Long-term performance of a novel communicating antitachycardia pacing–enabled leadless pacemaker and subcutaneous implantable cardioverter-defibrillator system: A comprehensive preclinical study

Karel T.N. Breeman, MD,* Bryan Swackhamer, BSChE,† Amy J. Brisben, PhD,† Anne-Floor B.E. Quast, MD, PhD,* Nathan Carter, MS,† Allan Shuros, MS,† Brian Soltis, MS,† Brendan E. Koop, PhD,† Martin C. Burke, DO,‡ Arthur A.M. Wilde, MD, PhD,* Fleur V.Y. Tjong, MD, PhD,*1 Reinoud E. Knops, MD, PhD*1

From the *Heart Center, Department of Clinical and Experimental Cardiology, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands, †Boston Scientific Corporation, St. Paul, Minnesota, and ‡CorVita Science Foundation, Chicago, Illinois.

BACKGROUND Subcutaneous implantable cardioverter-defibrillators (S-ICDs) and leadless pacemakers (LPs) are intended to diminish transvenous lead–related complications. However, S-ICDs do not deliver antibradycardia pacing or antitachycardia pacing, and currently, there is no commercially available coordinated leadless option for patients with defibrillator and (expected) pacing needs.

OBJECTIVE We evaluated the performance, safety, and potential replacement strategies of a novel modular cardiac rhythm management (mCRM) system, a wirelessly communicating antitachycardia pacing–enabled LP and S-ICD in a preclinical model.

METHODS LP implantation was attempted in 68 canine subjects, and in 38 an S-ICD was implanted as well. Animals were evaluated serially up to 18 months. At all evaluations, communication thresholds (CTs) between the devices, LP electrical parameters, and system-related complications were assessed. Different replacement strategies were tested.

RESULTS The LP was successfully implanted in 67 of 68 (98.5%) and the concomitant S-ICD in 38 of 38 (100%). mCRM communication was successful in 1022 of 1024 evaluations (99.8%). The mean CT was 2.2 ± 0.7 V at implantation and stable afterward (18 months: 1.8 ± 0.7 V). In multivariable analysis, larger LP-to-S-ICD angle and dorsal posture were associated with higher CTs. At implantation, the mean pacing capture threshold, impedance, and R-wave amplitude were 0.3 ± 0.1 V, 898.4 ± 198.9 Ω, and 26.4 ± 8.2 mV. The mean pacing capture threshold remained stable and impedance and R-wave amplitudes were within acceptable ranges throughout (0.7 ± 0.4 V, 619.1 ± 90.6 Ω, and 20.1 ± 8.4 mV at 18 months). Different replacement strategies seem feasible.

CONCLUSION This first mCRM system demonstrated excellent performance up to 18 months in a preclinical model.

KEYWORDS Leadless pacemaker; Antitachycardia pacing; Subcutaneous ICD; Modular therapy; Wireless communication

Introduction
Cardiac implantable electronic devices are increasingly used in patients with (a risk of) brady- or tachyarrhythmias. Patients with cardiac implantable electronic devices have a risk of complications that are mainly lead and pocket related.1 To address these transvenous lead–related complications, in the last 15 years, subcutaneous implantable cardioverter-defibrillators (S-ICDs) and leadless pacemakers (LPs) have been developed.2,3 However, the S-ICD is not yet suitable for patients requiring both defibrillator therapy and...
antibradycardia pacing and/or antitachycardia pacing (ATP). In those patients, a transvenous ICD is implanted, adding the risk of lead-related complications. Moreover, when patients requiring defibrillator therapy are expected to develop a future pacing need, physicians often prefer a transvenous ICD over the S-ICD. These preemptive transvenous ICD implantations also carry the risk of lead-related complications, while only a subset of patients will benefit from pacing therapy enabled by the lead. This urges the need for modular cardiac rhythm management (mCRM) strategy, in which only the device(s) indicated at that moment are implanted and additional devices implanted later when needed.

The first developed mCRM system is a novel LP in combination with an S-ICD. Similar to the currently available LPs, this LP is placed in the right ventricle (RV) and is capable of RV pacing. This LP can also coordinate with the S-ICD to deliver ATP. Notably, since this LP and the S-ICD can be implanted separately, patients may receive an S-ICD first and an LP later only when an indication develops, or vice versa. The preclinical short-term (≤90 days) performance and safety of this first mCRM system were promising. In this study, we evaluated the long-term preclinical performance and safety.

