Acute and Chronic Performance Evaluation of a Novel Epicardial Pacing Lead Placed by Percutaneous Subxiphoid Approach in a Canine Model

Running title: John et al.; Intra-pericardial Pacing Lead

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Abstract:

**Background** - Endovascularly implanted leads risk vascular injury and endocarditis, and can be difficult to locate in desired positions for LV pacing. We evaluated the acute and long-term stability, electrical performance and histo-pathology of a percutaneously placed intra-pericardial lead (IPL).

**Methods and Results** - Twelve adult mongrel dogs underwent defibrillator implants incorporating IPLs. Successful uncomplicated percutaneous implantation of an IPL was achieved in all. Early fluoroscopic shift noted with 3 of 6 of the initial version IPL-1 was not seen with the modified IPL-2. Mean ± 95% CI bipolar capture threshold @ 0.5msec pulse width for the IPL increased from 0.69 ± 0.14 V at implant to 1.50 ± 0.34 V (p = 0.003) at 12 weeks. The 12-week thresholds were higher for IPL compared to RV endocardial leads (0.75 ± 0.33 V, p = 0.001) but not different compared to coronary sinus leads (1.33 ± 0.58 V, p = 0.994). IPL impedance increased from 742 ± 46 ohms at implant to 1066 ± 207 ohms at 12 weeks (p = 0.007). R wave amplitude at 12 weeks was 8.37 ± 1.52 mV. There was no important phrenic nerve stimulation from IPL pacing. Histo-pathology in 8 animals showed adequate adhesion of the electrodes or mesh to the epicardium without damage to underlying vasculature. There was no evidence for late pericardial inflammation or effusion.

**Conclusions** - The IPL demonstrated adequate stability of position and acceptable electrical parameters without chronic pericardial inflammation in this canine model and offers a potential alternative to endocardial pacing leads.

**Key words**: pacing, epicardium, pericardium, epicardial pacing, pericardial lead, percutaneous epicardial pacing
Introduction

Cardiac implantable electronic devices (CIED) commonly utilize endovascular lead systems for sensing of native cardiac electrical activity and for delivery of therapy. However, concern for systemic infections and vascular injury have prompted the evolution of subcutaneous and epicardial systems.\textsuperscript{1, 2} The subcutaneous systems lack adequate long term pacing capability. Epicardial pacing and/or defibrillator leads are considered when endovascular access is limited, in the presence of recurrent infections from endovascular lines or leads and for cardiac re-synchronization therapy when adequate placement proves impossible via branches of the coronary sinus. However, surgical epicardial lead placement is associated with a higher morbidity and the leads have a higher rate of failure compared to endocardial leads.\textsuperscript{3, 4} An epicardial lead that can be delivered percutaneously therefore, has potential value. The pericardial space can be safely accessed via a subxiphoid approach for electrophysiology procedure, and can thus provide access for placement of pacing leads to the epicardial surface.\textsuperscript{5} In addition to sparing the vascular accesses, it offers the advantage of allowing for best pacing site(s) selection potentially based on hemodynamic response.

We evaluated the acute and long-term stability, electrical performance and histological features of a percutaneously placed epicardial lead system in canine models.

Methods

All animal experiments were performed in accordance with the Guide for the Care and Use of Laboratory Animals published by the U.S. National Institutes of Health and guidelines of the institution where the experiments were performed.\textsuperscript{6}

