Totally Leadless Biventricular Pacing Approach in Two Patients

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Why We Need to Propose Endocardial LV Pacing ?

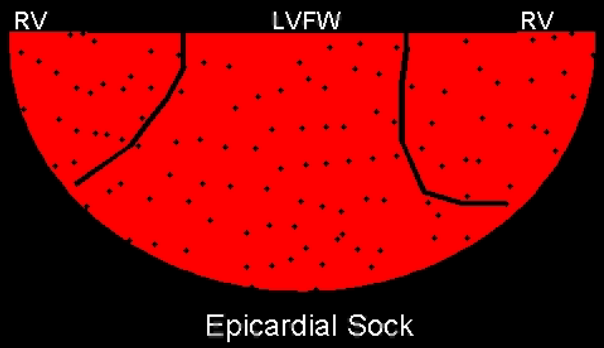
- *90-98% success rate with CS epicardial LV pacing but there are still implantation failures despite major improvements in the technology (*Failure of LV lead implantation (7%)[1]

- *Limitation due to the CS anatomy (small veins, tortuous veins, valves….)*
- *Limitation due to LV lead implantation complications*
  - CS dissection (1.3%) [1] coronary vein perforation (1.3%) [1]
  - High pacing threshold (acute and chronic)
  - Phrenic nerve stimulation (short and long terms)
  - LV lead dislodgement (short and long terms) (5.7%) [1]
  - Epicardial or non optimal pacing site ⟶ non response to CRT
  - X-rays exposure (patient, physician and staff)
  - In hospital-Death (0.3%) [1], 30-days mortality (0.7%) [1]

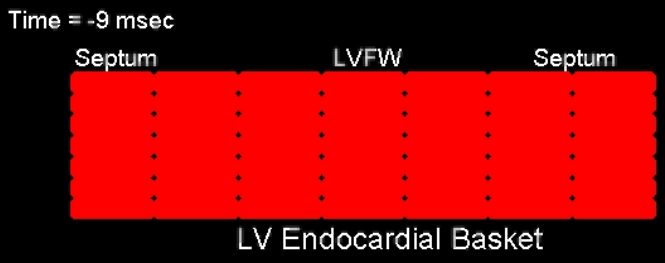
[1] *Van Rees. J Am Coll Cardiol 2011; 58: 995-1000*

Benefits of LV Endocardial Pacing
Physiology

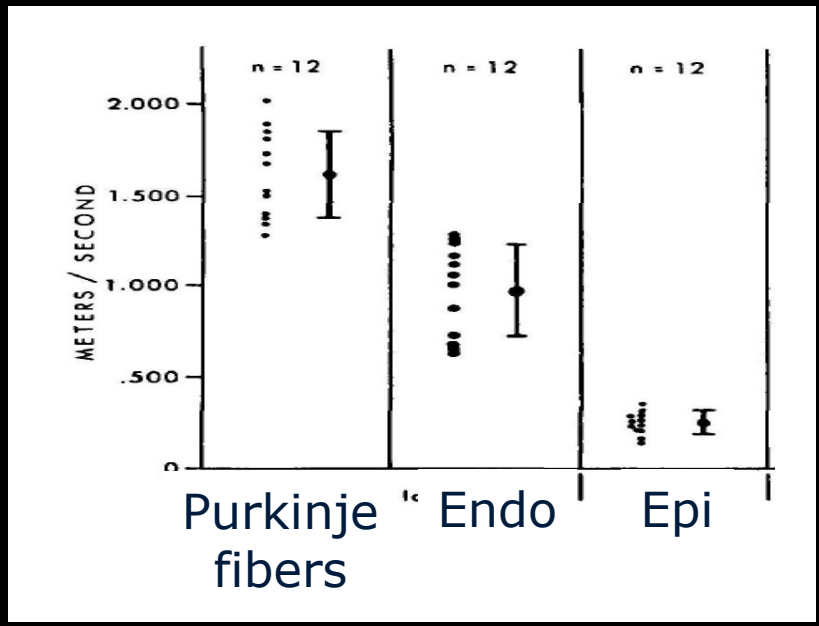
- Advantages of LV endocardial pacing:
  - Access to all regions of the LV
  - Faster impulse propagation in the endocardial than in the epicardial layers providing in theory a faster LV depolarization
  - More physiologic LV stimulation preserving the transmural activation and repolarization sequence



Epicardial Sock



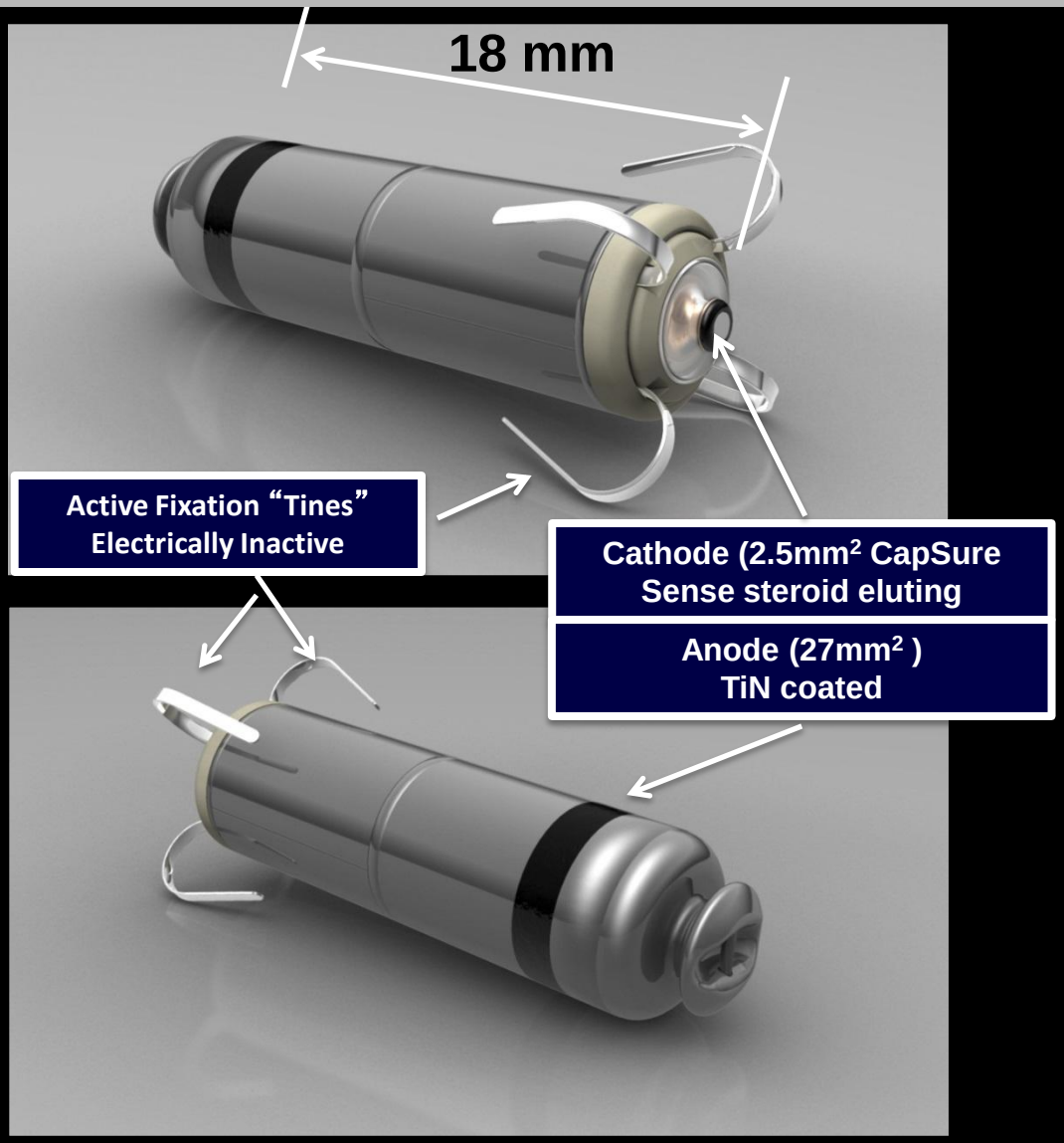
LV Endocardial Basket



RA Pacing

Myerburg et al., Circ. Res. 1978

MICRA TPS ™
Device Description

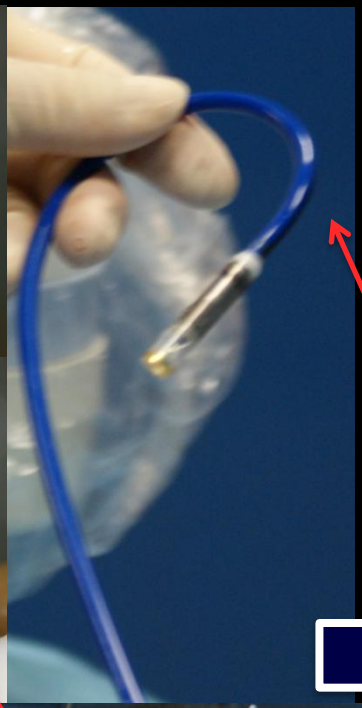


- Pacing Mode: VVIR
- Volume: 0.75cc
- Mass: 2g
- Length: 24mm
- Width: 20Fr
- Bipolar sensing (17mm spacing)

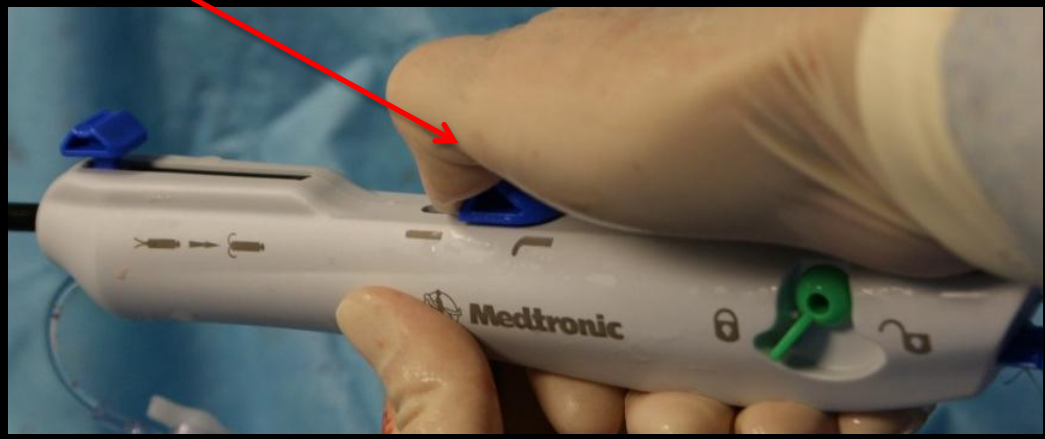
- Programmable
- Capture Management
- Rate Response
- Essential Diagnostics: battery status, pacing threshold, pacing impedance, % paced, longevity estimator
- Standard communication with 2090 programmer

