Novel therapies in cardiac rhythm management

The start of the leadless era

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Chapter 14

Acute and 3-Month Performance of a Communicating Leadless Antitachycardia Pacemaker and Subcutaneous Implantable Defibrillator


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Abstract
Objectives
The primary objective was to assess the acute and 3-month performance of the modular antitachycardia pacing (ATP)-enabled leadless pacemaker (LP) and subcutaneous implantable cardioverter-defibrillator (S-ICD) system, particularly device–device communication and ATP delivery.

Background
Transvenous pacemakers and implantable cardioverter-defibrillators (ICDs) have considerable rates of lead complications. We examined the next step in multicomponent leadless cardiac rhythm management: feasibility of pacing (including ATP) by a LP, commanded by an implanted S-ICD through wireless, intrabody, device–device communication.

Methods
The combined modular cardiac rhythm management therapy system of the LP and S-ICD prototypes was evaluated in 3 animal models (ovine, porcine, and canine) both in acute and chronic (90 days) experiments. LP performance, S-ICD to LP communication, S-ICD and LP rhythm discrimination, and ATP delivery triggered by the S-ICD were tested.

Results
The LP and S-ICD were successfully implanted in 98% of the animals (39 of 40). Of the 39 animals, 23 were followed up for 90 days post-implant. LP performance was adequate and exhibited appropriate VVI behavior during the 90 days of follow-up in all tested animals. Unidirectional communication between the S-ICD and LP was successful in 99% (398 of 401) of attempts, resulting in 100% ATP delivery by the LP (10 beats at 81% of the coupling interval). Adequate S-ICD sensing was observed during normal sinus rhythm, LP pacing, and ventricular tachycardia/ventricular fibrillation.

Conclusions
This study presents the preclinical acute and chronic performance of the combined function of an ATP-enabled LP and S-ICD. Appropriate VVI functionality, successful wireless device–device communication, and ATP delivery were demonstrated by the LP. Clinical studies on safety and performance are needed.
Introduction
Transvenous pacemakers and implantable cardioverter-defibrillators (ICDs) are effective treatment modalities for cardiac bradyarrhythmias and tachyarrhythmias (1–4). However, these systems are associated with device-related complications, mostly related to the transvenous leads, which result in morbidity and mortality. Transvenous pace and shock leads have shown high failure rates during long-term clinical follow-up (5–7). Device infections (sometimes involving the pocket but more so when systemic) are associated with a high risk of mortality (8). To reduce complications related to transvenous leads, both the leadless pacemaker (LP) and the subcutaneous implantable cardioverter-defibrillators (S-ICDs) were introduced and have shown clinical efficacy and safety (9–13). To date, these systems are only available for patients either requiring single-chamber right ventricular (RV) pacing or shock-only defibrillation therapy. Combined use of both devices could bring the benefits of leadless therapy to a larger patient population by providing both bradycardia pacing and defibrillation therapy. Limited evidence on the combined use of both devices has been reported in case studies (14,15). For patients in need of antitachycardia pacing (ATP) therapy, there are no leadless solutions available to date. We recently reported the first proof-of-concept study of a unidirectional LP and S-ICD that can deliver bradycardia pacing, ATP, and defibrillation therapy (16). These combined device systems require safe and reliable device–device communication and enable a novel treatment concept of modular cardiac rhythm management (CRM) therapy. The present preclinical study describes the acute and chronic performance of this modular CRM system. The objectives of this study were to assess the acute and chronic feasibility and performance of this novel modular CRM therapy, with regard to the following: 1) the performance of an ATP-enabled LP; 2) unidirectional device–device communication from an S-ICD to an LP; 3) S-ICD–triggered ATP delivery by an LP; and 4) S-ICD and LP rhythm discrimination during device–device communication, LP pacing, and ventricular fibrillation.

Methods
These data were collected prospectively involving both acute and chronic experiments in 3 animal models (ovine, n = 8; porcine, n = 5; and canine, n = 27). The protocols were pre-reviewed and acceptable to animal use and utilization ethics boards at both Academic Medical Center, University of Amsterdam (Amsterdam, the Netherlands) and Boston Scientific Corporation (St. Paul, Minnesota). They were to be conducted in compliance with the applicable government guidelines.

