Influence of pacing configurations, body mass index, and position of coronary sinus lead on frequency of phrenic nerve stimulation and pacing thresholds under cardiac resynchronization therapy

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Aims
Phrenic nerve stimulation (PNS) can affect, and in some cases considerably limit, the long-term success of cardiac resynchronization therapy (CRT) therapy. To address this common problem, the manufacturers of CRT devices offer a range of configurations aimed at preventing high left ventricular pacing thresholds (LVPTs) and PNS.

Methods and results
In 101 consecutive patients who had undergone implantation of a CRT system, we investigated prospectively the parameters LVPT and PNS threshold in relation to coronary sinus (CS) lead position, CS lead configuration, body position, and body mass index. With the configurations LV tip to right ventricular (RV) coil, LV tip to LV ring, and LV ring to RV coil, the LVPT and PNS threshold of patients with LV pacing were measured in the supine and left lateral body positions. The overall mean LVPT was lowest in LV tip to RV coil and highest in LV tip to ring configurations. The lowest PNS thresholds were measured in LV tip to RV coil and the highest in LV tip to ring configurations. The LVPT was not affected by body position and was stable in the standard supine and left lateral positions.

Conclusion
Flexible LV pacing configurations are a useful feature of CRT systems for preventing PNS. The optimal LV pacing configuration should be determined on the basis of individual patient testing.

Keywords
Cardiac resynchronization therapy • Congestive heart failure • Left ventricular pacing configurations • Phrenic nerve stimulation • Pacing threshold

Introduction
Phrenic nerve stimulation (PNS) is often problematic in the implementation of cardiac resynchronization therapy (CRT). The long-term benefit of CRT depends on left ventricular (LV) and biventricular pacing. The phrenic nerve runs on either side of the heart between the pericardium and parietal pleura (Figure 1). This thin relation between the left phrenic nerve and the posterior-lateral coronary sinus (CS) veins explains the frequent clinical incidence of PNS and resulting diaphragm irritation. Phrenic nerve stimulation can considerably limit or endanger the success of CRT therapy in the long term. In the Care-HF study, no statement on the frequency of PNS was made.¹ Several small studies have shown that PNS after implantation occurred in 4.0–9.2% of patients undergoing CRT, although a clear cause was not identified.² – ⁴ Moreover, there is little existing data on PNS associated with the left side position during chronic CRT therapy. In clinical practice a low stimulation output of the LV lead is often chosen to avoid PNS. Furthermore, the stimulation amplitude with a relatively long impulse duration of 1.0 ms for reduced amplitudes and a
low LV pacing threshold (LVPT) safety margin must be programmed regularly to avoid PNS. For that reason, we performed in this study all measurements with an impulse duration of 1.0 ms to focus to the PNS difficulty instead 0.5 ms as is generally used for pacing.

In this context, poor investigations of transitory exit blocks during chronic LV pacing exist. Only one small study has their influence on the long-term effectiveness of CRT examined.5 Many patients do not tolerate frequent PNS when lying on their left side. The decrease in safety margin leads to an increase in the frequency of PNS. To overcome this limitation, the CRT device manufacturers offer a number of different pacing configurations for CS leads. We investigated the influence of different pacing configurations on thresholds and PNS in relation to CS lead position and body mass index (BMI) in patients who had received a CRT device.

Methods

Study population

This prospective, non-randomized single-centre study enrolled patients with mild or severe symptomatic chronic heart failure (NYHA class II–IV), an ejection fraction of <35%, and a wide QRS complex (>130 ms). One hundred and one patients were successfully implanted with biventricular implantable cardioverter-defibrillator (ICD) or pacemaker devices. Before device implantation, patients underwent baseline evaluation, including demographics and medical history data collection, clinical examination, 12-lead electrocardiogram (ECG), estimation of NYHA functional class, and echocardiography recording. Patient demographics are shown in Table 1.