- Device will be deactivated at EOL

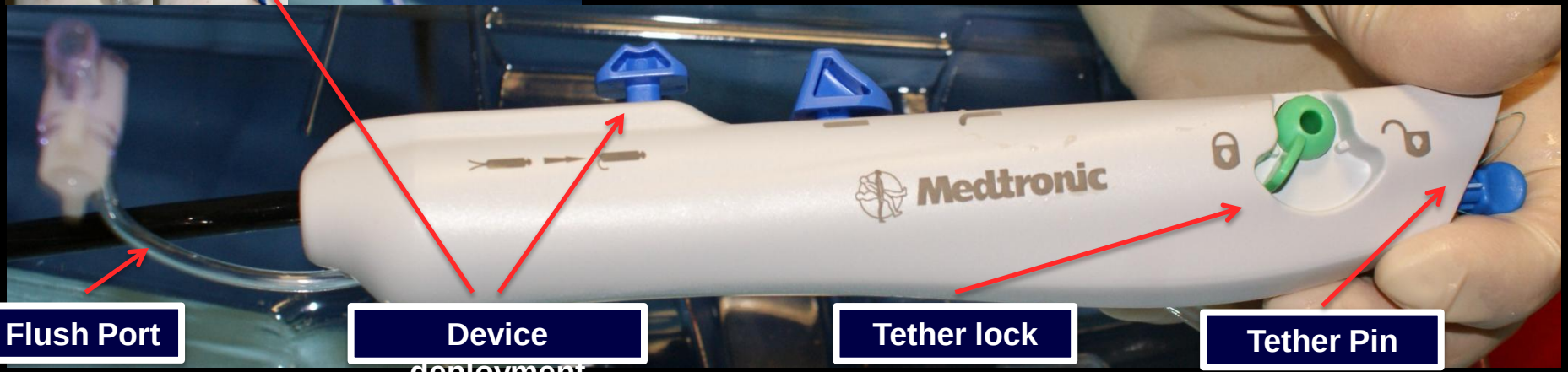
MICRA TPS ™
Delivery System



Deflectable Distal Curve



Curve deflection



Flush Port

Device deployment

Tether lock

Tether Pin

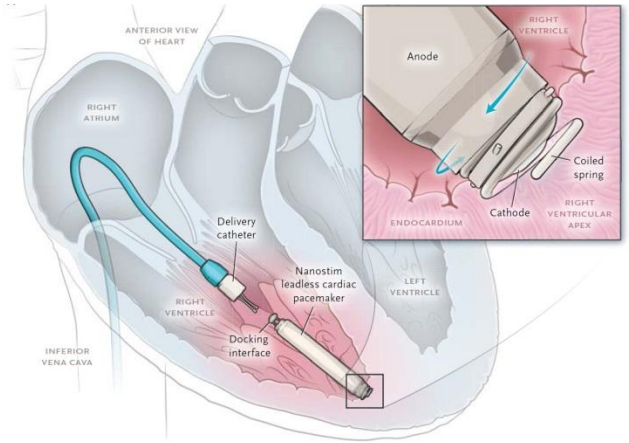
Leadless Pacemakers: *Clinical Oucome*

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*

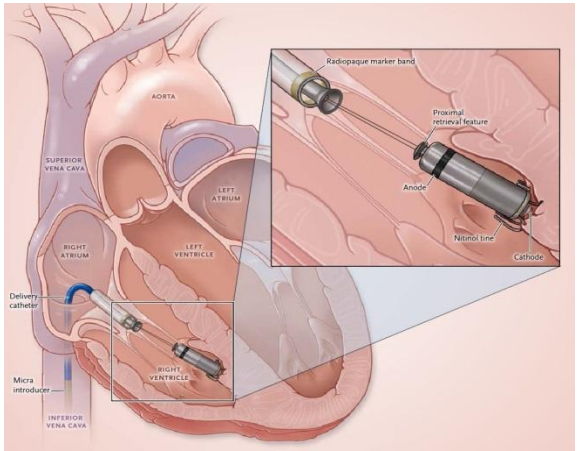


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

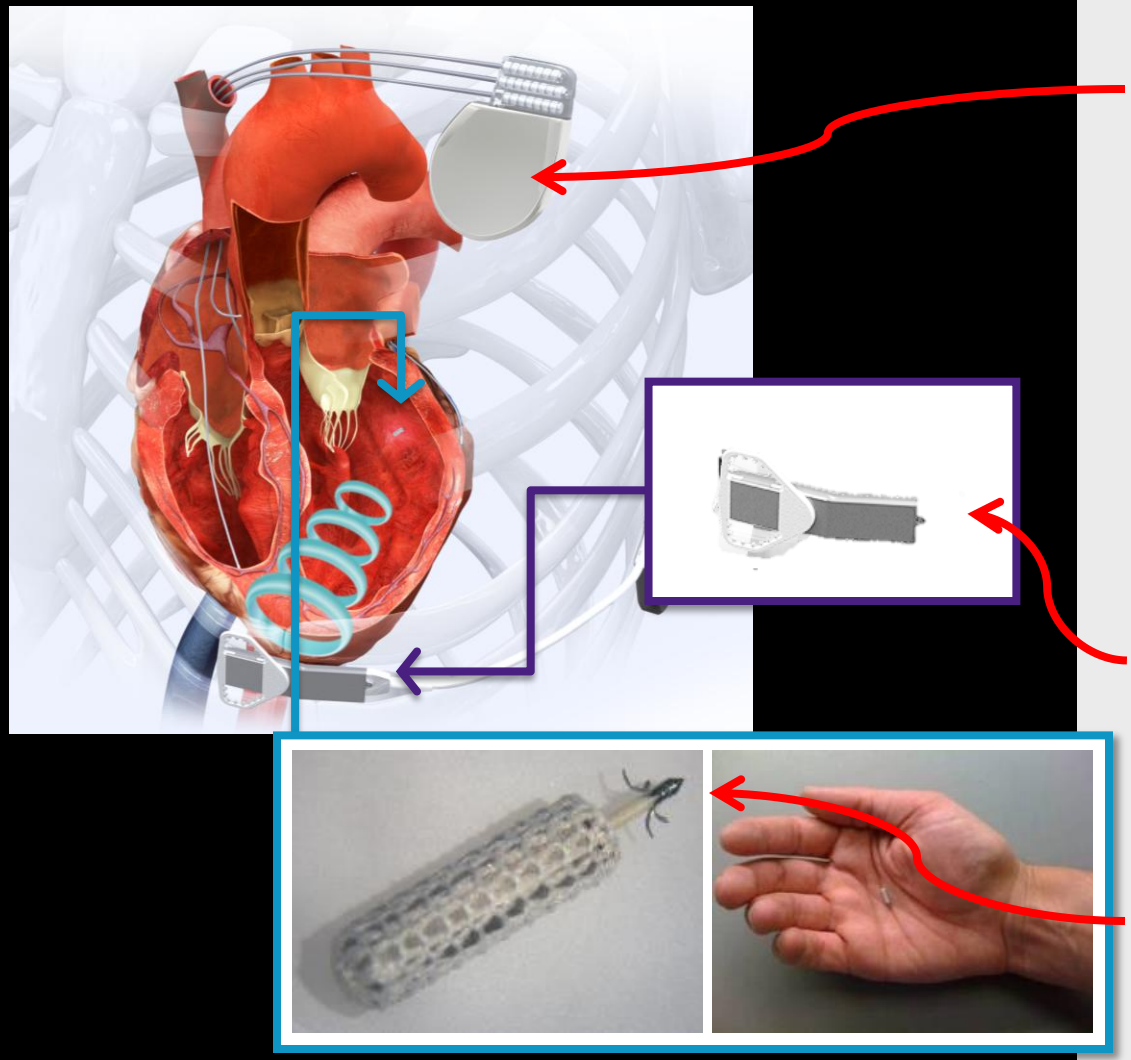
A Leadless Intracardiac Transcatheter Pacing System

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*



Wireless Endocardial LV Pacing for CRT

WiSE Technology



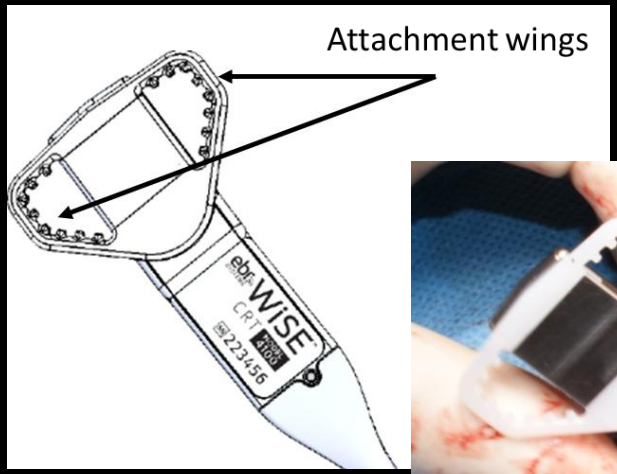
Conventional Device ("Co-Implant")
Provides RA and RV Pacing
(Pacemaker, ICD, CRT-p, CRT-D)

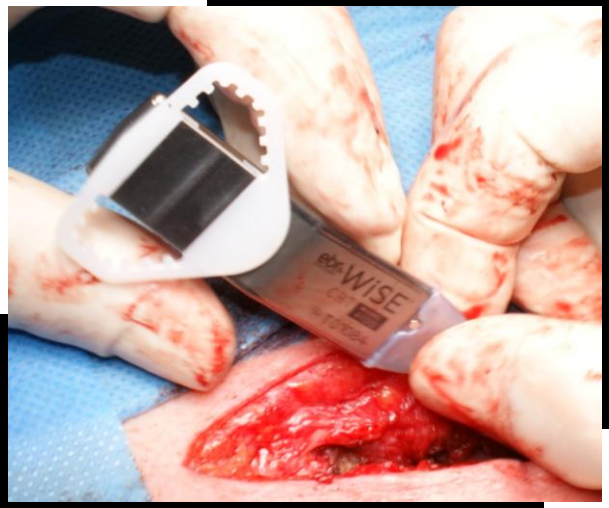
EBR's System Provides Synchronized Left Ventricular Pacing

- Phased Array Ultrasound Transmitter is Implanted in Intercostal Space

- Receiver Electrode (RE) is Implanted in LV Endocardially. Converts ultrasound energy to electrical pulse.

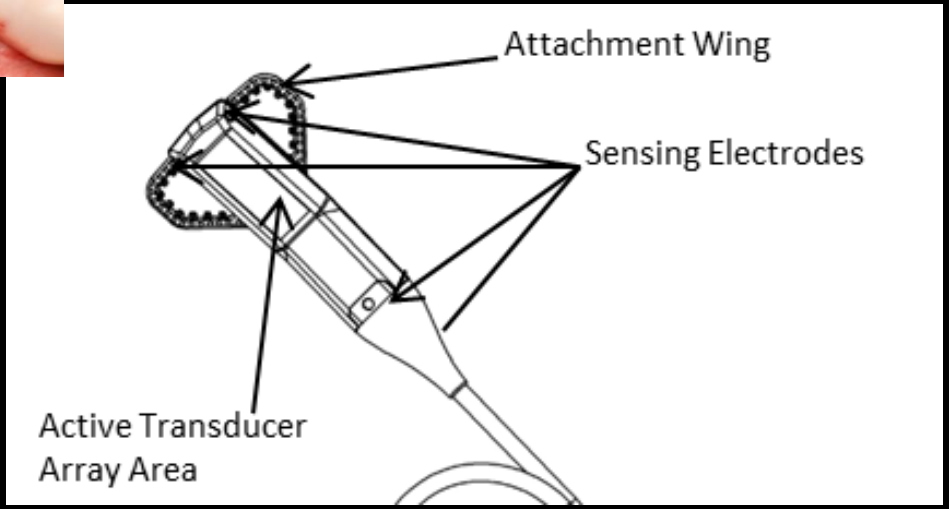
WiSE Technology Components:
Ultrasound Transmitter



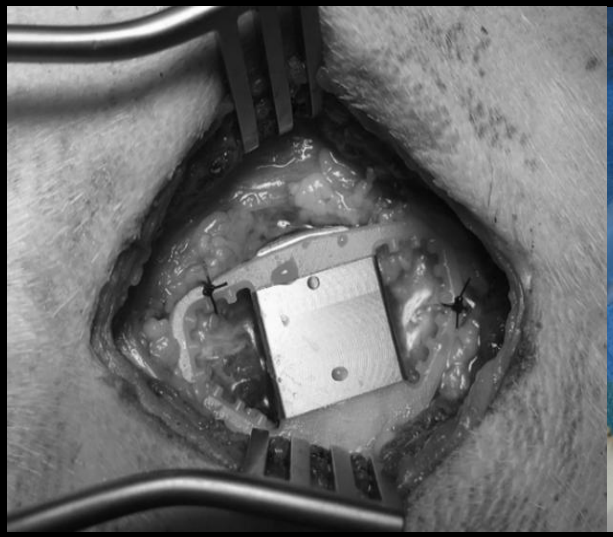


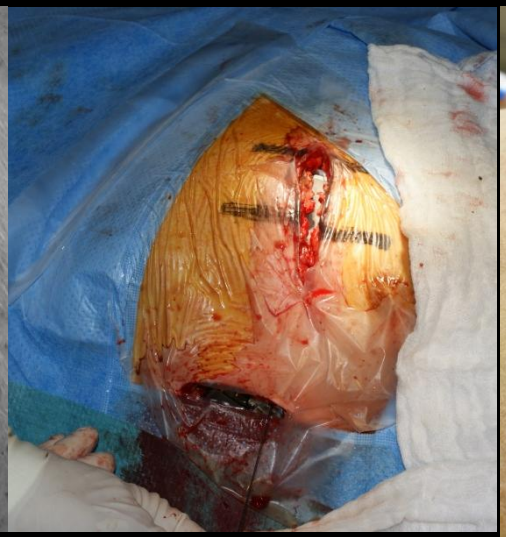
- Detects co-implant RV Pulse
  - Uses sensing electrodes
  - Discriminates RV pulse using pulse-width
  - Compatible with any co-implant / RV lead

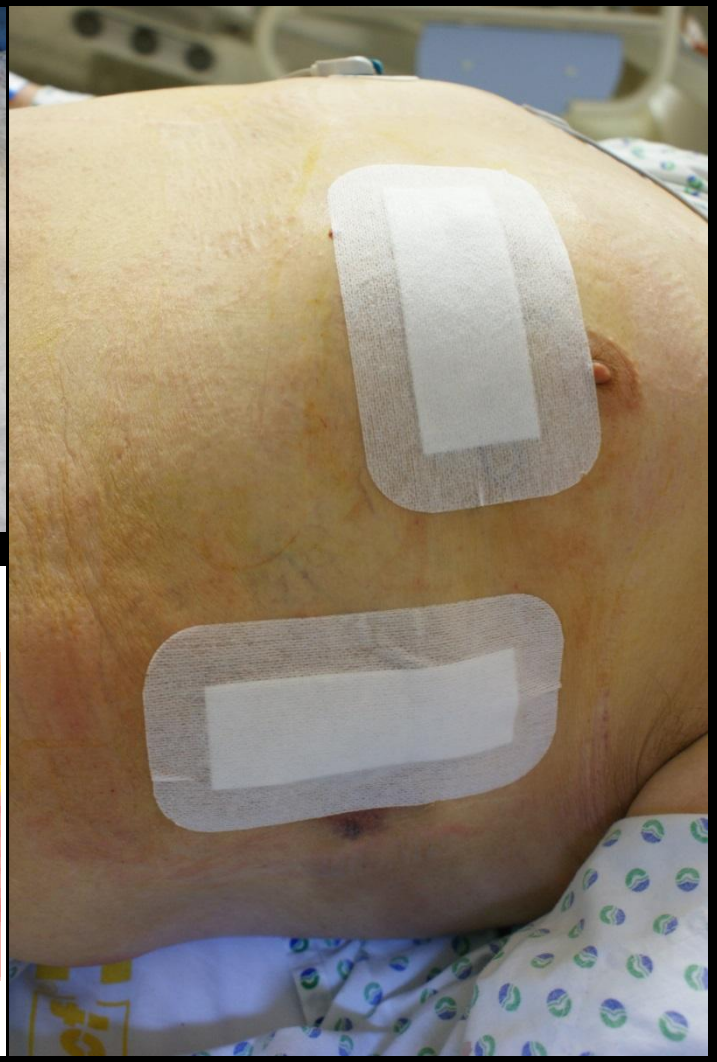
- Focuses and Steers Ultrasound Beam
  - Targeted beam improves power transfer efficiency
  - "Find" the RE (typ 3ms, max 10ms)
  - Send Pacing Pulse energy to RE location

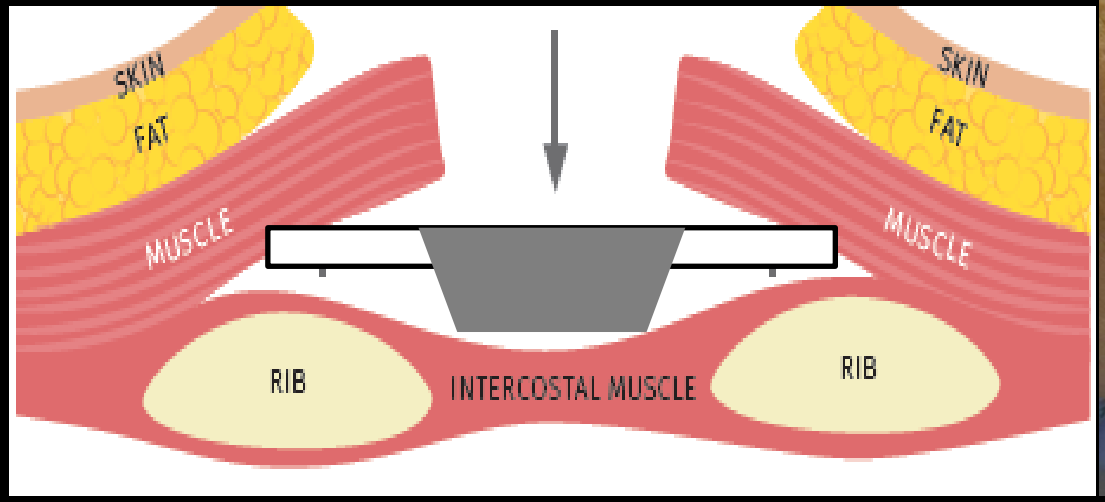


WiSE – Transmitter and Battery
Surgical Part of the Procedure

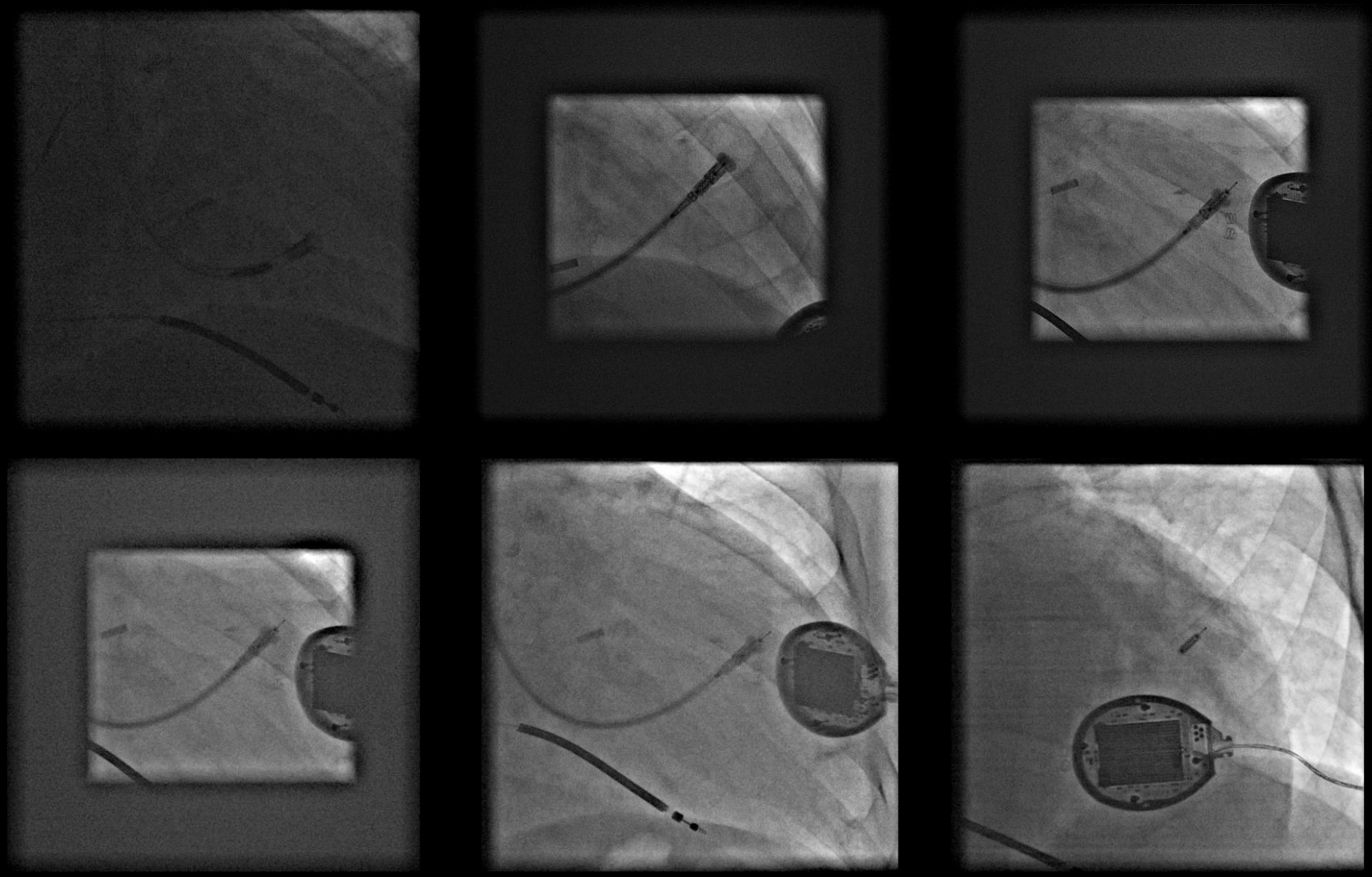








LV Electrode
Percutaneous Transaortic Implantation



MICRA & LV WiCS
Patient‘s Characteristics

Both patients got Micra TPS as part of the Micra Transcatheter pacing study
They developed HFrEF + > QRS: qualifying them for BiV pacing therapy

Only option for CRT, without losing the advantage of the resident MICRA was wireless LV pacing.

