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ORIGINAL RESEARCH

CIED - CRT

Acute Hemodynamic Effect of a Novel Dual-Vein, Multisite Biventricular Pacing Configuration

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ABSTRACT

BACKGROUND Biventricular pacing (BVP) from multiple left ventricular (LV) sites could enhance the efficacy of cardiac resynchronization therapy (CRT) by engaging a greater myocardial mass.

OBJECTIVES The goal of this study was to evaluate the acute hemodynamic effect of various multisite pacing (MSP) configurations against conventional BVP.

METHODS Twenty patients with nonischemic dilated cardiomyopathy and left bundle branch block (mean age: 59 ± 14 years; LV ejection fraction: 27% ± 6%; native QRS: 171 ± 16 milliseconds) were investigated during a routine CRT implant procedure. In addition to conventional right atrial and right ventricular leads, 2 quadripolar leads were placed in the distant coronary venous branches. LV hemodynamics was evaluated by using a micromanometer-tipped catheter during atrioventricular BVP with 4 LV lead configurations: single-lead conventional BVP; single-lead multipoint pacing; triventricular pacing from distal dipoles of 2 LV leads; and maximum MSP (MSP-Max) from 4 dipoles of 2 LV leads.

RESULTS Compared with right atrial pacing, any BVP configuration produced a significant increase in the maximal LV diastolic pressure rise ($LVdP/dT_{Max}$) (a median relative increase of 28% [IQR: 8%-45%], 25% [IQR: 18%-46%], 36% [IQR: 18%-54%], and 38% [IQR: 28%-58%], respectively; all, $P < 0.001$). MSP-Max but no other multisite BVP generated a significant increase of the maximal $LVdP/dT_{Max}$ than conventional BVP ($P = 0.041$). Increased $LVdP/dT_{Max}$ during MSP-Max was associated with greater LV diameter and lower LV ejection fraction, independently of the QRS width.

CONCLUSIONS The study shows the hemodynamic advantage of a novel dual-vein MSP-Max configuration that could be useful for CRT in patients with advanced LV remodeling. (J Am Coll Cardiol EP 2023;9:2329-2338) © 2023 by the American College of Cardiology Foundation.

Cardiac resynchronization therapy (CRT) is an established treatment for heart failure with reduced left ventricular (LV) ejection fraction (LVEF) and left bundle branch block (LBBB) that can improve the patient's survival, cardiac function, and well-being.[1] However, some individuals respond less favorably to CRT because of intrinsic factors such as non-LBBB morphology, ischemic

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

BVP = biventricular pacing

CRT = cardiac resynchronization therapy

LBBB = left bundle branch block

LV = left ventricular

LVEF = left ventricular ejection fraction

MPP = multipoint pacing

MSP = multisite pacing

MSP-Max = maximum multisite pacing

RV = right ventricular

TVP = triventricular pacing

etiology, or extensive LV dilatation.[2,3] In these clinical nonresponders, pacing from multiple LV sites (ie, multisite pacing [MSP]) may be a viable alternative to conventional single-site biventricular pacing (BVP).[4]

The hemodynamic benefit of MSP has been explained by engaging a greater myocardial mass and shortening of LV activation time.[4,5] Animal studies on MSP showed correlation of hemodynamic improvement with increasing number of LV pacing sites[6] and larger interelectrode distances,[7] whereas several (although not all) studies in humans reported greater acute improvement of LV contractility and better long-term response rates compared with conventional BVP, especially in patients with advanced LV remodeling.[8] These studies conducted pacing through 2 dipoles of a single quadripolar LV lead (multipoint pacing [MPP]),[5,8-13] or distal dipoles of 2 conventional LV leads placed in separate coronary veins (dual-vein or triventricular pacing [TVP]),[14-18] or through a combination of MPP and TVP.[19]

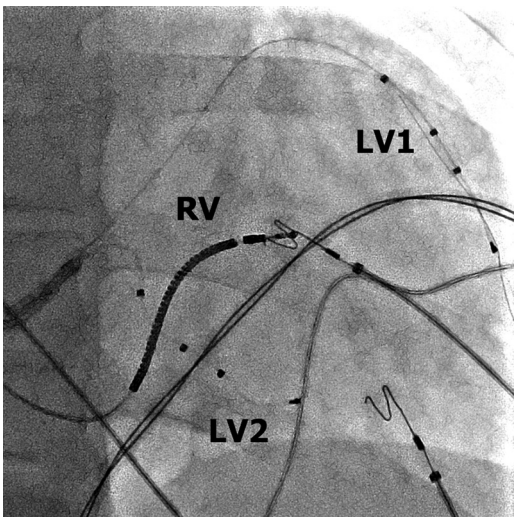
In the present study, we extended the combined TVP + MPP approach and developed a new maximum MSP configuration (MSP-Max) that uses pacing from 4 LV dipoles of 2 quadripolar LV leads. Based on the available evidence, we hypothesized that pacing by MSP-Max would generate a more significant acute hemodynamic response compared with that of conventional BVP and other MSP configurations. In addition, we verified whether the effect would be influenced by baseline LV remodeling.

