Cardiac resynchronization therapy with multipoint pacing via quadripolar lead versus traditional biventricular pacing: A systematic review and meta-analysis of clinical studies on hemodynamic, clinical, and prognostic parameters

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BACKGROUND Cardiac resynchronization therapy (CRT) is one of the cornerstones of heart failure (HF) therapy, as it has reduced mortality and morbidity and has shown improvement in functional capacity. Multipoint pacing (MPP) is a way of configuring CRT with the aim to improve the percentage of patients who respond to CRT.

OBJECTIVE To demonstrate the effectiveness of the MPP compared to traditional biventricular pacing (BiV).

METHODS We performed a systematic review and meta-analysis according to PRISMA guidelines of studies in which MPP vs BiV strategy were compared.

RESULTS MPP use is associated with a higher rate of patients experiencing functional improvement (odds ratio: 2.51, 95% confidence interval [CI], 1.56–4.06; $P = .0002$) and with higher delta LV dP/dt_{max} (mean difference, 1.82; 95% CI, 0.24–3.39; $P = .0240$) with respect to BiV. MPP and BiV have no significantly different effect on left ventricular end-systolic volume (LVESV) (mean difference, 0.39; 95% CI, -11.12 to 11.89; $P = .9475$); moreover, there is no significant difference between the 2 treatments regarding hospitalization for HF (odds ratio, 0.70; 95% CI, 0.32 to 1.54; $P = .3816$) and all-cause death (odds ratio, 0.81; 95% CI, 0.40 to 1.62; $P = .5460$). MPP is associated with a significantly lower projected battery longevity (mean difference -8.66 months; 95% CI, -13.67 to -3.66; $P = .00007$) with respect to BiV.

CONCLUSION MPP significantly improves functional class and acute hemodynamic parameters with respect to BiV. Prognostic indices and LVESV are not significantly influenced by MPP. MPP is associated with a significant reduction in projected battery longevity.

KEYWORDS Biventricular pacing; Cardiac resynchronization therapy; Heart failure; Meta-analysis; Multipoint pacing; Quadripolar lead; Systematic review

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Introduction

Heart failure (HF) is often associated with ventricular conduction abnormalities, namely bundle branch blocks and QRS duration >120 ms on 12-lead electrocardiography, that cause the so-called "ventricular dyssynchrony." It may complicate HF, causing impairment in ventricular systolic and diastolic function and increased duration of mitral regurgitation. Cardiac resynchronization therapy (CRT) is a modality of heart pacing therapy through the implantation of pacing leads both in the right ventricle and in the left ventricle (LV). It is one of the mainstays in the treatment of HF, and it is the treatment of choice in patients with symptomatic HF with reduced left ventricular ejection fraction (LVEF) refractory to guideline-directed medical therapy, and with ventricular dyssynchrony, as it has shown a reduction in mortality and morbidity and an improvement in functional capacity in these appropriately selected patients.[1] Yet not all those who receive this therapy respond adequately; indeed, between 30% and 40% of patients (so-called "nonresponders") do not show any improvement in hemodynamic parameters, reverse remodeling of the left ventricle, symptoms, and/or

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KEY FINDINGS

- According to our systematic review and meta-analysis, multipoint pacing (MPP) via quadripolar lead is associated with a significant improvement in clinical response and with a significant improvement in left ventricular (LV) dP/dt_{max} with respect to traditional biventricular pacing (BiV).
- MPP do not significantly affect LV end-systolic volume, hospitalization for heart failure, and all-cause death with respect to traditional BiV.
- BiV is associated with a higher projected battery longevity with respect to MPP.

prognosis.[2,3] The causes of this lack of improvement are likely to be multiple and linked both to patients' clinical features and to device features.[4] Wider QRS duration, presence of left bundle branch block, female sex, and nonischemic cardiomyopathy are associated with better CRT response, while narrower QRS duration, non–left bundle branch block, male sex, and ischemic cardiomyopathy, with wide scar area, are associated with worse response.[5]

In order to eliminate the residual degree of intraventricular dyssynchrony and to reduce the rate of CRT nonresponders, researchers devised a strategy of simultaneous stimulation of 2 distinct points of the LV.

A possible strategy consisted of an implantation of 2 distinct bipolar leads in the LV, and it was defined as multisite pacing. However, multisite pacing was burdened by longer implantation times and increased radiation exposure of the patient and the operators, increased pocket infections, more rapid battery drainage, and high procedural failure rate. For these reasons this strategy has not been implemented in clinical practice.[6,7]

Another strategy is constituted by multipoint pacing (MPP): it is a stimulation modality that aims to determine a more rapid and more physiological activation as compared to traditional single-site LV stimulation, through the recruitment of higher volumes of vital myocardium via the implantation of a single quadripolar lead[8,9] and stimulation in 2 cathodes out of the 4 electrodes of LV lead.

Implantation of a quadripolar LV lead in CRT has shown an indisputable clinical advantage over bipolar leads, and it has become the standard of care.[10]

Literature data on the possible benefit of MPP compared to traditional biventricular pacing (BiV) are scarce and contradictory, as they come mainly from small studies.

