ORIGINAL ARTICLE

Effective nonapical left ventricular pacing with quadripolar leads for cardiac resynchronization therapy

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KEY WORDS
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ABSTRACT

BACKGROUND Current guidelines recommend avoiding apical left ventricular (LV) pacing for cardiac resynchronization therapy (CRT).

AIMS We investigated the feasibility of nonapical pacing with the current quadripolar LV lead technology.

METHODS We analyzed consecutive patients who received CRT with an LV quadripolar lead. The post-implantation position of each electrode of the LV lead was designated as basal, mid, or apical. The pacing capture threshold (PCT) and phrenic nerve stimulation (PNS) threshold were assessed for each electrode.

RESULTS We enrolled 168 patients. A total of 8 CRT defibrillators were from Biotronik (with Sentus OTW QP leads), 98 were from Boston Scientific (with 21 Acuity X4 Spiral and 77 Acuity X4 Straight leads), and 62 from St. Jude Medical (with Quartet leads). The median (interquartile range) number of electrodes at nonapical segments per patient was 3 (1–4) with Biotronik Sentus leads, 4 (3–4) with spiral-design Boston Scientific leads, 4 (3–4) with straight Boston Scientific leads, and 3 (3–4) with St. Jude Medical Quartet leads ($P = 0.045$). Three patients (38%) with Biotronik Sentus leads, 21 (100%) with spiral-design Boston Scientific leads, 69 (90%) with straight-design Boston Scientific leads, and 49 (79%) with St. Jude Medical Quartet leads ($P < 0.001$) had at least 1 electrode located at nonapical segments linked with a PNS-PCT safety margin of more than 2 V. During the 6-month follow-up, PNS was detected in 4 patients and was eliminated with reprogramming. No significant changes in PCT were detected during follow-up.

CONCLUSIONS Quadripolar leads allowed nonapical pacing with acceptable electrical parameters in the majority of CRT recipients, although differences were found among the currently available devices.

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INTRODUCTION The pivotal role of cardiac resynchronization therapy (CRT) in symptomatic patients with chronic heart failure (HF), severely depressed left ventricular (LV) ejection fraction, and wide QRS with left bundle branch block morphology—despite optimal medical therapy—has clearly been established.[1,2] It has to be considered though, that a minority of patients

WHAT'S NEW?

This multicenter study is the first reported experience to compare the performance of the quadripolar left ventricular leads currently available on the market. These leads delivered effective pacing at nonapical left ventricular segments in the majority of patients, ensuring acceptable electrical parameters and therefore potentially leading to a lower risk of hospitalizations and death related to heart failure. Nonetheless, differences exist among the currently available electrode systems. Spiral-design leads may have better electrical performance at the proximal tip than at the distal tip and seem to have a greater number of effectively usable nonapical electrodes. These findings need to be properly assessed by evaluating the differences among the currently available systems according to their distinct designs and by characterizing the clinical long-term performance of these leads.

(approximately 34%) may show minimal clinical improvement after CRT implantation, with a progression in the New York Heart Association (NYHA) status demonstrated in about 51% of patients randomized to CRT as compared with 35% of controls (incremental effect 16%).[3,4] Other than peri-implant characteristics, QRS duration, and QRS morphology,[5] suboptimal positioning of the LV lead has been proposed as one possible cause of nonresponse to CRT.[6] The MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy) has shown that patients who undergo CRT implantation and have the LV lead positioned in the basal or mid-ventricular regions have a lower risk of HF hospitalization and death than patients in whom the LV lead is placed in apical positions.[7] Since ventricular electrical delay at the stimulation site is the most important mechanism to enhance CRT response in the presence of left bundle branch block,[8] pacing from mid-ventricular or basal regions that have been identified as the latest activated segments in patients with ventricular conduction disturbances may improve outcomes and quality of life in patients with HF. Moreover, an apical position of the LV lead may be in close proximity to the right ventricular lead, reducing the interelectrode distance and precluding resynchronization. Consequently, the current recommendations advocate avoiding apical LV pacing for CRT.[3] Furthermore, capturing a larger area of LV with multipoint pacing via quadripolar leads is associated with a significant reduction in cumulative HF hospitalizations and related costs after 1 and 2 years of follow-up.[9] In the present study, we sought to compare some currently available quadripolar leads targeting midventricular or basal LV regions.