MICRA Procedure details:

Case 1

70-y/o/m (AH + DM type 2) long standing persistent AF → fast response
Implantation of the Micra TPS +, AV node ablation → 5 months after
Patient developed HFrEF (LV EF 33%); NYHA III
RV paced QRS duration of 198 ms

Case 2

75-y/o/w (mi + tri annuloplasty + MAZE) long standing persistent AF.
Episodes of complete AVB. MICRA TPS implanted one year after surgery
Progression of HFrEF (LV EF 25%); NYHA III

MICRA & LV WiCS
Patient‘s Characteristics

In both patients we used a two-step approach. The transmitter and battery were implanted under general anesthesia.

WiSE Procedure details:

Case 1

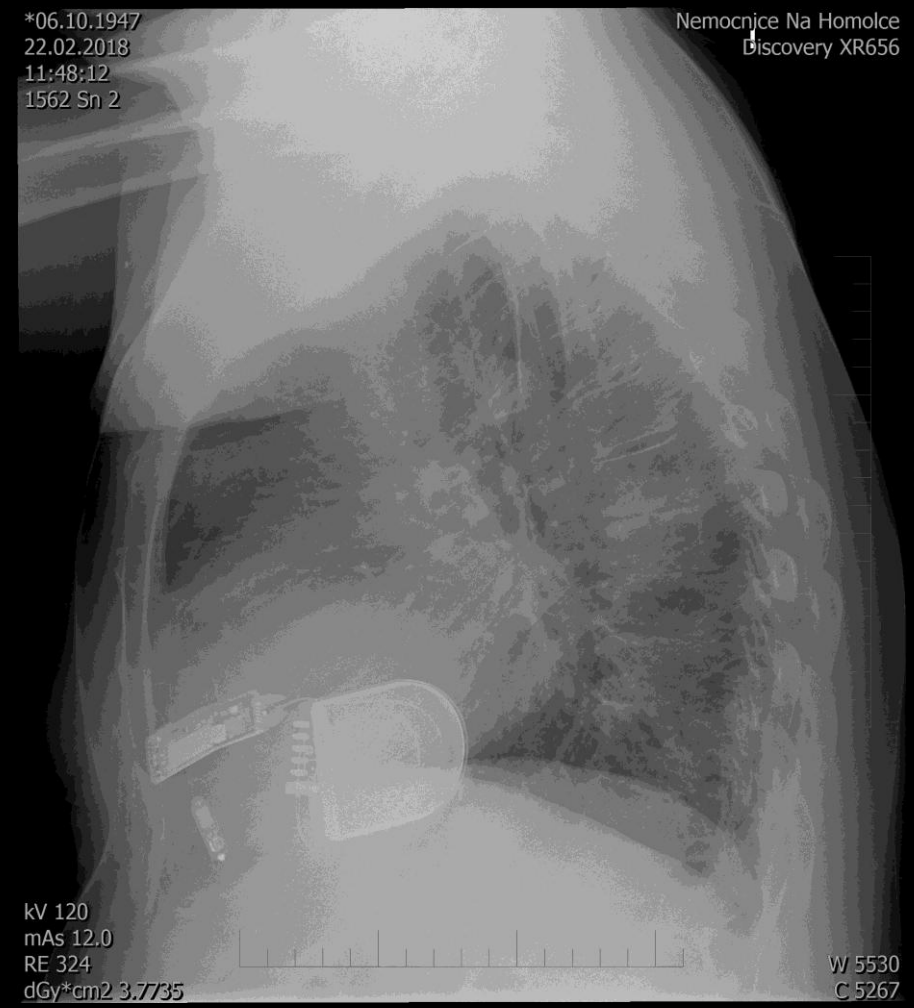
Surgical procedure time was 40 min. The transmitter was implanted into 7th intercostal space.
Transmitter procedure time was 16 min. + fluoroscopy 5 min.
a) shortening of QRS complex width from 198 ms to 120 ms
b) NYHA III→II

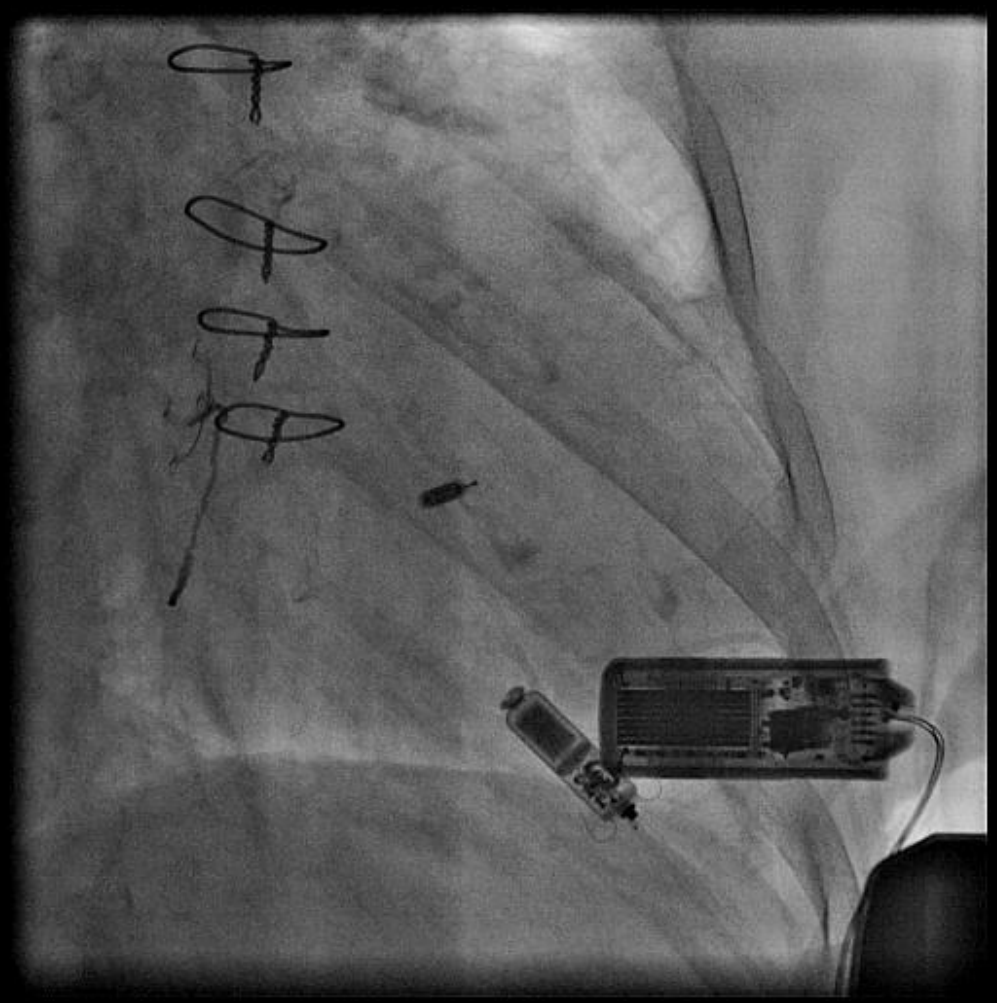
Case 2

Surgical procedure time was 55 min. The transmitter was implanted into 6th intercostal space.
Transmitter procedure time was 25 min. + fluoroscopy 6 min.
a) shortening of QRS complex width from 160 ms to 110 ms

Multichamber Leadless Pacing

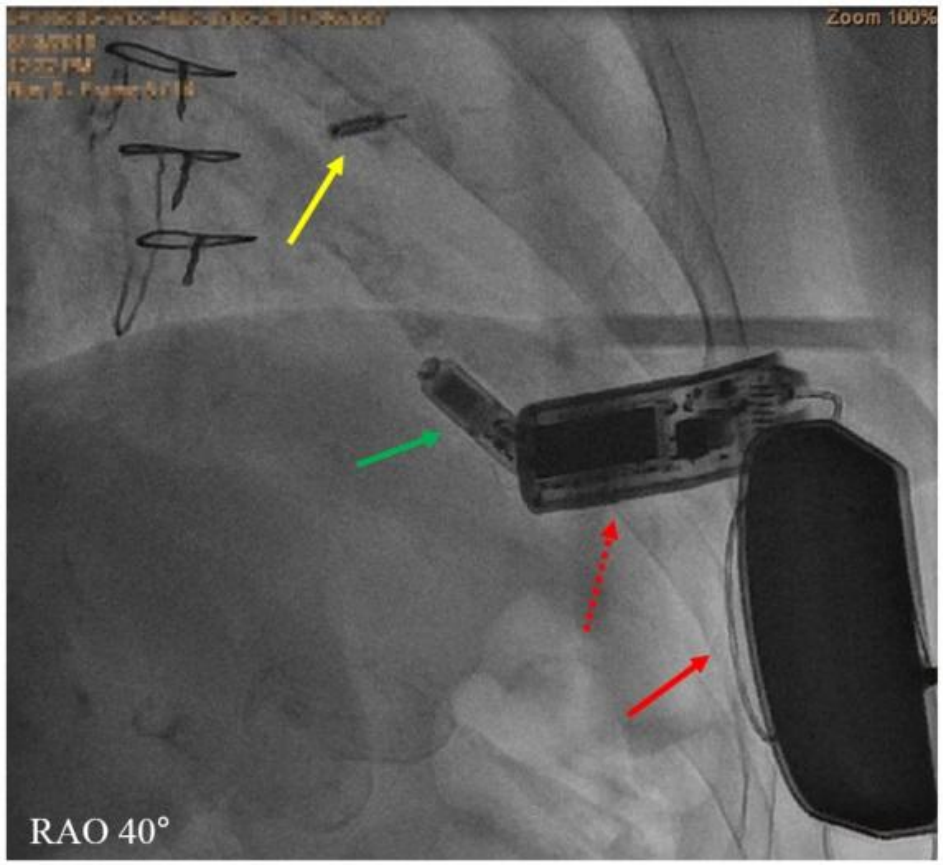
Micra TPS + WiSE

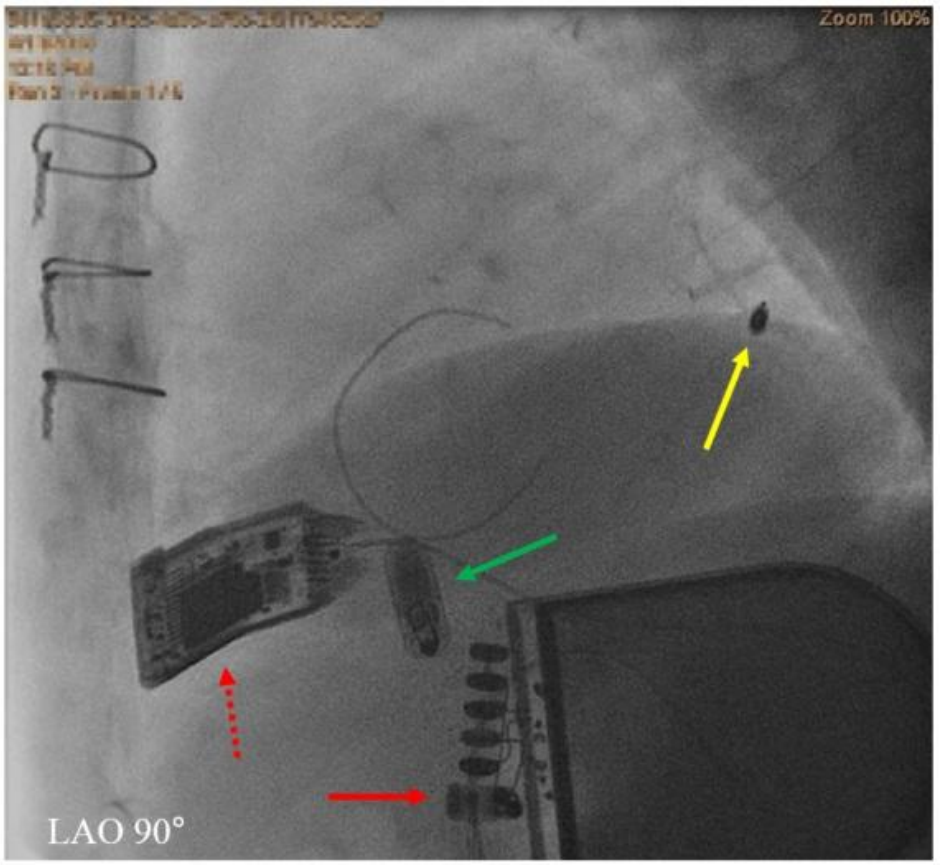




Multichamber Leadless Pacing

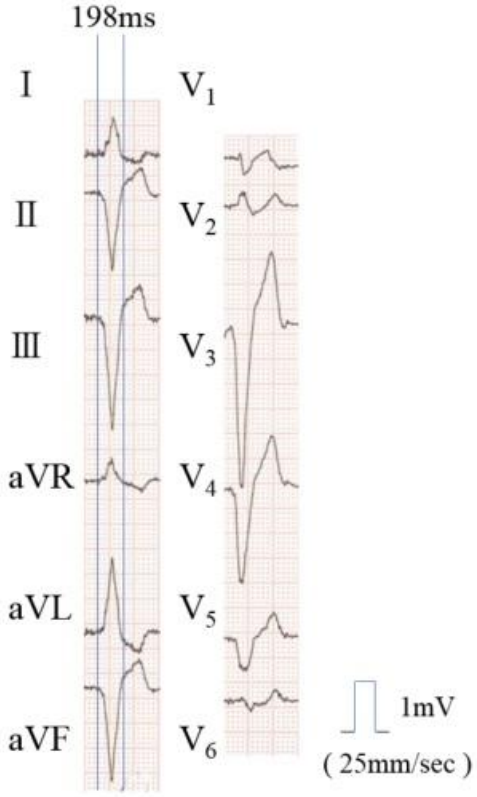
Micra TPS + WiSE



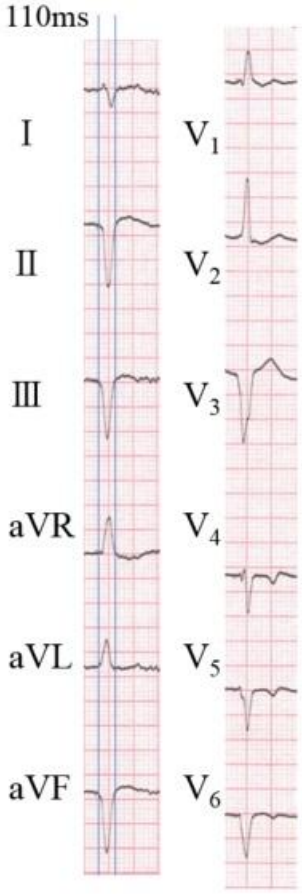


MICRA & LV WiCS
12 leads Electrocardiogram (Case 1)