However, the use of an MPP strategy is theoretically burdened, when compared to the traditional BiV, by a more complex programming in terms of search for an LV vector able to provide a more advantageous and less battery-consuming pacing.

First studies compared MPP to traditional BiV in several acute hemodynamic parameters: LVEF, cardiac index, stroke work, delta LV dP/dt_{max}, systolic blood pressure, radial strain, noninvasive radial artery tonometry parameters, end-diastolic and end-systolic volumes, and end-diastolic LV pressure. The results of these early studies generally showed a benefit of MPP over BiV, but the low number of patients studied and the various endpoints made this benefit not "generalizable."

Only a few studies compared MPP to traditional BiV in "hard" endpoint, such as clinical response, hospitalization for HF, and all-cause mortality. The results of these studies were contradictory and did not show a clear benefit of MPP over traditional BiV, focusing on reduced battery duration with MPP.[11–14]

We conducted a systematic review and meta-analysis of the literature on this topic to assess whether BiV with MPP may be preferable over traditional BiV, in clinical as well as in hemodynamic and prognostic index improvement. We also evaluated the impact of an MPP or BiV strategy on battery longevity.

Methods

The research reported in this paper adhered to PRISMA guidelines.[15] We searched the PubMed database until September 2020 with the following search criteria: "*multipoint pacing*," "*multipolar pacing*," and "*multisite pacing*." Inclusion criteria were as follows: (1) studies including patients who underwent CRT implant, comparing MPP via quadripolar lead vs traditional BiV; (2) studies including at least 1 of the following endpoints: (a) delta LV dP/dt_{max}, (b) LV end-systolic volume (LVESV), (c) (change in) functional capacity, (d) hospitalization for HF, (e) all-cause death, (f) projected battery longevity. Exclusion criteria were as follows: (1) unavailability of the full study text, (2) unavailability of analyzable data, (3) MPP not via a single quadripolar lead, (4) lack of clarity in the text on the possible use of the MPP mode of the quadripolar leads. We found a total of 15 studies and 1895 patients fitting inclusion criteria (Figure 1, Table 1). We used the Newcastle–Ottawa quality assessment scale to assess the quality of each study, assigning to each of them a grade between 6 and 8.

The primary endpoint was the clinical response (defined roughly as the change in New York Heart Association [NYHA] functional class). The secondary endpoints were (1) delta LV dP/dt_{max}, (2) LVESV, (3) hospitalization for HF, (4) all-cause death, and (5) projected battery longevity.

Two authors (C.M. and L.C.) screened the articles according to inclusion and exclusion criteria, and independently extracted the data. We resolved disagreements by consensus with a third investigator (E.D.G.).

Statistical analysis

Descriptive statistics are presented as means and standard deviations for continuous variables or number of cases (n). Statistical analysis is performed using the R environment (version 4.0.3). The *metabin* and *metacont* functions, which

