MHIF FEATURED STUDY:

COVID-PACT

OPEN AND ENROLLING:

EPIC message: *Research MHIF Patient Referral*

CONDITION:
Critically-ill patients hospitalized with COVID-19

PI:
Retu Saxena, MD

RESEARCH CONTACT:
Stephanie Ebnet, RN
Stephanie.Ebnet@allina.com | 612-863-6286

SPONSOR:
TIMI Study Group

DESCRIPTION:

Phase 2/3, randomized, open-label strategy trial to evaluate the efficacy and safety of antithrombotic therapy for prevention of arterial and venous thrombotic complications in critically-ill patients with COVID-19. Subjects are randomized to standard dose prophylactic versus therapeutic dose anticoagulation (Heparin or Lovenox) and antiplatelet (Plavix) versus no antiplatelet therapy. Subjects are followed for 28 days or until discharge (whichever occurs first). Several trials of anticoagulant intensity in COVID-19 have been completed, but the results of these trials have not yet resolved the uncertainty regarding the optimal dosing of anticoagulant therapy and not led to changes in professional society guidelines from those in place.

CRITERIA LIST/ QUALIFICATIONS:

Inclusion:

- ≥ 18 years old
- Acute infection with SARS-CoV2
- Currently admitted to the ICU or receiving ICU level cares ≤ 96 hours

Exclusion:

- Ongoing (>48 hours) or planned full-dose anticoagulation
- Ongoing or planned treatment with dual antiplatelet therapy
- Contraindication to antithrombotic therapy or high risk of bleeding
- History of heparin-induced thrombocytopenia
- Ischemic stroke within the past 2 weeks
- Pregnancy

MHIF FEATURED STUDY:

ACTIV-3

OPEN AND ENROLLING:

EPIC message: *Research MHIF Patient Referral*

CONDITION:	PI:	RESEARCH CONTACT:	SPONSOR:
Patients hospitalized for COVID-19	Jay Traverse, MD	Irena Davies Irena.Davies@allina.com | 612-863-4393	The University of Minnesota

DESCRIPTION: Phase 3 adaptive, double-blind, randomized placebo-controlled platform trial to evaluate the safety and efficacy of multiple investigational agents aimed at modifying the host immune response to SARS-CoV-2 infection or directly enhancing viral control in order to limit disease progression in patients hospitalized with COVID-19. Subjects are randomized to investigational agents available at our site versus placebo and receive single IV infusion. Subjects are followed for a total of 18 months with scheduled lab draws and follow-up visits.

CRITERIA LIST/ QUALIFICATIONS:

Inclusion:

- ≥ 18 years old
- Positive nucleic acid test (NAT) confirming SARS-CoV-2 infection ≤ 3 days of randomization **OR** positive NAT **and** progressive disease
- Symptoms attributable to COVID-19 first started within 12 days before randomization
- Requires admission for inpatient hospital acute medical care for COVID-19 infection

Exclusion:

- Received any SARS-CoV-2 hIVIG, convalescent plasma, or SARS-CoV-2 neutralizing monoclonal antibody anytime prior to admission
- Not willing to abstain from participation in other COVID-19 treatment trials until after Day 5 (with approval from study leadership)
- Presence at enrollment for stroke, meningitis, encephalitis, myelitis, MI, myocarditis, pericarditis, symptomatic CHF, arterial or deep vein thrombosis or PE
- Current requirement for invasive mechanical ventilation, ECMO, mechanical ventilator support, vasopressor therapy, initiation of RRT

Electrical Dyssynchrony and Cardiac Resynchronization Therapy:

Alan J. Bank, MD

Medical Director of Research

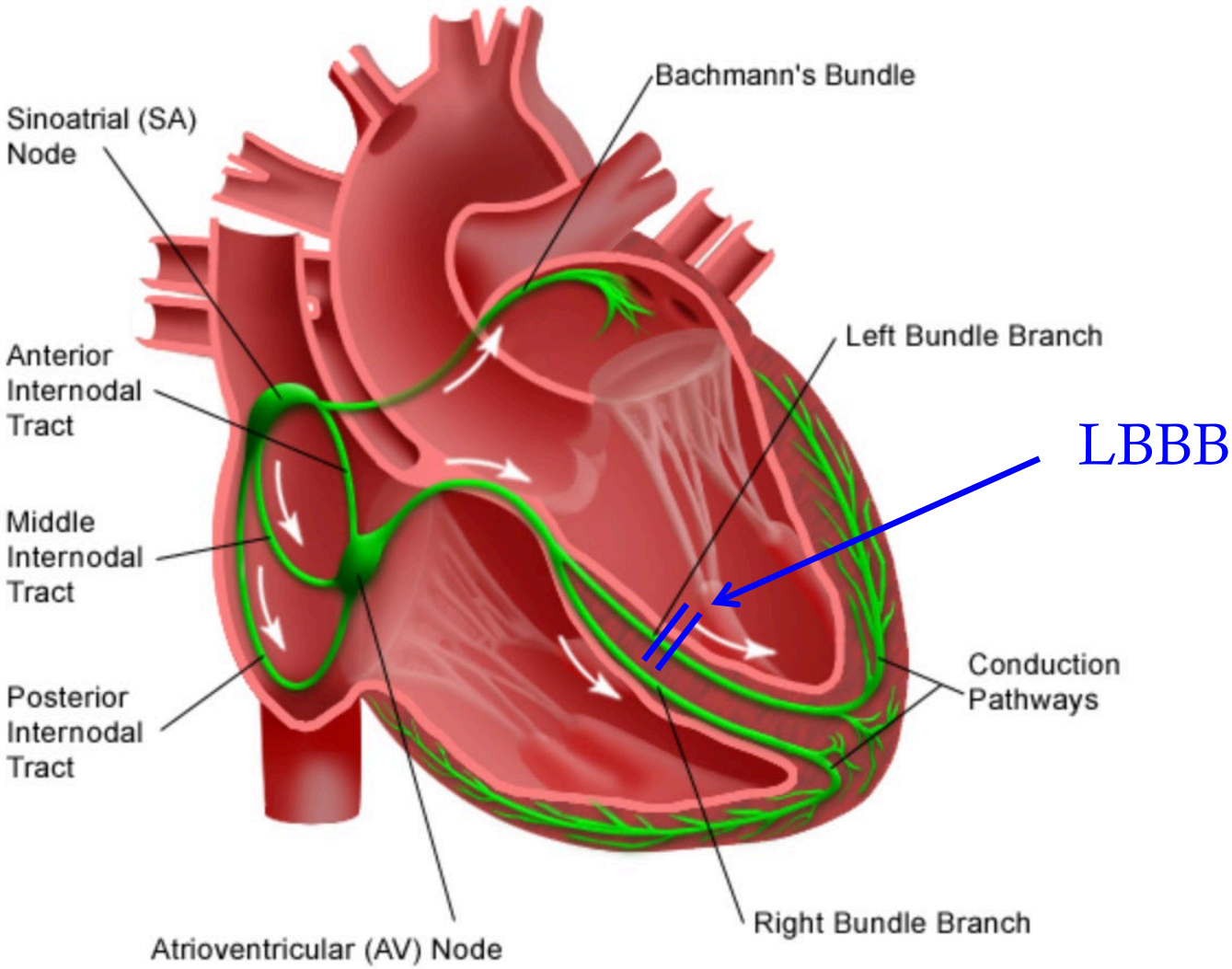
Minneapolis Heart Institute East at United Hospital

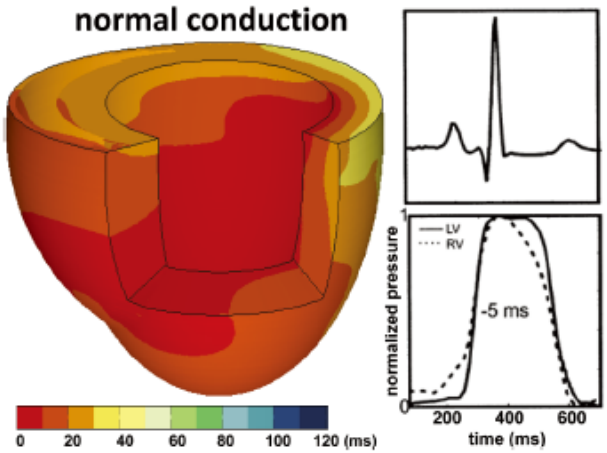
Allina Health

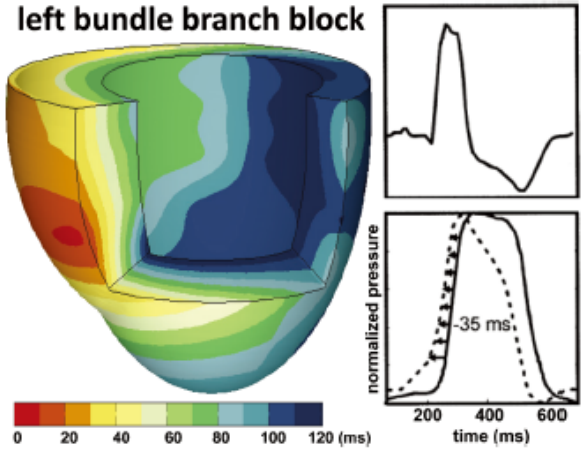
OUTLINE

1. THE PROBLEMS: Underutilization, Non-response/Incomplete-response
2. THE MECHANISM: Wavefront Fusion
3. THE MEASUREMENT: Cardiac Resynchronization Index (CRI)
4. THE GRAPHICS: Electrical Dyssynchrony Mapping (EDM)
5. THE OUTCOMES: Clinical and Echocardiographic
6. THE FUTURE: Clinical use for patient selection, lead location, optimization

Left Bundle Branch Block

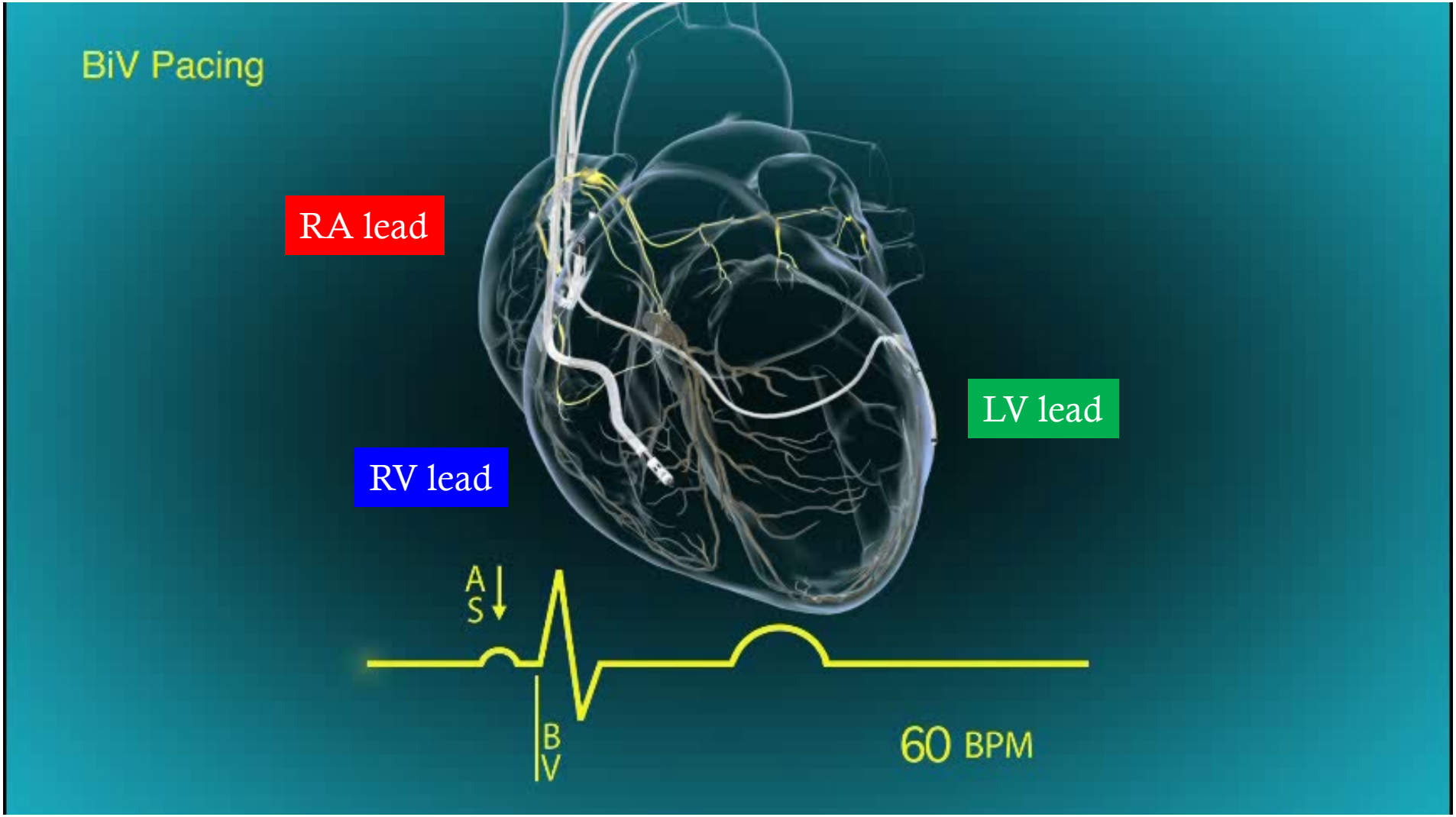






Videos courtesy of David Kass, John's Hopkin's University

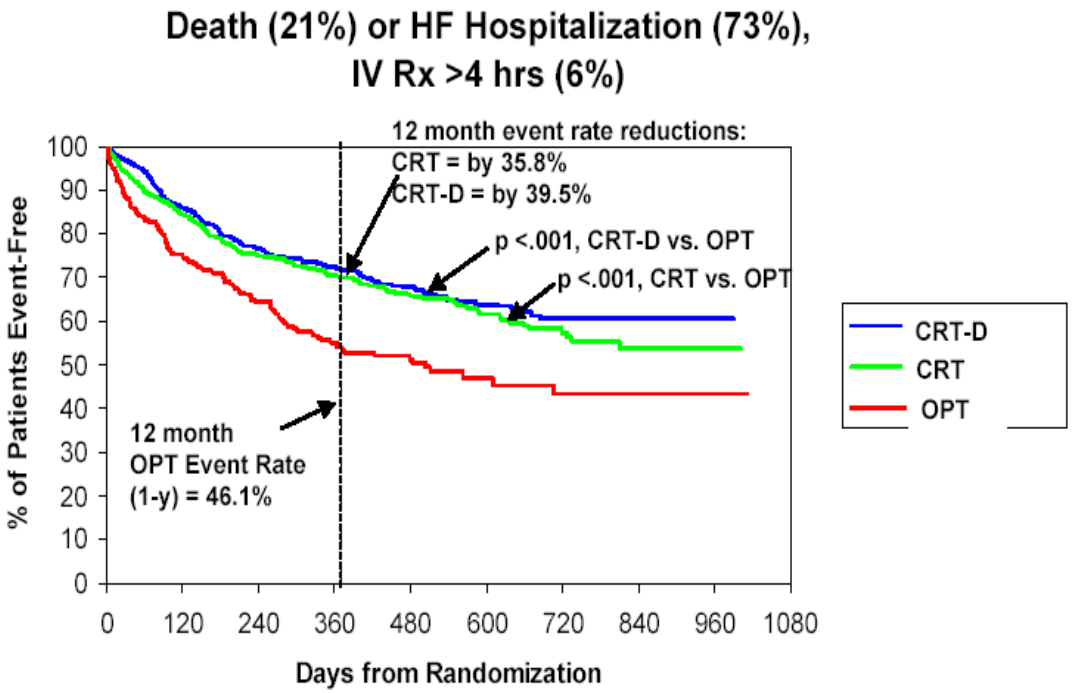
Cardiac Resynchronization Therapy (CRT) / Biventricular Pacing



CRT: Basic Facts

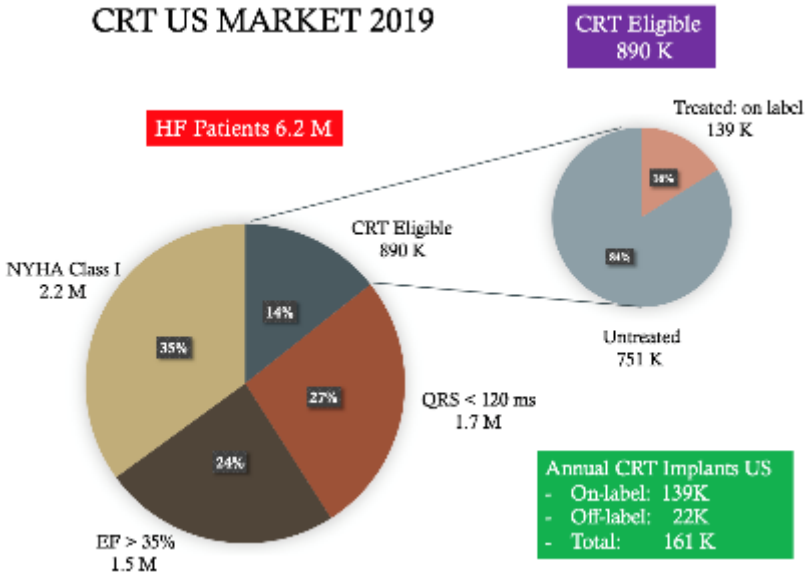
- Clinically available for ~ 20 years (with and without defibrillator)
- Indicated for patients with HF (EF < 35%) and conduction abnormalities (LBBB)
- Multicenter randomized trials > 10,000 patients with significant improvements in:
  - Symptoms and quality of life
  - Exercise capacity
  - Left ventricular size and function
  - Hospitalization rate
  - Mortality
- ~ 160K implants/year US (similar number OUS)
- > 2 million patients with CRT devices worldwide
- Annual sales revenue: ~ $3.2 billion

COMPANION CRT TRIAL



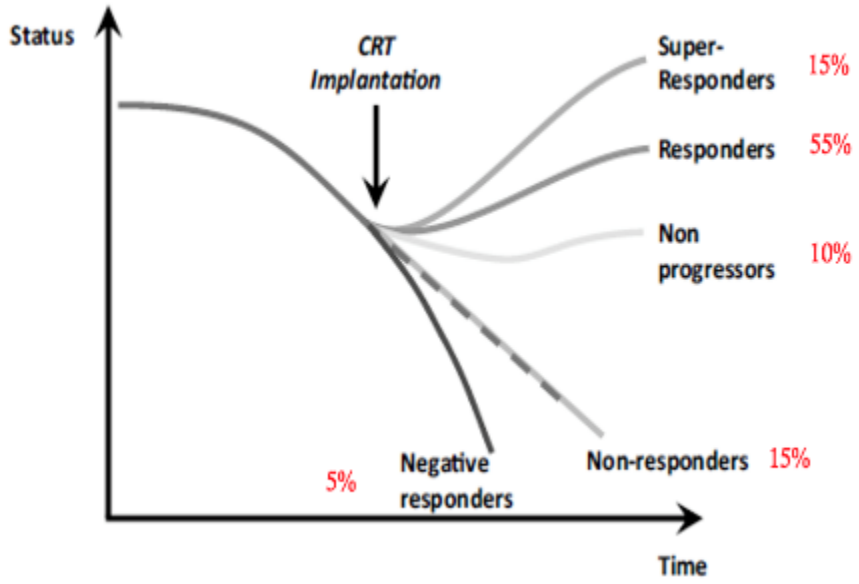
CRT: THE PROBLEMS

Underutilization (~16% penetrance)



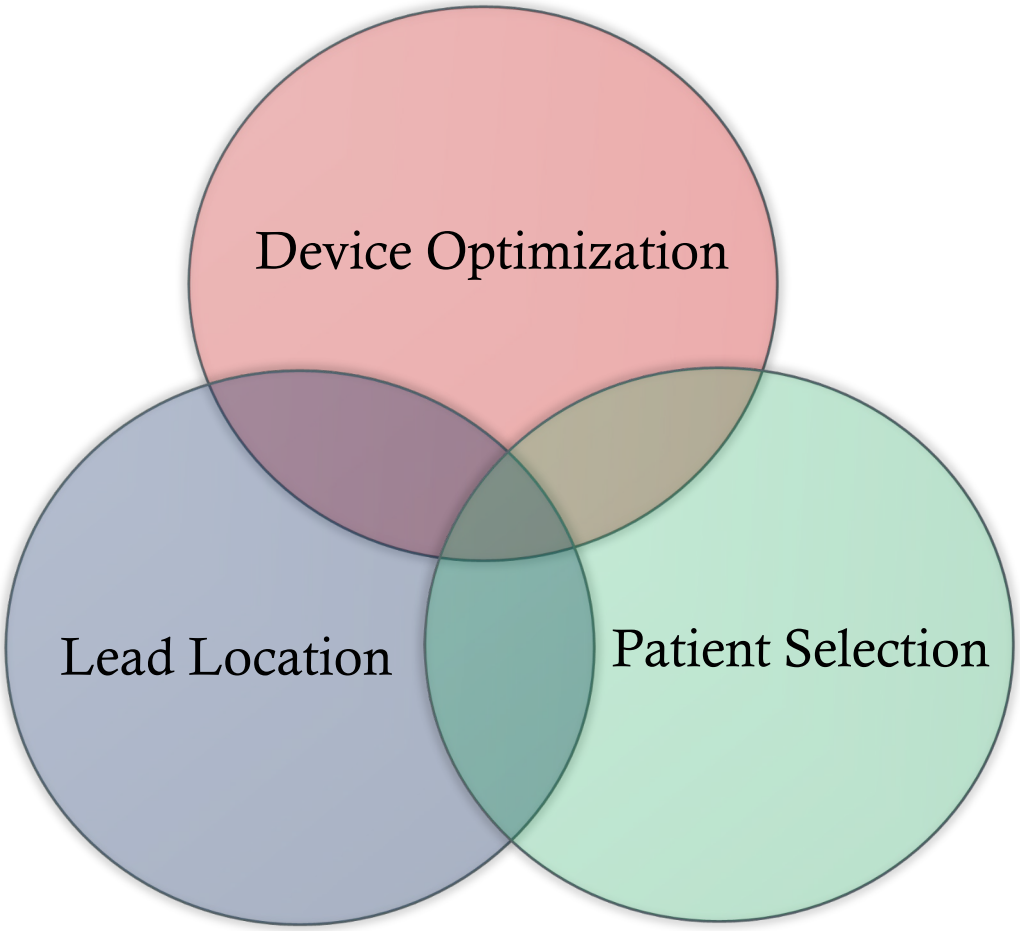
JP Morgan MedTech Research

Non-Response (~30%)



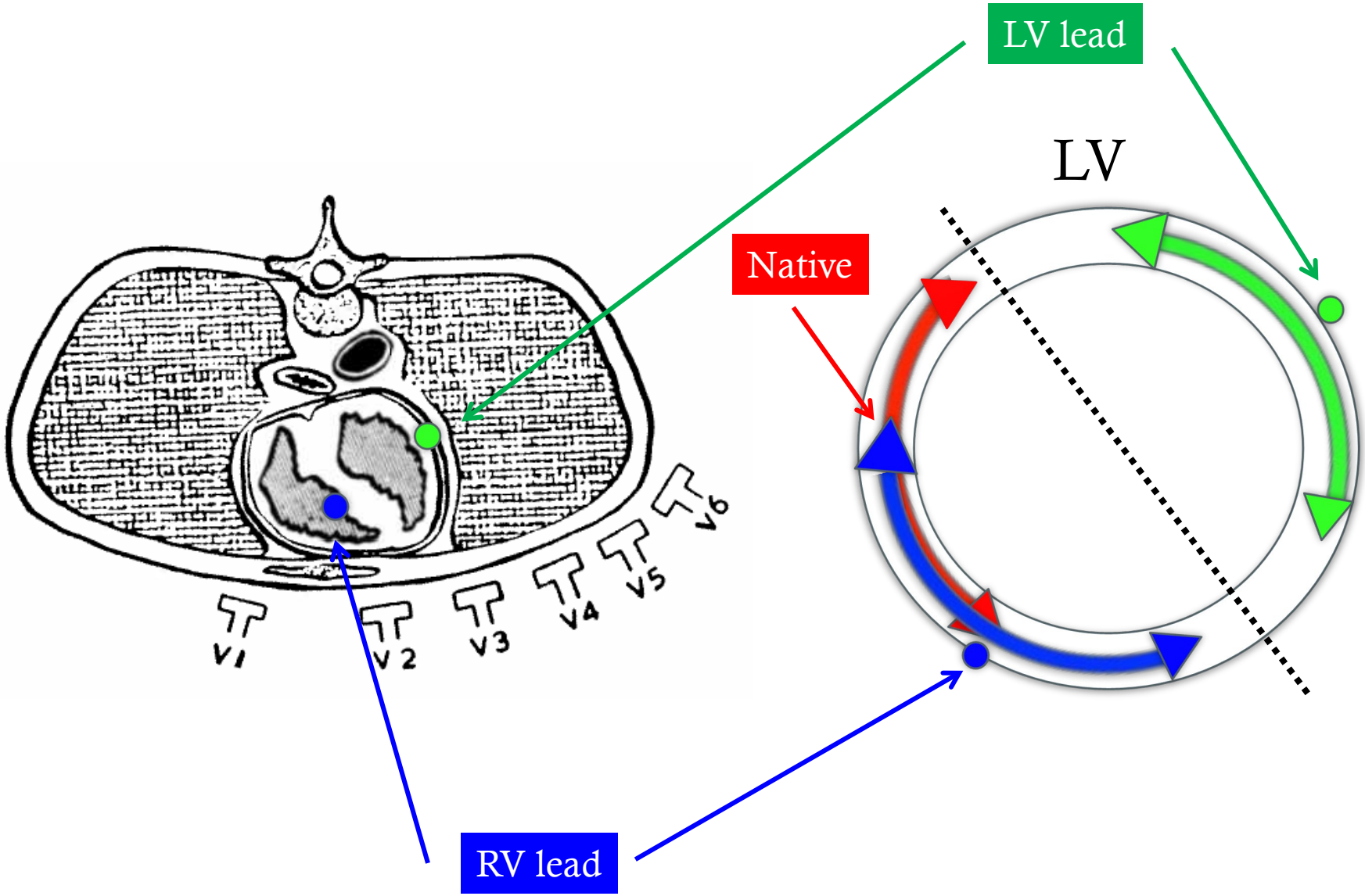
Steffel J, Ruschitzka F, Circ 2014;130:87-90

