# Pressure-Volume Loop Analysis of Multipoint Pacing With a Quadripolar Left Ventricular Lead in Cardiac Resynchronization Therapy

JACC: CLINICAL ELECTROPHYSIOLOGY VOL. 4, NO. 7, 2018

PUBLISHED BY ELSEVIER

# Pressure-Volume Loop Analysis of Multipoint Pacing With a Quadripolar Left Ventricular Lead in Cardiac Resynchronization Therapy

Wouter M. van Everdingen, MD, PhD,[a] Alwin Zweerink, MD,[b] Odette A.E. Salden, MD,[a] Maarten J. Cramer, MD, PhD,[a] Pieter A. Doevendans, MD, PhD,[a] Elien B. Engels, PhD,[c] Albert C. van Rossum, MD, PhD,[b] Frits W. Prinzen, PhD,[c] Kevin Vernooy, MD, PhD,[d] Cornelis P. Allaart, MD, PhD,[b] Mathias Meine, MD, PhD[a]

## ABSTRACT

**OBJECTIVES** This study aimed to compare multipoint pacing (MPP) to optimal biventricular pacing with a quadripolar left ventricular (LV) lead and find factors associated with hemodynamic response to MPP.

**BACKGROUND** MPP with a quadripolar LV lead may increase response to cardiac resynchronization therapy.

**METHODS** Heart failure patients with a left bundle branch block underwent cardiac resynchronization therapy implantation. Q to LV sensing interval divided by the intrinsic QRS duration was measured. Invasive pressure-volume loops were assessed during 4 biventricular pacing settings and 3 MPP settings, using 4 atrioventricular delays. Hemodynamic response was defined as change in stroke work (Δ%SW) compared with baseline measurements during intrinsic conduction. Δ%SW of MPP was compared with conventional biventricular pacing using the distal electrode and the electrode with highest Δ%SW (BIV-OPT).

**RESULTS** Forty-three patients were analyzed (age 66 ± 10 years, 63% men, 30% ischemic cardiomyopathy, LV ejection fraction 29 ± 8%, and QRS duration 175 ± 13 ms). Q to local LV sensing interval corrected for QRS duration was 84 ± 8%, and variation between LV electrodes was 9 ± 5%. Compared with conventional biventricular pacing using the distal electrode, MPP showed a significant higher increase of SW (Δ%SW +15 ± 35%; $p < 0.05$) with a large interindividual variation. There was no significant difference in Δ%SW with MPP compared with BIV-OPT (−5 ± 24%; $p = 0.19$). Male sex and low LV ejection fraction were associated with increase in Δ%SW due to MPP versus BIV-OPT in multivariate analysis, while ischemic cardiomyopathy was only associated in univariate analysis.

**CONCLUSIONS** Optimization of the pacing site of a quadripolar LV lead is more important than to program MPP. However, specific subgroups (i.e., especially men) may benefit substantially from MPP. (J Am Coll Cardiol EP 2018;4:881–9) © 2018 by the American College of Cardiology Foundation.

From the [a]Department of Cardiology, University Medical Center Utrecht, Utrecht, the Netherlands; [b]Department of Cardiology, Institute for Cardiovascular Research, VU University Medical Center, Amsterdam, the Netherlands; [c]Department of Physiology, CARIM, Maastricht University, Maastricht, the Netherlands; and the [d]Department of Cardiology, Maastricht University Medical Center, Maastricht, the Netherlands. This study was conducted with an unrestricted research grant from St. Jude Medical (St. Paul, Minnesota). Dr. Prinzen has received research grant support from Medtronic, Boston Scientific, St. Jude Medical, Abbott, LivaNova, Biosense Webster, Merck Sharp & Dohme, Biotronik, and EBR Systems; and has served as an advisor for Medtronic Inc. Dr. Vernooy has received speaker fees and research grants from St. Jude Medical. Dr. Meine has received research grant support from Boston Scientific and St. Jude Medical. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

All 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 *JACC: Clinical Electrophysiology* author instructions page.

Manuscript received October 27, 2017; revised manuscript received January 31, 2018, accepted February 2, 2018.

ISSN 2405-500X/$36.00 https://doi.org/10.1016/j.jacep.2018.02.005

JACC: CLINICAL ELECTROPHYSIOLOGY VOL. 4, NO. 7, 2018
JULY 2018:881–9

**ABBREVIATIONS AND ACRONYMS**

**Δ%SW** = change in stroke work

**AV** = atrioventricular

**BIV-CONV** = biventricular pacing with the distal electrode of a quadripolar lead

**BIV-OPT** = biventricular pacing with the electrode with highest increase in stroke work, of a quadripolar lead

**DCM** = dilated cardiomyopathy

**ECG** = electrocardiographic/electrocardiography

**EP** = electrophysiological

**ICM** = ischemic cardiomyopathy

**LBBB** = left bundle branch block

**MPP** = multipoint pacing

**QLV/QRSd** = Q to left ventricular sensing interval divided by the intrinsic QRS duration

**PV** = pressure-volume

**RA** = right atrial

**RV** = right ventricular

Cardiac resynchronization therapy (CRT) is an established therapy for patients with heart failure and left ventricular (LV) conduction delay (1). CRT aims to improve LV hemodynamic function by electromechanical resynchronization of LV contraction. Unfortunately, a considerable (30% to 40%) proportion of patients are considered nonresponders to CRT (2). Nonresponse has several causes, of which a suboptimal LV lead position is an important contributor (3). A suboptimal placed LV lead may reduce the effect of biventricular pacing on efficient electromechanical resynchronization (4). Several strategies have been suggested to optimize LV lead position, such as guided LV lead positioning, endocardial pacing, and multisite pacing (i.e., LV pacing in more than 1 vein) or multipoint pacing (MPP) (5,6). MPP implies pacing the LV free wall with 2 pacing stimuli, delivered by a single quadripolar LV lead. MPP may lead to a more homogeneous electromechanical activation and subsequently an additional improvement in LV function (4,7). MPP is proven to be beneficial compared with conventional biventricular pacing in terms of acute hemodynamic response, functional improvement, and reverse remodeling (5,8). Although these results are promising, most studies did not compare MPP with the most optimal setting of biventricular pacing, as obtained with a quadripolar LV lead. Moreover, hemodynamic response of MPP varies among patients (9), suggesting that patient specific differences (e.g., presence of ischemic cardiomyopathy or a low myocardial conduction velocity between electrodes) or therapy delivery (e.g., lead position) are factors contributing to the effect of MPP.