Device Description

The basic design for the intra-pericardial leads (IPL) used a diamond-shaped loop for stability at
the distal end and a pre-shaped lead body within the diamond loop in which the bipolar, non-steroid eluting, electrodes were located (figure 1). The electrodes were titanium nitride-coated platinum iridium, 5mm² in dimension and 16mm apart. These electrodes were insulated on their outer surface with a silicon-polyurethane copolymer; electrode contact with the myocardium was only possible on the internally facing surface. A polyester mesh to encourage tissue overgrowth and fixation surrounded the electrodes. The cable conductors were coated with co-polymer insulation (PTFE) and co-radially wound. These cables were wrapped around a central lumen that permits insertion of a stylet. Advancement of the stylet in the central lumen slenderized the distal end of the lead for introduction through a 13 Fr. sheath introducer. Retraction of the stylet restores the original diamond loop of the lead and allow for deployment of the stabilizing wings in a suitable location of the epicardial surface within the pericardium. The lead was 92 cm in length. The diameter of the body of the lead was 6 Fr. size. The proximal end has an IS-1 connector pin. This initial lead design (IPL-1) was implanted in 6 canines. Modifications were made to the initial design for implantation in the subsequent 6 experiments. The distal end of the main lead body was reduced to 5.5 Fr. size to allow more flexibility. The distal “nose” tip was reduced in length, the humps on the wings were increased, the polyester mesh adjacent to the electrodes was enlarged and the polyester “sock” proximal to the diamond geometry was lengthened. This modified version is referred to as IPL-2 (figure1).

Implant Procedure

Twelve adult mongrel dogs weighing 20-26 kg were implanted with an implantable cardioverter defibrillator with cardiac resynchronization therapy (CRT-D) under general anesthesia.

Using sterile technique with the animal in a supine position, a sub-xiphoid incision was made to the deep fascia and puncture of the pericardium was performed under fluoroscopy using
a Tuohy needle, aided by injection of contrast and use of a guide wire to confirm entry to the space. A dedicated short steerable sheath (Agilis PF Introducer, St Jude Medical) was used to deliver one IPL to the pericardial space and for positioning to overlie the lateral left ventricular epicardium, where satisfactory electrical performance was confirmed and registered. During the procedure, care was taken to prevent air from entering the pericardial space. If necessary, air was removed using the side port available on the Agilis PF Introducer and a syringe. Using the introducer and syringe in this manner also allowed to check for bleeding within the pericardial space. In an attempt to prevent lead migration, suture sleeves with three ligatures were used to affix the lead to subcutaneous tissue at the subxiphoid location. The lead was then tunneled submuscularly to an incision at the last rib space and then subcutaneously to a subcutaneous pocket for the CRT-D pulse generator, which was fashioned with blunt dissection in the left dorsal side of the thorax area. The incision at the sub-xiphoid access site was closed and sutured.

A standard cut-down of the left external jugular vein was performed. Under fluoroscopic guidance, one 7Fr defibrillation lead with bipolar sensing tip electrodes (St Jude Medical Models Riata 1580, 1581, or 7001) was placed in the right ventricle (RV) with the tip located in the RV apex for all twelve animals. Additional leads were placed for comparison with the IPL. For the first six animals, one active fixation sense/pace bipolar lead (St Jude Medical Model 1688T) was placed in the right atrium (RA). The remaining 6 animals received one bipolar lead (St Jude Medical Model 1058T) implanted into a branch of the coronary sinus (CS) overlying the left ventricle. The RV, RA, and CS leads were tunneled subcutaneously to the previously formed pocket on the left side of the chest and secured with suture sleeves. The RV lead was plugged into the respective port in the CRT-D device. The IPL was plugged into the LV port and the RA or CS lead was plugged into the RA port of the CRT-D device. The leads and device were implanted in the subcutaneous
pocket and the pocket was closed using standard surgical procedures.

**Intra-operative testing**

Standard measurement of all lead parameters including cathodal pacing thresholds (measured at 0.5 ms pulse width), pacing impedances, and intrinsic amplitudes were made in the bipolar mode. For IPL-2, measurements were also made in the unipolar mode to the RV coil. Phrenic nerve stimulation (PNS) was assessed while pacing via the IPL in bipolar mode up to a maximal output of 7.5 V at 0.5 msec.

