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Calcium Sensitizer Levosimendan on VF Vulverability during Therapeutic Hypothermia

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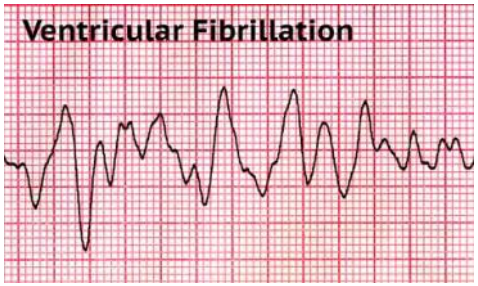
Korean Heart Rhythm Society
COI Disclosure

Name of First Author: Yu-Cheng Hsieh

The authors have no financial conflicts of interest to disclose concerning the presentation

VF and Sudden Cardiac Death



Acta Cardiol Sin. 2006;22:53-7.

ACLS Guidelines 2020

Part 3: Adult Basic and Advanced Life Support

2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

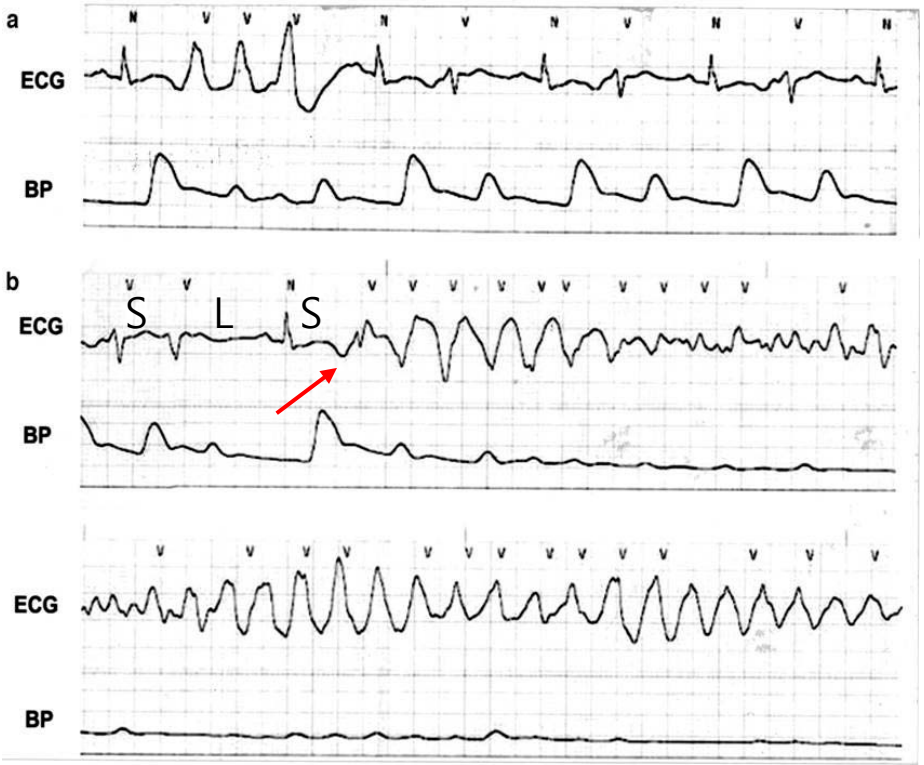
Recommendations for Performance of TTM		
COR	**LOE**	**Recommendations**
1	B-R	1. We recommend selecting and maintaining a constant temperature between 32°C and 36°C during TTM.
2a	B-NR	2. It is reasonable that TTM be maintained for at least 24 h after achieving target temperature.
2b	C-LD	3. It may be reasonable to actively prevent fever in comatose patients after TTM.
3: No Benefit	A	4. We do not recommend the routine use of rapid infusion of cold IV fluids for prehospital cooling of patients after ROSC.

Images in Cardiovascular Medicine

Therapeutic Hypothermia-Related Torsade de Pointes

Chien-Hua Huang, MD; Min-Shan Tsai, MD; Chiung-Yuan Hsu, MD; Wen-Jone Chen, MD, PhD

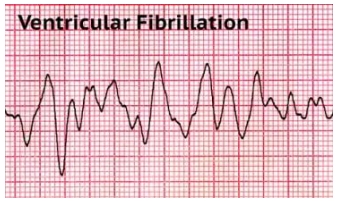
TH is neuro-protective, it might carry the risk of VF.



Circulation. 2006;114:e521-2.

Preventing Ventricular Arrhythmia during TH is clinically Important

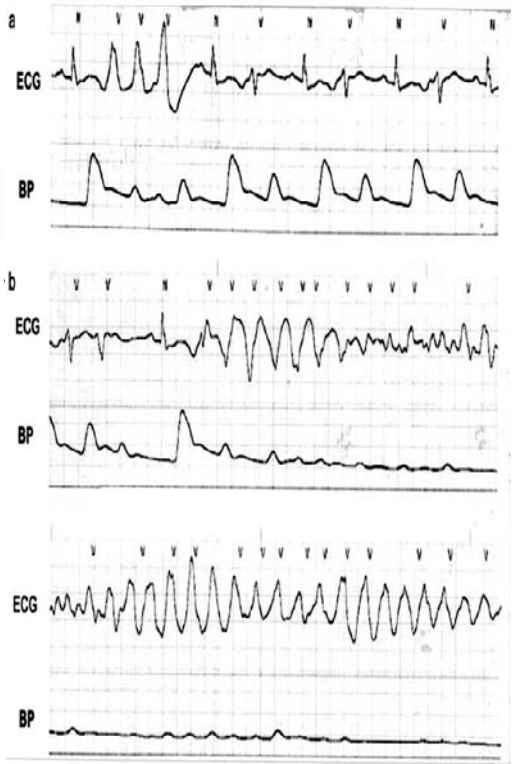
Ventricular Fibrillation (VF) and SCD



Therapeutic Hypothermia (TH)

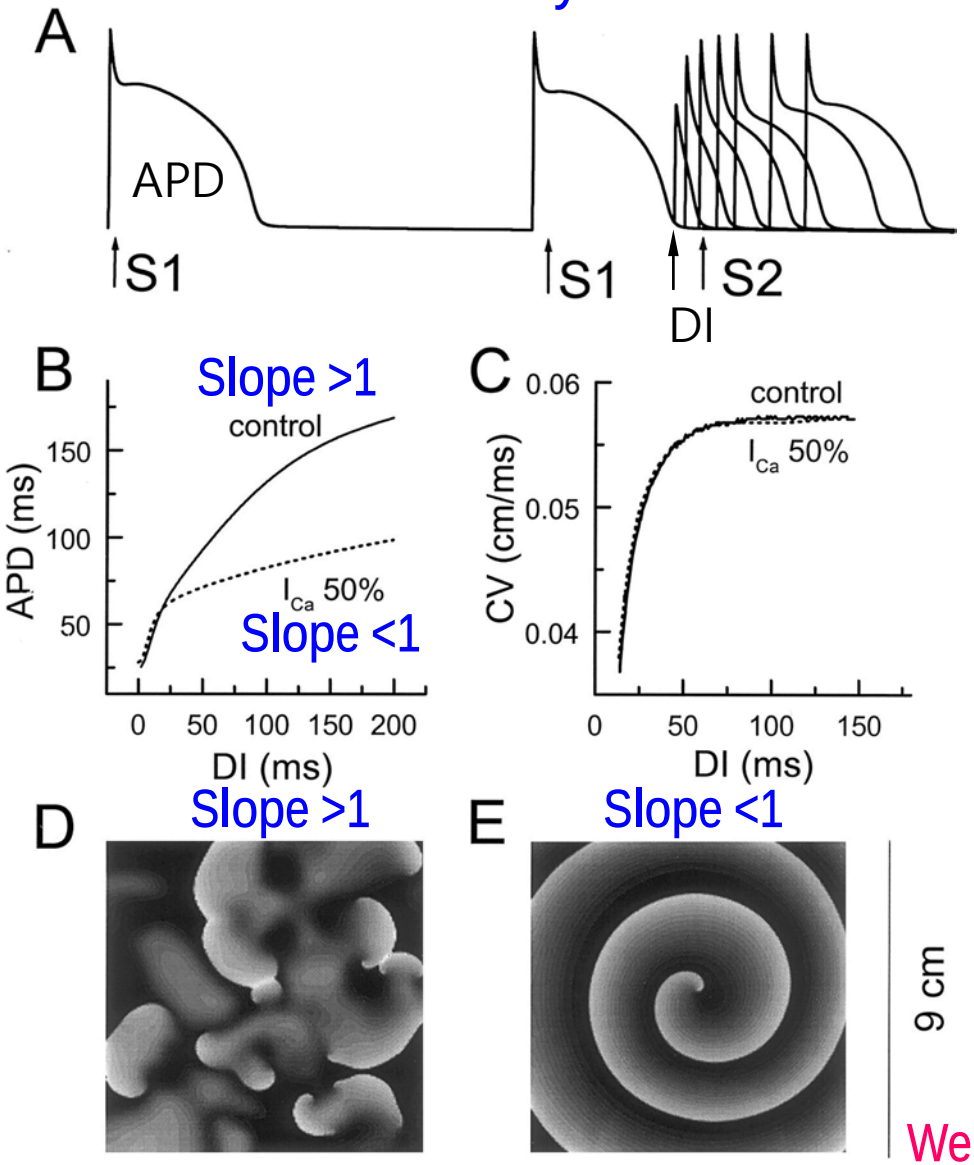
STOP

Ventricular Fibrillation (VF)



Circulation. 2006;114:e521-2.

