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The Micropacemaker Projects

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DISCLOSURES

- Issued and pending patents related to fetal micropacemaker
- Grant Funding: NIH, FDA, Coulter Foundation, Wright Foundation

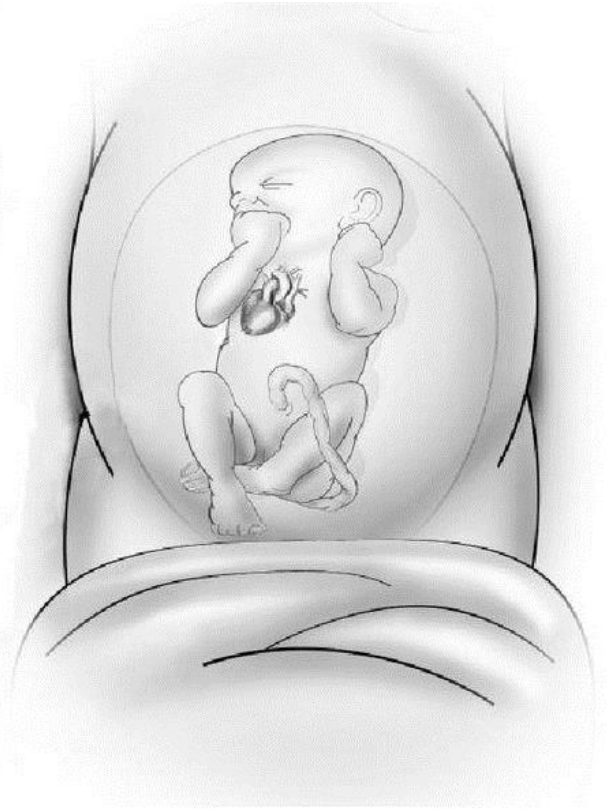
Fetal Heart Block

Incidence: 1:11,000 – 1:22,000 live births

Generally found in two settings:

1.) Maternal autoimmune disease

2.) Associated congenital heart disease (Heterotaxy / polysplenia)



Michaelsson et al. Cardiovasc Clin 1972;4:85 - 101.
Siren et al. J Rheumatol 1998;25:1862 - 1864.

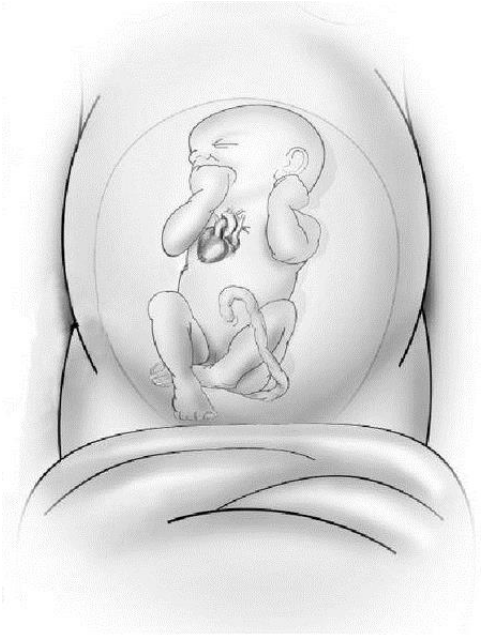
Maternal Autoimmune Disease

Antibodies cross the placenta, enter the fetal circulation and cause fetal injury, most often during the 16–24th gestational weeks.

Mortality rate varies from 10% - 29%.

Treatments: Fluorinated steroids, IVIG, plasmaphoresis, hydrochloriquine, b_2-Agonists

Mortality rates in setting of hydrops fetalis extremely high



Buyon et al. Systemic Lupus Erythematosus. 2011. p. 541-571.
Lee et al. Bailliere' s Clinical Rheumatology, Pregnancy and the Rheumatic Diseases. 1990. p. 69-84.
Lopez et al. Circulation. 2008; 118:1268–1275.
Jaeggi et al. Ultrasound Obstet Gynecol. 2005; 26:16–21.

Fetal Ventricular Pacing for Hydrops Secondary to Complete Atrioventricular Block

(J Am Coll Cardiol 1986;8:1434–6)

ROBERT J. CARPENTER, JR., MD, JANETTE F. STRASBURGER, MD,
ARTHUR GARSON, JR., MD, FACC, RICHARD T. SMITH, MD, FACC, RUSSELL L. DETER, MD,
H. TRISTAN ENGELHARDT, JR., PHD., MD

- 24 year old mother. 27 ½ weeks, Sjorgen’ s, 44 bpm.
- Bipolar **pigtail pacing catheter** placed through 19 gauge needle into right ventricle
- Medtronic external pulse generator
- Paced at 120 bpm. Threshold was 1.5 mA (paced at 6 mA)
- 4 hours and 15 minutes later, intermittent heart tones
  - increased output to 20 mA, but asystole seen on ultrasound.
- Autopsy: Lead remained in the right ventricle. No thrombi
  - Sero-sanguinous pericardial effusion.

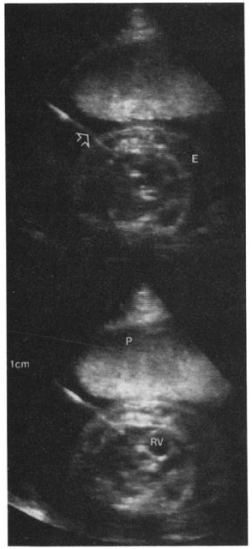


Figure 1. Two-dimensional fetal echocardiograms depicting the pacemaker lead passing through the chest wall and coiled in the right ventricle (RV). The **arrow** identifies the pacemaker cable; E = edema of chest wall; P = placenta.

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J. McCormack[b]
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In utero Pacing for Fetal Congenital Heart Block

Fetal Diagn Ther 1994;9:183–185

- 30 year old mother. 24 weeks, SLE
- Fetal umbilical vein punctured using 20 gauge needle. **Teflon coated pacing lead** (0.009 inch) placed into IVC 1 cm below diaphragm – then into right atrium and then right ventricle.
- Paced at 140 bpm - 5V at 0.5 ms. (0.5 V threshold)
- Lead loops in amniotic fluid. Medtronic Legend II pacemaker placed subcutaneously in the maternal abdominal wall.
- After 8 hours, heart rate 140 bpm. Soon thereafter, slow heart rate. Lead dislodgement suspected.
- 5 days later: Placental cord was punctured using 18 gauge Cook needle. Larger pacing wire placed (to possibly reduce risk of dislodgement). After puncture, while pushing pacing lead, heart rate fell and poor ventricular contraction seen on ultrasound. Asystole followed.
- Cord with no hemorrhage or tamponade. Bright yellow spot at RV apex (site of pacing contact).

Pacing via Open Fetal Surgery

Pacemaker implantation in 1 fetus (direct epicardial pacemaker placement)

Fetus did not survive the procedure

Silverman NH, Kohl T, Harrison MR, Hanley FL. Experimental fetal surgery in the animal model and in the human fetus. In: Imai Y, Momma K, editors. Proceedings of the Second World Congress of Pediatric Cardiology and Cardiac Surgery. Armonk (NY): Futura Publishing Co; 1998. p. 622-3.

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The Monolithic Fetal Pacemaker: Prototype Lead Design for Closed Thorax Deployment

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From the *University of Illinois College of Medicine, Chicago, Illinois, †Division of Cardiology, Department of Medicine, The State University of NY at Stony Brook, Stony Brook, New York, ‡The Heart Institute for Children, Hope Children's Hospital, Oak Lawn, Illinois, and the §Department of Obstetrics and Gynecology, Nassau County Medical Center, East Meadow, New York

(PACE 2003; 26[Pt. I]:805–811)

- Implanted in 11 rats
- Subcostal incision, diaphragm exposed, J-wire then lead advanced through diaphragm into thorax
- Placed close to mediastinum
- Connected to external pacemaker
- Pacing successful in 10 of 11

Figure 1. *Panel A shows the design of the unipolar catheter. This may have a lumen, in the preferred embodiment, in which case the device is hollow. Panel B shows the battery/pulse generator in the preferred embodiment.*

New lead for in utero pacing for fetal congenital heart block

Renato S. Assad, MD,[a] Paulo Zielinsky, MD,[b] Renato Kalil, MD,[b] Gustavo Lima, MD,[b] Anna Aramayo, MD,[b] Ari Santos, MD,[b] Roberto Costa, MD,[a] Miguel B. Marcial, MD,[a] and Sérgio A. Oliveira, MD,[a] São Paulo and Porto Alegre, Brazil

J Thorac Cardiovasc Surg. 2003 Jul;126(1):300-2.

