Cardiac resynchronization therapy (CRT) is an established treatment of heart failure because of left ventricular (LV) systolic dysfunction, with evidence of electric and mechanical dyssynchrony.1,2 The mechanism of improvement with CRT is based on the stimulation of the mostly delayed LV sites. 3–5 Phrenic nerve stimulation (PNS) is a major complication that may result in withdrawal of CRT. PNS is observed in 33% to 37% of patients, 6–8 and although it is actively addressed during implantation, 6 it may be difficult to overcome in the long-term management of CRT patients. 9–11 Indeed, ≈ 15% of patients need to be reevaluated after hospital discharge because of PNS occurrence at follow-up,9–11 and ≈ 6.6% eventually report PNS symptoms at long-term follow-up, despite multiple attempts to avoid PNS.10

Methods

This was an acute open-chest study on 6 anesthetized adult dogs. The dogs were premedicated with morphine (1 mg/kg IM), and anesthesia was induced with propofol (120 mg IV) and isoflurane to effect. ECG limb leads were placed and connected to an electrophysiology (EP) recording station (Prucka; GE Medical Systems) for monitoring. A jugular access was obtained, and a standard Attain catheter (model 6216A; Medtronic Inc, Minneapolis, MN) was introduced in the coronary sinus to perform a venogram (Figure 1A). An implantable cardioverter-defibrillator lead (model 6935; Medtronic Inc) was implanted in the right ventricle via jugular access to provide an anodal electrode for unipolar measurements and to guarantee backup pacing, if necessary.

Decapolar EP catheter with standard (2 mm-5 mm-2 mm) interelectrode spacing (model 041590CS, Torqr; Medtronic Inc) and modified (1 mm-5 mm-1 mm) interelectrode spacing was placed into a posterior/lateral cardiac vein in a randomized order in 6 anesthetized dogs via jugular access. The phrenic nerve was dissected via a left minithoracotomy and repositioned over the vein as close as possible to one of the electrodes. The presence of PNS was verified (ie, PNS threshold <2 V at 0.5 ms in unipolar configuration). Bipolar pacing was delivered using the electrode closest to the phrenic nerve as the cathode, and multiple bipolar electrode spacing configurations were tested. During bipolar pacing, PNS threshold increased as bipolar electrode spacing was reduced (P<0.05), whereas LV pacing thresholds did not change significantly (P>0.05). Compared with a standard bipolar electrode spacing of 20 mm for LV leads, 1 and 2 mm bipolar electrode spacing resulted in a PNS threshold increase of 5.5±2.2 V (P=0.003) and 2.8±1.7 V (P<0.001), respectively. Similarly, PNS threshold increased by 6.5±3.7 V with 1 mm and by 3.8±1.9 V with 2 mm bipolar pacing (both P<0.001), compared with unipolar pacing.

Conclusions—This study suggests that reducing LV bipolar electrode spacing from the standard 20 mm to 1 or 2 mm may significantly increase the PNS threshold without compromising LV pacing thresholds. (Circ Arrhythm Electrophysiol. 2012;5:815-820.)

Key Words: interelectrode spacing ■ cardiac resynchronization therapy ■ phrenic nerve stimulation

Cardiac resynchronization therapy (CRT) is an established treatment of heart failure because of left ventricular (LV) systolic dysfunction, with evidence of electric and mechanical dyssynchrony.1,2 The mechanism of improvement with CRT is based on the stimulation of the mostly delayed LV sites.3–5 Phrenic nerve stimulation (PNS) is a major complication that may result in withdrawal of CRT. PNS is observed in 33% to 37% of patients6–8 and although it is actively addressed in different ways during implantation,8 it may be difficult to overcome in the long-term management of CRT patients.9–11 Indeed, ≈ 15% of patients need to be reevaluated after hospital discharge because of PNS occurrence at follow-up,9–11 and ≈ 6.6% eventually report PNS symptoms at long-term follow-up, despite multiple attempts to avoid PNS.10

Clinical Perspective on p 820

Device manufacturers have developed approaches to manage PNS, such as electronic repositioning, multiple pacing vectors, and modification of the pacing output, but no definite solution has fully addressed this demanding challenge.12 We sought to investigate the physiological principles of PNS occurrence in an animal model to develop a comprehensive strategy aimed at PNS avoidance in the clinical practice.

Methods

This was an acute open-chest study on 6 anesthetized adult dogs. The dogs were premedicated with morphine (1 mg/kg IM), and anesthesia was induced with propofol (120 mg IV) and isoflurane to effect. ECG limb leads were placed and connected to an electrophysiology (EP) recording station (Prucka; GE Medical Systems) for monitoring. A jugular access was obtained, and a standard Attain catheter (model 6216A; Medtronic Inc, Minneapolis, MN) was introduced in the coronary sinus to perform a venogram (Figure 1A). An implantable cardioverter-defibrillator lead (model 6935; Medtronic Inc) was implanted in the right ventricle via jugular access to provide an anodal electrode for unipolar measurements and to guarantee backup pacing, if necessary.