Effects of APD and CV Restitution on Spiral-Wave Stability in Luo-Rudy Ventricular Action Potential Model



A steep action potential duration (APD) restitution (APDR) is associated with multiple wavebreak and arrhythmia.

Weiss et al. *Circulation* 1999;99:2819-26

Therapeutic Hypothermia (30°C) Enhances Arrhythmogenic Substrates, Including Spatially Discordant Alternans, and Facilitates Pacing-Induced Ventricular Fibrillation in Isolated Rabbit Hearts

Yu-Cheng Hsieh, MD; Shien-Fong Lin, PhD*; Tung-Chao Lin, MD;
Chih-Tai Ting, MD, PhD; Tsu-Juey Wu, MD, PhD

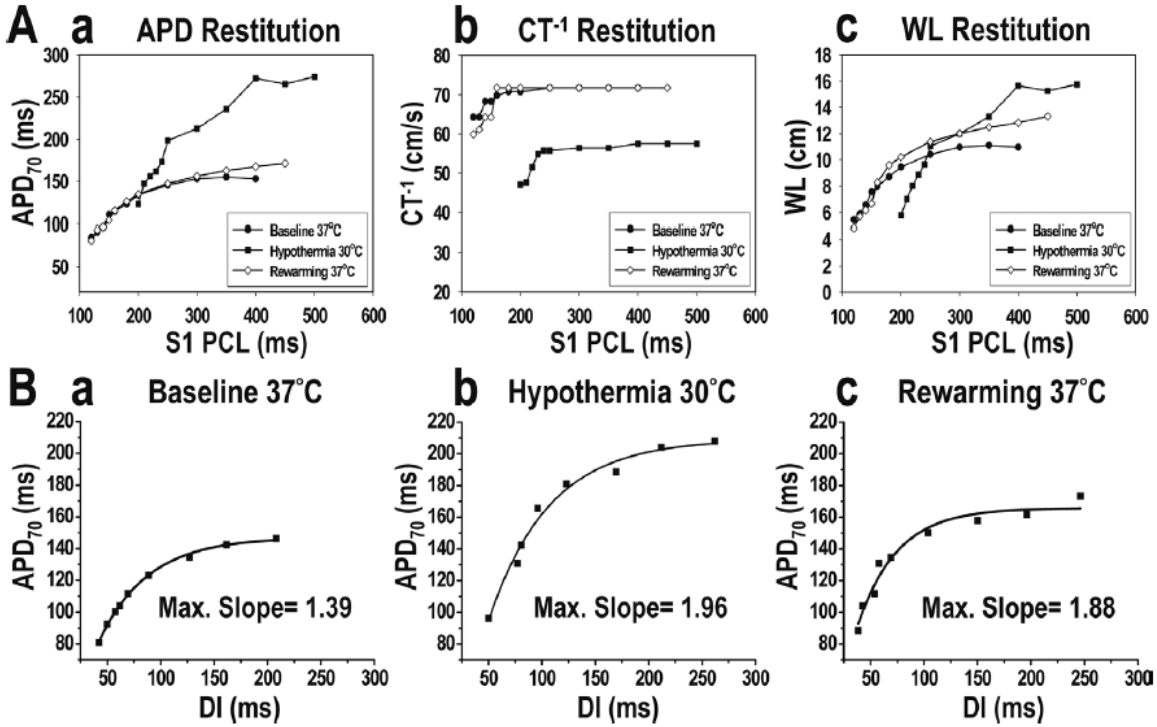
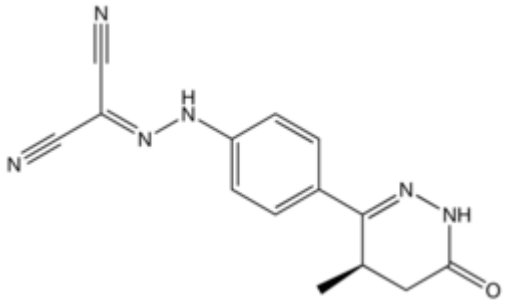


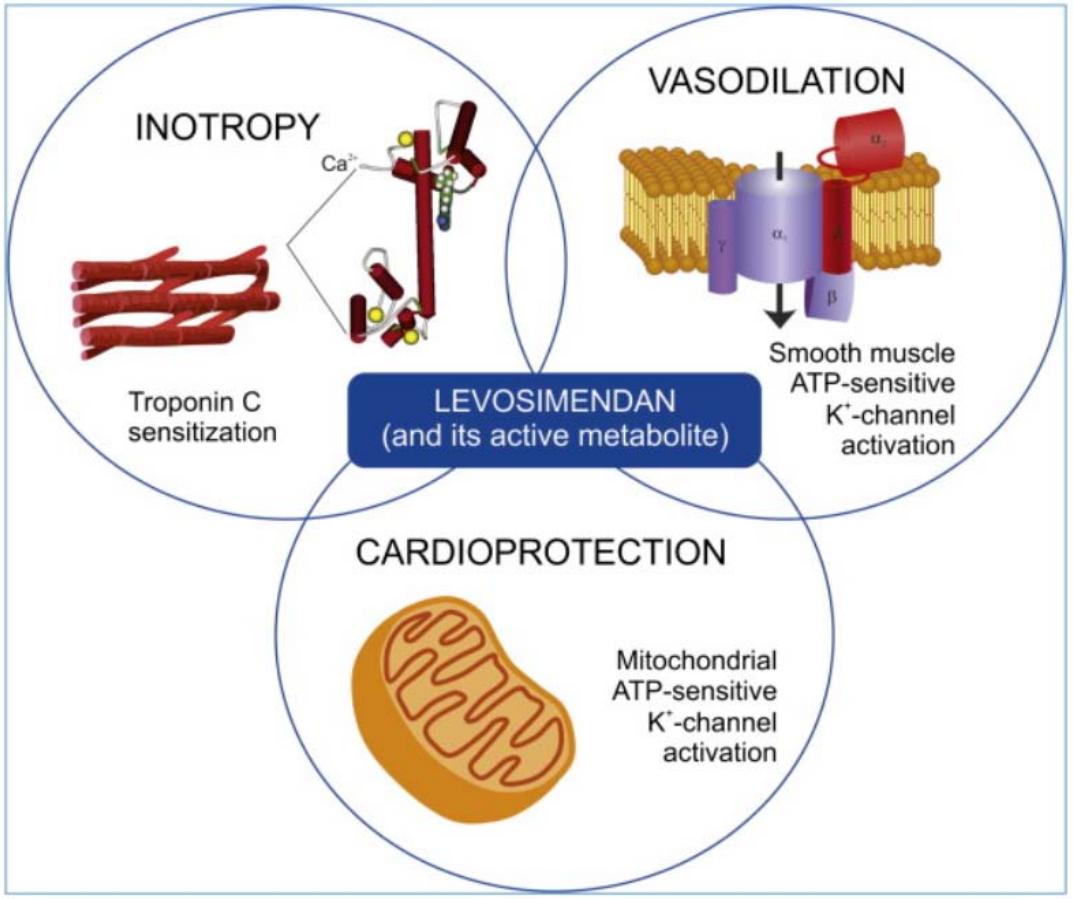
Figure 2. (A) Effects of hypothermia on APD, CT^{-1}, and WL restitutions. Data from heart no. 3 of Protocol II. (B) Effects of hypothermia on the maximum slope of APDR. Data from site a of heart no. 4 in Protocol II. See text for details.