Our research questions were as follows:

1. What is the long-term performance of the mCRM system in terms of device-device communication from the S-ICD to the LP and LP electrical parameters (pacing threshold, impedance, and R-wave amplitude)?
2. What is the long-term safety of the mCRM system in terms of complications, valvular function, and pericardial effusion due to fixation mechanism exposure?
3. Which replacement strategies are feasible for the LP?

Methods
In this preclinical prospective study, 68 canine subjects (52 [76%] male; mean age 454 ± 159 days; mean weight 30.0 ± 3.8 kg) were used (including 23 dogs with an mCRM system in which 3-month performance was described previously). The mCRM system and its operation are shown in Figure 1. Currently available EMBLEM S-ICDs (Boston Scientific, St. Paul, MN) underwent a firmware update, allowing the S-ICD to send ATP requests to the LP; thus, existing implanted S-ICDs can be used as an mCRM system. The S-ICD senses ventricular tachyarrhythmias identically to standard S-ICDs, but for termination, the S-ICD can send ATP requests to the LP through bursts of subthreshold low-voltage pulses from the S-ICD coil to the S-ICD pulse generator (PG) as a coded message (Figures 1B and 1C). This coded message is to be recognized by the LP, which is then triggered to provide ATP (Figure 1D). ATP can be requested before shock therapy when the arrhythmia is detected in the conditional shock zone or in parallel with charging for a shock when detected in the shock zone. Further device characteristics and implantation techniques have been described in detail previously. The 3-incision technique was used for the S-ICD implantations. The experiments consisted of primary single LP (EMPOWER, Boston Scientific) implantations with an S-ICD (EMBLEM) implanted in a subgroup and different replacement strategy experiments, with long-term follow-up. All preclinical experiments were conducted in compliance with applicable government guidelines. Experimental protocols were accepted by the ethical boards of American Preclinical Services (Minneapolis, MN) and Boston Scientific.

Experimental protocol primary single implantations
A primary single LP implantation procedure was attempted in all 68 animals, and in 38 concomitant S-ICD implantation was attempted (37 simultaneously with LP implantation, 1 after LP implantation). Animals were evaluated directly post-implantation and at follow-up visits after 3, 7, 14, 28, 45, 60, 75, and 90 days and every 3 months thereafter until killing. Evaluations after participation in different replacement strategies are described separately. At all evaluations, the performance of the mCRM system and the occurrence of clinical complications were assessed. In a subgroup, echocardiography was performed before implantation and during follow-up visits by using commercially available ultrasound (Vivid 9, General Electric, Fairfield, CT) and a 2.5-MHz transducer. Mitral regurgitation (MR) and tricuspid regurgitation (TR) severity were estimated visually using Doppler color flow.

mCRM performance parameters
The S-ICD-to-LP communication threshold (in volts) was defined as the minimum communication signal voltage of the ATP request resulting in the LP successfully receiving the signal for 2 consecutive attempts of a given signal voltage. A step-down/step-up testing protocol was followed, with intervals of 0.5 V and the starting signal voltage informed by previous experience. In anticipated clinical use, the minimum output will be 4.0 V and maximum output 7.0 V and the output will be programmed 1.0 V above the communication threshold at 1 month (safety margin). We programmed the output including safety margin accordingly (except for using the predischarge instead of 1-month visit). We defined successful communication as a communication threshold below the safety margin of the output. At predischarge, a threshold of ≤6.0 V was deemed successful to guarantee a 1.0 V safety margin.

As communication threshold is thought to be optimal when the long axis of the LP is aligned parallel to the S-ICD coil-PG communication vector to account for potential degradation in other orientations, the communication threshold was tested with the animals in dorsal, left lateral, and right lateral postures and the highest value was noted as threshold. In animals with both devices, the angle of the LP long axis to the S-ICD coil and whether the LP was within the space between the S-ICD coil and the generator in the dorsoventral view (Online
Supplemental Data 1) were assessed by radiography directly postimplantation. Pacing capture threshold (PCT; in volts) at 0.4 or 0.5 ms pulse width (results are pooled), pacing impedance (in ohms), and R-wave amplitudes (in millivolts) were also assessed. Acute experiments assessing ATP delivery, postshock LP performance, S-ICD rhythm discrimination, and communication during simulated ventricular tachycardias were also conducted and described previously.6

**Figure 1**  
A: Modular cardiac rhythm management system consisting of a leadless pacemaker (LP) and subcutaneous implantable cardioverter-defibrillator (S-ICD). B: Communication signal sent from the S-ICD to the LP. C: Communication vector between the S-ICD and the LP. D: Ventricular tachycardia (VT) terminated by S-ICD–requested antitachycardia pacing (ATP) delivered by the LP. Reproduced with permission of Tjong et al.7

**mCRM safety parameters**
Safety parameters were clinically evident complications during follow-up and valvular dysfunction or pericardial effusion assessed by echocardiography.