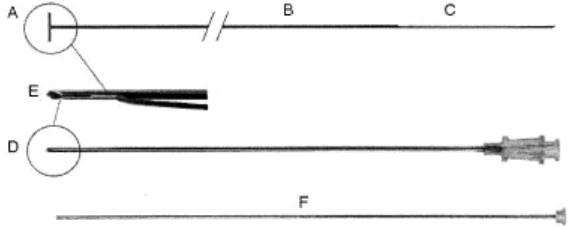

Figure 1. The introducer needle with the new T-bar lead: *A*, stainless steel bar; *B*, pacing wire with polypropylene coating; *C*, straight needle; *D*, 18-gauge introducer needle with a 25° beveled tip fashioned with a 7-mm longitudinal side slot cut from the heel of the bevel *(E)*; *F*, needle stylet.

- 36-year-old, 24 weeks gestation. HR 47 bpm.
- Hydrops, left atrial isomerism, AV septal defect.
- 15 cm, 18 gauge needle placed into left ventricular myocardium (4 attempts).
- A second lead placed in thoracic wall for bipolar stimulation.
- External Biotronic ERA 300 pacemaker (Subcutaneously in the maternal abdominal wall).
  - Paced at 140 bpm.
- Cardiac tamponade during procedure, managed with pericardiocentesis.
- First post-op day: recovery of myocardial function, mild pericardial effusion
- After 36 hours of pacing, ultrasound showed ventricular asystole and large effusion
- Autopsy: myocardial lead in place (as well as other lead in thoracic wall).

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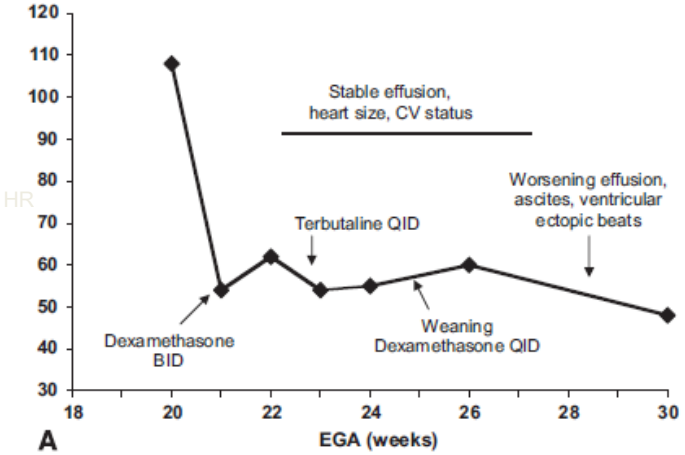
Fetal surgical management of congenital heart block in a hydropic fetus: Lessons learned from a clinical experience

Pirooz Eghtesady, MD, PhD,[a] Erik C. Michelfelder, MD,[b] Timothy K. Knilans, MD,[b] David P. Witte, MD,[c] Peter B. Manning, MD,[a] and Timothy M. Crombleholme, MD, FACS, FAAP,[d] Cincinnati, Ohio

The Journal of Thoracic and Cardiovascular Surgery • Volume 141, Number 3 835-837, 2011

- 32-year-old, 29 weeks gestation, Heart rate mid-40's
- Open fetal surgery
- St. Jude Microny pacemaker
  - Pacing at 65 bpm
- POD 1: Reaccumulation of small ascites.
  - Cardiac output up 150%
- POD 2: Continued oligohydramnios
  - Tried to accelerate pacing – unable to interrogate
- POD 5: fetal demise



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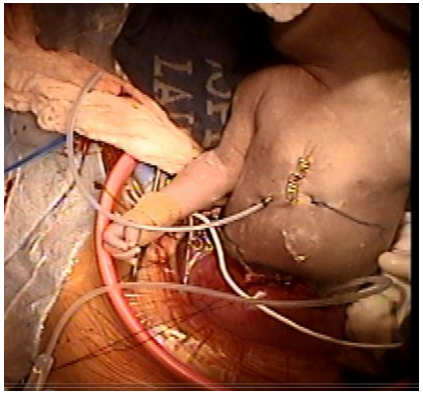
Fetal Diagnosis and Therapy

Novel Insights from Clinical Practice

Fetal Diagn Ther
DOI: 10.1159/000475815



Ex utero Intrapartum Treatment to Ventricular Pacing: A Novel Delivery Strategy for Complete Atrioventricular Block with Severe Bradycardia

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Johannes C. von Alvensleben[b, c] Regina Reynolds[a, b, g] Timothy M. Crombleholme[a, b–e]
Henry L. Galan[a, b, h]

21 year-old: Heart block at 18 6/7 weeks.
No response to IVIG / dexamethasone

26 weeks: HR 51; terbutaline started

36 weeks: HR 47 bpm. New small pericardial effusion

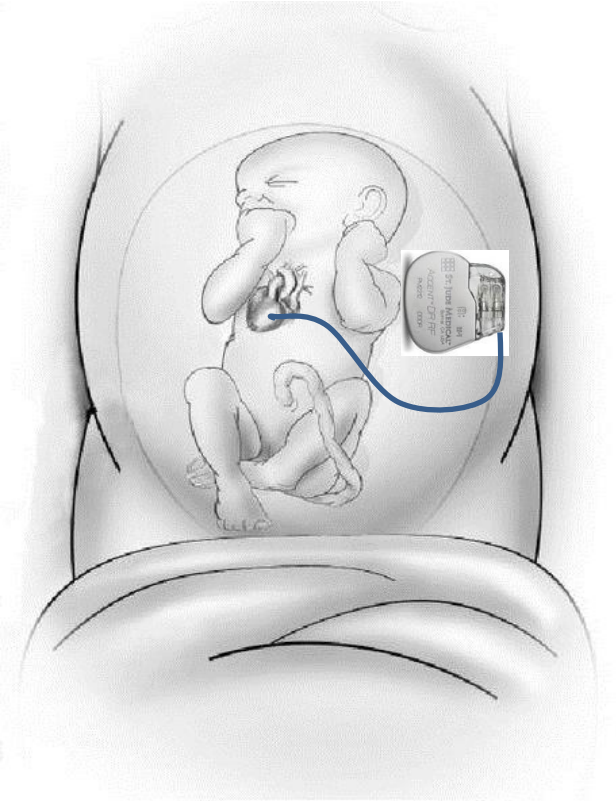
Ex utero intrapartum treatment (EXIT)

Temporary right ventricular lead placed through subxiphoid incision – pacing at 70 bpm

Delivered 55 minutes later

History of Fetal Pacing: Extracorporeal pacing system

- Place lead in fetus
- Attach to “standard” pacemaker in mother
- Failures presumed to be due to fetal movement and complications of fetal surgery



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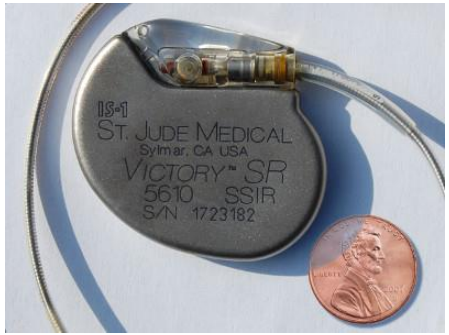
Challenges

- Pacing system needs to reside entirely within the fetus (not extracorporeal)
- Implant percutaneously in the fetus without open surgery
  - Preferably using tools already available for fetal interventions
- Adequate myocardial contact for capture
- Robust enough lead to tolerate >10,000,000 cardiac contractions (2-3 months)
- Adequate battery longevity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Sylmar, CA USA
VICTORY™ SR
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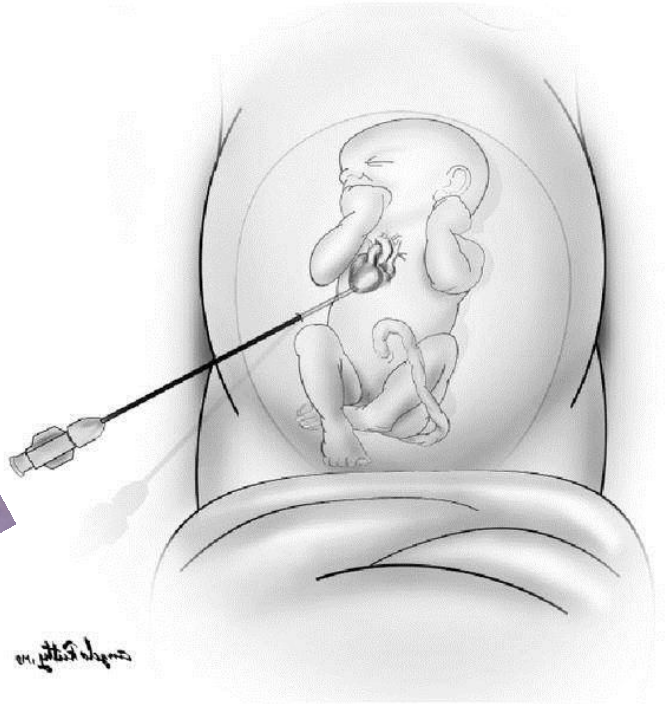
S/N 1723182