SEE PAGE 890

The aim of this study was to compare the short-term hemodynamic response of MPP, measured by invasive pressure-volume (PV) loops, with biventricular pacing using the electrode of quadripolar LV lead with highest increase in hemodynamic function. Patient characteristics as well as electrocardiographic (ECG) and electroanatomic parameters are correlated with MPP response. The hypothesis of this study is that patients with ischemic cardiomyopathy or those with a low myocardial conduction velocity between electrodes of a quadripolar LV lead will benefit from MPP because the additional pacing site may cause a faster or more homogeneous depolarization of the LV.

## METHODS

**PATIENT COHORT.** The OPTICARE-QLV (Optimization of Cardiac Resynchronization Therapy with a Quadripolar Left Ventricular Lead) trial is a multicenter observational study, which was performed in 3 university medical centers (University Medical Center Utrecht; VU University Medical Center, Amsterdam; and Maastricht University Medical Center, Maastricht; all in the Netherlands). Fifty-one patients planned for CRT implantation were prospectively enrolled. Inclusion criteria were moderate to severe heart failure (i.e., New York Heart Association functional class II or III), LV ejection fraction ≤35%, optimal pharmacological therapy, sinus rhythm, and a left bundle branch block (LBBB) according to the Strauss criteria (10). Exclusion criteria were presence of LV thrombus, severe aortic valve stenosis, or a mechanical aortic valve replacement. The study was performed according to the Declaration of Helsinki and in agreement with the local medical ethics committees. All subjects gave written informed consent.

**BASELINE CHARACTERISTICS.** Before implantation baseline characteristics were collected, among which laboratory tests (creatinine and B-type natriuretic peptide levels), age, sex, New York Heart Association functional class, PR interval, QRS duration, and QRS morphology. All patients underwent an echocardiographic examination and cardiac magnetic resonance imaging before CRT implantation. Derived LV volumes were used to calibrate the conductance catheter-derived volumes. Type of cardiomyopathy was classified as dilated cardiomyopathy (DCM) or ischemic cardiomyopathy (ICM) using the definition of Felker et al. (11). Patients with history of myocardial infarction or revascularization (coronary artery bypass grafting or percutaneous coronary intervention), with ≥75% stenosis of left main or proximal left anterior descending artery, or with ≥75% stenosis of 2 or more epicardial vessels were categorized as ICM.

**CRT IMPLANTATION.** CRT implantation was performed under local anesthesia. The right atrial (RA) and right ventricular (RV) leads were placed transvenously at conventional positions. The quadripolar LV lead (Quartet 1458Q, St. Jude Medical, St. Paul, Minnesota) was placed transvenously in one of the coronary veins overlying the LV free wall. An anterolateral, lateral, or posterolateral position was preferred. After electrophysiological measurements, the 3 leads were connected to a St. Jude Medical CRT device.

**ELECTROPHYSIOLOGICAL MEASUREMENTS.** Electrophysiological (EP) measurements were performed

**TABLE 1 Pacing Configurations**

| BIV | MPP |
|---|---|
| LV-D1 – 40 ms – RV (BIV-CONV) | LV-D1 – 5 ms – LV-P4 – 35 ms – RV (MPP1) |
| LV-M2 – 40 ms – RV | LV-D1 – 35 ms – LV-P4 – 5 ms – RV (MPP2) |
| LV-M3 – 40 ms – RV | LV-P4 – 35 ms – LV-D1 – 5 ms – RV (MPP3) |
| LV-P4 – 40 ms – RV | |

All pacing configurations were tested with 4 atrioventricular delays. In case of noncapture or phrenic nerve stimulation, a different electrode pair with largest interelectrode distance was used for multipoint pacing (MPP).

BIV-CONV = biventricular pacing with electrode D1 left ventricular pacing electrode; LV-D1 = left ventricular pacing with electrode D1; LV-M2 = left ventricular pacing with electrode M2; LV-M3 = left ventricular pacing with electrode M3; LV-P4 = left ventricular pacing with electrode P4; RV = right ventricular pacing.

using an onsite dedicated EP system. EP system settings (i.e., filter settings, gain, and sampling frequency) of the 3 participating centers were matched to study protocols. Using the EP system, simultaneous registrations of the 12-lead surface ECG and the 3 implanted leads were recorded. Temporary pacing was used to measure delays of specific pacing settings between electrodes, among which were the Q on the surface ECG to LV sensing delay (QLV) and the QLV interval divided by the intrinsic QRS duration (QLV/QRSd), and local myocardial conduction velocity (Online Appendix). Conduction time was measured as the pacing to sensing intervals between the 4 electrodes during LV only pacing with the separate electrodes (Online Figure 1). The distances between the electrodes were used to obtain the conduction velocity. Conduction velocity below 0.70 m/s was considered slow, whereas all other values were considered normal (12).

**HEMODYNAMIC MEASUREMENTS AND PACING PROTOCOL.** A dedicated PV loop conductance catheter (CD Leycom, Zoetermeer, the Netherlands) was placed in the LV cavity after right femoral artery access. For all pacing settings, including MPP, the RV coil was used as anode and the interventricular delay between first LV pacing site and RV was kept constant at 40-ms LV first (**Table 1**). Biventricular pacing was performed with each quadripolar electrode separately as LV pacing site. MPP was programmed in 3 settings: 1) distal and proximal simultaneously (i.e., 5-ms delay); 2) distal followed by proximal with a 35-ms delay; and 3) proximal followed by distal with a 35-ms delay. The observed conduction delay between the 2 electrodes used for MPP was above 35 ms in all cases. MPP was conducted with the electrodes with the largest anatomical distance (e.g., usually D1 and P4) or any other combination with acceptable pacing thresholds and without phrenic nerve stimulation.