Modular CRM therapy system
The modular ATP-enabled LP and S-ICD system (both, Boston Scientific Corporation, Marlborough, Massachusetts) are shown in Figure 1. The prototype modular CRM system comprises an S-ICD and a standard S-ICD electrode, an LP, a catheter-based delivery and retrieval system, and programmers with software dedicated for each device (Supplement Figure 1). The S-ICD pulse generator is a device based on the EMBLEM platform (Boston Scientific Corporation) with updated firmware to enable conducted communication to the LP. The LP is a rate-responsive, single-chamber pacemaker that has a self-contained battery and active-fixation nitinol tines.

Figure 1
The S-ICD uses unidirectional conductive communication to command the LP and radiofrequency signals to communicate with its programmer. The LP uses conductive communication to communicate with its programmer. During the course of the study, development of the LP was ongoing, and improvements in the microprocessor and software were introduced; no changes were made to the design or shape of the LP, the delivery catheter, or the S-ICD.

Implantation protocols

An ATP-enabled LP prototype was implanted in the RV apex, using a percutaneous, transfemoral approach through a 21-F introducer sheath using a designated delivery catheter with “telescope feature” for catheter extension (Figure 2). The LP was deployed by engaging 4 nitinol tines into the myocardium. After evaluating adequate fixation with gentle traction and obtaining satisfactory electrical measurements, the LP was released by removing the tether. The LP was interrogated, and baseline performance measures were obtained.

Figure 2

(A) The leadless pacemaker (LP) delivery catheter is advanced through 21-F introducer sheath in the inferior vena cava. (B) The delivery catheter is advanced and deflected in the right ventricle by using the telescope feature to extend the LP into the right ventricular apicoseptal region. (C) The LP is fixated with 4 nitinol tines that engage in the myocardial tissue. (D) Close-up of the LP fixation mechanism. (E) Implanted LP released from delivery catheter but still connected with tether to test electrical measurements and adequate fixation by gentle traction on the tether.

The S-ICD prototype was implanted under fluoroscopic guidance with the pulse generator placement in the left lateral side of the thorax and the coil on the contralateral side of the thorax (position ranging from right parasternal to right lateral side) to ensure an adequate shock and communication vector between coil and pulse generator, which would be representative of what is expected in chronic human use. During the course of the study, an external bandaging technique was introduced to stabilize the S-ICD in the pocket because of excessive motion of the S-ICD pulse generator in the canine skin pockets. A bandage was wrapped around the abdomen and back of the animal and on top of the S-ICD pocket to hold the S-ICD stable for postural changes of the animal during communication testing. The S-ICD uses 1 of 3 electrocardiographic recording “vectors” for heart rhythm discrimination. The most optimal sensing vector for each implant was chosen and programmed. S-ICD to LP communication was assessed and checked for interference, and heart rhythm discrimination was evaluated. A decapolar electrophysiology catheter (Polaris X Steerable Diagnostic Catheter, Boston Scientific Corporation, Marlborough, Massachusetts) was inserted into the left ventricle via left femoral artery access and used to pace the left ventricle to simulate monomorphic ventricular tachycardia (VT) morphology at rates in the therapy zone settings of the S-ICD.
Acute and 3-month modular CRM system performance

The purpose of the acute experiments was to assess the safety and feasibility of the ATP-enabled LP and S-ICD implantation to test unidirectional device–device communication, S-ICD–initiated ATP delivery, and S-ICD and LP rhythm discrimination during intrinsic rhythm, LP pacing, and ventricular fibrillation (VF). Healthy domestic ovine (mean weight 78 ± 12 kg), porcine (mean weight 65 ± 11 kg), and canine (mean weight 29 ± 3 kg) models were used. All but 23 canines were killed immediately after the experiments. In the chronic experiments, the 3-month safety and performance of the combined LP and S-ICD implants were assessed. The objectives of the acute experiments were assessed in this chronic model with a follow-up duration of 90 days using the remaining 23 healthy canines (mean weight 30 ± 3 kg). After successful implantation, the animals were recovered and followed up at serial time points. At 3, 7, 14, 28, 45, 60, and 75 days post-implant, the animals underwent follow-up evaluations that included clinical assessment, assessment of LP and S-ICD performance, and device–device communication. At 90 ± 14 days after implantation, ATP and shock, S-ICD rhythm discrimination, and post-shock LP performance testing was performed in 13 of 23 animals, which were hereafter immediately killed. The remaining 10 animals will be followed up for long-term safety and performance of the modular CRM system.

