Cardiology 2018

Children's Hospital Los Angeles — We Treat Kids Better

USC University of Southern California

Fetal Heart Block with Impending Fetal Hydrops…so frustrating

Jay D. Pruetz, MD
Associate Professor of Clinical Pediatrics
Associate Professor of Ob/Gyn
USC Keck School of Medicine
Director of the Fetal Cardiology Program
Division of Cardiology
Children's Hospital Los Angeles

Disclosures

- Issued and pending patents related to fetal micropacemaker
- Grant Funding: NIH, Coulter Foundation, Wright Foundation, USC CTSI
- You will be frustrated by this talk

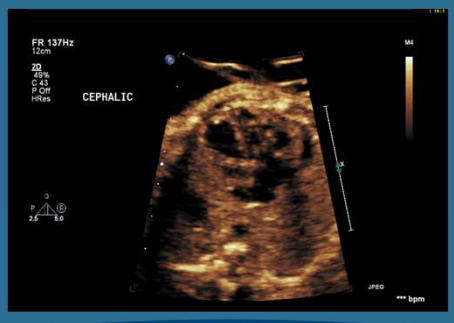
Outline

- Brief Overview of complete heart block in the fetus
  - Etiologies
  - Outcomes in CHD
  - Outcomes in Autoimmune Mediated
  - Outcomes in Hydrops
- Therapeutic approach
- Fetal Pacing Options
- New Approaches

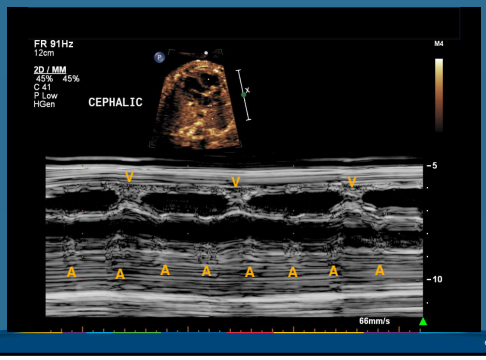
Just a routine day in the fetal echo clinic…

- Normal evaluations
  - A muscular VSD
  - TOF with mild PS
  - Set of Mono-Di Twins screen for TTTS
  - IVF pregnancy
- Then your last patient presents for routine exam due to Advanced Maternal Age and you see this…

Fetal Bradycardia



Fetal M-mode confirms CHB



Slide 1

1 Jay Pruetz, 1/28/2018

Fetal Complete Heart Block (CHB)

- Incidence: 1:11,000 – 1:22,000 live births
- Etiologies:
  - 1) Associated with CHD (~50%)
    - Heterotaxy / Polysplenia syndrome
    - L-TGA / CCTGA, CAVC, Ebstein's Anomaly
    - LV Non-compaction Cardiomyopathy
    - NKX2-5 Gene mutations (ASD, HLHS, CHB)
  - 2) Maternal autoimmune disease
    - SSA(Ro) and SSB(La) positive Antibodies
  - 3) Associated with Channelopathies
    - Long QT syndrome (bradycardia, 2:1 AVB)
    - Rare SCN5A, TRPM4, and KCNK17 mutations

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

CHB and CHD

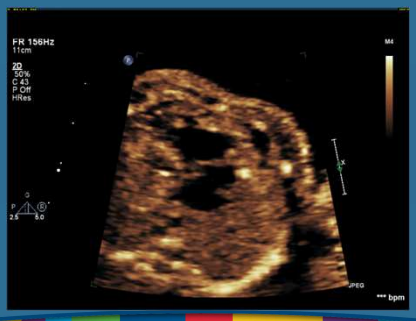
- Most common cardiac lesions associated with CHB:
  - Left Atrial Isomerism- LAI (synonymous with Polysplenia form of heterotaxy syndrome) ~60% of cases in a series of 116 fetuses w/ CHB
  - Discordant AV connections (CCTGA, LTGA or isolated ventricular inversion)
- These fetuses can often present with cardiomegaly, pericardial effusions and also hydrops.
- CHB also occurs less frequently in other heart lesions such as:
  - TOF, RV hypolasia, CAVC, DILV, and multiple cardiac rhabdomyomas

