Acute and 3-Month Performance of A Communicating Leadless Anti-Tachycardia Pacemaker and Subcutaneous Implantable Defibrillator

Fleur V.Y. Tjong, MD, Tom F. Brouwer, MD, Brendan Koop, PhD, Brian Soltis, MSc, Allan Shuros, MSc, Brian Schmidt, MSc, Bryan Swackhamer, MSc, Anne-Floor Quast, MD, Arthur A.M. Wilde, MD, PhD, Martin C. Burke, DO, Reinoud E. Knops, MD

PII: S2405-500X(17)30318-3
DOI: 10.1016/j.jacep.2017.04.002
Reference: JACEP 402

To appear in: JACC: Clinical Electrophysiology

Received Date: 21 March 2017
Revised Date: 24 April 2017
Accepted Date: 26 April 2017


This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Acute and 3-Month Performance of A Communicating Leadless Anti-Tachycardia Pacemaker and Subcutaneous Implantable Defibrillator

Fleur V. Y. Tjong, MD *, Tom F. Brouwer, MD *, Brendan Koop, PhD‡, Brian Soltis, MSc‡, Allan Shuros, MSc‡, Brian Schmidt, MSc‡, Bryan Swackhamer, MSc‡, Anne-Floor Quast, MD*, Arthur A.M. Wilde, MD, PhD*, Martin C. Burke, DO*, Reinoud E. Knops, MD*

*Academic Medical center, Amsterdam, The Netherlands; ‡Boston Scientific Corporation, St. Paul, MN, USA; CorVita Science Foundation , Chicago, IL, USA

Brief Title: Acute and 3-Month Performance of Leadless ATP Pacemaker & S-ICD

Disclosures: Dr. Tjong reports consulting fees from Boston Scientific Corporation, Inc. and St. Jude Medical. Dr. Burke reports consulting fees, research grants and honoraria for Boston Scientific, research grants with Medtronic and St. Jude Medical, and consulting fees and equity for AtaCor Medical. Dr. Knops reports consulting fees, research grants and honoraria for Boston Scientific, consulting fees research grants with Medtronic and St. Jude Medical. Prof. Wilde is a member of the Scientific Advisory Board of LivaNova. Mr. Koop, Mr. Soltis, Mr. Shuros, Mr. Schmidt, and Mr. Swackhamer are employees of Boston Scientific Corporation, Inc. The remaining authors have nothing to declare. Part of this study was funded by Boston Scientific Corp.

Corresponding Author:

Fleur V. Y. Tjong, MD

AMC Heart Center,
Department of Clinical and Experimental Cardiology, Academic Medical Center,
Meibergdreef 9, 1105 AZ, Room F3-240
Amsterdam, the Netherlands
Phone: +31-20-5669111; Fax: +31-20-6969704; Email: f.v.tjong@amc.nl
ABSTRACT

Background
Transvenous pacemakers and ICDs have considerable rates of lead complications. We examine the next step in multi-component leadless cardiac rhythm management: feasibility of pacing, including anti-tachycardia pacing (ATP), by a leadless pacemaker (LP), commanded by an implanted subcutaneous implantable cardioverter defibrillator (S-ICD) through wireless, intra-body, device-device communication. The primary objective is the acute and 3-month performance of the modular ATP-enabled LP and S-ICD system, particularly device-device communication and ATP delivery.

Methods
The combined modular cardiac rhythm management therapy system of LP and S-ICD prototypes was evaluated in three 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 (n=39/40). 23 out of the 39 animals were followed up for 90 days post-implant. LP performance was adequate and demonstrated appropriate VVI behavior during 90 days of follow-up in all tested animals. Unidirectional communication between the S-ICD and LP was successful in 99% (n=398/401) attempts resulting in 100% ATP delivery by the LP (10 beats at 81% of coupling interval). Adequate S-ICD sensing was observed during normal sinus rhythm, LP pacing, and VT/VF.

Conclusion
We present the preclinical acute and chronic performance of the combined function of an ATP-enabled LP and S-ICD. We demonstrated appropriate VVI functionality, successful wireless device-device communication and ATP delivery by the LP. Clinical studies on safety and performance are needed.