CRT: Clinical Issues to Address to Improve Underutilization and Non-Response

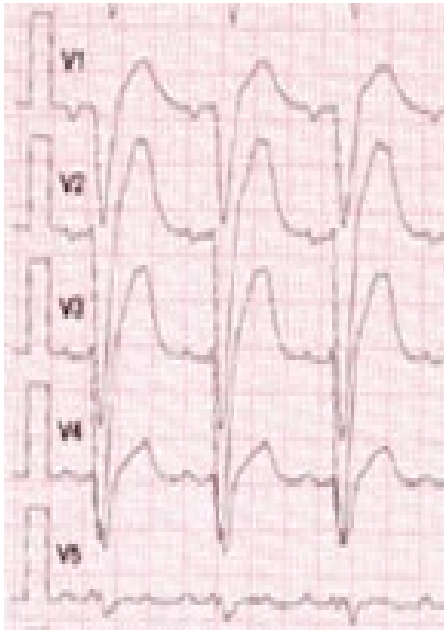


THE MECHANISM

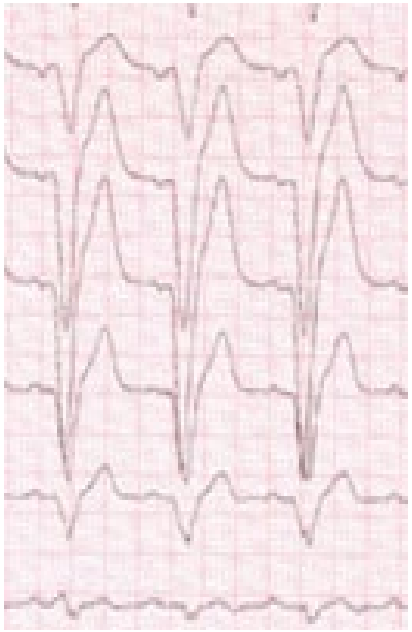
Wavefront Fusion in CRT



QRS Morphology and Electrical Wavefronts

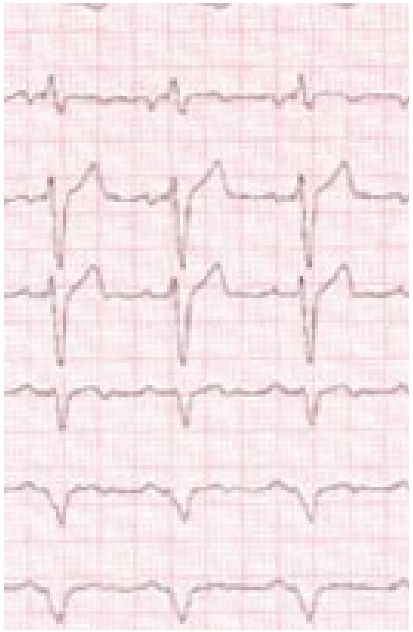


Native LBBB



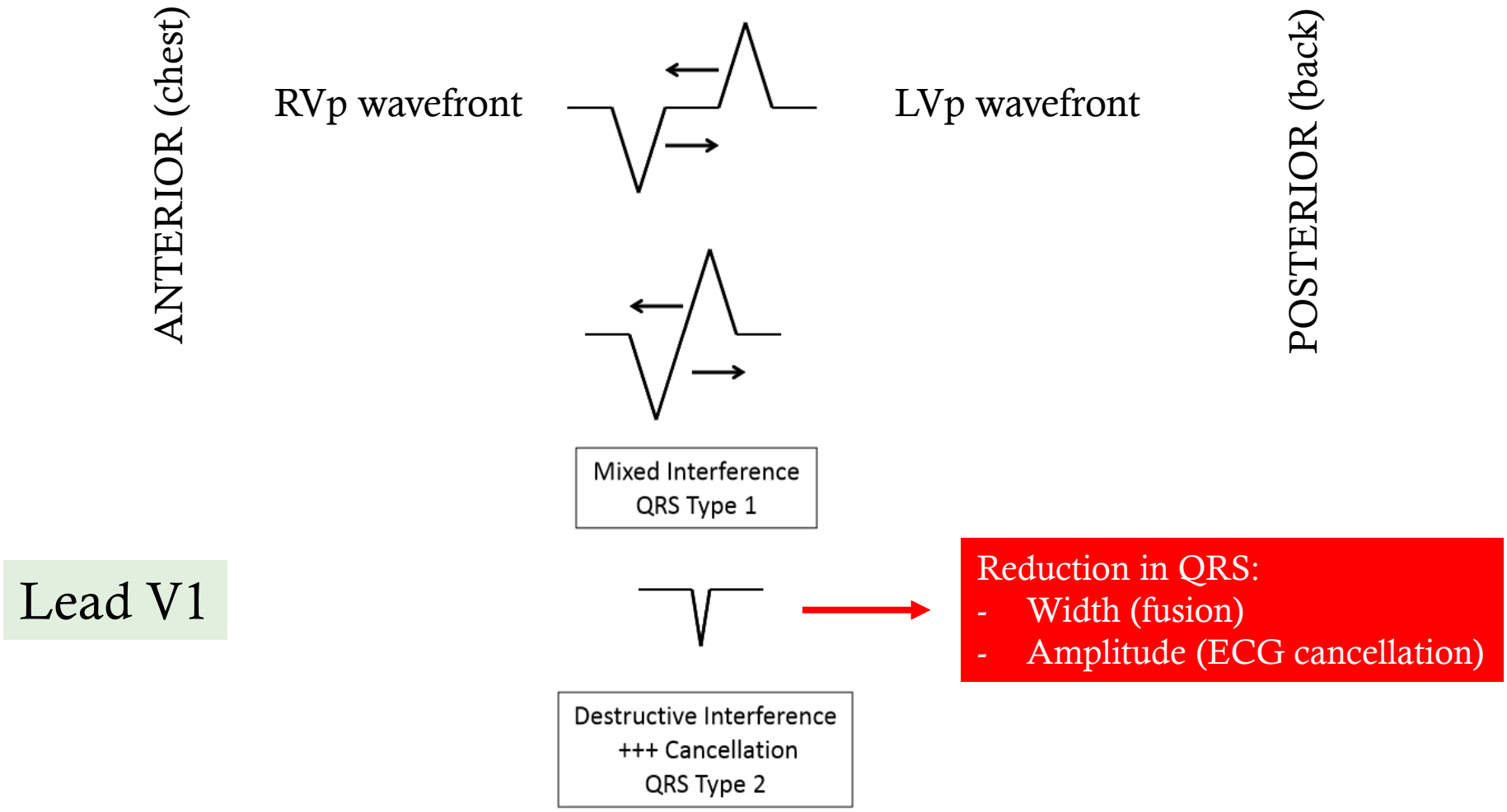
RV pacing

RBBB

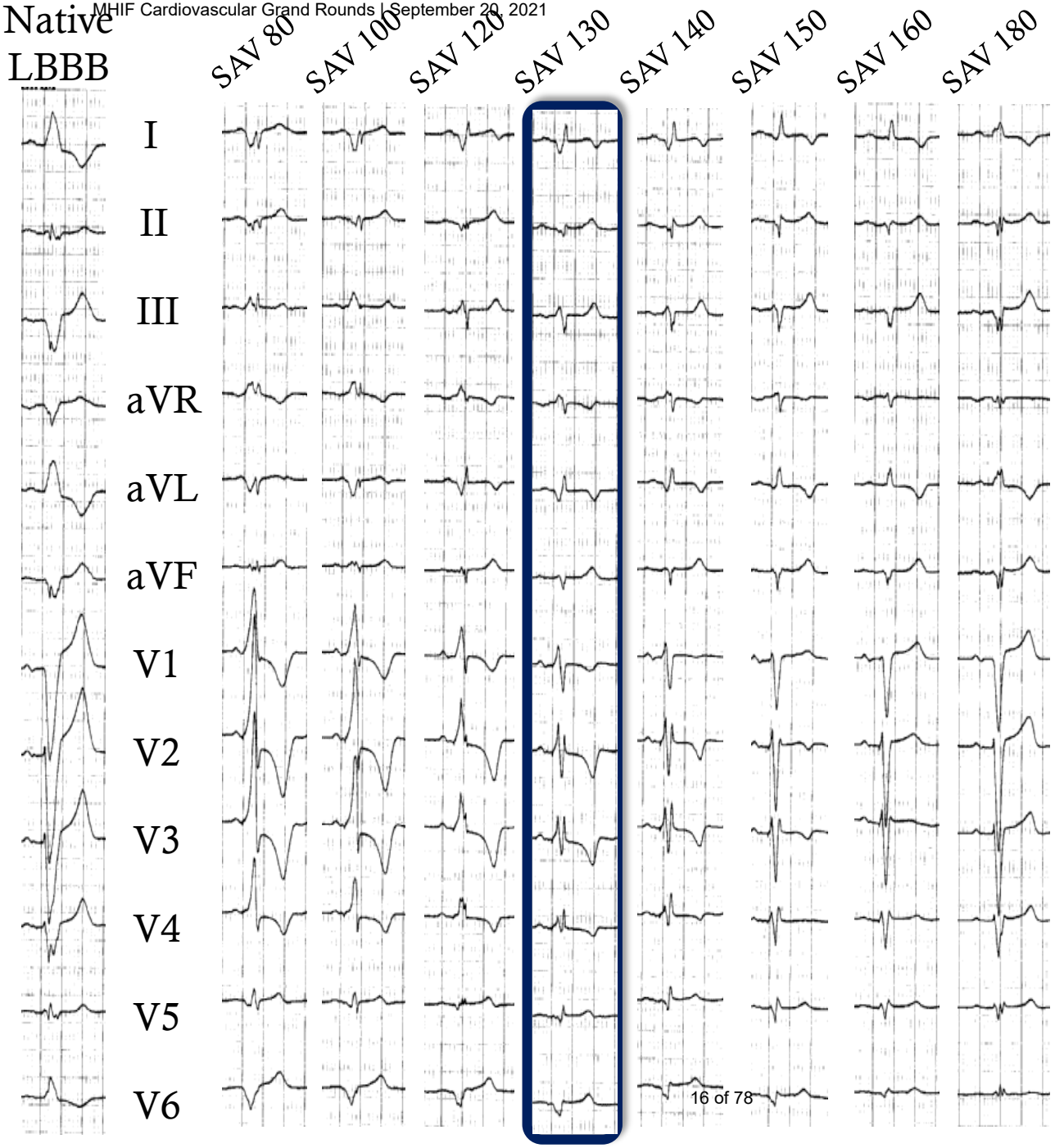


CRT

Wavefront Fusion and Electrocardiographic Cancellation



Adapted from: Sweeney MO, Hellkamp AS, Electrocardiographic Method of Wave Interference for Characterizing Ventricular Fusion During CRT



73 yr, Male
NICM, LBBB

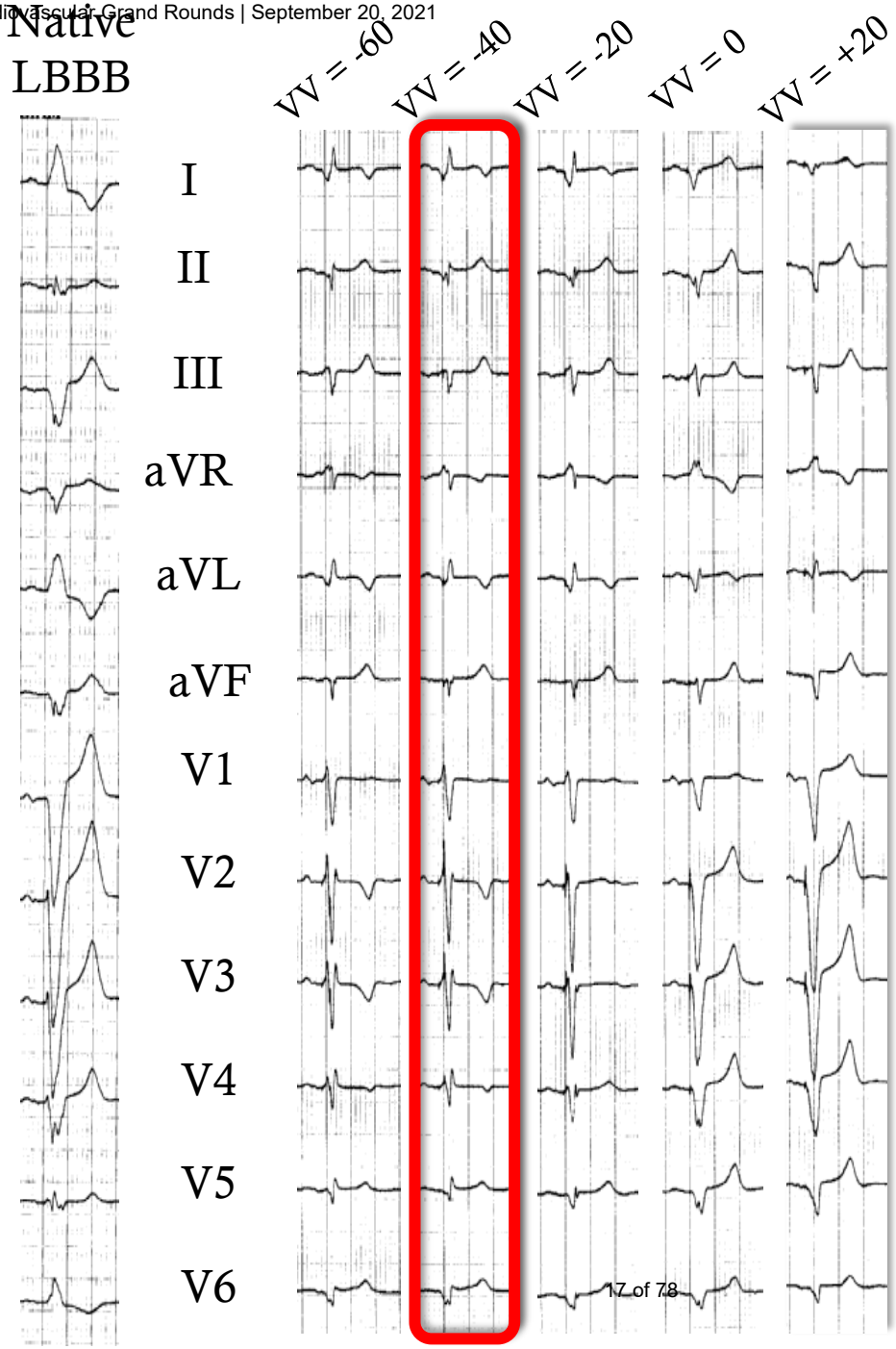
PR: 190 ms
QRSd: 170 ms

AsRVs – 190 ms
ApRVs – 230 ms

A-sensed LV-paced

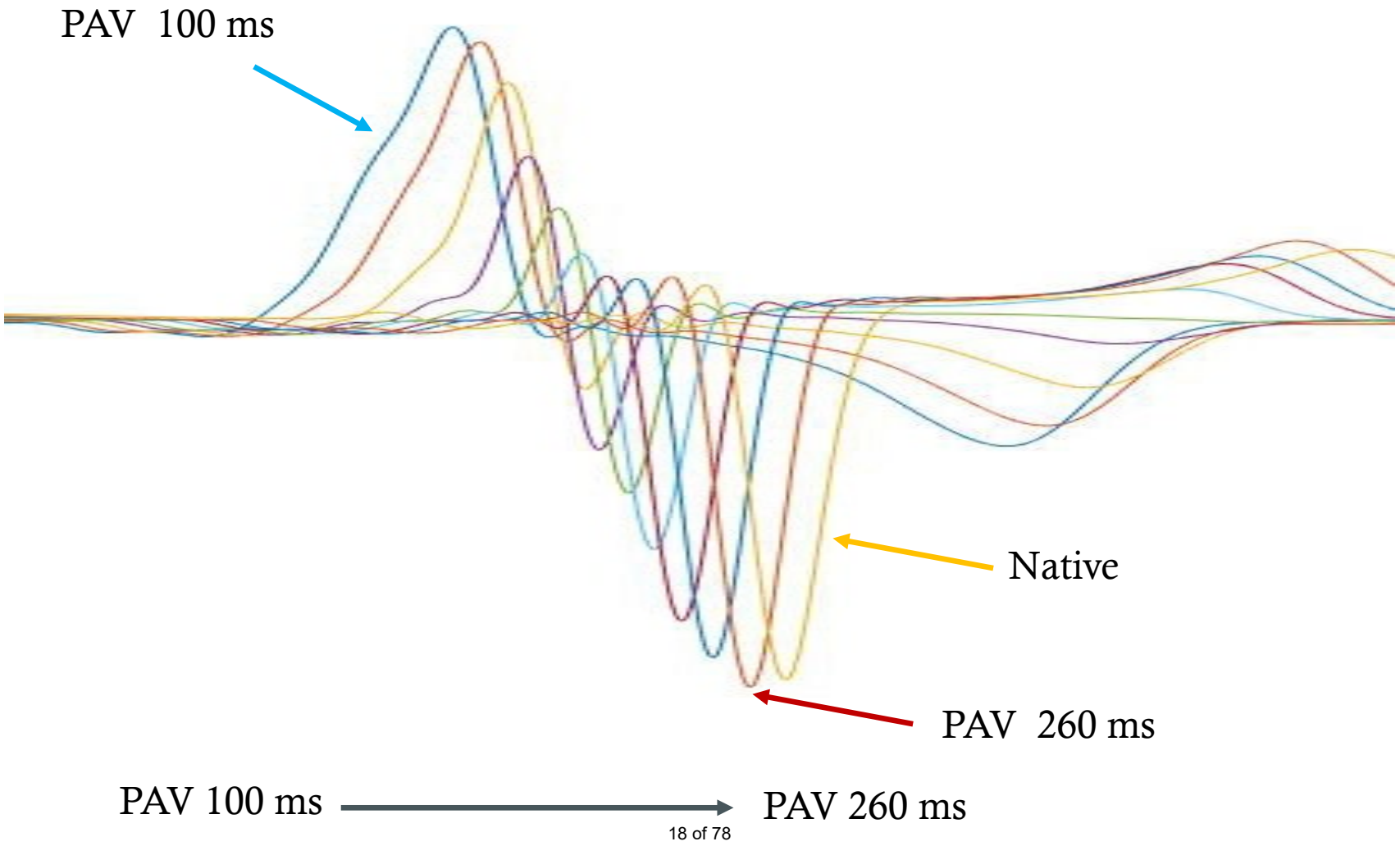
WHG

A-sensed BiV-paced (SAV 140)



WHG

Lead V1 during LV-only Pacing in Patient with Underlying LBBB

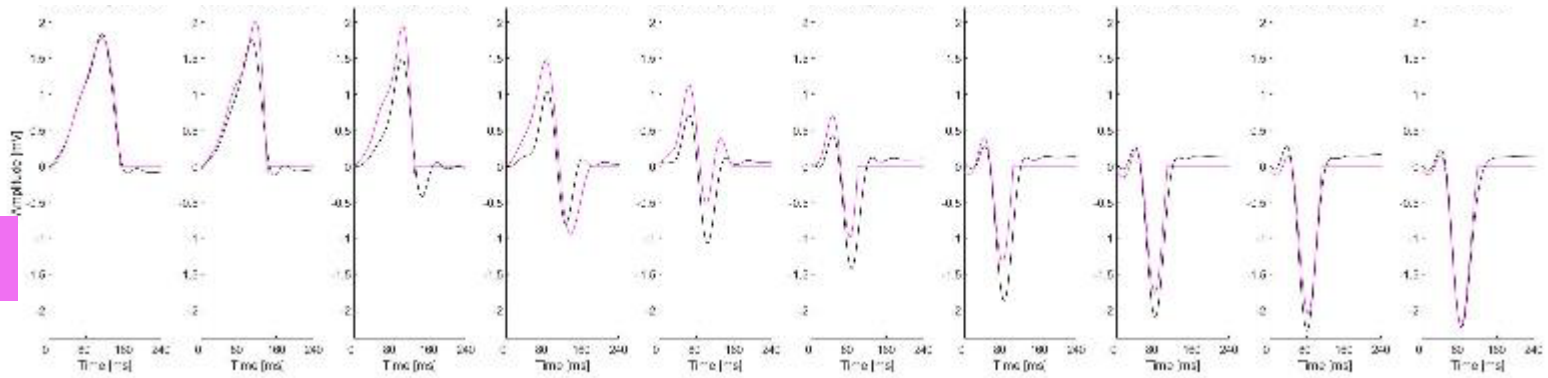


Fusion of Native and LVp (at short AVD) Wavefronts (Lead V1)

PAVD 100 120 140 160 180 * 200 220 240 260 Native

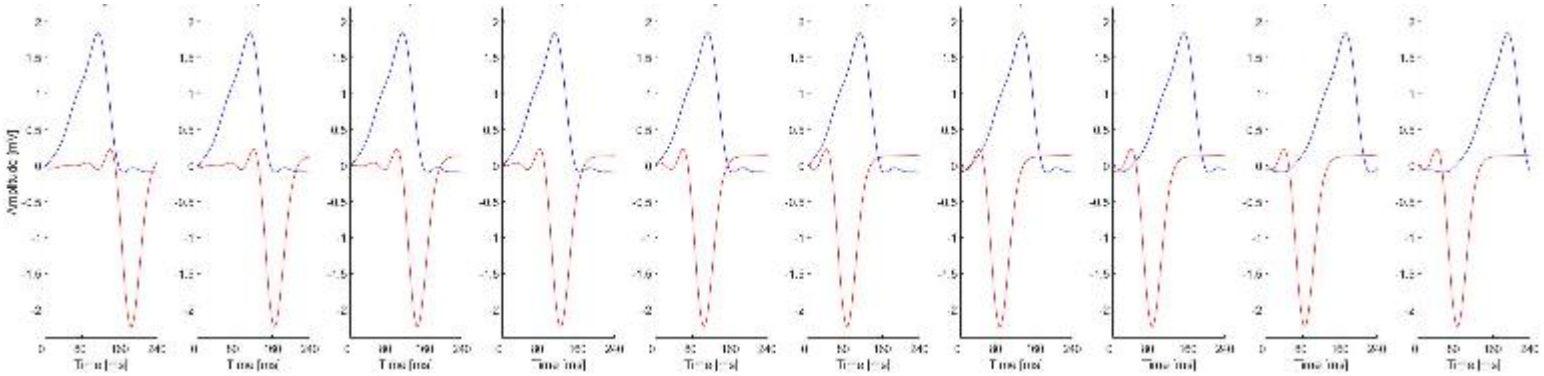
Measured Electrogram

Reconstructed Electrogram



LVp wavefront

Native wavefront



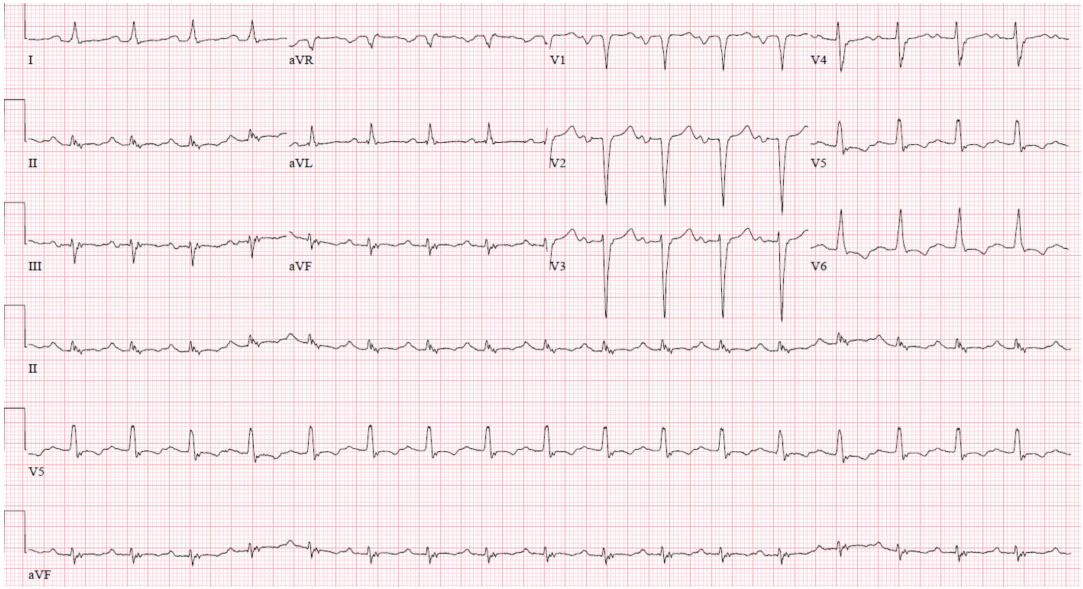
* Optimal PAVD = 190 ms (CRI > 90%)

THE MEASUREMENT
(of electrical dyssynchrony)

Electrical Dyssynchrony: QRS_d

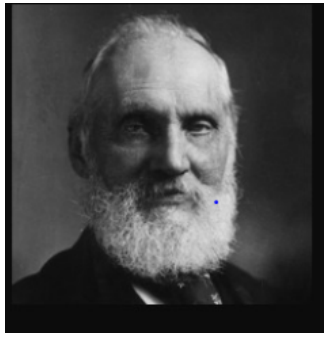
QRS_d has been the only measure of electrical dyssynchrony clinically available and used in the selection and management of CRT patients.

QRS_d serves as a surrogate for LV total activation time.



Measurement of QRS_d

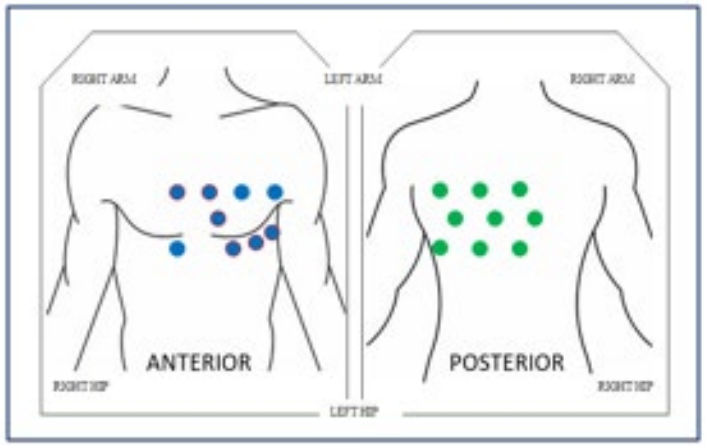
- Single lead? If so, which lead?
- Single beat or average multiple beats?
- Average all leads or longest QRS_d (global)?
- What defines start and end of QRS?
- Calipers or automated?
- Paper speed?
- Reproducibility: interobserver, intraobserver?



"To measure is to know; If you cannot measure it, you cannot improve it."

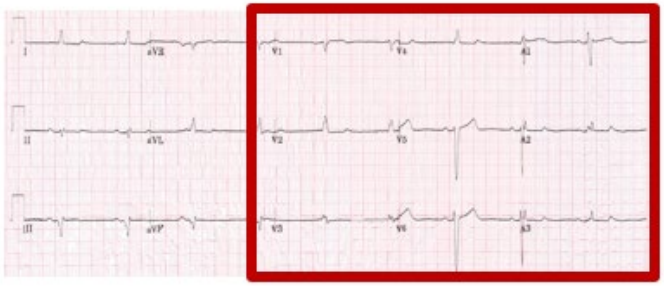
Lord Kelvin
1824-1907

Multi-lead ECG to Measure Dyssynchrony

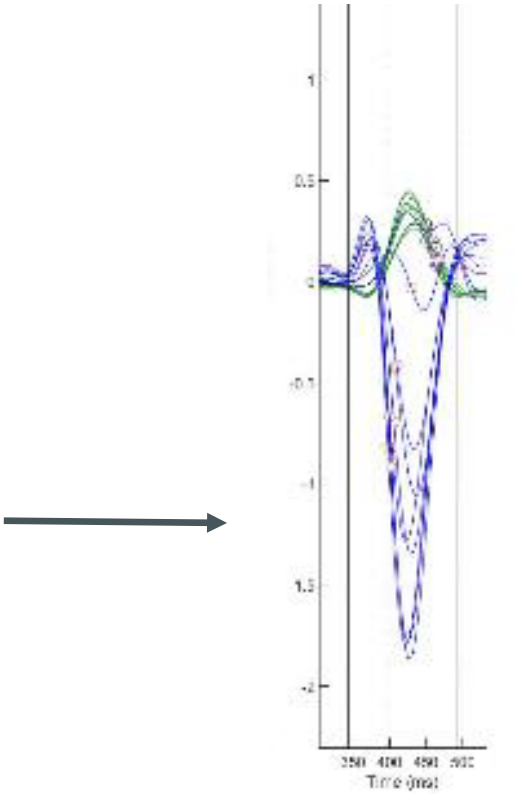


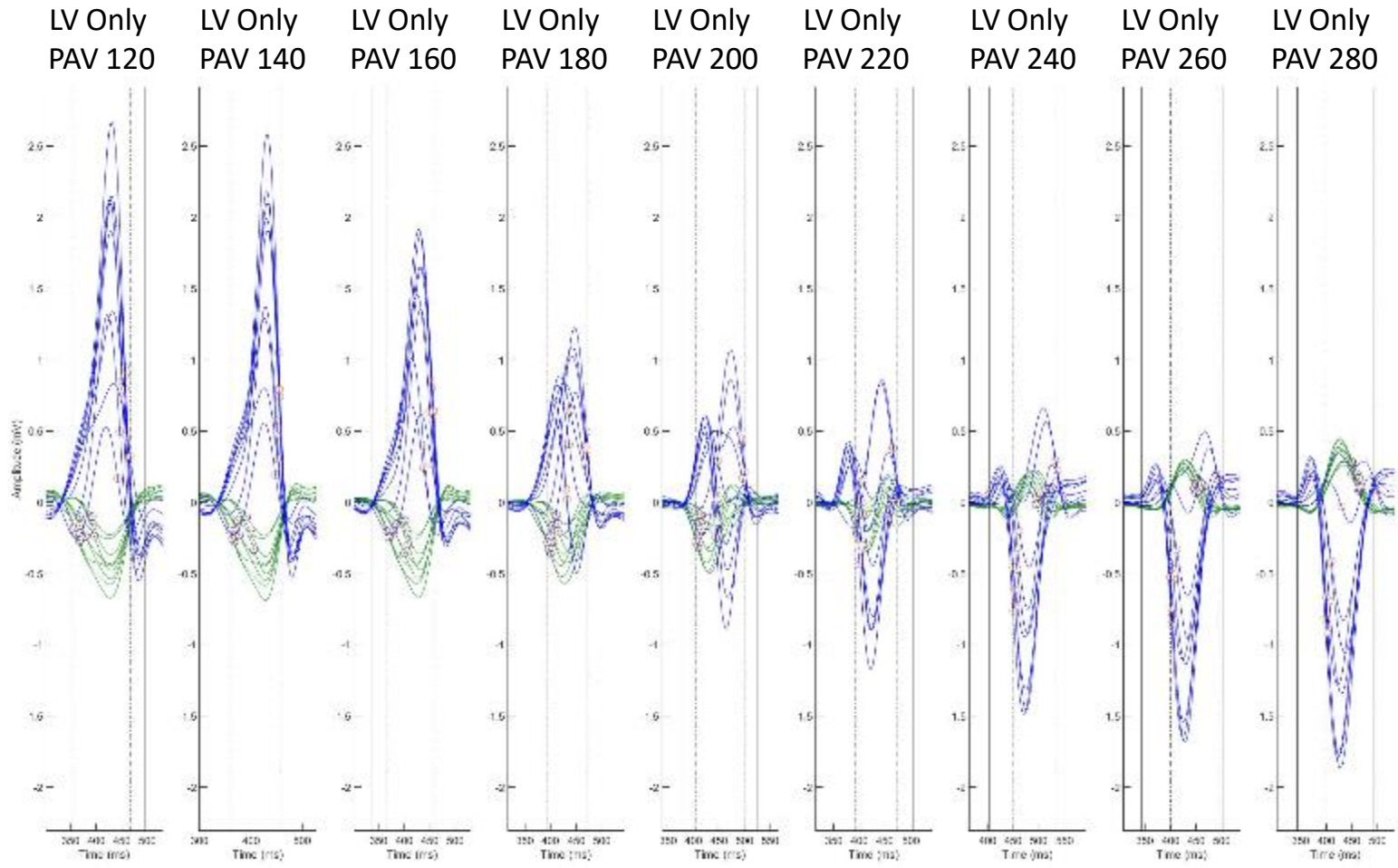
ANTERIOR

POSTERIOR



18 Unipolar Electrodes

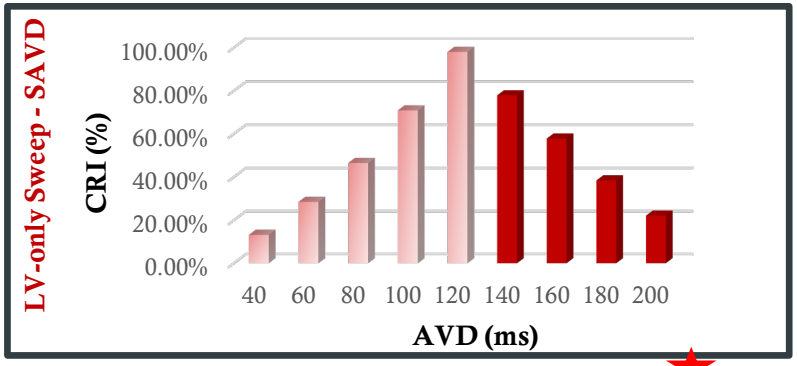


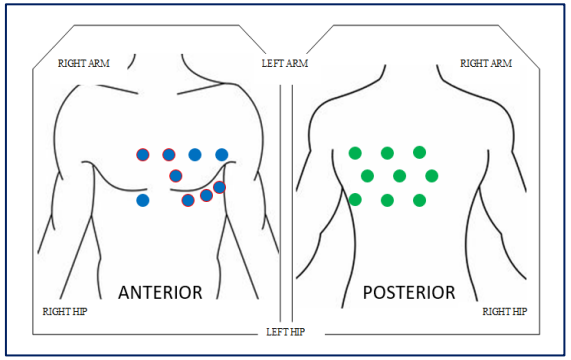


CRI (%)	-16	1	16	45	68	94	75	58	40

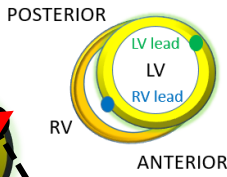
MRV

Cardiac Resynchronization Index

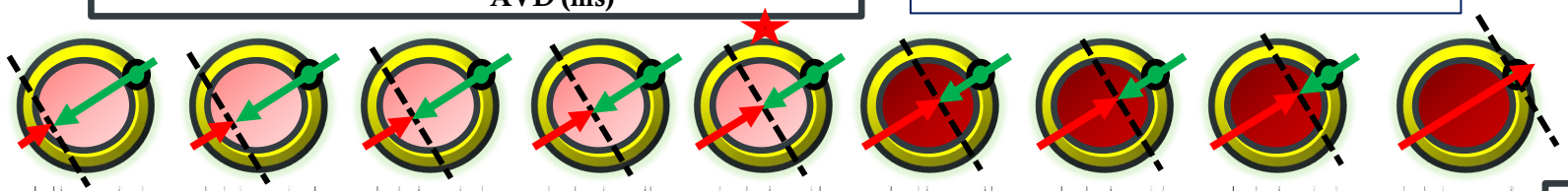




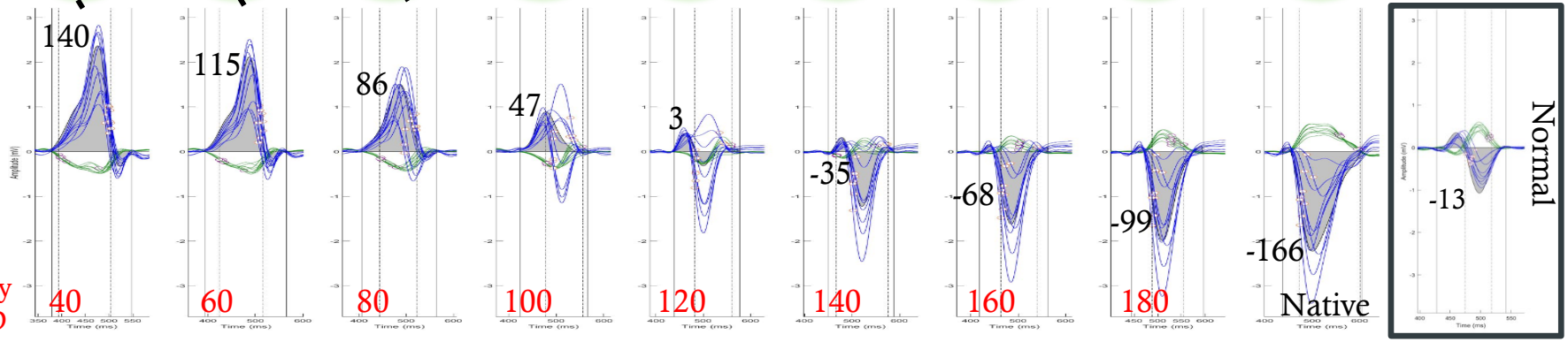
Multi-lead ECG Electrode Array



Wavefront Fusion



AUC (shaded)



