ELECTROPHYSIOLOGY

Effect of Steroid Elution on Electrical Performance and Tissue Responses in Quadripolar Left Ventricular Cardiac Vein Leads

ZHONGPING YANG, Ph.D.,* NICOLE KIRCHHOF, D.V.M.,† SHELBY LI, M.S.,* DOUGLAS HINE, M.S.,* and RICK MCVENES, B.S.*

From the *Cardiac Rhythm Heart Failure Research & Technology, Medtronic PLC, Mounds View, Minnesota; and †Physiological Research Laboratories, Medtronic PLC, Minneapolis, Minnesota

Introduction: The use of steroid elution (SE) electrode in a cardiac pacing lead is known to suppress myocardial inflammation to lower pacing thresholds (PTs). SE has been widely utilized on the distal electrode of left ventricular cardiac vein (LVCV) leads used in cardiac resynchronization therapy (CRT). However, no paired comparison in effect of SE has been studied in proximal electrodes of quadripolar LVCV leads.

Methods: We evaluated electrical performance and tissue responses of quadripolar LVCV lead electrodes with and without SE in two canine studies with a total of 14 canines. Extended bipolar PT and pacing impedance of the LVCV electrodes to right ventricle coil were collected via an implantable CRT device/programmer or a percutaneous threshold analyzer/pacing analyzer at weeks 0, 1, 2, 4, 6, 8, and 12. Gross and histopathological examinations of the canines were performed at the end of the studies.

Results: Our preclinical studies showed that SE had significant effects on the long-term pacing performance of quadripolar LVCV leads. The SE tip and ring electrodes reduced postimplant PT peak and chronic PT, P = 0.038. Histological examination of the perilead tissue capsules at 12 weeks showed a reduced thickness for the location of SE electrodes.

Conclusion: SE electrodes in quadripolar LVCV leads lower the PTs, and therefore may potentially reduce long-term current drain of CRT systems, thus improving the device longevity. These preclinical data serve as rationale to include SE on proximal electrodes for the Attain Performa LVCV leads and future quadripolar LVCV leads development. (PACE 2015; 38:966–972)

steroid elution, quadripolar left ventricular cardiac vein lead, pacing threshold

Introduction

Implantation of cardiac pacing leads is associated with an acute, locally restricted inflammation at the electrode-myocardium interface due to mechanical injury and biological responses. The tissue damage and inflammation not only result in myocardial fibrosis and encapsulation of the lead tip, but also in a rise of the postimplant pacing threshold (PT). This increase often persists and results in higher chronic pacing energy consumption. Since the early 1980s, it has been repeatedly demonstrated that steroid elution (SE) pacing leads have substantial electrical benefits compared to nonsteroid elution (NSE) leads. Benefits include low stable chronic PTs, elimination of inflammatory exit block, and resistance to PT rise due to systemic viral infections.

Apart from right atrial or right ventricular leads, SE has now also been utilized in the clinical practice in left ventricular (LV) leads. These leads are implanted into cardiac vein via the coronary sinus. It was demonstrated that left ventricular cardiac vein (LVCV) leads with SE from their distal electrode indeed remain electrically stable with excellent PTs over longer follow-up terms. In contrast to atrial and right ventricular leads, the electrical and morphological differences between SE and NSE proximal ring electrodes in LVCV leads have not been investigated. Moreover, newly
developed preshaped quadripolar LVCV leads with additional, more proximal ring electrodes have shown to achieve mechanical stability for all electrodes with or without SE.\textsuperscript{12,13} Likewise, the effect of SE in a vein that is more proximal and with relatively larger diameter, is yet to be tested.

In these two preclinical studies conducted in canines, we directly compared the electrical performance of SE and NSE in the proximal ring electrodes of quadripolar LVCV leads over 12 weeks, and examined the histomorphology of the electrode sites at the end of the study.

**Methods**

These studies series were conducted at the Medtronic Physiologic Research Laboratory (Coon Rapids, MN, USA), which is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AALAC). The study protocols were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC).