All chronic animals underwent standard transthoracic two-dimensional echocardiography at baseline pre-implant, immediately post-implant, and at day 90 by using a commercially available ultrasound system (Vivid 9, General Electric, Fairfield, Connecticut) with a 2.5-MHz transducer. Valvular regurgitation was estimated visually by using Doppler color flow. The following parameters were evaluated: valvular regurgitation severity (none, 0; mild, 1+; moderate, 2+; moderate to severe, 3+; and severe, 4+); RV long- and short-axis dimensions; left ventricular ejection fraction by biplane method of discs; heart function and wall motion by visual estimation; pericardial effusion by visual estimation; distance from tricuspid valve to device; and tricuspid valve interaction by visual estimation.

Device–device communication

Communication between the S-ICD and the LP is unidirectional, from S-ICD to LP, via electrically conducted signals. A series of short electrical pulses (the “ATP request”) is transmitted by the S-ICD using a vector (the “communication vector”) from the shocking coil to the can. The orientation of the LP relative to the communication vector of the S-ICD can affect its ability to sense the communication signals. Theoretically, optimal communication is achieved when the long-axis of the LP is positioned parallel to the communication vector; given anatomical constraints, this approach is also generally approximately perpendicular (90°) to the S-ICD coil (Supplemental Figure 2). The LP is designed to recognize the communication signals as being sent from the S-ICD and to distinguish communication signals from noise or other sources of electromagnetic interference. Device–device communication testing consisted of: 1) evaluation of successful communication between the S-ICD and LP during sinus rhythm and simulated VT; 2) evaluation of the communication threshold, defined as the minimum transmit amplitude for successful receipt of the ATP request by the LP; and 3) evaluation of the device orientation of the LP within the communication vector (measured by the angle between the long-axis of the LP and the S-ICD coil) (Supplemental Methods for extended description).

ATP therapy delivery by the LP

ATP therapy delivery success was defined as successful ATP delivery by the LP following an ATP request signal. In the acute experiments, this outcome was tested both on the manual ATP request and after an automated ATP request initiated by the modular CRM system during a simulated VT. In the chronic experiments, the full automated therapy sequence of the modular CRM system (ATP followed by S-ICD shock) was evaluated at 90 days post-implant. The S-ICD was programmed with a conditional shock zone of 170 to 220 beats/min (with 3 ATP requests, then shock), and a shock zone of >220 beats/min, and the left ventricular catheter was used to pace into the conditional shock zone and evaluate the S-ICD’s therapy response. Other scenarios were also evaluated, such as a single shock zone of >170 beats/min to evaluate a single ATP request and parallel charging for shock delivery. The number of successful ATP communications and ATP deliveries was recorded. If the heart rate was above the programmed LP tachycardia lower limit (e.g., 155 beats/min) when the series of pulses is received, the LP will deliver ATP in accordance with its programmed parameters (i.e., scheme, coupling/burst interval).
**Gross pathology examination**
In all chronic animals (n = 13) killed after 90 days of follow-up, a gross pathological examination was performed to assess the following: 1) LP fixation/position in the right ventricle; 2) the existence of tissue encapsulation of the LP; and 3) the existence of pericardial effusion/tine protrusion.

**Statistical analysis**
Descriptive statistics are presented as mean ± SD or median (interquartile range) for continuous variables and as frequencies and percentages for categorical variables. In the chronic experiments, the paired Student t test was used to compare means of continuous variables at specific time points; to test R-wave differences over time, a linear regression model was used. All analyses were conducted with SPSS version 20.0 (IBM SPSS Statistics, IBM Corporation, Armonk, New York).

**Results**

**Implantation of the modular CRM system**
In 38 animals, the LP was successfully implanted via the right femoral vein. In 1 animal, the catheter could not be introduced on the right side due to incompatible vessel diameter but was successfully implanted via the left side. One animal was replaced due to an aborted procedure because of a prototype catheter malfunction without an LP implant attempt. The LP was implanted in 24 (62%) in the RV apex, 14 (36%) in a low septal position, and 1 (2%) in the RV outflow tract. The duration of the implant procedure of the LP ranged between 59 and 119 min. Echocardiographic evaluation post-implant (n = 23) showed no pericardial effusion, no changes in tricuspid regurgitation, and no interaction of the LP with the tricuspid valve compared with baseline (Supplemental Table 1, Online Video 1). The mean distance of the LP to the tricuspid valve leaflets was 2.2 ± 0.6 cm. The S-ICD was successfully implanted in all 39 animals with the pulse generator on the left lateral side and the coil of the lead on the contralateral side (ranging from right parasternal to right lateral chest).

