Séminaire
Winter Arrhythmia
School
Annual Cardiac Arrhythmia Meeting
Division of Cardiology, University of Toronto

Leadless Pacing

François Philippon, MD, FRCPC, FHRS, FCCS

14th Annual
Collingwood, Ontario,
February 10 -12, 2017

INSTITUT UNIVERSITAIRE
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ET DE PNEUMOLOGIE
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SURGERY

VOL. 48 OCTOBER, 1960 No. 4

Original Communications

A TRANSISTORIZED, SELF-CONTAINED, IMPLANTABLE PACEMAKER FOR THE LONG-TERM CORRECTION OF COMPLETE HEART BLOCK

WILLIAM M. CHARDACK, M.D., ANDREW A. GAGE, M.D., AND WILSON GREATBATCH, M.S., BUFFALO, N. Y.

(From the Surgical Service, Buffalo Veterans Administration Hospital, and the Department of Surgery, University of Buffalo School of Medicine)

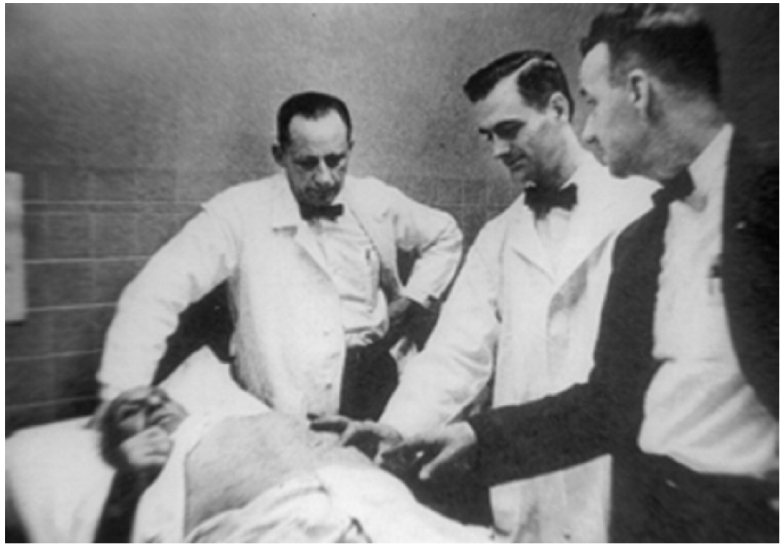

Figure 3. The "Bowtie Trio": William Chardack, Andrew Gage, and Wilson Greatbatch at the bedside of 1 of the first recipients of their permanent pacemaker. Source: Greatbatch Medical, courtesy of Curtis Holmes, PhD.

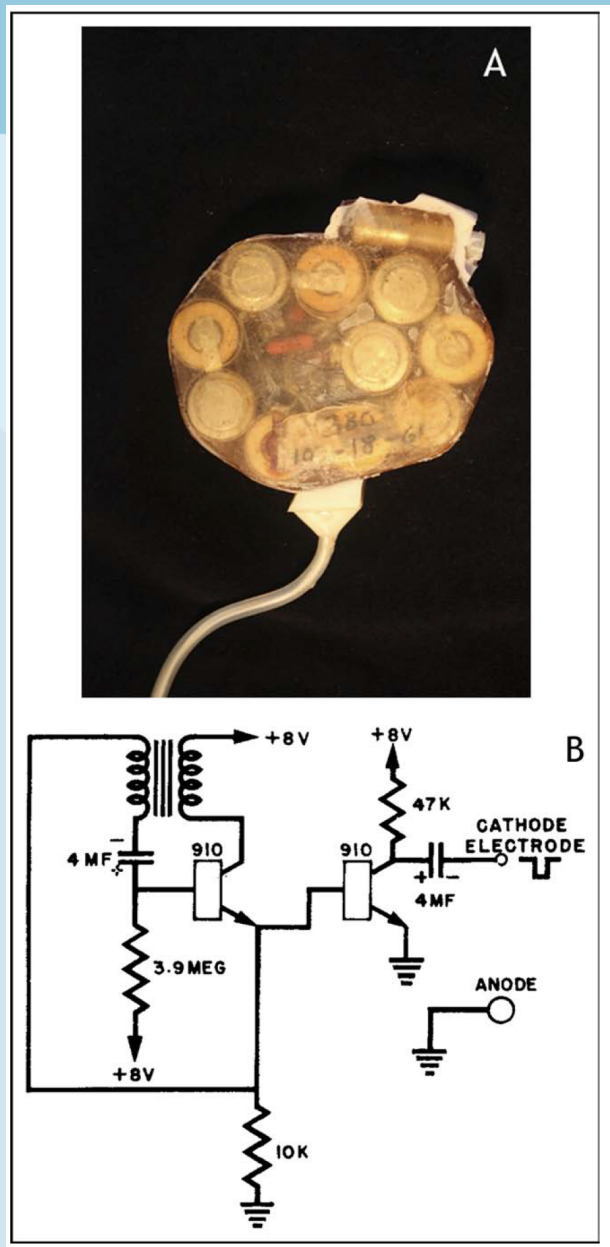

Figure 4. Design of the earliest Chardack-Greatbatch pacemakers. **(A)** The second pacemaker implanted in a human. The bulk of the device consists of the 10 mercury zinc cells connected in series. **(B)** Diagram of the simple but elegant circuitry within. Reprinted with permission from *Surgery*.[3]

(Am J Cardiol 2010;106:810–818)

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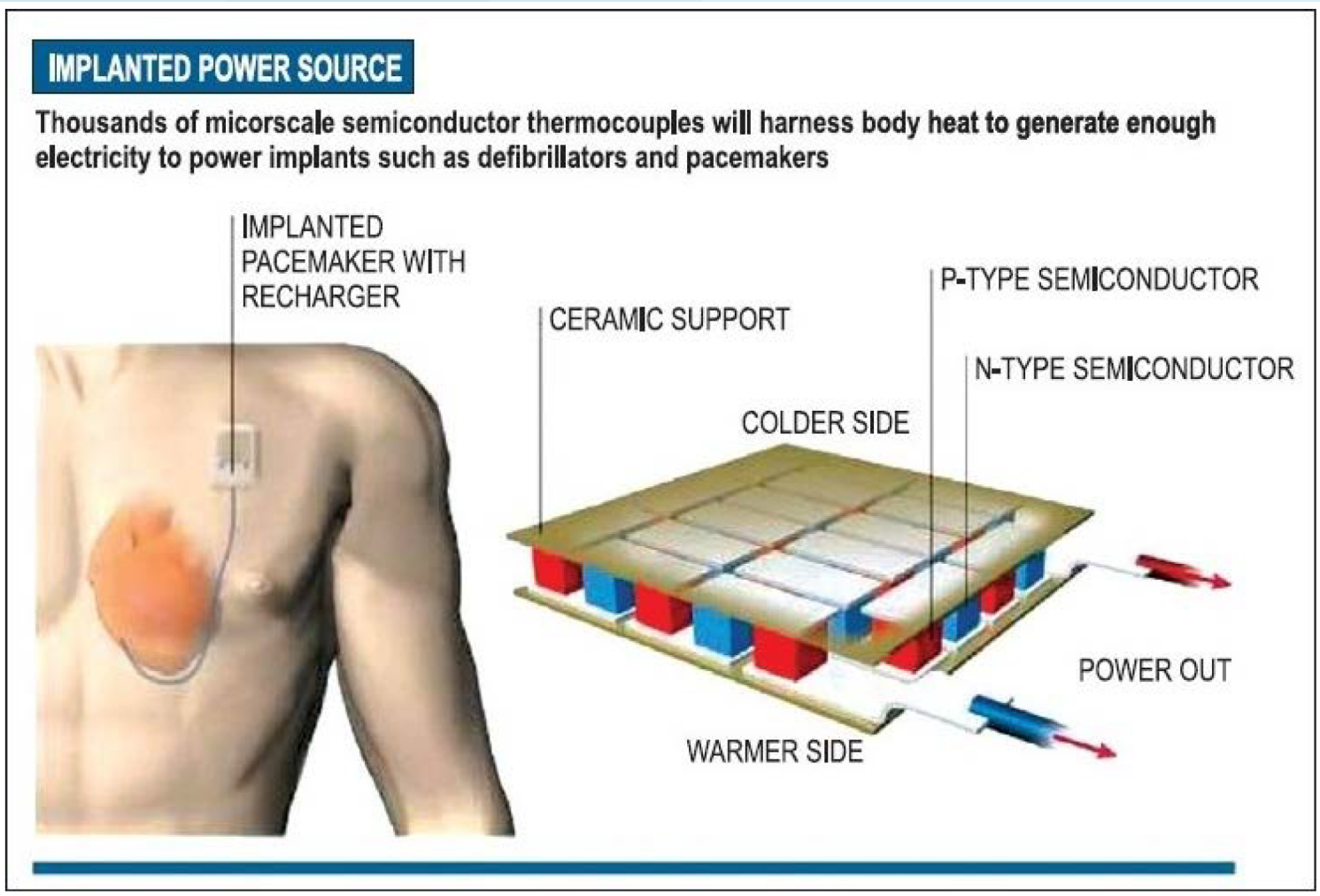
« Biothermal Pacing »



J Pharm Bioallied Sci. 2010 Jan-Mar; 2(1): 51–54.
doi: 10.4103/0975-7406.62713

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« Biological Pacing »

Stem Cell Reports. 2015 Jan 13;4(1):129-42. doi: 10.1016/j.stemcr.2014.11.004. Epub 2014 Dec 18.