Key words
S-ICD, Leadless Pacemaker, Modular Therapy, Wireless Communication, ATP
CONDENSED ABSTRACT

In this preclinical study (n=40), we demonstrated the safety and performance of the next step in multi-component leadless cardiac rhythm management: a communicating ATP-enabled leadless pacemaker commanded by an implanted subcutaneous implantable cardioverter defibrillator (S-ICD) through wireless, intra-body, device-device communication. Clinical studies on safety and performance are required before this modular treatment strategy can be applied in clinical practice.

ABBREVIATIONS

ATP  Anti-Tachycardia Pacing
CRM   Cardiac Rhythm Management
ICD   Implantable Cardioverter Defibrillator
LP    Leadless Pacemaker
RF    Radiofrequency
S-ICD  Subcutaneous Implantable Cardioverter Defibrillator
VVI   Single-chamber Pacemaker

Key Words: S-ICD, Leadless Pacemaker, Modular Therapy, ATP, Wireless Communication
Introduction

Transvenous pacemakers and implantable cardioverter-defibrillators (ICD) are effective treatment modalities for cardiac brady- 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, involving the pocket but more so when systemic, are associated with high risk of mortality (8).

To reduce complications related to transvenous leads both the leadless pacemaker (LP) and the subcutaneous ICD (S-ICD) 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 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 ATP therapy there are no leadless solutions available to date.

Recently, we reported the first proof-of-concept of a unidirectionally 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. In this preclinical study we present the acute and chronic performance of this modular CRM system.

Objectives

The objectives of this study are to assess the acute and chronic feasibility and performance of this novel modular CRM therapy, with regard to: 1) the performance of an ATP-enabled LP, 2) unidirectional device-device communication from S-ICD to LP, 3) S-ICD triggered ATP delivery by LP, 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 three 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, NL) and Boston Scientific Corp. (St. Paul, MN, USA) to be carried out in compliance with the applicable government guidelines.

**Modular Cardiac Rhythm Management (CRM) Therapy System**

The modular ATP-enabled LP and S-ICD system (both Boston Scientific Corp., Marlborough, MA, USA) are shown in Figure 1. The prototype modular CRM system consists of a S-ICD and a standard S-ICD electrode, LP, catheter based delivery and retrieval system, and programmers with software dedicated for each device (Supplemental Material, Figure S1). The S-ICD pulse generator is a device based on the EMBLEM™ platform 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. The S-ICD uses unidirectional conductive communication to command the LP and radiofrequency (RF) 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 right ventricular apex, using a percutaneous, transfemoral approach through a 21Fr introducer sheath using a designated delivery catheter with “telescope feature” for catheter extension (Figure 2). The LP was deployed by engaging four 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.

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, that 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 in order to hold the S-ICD stable for postural changes of the animal during communication testing. The S-ICD uses one out of three 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 EP catheter (Polaris X Steerable Diagnostic Catheter, Boston Scientific Corp., Marlborough, MA, USA) was inserted into the left ventricle (LV) via left femoral artery access and used to pace the LV 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, to test S-ICD initiated ATP delivery, and to test 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) were used. All but 23 canines were euthanized 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 follow-up duration of 90 days using the remaining 23 healthy canines (mean weight 30±3 kg). Following 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 animals underwent follow-up evaluations that included clinical assessment, assessment of LP and S-ICD performance, and device-device communication. At 90 days (+/-14 days) post-implant, ATP and shock, S-ICD rhythm discrimination, and post-shock LP performance testing was performed in 13 out of 23 animals, which were hereafter immediately euthanized. The remaining 10 animals will be followed for long-term safety and performance of the modular CRM system.
All chronic animals underwent standard transthoracic 2-dimensional echocardiography at baseline pre-implant, immediately post-implant and at day 90, using a commercially available ultrasound system (Vivid 9; General Electric, Fairfield, CT, USA) with a 2.5-MHz transducer. 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 discs (%); heart function and wall motion by visual estimation; pericardial effusion by visual estimation; distance from tricuspid valve to device (cm); 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 S-ICD’s communication vector can impact 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 is also generally approximately perpendicular (90°) to the S-ICD coil (**Supplemental Materials, Figure S2**). 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 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; 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).

**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 was tested both on 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 170-220 bpm (with 3 ATP requests then shock), and a Shock Zone of >220 bpm, and the LV 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 bpm 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 bpm) when the series of pulses is received, the LP will deliver ATP in accordance with its programmed parameters (i.e. scheme, coupling/burst interval, etc.).

Gross pathology examination

In all chronic animals (n=13) terminated after 90 days of follow-up, a gross pathological examination was performed to assess: 1) LP fixation/position in right ventricle 2) existence of tissue encapsulation of the LP, 3) existence of pericardial effusion / tine protrusion.