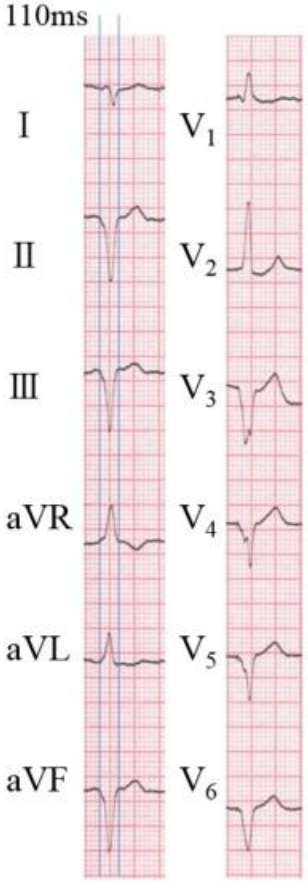
Baseline



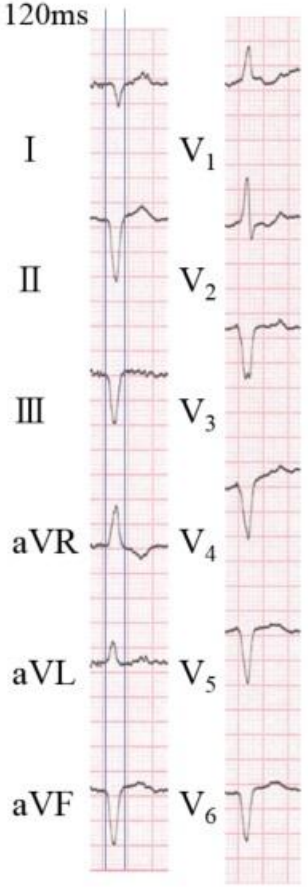
1 month



3 months

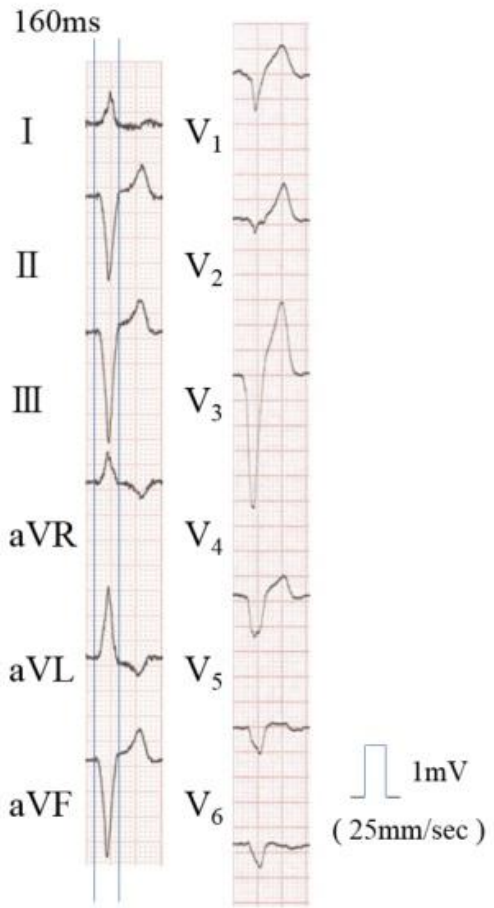


6 months

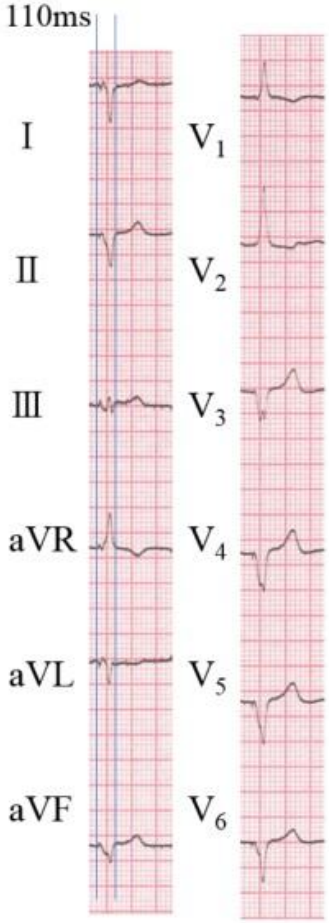


MICRA & LV WiCS
12 leads Electrocardiogram (Case 2)

