Electrical and Structural Remodeling of Rabbit Ventricles during Therapeutic Hypothermia: Role of Conduction Velocity on Ventricular Arrhythmogenesis

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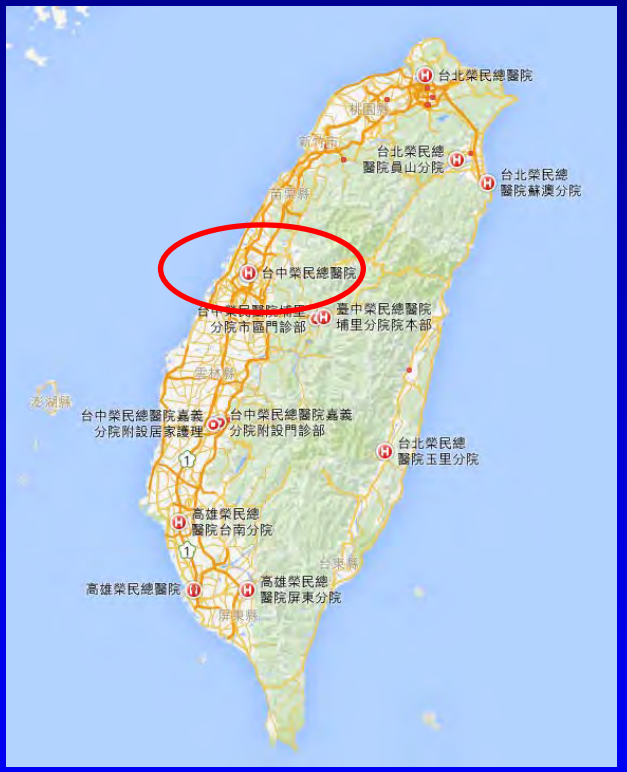


1462 Beds

738 Doctors

1736 Nurses

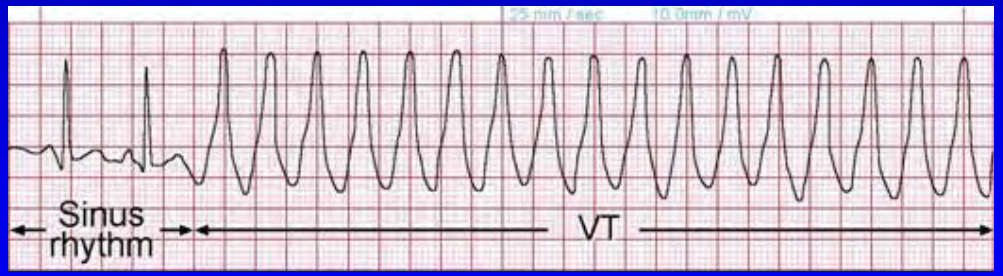
Outlines

- Background of Therapeutic Hypothermia (TH)
- Electrical Remodeling During Short-duration TH
- Structural Remodeling During Short-duration TH

