ABSTRACT

OBJECTIVES This study hypothesized that shielded electrodes could capture myocardium without extracardiac stimulation.

BACKGROUND Epicardial cardiac resynchronization therapy (CRT) permits unrestricted electrode positioning. However, this therapy requires surgical placement of device leads and risks unwanted phrenic nerve stimulation.

METHODS In 6 dog and 5 swine experiments, we used a percutaneous approach to access the epicardial surface of the heart and deployed novel leads housing multiple electrodes with selective insulation. Bipolar pacing thresholds at pre-specified sites were tested to compare electrode threshold data, facing both toward and away from the epicardial surface.

RESULTS In 151 paired electrode recordings (70 in 6 dogs; 81 in 5 swine), thresholds facing myocardium were lower than those facing away (median threshold of 0.9 [interquartile range (IQR): 0.4 to 1.6] mA vs. 4.6 [IQR: 2.1 to >10.0] mA, respectively, for dogs, p < 0.0001; and 0.5 [IQR: 0.2 to 1.0] mA vs 2.5 [IQR: 0.5 to 6.8] mA, respectively, for swine, p < 0.0001). Myocardial capture was feasible without extracardiac stimulation at all tested sites, with mean ± SE threshold margin of 3.6 ± 0.7 mA at sites of high output extracardiac stimulation (p = 0.004).

CONCLUSIONS Selective electrode insulation confers directional pacing to a multi-electrode epicardial pacing lead. This device has the potential for a novel percutaneous epicardial resynchronization therapy that permits placement at an optimal pacing site, irrespective of the anatomy of the coronary veins or phrenic nerves. (J Am Coll Cardiol EP 2015;1:273–83) © 2015 by the American College of Cardiology Foundation.

Cardiac resynchronization therapy (CRT) results in a significant reduction in mortality and symptoms in selected patients with heart failure (1). However, challenges remain with current approaches to resynchronization, including a high rate of non-responders due in part to anatomical limitations in negotiating the coronary venous system, resulting in suboptimal lead placement, phrenic stimulation precluding therapy delivery, and the risks and challenges associated with endovascular lead placement in specific patients such as those with congenital heart disease and patent foramen ovale (2,3). The alternative is the use of epicardial leads placed directly onto the left ventricle. However,
LEAD DESIGN AND PROTOTYPING. The novel partially insulated multi-electrode lead was designed to be introduced percutaneously into the pericardial cavity and permit multiple pacing vectors to be applied over a variably wide epicardial surface area. This was accomplished through use of an expanding design, which could be introduced into a sheath in a low-profile state and then expanded once deployed in the pericardium to permit pacing and sensing from desired regions (Figures 1 to 3). Electrodes were selectively insulated to direct the electric field toward myocardial tissue, permitting pacing without extracardiac stimulation and defibrillation without pain. The purpose of this initial study was to confirm that these self-expanding novel leads could be placed percutaneously in the pericardial space and thus could selectively pace myocardium while avoiding extracardiac stimulation, regardless of their position.

METHODS

ELECTROPHYSIOLOGY LABORATORY SETUP. All experiments were carried out in customized large-animal translational cardiac catheterization laboratories (Siemens, Erlangen, Germany) at the Cardiovascular Innovation Laboratory at Mayo Clinic, Rochester, Minnesota (canine studies) and at the Cardiovascular Animal Research Center in the Laboratory for Advanced Cardiovascular and Central Nervous System Interventions at the School of Veterinary Medicine, University of Veterinary and Pharmaceutical Sciences, Brno, Czech Republic (porcine studies). Electrophysiological studies were performed using the Cardiolab System (version 6.8.1 release 2, GE Healthcare, Wauwatosa, Wisconsin) using standard cardiac stimulators. Regular bipolar configurations between electrodes arranged in parallel between
lead arms (1-2, 3-4, 5-6, and 7-8) or serially along each arm (1-3, 2-4, and 1-5) were used (Figure 3). Sensed signals were gained 500 times and processed with 30- to 500-Hz band pass and 60-Hz notch filters.