METHODS

STUDY POPULATION. The study enrolled adult patients with heart failure with reduced LVEF due to idiopathic cardiomyopathy, who had sinus rhythm and LBBB and who underwent clinically indicated CRT. The hemodynamic study protocol was conducted during the implant procedures (January 2020-March 2022), during which the patients received a conventional permanent CRT device. Clinical checkup, echocardiography, and device interrogation were repeated after 6 months by examiners who were unaware of the hemodynamic data. Reduction of LV end-systolic diameter ≥15% at 6 months was considered a good response to CRT.[20]

The study was approved by the institutional ethics committee, and all patients signed informed consent.

FIGURE 1 Typical Positions of the Pacing Leads

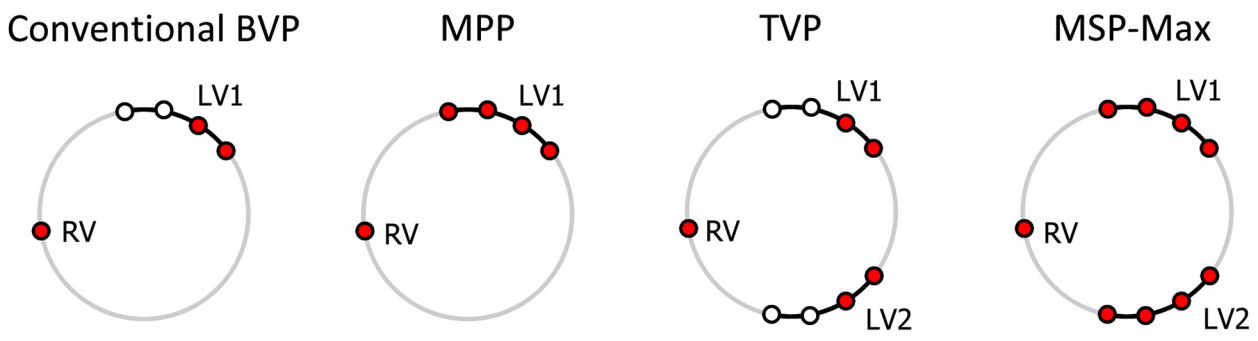


The figure shows a fluoroscopy image of a study patient with an optimal hardware setup with a wide separation of the left ventricular leads (LV1 and LV2). RV = right ventricle.

IMPLANT PROCEDURE AND INSTRUMENTATION. Conventional leads were positioned in the right atrial appendage and right ventricular (RV) mid septum. LV leads were implanted according to our previously described technique using electrophysiological guidance, balloon-occlusive angiography, and angiographic guidewires or subselectors when needed.[21] Two quadripolar leads (Quartet, Abbott) were introduced into distant coronary veins: one preferable position was in the anterior or anterolateral coronary vein and the other in the lateral or posterolateral vein, depending on the individual anatomy (Figure 1). A micromanometer-tipped pressure catheter (MicroCath, Millar) was inserted through a pig-tail catheter via transfemoral access into the left ventricle, and a sphygmomanometer cuff for continuous measurement of arterial blood pressure and stroke volume was strapped on the patient's third finger (Finometer Pro, FMS). After the hemodynamic study, the LV lead-generating lower $LVdP/dT_{Max}$ was removed, and the remaining LV lead was connected to a permanent CRT device.

PACING PROTOCOL. Patients were paced with the output of 5 V/0.75 millisecond at 90/min (or 10/min above the intrinsic heart rate) by 6 pacing configurations: right atrial pacing with native QRS, sequential RV pacing, conventional BVP, single-lead MPP,

FIGURE 2 Diagram Summary of the Used Biventricular Pacing Sequences



The diagram represents the biventricular pacing (BVP) sequences used. The red circles represent active electrodes of the left ventricular (LV) quadripolar leads. For simplification, the right atrial lead is not depicted, although all the configurations used atrioventricular sequential pacing with an atrioventricular delay of 150 milliseconds. Conventional BVP was performed from 1 right ventricular (RV) site and 1 LV site (distal dipole of the LV lead). Multipoint pacing (MPP) was performed from 1 RV site and 2 LV sites using a single quadripolar LV lead (proximal and distal dipoles of the LV lead). Triventricular pacing (TVP) was performed from 1 RV site and 2 LV sites using 2 LV leads (distal dipoles of 2 LV leads). Maximum multisite pacing (MSP-Max) was performed from 1 RV site and 4 LV sites using 2 quadripolar LV leads (proximal and distal dipoles of two LV leads).

dual-vein TVP, and MSP-Max; details are provided in Figure 2. Atrioventricular delay was set to 150 milliseconds, and RV-LV and intra-LV delays were set to 0 millisecond. BVP based on a single LV lead was conducted with the LV lead that generated greater $LVdP/dT_{Max}$. To ensure reliable capture from all electrodes, each electrode dipole was connected to a separate external pulse generator (Model 3085, Abbott) through a custom-made analog switcher. Each pacing sequence lasted approximately 1.5 minutes, and for each patient, the order of the sequences was changed randomly. To minimize measurement errors, the entire protocol was run twice.