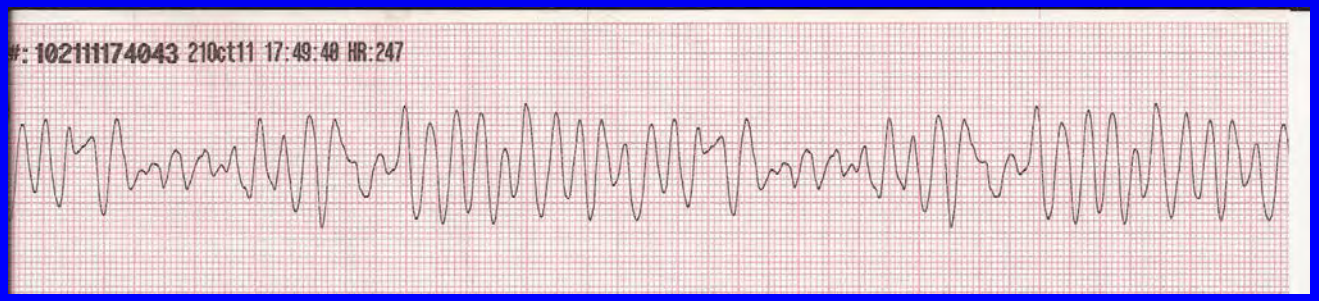
Lethal Ventricular Arrhythmias

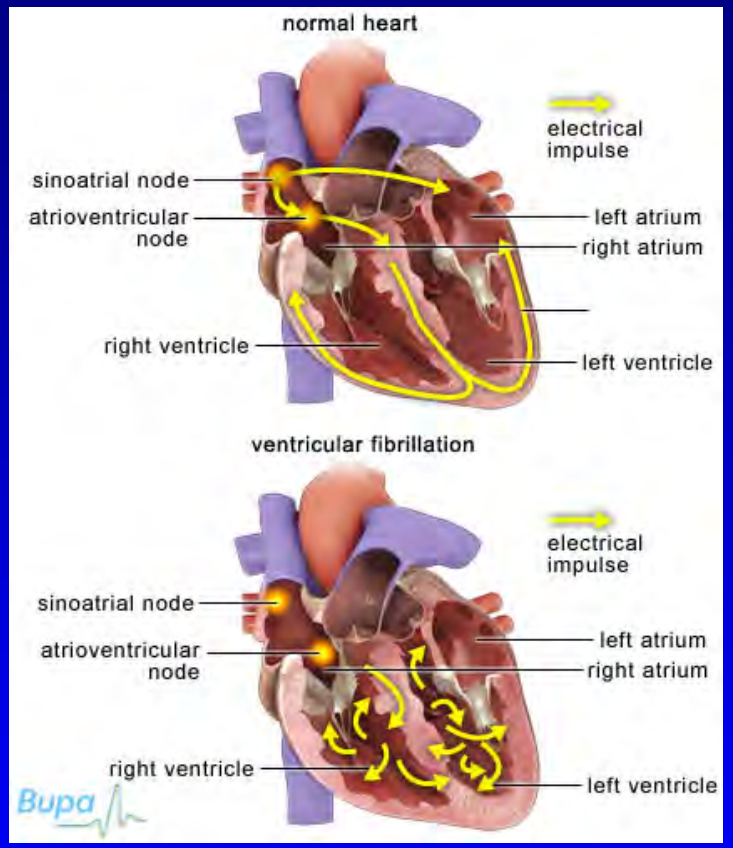
- Normal Rhythm

- Ventricular Tachycardia

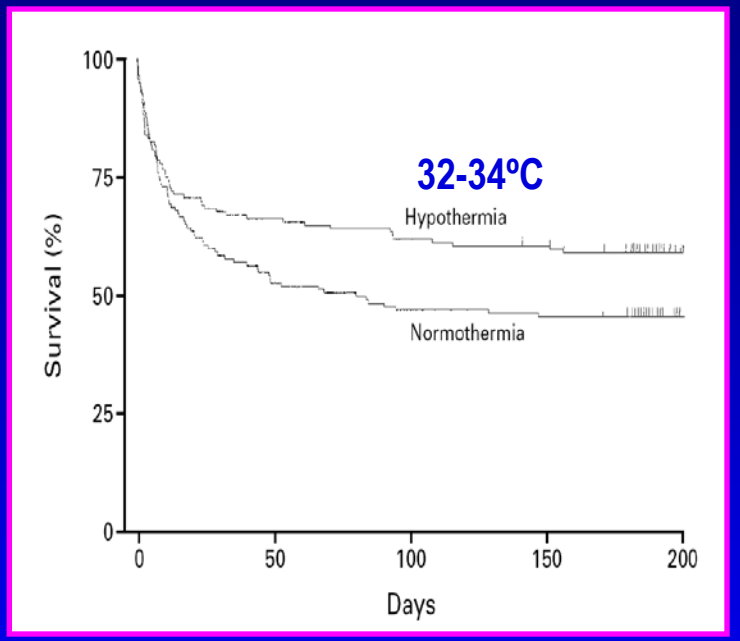


- Ventricular Fibrillation





Background



- TH has been demonstrated to improve neurological outcomes in patients randomized to TH (32-34˚C) after being resuscitated from out-of-hospital cardiac arrest VF.

NEJM 2002, 346:549-56

Part 9: Post–Cardiac Arrest Care

2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

Mary Ann Peberdy, Co-Chair*; Clifton W. Callaway, Co-Chair*; Robert W. Neumar; Romergryko G. Geocadin; Janice L. Zimmerman; Michael Donnino; Andrea Gabrielli; Scott M. Silvers; Arno L. Zaritsky; Raina Merchant; Terry L. Vanden Hoek; Steven L. Kronick

- **Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32-34 ºC for 12-24 h when the initial rhythm was ventricular fibrillation (VF).**

Circulation 2010;122;S768-S786

Part 9: Post–Cardiac Arrest Care

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- A number of potential complications are associated with cooling, including coagulopathy, arrhythmias, and hyperglycemia, particularly with an unintended drop below target temperature.

Circulation 2010;122;S768-S786

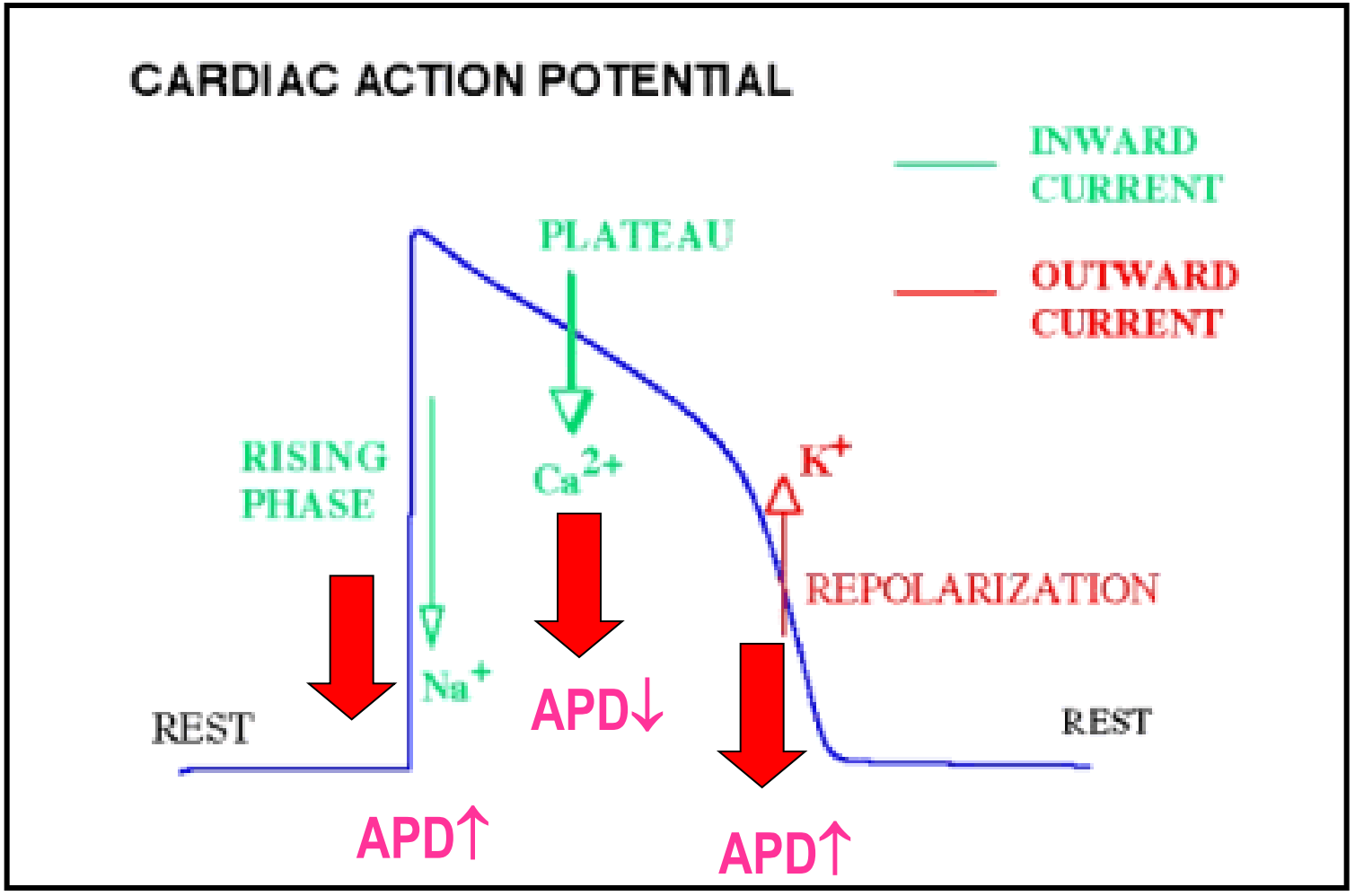
Therapeutic Hypothermia-Related Torsade de Pointes