METHODS

Patient selection, device implantation, and follow-up Consecutive adult patients successfully implanted with a CRT defibrillator (CRT-D) were enrolled in 9 different institutions. The patients gave their written informed consent and the study was approved by the local Ethics Committee. The CRT-Ds were implanted according to the standard practice of the individual center. Lead implantation stratified according to center preference is shown in Supplementary material, *Table S1*. A quadripolar LV lead, chosen by the implanting physician, was employed in all patients. The LV leads were deployed in the lateral or posterolateral branches of the coronary sinus. A preimplantation coronary venous angiogram was performed in at least 2 orthogonal views (left anterior oblique, 20° to 40°, and right anterior oblique, 20° to 40°). The final position of the LV lead was assessed with postimplantation fluoroscopic images in the same views. The positions of the LV leads on the LV surface were classified as basal, midventricular, or apical in the LV "long axis," and as anterior, lateral, or posterior in the LV "short axis."[10,11] The pacing capture threshold (PCT) was measured for each electrode, in either a bipolar or unipolar configuration, at 7.5 V or less, using a 0.5-ms pulse width. The presence of phrenic nerve stimulation (PNS) was evaluated by the same tests. In the interest of simplification, for the results of each electrode used as a cathode, we selected the pacing vector (cathode-anode couple) associated with the best electrical performance, defined as the largest PNS-PCT difference. A PNS--PCT difference greater than 2 V was considered acceptable in our evaluation.[12] During hospitalization, the optimization of pacing parameters and drug therapy was based on clinical evaluation. After CRT-D implantation and discharge, follow-up was performed according to the standard practice of the individual center.

Lead characteristics Commercially available transvenous leads were used in this study; an example of LV lead positioning is shown in FIGURE 1. The leads adopted in this series were Acuity X4 Spiral (Boston Scientific), Acuity X4 Straight (Boston Scientific), Quartet (St. Jude Medical), and Sentus OTW QP (Biotronik). The lead models differed in terms of the fixation design (a straight lead body for the Acuity X4 Straight, an S-curve design for the Sentus OTW QP and the Quartet, and a 3-dimensional helix for the Acuity X4 Spiral), tip diameter (2.6F for the Acuity family and 4F for both Sentus OTW QP and Quartet), maximum interelectrode spacing (36 mm for the Acuity X4 Straight, 47 mm for the Quartet, 50 mm for the Acuity X4 Spiral, and 61 mm for the Sentus OTW QP), and number of programmable pacing vectors (12 with the Biotronik system, 17 with the Boston Scientific systems, and 10 with the St. Jude Medical system).

Statistical analysis Continuous data are expressed as means (SD) for normally distributed continuous variables, or medians and interquartile ranges in the case of skewed distribution. The normality of distributions was tested

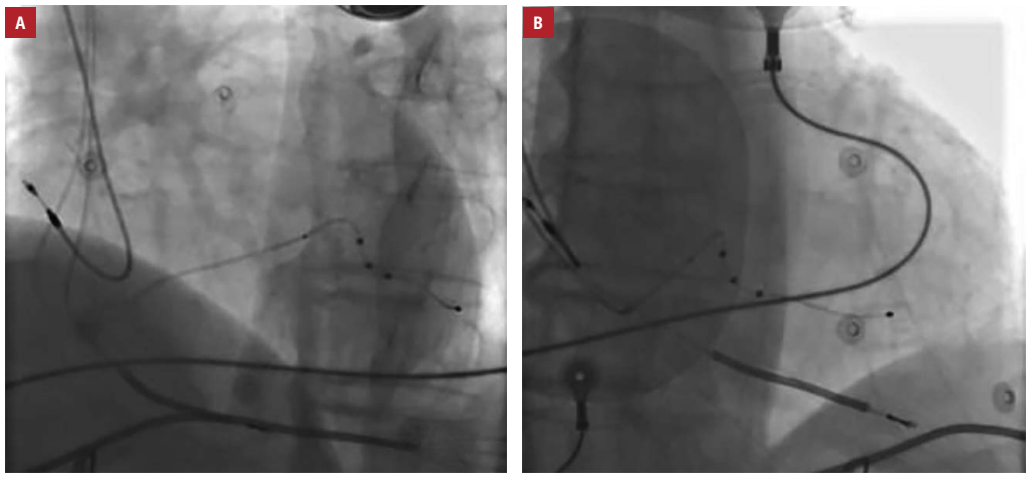

FIGURE 1 Example of left ventricular lead positioning: left anterior oblique (**A**) and right anterior oblique (**B**) views of Acuity X4 Spiral (Boston Scientific) positioning