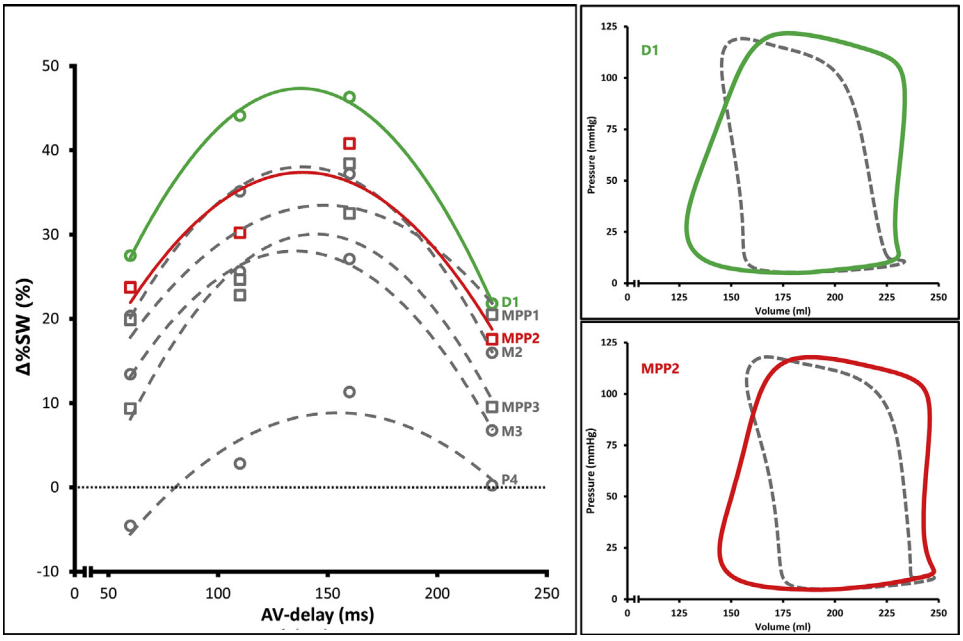
For each pacing mode, atrioventricular (AV) delays of 80%, 60%, 40%, and 20% of the patient's intrinsic AV conduction (i.e., RA pacing to RV sensing delay) were used. PV loops were recorded during pacing 5 to 10 beats/min above intrinsic rhythm, for 60 beats during pacing settings and for 30 beats during baseline references of RA pacing. Stroke work (SW) was calculated as the surface of the recorded PV loops. The change in SW (Δ%SW) of each pacing setting was calculated compared with the adjacent baseline references. The Δ%SW of the 4 different AV delays of a single pacing configuration were plotted, and a second-order polynomial line was fitted. The peak of the parabola was used as maximal increase in Δ%SW of the specific pacing setting (**Figure 1**). The same method was used for the maximal value of the first derivative of LV pressure ($dP/dt_{max}$). This method reduces measurement variability and allows for reliable estimation of the maximal achievable increase in SW (13). Patients were excluded from the final analysis if the PV loop during baseline measurements showed crossing sections and large end-diastolic tails. These loops are the result of poor measurement of volume changes and lead to underestimation of SW during intrinsic LBBB. Underestimation of baseline values leads to unreliable high increases in Δ%SW, because the PV loops often increase to normal shape during biventricular pacing.

Response to MPP was defined as Δ%SW compared with either conventional biventricular pacing using the most distal electrode (BIV-CONV), or as Δ%SW compared with biventricular pacing with the electrode of the quadripolar lead with highest Δ%SW (BIV-OPT).

**LEAD POSITION.** After lead placement, fluoroscopy images were made in the left anterior oblique 40° and in the right anterior oblique 30° angle to determine the specific position of each quadripolar LV lead electrode. The LV was divided into 6 segments in the circumferential direction (septal, anterior, anterolateral, lateral, posterolateral, and posterior) on the left anterior oblique view and in 3 segments (basal, mid, and apical) on the right anterior oblique view (14).

**STATISTICAL ANALYSIS.** Statistical analysis was performed using SPSS version 23.0 (IBM, Armonk, New York). Patients were classified with a benefit of MPP if Δ%SW of MPP was higher than Δ%SW of BIV-OPT; the remaining patients were classified as those without benefit of MPP. The univariate relation of predictors for Δ%SW due to MPP was analyzed using linear regression, both for change compared with BIV and compared with BIV-OPT. Univariate predictors

**FIGURE 1 Optimization Method Based on Pressure-Volume Loops**




The **left panel** shows optimization curves during all pacing modes in 1 patient. **Broken lines** represent parabolic curves fitted through the measured changes in stroke work (Δ%SW) compared with intrinsic conduction during 4 atrioventricular (AV) delays. In this patient biventricular pacing **(circles)** with D1 **(green)** was the optimal biventricular configuration and multipoint pacing (MPP) **(squares)** with D1-P4 with 35-ms delay between both pacing stimuli (MPP2) (**red**) was the best MPP configuration. The corresponding pressure-volume loops are displayed in the **right panels**, with **loops of broken lines** representing intrinsic conduction (right atrial pacing).

with a p value <0.10 were tested in a multivariate analysis. The relation of variables with response to MPP was analyzed using a *t* test or Mann-Whitney *U* test, dependent on normality of data, or a chi-square test in case of categorical variables. The optimal AV delays and hemodynamic effect of pacing strategies analyzed with a paired *t* test or Wilcoxon signed rank test, depending on normality of data. Mean ± SD or median (interquartile range_ are given, depending on normality of data. A p value <0.05 was considered significant for all tests.

## RESULTS

Fifty-one patients were included in the study, of whom 8 were excluded from this analysis. Three of the excluded patients had considerable underestimation of the PV loop during intrinsic rhythm. Two patients did not receive MPP due to a technical error during the pacing protocol. Three more patients were excluded due to large baseline drift of SW measurements between biventricular pacing and the MPP pacing configurations.

