Phrenic Stimulation
A Challenge for Cardiac Resynchronization Therapy

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Background—Phrenic stimulation (PS) may hinder left ventricular (LV) pacing. We prospectively observed its prevalence in consecutive patients with cardiac resynchronization therapy (CRT) devices.

Methods and Results—In the years 2003 to 2006, 197 patients received a CRT device. PS and LV threshold measurements were carried out at implantation and at 6-month follow-up. LV reverse remodeling was assessed by echocardiography before implantation and at follow-up. LV lead placement was lateral/posterolateral in 86% of patients. Both PS and LV reverse remodeling occurred most frequently at the lateral/posterolateral LV pacing sites ($P<0.001$). PS was detected in 73 (37%) of patients and was clinically relevant in 41 (22%). The detection of PS at implantation had a poor sensitivity, as it occurred only in left lateral or sitting position in 27 patients. Ten patients (5%) underwent repeated surgery and 4 (2%) had their CRT turned off because of PS. At follow-up, we could manage PS noninvasively in 32 patients with a small PS-LV threshold difference: in 20 by cathode programmability (3 also thanks to automatic management of LV output) and in 12 (without cathode programmability) by programming the LV output as threshold $1V$.

Conclusions—PS may seriously hinder CRT. A bipolar LV lead and cathode programmability are mandatory to avoid PS by changing the LV pacing vector at target sites for CRT. LV stability at target sites despite PS should also be pursued by these means. The automatic adjustment of LV pacing output is complementary in patients with a small PS-LV threshold difference. (Circ Arrhythmia Electrophysiol. 2009;2:402-410.)

Key Words: CRT ■ phrenic stimulation ■ reverse remodeling

Cardiac resynchronization therapy (CRT) is an important therapeutic option in patients with heart failure who have systolic left ventricular (LV) dysfunction and evidence of electric/mechanical dyssynchrony.1-2 The clinical benefit is strictly dependent on continuous LV stimulation at sites with delayed mechanical activity.3-6 Chung et al7 have recently reported that 45% of patients are nonresponders to CRT when efficacy is assessed by the objective measurement of LV function. Failure to ensure LV stimulation at the appropriate site because of a high pacing threshold and phrenic stimulation (PS) are important causes of failure to deliver CRT. Importantly, few data in literature address these aspects. Phrenic stimulation may seriously hinder LV stimulation and may prevent the optimal pacing sites for CRT from being reached. No study has prospectively investigated the prevalence of the PS phenomenon at implantation of a CRT device and at follow-up, to understand the limitation it poses to the effective delivery of CRT. The aim of our study was to understand the prevalence and the relevance of PS and to assess the practical solutions to overcome this problem. We also sought to understand the predictors of PS and of functional response to CRT with respect to the main patient characteristics and LV lead placement sites.

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Methods

In our early experience with biventricular stimulation (1999 to 2002), PS was a challenging problem owing to the technology available at that time. Since the release of CRT devices with separate ventricular outputs, we planned this prospective study of PS. Consecutive patients undergoing CRT device implantation from January 2003 to January 2007 were prospectively enrolled in the study. The purposes of this study were (1) to understand the prevalence of PS and whether different stimulation configurations or different electronic programming of the pacing strength yield any advantage in the event of PS, and (2) to understand the factors associated to CRT response.

Phrenic Stimulation

The evaluation of PS is part of our customary CRT implantation procedure and of routine device follow-up. PS is tested in all the patients starting from maximum pacing system analyzer output, 10 V
at 1.5 ms; in the event of PS occurrence, its threshold is measured in all the possible pacing configurations and compared with LV pacing threshold to ensure the feasibility of biventricular stimulation. PS and LV pacing threshold were measured in all the possible pacing configurations, according to LV lead type (unipolar or bipolar), both at 0.5-ms and 1.5-ms pulse width after a stepping down protocol starting from 10 V. Pulse voltage was decreased in 1-V steps until PS disappearance; stepping down was then resumed in 0.1-V steps starting from the upper step showing PS. The same protocol was used for LV pacing threshold measurement.

PS disappearance was defined as absence of muscular stimulation over a 20-minute observation period during respiratory changes (deep breath); LV threshold was defined as 100% stimulation during the same respiratory changes.

