Journal of Interventional Cardiac Electrophysiology (2019) 56:117–125
https://doi.org/10.1007/s10840-019-00592-1

REVIEWS

Multisite pacing via a quadripolar lead for cardiac resynchronization therapy

Alexandre Bodin[1] · Arnaud Bisson[1] · Clémentine Andre[1] · Bertrand Pierre[1] · Laurent Fauchier[1] · Dominique Babuty[1] · Nicolas Clementy[1]

Received: 8 March 2019 / Accepted: 10 July 2019 / Published online: 18 July 2019

Abstract
Cardiac resynchronization therapy is challenging. Up to 40% of patients are non-responder. Multisite pacing via a quadripolar lead, also called multipoint/multipole pacing (MPP), is a debated alternative. In this review, we summarize evidence in the literature, tips and pitfalls related to MPP programming, and the different algorithms of MPP in different manufacturers.

Keywords Biventricular pacing · Cardiac resynchronization therapy · Multipoint pacing · Multisite pacing

1 Introduction

Up to 40% of patients are non-responder to cardiac resynchronization therapy (CRT) [1–4]. Response to CRT depends on many variables including QRS duration, left bundle branch block morphology, left ventricular (LV) pacing site, and amount of scar tissue [5–12].

The concept of LV multisite pacing (MSP) uses 2 pacing cathodes to induce a larger LV depolarization wavefront and a subsequent shorter total LV activation time. MSP using 2 distinct bipolar leads linked through a Y connector initially proved to be associated with larger LV reverse remodeling than conventional biventricular (biV) pacing and an improved response to CRT especially in patients with posterolateral scar [13, 14]. MSP via multivein pacing has some clinical limitations: longer procedure times, higher radiation doses, limited venous anatomy, and the potential complications related to an additional lead (pocket bulk, need for Y connector and bipolar LV leads, faster battery drain).

MSP through a single quadripolar lead (using 2 pacing cathodes out of 4 electrodes), also called multipoint/multipole pacing (MPP), is an easier technique [15–17]. It also showed acute improvements in contractility, hemodynamics, and dyssynchrony as compared with biV pacing [18–33], especially in patients less likely to benefit from conventional CRT (narrower QRS, atypical LBBB morphology, type I LV activation, scar) [34–36].

We review evidence in literature, the potential tips and pitfalls related to MPP programming, and the different algorithms of MPP through a single quadripolar lead in different manufacturers.

2 Clinical observations in literature (Table 1)

MPP showed acute hemodynamics improvements compared with standard biV pacing: increased LV ejection fraction (LVEF), cardiac index, stroke work, and volume [21, 25]; increased LV dP/dt_{max} [18, 21–23] and systolic blood pressure [31]; improvement of radial strain [20, 25] and non-invasive radial artery tonometry parameters [30]; and reduction in end-diastolic and end-systolic volumes [27] and end-diastolic LV pressure [21].

MPP also showed a reduced QRS duration [23], a significant dyssynchrony echocardiographic parameter improvement [19], and a quicker activation of the LV [33] compared with biV pacing.

At 6 months and 1 year of follow-up, MPP activated after implantation showed a better CRT response rate with an improvement of clinical scores (NYHA, CCS, and Packer), an increase in LVEF, and a reduction of LV end-systolic volume compared with biV [24, 26, 29, 31].

✉ Alexandre Bodin
alexandre.bodin@etu.univ-tours.fr

[1] Service de Cardiologie, Centre Hospitalier Universitaire Trousseau et EA7505, Faculté de Médecine, Université François Rabelais, Tours, France