In the remaining 43 patients, 63% were men (n = 27), and 30% (n = 13) had an ischemic etiology of heart failure (Table 2). PR duration was 183 ± 32 ms, QRS duration was 175 ± 13 ms. QLV of the electrode with highest value was 147 ± 16 ms, with a QLV/QRSd ratio of 84 ± 8%. LV dimensions were enlarged (end-diastolic volume 208 ± 62 ml, LV end-systolic volume 154 ± 56 ml), and systolic function was impaired (LV ejection fraction 29 ± 8%). Cardiac magnetic resonance images were available in 40 patients, of whom 8 had evidence of delayed enhancement. There was no statistically significant difference in the number of patients with scar, nor was there a difference in scar size, between patients with and without a positive effect of MPP compared with BIV-OPT.

During biventricular pacing, the largest Δ%SW was achieved with electrode D1 in 15 (35%), M2 in 8 (19%), M3 in 5 (12%), and P4 in 15 (35%) patients. MPP was applied using electrode D1 and M3 in 3 (7%) patients and with D1 and P4 in all other patients. There was no statistical difference between MPP vectors regarding the Δ%SW (MPP1: 66 ± 59%, MPP2: 66 ± 57%, MPP3:

61 ± 56%; p = NS). Thirty-one (72%) patients showed a larger Δ%SW during MPP then during BIV-CONV pacing, and 17 (40%) showed a larger Δ%SW during MPP then during BIV-OPT (Table 3, Figures 2 and 3). MPP increased Δ%SW significantly (+15 ± 35%; p < 0.05) as compared with BIV-CONV pacing, but there was no significant change between MPP and BIV-OPT (−5 ± 24%; p = 0.19). The Δ%SW due to MPP compared with BIV-OPT was heterogeneous, being larger than 10% in 16 patients and larger than 10% in 9 patients, and in 18 patients showing a decrease in Δ% SW larger than 10%. A heterogeneous effect was also seen for percentage change in maximal rate of LV pressure rise (Figure 4). There was a large variation in response to MPP compared with BIV-OPT. Percentage change in maximal rate of LV pressure rise of MPP was not significantly different from BIV-CONV (−0.2 ± 4.0%; p = 0.71), whereas it was significantly lower for MPP compared with BIV-OPT (−1.8 ± 3.8; p < 0.01). There were no significant differences in the AV delay with highest Δ%SW between pacing configurations. The optimal AV delay for BIV-CONV was 133 ± 43 ms, for BIV-OPT was 120 ± 37 ms, and for MPP was 129 ± 36 ms (BIV-CONV vs. BIV-OPT: p = 0.15, BIV-CONV vs. MPP: p = 0.17, BIV-OPT vs. MPP p = 0.65).

Patients with a positive effect of MPP compared with BIV-OPT were more often men, had larger LV end-diastolic and end-systolic volumes, a lower LV ejection fraction, and lower myocardial conduction velocity (Table 2). Male patients and those with ICM also had a larger Δ%SW of MPP versus BIV-OPT (Figure 5). Increase in Δ%SW tended to be higher for those with low conduction velocity (p = 0.055). Patients with a positive response to MPP versus BIV-OPT tended to have distal electrodes (D1) in a mid position (15 mid and 2 apical), whereas patients with a negative response had a more evenly distributed D1 position (16 mid and 10 apical; p = 0.056). Univariate analysis of linear regression showed significant association of LV ejection fraction, type of cardiomyopathy, and sex, with Δ%SW of MPP versus BIV-OPT (Table 4). End-diastolic volume, QRS duration, QLV/QRSd, scar size, and conduction velocity were not associated with Δ%SW of MPP versus BIV-OPT. Multivariate analysis confirmed that LV ejection fraction and male sex were independent predictors for hemodynamic response of MPP compared with BIV-OPT, whereas type of cardiomyopathy was not included in the model.

**TABLE 2 Baseline Characteristics**

| | Analyzed Patients (N = 43) | Patients Without Benefit of MPP (n = 26) | Patients With Benefit of MPP (n = 17) | p Value |
|---|---|---|---|---|
| Age, yrs | 66 ± 10 | 66 ± 10 | 65 ± 9 | 0.750 |
| Male | 27 (63) | 13 (50) | 14 (82) | 0.032 |
| Cardiomyopathy (ICM) | 11 (26) | 6 (23) | 5 (29) | 0.642 |
| Scar | 8 (19) | 6 (24) | 2 (13) | 0.414 |
| Scar size* | 9 (2-19) | 9 (4-16) | 11 (1-20) | 1.000 |
| NYHA functional class | | | | |
| II | 29 (67) | 18 (69) | 12 (71) | 0.722 |
| III | 14 (33) | 8 (31) | 5 (29) | |
| PR duration, ms | 183 ± 32 | 181 ± 24 | 185 ± 41 | 0.717 |
| QRS duration, ms | 175 ± 13 | 173 ± 14 | 177 ± 12 | 0.280 |
| Max QLV, ms | 147 ± 16 | 146 ± 17 | 148 ± 15 | 0.691 |
| Max QLV/QRSd, % | 84 ± 8 | 85 ± 9 | 84 ± 5 | 0.624 |
| QLV/QRSd variation, % | 9 ± 5 | 10 ± 5 | 8 ± 4 | 0.187 |
| Conduction time, ms | 75 ± 21 | 69 ± 20 | 84 ± 21 | 0.034 |
| Conduction velocity, m/s | 0.60 ± 0.20 | 0.67 ± 0.28 | 0.51 ± 0.12 | 0.014 |
| LVEDV, ml | 209 ± 62 | 191 ± 43 | 235 ± 77 | 0.044 |
| LVESV, ml | 151 ± 57 | 134 ± 39 | 178 ± 70 | 0.029 |
| LVEF, % | 29 ± 8 | 31 ± 9 | 26 ± 6 | 0.031 |
| Creatinine, μmol/l | 87 ± 21 | 84 ± 24 | 92 ± 15 | 0.218 |
| log-BNP | 1.85 ± 0.49 | 1.8 ± 0.41 | 1.99 ± 0.60 | 0.212 |
| Medication | | | | |
| ACE inhibitor or ATII antagonist | 42 (98) | 26 (100) | 16 (94) | 0.211 |
| Beta-blocker | 36 (84) | 20 (77) | 15 (88) | 0.351 |
| Diuretics | 30 (70) | 16 (62) | 13 (76) | 0.307 |
| Aldosterone antagonists | 25 (58) | 16 (62) | 11 (65) | 0.834 |
| Anticoagulants | 27 (43) | 13 (50) | 13 (76) | 0.083 |
| Comorbidities | | | | |
| Hypertension | 15 (35) | 12 (46) | 3 (18) | 0.055 |
| Renal dysfunction | 3 (7) | 1 (4) | 2 (12) | 0.820 |
| Circumferential electrode position | | | | |
| Anterior | 0 | 0 | 0 | 0.152 |
| Anterolateral | 31 (19) | 22 (22) | 9 (14) | |
| Lateral | 96 (58) | 52 (51) | 44 (67) | |
| Posterolateral | 37 (22) | 24 (24) | 13 (20) | |
| Posterior | 3 (2) | 3 (3) | 0 | |
| Longitudinal electrode position | | | | |
| Basal | 55 (33) | 34 (34) | 21 (32) | 0.124 |
| Mid | 89 (53) | 49 (49) | 50 (76) | |
| Apical | 23 (14) | 18 (18) | 5 (8) | |

