Gap Junction and Ventricular Arrhythmia during Therapeutic Hypothermia

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Part 8: Post–Cardiac Arrest Care

2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

Clifton W. Callaway, Chair; Michael W. Donnino; Ericka L. Fink; Romegryko G. Geocadin; Eyal Golan; Karl B. Kern; Marion Leary; William J. Meurer; Mary Ann Peberdy; Trevon M. Thompson; Janice L. Zimmerman

• **Targeted Temperature Management (TTM)**
  – Comatose adult patients with ROSC after cardiac arrest have TTM (Class I, LOE B for VF/pVT OHCA)
  – Maintain a constant temperature between $32^\circ\text{C}$ and $36^\circ\text{C}$ during TTM (Class I, LOE B), for at least 24 hours after achieving TTM (Class IIa, LOE C)

_Circulation. 2015;132[suppl 1]:S465–S482_
Although TH is neuro-protective, it might carry the risk of VT/VF.
EP Lab, Taichung VGH

Langendorff setup with a two-camera optical mapping system

Optical mapping system software

Thermostatic perfusion / superfusion model

Langendorff perfused isolated rabbit heart

37°C

33°C or 30°C
Microvolt T-Wave Alternans

Physiological Basis, Methods of Measurement, and Clinical Utility—Consensus Guideline by International Society for Holter and Noninvasive Electrocardiology

CV slowing and spatial heterogeneities of CV restitutions were enhanced in MH and SH hearts, reversed after R.

Hsieh et al. Circ J. 2011;75(7):1706-16
Gap Junction and Conduction Velocity

- Gap junctions are membrane channels that mediate cell-to-cell movement of ions and small metabolites.
- Cardiac CV is determined by
  - Extra-cellular matrix
  - Phase 0 Na current
  - GJ coupling
- In the heart, GJ plays an important role in impulse conduction.
Hypothesis

- GJ remodeling in ventricles might occur shortly after the start of TH.
- GJ remodeling contributes to the conduction disturbance.
- Re-warming the hearts from SH can reverse the GJ remodeling and conduction disturbance.
T-Cx43 distribution (lateralization) increased during MH and SH

A
Baseline (37°C)  MH (33°C)  SH (30°C)  Rewarm (37°C)

B
T-Cx43 area (% tissue area)

C
% Lateral / Total T-Cx43
Not completely reversed after R
CV slowing and spatial heterogeneities of CV restitutions were enhanced in MH and SH hearts, reversed after R.

Hsieh et al. Circ J. 2011;75(7):1706-16
Interpretation

• In this acute model (minutes to hours), Cx43 lateralization was present regardless of a depressed (TH hearts) or recovered (R hearts) conduction.

  – Cx43 lateralization may not fully explain the CV change.
Hypothermia and GJ

- Short-duration (30 minutes) TH causes a prompt temperature-dependent Cx43 GJ remodeling.
- GJ remodeling alone might not play a major role in the conduction disturbance in this acute model.

Rotigaptide - a GJ enhancer

Gap junction modifier rotigaptide decreases the susceptibility to ventricular arrhythmia by enhancing conduction velocity and suppressing discordant alternans during therapeutic hypothermia in isolated rabbit hearts.

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Hsieh YC et al. Heart Rhythm 2016:13;251-261
Effects of Rotigaptide on APD (A,B) and CV (C,D) during MH and SH

* No significant effect on APD
* Partially restore conduction slowing

Figure 1
Effects of Rotigaptide on APD Alternans during MH and SH

Delay the onset of SDA during SH

Figure 4
Effects of Rotigaptide on the incidence of PVCs during MH and SH

Decrease the incidence of PVCs at SH

Figure 5
Major findings:

(1) Rotigaptide partially restored the conduction slowing, and completely abolishes the spatial heterogeneity of ventricular conduction during TH.

(2) Rotigaptide decreased the incidence of PVCs at TH.