Table 1 Clinical observations with MPP in literature

First author, year	Type of study, number of patients	Comparison	Main findings
Thibault et al. 2013 [18]	Prospective single-center, non-randomized clinical trial. $n = 19$.	Acute intraoperative assessment of LV hemodynamics of MPP and biV in the same patient.	- In 84% of patients, ≥ 2/4 MPP configurations increased LV dP/dt_{max} compared with biV pacing. - Pacing from the most distal and proximal electrodes was the most common optimal configuration, superior to biV pacing in 74% of patients.
Rinaldi et al. 2013 [19]	Prospective multicenter, observational study. $n = 41$.	Acute intraoperative assessment of echocardiographic dyssynchrony of MPP and biV in the same patient.	- Mean time-to-peak contraction of 12 LV segments (Ts-SD) was significantly lower for the optimal MPP configuration (35.3 ± 36.4 vs 50.2 ± 29.1 ms; $p = 0.01$). - At least 1 MPP configuration exhibited a significant dyssynchrony improvement in 63% of patients. - The mean number of LV segments with delayed longitudinal contractions was significantly reduced with the optimal MPP configuration (0.37 ± 7.99 vs 2.20 ± 0.19; $p < 0.001$).
Rinaldi et al. 2014 [20]	Prospective multicenter, observational study. $n = 40$.	Acute intraoperative assessment of echocardiographic radial strain and VTI in the left ventricular outflow tract (LVOT) of MPP and biV in the same patient.	- Mean peak radial strain: 18.3 ± 7.4% in MPP patients vs. 9.3 ± 5.3% in the biV group ($p < 0.001$). - LVOT mean ITV was obtained in 13 patients: 13.5 ± 2.7 cm in the MPP group vs. 10.9 ± 3.3 cm in the biV group ($p < 0.01$).
Pappone et al. 2014 [21]	Prospective single-center, observational study. $n = 42$.	Acute intraoperative assessment of LV hemodynamics of MPP and biV in the same patient.	Best MPP vs best biV: - Increase of dP/dt_{max}: 15.9 ± 10.0% vs 13.5 ± 8.8%; $p = 0.001$. - Increase of stroke work: 27.2 ± 42.5% vs 19.4 ± 32.2%; $p = 0.018$. - Increase of stroke volume: 10.4 ± 22.5% vs 4.1 ± 13.1%; $p = 0.003$. - Increase of LVEF: 10.5 ± 20.9% vs 5.3 ± 13.2%; $p = 0.003$. - Decrease of end-diastolic pressure: 18.2 ± 22.4% vs 8.7 ± 21.4%; $p = 0.001$.
Zanon et al. 2015 [22]	Prospective single-center, observational study. $n = 29$.	Acute intraoperative assessment of LV hemodynamics of MPP and biV in the same patient.	Increase in dP/dt_{max}: - All sites considered: 951 ± 193 mmHg/s at baseline, biV: 1144 ± 255 mmHg/s, MPP: 1178 ± 259 mmHg/s. - Best site considered: 942 ± 202 mmHg/s at baseline, biV: 1200 ± 267 mmHg/s, MPP: 1231 ± 267 mmHg/s.
Menardi et al. 2015 [23]	Prospective single-center, observational study. $n = 10$.	Acute intraoperative assessment of contact mapping and LV hemodynamics of MPP and biV in the same patient.	- Increased LV dP/dt_{max} (30 ± 13% vs. 25 ± 11%, $p = 0.041$). - Reduced QRS duration (22 ± 11% vs. 11 ± 11%, $p = 0.01$). - Decreased total endocardial activation time (25 ± 15% vs. 10 ± 20%, $p = 0.01$). - MPP resulted in a larger capture of LV mass during the first 25 ms

Table 1 (continued)