Hsieh, et al. Circ J. 2009;73:2214-22

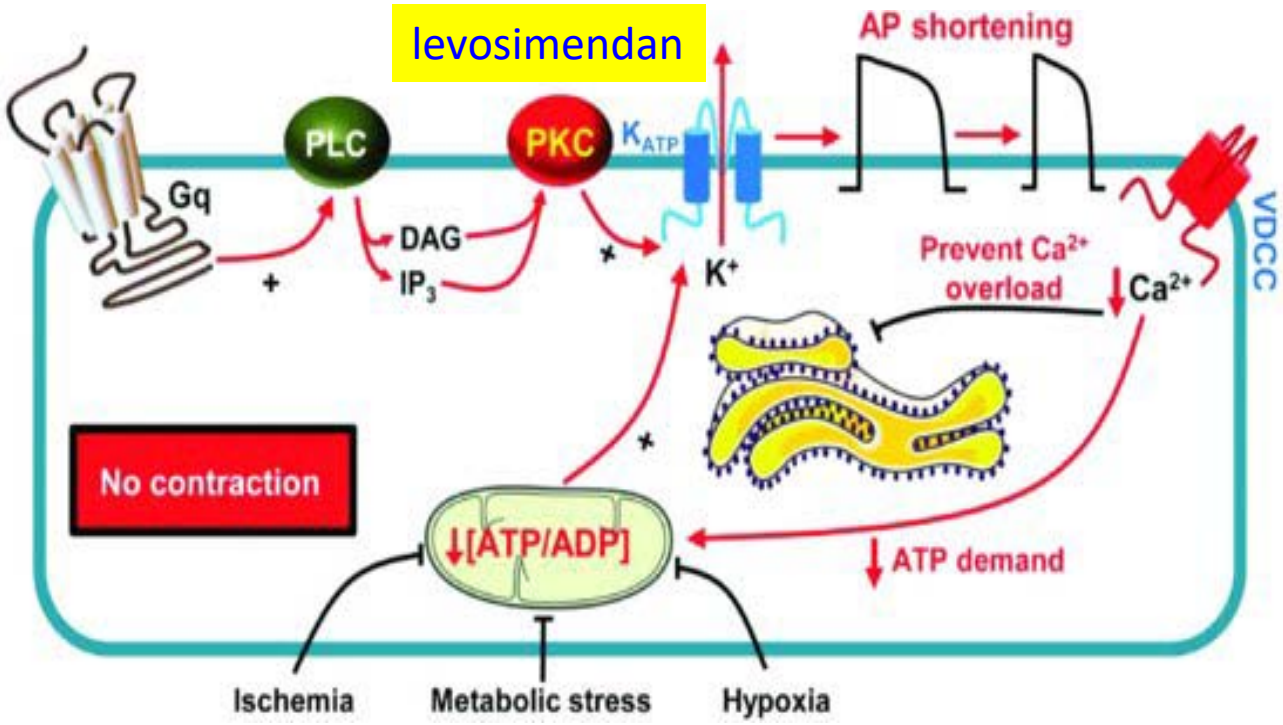
Levosimendan



Formula	$C_{14}H_{12}N_6O$
Molar mass	280.291 g·mol^{-1}



ATP-Sensitive K Channels and Their Physiological and Pathophysiological Roles



The calcium sensitizer levosimendan has been reported to shorten APD by enhancing ATP-sensitive K current.

Compr Physiol. 2018;8:1463-1511.

Background

- Therapeutic hypothermia (TH) increases ventricular arrhythmia (VA) risk by prolonging action potential duration (APD) and **steepening** the **APD restitution (APDR).**

- Levosimendan has been reported to shorten APD by enhancing ATP-sensitive K current and may affect the APDR.

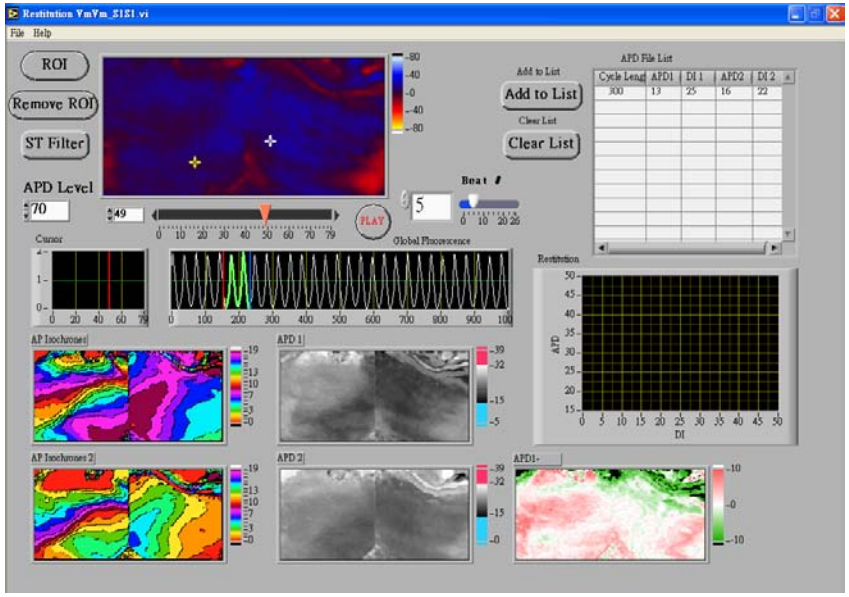
Hypothesis

- Levosimendan
  - shorten the already prolonged APD during TH
  - decreasing the maximal slope of APDR
  - prevent the occurrence of VA

Langendorff setup with a two-cameraoptical mapping system

Thermostatic perfusion / superfusion model

Optical mapping system software



Study protocol

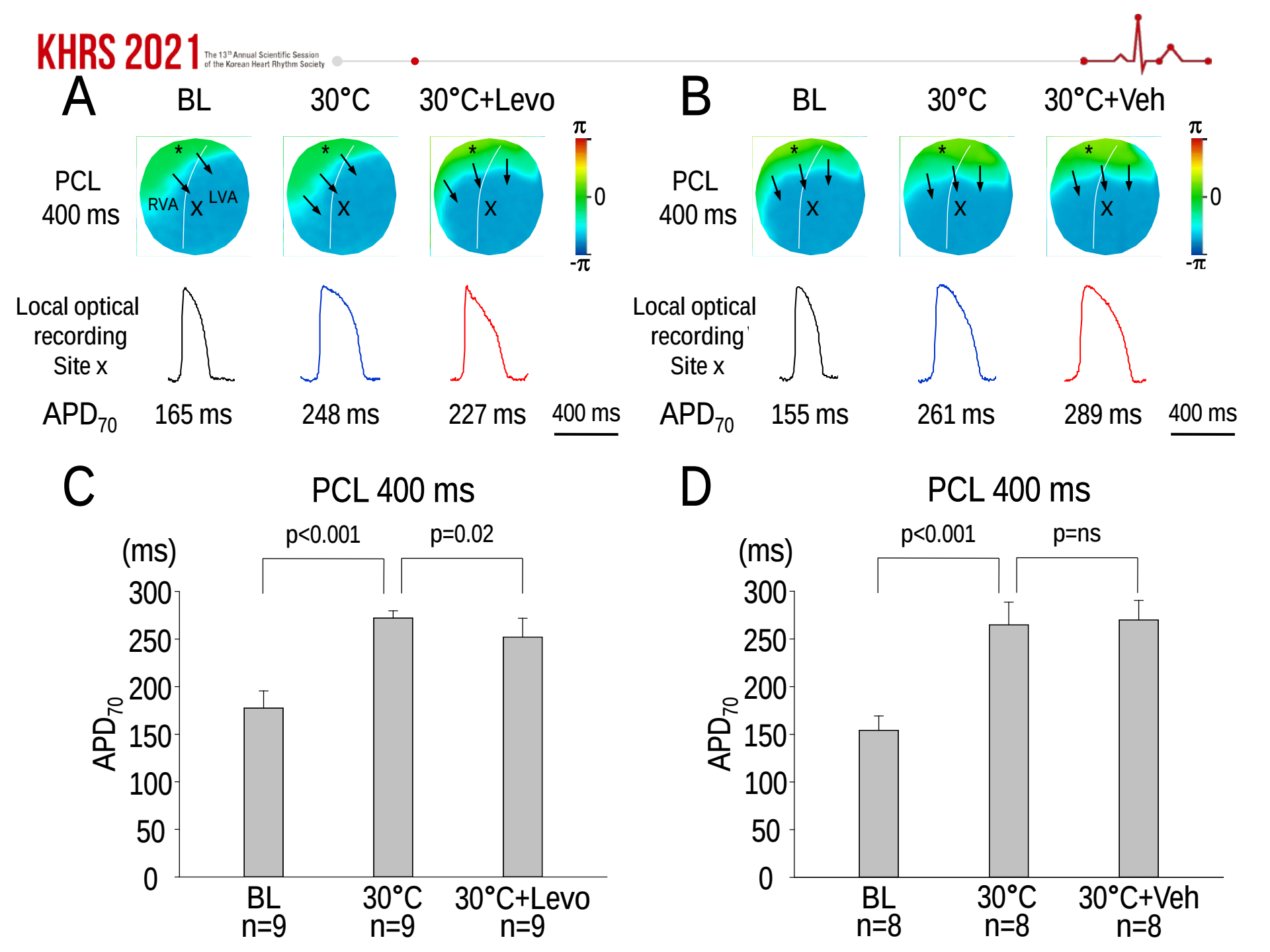
Levosimendan group (n=9)