by means of the nonparametric Kolmogorov-Smirnov test. Categorical data are expressed as numbers and percentages. Differences between continuous variables were analyzed using the *t* test for normally distributed variables and the Mann-Whitney test or the Wilcoxon nonparametric test for independent or paired samples, respectively, for non-normally distributed variables. Differences in proportions were compared with the χ^2 test or the Fisher exact test, as appropriate. One-way analysis of variance or the Kruskal-Wallis test was used to assess differences among groups, followed by the Student-Neuman-Keuls test for post hoc comparisons. A 2-tailed *P* value of less than 0.05 was considered significant for all tests (adjusted for multiple testing with Bonferroni correction; level of significance, 0.008). The STATISTICA software, version 7.1 (StatSoft, Inc., Dell Inc., Round Rock, Texas, United States) was used for the analysis.

TABLE 1 **Demographics and baseline clinical parameters of the study population (n = 168)**

Parameter		Value
Male sex, n (%)		113 (67)
Age, y, mean (SD)		72 (9)
Ischemic heart disease, n (%)		77 (46)
QRS duration, ms, mean (SD)		151 (27)
NYHA class, n (%)	II	91 (54)
	III	77 (46)
History of atrial fibrillation, n (%)		59 (35)
Hypertension, n (%)		111 (66)
Diabetes, n (%)		48 (28)
Chronic kidney disease, n (%)		49 (29)
Chronic obstructive pulmonary disease, n (%)		44 (26)
LV ejection fraction, %, mean (SD)		29 (6)
LVEDV, ml, mean (SD)		188 (63)
LVESV, ml, mean (SD)		148 (49)

Abbreviations: LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association

RESULTS

Study population

A total of 168 CRT-Ds were implanted in consecutive patients with HF and reduced ejection fraction. All patients were included in the analysis. The baseline clinical variables are summarized in TABLE 1. Eight CRT-Ds were from Biotronik (with Sentus OTW QP leads), 98 from Boston Scientific (with 21 Acuity X4 Spiral and 77 Acuity X4 Straight leads), and 62 from St. Jude Medical (with Quartet lead).

Positioning of left ventricular leads and location of pacing electrodes

The final locations of the LV lead tips are summarized in FIGURE 2. Specifically, the tip of the LV lead was deployed in an apical LV region in 90 patients (54%): 4 (50%) with the Biotronik Sentus, 9 (43%) with the Boston Scientific Acuity X4 Spiral, 35 (45%) with the Boston Scientific Acuity X4 Straight, and 42 (68%) with the St. Jude Medical Quartet (*P* = 0.04 overall). The spiral-design lead was more likely to target the basal left ventricle. This area has indeed been shown to provide better clinical outcomes. The distribution of all available pacing electrodes (1 distal tip and 3 proximal rings) across the LV segments is presented in FIGURE 3. The median number of electrodes at non-apical segments per patient was higher with both the spiral-design (4 [3–4]) and straight (4 [3–4]) Boston Scientific leads than with the other models of leads: Biotronik Sentus (3 [1–4]) and St. Jude Medical Quartet (3 [3–4]) (*P* = 0.045 overall; the Kruskal-Wallis test followed by pairwise comparisons).