The occurrence of PS that could not be managed because of a small difference compared with LV threshold could be solved by the implanting physician moving the LV lead to a different stimulation site; in this event, measurements were repeated at the new pacing site.

The LV lead placement was recorded at every tested pacing site by fluorography. In the event patients had PS during follow-up, they were evaluated for symptom assessment and problem solving. At 6-month follow-up, LV and PS threshold were measured by a step-down protocol starting from maximum device output at the same pulse widths as at implantation in all the pacing configurations available according to lead type and device programming capability. PS threshold was evaluated during respiratory changes in several body positions: supine, left lateral, right lateral, sitting, and standing. All the patients gave informed consent to the PS and ventricular threshold measurements.

**Response to CRT**

The study protocol included standard echocardiography and assessment of clinical parameters, symptoms, and New York Heart Association (NYHA) class, and 6-minute walking test at baseline and 6 months after CRT device implantation to assess the response to CRT.

**LV Lead Position**

We aimed at a lateral or posterior LV placement in all the patients, in which hemodynamic improvement has been reported to be maximum.3,4 LV lead placement was determined using biplane fluoroscopy classification (Figure 1) in the 45° left anterior oblique view (LAO) and in the 35° right anterior oblique view (RAO). In the LAO view, 2 sites were identified by vertical lines at clock positions 12 to 6 and 2 to 5 (Figure 1) to assess whether the lead placement was anterior/anterolateral (site 1) or lateral/posterolateral (site 2). In the RAO view, the LV pacing site was assessed in respect to the atrioventricular plane and the LV apex as being mid-basal (within mid-ventricular length) or mid-apical (from mid-ventricular to the apex). This topographic assessment was chosen after previous observations that clinical response to CRT is maximal when LV lead placement around the 3 o’clock position in the LAO view is achieved.8

Differently from Albertsen et al.,8 we divided the LV into 2 sites according to the variability of the left phrenic nerve course, as observed by Quintana et al.,9 which could yield different PS prevalence in very close LV sites.

**Echocardiographic Measurements**

The objective response to CRT was based on the extent of LV reverse remodeling at 6-month follow-up: Responders had to have an LV end-systolic volume (LVESV) reduction ≥15% and an absolute LV ejection fraction (LVEF) increase of ≥5%.

All patients were imaged before implantation and at 6-month follow-up, using a commercially available system (Philips Sonos 5500 Ultrasound System, Philips Ultrasound, Andover, Mass). Images were obtained using a 3.5-MHz transducer from the standard apical views (2- and 4-chamber).

LV volumes and LVEF were calculated according to the American Society of Echocardiography guidelines.10 Intraobserver and interobserver variability for assessment of LVESV and LVEF using Bland and Altman analysis expressed as mean difference of the 2 readings with 95% CIs and the limits of agreements with their 95% CIs were previously reported.11

**Statistical Analysis**

Continuous data are reported as median and interquartile ranges (25th to 75th percentiles), and categorical variables are reported as numbers and percentages. Univariate and multivariate logistic re-
Table 1. Patient Characteristics at Implantation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>197</td>
</tr>
<tr>
<td>Male</td>
<td>107 (54%)</td>
</tr>
<tr>
<td>Age, y</td>
<td>66 (57–72)</td>
</tr>
<tr>
<td>Ischemic etiology</td>
<td>73 (37%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>83 (42%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>76 (38%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>67 (34%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>51 (26%)</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.8 (12.7–14.7)</td>
</tr>
<tr>
<td>GFR, mL/min/1.73 m²</td>
<td>58.0 (46.0–72.0)</td>
</tr>
<tr>
<td>GFR &lt;30 mL/min/1.73 m²</td>
<td>13 (6%)</td>
</tr>
<tr>
<td>NYHA class III</td>
<td>163 (83%)</td>
</tr>
<tr>
<td>NYHA class IV</td>
<td>34 (17%)</td>
</tr>
<tr>
<td>6-M WT, m</td>
<td>367 (265–425)</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>164 (150–180)</td>
</tr>
<tr>
<td>LVES volume, mL</td>
<td>209 (150–279)</td>
</tr>
<tr>
<td>LVES volume, mL</td>
<td>178 (132–223)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>25 (21–29)</td>
</tr>
<tr>
<td>CRT-P</td>
<td>8 (4%)</td>
</tr>
<tr>
<td>CRT-D</td>
<td>189 (96%)</td>
</tr>
<tr>
<td>Severe mitral regurgitation</td>
<td>51 (26%)</td>
</tr>
<tr>
<td>Bipolar LV lead</td>
<td>119 (60%)</td>
</tr>
<tr>
<td>Unipolar LV lead</td>
<td>78 (40%)</td>
</tr>
</tbody>
</table>

GFR indicates glomerular filtration rate; 6-M WT, 6-minute walking test; ED, end-diastolic.