First author, year	Type of study, number of patients	Comparison	Main findings
			(35 ± 22%vs16 ± 8%; $p = 0.005$) and during the first 50 ms (78 ± 27% vs. 60 ± 23%; $p = 0.03$) of pacing, suggesting a quicker wave front propagation throughout the left ventricle.
Pappone et al. 2015 [24]	Prospective single-center, observational study. $n = 44$.	After implantation of a CRT device, 2 groups of patients were compared at 1 year: - biV with pressure-volume loop (PVL) optimization ($n = 22$). - MPP with PVL optimization ($n = 22$) CRT response was defined as a reduction of end-systolic volume ≥ 15%.	At 1 year: - 76% responders in the MPP groups vs. 57% responder in the biV group ($p = 0.33$). - ESV median: − 25% (IQR: − 39% to − 20%) in MPP patients vs − 18% (IQR: − 25% to– 2%) in the biV group ($p = 0.03$). - EF median: + 15% (IQR: 8 to 20%) in MPP patients vs +5% (IQR: − 1 to 8%) in the biV group ($p < 0.01$).
0sca et al. 2016 [25]	Prospective single-center, observational study. $n = 27$.	Acute intraoperative assessment of echocardiographic parameters of MPP and biV in the same patient.	- LVEF was increased in MPP and biV pacing vs. baseline: 38.4 ± 1.8%, 33.2 ± 1.8% and 26.1 ± 2.2, respectively ($p < 0.01$ vs. baseline). - Cardiac index (CI) was increased by 34.7 ± 5.1% and 21.8 ± 5.4% in MPP and biV configurations, respectively ($p = 0.19$) - Acute responders (CI increase ≥ 10%): MPP = 85.2% vs. conventional biV = 62.9%, $p < 0.001$. - Standard deviation of time-to-peak radial strain of 6 LV basal segments: Baseline 101 ± 9.7 ms, MPP 66 ± 8.03 ms ($p = 0.012$ vs. baseline) and biV 80.3 ± 9.2 ms ($p = 0.34$ vs. baseline,).
Zanon et al. 2016 [26]	Retrospective single-center, observational study. $n = 110$.	After implantation of a CRT device, 3 groups were compared at 1 year of follow-up: - STD: standard group with bipolar LV lead ($n = 54$) - OPT: group with bipolar or quadripolar LV lead with optimized pacing site defined as the greatest increase of LV dP/dt_{max}. ($n = 36$) - OPT+MPP: group with MPP and the same optimization. ($n = 20$)	At 1 year: - Reduction in NYHA class ≥ 1: OPT+MPP = 95.0%; OPT = 77.8%; STD = 66.7% ($p = 0.012$) - NYHA response with no HF-related hospitalization events or death (PACKER score = 0): OPT+MPP = 90.0%; OPT = 66.7%; STD = 59.3% ($p = 0.018$) - Reduction in end-systolic volume ≥ 15%: OPT+MPP = 90.0%; OPT = 72.2%; STD = 55.6% ($p = 0.04$)
Siciliano et al. 2016 [27]	Prospective single-center, observational study. $n = 11$.	Patients with MPP-enabled CRT devices underwent a three-dimensional echocardiography (3DE) and an echocardiographic particle imaging velocimetry (Echo-PIV) at 6 months follow-up during a pacing protocol with biV and MPP pacing.	- Reduction in end-diastolic and end-systolic volumes with MPP compared with biV ($p = 0.04$; $p = 0.03$, respectively). - LVEF and cardiac output were similar between MPP and biV. - There was also a trend towards improvement in strain between biV and MPP that did not reach statistical significance. - MPP reflected into a significant reduction of the deviation of global blood flow momentum compared

Table 1 (continued)

First author, year	Type of study, number of patients	Comparison	Main findings
			with biV ($p = 0.002$) indicating a systematic increase of longitudinal alignment from the base-apex orientation of the hemodynamic forces.
Niazi et al. 2017 [28]	Prospective multicenter, randomized, double-blind clinical trial. $n = 381$.	Clinical non-responders to standard biventricular pacing (biV) at 3 months defined using CCS score were randomized in 2 groups: - MPP arm ($n = 201$); - biV arm ($n = 180$).	- The primary safety endpoint was met with freedom from system-related complications of 93.2%. - The primary efficacy endpoint of the noninferiority comparison of non-responder rates between the 2 arms was met. - Patients randomized to MPP arm and programmed to pace from anatomically distant poles (MPP-AS = Cathode spacing ≥ 30 mm and 5 ms LV delay) responded to therapy at significantly higher rates than MultiPoint pacing–other programmed settings (MPP-Other): 87% were responders at 9 months, 100% designated as non-responders at 3 months converted to responders at 9 months, and 54% experienced an incremental response compared with MPP-Other. 92% of patients with *de novo* CRT-D implant were classified as responders compared with patients with MPP-Other.
Forleo et al. 2017 [29]	Prospective multicenter, observational registry. $n = 232$.	MPP was activated at discharge after CRT-D implantation ($n = 94$) and compared with standard biV ($n = 138$) at 6 months follow-up.	At 6 months: - CCS score improved in the MPP group (56 vs. 38%; $p = 0.009$). - EF was significantly higher in the MPP group than in the biV group ($39.1 \pm 9.6\%$ vs. $34.7 \pm 7.6\%$; $p = 0.001$). - MPP was a predictor of absolute increase in LVEF ≥ 5% at 6 months (OR = 2.5; 95% CI = 1.3–4.9; $p = 0.001$).
Ciconte et al. 2018 [30]	Prospective single-center, observational study. $n = 19$.	Patients with MPP-enabled CRT devices underwent non-invasive radial artery tonometry (RAT) during a pacing protocol with biV and MPP pacing.	MPP configuration with the greatest separation of LV cathodes and minimum intra-LV delay significantly improved: - Pre-ejection period (PEP) (mean PEP $-15 \pm 33\%$ in MPP vs. $-8 \pm 32\%$ in biV pacing, $p = 0.04$), - Ejection duration (ED) (mean ED $+8 \pm 8\%$ in MPP vs. $+4 \pm 7\%$ in biV pacing, $p = 0.02$), - PEP/ED (-0.07 ± 0.14 in MPP vs -0.04 ± 0.13 in biV pacing, $p = 0.02$).
Lercher et al. 2018 [31]	Prospective multicenter, non-randomized clinical trial. $n = 42$.	After successful implantation of a CRT device, various biV and MPP configurations were tested during a pacing protocol. Configuration with the best systolic blood pressure (SBP) elevation relative to reference was programmed.	- Greater SBP elevations were associated with the best MPP compared with the best biV configurations in 29 of 37 patients completing the pacing protocol (78%). - At 6 months: 23/27 (85%) MPP-programmed patients were

