Effect of Bipolar Electrode Spacing on Phrenic Nerve Stimulation and Left Ventricular Pacing Thresholds: An Acute Canine Study

Running title: Biffi et al.; Short bipolar pacing to avoid PNS in CRT

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Journal Subject Codes: [110] Congestive; [22] Ablation/ICD/surgery; [120] Pacemaker
Abstract:

Background - Phrenic Nerve Stimulation (PNS) is a common complication of cardiac resynchronization therapy (CRT) when left ventricular (LV) pacing occurs via a coronary vein. The purpose of this study was to evaluate effects of bipolar electrode spacing on PNS and LV pacing threshold.

Methods and Results - Electrophysiology (EP) catheters with standard (2mm-5mm-2mm) or modified (1mm-5mm-1mm) inter-electrode spacing was respectively inserted in a posterior/lateral cardiac vein in a randomized order in six anesthetized dogs via jugular access. The phrenic nerve was dissected via a left mini-thoracotomy and repositioned over the vein, as close as possible to one of the electrodes. The presence of PNS was verified (i.e. PNS threshold <2V 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), while LV pacing thresholds did not change significantly (p>0.05). Compared with a standard bipolar electrode spacing of 20mm for LV leads, 1mm and 2mm bipolar electrode spacing resulted in a PNS threshold increase of 5.5±2.2V (p=0.003) and 2.8±1.7V (p<0.001), respectively. Similarly, PNS threshold increased by 6.5±3.7V with 1mm and by 3.8±1.9V with 2mm bipolar pacing (both p<0.001), as compared to 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.

Key words: bipolar electrode spacing; cardiac resynchronization therapy; phrenic nerve stimulation
Cardiac resynchronization therapy (CRT) is an established treatment of heart failure due to left ventricular (LV) systolic dysfunction with evidence of electrical 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 33-37% of patients (6-8) and, although it is actively addressed in different ways during implantation (6), it may be difficult to overcome in the long-term management of CRT patients (9-11). Indeed, about 15% of patients need to be re-evaluated after hospital discharge because of PNS occurrence at follow up (9-11), and about 6.6% eventually report PNS symptoms at long-term follow up despite multiple attempts to avoid PNS (10).

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 physiologic 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 six anesthetized adult dogs. The dogs were premedicated with morphine (1mg/kg IM) and anesthesia was induced with propofol (120 mg IV) and isoflurane to effect. ECG limb leads were placed and connected to an EP recording station (Prucka, GE Medical Systems, US) for monitoring.

A jugular access was obtained and a standard Attain catheter (Model 6216A, Medtronic) was introduced in the coronary sinus to perform a venogram (Figure 1A). An ICD lead (Model...
6935, Medtronic) was implanted in the right ventricle (RV) via jugular access to provide an
anodal electrode for unipolar measurements and to guarantee backup pacing, if necessary.

Decapolar EP catheter with standard (2mm-5mm-2mm) inter-electrode spacing
(Medtronic Torqr, Model 041590CS) and modified (1mm-5mm-1mm) inter-electrode 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 mini-thoracotomy and
repositioned over the vein, as close as possible to one of the electrodes. Radiopaque markers
(Model V60 U-Clips, Medtronic) 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 (i.e. PNS
threshold <2V at 0.5 ms in unipolar configuration). Once the phrenic nerve was repositioned,
unipolar electrical measurements of PNS and LV pacing (LVP) thresholds were taken using all
the ten electrodes of the EP catheters as cathodes and the coil of the implanted RV 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 cathode (the
electrode closest to the phrenic nerve), in order to test nine bipolar electrode spacing
configurations of the decapolar EP catheters. In each configuration PNS and LV Pacing (LVP)
thresholds were measured at 0.5ms pulse width by an amplitude step down protocol from 10V to
0.1V by pacing at 130 bpm using the analyzer (Model 2290, Medtronic Inc). The LV pacing
impedance at 5V and 0.5 ms, and the R-Wave were also measured using the same pacing
analyzer in all bipolar configurations. The surface EKG 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 due to the fact that unipolar threshold greater than 10 V were censored. Additionally 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 utilized to understand the effect of electrode spacing on observed electrical 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 alpha level for the multiple comparisons made across pacing configuration. All P-values for the models described above were generated using Likelihood ratio tests. P-values < 0.05 were considered significant.

All analysis was performed in the statistical analysis software R version 2.14.2.

**Results**

LVP and PNS threshold were measured in 6 dogs; the 1/5/1 mm catheter was not used in 1/6
canines due to a surgical complication. Overall, 110 LVP threshold and 110 PNS threshold measurements were carried out on 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 threshold @ 0.5 ms to the RV coil. The PNS and LVP threshold was 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 and reached a maximum of 10 V@0.5 ms at the distance greater than 20 mm. However, the unipolar LVP thresholds appeared stable while cathode distance to the TPNE was less than 20mm then increasing while cathode distance to the TPNE was greater than 20mm. In fact, both unipolar PNS and LVP threshold showed large variability at TPNE distance > 20 mm likely due to phrenic nerve anatomy (i.e. divergence in the course of the phrenic nerve from coronary vein) (13) and to the larger vein diameter when located more proximally (i.e. 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 threshold, pacing impedance and R-wave**

Figure 3 shows the random correlation of bipolar PNS and LVP thresholds to the bipolar electrode spacing when the 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, Fig.3 B), while no association was found for LVP threshold (p=0.640; Figure 3A). Figure 4 and 5 show LV pacing impedance and R-wave amplitude relationship with the bipolar electrode...
spacing when the TPNE was used as the cathode. A decrease of LV pacing impedance and a
decrease of the intrinsic R-wave were respectively observed as the bipolar electrode spacing
shortened (p<0.001, Figure 4; p<0.001, Figure 5).