Implantation procedure

The devices and the pacing leads were implanted using standard techniques. In 34 of 101 patients a Medtronic InSync series ICD system was implanted (InSync Maximo®, Sentry®, Marquis®, or Concerto®). In 31 of 101 patients, a Boston Scientific ICD system (Contac Renewal® series) and in 24 of 101 patients a St Jude Medical Epic or Atlas HF® ICD system was implanted. Eleven of 101 patients received a CRT-P system (St Jude Medical; Frontier II®) and one patient received a Lumax® 340 ICD system produced by Biotronik. In contrast to this distribution, 59 patients received St Jude Medical Quicksite® LV lead series, 24 patients Boston Scientific Guidant Easytrak3/Acuaty® series, and 18 patients received Medtronic Attain® series.

According to the haemodynamic measurements by Butter et al.,7 and consistently with recent observations by Biffi et al.,8 LV lead placement in a posterior or lateral CS vein was planned before implantation. For CS lead placement classification in mid-basal and mid-apical position, the distance (L) from the atrioventricular line to the LV apex in left anterior oblique (LAO) and in right anterior oblique (RAO) CS angiography was estimated and is illustrated in Figure 2 according to Sanchez-Quintana et al. and Biffi et al.8–10 The distance (L) was divided into two part by a mid-ventricular line (M). The basal position was classified as mid-basal and the apical position classified as mid- apical CS lead position, referring to the CS lead tip.

Before patients were discharged, echo-directed adjustment or an invasive haemodynamic optimization of the atrioventricular pacing interval was performed to optimize haemodynamic function.

Left ventricular pacing threshold and phrenic nerve stimulation testing

According to clinical practice, routine follow-ups were scheduled 1–3 days after implantation, 1 month after implantation, and at 3-month intervals after that (4-month after implantation). Additional follow-ups were performed following ICD discharge or on the basis of patient complaints. In all 101 patients who received a CRT device, we

Table 1  Demographics

<table>
<thead>
<tr>
<th>Patients</th>
<th>n = 101</th>
</tr>
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<tbody>
<tr>
<td>Male/female</td>
<td>76/25</td>
</tr>
<tr>
<td>Age (years)</td>
<td>69.10 ± 8.33</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>83.5 ± 14.0</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.74 ± 0.07</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.56 ± 3.92</td>
</tr>
<tr>
<td>Aetiology (CAD/DCM)</td>
<td>55/46</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>25.93 ± 6.74</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>159.05 ± 19.56</td>
</tr>
<tr>
<td>CS lead position basal/mid</td>
<td>52/49</td>
</tr>
<tr>
<td>CS lead uni-/bipolar</td>
<td>5/96</td>
</tr>
<tr>
<td>Device: Medtronic/Boston/St Jude/Biotronik</td>
<td>34/31/35/1</td>
</tr>
<tr>
<td>CS lead type: Quicksite/Easytrak/Attain</td>
<td>59/24/18</td>
</tr>
</tbody>
</table>
investigated the LVPT and PNS in different configurations at the first follow-up, 1–3 days after implantation, 1 month after implantation, and at 3-month intervals after that. The different CS lead configurations were LV tip to right ventricular (RV) coil, LV tip to LV ring, and LV ring to RV coil in the case of Boston Scientific Guidant devices. All configurations were tested on a standard examination bed with a top angle of 30° in the supine and left lateral body positions. Left ventricular pacing thresholds were tested in DDD pacing mode, LV alone, 100 b.p.m., and impulse duration of 1.0 ms. The minimal amplitude of effective depolarization in volt (V) was defined as LVPT. The minimal amplitude (V) was defined as PNS threshold when the patient reported regular sensations at each follow-up. The BMI was calculated as the patient’s body weight (in kilograms) divided by body height squared (in metres).