Lopes et al. 2008

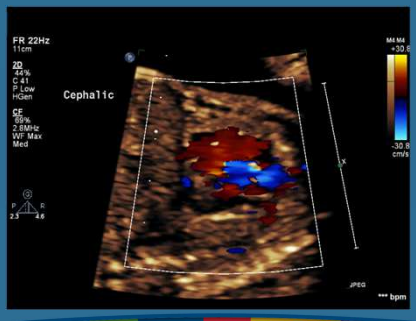
CHB and Complex CHD

- LAI/Polysplenia is associated with multiple abnormalities including:
  - CHB and/or sinus bradycardia (displaced, hypoplastic or absent SA and/or AV nodes)
  - Bilateral LAA
  - Interrupted IVC
  - Bilateral SVC
  - AV Canal defect
  - OFT anomalies
  - Situs anomalies
  - Two lobed lungs with bilateral left bronchial anatomy
  - Malrotation of the bowel
  - Biliary atresia

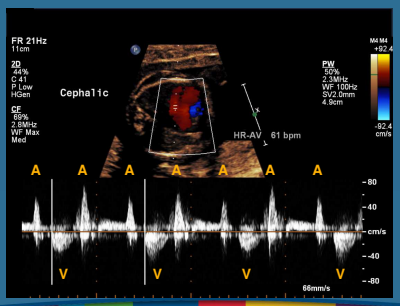
Polysplenia: CAVC, Interrupted IVC with hemiazygous continuation and CHB



Polysplenia: CAVC, Interrupted IVC with hemiazygous continuation to LSVC and CHB



Polysplenia: CAVC, Interrupted IVC with hemiazygous continuation to LSVC and CHB



13

CHB and Complex CHD

- Treatment Options Very limited
  - Observation
  - Sympathomimetics for HR <55bpm
  - Premature delivery for pacing?
  - In-utero pacing?

14

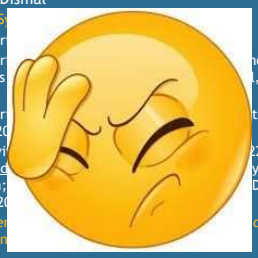
AHA 2014 Scientific Statement: Diagnosis and Treatment of Fetal Cardiac Disease

			COR/LOE	
AV block	Immune mediated (SSA/SSB antibody)	Observation	I/A	Structurally normal heart May have concomitant EFE or myocardial or valvar dysfunction
		Dexamethasone For second-degree block or first-degree block with findings of cardiac inflammation	IIb/B	Note: for idiopathic AV block or AV block resulting from damage to a normal AV node (ie, SSA/SSB antibody negative block), observation only, dexamethasone not recommended
		For CHB as prevention for death or cardiomyopathy	IIb/B	
		IVIG (note: IVIG as prophylaxis is not recommended)	IIb/C	
		Sympathomimetics for rate <55 bpm or higher rates with associated	IIa/C	
	Developmental abnormality of the AV node	Observation	I/A	Associated cardiac defects (CC-TGV, left atrial isomerism, AVSD, DORV)
		Sympathomimetics for rate <55 bpm or higher rates with associated CHD, cardiac dysfunction, or hydrops	IIa/C	
	Channelopathies (including NKX2.5, LQTS)	Observation	I/A	May be associated with structural cardiac defects, progressive conduction system disease, or dilated cardiomyopathy (Lenegre syndrome)
		Avoid QT-prolonging drugs	I/A	
		Surveillance for VT	I/A	