SHOX2 Overexpression Favors Differentiation of Embryonic Stem Cells into Cardiac Pacemaker Cells, Improving Biological Pacing Ability.

Ionta V[1], Liang W[2], Kim EH[2], Rafie R[2], Giacomello A[3], Marbán E[2], Cho HC[4].

Author information

Abstract

When pluripotency factors are removed, embryonic stem cells (ESCs) undergo spontaneous differentiation, which, among other lineages, also gives rise to cardiac sublineages, including chamber cardiomyocytes and pacemaker cells. Such heterogeneity complicates the use of ESC-derived heart cells in therapeutic and diagnostic applications. We sought to direct ESCs to differentiate specifically into cardiac pacemaker cells by overexpressing a transcription factor critical for embryonic patterning of the native cardiac pacemaker (the sinoatrial node). Overexpression of SHOX2 during ESC differentiation upregulated the pacemaker gene program, resulting in enhanced automaticity in vitro and induced biological pacing upon transplantation in vivo. The accentuated automaticity is accompanied by temporally evolving changes in the effectors and regulators of Wnt signaling. Our findings provide a strategy for enriching the cardiac pacemaker cell population from ESCs.

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor*

Gene Therapy and Biological Pacing

Michael R. Rosen, M.D.

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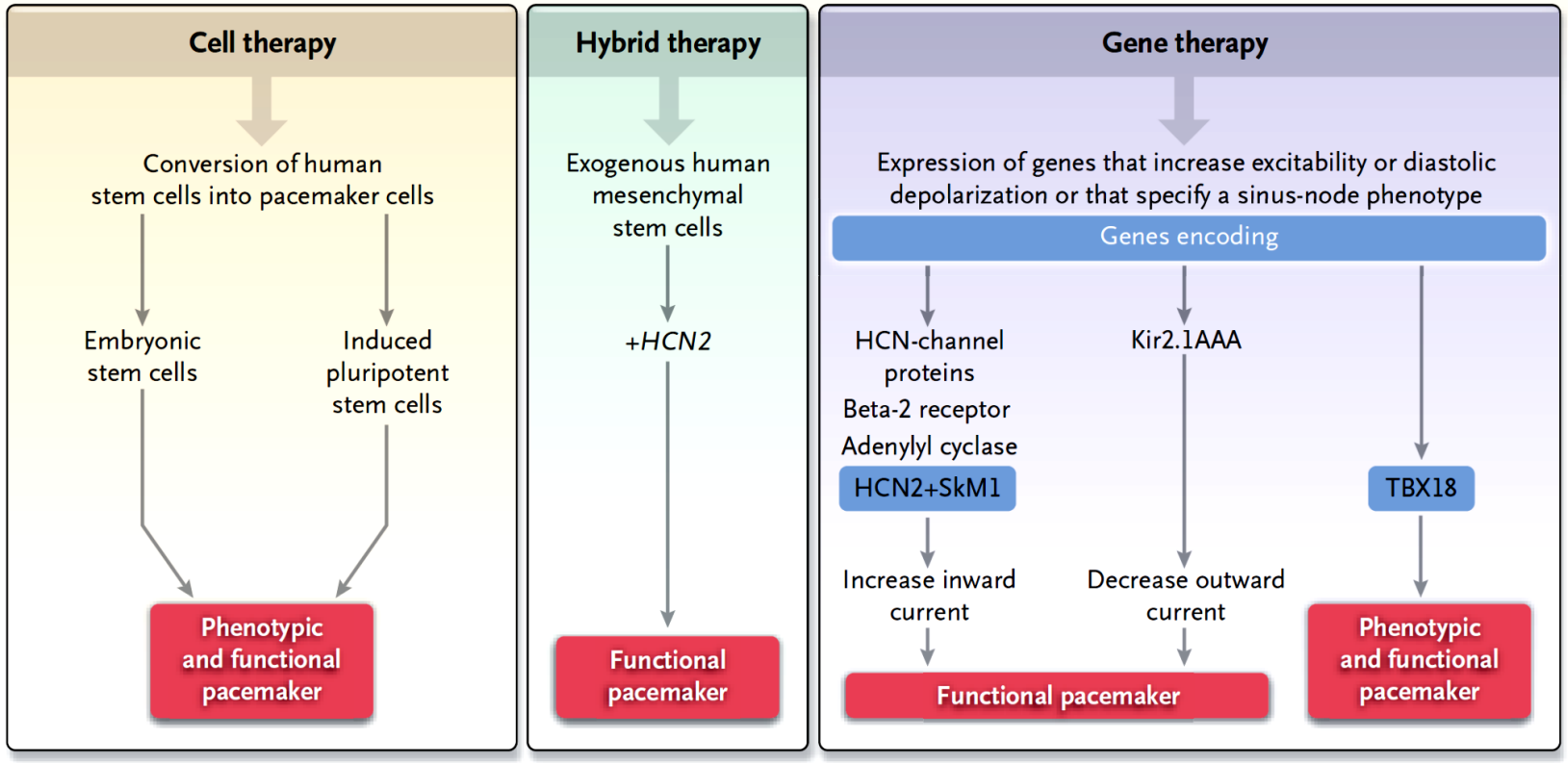


Figure 1. Approaches to Biological Pacing.

Cell therapy, gene therapy, and a hybrid approach have been used to create biological pacemakers in which the outcome is a cell that has the properties and function of a phenotypic pacemaker or that retains its adult phenotype but still takes on pacemaker function. Human embryonic stem cells or induced pluripotent stem cells engineered from mature fibroblasts or keratinocytes have been used to create a cardiac phenotypic and functional pacemakers in large animals. In hybrid therapy, a human mesenchymal stem cell loaded with the pacemaker gene *HCN2* (hyperpolarization-activated, cyclic nucleotide-gated channel 2) is implanted in the myocardium to induce pacemaker function. The gene encoding transcription factor TBX18 has also been used to engineer phenotypic and functional pacemaker cells from myocardial cells in situ. Gene therapies have used viral vectors or other means to overexpress the ion channels of the HCN pacemaker family, the skeletal-muscle sodium channel (SkM1), or the beta-2 receptor or adenylyl cyclase to increase inward current during diastole and have used the potassium-channel Kir2.1AAA to decrease outward current during diastole. Cell therapy, gene therapy, and hybrid therapy all increase pacemaker rate. Pacemaker function most closely approximating that envisioned as ideal occurs through the two gene therapies highlighted in blue.

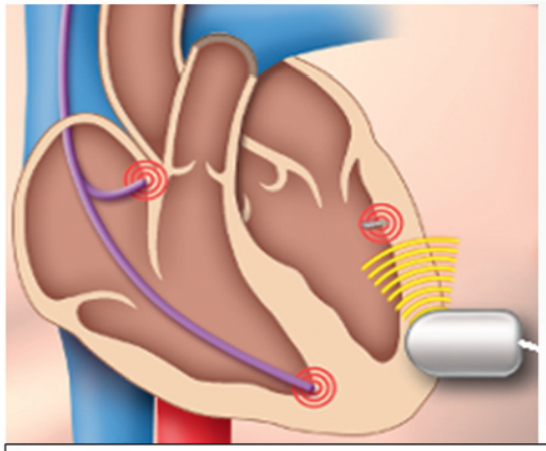
Key points

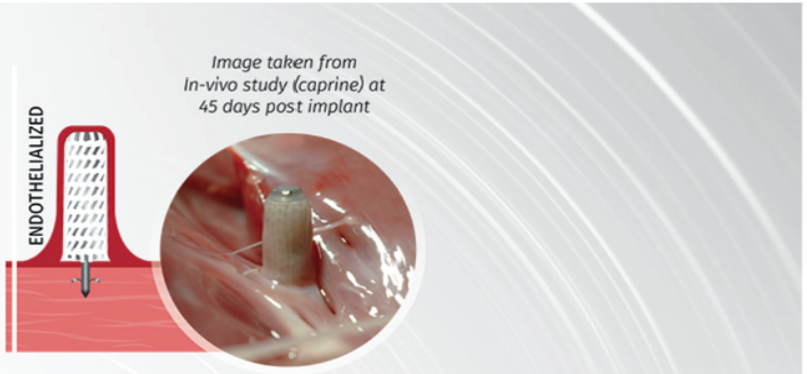
- Biological pacing is a disruptive technology that aims first to improve upon, then to supplement and, eventually, to replace electronic pacing
- Biological pacing utilizes the tools of gene and cell therapy to introduce pacemaker function to preselected regions of the heart
- Gene therapy focuses on delivery via viral vectors; whereas cell therapy uses either mesenchymal stem cells as delivery systems or cells with sinoatrial node-like properties derived from pluripotent stem cells
- Proof-of-concept has been achieved in studies of large animals in complete heart block and, in some instances, sinoatrial node dysfunction
- Substantial barriers remain to be overcome before clinical trials of biological pacing can be begun, but the field is advancing steadily towards this goal