**Experimental protocol replacement strategies**
The feasibility of different replacement strategies was assessed. LP retrieval was attempted under fluoroscopy in
28 animals, and in 2 a new LP was implanted after retrieval. Either a single-loop snare, triloop snare, or both were used. To study the abandonment strategy, an adjacent second LP was placed after 90 days in 5 animals and 3 LPs were implanted simultaneously in 4 animals. Afterward, electrical performance of all implanted LPs, clinical complications, and echocardiographic parameters were assessed similarly to primary single implants. In animals with 2 LPs in situ, the communication threshold of the S-ICD with both LPs was also tested (in 4 of 5 animals owing to 1 anesthetic death before testing). In clinical practice, though, the abandoned LP would need to be deactivated. Of note, secondary LPs were implanted via the left femoral vein as the right femoral vein would need to be deactivated. Of note, secondary LPs were implanted via the left femoral vein as the right femoral vein (RFV) was ligated after primary LP implantation in this model.

Necropsy
Animals with ≥1 successfully implanted LP (n = 65; 2 are still alive) were killed after varying time intervals, followed by necropsy. A single LP was in situ at necropsy in 39 animals, 2 or 3 LPs were in place in 4 animals, and the remaining 18 animals underwent successful LP retrieval before necropsy (alive: n = 17; postmortem: n = 1). In animals with a single LP in situ, pericardial fluid volume and color (hemorrhagic, serosanguinous, and serous) and epicardial fixation mechanism exposure were assessed. In all animals, degree of LP encapsulation was assessed by direct measurement or measuring length of remaining encapsulating tissue after retrieval.

Statistical analysis
Descriptive statistics are presented as mean ± SD or median (interquartile range [IQR]) for continuous variables and as frequency (percentage) for categorical variables. Differences in communication threshold, PCT, impedance, and R-wave amplitude over time were assessed using paired t tests (short-term: day 0 to day 90; long-term: day 90 to 18 months). Multivariable analysis was performed to assess factors influencing the communication threshold. The correlation between the degree of encapsulation and the terminal communication threshold was assessed using the Spearman correlation. Wilcoxon signed rank, Wilcoxon rank sum, χ², and Friedman tests were used for testing for differences between groups and between follow-up moments. In most analyses, certain animals were excluded because of diverse reasons (see Online Supplemental Data 2 for further details).

Results
mCRM system implantation
LP implantation was successful in 67 of 68 animals (99%). In the unsuccessful implant, the delivery catheter sleeve of a prototype catheter design detached from the catheter, embolized to the pulmonary arteries, and could not be retrieved percutaneously, after which the animal was killed. In the successful implants, the RFV was used except for 2 where the left femoral vein was used because of the small RFV vessel size. The LPs were implanted in the RV apex (n = 59 [88.1%]), RV septum (n = 3 [4.5%]), RV apical septum (n = 2 [3.0%]), anterolateral wall (n = 2 [3.0%]), and free wall (n = 1 [1.5%]). The number of necessary (ie, PCT >1.0 V@0.5 ms, not for research purposes) deployment attempts was 1 in 88%, 2 in 10%, and 3 in 2%. The implant duration was 84 ± 30 minutes (includes acute experiments), and the fluoroscopy duration was 8 ± 6 minutes.

S-ICD implantations were successful in all 38 animals. The PG was positioned on the left lateral side, of which 8 in a Parsonnet pouch and the coil on the right lateral side adjacent to the sternum. The average angle between the LP and the S-ICD coil was 25° ± 8°. In the dorsoventral view, the LP was located in between the S-ICD coil and the generator in 6 ("straddling," 16%) and outside the space between the S-ICD coil and the generator in 18 (47%). All successful LP implantations and S-ICD implantations were uncomplicated.