15

Prognosis for Complex CHD and CHB

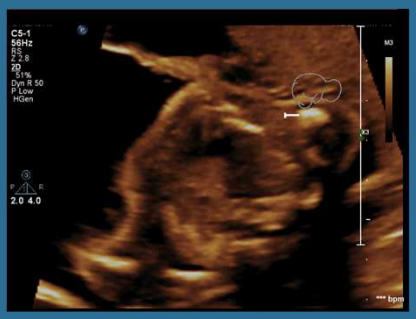
- Outcomes are Dismal
  - Heterotaxy S
    - 100% Mor
    - 100% Mor
    - 100% Mor
    - 63% Survi
  - Few treatme



onths. Prenatal
, Ann Thorc Surg
th RAI (Taketazu et
22/91 LAI patients
ydrops; 20% had HR
Diaz et al. Pediatr
despite advances in

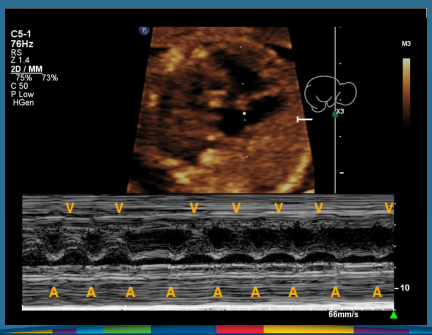
16

CCTGA and 2nd degree AVB



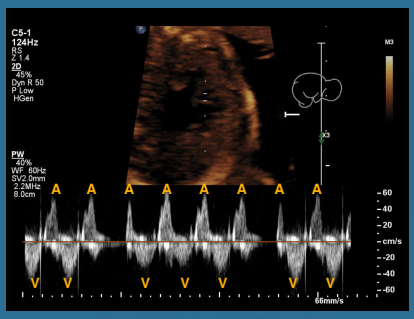
17

CCTGA and 2nd degree AVB



18

CCTGA and 2nd degree AVB



19

20

CCTGA and CHB

- CHB can develop during fetal life; true incidence is unknown
- CCTGA is associated with other lesions: VSD, PS, and Ebstein-like anomaly of the tricupsid valve.
- Abnormal development of the central fibrous body of the AVN with lack of union between the AVN and AV Bundle due to malalignment of the atrial and inlet ventricular septum. This disrupts the normal conduction tracts leading to progressive AV block.
- Lifelong risk of developing CHB is 1% annually and roughly 50% develop CHB by age 50 (Warnes et al, Circ 2006)
- In series of 54 patients with CCTGA 30% were prenatally Dx and only one had CHB. In group 4 deaths reported (14% mortality), of which 3 had CHB (Wan et al, AJC 2009)

21

AHA 2014 Scientific Statement: Diagnosis and Treatment of Fetal Cardiac Disease

COR/LOE

AV block	Immune mediated (SSA/SSB antibody)	Observation	I/A	Structurally normal heart May have concomitant EFE or myocardial or valvar dysfunction
		Dexamethasone For second-degree block or first-degree block with findings of cardiac inflammation	IIb/B	Note: for idiopathic AV block or AV block resulting from damage to a normal AV node (ie, SSA/SSB antibody negative block), observation only, dexamethasone not recommended
		For CHB as prevention for death or cardiomyopathy	IIb/B	
		IVG (note: IVG as prophylaxis is not recommended)	IIb/C	
		Sympathomimetics for rate <55 bpm or higher rates with associated cardiac dysfunction or hydrops	IIa/C	
	Developmental abnormality of the AV node	Observation	I/A	Associated cardiac defects (CC-TGV, left atrial isomerism, AVSD, DORV)
		Sympathomimetics for rate <55 bpm or higher rates with associated cardiac dysfunction, or hydrops	IIa/C	
	Channelopathies (including NKX2.5, LQTS)	Observation	I/A	May be associated with structural cardiac defects, progressive conduction system disease, or dilated cardiomyopathy (Lenegre syndrome)
		Avoid QT-prolonging drugs	I/A	
		Surveillance for VT	I/A	

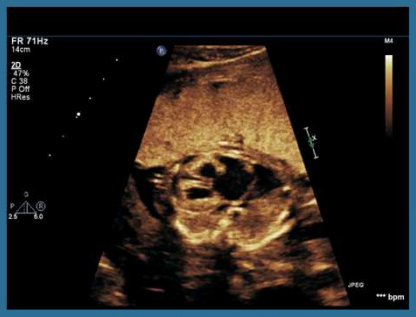
22

Follow Up study of polysplenia (LAI) patient with CHB

- On prior exam
  - Ventricular rate was 65bpm
  - Trivial pericardial effusion
  - Normal ventricular function
  - No other effusions or edema noted
  - Fetus was growing appropriate for EGA