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

Circulation 2006; 114: e521-2

Electrical Remodeling During TH in Rabbit Ventricles

Hypothermia on Cardiac Action Potential



Electrical Remodeling During TH

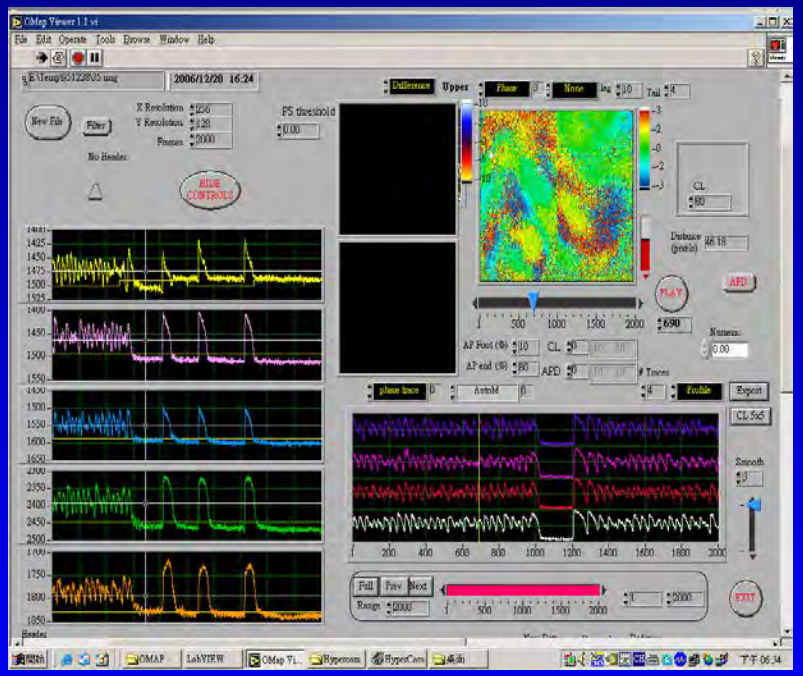
- 30˚C is the lowest temperature proven to be feasible in clinical practice.

- We hypothesize that TH at 30˚C
  - Enhances wavebreaks during VF and S1 pacing
  - Facilitates pacing-induced cardiac alternans
  - Increases the vulnerability of pacing-induced VF

EP Lab (Prof. Wu TJ), Taichung VGH

Thermostatic perfusion/ superfusion

Optical mapping system software



Two-camera optical mapping system

Protocol I: Restitution Curves

To determine ERP, APD and CT^{-1} restitution curves at baseline, during TH and after rewarming. (n=6).

S_1 pacing with PCLs from 500 to 110 ms (RVOT) (S_1 pacing method)

↓

Baseline (37ºC, 5 min)