LV-only SAVD

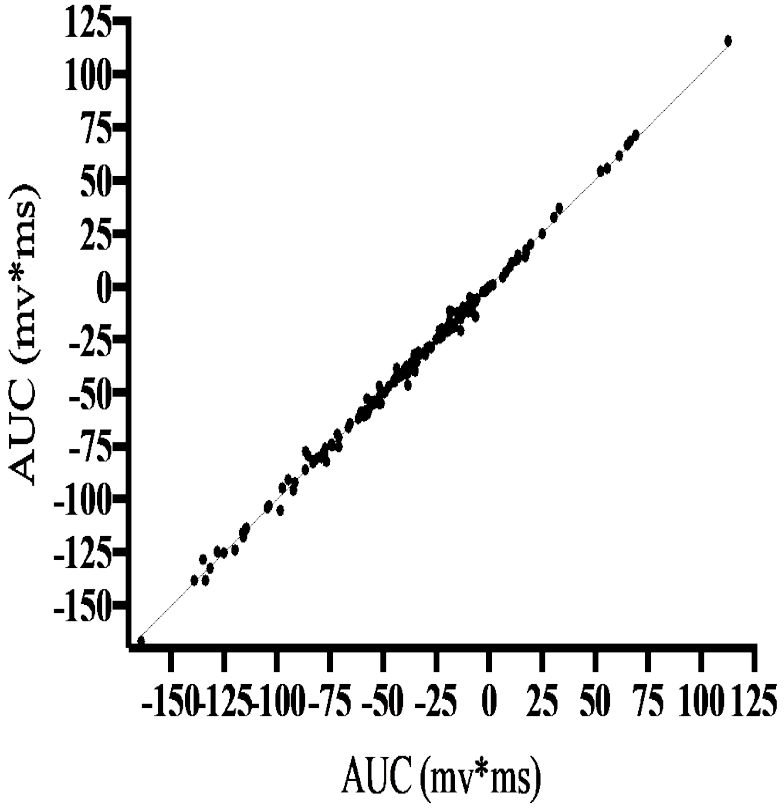
40 60 80 100 120 140 160 180 Native

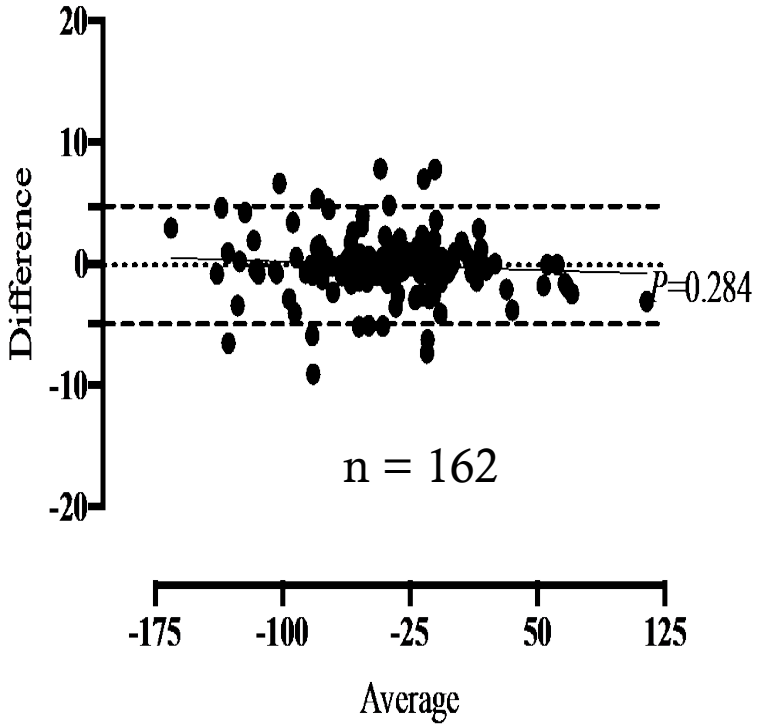
CRI: % change in AUC at any given setting compared to native

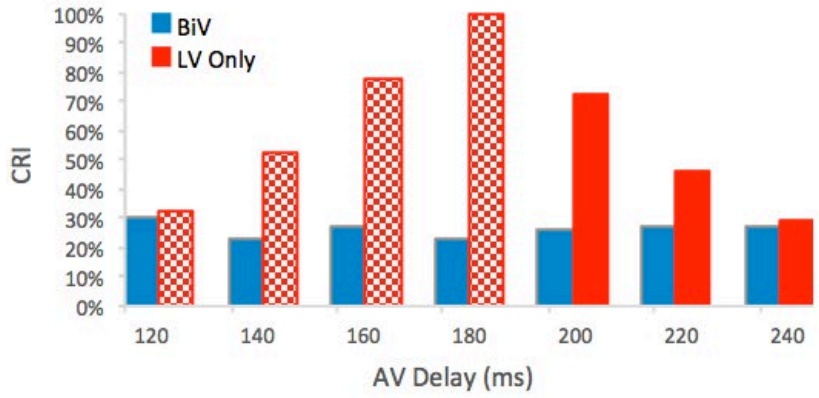
$$CRI = \left| \frac{AUC_{native} - AUC_{x}}{AUC_{native}} \right| \times 100$$

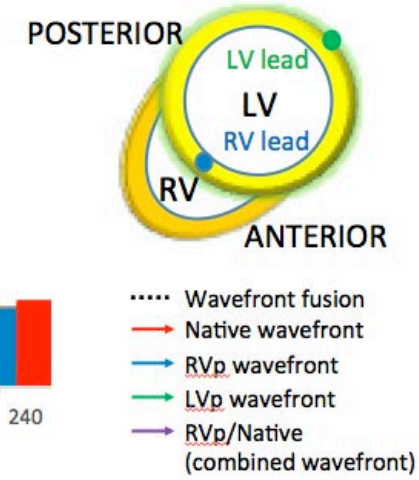
CJC-056R

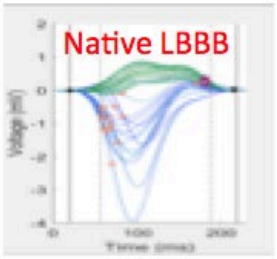
Short-term Reproducibility of AUC Measurement

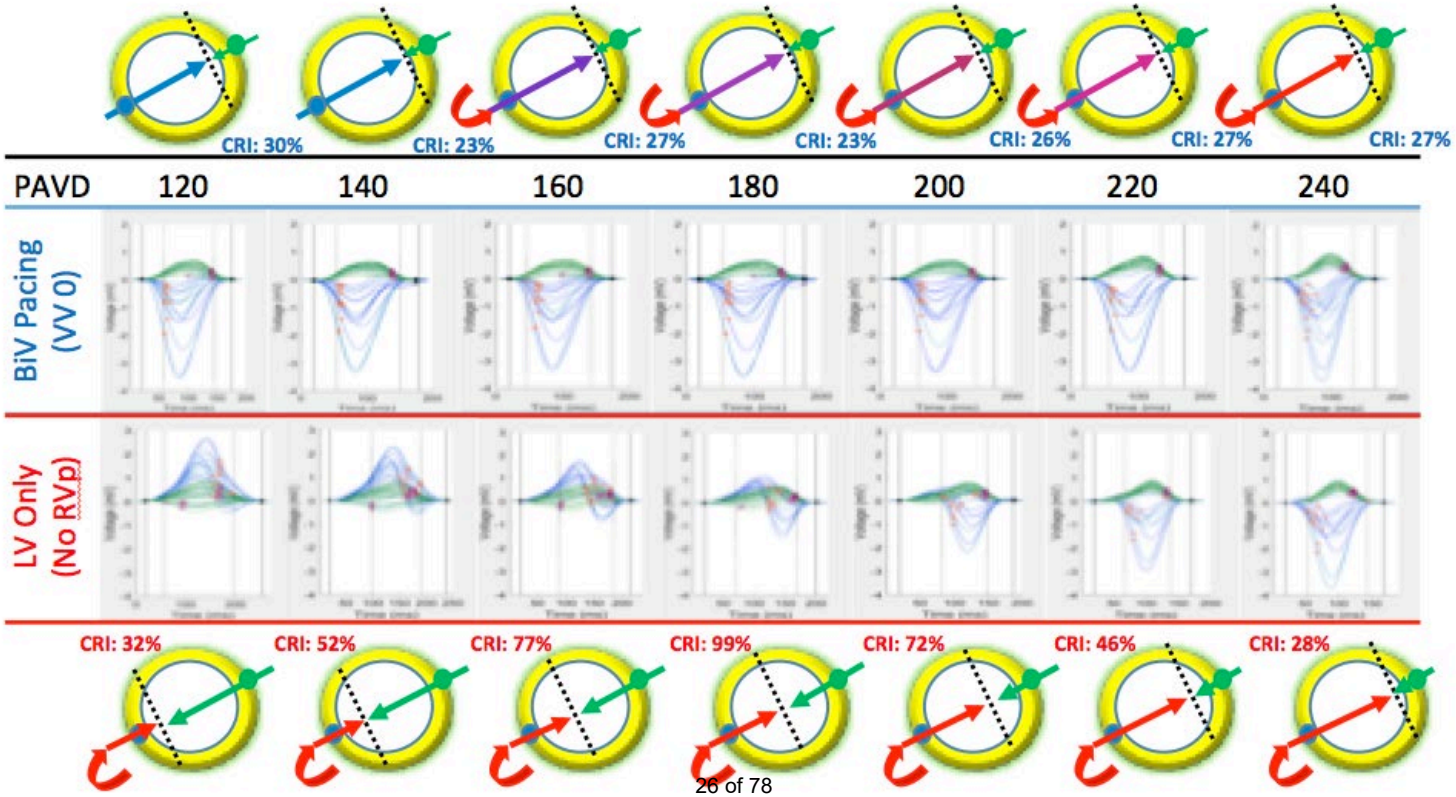












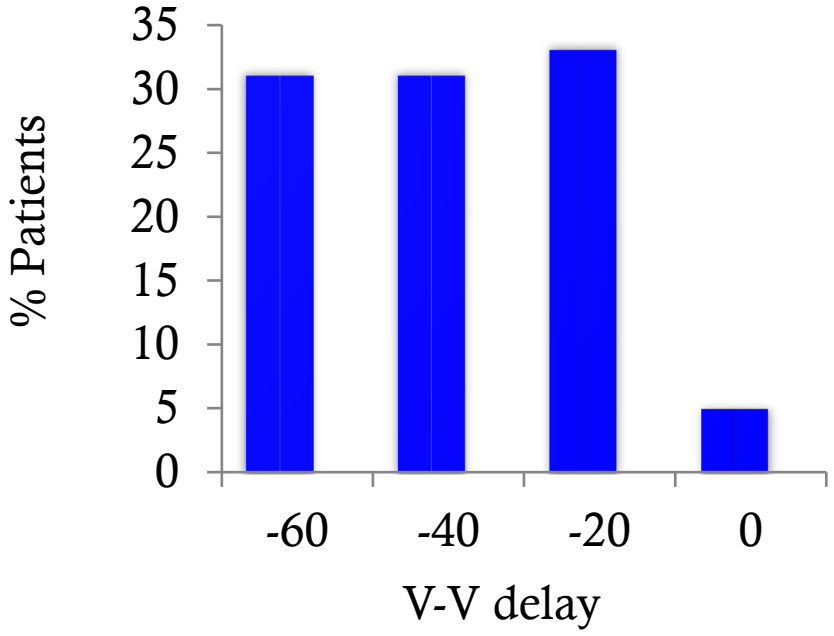
Bank AJ, et al, J Electrocardiology 2020

Fusion of Intrinsic, LVp and RVp Wavefronts:

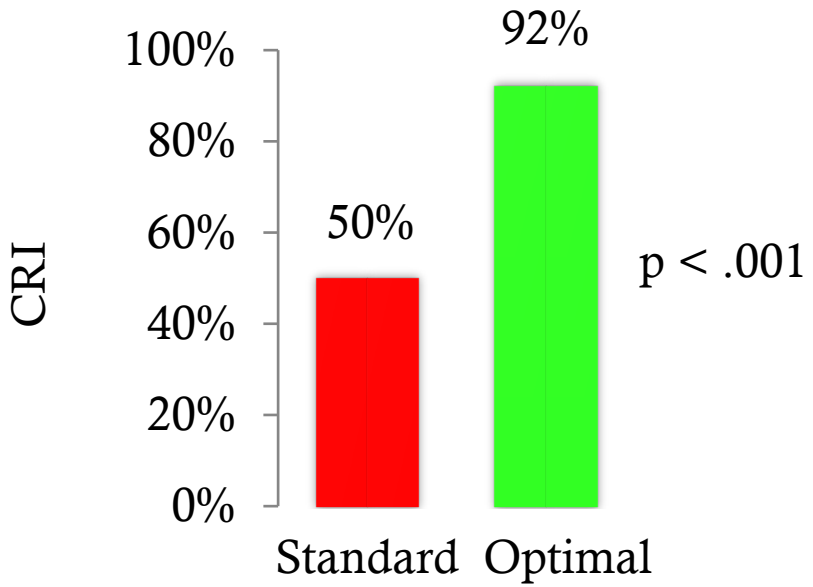
BiV Pacing in Patients with NSR and Intact AV Conduction

- Sequential BiV pacing
  - best CRI 83.9 +/- 13% at LV = - 40.2 +/- 20 ms

LV Preactivation Needed To Achieve Best CRI



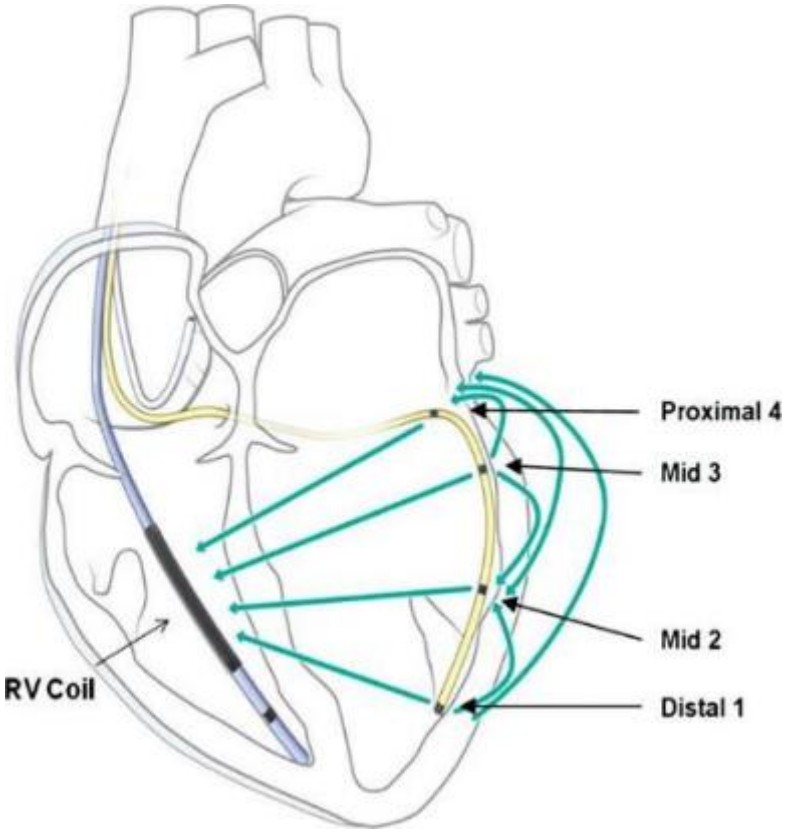
Effects of CRT Optimization



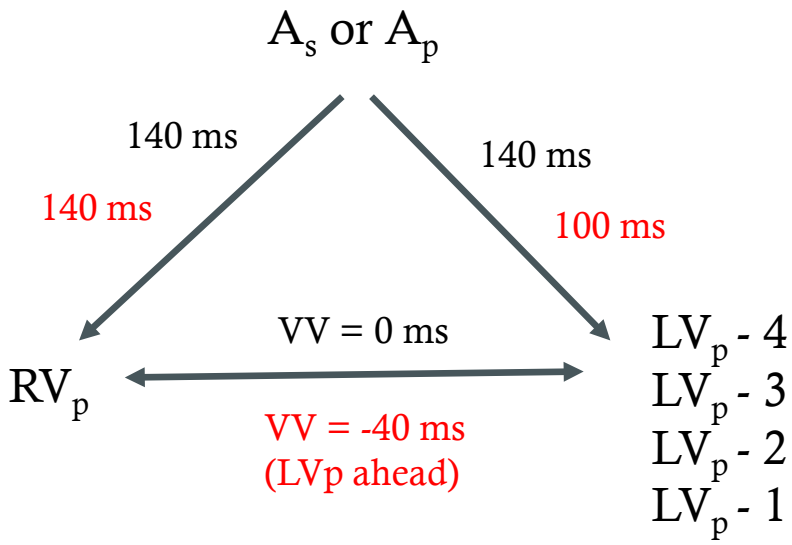
Bank AJ, et al, J Electrocardiology 2020

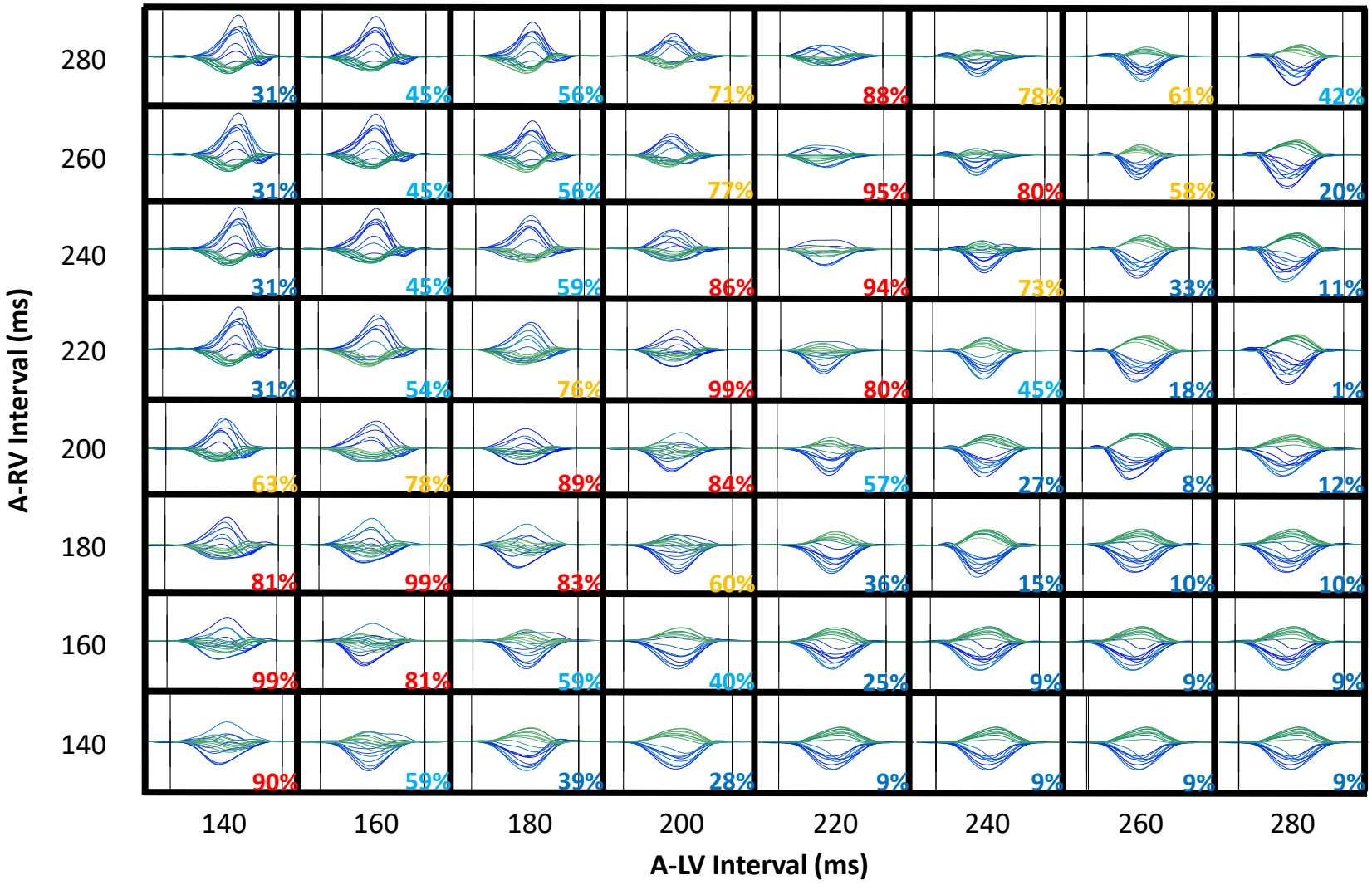
THE GRAPHICS
Electrical Dyssynchrony Mapping (EDM)

CRT Programming (1000's of options)

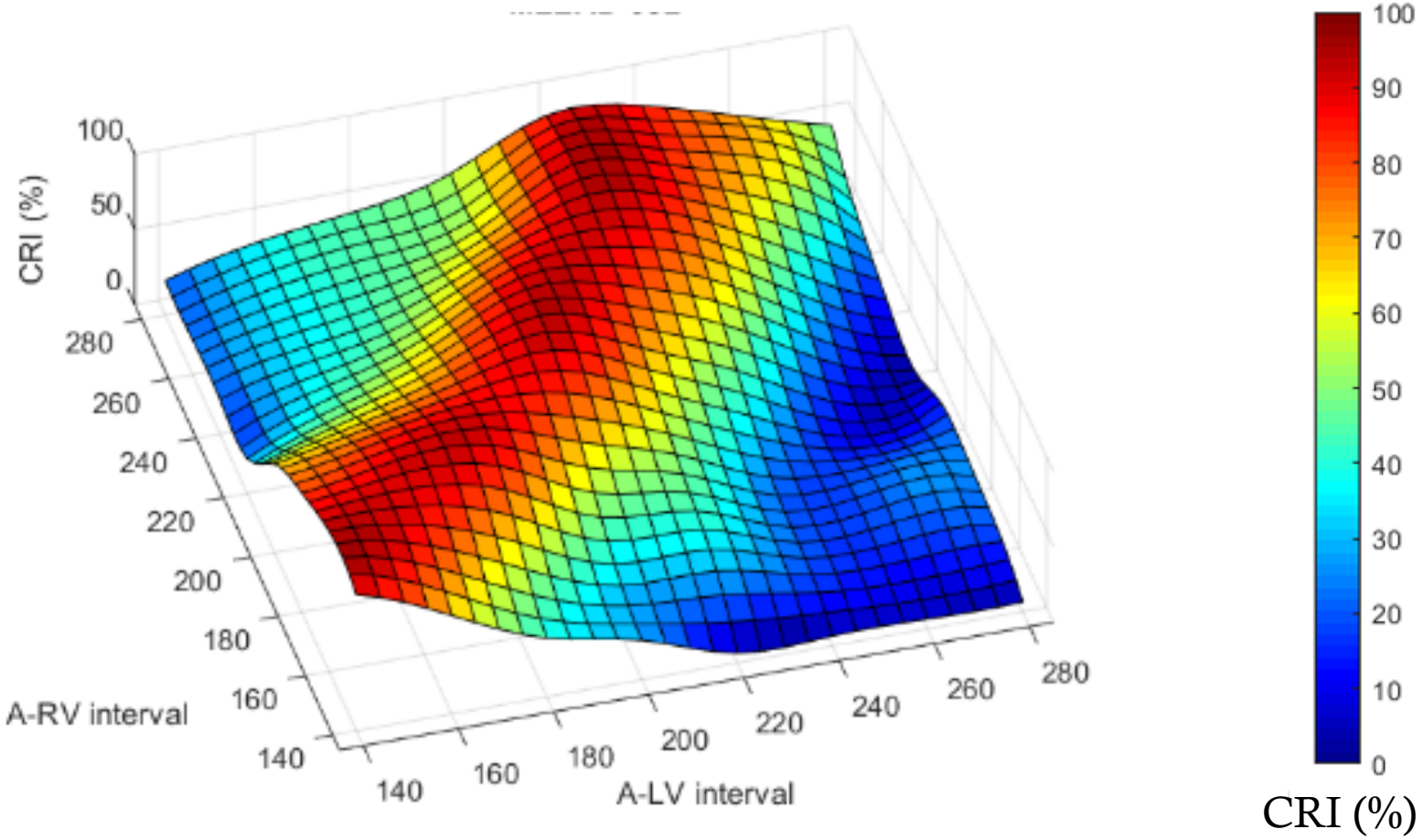


- Atrial-Ventricular Delay (AVD)
- Ventricular-Ventricular Delay (VVD)
- Atrial sensing vs Atrial pacing
- Biventricular vs. LV-only
- Quadripolar Electrode



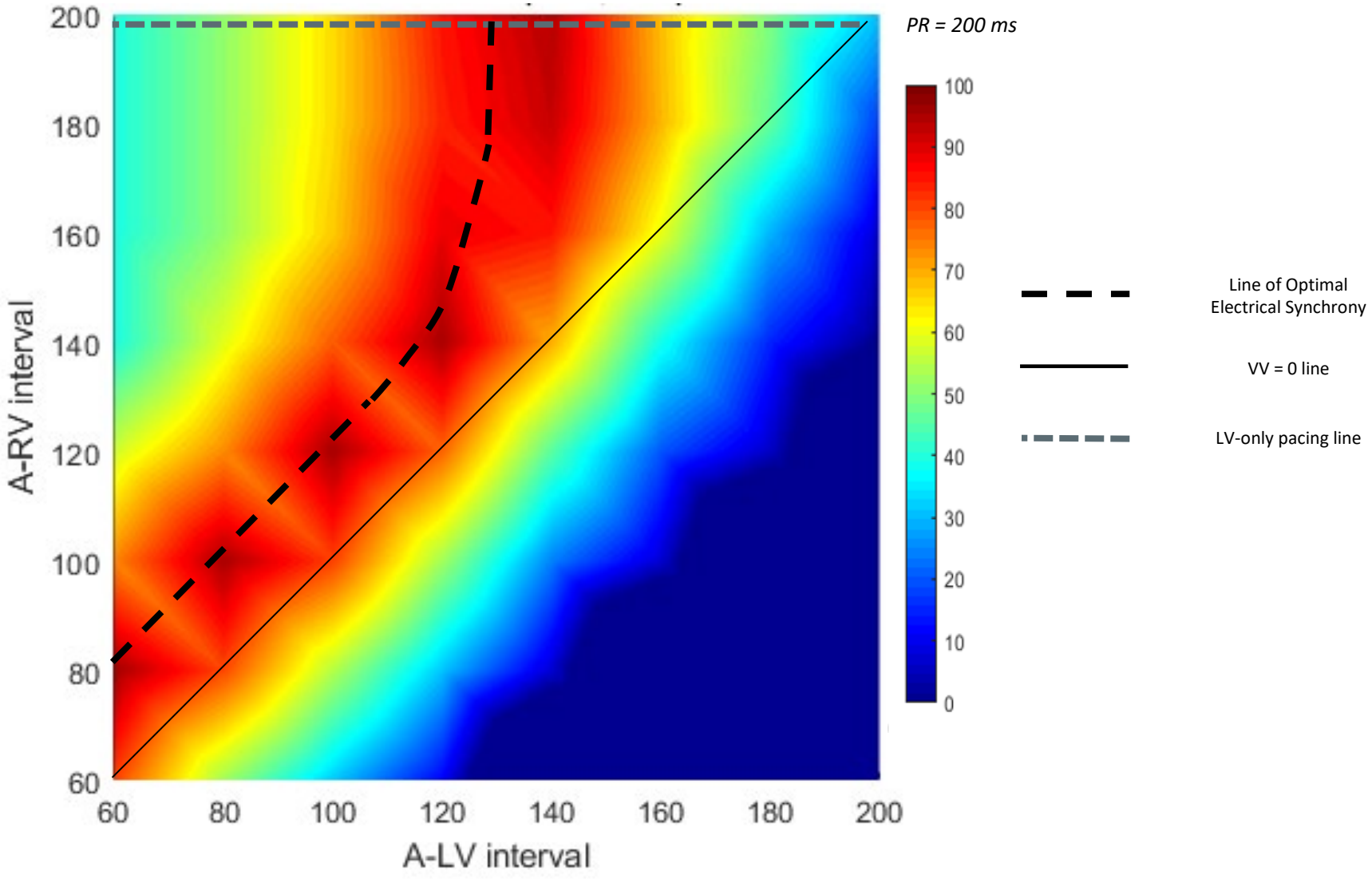

A-RV Interval (ms)
280
260
240
220
200
180
160
140
31% 45% 56% 71% 88% 78% 61% 42%
31% 45% 56% 77% 95% 80% 58% 20%
31% 45% 59% 86% 94% 73% 33% 11%
31% 54% 76% 99% 80% 45% 18% 1%
63% 78% 89% 84% 57% 27% 8% 12%
81% 99% 83% 60% 36% 15% 10% 10%
99% 81% 59% 40% 25% 9% 9% 9%
90% 59% 39% 28% 9% 9% 9% 9%
140 160 180 200 220 240 260 280
A-LV Interval (ms)