Medtronic’s quadripolar LVCV lead family includes a canted polyurethane insulated lead with co-radial conductors design having four 5.8 mm\textsuperscript{2} TiN-coated platinum/iridium ring electrodes (LV1-LV4). LV1 is positioned at the distal tip of the lead, LV2 is 21 mm proximal from LV1, LV3 is 1.3 mm proximal from LV2, and LV4 is 21 mm proximal from LV3. The lead body has a 5.3-French proximal and 4.1-French distal diameter. The SE quadripolar lead (model 4298) has a dexamethasone-loaded monolithic-controlled release device (MCRD) in all four electrodes (Fig. 1A). The NSE quadripolar lead (model 4298NSE) has only its tip electrode (LV1) containing a dexamethasone MCRD (Fig. 1B). The three proximal electrodes are steroid free in this design. All LVCV leads ended with an IS-4 connector (Fig. 1).

Fourteen purpose bred, adolescent dogs of either sex, weighing between 20 kg and 35 kg, were used in these studies. All surgeries were conducted in deep anesthesia. Before LVCV lead implantation, a retrograde coronary venogram was performed in each dog. The leads were implanted using stylet-guided or over-the-wire technique via an intercostal thoracotomy and access to the costocervical vertebral trunk near the superior vena cava. For monitoring purposes, an implantable cardioverter defibrillator lead (Sprint Quattro\textsuperscript{⃝}, Medtronic) was placed in the right ventricle (RV) after access from the right jugular vein. The 4298NSE leads were connected to a custom-designed percutaneous threshold analyzer (PTA). The 4298 leads were connected to a cardiac resynchronization therapy (CRT) device (CRT-D) (Viva Quad XT CRT-D, Medtronic). At the end of the implant surgery, a lateral fluoroscopic projection was used to document the lead locations. Sedated electrical monitoring was performed at 0-, 1-, 2-, 3-, 4-, 6-, 8-, 10-, and 12-week postimplant for each dog. From the PTA or the CRT-D, extended bipolar PTs and pacing impedance (PI) of the LV electrodes to RV Coil were collected with a Medtronic PTA/2290 Analyzer or CRT-D/2090 programmer.

After the final electrical monitor at 12-week postimplant, each dog was heparinized and then euthanatized with an overdose of barbiturate. All dogs underwent a necropsy where the heart with the leads in place was collected and fixed in 10% neutral-buffered formalin. During fixed-tissue trim, the LVCV lead tip and the four electrode positions were determined, the cardiac tissue in contact with the lead electrodes was marked, and the leads were carefully removed, leaving the perilead tissue capsule in the vein. Cross-section profiles containing the tissue capsule, the vein, and adjacent tissues at the level of the electrode sites were generated. Two of the dogs implanted with a 4298NSE lead were excluded from histological analysis as their leads were extracted \textit{in vivo} and the electrode locations could not be determined for this examination. These histology specimens were then dehydrated, paraffin embedded, serially sectioned at approximately 5 \textmu m, and stained with hematoxylin and eosin and Masson’s trichrome. Histopathological assessment of the electrode sites focused on the semiquantitative scoring of the inflammation in the perilead fibrous tissue capsule (0 = absent, 1 = minimal, 2 = mild, 3 = moderate, and 4 = severe), the maturity of the fibrous tissue capsule (0 = 95–100% mature, 1 = 50–94% mature, and 2 = 0–49% mature), and the measurement of the thickness of the fibrous tissue capsule (\textit{w} = width of the capsule at a...
region estimated visually to be average or near average for that capsule). During the assessment, the pathologists were blinded to the presence or absence of SE at the respective electrode sites.

**Statistical Analysis**

Data on LV PTs and PI are summarized by electrode for each time point over the study duration for both experimental groups. Because multiple measurements were taken from each dog longitudinally in the experiment, we employed a Linear Mixed effects model to compare the differences between SE and NSE electrodes in terms of PT and PI. The effect was tested after adjusting for the random effect (dog) and the fixed effects (electrode location and week postimplant). The difference in perilead fibrous tissue thickness at week 12 between SE and NSE groups was also tested similarly with tissue thickness as the response variable, and SE or NSE electrodes as covariates. The statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and a $P < 0.05$ was considered significant.

**Results**

**Lead Implant Position**

All LVCV leads were implanted in the anterior interventricular vein (AIV) for uniform implant site comparison. The lead tip positioning reached barely into the apical half of the heart due to the dog’s cardiovascular anatomy (Fig. 2). The distal three electrodes (LV1–LV3) were always located in the AIV or in one of its main tributaries; however, the LV4 was often found in the great cardiac vein. None of the LVCV leads had dislodged when their cardiac location at the study termination was compared to the fluoroscopic images taken immediately after implantation.