**ANIMAL PREPARATION.** The study was approved by the Mayo Clinic Animal Care and Use Committee and the Ethics Committee of the University of Veterinary and Pharmaceutical Sciences, Brno, Czech Republic. Six male mongrel dogs (mass of 30.2 ± 3.6 kg) and 5 female swine (47.6 ± 4.8 kg), all in sinus rhythm on study initiation, were maintained under general anesthesia using ketamine (10 mg/kg) and diazepam (0.5 mg/kg) and mechanical ventilation with 1% to 3% isoflurane. Paralytic agents were not used. Continuous surface electrocardiography (ECG) was monitored with placement of standard limb leads and a V1 chest lead. Continuous intra-arterial blood pressure was monitored using a 9-F left femoral artery sheath. An intracardiac echocardiography (ICE) catheter was introduced through a 1-2F sheath placed in the right external jugular vein. Two 9-F sheaths were placed, one in each of the right and left femoral veins for additional endovascular access. Sheaths were placed using Seldinger technique.
PERCUTANEOUS PERICARDIAL ACCESS. Percutaneous pericardial access of the anterior surface of the heart was obtained using the technique described by Sosa (6) and, upon progressive dilatation of the access site with serially larger diameter dilators, 1 to 2 of the prototype steerable sheaths were deployed in the pericardial space. Pneumopericardium and pericardial effusions were monitored for using ICE and fluoroscopy and controlled using pericardial aspiration from the sheath. The novel leads were introduced into the sheath, which was steered under fluoroscopic guidance to guide the lead to standardized locations over the right ventricular outflow tract (RVOT), anterolateral left ventricular free wall (LV), and left atrial appendage (LAA). The radiopaque marker was used to ascertain which direction the exposed electrode surfaces faced (Figure 3).

EPICARDIAL PACING AND EXTRACARDIAC STIMULATION. Bipolar pacing was tested in regions with adequately sensed signals and no significant mechanical or electrical interference. Pulsed square waves of 2-ms duration were delivered at a regular frequency of 15% above basal heart rate, starting at an output of 10 mA and reducing gradually until capture threshold was reached. Capture was confirmed by a concordant change in surface ECG and arterial pressure waveform rates. Paced QRS complex and epicardial electrograms were compared to those sensed in intrinsic rhythm to differentiate atrial and/or ventricular capture (Online Figure 2).

Sensed signals were analyzed offline for slew, ensuring that signals of <0.5 mV from uninsulated electrode surfaces facing the myocardial surface were excluded from analysis. Slew was measured at the highest frequency near-field electrogram deflection.

Extracardiac stimulation (both phrenic and chest wall musculature) was noted using inspection, palpation, and fluoroscopy while pacing. If stable extracardiac stimulation was noted, the capture threshold was determined as the pacing output at which no further extracardiac stimulation occurred. If no extracardiac stimulation was noted during standard pacing maneuvers, then phrenic location and integrity were confirmed by high output pacing with electrodes facing away or using a pacing probe through the lead’s central channel.

Using side-by-side fluoroscopic images to ensure comparable catheter location, leads were rotated such that the electrodes were turned from facing the heart.
to facing the serosal surface of the parietal pericardium, and the above-described protocol was repeated to generate paired sensing and pacing data. At the end of the procedure, a standard endovascular electrophysiology catheter was introduced into the ventricle, and the animal was sacrificed by inducing ventricular fibrillation through either rapid ventricular pacing or application of direct current. Necropsy was performed immediately upon death to assess pericardial access and document injury to cardiac and extracardiac structures.

**STATISTICAL ANALYSIS.** Statistical analysis was performed using JMP version 10.0.0 software (SAS Institute Inc., San Francisco, California). Non-normally distributed data were expressed as medians and interquartile ranges (IQRs). Paired readings of slew and pacing thresholds were assessed using the Wilcoxon signed rank test. Correlation between slew and threshold was compared using Spearman rho. Differences in lead parameters between sites and electrodes were compared using the Wilcoxon rank sum test. The null hypothesis was rejected at a 2-tailed p value of <0.05.