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Design and Testing of a Percutaneously Implantable Fetal Pacemaker

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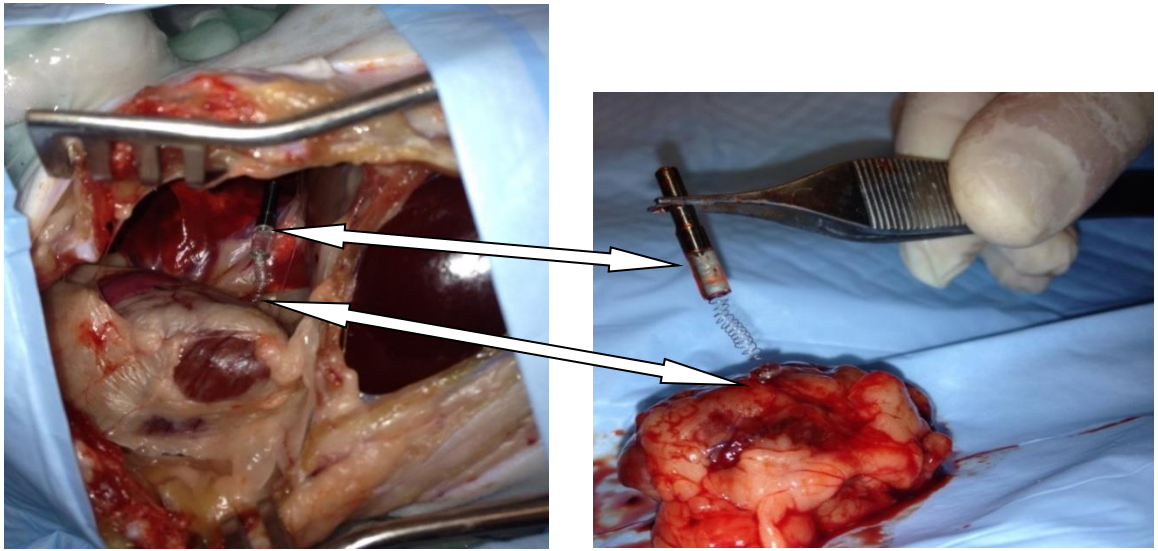
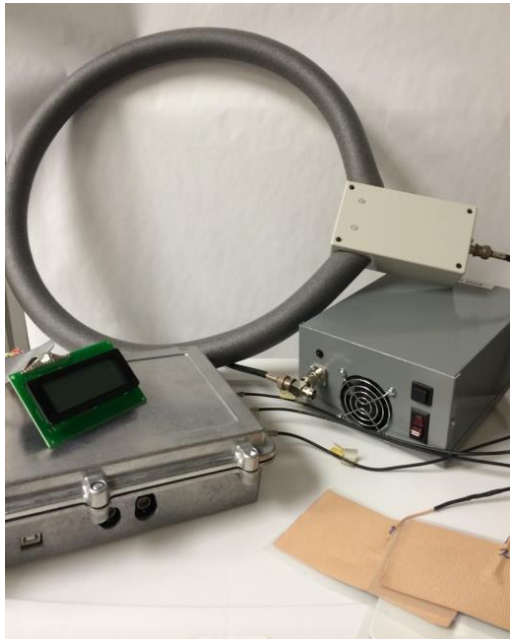
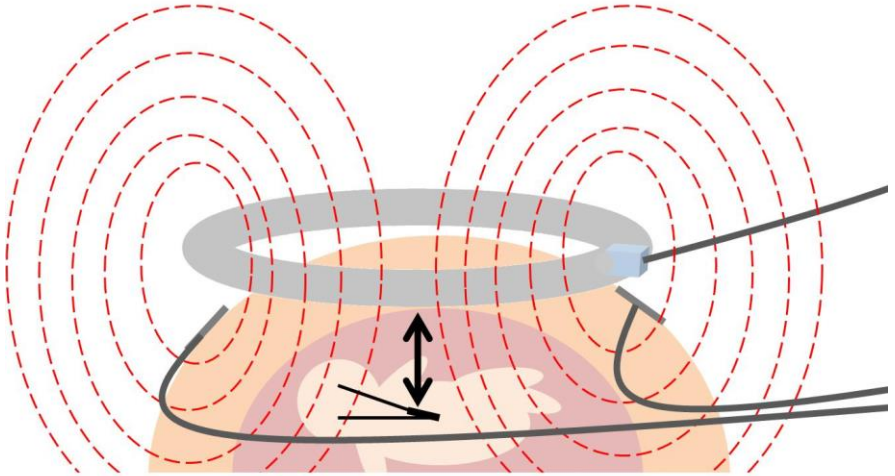
(*Received 16 May 2012; accepted 14 July 2012*)



Implanted percutaneously in an adult rabbit via subxyphoid approach using ultrasound guidance

Battery Longevity: Wireless Recharging System





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Preclinical testing and optimization of a novel fetal micropacemaker

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From the [*]Division of Cardiology, Children's Hospital Los Angeles; and Keck School of Medicine, University of Southern California, Los Angeles, CA, [†]Department of Biomedical Engineering, University of Southern California, Los Angeles, California, [‡]C.W. Steers Biological Resources Center, Los Angeles Biomedical Research Institute, Harbor–University of California, Los Angeles, Torrance, California, and [§]Department of Obstetrics and Gynecology, Keck School of Medicine, University of Southern California, Los Angeles, California.

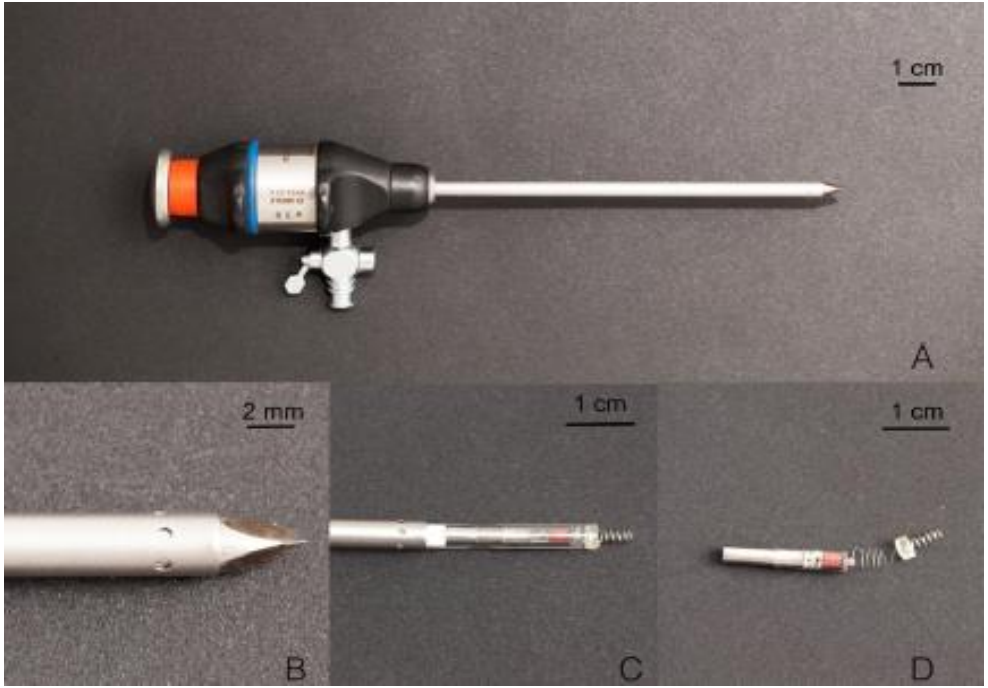
- 7 fetal sheep
- 112-128 days gestation (normal gestation is 145-150 days)
- Micropacemaker: VOO 100-110 bpm
- Uterus surgically exposed for procedures

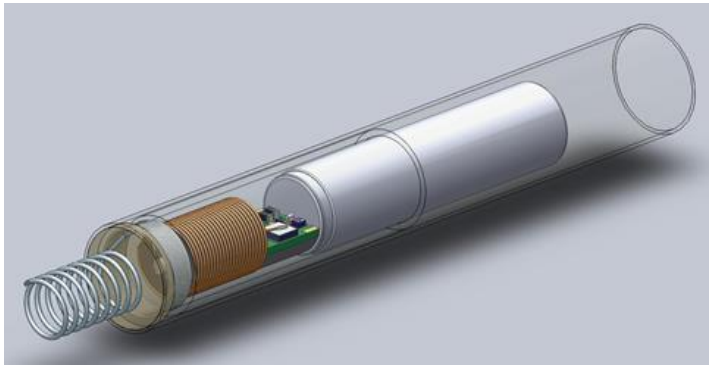
  Leads sewn on fetal chest for fetal ECG (to determine pacing / capture)