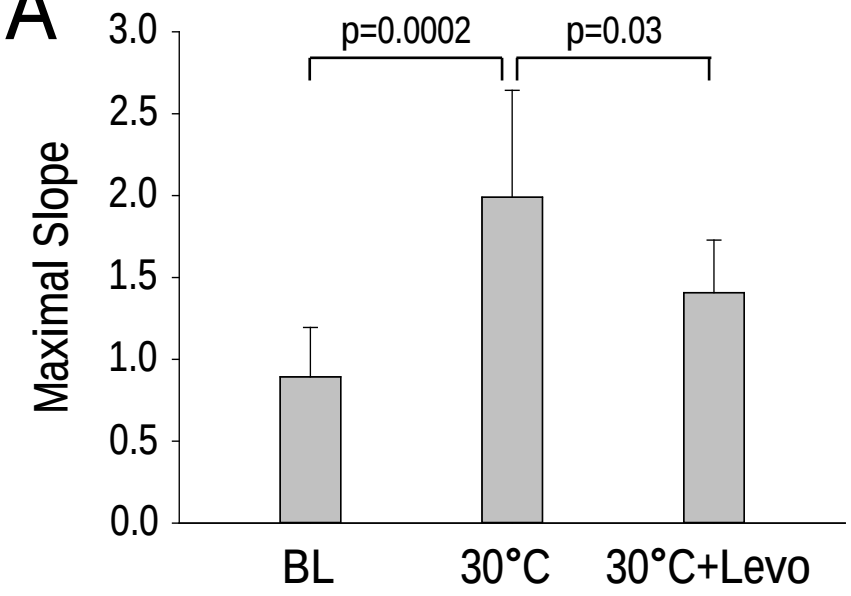
Baseline → 15 min: TH (30°C) → 30 min: TH (30°C) + *Levosimendan 0.5uM*

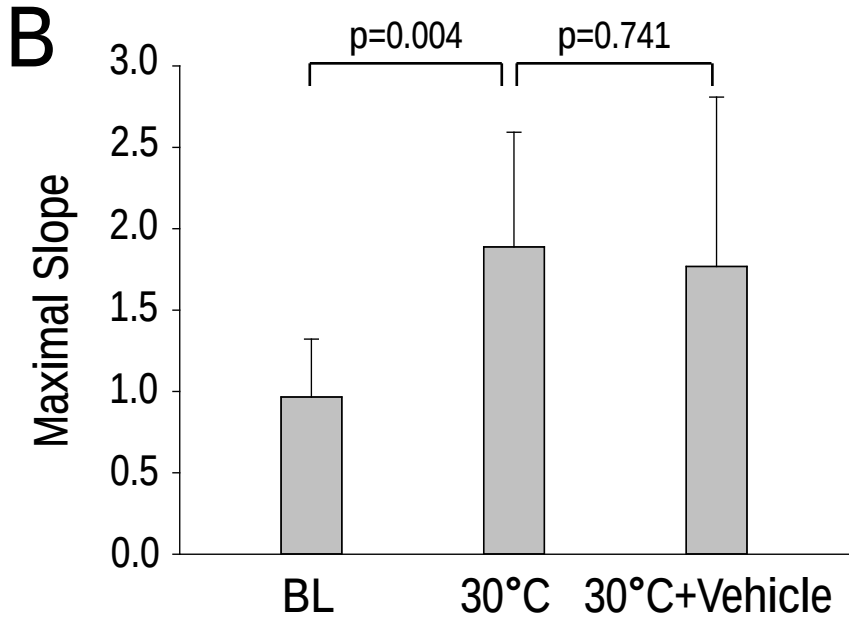
Control group (n=8)

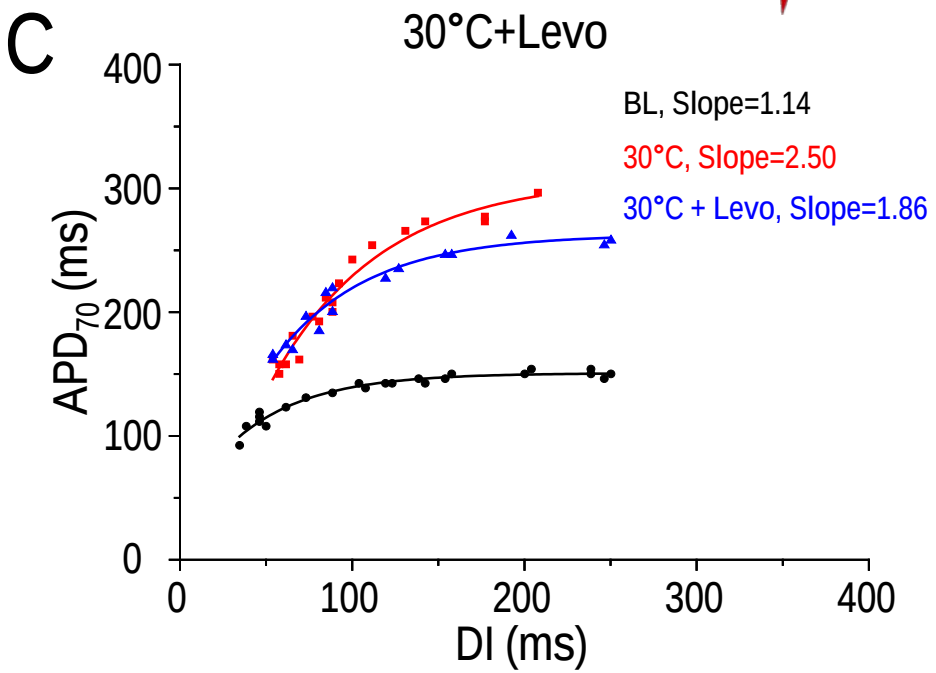
Baseline → 15 min: TH (30°C) → 30 min: TH (30°C) + *Vehicle*

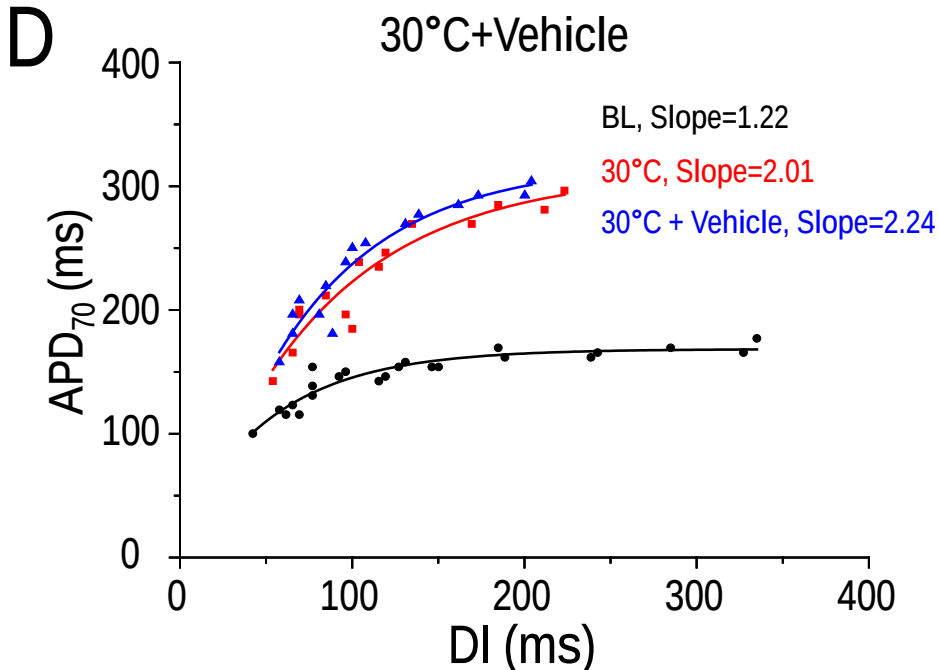
*30°C is lowest feasible temperature for therapeutic hypothermia.