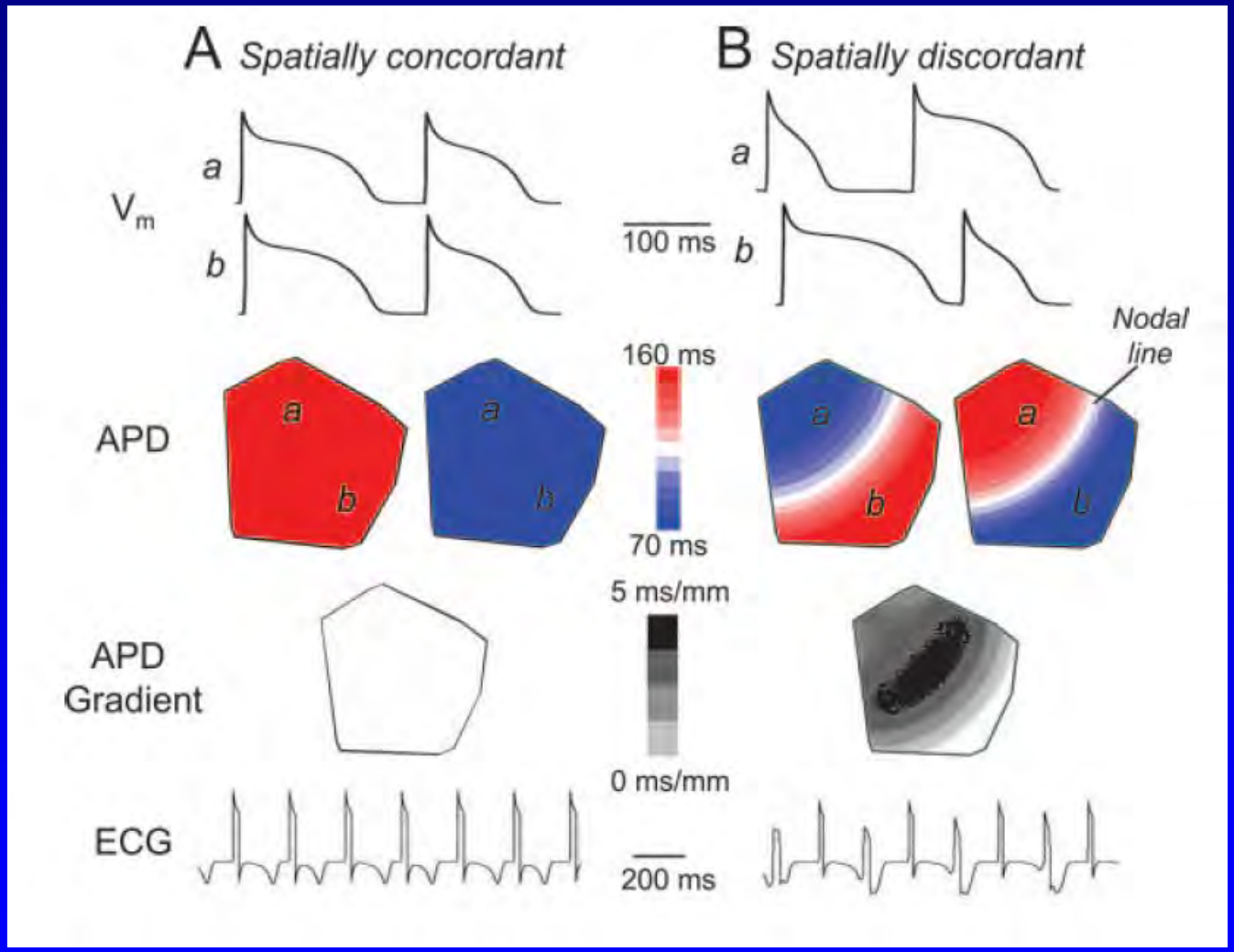
↓

TH (30ºC, 5 min)

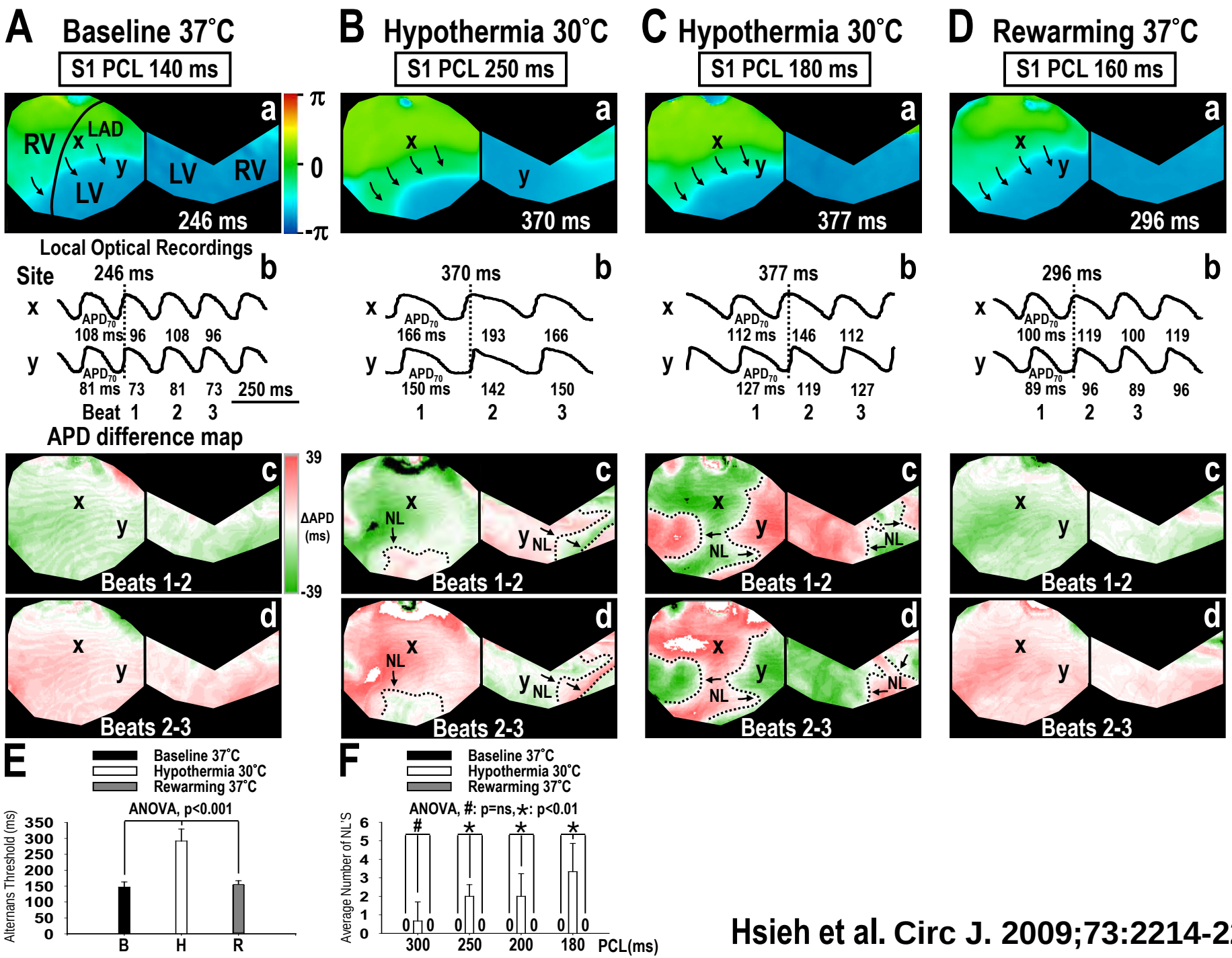
↓

Re-warming (37ºC, 5 min)