Values are mean ± SD, n (%), or median (interquartile range). MPP responders and nonresponders are defined by a positive or negative change in stroke work (Δ%SW) between BIV with the electrode with highest Δ%SW and highest increase in Δ%SW with MPP. The p value of the comparison of patients with a benefit and those without a benefit of MPP compared with optimal Δ%SW with biventricular pacing (BIV-OPT) is depicted in the last column. *Scar size in patients with scar on late gadolinium-enhanced images.

ACE = angiotensin-converting enzyme; ATII = angiotensin receptor II; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; ICM = ischemic cardiomyopathy; log-BNP = 10th logarithmic conversion of brain natriuretic peptide; NYHA = New York Heart Association; QLV = Q to LV sensing delay. QLV/QRSd = ratio between QLV and intrinsic QRS duration; SW = stroke work; other abbreviations as in Table 1.

## DISCUSSION

The acute hemodynamic response of MPP compared with BIV-CONV showed a significant improvement. The effect of MPP compared with BIV-OPT showed no overall benefit. These findings indicate that optimization of the LV site for BIV-OPT is of primary importance. MPP may have additional benefit in a subselection of patients, specifically men and those having a low LV ejection fraction.

**TABLE 3 Effect of Pacing Strategies on Acute Hemodynamic Response**

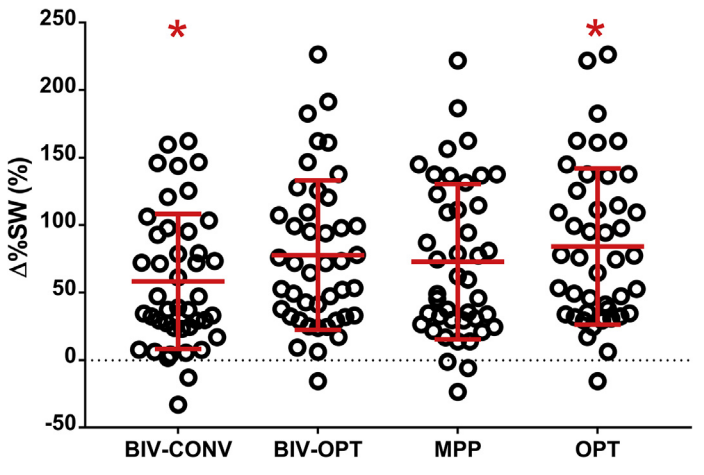
| | All Patients (N = 43) | Patients Without Benefit of MPP (n = 26) | Patients With Benefit of MPP (n = 17) | p Value |
|---|---|---|---|---|
| Strategy | | | | |
| BIV-CONV, Δ%SW | 58 ± 50 | 55 ± 53 | 64 ± 46 | 0.568 |
| BIV-OPT, Δ%SW | 78 ± 55 | 78 ± 59 | 78 ± 50 | 0.960 |
| MPP, Δ%SW | 73 ± 58 | 59 ± 56 | 94 ± 56 | 0.035 |
| Differences | | | | |
| BIV-OPT vs. BIV-CONV, Δ%SW | 19 ± 27* | 25 ± 5* | 14 ± 29† | 0.170 |
| MPP vs. BIV-CONV, Δ%SW | 15 ± 35† | 5 ± 32 | 30 ± 34* | 0.012 |
| MPP vs. BIV-OPT, Δ%SW | −5 ± 24 | −19 ± 18* | 16 ± 15* | <0.001 |

Values are mean ± SD. MPP responders and nonresponders are defined by a positive or negative Δ%SW between biventricular pacing with the electrode with highest Δ%SW and highest increase in Δ%SW with MPP. In the last column, the p value is depicted for the comparison of MPP responders and nonresponders. Effects between groups were compared with a Mann-Whitney *U* test and corresponding p values are shown in the rightmost column. Effects within a group were compared with a Wilcoxon signed rank test. *p < 0.05 between 2 strategies. †p < 0.001 between 2 strategies.

Abbreviations as in Tables 1 and 2.

