Phrenic stimulation: a challenge for cardiac resynchronization therapy.

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Abstract

**Background.** Phrenic stimulation (PS) may hinder left ventricular (LV) pacing. We prospectively observed its prevalence in consecutive CRT patients.

**Methods and Results.** In the years 2003-2006, 197 patients received a CRT device. PS and LV threshold measurements were carried out either at implantation and at 6-months 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. 10 patients (5%) underwent repeated surgery, and 4 (2%) had CRT turned off, because of PS. At follow-up, we could manage PS non-invasively 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 complimentary in patients with a small PS-LV threshold difference.

**Key Words:** CRT, Phrenic stimulation, reverse remodeling.
Cardiac resynchronization therapy (CRT) is an important therapeutic option in heart failure patients with systolic left ventricular (LV) dysfunction and evidence of electrical/mechanical dyssynchrony. (1,2) The clinical benefit is strictly dependent on continuous LV stimulation at sites with delayed mechanical activity. (3-6) Chung et al. (7) have recently reported that 45% of patients are non-responders 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 or of 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 also prevent to reach the optimal pacing sites for CRT. No study has prospectively investigated the prevalence of the PS phenomenon either 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 phrenic stimulation and of functional response to CRT with respect to the main patients’ characteristics and LV lead placement sites.

METHODS
In our early experience with biventricular stimulation (1999-2002) 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 a 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; 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 (PSA) output, 10V@1.5ms: in the event of PS occurrence, its threshold is measured in all the possible pacing configurations, and compared to left ventricular 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 0.5ms and 1.5 ms pulse width following a stepping down protocol starting from 10V. Pulse voltage was decreased in 1V steps until PS disappearance: stepping down was then resumed in 0.1V 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” 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 to 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 experienced PS during follow-up, they were evaluated for symptoms assessment and problem solving.

At six months 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. Differently compared to implantation, PS threshold was evaluated during respiratory changes in several body positions: supine, left lateral, right lateral, sitting, 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 NYHA class, 6 minutes walking test either 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, where the hemodynamic improvement has been reported to be maximum (3,4). LV lead placement was determined using biplane fluoroscopy classification (Fig.1) in the 45° left anterior oblique view (LAO) and in the 35° right anterior oblique view (RAO). In LAO, 2 sites were identified by vertical lines at hours 12-6 and 2-5 (Fig.1) to assess whether the lead placement was anterior/antrolateral (site 1), or lateral/posterolateral (site 2). In RAO view the LV pacing site is assessed 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 following previous observations that clinical response to CRT is maximal when LV lead placement around the 3 o’clock site in LAO view is achieved.(8)

Differently from Albertsen et al (8), we divided the LV in 2 sites according to the variability of the left phrenic nerve course, as observed by Quintana et al. (9), that 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-months follow up: responders had to have a LVESV reduction ≥15% and an absolute LVEF increase ≥ 5%.

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

LV volumes and LVEF were calculated according to the American Society of Echocardiography guidelines.(10) Intra- and inter-observer variability for assessment of LVESV and LVEF using Bland & Altman analysis expressed as mean difference of the two readings with 95% confidence interval (CI) and the limits of agreements with their 95% CI, were previously reported.(11)
Statistical analysis

Continuous data are reported as median and interquartile range (25th-75th percentile) and categorical variables are reported as numbers and percentages. A uni- and multivariable logistic regression analysis using a backward selection procedure, including hemoglobin level at baseline, ischemic etiology, 6 minutes walking test at baseline, QRS width at baseline, LVESV and LVEF at baseline, and LV lead site, was performed to identify predictors of response to CRT. A uni- and multivariable logistic regression analysis using a backward selection procedure, including ischemic etiology, QRS width at baseline, LVESV and LVEF at baseline, and LV lead site, was performed to identify predictors of PS. Data within patient groups were compared by use of Wilcoxon signed rank test or McNemar chi-squared test as appropriate (reported in text or tables). All statistical tests were 2-sided, and a p value <0.05 was considered significant. A statistical software program SPSS 14.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis.