**Acute modular CRM performance**
During acute testing, the LP bradycardia pacing functionality was assessed in all 39 animals. The mean pacing threshold, R-wave amplitude, and impedance at implant were 0.53 ± 0.42 V at 0.5 ms, 19.9 ± 9.9 mV, and 727 ± 193 Ω, respectively. Pacing threshold testing was performed at 0.4 ms (n = 11) or 0.5 ms (n = 28) pulse width; for this analysis, these values are pooled, and the R-wave amplitude measurements in the canine (n = 26) models were right-censored at 25 mV. S-ICD heart rhythm discrimination was correct during intrinsic and LP pacing above the intrinsic rate and did not result in oversensing (Figure 3). Induction of VF in the presence of ventricular asynchronous pacing at 60 ppm was performed in 7 animals to verify proper discrimination and therapy delivery by the S-ICD (Supplemental Figure 3).

**Figure 3**

![Primary Vector (Sense B to Can)](Primary Vector (Sense B to Can))

![Secondary Vector (Sense A to Can)](Secondary Vector (Sense A to Can))

![Alternate Vector (Sense A to Sense B)](Alternate Vector (Sense A to Sense B))

**NSR**

**LP Pacing**
Unidirectional device–device communication from the S-ICD to the LP via conductive communication was attempted in all implanted animals and was successful in 306 (99%) of 309 communication attempts in the dorsal position of the animals.

All ATP requests that were triggered by the S-ICD and received by the LP (306 of 306) resulted in ATP therapy delivery. Figure 4 displays an example of successful ATP delivery by the LP. ATP therapy consisted of 10 beats of pacing at the maximum pacing output of 5 V at 1 ms timed at 81% of the previous coupling interval. An example of the complete therapy sequence (3 times ATP therapy bursts followed by an S-ICD shock) can be appreciated in Online Video 2 (only online).

Figure 4

![Figure 4](image_url)

In all animals with anteroposterior fluoroscopy images (n = 23) obtained at implantation, the device orientation of the LP was assessed. The median angle of the LP to the S-ICD coil was 28° (range 4 to 39°). The device–device communication was successful in all of these animals, with a mean communication threshold of 2.5 ± 0.8 V.

3-month modular CRM performance

All but 1 animal (22 of 23 [96%]) completed the 90-day follow-up of the modular CRM system. In the 1 animal, only chronic LP performance was obtained due to removal of the S-ICD at day 9 post-implant because of a pocket infection. In 9 other animals, a local S-ICD pocket infection was suspected but did not lead to device removal or systemic infection in these animals. Potential causes of these infections were suboptimal sterile conditions of the animal operating room, no use of pre-operative antibiotics, and bandage technique. Several precautions were introduced to minimize the risk for infection in subsequent animal implants. The chronic electrical performance of the LP showed a small increase in pacing threshold (p < 0.001) and a decrease in R-wave amplitude (p = 0.001) and impedance (p = 0.04) between baseline and 90 days of follow-up (Table 1). The electrical measurements at 7, 28, and 90 days, respectively, were as follows: mean pacing threshold (at 0.5 ms), 0.56 ± 0.37 V (n = 20), 0.54 ± 0.30 V (n = 20), and 0.72 ± 0.45 V (n = 19); mean R-wave amplitude, 26.3 ± 6.8 mV (n = 14), 25.0 ± 9.4 mV (n = 15), and 23.3 ± 9.4 mV (n = 23); and mean impedance, 785 ± 129 Ω (n = 14), 827 ± 105 Ω (n = 20), and 728 ± 141 Ω (n = 22) (Supplemental Figure 4). R-wave measurements were clipped at 25 mV. Several data points at different time points were excluded from the analysis based on the following reasons: LP prototypes without steroid-eluting drug on electrode (n = 3), suspected prototype LP malfunction (n = 1), and inaccurate measurements of R wave and impedance due to prototype programmer software coding errors (n = 9).
Table 1