Results

One hundred ninety-seven consecutive patients undergoing a CRT device implantation from January 2003 to January 2007 were enrolled into the study. One hundred eighty-nine of 197 received a CRT-D device, whereas 8 of 197 received a CRT-P device. Ischemic etiology, defined as a history of myocardial infarction with documented coronary artery disease, was observed in 73 of 197 patients; nonischemic dilated cardiomyopathy was observed in 124 of 197. Twelve of 197 patients enrolled did not attend the 6-month follow-up: Their data are available at implantation only. The study population characteristics are reported in Table 1. Over a 24-month follow-up (range, 12 to 37), 16 patients died and 4 underwent heart transplantation.

The LV lead was chosen according to the size of the target coronary vein and according to the implanting physician’s preference. Six different types of LV lead by 3 manufacturers were used: 2 unipolar (Attain OTW 4193 by Medtronic and Aescula 1055K by St Jude Medical), and 4 bipolar (Attain OTW 4194 by Medtronic; Quicksite 1055T by St Jude Medical; Easytrack 2 and Acuity by Boston Scientific). Thus, all the patients could be paced in the “extended bipolar” configuration (LV tip to right ventricular [RV] coil/ring), whereas only 119 of 197 (60%) could be paced in the “true bipolar” (LV tip to ring) configuration.

Fifty-one of 112 patients with a CRT-D and 6 of 8 with a CRT-P device had a bipolar LV lead and devices featuring cathode programmability (capability to program either the proximal or the distal LV lead electrode as cathode). Matched evaluation at implantation and at follow-up of multiple pacing configurations was possible in 54 of 185 (29%) patients.

Response to CRT

Overall, there were 128 of 185 (69%) CRT responders as assessed by 6-month echocardiography, and 133 of 185 (72%) improved by at least 1 NYHA class. One hundred fifteen of 128 (90%) echocardiographic responders improved by at least 1 NYHA class, whereas only 18 of 57 (32%) nonresponders at echocardiography improved by 1 NYHA class ($\chi^2, P<0.001$). The LV lead placement was lateral or posterolateral according to the LAO view in 170 of 197 (86%) patients and mid-apical according to the RAO view in 129 of 197 (65%) patients (Figures 1 and 2).

CART responders at echocardiography were 119 of 160 (74%) among patients whose LV lead was placed at site 2 versus 9 of 25 (36%) placed at site 1 in the LAO view ($\chi^2, P<0.001$). CART responders were 92 of 120 (77%) when the LV lead was mid-apical versus 36 of 65 (55%) mid-basal in the RAO view ($\chi^2, P=0.003$). Combining LV lead classification in the LAO and RAO view (Figure 2) response to CRT at echocardiography was 2 of 9 (22%) in site 1 mid-apical, 7 of 16 (44%) in site 1 mid-basal, 29 of 49 (59%) in site 2 mid-basal, and 90 of 111 (81%) in site 2 mid-apical ($\chi^2, P<0.001$). LV lead placement at site 2 mid-apical was the strongest predictor of 6-month echocardiographic response to CRT at multivariable regression analysis (Table 2).

Phrenic Stimulation

PS at implantation or during follow-up in the overall study population was detected in 73 (37%) patients. PS was exclusively observed when the LV lead was placed in site 2. At
multivariable analysis, the mid-apical position was the strongest predictor of PS at implantation or in the follow-up (Table 3). PS at follow-up was investigated during respiratory changes in several body positions, which yielded different sensitivity: supine, 59%; standing, 13%; left lateral, 72%; right lateral, 19%; and sitting, 36%. Those patients who could not be identified in the supine position had PS in the left lateral position (16 patients) or sitting position (11 patients).