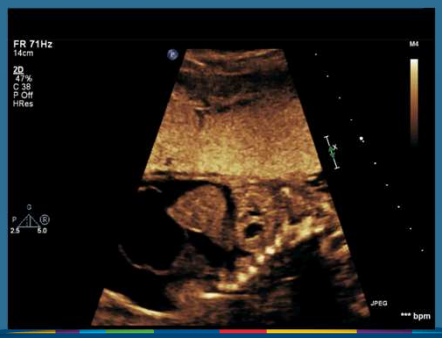
23

Polysplenia: CAVC, CHB and hydrops

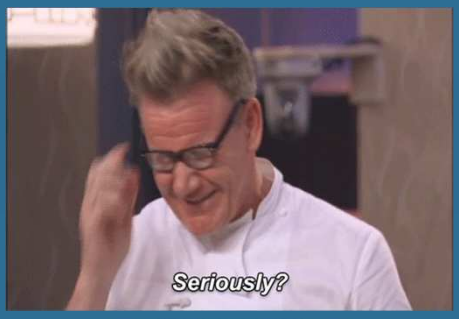


24

Polysplenia: CAVC, CHB and hydrops



25



26

Hydrops Defined

- Non-immune hydrops (NIHF) is the presence of two or more abnormal fetal fluid collections in the absence of red cell alloimmunization
  - Ascites, Pleural effusion, Skin/scalp edema, Pericardial effusion
- NIHF accounts for ~ 90% of cases of hydrops with the most common etiologies being cardiovascular(~20%), chromosomal (~13%), and hematologic abnormalities (~10%)
- Polyhydramnios and preterm birth occur frequently with NIHF
- Prognosis of NIHF due to cardiac abnormalities is poor, with combined fetal and infant mortality reported as ~92%
- Cardiac hydrops can be due to cardiac dysfunction, structural anomalies, severe bradycardia (CHB) and persistent tachycardia

Society for Maternal-Fetal Medicine (SMFM) Clinical Guideline #7: nonimmune hydrops fetalis. Society for Maternal-Fetal Medicine (SMFM); Mary E. Norton, MD; Suneet P. Chauhan, MD; and Jodi S. Dashe, MD. 2014

27

Hydrops in CHB

- Cardiac hydrops is caused by fetal heart failure
  - End Stage Manifestation of elevation in venous pressure seen in conjunction with failure of the fetal heart to provide adequate oxygen delivery to the fetus
- Hydrops occurs more often when the fetal HR drops below 55bpm (Breur et al. 2008)
- When hydrops occurs it portends a poor outcome…

Society for Maternal-Fetal Medicine (SMFM) Clinical Guideline #7: nonimmune hydrops fetalis. Society for Maternal-Fetal Medicine (SMFM); Mary E. Norton, MD; Suneet P. Chauhan, MD; and Jodi S. Dashe, MD. 2014

28

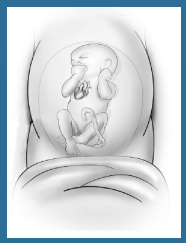
CHB with Hydrops

- Lopes et al. 2008
  - 11 of 57 CHB with hydrops (19.3%)
    - Mortality was 100%
    - 6 of 11 (55%) had fetal demise
    - 5 of 11 (45%) postnatal death
- Ho et al. 2015
  - CHB with Hydrops 16 of 85 (19%)
    - 8 (50%) had fetal demise
    - 5 (31%) died in early postnatal life
    - 3 (19%) are alive with pacemakers and without evidence of dilated cardiomyopathy

Ho et al. Am J Cardiol 2015;116:142-147.