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<th>Acute Performance (n=40)</th>
<th>3-Month Performance (n=23)</th>
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<td>Implant characteristics</td>
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<td>Implant success, n (%)</td>
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<td>RV apex, n (%)</td>
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<td>LP electrical performance</td>
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<td>Pacing threshold, V at 0.5 ms</td>
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<td>R-wave amplitude, mV</td>
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<td>Impedance, Ohms</td>
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<td>Pre-/post-shock change in impedance, Ohms</td>
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* Pacing threshold data from 3 animals were excluded because LP prototypes did not have steroid eluting electrode.
† R-wave and impedance data from 7 animals at Baseline, 9 animals at Day 7, and 7 animals at Day 28 were excluded due to programmer software malfunction.
‡ Impedance and pacing threshold data from 1 animal was excluded due to suspected device malfunction at Day 90.
§ P-value between baseline and 90 days, for pacing threshold and impedance tested with t-test, for R-wave calculated with a linear regression analysis.

Acute and 3-Month LP Performance

Echocardiographic evaluation at 90 days (n = 17) revealed no pericardial effusion or mean change in tricuspid regurgitation; interaction between the tricuspid valve was noted in 2 animals (12%), leading to an increase in tricuspid regurgitation in 1 animal (Supplemental Table 1, Online Video 1).

The chronic device–device communication success was 100% (92 of 92 attempts) (Figure 5). In addition, 100% of the communication signals were successfully translated into ATP delivery by the LP. The mean communication thresholds decreased from baseline to 90-day follow-up in all 3 postures: 2.5 ± 0.8 V to 1.6 ± 0.6 V for the dorsal (supine) position, 1.9 ± 0.4 V to 1.6 ± 0.5 V for the left lateral position, and 1.8 ± 0.4 V to 1.4 ± 0.5 V for the right lateral position. All communication thresholds at 90 days were below the nominal threshold of 4 V.
Acute and chronic device–device communication success from the S-ICD to the LP. Communication thresholds are displayed during 90 days of follow-up in 3 postures: dorsal, left lateral, and right lateral. The communication signal amplitude can range from 0 to 7 V, and the nominal setting is 4 V. Abbreviations as in Figure 3.

Post-shock LP performance was assessed in 7 of 39 animals and showed no alterations in electrical performance: mean change in pacing threshold of $0.0 \pm 0.3$ V at 0.5 ms and a mean change in impedance of $-4 \pm 57$ $\Omega$, respectively. Furthermore, no dislocations or device resets were noted.

**Gross pathology examination**
At necropsy, the LP was observed to be implanted in the RV apicoseptal region in 46% (6 of 13) of the animals and in the RV free wall in the remaining 54%. Device encapsulation of the LP ranged from 0% to 100%, with a median of 70% (Figure 6). Three of the 13 LPs did not have any encapsulation, 5 were partially covered (10% to 90%), and 5 LPs were completely encapsulated. In none of the animals was substantial pericardial effusion (>10 ml) observed. In 3 animals (3 of 13 [23%]), a single tine was observed on the epicardial surface, with no pericardial effusion.

**Figure 6**

A) Gross pathological examination of an incised right ventricle exposing a leadless pacemaker (LP) implanted for 90 days with no evidence of device encapsulation. (B) The LP is fully encapsulated 90 days post-implant.

**Discussion**

**Main findings**
There were 4 important findings in this preclinical study on a modular CRM system, consisting of an S-ICD that can unidirectionally command a novel LP. First, an LP was successfully implanted in 98% of the animals (39 of 40). Second, unidirectional conductive communication between the S-ICD and LP was successful in all implanted animals. Third, ATP was successfully delivered both when commanded manually via the S-ICD and automatically when the S-ICD detected a simulated VT at a rate within the programmed therapy zone. Finally, LP pacing did not have a negative impact on S-ICD sensing of the cardiac rhythm, either at rest or during (simulated) ventricular arrhythmias.
Modular CRM implantation, safety, and performance

LP implantation was feasible via the femoral vein, despite the relatively large-sized catheters compared with the smaller sized venous anatomy of these animals. These outcomes are similar to the high implantation success rates (95.8% to 99.2%) of the currently available LP systems in human with varying body habitus (11,12) using similarly sized introducer sheaths (18-F to 23-F). The delivery catheter has a unique telescoping extension feature that enables advancement of its distal portion while maintaining a stable position of its proximal portion deflect-ed in the right atrium. This limits forward pressure on the RV apex during implantation and allows flexibility to accommodate various cardiac anatomies.