**RESULTS**

**EPICARDIAL LEAD PLACEMENT.** Successful epicardial access and placement of 1 to 2 epicardial sheaths was achieved for all animals. The steerable sheaths allowed for easy maneuverability of the pacing leads within the pericardial space and for placement over the RVOT, anterolateral LV, and LAA, while the nitinol loops leveraged the pericardium to provide lead stability.

**INSULATED SENSING AND PACING.** Data from a total of 151 paired electrode recordings were analyzed.
(70 in dogs and 81 in swine) to compare pacing thresholds when the exposed electrode surfaces were directed toward the myocardial surface versus facing away. In both of the animal models, the pacing threshold was significantly lower when facing the myocardium than when facing away (median dog threshold of 0.9 [IQR: 0.4 to 1.6] mA vs. 4.6 [IQR: 2.1 to >10.0] mA, p < 0.0001; and median swine threshold of 0.5 [IQR: 0.2 to 1.0] mA vs. 2.5 [IQR: 0.5 to 6.8] mA, respectively, p < 0.0001) (Figure 4).

With electrodes directed toward myocardium, capture was feasible without extracardiac stimulation (either phrenic or chest wall musculature) at the pacing sites in all experiments, including sites in juxtaposition with the phrenic nerve. With high output, extracardiac capture with electrodes facing myocardium was noted at 4 of 70 sites (5.7%) in canine and 5 of 81 sites (6.2%) in porcine experiments. Thresholds were significantly lower for myocardial than extracardiac capture (0.3 [IQR: 0.1 to 1.5] mA vs. 5 [IQR: 1.7 to 7.0] mA; threshold margin of 3.6 ± 0.7 mA, p = 0.004).

Analysis of sensed epicardial signals in canine experiments demonstrated a clear, high frequency signal after an initial low frequency signal, which presumably represented near-field epicardial activation following initial far-field endocardial activation, permitting analysis of slew on the near-field component (Figure 5). There were significant differences between sensed signals obtained from electrodes directed onto the myocardium and those obtained from electrodes facing away (median of 3.4 [IQR: 1.4 to 6.5] V/s toward vs. 1.7 [IQR: 1.0 to 2.7] V/s away; p < 0.0001) and an inverse correlation between slew and myocardial pacing threshold (Spearman’s rho = −0.401, p = 0.0002). In contrast, sensed signals obtained in porcine experiments were multicomponent, with multiple discreet, high-frequency components, which rendered slew analysis unreliable, despite a visible reduction in signal frequency when electrodes were directed away (Figure 6).

**Effect of Lead Position and Interelectrode Distance on Lead Function.** Depending on electrode position, pacing captured the atrium (when electrodes were over the appendage or atrial tissue) or the ventricle. The lower pacing thresholds with electrodes facing the myocardium were consistently present, regardless of pacing site or electrode vector. In dogs, there was more variability in thresholds when pacing thresholds were obtained at the LAA than at the RVOT and LV; whereas in swine, there was less variability at the LAA as compared than at the RVOT and LV (Figure 7). We noted a difference in anatomical approach in navigation to the prespecified pacing sites between the two species. To reach the LAA in dogs, the lead had to be maneuvered to a leftward posterolateral position, whereas in swine, a more anterior approach was often sufficient and required less distortion of the lead, particularly the distal-most electrode bipole, which had the least accuracy, particularly in canine experiments (Figure 7). To confirm that the increased thresholds noted on the distal-most electrodes were not due to increased interelectrode distance, we repeated threshold testing for electrodes with arms apart vs. together over the RVOT in a single canine experiment. There were no significant differences between thresholds of parallel bipoles (apart: 0.55 [IQR: 0.35 to 1.4] vs. together: 0.95 [IQR: 0.3 to 3.2], p = 0.31).