Fluoroscopic imaging in the anterior posterior and lateral views, were stored to document the initial position of the IPL. With the animal in a lateral position, the stability of the IPL was challenged with the vigorous skeletal muscle contractions associated with 2 high energy R-wave synchronized shocks at 20 and 30 J delivered successively. After these shocks, repeat fluoroscopy images were obtained to record and any shift in position of the IPL.

**Follow Up**

Following the implantation procedure and testing, the animals were recovered and maintained in a standard animal housing facility. Electrical parameters of all leads that included bipolar cathodal pacing thresholds (at 0.5 ms pulse duration), impedances and intrinsic amplitudes were recorded at weekly intervals for 6 weeks, two weekly intervals to 12 weeks, at 4 weekly intervals to week 104, and thereafter, every 6 weeks to the latest time point or to the point of sacrifice. At each pacing check, fluoroscopy images along the same 4 images recorded intra-operatively were collected for offline analysis. In addition, PNS was assessed at each pacing check through visual observation coupled with palpation of the diaphragm during testing. Lastly, two synchronized programmer shocks as during the intra-operative testing, were delivered at week 4 and 12.
Explants and Pathological Examination

Out of the 12 canines, planned explant and pathological studies were performed in 5 animals at weeks 12, 12, 28, 40, and 104 weeks. Two animals were euthanized at weeks 152 and 176 for methicillin resistant staphylococcal infections, one involving the pericardium and the second for methicillin resistant staphylococcal bacteremia. One animal was euthanized for failure to thrive at 188 weeks. Pathological evaluation was available in all 8 animals.

Following euthanasia, the device was explanted. The leads were disconnected from the pulse generator and the IPL was dissected along the lead path to the entry site of the sub-xiphoid lead and photographed. A section of the rib cage was removed for clear view of the thoracic cavity and heart. The condition of the pericardial sac was also noted and photographed. The heart and leads were removed intact from the chest, rinsed and examined. After examination, the heart with leads attached was placed in formalin and prepared for histologic evaluation.

Pathology

Gross examination of the pericardium, heart surface, and IPL was conducted on each heart. The pericardium was removed, where possible, to determine the degree of pericardial/epicardial adhesions and to expose the IPL. Gross photographs were taken to document the findings. The IPL including tissues adjacent to the two electrodes and the polyester mesh were dissected free of the remainder of the heart, and were processed, infiltrated, and embedded in methyl methacrylate (MMA). Following MMA polymerization, radiographs were prepared and used to identify target section areas. Ground sections (~50 μm thick) were prepared and surface-stained (~6 μm) with hematoxylin & eosin. Microscopic examination included cross-sections of proximal and distal electrodes. Whole slide images were prepared using Aperio ScanScope CS (Vista, California) running Spectrum software at 20x equivalent magnification. Once scanned,
digital jpg images were prepared at various magnifications using Aperio ImageScope (V 11.1.2.760). For all digital images, a calibrated axis was included as a scale bar.

**Statistical Analysis:**

Because of the uneven explant schedule of the animals, all analyses of lead parameters were analyzed only over the initial 12 weeks of implantation, the period over which all animals endured. To address non-normal data, a square root transformation was applied to all lead parameters. Changes in IPL-1 and IPL-2 parameters were taken together over these 12 weeks and were assessed using F tests from a repeated measures model assuming compound symmetry of the correlation matrix. To assess a few judiciously selected time points at which IPL parameters might have changed, paired t-tests were used to compare IPL parameters at implant versus 1, 4, and 12 weeks post-implant. Differences in lead parameters between the IPL-1 and IPL-2 leads were assessed using F tests associated with the lead main effect from the repeated measures model.

From the six animals implanted with IPL-2 leads, the IPL-2 pacing parameters were compared to those of the endocardial RV and endovascular CS leads. Paired t-test comparisons of the lead parameters of the IPL-2, endocardial RV, and epicardial CS leads were made at implant and 1, 4, and 12 weeks using a Tukey-Kramer adjustment for multiplicity. Statistical significance for all comparisons was taken as P <0.05. Continuous variables are expressed as mean ± 95% confidence interval (CI) when compared, mean ± standard deviation when purely descriptive, or median and interquartile range as appropriate.