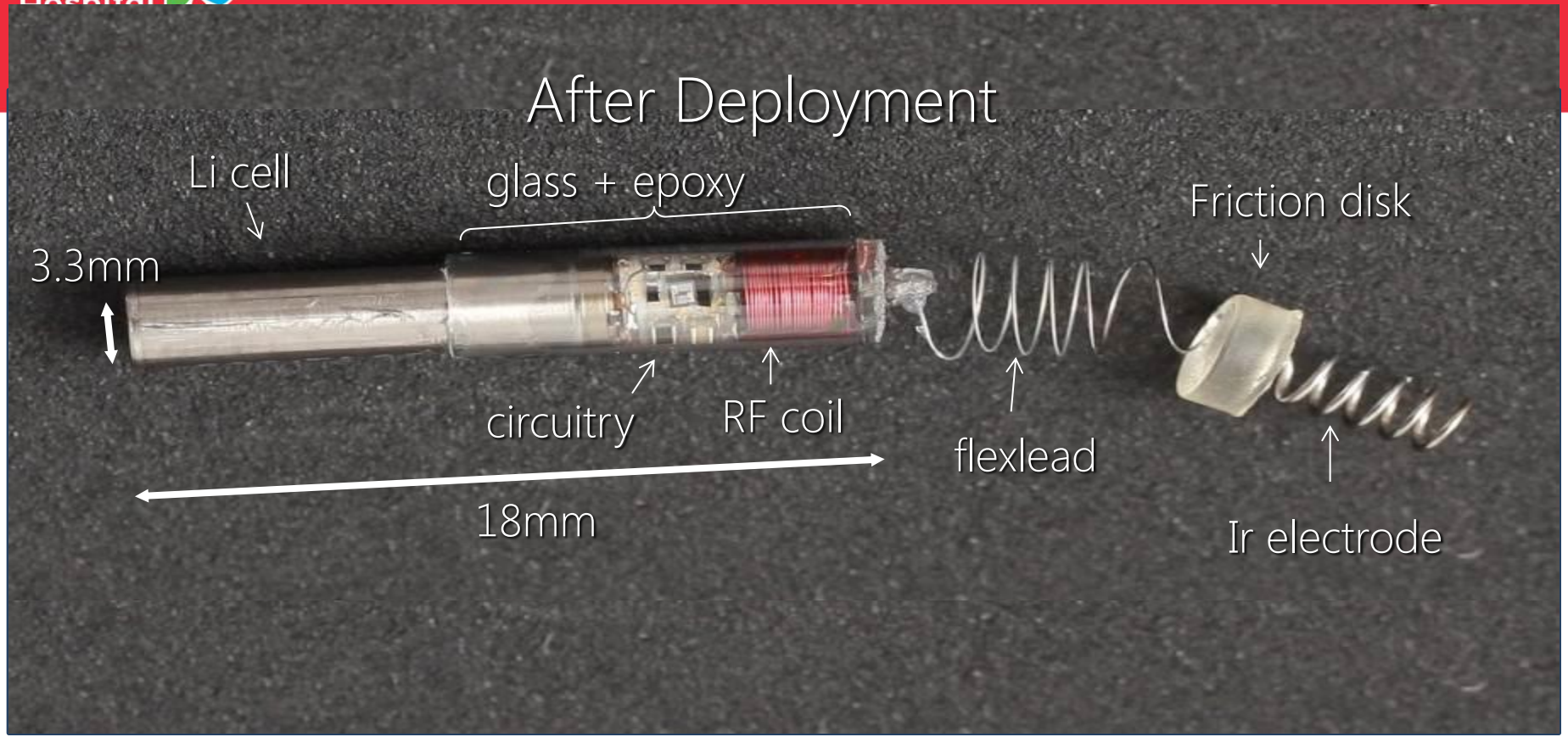
Heart Rhythm 2015; 12:1683-1690

Device and Equipment

4.5 mm external diameter (3.8 mm internal diameter) implantation trocar and cannula






After Deployment
Li cell
glass + epoxy
Friction disk
3.3mm
circuitry
RF coil
flexlead
18mm
Ir electrode

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Sheep Model Limitations

- Lack of pericardial effusion
- Shape of fetal sheep thorax
- No heart block
- More invasive (opening of uterus for placement of ECG electrodes)

Implantation

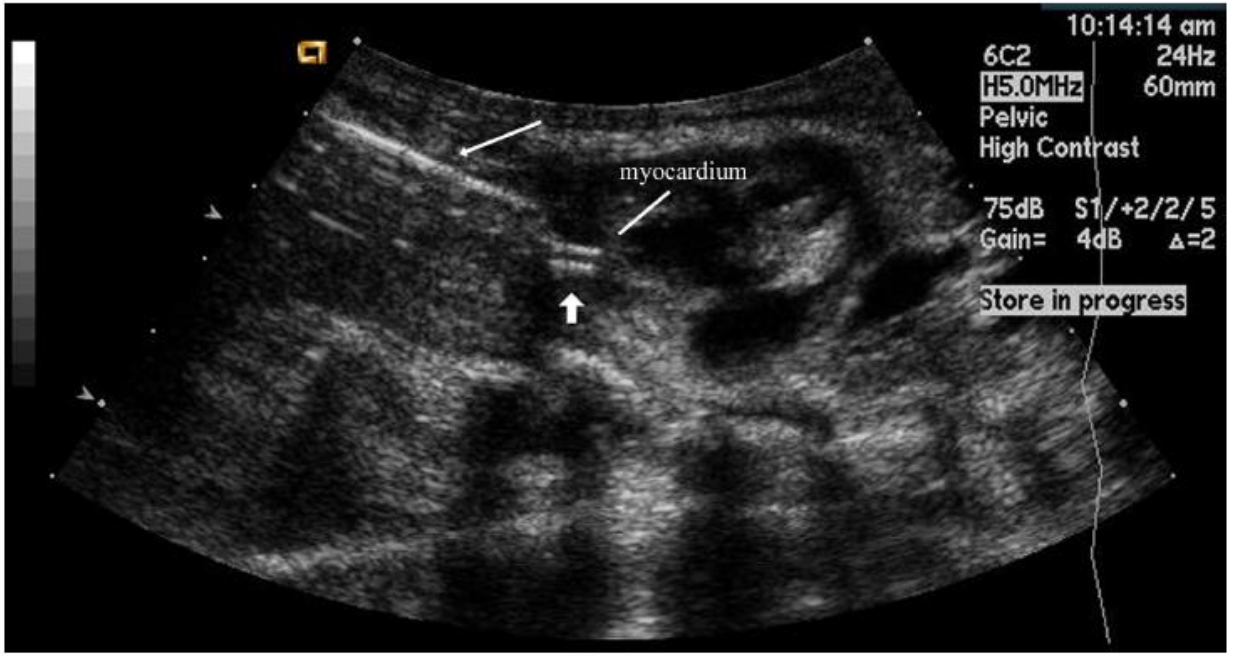

Figure 2 Micropacemaker deployment: Ultrasound image showing implanted electrode (thick arrow) and implantation cannula (thin arrow) just after deployment of the micropacemaker.

Major Challenge = No pericardial effusion

Creation of pericardial effusion

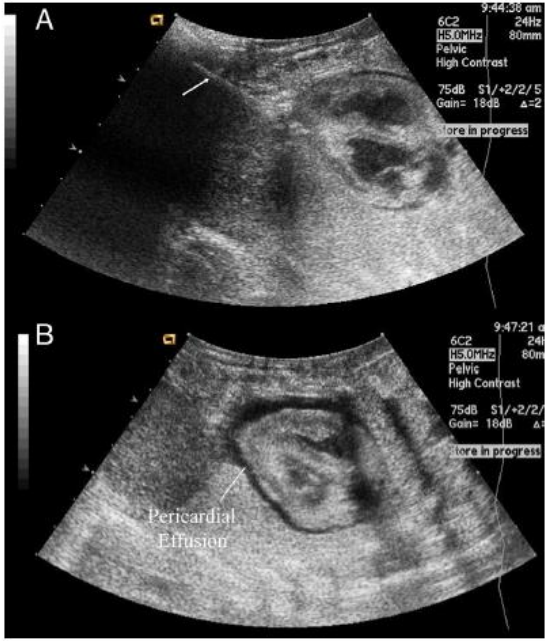

Figure 3 Creation of pericardial effusion. **A:** A long needle *(arrow)* is inserted into the pericardial space under ultrasound guidance. **B:** Saline is injected to create a transient pericardial effusion.