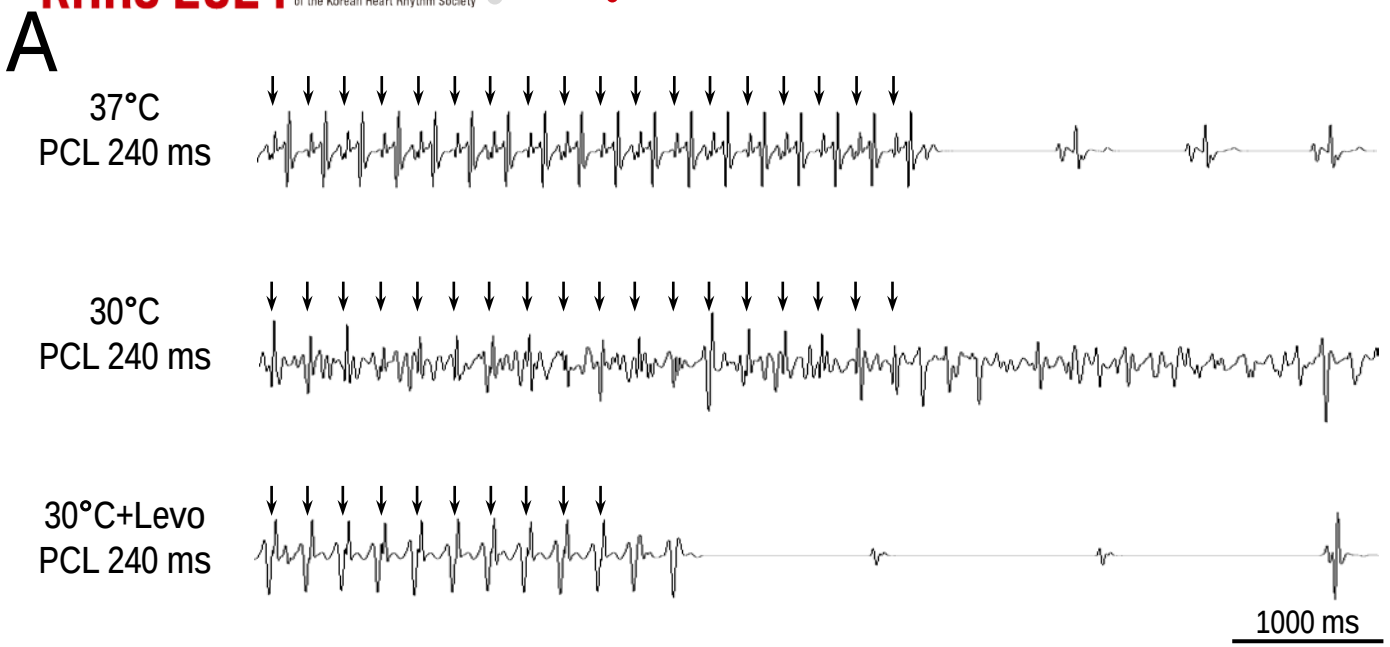

A
BL
30°C
30°C+Levo
PCL
400 ms
RVA
LVA
X
π
0
-π
Local optical
recording
Site x
APD70
165 ms
248 ms
227 ms
400 ms
B
BL
30°C
30°C+Veh
PCL
400 ms
X
π
0
-π
Local optical
recording
Site x
APD70
155 ms
261 ms
289 ms
400 ms
C
PCL 400 ms
p<0.001
p=0.02
(ms)
300
250
200
150
100
50
0
APD70
BL
n=9
30°C
n=9
30°C+Levo
n=9
D
PCL 400 ms
p<0.001
p=ns
(ms)
300
250
200
150
100
50
0
APD70
BL
n=8
30°C
n=8
30°C+Veh
n=8

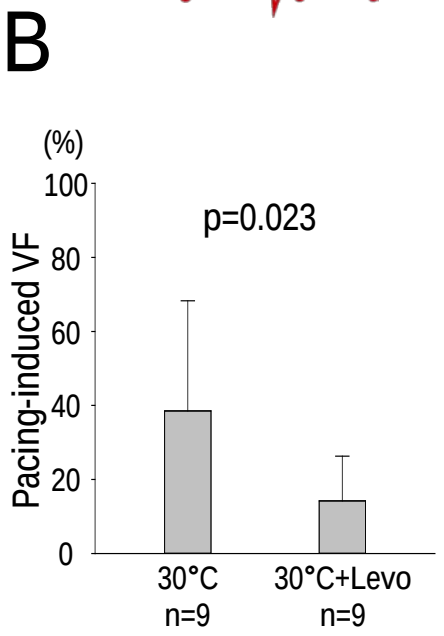

A
p=0.0002
p=0.03
Maximal Slope
3.0
2.5
2.0
1.5
1.0
0.5
0.0
BL
30°C
30°C+Levo

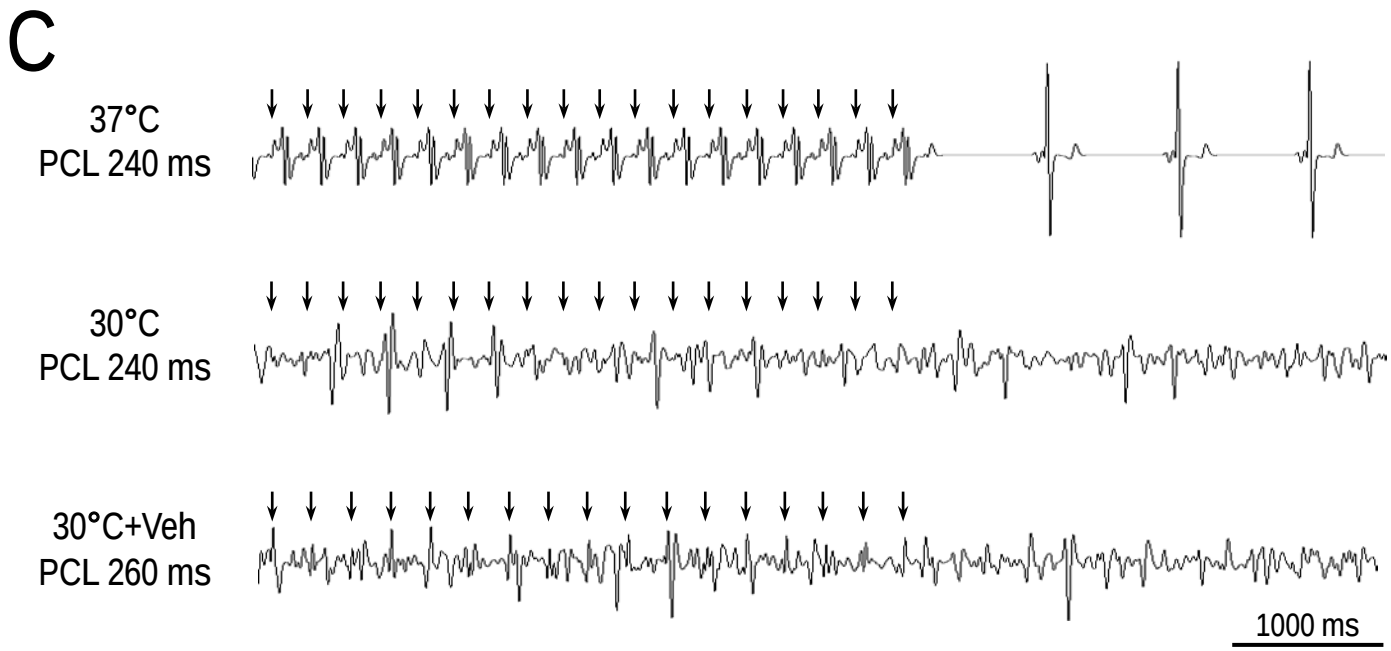

B
p=0.004
p=0.741
Maximal Slope
3.0
2.5
2.0
1.5
1.0
0.5
0.0
BL
30°C
30°C+Vehicle

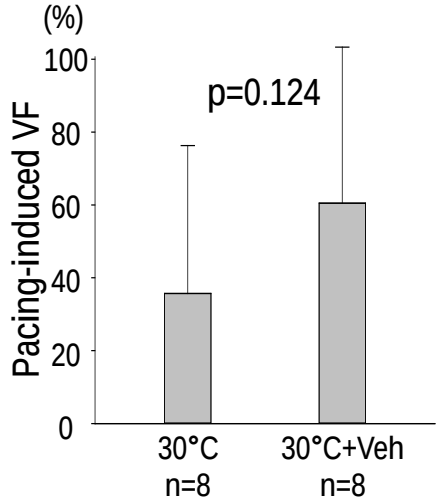

C
30°C+Levo
BL, Slope=1.14
30°C, Slope=2.50
30°C + Levo, Slope=1.86
APD70 (ms)
400
300
200
100
0
0
100
200
300
400
DI (ms)