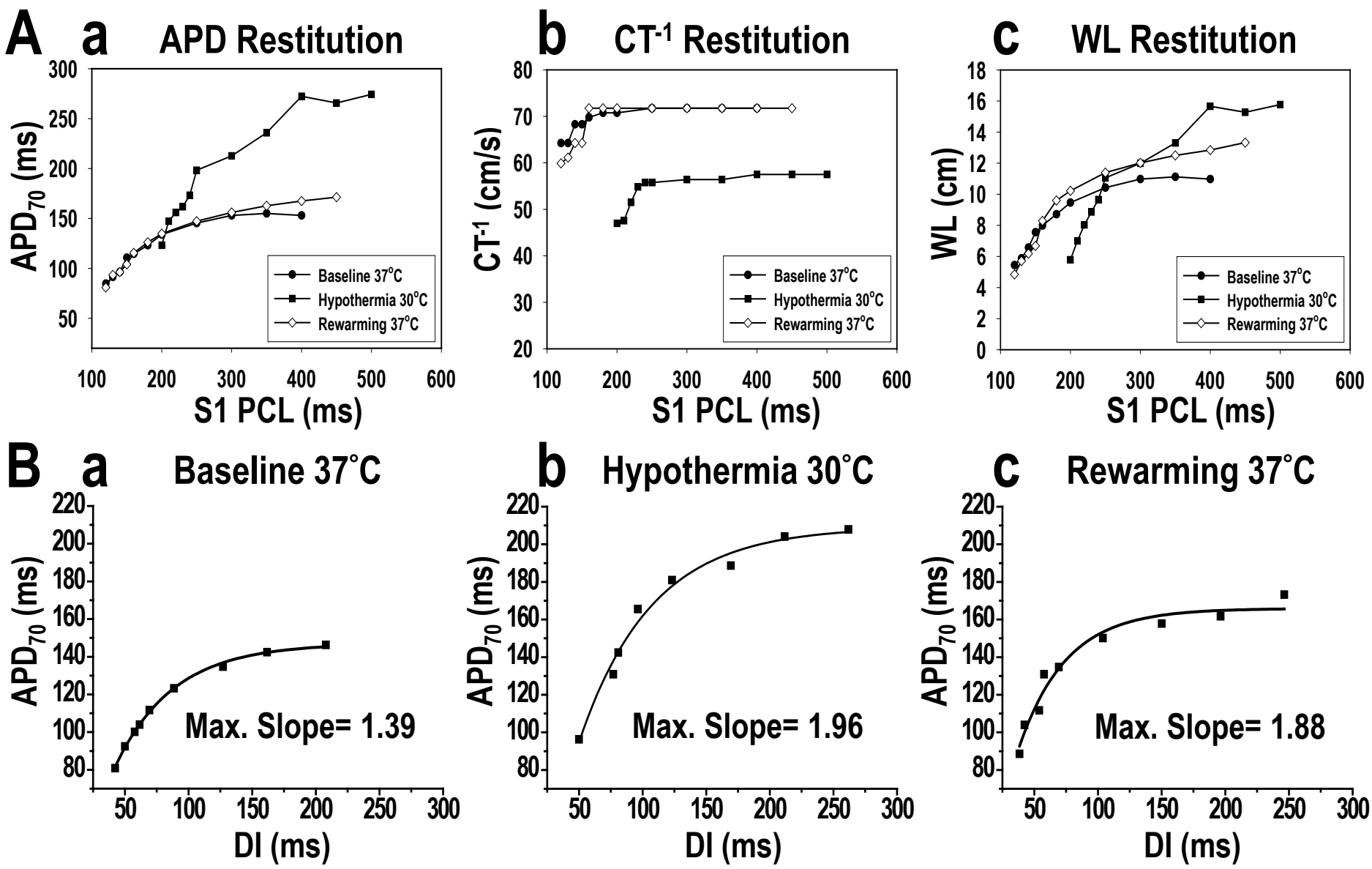
Spatially Concordant/Discordant Alternans



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



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



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

Protocol II: Effect of TH on VF Activations

To observe the wavefront characteristics during VF under TH (30ºC)

(n=7)

Baseline VF by burst pacing from RVOT

↓

Baseline (37ºC 5 mins)

↓

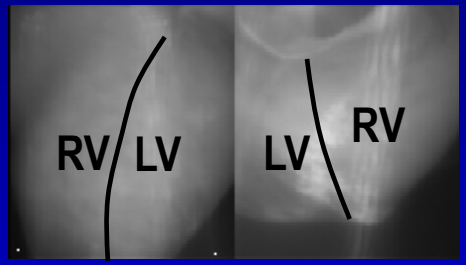
TH (30ºC for 15 mins)

↓

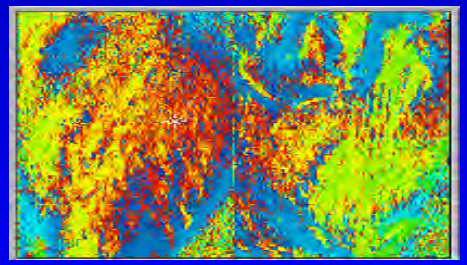
Re-warming (37ºC for 15 mins)