There were no cardiac adverse events related to the implant procedure; specifically, no occurrence of pericardial effusion or device dislodgements, confirmed by echocardiography and necropsy. In the chronic animal model, tine protrusion from the epicardium was observed at necropsy in 3 animals without pericardial effusion. This outcome suggests that with the tine fixation mechanism, protrusion through the myocardium can occur. The human Micra study reported a pericardial effusion rate of 1.6% without tamponade using a similar fixation mechanism (nitinol tines) and suggests an increased risk for cardiac perforation compared with transvenous pacemaker leads; data on tine protrusion were not reported (12). A more septal or apico-septal implant location may mitigate this risk. The S-ICD pocket infections were likely due to suboptimal sterile conditions, and none of the infections was systemic. We expect the infection rate of the individual components of this modular system will be similar to the currently reported S-ICD and LP infection rates (10,17,18).

The electrical performance of the LP was adequate and showed a slight increase in pacing threshold and a decrease in impedance and R wave during 90 days of follow-up. The results and trends were similar to other LP systems tested in animals (19). The long-term electrical performance of this system will be evaluated in ongoing chronic animal experiments. Human data with LP and conventional transvenous pacemakers with active-fixa-tion pacemaker leads show similar stable electrical performance (11,12,20). S-ICD sensing was adequate in all animals in at least 1 sensing vector. No inappropriate sensing or therapy was observed during LP pacing at rest, during communication, or during ventricular arrhythmias. A previous case series reporting outcomes in S-ICD with concomitant transvenous pacemakers demonstrated similar results (21), but these findings must be confirmed in large clinical cohorts with long follow-up.

Device–device communication

The modular CRM system uses a novel concept of intrabody device–device communication to enable coordinated leadless pacing and defibrillation therapy. Conducted communication has been proven to be a successful tech-nology in intrabody communication, using the body tissue as a conductor (11,13,22). Currently, similar conducted signals are used for S-ICD lead impedance measurements and have little impact on battery longevity, and they do not cause undesired tissue stimulation. The unidirectional communication signals are sent from the S-ICD coil to the S-ICD pulse generator, creating a communication vector between the S-ICD coil and can. The RV position of the LP is within this communication vector, assuming normal human anatomy. The optimal position of the long-axis of the LP is parallel to the communication vector, resulting in the largest voltage difference between anode and cathode.

In this study, we showed that unidirectional device–device communication was successful in all animals, with a high success rate of 99% of all communication attempts. The unsuccessful communication attempts (3 of 309) all occurred in 1 ovine subject during the first experiment performed. In this animal, the S-ICD lead was placed in a suboptimal position (high lateral in the right axillary midline and slightly curved) and not representative of the human situation, which is believed to be the reason for the failed attempts. The mean communication threshold was below the nominal setting of 4 V, which is currently used in the S-ICD lead impedance measurements and causes no muscle stimulation. The unfavorable device orientation in these animals (vertical position) did not seem to adversely affect communication success. This finding is reassuring, considering the expected device orientation in humans, which will be more horizontal and parallel to the communication vector, and thus more
favorable. Electromagnetic interference could hypothetically disturb the conducted device–device communication. This situation was not observed in our chronic animal study; however, no electromagnetic interference tests were performed. Two safety features were developed to minimize the risk of communication interference: first, a specific communication protocol (signal sequence) is used by the S-ICD and recognized by the receiving LP. Second, the LP has a built-in safety feature that inhibits ATP if the intrinsic heart rhythm is below a predefined threshold (e.g. 155 beats/min).