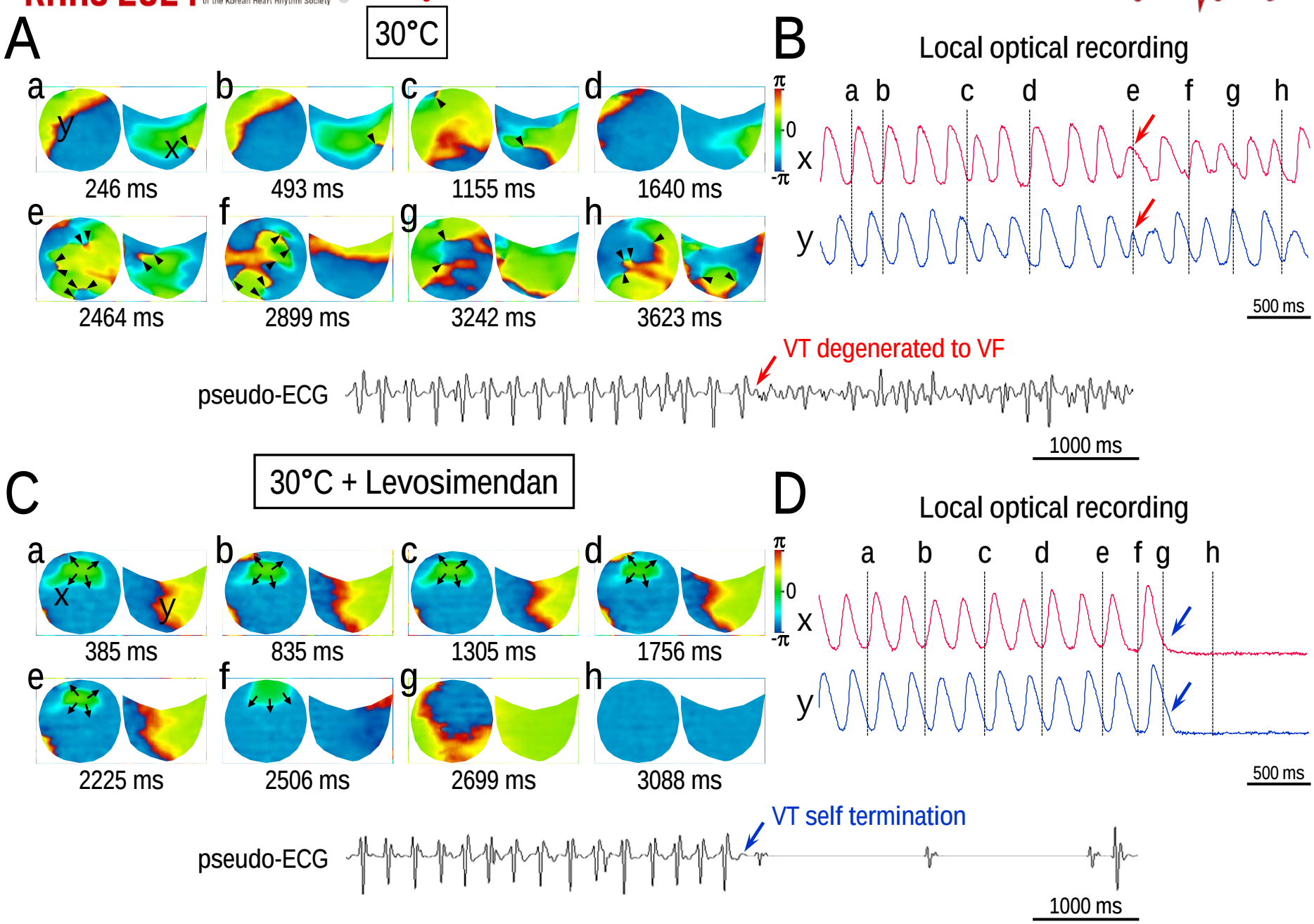

D
30°C+Vehicle
BL, Slope=1.22
30°C, Slope=2.01
30°C + Vehicle, Slope=2.24
APD70 (ms)
400
300
200
100
0
0
100
200
300
400
DI (ms)


A
37°C
PCL 240 ms
30°C
PCL 240 ms
30°C+Levo
PCL 240 ms
1000 ms


B
(%)
Pacing-induced VF
100
80
60
40
20
0
p=0.023
30°C
n=9
30°C+Levo
n=9


C
37°C
PCL 240 ms
30°C
PCL 240 ms
30°C+Veh
PCL 260 ms
1000 ms


D
(%)
Pacing-induced VF
100
80
60
40
20
0
p=0.124
30°C
n=8
30°C+Veh
n=8


A
30°C
a
b
c
d
246 ms
493 ms
1155 ms
1640 ms
e
f
g
h
2464 ms
2899 ms
3242 ms
3623 ms
B
Local optical recording
π
0
-π
x
y
a b c d e f g h
500 ms
VT degenerated to VF
pseudo-ECG
1000 ms
C
30°C + Levosimendan
385 ms
835 ms
1305 ms
1756 ms
2225 ms
2506 ms
2699 ms
3088 ms
D
Local optical recording
VT self termination
pseudo-ECG
1000 ms

Results

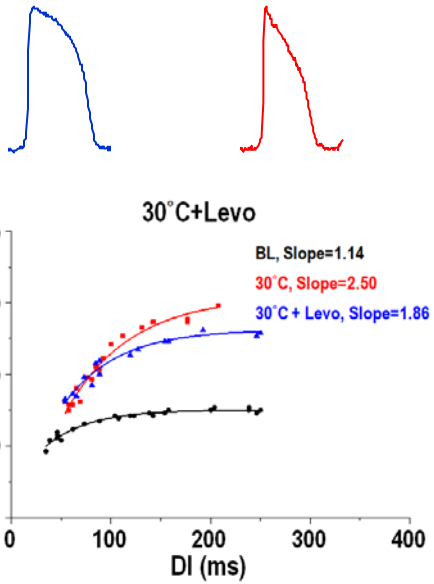
- Levosimendan decreases the maximal slope of APDR from 1.99 ±0.65 at TH to 1.41±0.32 after adding levosimendan (p=0.034).
- The VF inducibility was decreased by levosimendan from 39±30% at 30°C to 14±12% with levosimendan (p=0.023).
- In control hearts, the maximal slope of APDR (p=0.75) and VF inducibility (p=0.12) were not changed by vehicle during TH.

Possible Mechanisms (1)

Therapeutic Hypothermia (30°C)

Levosimendan

Therapeutic Hypothermia (30°C)



APD Prolongation

Steepen APDR

Enhance SDA

Promote VA

APD shortening

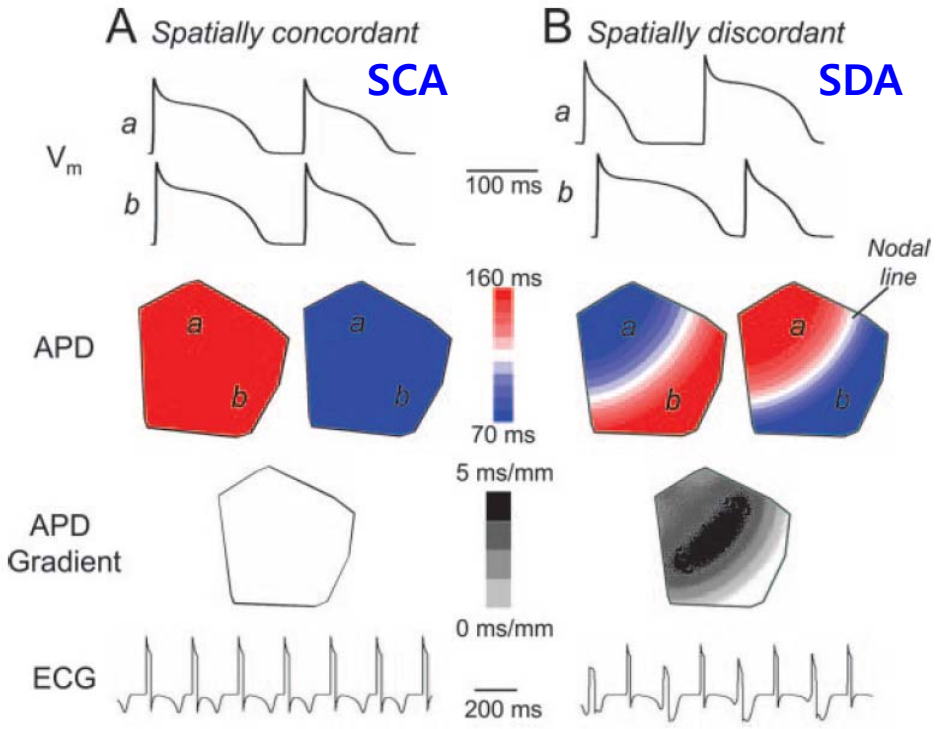
Flattened APDR

Suppress SDA

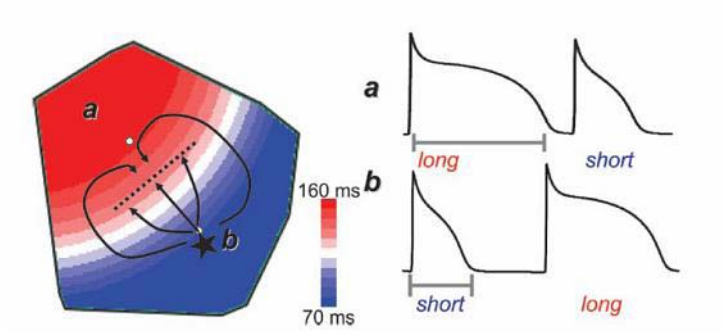
Prevent VA

Possible Mechanisms (2)