**Results**

All 12 implants were achieved without complications with placement of the IPL in the desired location to overlie the left ventricular epicardial surface, 6 with the initial IPL-1 design and 6
subsequently with the IPL-2 design. Procedure time (from when the Agilis PF Introducer was positioned within the intrapericardial space until the final positioning and electrical testing) for placement of all IPLs was 14 (12-22) minutes. No acute complications occurred during lead placement. In particular, no animal had significant pericardial bleeding leading to cardiac tamponade or arrhythmias.

Stability of Intrapericardial Leads:

None of the IPL-1 nor IPL-2 leads were judged to have dislocated upon delivery of the intra-operative defibrillation shocks. However, three of the six IPL-1 leads were identified having shifted implant position by fluoroscopic imaging comparison over the follow up period; two were noted to have shifted at 1 week post-implant, and the other at 2 weeks post implant but without significant changes in electrical parameters. After this initial observation, all IPL-1 leads remained stable in subsequent follow up. All six IPL-2 leads remained stable, with no identifiable shift in lead position over the duration of the follow up (figure 2).

Electrical Performance

The bipolar pacing impedances, capture thresholds, and R wave amplitudes over the course of follow up of 158 weeks for all the IPLs are shown in Figure 3. The impedance and capture thresholds from the IPLs, taken together, exhibited significant increases over the 12 week maturation period (F test P < 0.001 for the effect of implant duration on each of impedance and threshold). The IPLs sensing amplitudes did not exhibit a significant change over the 12 week maturation period (F test p=0.053). Bipolar capture threshold @ 0.5msec pulse width for all IPLs was 0.69 ± 0.14 V at implant and 1.50 ± 0.34 V at 12 weeks (t test p = 0.003). Pacing lead impedance for all IPL leads was 742 ± 46 ohms at implant and increased to 1066 ± 207 ohms at 12 weeks (t test p = 0.007). R wave amplitude at implant was 12.6 ± 3.1 mV and decreased to 8.4
± 1.5 mV (t test p = 0.034). There was no difference in the electrical performance of the IPL-1 versus the IPL-2 over 12 weeks in capture threshold, R wave amplitude and impedance (F tests p = 0.206, 0.778, and 0.493 respectively).

Comparisons of the IPL-2 pacing parameters to those of the RV and CS LV leads at implant and 1, 4, and 12 weeks are shown in Figure 4. Compared to the endocardial active fixation RV lead, IPL-2 had higher capture thresholds at 1, 4, and 12 weeks. However, there were no differences in the IPL-2 capture thresholds compared with those of the endovascular CS lead at any of the time points. Pacing impedances for the IPL-2 were higher than those of the RV lead at implant, 1, 4, and 12 weeks, but not different than those of the CS lead. R wave sensing for the IPL-2 was comparable to the RV lead and significantly higher than that of the CS lead across the observational period.

Pacing and sensing were tested in the unipolar mode for both proximal and distal electrodes to the RV coil for IPL-2. Highest unipolar pacing threshold at 0.5 msec and lowest R wave for either electrode was 1.0 ± 0.6 V and 14.4 ± 2.9 mV respectively at 12 weeks. Unipolar lead impedances for distal and proximal electrodes were 502 ± 100 and 542 ± 48 ohms respectively at 12 weeks.

None of the 12 animals exhibited PNS intra-operatively, at the stimulus strength of 7.5 V at 0.5 msec. Over the course of follow-up, 11 of the 12 animals did not exhibit any instances of PNS. One animal, implanted with IPL-1, exhibited PNS at pacing amplitudes between 6.0 – 7.5 V during 6 of its 40 follow-up evaluations.