**ATP therapy**
This study reported a high success rate (100%) of ATP delivery by the LP when commanded by the S-ICD. The ATP settings of the LP are programmable, similarly to conventional transvenous pacemakers. In this first iteration of the modular CRM system, ATP can be programmed with up to 3 bursts of ATP in the conditional shock zone (10 beats at 5 V at 1 ms at varying coupling intervals ranging from 50% to 94%) followed by a S-ICD shock. When programmed in the conditional shock zone (fast VT zone), time to first therapy (ATP) will be shorter in this modular CRM system compared with S-ICD therapy alone because ATP delivery does not require charging of the high-voltage capacitor. In the shock zone (VF zone), 1 burst of ATP will be delivered during charging similar to transvenous ICDs. A delayed therapy response is therefore not expected in this modular CRM system. The impact of both conductive communication and ATP bursts on S-ICD and LP battery longevity is expected to be negligible. For instance, 1,000 bursts of ATP per year would result in an approximately 1.5-week LP longevity decrease, whereas 1 h of conductive telemetry per year would result in about 2 months of LP longevity decrease with conservative assumptions. Post-shock pacing by the LP is available when programmed to a demand pacing mode (e.g., VVI) and will occur according to programmed settings.

ATP continues to be an important programming feature for patients with transvenous ICDs, and the modular CRM combination presented here allows for ATP to be delivered to S-ICD patients when it is clinically necessary. The incidence of recurrent monomorphic VT in a pooled analysis (10) presented in a contemporary S-ICD population (young, with mixed substrates) has been estimated at 0.4% per annum. Poole and Gold (23) estimated that the annual need for ATP (using SCD-HeFT [Sudden Cardiac Death in Heart Failure Trial] event rates) would be 1.2% per annum. These risk adjustments are small and programming dependent but illustrate a use for ATP in selected patients after implantation of an S-ICD or a tricuspid valve–ICD.

**Future perspective**
With the introduction of this modular CRM system, new opportunities are available to further individualize patient treatment. The modular CRM system presented here is compatible with the EMBLEM S-ICD platform being implanted today. Thus, the LP module can be added to patients in need of ATP who already have an S-ICD, either at initial implantation or as their cardiac substrate and prescriptive needs evolve. Similarly, a patient who undergoes implantation with an LP for bradycardia treatment can receive an S-ICD when an ICD indication arises in the future. A modular CRM system with forward and backward engineering allows for tailored therapy with fewer hardware needs and is the future of device-based arrhythmia therapies. Furthermore, the development of bidirectional device–device communication can enable future iterations of this modular CRM system to enhance S-ICD rhythm discrimination via LP rhythm confirmation. This scenario would potential result in further reduction of oversensing issues (e.g. T-wave oversensing) and inappropriate therapy. The first-in-man trials with a validated and verified modular CRM system are planned and will be the first to combine LP therapy and ICD therapy in a coordinated fashion. The safety and performance results of this modular system are required to consider clinical adoption.

**Conclusions**
We present the preclinical acute and chronic performance of the combined implantation of an ATP-enabled LP and S-ICD. Appropriate VVI functionality, successful wireless device–device communication, and ATP delivery were demonstrated by the LP. Clinical studies on safety and performance are needed.
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Supplemental Materials

Methods

Device communication testing

Communication transmit success was tested at implant and each follow-up by sending ATP requests at varying transmit amplitudes from S-ICD to the LP during normal sinus rhythm in three animal postures (supine, left lateral, right lateral). A counter in the LP was utilized to verify successful receipt of an ATP request. Varying the transmit amplitude of the S-ICD’s ATP request allowed the measurement of a communication threshold: the minimum transmit amplitude for successful receipt of the ATP request by the LP. Final determination of the communication threshold was accomplished by stepping down the transmit amplitude to communication failure, then stepping back up to reconfirm communication success. The transmit amplitude setting is programmable from 1-7 V, in 0.5 V increments, and refers to the S-ICD’s charge voltage to send each pulse of the ATP request.

Successful communication between the S-ICD and LP is impacted by the position of the LP in the communicating vector between the S-ICD coil and S-ICD generator. Theoretically, optimal communication is achieved when the long axis of the LP is positioned parallel to the communication vector; given anatomical constraints, this is also generally perpendicular to the S-ICD coil. This position was assessed by measuring the angle between the long axis of the LP and the S-ICD coil in anterior-posterior (AP) fluoro images obtained during implant.
Supplemental Table 1. Transthoracic echocardiography results from the chronic canine model at 90 days