3D Graph of CRI in Patient with LBBB and CRT



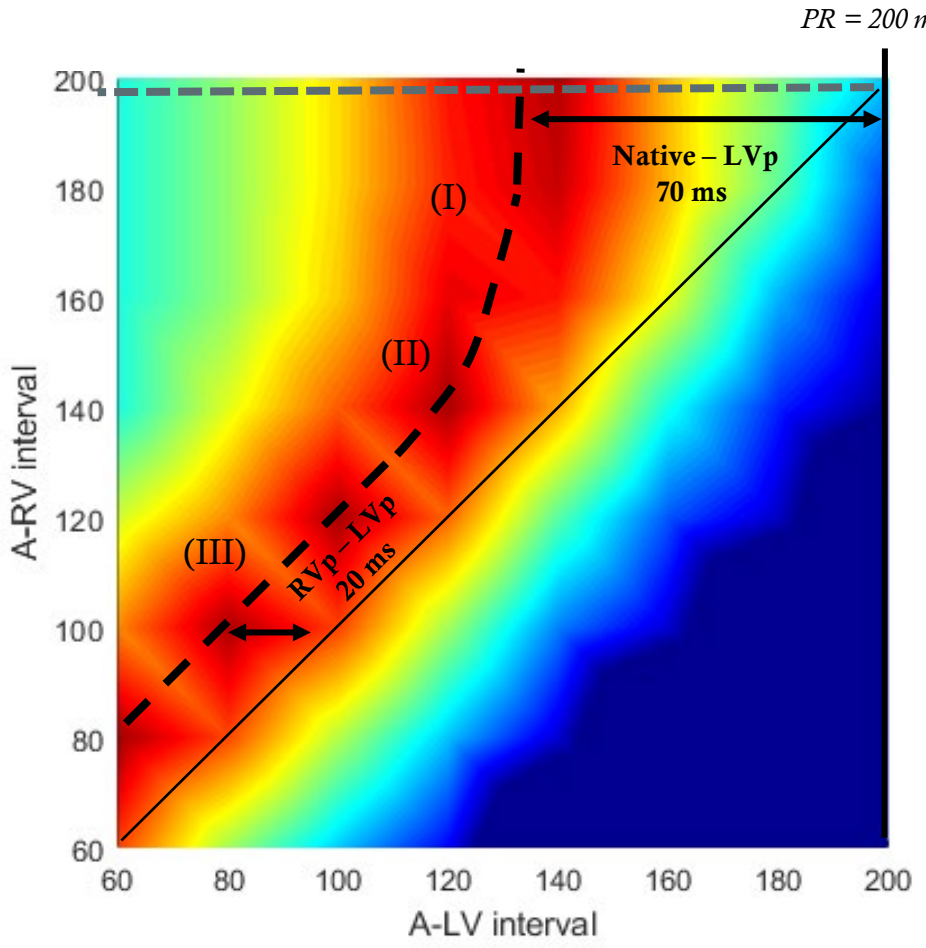
Optimal electrical synchrony occurs in a curvilinear line running through the middle of the red area (peak CRI)

Electrical Dyssynchrony Map (EDM) in 62 y/o M with LBBB, QRSd 178 ms



HEO

Electrical Dyssynchrony Map (EDM) in 62 y/o M with LBBB, QRSd 178 ms



(I) **Native + LVp Wavefront Fusion**

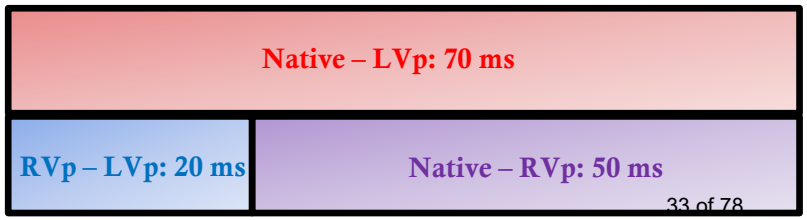
(II) **Native + RVp + LVp Triple Wavefront Fusion**

(III) **RVp + LVp Wavefront Fusion**

Line of Optimal Electrical Synchrony

VV = 0 line

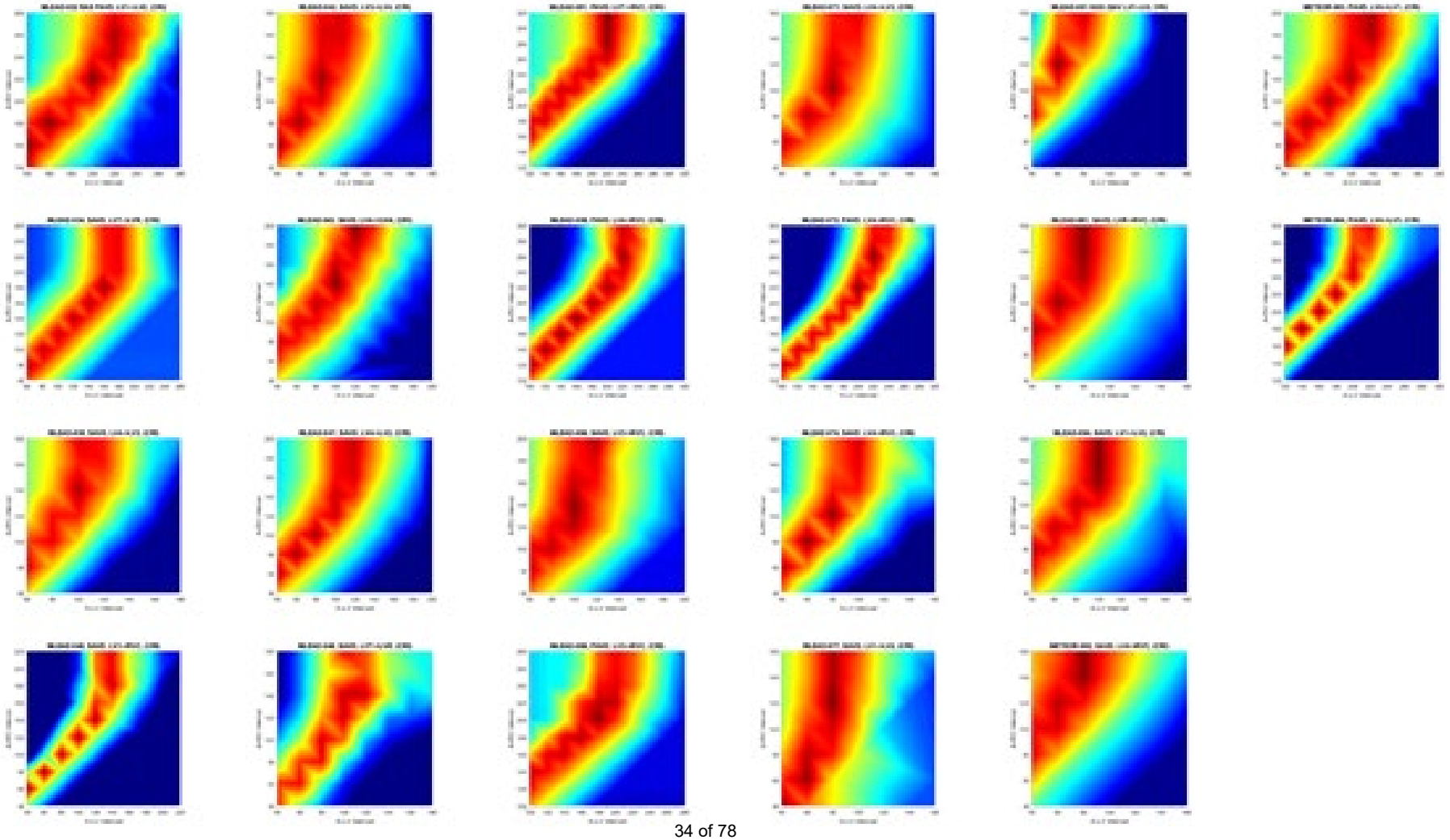
LV-only pacing line



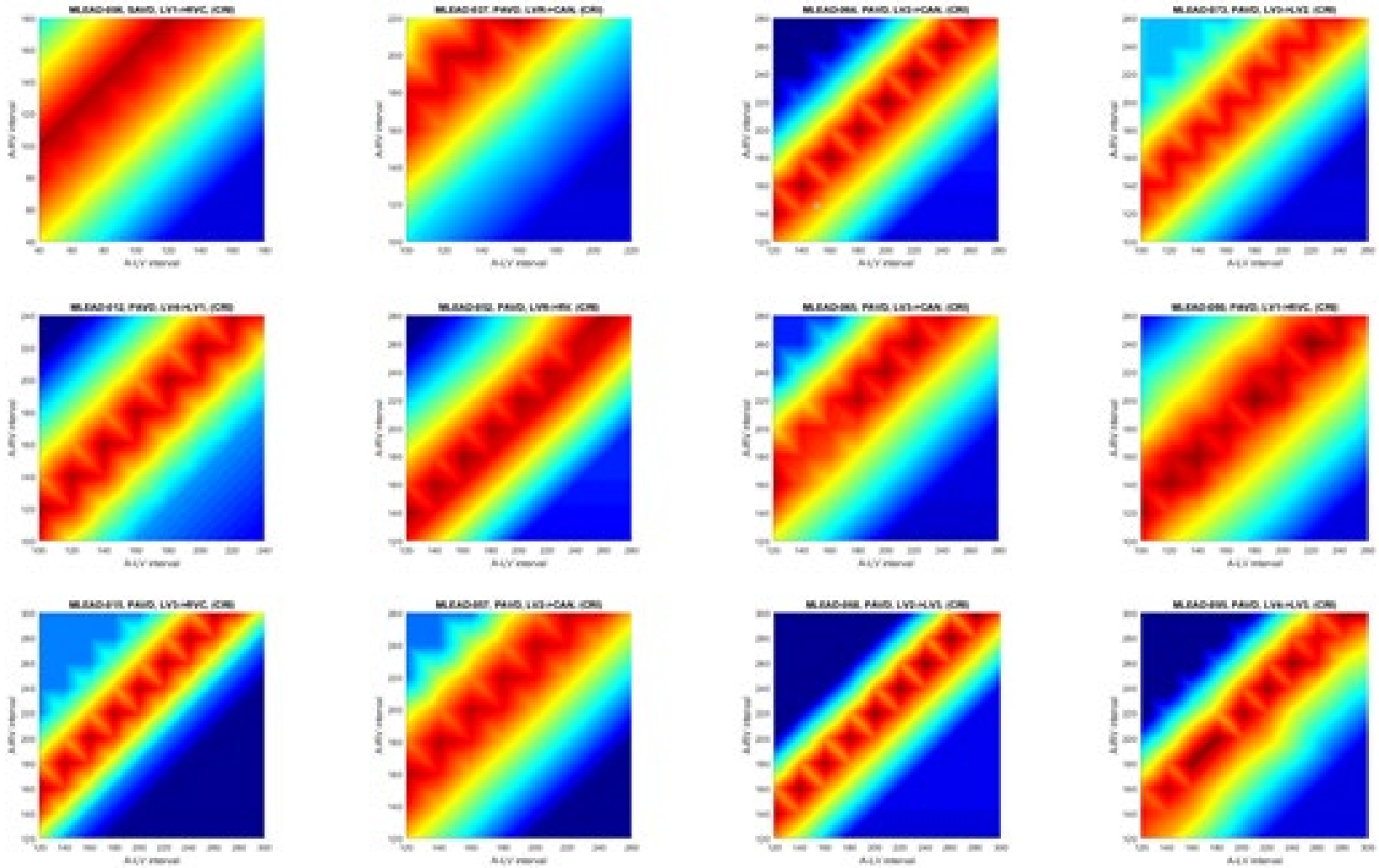
LBBB Patients with Intact AVN Conduction:

1. Short AVD: RVp and LVp wavefronts
2. Intermediate AVD: all 3 wavefronts
3. Long AVD: LVp and native wavefronts

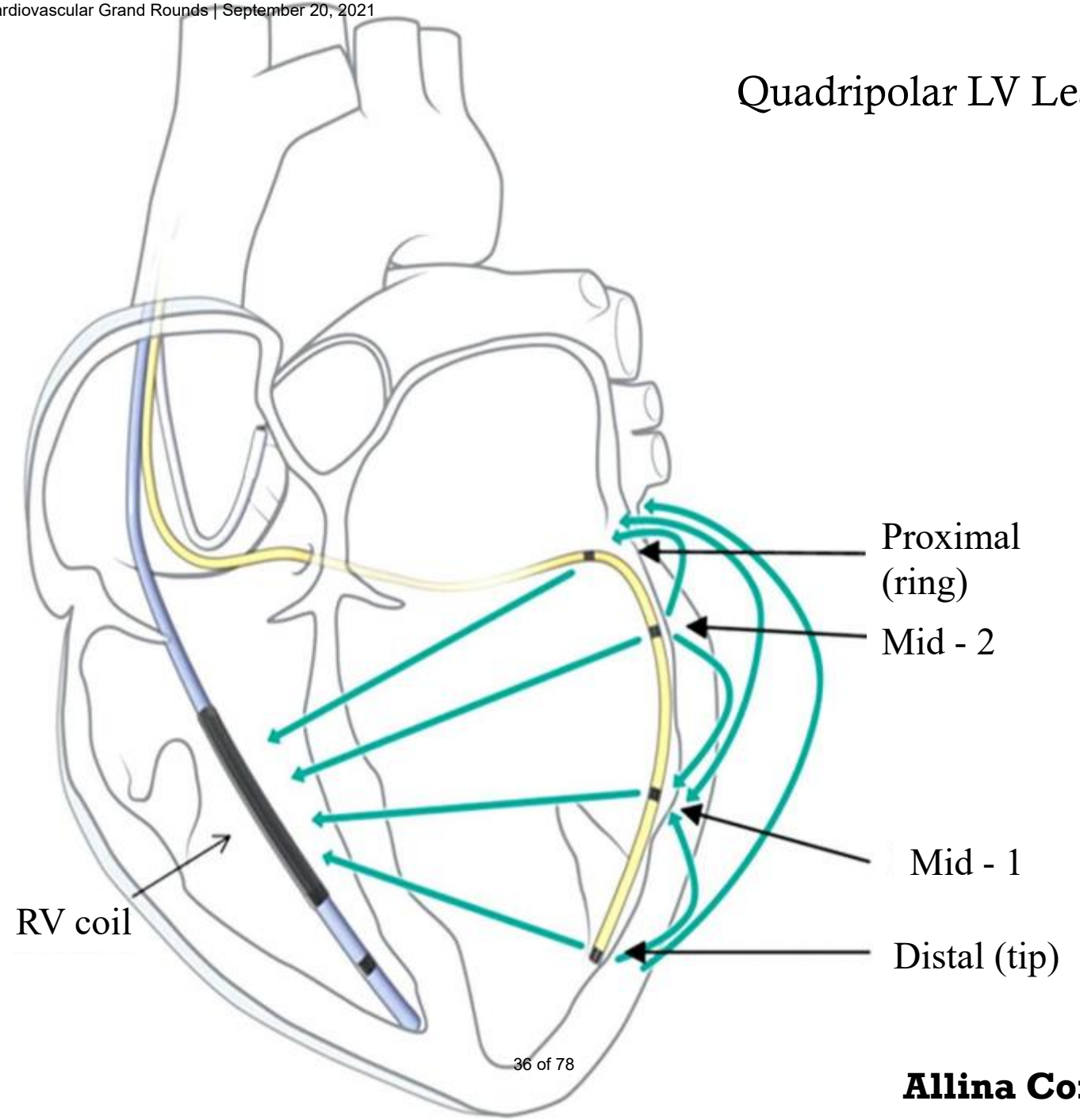
Fusion



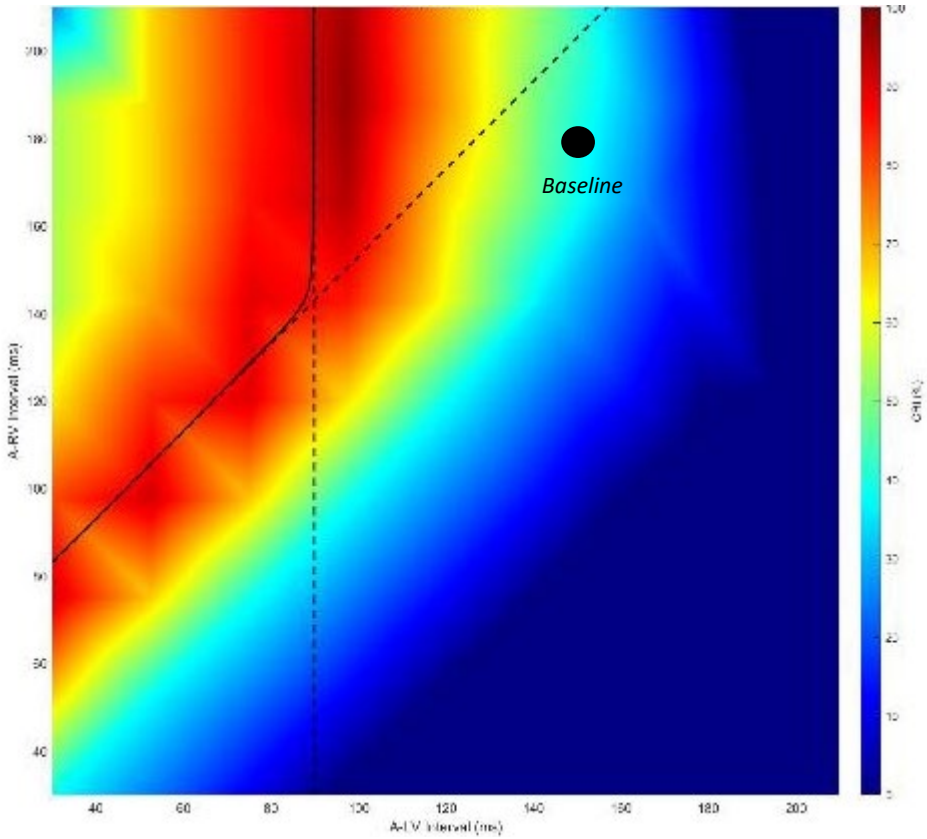
CHB Patients: fusion of RVp and LVp wavefronts



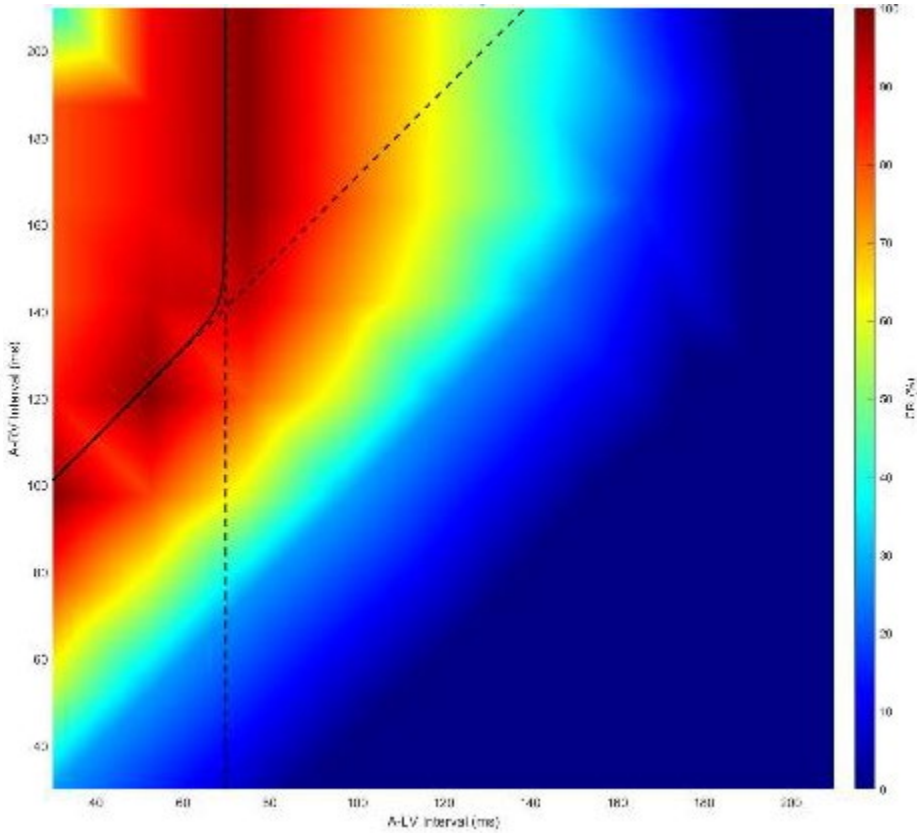
Quadripolar LV Leads



Changing Pacing Cathode of Quadripolar Lead:
RVp and Native Wavefronts identical but LVp wavefront shifted by 20 ms



LV2 -> LV4



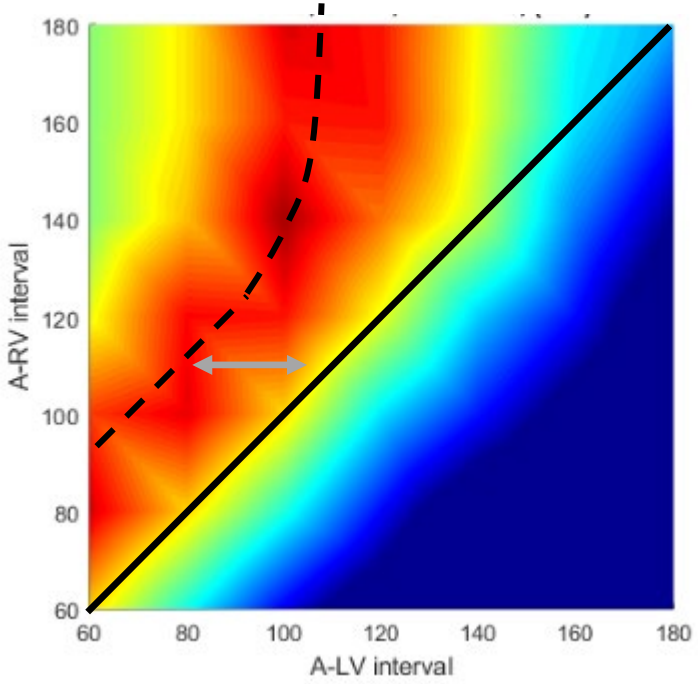
LV1 -> CAN

Wavefront timing:

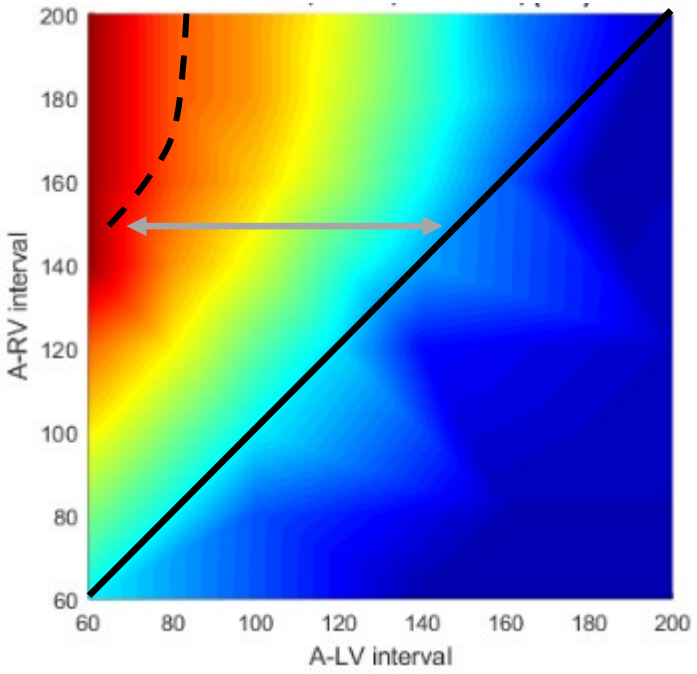
50 ms	RVp to LVp	70 ms
110 ms	Native to LVp	130 ms
60 ms	Native to RVp	60 ms

Quadripolar Lead: Electrical Synchrony at Different Vectors

- LV4 --- need 30 ms LV preactivation
- LV1 --- need 80 ms LV preactivation

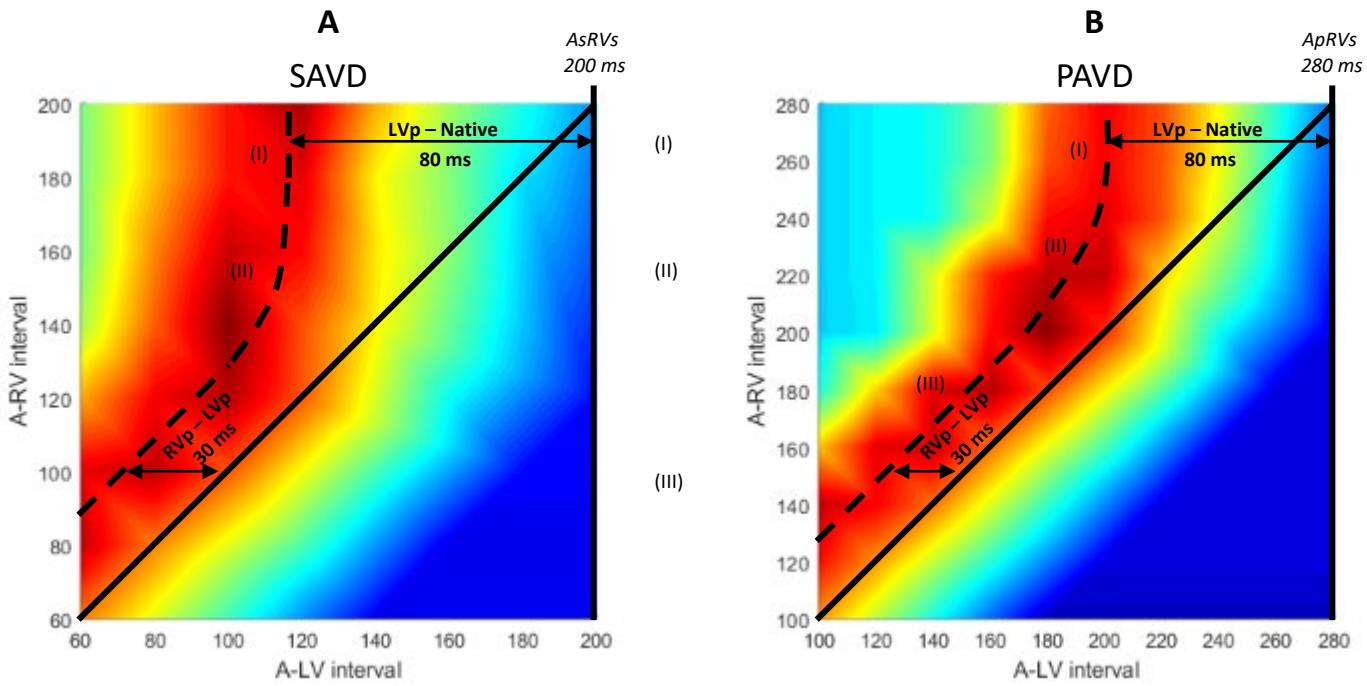


Pacing vector:
LV4 to LV3



Pacing vector:
LV1 to LV4

Atrial Sensing vs. Atrial Pacing:
Changing Native Wavefront Only

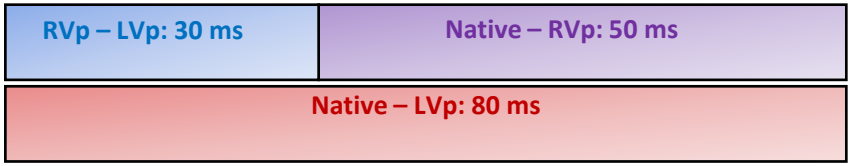


Fusion

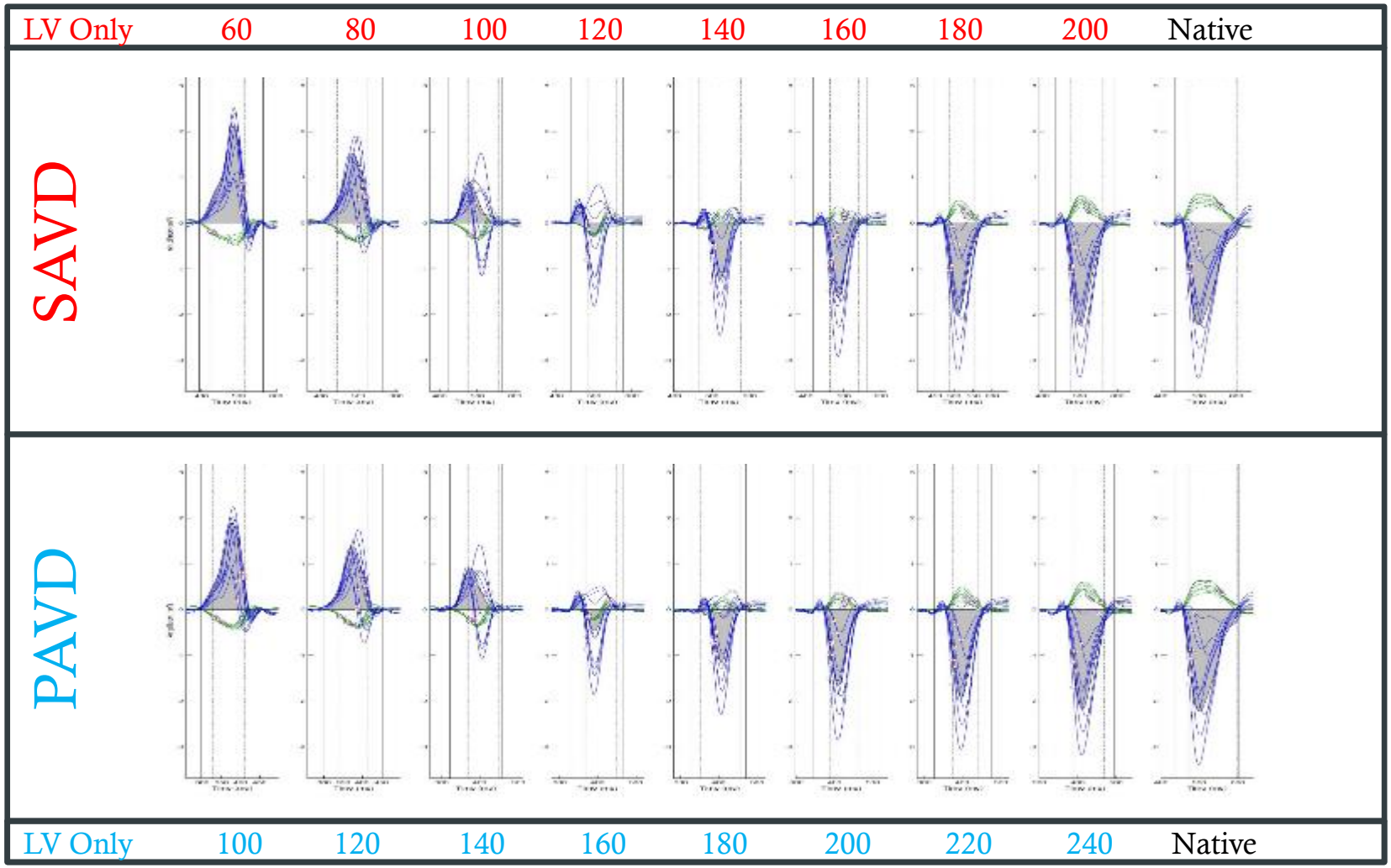
(I) LVp - Native

(II) Triple (LVp, Native, RVp)

