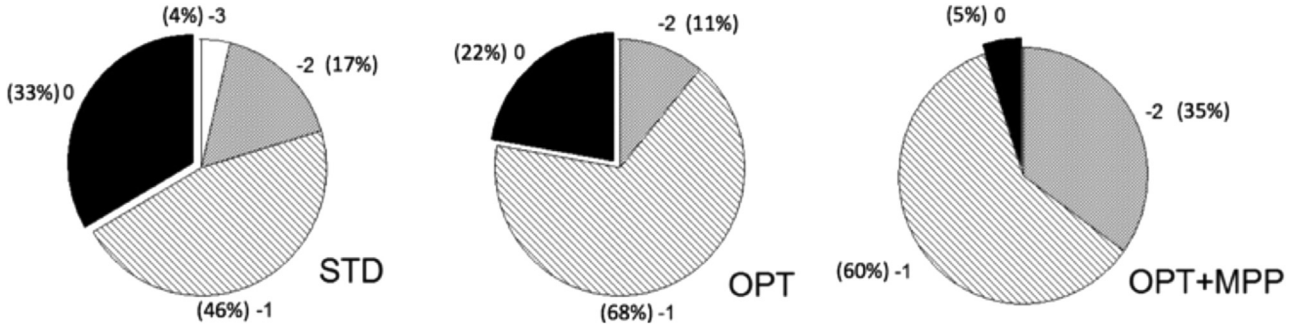

Figure 3 Reduction in NYHA class (NYHA class at follow-up minus baseline NYHA class). The black slice indicates patients who did not show any improvement in NYHA class. MPP = multipoint pacing; NYHA = New York Heart Association; OPT = optimized; STD = standard.

Table 4 Multivariate analysis showing independent predictors of ESVi response, NYHA response and Packer's response.

Logistic regression dependent variable: ESVi response				
Correct Classification= 69.1%, Chi-square=19.1, df=4, p=0.001				
		95% C.I. for OR		
Factors	OR	Lower	Upper	p
CRT: OPT vs STD	2.16	0.82	5.70	0.118
OPT + MPP vs STD	9.53	1.84	49.27	0.007
Hypertension	3.03	1.01	9.10	0.048
PCI-CABG	0.33	0.13	0.81	0.016
Logistic regression dependent variable: NYHA response				
Correct Classification= 81.8%, Chi-square=30.3,df=4, p=0.0001				
		95% C.I. for OR		
Factors	OR	Lower	Upper	p
CRT: OPT vs STD	1.38	0.45	4.23	0.568
OPT + MPP vs STD	9.59	1.06	86.69	0.044
NYHA pre	8.83	2.93	26.61	0.001
GFR < 30	0.18	0.04	0.80	0.024
Logistic regression dependent variable: PACKER's response				
Correct Classification= 80.1%, Chi-square=49.6,df=4, p=0.001				
		95% C.I. for OR		
Factors	OR	Lower	Upper	p
CRT: OPT vs STD	1.20	0.39	3.75	0.742
OPT + MPP vs STD	7.95	0.88	71.58	0.064
NYHA pre	9.64	2.98	31.23	0.001
GFR < 30	0.01	0.001	0.13	0.001

CABG = coronary artery bypass graft; CI = confidence intervals; CRT = cardiac resynchronization therapy; ESVi = end-systolic volume index; GFR = glomerular filtration rate; MPP= multipoint pacing; NYHA = New York Heart Association; OPT = optimized; OR= odds ratio; PCI = percutaneous coronary intervention; STD = standard.

specific anatomical locations across the patient population. This finding is consistent with the difficulty of identifying superior LV pacing sites on the basis of anatomical criteria alone, as experienced in previous studies,[9] and supports the notion that LV lead positioning needs to be optimized individually.

Study limitations

This study was limited to a single center in order to maintain consistency in terms of lead placement and data collection. As a consequence, the patient sample size was limited, although comparable to that of previous MPP studies. As we had observed the acute clinical benefits of MPP in our previous study,[11] we chose not to withhold MPP therapy for the sake of randomizing patients. Although patients were not randomized to each group, none of the baseline characteristics that differed among the study groups were ultimately identified as potential predictors of response rate. Moreover, the distribution of LV lead location was similar between groups, strengthening the concept of a patient-specific best position. But this concept also needs to be confirmed in a randomized clinical trial. Another limitation could be the inclusion of patients in different periods of time. This was the result of a change in our implantation procedure from a conventional to an optimized approach. However, indications for CRT in our clinical practice did not change in this period, as demonstrated by the absence of significant differences in 3 groups.

Another potential limitation is the lack of information of scar burden because magnetic resonance imaging examination was not part of the preimplantation screening in all 3 groups.

In light of the inherent limitations of this study, its implications should be confirmed in a larger, randomized, prospective, multicenter study.

Conclusion

The results of this follow-up study demonstrate the long-term superiority of LV site optimization plus MPP over conventional CRT. Combining MPP with acute optimization, both electrical and hemodynamic, was found to be able to reverse the long-term progression of HF and to improve clinical outcomes, resulting in response rates of around 90%.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.hrthm.2016.05.015.

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