Of 73 patients with PS, 40 had a unipolar LV lead (Figure 3). In 10 patients who had a PS threshold ≥2 V, PS was solved at implantation by changing the target coronary vein in 4 and by pulling the LV lead tip to a less distal position in 6. LV lead dislodgement occurred in 2 of 6 latter patients; repositioning was required. Despite an appropriate PS-LV threshold difference at implantation, 14 of 40 (35%) complained of PS in the 1st-month follow-up: 9 could avoid PS by programming the LV output as threshold ≥1 V without compromising the efficacy of CRT, whereas 5 needed repeated surgery for lead repositioning (1 had LV lead dislodgement after the lead was pulled back to a mid-basal position at implantation), and 1 had the CRT turned off.

The remaining 33 patients had a bipolar LV lead, hence they had enhanced possibilities to manage PS (Figure 3): 17 of 23 patients whose device was capable of cathode programmability were able to avoid PS by a pacing configuration other than LV tip-ring, thereby increasing the difference between PS and LV threshold; nonetheless, 4 with a small PS-LV threshold difference (<2 V) despite cathode programmability had PS solved by automatic management of LV stimulation (Left Ventricular Capture Management, Medtronic Inc, Minneapolis, Minn). Patients without cathode programmability had a more difficult workup because of PS: 3 had the LV output programmed below a 100% safety margin, whereas 3 needed repeated surgery for lead repositioning (1 had LV lead dislodgement after the lead was pulled back to a mid-basal position at implantation), and 1 had the CRT turned off.

PS was successfully managed noninvasively at follow-up in 32 of 185 patients (17%) (16 had the LV output below a 100% safety margin), whereas 10 (5%) underwent repeated surgery and 4 (2%) had the CRT turned off because of PS. All PS-related lead repositioning or dislodgements caused by a mid-basal placement occurred in patients whose device had no cathode programmability.

During long-term follow-up, 13 patients who had been evaluated for management of PS after implantation sporadically reported PS-related symptoms (PS threshold was at least 2 V above LV output in 10 of 13 patients): 9 of 13 had no cathode programmability. At the last follow-up visit, none of them reported intolerable PS that required interventions, whereas 3 required a change of LV pacing configuration 3, 6, and 12 months, respectively, after implantation.

LV Stimulation Threshold and Phrenic Threshold
Because of the different possibilities for LV stimulation, the results are reported both at implantation and at 6-month

<table>
<thead>
<tr>
<th>Phrenic Stimulation</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, g/dL</td>
<td>0.97 (0.91–1.03)</td>
<td>0.37 (0.06–2.35)</td>
</tr>
<tr>
<td>Ischemic etiology</td>
<td>0.51 (0.27–0.96)</td>
<td>0.036 (0.99–1.01)</td>
</tr>
<tr>
<td>6-Min. walking test</td>
<td>1.00 (0.99–1.01)</td>
<td>0.91 (0.06–2.35)</td>
</tr>
<tr>
<td>GRS width at baseline, m</td>
<td>1.00 (0.99–1.01)</td>
<td>0.74 (0.99–1.01)</td>
</tr>
<tr>
<td>LVES volume at baseline, mL</td>
<td>0.99 (0.99–1.00)</td>
<td>0.24 (1.00–1.04)</td>
</tr>
<tr>
<td>LVEF at baseline, %</td>
<td>1.00 (0.95–1.04)</td>
<td>0.89 (0.60–5.83)</td>
</tr>
<tr>
<td>Site 1 mid-basal</td>
<td>1.87 (0.60–5.83)</td>
<td>0.28 (1.87–5.83)</td>
</tr>
<tr>
<td>Site 1 mid-apical</td>
<td>5.51 (1.84–16.49)</td>
<td>0.002 (5.51–16.49)</td>
</tr>
</tbody>
</table>

OR indicates odds ratio.
follow-up with regard to pacing configuration: extended bipolar, true bipolar, and “best performing,” as allowed by cathode programmability (defined as the configuration with the largest PS-LV threshold difference), to understand the specific benefit of the technological improvements that occurred through the past years.