(III) RVp - LVp

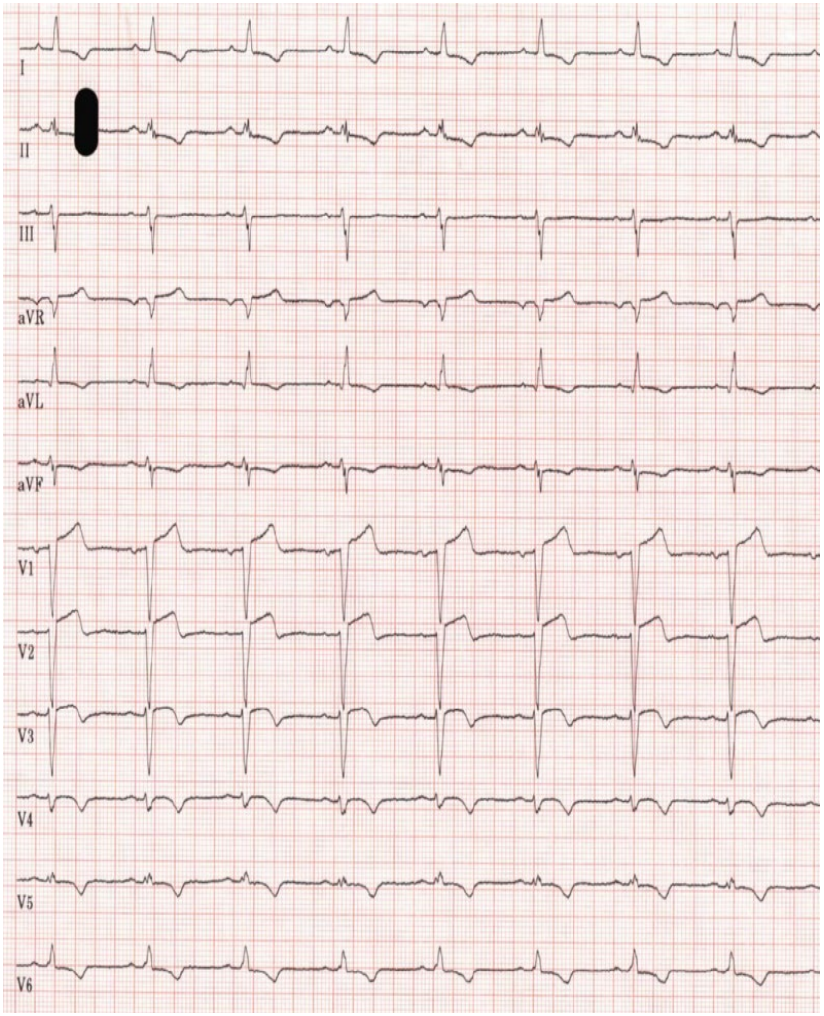


MLEAD-056-R

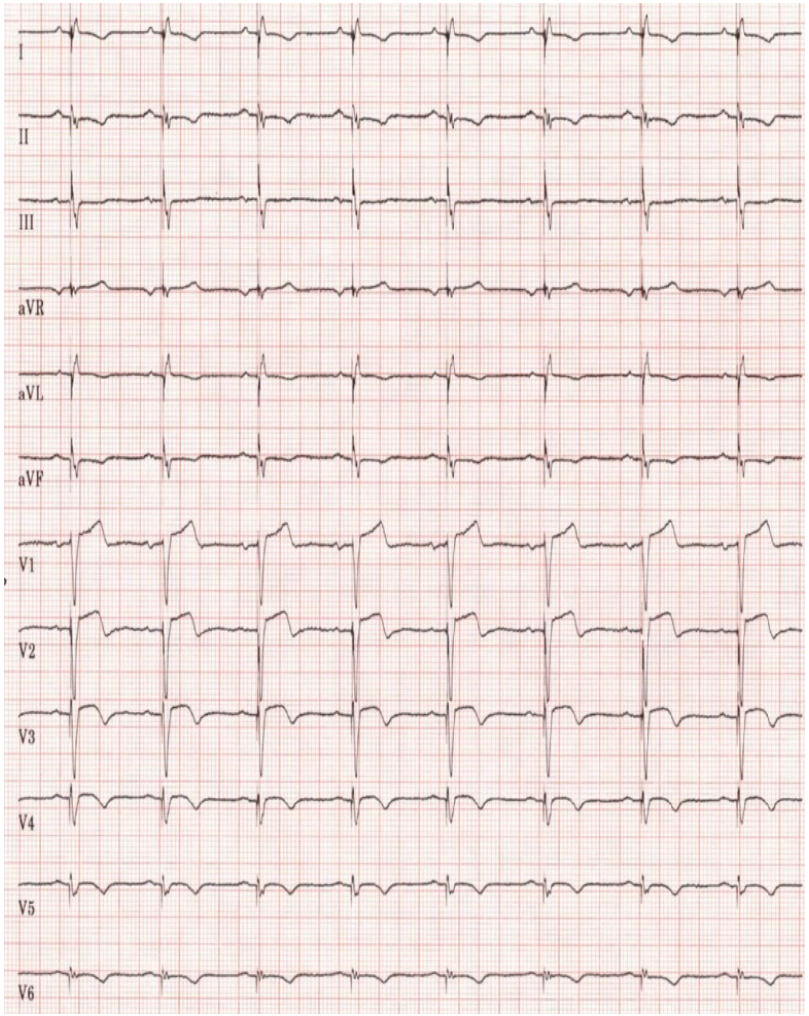


Narrow QRS and Electrical Dyssynchrony

CRT Optimization in a Patient with EF 15% and Narrow QRS (110 ms)



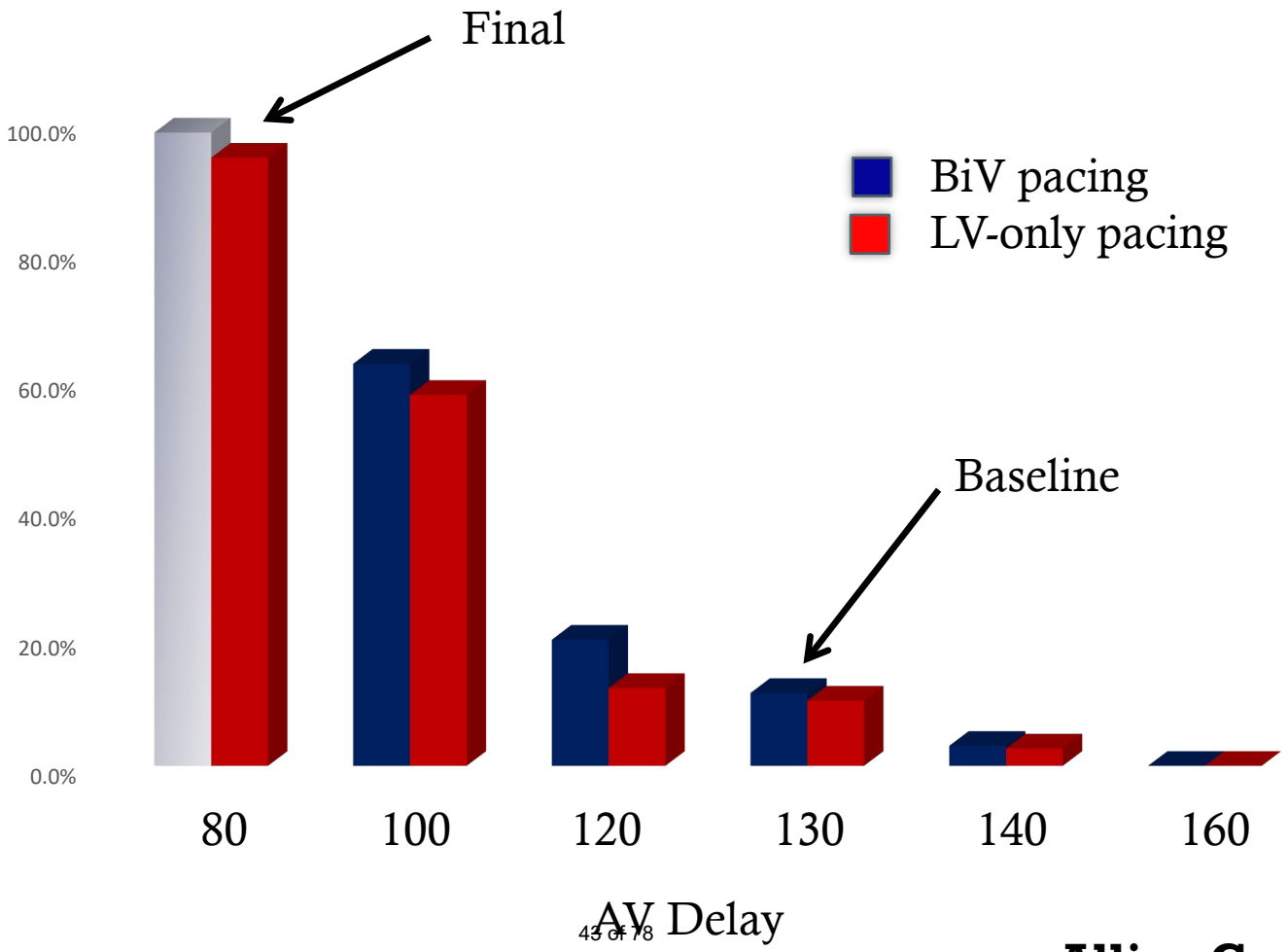
Native



Baseline: AVD 130 ms, VV = 0

JMF

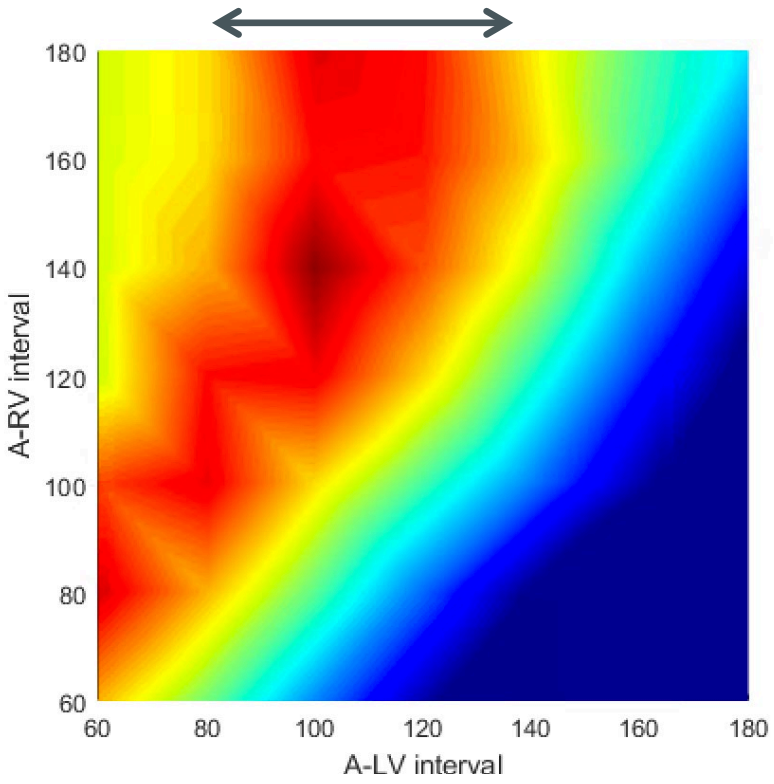
CRT Optimization in a Patient with EF 15% and Narrow QRS (110 ms)



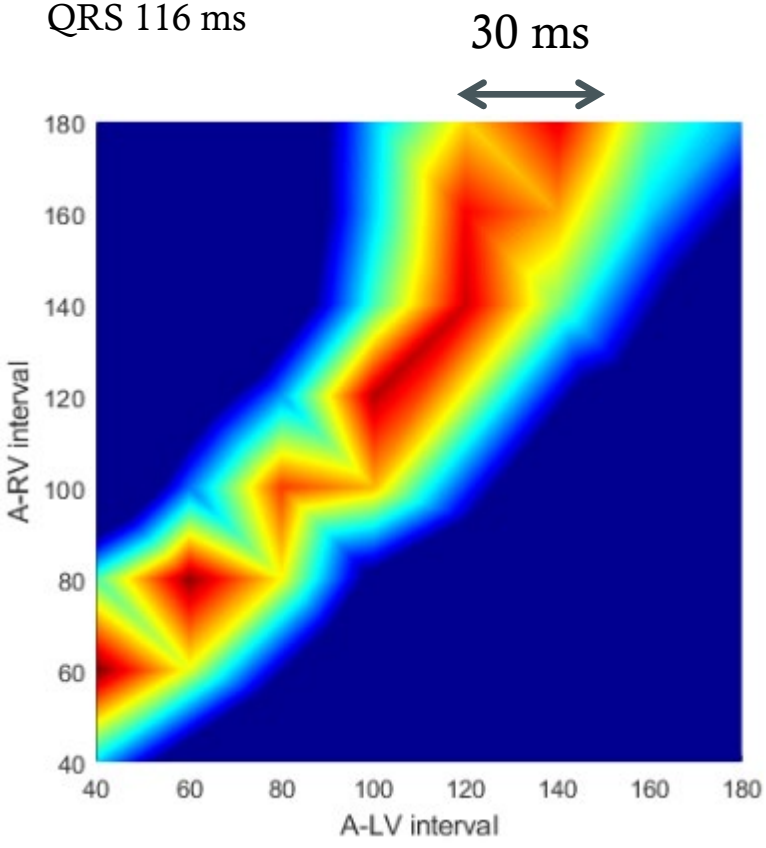
JMF

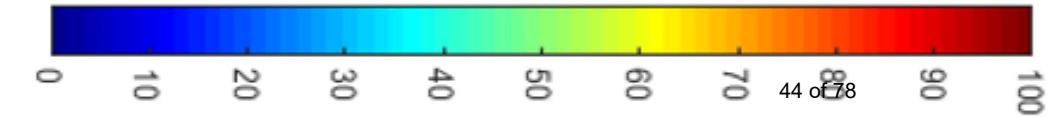
Resynchronization Window

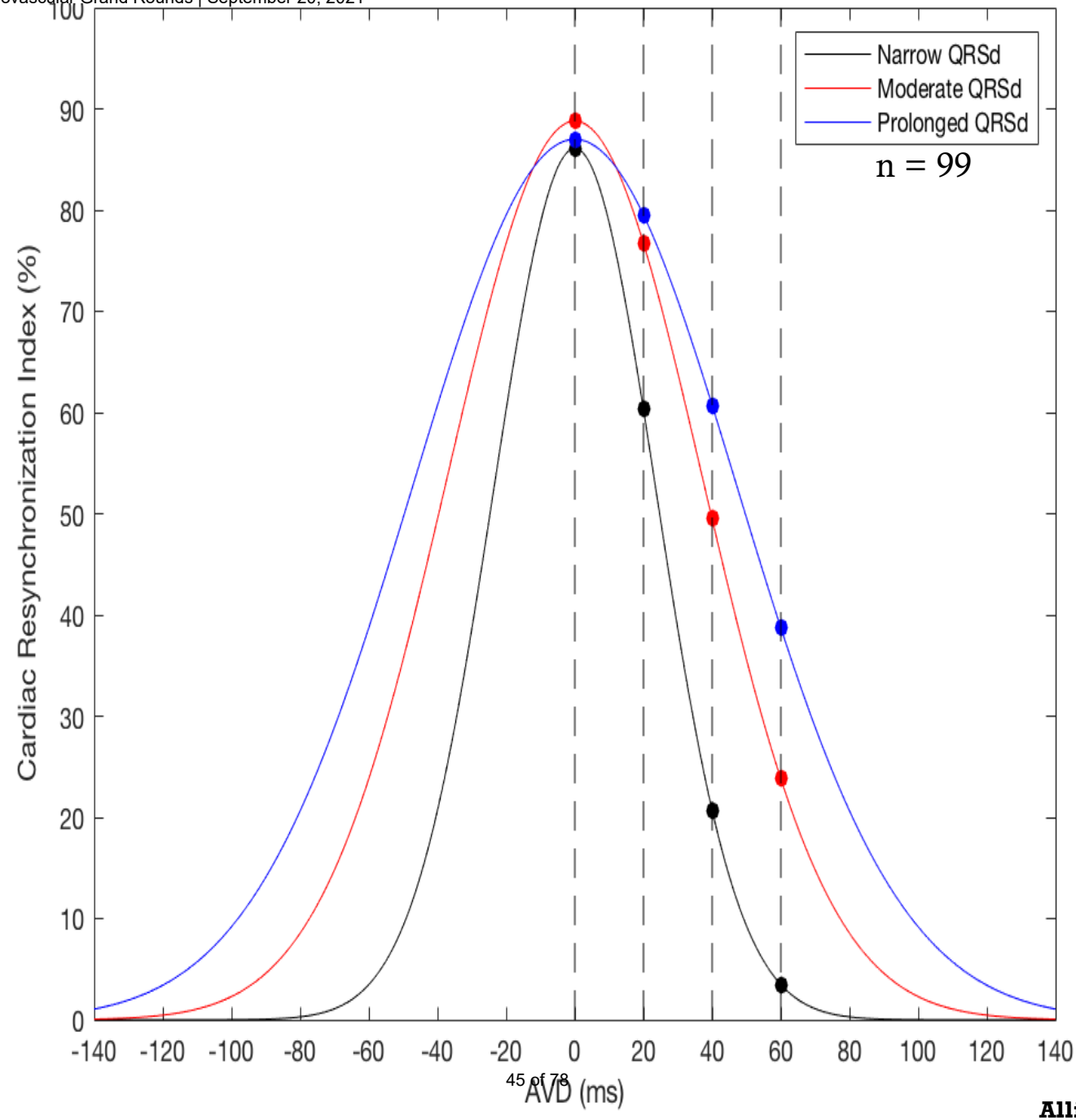
LBBB
QRS 160 ms



IVCD (LBBB-like)
QRS 116 ms

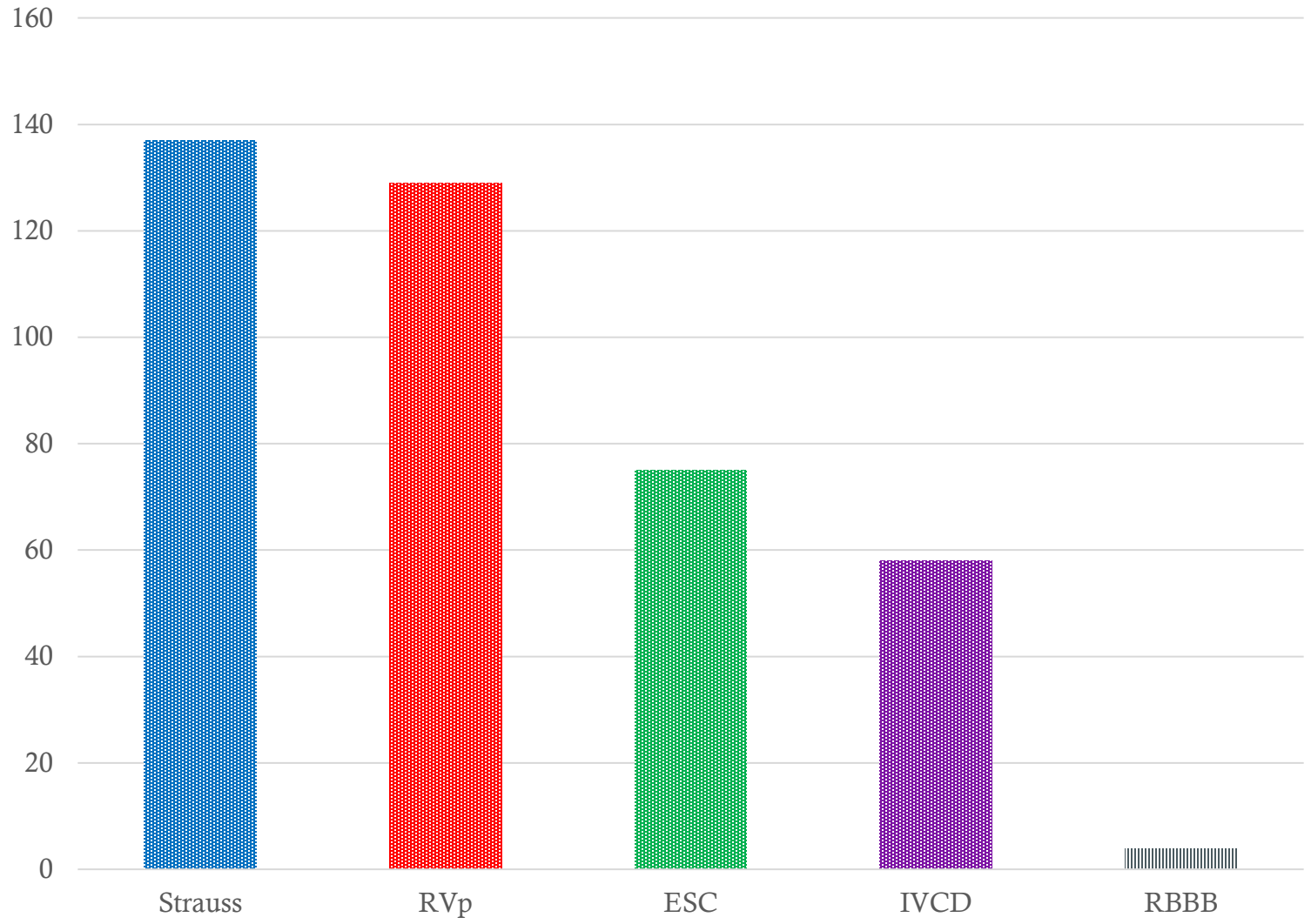




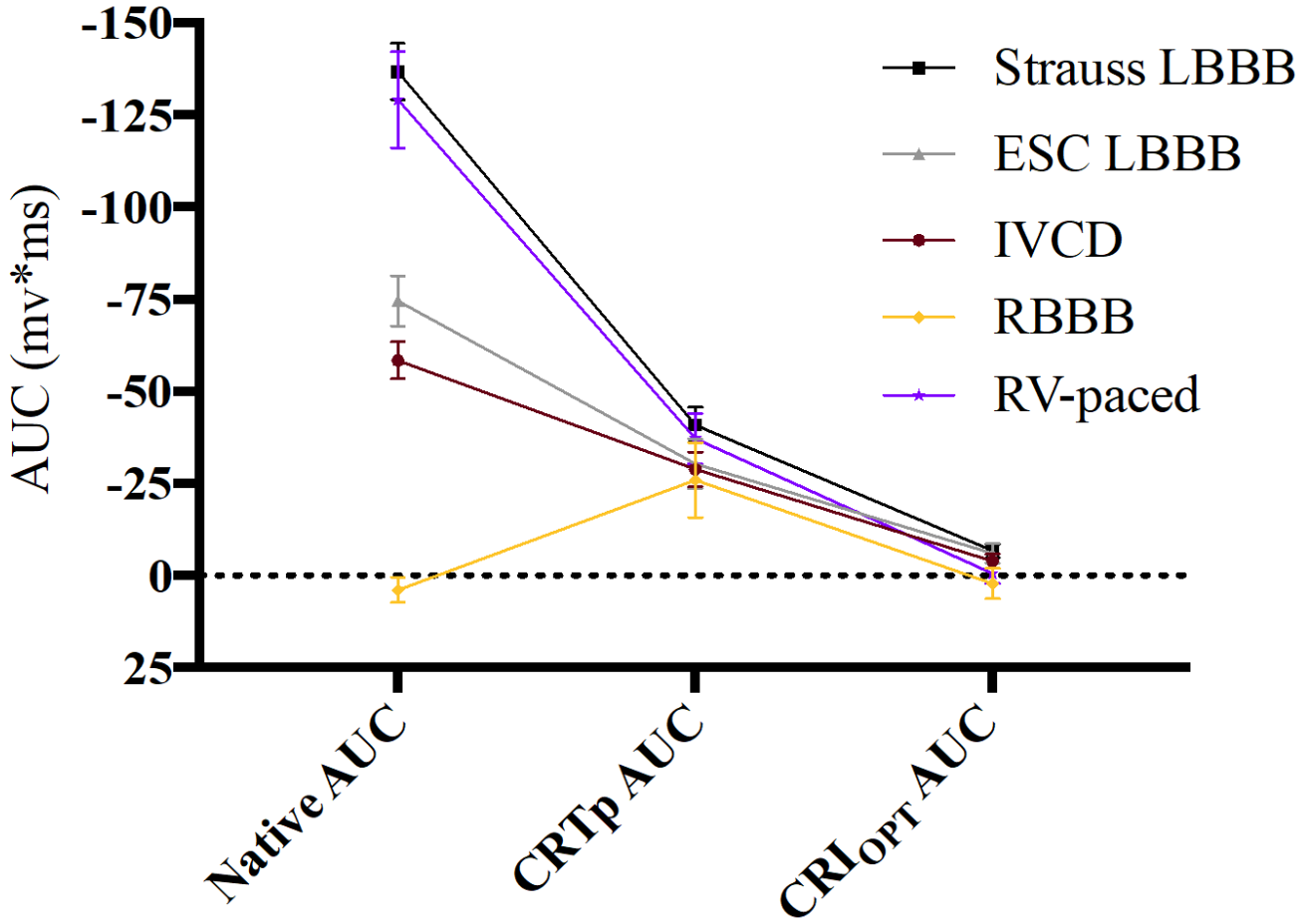


Selection of Patients for CRT

Native AUC for Different QRS Morphologies



Change in AUC with CRT (Baseline and Optimal)

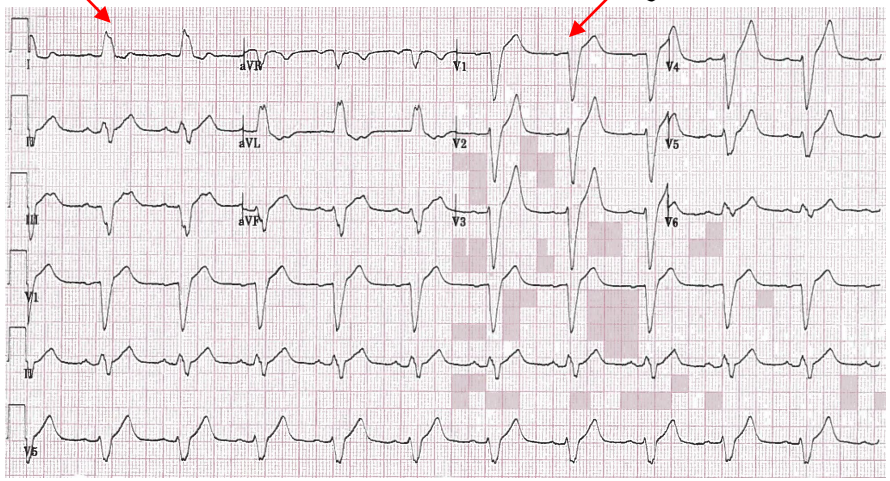


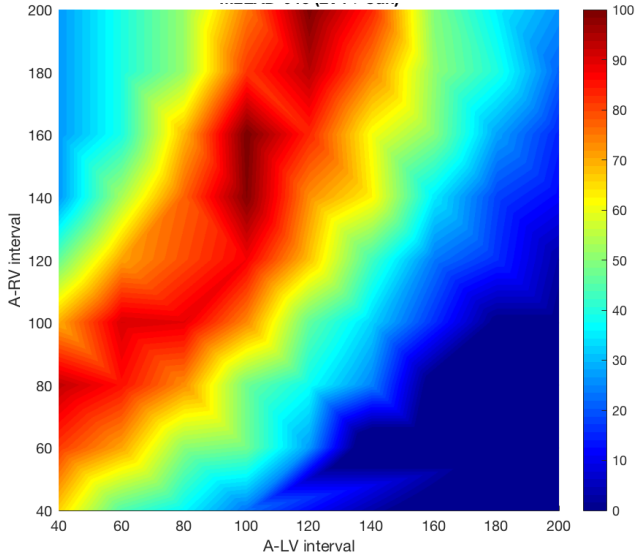
Mid-QRS notching

Strauss LBBB QRS morphology

QRS_d 150

QS





JRH

IVCD QRS morphology

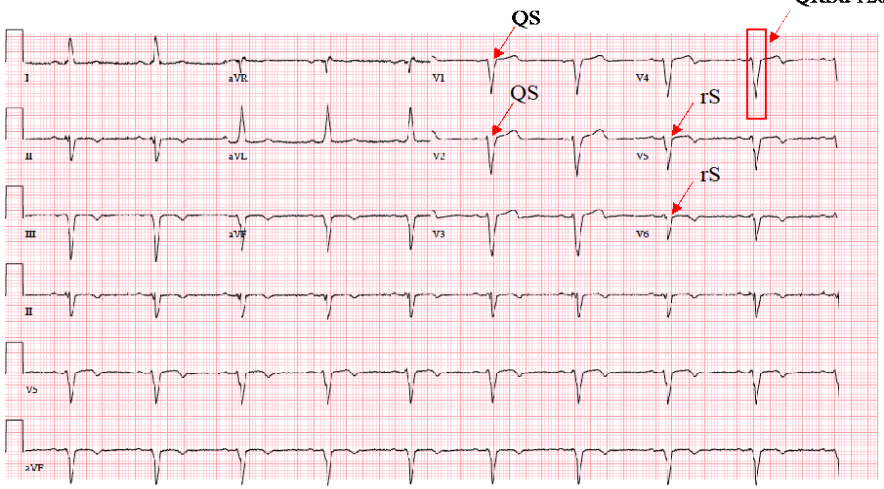
QRSd 120

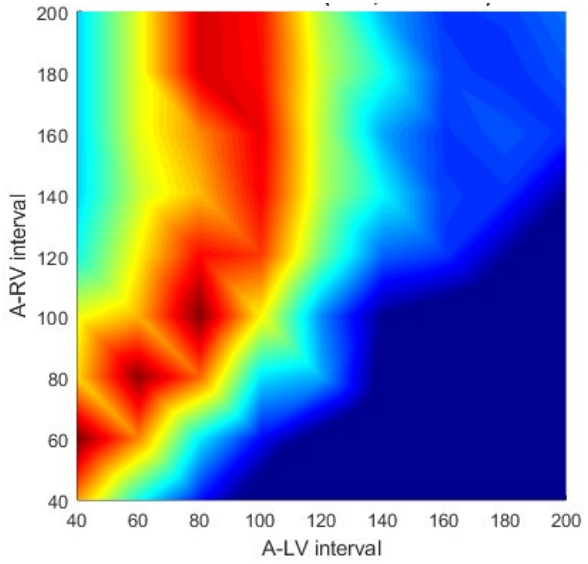
QS

QS

rS

rS

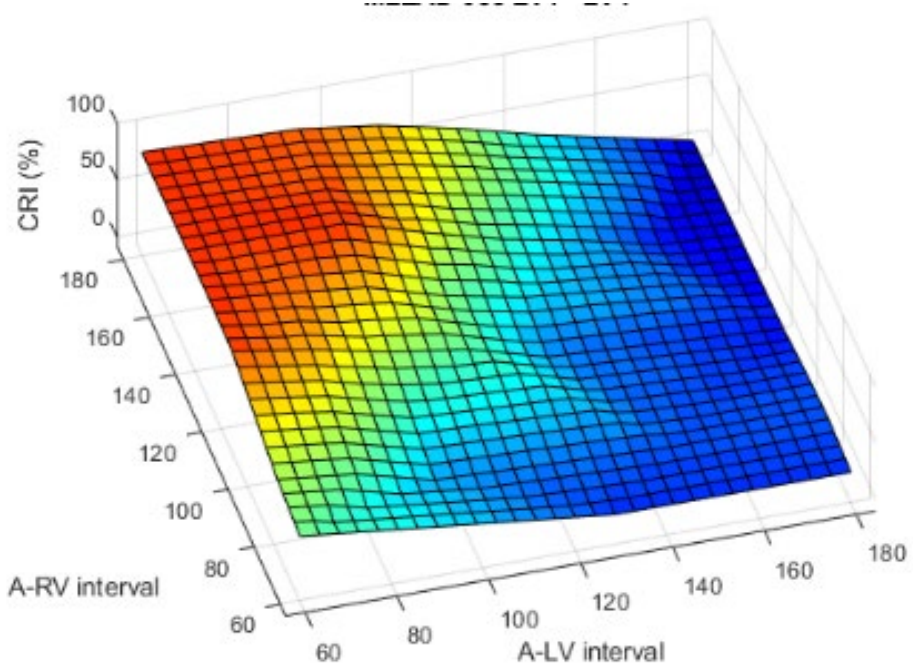




KAH

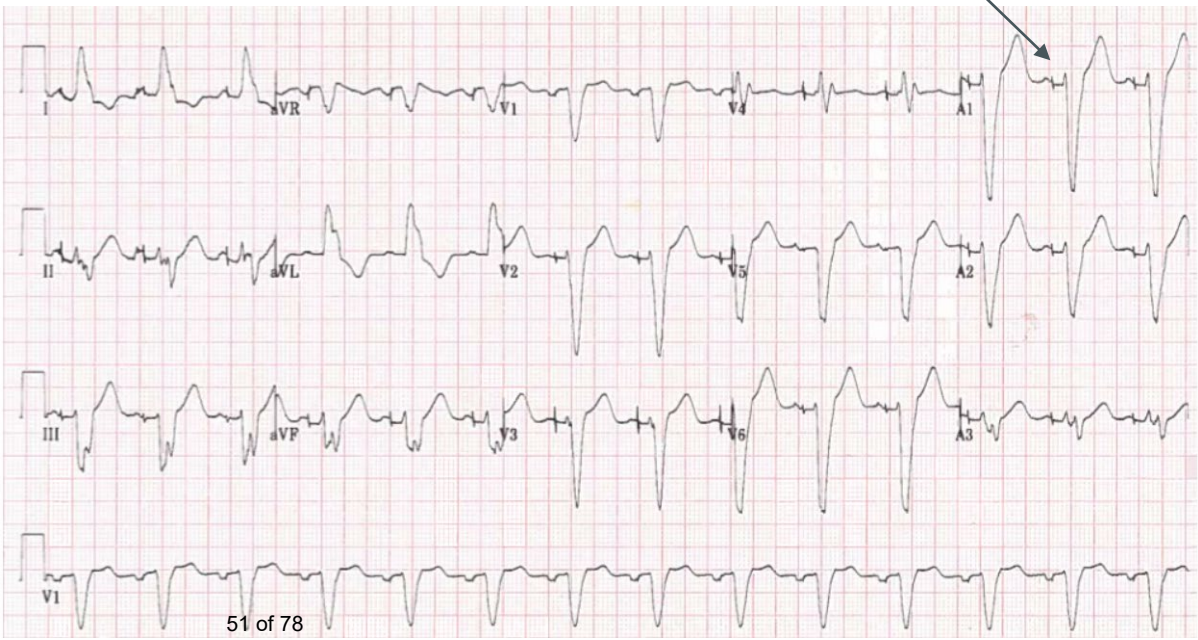
Assessment of LV Lead Location from EDM's