Decapolar EP catheter with standard (2 mm-5 mm-2 mm) interelectrode spacing (model 041590CS, Torqr; Medtronic Inc) and modified (1 mm-5 mm-1 mm) interelectrode spacing was placed into a posterior/
lateral cardiac vein, respectively, in a randomized order under fluoroscopic guidance. The phrenic nerve was dissected via a left minithoracotomy and repositioned over the vein as close as possible to one of the electrodes. Radiopaque markers (model V60 U-CIps; Medtronic Inc) were placed next to the nerve to document nerve location on fluoroscopy after the chest was closed (Figure 1B). During pacing, PNS was detected using tactile feel by placing a hand directly on the chest, and the presence of PNS was verified (ie, PNS threshold <2 V at 0.5 ms in unipolar configuration). Once the phrenic nerve was repositioned, unipolar electric measurements of PNS and LV pacing (LVP) thresholds were taken using all the 10 electrodes of the EP catheters as cathodes and the coil of the implanted right ventricle lead as anode. The electrode on the EP catheters with the lowest PNS threshold in unipolar configuration was identified as the targeted phrenic nerve electrode (TPNE), which was considered to be closest to the phrenic nerve (Figure 1B). Finally, bipolar pacing was delivered using TPNE as the cathode (the electrode closest to the phrenic nerve) to test 9 bipolar electrode spacing configurations of the decapolar EP catheters. In each configuration, PNS and LVP thresholds were measured at 0.5 ms pulse width by an amplitude step-down protocol from 10 to 0.1 V by pacing at 130 beats per minute using the analyzer (model 2290; Medtronic Inc). The LVP impedance at 5 V and 0.5 ms and the R wave were also measured using the same pacing analyzer in all bipolar configurations. The surface ECG was used during the stimulation protocol to validate true LV capture; anodal stimulation was always discarded for the measurement of LVP threshold. The actual bipolar electrode spacings were also measured on the EP catheter in all bipolar configurations. This study setting closely mimics clinical practice in the worst-case scenario, where the pacing lead is in proximity of the phrenic nerve. The study was reviewed and approved by Medtronic’s Institutional Animal Care and Use Committee.

Statistical Analysis

A parametric survival model was used to study the effect of cathode distance from phrenic nerve for the unipolar configuration because of the fact that unipolar threshold >10 V was censored. In addition, a random-effects term was incorporated into the survival model to account for the multiple observations within a canine. A linear mixed-effects model with canines as the random effect was used to understand the effect of electrode spacing on observed electric measurements and safety margin. Natural cubic splines with 2 knots located at the 1/3 and 2/3 percentiles of the predictor variables were used to address nonlinear relationships in both models described above. To compare the effect of pacing configuration on thresholds for both PNS and LV, a linear mixed-effects model that accounts for different variances across the different levels of the predictor was used to account for the observed heteroscedasticity across the pacing configurations. A Bonferroni correction was applied to the α level for multiple comparisons made across pacing configuration. All P values for the models described above were generated using likelihood ratio tests. P<0.05 was considered significant. All analysis was performed in the statistical analysis software R version 2.14.2 (SAS Institute, Cary, NC).

Results

LVP and PNS thresholds were measured in 6 dogs; the 1/5/1 mm catheter was not used in 1/6 canines because of a surgical complication. Overall, 110 LVP threshold and 110 PNS threshold measurements were carried out in the 6 animals.

Effect of Cathode Distance From Phrenic Nerve in the Unipolar Configuration

Figure 2 shows the effect of cathode distance from the TPNE (phrenic nerve) location on the unipolar PNS and LVP thresholds at 0.5 ms to the right ventricle coil. The PNS and LVP thresholds were positively correlated with the cathode distance from the TPNE (P<0.001, respectively). The effect of cathode distance from the TPNE on the unipolar PNS threshold is significantly stronger than that on the LVP threshold (P<0.001). The unipolar PNS thresholds rapidly increased while the cathode moving away from the TPNE reached a maximum of 10 V at 0.5 ms at a distance >20 mm. However, the unipolar LVP thresholds appeared stable.

Figure 1. Fluoroscopic image of the coronary vein angiogram (A) and of catheter and phrenic nerve location (B). TPNE indicates targeted phrenic nerve electrode.