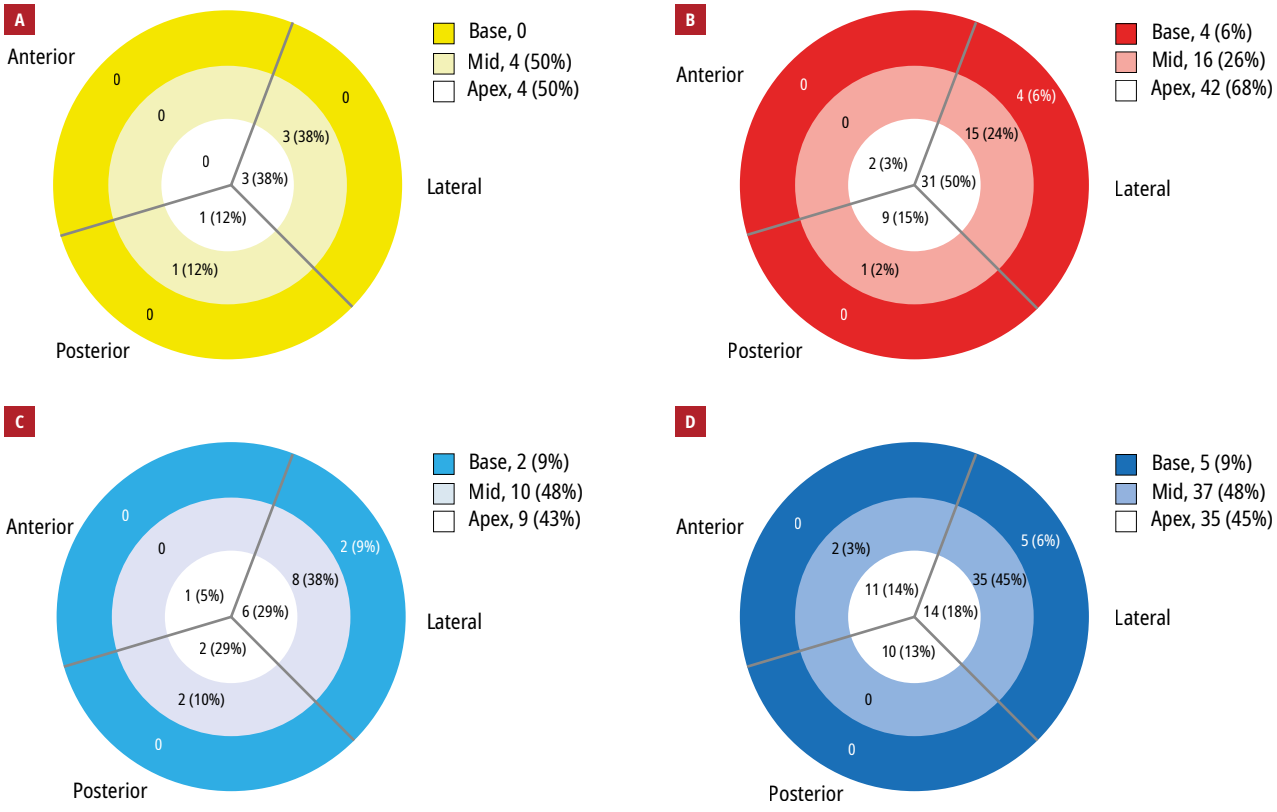

FIGURE 2 Distribution of the left ventricular lead tip position by lead model: **A** – Biotronik Sentus (n = 8); **B** – St. Jude Medical Quartet (n = 62); **C** – spiral-design Boston Scientific (n = 21); **D** – straight-design Boston Scientific (n = 77).