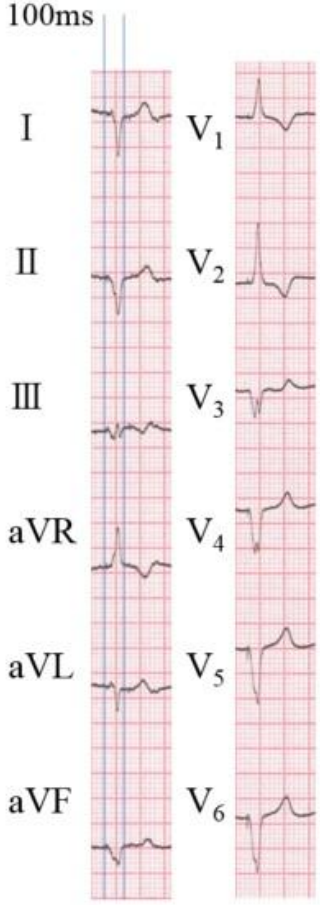
Baseline



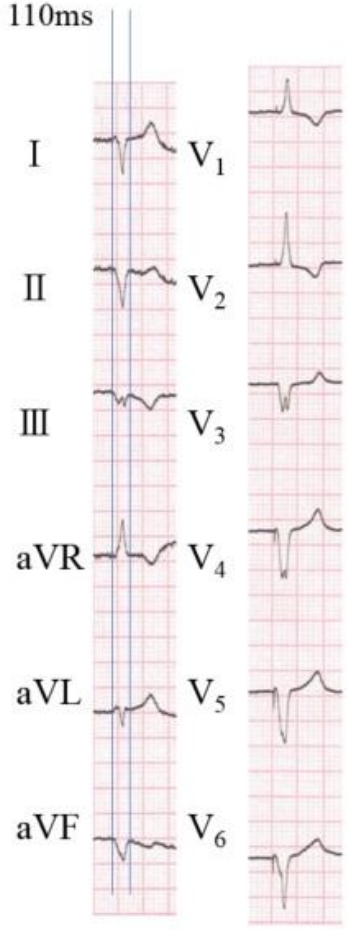
1 month



3 months

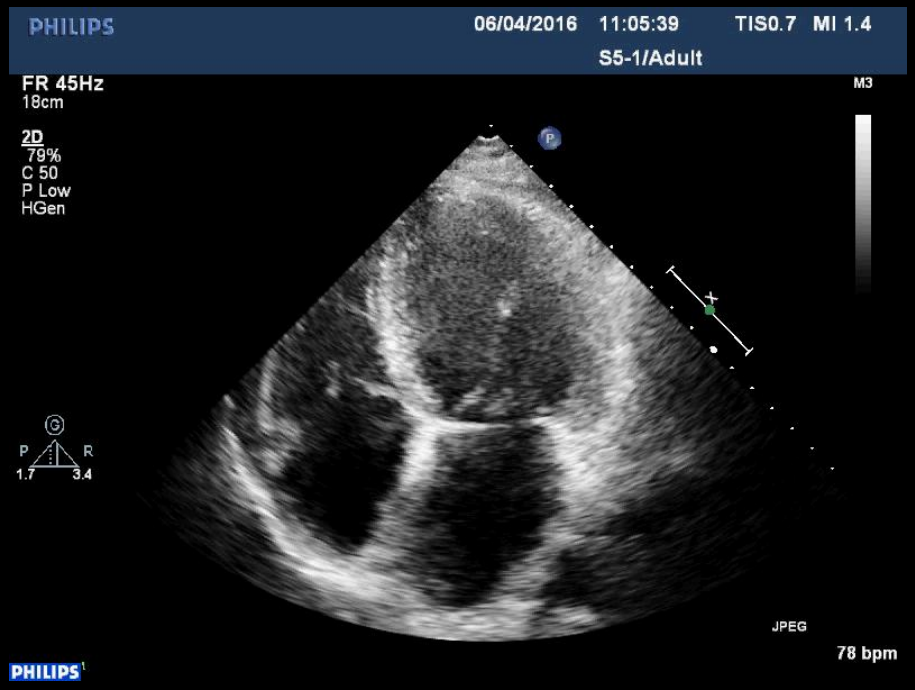


6 months

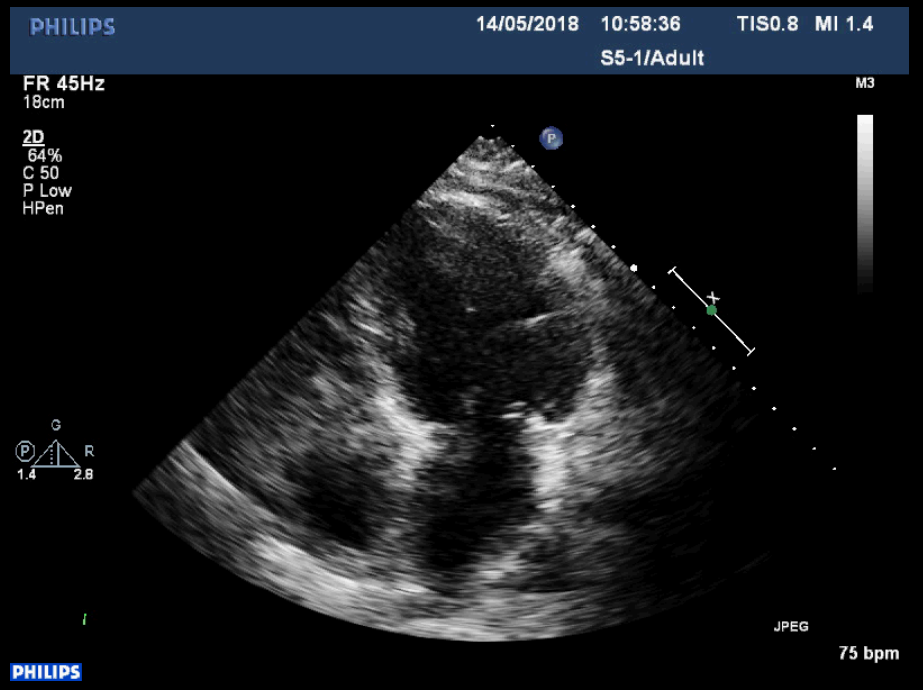


MICRA & LV WiCS
A4C Echocardiography

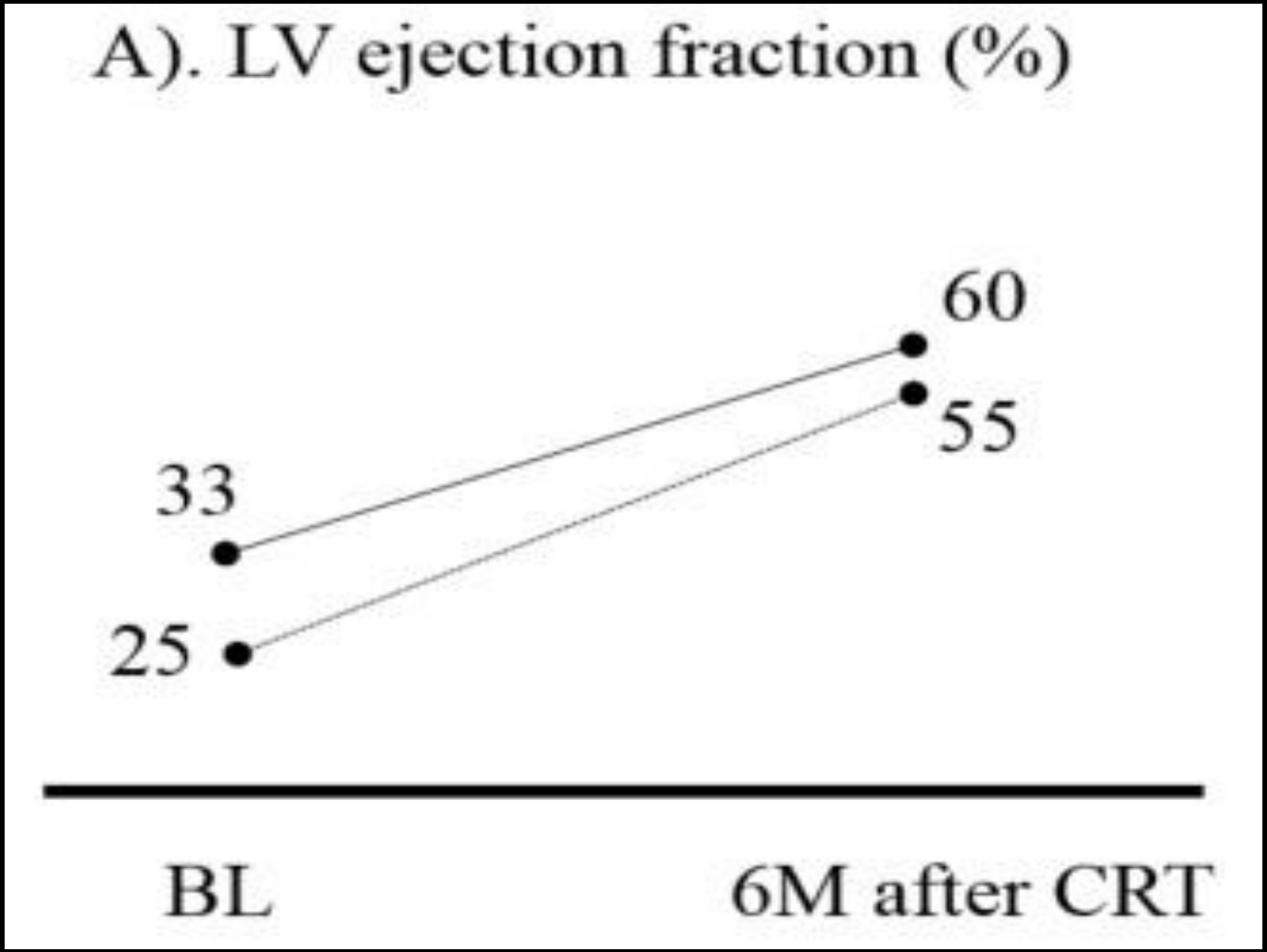
before



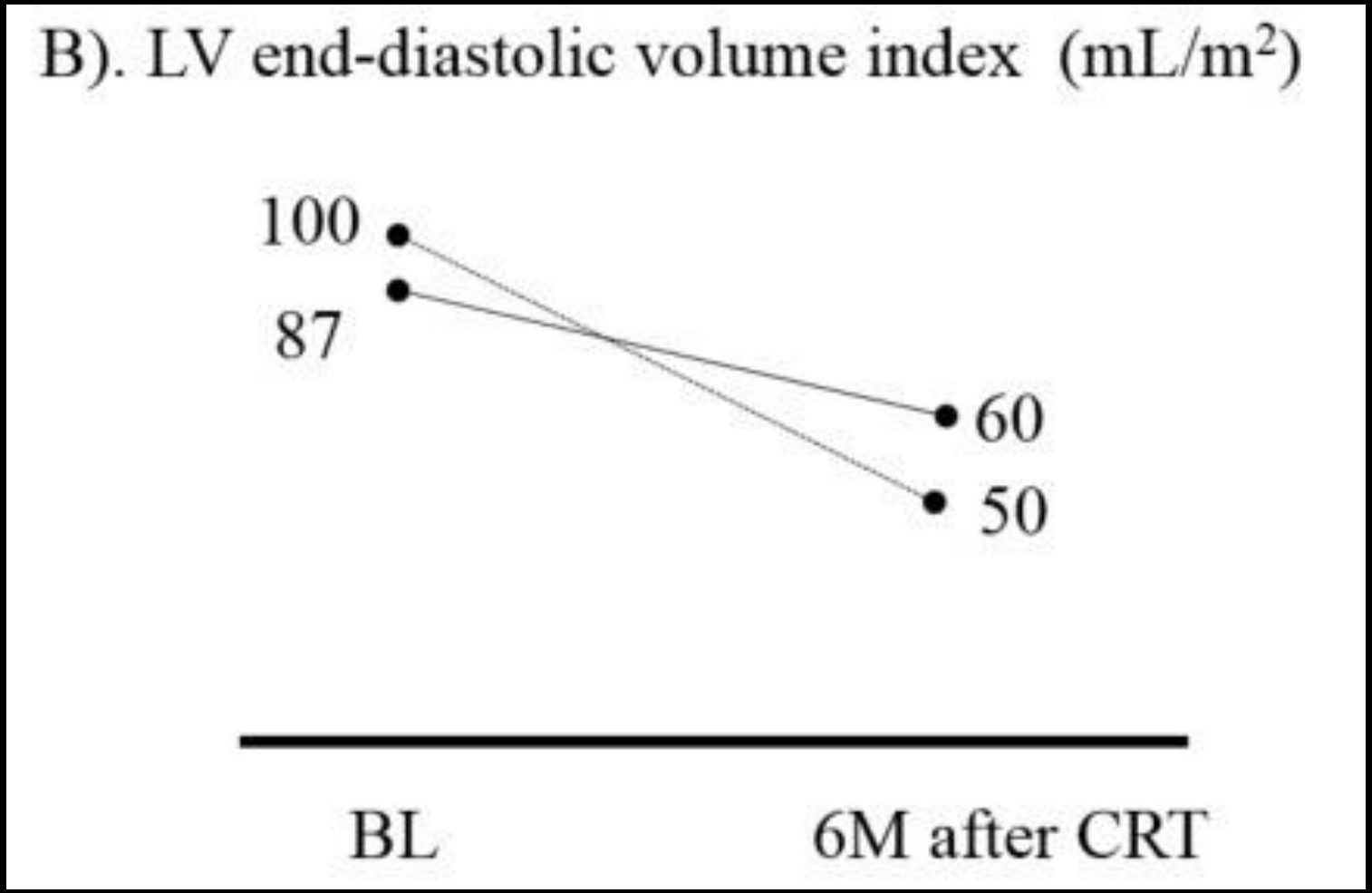
6 months after



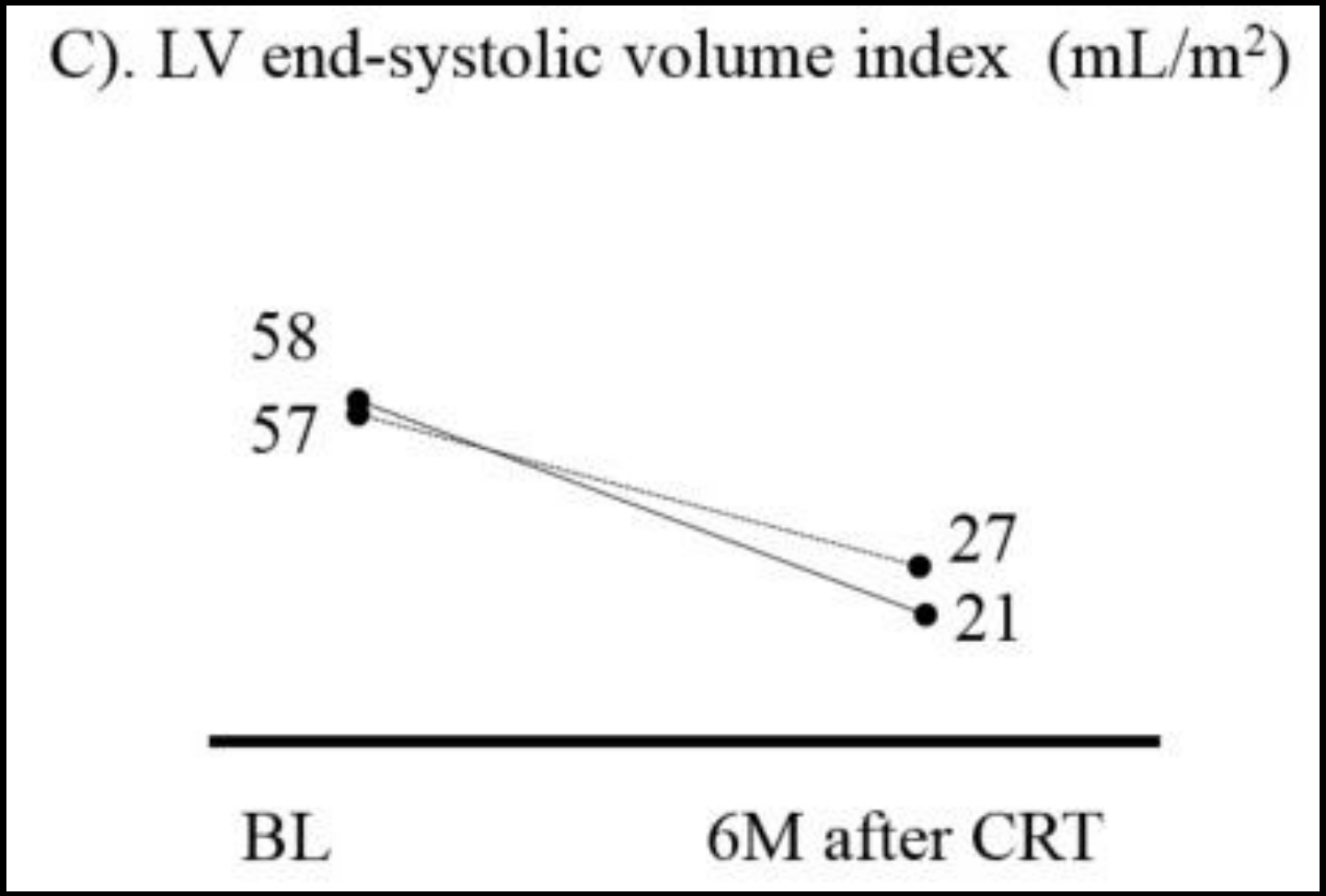
MICRA & LV WiCS
LV Ejection Fraction Improvement



MICRA & LV WiCS
LV EDVi Improvement

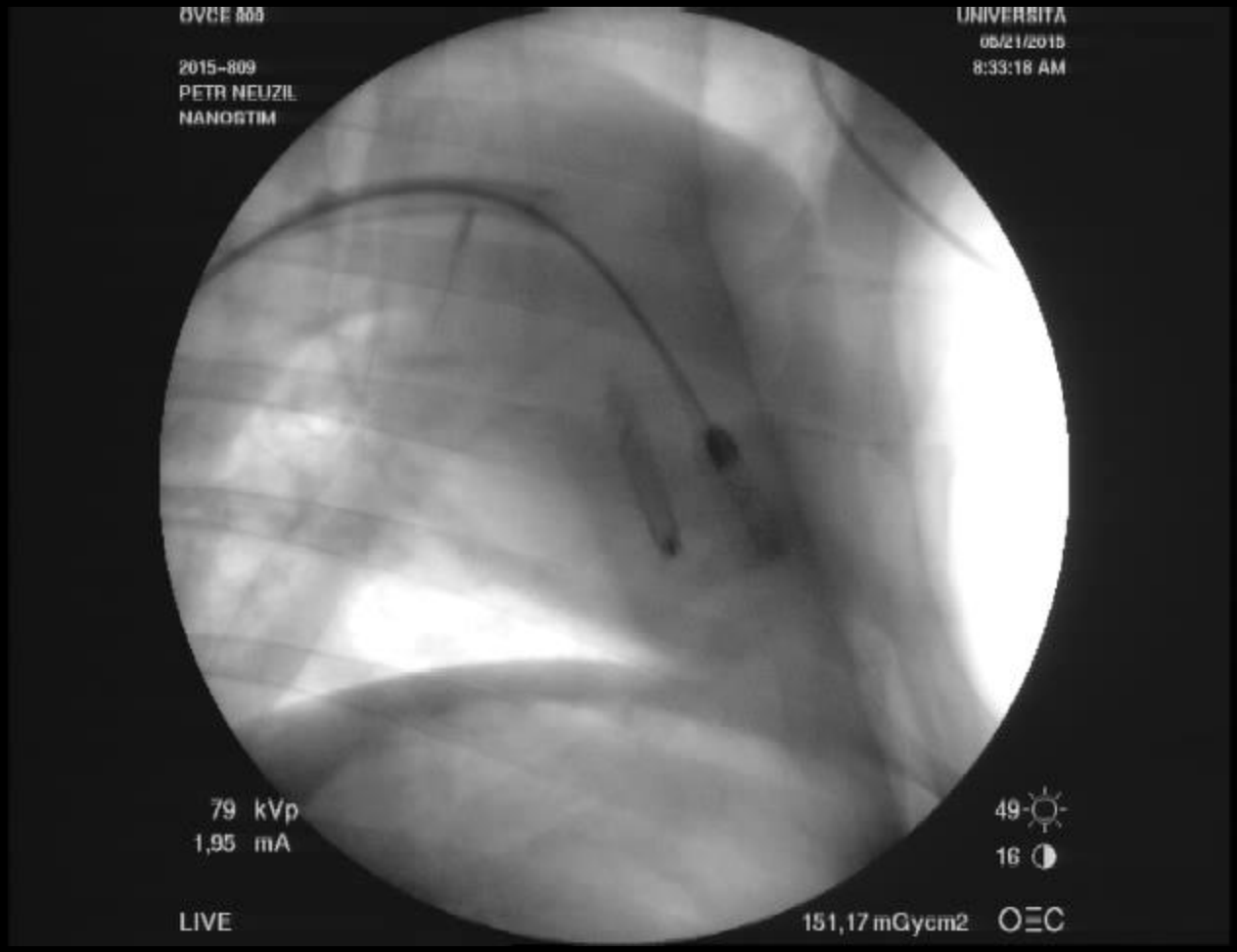


MICRA & LV WiCS
LV ESVi Improvement



Multichamber „True“ Leadless Pacing

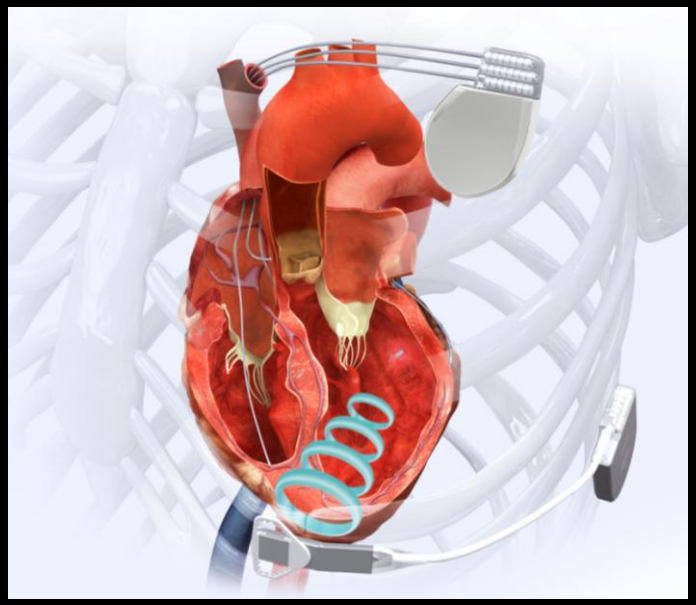
Preclinical experiments



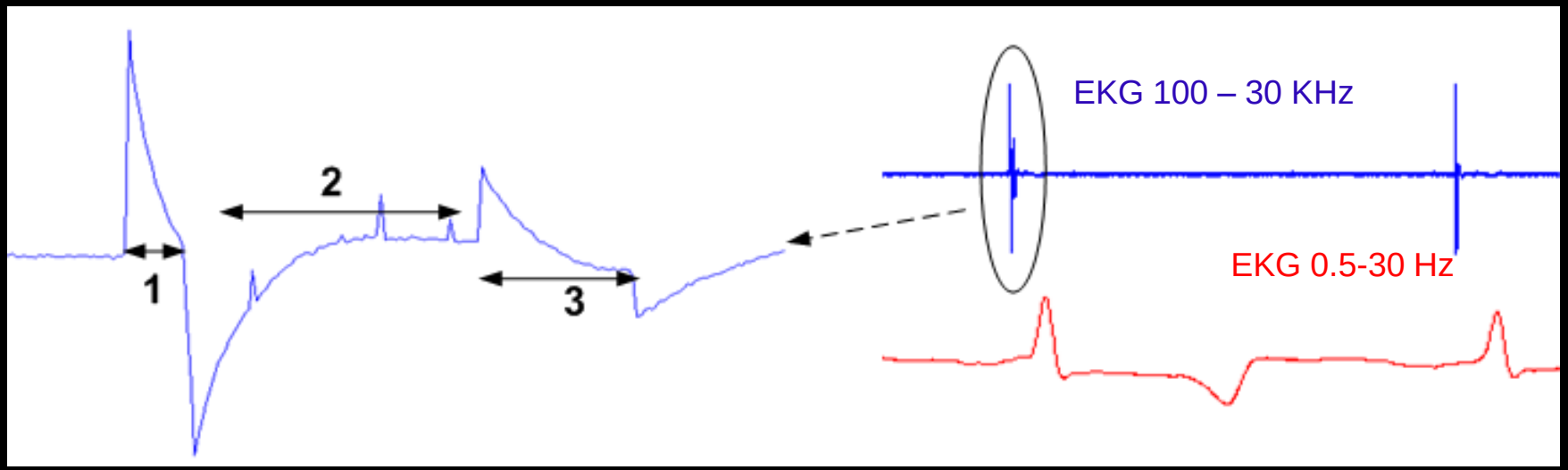
Conclusion

- This first report of a totally leadless approach for cardiac resynchronization therapy showed safety and efficacy. More studies are required to confirm that approach as an alternative to the standard transvenous resynchronization.
- A completely leadless configuration of biventricular pacing was found to be safe and effective in these two patients. Leadless biventricular pacing utilizing a wireless LV electrode may be particularly attractive for patients with both AF and CHF who do not respond to pharmacological rate control therapy and are not suitable for ablation therapy.
- In these two cases we demonstrated high level of synchronization between leadless RV and wireless LV devices.