If a bipolar lead was implanted (92 patients), the CS lead configuration of LV tip to LV ring with 100% safety margin was programmed primarily at the first follow-up 1–3 days after implantation as a chronic LV output. In the case of a unipolar CS lead (nine patients), it was programmed primarily LV tip to RV coil with 100% safety margin as a chronic LV output. In the case of clinical PNS, LV pacing configuration with highest safety margin was programmed. During implantation procedure, the accepted safety margin was from minimally $3 \text{ V}$ to avoid a CS lead revision. If this lay underneath, CS lead revision was arranged during implantation. At each follow-up visit, the device was examined for proper functioning as well as to review the arrhythmic episodes detected and treated by the ICD. When necessary, the parameters of the device were reprogrammed.

**Statistical analysis**

The LVPT and PNS are expressed as mean ± SD. The distribution of the collected data was tested using the Anderson–Darling normality test, the Lilliefors (Kolmogorov–Smirnov) normality test, and the Shapiro–Wilk normality test. Only the BMI was normally distributed. A $p$-value of 0.05 is considered statistically significant. Results were compared using a two-sided paired Wilcoxon test. Pearson’s correlation coefficient was calculated to evaluate the correlation between the changes.

**Results**

**Coronary sinus lead implantation and position**

In no patient, the CS lead was implanted in an anterolateral CS vein. In 10 patients, a CS lead repositioning was required because of low PNS threshold and safety margin (<3 V) during implantation procedure. Seven of these 10 patients were initially implanted in mid-apical CS position. Only one of these patients complained of PNS in the further course. In 52 of 101 patients, the LV leads were stably implanted in the mid-basal position in the posterior or lateral vein (Figure 2). In 49 patients, a mid-apical posterior or lateral position was chosen by the physicians and necessitated by the anatomy (Table 2). For the mid-apical posterolateral position of the LV lead, a trend towards higher LVPT ($P = 0.16$) was measured: $1.2 \pm 0.8$ V to basal $1.0 \pm 0.6$ V in the LV tip to RV coil configuration (Figure 3) at first month after implantation. But a significantly higher PNS threshold was examined for mid-basal ($3.4 \pm 1.7$ V) to mid-apical posterolateral vein ($2.8 \pm 1.4$ V) in the LV tip to RV coil configuration ($P = 0.04$). No significant differences were measured in LV tip to LV ring or LV ring to RV coil configurations as well as in all left lateral positions. The different CS lead types did not significantly influence either LVPT or PNS threshold.

No correlation between LVPT, PNS threshold, BMI, reduction of LV end-diastolic diameter, or LV ejection fraction after 3 month was observed either in the supine or in the left lateral body position ($P > 0.4$).

In 5 of 101 patients, the anatomy of the CS vein only allowed a stable lead position with a unipolar CS lead.
On inquiry, 33 of 101 patients described PNS at the 1-month follow-up after implantation. Nine of those 33 patients complained of frequent and annoying PNS. Two of them already came too early after 1 or 4 days after first follow-up because of PNS in our clinic. The nine patients report already without any question about PNS. Only in one case was it necessary to perform an LV lead repositioning procedure since all reprogramming attempts to overcome PNS failed. In 32 of the 33 patients, reprogramming of the LV lead configuration was sufficient to control PNS. In the last follow-up 4-month after implantation, only three of initial 33 patients reported PNS, 1 day per week, which did not negatively affect their quality of life.

Coronary sinus lead configuration

The LVPTs and PNS threshold did not differ within single follow-ups significantly. Exemplarily, the measuring values are compared here at 1 month after implantation. In all 101 patients in the standard supine body position, the LVPT was $1.1 \pm 0.7$ V with the LV tip to RV coil configuration—significantly lower than the threshold $1.2 \pm 0.8$ V for the LV tip to LV ring configuration ($P = 0.001$) at first month after implantation (Figure 4). However, in the LV tip to LV ring configuration, PNS threshold was $3.9 \pm 1.6$ V, which is significantly higher than in the LV tip to RV coil configuration at $3.1 \pm 1.6$ V ($P = 0.001$).