**Gross Pathology and Histology**

Pathological data were available on all 8 euthanized animals at time periods ranging between 12 and 188 weeks (supplemental table). Figure 5 shows a gross appearance of the posterior surface...
of an explant at 104 weeks. The entire lead including the wing and electrodes could be visualized in this specimen with minimal pericardial thickening or fibrosis. In gross examination, none of the animals developed a pericardial effusion.

There was variable degrees of adhesion and thickening of the pericardium with mild inflammatory changes seen in the early explants. However, there was no evidence of inflammation in the planned explants beyond 40 weeks. In all histological studies, there was good adhesion of the electrodes or mesh with the epicardium without damage to underlying blood vessels (figure 6). No major epicardial vessels were directly beneath the pacing electrodes or mesh. In one IPL-1 explant, there was 3mm of epicardial fat separating the proximal electrode from the epicardium (figure 7). Despite this separation, there was adequate pacing threshold with this lead. The distal electrode in this explant was firmly opposed to the epicardium allowing for excellent pacing and sensing thresholds in the bipolar mode. Aside from this one electrode overlying 3 mm epicardial fat, the thickness of fibrotic encapsulation around the electrodes separating them from the epicardium in the IPL-1 explants was 1 mm for 1 electrode, 0.4 – 0.5 mm for 3 electrodes, and <0.1 mm for the remaining electrodes. For the two IPL-2 explants, the encapsulation thicknesses around the four electrodes were all ≤0.1 mm.

In the explants after euthanization for MRSA infection, there was dense pericardial thickening and adhesions to the epicardium. However, there was no evidence for pericardial effusion.

**Discussion**

This report represents the first systematic evaluation of a passive fixation lead system designed for easy percutaneous delivery to the epicardial surface. The present series of experiments provide data on two versions of the epicardial bipolar pacing lead. The main findings are as
follows: 1) Epicardial placement of the IPL can be safely achieved in canine models using a sub-xiphoid approach and dedicated tools to direct placement in areas where adequate pacing and sensing thresholds are obtained. 2) Although IPL-1 lead design was associated with early dislodgement within the pericardial space, subsequent modifications in the IPL-2 design provided for lead stability. 3) IPL pacing thresholds and impedance were comparable to endovascular CS leads for LV pacing, but higher than the endocardial RV leads. Sensing for the IPL-2 was similar to that of the RV leads. 4) Gross and histological examination of planned and unplanned explants showed early inflammatory changes but free of the development of effusion and adequate fixation of the electrodes to the epicardial surface without damage to myocardium or blood vessels.

Despite the greater ease of transvenous implants, incidence of cardiac implantable electronic device (CIED) infections with endocarditis has risen over the years with higher rates for patient on dialysis. In addition, chronic upper extremity vascular occlusion and inadequate left ventricular branches to the coronary sinus for LV pacing necessitate the use of epicardial pacing wires. Surgical epicardial lead placement is associated with a higher upfront morbidity and mortality. Hence, an intra-pericardial lead that can be introduced percutaneously has appeal. Leads have been placed in pediatric patients by percutaneous sub-xiphoid pericardial access or via a small surgical subxiphoid incision to access the pericardial space. In the adult population, surgical access requires more extensive dissection. However, percutaneous pericardial access is now commonly utilized for epicardial ablation of arrhythmias and can be safely achieved in patients without prior cardiac surgery or pericardial disease. In the present study using canine models, successful placement of a novel IPL in a desired location in the pericardial space to overlie the posterior lateral LV was successfully achieved in all 12 dogs.
Electrical measurements in the IPL-lead remained stable over several months after implantation despite the lack of steroid elution in these leads. While the chronic thresholds in the IPL-2 leads were consistently higher than the endocardial RV active fixation lead, the maximum capture threshold registered was 2.5V at 0.5 msec and still within the acceptable limits for an epicardial pacing lead. It was comparable to that of the LV leads placed via the coronary sinus. Histologically, varying degrees of fibrosis and epicardial fat were present beneath the electrodes. The bipolar design of the IPL leads would be expected to allow successful pacing capture and sensing from at least one of the electrodes.