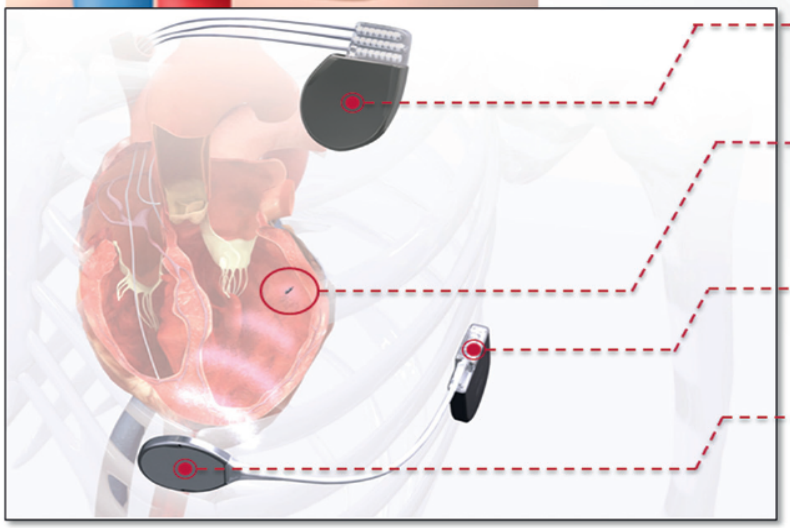
Rosen, M. R. *et al*. *Nat. Rev. Cardiol.* **8**, 656–666 (2011);

Ultrasound

FIGURE 17 Multicomponent Leadless Pacing System







CO-IMPLANT DEVICE
Co-implanted pacemaker, ICD or CRT paces the right ventricle.

RECEIVER ELECTRODE
Implanted onto the endocardium, the receiver electrode converts ultrasound energy into electrical energy to pace the left ventricle.

BATTERY
Implanted subcutaneously on the left mid axillary line, powers the transmitter.

TRANSMITTER
Phased array ultrasound transmitter is implanted sub-muscular over a cardiac echo window. Synchronizes with an RV pacing pulse to transmit ultrasound energy to the receiver electrode to provide Bi-V endocardial pacing.

The battery/transmitter unit detects the pacing stimulus from the coimplant, and an ultrasound pulse is sent to the receiver electrode, which converts the ultrasound energy to a pacing pulse. ICD = implantable cardioverter-defibrillator; other abbreviations as in Figures 1 and 3.

JACC VOL. 69, NO. 2, 2017
JANUARY 17, 2017:211-35

« LeadLess Pacing »

St-Jude Medical
CE mark Oct 2013
Advisory 28 octobre 2016

Medtronic
FDA approved 2016
Approved Health Canada, October 2016

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Comparison of Nanosim leadless cardiac pacemaker (LCP) and Micra Transcatheter pacing system (TPS) features

	LCP	TPS
Length (mm)	41.4	25.9
Volume (cm3)	1	0.8
Weight (g)	2	2
Fixation mechanism	Screw-in helix	Nitinol tines
Pacing mode	VVI/R	VVI/R
Sensor	Temperature	Accelerometer
Battery Longevity (years)	9.8 (2.5 V @0.4 ms)* 14. 7 (1.5 V @ 0.24 ms)	4.7 (2.5 V @ 0.4 ms)* 10 (1.5 V @ 0.24 ms)

Am J Cardiol 2017;119:145e148

Summary of Nanostim leadless cardiac pacemaker (LCP) and Micra Transcatheter pacing system (TPS) investigational device exemption (IDE) trials

Variables	Trials	
	Leadless II-LCP (n=526)	Micra-TPS (n=725)
Implant Success	95.8%	99.2%
Thresholds @ Implant (V@ms)	0.82 @ 0.4	0.63 @ 0.24
Threshold @ 6 Months (V@ms)	0.53 @ 0.4	0.54 V @ 0.24
Complication Rates (6 months)	6.5%	4%
Pericardial Effusion	1.5%	1.6%
Groin Complication	1.2%	0.7%
Device Dislodgement	1.1%	0%

Am J Cardiol 2017;119:145e148

Micra™ (Medtronic)

Device Features

Size

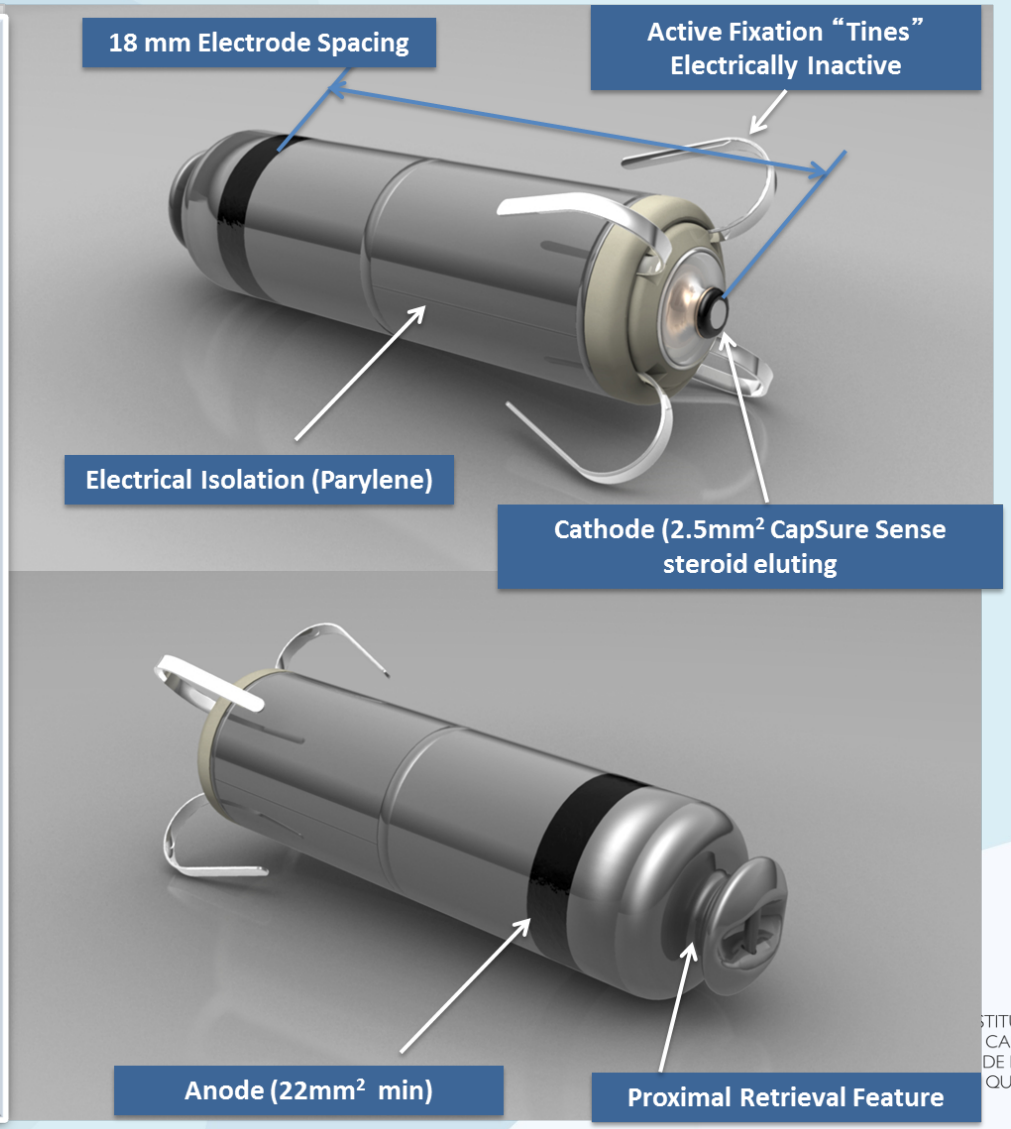
- Volume: 0.75cc
- Mass: 2g
- Length: 25.9mm
- Width: 20Fr