Table 1 (continued)

First author, year	Type of study, number of patients	Comparison	Main findings
			classified as CRT responders (ΔLVESV = 31 ± 20%).
Leclercq et al. 2019 [32]	Prospective multicenter, randomized clinical trial. $n = 544$.	Non-responders to biV at 6 months defined as reduction < 15% in left ventricular end-systolic volume (LVESV) were randomized in 2 groups: - MPP ($n = 236$); - biV ($n = 231$).	- No difference was observed in non-responder to responder conversion rate between MPP and biventricular pacing (31.8% and 33.8%, $p = 0.72$). - In the MPP arm, 68 (29%) patients received MPP programmed with a wide LV electrode anatomical separation (≥ 30 mm) and shortest LV1–LV2 and LV2–RV timing delays (MPP-AS); 168 (71%) patients received MPP programmed with other settings (MPP-Other). - MPP-AS elicited a significantly higher non-responder conversion rate compared with MPP-Other (45.6% vs. 26.2%, $p = 0.006$) and a trend in a higher conversion rate compared with biventricular pacing (45.6% vs. 33.8%, $p = 0.10$).
Sieniewicz et al. 2019 [33]	Prospective single-center, observational study. $n = 5$.	Acute evaluation MPP and biV with electrocardiographic imaging (ECGi) the day after implantation of CRT device.	In 2/5 subjects, MPP resulted in more rapid activation of the left ventricle compared with standard CRT. In the 3 other patients, the use of MPP did not appear to acutely improve electrical resynchronization.

Randomized clinical trials were designed with activation of MPP in non-responder patients to CRT. The MPP IDE [28] study showed that MPP was safe and non-inferior to standard biV pacing. MPP from anatomically distant poles (MPP-AS) with a cathode spacing ≥ 30 mm and 5 ms LV delay showed also a better response rate compared with MPP with other settings. The phase I of More-CRT MPP study [32] did not show advantage of indiscriminate programming of MPP on LV reverse remodeling compared with biV pacing in echocardiographic non-responders to CRT. However, MPP-AS might be beneficial in selected patients and a phase II is in progress.

3 Tips and pitfalls for MPP

Choice of both LV vector is crucial Every LV vectors are not programmable in MPP configuration as shown in Table 2. The farthest anatomic distance may achieve a better response to CRT with cathode spacing ≥ 30 mm [28]: when possible, consider pacing from most distal and proximal electrodes [18]. Another way to choose the vectors is to choose the first and last activated sites during RV-LV delay measurement [37]. 12-Derivation electrocardiogram during MPP configuration testing in order to choose minimal QRS width seems time-consuming but could be efficient in selected patients [29]. Pressure-volume loop [24] and invasive dP/dT [26] are neither feasible nor relevant in clinical practice and belong to clinical research field [30]. Favoring the true bipolar vector may be beneficial.

Pacing delay between the two chosen LV vectors is also a key-point Minimal programmable or simultaneous delay appears to be more efficient except in case of extensive fibrosis [28].

Threshold and battery longevity is impacted MPP significantly reduces battery longevity compared with biV. When MPP LV vector ≤ 4 V is achieved, the decrease in battery longevity is reasonable [36]. Auto-threshold LV tests and adjustment permit to minimize battery consumption.

4 MPP algorithms

Main characteristics of devices and quadripolar lead used in MPP are reported in Table 2.