**EFFECT OF MPP.** Although MPP was beneficial compared with conventional CRT, we found a heterogeneous and nonsignificant hemodynamic effect of MPP compared with CRT with the optimal configuration of a quadripolar LV lead. Because we optimized the AV delay and tested each pacing site of a quadripolar LV lead for biventricular pacing, the additional effect of MPP compared with BIV-OPT was low in our study. Our results are however comparable to a study in which AV delay optimization was used and all biventricular pacing sites were compared with MPP (15). Although some studies also indicate that response to MPP is heterogeneous among patients (9,15), Zanon et al. (5) found a small but significant increase in acute hemodynamic response (i.e., $dP/dt_{max}$) with MPP compared with unifocal LV paced sites in all patients. We used both SW and $dP/dt_{max}$ and found a variation in the effect of MPP with both indices (Figures 3 and 4). Pappone et al. (8) also used SW derived from PV loops and showed that the best of 7 MPP settings improved hemodynamic function more than biventricular pacing with only the distal or proximal electrode of a quadripolar LV lead. These findings are in line with our results, as we found that MPP resulted in higher Δ%SW benefit than BIV-CONV. Because we found no benefit of 3 MPP settings compared with 4 BIV settings, a single optimized pacing site may be ideal for CRT. The presence of an ideal location for biventricular pacing that cannot be improved by multiple LV pacing sites has been put forward by Ploux et al. (4). Finding the optimal biventricular pacing configuration is of primary importance. Although we still need tools to select the optimal biventricular pacing configuration, 1 well-placed lead is potentially better than adding extra pacing sites to a suboptimal placed lead. Generally, patients benefit most from an optimized single LV pacing site, but some benefit from MPP. The effect of LV pacing site optimization is therefore heterogeneous and requires a patient-tailored approach.

**FIGURE 2 Acute Hemodynamic Effect of 4 Optimization Strategies**




Acute hemodynamic effect in Δ%SW of biventricular pacing with the distal electrode, with the optimal electrode, MPP, or the optimal setting. The optimal setting is either MPP or biventricular pacing with the optimal electrode. *p < 0.01 compared with all other strategies. Abbreviations as in Figure 1.

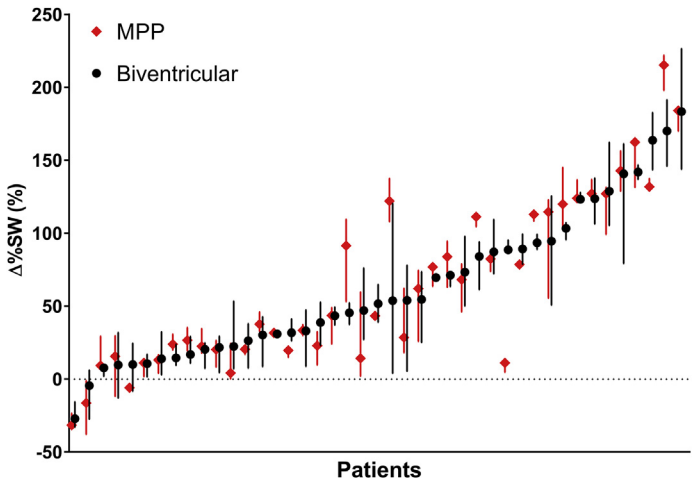
**PREDICTING MPP RESPONSE.** Specific subsets of patients may benefit from MPP, because we observed that male patients especially and those with lower LV ejection fraction benefited from MPP. Sex was the strongest predictor in the multivariate analysis, possibly because men more often had ICM (50% vs. 13%; p = 0.17) and larger hearts (LV end-diastolic volume: 223 ± 68 ml vs. 184 ± 42 ml; p < 0.05). The additional electrical wave front of MPP may lead to a more homogeneous or faster depolarization of the enlarged LV free wall. Also, differences in cardiac size have shown to modify the effect of QRS duration on CRT response (16,17). Although LV end-diastolic volume was higher in MPP responders, LV end-diastolic volume did not have an association with Δ%SW of MPP versus BIV-OPT in our study. MPP could also be beneficial in ventricles with heterogeneous conduction, potentially caused by myocardial fibrosis. The direct effect of scar burden on the hemodynamic benefit of MPP was shown in computer simulations (18). These results were confirmed in a patient study with posterolateral scar (19), and in patients with ICM in general in other studies (15,20). Sohal et al. (20) observed that only non-LBBB patients converted from hemodynamic nonresponders with

conventional CRT to multisite pacing responders. This may partly be explained by the prevalence of ICM, which is higher in non-LBBB patients, resulting in a more heterogeneous conduction of the LV (21). Because we only included patients with a strict LBBB using the Strauss et al. criteria (10), the prevalence of patients with substantial myocardial scar in our study was relatively low. Implementation of our methods in CRT candidates without strict LBBB is of interest, because the scar burden is potentially larger in these patients (18).

We used the electrodes with largest interelectrode distance for MPP, which were the most valuable electrodes for MPP in prior studies (9,22). The results of Niazi et al. (22) confirm that the MPP vector with the largest anatomic separation has favorable effects on long-term clinical response, compared with other MPP vectors. Because the effect of MPP with a quadripolar LV lead may be dependent on the electrode spacing, the effect of interelectrode distance and the number of electrodes on an LV lead are also of interest for future work. Several manufacturers, including the one used in this study, have developed quadripolar leads with varying electrode spacing. Larger electrode spacing may facilitate a better distribution of electrodes over the LV wall. Nonetheless, the effective electrode spacing is limited by the coronary venous anatomy. Large electrode spacing may result in noncapture in case of short tributary branches. We already observed noncapture on the proximal electrode in 3 patients with the electrode spacing (i.e., 47 mm) of the current quadripolar lead.