Optical Mapping During Burst Pacing

Mapped Area

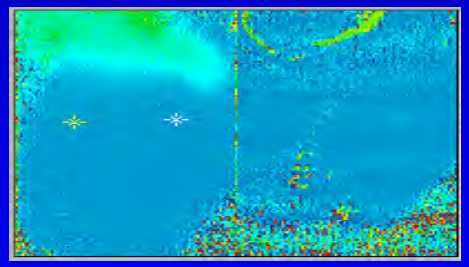


Baseline
37˚C



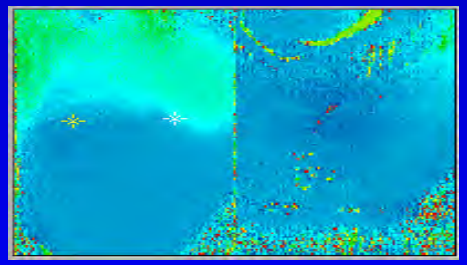
No wavebreak during pacing

Severe Hypothermia
30˚C

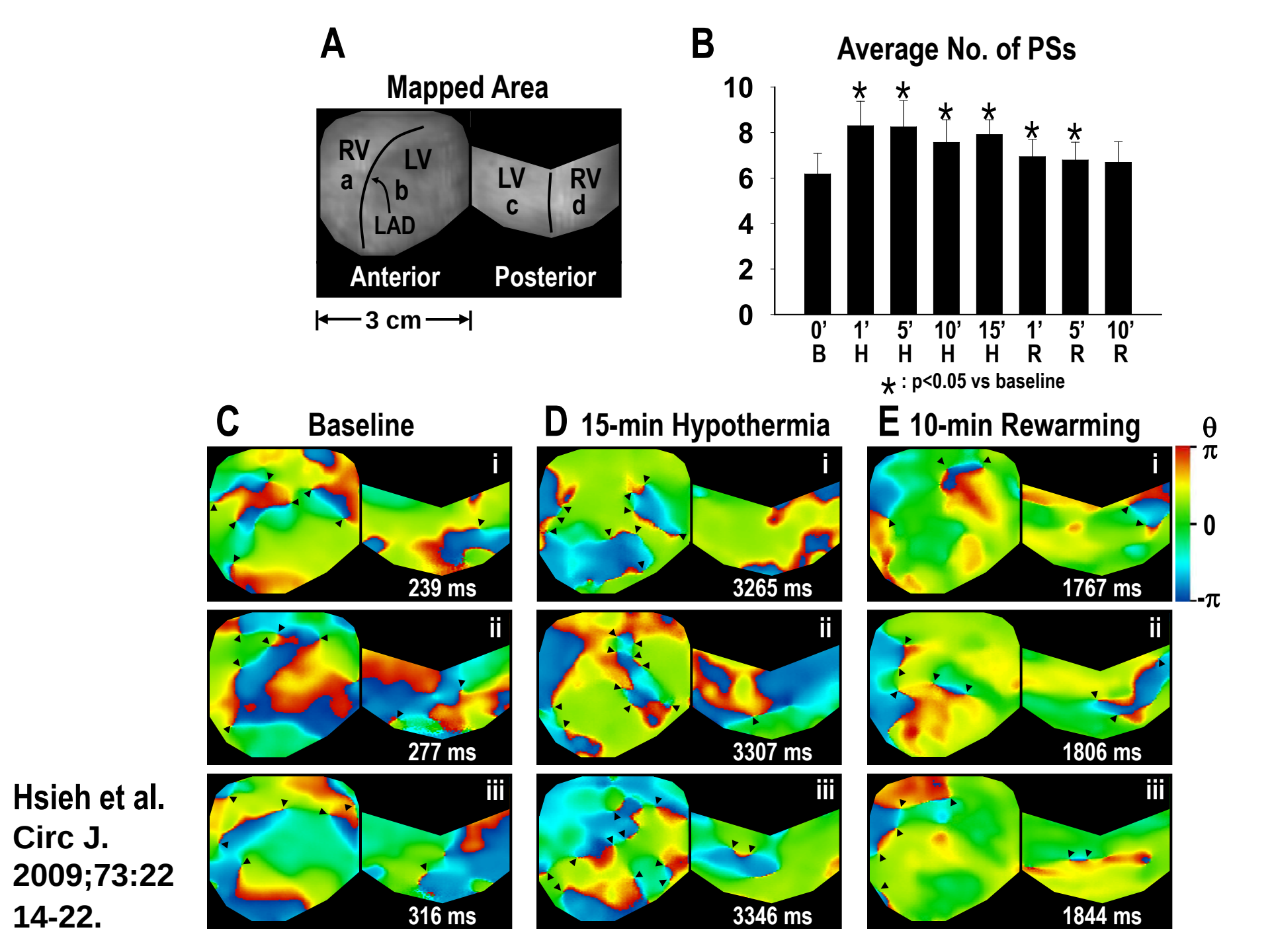


The pacing wavefronts always broke into multiple wavelets and became self-perpetuated, leading to VF maintenance.

Rewarming
37˚C



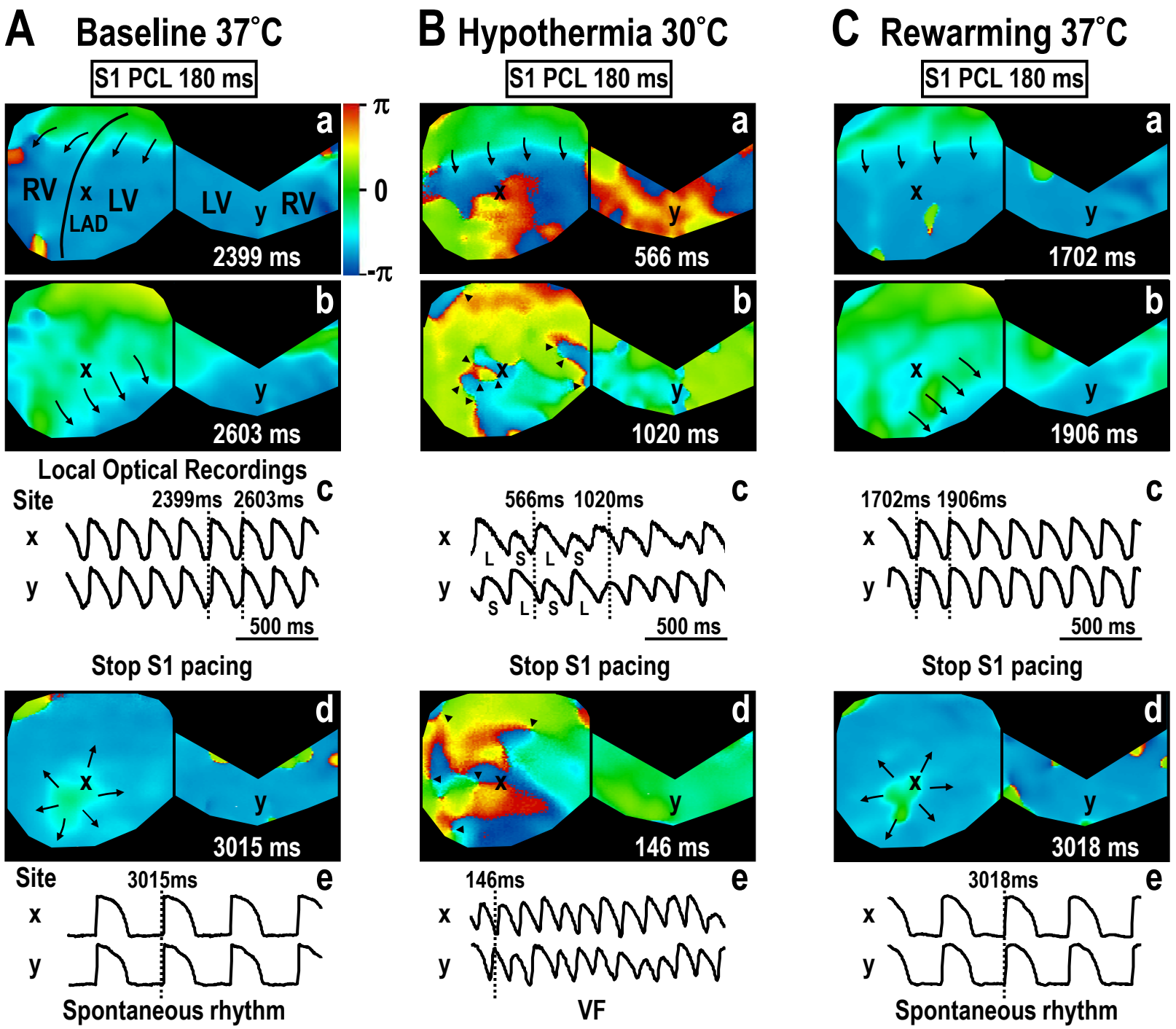
once epicardial wavebreak occurred, it always vanished without perpetuation.