Maternal Autoimmune Disease

- **Antibodies reactive to Ro and/or La ribonucleoproteins cross the placenta, enter the fetal circulation and cause fetal injury, most often during the EGA 16–24^{wks}**
- **Fetuses at risk for hydrops and fetal demise w/ FHR < 50bpm**
- **Mortality rate varies from 10% - 29%, increased in setting of hydrops fetalis**
- **Patients with CHB Require permanent pacemaker after birth, but overall have a good prognosis with near normal life expectancy.**



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.

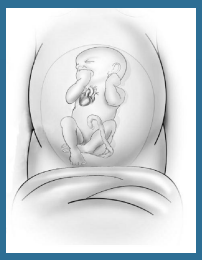
Treatment Strategies

Prevent Progression, Reverse Course and Prophylaxis
- •Fluorinated Steroids (Dex)
- •Intravenous Immunoglobulin (IVIG)
- •Plasmaphoresis
- •Hydrochloriquine

Manage Bradycardia
- •b_2-Agonists
- •Fetal Pacing

Early/Premature Delivery

EXIT Procedure



Michaelsson et al. Cardiovasc Clin 1972;4:85 – 101.
Siren et al. J Rheumatol 1998;25:1882 – 1884.

AHA 2014 Scientific Statement: Diagnosis and Treatment of Fetal Cardiac Disease

CORLOE

AV block	Immune mediated (SSA/SSB antibody)	Observation	I/A	Structurally normal heart
		Dexamethasone For second-degree block or first-degree block with findings of cardiac inflammation	IIb/B	May have concomitant EFE or myocardial or valvar dysfunction
		For CHB as prevention for death or cardiomyopathy	IIb/B	Note: for idiopathic AV block or AV block resulting from damage to a normal AV node (ie, SSA/SSB antibody negative block), observation only, dexamethasone not recommended
		IVIG (note: IVIG as prophylaxis is not recommended)	IIb/C	
		Sympathomimetics for rate <55 bpm or higher rates with associated cardiac dysfunction or hydrops	IIa/C	
	Developmental abnormality of the AV node	Observation	I/A	Associated cardiac defects (CC-TGV, left atrial isomerism, AVSD, DORV)
		Sympathomimetics for rate <55 bpm or higher rates with associated CHD, cardiac dysfunction, or hydrops	IIa/C	
	Channelopathies (including NKX2.5, LQTS)	Observation	I/A	May be associated with structural cardiac defects, progressive conduction system disease, or dilated cardiomyopathy (Lenegre syndrome)
		Avoid QT-prolonging drugs	I/A	
		Surveillance for VT	I/A	

32

Do Steroids Help?

33

Early Studies Showed Promise

- Early Studies Showed Promise
  - Improved outcomes reported with maternal steroids in autoimmune heart block including resolution of hydrops
  - Perceived benefit of reducing autoantibody load and treating the an acute inflammatory process resulting in myocarditis

  Copel et al. Am J Obstet Gynecol 1995;
  Jaeggi et al. Circ 2004; Fesslova et al. Cardiol Young 2009
- Subsequent studies showed no positive impact on intrauterine survival, postnatal survival, or development of cardiomyopathy
  - Steroids used in 38% of effected cases in Europe showed no difference in outcomes
  - PRIDE Study showed no difference in outcomes
  - Hydrops can improve/resolve during pregnancy in 76% of treated and 23% of non-treated cases, but conferred no improvement in outcome.

  Eliasson et al. Circ 2011; Friedman et al. Am J Cardiol 2009; Fesslova et al. Cardiol Young 2009; Ciardulli et al. The Journal of Mat-Fetal & Neo Medicine 2017

34

PRIDE STUDY

Summary of Outcomes

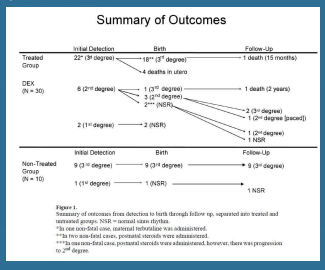


Figure 1.
Summary of outcomes from detection to birth through follow up, separated into treated and untreated groups. NSR = normal sinus rhythm.
*In one non-fetal case, maternal terbutaline was administered.
**In two non-fetal cases, postnatal steroids were administered.
***In one non-fetal case, postnatal steroids were administered, however, there was progression to 2nd degree.