The histological reaction to endocardial leads is well documented in animals and human studies. Typically, there is thrombus formation, localized inflammatory process with granulation tissue and gradual replacement with fibrous tissue. Defibrillation leads incite a greater fibrotic reaction compared to pacemaker leads. The findings relating to the passive fixation IPL leads followed a similar pattern but without the initial thrombosis. There was variable fibrotic reaction that resulted in adequate fixation of the electrodes and the surrounding mesh to the epicardial surface and/or pericardium. The fibrous tissue at the interface appears to be minimal and does not influence the electrical measurements over the longer term. No epicardial vessels were entrapped beneath the lead in these experiments but second-order arterioles and venules beneath the electrodes were not affected.

Potential problems relating to an IPL lead include the issue of access to the pericardial space. In adults, access to the pericardial space for epicardial ablation for ventricular tachycardia was first described by Sosa et al. in 1996 and increasingly utilized for ablation. Nevertheless, a “dry” pericardial tap can be associated with complications that include intra-abdominal bleeding, laceration of the liver, injury to the coronary arteries and cardiac perforation.
RV puncture is the most common complication encountered in 4.5% of 215 consecutive cases in a series by Sosa et al. However, RV puncture rarely causes continued bleeding and often seals spontaneously. In the absence of prior pericardial inflammation or cardiac surgery, catheters and sheaths can be moved about freely within the pericardial space to deploy a lead in a desired area. In this series, we chose the posterior lateral LV for lead location because this is the area where activation commonly occurs latest during left bundle branch block and is thus, a good location for pacing for cardiac resynchronization therapy. The issue of extracardiac stimulation eg. phrenic nerve, is theoretically eliminated by the lead design that employs insulation over the outer surface of the electrodes. In this series, no late migration of the lead was seen. However, migration is possible in the presence of undetected pericardial effusion. Finally, in the event of infection that involves the pericardial space, removal will most likely entail surgical intervention. In the early stages, advancement of a sheath over the lead for retraction may be possible but we have no information regarding safety of this technique. In the present series, two animals developed staphylococcal infection, involving the pericardium in one and requiring euthanization at weeks 152 and 176. These were likely due to secondary seeding of the devices from an unidentified primary source.

**Limitations**

Complete data on the 12 animals is only available to 12 weeks and hence the demonstrated stability and performance of this lead is short term. Planned and unplanned sacrifices at various time points have however, provided data on histo-pathology spanning 12 to 188 weeks. Four surviving animals have continued to demonstrate adequate lead performance. Finally, epicardial fat layers may be thicker in the human heart with possible interference with pacing capture although it is unusual to encounter significant adipose tissue over low posterior-lateral LV where
IPL were positioned in the present series of experiments.

Conclusion

In this first systematic study of a novel percutaneously introduced IPL in the canine model, we have demonstrated adequate stability of the lead in the pericardial space without dislodgement, adequate pacing and sensing threshold and no damage to the epicardial surface or underlying small blood vessels. An IPL lead has potential applications in cardiac pacing when transvenous access is not possible or desirable.

Conflict of Interest Disclosures: Roy M. John has received modest honoraria for lectures from St. Jude Medical, Inc., Medtronic, Inc., and Boston Scientific, Inc. Kevin Morgan and Michael E. Benser are employees of St. Jude Medical, Inc. Pierre Jais is a consultant to Biosense Webster, Inc., and St. Jude Medical, Inc. Lucas H. Brennecke has nothing to disclosure.

Reference:


Figure Legends:

Figure 1: Ventral view (left panel) and a schematic of a cross section at the electrode (right panel) of the intrapericardial lead version 2 (IPL-2). Right panel: 1 = A layer of insulation overlying the outer surface of the electrode to prevent phrenic nerve capture. 2 = Polyester mesh surrounding the electrode. 3 = Active electrode to contact with the epicardial surface. Note the central bore in the electrode for steroid (not incorporated in the IPLs tested in this study). 4 = Weld of the conductor coil to the ring of the electrode. 5 = Central lumen of the lead.