- Insertion of Touhy needle into pericardial space
  - Saline hand infused in slow boluses
- Improved access to epicardial surface
- Improved imaging

- Performed in last 4 sheep

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Sheep Model Limitations

- Lack of pericardial effusion
- Shape of fetal sheep thorax
- No heart block in model
- More invasive (opening of uterus for placement of ECG electrodes)

Capture demonstrated (VOO)

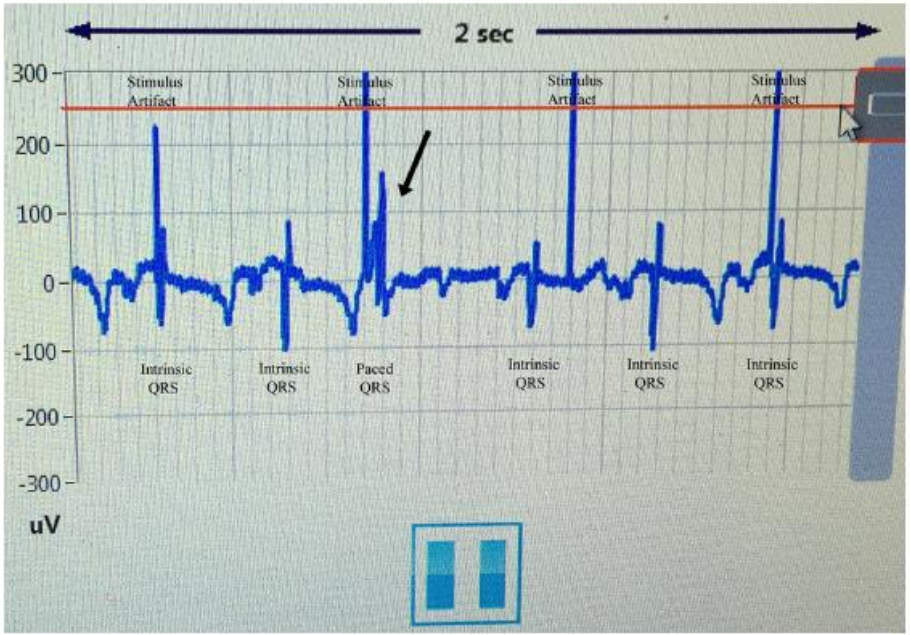

Figure 4 Fetal ECG demonstrating ventricular capture. Stimulus artifacts from the pacemaker march out at a pacing rate of 118 bpm while the intrinsic fetal heart rate is 170 bpm. Advancement of the QRS *(arrow)* is seen immediately after a stimulus artifact when ventricular capture occurs.

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Fetal Sheep Outcomes

Table 1 Implantation and follow-up

Animal no.	Gestational age at implantation (days)	Device follow-up time (days)	Total procedural time (hours:minutes)	Open uterus time (hours:minutes)	No. of devices	Successful capture?	Implantation comments	Follow-up
1	112	19	2:15	1:49	1	Yes	Failure of electronics causing intermittent pacer output.	POD1: Effusions (pericardial and pleural) seen POD12: Complete resolution of effusions POD19: Euthanasia
2	127	N/A	2:50	2:24	3	No	Electrode screws did not penetrate epicardial surface	
3	128	N/A	1:40	1:23	2	No	First device did not contact epicardial surface Second device placement resulted in myocardial perforation and cardiac tamponade	
4	127	5	2:25	0:45	1	Yes	Pericardial effusion created (40 mL)	POD1 and POD3: Capture and good fetal health POD5: Animal found delivered and deceased
5	128	15	2:30	0:23	2	Yes	Pericardial effusion created (40 mL) Capture seen on first device after implantation and capture of second device	POD1: Good fetal health, 1 device captures POD7: Good fetal health, no capture POD12: 2 devices recharged, no capture POD15: Elective termination
6	120	5	0:50	0:20	1	Yes	Pericardial effusion created (40 mL)	POD2: Intermittent capture, good health POD5: Fetal death, sheep in labor
7	125	6	1:30	0:17	1	Yes	Pericardial effusion created (50 mL)	POD2: No capture, good fetal health POD6: Fetal death, sheep in labor

POD = postoperative day.

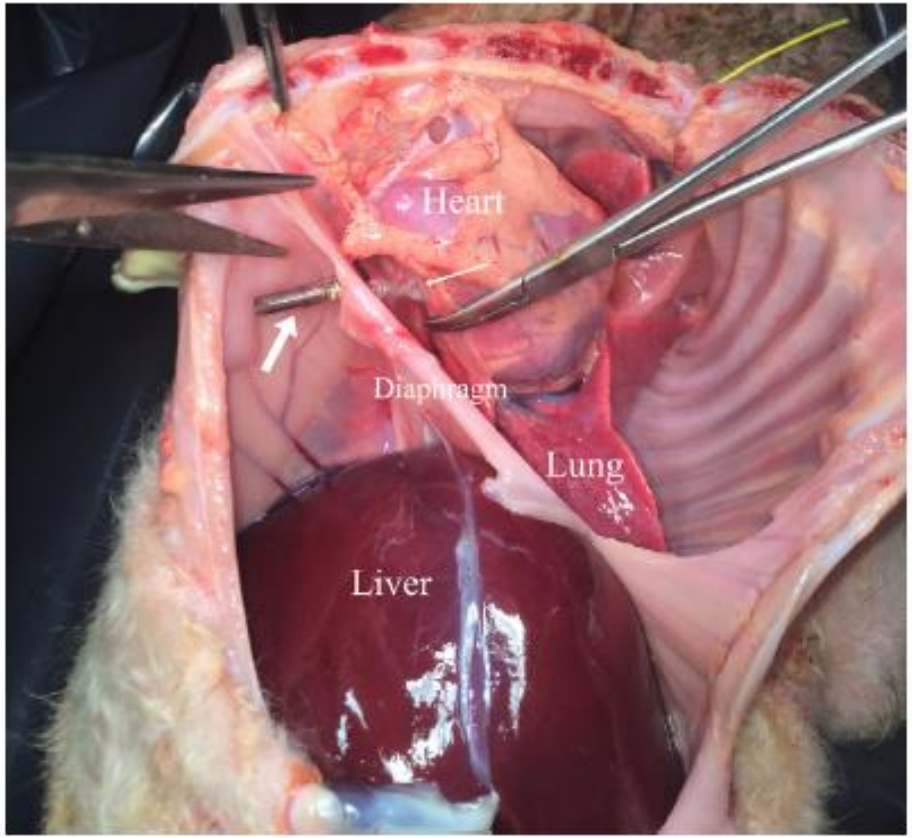


Figure 5 Necropsy in sheep no. 4 demonstrating the micropacemaker device *(large arrow)* lying through the diaphragm. The electrode is seen penetrating the left ventricular epicardium *(small arrow)*.

Figure 7 Radiograph of fetal heart specimen (sheep no. 4) fixed in formaldehyde. The electrode is connected to the micropacemaker via an intact flexible lead.

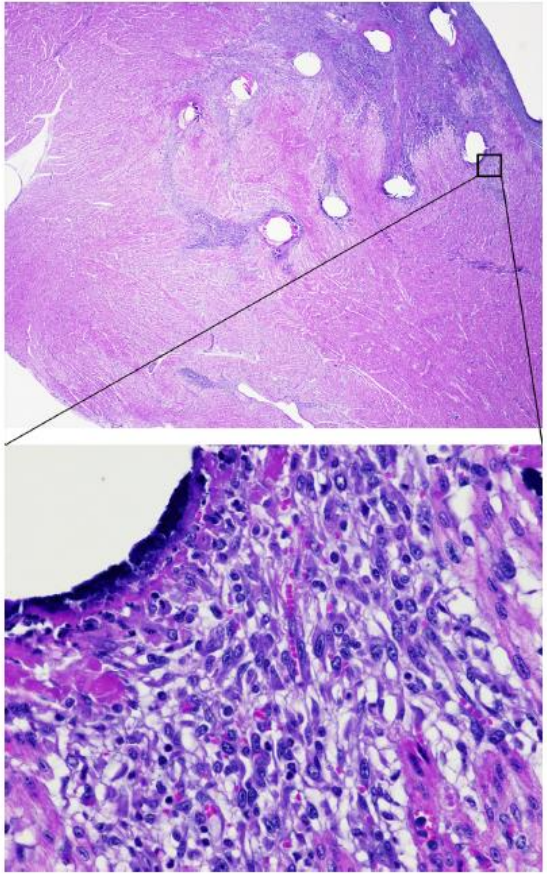


Figure 6 Histology at implantation site. Histology from sheep no. 4 demonstrating the path of the electrode (seen as round voids) as it tunneled into the myocardium. There is moderate myocardial degeneration and necrosis with a mixed inflammatory reaction, including macrophages, lymphocytes, and neutrophils.