Results

One hundred and ninety-seven consecutive patients undergoing a CRT device implantation from January 2003 to January 2007 were enrolled into the study. 189/197 received a CRT-D device, whereas 8/197 received a CRT-P device. Ischemic etiology, defined as a history of myocardial infarction with documented coronary artery disease, was observed in 73/197 patients; non-ischemic dilated cardiomyopathy was observed in 124/197. Twelve of 197 patients enrolled did not attend the 6-months follow up: their data are available at implantation only. The study population characteristics are reported in Table 1. Over a 24 (12-37) months follow up, 16 patients died and 4 underwent heart transplantation.

The LV lead was chosen according to the size of the target coronary vein and to the implanting physician 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 RV coil/ring), whereas only 119/197 (60%) could be paced in the “true bipolar” (LV tip to ring) configuration.

51/112 patients with a CRT-D and 6/8 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 54/185 (29%) patients.

**Response to CRT**

Overall, there were 128/185 (69%) CRT responders as assessed by 6-months echocardiography, and 133/185 (72%) improved at least 1 NYHA class. 115/128 (90%) echocardiographic responders improved at least 1 NYHA class, whereas only 18/57 (32%) non-responders at Echocardiography improved 1 NYHA class (Chi-squared, p <0.001). The LV lead placement was lateral or posterolateral according to LAO view in 170/197 (86%) patients, and mid-apical according to RAO view in 129/197 (65%) patients (Figure 1, 2).

CRT-responders at echocardiography were 119/160 (74%) among patients whose LV lead was placed at site 2 vs. 9/25 (36%) at site 1 in LAO view (Chi squared, p < 0.001). CRT-responders were 92/120 (77%) when the LV lead was mid-apical vs. 36/65 (55%) mid-basal in RAO view (Chi squared, p = 0.003). Combining LV lead classification in LAO and RAO view (Figure 2) response to CRT at echocardiography was: 2/9 (22%) in site 1 mid-apical, 7/16 (44%) in site 1 mid-basal, 29/49 (59%) in site 2 mid-basal, and 90/111 (81%) in site 2 mid-apical (Chi squared, p <0.001). LV lead placement at site 2 mid-apical was the strongest predictor of 6-months 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 mid-apical position was the strongest predictor of PS at implant or in the follow-up (Table 3).

PS at follow-up was investigated during respiratory changes in several body positions, that yielded different sensitivity: supine 59%, standing 13%, left lateral 72%, right lateral 19%, sitting 36%. Those patients who could not be identified in supine had PS in left lateral position (16 patients) or sitting (11 patients).

Over 73 patients with PS, 40 had a unipolar LV lead (Fig.3). In 10 patients who had a PS threshold ≤2V, 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 2/6 latter patients: repositioning was required. Despite an appropriate PS-LV threshold difference at implantation, 14/40 (35%) complained of PS in the 1st month follow-up: 9 could avoid PS by programming the LV output as threshold +1V without compromising the efficacy of CRT, whereas 5 needed repeated surgery for lead repositioning. Eventually, 3 had LV stimulation turned off because of impossibility to avoid PS. The other 15 patients had the LV output programmed at least 1.5V lower than PS threshold.

The remaining 33 patients had a bipolar LV lead, hence they had enhanced possibilities to manage PS (Fig.3): 17/23 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 (<2V) despite cathode programmability had PS solved by automatic management of LV stimulation (Left Ventricular Capture Management, LVCM, Medtronic Inc., Minneapolis). Patients without cathode programmability had a more difficult work-up 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 pulling back the lead to a mid-basal position at implantation), and 1 had CRT turned off.
Overall, 32/185 (17%) had PS managed successfully non-invasively at follow-up (16 had the LV output below a 100% safety margin), whereas 10 (5%) underwent repeated surgery, and 4 (2%) had CRT turned off because of PS. All PS-related lead repositioning or dislodgements due to a mid-basal placement occurred in patients whose device had no cathode programmability.