Statistics

Descriptive statistics are presented using mean ± SD or median (interquartile range; IQR) for continuous variables and as frequencies and percentages for categorical variables. In the chronic experiments, the paired t test was used to compare means of continuous variables at specific time points and to test R-wave differences over time a linear regression model was used. All analyses were conducted with SPSS version 20.0 (SPSS Inc, Chicago, IL, USA).

Results

Implantation of modular CRM system

In 38 animals the LP was successfully implanted via the right femoral vein. In one 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 due to prototype catheter malfunction without an LP implant attempt. The LP was implanted in 24 (62%) in the RV apex, 14 (36%) in low septal position, and one (2%) in the right ventricular outflow tract. The implant procedure duration of the LP ranged between 59 and 119 minutes. Echocardiographic evaluation post-implant (n=23) showed no pericardial effusion, no changes in tricuspid regurgitation
(TR) and no interaction of the LP with the tricuspid valve (TV) compared to baseline (Supplemental Material, Table S1, Video 1). The mean distance of the LP to the TV 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 (=11) or 0.5 ms (n=28) pulse width, for this analysis these values are pooled and the R-wave amplitude measurements in canine (n=26) were right-censored at 25mV.

S-ICD heart rhythm discrimination was correct during intrinsic and LP pacing above the intrinsic rate and did not result in over-sensing (Figure 3). Induction of VF in the presence of VOO pacing at 60 ppm was performed in 7 animals to verify proper discrimination and therapy delivery by the S-ICD (Supplemental Material, Figure S3).

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

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

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

All but one animal (n=22/23, 96%) completed the 90 day follow-up of the modular CRM system. In this one 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 pre-cautions 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 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 days, 28 days, and 90 days, respectively, were: mean pacing threshold (at 0.5 ms): 0.56 ± 0.37 V (n=20), 0.54 ± 0.30 V (n=20), 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), 23.3 ± 9.4 mV (n=23); and mean impedance: 785 ± 129 Ω (n=14), 827 ± 105 Ωs (n=20), 728 ± 141 Ω (n=22) (Supplemental Material, Figure S4). R-wave measurements were clipped at 25mV. 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), inaccurate measurements of R-wave and impedance due to prototype programmer software coding errors (n=9).

Echocardiographic evaluation at 90 days (n=17) showed no pericardial effusion, or mean change in TR; in 2 animals (12%) interaction between the TV was noted leading to increase in TR in one animal (Supplemental Material; Table S1, Video S1).

The chronic device-device communication success was 100% (92/92 attempts) (Figure 5, panel A). Also, 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 three postures: 2.5 ± 0.8 V to 1.6 ± 0.6 V for dorsal (supine) position, 1.9 ± 0.4 V to 1.6 ± 0.5 V for left lateral position, and 1.8 ± 0.4 V to 1.4 ± 0.5 V for right lateral position (Figure 5, Panel B). All communication thresholds at 90 days were below the nominal threshold of 4V.
Post-shock LP performance was assessed in 7 out of 39 animals and showed no alterations in electrical performance: mean change in pacing threshold of 0.0 ± 0.3V at 0.5 ms and mean change in impedance of -4 ± 57 Ω, 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% (6/13) 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 out of 13 LPs did not have any encapsulation, five were covered partially (10-90%) and five LPs were completely encapsulated. In none of the animals was substantial pericardial effusion (>10ml) observed. In three animals (n=3/13, 23%) a single tine was observed on the epicardial surface, without the existence of pericardial effusion.

**Discussion**

**Main findings**

There were four 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 (n=39/40). 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 implant, safety and performance**

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

There were no cardiac adverse events related to the implant procedure; specifically no occurrences of pericardial effusion or device dislodgements, confirmed by echocardiography and necropsy. In the chronic animal model tine protrusion from the epicardium was observed in three animals without pericardial effusion at necropsy. This 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 to transvenous pacemaker leads, but data on tine protrusion is not reported (12). A more septal or apicoseptal implant location may mitigate this risk.