Capabilities

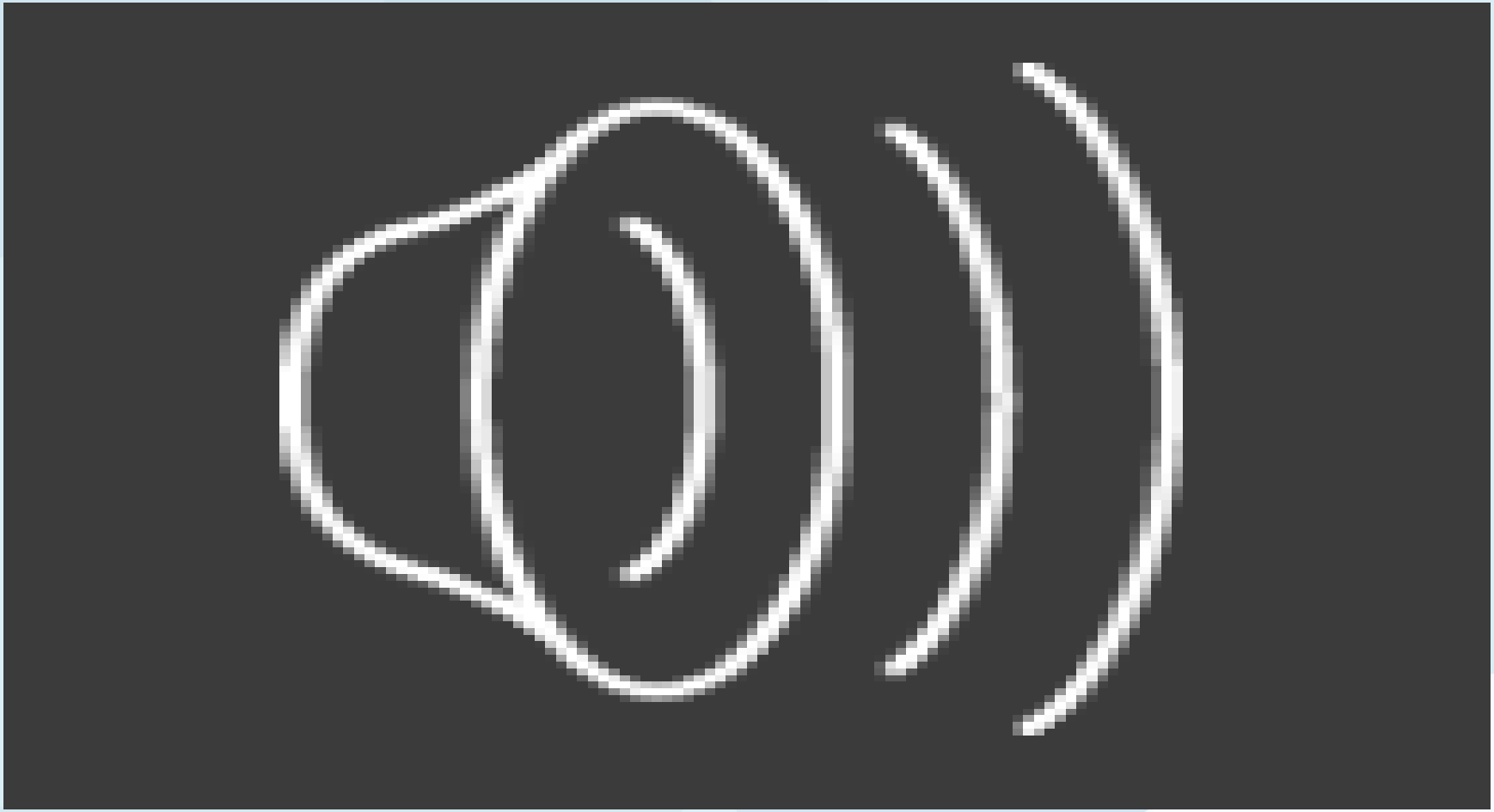
- Pacing Mode: VVIR
- Bipolar sensing (18mm spacing)
- Programmable (RF communication with programmer)
- Capture Management
- Rate Response
- *Essential Diagnostics*: battery status, pacing threshold, pacing impedance, % paced
- Device can be manually deactivated and automatically deactives at EOS

Battery

- 9.6 / 7.1 year longevity
  - 1.5V / 2.0V threshold if 100% paced @ 60 bpm



Implantation



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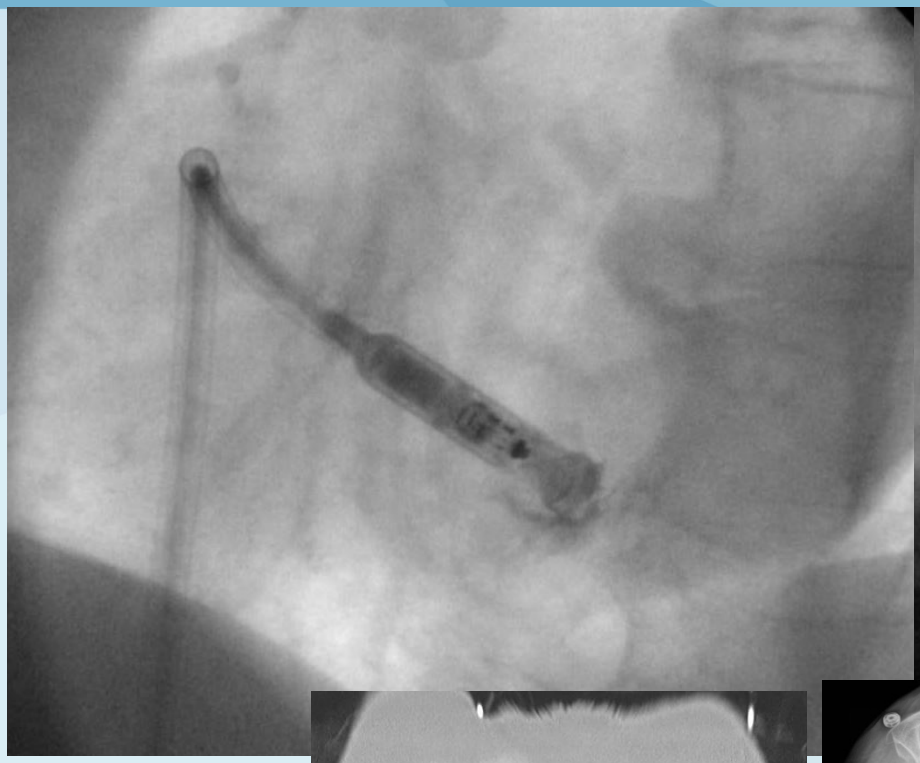
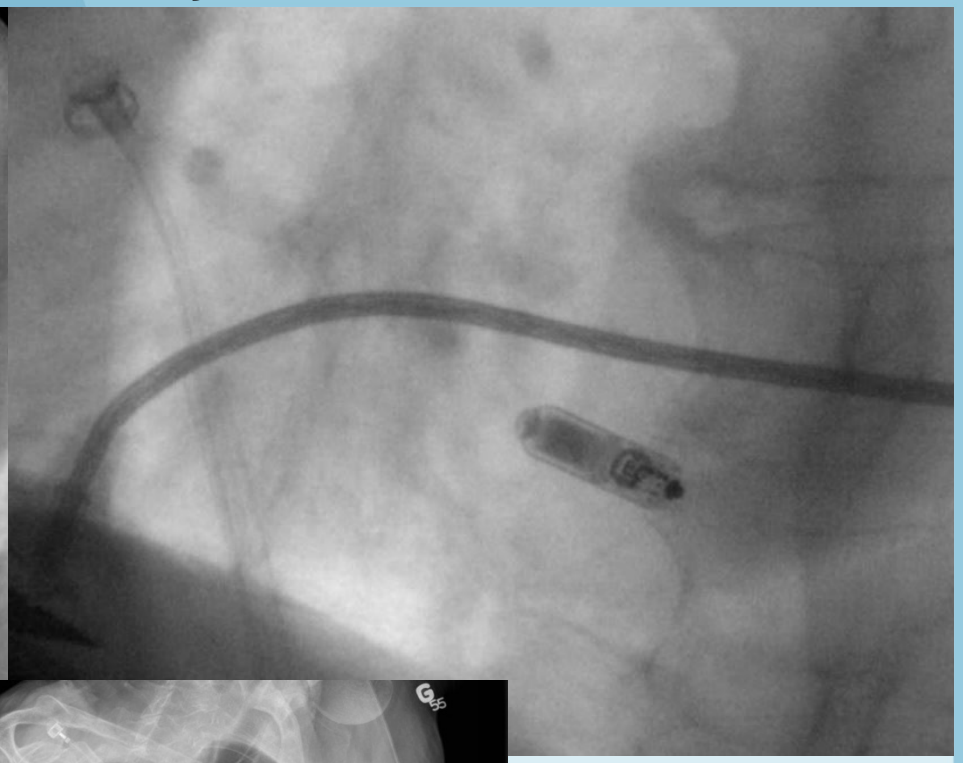
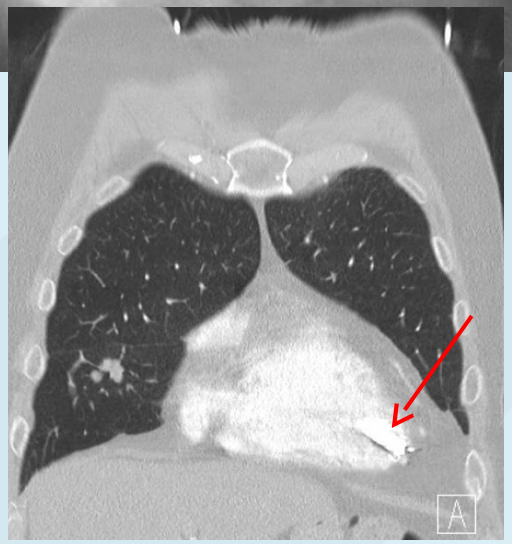
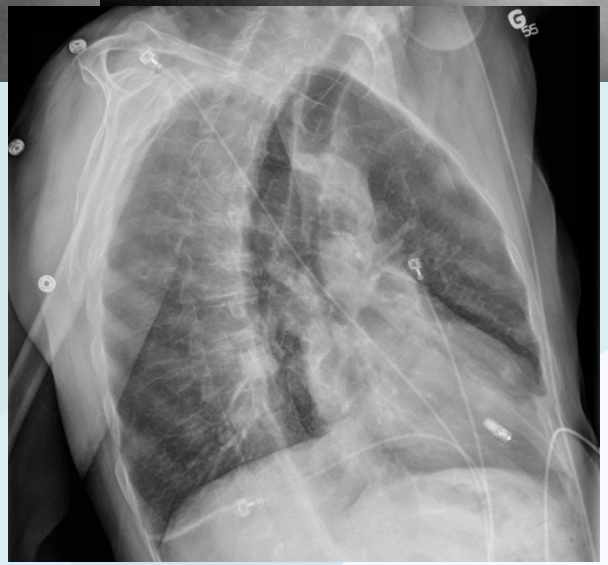
MICRA (IUCPQ,Janv 2015)