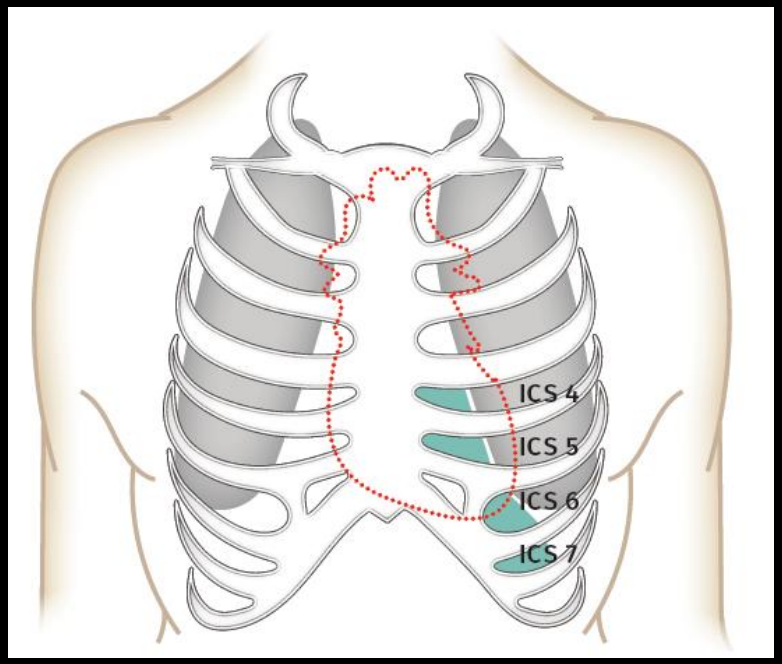
WiSE-LV System
Synchronization & Timing for CRT



1. Detect Co-implant RV output
   - Pacemaker, ICD, or CRT
   - Pulse-width measured to discriminate RV vs. RA
2. Locate/Target Electrode – “search”
   - 16 µs ultrasound pulses
   - sensed amplitude response discriminates position
3. Send pacing energy
   - Programmable PW 0.1-2.0ms and Transmit level
   - Typically 3ms after RV pulse, max ~12ms



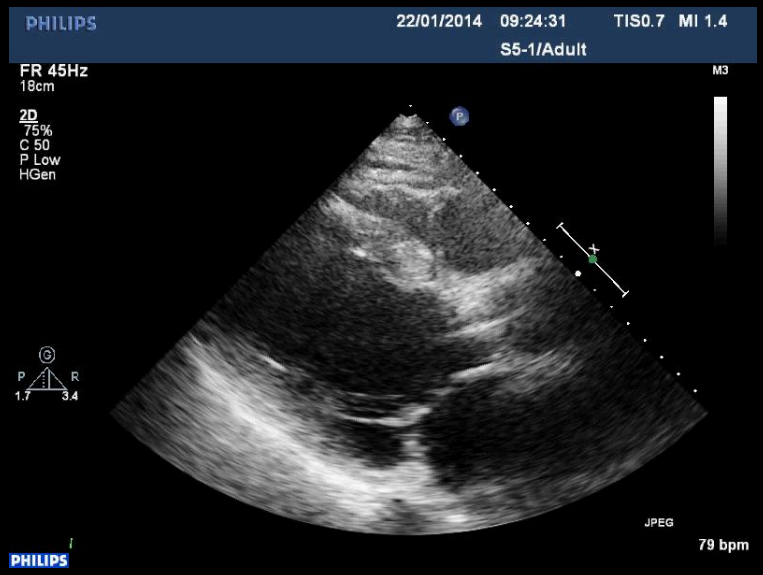
Transthoracic Echocardiography: Examples of acustic window detection

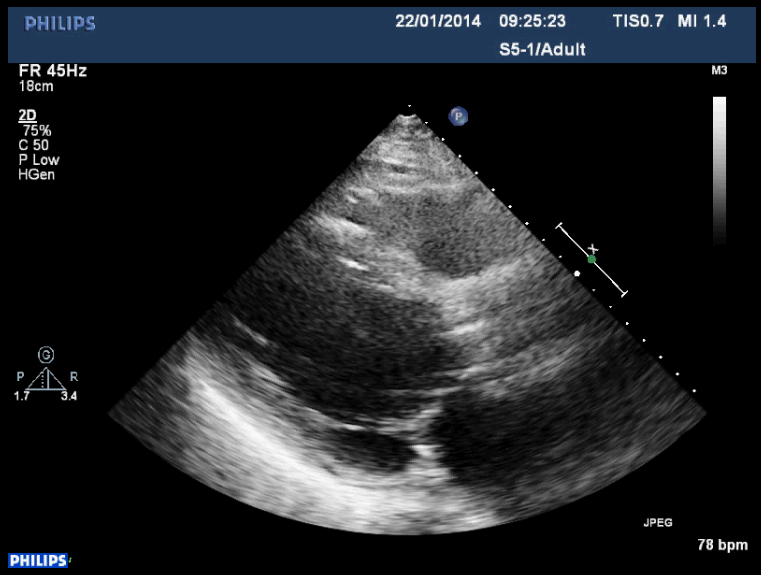


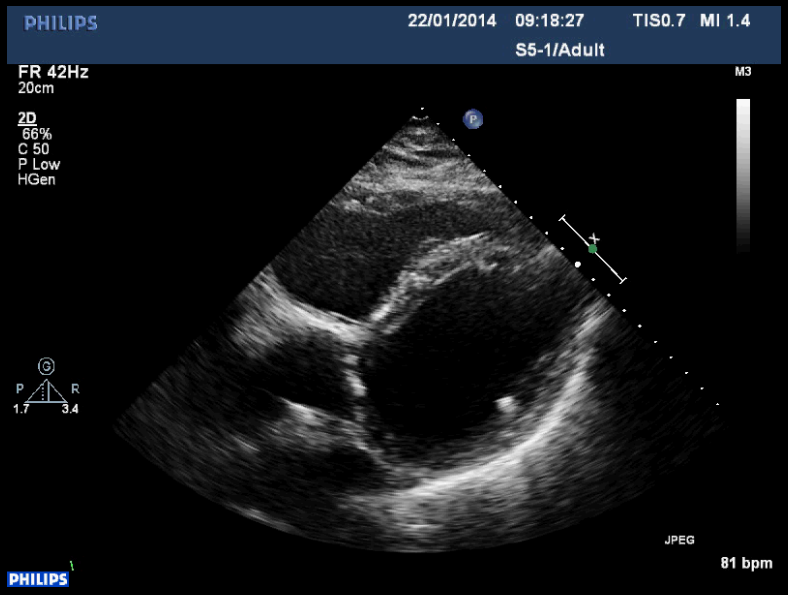
Transmitter is most commonly placed in a patient's 6th intercostal space (ICS)

- Identify optimal transmitter position, acoustic window, AW
  - Assess intercostal space 4-7 with TTE
  - Ensure no lung or rib obstruction preventing ultrasound transmission to potential receiver electrode site
  - Minimum 1 x 3.5cm window
- Additional assessment of:
  - LV wall thickness
  - Areas of ischemia
  - Potential electrode placement

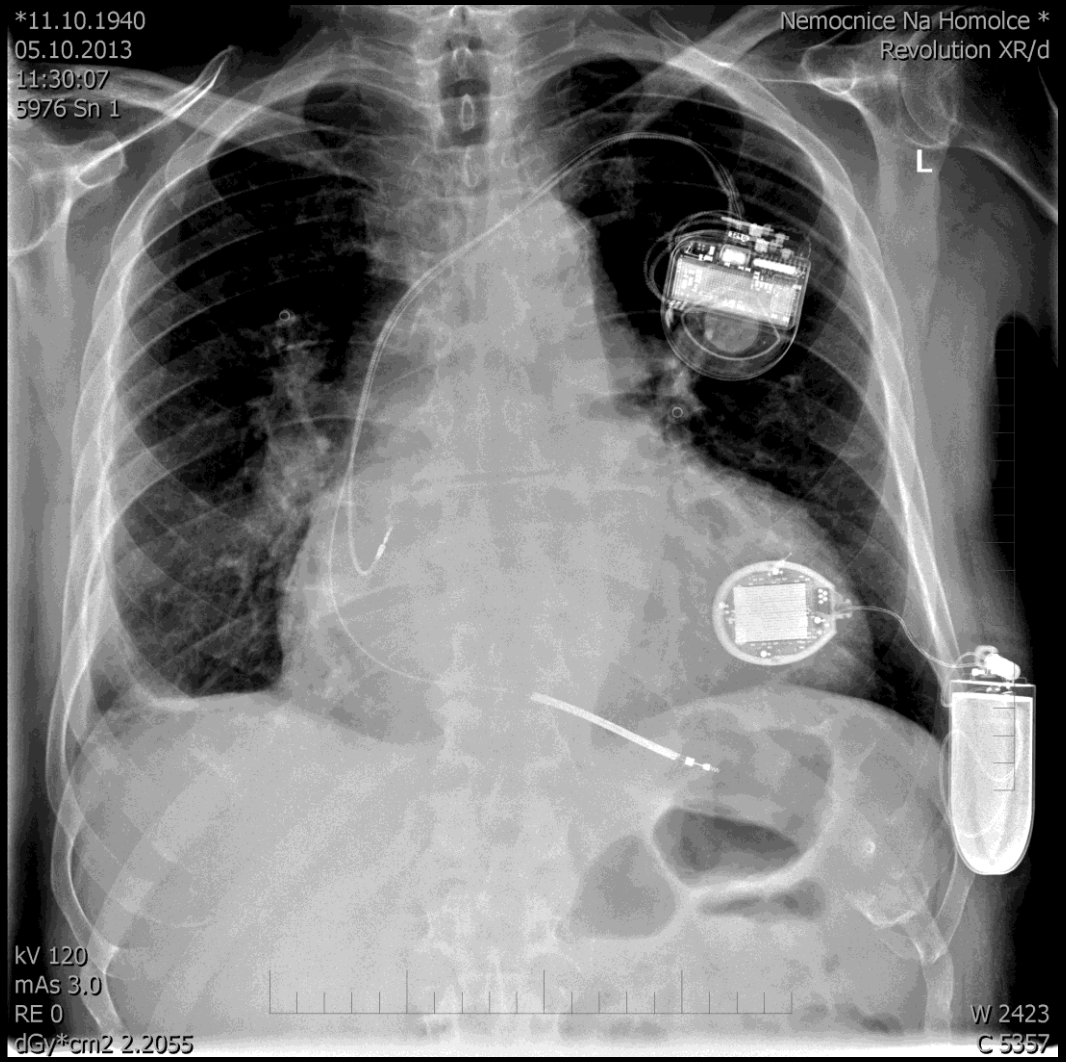
Transthoracic Echocardiography:
Examples of acustic window detection