Left ventricular ring to right ventricular coil configuration

Thirty-one of 101 patients received a Boston Scientific Guidant ICD system (Contac Renewal®); this additionally allows an LV ring to RV coil configuration. In the LV ring to RV coil configuration, no differences in LVPT were found when compared with LV tip to RV coil ($1.2 \pm 0.9$ to $1.1 \pm 0.8$ V, $P = 0.4$) and LV tip to LV ring ($1.2 \pm 0.9$ V, $P = 0.8$) configurations (Figure 4). Phrenic nerve stimulation threshold was, however, significantly higher in LV ring to RV coil than in the LV tip to RV coil configuration ($3.6 \pm 1.3$ to $3.1 \pm 1.6$ V, $P = 0.01$). No significant difference in PNS threshold was measured in comparison with the LV tip to LV ring configuration ($P = 0.76$). In two patients, the LV ring to RV coil configuration prevented repositioning of the LV lead caused by higher PNS threshold.

Body position

In all 101 patients, we observed no significant differences in LVP thresholds between the standard supine and left lateral body
positions (Table 3). However, a significant decrease in PNS threshold was observed in the left lateral body position for LV tip to RV coil ($P=0.001, 3.1+1.6$ to $2.2+0.9$ V), for LV tip to LV ring ($P=0.001, 3.9+1.6$ to $3.0+1.0$ V), and for LV ring to RV coil ($P=0.001, 3.6+1.3$ to $2.7+0.9$ V) configurations (Figure 5).

**Discussion**

**Coronary sinus lead configuration**

In clinical practice, a low stimulation output of the LV lead is often chosen to avoid PNS. Also Biffi et al. have measured LVPTs and PNS thresholds with an impulse width of 0.5 and 1.0 ms. Further, Biffi et al. detected a higher safety margin with 1.5 ms than with 0.5 ms impulse width. With 1.5 ms impulse width, at least two patients had less safety margin, 100%, than with standard 0.5 ms impulse width.

Phrenic nerve stimulation is a frequent complication of transvenous implantation of LV CS leads. With 0.9–4.9% of the CRT patients, PNS cannot be avoided by programming and consequently a lead replacement is necessary in these patients. In contrast to the usual 7.5 or 10 V testing during implantation, in this study, we examined the clinically relevant PNS threshold at first and at 4-month follow-up after implantation. We defined PNS threshold as regular sensations reported by the patient and confirmed by the physician on physical examination of the patient during follow-ups. Gurevitz et al. reported a PNS rate of 18.5% (17 of 92 patients) in the supine and Schwierz et al. ~13.9% during the implantation procedure. In our group of patients, a lower PNS rate of 9% (9 of 101 patients complained of PNS) or 30% ($+24$ of 101 patients reported PNS) was reported during chronic CRT therapy. Furthermore, we achieved a successful stable transvenous CS lead implantation in a posterolateral or lateral vein in all patients (100%). Schwierz et al. had to implant CS leads in an anterolateral vein in 9.3% and Gurevitz et al. reported that successful stable transvenous CS lead implantation had failed in 14% due to difficult anatomy. In correspondence to our results, Biffi et al. detected PNS in 37% of patients and in 22% it was clinically relevant. In the study of Biffi et al., a CS lead revision became necessary in 10 patients (5%). In our study, CS lead revision became inevitable in one patient (1%) and in no patient CRT turned off.

**Left ventricular ring to right ventricular coil configuration**

Gurevitz et al. examined the influence of a bipolar LV tip to LV ring and the LV ring to RV coil configuration for PNS threshold in 92 patients. The relevant PNS could be lowered from LV tip to RV coil configuration (PNS rate, 24%) to LV tip to LV ring and the LV ring to RV coil configurations (PNS rate, 12%). No clear difference was observed between the LV tip to LV ring and the LV ring to RV coil configurations. In our data, no differences were found in relation to LVPT. Although the LV tip to LV ring

<table>
<thead>
<tr>
<th>LVPT</th>
<th>PNS threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVTIP/RVCOIL, n = 101</td>
<td>LVTIP/LVRING, n = 96</td>
</tr>
<tr>
<td>Supine</td>
<td>1.1 ± 0.7</td>
</tr>
<tr>
<td>Left</td>
<td>1.1 ± 0.6</td>
</tr>
<tr>
<td>Difference</td>
<td>0.1 ± 0.2</td>
</tr>
<tr>
<td>P-value</td>
<td>0.07</td>
</tr>
</tbody>
</table>