DATA ACQUISITION AND PROCESSING. Analog signals from the LV pressure catheter and continuous sphygmomanometer were recorded at 1 kHz using a data acquisition system (PowerLab, ADInstruments) and analyzed in dedicated software (LabChart 8, ADInstruments). Measured hemodynamic variables included $LVdP/dT_{Max}$, LV end-diastolic pressure, and tau obtained from the pressure catheter; arterial systolic, mean, and pulse pressure acquired by using a sphygmomanometer; and stroke volume obtained by analysis of the arterial pressure waveform using a 3-parameter Windkessel model implemented in the software. For each pacing sequence, a 30-second steady-state interval was analyzed beat-by-beat and averaged over the selected interval, then averaged over 2 sequence runs. Electrocardiography was recorded at 1 kHz by using the CardioLab system (GE Healthcare). QRS and Q-LV intervals were obtained from the average of 3 measurements by an electronic caliper, as previously described.[21]

STATISTICAL ANALYSIS. Continuous variables are reported as mean ± SD or median (IQR). Comparisons of hemodynamic variables between various pacing configurations were performed by using a paired Student's t-test with the Holms correction for repeated measures. The primary endpoint was the change in $LVdP/dT_{Max}$ during BVP compared with right atrial pacing. Baseline factors associated with the change in $LVdP/dT_{Max}$ were evaluated by linear regression for continuous variables and logistic regression for categorical variables. Correlations between $LVdP/dT_{Max}$ and noninvasive hemodynamic variables were evaluated by using Pearson's test with pooled data from all patients at all pacing configurations. The pooled data were also used for linear regression to evaluate the relation among $LVdP/dT_{Max,}$ (as a dependent variable) and QRS duration, QRS change, and BVP as independent variables.

The analyses were performed in R version 4.1 (R Foundation for Statistical Computing). The values of $P < 0.05$ were considered statistically significant.

RESULTS

STUDY POPULATION. From the initially enrolled 22 consecutive patients, 2 patients were excluded during the implantation procedure for unattainable myocardial capture from one of the proximal LV dipoles. The final study population comprised 20 patients with a completed study protocol (Table 1).

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TABLE 1 Patient Clinical Characteristics (N = 20)

Age, y	62 ± 13
Female	7 (35.0)
Body mass index, kg/m^2	28 ± 4
Arterial hypertension	11 (55.0)
Diabetes mellitus	5 (25.0)
Coronary artery disease	1 (5.0)
NYHA functional class I-IV	2 ± 1
HF diagnosis duration, y	1.5 (0.5-3.2)
Previous hospitalization for acute HF	6 (30.0)
ACE inhibitor/ARB/ARNI	19 (95.0)
Beta-blockers	17 (85.0)
Mineralocorticoid receptor antagonists	16 (80.0)
Loop diuretics	16 (80.0)
Antiarrhythmic drugs	4 (20.0)
B-type natriuretic peptide, μg/L	231 (131-375)
LV ejection fraction, %	25 ± 5
LV end-diastolic diameter, mm	65 ± 8
LV end-systolic diameter, mm	49 ± 8
Native QRS width, ms	177 ± 15
Native QLV delay, ms	133 ± 24
QLV/QRS ratio	0.74 ± 13

Values are mean ± SD, n (%), or median (IQR).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; HF = heart failure; LV = left ventricular.

All patients had idiopathic dilated cardiomyopathy (LV diastolic diameter ranging from 58-90 mm) and a typical LBBB (a mean QRS of 177 ± 15 milliseconds). One patient had a history of coronary artery stenting of chronic stenosis of the circumflex artery (single-vessel disease) without a prior myocardial infarction. All patients were in sinus rhythm throughout the study.

IMPLANTATION PROCEDURE. Implantation of the 2 LV leads into separate coronary vein branches was successful in all cases. The achieved locations of the first LV leads (as appearing in right anterior oblique and left anterior oblique sciascopy views) were: lateral-medial (n = 5 [25%]), lateral-apical (n = 1 [5%]), anterior-basal (n = 5 [25%], anterior-medial (n = 7 [35%]), and anterior-apical (n = 2 [10%]). The locations of the second LV leads were: posterior-medial (n = 6 [30%]), posterior-apical (n = 5 [25%]), lateral-medial (n = 8 [40%]), and lateral-apical (n = 1 [5%]). The average duration of the entire implantation procedure, including the hemodynamic study, was 118 ± 21 minutes. The total fluoroscopic time reached 20 ± 8 minutes, and the radiation dose was 506 ± 207 μGy/m^2. No procedure-related complications occurred.

QRS AND HEMODYNAMICS DURING BVP. Compared with right atrial pacing, QRS complexes were significantly prolonged during RV pacing and significantly shortened during any BVP configuration (Table 2, Figure 3A). Paced QRS were shorter during TVP and MSP-Max compared with conventional BVP by a median of -10 milliseconds [IQR: -7 to -17 milliseconds] and -14 milliseconds [IQR: -10 to -18 milliseconds] (both, $P < 0.001$), whereas there was no significant difference in QRS duration between conventional BVP and MPP (Table 2, Figure 3A).