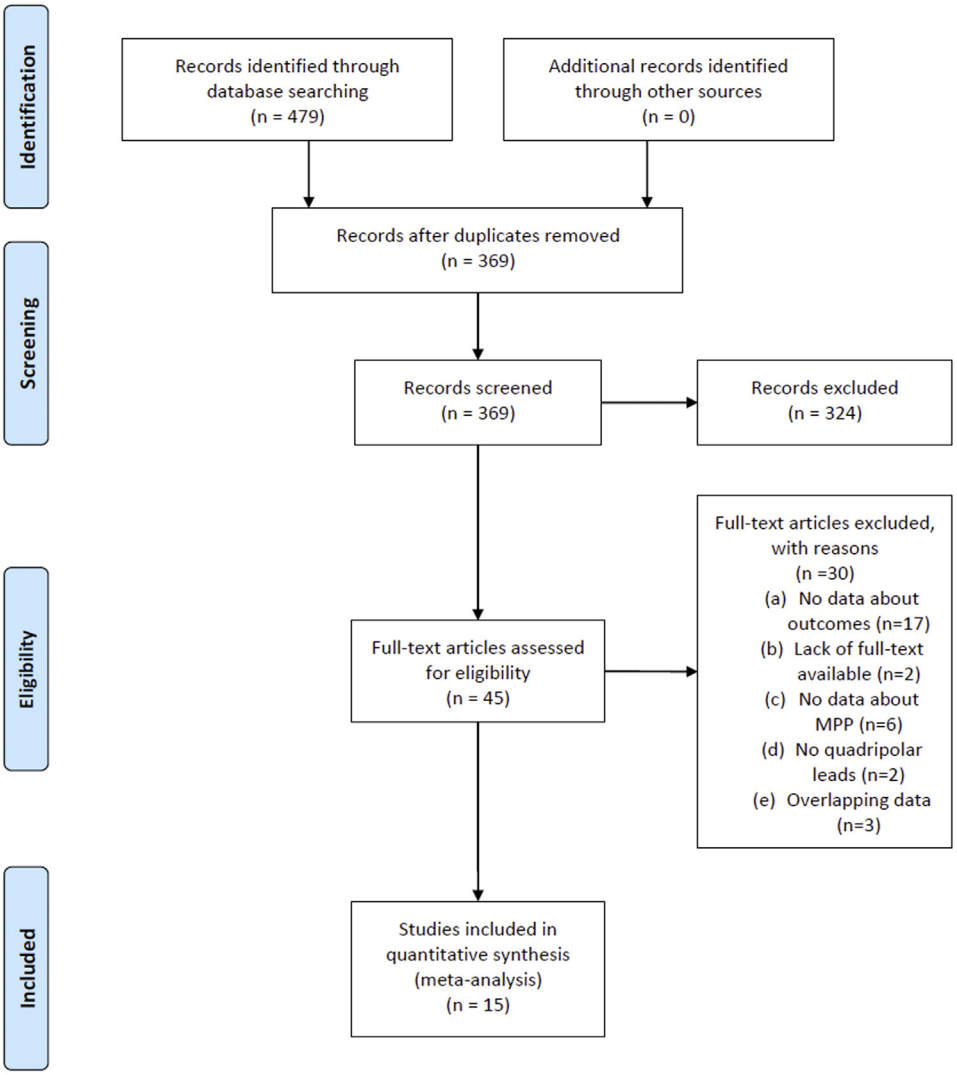

Figure 1 PRISMA algorithm for the selection of the studies. MPP: multipoint pacing.

are implemented in the R package *meta*,[16] are used for meta-analysis of binary and continuous outcome data, respectively.

As suggested by the recent literature,[17] the conceptual assumptions for using the fixed-effect model are very strong. Generally, the similarity of all the studies included in the meta-analysis is very difficult to satisfy. Effectively, there are often several sources of heterogeneity, including differences in the treatment, the treated population, the study design, or the data analysis method.

For this reason, random effects meta-analysis based on estimates and their standard errors are implemented. To assess the consistency across studies, the I^2 statistic is adopted with 25%, 50%, and 75% suggesting low, moderate, and high heterogeneity degrees, respectively. However, I^2 should be presented and interpreted cautiously in small meta-analyses.[18] For this reason, 95% confidence intervals (95% CI) are presented in addition to the point estimate.

The χ^2-based Q test was also applied to look for heterogeneity of effects among studies. As suggested by Sutton and colleagues,[19] the statistical power of the test is in most cases very low owing to the small number of studies; therefore, the Q statistic is not statistically significant at conventional levels of significance such as 0.05, and a cut-off significance level of 0.10 is used to suggest the presence of significant heterogeneity. The τ^2 statistic is also presented to check the variance of the true effects. The Mantel-Haenszel and inverse variance estimation methods are used for pooling results of binary and continuous outcomes, respectively.

Funnel plots are presented as a graphical tool for the evaluation of possible publication bias. The *funnel* function in the R package *metafor*[20] is used to check for publication bias. The *metabias* function, which is implemented in the R package *meta*, is adopted to compute the Begg test; the latter, implemented using rank correlation, is used to test for funnel plot asymmetry. A 2-tailed P value of $\leq .05$ was considered statistically significant. Following the recommendations of Sterne and colleagues,[21] a test for funnel plot asymmetry should be conducted only if the number of studies is

Table 1 Studies in meta-analysis and baseline characteristics

	Author (year)	Year	Study quality Newcastle–Ottawa quality assessment scale	Country	Number of patients	Study type	Age (years)		LVEF (%)		LVESV (mL)		NYHA class[†] (n patients)	
							BiV	MPP	BiV	MPP	BiV	MPP	BiV	MPP
1	Thibault et al (2013)[29]	2013	7	Canada	21	Prospective single-center, observational study	60 ± 14		22 ± 5		/[‡]	/	II: 2 III: 19	
2	Menardi et al (2015)[31]	2015	6	Italy	10	Prospective single-center, observational study.	69 ± 9		27 ± 5		/	/	/	/
3	Pappone et al (2014–2015)[22,30]	2015	7	Italy	44	Prospective single-center, observational study	67 ± 8	66 ± 8	30 ± 6	27 ± 7	169 ± 107	182 ± 56	III: 21	III: 19
4	Zanon et al (2015)[32]	2015	6	Italy	29	Prospective single-center, observational study	72 ± 12		29 ± 7		/	/	II: 5, III: 24	
5	Bencardino et al (2016) [23]	2016	6	Italy	43	Randomized open-label	68 ± 11	71 ± 6	27 ± 3	25 ± 6	140 ± 51	169 ± 95	III: 11, IV: 9	III: 12, IV: 11
6	Sterlinski et al (2016) [33]	2016	6	Multicenter	24	Prospective multicenter, observational registry	61 ± 13		24 ± 6		/	/	II: 1, III: 19	
7	Zanon et al (2016)[24]	2016	8	Italy	110	Retrospective single-center, observational study	73 ± 8	67 ± 13	31 ± 6	27 ± 4	71 ± 28 (indexed)	73 ± 28 (indexed)	II:5, III:30, IV:1	II:3, III:16, IV:1
8	Gu et al (2017)[26]	2017	7	China	52	Double-blinded randomized trial	56 ± 11	59 ± 9	28 ± 7	28 ± 7	186 ± 73	173 ± 69	II:9 , III:16 , IV:1	II:10 , III:15 , IV:1
9	Niazi et al (2017)[27]	2017	7	USA	381	Prospective multicenter, randomized, double-blind clinical trial.	68 ± 10	67 ± 10	/	/	/	/	I:25, II:52 , III:113 , IV:11	I:11, II:59 , III:105 , IV:5
10	Akerstroem et al (2018)[36]	2018	6	Spain	46	Prospective multicenter, observational, cross sectional	67 ± 8		26 ± 8		/		I:3, II:20, III:23, IV:0	
11	Leclercq et al (2019)[34]	2019	8	Multicenter	544	Prospective multicenter, randomized clinical trial	68 ± 11	68 ± 10	26 ± 8	26 ± 8	163 ± 68	165 ± 65	II:112, III:113, IV:6	II:106, III:123, IV:7
12	Schiedat et al (2020)[28]	2019	7	Germany	41	Prospective single-center, observational study	70 ± 7		26 ± 8		134 ± 54		II: 13, III: 28	
13	D'Onofrio et al (2021)[38]	2020	7	Italy	167	Prospective observational study	71 ± 10		29 ± 6		133 ± 63		II: 90, III: 77	
14	Forleo et al (2017–2019–2020)[25,35,37]	2020	7	Italy	318	Prospective multicenter, observational registry	71 ± 9	70 ± 11	28 ± 6	28 ± 6	/	/	I-II: 69, III-IV: 112	I-II: 34, III-IV: 75
15	Garcia Guerrero et al (2020)[39]	2020	6	Spain	65	Single-center evaluation of a clinical trial	/	/	/	/	/	/	/	/