**Figure 4** Different LV lead configuration compared with LVPT and PNS threshold at 1-month follow-up after implantation.
configuration is, in many patients, superior to the LV ring to RV coil configuration with regard to PNS threshold, in isolated cases, an advantage could nevertheless be ascertained for the LV ring to RV coil configuration. In two patients, LV ring to RV coil configuration was even able to prevent lead replacement. A possible explanation for higher PNS threshold of LV ring to RV coil is a more basal position of the ring compared with the tip of the CS lead in relation to the anatomical course of the CS vein. In addition, some investigations point to an important positive therapeutic effect measured in increased aortic velocity–time integral by anodal capture of LV.18,19 But LV pacing should be confirmed in LV tip to RV coil and LV ring to RV coil configurations to exclude single RV pacing by 12-channel ECG. It should be noted that LV ring to RV coil configuration offers additional programmable configurations for lead complications and a greater possibility of avoiding CS lead replacements.

Body position and coronary sinus lead position

No significant difference in LV thresholds was observed based on body position. Therefore, the threshold recorded during the implantation procedure in the standard supine position can also be used as a reference threshold for the lateral position. There is no need for further LV threshold testing in the lateral body position for effective LV pacing during follow-ups. However, regardless of the CS lead configuration, PNS threshold decreased by around 0.9 V from the supine to the lateral body position, which is relevant in the long run for patient acceptance of the CRT device. Some patients grow accustomed to avoiding the left sleeping position; other patients do not tolerate frequent night PNS. This point has to be taken into consideration for calculation of the individual safety margin of chronic LV pacing. Besides, no correlation between BMI and PNS threshold was observed.

In correspondence to Biffi et al.8 for the mid-apical posterolateral position of LV lead, there was a smaller safety margin compared with the mid-basal position in LV tip to RV coil configuration (Figure 3). In contrast to Biffi et al.,8 no CS lead was implanted anterolaterally in our study (in Biffi et al., 14% were anterolateral CS leads).

Further three-dimensional mapping procedures will be investigated in order to improve the optimal CS lead position in further studies.20 According to our practice during implantation, a PNS threshold under 10 V testing is not an obstacle for a stable CS lead positioning. Nevertheless, our data suggest a safety ratio of >3 is desirable to reduce PNS.

Configuration recommendation

The true bipolar configuration LV tip to LV ring resulted in a significantly higher PNS threshold. For that reason, almost all patient devices were programmed with the LV tip to LV ring configuration for chronic pacing. Frequently, the safety margin in LV tip to RV coil configuration is not sufficient and clinically relevant PNS threshold follows.

In practice, the patient’s perception of PNS and its limitations vary widely. Phrenic nerve stimulation acceptance and the optimal configuration should therefore be evaluated on a case-by-case basis.

Limitations

Statistical limitations were to be expected due to the single-centre study and the non-blinded character of the PNS threshold testing. Additional different CS lead types, their structure, devices of different manufactures, the different electrode surface area, and inter-electrode distance according to the individual CS anatomy may influence both PNS threshold and LVPT. Individual differently pericardial fat could have an insulation effect of LV stimulation concerning the PNS threshold. The pericardial layer of fat was not determined before implantation CRT devices by magnetic resonance imaging.

Conclusion

Phrenic nerve stimulation is a common problem when targeting the proper LV site for CRT and has been previously underreported in literature. The different LV pacing configurations are a useful feature of CRT systems to prevent PNS threshold. The implantation of a bipolar CS lead should aim always to have several configurations for flexibility of programming. The maximum safety ratio was calculated in the LV tip to LV ring configuration. The optimal LV pacing configuration should be individually tested in patients. The BMI of heart failure patients does not influence either PNS threshold or LVPTs.

Conflict of interest: none declared.
References