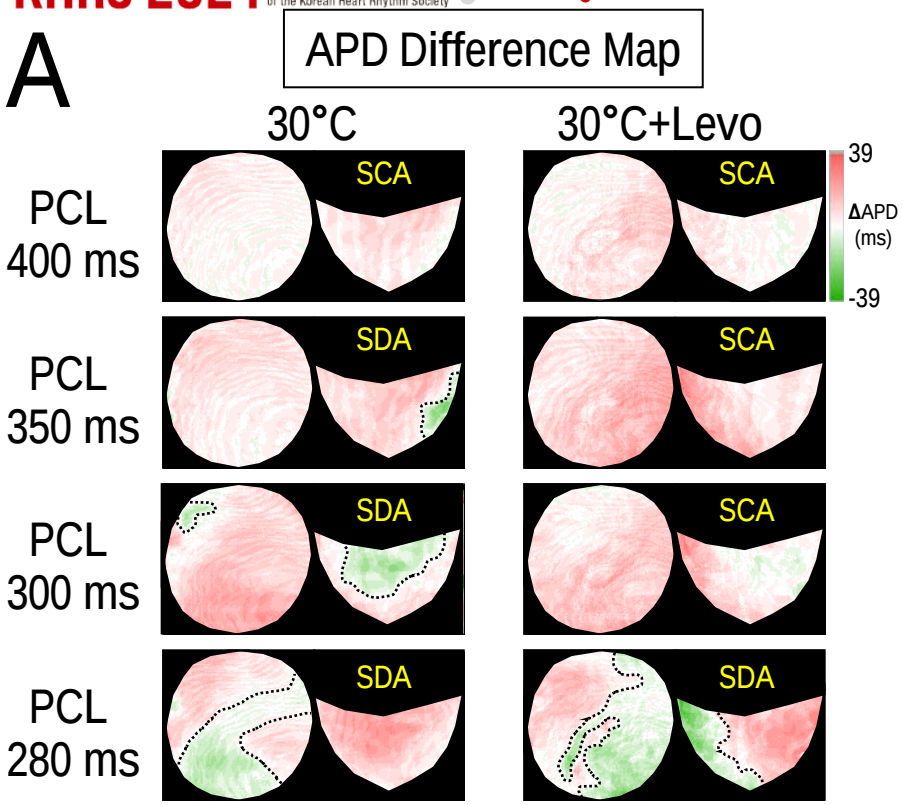
A **steep APD restitution** is associated with spatially discordant alternans (SDA)

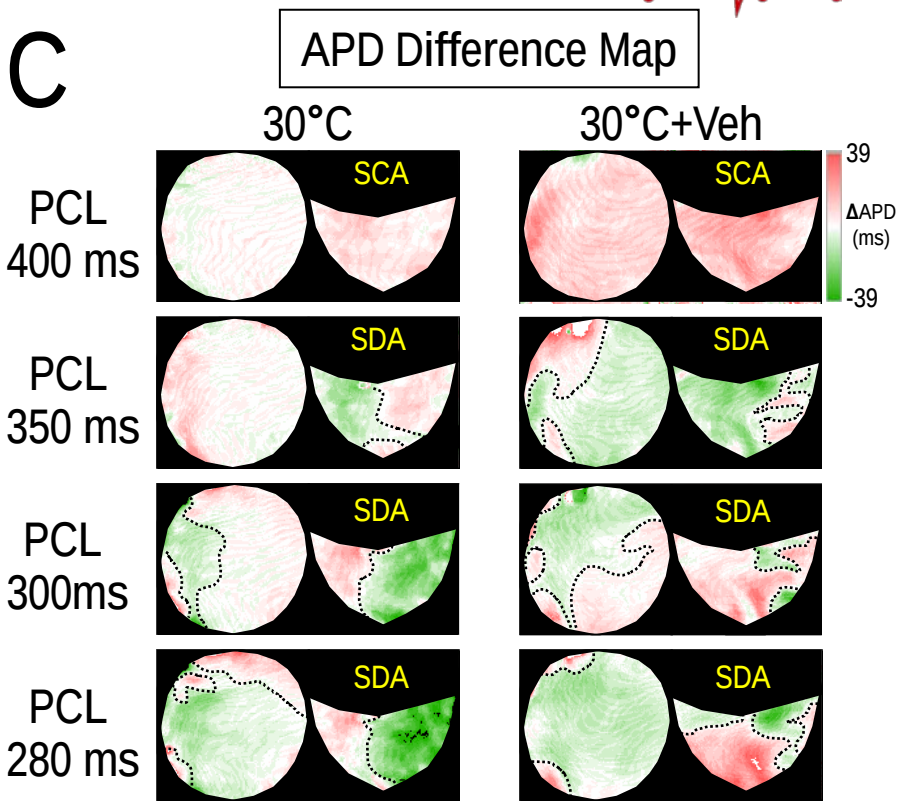


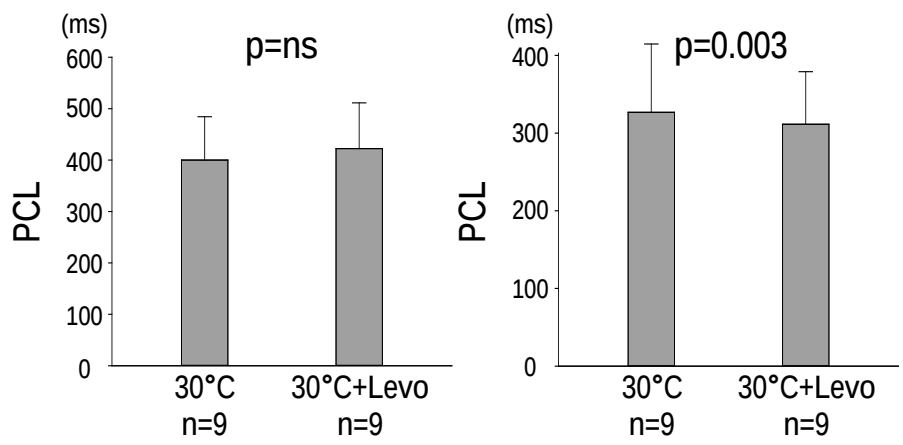
SDA is more arrhythmogenic than SCA !!