Long-term mCRM system performance
Communication between the S-ICD and the LP (baseline: n = 38) was successful in 1022 of 1024 attempts (99.8%). The 2 unsuccessful attempts were due to increased communication thresholds: 6.0 V at day 7 in 1 dog and 5.0 V at day 75 in another. Although the thresholds were below 7.0 V (maximum output), we considered those unsuccessful because the thresholds exceeded the programmed output value, including a safety margin of 1.0 V, per the anticipated clinical programming strategy. In both cases, behavior was transient, returning to an adequate value at subsequent follow-up. Of note, the unsuccessful attempts were in the left lateral and dorsal postures and the simultaneously measured thresholds in other postures were normal for those animals. Of the successful communication attempts, 1018 of 1022 (99.6%) were below 4.0 V (minimal programmable value) and 4 were between 4.0 and 7.0 V. The mean communication threshold up to 18 months is shown in Figure 2. The communication threshold at implantation was 2.2 ± 0.7 V, which decreased significantly to 1.6 ± 0.6 V at day 90 (P < .001), did not change significantly thereafter, and was 1.8 ± 0.7 V at 18 months (P = .092). In 1 animal, results were available up to 36 months, with communication thresholds of 2.0 V at day 0, 1.0 V at day 90, 2.0 V at 18 months, and 1.5 V at 36 months. The communication did not cause muscle stimulation. The S-ICD system did not migrate in 3 (8%), migrated minimally in 10 (27%), moderately in 18 (49%), and significantly in 2 (5%).

Multivariable analysis of the predefined variables potentially affecting communication threshold is shown in Figure 3. Adjusted for baseline communication threshold and day of testing, larger angle between the LP and the S-ICD coil and dorsal posture were predictive of a higher communication threshold. There was no significant correlation between the degree of encapsulation (in percentage) at killing and the last measured communication threshold (P = .69).
Pacing threshold, impedance, and R-wave amplitude (baseline: n = 67) are shown up to 18 months after implantation in Figure 4. The mean PCT was low and increased significantly from day 0 to day 90 (0.3 ± 0.1 and 0.8 ± 0.6 V; $P < .001$) and was stable from day 90 to 18 months (0.7 ± 0.4 V at 18 months; $P = .700$). Impedance decreased significantly from day 0 to day 90 (898.4 ± 198.9 and 766.5 ± 178.8 Ω; $P < .001$) and decreased further up to 18 months (619.1 ± 90.6 Ω at 18 months; $P < .001$). R-wave amplitude decreased slightly from day 0 to day 90 (26.4 ± 8.2 and 24.1 ± 7.7 mV; $P = .102$) and decreased significantly from day 90 to 18 months (20.1 ± 8.4 mV at 18 months; $P = .027$).

mCRM system long-term safety
Two LP-related complications occurred. Both were prototype accelerometer (used for rate-responsive pacing) malfunctions that caused premature battery depletion with loss of communication after 12–15 months in 1 animal. Design changes were made to the accelerometer, and the performance was verified by extensive bench testing. Thirteen S-ICD–related complications occurred—all pocket/incision infections. Eleven were managed by antibiotics; in 2 cases extraction was necessary (at days 9 and 345). Most infections were observed in early concomitant LP and S-ICD implantations, after which the implant procedure was revised (see Discussion), and fewer infections were seen afterward.

Echocardiography in all animals with a single LP showed no increase in TR at 90 days and 18 months ($P = .317$ and $P = .705$, respectively). MR was increased only at 90 days ($P = .002$) but not at 18 months ($P = .317$) (Figure 5; severe TR was not seen). The percentage of animals paced during transthoracic echocardiography (TTE) examination was 0% at day 0, 60% at day 90, and 44% at 18 months ($P = .03$).

Directly postimplantation, no pericardial effusion was seen in animals with a single LP in situ (n = 63). At TTE during follow-up (90 days: n = 37; 18 months: n = 25), no

---

**Figure 2** Modular cardiac rhythm management communication threshold stability up to 18 months. Error bars represent mean ± SD. S-ICD = subcutaneous implantable cardioverter-defibrillator.