Table 2 Main characteristics of MPP

	Multipoint of Abbott	Multipole of Biotronik	Double-cathode stimulation of Boston	Multipoint of Medtronic	Multipoint of Microport
MPP-capable CRT devices	Quadra Assura™ CRT-D Quadra Allure™ RF CRT-P	Ilivia 7™ CRT-D Intica 7™ CRT-D Acticor 7™ CRT-D	Resonate X4™ CRT-D Momentum X4™ CRT-D Charisma X4™ CRT-D Vigilant X4™ CRT-D	Claria™ CRT-D Amplia™ CRT-D Percepta™ CRT-P Serena™ CRT-P	Platinium 4LV SonR™ CRT-D
Quadripolar LV lead	Quartet™	Sentus™	Acuity X4™	Attain performa™ Attain stability Quad™	–
Electrode spacing	- 1458Q and 1457Q: 20–10–17 mm - 1456Q: 20–10–10 mm - 1458QL: 20–27–13 mm	- L and S: 21–20–20 mm - L-xx/49 and S-xx/49: 21–15–10 mm	- Spiral L: 35.5–7.5–7.5 mm - Spiral S: 20.5–7.5–7.5 mm - Straight: 12–12–12 mm	4298, 4398 (Straight), 4598 (S), 4798: 21–1.3-21 mm	–
Lead diameter	4.7F body 4.0F electrode	4.8F body 4.8F electrode	5.2F body 3.9F electrode	Attain performa™: 5.3F Body / 5.1F electrode Attain stability Quad™: 4.4F Body/5.1F electrode	–
Fixation	Passive	Passive	Passive	Attain performa: Passive Attain stability: active (helix)	–
CRT-P	Yes	No	No	Yes	No
Numbers of vectors available	10 for CRT-D 14 for CRT-P	12	17	16	14
Programmable vector in MPP	CRT-D: LV1: 10 LV2: 7 or 8 CRT-P: LV1: 14 LV2: 10 or 11	LV1: 12 LV2: 11	LV1: 17 vectors LV2: 13 vectors	CRT-D: Unipolar vectors using RV coil CRT-P: LV1: 9 LV2: 6	LV1: 8 vectors LV2: 6 vectors
Number of possible MPP configuration	CRT-D: 70 to 80 CRT-P: 140 to 154	131	216	CRT-D: 5 CRT-P: 54	48
Inter-ventricular delay (RV-LV)	5–80 ms	0-50 ms (VV delay after Vp can be set, while VV delay after Vs is fixed at 0 ms)	5-100 ms	10-80 ms	0-64 ms
Intra-ventricular delay (LV1-LV2)	5–50 ms	0-100 ms	0-95 ms	CRT-D: 0 ms CRT-P: 10-80 ms	0 ms
Programming	biV or LV	biV	biV or LV	biV	biV or LV
LV vector analysis	CRT Toolkit™ VectSelect Quartet™	LV Vector Opt™	LV Vector guide™	Vector Express™	LV vectors selection tool
MPP-optimization algorithm	Multipoint™	–	SmartVector™ and Smartoffset™	–	–
LV automatic threshold test	LVCap™ confirm	Captur control™	Pacesafe™ available for LV1 only	LV Capture management™	No
Other CRT features	Syncav™ QuickOpt™	Triggering Negative AV hysteresis	Smart Delay™	Adaptiv CRT™ Effectiv CRT™	SonR™ Brady-tachy overlap (BTO™)

4.1 Abbott devices

Automatic measurements of RVP-to-LVS or RVS-to-LVS delay and LV thresholds through CRT Toolkit™ and VectSelect Quartet™ algorithms, respectively, help selecting the adequate pacing electrodes with a good compromise between electrically distant sites and an acceptable battery longevity.

The Multipoint™ pacing is available only for heart rates ≤ 110 beats per minute (bpm), with automatic switch towards conventional biV pacing from 111 bpm to upper pacing rate. The device permits to pace RV and then LV and vice versa. The choice of the two LV vectors can be manual or with two proposed configurations: wider cathode spacing or shortest and longest activation time.

4.2 Biotronik devices

LV Vector Opt™ After an automatic measurement of RVP-to-LVS delay, LV threshold with PNS threshold and impedance are manually measured.

Via multipole pacing™, the device also permits to firstly pace the RV or the LV. However, the LV vector choice is only manual.

4.3 Boston devices

LV Vectorguide™ RVS-to-LVS delay is averaged over several cardiac cycles (at least 3 RV events, up to 10) for each selected vector. Any unstable RV intervals (> 20% RV-RV) are eliminated. An RVS-LVS interval is not valid if it is > 10 ms (±) from the median.

Other invalid events are excluded from the delay measurement: RV pace, RV sensed event > 110 bpm, PVC, RV sense following a PVC, LVS is 100 ms or earlier than the RVS or LVS is 200 ms or later than the RVS, more than one LVS is within − 100 ms and + 200 ms of the RVS, RVS, or LVS that occur during noise.

A negative value for the RVS-LVS delay indicates that the LVS precedes the RVS.

LV impedance is measured for each selected vector and phrenic nerve stimulation identified by the physician for each selected vector.