LV Lead Latency and EDM



LV1 to LV4

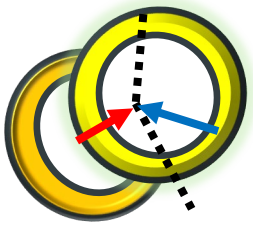
LV lead latency 80 ms



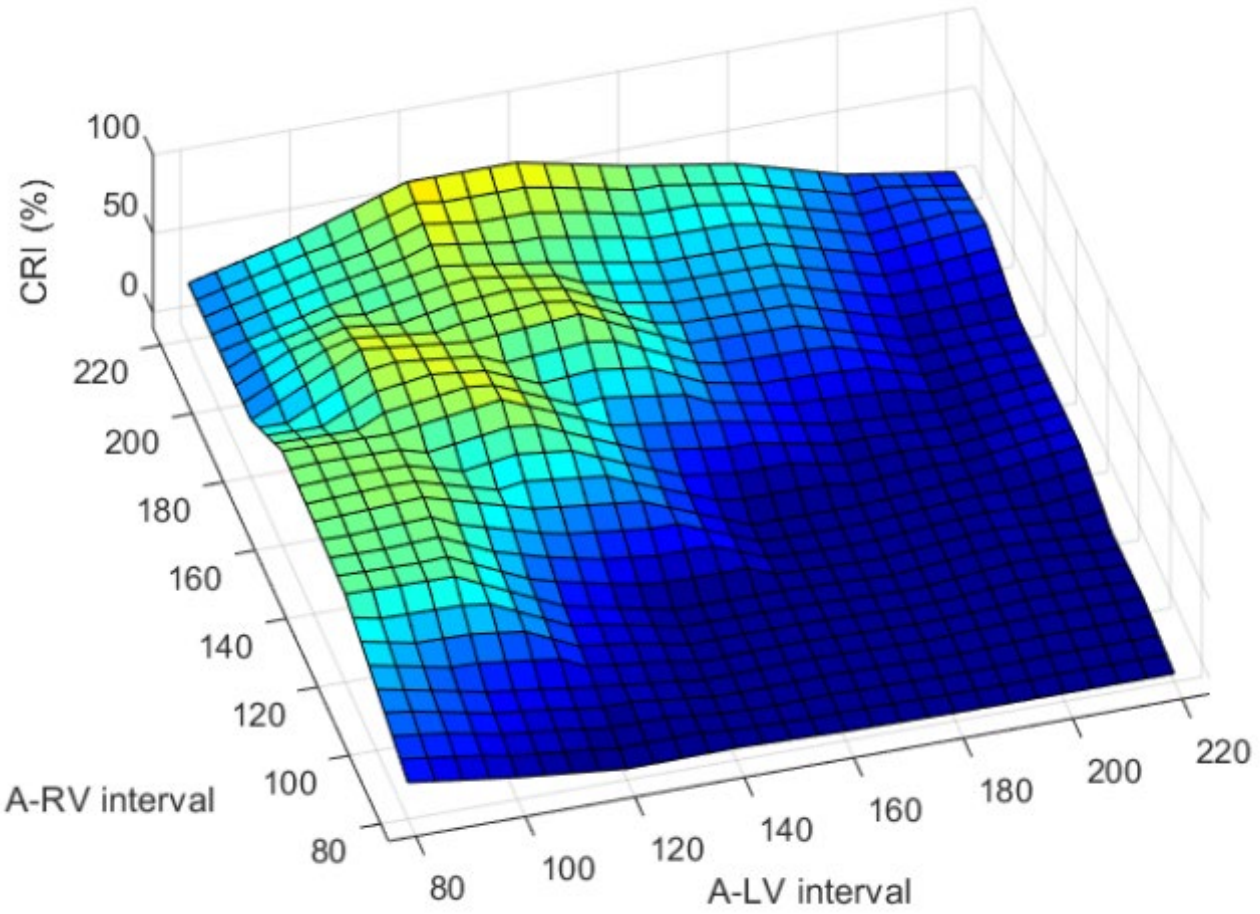
JLK

Assessment of LV lead location

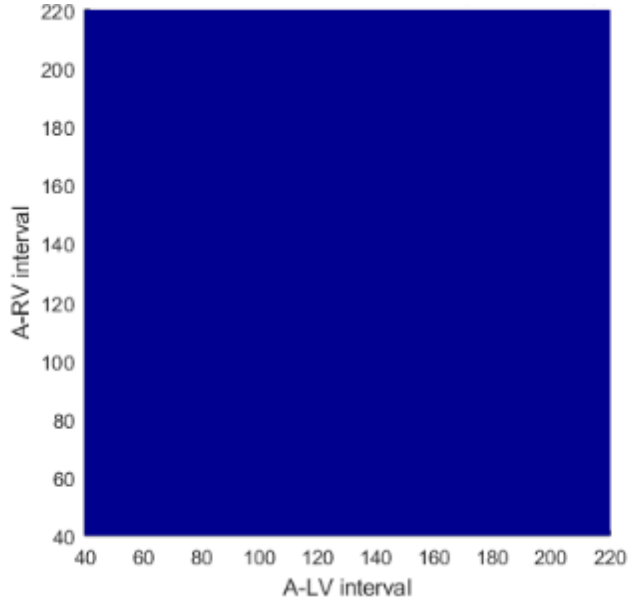
Posterior



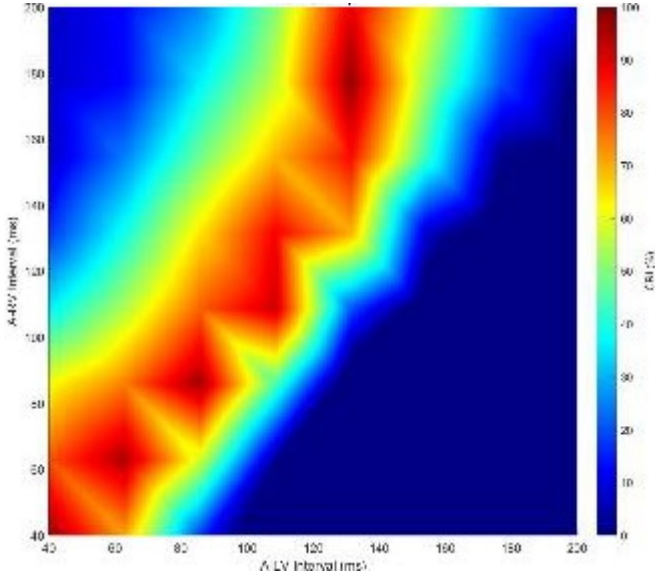
Anterior



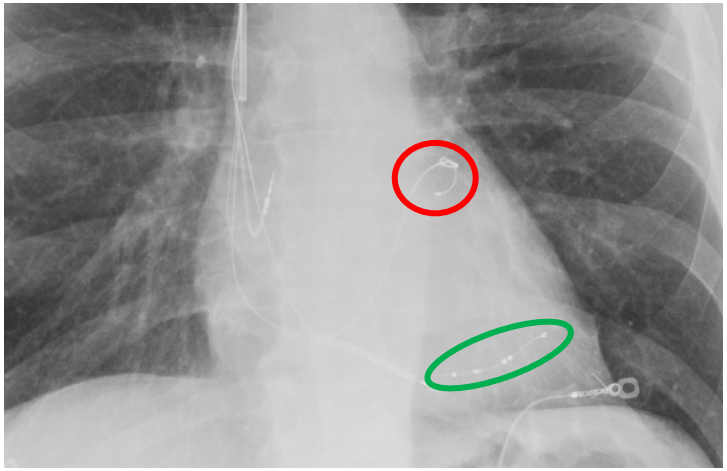
Maximum CRI is ~ 50-60% (yellow on map) due to anterior LV lead position and inability to get good wavefront fusion at any device setting

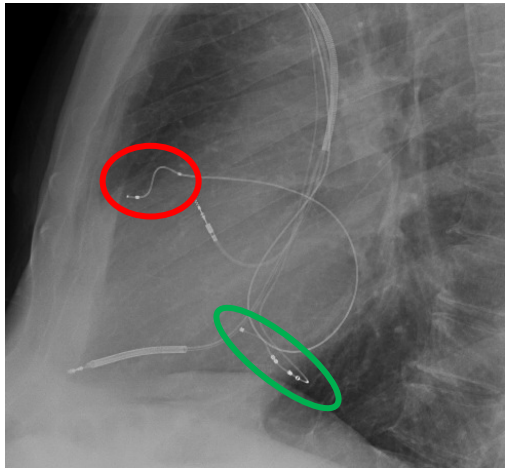


Pre - LV lead revision

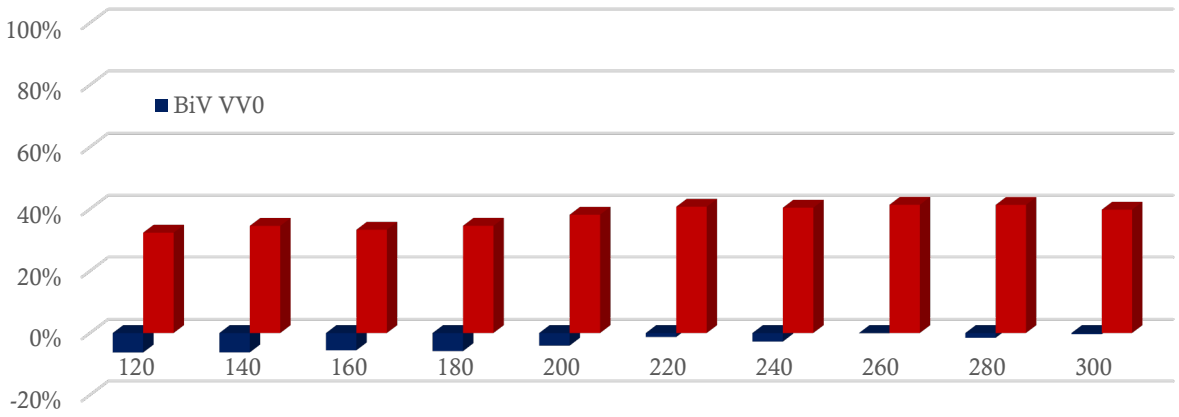


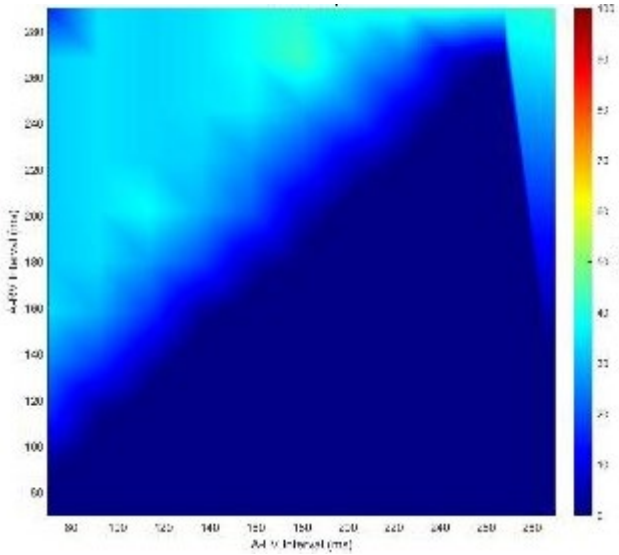
Post - LV lead revision





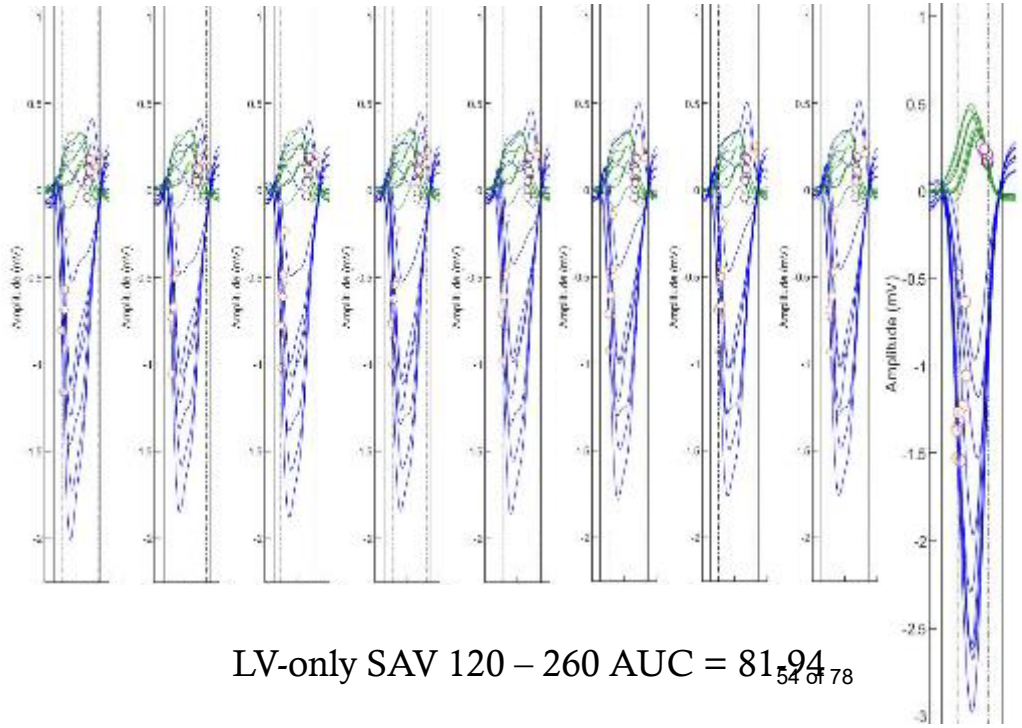
71 y/o M with EF 40%, CHB, increased HF symptoms





RV-only AUC = 156

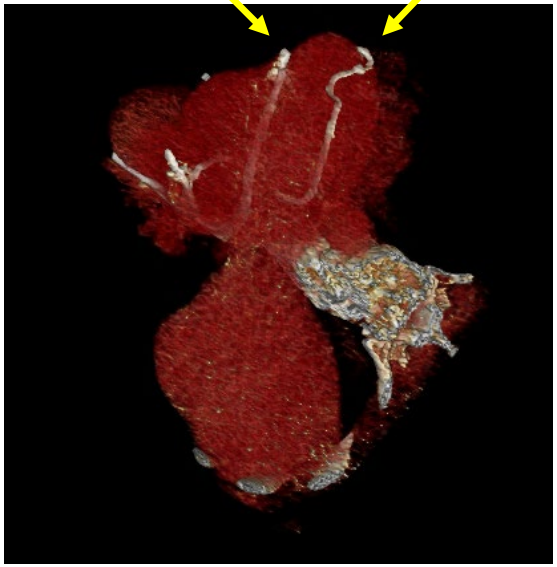
LV-only pacing



LV-only SAV 120 – 260 AUC = 81-94

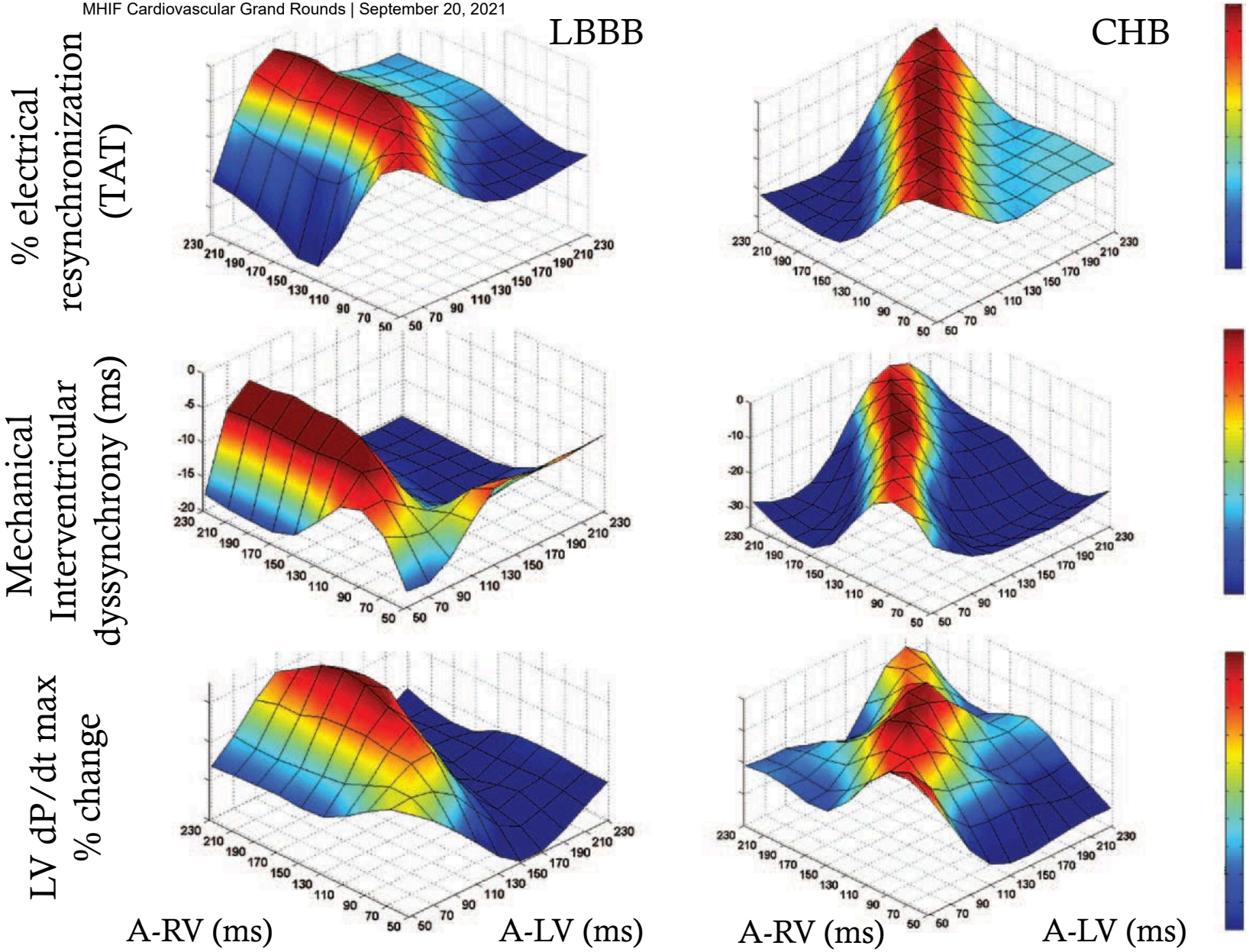
RV lead

LV lead

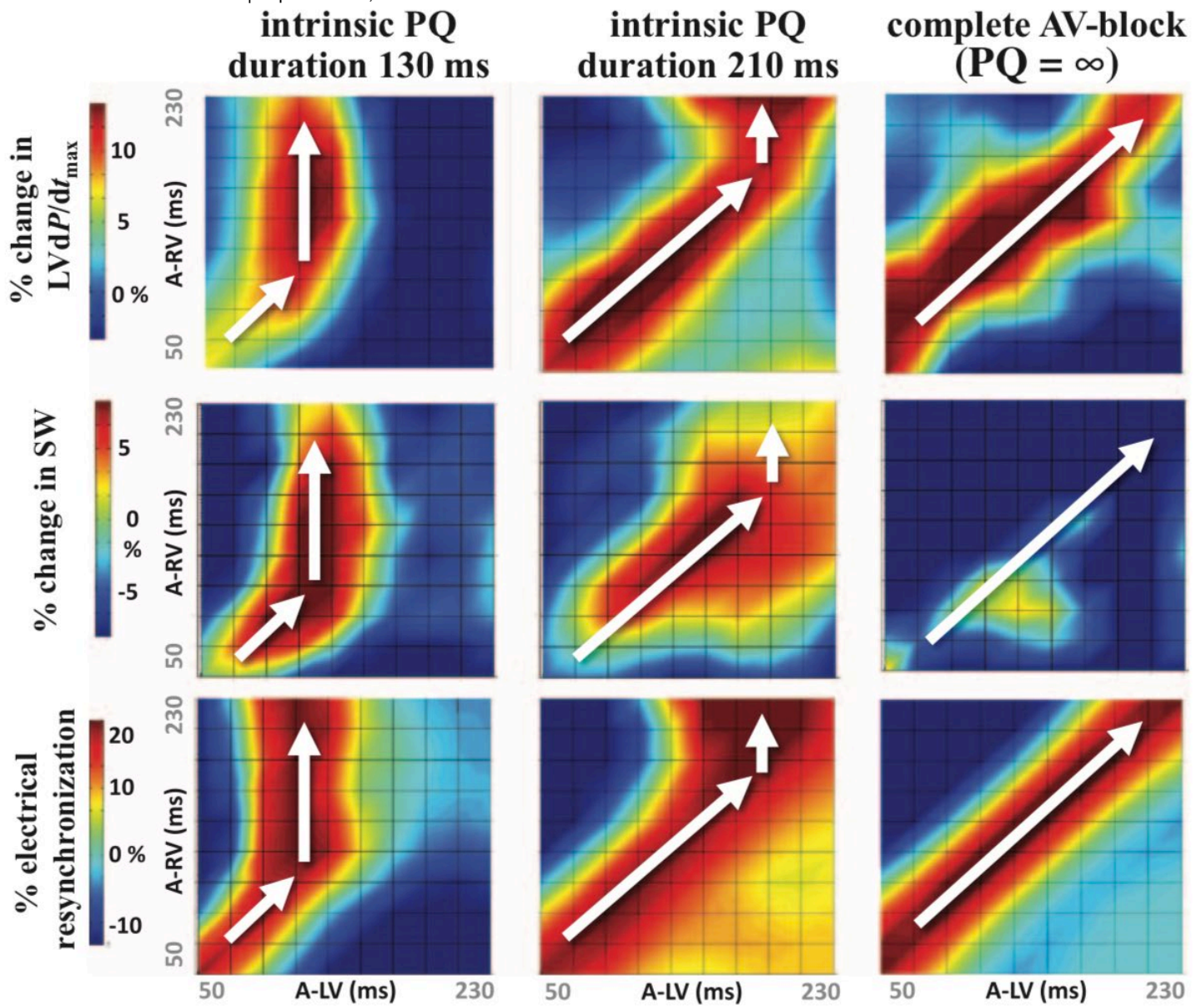


RJM

THE OUTCOMES



Strik M, et al. Interplay of Electrical Wavefronts as Determinants of the Response to CRT in Dyssynchronous Canine Hearts. Circ Arrhythm Electrophysiol 2013;6:924-31.

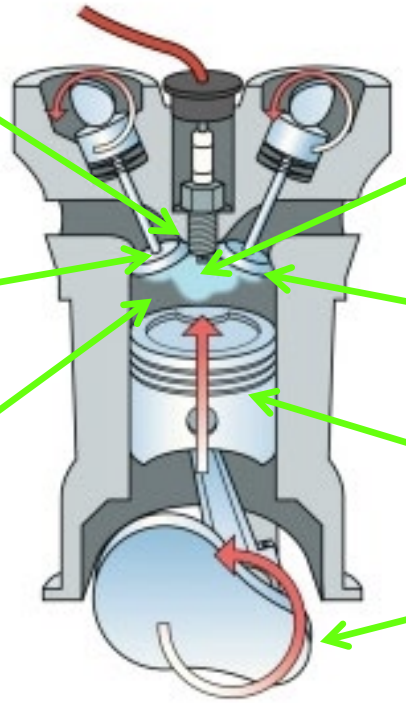


Strik M, et al. Interplay of Electrical Wavefronts as Determinants of the Response to CRT in Dyssynchronous Canine Hearts. Circ Arrhythm Electrophysiol 2013;6:924-31.

Sparkplug Timing and Engine Efficiency/Power

Sparkplug

Fires at 10° before top dead center with mixture fully burnt at 20° after top dead center



Air-Fuel Mixture

Intake Valve

Outtake Valve

Piston

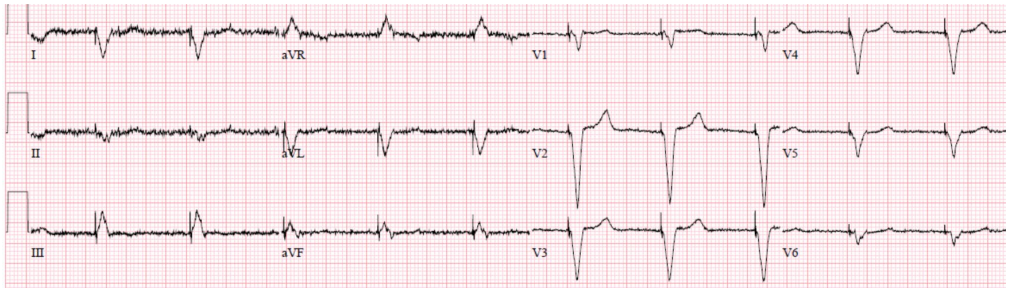
Cylinder

Crankshaft

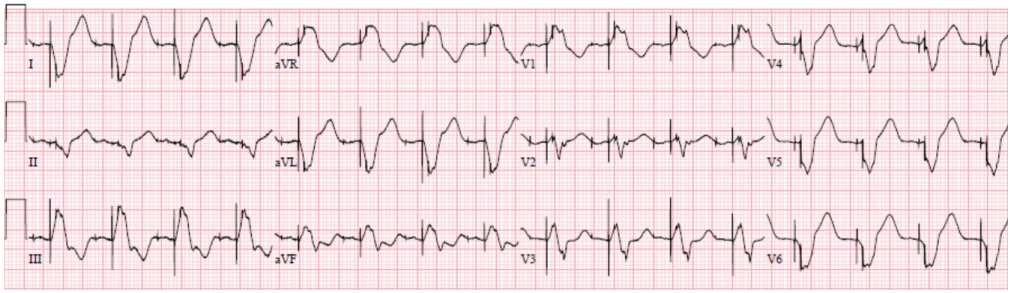
At 900 rpm the crank rotates one degree in 0.185 msec.

By advancing the timing 4 degrees, you start ignition 0.74 msec sooner.