**Complications and Necropsy Findings.** Successful entry into the anterior pericardial space through the connective tissue superficial to the diaphragm was confirmed in all animals (Figure 8). There were no significant arrhythmias caused by lead placement and pacing. Sheath- and access-related trauma were seen in 3 experiments. In one, inadvertent laceration of the distal left anterior descending artery during serial sheath dilatation was tolerated hemodynamically once pericardial blood was aspirated, allowing for successful completion of the study. In another, the study was performed with
a wire entrapped in the left ventricle after inadvertent entry and knotting therein after ensuring that it was not causing ventricular ectopy, mitral regurgitation, or ventricular dysfunction. In a third, there was inadvertent puncture and exit of the sheath through the pericardium overlying the left atrial appendage, which resulted in the inability to manipulate the lead over the appendage for sensing and pacing due to exit from the pericardium each time. Isolated minor abrasions on the inferior surface of the heart were noted in four experiments and were of uncertain significance, possibly created during sheath placement, with no bleeding or evidence of myocardial injury during the procedure. There were no pacing-related complications in any experiment.

DISCUSSION

The 2 main findings of our study are: 1) epicardial pacing via subxiphoid percutaneous access is feasible using novel self-expanding leads that collapse for sheath placement and expand in the pericardium; and 2) insulated electrodes confer directionality and preference to pacing the myocardial surface and permitting epicardial pacing without extracardiac stimulation, even when the electrodes are positioned directly opposite the phrenic nerve. A standardized experimental protocol and prototypes yielded comparable results at 2 separate experimental sites located on separate continents, with multiple operators involved, and with different large animal models used, suggesting a robustness to this approach and a
shallow learning curve. To the best of our knowledge, this is the first reported use of percutaneously placed, insulated epicardial electrodes to confer directional pacing for these purposes.

Previous studies have reported the use of subxiphoid and subcostal surgical approaches for epicardial pacing (9–11) and, together with our report on a completely percutaneous approach, support the utility of the pericardial space as a vantage point for bioelectrical therapies for heart failure. Specifically for pacing for CRT, these therapies include access to left-sided chambers without the limitations set by coronary sinus anatomy, avoid bloodstream infections due to endovascular foreign material, or lead thromboembolism (3). This may be particularly relevant to patients with an especially high risk of adverse events from endocardial leads, such as those with cyanotic congenital heart disease, intracardiac shunts, or bloodstream infections (2). Furthermore, coronary sinus leads have a significant failure rate due to both dislodgement and from revisions necessitated by symptomatic extracardiac stimulation, although similar long-term experience using percutaneous epicardial leads is lacking in comparison.

We designed our leads to harness the pericardium for mechanical support, introduced supportive nitinol loops to provide additional lead and lead arm stability, and contoured the lead to the natural curvature of the cardiac surface. These actions together resulted in good lead stability and function at the areas of interest. A combination of fluoroscopic and electrical navigation was sufficient for accurate placement, and ICE was used to monitor for complications to chambers, valves, and pericardium. The use of steerable sheaths greatly facilitated maneuverability of leads, and the successful use of this strategy for epicardial ablation has been previously reported (12). We investigated whether our data were influenced by differences in interelectrode distances between the parallel bipolar configuration, with the more distal electrode pair being farther apart than

![Comparison of Sensed Epicardial Signals in Dogs Versus Those in Swine](image-url)
the proximal pair (Figures 1 and 3) and were not able to demonstrate this. We did find, however, that, owing to the size and shape of the forked design, the distal-most pair had a higher threshold, most likely due to interaction with the valvular annuli and great vessels and over corners that needed to be negotiated, a finding which is being incorporated into designing the next prototypes for chronic, indwelling use.

Because of the course of the phrenic nerves in intimate proximity to the pericardium (13) and other electrically active thoracic structures in close vicinity (nerves and skeletal muscle), preventing phrenic and extracardiac stimulations are important considerations as epicardial pacing strategies are developed. With coronary sinus lead placement, phrenic stimulation affects approximately 15% to 30% of patients (14,15), requiring either repositioning the lead or electrically reprogramming another vector, both of which may result in lead dysfunction (16,17). Detecting phrenic stimulation at implantation has intimate proximity to the pericardium (13) and other indwelling use.