During long term follow-up 13 patients who had been evaluated to manage PS after implantation sporadically reported PS-related symptoms (PS threshold was at least 2V above LV output in 10/13 patients): 9/13 had no cathode programmability.

At last follow-up visit none of them reported intolerable PS that required interventions, whereas 3 required a change of LV pacing configuration respectively 3, 6, and 12 months following implantation.

**LV stimulation threshold and phrenic threshold**

Owing to the different possibilities for LV stimulation, the results are reported both at implantation and at 6 months 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 technologic improvements that occurred through the past years.

*“Extended bipolar” (LV tip to RV coil/ring) configuration.*

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

In patients who exhibited PS at implantation LV threshold was 1.0 (0.6-1.4) V@0.5ms, or 0.6 (0.5-1.0) V@1.5ms, whereas PS threshold was 3.8 (2.0-6.0) V@0.5ms or 3.0 (1.6-5.0) V@1.5ms.
At implantation, PS threshold was ≥6V in 14/48 pts with PS (29%), between 3 and 6 V in 20/48 pts (42%), and ≤3V in 14/48 pts (29%) at 0.5 ms pulse width, whereas it was ≥6V in 8/48 pts (17%), between 3 and 6 V in 19/48 pts (39%), and ≤3V in 21/48 pts (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 follow-up. This phenomenon was never associated to LV lead dislodgement; indeed PS occurred early after implantation (1 day to 3 weeks) in left lateral or sitting position (not feasible at implantation). At follow-up LV threshold was 1.0 (0.8-2.1) V@0.5ms, or 0.8 (0.5-1.5) V@1.5ms in the overall population.

In 54 patients with detectable PS at follow-up, LV threshold was 1.0 (0.8-1.5) V@0.5ms, or 0.8 (0.5-1.3) V@1.5ms, whereas PS threshold was 3.8 (2.5-5.5) V@0.5ms, or 3.0 (1.9-4.8) V@1.5ms. At follow-up, PS threshold was ≥6V in 12/54 patients (22%), between 3 and 6 V in 18/54 patients (33%), and ≤3V in 24/54 patients (45%) at 0.5 ms pulse width, whereas it was ≥6V in 5/54 (9%), between 3 and 6 V in 22/54 (41%), and ≤3V in 27/54 (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 margin are reported in Table 4.

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

“True Bipolar” (LV tip to ring) configuration

This pacing configuration is available only with bipolar leads. Following data are reported in the LV tip-ring configuration as compared to the “extended bipolar” configuration to understand the benefit of bipolar over unipolar leads. PS was detected in 33/119 (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 (0.5-1.6) V@0.5ms, or 0.9 (0.5-1.4) V@1.5ms, whereas PS threshold was 5.0 (2.4-6.0) V@0.5ms, or 3.8 (2.0-5.9) V@1.5ms. At
implantation, PS threshold was ≥ 6V in 11/33 (33%) of patients, between 3 and 6 V in 11/33 (33%) of patients, and < 3V in 11/33 (33%) of patients at 0.5 ms pulse width, whereas it was ≥ 6V in 8/33 (24%) of patients, between 3 and 6 V in 9/33 (27%) of patients, and < 3V in 16/33 (49%) of patients at 1.5 ms pulse width.

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

At follow-up, PS threshold was ≥6V in 4/27 pts (15%), between 3 and 6 V in 7/27 pts (26%), and ≤ 3V in 16/27 pts (59%) at 0.5 ms pulse width, whereas it was ≥ 6V in 2/27 (7%), between 3 and 6 V in 8/27 pts (30%), and ≤ 3V in 17/27 pts (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 margin are reported in Table 5 in both pacing configurations: no consistent benefit is observed by pacing in the “true Bipolar” compared to the “extended bipolar” configuration.

