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

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**Short title:** Nonapical LV pacing with quadripolar leads for CRT
CONFLICT OF INTEREST:

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**WHAT’S NEW?**

This multicenter study is the first reported experience comparing the performance of currently available quadripolar left ventricular (LV) leads. These leads allowed to deliver effective pacing at non-apical LV segments in the majority of patients, ensuring acceptable electrical parameters and therefore potentially leading to a lower risk of heart failure (HF) hospitalizations and death. Nonetheless, differences exist among currently electrodes available systems. Spiral-design leads may have better electrical performance at the proximal than at the distal tip and seem to show a higher number of effectively usable non-apical electrodes. These findings need to be properly assessed, evaluating differences among current available systems with distinct designs as well as characterizing clinical long-term performance of these leads.

**Keywords:** cardiac resynchronization therapy; heart failure; left ventricular function; defibrillators.
ABSTRACT

Background: Current guidelines recommend to avoid apical left ventricular (LV) pacing for cardiac resynchronization therapy (CRT).

Aim: We investigated the feasibility of non-apical pacing with current quadripolar LV lead technology.

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

Results: We enrolled 168 patients. Eight CRT-D were from Biotronik (with Sentus OTW QP lead), 98 from Boston Scientific (21 Acuity X4 Spiral, 77 Acuity X4 Straight leads), and 62 from St Jude Medical (with Quartet lead). The median [25-75 percentile] number of electrodes at non-apical segments per patient was: 3 [1-4] with Biotronik Sentus, 4 [3-4] with spiral-design Boston Scientific leads, 4 [3-4] with straight Boston Scientific, 3 [3-4] with St Jude Medical Quartet ($P = 0.045$). Three (38%) patients with Biotronik Sentus, 21 (100%) with spiral-design Boston Scientific, 69 (90%) with straight-design Boston Scientific, and 49 (79%) with St Jude Medical Quartet ($P < 0.001$) had at least one electrode located at non-apical segments linked with a PNS-PCT safety margin > 2 V. During the 6-months follow-up, PNS was detected in 4 patients and was eliminated with reprogramming. No significant changes in PCT were detected from baseline to follow-up.

Conclusions: Quadripolar leads allowed non-apical pacing with acceptable electrical parameters in the majority of CRT recipients, although dissimilarity appeared among currently available devices.
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 broadened 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 (approximately 34%) may barely clinically improve after CRT implantation, with a New York Heart Association (NYHA) status progress described in about 51% of patients randomized to CRT vs. 35% of control (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 of the possible causes of non-response to CRT [6]. MADIT-CRT trial have shown that patients who undergo CRT implantation and have the LV lead positioned in basal or mid-ventricular regions, have lower risk of HF hospitalization and death, compared with patients with the LV lead 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 LBBB [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 HF patients outcomes and quality of life. Moreover, an apical position of the LV lead may be in close spatial relation with the right ventricular lead, reducing the interelectrode distance and precluding resynchronization. Consequently, current recommendations advocate avoiding apical LV pacing for CRT [3]. Furthermore, capturing a larger area of LV with multipoint pacing (MPP) via quadripolar leads is associated with a significant reduction in cumulative HF hospitalizations and related costs after one and two years of follow-up [9]. In the current study, we sought to compare some currently available quadripolar leads targeting mid-ventricular or basal LV regions.
METHODS

Patient selection, device implantation and follow-up

Consecutive adult patients successfully implanted with a CRT-D were enrolled in nine different Institutions. Enrolled patients gave written informed consent. The study was approved by the Local Ethics Committee. CRT-D implantation was performed according to the standard practice of the individual center. A LV quadripolar lead was employed for all patients and implanting physician chose the LV lead. LV leads were deployed in lateral or posterolateral branches of the coronary sinus. A preimplantation coronary venous angiogram, performed in at least 2 orthogonal views (left anterior oblique, 20° to 40°, and right anterior oblique, 20° to 40°) was performed. The final position of the LV lead was assessed with post-implantation 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 with the same testing. For the purpose of simplification, for each electrode used as cathode we considered the results obtained by selecting the pacing vector (cathode-anode couple) associated with the best electrical performances, defined as the largest PNS-PCT difference. A PNS-PCT difference was greater than 2 V was considered acceptable in our evaluation [12]. During hospitalization, 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), Sentus OTW QP (Biotronik). The lead models differed as regard to the fixation design (straight lead body for the Acuity X4 Straight, S-curve design for the Sentus OTW QP and the Quartet, 3-dimensional helix for the Acuity X4 Spiral), the tip diameter (2.6 F for the Acuity family and 4 F for both Sentus OTW QP and Quartet), and the maximal interelectrode spacing (36mm for the Acuity X4 Straight, 47mm for the Quartet, 50mm for the Acuity X4 Spiral, 61 mm for the Sentus OTW QP), the number of programmable pacing vectors (12 with Biotronik systems, 17 with Boston Scientific systems and 10 with St Jude Medical CRT-D).