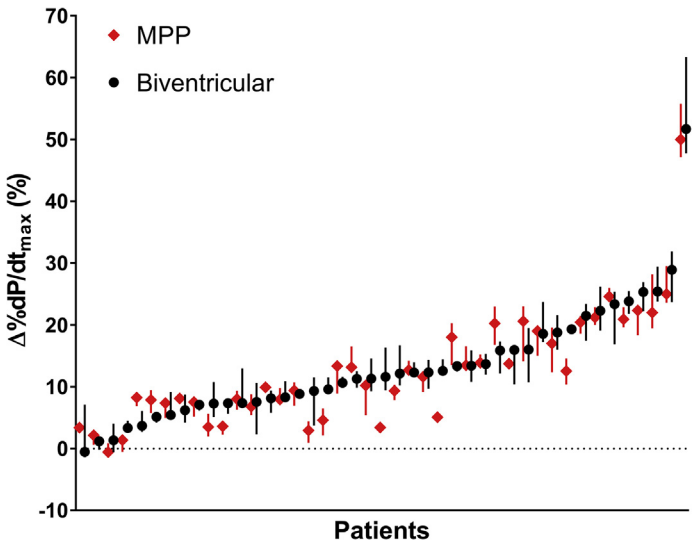
MPP may be used to further optimize hemodynamic response in subgroups of patients. However, in the current patient population (i.e., strict LBBB), only 1 patient converted from nonresponder with BIV-OPT to a responder with MPP using the 20% increase in Δ% SW cutoff value defined by De Roest et al. (23) (Δ%SW of BIV-OPT: 9%, MPP: 29%). However, 3 patients became nonresponders with MPP, whereas they were classified as responders to BIV-OPT. Although translation of short-term response to long-term effects is difficult, other studies show that MPP may improve CRT response in individual patients (22). Physicians should therefore first test the acute effect of biventricular pacing with each separate electrode of the quadripolar lead. MPP may then be implemented if the benefit of biventricular pacing is lower than desired, especially in patients with an ischemic etiology of heart failure, men, and those with very low LV ejection fraction. Nevertheless, MPP should not be programmed blindly, because it can have a detrimental effect on hemodynamic response. The hemodynamic effect of MPP should therefore always be tested, moreover because it increases battery drainage. Because PV loop recordings are not standard clinical practice, testing of the hemodynamic

**FIGURE 3** Acute Hemodynamic Effect of Biventricular Pacing and MPP Per Patient



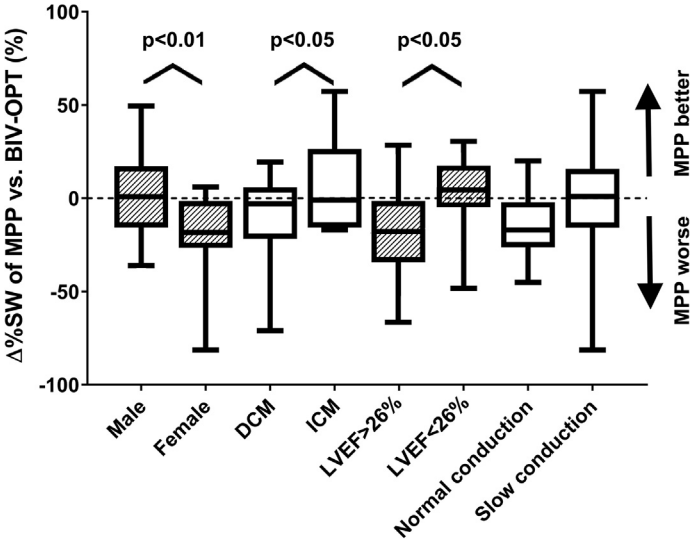

Δ%SW of biventricular pacing **(black circles)** and MPP **(red diamonds)**. The **symbols** depict the median value of the 4 biventricular pacing settings and of the 3 MPP settings, whereas lowest and highest values of biventricular pacing and MPP are displayed by **bars**. BIV-CONV = biventricular pacing with the distal electrode; BIV-OPT = biventricular pacing with the optimal electrode; OPT = optimal setting; other abbreviations as in Figure 1.

**FIGURE 4** Change in $dP/dt_{max}$ of Biventricular Site Pacing and MPP Per Patient




Percentage change in maximal rate of left ventricular pressure rise (%$dP/dt_{max}$) of biventricular pacing **(black circles)** and MPP **(red diamonds)** is given. The medians of 4 biventricular pacing settings and 3 MPP settings are displayed by the symbol, whereas lowest and highest values are displayed by bars. Abbreviations as in Figures 1 and 3.

**FIGURE 5 Response to MPP Versus BIV-OPT for 4 Categorical Variables**




Δ%SW of MPP versus optimal biventricular pacing with 1 of the electrodes of the quadripolar lead (BIV-OPT). Conduction velocity is categorized in fast (≥0.7 m/s) and slow (<0.7 m/s) myocardial conduction. DCM = dilated cardiomyopathy; ICM = ischemic cardiomyopathy; LVEF = left ventricular ejection fraction; other abbreviations as in Figures 1 and 3.

effect of MPP should be performed preferably by noninvasive assessment of cardiac function such as the plethysmographic method of Kyriacou et al. (24).

**STUDY LIMITATIONS.** There are some limitations to take into account. Owing to the use of invasive measurements, the sample size of this study is relatively small, and the time period of inclusion relatively long. Due to the strict LBBB criteria, patients with ICM and pronounced areas of scar were prone to be excluded, although they may benefit more from MPP. The results regarding patients with ICM should therefore be interpreted with caution. Although patients with ICM often had only small areas of myocardial scar, the etiology of heart failure in these patients is different from DCM. PV loop analysis with various AV delays and pacing modes was time consuming. The study protocol was therefore shortened by the use of a fixed offset of 40-ms LV first because it is preferable in most CRT patients (25). The fixed offset might have influenced results because it has not been specifically tested for MPP. Due to the implantation protocol, most LV leads were placed in a favorable segment (i.e., anterolateral, lateral, or posterolateral). The intra- and interindividual differences between studied parameters was therefore relatively small, although it also reflects clinical practice. Although randomization is preferred to reduce bias by baseline drift of the catheter, pacing configurations were performed in a fixed order to reduce programming errors. PV loop recording of MPP was therefore always performed after biventricular pacing modes. The effect of baseline drift was compensated by the repeated reference measurements before and after each pacing configuration. Furthermore, to minimize the effect that excessive baseline drift might have on the results, 3 patients with considerable drift between BIV modes and MPP were excluded from the analysis. Last, ECG recordings were not systematically collected during PV loop measurements, and therefore no comment can be made on the applicability of ECG parameters for optimization of CRT.