Hemodynamic changes at the different pacing configurations are summarized in Table 2 and Figure 3B. Compared with right atrial pacing, any BVP induced a significant increase in LVdP/dTMax; however, the increase was greatest during MSP-Max (median percent change, conventional BVP: 28% [IQR: 8%-45%]; MPP: 25% [IQR: 18%-46%]; TVP: 36% [IQR: 18%-54%]; and MSP-Max: 38% [IQR: 28% to 58%]; all, $P < 0.001$). LVdP/dTMax during MSP-Max was significantly greater compared with conventional BVP (by a median of 9% [IQR: 2% to 13%]; adjusted $P = 0.041$), whereas there was no significant difference in LVdP/dT_{Max} among conventional BVP and other MSP configurations (Table 2). No BVP configuration significantly affected LV diastolic function, as represented by the LV end-diastolic pressure and tau.

Of the noninvasive hemodynamic variables, only the mean arterial pressure increased significantly during TVP and MSP-Max (Table 2). No significant changes were observed in any other noninvasive hemodynamic variables for any pacing configuration. Moreover, there was only a modest correlation between LVdP/dT_{Max} and noninvasively measured mean arterial pressure, systolic pressure, or pulse pressure (n = 120, $r = 0.31$, $r = 0.30$, and $r = 0.20$; $P < 0.001$, $P < 0.001$, and $P = 0.043$, respectively), and no correlation was found between LVdP/dT_{Max} and noninvasive stroke volume ($r = 0.10$; $P = 0.30$).

FACTORS ASSOCIATED WITH A GREATER INCREASE IN LVdP/dT_{Max}. From the baseline variables listed in Table 1, only greater LV end-diastolic diameter and lower LVEF were significantly associated with the increase in LVdP/dT_{Max} and only during TVP and MSP-Max (β, 1.6 [95% CI: 0.2-2.9] and 1.5 [95% CI: 0.3-2.8] for LV end-diastolic diameter, and -2.6 [95% CI: -4.6 to -0.6] and -2.2 [95% CI: -4 to -0.2] for LVEF, respectively). Of note, LV end-diastolic diameter did not differ between male (66 ± 10 mm, n = 13) and female (64 ± 7 mm, n = 7) subjects.

TABLE 2 QRS Width and Hemodynamics and During Different Pacing Configurations

	RA Pacing (Native QRS)	RV Pacing	Conventional BVP	MPP	TVP	MSP-Max
QRS width, ms	177 ± 15	192 ± 20 [b,f]	165 ± 18[a]	157 ± 12[c]	151 ± 11[c,f]	149 ± 9 [c,f]
LVdP/dT$_{Max}$, mm Hg/s	1,884 ± 545	2,027 ± 687	2,440 ± 809[c]	2,541 ± 696[c]	2,533 ± 795[c]	2,685 ± 847[c,d]
SBP, mm Hg	127 ± 26	128 ± 24	130 ± 25	131 ± 24	132 ± 26	130 ± 29
PP, mm Hg	56 ± 19	56 ± 18	58 ± 19	58 ± 19	58 ± 21	59 ± 20
MAP, mm Hg	87 ± 19	89 ± 20	89 ± 19	89 ± 19	91 ± 19[a,e]	91 ± 18[a,d]
Stroke volume, mL	62 ± 14	61 ± 14	64 ± 14	61 ± 14[d]	62 ± 12	63 ± 13
LV EDP, mm Hg	16 ± 7	16 ± 7	15 ± 8	15 ± 8	15 ± 8	16 ± 8
LV tau index, ms	0.29 ± 0.23	0.24 ± 0.19	0.18 ± 0.09	0.32 ± 0.64	0.41 ± 1.18	2.52 ± 10.3

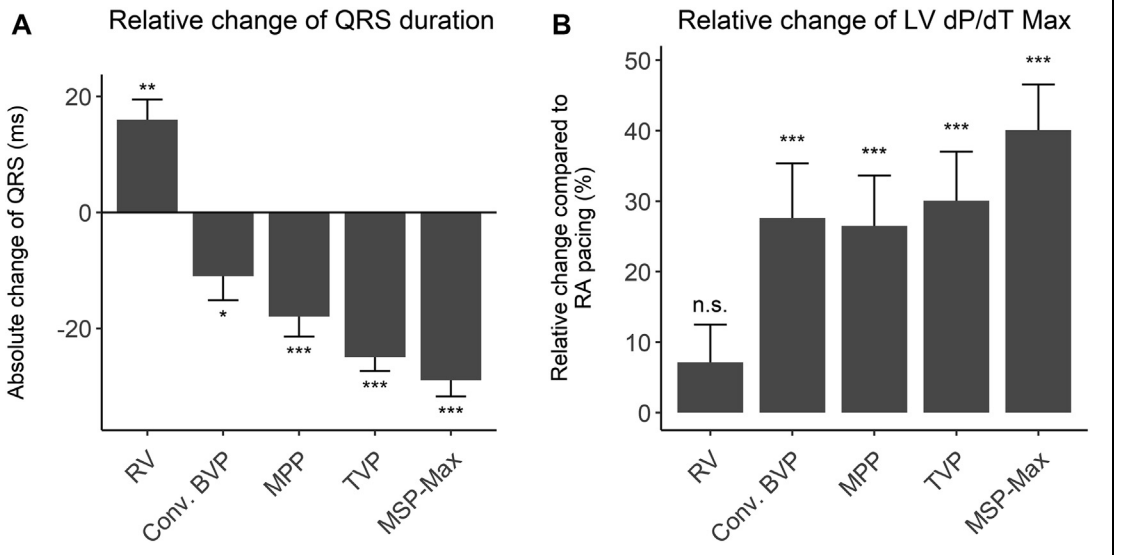
Values are mean ± SD. [a,b,c]Adjusted $P < 0.05/P < 0.01/P = 0.001$ against right atrial (RA) pacing. [d,e,f]Adjusted $P < 0.05/P = 0.01/P = 0.001$ against conventional biventricular pacing (BVP).