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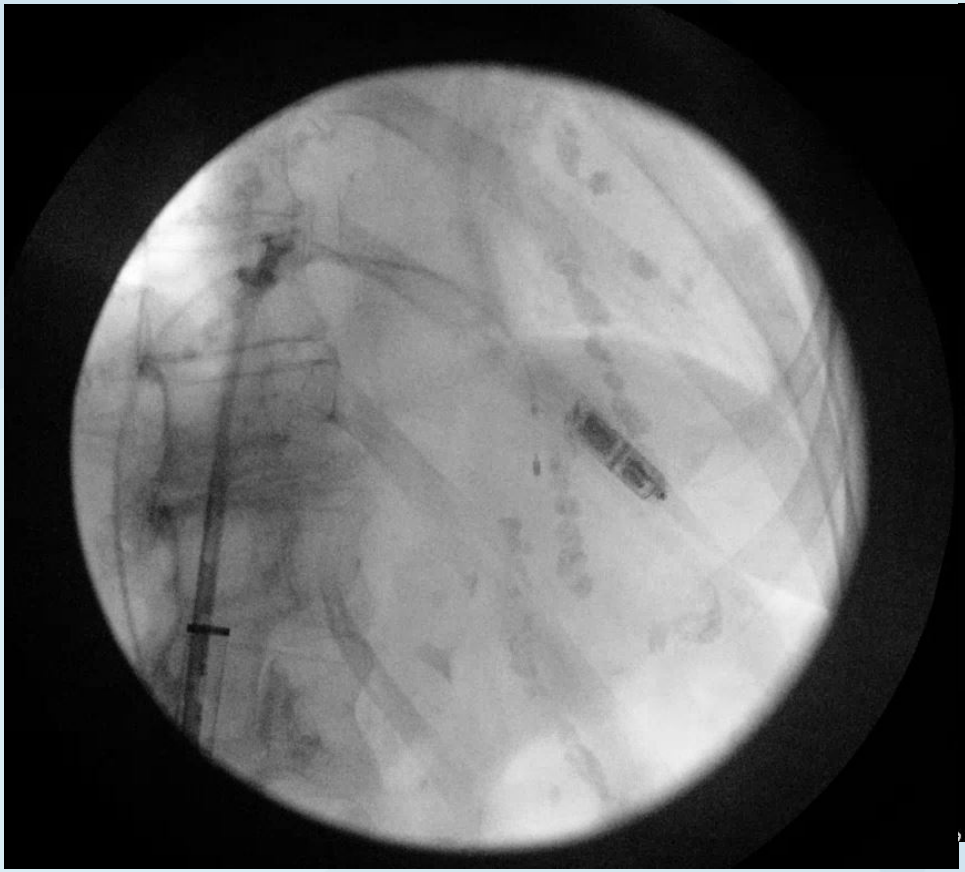
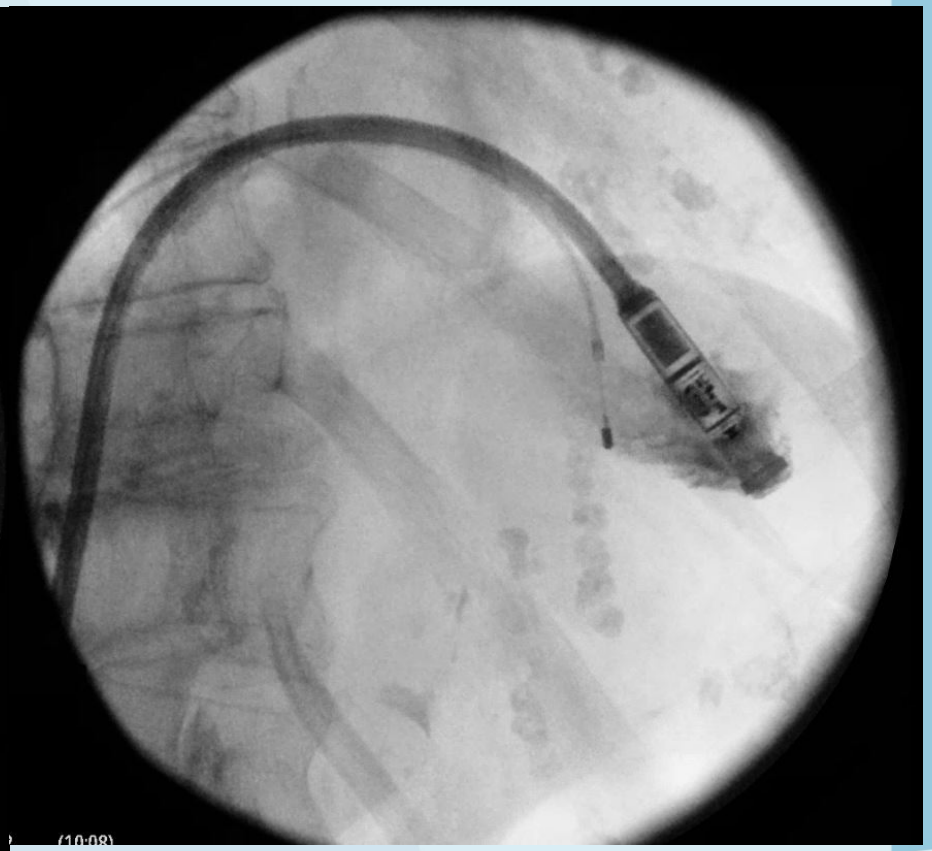
IUCPQ Oct 27, 2016