Figure 2. Effect of cathode distance from the phrenic nerve on both left ventricular pacing (A) and phrenic nerve stimulation (B) unipolar threshold. The dashed lines represent the effect in each animal, and the solid line represents the overall trend in the study. TPNE indicates targeted phrenic nerve electrode.
while the cathode distance to the TPNE was <20 mm, then increased while the cathode distance to the TPNE was >20 mm. In fact, both unipolar PNS and LVP thresholds showed large variability at TPNE distance >20 mm, likely because of phrenic nerve anatomy (ie, divergence in the course of the phrenic nerve from coronary vein) and to the larger vein diameter when located more proximally (ie, poor electrode contact): in this experimental setting, the TPNE was located at the distal end of the decapolar catheter.

**Effect of Bipolar Electrode Spacing on Bipolar PNS and LVP Thresholds, Pacing Impedance, and R Wave**

Figure 3 shows the random correlation of bipolar PNS and LVP thresholds to the bipolar electrode spacing when TPNE was used as the cathode (the electrode closest to phrenic nerve). PNS threshold was significantly inversely related to bipolar electrode spacing ($P<0.001$; Figure 3B), whereas no association was found for LVP threshold ($P=0.640$; Figure 3A). Figures 4 and 5 show LVP impedance and R-wave amplitude relationship with the bipolar electrode spacing when TPNE was used as the cathode. A decrease in LVP impedance and a decrease in the intrinsic R wave were, respectively, observed as the bipolar electrode spacing shortened ($P<0.001$; Figure 4 and $P<0.001$; Figure 5).

Figure 6 summarizes the comparison of pacing configurations: the unipolar pacing was compared, respectively, with the 1-mm spaced, 2-mm spaced, and 20-mm spaced (the last one is commonly available in clinical practice using market-released LV leads) bipolar pacing using TPNE as the cathode. The pacing configuration affected the PNS thresholds ($P<0.001$). However, the pacing configuration did not affect LVP thresholds ($P=0.130$). Compared with 20 mm of standard bipolar electrode spacing, 1 and 2 mm bipolar electrode spacing resulted in a PNS threshold increase of 5.5±2.2 V ($P=0.003$) and 2.8±1.7 V ($P<0.001$), respectively. Similarly, PNS threshold increased by 6.5±3.7 V with 1 mm and by 3.8±1.9 V with 2 mm bipolar pacing (both $P<0.001$), compared with unipolar TPNE pacing. The trend of the bipolar configuration was clear: a shorter electrode spacing resulted in significantly higher PNS thresholds (Figure 6).

**Effect of Bipolar Electrode Spacing on Safety Margin of Bipolar PNS to LVP**

Figure 7 shows the significant relationship of the difference between the bipolar PNS and LVP thresholds to the bipolar electrode spacing, with TPNE as the cathode. The difference between PNS and LVP thresholds is significantly inversely related to the bipolar electrode spacing ($P<0.001$).

![Figure 3](http://circep.ahajournals.org/)

**Figure 3.** Effect of bipolar electrode spacing on bipolar left ventricular pacing (A) and phrenic nerve stimulation (B) threshold. The dashed lines represent the effect in each animal, and the solid line represents the overall trend in the study.

![Figure 4](http://circep.ahajournals.org/)

**Figure 4.** Effect of bipolar electrode spacing on pacing impedance. The dashed lines represent the effect in each animal, and the solid line represents the overall trend in the study.

![Figure 5](http://circep.ahajournals.org/)

**Figure 5.** Effect of bipolar electrode spacing on R-wave amplitude. The dashed lines represent the effect in each animal, and the solid line represents the overall trend in the study.
Figure 8 shows the effect of the bipolar electrode spacing on the probability to achieve a safety margin >3 V in the worst-case scenario, using TPNE as the cathode (closest to phrenic nerve). This safety margin is obtained reliably in all the cases using 1 mm bipolar electrode spacing. The success rate dropped dramatically for bipolar electrode spacing >6 mm, which are those typically used for LV leads in clinical practice.

**Discussion**

The main finding of our study is that both the distance from the LV cathode to the phrenic nerve and bipolar electrode spacing affect the PNS threshold: the farther the LV cathode from the phrenic nerve or the shorter the bipolar electrode spacing, the lower the chance of PNS. The difference between PNS threshold and LVP threshold was used to provide a PNS safety margin to relate the results to clinical practice. Indeed, a difference ≥3 V is associated with freedom from PNS-related complications in the majority of clinical reports, which involved ≈600 patients. This safety margin was obtained reliably in all the cases using 1 mm bipolar electrode spacing and keeping TPNE as the cathode (Figure 8). The success rate dropped dramatically for bipolar electrode spacing >6 mm, which are those typically used for LVP in clinical practice. Two strategies for PNS management are highlighted by this study: placing the LV cathode remote from the TPNE or shortening the bipolar electrode spacing with the LV cathode at TPNE.

PNS needs to be managed at the same pacing sites that are deemed optimal for CRT. When PNS is detected at implantation, several approaches are used: moving the lead to a different position in the vein, programming the LV cathode to a different electrode in devices featuring this technology, or lowering the LV output to avoid PNS when the other options have failed. LV lead repositioning to another vein is the last resort and is possible only when other coronary veins are suitable for LV lead placement.