The S-ICD pocket infections are likely due to suboptimal sterile conditions and none of the infections were 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 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). 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-fixation pacemaker leads and show similar stable electrical performance (11, 12, 20). S-ICD sensing was adequate in all animals in at least one 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 this 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 technology in intrabody communication, utilizing 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 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 right ventricular 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 (3/309) all occurred in one 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 to 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 impact communication success. This is reassuring, considering the expected device orientation in humans, which will be more horizontal and parallel to the communication vector, and thus more favorable. Electronic magnetic interference could hypothetically disturb the conducted device-device communication. This was not observed in our chronic animal study, however no EMI tests were performed. Two safety features are 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. Secondly, the LP has a built-in safety feature that inhibits ATP if the intrinsic heart rhythm is below a predefined threshold (e.g. 155 bpm).

**ATP therapy**

We demonstrated 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 three 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 to S-ICD therapy alone, as ATP delivery does not require charging of the high voltage capacitor. In the Shock Zone (VF zone), one burst of ATP will be delivered during charging similar to transvenous ICDs. Therefore, a delayed therapy response is 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, 1000 bursts of ATP per year would result in an approximately 1.5 week LP longevity decrease, while one hour of conductive telemetry per year would result in about two months 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 transvenous ICD patients 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 et al. (23) estimates that the annual need for ATP using The Sudden Cardiac Death in Heart Failure Trial event rates to be 1.2% per annum. These risk adjustments are small and programming dependent but demonstrate a use for ATP in selected patients following implant of an S-ICD or a TV-ICD.

**Future perspective**

With the introduction of this modular CRM system new opportunities are provided to further individualize patient treatment. The modular CRM system presented here is compatible with the EMBLEM™ S-ICD platform being implanted today. In other words, the LP module can be added to patients in need of ATP who already have an S-ICD, either at initial implant or as their cardiac substrate and prescriptive needs evolve. Similarly, a patient implanted 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 bi-directional device-device communication can enable future
iterations of this modular CRM system to enhance S-ICD rhythm discrimination via LP rhythm confirmation, potentially resulting 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.

**Conclusion**

We present the preclinical acute and chronic performance of the combined implant of an ATP-enabled LP and S-ICD. We demonstrated appropriate VVI functionality, successful wireless device-device communication and ATP delivery by the LP. Clinical studies on safety and performance are needed.

**Perspectives**

**Competencies in Medical Knowledge:** The novel modular CRM system provides coordinated leadless bradycardia along with anti-tachycardia pacing that uses the subcutaneous defibrillation system thereby minimizing intracardiac hardware. Utilizing this modular approach of therapy has the potential to optimize individualized patient treatment strategies.

**Translational outlook I:** This preclinical study with prototype technology demonstrated safety and adequate performance as an entire modular CRM system. However, before clinical adoption can be considered, long-term performance results and human clinical studies, using more developed and validated modular CRM systems, are required.

**Translational outlook II:** Common pathways of bi-directional device-device communication as a human body network has the potential to intelligently enhance chronic cardiac care in high risk patients. Basic examples of this potential include enhanced S-ICD rhythm discrimination, decrease in over-sensing issues and inappropriate therapy, and further expansion of modular cardiac rhythm artificial intelligence.

**REFERENCES**


20. Kistler PM, Liew G, Mond HG. Long-Term Performance of Active-Fixation Pacing Leads:
A Prospective Study. PACE 2006; 29:226–230


23. Poole JE, Gold MR. Who should receive the subcutaneous implanted defibrillator? The subcutaneous implantable cardioverter defibrillator (ICD) should be considered in all ICD patients who do not require pacing. Circulation 2013; 6: 1236-1245.
### Table 1. Acute and 3-Month LP performance

<table>
<thead>
<tr>
<th></th>
<th>Acute Performance (n=40)</th>
<th>3-Month Performance (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ovine</td>
<td>Swine</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>Baseline</td>
</tr>
<tr>
<td><strong>Implant characteristics</strong></td>
<td>n=8</td>
<td>n=5</td>
</tr>
<tr>
<td>Implant success, n (%)</td>
<td>8 (100)</td>
<td>5 (100)</td>
</tr>
<tr>
<td><strong>LP position</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- RV apex, n (%)</td>
<td>8 (100)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>- RV apical septum, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>- RV outflow tract, n (%)</td>
<td>0 (0)</td>
<td>1 (20)</td>
</tr>
<tr>
<td><strong>LP electrical performance</strong></td>
<td>n=8</td>
<td>n=5</td>
</tr>
<tr>
<td>Pacing threshold, V at 0.5 ms</td>
<td>1.10 ± 0.81</td>
<td>0.53 ± 0.49</td>
</tr>
<tr>
<td>R-wave amplitude, mV</td>
<td>6.6 ± 1.4</td>
<td>28.3 ± 5.8</td>
</tr>
<tr>
<td>Impedance, Ohms</td>
<td>665 ± 225</td>
<td>753 ± 118</td>
</tr>
<tr>
<td><strong>LP post-shock performance</strong></td>
<td>n=8</td>
<td>n=2</td>
</tr>
<tr>
<td>Pre- to post-shock change in pacing threshold, V at 0.5 ms</td>
<td>0 ± 0.5</td>
<td>0.1 ± 0.1</td>
</tr>
<tr>
<td>------------------------------------------------------</td>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>Pre- to post-shock change in impedance, Ohms</td>
<td>+18 ± 49</td>
<td>+26 ± 40</td>
</tr>
</tbody>
</table>