EDP = end-diastolic pressure; LV = left ventricular; LVDP/dT$_{Max}$ = maximal LV diastolic pressure; MAP = mean arterial pressure; MPP = multipoint pacing; MSP-Max = maximum multisite pacing; PP = pulse pressure; RV = right ventricular; SBP = systolic blood pressure; TVP = triventricular pacing.

In univariate regression analyses of pooled data from all sequences (n = 120), the only factors associated with the increase in LVdP/dT$_{Max}$ were the QRS duration, the absolute change of QRS duration, and pacing with any BVP configuration (β, -0.4 [95% CI: -0.7 to 0.2], -0.5 [95% CI: -0.8 to -0.3], and 576 [95% CI: 404-748]).

FOLLOW-UP AT 6 MONTHS. Clinical follow-up at 6 months, including echocardiography and device interrogation, was available in all patients. No delayed device-related infection or device failures were observed. Good response to conventional CRT was noted in 13 (65%) patients, whereas 7 (35%) patients responded poorly. A comparison between the

FIGURE 3 Effect of Multisite Pacing on QRS Duration and Hemodynamics



Absolute change of QRS width (A) and percent change in LVdP/dT$_{Max}$ (B) during different pacing configurations compared with right atrial pacing with native QRS. */**/***Adjusted $P < 0.05/0.01/0.001$. Details on the pacing configurations are provided in Figure 2. Conv. BVP = conventional biventricular pacing; RV = right ventricular pacing; other abbreviations as in Figure 2.

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responders and poor responders is presented in Supplemental Table 1. In a pooled analysis of all BVP configurations (80 data points), LVdP/dT_{Max} measured during BVP at baseline predicted good response to conventional CRT and relative change of LV end-systolic diameter (OR: 1.1 [95% CI: 1.02-1.21] and 2.0 [95% CI: 1.3-3.2] per 100 mm Hg/s, respectively). This relationship did not reach statistical significance when each BVP configuration was analyzed separately (20 data points).

DISCUSSION

This study evaluated acute hemodynamic effects of conventional BVP and 3 different MSP configurations in patients with dilated cardiomyopathy and LBBB. Although there was a significant increase in LV contractility during any of the BVP configurations, the greatest improvement was achieved by the newly proposed MSP-Max configuration that used 4 dipoles of 2 LV leads. In fact, our findings indicate hemodynamic superiority of MSP-Max over conventional BVP, which can be explained by more effective electric activation of a larger myocardial mass. Moreover, there was a significant association between LV diastolic diameter and improvement in LV contractility during TVP and MSP-Max, suggesting a possible role of the dual-vein approach in patients with advanced LV remodeling. In this limited sample, LVdP/dT_{Max} measured during BVP at baseline seemed to be associated with response to CRT at 6 months. However, the study found a limited effect of BVP on noninvasive hemodynamic parameters and a weak correlation of the noninvasive parameters with LVdP/dT_{Max}. These findings have relevant implications for assessment of hemodynamics in future studies on MSP (**Central Illustration**).

MPP VS CONVENTIONAL BVP. The concept of MSP has been explored for more than a decade in an effort to surpass the response rate of CRT. It is presumed that pacing from multiple LV sites can engage larger myocardial mass, thereby improving intra-LV synchrony with ensuing shorter LV activation time.[4] One approach to MSP is pacing from multiple dipoles of a single quadripolar LV lead, MPP. Four invasive hemodynamic studies reported greater acute improvement of LV contractility by MPP compared with conventional BVP.[9,12,13,19] Pappone et al[22] followed up their patients for additional 12 months and observed greater LV reverse remodeling in the MPP group compared with the conventional BVP group. Another study reported more pronounced LV reverse remodeling and an improved composite clinical score at 3 months with MPP, although this was mostly observed in patients with more advanced baseline LV remodeling.[8]