All data are expressed as mean ± standard deviation (as not specified elsewhere).

BiV = biventricular pacing; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MPP = multipoint pacing; NYHA = New York Heart Association.

[†]Class I: no limitation of physical activity; class II: slight limitation of physical activity; class III: marked limitation of physical activity; class IV: unable to carry on any physical activity without discomfort.

[‡]Data not expressed in full text.

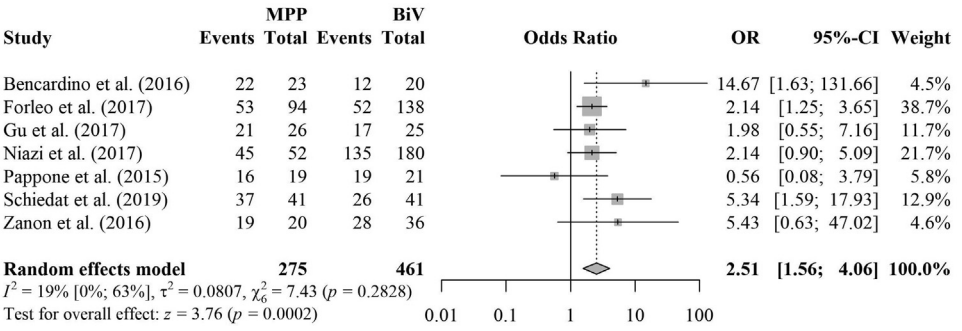

Figure 2 Forest plot for clinical response. Odds ratio of clinical response between the multipoint pacing (MPP) group and biventricular pacing (BiV) group.

considerable. For this reason, even if a larger number of studies should be advisable, we consider a minimum number of studies equal to 3 before considering the above test for asymmetry.

Results

MPP improves clinical response

Seven studies involving 736 patients reported the effect of MPP and BiV on clinical response.[22–28] Indeed, I^2 = 19% and χ^2-based Q test displays a P value higher than .10, highlighting the presence of homogeneous studies (Figure 2). Compared with the BiV group, patients who received MPP therapy are associated with a higher clinical response (odds ratio [OR] = 2.51; 95% CI, 1.56–4.06; P = .0002; Figure 2).

MPP is associated with higher delta LV dP/dtmax

Five studies were considered for understanding the difference between BiV and MPP regarding delta LV dP/dt_{max}.[29–33] A total number of 128 patients have been subjected to both treatments. We underline that all the studies considered for meta-analysis reported a difference favoring the experimental group (MPP). Therefore, the pooled mean difference highlights that MPP is associated with higher delta LV dP/dt_{max} (mean difference [MD], 1.82; 95% CI, 0.24–3.39; P = .0240; I^2 = 0%; Figure 3).

MPP and BiV have no significantly different effect on LVESV

Three articles are considered to capture the pooled effect of LVESV.[22,26,34] Gu and colleagues[26] and Pappone and colleagues[22] found negative mean differences indicating that BiV increases LVESV. However, Leclercq and colleagues[34] presented opposite results but with a higher sample size and thus lower variability in the estimated MD. For this reason, the pooled MD is strongly influenced by the result of the latter study with 85.6% weight. In summary, the pooled MD is positive even if not statistically significant (MD, 0.39; 95% CI, -11.12 to 11.89; P = .9475; Figure 4). Thus, we can conclude that MPP and BiV have no significantly different effect on LVESV.

MPP and BiV do not significantly influence hospitalization for HF

Two researches are considered to understand the effect of MPP and BiV on hospitalization for HF.[34,35] OR is used as the effect measure. Forleo and colleagues[35] presented risk ratio = 0.50, indicating that MPP decreases hospitalization for HF, whereas Leclercq and colleagues[34] found risk ratio = 1.03, showing no significant differences between treatments. In summary, MPP and BiV do not significantly affect hospitalization for HF (OR = 0.70; 95% CI, 0.32–1.54; P = .3816; Figure 5).