- Dexamethasone (DEX) did not reverse CHB or change outcomes at 1yr of age
- Dex may reverse 1st and 2nd Degree AVB in rare cases
- Risks of prematurity and SGA in Dex group.

Friedman et al. Am J Cardiol 2009

35

What can we agree on?

- The challenges:
  - No reliable way to predict which cases of 1st or 2nd degree AVB will progress to CHB
    - Anti-Ro/SSA >100U/ml ? (Jaeggi et al. 201) Or is is SSB >100U/ml ? (Tunks et al. 2013)
    - Prolonged AV interval often reverts back to NSR
  - Progression to CHB can occur over a very short period of time, hours to days, making surveillance difficult
  - Once CHB occurs it does not revert back to normal rhythm, either spontaneously or with maternal medical therapy.

Friedman et al. Am J Cardiol 2009
Jaeggi et al. Obstet Gynecol 2004
Sonesson et al. Arthritis Rheum 2004
Saleb et al. Arthritis Rheum 1999
Fesslova et al. Cardiol Young 2009
Jaeggi et al. J Am Coll Cardiol 2011

36

Mixed Results with Steroids

- There may be some benefit in patients with myocardial dysfunction from associated myocarditis.
- There may be a benefit if progression to CHB is identified and treated immediately with steroids, <24hrs
- Still have no good way to predict which cases will progress to hydrops, and then which cases of hydrops will either resolve or result in fetal loss…
- Downsides to steroid use:
  - Maternal Risks (Diabetes, Hypertension, Mental health effects)
  - Fetal Risks (prematurity, growth restriction, neurologic developmental impairment)

Wapner et al. NEJM 2007
Friedman et al. Am J Cardiol 2009
Modi et al. Pediatr Res 2011
Skog et al. Pediatrics 2008
Eliasson et al. Circ 2011

37

What if we add Beta-stimulation or IVIG

- Maternal Salbutamol was thought to increase the fetal ventricular rate and subsequently improve myocardial function (Groves et al. Circ 1995).
- Early data suggests the combination of steroids with Salbutamol has a beneficial effect on outcome (Jaeggi et al. Circ 2004).
  - Increased survival rates at 1 year 80% historically (1990-1997) to 95% (1997-2003)
- Addition of IVIG in cases of significant myocardial dysfunction and endocardial fibroelastosis in CHB
  - Prevention of progression to dilated cardiomyopathy, more studies needed to prove effect.

38

39

What about fetal pacing?

- In cases already progressed to CHB with very low ventricular escape rate (<50bpm) and evidence of CHF or Hydrops that are refractory to standard therapies
- Concept to provide temporary pacing for duration of pregnancy with conversion to conventional pacemaker after birth
- Fetal pacing has potential to:
  - Increase baseline fetal HR, improve CO and fetal tissue oxygenation
  - Allow to time for hydrops or CHF to resolve if pacing continued for several weeks or more
  - Allow time for baby to grow/develop closer to term

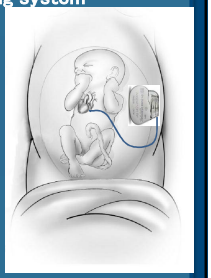
40

Summary of Previous Attempts at Fetal Pacing

Study		Probable Failure Reason
Carpenter 1986		Unknown
Walkinshaw 1994		Displacement and complications
Silverman 1998		Complications
Assad 2003		Fetal complications
Eghtesady 2011		Multi-organ Failure

Problems with traditional approach with extracorporeal pacing system

- Place lead in fetus and attach to "standard" pacemaker in mother
- Most failures presumed to be due to fetal movement and complications of fetal surgery
- Fetal Pacing
  - No reports of survival beyond the perioperative period