Extended Bipolar (LV Tip to RV Coil/Ring) Configuration

By using the following data, we observed the impact of PS if this was the only available LV pacing configuration because it is the default setting in all CRT devices. In this configuration, PS was detected in 48 of 197 (24%) patients during the implantation procedure, whereas it was observed in 54 of 185 (29%) at follow-up. LV threshold was 1.0 V (range, 0.6 to 1.5) at 0.5 ms or 0.6 V (range, 0.4 to 1.0) at 1.5 ms in the overall population.

In patients who exhibited PS at implantation, LV threshold was 1.0 V (range, 0.6 to 1.4) at 0.5 ms or 0.6 V (range, 0.5 to 1.0) at 1.5 ms, whereas PS threshold was 3.8 V (range, 2.0 to 6.0) at 0.5 ms or 3.0 V (range, 1.6 to 5.0) at 1.5 ms.

At implantation, PS threshold was ≥6 V in 14 of 48 patients with PS (29%), between 3 and 6 V in 20 of 48 patients (42%), and ≤3 V in 14 of 48 patients (29%) at 0.5-ms pulse width, whereas it was ≥6 V in 8 of 48 patients (17%), between 3 and 6 V in 19 of 48 patients (39%), and ≤3 V in 21 of 48 patients (44%) at 1.5-ms pulse width.

Although PS was solved at implantation in 10 patients with a unipolar lead, PS was newly observed in 20 patients within the first month of follow-up. This phenomenon was never associated with LV lead dislodgement; indeed, PS occurred early after implantation (1 day to 3 weeks) in the left lateral or sitting position (not feasible at implantation). At follow-up, LV threshold was 1.0 V (range, 0.8 to 2.1) at 0.5 ms or 0.8 V (range, 0.5 to 1.5) at 1.5 ms in the overall population.

In 54 patients with detectable PS at follow-up, LV threshold was 1.0 V (range, 0.8 to 1.5) at 0.5 ms or 0.8 V (range, 0.5 to 1.3) at 1.5 ms, whereas PS threshold was 3.8 V (range, 2.5 to 5.5) at 0.5 ms or 3.0 V (range, 1.9 to 4.8) at 1.5 ms.

At follow-up, PS threshold was ≥6 V in 12 of 54 patients (22%), between 3 and 6 V in 18 of 54 patients (33%), and ≤3 V in 24 of 54 patients (45%) at 0.5-ms pulse width, whereas it was ≥6 V in 5 of 54 (9%), between 3 and 6 V in 22 of 54 (41%), and ≤3 V in 27 of 54 (50%) at 1.5-ms pulse width.

For the practical purpose of programming the LV output, the difference between PS and LV threshold and the number of patients with PS threshold ≥100% LV safety margins are reported in Table 4.

Of 54 patients who had detectable PS in this configuration, 11 (20%) could not be paced by a 100% safety margin at follow-up despite the most convenient output for LV stimulation (1.5-ms pulse width, Table 4).

True Bipolar (LV Tip to Ring) Configuration

This pacing configuration is available only with bipolar leads. The following data are reported in the LV tip-ring configuration as compared with the extended bipolar configuration to
understand the benefit of bipolar over unipolar leads. PS was detected in 33 of 119 (28%) patients at implantation. PS was solved by placing the lead in another side branch within the same coronary vein in 6 patients and changing the target vein in 4 patients. LV threshold was 1.0 V (range, 0.5 to 1.6) at 0.5 ms or 0.9 V (range, 0.5 to 1.4) at 1.5 ms, whereas PS threshold was 5.0 V (range, 2.4 to 6.0) at 0.5 ms or 3.8 V (range, 2.0 to 5.9) at 1.5 ms. At implantation, PS threshold was ≥6 V in 11 of 33 (33%) patients, between 3 and 6 V in 11 of 33 (33%) patients, and <3 V in 11 of 33 (33%) patients at 0.5-ms pulse width, whereas it was ≥6 V in 8 of 33 (24%) patients, between 3 and 6 V in 9 of 33 (27%) patients, and <3 V in 16 of 33 (49%) patients at 1.5-ms pulse width.