Significant inflammatory response seen at electrode-myocardial interface

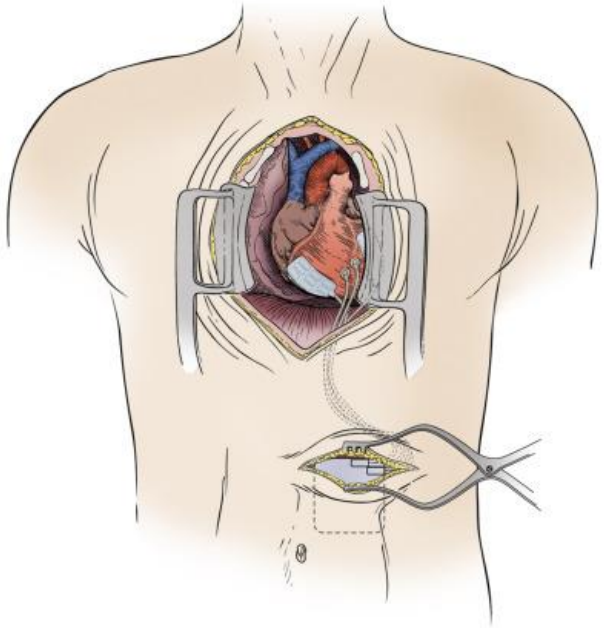
Lesson learned: need steroid-eluting plug

Device Challenges and Solutions

- Electrical failure in first experiment → Circuit board optimized
- Screw electrode blunted → Modified tip bevel and storage container for device
- Broken flexible lead → Modified welding technique
- Inflammation at electrode-myocardium interface → Steroid eluting plug
- Recharging challenges → Engineering modifications performed to ferrite (RF) coil

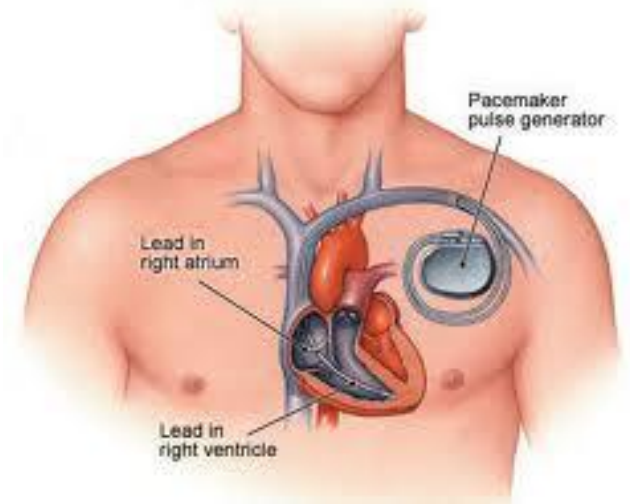
Standard Pacing

Epicardial



Belott et al. Clinical Cardiac Pacing: Defirillation and Resynchronization Therapy (Fifth Edition) 2017

Transvenous



http://heartcenteraz.com/cardiovascular-services/electrophysiology-procedures/

Lead challenges

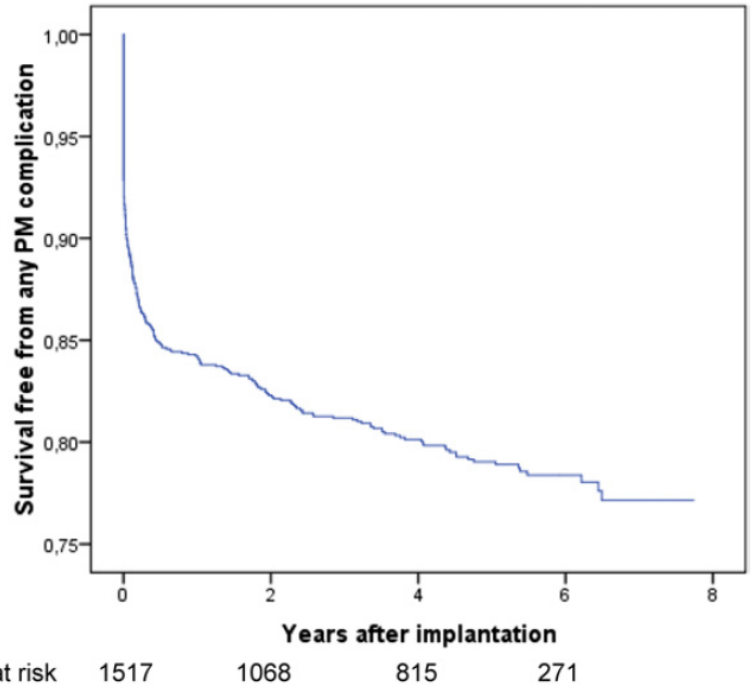


Figure 1 Kaplan-Meier curve with survival free from any pacemaker complication during a mean follow-up of 5.8 years.

Complications after pacemaker placement:

- Within 2 months: 12.4% with complications
- Later complications: 9.4% (majority lead-related)

Udo et al. *Heart Rhythm*. 2012;9:728-735

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Table 3 Complications within 2 months and during long-term follow-up occurring in 1517 patients with a first pacemaker

	Within 2 months		During follow-up	
	n	%	n	%
Traumatic complications—total	42	2.77	1	0.07
Perforation of cardiac structure	6	0.40	1	0.07
Pneumo(hemo)thorax	34	2.24	0	0
Pericardial effusion	2	0.13	0	0
Lead related complications—total	84	5.54	84	5.54
Lead fracture*	2	0.13	6	0.40
Lead dislocation or disconnection*	50	3.30	24	1.58
Insulation problem*	4	0.26	11	0.73
Infection (ie, lead endocarditis)*	0	0	3	0.20
Stimulation threshold problem	12	0.79	26	1.71
Diaphragm or pocket stimulation	11	0.73	10	0.66
Diaphragm or pocket stimulation*	0	0	1	0.07
Other†	5	0.33	3	0.20
Pocket complications—total	72	4.75	49	3.23
Hematoma	44	2.90	1	0.07
Difficult to control bleeding*	4	0.26	2	0.13
Infection	10	0.66	4	0.26
Infection*	4	0.26	8	0.53
Discomfort due to pocket or pacemaker	1	0.07	17	1.12
Discomfort due to pocket or pacemaker*	2	0.13	9	0.59
Skin erosion	7	0.46	8	0.53
Pulse generator problem—total	5	0.33	23	1.52
Problem with connection screw	5	0.33	0	0
Manufacturer recall	0	0	5	0.33
Manufacturer recall*	0	0	6	0.40
Reset to default settings	0	0	4	0.26
Device cannot be programmed	0	0	2	0.13
Pacemaker tachycardia	0	0	2	0.13
Malfunction of software algorithm	0	0	4	0.26
Total number of complications in need of reoperation	64	4.22	61	4.02
Number of patients experiencing a complication	188	12.4	140	9.20

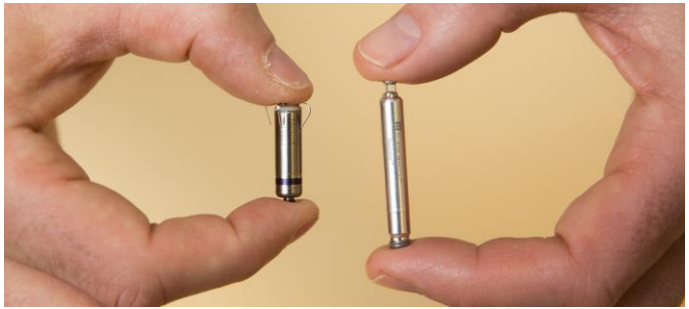
*Complication is managed with reoperation. Numbers do not add up, because patients can experience multiple complications.
†See text for details.