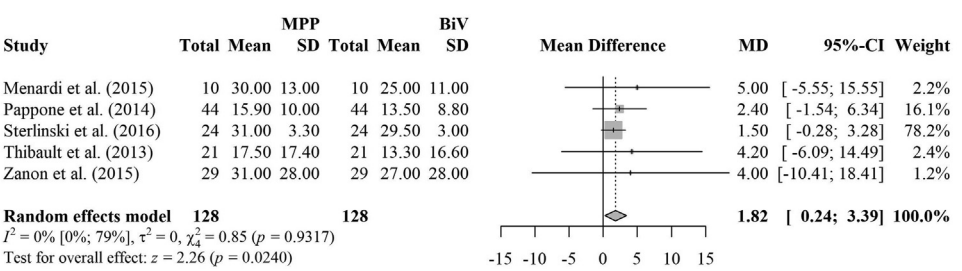

Figure 3 Forest plot for delta LV dP/dt_{max}. Mean difference of clinical response between the multipoint pacing (MPP) group and biventricular pacing (BiV) group.

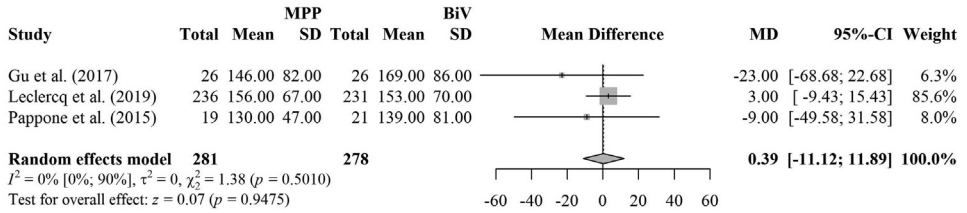

Figure 4 Forest plot for left ventricular end-systolic volume. Mean difference of clinical response between the multipoint pacing (MPP) group and biventricular pacing (BiV) group.

MPP and BiV do not significantly affect all-cause death

Two research papers are used to comprehend the effect of the different treatments on all-cause death.[27,35] OR is used as the effect measure. The pooled OR is not statistically significant (OR = 0.81; 95% CI, 0.40–1.62; P = .5460; Figure 6). I^2 = 0% suggests no heterogeneity and χ^2-based Q test shows P = .8938.

MPP is associated with significantly lower projected battery longevity

Four studies, including a total of 793 patients, reported the effect of MPP with respect to BiV on projected battery longevity.[36–39] I^2 = 87% and χ^2-based Q test displays a P value <.0001, highlighting presence of heterogeneity (Figure 7). These data could be explained by the following arguments: (1) different MPP configurations may have been used among the 4 studies, and (2) the average difference in projected battery longevity found in the study by D'Onofrio and colleagues[38] clearly differs from the results of the other 3 studies. Compared with the BiV group, patients who received MPP therapy are associated with significantly lower projected battery longevity (MD = -8.66; 95% CI, -13.67 to -3.66; P = .0007).

Publication bias

A visual interpretation of funnel plots (Figure 8 and Supplemental Figures 1–5) does not suggest publication bias. Sterne and colleagues[21] suggested that to get a robust test, a number of studies close to 10 should be recommendable; however, the Begg test was implemented for those analyses with more than 3 studies. The latter confirms that publication bias is not a concern in our meta-analysis (P values >.05).

Discussion

We performed a systematic review and meta-analysis on the effects of MPP compared to traditional BiV with the main purpose of investigating the clinical response, defined as improvement of functional class. Then we focused on hemodynamic effects (both short-term—delta LV dP/dt_{max}—and medium-term—LVESV) on prognostic effects and on projected battery longevity. Only a few similar works have been done previously. However, they are not comparable to ours as (1) some of them have a different definition of clinical response; (2) they do not consider hemodynamic parameters in the short term and some of them do not consider LV reverse remodeling; (3) in analyzing the outcome data, some of them include the comparison between bipolar and quadripolar leads, therefore determining completely different results; (4) they do not consider the comparison of the projected battery longevity; and (5) we do not perform any subgroup analysis.[11,13,40–42]

We find that, in terms of functional performance, MPP is associated with a higher percentage of responders than BiV.

Acute and medium-term hemodynamic performance data are more abundant and encouraging. According to our research, use of MPP is associated with an improvement in hemodynamic parameters, but it is not associated with a "reverse remodeling" of the LV, as it determines only a slight and nonsignificant reduction in LVESV.