Variability in pacing thresholds from electrodes directed toward myocardium at different anatomical sites (top) and between electrode configurations (bottom). Box and whisker plots summarize individual pacing thresholds from all experiments (6 dogs with 70 data points, 5 pigs with 81 data points), with median, first, and third quartiles marked by the middle band and top and bottom of the box, respectively, range is marked by the whiskers, and potential outliers by disconnected points. Note, LAA was the site with greatest variability in pacing threshold in dogs and least variability in swine, and the distal-most electrode pair (1-2) had greatest variability (see text for details). Numbers represent epicardial electrode configuration as shown in Figure 3. LAA = left atrial appendage; LV = left ventricle; RVOT = right ventricular outflow tract. (Figures 7 and 8)
human implementation. Based on comparably similar performance in both of the large-animal species in this study, we predict that the currently prototyped platform would require minimal modification for clinical use. The complications seen were all related to pericardial access and sheath deployment, which suggests that an alteration to sheath profile may be required. In addition, future studies are ongoing and/or planned to establish the medium to long-term effectiveness, stability, safety, and tolerability of a chronic lead design. Prototyping and testing of a screw-in mechanism and imaging guidance to identify and thereby avoid coronary vasculature are currently under way.

**STUDY LIMITATIONS.** We did not investigate the effects of pacing on cardiac activation and recovery (31) or the various forms of dys-synchrony (atrio-ventricular, interventricular, and intraventricular), nor have we fully explored the utility of this approach for ablation, defibrillation, or autonomic modulation (32,33). Given the growing understanding of autonomic modulation of arrhythmogenesis, selectively insulated electrodes facing away from the myocardium may be useful for adjunctive autonomic stimulation as part of an implanted system. Long-term human application will also have to consider the relative risks and benefits of such an approach once prototype refinement is finalized, as well as the challenges in pericardial access imparted by cardiac surgery, thoracic irradiation, and prior pericarditis.

**CLINICAL IMPLICATIONS.** This novel multi-electrode lead with insulated electrodes demonstrates effective myocardial pacing in preclinical large animal studies without extracardiac stimulation. This device has the potential for a novel percutaneous epicardial resynchronization therapy that permits placement at an optimal pacing site, irrespective of the anatomy of the coronary veins or phrenic nerves.

**CONCLUSIONS**

A novel, percutaneously placed multi-electrode epicardial pacing lead confers directional pacing to the myocardial surface. Combined with the use of a steerable sheath, effective myocardial pacing at multiple sites was possible with good lead stability and without extracardiac stimulation. This strategy may prove promising for a percutaneous epicardial atrial and ventricular pacing device.

**REPRINT REQUESTS AND CORRESPONDENCE:** Dr. Samuel J. Asirvatham, Division of Cardiovascular Diseases, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905. E-mail: asirvatham.samuel@mayo.edu.

**PERSPECTIVES**

**COMPETENCY IN MEDICAL KNOWLEDGE:** A novel, self-expandable lead designed for percutaneous epicardial pacing with multiple electrodes, shaped and directed to maximize myocardial contact and selectively insulated to minimize extracardiac pacing, allowed for directionality and preference to pacing the myocardial surface. This permitted epicardial pacing without extracardiac stimulation, even when the electrodes are positioned directly opposite the phrenic nerve.

**TRANSLATIONAL OUTLOOK:** This innovation provides a therapeutic approach for epicardial pacing which overcomes current limitations of cardiac resynchronization therapy, including a high rate of non-responders due in part to suboptimal lead placement afforded by coronary venous anatomy; phrenic stimulation; and vascular lead complications.
REFERENCES


KEY WORDS: bioelectrical therapy, biventricular pacing, cardiac resynchronization therapy, epicardial mapping, epicardial pacing, minimally invasive, multisite pacing, pericardial intervention, phrenic nerve stimulation, steerable pericardial sheath

APPENDIX For supplemental figures and videos, please see the online version of this article.