**Figure 3** Multivariable analysis of the predictors of the communication threshold. LP = leadless pacemaker; mCRM = modular cardiac rhythm management; RVA = right ventricular apex; RVAS = right ventricular apical septum; RVFW = right ventricular free wall; S-ICD = subcutaneous implantable cardioverter-defibrillator; wrt = with respect to.
pericardial effusion was seen either. In 39 dogs with a single LP in situ at necropsy (median 365 [IQR 90–540] days after implantation), fixation mechanism exposure on the epicardium was seen in 8 (21%). TTE at baseline and either 90 days or 18 months was available for all 8. Fixation mechanism exposure was not associated with pericardial fluid volume (P = .814) or color (P = .590). For 2 animals, pericardial fluid volume and color were not available; fixation mechanism exposure was not observed in either of these cases. The implant location was the RV apex in 38 and RV septum in 1; fixation mechanism exposure was seen in only apically implanted LPs.

mCRM system replacement strategies
Single implanted LP retrieval was attempted in 28 animals after a median of 540 (IQR 7–562) days. Retrieval was successful in 17 of 28 (61%). Unsuccessful retrievals were most commonly due to complete encapsulation (5 of 28) and tissue within the LP snare groove (3 of 28); in 1 case it was attributed to limited maneuverability due to the small animal cardiac anatomy, and in 2 the cause was unknown (no tissue encapsulation). There was no significant difference in the degree of encapsulation in animals killed at 90–120 days vs 18–19 months (median 53% [IQR 22%–100%] vs 56% [IQR 31%–96%];

Figure 4  (A) Leadless pacemaker (LP) pacing threshold, (B) impedance, and (C) R-wave amplitude stability over time up to 18 months. Error bars represent mean ± SD.
In failed retrievals, there was a significantly higher degree of encapsulation than in successful retrievals (median 79% [IQR 47%–100%] vs 25% [IQR 0%–53%]; P < .001; Figure 6B). There were no procedural complications at retrieval.

A new LP was implanted immediately before retrieval of the first LP at 18 months in 2 animals. Both implantations and subsequent retrievals were successful without complications. One new LP was implanted in the RV septum and 1 in the RV free wall. Subsequently, follow-up was 90 days in 1 and 18 months in the other animal. Pacing threshold, impedance, and R-wave amplitude were constantly within acceptable ranges.

A new second LP was successfully placed alongside the first at 90 days in 5 animals. One complication occurred in which an animal suffered anesthetic death 2.5 hours after implantation. Communication threshold and electrical parameters of the first and second LPs were tested up to 18 months after primary LP implantation. The communication was successful in 70 of 72 attempts (97%). The 2 unsuccessful attempts were in the same animal at different follow-up visits in different postures, and both unsuccessful attempts were ≤7.0 V. No unusual LP location or other clear explanation was identified. Pacing threshold, impedance, and R-wave amplitude of both LPs were constantly within acceptable ranges.

In 4 animals, 3 LPs were implanted simultaneously. In 1 animal, follow-up was 28 days; and in 3, 90 days. There were no complications. PCT was acceptable in all but 1 LP, in which a maximum threshold of 4.5 V was seen at 28 days, which decreased to 3.5 V at 90 days. However, the mean decrease in PCT up to 90 days was comparable to primary single LPs (0.5 V). Impedance and R-wave amplitude were within acceptable ranges.

Discussion

A previous animal study demonstrated successful short-term (≤90 days) performance of the first developed mCRM system consisting of a novel LP and S-ICD. This subsequent animal study provides 3 key findings: (1) the mCRM system has excellent long-term (up to 18 months) performance with low stable communication thresholds for device-device communication and adequate LP electrical parameters, (2) long-term safety was acceptable, with most complications related to animal anatomy and physiology or prototype LP and delivery catheters as well as absence of pericardial complications despite fixation mechanism exposure in 21%, and (3) different replacement strategies are feasible.

The key feature of the mCRM system is the wirelessly conducted unidirectional communication from the S-ICD to the LP to deliver ATP. In our study, communication was successful in 99.8% of attempts. The overall communication threshold was consistently lower than the minimum programmable value. We found the communication threshold to be independent of the LP location in relation to the S-ICD on dorsoventral radiography and the degree of S-ICD system migration. Only a larger angle between the LP and the S-ICD coil and dorsal posture were predictive of higher thresholds. These suggest that although in theory, a larger angle should cause lower communication thresholds because the LP sensing dipole would be more parallel to the communication vector, this has limited clinical relevance. The 2 unsuccessful communication attempts were unrelated to angle, posture, or follow-up time point; thus, multivariable analysis results did not provide a root cause for these unsuccessful attempts. As behavior was transient without intervention, we think the likeliest cause would be varying of the precise S-ICD can location during testing, perhaps related to relatively loose subcutaneous tissue in the canine model. A potential solution in clinical practice would be to increase the safety margin of the output value. The effect of communication on S-ICD longevity is expected to be negligible owing to the low signal amplitude and short pulse width, even if a higher output is necessary in humans. An upcoming clinical trial will evaluate communication results in patients.
The LP showed adequate long-term pacemaker functionality through 18 months. Most importantly, PCT increased up to 90 days but was stable afterward. While impedance and R-wave amplitude decreased over time, the values were within acceptable ranges. Electrical parameters were comparable to earlier preclinical and clinical studies in transvenous pacemakers and LPs.10–13