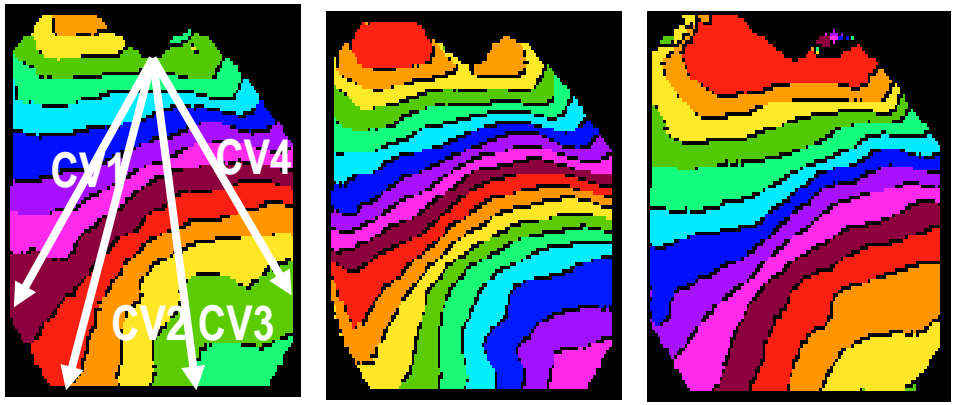
Hsieh et al. Circ J. 2009;73:2214-22.

Pacing-induced VF Episodes

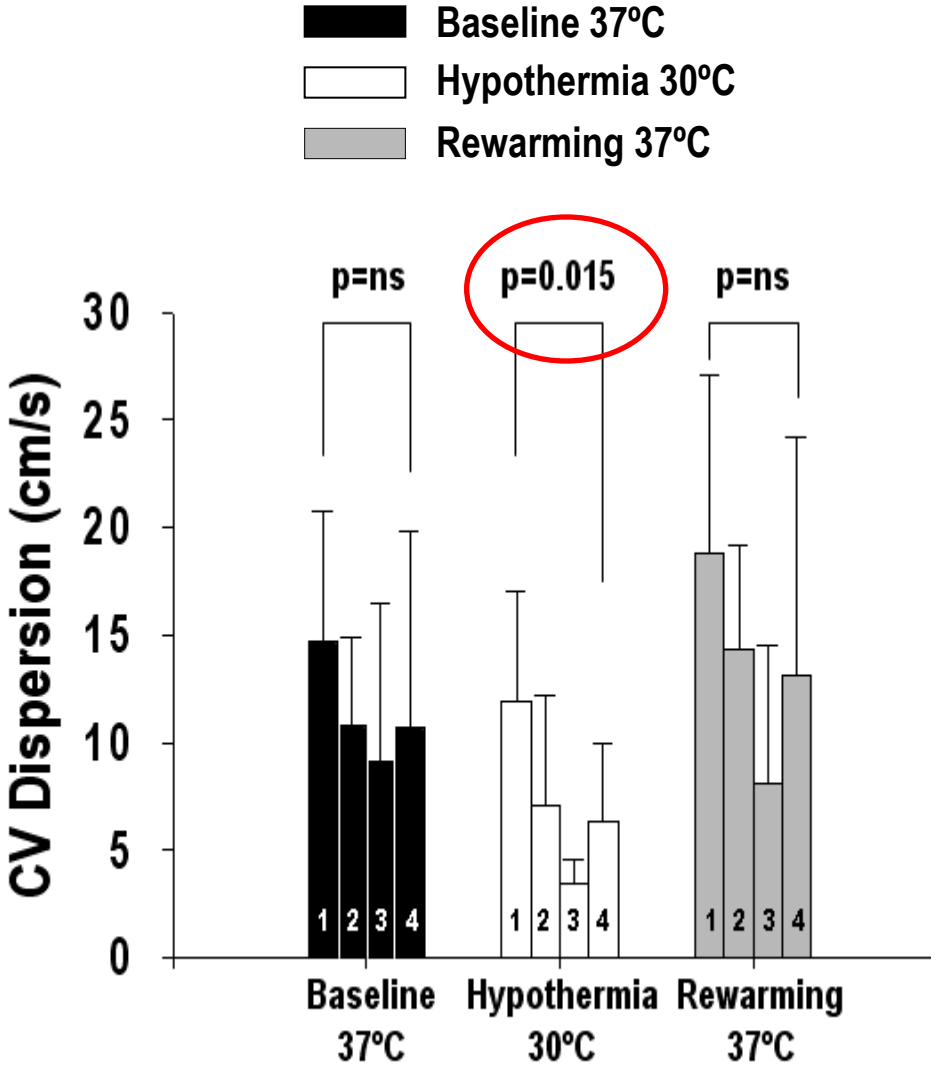
- During S_1 pacing, there was no VF episode inducible at B or R (n=6).
- During TH, a total of 6 sustained VF episodes were induced in 3 hearts (p=0.027).
- In 5 of these 6 VF episodes, SDA was observed during S1 pacing before VF formation.