LV threshold tests are automatic only on Autogen devices. They can be made manually or via Quickcapture™ test (runs at same output for each selected LV vector and permits to quickly note capture/no capture).

Smart Vector™ Activation sequence's choice depends on RVS-LVS delay: if ≥ − 20 ms then LV1➔LV2➔RV, if < − 20 ms then RV➔LV1➔LV2. Vector's choice is made after elimination of vector with PNS, extreme impedance, LV threshold > 4.5 V, and missing data.

LV1 vector will favor the cathode with the longest RVS-LVS delay. If all RVS-LVS delays are equal, then priority for the best LV threshold. If all LV thresholds are equal, priority for the most basal cathode and for the anode: RV > $LV_{distal4}$ > $LV_{medial3}$ > $LV_{medial2}$ > box. For the LV2 vector, the farthest anatomic electrode from LV1 and the anode with the lowest threshold will be chosen.

LV1 threshold can be programmed on automatic (Pacesafe™) but not LV2 (results of Vectorguide™ + 1.5 V).

Smart Offset™ Intra-ventricular pacing delays are automatically adjusted on RVS-to-LVS delay (between 0 and 10 ms). Inter-ventricular pacing delay is 5 ms. A fully manual programing is also possible.

4.4 Medtronic devices

Vector Express™ Pacing threshold and impedance are automatically tested for each selected pacing polarities associated with a test looking for PNS. The calculated relative longevity is based on the current battery status and on typical (not actual) parameter settings and device events with a 1.5 V ventricular safety margin (different from remaining longevity).

LV Capture Management™ permits a monitoring of pacing amplitude threshold and adjustment of LV outputs (automatic threshold measurement daily). It will operate twice when MPP is on and then utilize the higher of the two LV cathode thresholds.

RV-LV sequence, LV vector's choice, and delays programing are manual.

4.5 Microport devices

LV Vectors Selection Tool™ Manual pacing threshold and impedance for each LV vectors and test looking for PNS.

SonR™ is a peak endocardial acceleration-based optimization method. The peak endocardial acceleration (PEA) sensor is embedded in the tip of the RA lead and permits adjustment of the PEA in order to determine the optimal LV configuration (highest PEA value, closely correlated with LV dP/dt_{max}, for all scanned configurations).

RV-LV sequence, LV vector's choice, and delays programing are also manual.

5 Conclusion

MPP via quadripolar showed an improvement in hemodynamics and functional status but still needs more morbimortality evidence. Programing is challenging and may be crucial to evaluate MPP in further clinical studies.

Compliance with ethical standards

Conflict of interest LF: consultant or speaker for Bayer, BMS/Pfizer, Boehringer Ingelheim, Livanova, Medtronic, and Novartis. DB: speaker for BMS/Pfizer and Medtronic. NC: consultant or speaker for Boston Scientific and Medtronic. Other authors—no conflicts of interest.

Abbreviations *biV,* biventricular; *CRT,* cardiac resynchronization therapy; *LV,* left ventricular; *LV1,* first LV vector; *LV2,* second LV vector; *LVP,* left ventricle paced; *LVS,* left ventricle sensed; *LVEF,* left ventricle ejection fraction; *LBBB,* left bundle branch block; *MPP,* multipoint/multipole pacing; *MPP-AS,* multipoint pacing–anatomic separation/minimal intraventricular timing delay; *PNS,* phrenic nerve stimulation; *PVC,* premature ventricular complexes.; *RVP,* right ventricle paced; *RVS,* right ventricle sensed

