**MHIF FEATURED STUDY:**
**COVID-PACT**

**CONDITION:**
Critically-ill patients hospitalized with COVID-19

**PI:**
Retu Saxena, MD

**RESEARCH CONTACT:**
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**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

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.

CONDITION: Patients hospitalized for COVID-19

PI: Jay Traverse, MD

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SPONSOR: The University of Minnesota

OPEN AND ENROLLING:
EPIC message: Research MHIF Patient Referral

CRITERIA LIST/QUALIFICATIONS:

Inclusion:
• \( \geq 18 \) years old
• Positive nucleic acid test (NAT) confirming SARS-CoV-2 infection \( \leq 3 \) 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

LBBB
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
Death (21%) or HF Hospitalization (73%), IV Rx >4 hrs (6%)

12 month event rate reductions:
- CRT = by 35.8%
- CRT-D = by 39.5%
- p < .001, CRT-D vs. OPT
- p < .001, CRT vs. OPT

12 month OPT Event Rate (1-y) = 46.1%
CRT: THE PROBLEMS

Underutilization (~16% penetrance)  Non-Response (~30%)

CRT US MARKET 2019

- HF Patients 6.2 M
- NYHA Class I 2.2 M
- CRT Eligible 890 K
- CRT Eligible 890 K
- QRS < 120 ms 1.7 M
- EF > 35% 1.5 M

Treated: on label 139 K
Untreated 751 K

Annual CRT Implants US
- On-label: 139K
- Off-label: 22K
- Total: 161 K

Status

- Super-Responders 15%
- Responders 55%
- Non-progressors 10%
- Negative responders 5%
- Non-responders 15%

Time

JP Morgan MedTech Research
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
Native LBBB

73 yr, Male
NICM, LBBB

PR: 190 ms
QRSd: 170 ms

AsRVs – 190 ms
ApRVs – 230 ms

A-sensed LV-paced
A-sensed BiV-paced (SAV 140)
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 |

* 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
Cardiac Resynchronization Index

CRI (Cardiac Resynchronization Index): % change in AUC at any given setting compared to native.

\[
CRI = \left( \frac{AUC_{\text{native}} - AUC_x}{AUC_{\text{native}}} \right) \times 100
\]

AUCnative: Native Area Under the Curve
AUCx: Area Under the Curve at any given setting

LV-only Sweep - SAVD
LV-only SAVD and Wavefront Fusion

AVD (ms) vs. CRI (%):
- 40
- 60
- 80
- 100
- 120
- 140
- 160
- 180
- 200

AVD (ms): 115, 86, 47, 3
CRI (%): -35, -68, -99, -166

Multi-lead ECG Electrode Array

AUC (shaded) vs. LV-only SAVD

Normal, -13
Short-term Reproducibility of AUC Measurement

![Graph showing the reproducibility of AUC measurement](image)

- **AUC (mv*ms)**
- **Difference**

- **n = 162**
- **p = 0.284**
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

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

140 ms 140 ms
140 ms
100 ms

$V V = 0 \text{ ms}$
$V V = -40 \text{ ms}$
(LV$_p$ ahead)

$A_s$ or $A_p$

RV$_p$

LV$_p$ - 1
LV$_p$ - 2
LV$_p$ - 3
LV$_p$ - 4
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
Electrical Dyssynchrony Map (EDM) in 62 y/o M with LBBB, QRSd 178 ms

- Native – LVp: 70 ms
- Native – RVp: 50 ms
- RVp – LVp: 20 ms

**Line of Optimal Electrical Synchrony**

**VV = 0 line**

**LV-only pacing line**

(I) Native + LVp Wavefront Fusion

(II) Native + RVp + LVp Triple Wavefront Fusion

(III) RVp + LVp Wavefront Fusion
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
Changing Pacing Cathode of Quadripolar Lead:
RVp and Native Wavefronts identical but LVp wavefront shifted by 20 ms

Wavefront timing:

- LV2 -> LV4
  - 50 ms
  - 110 ms
  - 60 ms
- LV1 -> CAN
  - RVp to LVp: 70 ms
  - Native to LVp: 130 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
Atrial Sensing vs. Atrial Pacing: Changing Native Wavefront Only

**A**

SAVD

AsRVs 200 ms

---

LVp – Native 80 ms

---

**(I)**

LVp – Native 80 ms

**(II)**

RVp – LVp 30 ms

**(III)**

---

**B**

PAVD

ApRVs 280 ms

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LVp – Native 80 ms

---

**(I)**

LVp – Native 80 ms

**(II)**

RVp – LVp 30 ms

**(III)**

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**Fusion**

(I) LVp - Native

(II) Triple (LVp, Native, RVp)

(III) RVp - LVp

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<table>
<thead>
<tr>
<th>RVp – LVp: 30 ms</th>
<th>Native – RVp: 50 ms</th>
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<tr>
<td>Native – LVp: 80 ms</td>
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Narrow QRS and Electrical Dyssynchrony
CRT Optimization in a Patient with EF 15% and Narrow QRS (110 ms)
CRT Optimization in a Patient with EF 15% and Narrow QRS (110 ms)
Resynchronization Window

LBBB
QRS 160 ms

IVCD (LBBB-like)
QRS 116 ms

55 ms

30 ms
Cardiac Resynchronization Index (%) vs. AVD (ms)

- Black: Narrow QRSd
- Red: Moderate QRSd
- Blue: Prolonged QRSd

Sample data points for each category are marked with different colors and markers.

Sample size: n = 99
Selection of Patients for CRT
Native AUC for Different QRS Morphologies

- Strauss
- RVp
- ESC
- IVCD
- RBBB
Change in AUC with CRT (Baseline and Optimal)
Strauss LBBB QRS morphology

IVCD QRS morphology
Assessment of LV Lead Location from EDM’s
LV Lead Latency and EDM

LV lead latency 80 ms

LV1 to LV4
Assessment of LV lead location

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

LV-only SAV 120 – 260 AUC = 81.94

RV-only AUC = 156

RV lead
LV lead
THE OUTCOMES
Sparkplug Timing and Engine Efficiency/Power

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

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

At 900 rpm the crank rotates one degree in 0.185 msec.
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%
72 y/o F with Class III HF, IDCM, EF 15-20%
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-optimization
(LV-only, SAV 120 ms)

Post-optimization
(LV-only, SAV 100 ms)
77 y/o M with Systolic HF and CRT Referred for CRT Optimization

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%
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)
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)
EF response 1 year post-CRT

No Scar

- Not Optimized: 15 ± 9
- ECG Optimized: 12 ± 11

Midwall Stripe

- Not Optimized: 2 ± 9
- ECG Optimized: 12 ± 12

Scar

- Not Optimized: 6 ± 11
- ECG Optimized: 0 ± 7

p values:
- No Scar: p=0.5
- Midwall Stripe: p=0.01
- Scar: p=0.02
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

MultiLead ECG To Effectively Optimize Resynchronization 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

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


**Device Companies**
Increase in indicated patients Expansion of indications

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

10% ↓ in non-responder rate
3500 less hospitalizations/yr
543 less deaths/yr

10% ↓ in non-responder rate
~$62 million ↓ in annual cost of care

10% ↑ in projected market growth
$3.95 billion ↑ revenue over 10 years