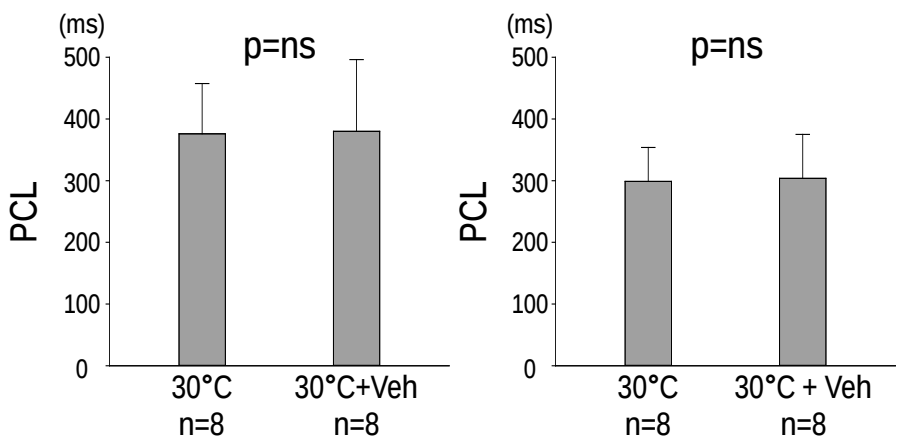


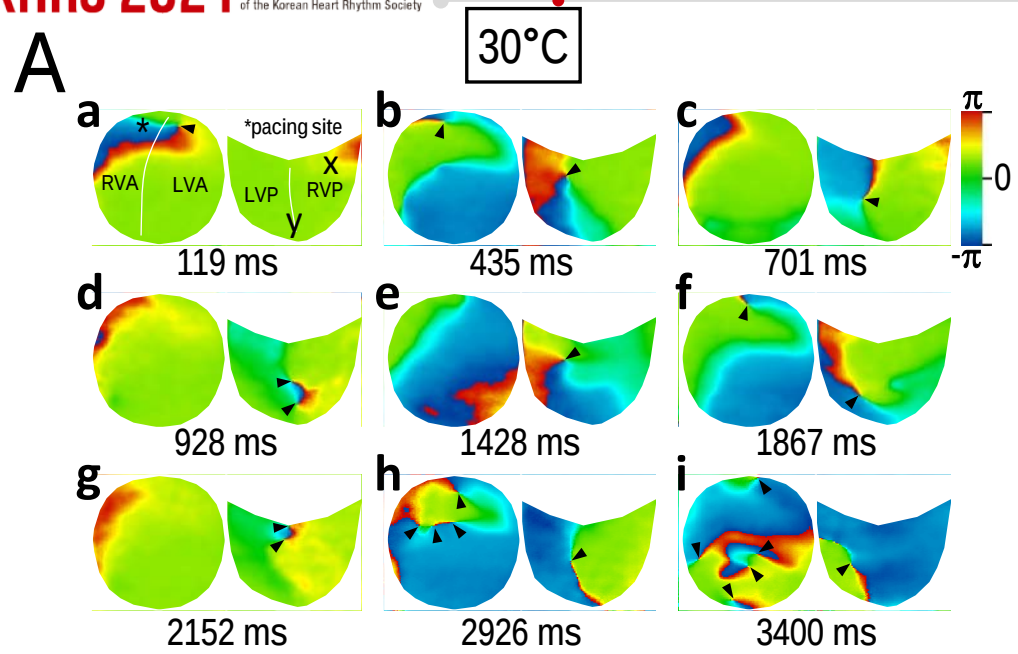
Weiss et al. Circ Res. 2006;98:1244-1253.

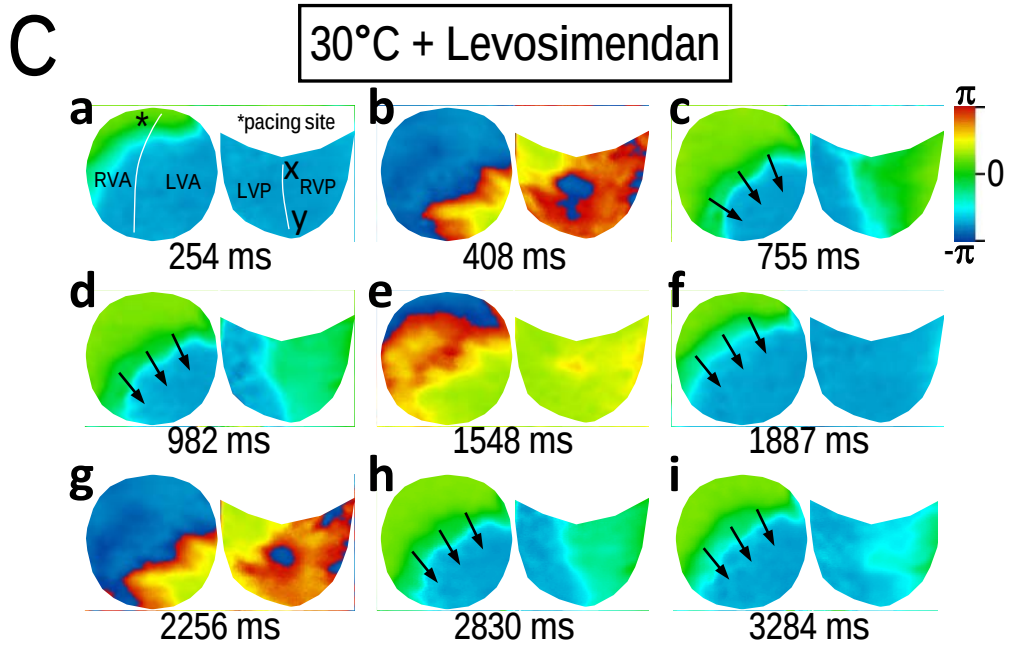

A
APD Difference Map
30°C
30°C+Levo
PCL 400 ms
PCL 350 ms
PCL 300 ms
PCL 280 ms
SCA
SDA
39
ΔAPD (ms)
-39

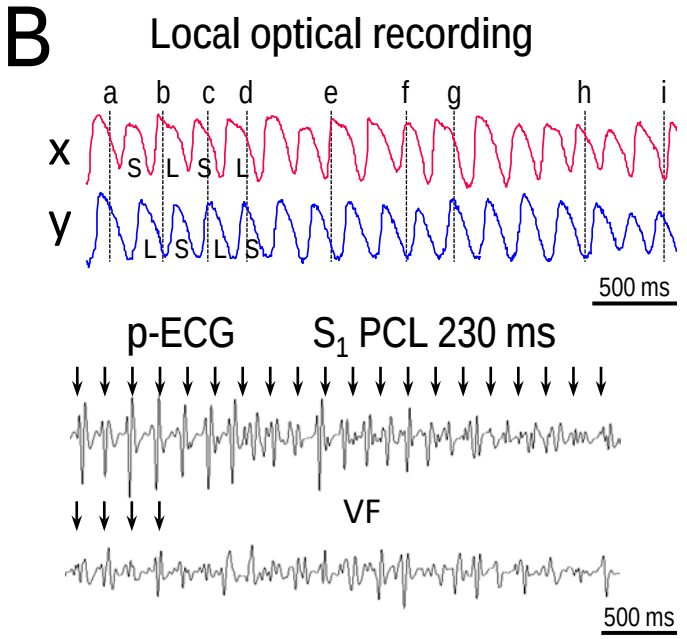

C
APD Difference Map
30°C
30°C+Veh
PCL 400 ms
PCL 350 ms
PCL 300ms
PCL 280 ms
SCA
SDA
39
ΔAPD (ms)
-39

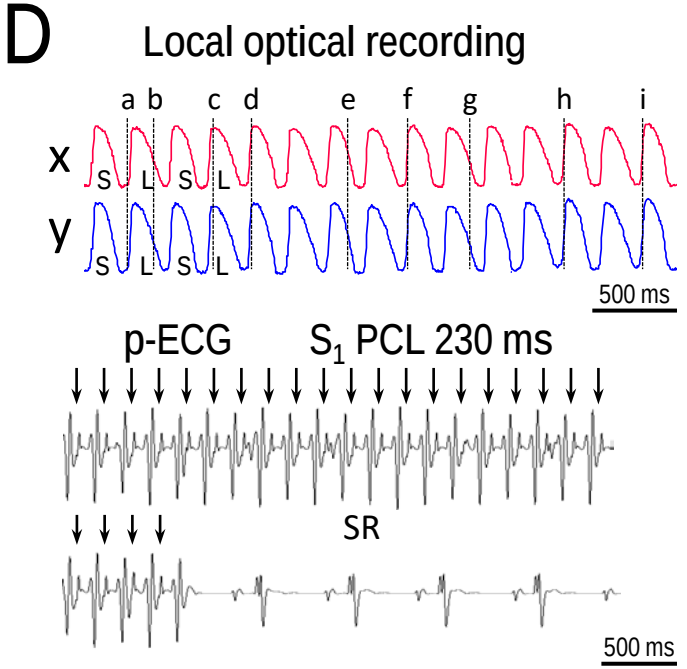

B
APD alternans threshold
SDA threshold
(ms)
PCL
p=ns
p=0.003
30°C
30°C+Levo
n=9
n=9


D
APD alternans threshold
SDA threshold
(ms)
PCL
p=ns
p=ns
30°C
30°C+Veh
30°C + Veh
n=8
n=8
n=8


A
30°C
a
b
c
d
e
f
g
h
i
*pacing site
RVA
LVA
LVP
RVP
x
y
119 ms
435 ms
701 ms
928 ms
1428 ms
1867 ms
2152 ms
2926 ms
3400 ms
π
0
-π


C
30°C + Levosimendan
a
b
c
d
e
f
g
h
i
*pacing site
RVA
LVA
LVP
RVP
x
y
254 ms
408 ms
755 ms
982 ms
1548 ms
1887 ms
2256 ms
2830 ms
3284 ms
π
0
-π


B
Local optical recording
a b c d e f g h i
x
y
S L S L
L S L S
500 ms
p-ECG
S1 PCL 230 ms
VF
500 ms


D
Local optical recording
a b c d e f g h i
x
y
S L S L
S L S L
500 ms
p-ECG
S1 PCL 230 ms
SR
500 ms

Limitation

- Whether the results also apply to failing hearts, or at 33C remains to be explored.
- Other effects than ATP-sensitive K current opener with levosimendan on VA deserved further investigation.

Conclusion

- Levosimendan might protect the hearts against VA during TH by flattening the APDR.

- Enhancing ATP-sensitive K current with levosimendan during TH might be a novel approach to prevent VA during TH.

Clinical Implication

- In patients with cardiac arrest and HF undergoing TH, levosimendan might prevent VA.


OFFICE HOURS
Thank you !!