**Lead Electrical Performance**

**Pacing Threshold (PT)**

The PTs of the SE LV1 of both model 4298 and 4298NSE leads were stable and similar from implant to week 12 regardless of the monitoring device used. The average LV 1 PT values ranged 0.4–0.7 V @ 0.5 ms (Fig. 3A). Stable PT values were observed for SE LV2, LV3, and LV4 on the 4298 leads throughout the study phase (Figs. 3B–D). Average PT ranges 0.6–0.9 V @ 0.5 ms for LV2, 0.6–1.0 V @ 0.5 ms for LV3, and 1.5–2.3 V @ 0.5 ms for LV4. In contrast, the average PT of all NSE electrodes were higher and peaked at the 2-week postimplant then stabilized at the 12-week postimplant. Average NSE electrode PTs ranged 0.6–1.4 V @ 0.5 ms for LV2, 0.7–1.7 V @ 0.5 ms for LV3, and 0.9–2.5 V @ 0.5 ms for LV4.

The overall SE significantly lowered the PTs in the quadripolar LVCV lead, determined by the Linear Mixed Model, $P = 0.038$. It should be noted that the SE effects on the PTs were significantly different on the different electrodes ($P < 0.0001$), suggesting a dependency on the relative location of the electrode in the cardiac vein. The LV4 often located in the great cardiac vein. The SE LV4 reduced the postimplant PT peak but had the similar chronic PTs as compared to its NSE LV4.
Pacing Impedance

The average PIs of the LV1 on the 4298NSE leads were higher than those on the 4298 leads but both were stable over 12-week study duration (Fig. 4A). Both of the SE LV1 were identical and their locations in the cardiac veins were similar. This difference in PI observed in the study duration was because of the different monitoring methods used in the PI measurements, the 4298 leads via CRT-D device and the 4298NSE lead via the PTA, in the studies. The average PIs of the remaining three electrodes of the 4298 lead (LV2, LV3, and LV4) were similar and fairly stable (Figs. 4B–D). In contract, the average PIs of LV2, LV3, and LV4 of the 4298NSE leads significantly increased over time, $P < 0.0001$, suggesting there is a difference in PIs between SE and NSE groups as time goes.

Histological Findings

After 12 weeks, an almost continuous tissue capsule had formed around the intravenous leads. This capsule was made of circumferentially arranged collagen fibers (blue color on Masson’s trichrome stain, Figs. 5A and B) and widely attached or even merged with the wall of the lead bearing vein portion. Any nonencapsulated remainder of the lead’s circumference was separated from the venous endothelium by a narrow void that occasionally contained erythrocytes. The tissue capsules were in most cases composed of poorly cellular, highly fibrillar (mature) fibrous tissue; less often the fibrous tissue contained more cells (partly mature). Besides fibrocytes, inflammatory cells such as macrophages, lymphocytes, and plasma cells were sometimes encountered within the capsular collagen fibers. In general, macrophages were the most abundant cell type besides fibrocytes. Histomorphological comparison of the perilead capsule that had formed around SE or NSE electrodes did not show differences in capsular inflammation. But the SE was associated with an average reduction of the capsular thickness of 0.03 mm for LV2, 0.07 mm for LV3, and 0.11 mm for LV4 at week 12 (Fig. 6). The effect of SE on reduction in tissue sheath thickness was statistically significant ($P = 0.0005$). The underlying myocardium was within normal limits for each LV1, LV2, and LV3 specimen. Importantly, the venous segments harboring the LV4 usually were not contacting the myocardium, but were mainly surrounded by epicardial fat tissue.
Discussion

Electrical Effect of SE

This 12-week long preclinical study compared SE and NSE electrodes (LV2, LV3, and LV4) of quadripolar LVCV leads for differences between their PTs and PIs. Results from weekly monitors showed significant reductions of the PTs from SE to NSE electrodes in the LV2 and LV3 position. This PT difference was the greatest at 2 weeks postimplant, and was still apparent at the end of the studies at 12 weeks. PIs were more stable for SE electrodes during the postimplant follow-up phase whereas the NSE electrodes showed a gradual PI rise, most likely due to more fibrotic tissue gradually grown around these proximal NSE electrodes.