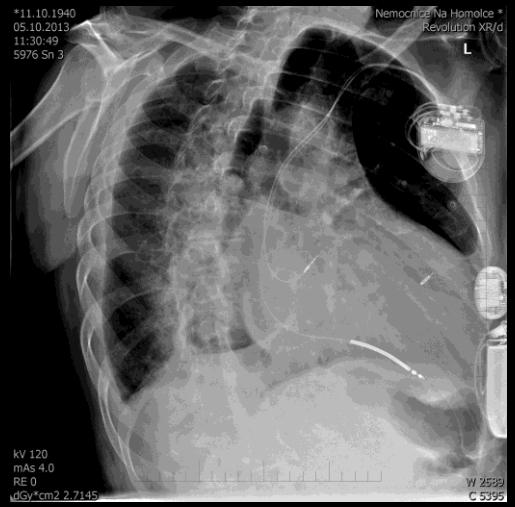


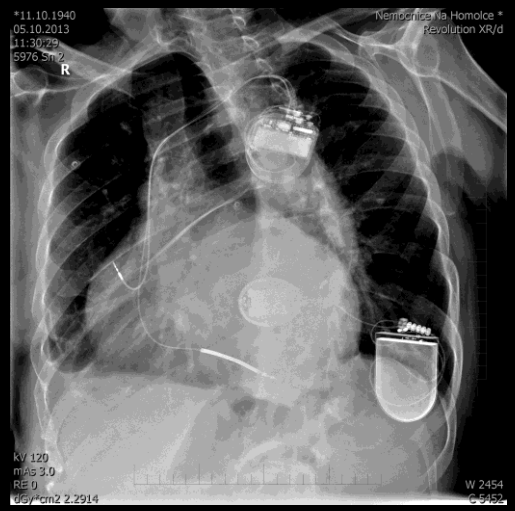




WiSE – System Insertion
Fluoroscopy in Different Projections

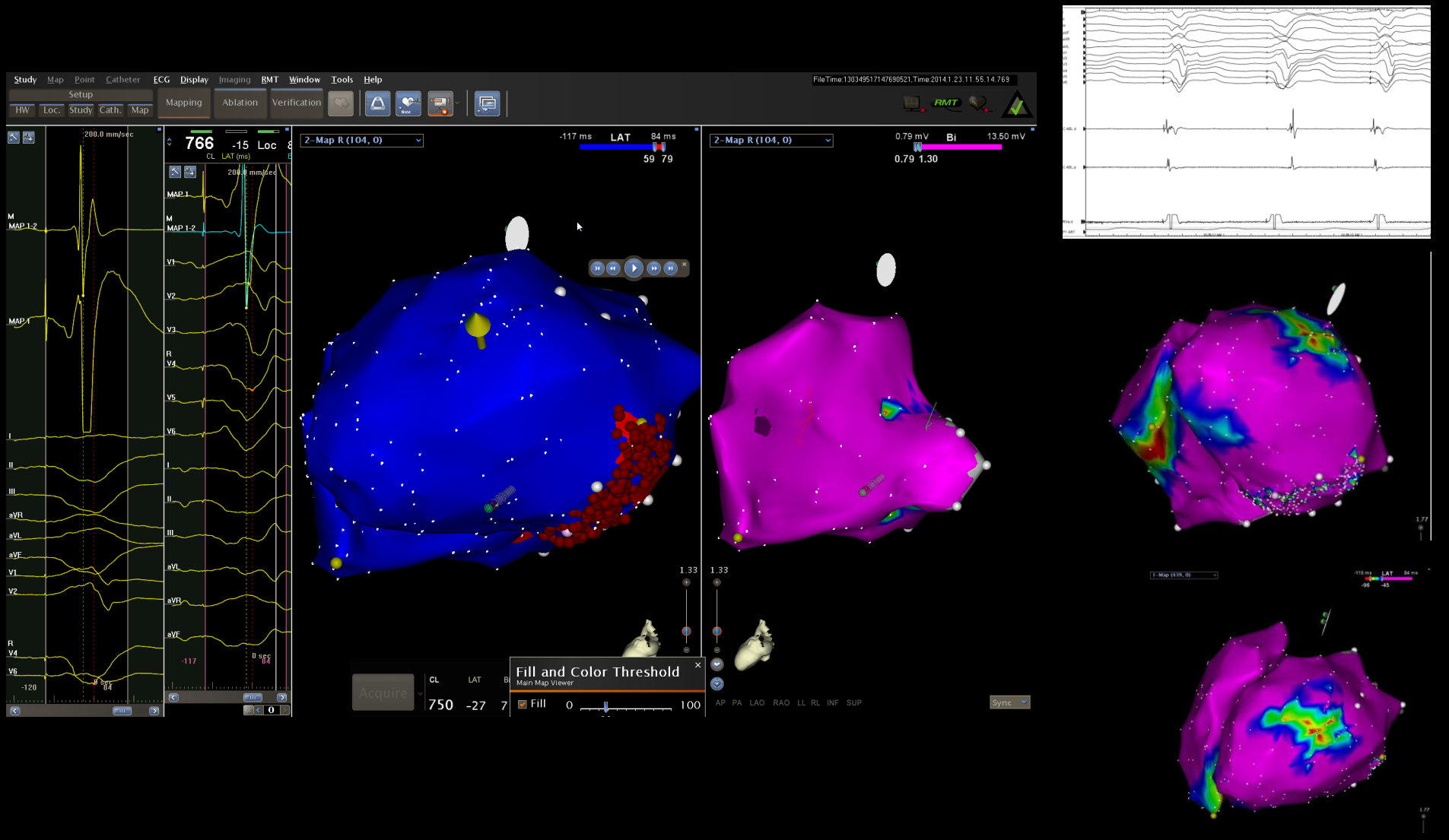




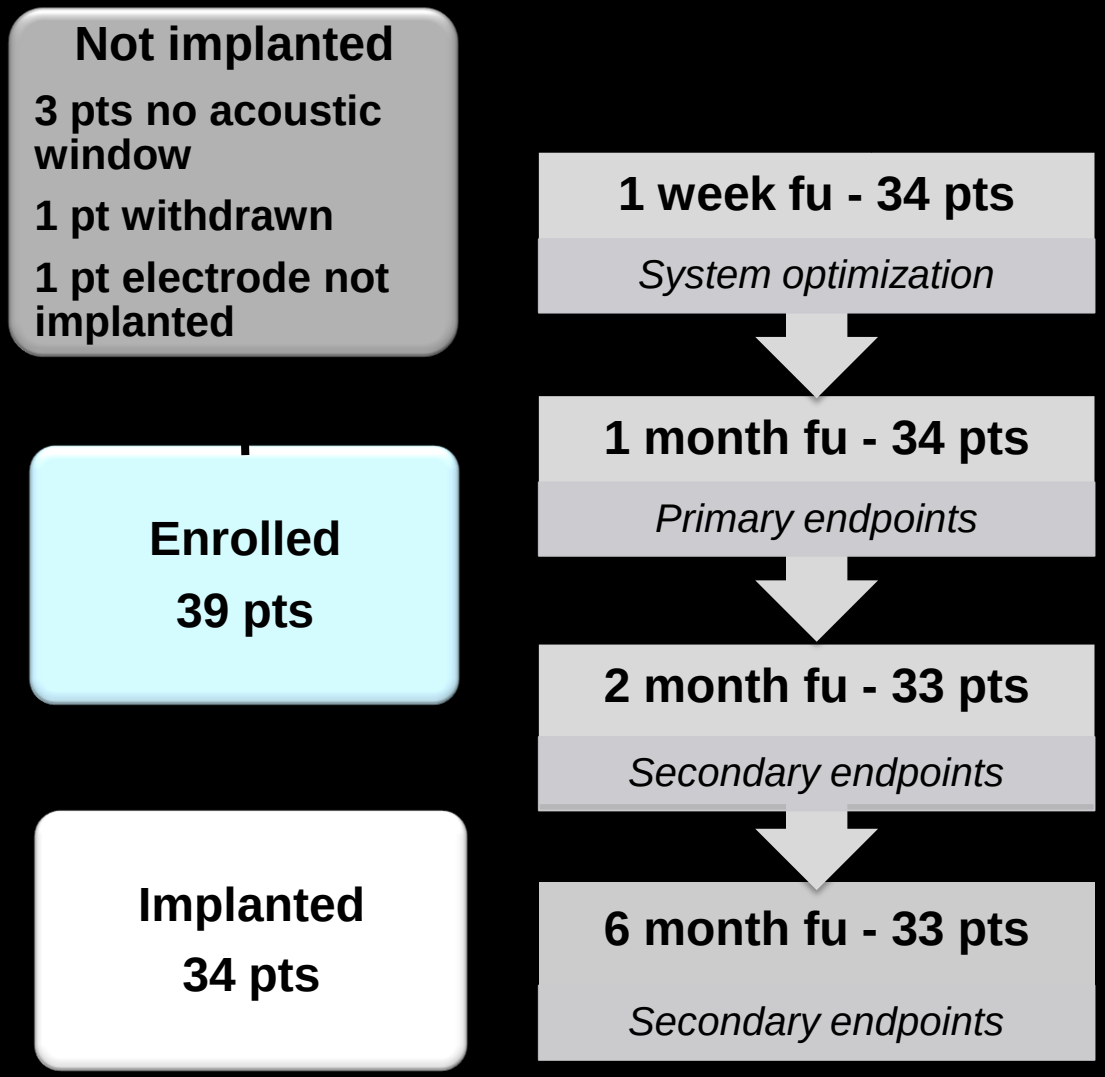


CARTO Electroanatomical Mapping

8 months after Implantation



SELECT-LV Study
Patient's Flowchart



SELECT-LV pts reaching12m: Demographics

Demographics	Mean ± SD
Age, years	65.5 ± 8.0
Ejection fraction,%	26.0 ± 6.2%
NYHA	2.6 ± 0.6
Intrinsic pre-imp QRS duration, ms	170 ± 29
Gender, male : female	29 (85%) : 5 (15%)
ICM / NICM / Both	15 (44%) / 15 (44%) / 4 (12%)
Upgrade / Non-responder / Untreated	3 (8.8%) / 10 (29.4%) / 21 (61.8%)
Pts taking anticoagulant pre-implant	22 (64.7%)

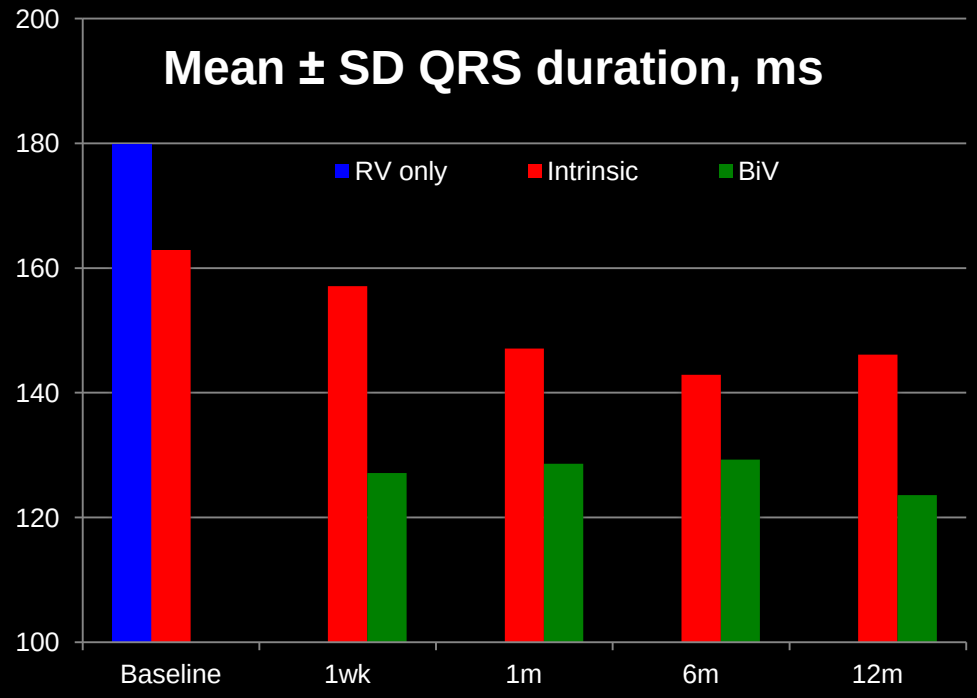
SELECT-LV pts reaching12m: Clinical Events

Clinical events	
Suspected infection	(3 patients)
Haematoma at pulse generator pocket	
Acute CVA - pt not compliant with anticoagulant regimen	
Pseudo aneurysm	
Heart failure hospitalisation	(Repeated in 1 patient)
Death, heart failure	(2 patients)
Premature battery depletion	(2 patients)
Arrhythmic storm	(2 patients)
VF and adequate ICD therapy	

- No cardiac perforation
- No electrode dislodgments

SELECT-LV pts reaching12m: Performance - BiV Pacing

- BiV pacing capture on 12 lead ECG at 1, 6 and 12m
  - 100%, 97% and 96% of evaluable pts

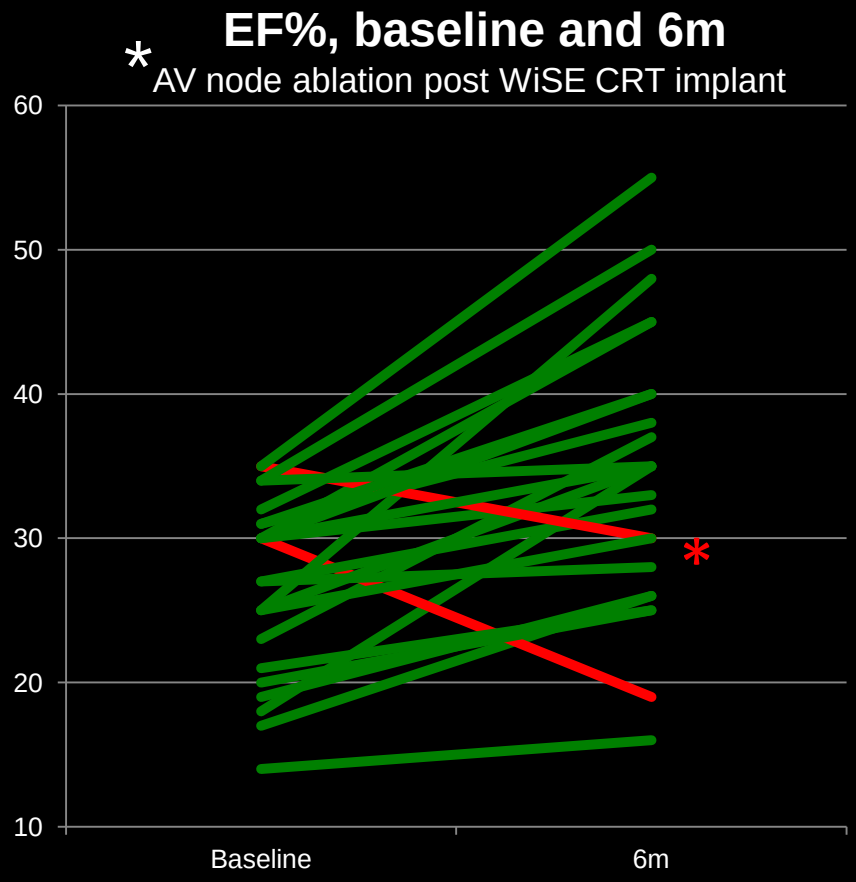


- ***Mean BiV QRS reduced at 1, 6 and 12m vs:***
  - ***Baseline RV:***

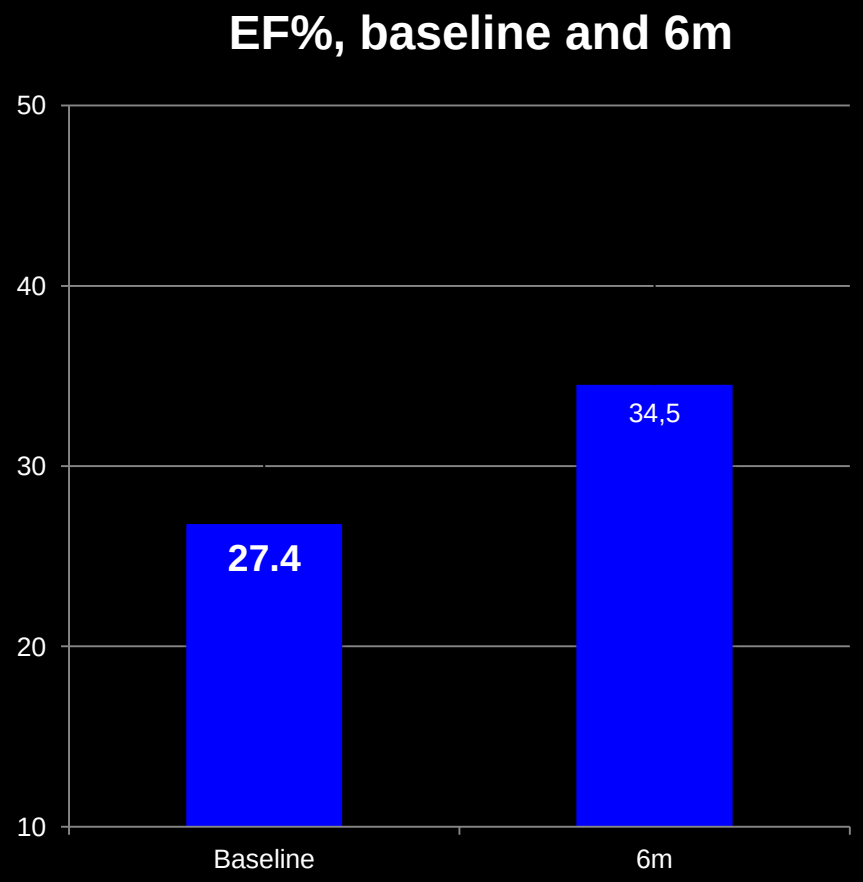
  51, 51 and 56 ms
  - ***Intrinsic:***

  34, 34 and 39 ms
- **Intrinsic QRS reduced over the time**

SELECT-LV pts reaching12m: Preliminary Efficacy



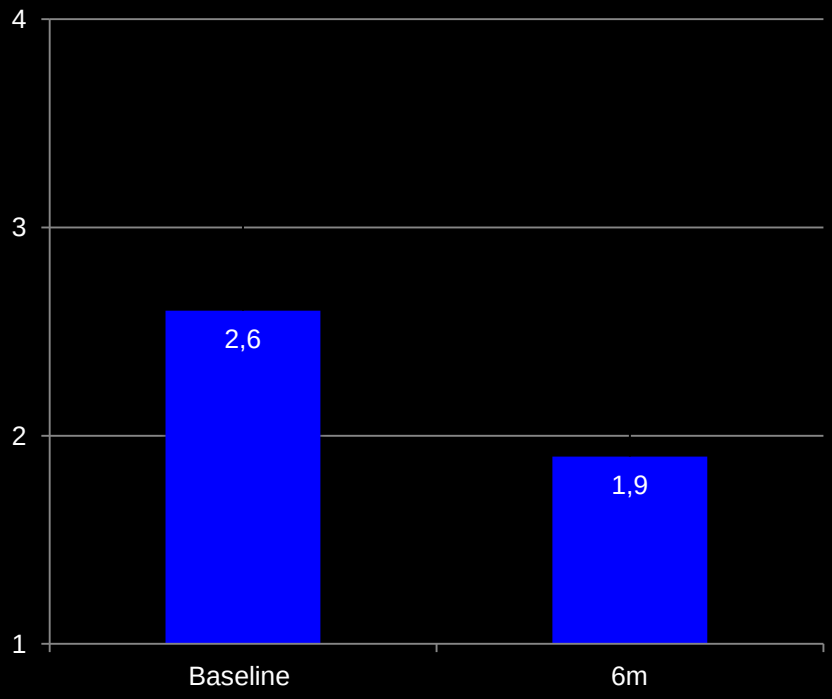
68% pts ≥5% increase



Mean ± SD difference at 6m = 7.1 ± 8.0

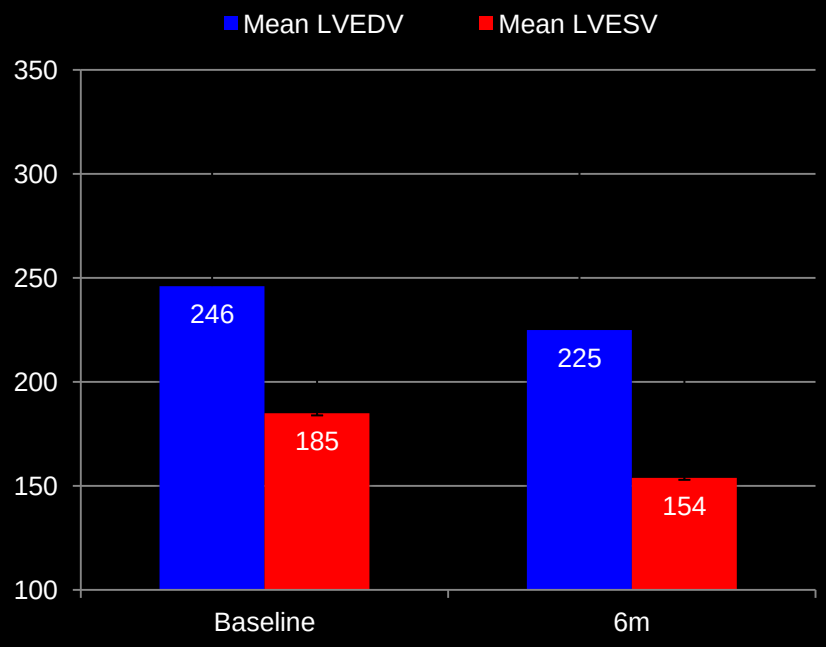
SELECT-LV pts reaching12m: Preliminary Efficacy