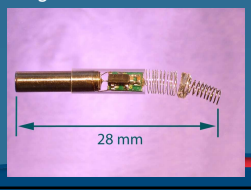


Pacing of Fetus with CHB and Hydrops

- Lessons learned from this case and literature
  - Hydrops associated with poor perinatal outcomes
    - Presence of severe cardiomyopathy and chronic multiorgan failure occurs with longstanding CHB and Hydrops
  - Inefficacy of current medical management regimens
  - Limitations of current technology and approach
    - Lead displacement and/or device malfunction

New Innovation in Pacing

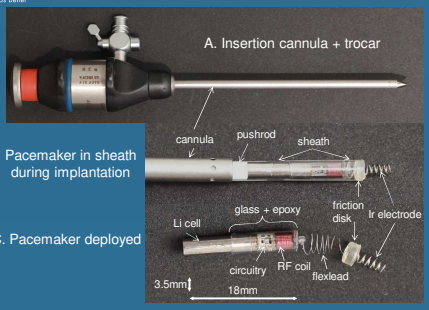
- Developed a self contained, fully implantable fetal pacemaker that could avoid the problems with prior fetal pacemaker attempts that failed due to lead dislodgement by fetal movement.
- Implantation via a minimally invasive method using current fetal intervention techniques and tools that limit surgical risk.



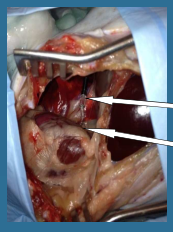
Development of Fetal Micropacemaker

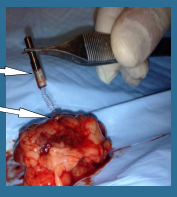
- Pacing system desiged to reside entirely within the fetus (not extracorporeal)
  - Miniaturization of pacemaker with novel design of single unit including implantable lead, flexible lead, electronics and battery.
- Implanted percutaneously in the fetus without open surgery
  - Using current fetal intervention tools and delivery method to minimize risk to fetus and mother by using minimally invasive, percutaneous techniques
- Provides adequate myocardial contact for capture
- Robust enough lead to tolerate >10,000,000 contractions (2–3 months)
- Maximize battery longevity, but with recharging capabilities

Tools for Implantation



Design and Testing of a percutaneously implantable fetal pacemaker





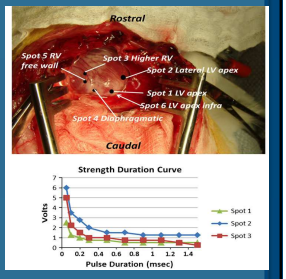
Implanted fetal micropacemaker percutaneously into an adult rabbit via subxyphoid approach using US guidance.

Loeb et al. Annals of Biomed Engineering 2012

Optimization of Device in Animal Model

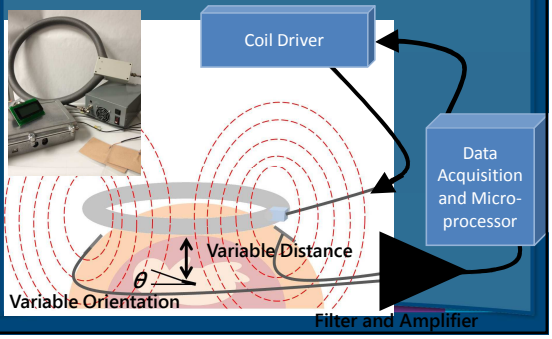
First Prototype

- **Validated electrode design and electrical pacing requirements in 3 rabbits**
- **Tested multiple screw configurations and optimal pacing site locations on the heart**
- **Determined capture thresholds and impedances**