Figure 2: Anterior-posterior fluoroscopic views at implant and at 116 weeks of an IPL-2 lead implant. The epicardial lead overlies the posterior lateral LV with no discernible change in position over the period of monitoring. RV = right ventricular; CS = coronary sinus; IPL-2 = intrapericardial lead version 2.

Figure 3: Bipolar pacing capture threshold, R-wave sensing amplitude and pacing impedance for the IPL leads. Each P value versus implant (t tests). The data represent 12 animals through 12 weeks; 10 animals through 28 weeks; 9 through 40; 8 through 104; 7 through 152; and 6 through
158. Data represented as mean ± 95% CI.

**Figure 4:** Comparisons of bipolar capture threshold, R wave sensing amplitude, and pacing impedance of IPL-2 with RV and CS leads from implant through 12 weeks. The top row of P values in each graph represents IPL-2 vs CS lead (t tests); the bottom row represents IPL-2 vs endocardial RV lead (t tests). Data represented as mean and 95% CI.

**Figure 5:** Gross appearance of an explanted heart at 104 weeks. The posterior view of the heart is shown. The lead with the electrodes, stabilizing wings can be visualized through a translucent pericardium that demonstrated minimal thickening.

**Figure 6:** Histological appearance of the proximal electrode and its interface with the myocardium at 104 weeks in low power (left panel) and high power (right panel). Dense fibrous tissue lines the polyester mesh. No inflammatory cells were present. The base of the electrode was separated from the the epicardial myocardium by 3 mm of fat despite which there was adequate bipolar capture due to excellent apposition of the distal electrode. A small arteriole within the epicardial fat showed no abnormality from the overlying electrode.

**Figure 7:** Histological appearance of the distal electrode and its interface with the myocardium in the same specimen as in figure 6. Both the low (left panel) and high (right panel) power images show close apposition of the electrode to the myocardial surface with a thin fibrous layer separating the electrode and the myocardium. The polyester mesh is encased in fibrous tissue and separated from the myocardium by epicardial fat.
Pre-shaped lead body

Stabilizing loop

Pacing electrodes with surrounding polyester mesh
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SUPPLEMENTAL MATERIAL