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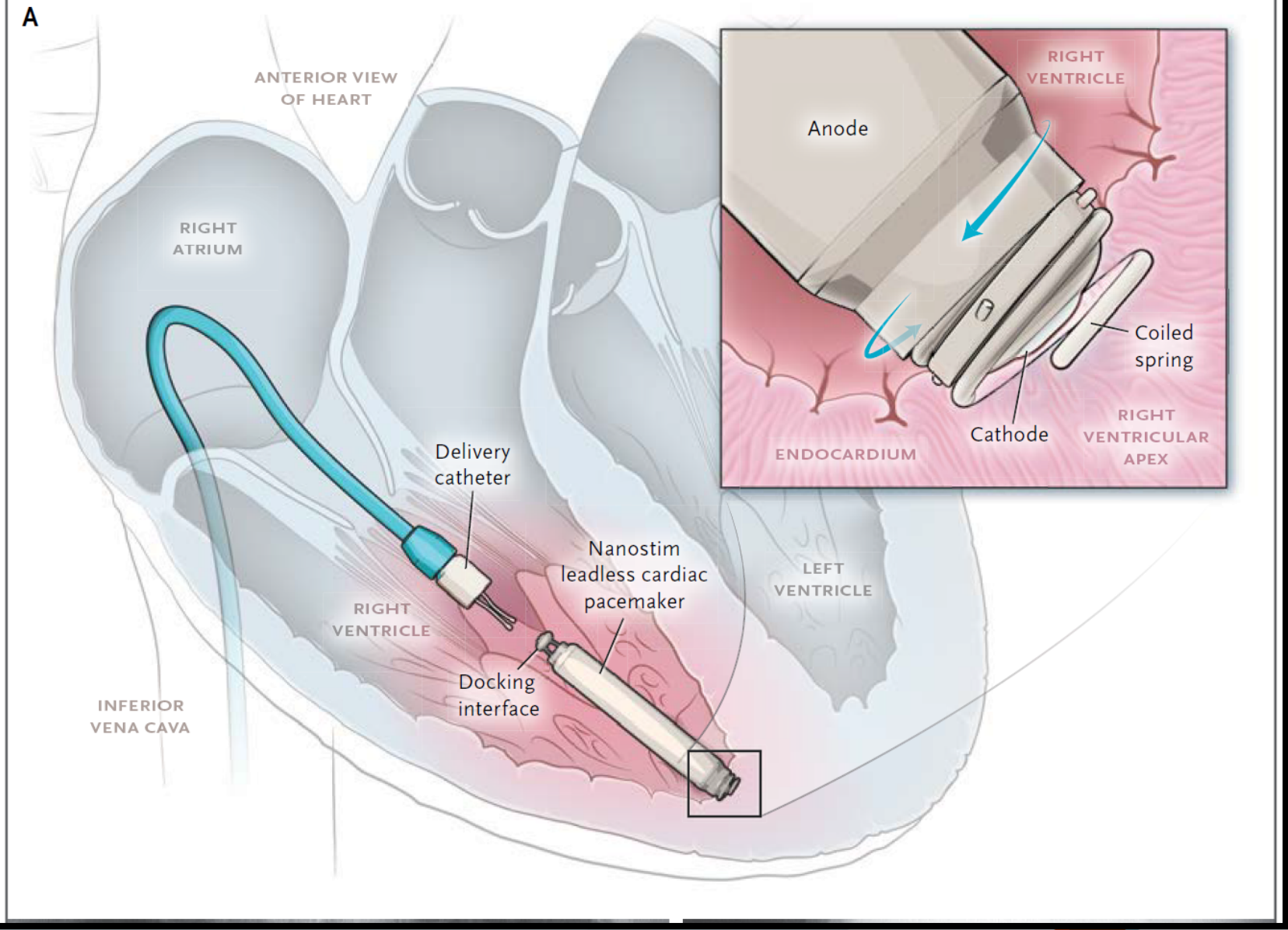
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Percutaneous Implantation of an Entirely Intracardiac Leadless Pacemaker

Vivek Y. Reddy, M.D., Derek V. Exner, M.D., M.P.H., Daniel J. Cantillon, M.D., Rahul Doshi, M.D., T. Jared Bunch, M.D., Gery F. Tomassoni, M.D., Paul A. Friedman, M.D., N.A. Mark Estes, III, M.D., John Ip, M.D., Imran Niazi, M.D., Kenneth Plunkitt, M.D., Rajesh Banker, M.D., James Porterfield, M.D., James E. Ip, M.D., and Srinivas R. Dukkipati, M.D., for the LEADLESS II Study Investigators*

N ENGL J MED 373;12 NEJM.ORG SEPTEMBER 17, 2015



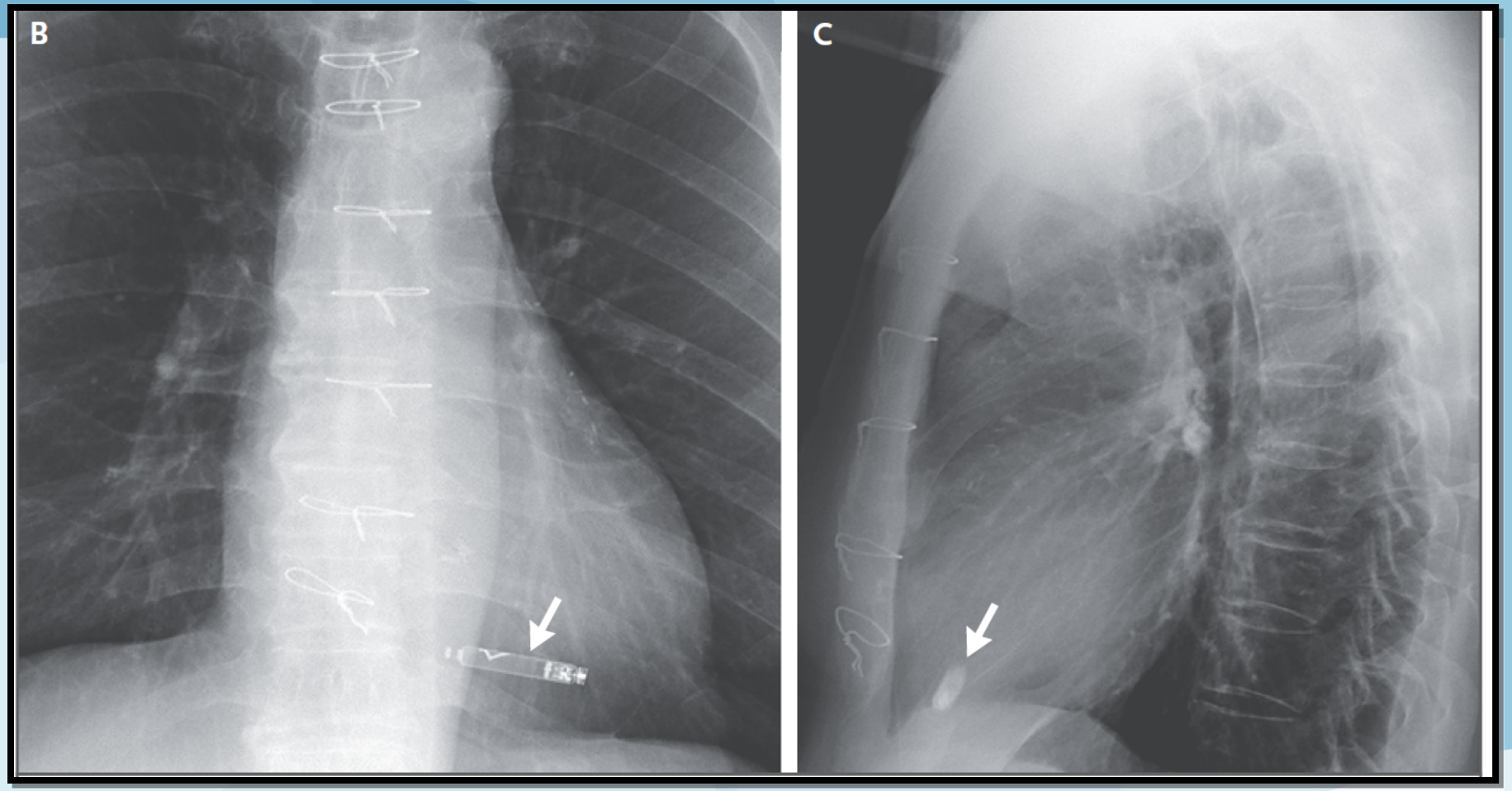


Table 1. Patient Characteristics at Baseline and Procedural Characteristics.*

Characteristic	Primary Cohort (N = 300)	Total Cohort (N = 526)
Patient characteristics		
Age — yr		
Mean	75.7±11.6	75.8±12.1
Range	30–96	19–96
Body-mass index†		
Mean	29.2±7.3	28.7±6.8
Range	15.8–60.3	15.2–60.3
Sex — no. (%)		

Table 1. (Continued.)