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

Figure 8 shows the effect of the bipolar electrode spacing on the probability to achieve a
safety margin greater than 3 V at the worst case scenario, using the TPNE as the cathode (closest
to phrenic nerve). This safety margin is obtained reliably in all the cases using 1mm bipolar
electrode spacing. The success rate dropped dramatically for bipolar electrode spacing > 6 mm,
which are those typically employed 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” in order to relate the results to clinical practice. Indeed, a difference $\geq 3\text{V}$ is associated with freedom from PNS-related complications in the majority of clinical reports (6, 8, 10, 11), which involved about 600 patients. This safety margin was obtained reliably in all the cases using 1 mm bipolar electrode spacing and keeping the TPNE as cathode (Fig.8). The success rate dropped dramatically for bipolar electrode spacing $> 6\text{ mm}$, which are those typically employed for LV pacing 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 (6, 7, 9, 11). 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 (6, 11, 14). 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 (6, 8). Surgery increases the risk of complications due to increased risk of infection (15). Abandoning the target site or loss of capture because of a high LVP threshold may
cause failure to achieve CRT and clinical improvement (4,5).

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 re-programming the LV cathode in multi-electrode leads in order to maintain lead stability and decrease the risk of lead dislodgement (6, 8–10, 14). This strategy has not proved to ensure PNS avoidance in 100% of patients (10–12, 16), 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 needs to be at least 20–30 mm far from the TPNE. To overcome this limitation, a quadripolar S-shaped LV lead that spans a length of approximately 50 mm from the tip to the proximal electrode and allows 10 pacing configurations has been developed (16). The preliminary short-term experience with this lead in highly trained centers reported that during implantation 5/75 (6.6%) patients had the lead placed at a vein different than the target one because of PNS that could not be managed by re-programming (16). Moreover, the incidence of PNS at 7.5V when programming the LV cathode 30 mm or 47 mm from the lead tip was 14% and 23%, respectively, with an average PNS threshold around 5 ± 2 V (16). The LVP threshold in those settings was respectively 2.5V and 3.5V on average, meaning that a 3V difference between PNS and LVP threshold was not obtained in all patients, and that PNS avoidance was a trade-off with a high LVP threshold. This represents a potential limitation in managing PNS at follow up (10). Hence, owing to the variability of both coronary vein and phrenic nerve anatomy, a strategy
based on a multi-electrode 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 above 3V at a spacing < 2mm (Fig. 7,8). 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 non-response to CRT (5, 17-20), which carries the risk of significant morbidity and mortality (1, 2, 5, 19, 20). Furthermore, this approach is neutral on the LVP threshold compared to longer/standard electrode spacing (Fig. 6B), thus minimizing the risk of a high LVP threshold and loss of ventricular capture when pacing elsewhere than lead tip (16). Our results are in complete agreement with the recently published experience by Wecke et al (21) that reported similar results in a canine model, using a networked multi-electrode LV lead. They demonstrated (21) that a very short pacing dipole (≤1mm), 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 multi-electrode 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 multi-electrode or active fixation leads, where all the 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 (21) might be vulnerable to the risks of any new highly sophisticated electronic
Study Limitations: This was an acute animal study which requires confirmation firstly 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 due to ischemic scars, that could possibly alter the study results. We used commercially available electrophysiology 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 LV pacing threshold compared to conventional LV pacing leads due to 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.

Conflict of Interest Disclosure: 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.

References:


Figure Legends:

Figure 1. Fluoro image of the coronary vein angiogram (A) and of catheter and phrenic nerve location (B)

Figure 2. Effect of cathode distance from the phrenic nerve on both LVP (A) and PNS (B)
unipolar threshold. The dashed lines represent the effect in each animal and the solid line represents the overall trend in the study.

**Figure 3.** Effect of bipolar electrode spacing on bipolar LVP (A) and PNS (B) threshold. The dashed lines represent the effect in each animal and the solid line represents the overall trend in the study.

**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.** 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 6.** Comparison of pacing configurations of bipolar and unipolar PNS (A) and LVP (B) using the TPNE as a cathode. The solid lines represent 95% confidence intervals.

**Figure 7.** Relationship of the difference between bipolar PNS and LVP threshold. The dashed lines represent the effect in each animal and the solid line represents the overall trend in the study.

**Figure 8.** Probability of a PNS-LVP threshold difference >3 V, with bipolar electrode spacing.
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_Circ Arrhythm Electrophysiol._ published online July 11, 2012;
_Circulation: Arrhythmia and Electrophysiology_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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