**“Cathode Programmability”**

Most recent CRT devices allow cathode programmability to minimise PS by programming either the distal or the proximal LV electrode as cathode. This feature allows to pace 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 employed 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, 57/119 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. 17/23 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” pacing configuration at implant was: LV ring to Can (8% patients), LV ring to RV coil (43% patients), LV tip to RV coil (36% patients), LV tip to ring (13% patients). During follow-up it was: LV tip to can (5% patients), LV ring to RV coil (40% patients), LV tip to RV coil (40% patients), LV tip to ring (15% patients). In the best performing configuration PS was completely abolished at maximum device output in 6/23 patients, and the PS-LV threshold difference was significantly increased in all the other patients (Table 6).

CRT was never turned off, nor was the target pacing site changed because of PS, owing to the enhanced possibility to overcome this challenge. No reoperation occurred at follow up.

DISCUSSION

In this prospective evaluation we observed that PS is a very important clinical issue, as it occurs most frequently at the same pacing sites where reverse remodeling occurs following CRT delivery (fig.2, tab. 2-3). 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 also 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 al. (12) 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 non-invasively in 33 patients (18%) or invasively in 10 patients (5%). Three lead dislodgments occurred because of a proximal lead placement to avoid PS; 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 10V (13), hence PS prevalence was 3% at follow up. In multicenter studies, PS prevalence ranged from 2% in Knight’s report (14) to 10% in Ellery’s (15). In our population, it was detected in 37% of patients (implantation and follow-up), but it was clinically relevant only in 22% (41/185) of patients. This figure is similar to the report by Gurewitz et al. (16) who observed clinically relevant PS in 19% (17/92) 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 course (9) is a reasonable explanation for the occurrence of PS (table 3), as 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) Consistently with this interpretation, both in Knight (14) and Ellery (15) 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 under-detected or underreported in previous observations, and that its prevalence among studies depends on the target site for CRT which is 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 left ventricular volume and function was closely related to pacing site (Tab.2, Fig.2), according to pioneering experience in CRT and to most recent studies (3-7). Ypenburg et al (5) 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, as only 81% of patients in site 2 were CRT responders (fig.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 (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 (13) might prevent to achieve 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 (14). Gurewitz et al (16) reported a significantly higher success rate to target posterolateral pacing sites (95% patients) when cathode programmability was made available, compared to former device technology (77% 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 at implantation to minimize the risk of PS, whereas lead repositioning should be performed as the last resort (18). As observed in our experience, 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 PS-LV threshold ≤2V, and may be considered as complimentary to cathode programmability in this instance. Moreover, the difference PS-LV threshold shows a trend toward a decrease at follow-up (1.5V on average) in all the pacing configurations (Tab. 6), a fact that makes automatic verification of stimulation even more attractive in selected patients who have a PS-LV difference ≤3.5V. Indeed, despite LV threshold shows little variability in the majority of patients, fluctuations ≥1.5V were reported in 8% of patients (19). Such an event could threaten PS in those patients without cathode programmability, who have a median PS-LV difference about 1.5V (table 5, table 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 0.5ms programming (patients who could be paced by a 100% safety margin) was observed (Tab. 6).

The use of a bipolar LV lead without cathode programmability does not improve the management of PS, as 22% (26/119) of patients with a bipolar lead have clinically relevant PS compared to 19% (15/78) with a unipolar lead; a 100% safety margin cannot be programmed in 25-30% of these patients (Tab 5). Patients with a unipolar lead had the highest rate of detectable PS (40/78 patients), repeated surgery (7/78), and CRT turnoff (3/78) 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 needs to be managed in 22% of patients in the range 0.5V-6V, despite it is actively dealt with at implantation. Our observations suggest to place 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 attaining PS. Automatic management of the LV output may also be useful in a minority of patients. Placing the LV lead at proximal or unstable sites should be avoided, as it carries an 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.