Characteristic	Primary Cohort (N = 300)	Total Cohort (N = 526)
Procedural characteristics§		
Duration of implantation — min		
Total: sheath insertion to removal	50.0±27.3	46.5±25.3
Procedure: insertion of delivery catheter to removal	30.4±18.2	28.6±17.8
Duration of fluoroscopy — min	14.9±9.4	13.9±9.1
Device repositioning — no. of patients/total no. (%)		
None	199/289 (68.9)	354/504 (70.2)
1	53/289 (18.3)	89/504 (17.7)
2	24/289 (8.3)	39/504 (7.7)
>2	13/289 (4.5)	22/504 (4.4)
Final device position in right ventricle — no. of patients/total no. (%)		
Apex	140/289 (48.4)	192/504 (38.1)
Apical septum	5/289 (1.7)	96/504 (19.0)
Outflow, septum, or other	144/289 (49.8)	215/504 (42.7)
Missing data	0/289	1/504 (0.2)

Table 2. Device-Related Serious Adverse Events.*

Event	Primary Cohort (N = 300)			Total Cohort (N = 526)		
	No. of Events	No. of Patients	Event Rate %	No. of Events	No. of Patients	Event Rate %
Total	22	20	6.7	40	34	6.5
Cardiac perforation						
Cardiac tamponade with intervention	1	1	0.3	5	5	1.0
Cardiac perforation requiring intervention	1	1	0.3	1	1	0.2
Pericardial effusion with no intervention	2	2	0.7	2	2	0.4
Vascular complication						
Bleeding	2	2	0.7	2	2	0.4
Arteriovenous fistula	1	1	0.3	1	1	0.2
Pseudoaneurysm	1	1	0.3	2	2	0.4
Failure of vascular closure device requiring intervention	0	0	0	1	1	0.2
Arrhythmia during device implantation						
Asystole	1	1	0.3	1	1	0.2
Ventricular tachycardia or ventricular fibrillation	1	1	0.3	2	2	0.4
Cardiopulmonary arrest during implantation procedure	0	0	0	1	1	0.2
Device dislodgement	5	5	1.7	6	6	1.1
Device migration during implantation owing to inadequate fixation	0	0	0	2	2	0.4
Pacing threshold elevation with retrieval and implantation of new device	4	4	1.3	4	4	0.8

ST. JUDE MEDICAL

St. Jude Medical
15900 Valley View Court
Sylmar, CA 91342 USA
Main 818 362 6822
Fax 818 364 5814

Important Medical Device Advisory

Battery Malfunction for Nanostim Leadless Cardiac Pacemaker (LCP)

Model Number S1DLCP

27 October, 2016

Canadian Heart Rhythm Society
Société canadienne de rythmologie

October 28th 2016

Canadian Heart Rhythm Society
Device Committee

RE: ADVISORY: Battery Malfunction, St. Jude Medical NanoStim™ Leadless Cardiac Pacemaker System.

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AFFILIÉ À UNIVERSITÉ LAVAL

ORIGINAL ARTICLE

A Leadless Intracardiac Transcatheter Pacing System

Dwight Reynolds, M.D., Gabor Z. Duray, M.D., Ph.D., Razali Omar, M.D., Kyoko Soejima, M.D., Petr Neuzil, M.D., Shu Zhang, M.D., Calambur Narasimhan, M.D., Clemens Steinwender, M.D., Josep Brugada, M.D., Ph.D., Michael Lloyd, M.D., Paul R. Roberts, M.D., Venkata Sagi, M.D., John Hummel, M.D., Maria Grazia Bongiorni, M.D., Reinoud E. Knops, M.D., Christopher R. Ellis, M.D., Charles C. Gornick, M.D., Matthew A. Bernabei, M.D., Verla Laager, M.A., Kurt Stromberg, M.S., Eric R. Williams, B.S., J. Harrison Hudnall, B.S., and Philippe Ritter, M.D., for the Micra Transcatheter Pacing Study Group*

N Engl J Med 2016;374:533-41.