NYHA, Baseline and 6m



52% pts ≥ 1 class improvement

End systolic and diastolic volumes, ml, baseline and 6m



53% pts ≥15% improvement in LVESV

SELECT-LV pts reaching12m: Preliminary Efficacy - Clinical Composite Score

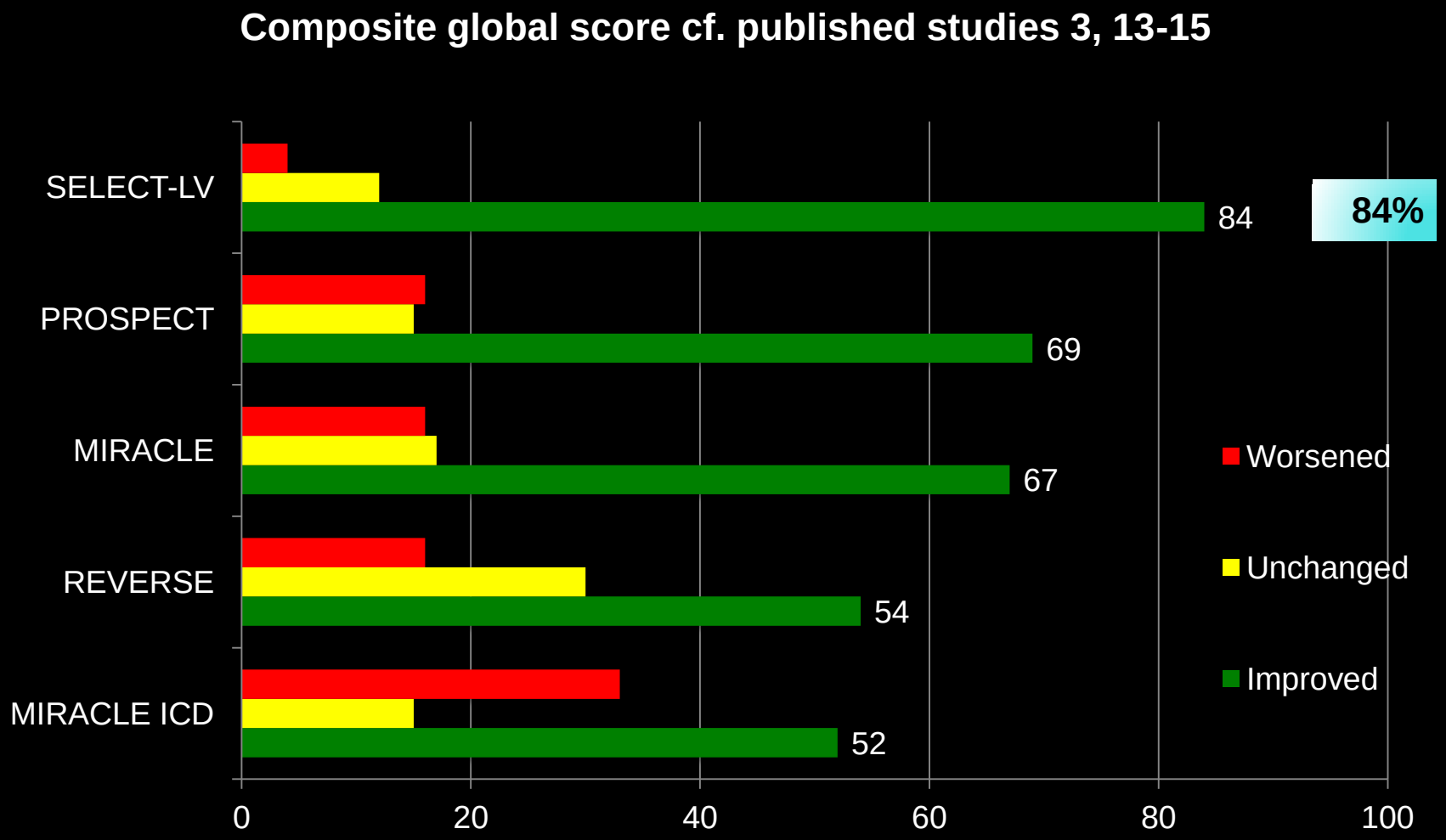
- 25 pts to date followed for 12m study duration
  - No pts died within study period
  - 1 pt hospitalised for HF on 2 occasions
  - NYHA mean ± SD decrease from 2.7 ± 0.6 to 1.8 ± 0.7
    - 6 (24%) pts decreased by 2 classes
    - 11 (44%) pts decreased by 1 class
    - 7 (28%) pts unchanged
    - 1 (4%) pts increased by 1 class
  - Pt global assessment
    - 16 (76.2%) pts improved, 3 (14.3%) unchanged, 2 (9.5%) worsened

Clinical composite score

76% (19) pts improved
16% (4) pts unchanged
8% (2) pts worsened

Packer M et al., J Cardiac Failure 2001; 7: 176-182.

SELECT-LV pts reaching12m: Clinical Composite Score



3. Leon AR et al., JACC 2005; 46: 2348-2356.
13. Chung E et al., Circulation 2008; 117: 2608-2616.
14. Linde C et al., JACC 2008; 52: 1834-1843.
15. Young JB et al., JAMA 2003; 289: 2685-2694.

SOLVE – CRT
IDE Randomised Trial

Stimulation **O**f the **L**eft **V**entricular **E**ndocardium for **C**ardiac **R**esynchronization **T**herapy in Non-Responders & Previously Untreatable Patients:

- Prospective, two-arm, randomized, double blind, multi-center pivotal trial
- 350 patients, 45 Centers
  - All patients get WiSE, Randomized 1:1 Sense Mode vs WiSE ON

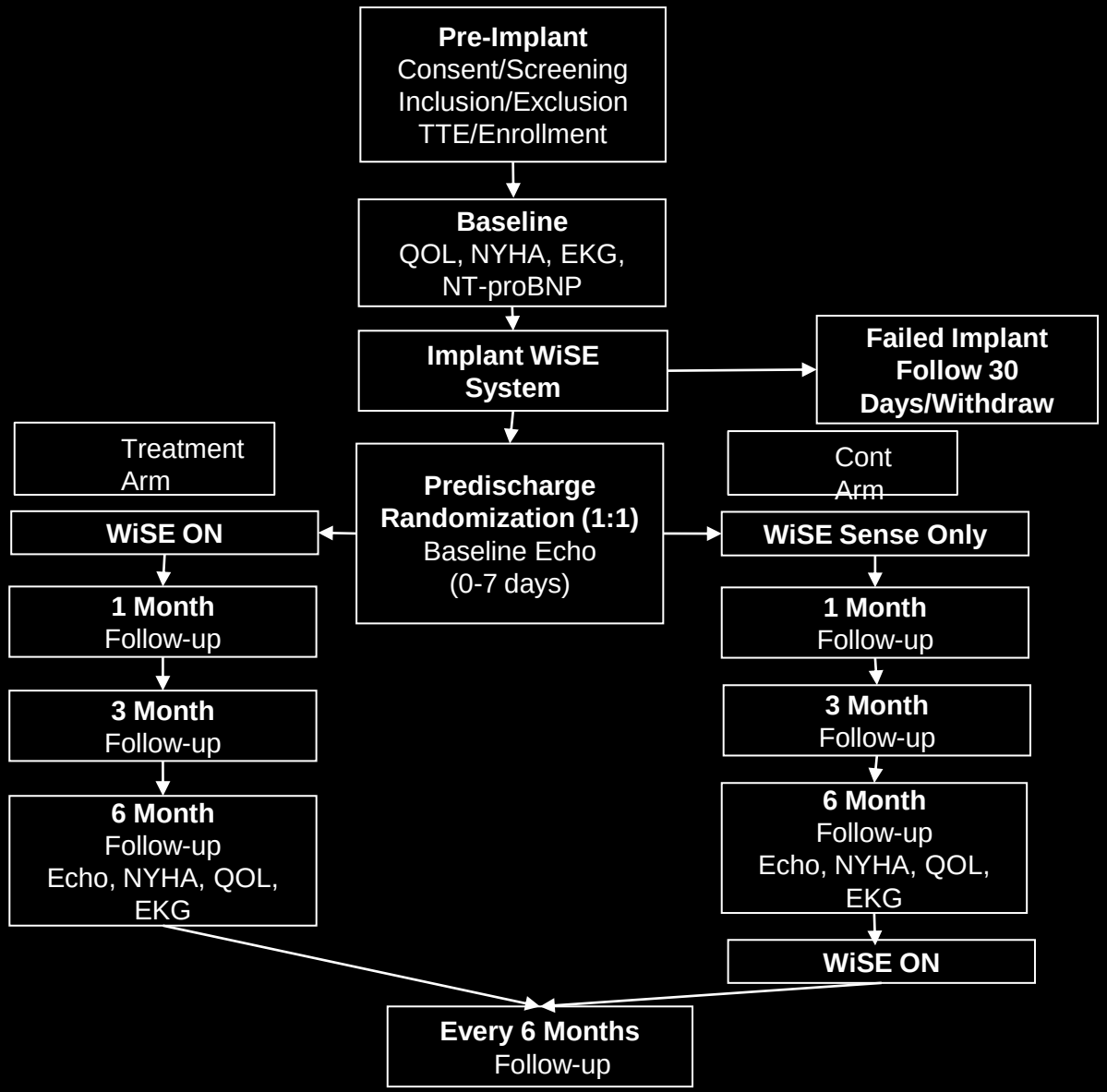
Purpose:

- To demonstrate the safety and effectiveness of the WiSE

Population:

- Indicated for CRT Non-Responders or Previously Untreatable and meeting established CRT treatment criteria.
- The WiSE provides endocardial LV stimulation, synchronized to the RV pacing pulse of a commercially-available implanted pacemaker, ICD, CRT-P, or CRT-D to achieve CRT.

SOLVE-CRT Trial: Design



SOLVE-CRT Trial: Inclusion Criteria

1. **Current guidelines (except blue):**
   a. Class I: NYHA II, III, IV, EF ≤ 35%, LBBB, QRS≥150ms
   b. Class IIa (1): NYHA II, III, IV, EF≤35%, LBBB, QRS≥130 to <150ms
   c. Class IIa (2): NYHA II, III, IV, EF≤35%, non-LBBB, QRS≥150ms
2. **'Non-responder': Have a CRT system that is functional and despite Guideline Directed Medical Therapy (GDMT), optimal programming the patient has not responded to therapy for a minimum of 6M. Non-response is defined as remaining clinically unchanged or worsened:**
   a. EF has remained unchanged or worsened, and
   b. The patient's clinical status based in the totality of available clinical evidence (such as NYHA Class, exercise tolerance, QOL, or global assessment) has remained unchanged or worsened, as determined by the local **Site Enrolment Committee**

OR

'Previously Untreatable': Patients who have a full or partial CRT system,

a. Patients in whom CS lead implantation for CRT has failed
b. CS lead implanted but has been programmed OFF
c. High risk upgrades: relative contraindications to CS lead implant

Conclusion

- WiSE CRT shows promising efficacy in pts unable to benefit from conventional CRT, non responders / upgrades
- Multi-centre experience in a small number of pts has demonstrated feasibility, utility and long term outcome of endocardial LV pacing to achieve CRT
  - BiV pacing achieved in 100, 100, 97 and 96% of pts at 1 week, 1, 6 and 12m
  - Mean BiV QRS duration reduced by 1 week and maintained at 12m
  - Intrinsic QRS duration reduced, demonstrating electrical reverse remodelling
  - Mean LV EF increased
  - Mean NYHA reduced
  - Mean end systolic / diastolic volumes reduced
  - Clinical composite score improved

Drug Management during Study

Table 1: Recommendations for Management of antiplatelet and anticoagulation therapy[1]				
Chronic Therapy	**Pre-Implant**	**Implant**	**Pre-discharge**	**Follow-up**
Either no antiplatelet or antithrombin therapy or ASA alone	ASA and clopidogrel loading dose	Heparin	ASA and clopidogrel	ASA (6M)[2] and clopidogrel (3M)
NOAC/DOAC	D/C 2-3 days ASA and clopidogrel loading dose	Heparin	Restart NOAC/DOAC ASA and clopidogrel	NOAC/DOAC ASA (6M) and clopidogrel (3M)
Antithrombin	D/C 2-3 days ASA and clopidogrel loading dose	Heparin	Restart Antithrombin ASA and clopidogrel	Antithrombin ASA (6M) and clopidogrel (3M)
ASA and clopidogrel	ASA and clopidogrel loading dose	Heparin	ASA and clopidogrel	ASA (6M)[2] and clopidogrel (3M)[2]

SELECT-LV Study Results

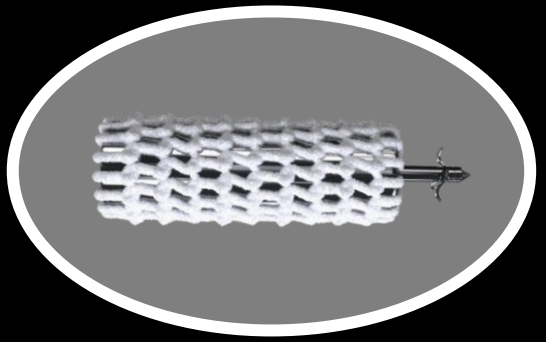
- 39 pts completed enrollment and screening
  - 3 pts failed acoustic window screening
  - 1 pt withdrew consent
- 34 (97.1%) of 35 attempted implants successful
- **25 pts followed for >12m**

WiSE CRT System
Electrode

Small Size

Designed for LV placement while avoiding need for chronic anticoagulation

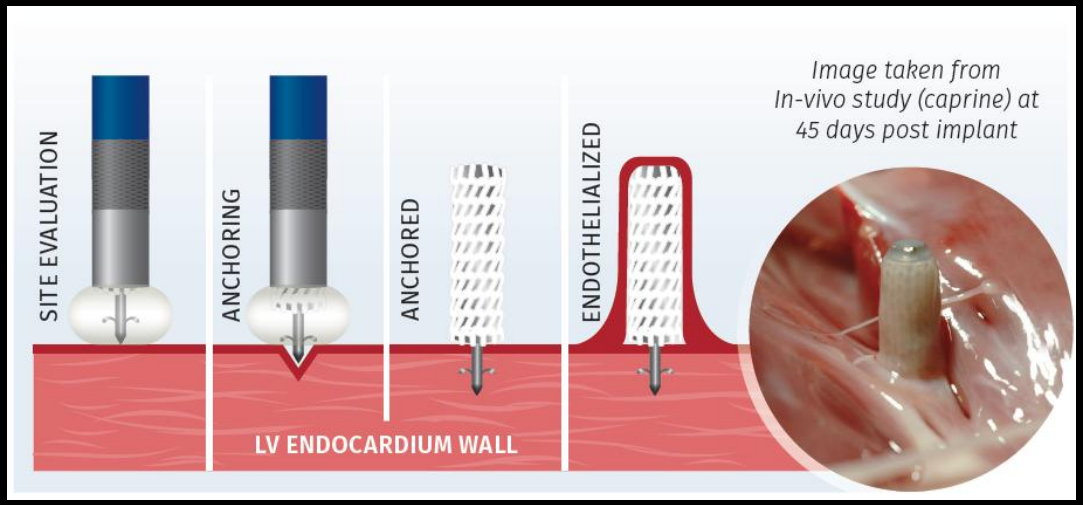
LENGTH OF BODY: **9.1mm**
DIAMETER: **2.7mm**
WEIGHT: **0.12 g**
VOLUME: **0.05 cc**



Secure Attachment

Endothelialises for a low risk of thromboembolic events

- Anchors onto endocardial wall with 5 nitinol tines
- Passive device with no need for replacement
- Full endothelialisation in animal testing at 30 to 45 days [11]



Echt DS, Moore D, Cowan M, Valli VE, Whitehair JG, Willis NP. Heart Rhythm 2010; S451-2.