Conflict of Interest: none

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Table 1. Patients characteristics at implantation.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tr>
<td>Number of patients</td>
<td>197</td>
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<tr>
<td>Male</td>
<td>107 (54%)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>66 (57-72)</td>
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<td>Ischemic etiology</td>
<td>73 (37%)</td>
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<td>Hypertension</td>
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<td>Hypercholesterolemia</td>
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<td>Diabetes</td>
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<td>Hemoglobin (g/dl)</td>
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<td>GFR&lt;30 ml/min/1.73m²</td>
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<td>LVES Volume (ml)</td>
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<td>LVEF (%)</td>
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<td>CRT-D</td>
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<td>Severe Mitral Regurgitation</td>
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</tbody>
</table>

EF = Ejection Fraction; ED = End Diastolic; ES = End Systolic; GVF = Glomerular Filtration Rate; LV = Left Ventricular; PS = Phrenic Stimulation; SM = Safety Margin; 6MWT = Six Minute Walking Test.
Table 2. Predictors of Echocardiographic response to CRT

<table>
<thead>
<tr>
<th>Response to CRT</th>
<th>Univariate analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>0.97</td>
<td>0.91-1.03</td>
</tr>
<tr>
<td>Ischemic etiology</td>
<td>0.51</td>
<td>0.27-0.96</td>
</tr>
<tr>
<td>6 minutes walking test at baseline (m)</td>
<td>1.00</td>
<td>0.99-1.01</td>
</tr>
<tr>
<td>QRS width at baseline (ms)</td>
<td>1.00</td>
<td>0.99-1.01</td>
</tr>
<tr>
<td>LVES volume at baseline (ml)</td>
<td>0.99</td>
<td>0.99-1.00</td>
</tr>
<tr>
<td>LVEF at baseline (%)</td>
<td>1.00</td>
<td>0.95-1.04</td>
</tr>
<tr>
<td>Site 1 mid-basal</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Site 1 mid-apical</td>
<td>0.37</td>
<td>0.06-2.35</td>
</tr>
<tr>
<td>Site 2 mid-basal</td>
<td>1.87</td>
<td>0.60-5.83</td>
</tr>
<tr>
<td>Site 2 mid-apical</td>
<td>5.51</td>
<td>1.84-16.49</td>
</tr>
</tbody>
</table>

CI = confidence interval; CRT = cardiac resynchronization therapy; EF= Ejection Fraction; ES= End Systolic; LV = left ventricular; OR = odd ratio.
Table 3. Predictors of Phrenic stimulation at lateral/posterolateral sites.

<table>
<thead>
<tr>
<th>Phrenic stimulation</th>
<th>Univariate analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Ischemic etiology</td>
<td>1.01</td>
<td>0.55-1.84</td>
</tr>
<tr>
<td>QRS width at baseline (ms)</td>
<td>1.00</td>
<td>0.98-1.01</td>
</tr>
<tr>
<td>LVES volume at baseline (ml)</td>
<td>1.00</td>
<td>0.99-1.01</td>
</tr>
<tr>
<td>LVEF at baseline (%)</td>
<td>0.97</td>
<td>0.93-1.02</td>
</tr>
<tr>
<td>Mid-apical LV lead placement</td>
<td>4.23</td>
<td>2.03-8.1</td>
</tr>
</tbody>
</table>

CI = confidence interval; EF = Ejection Fraction; ES = End Systolic; LV = left ventricular; OR = odd ratio.
Table 4. Stimulation in the LV tip to RV ring/coil configuration in patients with detectable PS.

<table>
<thead>
<tr>
<th></th>
<th>Implant (n=48)</th>
<th>Follow-up (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5ms Pulse Width</td>
<td>1.5ms 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>

LV = Left Ventricular; ES = End Systolic; ED = End Diastolic; EF = Ejection Fraction; PS = Phrenic Stimulation; SM = Safety Margin

*: Wilcoxon signed rank test
†: McNemar chi-squared test
Table 5. Stimulation in patients with a bipolar LV lead who had detectable PS.