PS was detected in 27 of 108 (25%) patients at follow-up: 7 patients (6%) had newly developed PS at follow-up, 3 had the LV output programmed as threshold +1 V, 3 underwent repeated surgery to find a different LV lead placement, and 1 had the CRT turned off because of the absence of another suitable coronary vein. LV threshold at follow-up was 1.4 V (range, 0.8 to 1.8) at 0.5 ms or 1.0 V (range, 0.6 to 1.4) at 1.5 ms, whereas PS threshold was 3.5 V (range, 2.0 to 6.0) at 0.5 ms or 3.0 V (range, 2.0 to 5.1) at 1.5 ms.

At follow-up, PS threshold was ≥6 V in 4 of 27 patients (15%), between 3 and 6 V in 7 of 27 patients (26%), and ≤3 V in 16 of 27 patients (59%) at 0.5-ms pulse width, whereas it was ≥6 V in 2 of 27 (7%), between 3 and 6 V in 8 of 27 patients (30%), and ≤3 V in 17 of 27 patients (63%) at 1.5-ms pulse width.

The difference between PS and LV threshold and the number of patients with PS threshold ≤100% LV safety margins are reported in Table 5 in both pacing configurations: No consistent benefit was observed by pacing in the true bipolar compared with the extended bipolar configuration.

**Cathode Programmability**

Most recent CRT devices allow cathode programmability to minimize PS by programming either the distal or the proximal LV electrode as cathode. This feature allows pacing from the farthest electrode with respect to the phrenic nerve at no compromise with lead stability (the tip is wedged distal in the vein). CRT-D devices used in these patients allowed 3 (Medtronic: LV tip/LV ring to RV coil, LV tip to ring) to 4 (Boston: LV tip/LV ring to RV coil, LV tip to ring, LV ring to tip) pacing configurations. Boston CRT-P devices also allowed LV tip/LV ring to can pacing, for a total of 6 pacing configurations. Among our patients with a bipolar LV lead, 57 of 119 received CRT devices capable of cathode programmability, so that several pacing configurations could be tried to avoid PS. Both LV and PS threshold showed marked differences in the specific pacing configurations, owing to the anode size and to the cathode contact with LV epicardium. It is indeed conceivable that the cathode contact differs when pacing occurs at the proximal LV electrode or in a large coronary vein. Among these 57 patients, 23 (40%) had detectable PS. Seventeen of 23 had PS that prevented CRT delivery in the true bipolar configuration.

We compared the extended bipolar configuration with the true bipolar (LV tip-ring) and the best performing configuration, defined as the one with the largest PS-LV threshold difference (Table 6). According to this definition, the best performing configuration at implantation was LV ring to can (8% of patients), LV ring to RV coil (43% of patients), LV tip to RV coil (36% of patients), and LV tip to ring (13% of patients). During follow-up it was LV tip to can (5% of patients), LV ring to RV coil (40% of patients), LV tip to RV coil (40% of patients), and LV tip to ring (15% of patients). In the best performing configuration, PS was completely

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**Table 4. Stimulation in Patients With a Bipolar LV Lead Who Had Detectable PS**

<table>
<thead>
<tr>
<th>Pacing Configuration</th>
<th>Implantation (n=48)</th>
<th>Follow-Up (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5-ms Pulse Width</td>
<td>1.5-ms Pulse Width</td>
</tr>
<tr>
<td>PS-LV threshold, V</td>
<td>2.5 (1.0–4.4)</td>
<td>2.3 (0.8–4.0)</td>
</tr>
<tr>
<td>PS ≤100% SM (patients)</td>
<td>14 (29%)</td>
<td>10 (21%)</td>
</tr>
</tbody>
</table>

SM indicates safety margin.

*Wilcoxon signed rank test.
†McNemar χ² test.

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**Table 5. Stimulation in Patients With a Bipolar LV Lead Who Had Detectable PS**

<table>
<thead>
<tr>
<th>Pacing Configuration</th>
<th>Implantation (n=33)</th>
<th>Follow-Up (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5-ms Pulse Width</td>
<td>1.5-ms Pulse Width</td>
</tr>
<tr>
<td>LV tip to RV coil/ring</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS-LV threshold, V</td>
<td>2.5 (0.9–4.6)</td>
<td>2.5 (0.9–4.5)</td>
</tr>
<tr>
<td>PS ≤100% SM (patients)</td>
<td>9 (27%)</td>
<td>6 (18%)</td>
</tr>
<tr>
<td>LV tip to ring</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS-LV threshold, V</td>
<td>2.7 (1.2–4.4)</td>
<td>3.1 (1.1–4.3)</td>
</tr>
<tr>
<td>PS ≤100% SM (patients)</td>
<td>7 (21%)</td>
<td>6 (18%)</td>
</tr>
</tbody>
</table>

SM indicates safety margin.