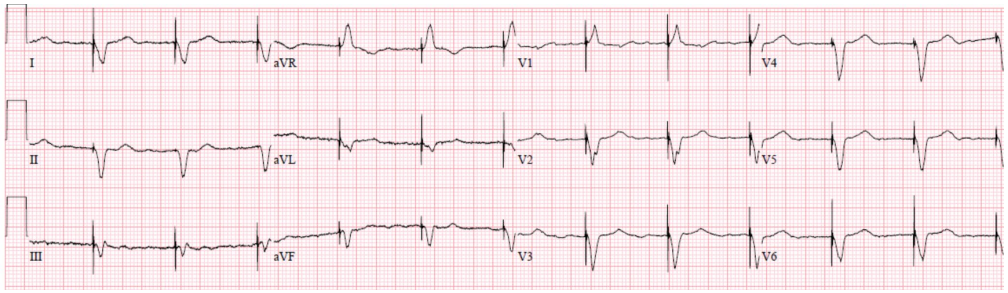
Electrical/Mechanical Dyssynchrony: Practical Clinical Tips to Identify Patients Needing Optimization



DMP



JGB

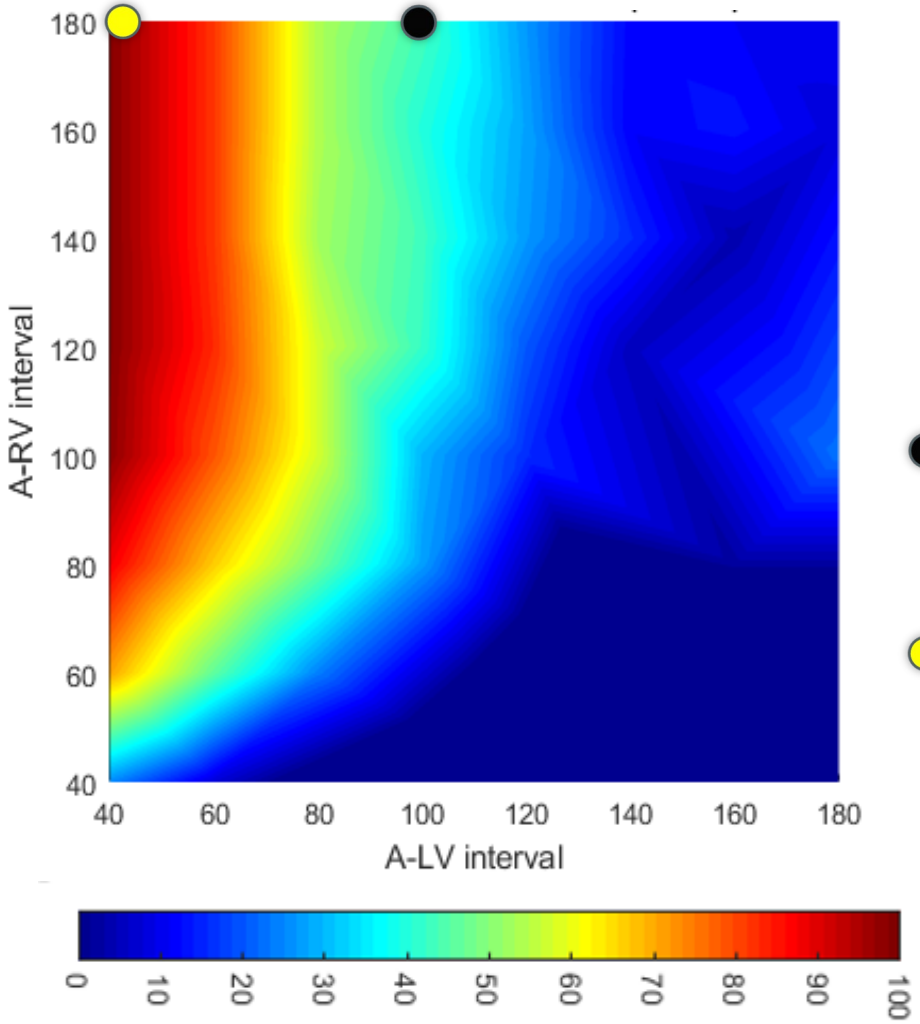


TJD

SLD

1. Order/review 12-lead ECGs on all patients post-CRT
2. Is QRS really wide? Is QRS amplitude high?
3. Are there deep Q waves in multiple chest leads?
4. Is net AUC V1-6 markedly negative or positive?
5. Is EF low?
6. Is there evidence of mechanical dyssynchrony on echo?
   - Dyssynchronous septum/anteroseptum/ inferior wall
   - "Shudder of septum/anteroseptum
   - Apical rocking
   - "Hula hoop" motion of LV

Treatment of Non-Responder

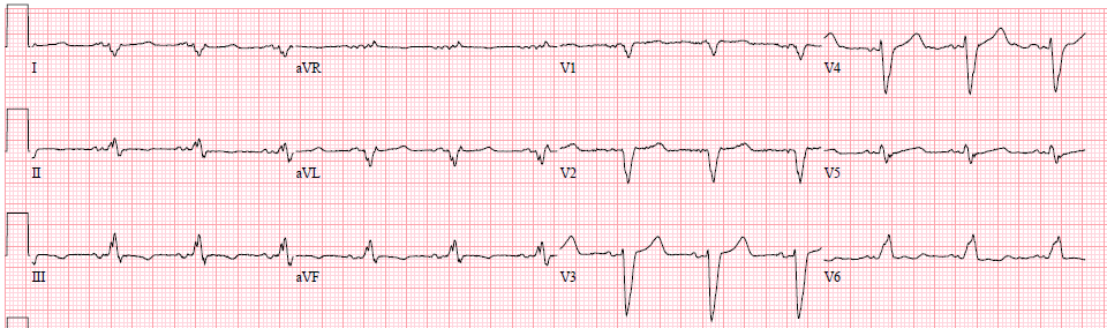


72 y/o F with NICM

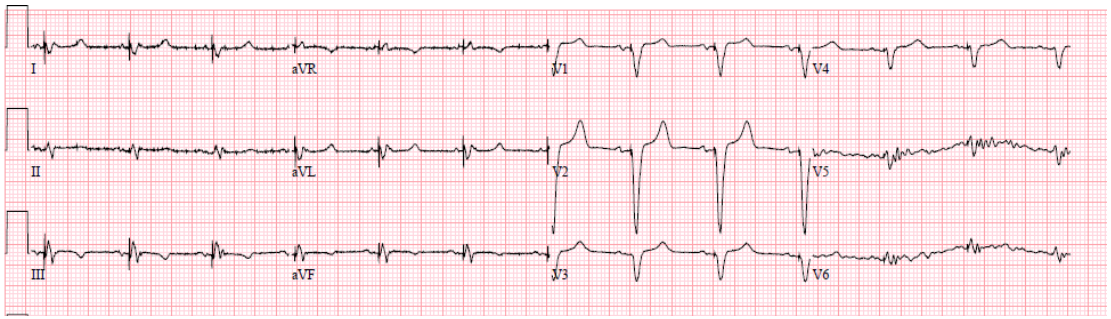
- Baseline: aCRT LV-only SAV 100
  EF 15-20%
- Final: LV-only SAV 40
  EF 35-40%

72 y/o F with Class III HF, IDCM, EF 15-20%

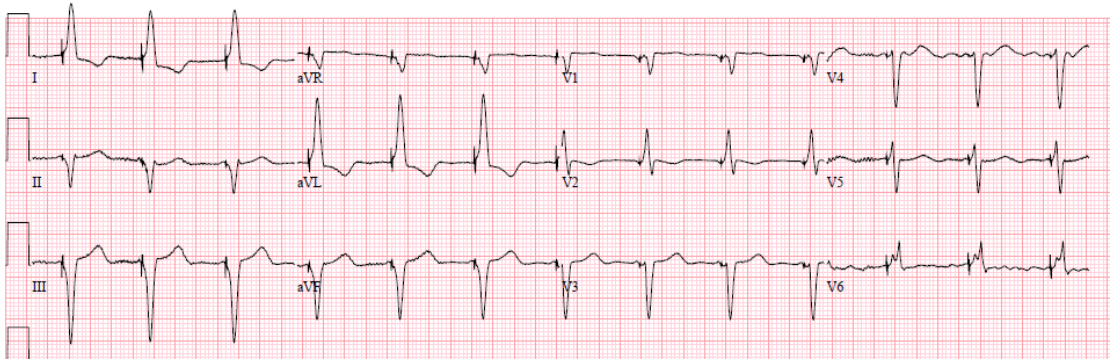
Pre-CRT
(LBBB: QRS 130)



~ 3 months Post-CRT
(non-response)

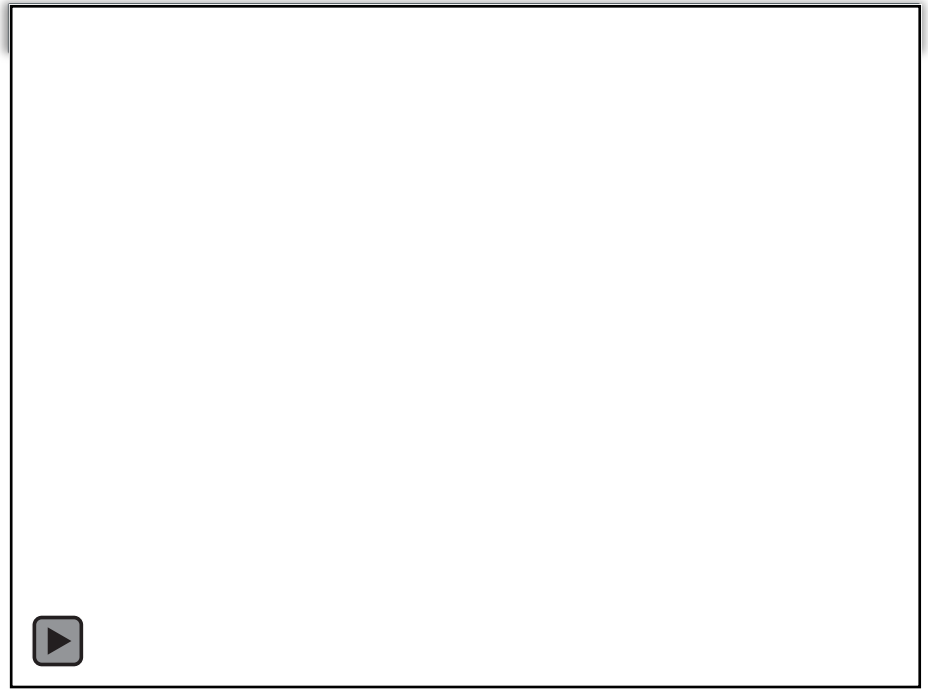


Post-Optimization

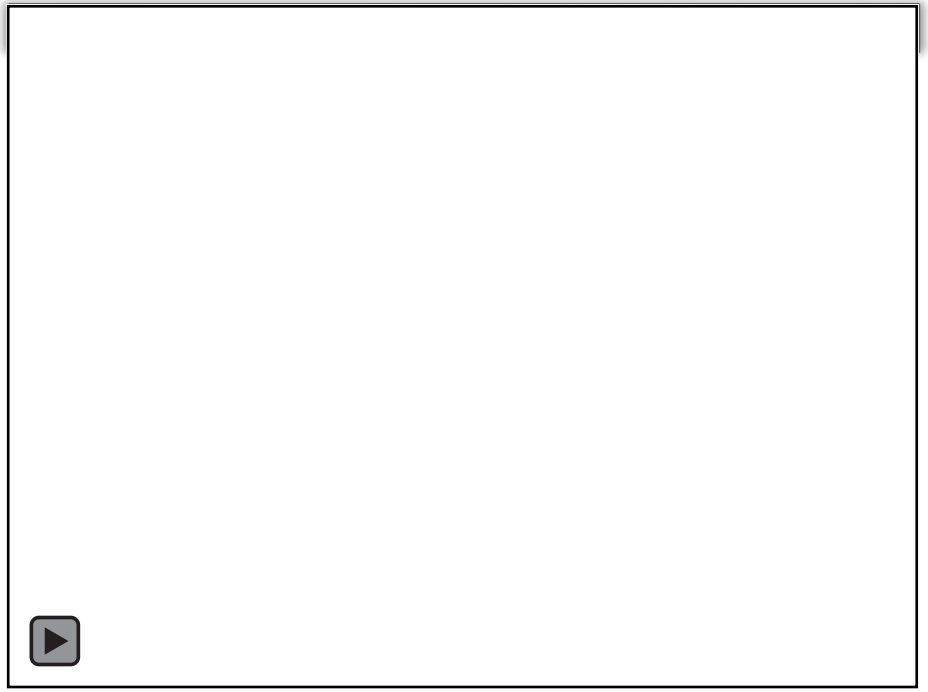


KJB

72 y/o F with Class III HF, IDCM, EF 15-20%



Pre-Optimization

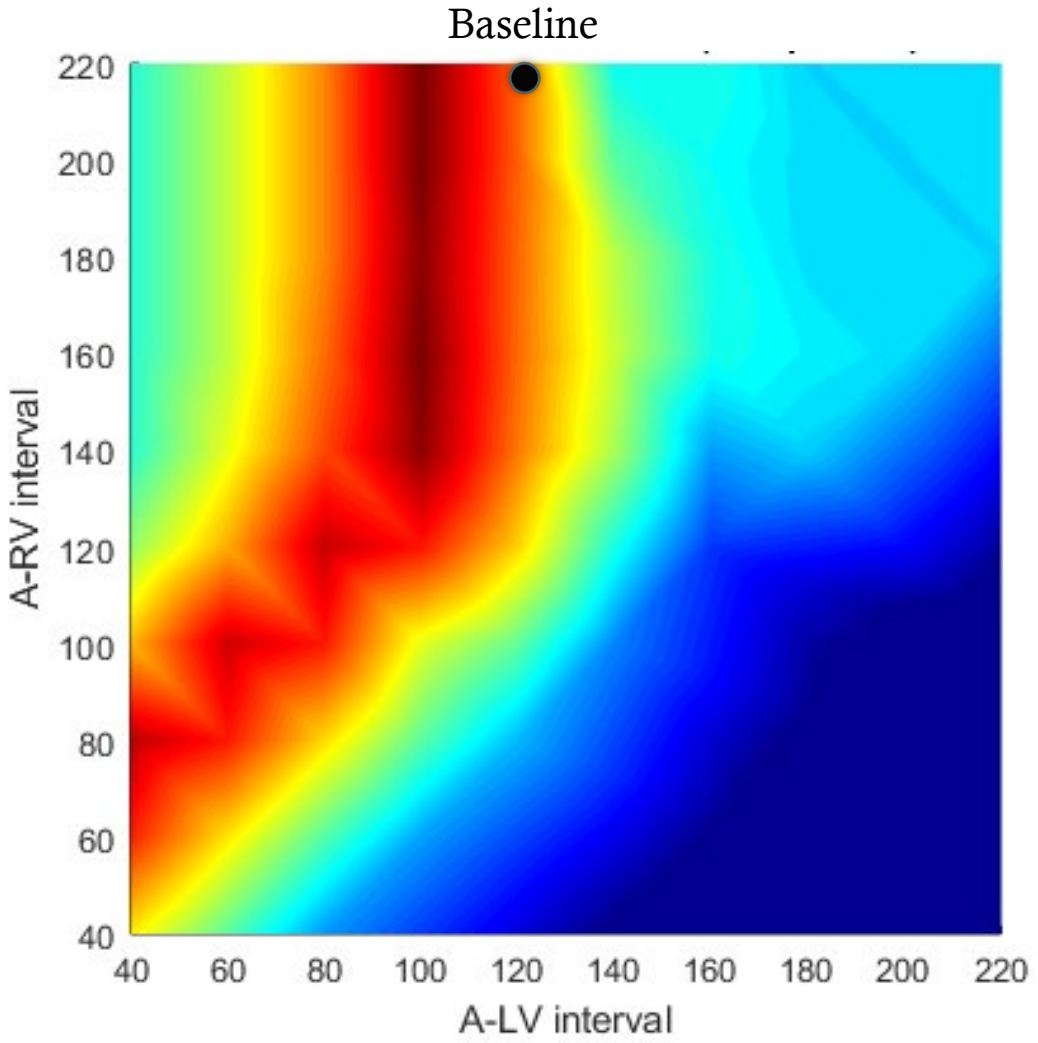


Post-Optimization

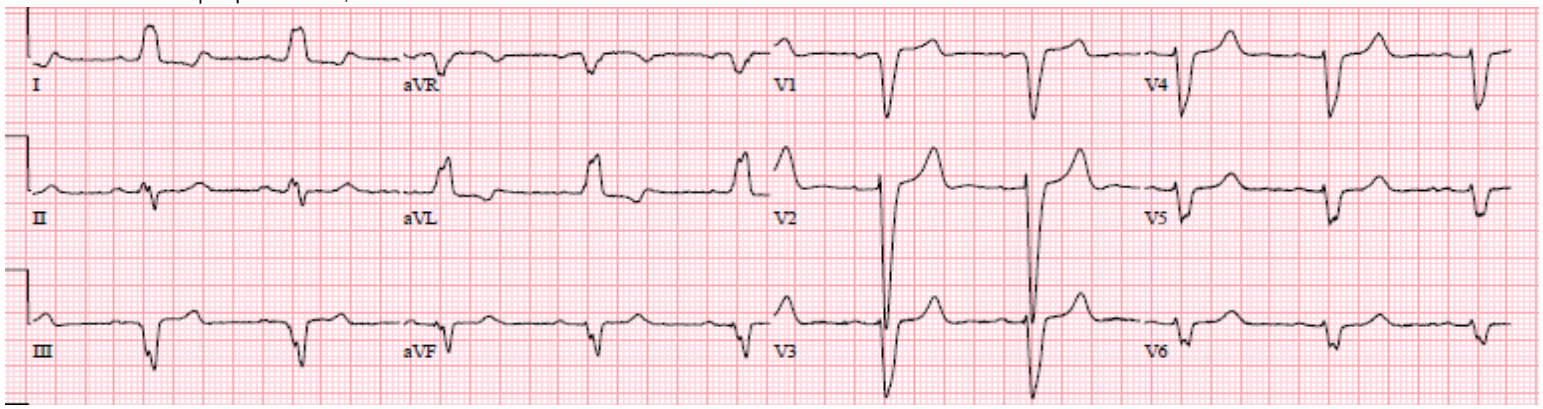
KJB

71 y/o F with NICM and non-response to CRT

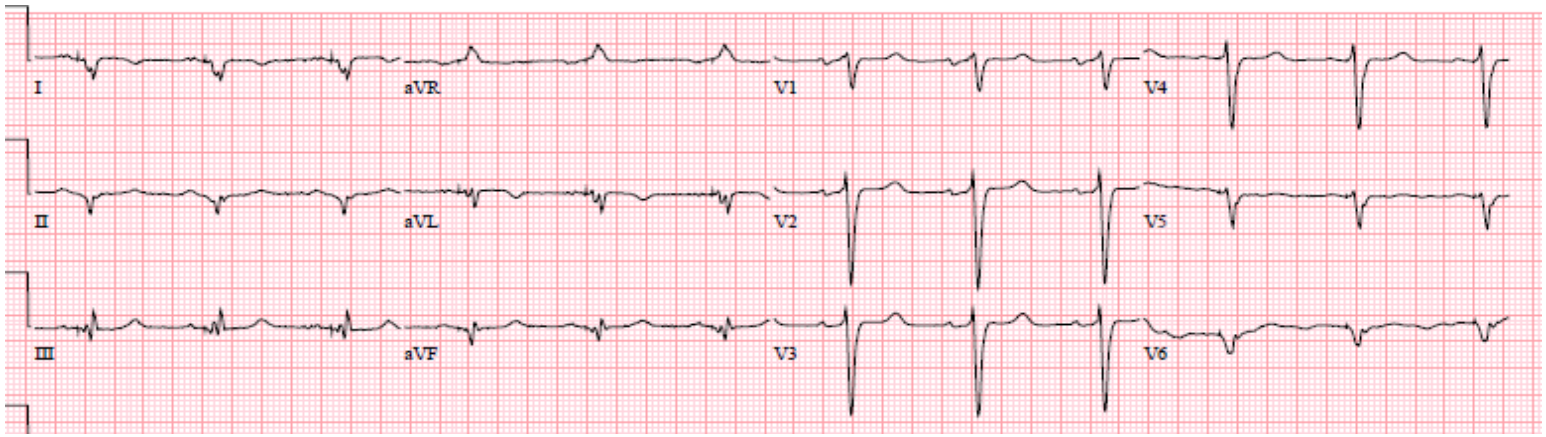
- LBBB with PR 180, QRS 160
- EF 20-25% pre- and post-CRT



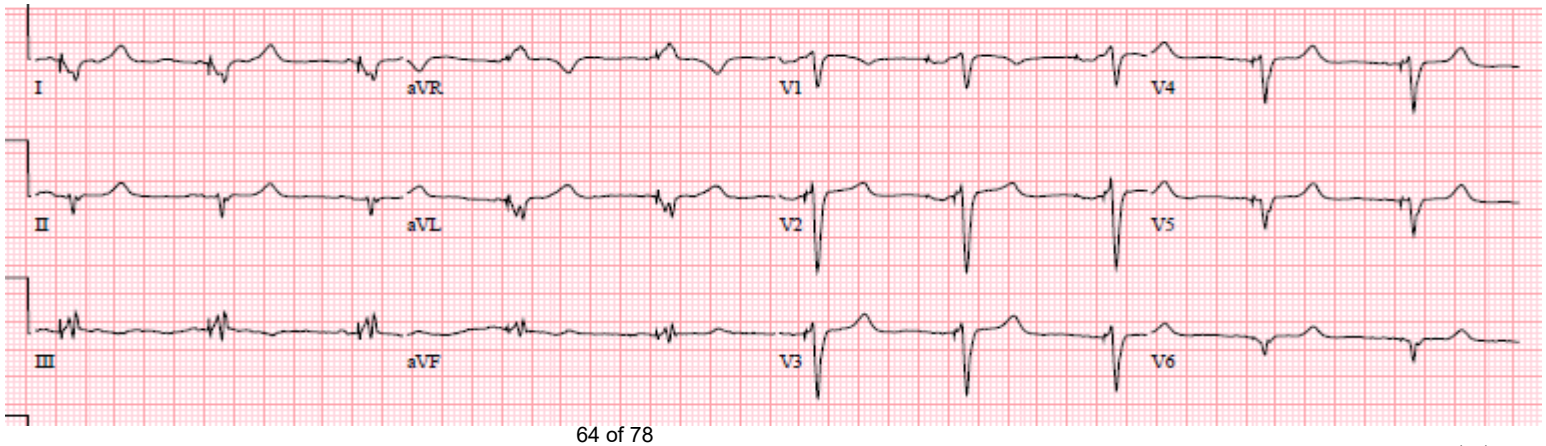
Pre-CRT



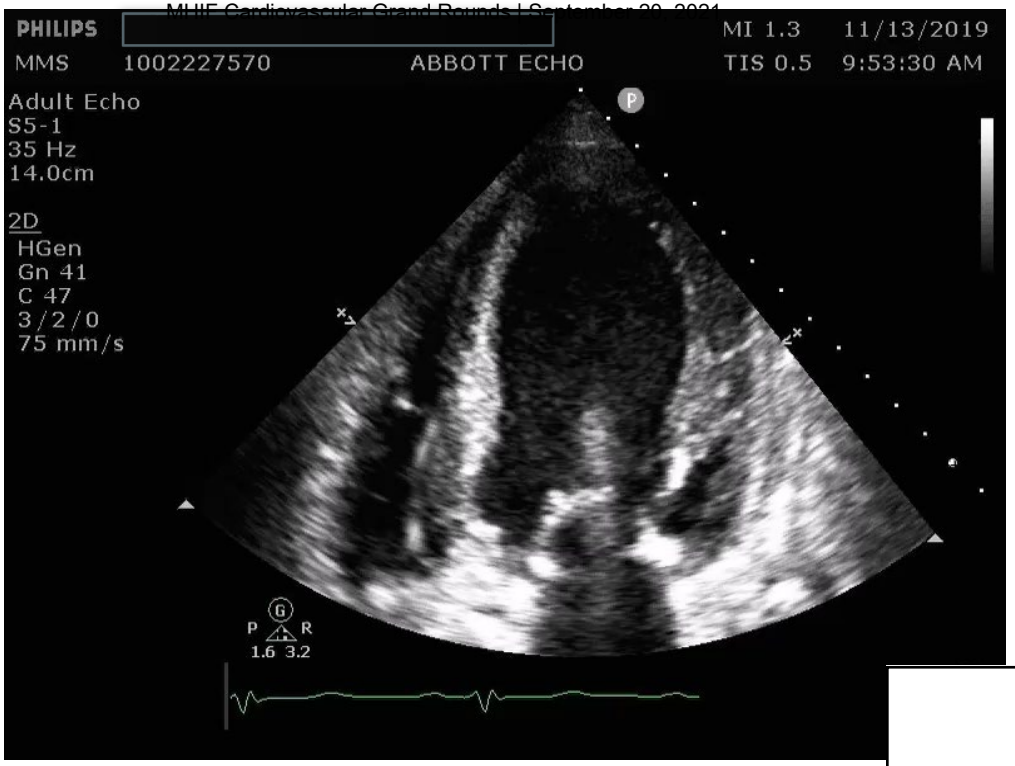
Post-CRT



Post-optimization



AAR

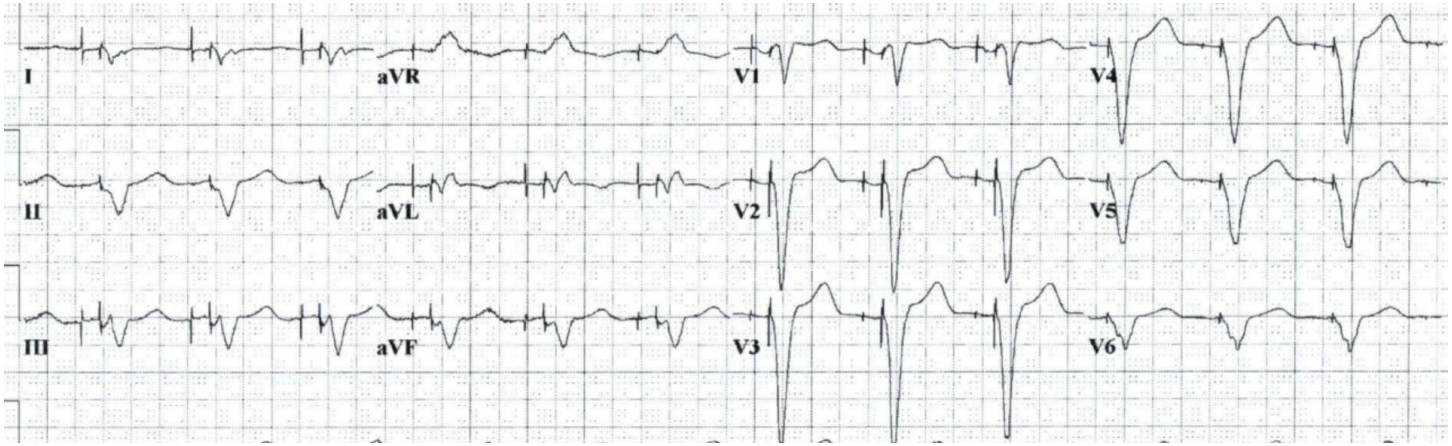


Pre-optimization
(LV-only, SAV 120 ms)

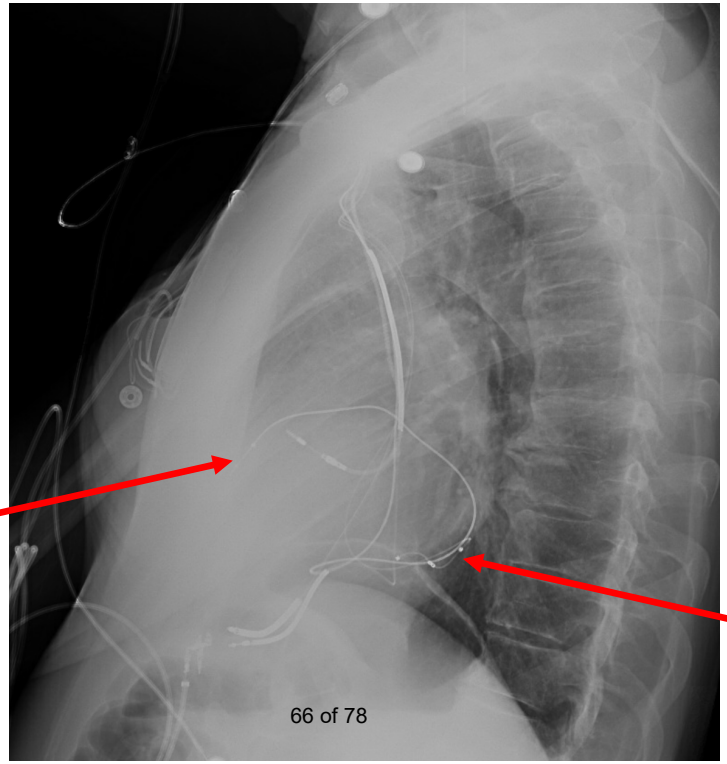
Post-optimization
(LV-only, SAV 100 ms)

AAR

77 y/o M with Systolic HF and CRT Referred for CRT Optimization



Chest

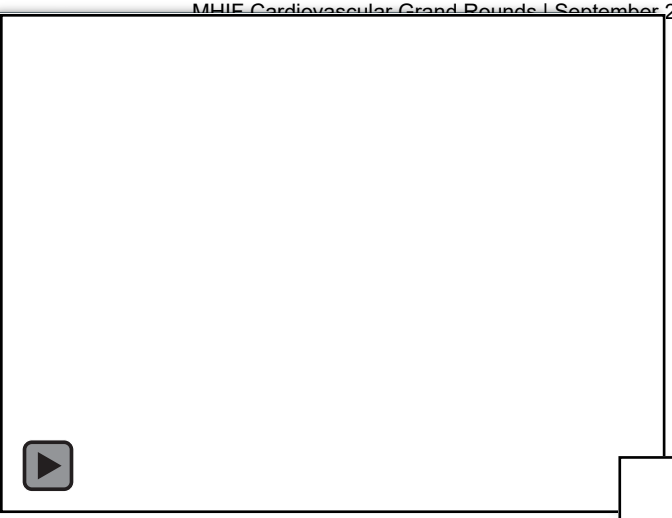


Back

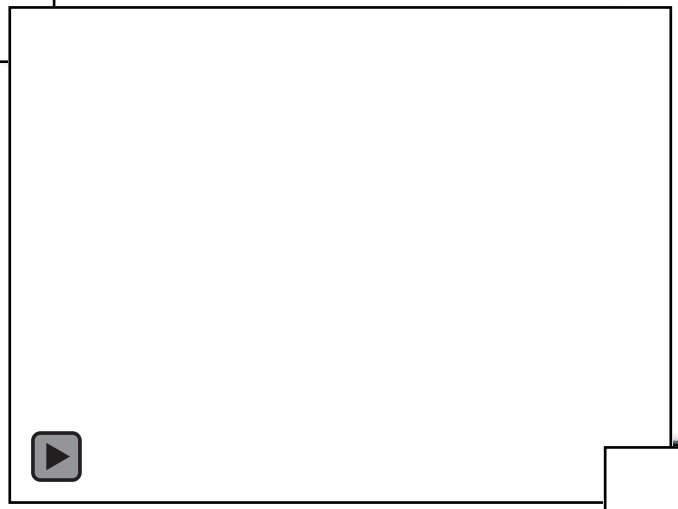
LV lead: old (2005)