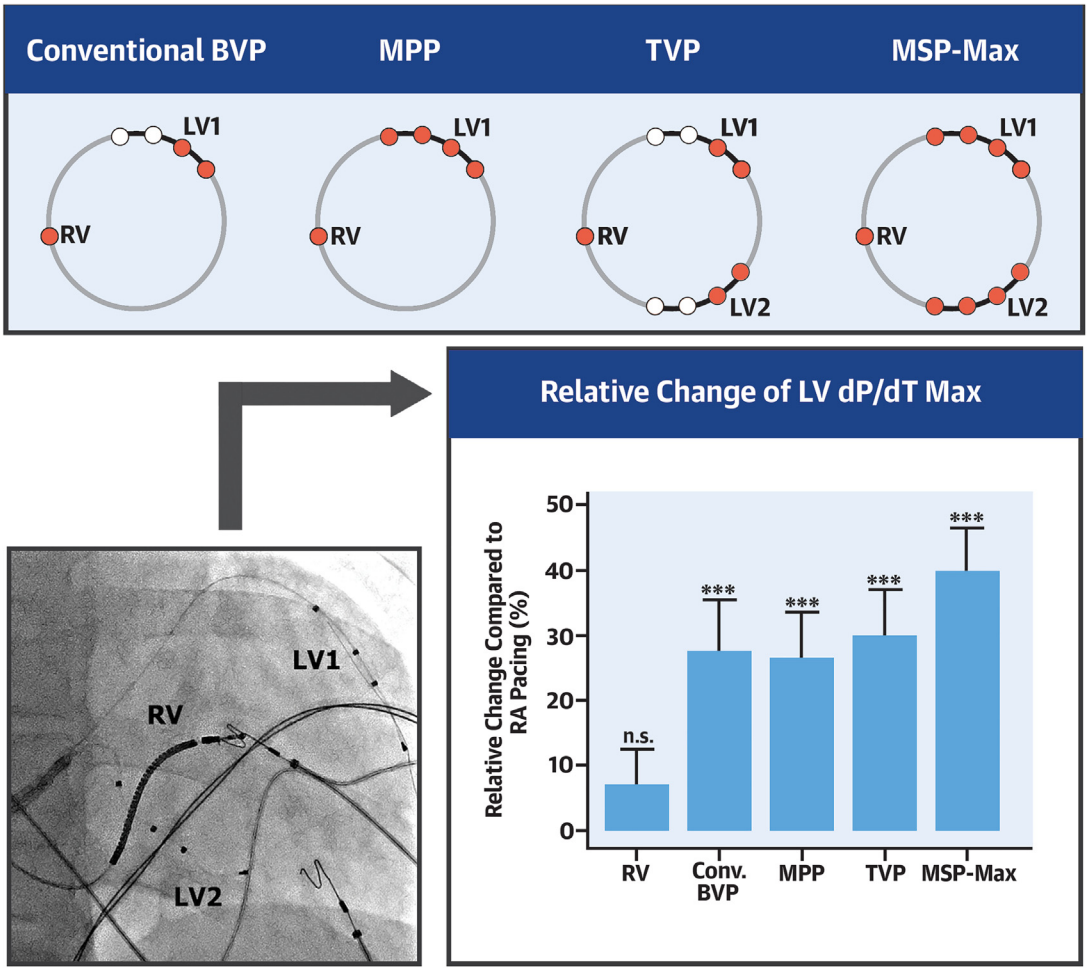
In contrast, 3 comparable hemodynamic studies together with our study found significant differences in LVdP/dT_{Max} between MPP and right atrial pacing but did not confirm hemodynamic superiority of MPP over conventional BVP.[5,10,11] We can only speculate that the lack of hemodynamic advantage of MPP found in the present study may be related to the distinct population of our patients with dilated cardiomyopathy who could have better responded to conventional BVP than patients with ischemic scar.[23] Given the conflicting evidence, further studies are needed to establish the role of MPP in clinical practice.

DUAL-VEIN APPROACH VS CONVENTIONAL BVP. Another strategy of MSP is implantation of a second LV lead to a separate coronary vein branch, the so-called dual-vein approach. The delayed effect of the dual-vein approach has been tested by 5 randomized trials with 3 to 12 months of echocardiographic follow-up. The pacing was carried through 1 RV site and 2 LV sites (ie, TVP). Three of the trials observed greater improvement of LVEF in the TVP group,[16-18] and 2 of them found additional improvement in functional capacity.[17,18] In contrast, the V3 and STRIVE-HF (Triventricular Pacing in Heart Failure) trials found no difference between the 2 groups in a composite clinical score, functional capacity, or LV remodeling.[14,15] However, the V3 trial could have been biased by selecting nonresponders to conventional BVP.

In the current study, the difference in LVdP/dT_{Max} between TVP and BVP did not reach statistical significance. Similarly as for MPP, this could have been related to an already good response to conventional BVP that was difficult to exceed. Nevertheless, our study contributes an important finding of greater hemodynamic response to dual-vein MSP in patients with larger LV diameter and lower LVEF. This association could be explained by the fact that a larger LV surface requires more pacing sites and wider electrode separation to effectively improve LV activation.[7,8] The finding also suggests the possible use of dual-vein MSP in patients with more advanced LV remodeling.