*Wilcoxon signed rank test.
†McNemar χ² test.
abolished at maximum device output in 6 of 23 patients, and the PS-LV threshold difference was significantly increased in all the other patients (Table 6). The CRT was never turned off, nor was the target pacing site changed because of PS because of the enhanced possibility of overcoming this challenge. No reoperation occurred at follow-up.

Discussion

In this prospective evaluation, we observed that PS is a very important clinical issue because it occurs most frequently at the same pacing sites where reverse remodeling occurs after CRT delivery (Figure 2 and Tables 2 and 3). This requires that CRT devices are equipped with technological features to avoid PS as much as possible. During implantation, PS compelled us to try several pacing sites in the target area when changing the pacing vector was not feasible and to change the target area in 8 patients, with a possible negative outcome on reverse remodeling. This aspect is of major importance: D’Ivernois et al12 recently reported that 30% of LV leads are placed outside the target vein deemed optimal for CRT due to technical difficulties, but no mention to PS was made. At implantation, we managed to solve PS by changing lead placement in 10 patients with unipolar leads and in 10 with bipolar leads who had no cathode programmability. Despite the laboring process to avoid PS at implantation, during follow-up 14 patients with unipolar leads and 27 patients with bipolar leads (22% of the overall population) encountered significant problems due to PS that were resolved either noninvasively in 33 patients (18%) or invasively in 10 patients (5%). Three lead dislodgments occurred because of a proximal lead placement to avoid PS; the CRT was turned off in 2% of patients because of PS.

PS Prevalence in CRT Patients

The prevalence of PS is extremely variable in CRT studies, depending on whether it was extensively investigated and actively avoided at implantation or not, as reported by Alonso et al.13 In their study, the LV lead placement was systematically changed whenever PS was detected starting from 10 V13; hence, PS prevalence was 3% at follow up. In multicenter studies, PS prevalence ranged from 2% in the Knight et al14 report to 10% in the report by Ellery et al.15 In our population, it was detected in 37% of patients (implantation and follow-up), but it was clinically relevant only in 22% (41 of 185) of patients. This figure is similar to the report by Gurewitz et al.16 who observed clinically relevant PS in 19% (17 of 92) of their patients. We believe this is related to the similar rate of lateral/posterolateral LV lead placement (86%) achieved in both studies: As we observed, the proximity to the left phrenic nerve course6 is a reasonable explanation for the occurrence of PS (Table 3) because it passes alongside the obtuse margin of the heart in 79% of cases.9 Observations reporting a lower PS prevalence may not have achieved a similar rate of placement in these target sites for CRT.12

Consistent with this interpretation, both in the Knight et al14 and Ellery et al15 reports, PS occurred in patients with a posterior LV lead placement. In the multicenter EASYTRACK lead investigation,17 a posterior LV lead placement was avoided; hence, PS occurrence was 2%. It appears that PS has been largely underdetected or underreported in previous observations and that its prevalence among studies depends on the target site for CRT aimed at and on the efforts made to detect and avoid PS at implantation.