Table: Time to explant for each experiment, gross and histological findings at pathological examination.
<table>
<thead>
<tr>
<th>Animal No. and type of lead</th>
<th>Explant time</th>
<th>Reason for Explant</th>
<th>General Gross Appearance</th>
<th>Pericardium Gross</th>
<th>Presence of fluid</th>
<th>Histology (presence of fibrosis and extent)</th>
<th>Inflammation yes/no</th>
<th>Underlying myocardium</th>
<th>Epicardial fat/Vessels</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 IPL-1</td>
<td>12 wks</td>
<td>Planned</td>
<td>Mild epicardial bruising beneath distal electrode</td>
<td>Multifocal areas of fibrinous adhesion between epicardium and pericardium</td>
<td>no</td>
<td>Proximal electrode attached to epicardium by mild to moderate fibrous connective tissue and small areas of loose connective tissue.</td>
<td>Small numbers of lymphocytes and plasma cells. Mild to moderate granulomatous inflammation surrounding mesh on epicardial surface.</td>
<td>Normal</td>
<td>No fat or vessels</td>
</tr>
<tr>
<td>2 IPL-1</td>
<td>12 wks</td>
<td>Planned</td>
<td>Both electrodes firmly attached to epicardium and pericardium</td>
<td>Unremarkable</td>
<td>no</td>
<td>Electrodes firmly compressed against epicardium with thin fibrous capsule around the mesh</td>
<td>Mild inflammatory cell infiltration</td>
<td>Underlying myocardium normal</td>
<td>Epicardial fat present and small arteriole within fat unremarkable</td>
</tr>
<tr>
<td>3 IPL-2</td>
<td>28 wks</td>
<td>Planned</td>
<td>Grossly unremarkable</td>
<td>Minimal fibrosis all around lead body from site of entry into pericardium.</td>
<td>no</td>
<td>Fibrous tissue (&lt;100µm) between electrodes and epicardium, Both electrodes separated</td>
<td>Macrophages and giant cell infiltration beneath mesh that had separated</td>
<td>Normal</td>
<td>Small venule and arterioles beneath within epicardial fat between</td>
</tr>
<tr>
<td></td>
<td>IPL-1</td>
<td>40 wks</td>
<td>Planned</td>
<td>Electrodes firmly adherent to epicardium and mesh encapsulated in fibrous tissue. from epicardium</td>
<td>Minimal fibrosis between electrodes and epicardium but electrodes and mesh encased in fibrous capsule.</td>
<td>Minimal fibrosis under electrodes (&lt; 1 mm). No inflammatory cell infiltrate.</td>
<td>Normal myocardium</td>
<td>No blood vessels in vicinity of electrodes/mesh.</td>
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<tr>
<td>4</td>
<td>IPL-1</td>
<td>104 wks</td>
<td>Planned</td>
<td>Translucent pericardium with no adhesions. Significant pericardial fibrosis of adhesions around the electrodes but some fibrosis around entry of lead to pericardial space. No inflammation.</td>
<td>No significant fibrotic reaction around electrodes but mesh attached to myocardium with mild fibrosis. No inflammation.</td>
<td>Normal myocardium. Proximal electrode separated from myocardium by 3 mm of fat. Small arteriole and vein unremarkable. Distal electrode in direct contact with myocardium with 50µm of fibrosis.</td>
<td>No fat or vessels beneath.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>IPL-1</td>
<td>152 wks</td>
<td>Euthanized for MRSA Infection</td>
<td>Epicardium deep red and had extensive pericardial fibrosis. Both</td>
<td>No obvious fibrosis externally. Extensive fibrinous pericardial adhesion to epicardium all around the heart.</td>
<td>Normal.</td>
<td>No blood vessels in vicinity of electrodes/mesh.</td>
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<tr>
<td>6</td>
<td>IPL-2</td>
<td></td>
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<td></td>
<td>No fat or vessels beneath.</td>
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<tr>
<td>Animal</td>
<td>Duration</td>
<td>Euthanizing Reason</td>
<td>Observations</td>
<td>Electrode Attachment</td>
<td>Fibrosis</td>
<td>Adhesion</td>
<td>Myocardium</td>
<td>Fat Thickness</td>
<td>Inflammation</td>
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<tr>
<td>7 IPL-1</td>
<td>176 wks</td>
<td>Euthanized for MRSA bacteremia</td>
<td>Minimal fibrotic reaction externally but pericardium firmly attached to epicardium over most of the heart</td>
<td>Both electrodes attached by fibrosis to epicardium and pericardium</td>
<td>no</td>
<td>Minimal fibrosis around polyester mesh attaching mesh to epicardial surface.</td>
<td>No inflammation</td>
<td>Myocardium beneath electrodes and mesh was normal.</td>
<td>0.8 mm of fat beneath electrode but no inflammatory infiltrate. Venule 0.5 mm from electrode in fat unremarkable.</td>
</tr>
<tr>
<td>8 IPL-1</td>
<td>188 wks</td>
<td>Euthanized for lymphoma</td>
<td>Extensive pericardial thickening and fibrosis</td>
<td>Pericardium adhered to epicardium. Electrodes encapsulated by fibrous tissue but poor attachment to epicardium</td>
<td>no</td>
<td>Mild fibrosis around proximal electrode but none around distal electrode</td>
<td>No</td>
<td>Normal myocardium</td>
<td>Electrodes separated from myocardium by 200µm of fat and connective tissue. No blood vessels</td>
</tr>
</tbody>
</table>