References

1. Young JB, Abraham WT, Smith AL, Leon AR, Lieberman R, Wilkoff B, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. JAMA. 2003;289(20):2685–94. https://doi.org/10.1001/jama.289.20.2685.
2. Birnie DH, Tang AS. The problem of non-response to cardiac resynchronization therapy. Curr Opin Cardiol. 2006;21(1):20–6.
3. Chung ES, Leon AR, Tavazzi L, Sun J-P, Nihoyannopoulos P, Merlino J, et al. Results of the predictors of response to CRT (PROSPECT) trial. Circulation. 2008;117(20):2608–16. https://doi.org/10.1161/CIRCULATIONAHA.107.743120.
4. Auricchio A, Prinzen FW. Non-responders to cardiac resynchronization therapy: the magnitude of the problem and the issues. Circ J. 2011;75(3):521–7.
5. Butter C, Auricchio A, Stellbrink C, Fleck E, Ding J, Yu Y, et al. Effect of resynchronization therapy stimulation site on the systolic function of heart failure patients. Circulation. 2001;104(25):3026–9.
6. van Campen CMC, Visser FC, de Cock CC, Vos HS, Kamp O, Visser CA. Comparison of the haemodynamics of different pacing sites in patients undergoing resynchronisation treatment: need for individualisation of lead localisation. Heart. 2006;92(12):1795–800. https://doi.org/10.1136/hrt.2004.050435.
7. Becker M, Franke A, Breithardt OA, Ocklenburg C, Kaminski T, Kramann R, et al. Impact of left ventricular lead position on the efficacy of cardiac resynchronisation therapy: a two-dimensional strain echocardiography study. Heart. 2007;93(10):1197–203. https://doi.org/10.1136/hrt.2006.095612.
8. Bleeker GB, Kaandorp TAM, Lamb HJ, Boersma E, Steendijk P, de Roos A, et al. Effect of posterolateral scar tissue on clinical and echocardiographic improvement after cardiac resynchronization therapy. Circulation. 2006;113(7):969–76. https://doi.org/10.1161/CIRCULATIONAHA.105.543678.
9. Spragg DD, Dong J, Fetics BJ, Helm R, Marine JE, Cheng A, et al. Optimal left ventricular endocardial pacing sites for cardiac resynchronization therapy in patients with ischemic cardiomyopathy. J Am Coll Cardiol. 2010;56(10):774–81. https://doi.org/10.1016/j.jacc.2010.06.014.
10. Derval N, Steendijk P, Gula LJ, Deplagne A, Laborderie J, Sacher F, et al. Optimizing hemodynamics in heart failure patients by systematic screening of left ventricular pacing sites: the lateral left ventricular wall and the coronary sinus are rarely the best sites. J Am Coll Cardiol. 2010;55(6):566–75. https://doi.org/10.1016/j.jacc.2009.08.045.
11. Singh JP, Klein HU, Huang DT, Reek S, Kuniss M, Quesada A, et al. Left ventricular lead position and clinical outcome in the multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy (MADIT-CRT) trial. Circulation. 2011;123(11):1159–66. https://doi.org/10.1161/CIRCULATIONAHA.110.000646.
12. 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(6):873–9. https://doi.org/10.1093/europace/eut420 .
13. Leclercq C, Gadler F, Kranig W, Ellery S, Gras D, Lazarus A, et al. A randomized comparison of triple-site versus dual-site ventricular stimulation in patients with congestive heart failure. J Am Coll Cardiol. 2008;51(15):1455–62. https://doi.org/10.1016/j.jacc.2007.11.074.
14. Ginks MR, Duckett SG, Kapetanakis S, Bostock J, Hamid S, Shetty A, et al. Multi-site left ventricular pacing as a potential treatment for patients with postero-lateral scar: insights from cardiac magnetic resonance imaging and invasive haemodynamic assessment. Europace. 2012;14(3):373–9. https://doi.org/10.1093/europace/eur336 .
15. Rogers DPS, Lambiase PD, Lowe MD, Chow AWC. A randomized double-blind crossover trial of triventricular versus biventricular pacing in heart failure. Eur J Heart Fail. 2012;14(5):495–505. https://doi.org/10.1093/eurjhf/hfs004.
16. Lenarczyk R, Kowalski O, Sredniawa B, Pruszkowska-Skrzep P, Mazurek M, Jędrzejczyk-Patej E, et al. Implantation feasibility, procedure-related adverse events and lead performance during 1-year follow-up in patients undergoing triple-site cardiac resynchronization therapy: a substudy of TRUST CRT randomized trial. J Cardiovasc Electrophysiol. 2012;23(11):1228–36. https://doi.org/10.1111/j.1540-8167.2012.02375.x.
17. Bordachar P, Gras D, Clementy N, Defaye P, Mondoly P, Boveda S, et al. Clinical impact of an additional left ventricular lead in cardiac resynchronization nonresponders: the V3trial. Heart Rhythm. 2017;15:870–6. https://doi.org/10.1016/j.hrthm.2017.12.028.
18. 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(7):984–91. https://doi.org/10.1093/europace/eus435 .
19. 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(11):731–8. https://doi.org/10.1016/j.cardfail.2013.10.003.
20. 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(1):75–80. https://doi.org/10.1007/s10840-014-9891-1.
21. 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(3):394–401. https://doi.org/10.1016/j.hrthm.2013.11.023.
22. 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(5):975–81. https://doi.org/10.1016/j.hrthm.2015.01.034.
23. Menardi E, Ballari GP, Goletto C, Rossetti G, Vado A. Characterization of ventricular activation pattern and acute hemodynamics during multipoint left ventricular pacing. Heart Rhythm. 2015;12(8):1762–9. https://doi.org/10.1016/j.hrthm.2015.04.029.