Previous studies had already shown objective improvement of LVEF with MPP. In our work we did not consider this endpoint, since we realized that a further analysis would not add anything to what other authors have already discovered.[40]

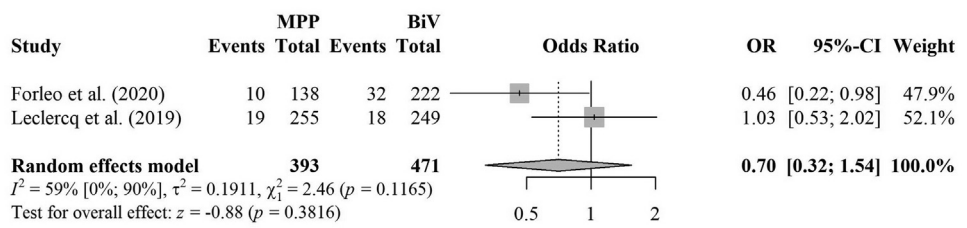

Figure 5 Forest plot for hospitalization for heart failure. Risk ratio of clinical response between the multipoint pacing (MPP) group and biventricular pacing (BiV) group.

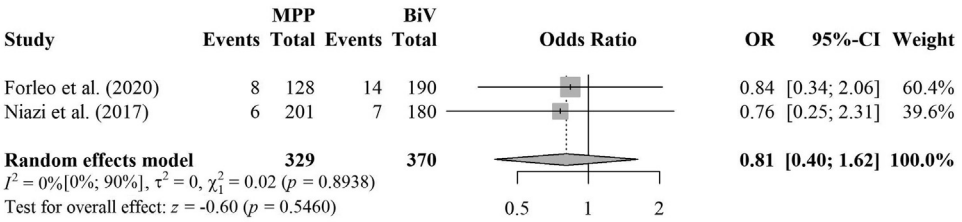

Figure 6 Forest plot for all-cause death. Odds ratio of clinical response between the multipoint pacing (MPP) group and biventricular pacing (BiV) group.

Meta-analysis of the 2 studies that analyzed hospitalization for HF and of the 2 studies that analyzed death from all causes were conflicting and did not reveal any significant difference in the endpoints. This finding is burdened by the limited number of studies and of patients that include outcome endpoints; this constitutes a major limitation for our analysis.

Projected battery longevity data show an undisputed advantage of traditional BiV over MPP. However, it should be emphasized that this advantage can be reduced by more advantageous stimulation configurations, and that the net advantage of BiV over MPP is limited (mean difference of 8.6 months).

Some clinical trials involving MPP are ongoing, or, to our knowledge, their results have not been published yet. The most important of them, already registered on clinicaltrials.gov, are the MORE-CRT-MPP PHASE II trial[43] (a large clinical study whose primary outcome is the response to CRT after 6 months of MPP), IMAGE-CRT[44] (a cohort study whose primary outcome is the CRT response of a type of MPP configuration), MPP Narrow QRS[45] (a randomized clinical trial involving patients with narrow QRS—100 to 130 ms—whose primary outcome is "reverse remodeling" with MPP vs implantable cardiac defibrillator), and the HUMVEE trial[44,46] (a case-crossover prospective study whose primary outcomes are the improvement of ventriculoarterial coupling and the improvement of energy efficiency). The results of these studies and of other clinical trials will certainly help clarify the questions that remain open after our review work.

MPP has been shown to be a pacing modality of great interest to improve the rate of CRT responders, as well as other emerging modalities (eg, LV-only pacing).

To our knowledge, subgroups of patients who benefit more from MPP than from BiV have not been adequately identified. However, MPP was designed, at least theoretically, for those patients who are expected to be "nonresponders" (particularly ischemic patients with large areas of scar).

It is also possible that the clinical results of MPP will be further improved by the development of new technologies capable of improving (1) the choice of the programmed AV delay, (2) the choice of the LV vector, and (3) the automatic programming of the thresholds of the LV, in order to reduce battery consumption.

Conclusion

In light of this evidence, the MPP mode, despite the need for better validation, appears to be advantageous in improving functional class and in improving some acute hemodynamic parameters, even if "reverse remodeling" and prognostic indices—namely LVESV, all-cause mortality, and hospitalization for HF—do not seem to be significantly influenced by MPP with respect to BiV. MPP is associated with a significant reduction in projected battery longevity, with a mean difference of 8.6 months. Conclusive data deriving from newer randomized trials are expected to clarify the prognostic impact of MPP over BiV pacing.

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Disclosures

The authors have no conflicts of interest to disclose.

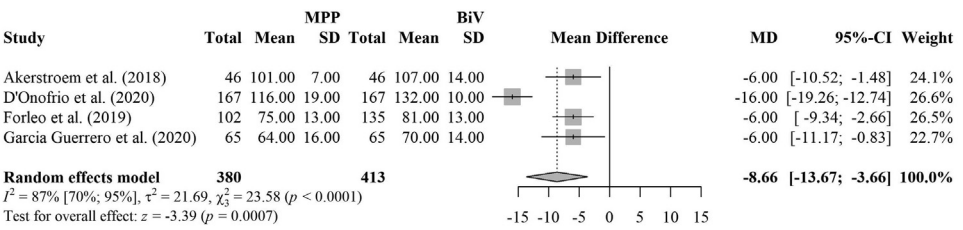

Figure 7 Forest plot for projected battery longevity. Mean difference of clinical response between the multipoint pacing (MPP) group and biventricular pacing (BiV) group.