A few complications occurred in this study. As most complications were related to animal anatomy and physiology and prototype device, those are not anticipated in human use of an improved design. A prototype LP delivery catheter malfunctioned, after which design changes were made. A prototype accelerometer malfunction was found; root cause analysis demonstrated a design flaw, which was corrected, and the resulting performance was verified by extensive bench testing. Other complications such as vascular complications, perforations, or pericardial effusion were not seen at LP implantation nor during follow-up. Fixation mechanism exposure was seen at necropsy in 21%, but apparently did not cause pericardial effusion or clinical signs of other

![Figure 6](Image)

A: Leadless pacemaker (LP) encapsulation degree after different implant durations, with exemplary necropsy depictions of complete encapsulation (necropsy at 91 days) and little (19%) encapsulation (necropsy at 540 days). B: Retrieval success for different encapsulation degrees.
pericardial complications. This is in line with a preclinical (porcine) study of the Micra LP (Medtronic, Minneapolis, Minnesota), which also uses a tine-based fixation mechanism: fixation mechanism exposure was seen in 7 of 10 pigs, and no pericardial effusion was noted.\textsuperscript{12} In clinical LP studies, fixation mechanism exposure has not been studied yet but pericardial effusion occurred in 0.4%–1.6% of patients.\textsuperscript{2,14} Only S-ICD complications were infections, which were determined to be partly due to the order of operations, for example, with conducted telemetry cable placement near the S-ICD incisions, and partly due to the canine model, with the caudal sternal incision particularly subject to disturbance in the prone posture. The procedure was subsequently revised to closely resemble clinical conditions with beneficial reduction in the number of infections. S-ICD system migration occurred frequently in this study. Clinical studies report only low rates (<2%) of S-ICD migration necessitating surgical intervention.\textsuperscript{15} We therefore think that the presently described migration rate is due to the canine anatomy (loose subcutaneous tissue) and physiology (more ribcage motion). Regardless, our multivariable analysis demonstrated that S-ICD migration did not affect communication thresholds. No significantly increased TR or MR was seen at 18 months. At 90 days, more MR was seen, which could be explained by the higher number of paced animals.

Optimal LP replacement strategy is not yet defined, but both replacing the LP and abandoning and implanting an adjacent LP were proven feasible in our small-scale experiments. Retrieval failures due to tissue overgrowth were common, while dwelling time was only up to 18 months. Retrievals in humans may be successful more often, as the dedicated retrieval catheter is designed for the human anatomy and not for the smaller canine anatomy. Other LPs have demonstrated a high (85%–90%) retrieval success rate up to 4 years, despite signs of encapsulation.\textsuperscript{16–18} Conversely, retrieval failure may occur more often after a longer dwelling time, which is to be expected in human use. Therefore, in longer-term implanted devices, the abandonment strategy may be an important alternative. In animals with 2 or 3 simultaneously dwelling LPs, electrical performance was similar to primary single LPs. Only in 1 animal with 3 LPs, the PCT of 1 LP was unacceptably high, possibly because of mechanical interaction between the coimplanted LPs in an animal RV that is smaller than the typical human RV. There are no data on the simultaneous presence of 3 LPs in humans, but in a group of patients with 2 LPs, no mechanical or electrical interactions were noted.\textsuperscript{16}

This study has several limitations and uncertainties. The implant duration underestimates the duration expected in humans, as it also encompassed acute experiments in some animals. The predischARGE visit was performed at day 0 and not at day 1 to minimize animal suffering. Further, LP performance cannot be directly extrapolated to humans: for instance, the R-wave amplitude is known to be higher in canine subjects. In addition, most LPs were implanted in the RV apex as a consequence of the animal model; ideally in human subjects, LP implants would target the RV septum.