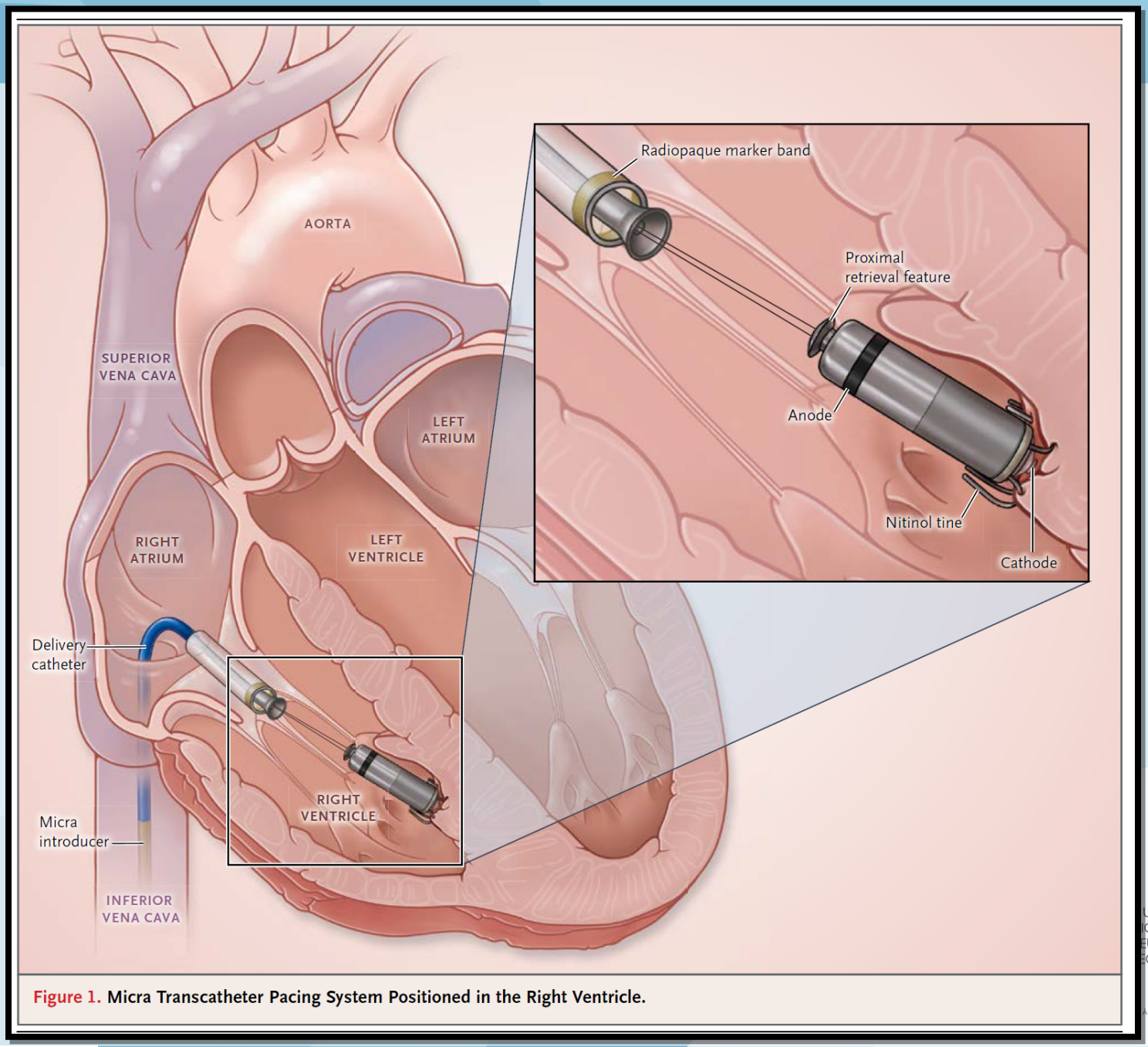


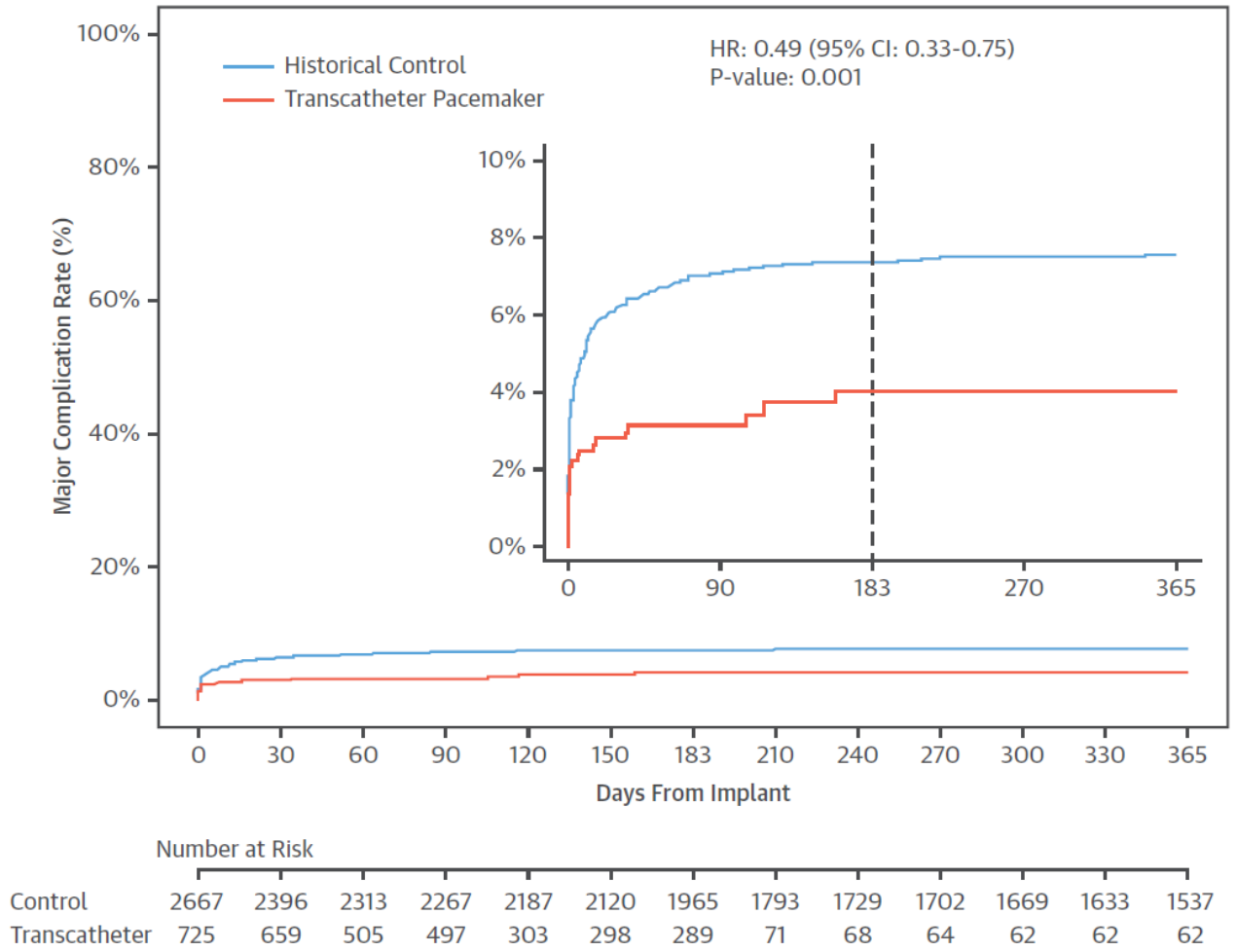
Figure 1. Micra Transcatheter Pacing System Positioned in the Right Ventricle.

N Engl J Med 2016;374:533-41.

Table 2. Major Complications in 725 Patients Who Underwent a Transcatheter Pacemaker Implantation Attempt.

Adverse Event	No. of Events Associated with Major Complication Criterion*						No. of Patients (%)†
	Death	Loss of Device Function	Hospitalization	Prolonged Hospitalization‡	System Revision	Total Events	
Embolism and thrombosis	0	0	1	1	0	2	2 (0.3)
Deep vein thrombosis	0	0	0	1	0	1	1 (0.1)
Pulmonary thromboembolism	0	0	1	0	0	1	1 (0.1)
Events at groin puncture site: atrioventricular fistula or pseudoaneurysm	0	0	2	3	0	5	5 (0.7)
Traumatic cardiac injury: cardiac perforation or effusion	0	0	3	9	0	11	11 (1.6)
Pacing issues: elevated thresholds	0	1	2	1	2	2	2 (0.3)
Other events	1	0	5	4	1	8	8 (1.7)
Acute myocardial infarction	0	0	0	1	0	1	1 (0.1)
Cardiac failure	0	0	3	2	0	3	3 (0.9)
Metabolic acidosis	1	0	0	0	0	1	1 (0.1)
Pacemaker syndrome	0	0	1	0	1	1	1 (0.2)
Presyncope	0	0	0	1	0	1	1 (0.1)
Syncope	0	0	1	0	0	1	1 (0.1)
Total	1	1	13	18	3	28	25 (4.0)

FIGURE 16 Complications With Transcatheter Leadless Pacemakers Versus Historical Transvenous Control Subjects



In this Micra TPS (Medtronic, Minneapolis, Minnesota) study post hoc analysis, the 725 study patients were compared with 2,667 patients who received transvenous pacemakers in previous studies as a historical control cohort. Leadless study patients were older and had more comorbidities than control subjects. At 6-month follow-up, patients with leadless pacemakers had significantly fewer major complications than control patients (HR: 0.49; $p < 0.001$), with study patients experiencing fewer hospitalizations, system revisions, and dislodgments. Reprinted with permission from Reynolds et al. (63). Abbreviations as in Figure 4.

Right Ventricular Anatomy Can Accommodate Multiple Micra Transcatheter Pacemakers

PAMELA OMDAHL, M.B.A.,* MICHAEL D. EGGEN, PH.D.,* MATTHEW D. BONNER, PH.D.,* PAUL A. IAIZZO, PH.D.,† and KENT WIKA, M.S.*

From the *Medtronic, PLC., Mounds View, Minnesota; and †Department of Surgery, University of Minnesota, Minneapolis, Minnesota

Methods: *A total of six human cadaver hearts were obtained from the University of Minnesota Anatomy Bequest Program; the seventh heart was a heart not deemed viable for transplant obtained from LifeSource and then reanimated using Visible Heart® methodologies. Each heart was implanted with multiple Micras using imaging and proper delivery tools; in these, the right ventricular volumes were measured and recorded. The hearts were subsequently dissected to view the right ventricular anatomies and the positions and spacing between devices.*

Results: *Multiple Micra devices could be placed in each heart in traditional, clinically accepted pacing implant locations within the RV and in each case without physical device interactions. This was true even in a human heart considered to be relatively small.*

Conclusions: *Although this technology is new, it was demonstrated here that within the human heart's RV, three Micra devices could be accommodated within traditional pacing locations: with the potential in some, for even more. (PACE 2016; 39:393–397)*

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Long-term Outcomes in Leadless Micra Transcatheter Pacemakers with Elevated Thresholds at Implantation: Results from the Micra TPS Global Clinical Trial

Results: Among 711 Micra patients, 83 (11.7%) had an implant threshold >1.0 V at 0.24 msec. Among 538 Capture patients, 50 (9.3%) had an implant threshold of >1.0 V at 0.40 msec. There were no significant differences in patient characteristics between those with and without an implant threshold >1.0 V, with the exception of LVEF in the Capture cohort (lower with high thresholds, 53% vs 58%, p=0.011). Patients with implant thresholds >1.0 V decreased significantly (p<0.001) in both cohorts. Micra patients with high and very-high thresholds decreased significantly (p<0.01) by 1-month with 87% and 85% having 6-month thresholds lower than the implant value. However, when the capture threshold at implant was >2V only 18.2% had a threshold ≤1V at 6-months and 45.5% had a capture threshold >2V.

Heart Rhythm, in press 2017

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BASIC SCIENCE

Combined leadless pacemaker and subcutaneous implantable defibrillator therapy: feasibility, safety, and performance

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Methods and results

The study consists of two parts. *Animal experiments*: Two sheep were implanted with both an S-ICD and LP (Nanostim, SJM), and the objectives above were tested. *Human experience*: Follow-up of one S-ICD patient with bilateral subclavian occlusion who received an LP and two LP (all Nanostim, SJM) patients (without S-ICD) who received electrical cardioversion (ECV) are presented. *Animal experiments* : Simultaneous device-programmer communication was successful, but LP-programmer communication telemetry was temporarily lost (2 ± 2 s) during ventricular fibrillation (VF) induction and 4/54 shocks. Leadless pacemaker communication and pacing did not interfere with S-ICD rhythm discrimination. Additionally, all VF episodes ($n = 12/12$), including during simultaneous LP pacing, were detected and treated by the S-ICD. Post-shock LP performance was unaltered, and no post-shock device resets or dislodgements were observed (24 S-ICD and 30 external shocks). *Human experience* : The S-ICD/LP patient showed adequate S-ICD sensing during intrinsic rhythm, nominal, and high-output LP pacing. Two LP patients (without S-ICD) received ECV during follow-up. No impact on performance or LP dislodgements were observed.

Conclusion

Combined LP and S-ICD therapy appears feasible in all animal experiments ($n = 2$) and in one human subject. No interference in sensing and pacing during intrinsic and paced rhythm was noted in both animal and human subjects. However, induced arrhythmia testing was not performed in the patient. Defibrillation therapy did not seem to affect LP function. More data on safety and performance are needed.

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Exclusive: Details on Boston Scientific's Leadless Pacer Emerge

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The Empower leadless pacemaker from Boston Scientific