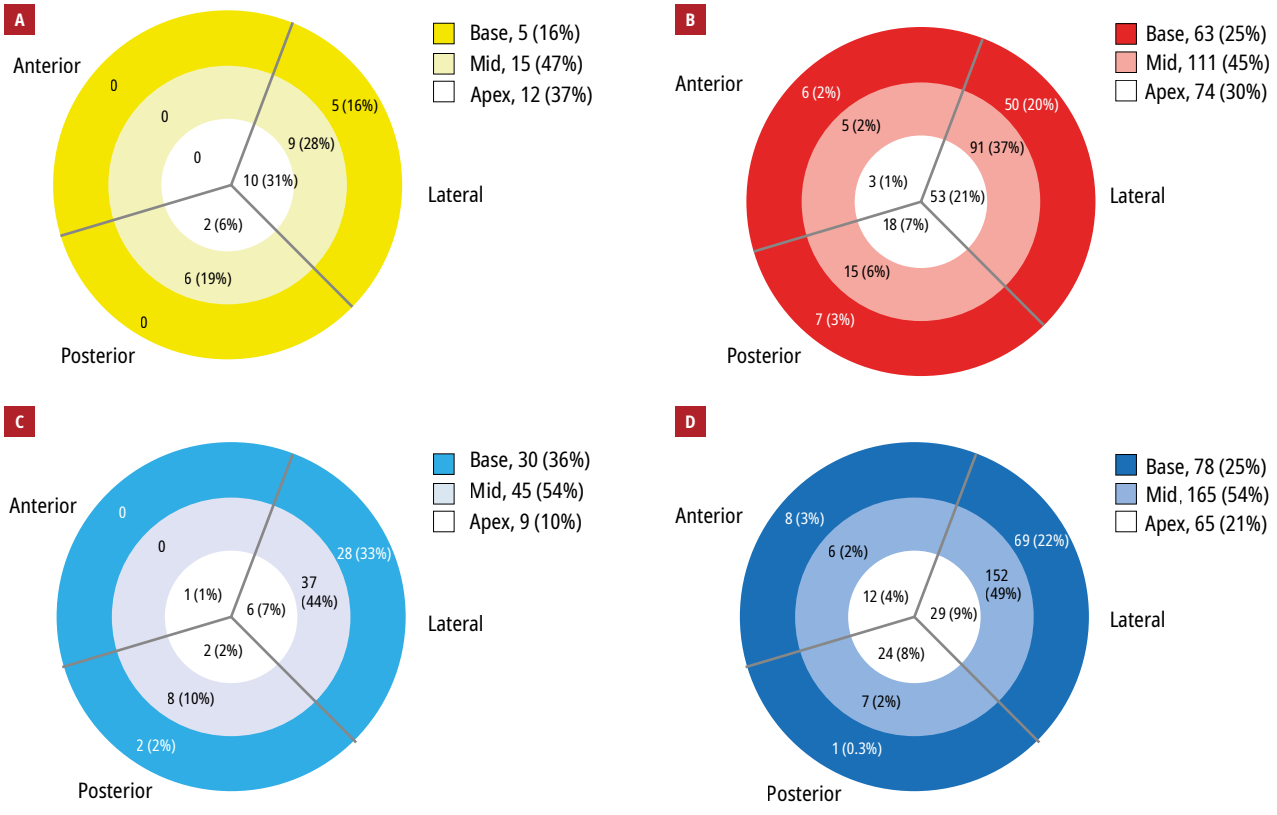

FIGURE 3 Distribution of all available pacing electrodes (1 distal tip and 3 proximal rings) over the left ventricular segments by lead model: **A** – Biotronik Sentus (n = 32); **B** – St. Jude Medical Quartet (n = 248); **C** – spiral-design Boston Scientific (n = 84); **D** – straight-design Boston Scientific (n = 308)

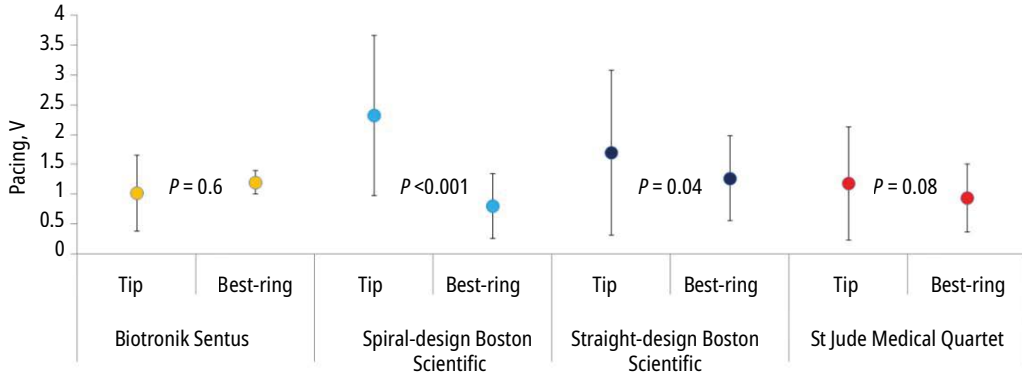

FIGURE 4 Pacing capture threshold comparisons between the electrodes at the distal tip and at the best of proximal rings by lead model. The circles indicate means and the whiskers indicate SD.

Electrical performance In the study population, the mean (SD) PCT was 1.6 (1.3) V at the tip electrode, 1.3 (0.8) V at ring 1, 1.8 (1.2) V at ring 2, and 2.4 (1.6) V at ring 3. The PCT values at the distal tip and proximal rings are presented in FIGURE 4. With the Biotronik or St. Jude Medical leads, the mean PCT was comparable between pacing configurations that used the tip or a ring as a cathode. By contrast, with the Boston Scientific lead models, the adoption of a ring as a cathode resulted in lower PCT, in particular with the spiral-design leads (P <0.001 and P = 0.04 for comparisons of spiral-design leads and straight-design leads, respectively).