(3) Rotigaptide delayed the onset of arrhythmogenic SDA at SH, and decreased the susceptibility to pacing-induced VF during MH / SH.

Enhancing cell-to-cell coupling by rotigaptide might be a novel approach to prevent recurrent VA in patients undergoing TH.
Rotigaptide on beat-to-beat ECG morphologic variation (Divergence) and Ventricular Arrhythmia during Hypothermia
The Use of Signal Analyses of Ventricular Tachycardia Electrograms to Predict the Response of Antitachycardia Pacing in Patients with Implantable Cardioverter-Defibrillators

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Divergence

- Beat-to-beat morphologic variation
- A template ECG was constructed by averaging all the normalized ventricular EGMs

\[
\text{Divergence} = \frac{1}{N} \sum_{i=1}^{N} d(X_i, \bar{X})
\]

- Divergence will be of zero for an episode with identical ventricular ECG.

Hypothesis:

Is ECG divergence associated intra-cardiac wavebreaks?
A total of 122 optical/p-ECG recordings were evaluated.

Hsieh et al. Unpublished Data 2019
A

\[ *p=0.036 \]

B

\[ p=0.032 \]

*Fisher's exact test

Hsieh et al. Unpublished Data 2019
A

No Roti

Divergence = 0.1006

B

Roti

Divergence = 0.0515

Hsieh et al. Unpublished Data 2019
A

- VF, No Roti
- VF, Roti
- No VF, No Roti
- No VF, Roti

Divergence

(b eyes)

B

p=0.02

p=0.004

p=0.04

p=0.41

No VF, No Roti (N=28)
No VF, Roti (N=33)
VF, No Roti (N=34)
VF, Roti (N=17)

Hsieh et al. Unpublished Data 2019
A

- VF, No Roti
- VF, Roti
- No VF, No Roti
- No VF, Roti

WBs/phase map

B

- No VF, No Roti (N=28)
- No VF, Roti (N=33)
- VF, No Roti (N=34)
- VF, Roti (N=17)

p = 0.03
p = 0.96

P < 0.001
p = 0.005

Hsieh et al. Unpublished Data 2019
Figure 6

A. Phase Maps during S1 Pacing

0 ms  400 ms  778 ms

1170 ms  1559 ms  1902 ms

B. S1 Pacing CL = 280 ms

p-ECG Burst pacing

p-ECG Stop pacing

Local optical Recording

500 ms

C. S1 Pacing CL = 280 ms

D. S1 Pacing CL = 280 ms
Figure 5

A  Phase Maps during S1 Pacing

0 ms  385 ms  770 ms

1155 ms  1540 ms  1925 ms

B  S1 Pacing CL= 220 ms

p-ECG Burst pacing

p-ECG Stop pacing

Local optical Recording

500 ms

C  S1 Pacing CL= 220 ms

Divergence

D  S1 Pacing CL= 220 ms

WB Number
Epicardial WBs

Divergence

$y = 0.0752x + 0.0757$

$p < 0.001$

Hsieh et al. Unpublished Data 2019
Major Findings

• Ventricular **beat-to-beat morphological variation** evaluated by divergence is significantly correlated with **epicardial WBs** during ventricular pacing at TH.
Spatially discordant alternans

No Roti

Spatially concordant alternans/No alternans

Roti

Hsieh et al. Unpublished Data 2019
Clinical Implication

• In patients with an ICD/CRTD for VA, the episodes of successful/failed ATP therapy should be carefully examined.

• The presence of high divergence during ATP might indicate epicardial WBs formation at ATP and should be categorized into high-risk group and reduce the ATP attempts.
Conclusions

- The GJ modifier (rotigaptide) protects the heart against VA during TH.
- Enhancing cell-to-cell coupling by rotigaptide might be a novel approach to prevent recurrent VA in patients undergoing TH.
- ECG divergence might be caused by discordant alternans (DA), and is correlated epicardial WBs.
- Rotigaptide might decreases ECG divergence and DA, and prevent pacing-induce VF.
Thank you!!