Loeb et al., Annals Biomed. Engng. 2012

Developed wireless recharging system to address battery longevity limitations

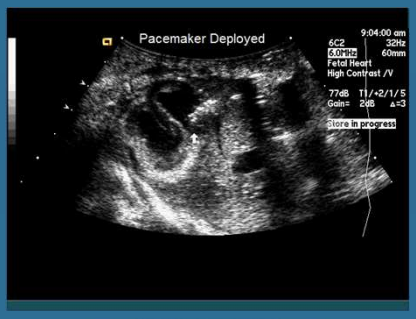


Preclinical testing and optimization of a novel fetal micropacemaker

- 7 fetal sheep *at* 112–128 days gestation
- Micropacemaker: VOO 100–110 bpm
- Uterus surgically exposed
  - **Leads sewn on fetal chest for ECG to determine pacing / capture**
  - **Fetal subxyphoid area exposed for implantation in first 3 animals**
  - **Insertion through closed uterine wall in last 4 animals**
- **Successful capture in last 4 animals**
  - **Longest pacing period was 2 days**

Bar-Cohen et al. Heart Rhythm 2015

Fetal Pacemaker Deployment

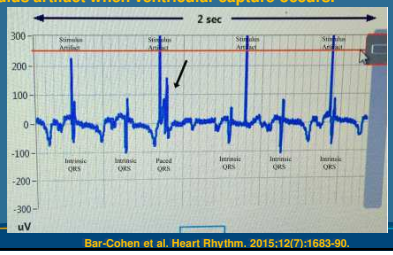


Bar-Cohen et al, Heart Rhythm 2015

51

Pacing a Fetal Sheep

- **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 170bpm.**
- **Advancement of the QRS (arrow) is seen immediately after a stimulus artifact when ventricular capture occurs.**



Bar-Cohen et al. Heart Rhythm. 2015;12(7):1683-90.

Fetal Sheep Outcomes

Table 1 Implantation and follow-up

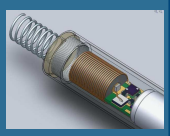
Animal no.	Gestational age at implantation (days)	Device follow-up time (days)	Total procedural time (hours:minutes)	Open uterus time (hours:minutes)	No. of devices	Successful capture?	Implantation comments	Follow-up
1	112	19	2:15	1:49	1	Yes	Failure of electronics causing intermittent pacer output.	POD1: 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.

Bar-Cohen et al. Heart Rhythm. 2015;12(7):1683-90.

Current Status

- Functional fetal micro-pacemaker device developed and tested through the support of NIH RO1 grant over 3yrs
- Electronics, device, leads, & electrode structure refined over multiple experiments resulting in a fully functional system
- External recharging system developed to recharge pacemaker through the maternal abdomen
- Obtained FDA qualification under the Humanitarian Device Exemption



54

Fetal Micro-pacemaker Next Steps

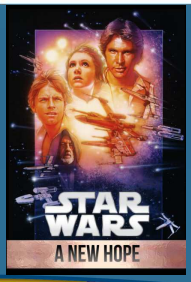
- Prepared for first in-utero human trial of fetal micropacemaker. IRB Protocol in place
- Fabrication of functional, clinical grade, fetal micro-pacemaker devices completed (5 on shelf)
- Plan for 5 Year study period with target enrollment of 10 patients to investigate safety and probable benefit of pacing a fetus with heart block and hydrops fetalis.
- Goal will be successful fetal micropacemaker implantation and function with fetal survival to a viable birth.

55

Summary

- CHB with impending hydrops is frustrating
- Once hydrops develops the prognosis is poor
- Need better measures to predict progression of CHB cases to hydrops and better therapies to treat severe bradycardia in cases of CHB
- There is hope for better outcomes with combination drug therapies and new fetal pacing options on the horizon.

Cardiology 2018



56

Thank you!

Clinical Team

- Yaniv Bar-Cohen, MD (Pediatric EP)
- Ramen Chmait, MD (Fetal Surgeon)
- Michael Silka, MD (Pediatric EP)
- Jay Pruetz, MD (Fetal Cardiologist)
- Allison Hill, MD (Pediatric EP)

Advisory and Regulatory

- Jessica Rousset
- Shraddha More
- Francis Richmond, PhD
- Christine Matheson

Engineering

- Jerry Loeb, MD
- Adriana Nicholson, PhD
- Li Zhou, PhD
- Kaihui Zheng
- Michael Lu
- Ray Peck
- Glen Griffith
- Viktoira Norekyan
- Sara Rabin