<table>
<thead>
<tr>
<th>Pacing configuration</th>
<th>Implant (n=33)</th>
<th>Follow-up (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5ms Pulse Width</td>
<td>1.5ms Pulse Width</td>
</tr>
<tr>
<td>LV tip to RV coil/ring</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>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>

LV = Left Ventricular; PS = Phrenic Stimulation; SM = Safety Margin; RV = Right Ventricular
*: Wilcoxon signed rank test
†: McNemar chi-squared test

LV = Left Ventricular; PS = Phrenic Stimulation; SM = Safety Margin; RV = Right Ventricular
*: Wilcoxon signed rank test
†: McNemar chi-squared test
Table 6. Stimulation in patients with a bipolar LV lead and a CRT device capable of cathode programmability who had detectable PS.

<table>
<thead>
<tr>
<th>Pacing configuration</th>
<th>Implant (n=23)</th>
<th>Follow-up (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5 ms Pulse Width</td>
<td>1.5 ms Pulse Width</td>
</tr>
<tr>
<td><strong>LV tip-RV coil/ring</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS – LV threshold (V)</td>
<td>2.4 (0.6-4.7)*</td>
<td>2.2 (0.6-4.7)*</td>
</tr>
<tr>
<td>LV tip to ring</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS – LV threshold (V)</td>
<td>2.7 (1.4-4.3)*</td>
<td>3.1 (1.8-4.2)*</td>
</tr>
<tr>
<td>Best Performing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS – LV threshold (V)</td>
<td>5.0 (2.9-8.6)</td>
<td>5.0 (3.4-7.3)</td>
</tr>
</tbody>
</table>
| LV = left ventricular; PS = phrenic stimulation; SM = safety margin; RV = right ventricular; *: p <0.01 vs. Best Performing at implant (Wilcoxon signed rank test); †: p <0.05 vs. Best Performing at follow-up (Wilcoxon signed rank test); ‡: p = 0.031 vs. Best performing at implant (McNemar chi-squared test); ¶: p <0.001 vs. Best performing at implant (McNemar chi-squared test)
Figure Legends

Fig. 1. Lead Placement classification scheme: 35° Right Anterior Oblique (RAO) and 45° Left Anterior Oblique (LAO) views displaying the LV lead placement. In RAO the placement could be Mid-Apical (A) or Mid-Basal (B). In LAO the placement could be anterior/anterolateral (site 1) or lateral/posterolateral (site 2).

Fig 2. Number of patients and number of CRT responders at each LV lead implantation site (see Fig 1 for sites).

Fig 3. Actions taken to avoid PS in the 73 patients respect to lead type (Unipolar/Bipolar) and device capability (Cathode programmability / No cathode programmability), and clinical outcome.
PS at implantation 73 pts

Unipolar LV lead 40 pts

Bipolar LV lead 33 pts

No cathode programmability 10 pts

Cathode programmability 23 pts

LV tip/ring to can 2 pts
LV ring to RV 9 pts
LV tip to RV 8 pts
LV tip to ring 4 pts

LV site change during implantation 10 pts

No site change during implantation 30 pts

2 pts 5 pts 3 pts

LV output <100% SM TOTAL = 14 patients

CRT turned off TOTAL = 4 pts

Reoperation for LV lead replacement during follow-up TOTAL = 10 pts
Phrenic Stimulation: A Challenge for Cardiac Resynchronization Therapy
Mauro Biffi, Carlotta Moschini, Matteo Bertini, Davide Saporito, Matteo Ziacchi, Igor Diemberger, Cinzia Valzania, Giulia Domenichini, Elena Cervi, Cristian Martignani, Diego Sangiorgi, Angelo Branzi and Giuseppe Boriani

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