Response to CRT and PS Management

We observed that the improvement of LV volume and function was closely related to pacing site (Table 2 and Figure 2), according to pioneering experience in CRT and most recent studies.3-7 Ypenburg et al16 observed that the most delayed LV site may not be lateral or posterior in up to 30% of patients; this could explain either the lack of reverse remodeling at these pacing sites or the reverse remodeling occurring at anterolateral sites. Our findings are consistent with their observation because only 81% of patients in site 2 were CRT responders (Figure 3). Thus, the lack of reverse remodeling may be only partly related to the PS phenomenon in the event
the target pacing site is not attained.\textsuperscript{5,6,12} In our experience, an increased risk of loss of CRT/lead dislodgement occurred when the LV lead was replaced to a suboptimal site because of PS: Changing the target site whenever PS is detected at implantation\textsuperscript{13} might prevent achieving the clinical benefit of CRT, whereas moving the lead to a less distal site within the target vein may pose a stability issue with an increased postoperative dislodgement risk.\textsuperscript{14} Gurewitz et al\textsuperscript{16} reported a significantly higher success rate to target posterolateral pacing sites (95\% of patients) when cathode programmability was made available, compared with former device technology (77\% of patients). Moreover, cathode programmability enhances the possibility to achieve a stable lead placement in the target coronary vein while avoiding PS by the appropriate pacing configuration. Thus, selecting a CRT device featuring cathode programmability should be the first step in implantation to minimize the risk of PS, whereas lead repositioning should be performed as the last resort.\textsuperscript{18} We observed that PS evaluation at implantation is not 100\% predictive, owing to the body position (detected only after implantation in 27 patients), a fact that reinforces the need for cathode programmability. Automatic verification of capture helped to manage 4 patients who had a difference in PS-LV threshold of $\leq 2$ V and may be considered as complementary to cathode programmability in this instance. Moreover, the difference in PS-LV threshold shows a trend toward a decrease at follow-up (1.5 V on average) in all the pacing configurations (Table 6), a fact that makes automatic verification of stimulation even more attractive in selected patients who have a PS-LV difference $\leq 3.5$ V. Although LV threshold shows little variability in the majority of patients, fluctuations $\geq 1.5$ V were reported in 8\% of patients.\textsuperscript{19} Such an event could threaten PS in those patients without cathode programmability, who have a median PS-LV difference of approximately 1.5 V (Tables 5 and 6). Programming the LV pulse width at a greater duration lowered both the LV and the PS threshold voltage, so that no consistent benefit over a 0.5-ms programming (patients who could be paced by a 100\% safety margin) was observed (Table 6).

The use of a bipolar LV lead without cathode programmability does not improve the management of PS, as 22\% (26 of 119) of patients with a bipolar lead have clinically relevant PS compared with 19\% (15 of 78) with a unipolar lead; a 100\% safety margin could be programmed in 25\% to 30\% of these patients (Table 5). Patients with a unipolar lead had the highest rate of detectable PS (40 of 78 patients), repeated surgery (7 of 78), and CRT turnoff (3 of 78) because of PS.

**Practical Implications**

The goal of CRT is the improvement of symptoms and of LV function. PS is most likely to occur at the most appropriate sites for CRT and must be managed in 22\% of patients in the range 0.5 to 6 V, even when actively dealt with at implantation. Our observations suggest placing the LV lead in the optimal stable site for CRT delivery despite PS, because reverse remodeling may be achieved in up to 81\% of patients. The use of a bipolar lead and of a device capable of cathode programmability are mandatory to increase the PS-LV threshold difference so that accommodation of LV threshold fluctuations can be achieved without PS. Automatic management of the LV output also may be useful in a minority of patients. Placing the LV lead at proximal or unstable sites should be avoided because of the unacceptable risk of dislodgement. It is speculative that automatic PS detection and switching to an alternative pacing configuration could be a useful built-in feature to manage those patients with a small PS-LV threshold difference.

**Disclosures**

None.

**References**


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CLINICAL PERSPECTIVE

The prevalence of phrenic stimulation in patients receiving cardiac resynchronization therapy (CRT) is extremely variable in published reports, depending on whether it was extensively investigated and actively avoided at implantation or not. It also appears that it has been largely underdetected or underreported and that its prevalence depends on the target site for CRT and on the efforts made to detect and avoid phrenic stimulation (PS) at implantation. We found that PS is clinically relevant in 22% of CRT patients despite efforts that were made at implantation to avoid it and that it occurs at the same pacing sites where the likelihood of achieving a favorable CRT response (left ventricular [LV] reverse remodeling) is highest. The management of patients with PS may involve lead dislodgement when the LV lead is placed at a proximal LV pacing site; reoperation to change the pacing site; and/or LV pacing by a small safety margin. We observed that the use of a bipolar LV lead and of a CRT device with cathode programmability allowed management of PS in all patients by increasing the difference between the threshold for PS and the ventricular pacing threshold. LV stimulation can thus be accomplished without changing the target pacing site for CRT or increasing the risk of adverse events at follow-up.
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