**TABLE 4 Univariate and Multivariate Models for Predictors of Response to MPP Versus BIV-OPT**

| | B | SE | r | p Value |
|---|---|---|---|---|
| Univariate analysis | | | | |
| Male | 19.16 | 6.95 | 0.40 | 0.009 |
| Cardiomyopathy (ICM) | 17.05 | 7.95 | 0.32 | 0.038 |
| Scar size | 0.03 | 0.71 | 0.01 | 0.970 |
| LVEDV | 0.06 | 0.06 | 0.16 | 0.306 |
| LVEF | −0.95 | 0.42 | 0.33 | 0.030 |
| Conduction velocity | −0.17 | 0.16 | 0.17 | 0.293 |
| QLV/QRSd | 3.12 | 47.10 | 0.01 | 0.948 |
| QRS duration | −0.07 | 0.28 | 0.04 | 0.793 |
| Multivariate analysis | | | | |
| Male | 17.59 | 6.72 | 0.40 | 0.012 |
| LVEF | −0.83 | 0.40 | 0.49 | 0.042 |
| Cardiomyopathy (ICM) | — | — | — | 0.184 |

Univariate analysis depicts the values of linear regression of the specific parameter and Δ%SW between MPP and BIV-OPT. Multivariate forward analysis incorporates the parameters with a $p < 0.10$ in the univariate analyses. The r value of the multivariate analysis indicates the r value of the model with incorporation of that parameter. Sex was incorporated first, LVEF second.

Abbreviations as in Tables 1 and 2.

## CONCLUSIONS

In patients with typical LBBB, the acute hemodynamic response of MPP compared with BIV-CONV showed a significant improvement. The effect of MPP compared with BIV-OPT showed no overall benefit. Therefore, optimization of the LV site for biventricular pacing with a quadripolar lead is of primary importance. Nevertheless, MPP may have additional benefit in a specific subselection of patients.

**ADDRESS FOR CORRESPONDENCE:** Dr. Wouter M. van Everdingen, Department of Cardiology, University Medical Centre Utrecht, Heidelberglaan 100, P.O. Box 85500, 3508 GA, Utrecht, the Netherlands. E-mail: w.m.vaneverdingen@umcutrecht.nl.

## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** Overall, optimizing biventricular pacing with a quadripolar LV lead is of primary importance for CRT patients. Nevertheless, some patients may improve with MPP as compared with optimal biventricular pacing.

**TRANSLATIONAL OUTLOOK:** Studies in specific subgroups (e.g., non-LBBB patients and patients with ischemic cardiomyopathy) are needed to improve understanding of therapeutic targets for MPP.

## REFERENCES

**1.** Russo AM, Stainback RF, Bailey SR, et al. ACCF/HRS/AHA/ASE/HFSA/SCAI/SCCT/SCMR 2013 appropriate use criteria for implantable cardioverter-defibrillators and cardiac resynchronization therapy. J Am Coll Cardiol 2013;61:1318–68.

**2.** Wilkoff BL, Fauchier L, Stiles MK, et al. 2015 HRS/EHRA/APHRS/SOLAECE expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing. Europace 2016;18:159–83.

**3.** 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;53:765–73.

**4.** 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;11:119–25.

**5.** 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;12:975–81.

**6.** 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 2014:873–9.

**7.** van Everdingen WM, Cramer MJ, Doevendans PA, Meine M. Quadripolar leads in cardiac resynchronization therapy. J Am Coll Cardiol EP 2015;1:225–37.

**8.** 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.

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

**10.** Strauss DG, Selvester RH, Wagner GS. Defining left bundle branch block in the era of cardiac resynchronization therapy. Am J Cardiol 2011;107:927–34.

**11.** Felker GM, Shaw LK, O'Connor CM. A standardized definition of ischemic cardiomyopathy for use in clinical research. J Am Coll Cardiol 2002;39:210–8.

**12.** Anderson KP, Walker R, Urie P, Ershler PR, Lux RL, Karwandee SV. Myocardial electrical propagation in patients with idiopathic dilated cardiomyopathy. J Clin Invest 1993;92:122–40.

**13.** Sohaib SM, Whinnett ZI, Ellenbogen KA, et al. Cardiac resynchronisation therapy optimisation strategies: systematic classification, detailed analysis, minimum standards and a roadmap for development and testing. Int J Cardiol 2013;170:118–31.

**14.** Bogaard MD, Doevendans PA, Leenders GE, et al. Can optimization of pacing settings compensate for a non-optimal left ventricular pacing site? Europace 2010;12:1262–9.

**15.** 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.

**16.** Zweerink A, Wu L, de Roest GJ, et al. Improved patient selection for cardiac resynchronization therapy by normalization of QRS duration to left ventricular dimension. Europace 2017;19:1508–13.

**17.** Varma N, Lappe J, He J, Niebauer M, Manne M, Tchou P. Sex-specific response to cardiac resynchronization therapy. J Am Coll EP 2017;3:844–53.

**18.** Niederer SA, Shetty AK, Plank G, et al. Biophysical modeling to simulate the response to multisite left ventricular stimulation using a quadripolar pacing lead. Pacing Clin Electrophysiol 2012;35:204–14.

**19.** 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 2011;14:373–9.

**20.** 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;12:2449–57.

**21.** Zareba W, Klein H, Cygankiewicz I, et al. effectiveness of cardiac resynchronization therapy by QRS morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). Circulation 2011;123:1061–72.

**22.** Niazi I, Baker J II, Corbisiero R, et al. Safety and efficacy of multipoint pacing in cardiac resynchronization therapy. J Am Coll EP 2017;3:1510–8.

**23.** de Roest GJ, Allaart CP, Kleijn SA, et al. Prediction of long-term outcome of cardiac resynchronization therapy by acute pressure-volume loop measurements. Eur J Heart Fail 2013;15:299–307.

**24.** Kyriacou A, Pabari PA, Whinnett ZI, et al. Fully automatable, reproducible, noninvasive simple plethysmographic optimization: proof of concept and potential for implantability. Pacing Clin Electrophysiol 2012;35:948–60.

**25.** Bogaard MD, Meine M, Tuinenburg AE, Maskara B, Loh P, Doevendans PA. Cardiac resynchronization therapy beyond nominal settings: who needs individual programming of the atrioventricular and interventricular delay? Europace 2012;14:1746–53.

**KEY WORDS** acute hemodynamic response, cardiac resynchronization therapy, multipoint pacing, pressure-volume loops, quadripolar lead

**APPENDIX** For an expanded Methods section as well as a supplemental figure, please see the online version of this paper.