The median (SD) number of cathodes associated with an acceptable pacing configuration (ie, a PNS-PCT of >2 V) was 4 (3–4): 2 (1–2) with the Biotronik Sentus, 4 (3–4) with the spiral-design Boston Scientific, 4 (3–4) with the straight-design Boston Scientific, and 3 (2–4) with the St. Jude Medical Quartet leads (P >0.05, the Kruskal-Wallis test). The number of patients with at least 1 electrode at nonapical segments associated with a PNS-PCT safety margin of more than 2 V was 142 (85%): 3 (38%) with the Biotronik Sentus, 21 (100%) with the spiral-design Boston Scientific, 69 (90%) with the straight-design Boston Scientific, and 49 (79%) with St. Jude Medical Quartet leads (P <0.001 overall, followed by pairwise comparisons).

Follow-up During the 6-month follow-up, PNS was detected in 4 patients. For each of them, alternative acceptable configurations were available and the PNS was eliminated after reprogramming. In the study cohort, the median change in PCT from baseline to follow-up was 0 V (–0.5 to 0.3) at the tip electrode, 0.2 (–0.2 to 0.5) at ring 1, 0.1 (–0.2 to 0.5) at ring 2, and 0.1 (–0.3 to 0.8) at ring 3 (P >0.05 for all changes; the Wilcoxon nonparametric test).

DISCUSSION

In CRT implantations, the use of quadripolar LV leads have become the first-line strategy, since their use is associated with lower total mortality, cardiac mortality, and less HF hospitalizations.[13] Quadripolar LV leads enable better reverse remodeling than conventional bipolar leads, due to the lower dislodgement rate from the targeted stimulation site.[14] Having multiple pacing options allows the electrophysiologist to deal with the issues represented by PNS and high PCT, as well as enhancing the likelihood of successfully pacing nonapical LV segments. Currently, a multitude of designs for quadripolar LV leads are available to the clinician, including leads allowing multipoint pacing, which can shorten the QRS interval, reduce LV dyssynchrony, and increase the LV ejection fraction.[15] The distinctive features might result in differences in procedural and clinical outcomes among different leads, especially in the setting of varying coronary sinus anatomy.

This is the first analysis in a real-world European setting to show that differences exist among the currently available leads in their ability to target mid-ventricular or basal LV regions. This multicenter experience shows that the currently available quadripolar LV leads can deliver effective pacing at nonapical LV segments in approximately 85% of patients.

The lead models included in this analysis differed in regard to several characteristics (eg, the fixation design, tip diameter, interelectrode spacing, and number of programmable pacing vectors) and presented differences in the ability to deliver nonapical LV pacing. Specifically, spiral-design leads had a higher number of effectively usable nonapical electrodes. This finding was somewhat expected, given that the leads were not comparable with regard to interelectrode distance and geometry. The spiral lead was designed to ensure stability and low PCT even if it is not wedged distally; therefore, the tip of the lead was less likely to be deployed in an apical LV region. In addition, the longer spacing between the distal and proximal electrodes resulted in a higher probability that the proximal electrodes would be located at basal segments. Electrical performance, as expressed by the mean

pacing threshold at basal ventricular segments, was significantly better with the spiral-design leads. This is attributable to the lead design, which was developed to maintain the basal electrodes in closer contact with the vessel lumen. Nonetheless, although the pacing values seem to favor spiral leads, the small difference detected may not significantly impact clinical practice.

Our results confirm the previous findings of the LILAC (Left Ventricular Three-Dimensional Quadripolar Lead Acute Clinical) study,[16] which evaluated the acute performance of 3 quadripolar LV prototype leads and found that acceptable PCT without PNS was achieved in the first implanted target vein with a spiral lead design in more than 90% of patients. Indeed, it was shown that an excellent contact between the electrode and the myocardium—at least at 1 proximal electrode, leading to adequate PCT—is possible with a 3-dimensional spiral design, irrespective of the diameter of the vein or the location of the lead (proximal or distal). Moreover, LV stimulation at basal sites might also be the ideal location to manage PNS, as PNS was found to occur more frequently at apical or mid LV sites.[17,18] Similarly, the NAVIGATE X4 (Evaluation of ACUITY X4 Quadripolar Coronary Venous Leads and RELIANCE 4-FRONT Defibrillation Leads) clinical trial showed lower PCT from proximal electrodes spaced around a helical bias of spiral leads than from the distal electrode.[19] In the trial, this resulted in devices most commonly permanently programmed to pace from a proximal electrode, thereby increasing the probability of avoiding pacing from apical regions of the LV.