<table>
<thead>
<tr>
<th>Time point</th>
<th>N</th>
<th>RV Long Axis (cm)</th>
<th>RV Short Axis (cm)</th>
<th>RV Area (cm²)</th>
<th>RA Long Axis (cm)</th>
<th>RA Short Axis (cm)</th>
<th>RA Area (cm²)</th>
<th>Tricuspid annular plane systolic excursion (TAPSE) (mm)</th>
<th>Distance from Tricuspid Valve to Device (cm)</th>
<th>LVEF (%)</th>
<th>Pericardial Effusion</th>
<th>Tricuspid Valve Interaction</th>
<th>Tricuspid Regurgitation (severity scale 0 to 4)</th>
<th>Mitral Regurgitation (severity scale 0 to 4)</th>
<th>Aortic Regurgitation (severity scale 0 to 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Implant</td>
<td>23</td>
<td>5.3 ± 0.3</td>
<td>2.5 ± 0.2</td>
<td>9.6 ± 1.2</td>
<td>3.0 ± 0.2</td>
<td>3.0 ± 0.3</td>
<td>7.1 ± 1.7</td>
<td>11.0 ± 1.7</td>
<td>NA</td>
<td>49 ± 7.5</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Post-Implant</td>
<td>23</td>
<td>5.4 ± 0.4</td>
<td>2.5 ± 0.3</td>
<td>9.5 ± 1.1</td>
<td>3.1 ± 0.2</td>
<td>3.0 ± 0.2</td>
<td>7.5 ± 1.0</td>
<td>11.6 ± 1.8</td>
<td>3.3 ± 0.6</td>
<td>47 ± 6.4</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>90-days Post-Implant</td>
<td>17</td>
<td>5.3 ± 0.3</td>
<td>2.4 ± 0.2</td>
<td>9.6 ± 1.3</td>
<td>2.8 ± 0.2</td>
<td>2.9 ± 0.2</td>
<td>8.9 ± 0.7</td>
<td>11.6 ± 1.8</td>
<td>2.1 ± 0.8</td>
<td>41 ± 6.7</td>
<td>None</td>
<td>1/13*</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

Animals underwent standard transthoracic 2-dimensional echocardiography using a commercially available ultrasound system (Vivid 6, General Electric, Fairfield, CT) and a 25-MHz transducer. Images included parasternal, apical, and subcostal views. Valvular regurgitation was estimated visually using Doppler color flow. The following parameters were evaluated: valvular regurgitation severity (none 0, mild 1+, moderate 2+, moderate-severe 3+, and severe 4+); RV long and short axis dimensions; LV ejection fraction (EF) by biplane method of disks (%); pericardial effusion by visual estimation; distance from tricuspid valve to device line; tricuspid valve interaction by visual estimation. *Leaflets appear to be in contact with device when valve is open.
Supplemental Figure 1

LP system overview In this Figure the LP system is displayed: 1) the LP measures 31.9 mm x 6mm and has a volume of 0.8cc, is fixated using active fixation nitinol tines and has a distal snare port allowing for device retrieval; 2) the designated steerable delivery catheter with unique telescope feature; 3) dedicated programmers for the S-ICD (Model 3200-S-ICD) and LP (BSC 3300 LATITUDE). © 2017 Boston Scientific Corporation or its affiliates. All rights reserved. Used with permission of Boston Scientific Corporation
Device orientation LP within communication vector. In this fluoroscopy image the modular CRM system is implanted. The communication vector between S-ICD coil and S-ICD can is schematically displayed using white arrows. The LP is implanted in the right ventricle and the angle between the long axis of the LP and the communication vector is indicated with $\alpha$. 
**Supplemental Figure 3**

S-ICD Rhythm discrimination during VF and concomitant LP VOO pacing. The S-ICD rhythm detection is displayed with green S-ICD tachymarkers during ventricular fibrillation (VF) and concomitant VOO LP pacing (red arrows). The dotted blue line represents the moment when the S-ICD starts charging to deliver shock therapy. This figure illustrates adequate S-ICD VF detection during concomitant LP pacing.

**Supplemental Figure 4**

3-month electrical performance LP. In this graph the LP electrical 90-day performance is displayed. On the left Y-axis the LP pacing threshold in V at 0.5 ms is displayed in black. On the right Y-axis the impedance measurements are displayed in Ω. * denotes a p-value of < 0.001 between implant and 90 days. + denotes a p-value of 0.04 between implant and 90 days.