Statistical analysis
Continuous data were expressed as mean (SD) for normally distributed continuous variables, or medians and interquartile range (25th-75th percentile) in the case of skewed distribution. Normality of distribution was tested by means of the nonparametric Kolmogorov-Smirnov test. Categorical data were expressed as percentages. Differences between continuous variables were performed using a Student T test for Gaussian variables, and a Mann Whitney U Test or Wilcoxon non-parametric test for non-Gaussian variables, respectively for independent or paired samples. Differences in proportions were compared by applying Chi-square analysis or Fisher’s exact test, as appropriate. One-way analysis of variance or Kruskal-Wallis test was used to test for differences among groups, followed by Student–Neuman–Keuls test for post hoc comparisons. A two sided $P$ value <0.05 was considered significant for all tests (adjusted for multiple testing by Bonferroni correction – level of significance: 0.008). STATISTICA software, version 7.1 (StatSoft, Inc.) was used for the analysis.
RESULTS

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

Positioning of LV leads and location of pacing electrodes
The final locations of the LV lead tips are summarized illustrated in Figure 2. Specifically, the tip of the LV lead was deployed in an apical LV region in 90 (54%) patients: 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 (overall \( P = 0.04 \)). The distribution of all available pacing electrodes (1 distal tip and 3 proximal rings) over the LV segments, stratified by lead model, is reported in Figure 3. The median number of electrodes at non-apical segments per patient was higher with spiral-design (4 [3-4]) and straight (4 [3-4]) Boston Scientific leads than with the other lead models: Biotronik Sentus (3 [1-4]), St Jude Medical Quartet (3 [3-4]) (\( P = 0.045 \), overall Kruskal-Wallis test followed by pairwise comparisons).

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 distal tip and proximal rings are reported in Figure 4. With Biotronik or St Jude Medical leads, the mean PCT was comparable between pacing configurations that used the tip or a ring as cathode. By
contrast, with Boston Scientific lead models the adoption of a ring as cathode resulted in lower PCT, in particular with spiral-design leads ($P < 0.001$ and $P = 0.04$ for two groups comparisons considering spiral-design lead and straight-design lead, respectively).

The median number of cathodes associated with an acceptable pacing configuration (i.e. PNS-PCT > 2V) was 4 [3-4] (2 [1-2] with Biotronik Sentus, 4 [3-4] with spiral-design Boston Scientific, 4 [3-4] with straight-design Boston Scientific, 3 [2-4] with St Jude Medical Quartet; $P > 0.05$, Kruskal-Wallis test). The number of patients with at least one electrode at non-apical segments associated with a PNS-PCT safety margin > 2 V was 142 (85%): 3 (38%) with Biotronik Sentus, 21 (100%) with spiral-design Boston Scientific, 69 (90%) with straight-design Boston Scientific, and 49 (79%) with St Jude Medical Quartet ($P < 0.001$, overall p-value followed by pairwise comparisons).

*Follow-up*

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

**DISCUSSION**

In CRT implantations, the use of quadripolar LV leads have become the first-line strategy, since their use is associated with a lower total mortality, cardiac mortality, and HF hospitalization [13]. LV quadripolar leads enable a better reverse remodeling compared to conventional bipolar leads, due to a decreased dislodgement rate from the targeted stimulation
Multiple pacing options let the electrophysiologist to handle issues represented by PNS and high PCT, as well as enhancing the likelihood of successfully pacing non-apical LV segments. Currently, a multitude of different designed quadripolar LV leads are available for the clinician, including leads allowing multipoint pacing, that enables to shorten the QRS interval, reducing LV dyssynchrony and increasing LV ejection fraction [15]. The distinctive features might result in differences in procedural and clinical outcomes among leads, especially in the settings of different CS anatomy. For the first time in a real-world European setting, our analysis reveals that differences exist among currently available leads in the ability of targeting mid-ventricular or basal LV regions. This multicenter experience shows that currently available quadripolar LV leads allow to deliver effective pacing at non-apical LV segments in approximately 85% of patients. The lead models included in this analysis differed as regard to several characteristics (e.g. the fixation design, the tip diameter, the interelectrode spacing, the number of programmable pacing vectors) and presented differences in the ability to delivery non-apical LV pacing. Specifically, spiral-designed leads showed a higher number of effectively usable non-apical electrodes. This finding was not unexpected 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 not wedged distally, therefore the tip of the lead was less likely deployed in an apical LV region. In addition, the longer spacing between distal and proximal electrodes resulted in a higher probability to target proximal electrodes at basal segments. Electrical performance, as expressed in mean pacing threshold at basal ventricular segments, was significantly better with spirally designed 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 pacing values seem to favor spiral leads, the small difference detected may not significantly impact clinical practice.
Our results confirm previous findings of the Left Ventricular Three-Dimensional Quadripolar Lead Acute Clinical (LILAC) Study [16]. The study evaluated the acute performance of 3 investigational quadripolar LV prototype leads and found that, with a spiral lead design, acceptable PCT without PNS was achieved in more than 90% of patients in the first implanted target vein. Indeed, it was shown that excellent electrode-myocardium contact, at worst at one proximal electrode, leading to adequate PCT, is provided with a 3D spiral design, irrespective of the diameter of the vein and of the lead location (proximal or distal). Moreover, LV stimulation at basal sites might also be the ideal location to manage the PNS, as the PNS occurrence was found more frequently at apical or mid LV sites [17,18]. Similarly, the NAVIGATE X4 clinical trial showed lower PCT from proximal electrodes spaced around the helical bias of spiral leads than from the distal electrode [19]. In the trial, this resulted in devices permanently programmed most commonly to pace from a proximal electrode, thereby increasing the probability to avoid pacing from apical regions of the LV.