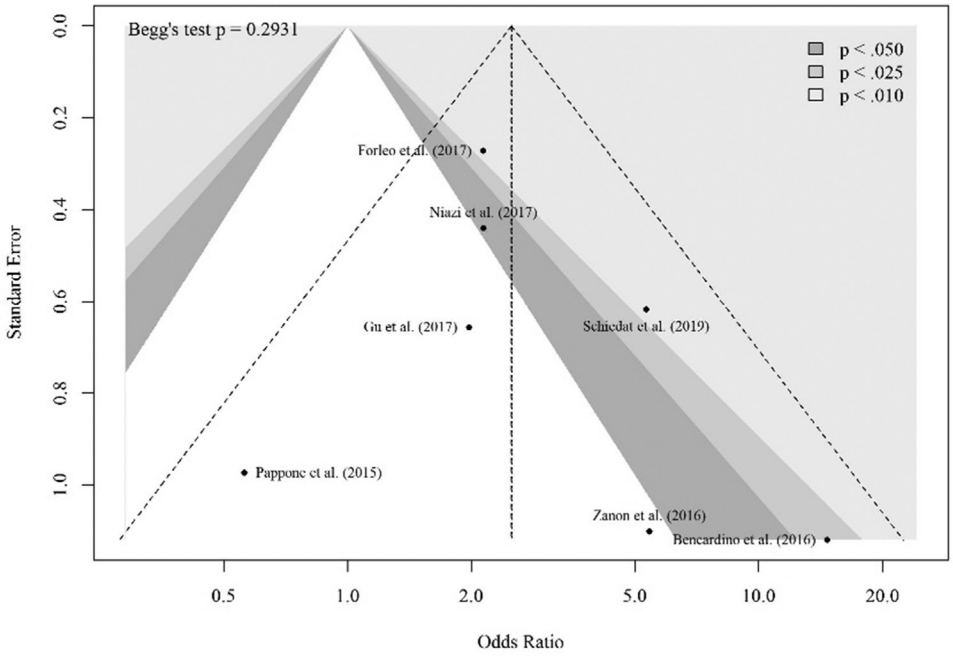

Figure 8 Funnel plot for clinical response. Begg's test confirms that there is no publication bias.

Authorship

All authors attest they meet the current ICMJE criteria for authorship.

Ethics Statement

The research reported in this paper adhered to PRISMA guidelines.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2021.09.012.

References

1. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129–2200.
2. Ypenburg C, van Bommel RJ, Borleffs CJ, et al. Long-term prognosis after cardiac resynchronization therapy is related to the extent of left ventricular reverse remodeling at midterm follow-up. J Am Coll Cardiol 2009;53:483–490.
3. Daubert C, Behar N, Martins RP, Mabo P, Leclercq C. Avoiding non-responders to cardiac resynchronization therapy: a practical guide. Eur Heart J 2017;38:1463–1472.
4. Mullens W, Grimm RA, Verga T, et al. Insights from a cardiac resynchronization optimization clinic as part of a heart failure disease management program. J Am Coll Cardiol 2009;53:765–773.
5. Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J 2013;34:2281–2329.
6. Padeletti L, Colella A, Michelucci A, et al. Dual-site left ventricular cardiac resynchronization therapy. Am J Cardiol 2008;102:1687–1692.
7. Ginks MR, Duckett SG, Kapetanakis S, 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;14:373–379.
8. Leclercq C, Gadler F, Kranig W, et al. A randomized comparison of triple-site versus dual-site ventricular stimulation in patients with congestive heart failure. J Am Coll Cardiol 2008;51:1455–1462.
9. Lenarczyk R, Kowalski O, Kukulski T, et al. Triple-site biventricular pacing in patients undergoing cardiac resynchronization therapy: a feasibility study. Europace 2007;9:762–767.
10. Leyva F, Zegard A, Qiu T, et al. Cardiac resynchronization therapy using quadripolar versus non-quadripolar left ventricular leads programmed to biventricular pacing with single-site left ventricular pacing: impact on survival and heart failure hospitalization. J Am Heart Assoc 2017;6(10).
11. Bodin A, Bisson A, Andre C, et al. Multisite pacing via a quadripolar lead for cardiac resynchronization therapy. J Interv Card Electrophysiol 2019;56:117–125.
12. Muller-Leisse J, Zormpas C, Konig T, Duncker D, Veltmann C. [Multipoint pacing-more CRT or a waste of battery power?]. Herz 2018;43:596–604.
13. Antoniadis AP, Sieniewicz B, Gould J, et al. Updates in cardiac resynchronization therapy for chronic heart failure: review of multisite pacing. Curr Heart Fail Rep 2017;14:376–383.
14. Thibault B, Mondesert B, Cadrin-Tourigny J, Dubuc M, Macle L, Khairy P. Benefits of multisite/multipoint pacing to improve cardiac resynchronization therapy response. Card Electrophysiol Clin 2019;11:99–114.
15. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097.
16. Balduzzi S, Rucker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evidence-Based Mental Health 2019;22:153–160.
17. Spineli LM, Pandis N. The importance of careful selection between fixed-effect and random-effects models. Am J Orthod Dentofacial Orthop 2020;157:432–433.
18. von Hippel PT. The heterogeneity statistic I(2) can be biased in small meta-analyses. BMC Med Res Method 2015;15:35.
19. Sutton AJ, Song F, Gilbody SM, Abrams KR. Modelling publication bias in meta-analysis: a review. Stat Methods Med Res 2000;9:421–445.
20. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw 2010;36:1–48.
21. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011;343:d4002.