* 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.
FIGURE TITLES AND LEGENDS

Figure 1. Communicating ATP-enabled LP and S-ICD
Panel A. Overview of modular CRM system prototypes with detailed image of the novel ATP-enabled LP (dimensions 31.9 mm length x 6.0 mm diameter, 0.8 cc volume). Panel B. Schematic depiction of human modular CRM system implant. Panel C. Fluoroscopy imaging of implanted modular CRM system and left ventricular pacing catheter in canine subject in anterior posterior view.

Figure 2. Implantation of the LP
Panel A. LP delivery catheter is advanced through 21Fr introducer sheath in the inferior vena cava. Panel B. Delivery catheter is advanced and deflected in the right ventricle (RV) using the telescope feature to extend the LP into the RV apicoseptal region. Panel C. The LP is fixated with 4 nitinol tines that engage in the myocardial tissue. Panel D. Close up of the LP fixation mechanism. Panel 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.

Figure 3. S-ICD rhythm discrimination during high rate LP pacing
S-ICD rhythm discrimination during normal sinus rhythm (NSR) and during high rate LP pacing showing adequate rhythm discrimination in all three S-ICD sensing vectors.

Figure 4. ATP delivery by the LP commanded by the S-ICD
In this Figure a modular CRM therapy sequence is displayed: a simulated monomorphic ventricular tachycardia triggers an ATP-request from the S-ICD which results in 10 beats of ATP delivered by the LP.

Figure 5. Device-device communication between S-ICD and LP
Panel A. Acute and chronic device-device communication success from S-ICD to LP. Panel B. Communication thresholds are displayed during 90 days of follow-up in three 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.

Figure 6. Gross pathology examination of LP implantation after 90 days
Panel A shows a gross pathological examination of an incised right ventricle exposing an LP implanted for a duration of 90 days with no evidence of device encapsulation. Panel B shows an LP that is fully encapsulated 90 days post-implant.

**Video 1. Echocardiography of LP implant**

In this long-axis echocardiographic view the LP can be observed anchored in the right ventricular (RV) apex. There is no interference observed with the tricuspid valve or other structures in the RV.

**Video 2. ATP and shock therapy sequence**

In this video an ATP and shock therapy sequence is delivered by the modular CRM system. On the left the live electrocardiogram can be observed, on the right the live fluoroscopy imaging during this therapy sequence. Three ATP bursts are delivered by the LP followed by a shock delivered by the S-ICD.
<table>
<thead>
<tr>
<th>Vector Type</th>
<th>NSR</th>
<th>LP Pacing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Vector (Sense B to Can)</td>
<td><img src="image1" alt="Graph" /></td>
<td><img src="image2" alt="Graph" /></td>
</tr>
<tr>
<td>Secondary Vector (Sense A to Can)</td>
<td><img src="image3" alt="Graph" /></td>
<td><img src="image4" alt="Graph" /></td>
</tr>
<tr>
<td>Alternate Vector (Sense A to Sense B)</td>
<td><img src="image5" alt="Graph" /></td>
<td><img src="image6" alt="Graph" /></td>
</tr>
</tbody>
</table>
A

<table>
<thead>
<tr>
<th></th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>39</td>
<td>23</td>
</tr>
<tr>
<td>Device-device communication success, n/N (%)</td>
<td>306/309 (99)</td>
<td>92/92 (100)</td>
</tr>
</tbody>
</table>

B

- Dorsal (Supine)
- Left Lateral
- Right Lateral

Communication Threshold (V) vs. Days from Implant

Error bars = +/- Standard Deviation