24. Pappone C, Ćalović Ž, Vicedomini G, Cuko A, McSpadden LC, Ryu K, et al. Improving cardiac resynchronization therapy response with multipoint left ventricular pacing: twelve-month follow-up study. Heart Rhythm. 2015;12(6):1250–8. https://doi.org/10.1016/j.hrthm.2015.02.008.
25. Osca J, Alonso P, Cano O, Andrés A, Miro V, Tello MJS, 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. 2016;18(4):560–7. https://doi.org/10.1093/europace/euv211 .
26. 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(8):1644–51. https://doi.org/10.1016/j.hrthm.2016.05.015.
27. Siciliano M, Migliore F, Badano L, Bertaglia E, Pedrizzetti G, Cavedon S, et al. Cardiac resynchronization therapy by multipoint pacing improves response of left ventricular mechanics and fluid dynamics: a three-dimensional and particle image velocimetry echo study. Europace. 2016. https://doi.org/10.1093/europace/euw331 .
28. Niazi I, Baker J, Corbisiero R, Love C, Martin D, Sheppard R, et al. Safety and efficacy of multipoint pacing in cardiac resynchronization therapy: the MultiPoint pacing trial. JACC Clinical electrophysiology. 2017;3(13):1510–8. https://doi.org/10.1016/j.jacep.2017.06.022.
29. Forleo GB, Santini L, Giammaria M, Potenza D, Curnis A, Calabrese V, 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. 2017;19(7):1170–7. https://doi.org/10.1093/europace/euw094 .
30. Ciconte G, Ćalović Ž, Vicedomini G, Cuko A, McSpadden LC, Jiang C, et al. Multipoint pacing improves peripheral hemodynamic response: noninvasive assessment using radial artery tonometry. PACE. 2018;41(2):106–13. https://doi.org/10.1111/pace.13254 .
31. Lercher P, Lunati M, Rordorf R, Landolina M, Badie N, Qu F, et al. Long-term reverse remodeling by cardiac resynchronization therapy with MultiPoint Pacing: a feasibility study of noninvasive hemodynamics-guided device programming. Heart Rhythm. 2018;15(12):1766–74. https://doi.org/10.1016/j.hrthm.2018.06.032.
32. Leclercq C, Burri H, Curnis A, Delnoy PP, Rinaldi CA, Sperzel J, et al. Cardiac resynchronization therapy non-responder to responder conversion rate in the more response to cardiac resynchronization therapy with MultiPoint Pacing (MORE-CRT MPP) study: results from phase I. Eur Heart J. 2019. https://doi.org/10.1093/eurheartj/ehz109.
33. Sieniewicz BJ, Jackson T, Claridge S, Pereira H, Gould J, Sidhu B, et al. Optimization of CRT programming using non-invasive electrocardiographic imaging to assess the acute electrical effects of multipoint pacing. J Arrhythm. 2019;35(2):267–75. https://doi.org/10.1002/joa3.12153.
34. Sohal M, Shetty A, Niederer S, Lee A, Chen Z, Jackson T, et al. Mechanistic insights into the benefits of multisite pacing in cardiac resynchronization therapy: the importance of electrical substrate and rate of left ventricular activation. Heart Rhythm. 2015;12(12):2449–57. https://doi.org/10.1016/j.hrthm.2015.07.012.
35. Gasparini M, Galimberti P, Bragato R, Ghio S, Raineri C, Landolina M, et al. Multipoint pacing versus conventional ICD in patients with a narrow QRS complex (MPP narrow QRS trial): study protocol for a pilot randomized controlled trial. Trials. 2016;17(1):572. https://doi.org/10.1186/s13063-016-1698-1.
36. Akerström F, Narváez I, Puchol A, Pachón M, Martín-Sierra C, Rodríguez-Mañero M, et al. Estimation of the effects of multipoint pacing on battery longevity in routine clinical practice. Europace. 2017;20:1161–7. https://doi.org/10.1093/europace/eux209 .
37. Zanon F, Baracca E, Pastore G, Fraccaro C, Roncon L, Aggio S, et al. Determination of the longest intrapatient left ventricular electrical delay may predict acute hemodynamic improvement in patients after cardiac resynchronization therapy. Circ Arrhythm Electrophysiol. 2014;7(3):377–83. https://doi.org/10.1161/CIRCEP.113.000850.