	Within 2 months		During follow-up	
	n	%	n	%
Lead related complications—total	84	5.54	84	5.54
Lead fracture*	2	0.13	6	0.40
Lead dislocation or disconnection*	50	3.30	24	1.58
Insulation problem*	4	0.26	11	0.73
Infection (ie, lead endocarditis)*	0	0	3	0.20
Stimulation threshold problem	12	0.79	26	1.71
Diaphragm or pocket stimulation	11	0.73	10	0.66
Diaphragm or pocket stimulation*	0	0	1	0.07
Other†	5	0.33	3	0.20

Udo et al. *Heart Rhythm*. 2012;9:728-735

Standard Pacing

- Implantation of a myocardial lead attached to a remote pacing device
- Leadless Pacemakers have been added
- Pacing devices attached to the right ventricular myocardium and reside in endovascular space
- Complications include device dislodgement, perforation at implant



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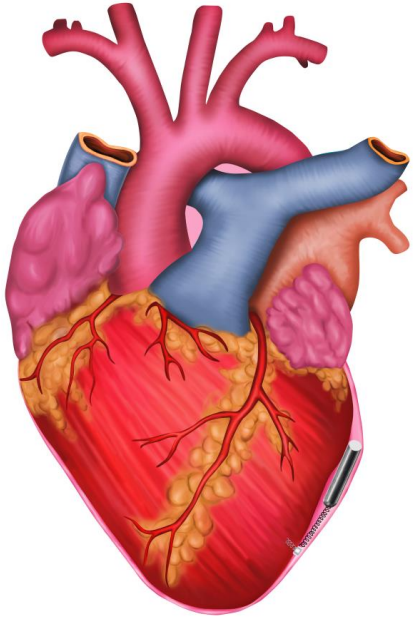
Circulation: Arrhythmia and Electrophysiology

ORIGINAL ARTICLE

Minimally Invasive Implantation of a Micropacemaker Into the Pericardial Space



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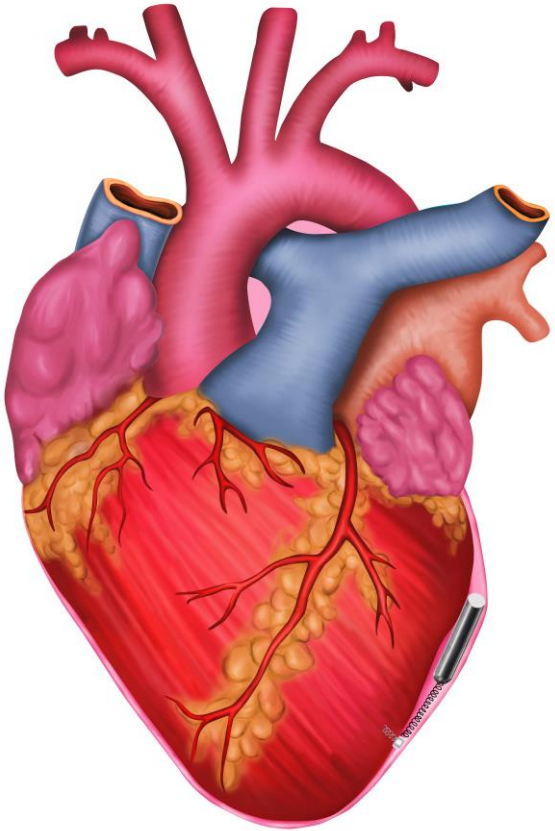
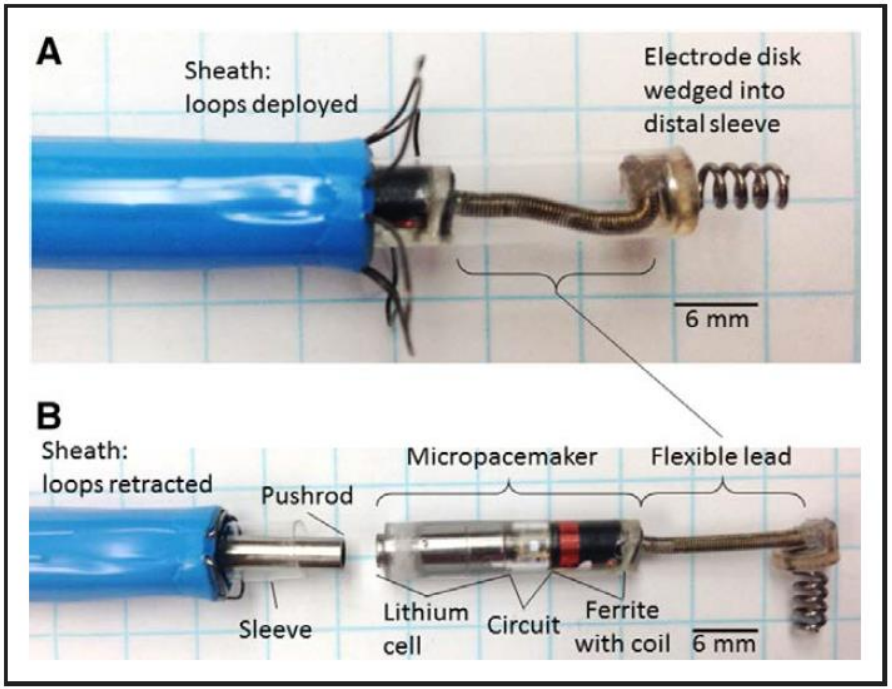
Circ Arrhythm Electrophysiol. 2018;11:e006307

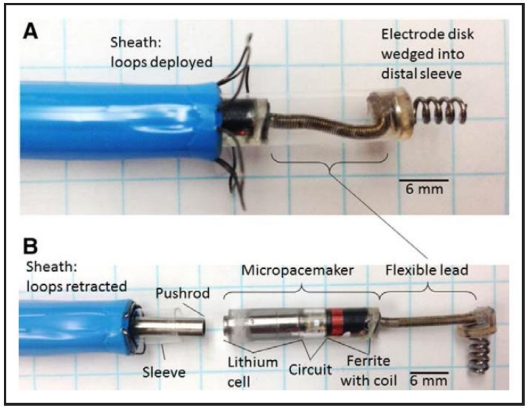
Implantation Equipment





Implantation Steps

- Access Pericardial Space via subxyphoid needle puncture
- Place long sheath into pericardial space
- Deploy sheath retaining loops to secure placement within pericardial sheath
- Position tip of long sheath at desired implantation site
- Place miniature camera catheter into sheath to visualize epicardial surface



- Insert implantation sleeve (with micropacemaker) and rotate clockwise to implant electrode
- Pull on secured long sheath and push out micropacemaker into pericardial space using pushrod
- Release retaining loops and remove long sheath

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Procedure Results: 6 pigs

Pig No.	Weight at Implant, kg	Weight at Explant, kg	Device Follow-Up Time, d	Procedure Time, h	Location of Electrode	No. of Devices Attempted	Successful Implant	Comments
1	27.8	40.5	33	1:24	NA	2	No	2 device implants attempted, but both outside of pericardial space.
2	33.6	33.6	NA	1:05	Anterior of RV apex	2	No	Both implants in pericardial space, but electrode not into myocardium.
3	32.7	50	56	1:00	Near LV apex	2	Yes	First device in pericardium. Second device outside pericardium, but electrode in epicardium.
4	34.4	43.5	27	1:35	Diaphragmatic surface	1	No	Electrode in myocardium, but device outside of pericardial space.
5	34.1	46	30	1:28	Near LV apex	1	Yes	Appropriate placement.
6	27.4	45.1	28	0:50	Near RV apex	1	Yes	Appropriate placement of functional device.

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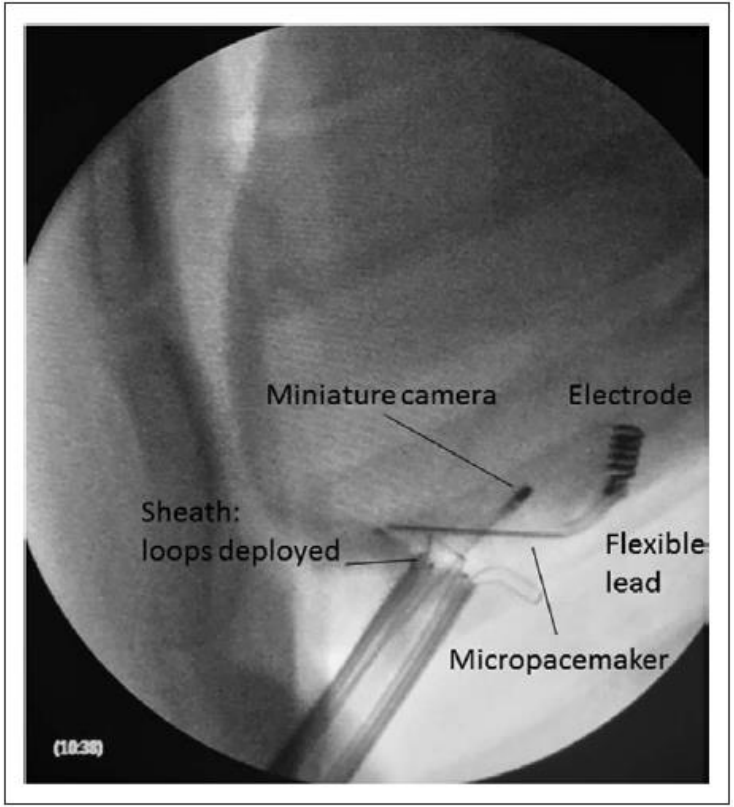