LV lead: new (7/16)

11 years post-CRT: poor LV lead position
EF 20%



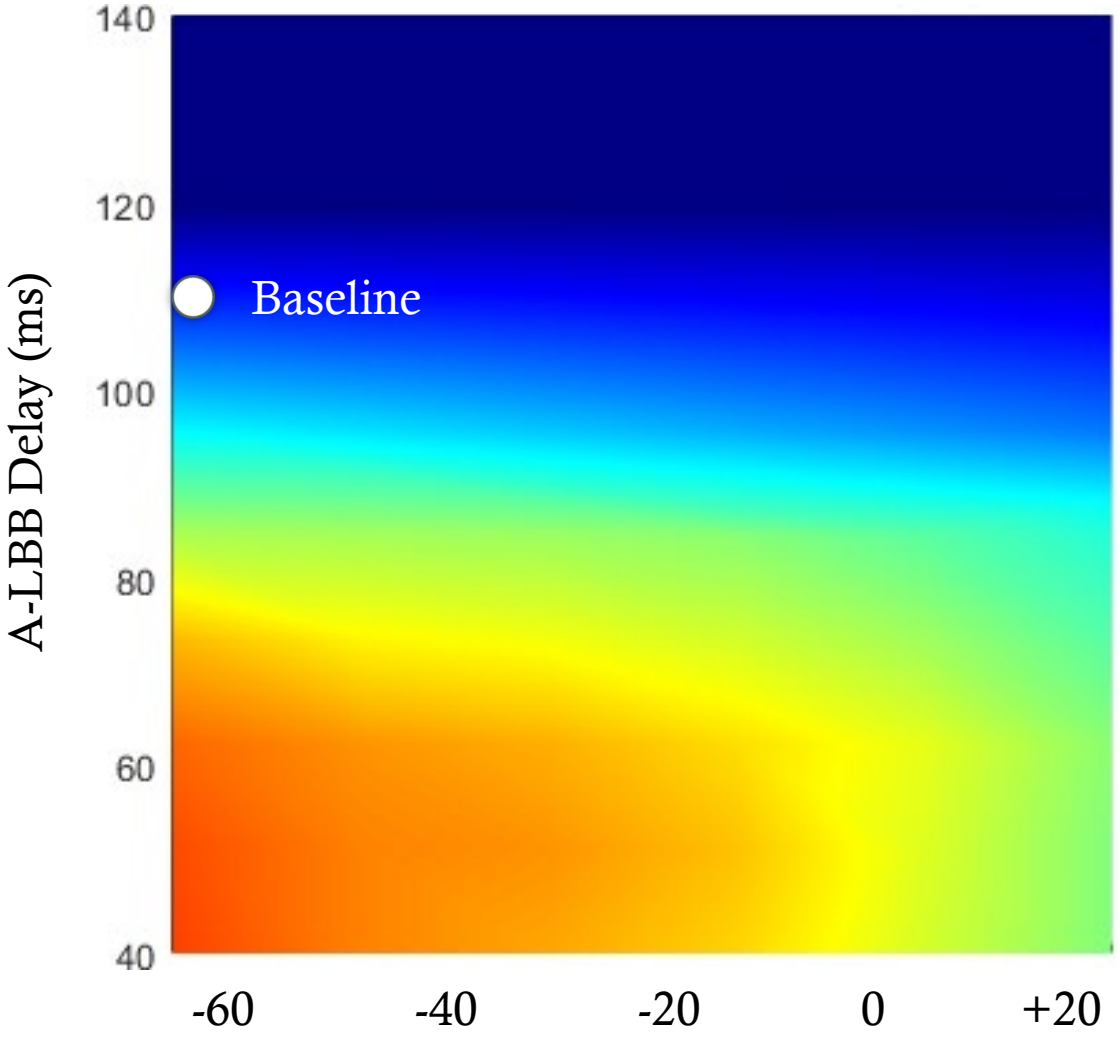
Post LV lead revision: VV = 0
EF 30%

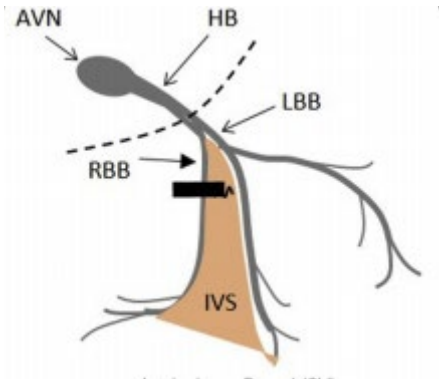


Post CRT Optimization: LV-only pacing
EF 38%

RAS

Patient with Underlying LBBB; LBB area and RV Pacing Leads





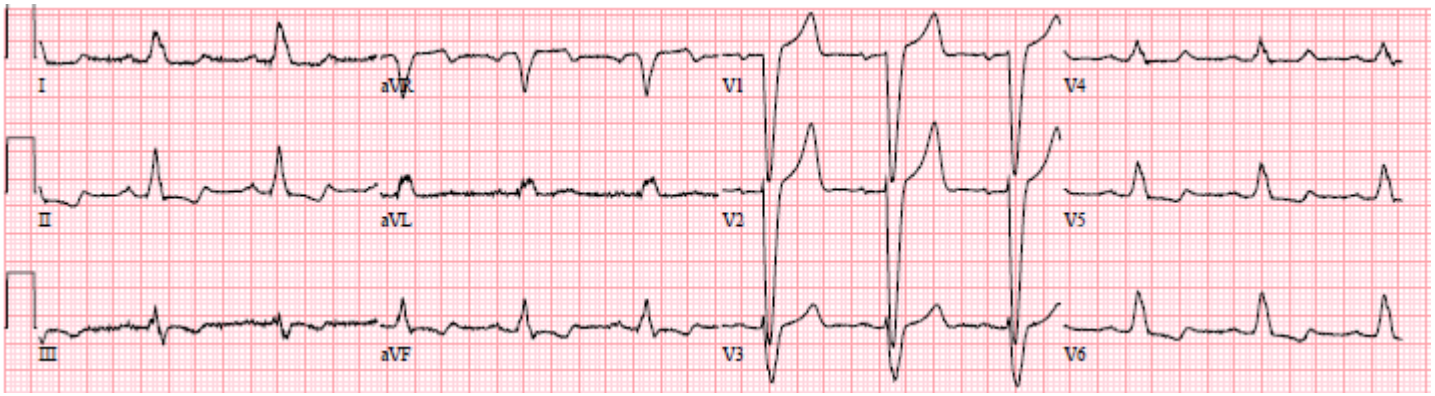
Best setting is with:

1. Very short AVD (no native wavefront)

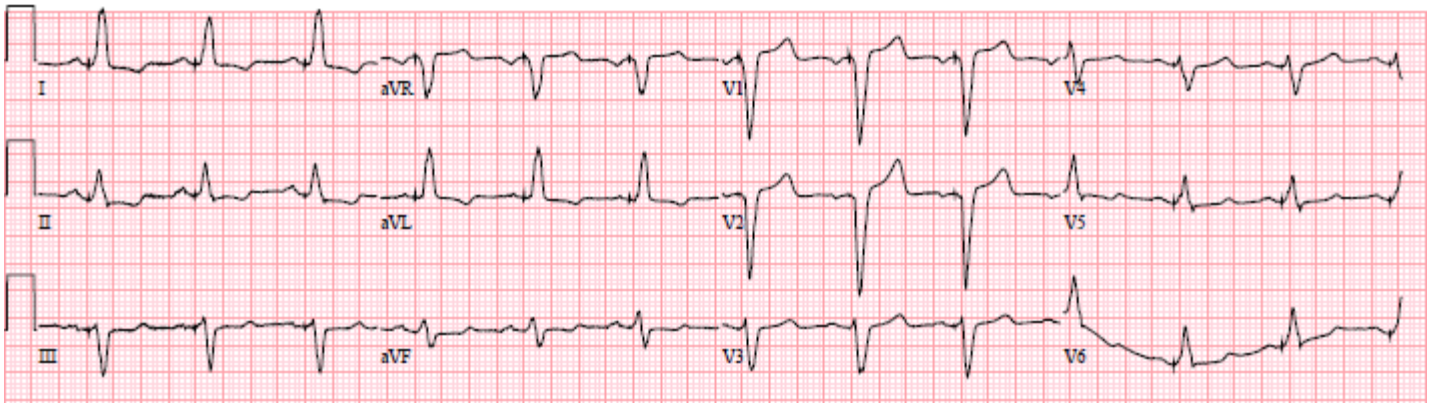
2. LBB way ahead of RV (no RVp wavefront)

SJJ

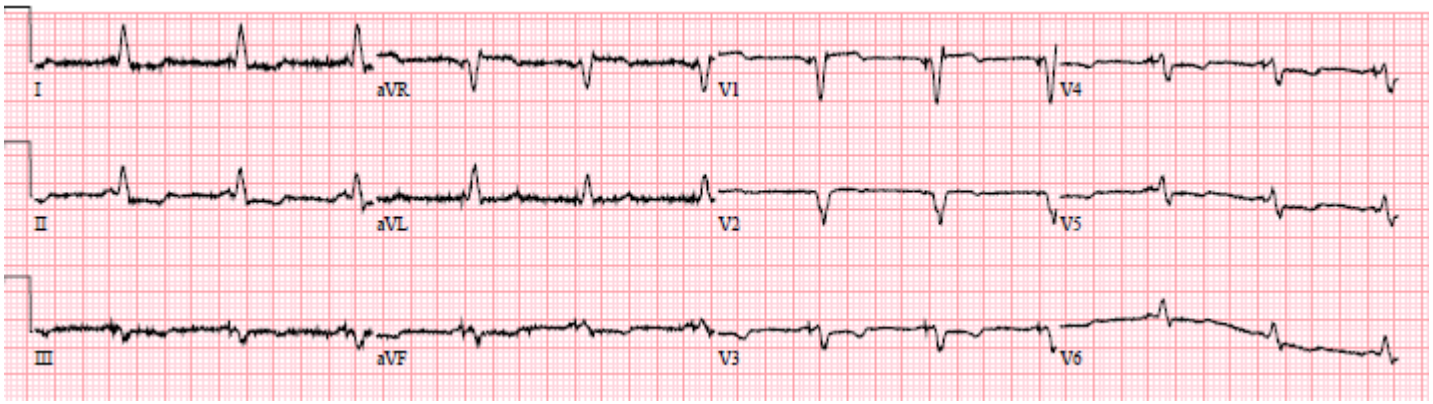
Pre-CRT



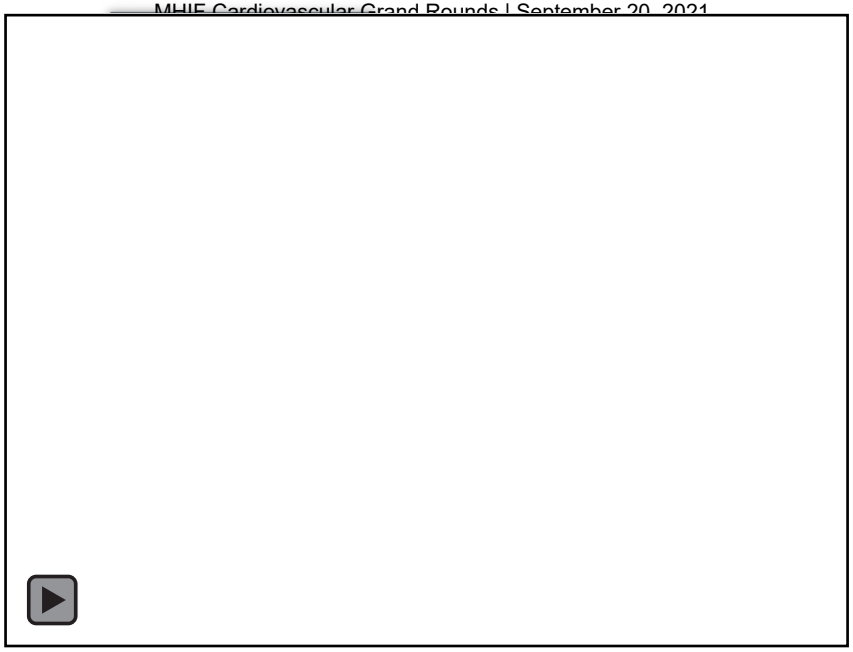
Post-CRT
LBBp, AVD120

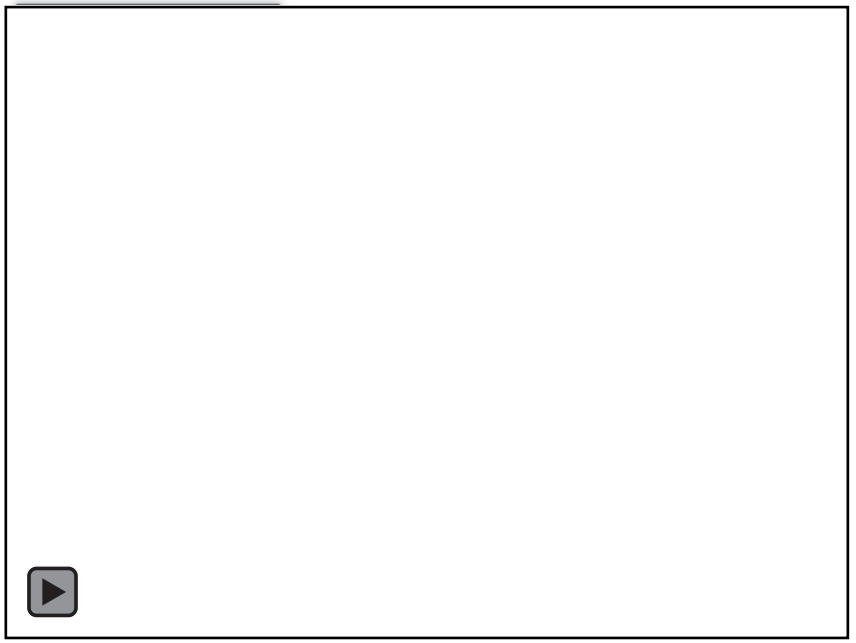


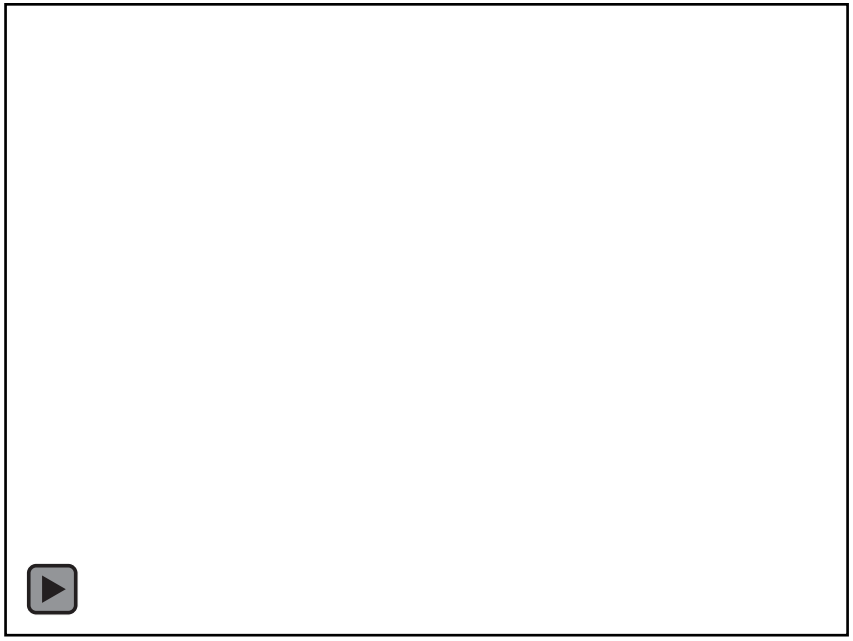
Post-optimiz.
LBBp, AVD 40



SJJ



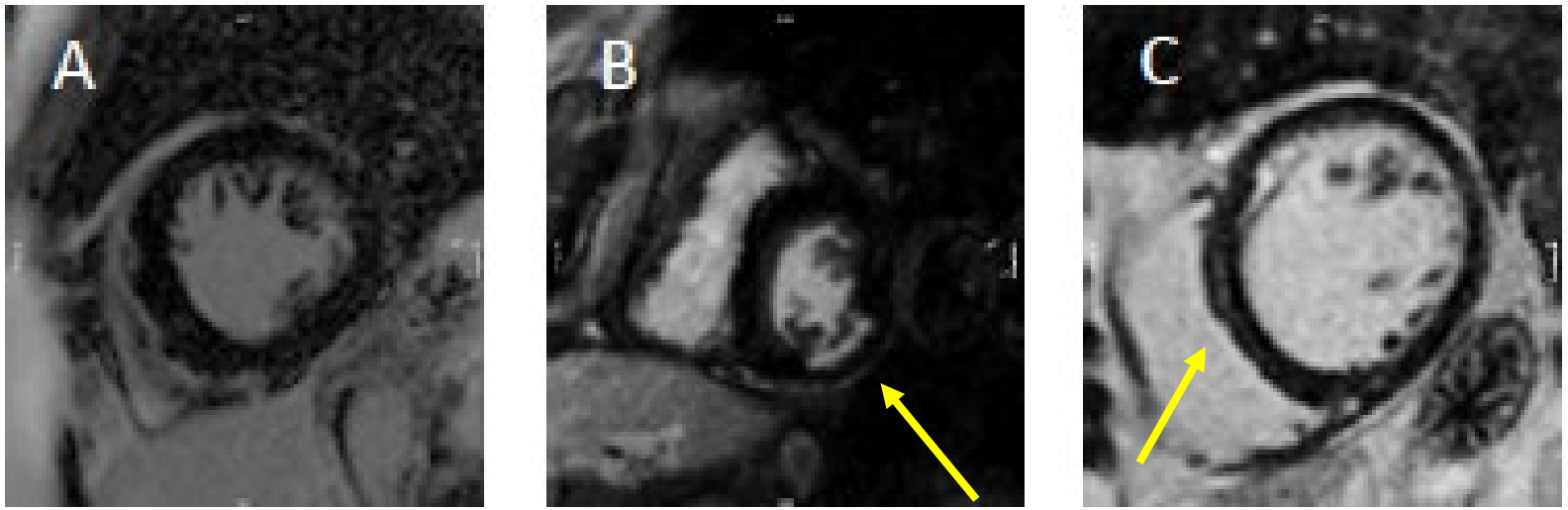




SJJ

Effects of 12-lead ECG Optimization of CRT on Patients with and without Delayed Enhancement on Cardiac MRI

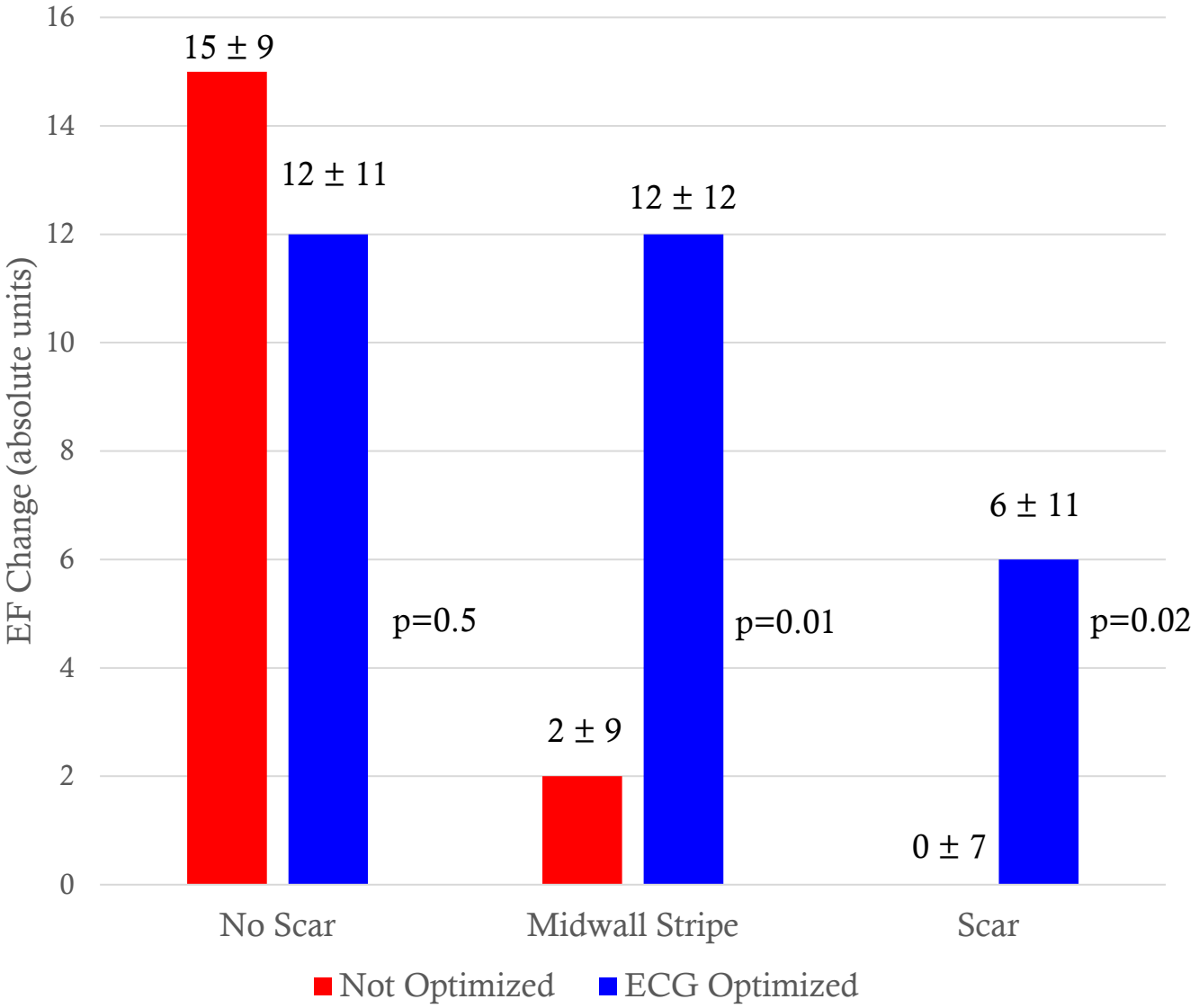
- Retrospective study of 130 patients with CRT
- 2007-13: not optimized (standard CRT programming)
- 2014-17: 12-lead ECG optimized (often LV-only or LV preactivation



No DE	Scar	Midwall fibrosis
n = 44	n = 56	n = 30

Gage RM ….Bank AJ. JAHA Open Access 2018

EF response 1 year post-CRT



Gage RM……Bank AJ. JAHA 2018

CRT Research Studies Using EDM's

Multi-lead ECG (M-LEAD) Research Study

- Focus on non-responders to CRT (but can enroll any patient with CRT device)
- Generate EDM, program all patients to best setting, compare pre- and 6 month post-optimization echos
- Enrolled > 140 patients

Multi**L**ead **E**CG **T**o **E**ffectively **O**ptimize **R**esynchronization in New **CRT** Recipients: METEOR-CRT

- Randomized double-blind trial of programming to best device setting based on EDM vs. standard setting for 6 months and then all patients programmed to best setting after 6 months
- Echo, NYHA class, Questionnaire pre-CRT and at 6 and 12 months
- Enrolled 25 patients with 120 planned
- Anticipate having 5-6 sites across the country

Cardiac MR in Non-responders to CRT

- Patients with EF < 40% post-CRT randomized to best device setting based on EDM vs. standard setting
- MRI at baseline and at 6 months post-randomization
- MRI at 3 settings: Native (CRT OFF), current setting, best setting
- Just starting enrollment

THE FUTURE

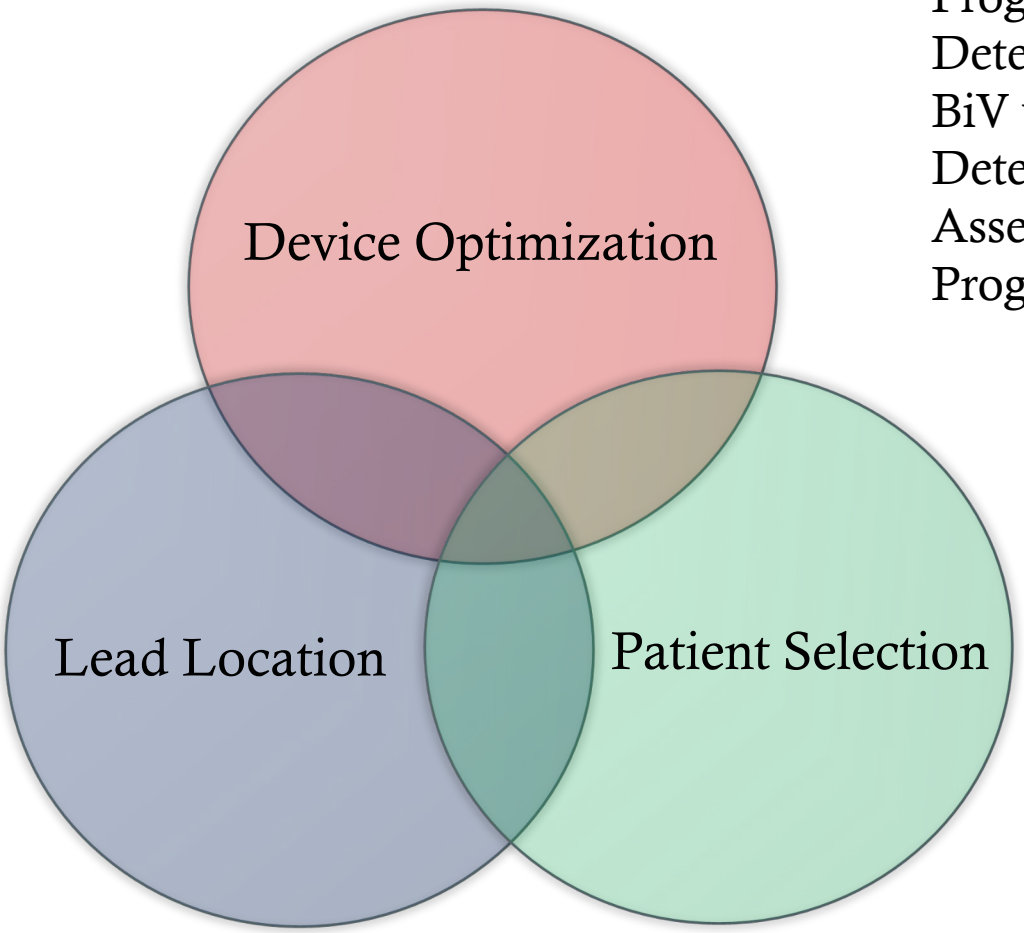
Clinical Use of EDM Technology in Future

- Incorporate EDM technology into programmers
- Automatically run through individualized settings and generate EDM (like Vector-Express)

Advantages of EDM for Clinical Use in CRT

- Cost-effective: no disposable supplies, equipment not expensive
- Automated: no observer bias
- Time efficient: generate EDM in ~ 40 minutes
- Non-invasive: no imaging study or dye needed
- Reproducible: highly
- Physiologic: consistent with wavefront fusion
- Physician-independent: no MD supervision needed during acquisition of data

EDM Impact on CRT



Program optimal AVD/VVD
Determine As and Ap AVDs
BiV vs. LV-only programming
Determine optimal quad electrode
Assess need for new lead
Program LBB area pacing

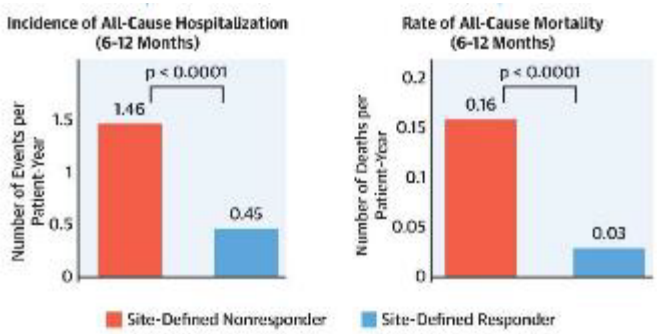
Broaden CRT criteria
(narrow QRS, L-IVCD)
Assess native dyssynchrony

Assist lead location at implant
Determine if lead location is cause of non-response

What is the Value of our New Technology?

Patients

Clinical Outcomes:
responders vs non-responders



10% ↓ in non-responder rate

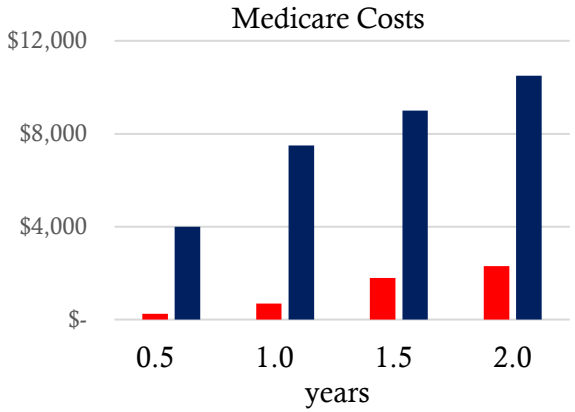
↓

3500 less hospitalizations/yr
543 less deaths/yr

Health Care System

Cumulative cost of care: responders vs. non-responders (Medicare and Private Insurance)

Varma, N. et al. J Am Coll Cardiol. 2019;74(21):2588-603.



10% ↓ in non-responder rate

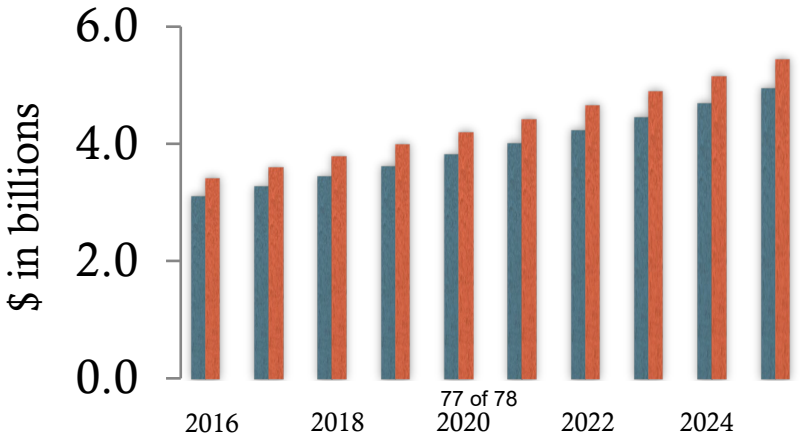
↓

~$62 million ↓ in annual cost of care

Device Companies

Increase in indicated patients
Expansion of indications

Assumptions:
- 100,000 implants/yr
- 35% NR rate



10% ↑ in projected market growth

↓

$3.95 billion ↑ revenue over 10 years

CRT Program: Vision