Zanon et al[19] combined MPP by a quadripolar LV lead with TVP by a second LV lead. The combination of TVP and MPP generated a greater acute increase in LV contractility than conventional BVP or TVP alone. This finding corroborates results of an experimental animal study, in which progressive pacing from up to

CENTRAL ILLUSTRATION Summary of Methods and Results



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The upper panel shows evaluated pacing configurations: conventional biventricular pacing (BVP), multipoint pacing (MPP) using 2 dipoles of 1 quadripolar left ventricular (LV) lead, triventricular pacing (TVP) using distal dipoles of 2 LV leads, and a novel maximum multisite pacing (MSP-Max) using 4 dipoles of 2 quadripolar LV leads. The lower left panel shows hardware setup as appearing on sciascopy. The lower right panel shows the relative increase in $LVdP/dT_{Max}$ during the evaluated pacing configurations. *** $P < 0.001$ compared to RA pacing. $LVdP/DT_{max}$ = maximal LV diastolic pressure; n.s. = not significant; RV = right ventricle.

9 LV epicardial sites led to an incremental increase in $LVdP/dT_{Max}$.[6] Our study extended these observations. By adding an additional LV site, whereby obtaining 5 ventricular pacing sites, we showed significantly greater improvement in LV contractility that went beyond conventional BVP and all other MSP configurations.

CLINICAL FEASIBILITY OF DUAL-VEIN MSP. It is conceivable that implantation of an additional LV lead could increase the risk of periprocedural complications. However, except for 1 study in which complications were observed in up to 20% of patients,[14] most studies on dual-vein pacing reported a high success rate and a low rate of

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complications.[16,17,19] Our study adds important safety data to the evidence base. We showed that the implantation of 2 LV leads could be achieved in 22 consecutive cases without any clinical complications. Technically, the implant procedure was successful in 20 of the patients (91%), as there were 2 cases of unattainable capture from one of the LV lead dipoles. Our data, together with the prevailing evidence, indicate the feasibility and acceptable safety of dual-vein CRT.

TECHNICAL CONSIDERATIONS. Although there are clinically available CRT devices that enable controlling different vectors of a single quadripolar LV lead, it should be emphasized that currently there is no clinically available 4-channel CRT device that could separately control right atrial, RV, and 2 LV leads. In the previous studies, this technical hurdle was partially overcome by connecting 2 LV leads through a Y-connector.[14-19] However, such an approach requires equal electrical impedance on all LV dipoles used. Any impedance mismatch would cause preferential flow of the electric current through the LV lead with the lower resistance, thereby hampering capture by the other LV lead or causing premature battery depletion due to the required higher voltage output. Implantation of 2 LV leads could also carry an increased risk of delayed lead dislocation. Conversely, this complication could be prevented by using new-generation quadripolar leads with active fixation.[24] Hopefully, studies such as the current one will stimulate device manufacturers to develop new CRT systems for dual-vein MSP.

STUDY LIMITATIONS. The small sample size limited analyses of baseline predictors of acute hemodynamic response to MSP or baseline predictors of long-term LV reverse remodeling. Nevertheless, the study was adequately powered for the evaluation of significant within-subject changes in $LVdP/dT_{Max}$, which was the main hemodynamic endpoint. Although the relation between acute increase in $LVdP/dT_{Max}$ during conventional CRT procedure and long-term LV reverse remodeling has been previously reported,[20] it would need to be explicitly confirmed for MSP-Max. In our limited sample size, we observed a significant association between BVP and future response to conventional BVP. However, the study was not designed for evaluation of the long-term effect of the individual MSP configurations. We did not measure the achieved interelectrode distances, which could potentially bring more insights into the effect of MSP. Such analysis would require dedicated sciascopy projections or computed tomography imaging, which were not designed in the study protocol.

To identify best responders to the MSP, we believe further studies should also implement electrocardiographic imaging and measurement of paced LV conduction times.[25] It should also be highlighted that our study investigated only patients with idiopathic dilated cardiomyopathy. Although this approach avoided the bias of inefficient pacing from postinfarct scar,[23] it limits the applicability of the results to this specific patient population. Lastly, to ensure similar conditions across the study group, we set a fixed atrioventricular delay of 150 milliseconds for the BVP sequences. It is conceivable that optimization of the atrioventricular delay for each patient could further improve the hemodynamic response.[26]

CONCLUSIONS

Dual-vein MSP with a novel MSP-Max configuration generated significantly greater acute increase in LV contractility than conventional BVP, especially in patients with greater LV diameter and lower LVEF. Conversely, the single-lead MPP approach did not seem to be hemodynamically superior. These preliminary findings provide foundations for designing new strategies for nonresponders to conventional CRT due to advanced LV remodeling.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with more advanced LV remodeling seem to have hemodynamic benefit from dual-vein MSP, particularly from a newly proposed MSP-Max pacing configuration. Clinical nonresponders to conventional BVP due to advanced LV remodeling could be considered for implantation of a second LV lead and MSP-Max as an alternative strategy. However, such a strategy would need to be confirmed in a large, long-term prospective trial.

TRANSLATIONAL OUTLOOK: This study provides the clinical rationale for the manufacturers of CRT devices to develop new solutions that would enable reliable long-term dual-vein MSP in clinical practice. Further research would need to verify the benefits, longevity, and cost-efficacy of such devices.