Positioning LV leads at an effective location is a prerequisite for effective CRT. Quadripolar LV leads were developed to prevent high PCT and PNS by allowing more options in lead placement and programming capability. In recent years, there has been a growing body of evidence from several studies which emphasizes the efficacy of quadripolar LV leads; this has led to their widespread adoption in the clinical setting of CRT, being associated with low rates of dislocation and PNS at follow-up.[20-22] Indeed, while PNS was detected in 4 of 168 patients (2.4%), no evident and significant LV lead dislodgment leading to reintervention was detected, either immediately after the procedure or during the 6-month follow-up in our cohort; this was also witnessed by PNS resolving after reprogramming in all cases, although chest x-ray data were not systematically collected during follow-up. These data are in line with other studies that analyzed dislodgement and malfunction of these leads jointly, such as Ghani et al,[23] who reported that a global rate of LV lead dislodgement or malfunction within the first year was 1.4% and Bulava et al,[24] who reported a rate of 1.1% for LV dislodgment with a loss of capture and need for repositioning. The low rates of complications, circumventing the need for reintervention, might be partially explained by the novelty of our data in comparison to older reports, corroborating the downward trend of CRT issues with more recent implantations, as postulated by Alonso et al.[25]

Moreover, the programming flexibility of quadripolar leads has also been associated with fewer hospitalizations and reduced mortality.[26] It is possible that avoiding the apical region could enhance the overall response to CRT therapy,[7,27] making this an even more cost-effective strategy.[28,29] These positive results may be explained by the latest activated LV segments being present at the mid-ventricular or basal regions,[8,30] while more apical pacing sites may be in close proximity to the RV lead, precluding resynchronization. In this study, we confirmed that apical pacing could be successfully avoided, as we evaluated the location of each electrode of the LV lead with post-implantation fluoroscopic images. We tested each electrode (selected as a cathode) by choosing the pacing vector (the corresponding anode) associated with the best electrical performance, that is, the largest PNS-PCT difference. This resembles the approach used in clinical practice, when operators would test more pacing configurations to achieve acceptable PCT at the best anatomical location. This method is also facilitated by contemporary device algorithms that automatically test multiple pacing configurations and suggest viable options at implantation and at follow-up device interrogation.

Limitations Our study has some significant limitations. Due to its nonrandomized, retrospective, observational nature, it may be subject to confounders and relevant selection bias, although it should be pointed out that we included consecutive patients in order to minimize this issue. The initial choice of the lead type was based on availability at the time of implantation rather than patient-specific variables [7] and the number of leads from different producers makes it difficult to draw definite conclusions from this comparison. Indeed, the sample size in our study was relatively small and not balanced between the groups. The independent analysis of the prospectively collected, postoperative fluoroscopic images by a core center is simple and widely applicable, though it has some limitations.[11] Significant differences exist among the designs of the currently available electrode systems, especially considering the one with a spiral distal part and the 3 with a straight ending. In our analysis, the straight leads were from 3 manufacturers and had different sizes, designs, and intraelectrode distances, thus making our comparison very complicated and unable to provide definite conclusions on this topic; the differences between lead types require further investigations. Also, this study does not address lead-related differences in the overall response to

CRT and lacks clinical data on short- and long-term follow-up. Therefore, additional supporting clinical studies with follow-up data are required to evaluate differences in clinical and procedural outcomes among the currently available quadripolar leads.

Conclusions This multicenter study is the first reported experience to compare the performance of currently available quadripolar LV leads. As expected due to their design, these leads allowed effective pacing to be delivered at nonapical LV segments in the majority of patients, ensuring acceptable electrical parameters and therefore potentially leading to a lower risk of HF hospitalization and death. These leads were invented to provide stability of the leads' location and the ability to stimulate from different sites; these features were in fact reflected in our data. Additional supporting studies are clearly needed to properly assess differences among the currently available systems with different designs and to characterize the long-term clinical performance of these leads.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/kardiologiapolska.

ARTICLE INFORMATION

CONFLICT OF INTEREST ML and SV are employees of Boston Scientific, Inc. LS received speaker honorarium from St. Jude Medical, Boston Scientific, and Biotronik. Other authors declare no conflict of interest.

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