Each of these approaches has its own drawbacks: LV lead placement at an alternative site poses an increased risk of a suboptimal LVP threshold and of LV lead dislodgement, with need for repeated surgery. Surgery increases the risk of complications because of increased risk of infection. Abandoning the target site or loss of capture because of a high LVP threshold may cause failure to achieve CRT and clinical improvement. Our observations highlight the need to develop new strategies for PNS management through implant techniques and lead technology.

**Impact of Cathode Distance From the Phrenic Nerve in Unipolar Configuration**

PNS threshold has a linear relationship with distance from the phrenic nerve (Figure 2). This is the physiological background for the strategy most commonly used in clinical practice to avoid PNS: placement of the LV cathode far from the phrenic nerve. Nowadays, this is achieved by reprogramming the LV cathode in multielectrode leads to maintain lead stability and decrease the risk of lead dislodgement. This strategy has not proved to ensure PNS avoidance in 100% of patients, most likely owing to the electrode spacing of bipolar LV leads that ranges from 10 to 20 mm, whereas our observation
dictates that the LV cathode be at least 20 to 30 mm from the TPNE. To overcome this limitation, a quadripolar S-shaped LV lead that spans a length of ≈50 mm from the tip to the proximal electrode and allows 10 pacing configurations has been developed. The preliminary short-term experience with this lead in highly trained centers is that during implantation, 5 of 75 (6.6%) patients had the lead placed at a vein different than the target one because of PNS that could not be managed by reprogramming. Furthermore, the incidence of PNS at 7.5 V when programming the LV cathode 30 or 47 mm from the lead tip was 14% and 23%, respectively, with an average PNS threshold around 5±2 V. The LVP threshold in those settings was, respectively, 2.5 and 3.5 V on average, meaning that a 3-V difference between PNS and LVP thresholds was not obtained in all patients and that PNS avoidance was a trade-off with high LVP threshold. This represents a potential limitation in managing PNS at follow-up. Hence, owing to the variability of both coronary vein and phrenic nerve anatomy, a strategy based on a multielectrode LV lead with conventional bipolar electrode spacing in the range of 10 to 20 mm does not seem to provide a comprehensive approach to manage PNS.

Impact of Electrode Spacing on PNS Threshold and Implications for a PNS-Avoidance Strategy

We observed an inverse relationship of PNS threshold with bipole electrode spacing (Figure 3B) that warrants a PNS-LVP threshold difference >3 V at a spacing <2 mm (Figures 7 and 8).

This allows the implanting physician to keep the LV cathode at the target site for CRT (though being the TPNE), thus minimizing the risk of nonresponse to CRT, which carries the risk of significant morbidity and mortality. Furthermore, this approach is neutral on the LVP threshold compared with longer/standard electrode spacing (Figure 6B), thus minimizing the risk of high LVP threshold and loss of ventricular capture when pacing elsewhere than lead tip.

Our results are in complete agreement with the recently published experience by Wecke et al that reported similar results in a canine model, using a networked multielectrode LV lead. They demonstrated that a short pacing dipole (≤1 mm), obtained by pacing between adjacent segments of networked electrodes, can achieve PNS avoidance in 100% of the worst-case scenarios (phrenic nerve dissected and positioned above the LV lead).

Practical Implications

We believe that our study provides the rationale for the development of multielectrode LV leads with a 1 to 2 mm bipolar electrode spacing to maximize PNS management either at implant or at follow-up. The short-spaced dipole could be part of either multielectrode or active fixation leads, where all efforts are focused to avoid both a high LVP threshold and PNS at the same time. The advantage of such an approach is the use of an already established and reliable LV lead technology, whereas the new lead technology described by Wecke et al might be vulnerable to the risks of any new highly sophisticated electronic technology.

Study Limitations

This was an acute animal study that requires confirmation first in acute human studies and later during long-term follow-up. The healthy animals used in the study could not mimic a high LVP threshold caused by ischemic scars, which could possibly alter the study results. We used commercially available EP catheters, both standard and modified, to provide a shorter bipolar electrode spacing instead of leads designed for chronic pacing. This catheter and electrode design may have increased the LVP threshold compared with conventional LVP leads because of unpredictable electrode contact with the myocardium. PNS was determined via tactile feel, and this may not reflect the clinical perception of PNS felt by patients. The phrenic nerve was surgically repositioned over a coronary vein, and this difference from physiological conditions could impact the contact between the nerve and the catheter within the vein.

Disclosures

Dr Biffi has received modest honoraria from Medtronic, Boston Scientific, and Biotronik for scientific presentations at Medical Simposia and for Educational Activity. All the other authors are employees of Medtronic.

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