LV lead positioned at an effective location is a prerequisite for effective CRT. Quadripolar LV leads have been developed to prevent high PCT and PNS, by allowing more choices in lead placement location and programming capability. In the last years, there was a growing number of evidences from several studies, which emphasized the efficacy of quadripolar LV leads and led to their widespread adoption in the clinical practice of CRT, being associated with low rates of dislocations and PNS at follow-up [20–22]. Indeed, while PNS was detected in 4/168 patients (2.4%), no evident and significant LV lead dislodgment leading to reintervention was detected immediately after the procedure or during the 6-month follow-up in our cohort, as also witnessed by PNS solving 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] that reported a global rate of LV lead dislodgement or malfunction within the
first year of 1.4% and Bulava et al. that reported 1.1% of LV dislodgment with loss of capture and need for repositioning [24]. The low rates of complications leading to no need for reintervention might be partially explained by the novelty of our data, when compared to older reports, corroborating the downward trend of CRT issues related to more recent implantations, as postulated by Alonso et al. [25].

Moreover, the quadripolar leads programming flexibility has also been associated with lower 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 presence of the latest activated LV segments at mid-ventricular or basal regions [8,30] while more apical pacing sites may be in close spatial relation with 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, through analysis of post-implantation fluoroscopic images. We tested each electrode (selected as cathode) by choosing the pacing vector (the corresponding anode) associated with the best electrical performances, i.e. 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 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 non-randomized, retrospective, observational nature, it may be subject to confounders and relevant selection bias, although it has to be underlined 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 of different producers included makes difficult to draw definite conclusions from this comparison. Indeed, the sample size of our study was relatively small and not balanced among groups. The independent analysis, by a core center, of the prospectively collected, postoperative fluoroscopic images is simple and widely applicable, though has some limitations [11]. Significant differences exist among currently electrodes available systems, especially for their design with the spiral distal part and three with straight ending. Nevertheless, in our analysis the straight leads were from three manufactures of different size, design and intraelectrode distance, thus making our comparison very complicated and uncapable to provide definite conclusions on this topic; differences between lead types require further investigations. Also, this study does not address lead-related differences in the overall response to CRT therapy and lacks of 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 currently available quadripolar leads.

Conclusions

This multicenter study is the first reported experience comparing the performance of currently available quadripolar LV leads. As expected due to their design, these leads allowed to deliver effective pacing at non-apical LV segments in the majority of patients, ensuring acceptable electrical parameters and therefore potentially leading to a lower risk of HF hospitalizations and death. These leads were invented to provide stability of lead location and capability to stimulate from different sites; indeed these features were reflected in our data. Additional supporting studies are clearly needed to properly assess differences among current available
systems with different designs as well as characterizing clinical long-term performance of these leads.
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Table 1. Demographics and baseline clinical parameters of the study population.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>(n = 168)</th>
</tr>
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<tbody>
<tr>
<td>Male gender</td>
<td>113 (67%)</td>
</tr>
<tr>
<td>Age, years</td>
<td>72 (9)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>77 (46%)</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>151 (27)</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
</tr>
<tr>
<td>- Class II</td>
<td>91 (54%)</td>
</tr>
<tr>
<td>- Class III</td>
<td>77 (46%)</td>
</tr>
<tr>
<td>History of atrial fibrillation</td>
<td>59 (35%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>111 (66%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>48 (28%)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>49 (29%)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>44 (26%)</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>29 (6)</td>
</tr>
<tr>
<td>LVEDV, ml</td>
<td>188 (63)</td>
</tr>
<tr>
<td>LVESV, ml</td>
<td>148 (49)</td>
</tr>
</tbody>
</table>

Data are expressed as mean (standard deviation) or number (percentage).

NYHA = New York Heart Association; LV = Left ventricular; LVEDV = Left ventricular end-diastolic volume; LVESV = Left ventricular end-systolic volume.
**Figure 1.** Panel A, B. Example of left ventricular lead positioning: left anterior oblique (LAO) and right anterior oblique (RAO) views of Acuity X4 Spiral, Boston Scientific positioning.
Figure 2. Panels A, B, C, D. Distribution of the left ventricular lead tip position. The spiral designed lead was more likely to target the basal left ventricle. This area has indeed been shown to provide better clinical outcomes.
Figure 3. Panels A, B, C, D. Distribution of all available pacing electrodes (1 distal tip and 3 proximal rings) over the left ventricular segments, stratified by lead model.
Figure 4. Pacing capture threshold comparisons between the electrodes at the distal tip and at the best of proximal rings, stratified by lead model. Data are presented as mean (standard deviation).