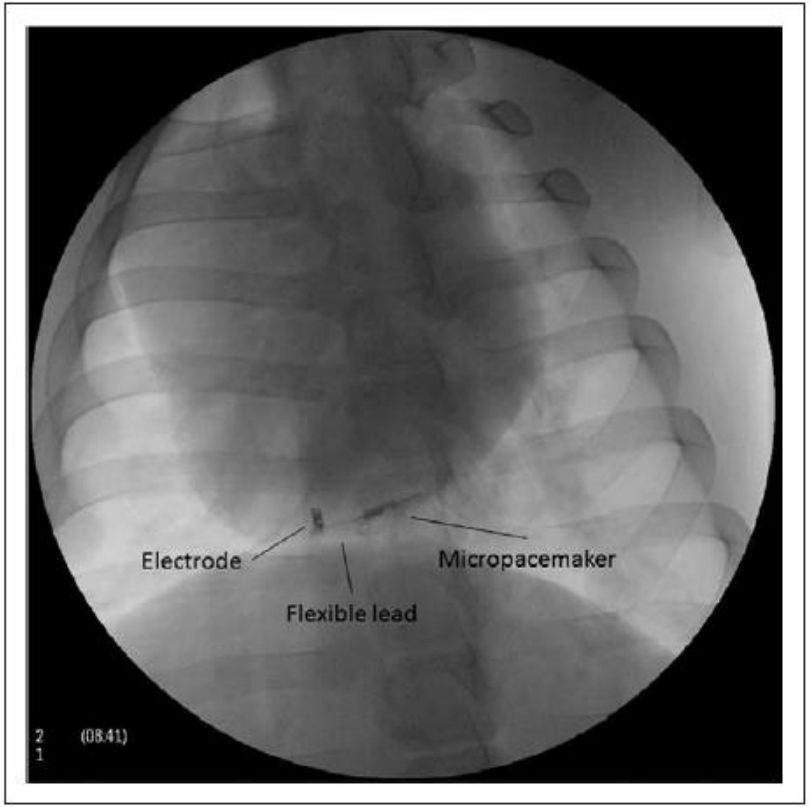

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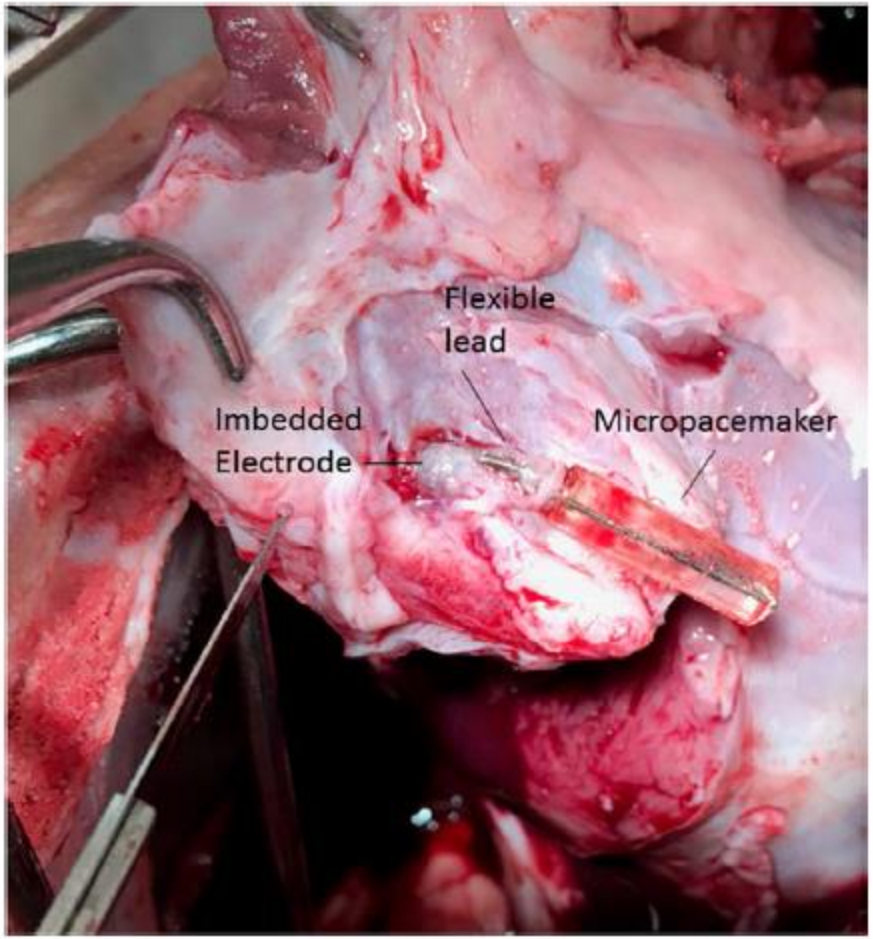

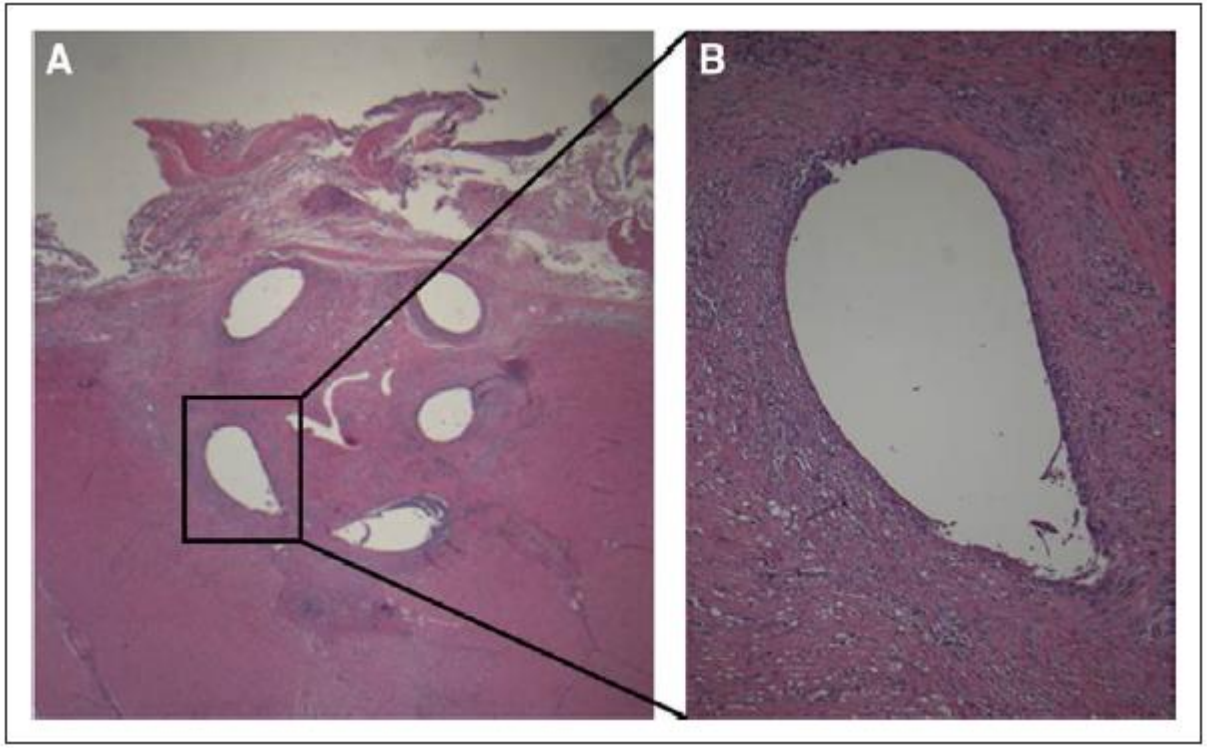
A
B

Thank you!

Clinical

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- Michael Silka, MD (pediatric EP)
- Jay Pruetz, MD (fetal cardiologist)
- Allison Hill, MD (pediatric EP)

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- Li Zhou, PhD
- Kaihui Zheng
- Michael Lu
- Ray Peck
- Glen Griffith
- Viktoira Norekyan
- Sara Rabin
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Conclusion

- Percutaneously implantable fetal micropacemaker may offer solution for hydropic fetuses with complete AV block
  - First human implantation is hopefully near
  - Requirements: Hydropic fetus with pericardial effusion, no significant CHD, ~18-32 weeks gestation, single gestation

- Percutaneously implantable pericardial micropacemaker may offer less invasive pacing solution for children and adults, especially those requiring epicardial pacemakers

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Thank you!