22. Pappone C, Calovic Z, Vicedomini G, 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 2015;26:58–63.
23. Bencardino G, Di Monaco A, Russo E, et al. Outcome of patients treated by cardiac resynchronization therapy using a quadripolar left ventricular lead. Circ J 2016;80:613–618.
24. Zanon F, Marcantoni L, Baracca E, 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;13:1644–1651.
25. 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 2017;19:1170–1177.
26. Gu M, Jin H, Hua W, et al. Repetitive optimizing left ventricular pacing configurations with quadripolar leads improves response to cardiac resynchronization therapy: a single-center randomized clinical trial. Medicine 2017;96:e8066.
27. Niazi I, Baker J 2nd, Corbisiero R, et al. Safety and efficacy of multipoint pacing in cardiac resynchronization therapy: the MultiPoint Pacing Trial. JACC Clin Electrophysiol 2017;3:1510–1518.
28. Schiedat F, Schone D, Aweimer A, et al. Multipoint left ventricular pacing with large anatomical separation improves reverse remodeling and response to cardiac resynchronization therapy in responders and non-responders to conventional biventricular pacing. Clin Res Cardiol 2020;109:183–193.
29. Thibault B, Dubuc M, Khairy P, et al. Acute haemodynamic comparison of multisite and biventricular pacing with a quadripolar left ventricular lead. Europace 2013;15:984–991.
30. Pappone C, Calovic Z, Vicedomini G, 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.
31. 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;12:1762–1769.
32. Zanon F, Baracca E, Pastore G, 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;12:975–981.
33. Sterlinski M, Sokal A, Lenarczyk R, et al. In heart failure patients with left bundle branch block single lead multispot left ventricular pacing does not improve acute hemodynamic response to conventional biventricular pacing. A multicenter prospective, interventional, non-randomized study. PloS One 2016;11:e0154024.
34. Leclercq C, Burri H, Curnis A, 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;40:2979–2987.
35. Forleo GB, Santini L, Calo L, et al. Clinical and economic impact of multipoint left ventricular pacing: a comparative analysis from the Italian registry on multipoint pacing in cardiac resynchronization therapy (IRON-MPP). J Cardiovasc Electrophysiol 2020;31:1166–1174.
36. Akerstrom F, Narvaez I, Puchol A, et al. Estimation of the effects of multipoint pacing on battery longevity in routine clinical practice. Europace 2018;20:1161–1167.
37. Forleo GB, Gasperetti A, Ricciardi D, et al. Impact of multipoint pacing on projected battery longevity in cardiac resynchronization therapy. An IRON-MPP study sub-analysis. J Cardiovasc Electrophysiol 2019;30:2885–2891.
38. D'Onofrio A, Bertini M, Infusino T, et al. Single- and multi-site pacing strategies for optimal cardiac resynchronization therapy: impact on device longevity and therapy cost. J Interv Card Electrophysiol 2021;60:195–203.
39. Garcia Guerrero JJ, Fernandez de la Concha Castaneda J, Chacon Pinero A, et al. Extending multipoint pacing CRT battery longevity by swapping left ventricular pulse configurations. J Interv Card Electrophysiol 2020;57:481–487.
40. Hu F, Zheng L, Ding L, et al. Clinical outcome of left ventricular multipoint pacing versus conventional biventricular pacing in cardiac resynchronization therapy: a systematic review and meta-analysis. Heart Fail Rev 2018;23:927–934.
41. Mehta VS, Elliott MK, Sidhu BS, et al. Multipoint pacing for cardiac resynchronisation therapy in patients with heart failure: a systematic review and meta-analysis. J Cardiovasc Electrophysiol 2021;32:2577–2589.
42. Bessa A, Mendes Pimentel PG, Da Silva Menezes Junior A, et al. Effectiveness of multipoint cardiac resynchronizing therapy in heart failure: a systematic review and meta-analysis of randomized controlled trials. Expert Rev Cardiovasc Ther 2021;19:655–665.
43. Leclercq C, Burri H, Curnis A, et al. Rationale and design of a randomized clinical trial to assess the safety and efficacy of multipoint pacing therapy: MOre REsponse on Cardiac Resynchronization Therapy with MultiPoint Pacing (MORE-CRT MPP-PHASE II). Am Heart J 2019;209:1–8.
44. Solimene F, Nigro G, Canciello M, et al. Design and rationale of the Impact of MultiPoint pacing in CRT patients with reduced RV-to-LV delay (IMAGE-CRT) study. J Cardiovasc Med 2020;21:250–258.
45. Gasparini M, Galimberti P, Bragato R, 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;17:572.
46. Chrysohoou C, Dilaveris P, Antoniou CK, et al. Heart failure study of multipoint pacing effects on ventriculoarterial coupling: rationale and design of the HUMVEE trial. Ann Noninvasive Electrocardiol 2018;23:e12510.