REFERENCES

1. Glikson M, Nielsen JC, Kronborg MB, et al. 2021 ESC guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J*. 2021;42:3427–3520.

2. Carluccio E, Biagioli P, Alunni G, et al. Presence of extensive LV remodeling limits the benefits of CRT in patients with intraventricular dyssynchrony. *J Am Coll Cardiol Img*. 2011;4:1067–1076.

3. Varma N, Lappe J, He J, Niebauer M, Manne M, Tchou P. Sex-specific response to cardiac resynchronization therapy: effect of left ventricular size and QRS duration in left bundle branch block. *J Am Coll Cardiol EP*. 2017;3:844–853.

4. Rinaldi CA, Burri H, Thibault B, et al. A review of multisite pacing to achieve cardiac resynchronization therapy. *Europace*. 2015;17:7–17.

5. Sohal M, Shetty A, Niederer S, 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;12:2449–2457.

6. Ploux S, Strik M, van Hunnik A, van Middendorp L, Kuiper M, Prinzen FW. Acute electrical and hemodynamic effects of multisite left ventricular pacing for cardiac resynchronization therapy in the dyssynchronous canine heart. *Heart Rhythm*. 2014;11:119–125.

7. Heckman LIB, Kuiper M, Anselme F, et al. Evaluating multisite pacing strategies in cardiac resynchronization therapy in the preclinical setting. *Heart Rhythm O2*. 2020;1:111–119.

8. Varma N, Baker J 2nd, Tomassoni G, et al. Left ventricular enlargement, cardiac resynchronization therapy efficacy, and impact of multipoint pacing. *Circ Arrhythmia Electrophysiol*. 2020;13:e008680.

9. 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.

10. Shetty AK, Sohal M, Chen Z, et al. A comparison of left ventricular endocardial, multisite, and multipolar epicardial cardiac resynchronization: an acute haemodynamic and electroanatomical study. *Europace*. 2014;16:873–879.

11. 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.

12. 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.

13. 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.

14. Bordachar P, Gras D, Clementy N, et al. Clinical impact of an additional left ventricular lead in cardiac resynchronization therapy nonresponders: the V(3) trial. *Heart Rhythm*. 2018;15:870–876.

15. Gould J, Claridge S, Jackson T, et al. Standard care vs. TRIVEntricular pacing in Heart Failure (STRIVE HF): a prospective multicentre randomized controlled trial of triventricular pacing vs. conventional biventricular pacing in patients with heart failure and intermediate QRS left bundle branch block. *Europace*. 2022;24:796–806.

16. 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.

17. Lenarczyk R, Kowalski O, Kukulski T, et al. Mid-term outcomes of triple-site vs. conventional cardiac resynchronization therapy: a preliminary study. *Int J Cardiol*. 2009;133:87–94.

18. Rogers DP, Lambiase PD, Lowe MD, Chow AW. A randomized double-blind crossover trial of triventricular versus biventricular pacing in heart failure. *Eur J Heart Failure*. 2012;14:495–505.

19. Zanon F, Marcantoni L, Baracca E, et al. Hemodynamic comparison of different multisites and multipoint pacing strategies in cardiac resynchronization therapies. *J Interv Cardiac Electrophysiol*. 2018;53:31–39.

20. Sohal M, Hamid S, Perego G, et al. A multicenter prospective randomized controlled trial of cardiac resynchronization therapy guided by invasive dP/dt. *Heart Rhythm O2*. 2021;2:19–27.

21. Sedlacek K, Jansova H, Vancura V, Grieco D, Kautzner J, Wichterle D. Simple electrophysiological predictor of QRS change induced by cardiac resynchronization therapy: a novel marker of complete left bundle branch block. *Heart Rhythm*. 2021;18:1717–1723.

22. Pappone C, Calovic Z, Vicedomini G, et al. Improving cardiac resynchronization therapy response with multipoint left ventricular pacing: twelve-month follow-up study. *Heart Rhythm*. 2015;12:1250–1258.

23. Ginks MR, Shetty AK, Lambiase PD, et al. Benefits of endocardial and multisite pacing are dependent on the type of left ventricular electric activation pattern and presence of ischemic heart disease: insights from electroanatomic mapping. *Circ Arrhythmia Electrophysiol*. 2012;5:889–897.

24. Chapman M, Bates MGD, Behar JM, et al. A novel quadripolar active fixation left-ventricular pacing lead for cardiac resynchronization therapy: initial United Kingdom experience. *J Am Coll Cardiol EP*. 2019;5:1028-1035.

25. Wisnoskey BJ, Varma N. Left ventricular paced activation in cardiac resynchronization therapy patients with left bundle branch block and relationship to its electrical substrate. *Heart Rhythm O2*. 2020;1:85-95.

26. Varma N, O'Donnell D, Bassiouny M, et al. Programming cardiac resynchronization therapy for electrical synchrony: reaching beyond left bundle branch block and left ventricular activation delay. *J Am Heart Assoc*. 2018;7.

KEY WORDS cardiac resynchronization therapy, heart failure, hemodynamics, multipoint pacing, multisite pacing

APPENDIX For a supplemental table, please see the online version of this article.