Effect of Electrode Position

In contrast to the distal electrodes, the effect of the SE on PTs of the proximal electrodes is dependent on the electrode locations in the dogs (Figs. 3B–D). The LV2 and LV3 along with the distal LV1 were all implanted in the narrow-lumen...
AIV or its tributaries, but the LV4 were mainly located in the wider caliper, more proximal great cardiac vein. It is assumed that a reduction in contact to the venous wall due to the wider diameter and the presence of fully circumferential, perivenous epicardial fat tissue in this more basal location caused this finding in dogs.

In addition, no significant difference in PT between SE electrodes on the same lead (LV2 and LV3) or between the LVCV leads (LV1; Fig. 3) was found. These results show that SE from intravenous electrodes of LVCV leads that are in close apposition to the venous wall and have no fatty tissue between the vein and the myocardium can effectively suppress a PT rise that is characteristically observed in the postimplant NSE leads. These results are consistent with the results of SE or NSE endocardial pacing lead electrodes where the lead-tip electrode is not within a cardiac vein, but in direct contact with the myocardium.\(^1\)

**Histomorphological Effect of SE around Pacing Electrodes**

Previous reports\(^6\) showed that local SE from passive-fixation, endocardial pacing leads implanted in dogs over 3–6 weeks significantly lowered PTs. The authors postulated that for SE electrodes the concurrently observed reduced formation of connective tissue and inflammatory response around the stimulating electrodes allowed for cardiac pacing with lower PT levels. It has been described that the connective tissue around the lead tip forms as part of a foreign body response\(^14\) and after microinjury to the local tissues with subsequent organization of the deposited thrombus via a macrophage-dominated phase that eventually creates a fibrous capsule. This subsequent fibrosis concludes the adverse electrical remodeling as cardiomyocytes are nonregenerative cells and the “status quo ante” cannot be regained.\(^15\) Steroids and their well-documented antiinflammatory properties clearly mitigate these undesired events and lead to earlier stabilization.\(^16\)

The current studies examined via histopathology 12-week-old implants of LVCV leads in dogs. This time point is assumed to be representative of the long-term histomorphology of a perilead fibrous capsule. Indeed, the persistence of low PT for the SE electrodes in the AIV at 12 weeks was clearly reflected in the concurrent observation of their reduced capsular thickness compared to NSE electrodes. The same difference in capsular thickness was previously reported for SE and NSE endocardial leads,\(^6\) but at 3 weeks and at 6 weeks postimplant. At these significantly earlier time points, the unaltered encapsulation process is characterized by a more inflammatory component and is not yet completed. These authors also showed that the capsular thickness is actually higher at 3 weeks than at 6 weeks. Therefore, differences from SE should be more easily noticeable at earlier stages after implantation. Based on these findings from the short-term implants, and the presented findings for long-term implants, it now can be extrapolated that early mitigation of a rise in PTs, together with...
a reduction of the local inflammatory response that is immediately achieved from SE of pacing electrodes, will have long-term benefits for the therapy recipient.

### Practical Implications

Since the first generation of CRT devices were manufactured more than two decades ago, great advancements have been achieved in LVCV leads, especially with the recent market release of quadripolar LVCV leads from multiple manufactures. We investigated the effect of SE for LV pacing using the paired quadripolar leads in our study with comparative statistics. The results provided evidence that all the SE distal and proximal electrodes in LVCV leads are effective to reduce PTs of the LVCV electrodes in the cardiac vein. The lower PTs do not only potentially reduce long-term pacing energy consumption of CRT systems but also provide higher likelihood to avoid phrenic nerve stimulation at the same time. Additionally, with a quadripolar lead, lower PTs at the proximal electrodes may provide opportunities for mid to basal pacing in human use.

### Study Limitations

The paired SE and NSE LVCV leads in the animal study demonstrated the beneficial effect of all the SE electrodes that require confirmation first in short-term human studies and later during long-term follow-up. The anatomy of the healthy animals used in the study may not be the same as in patients. This could possibly alter the study results since the PTs and the tissue responses were dependent on the electrode anatomical location in the cardiac vein.

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