A
Baseline 37°C
S1 PCL 180 ms
a
RV
x
LV
LAD
LV
y
RV
2399 ms
π
0
-π
b
x
y
2603 ms
Local Optical Recordings
Site
2399ms
2603ms
c
x
y
500 ms
Stop S1 pacing
d
x
y
3015 ms
Site
3015ms
e
x
y
Spontaneous rhythm
B
Hypothermia 30°C
S1 PCL 180 ms
a
x
y
566 ms
b
x
y
1020 ms
566ms
1020ms
c
x
L
S
L
S
y
S
L
S
L
500 ms
Stop S1 pacing
d
x
y
146 ms
146ms
e
x
y
VF
C
Rewarming 37°C
S1 PCL 180 ms
a
x
y
1702 ms
b
x
y
1906 ms
1702ms
1906ms
c
x
y
500 ms
Stop S1 pacing
d
x
y
3018 ms
3018ms
e
x
y
Spontaneous rhythm

Spatial heterogeneity of CV restitutions



Baseline 37ºC Hypothermia 30ºC Rewarming 37ºC



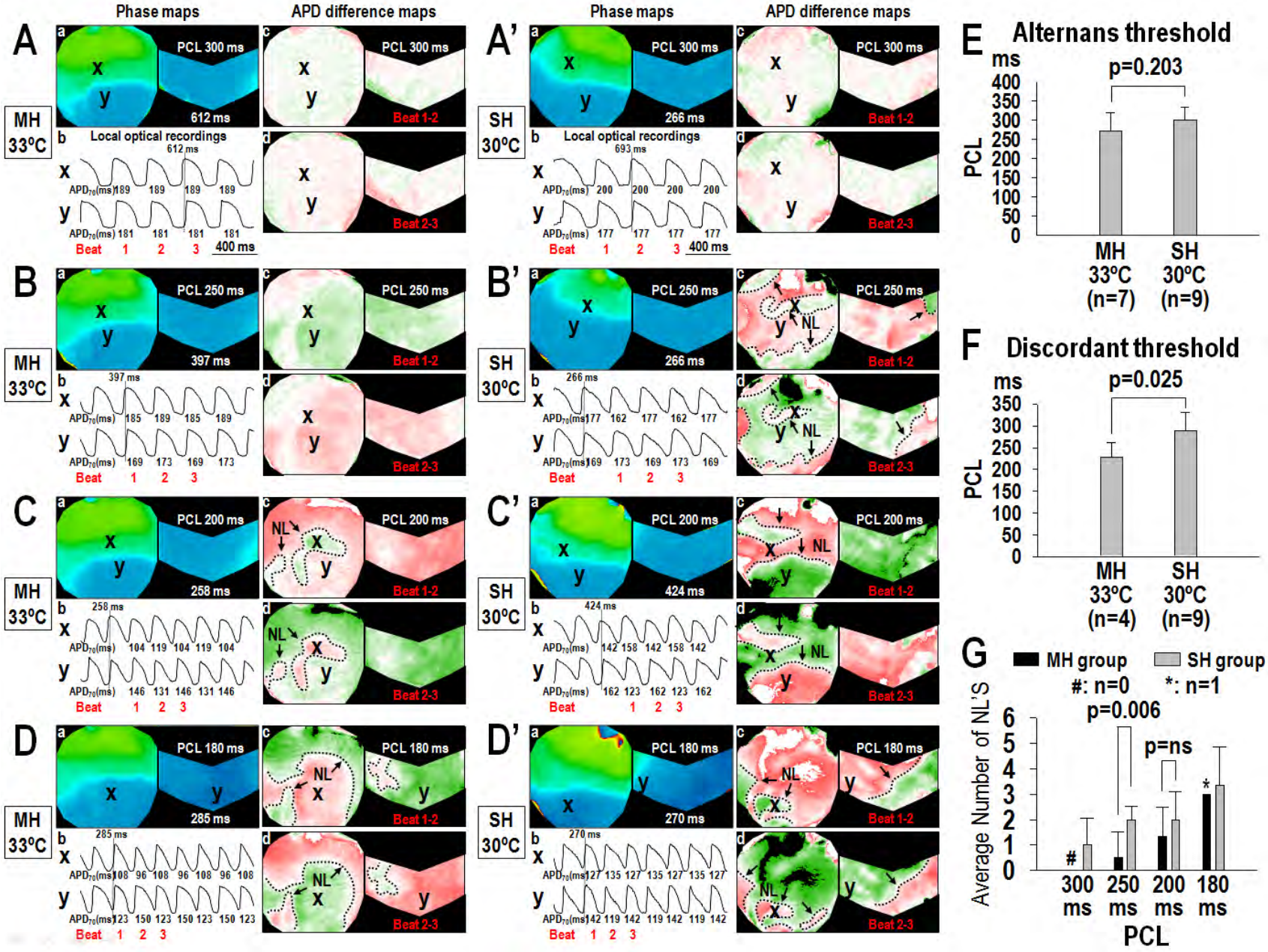
Hsieh et al. Circ J. 2009;73:2214-22.

Major Findings

- **TH (30ºC) increases wavebreaks during VF**
- **TH (30ºC) enhances proarrhythmic parameters**
  - ↓CV, ↓WL
  - ↑spatial heterogeneity of CV restitution
- **TH (30ºC) results in earlier onset of APD alternans, which are predominated by SDA.**
- **TH (30ºC) increases the vulnerability of pacing-induced VF.**

Clinical Implication

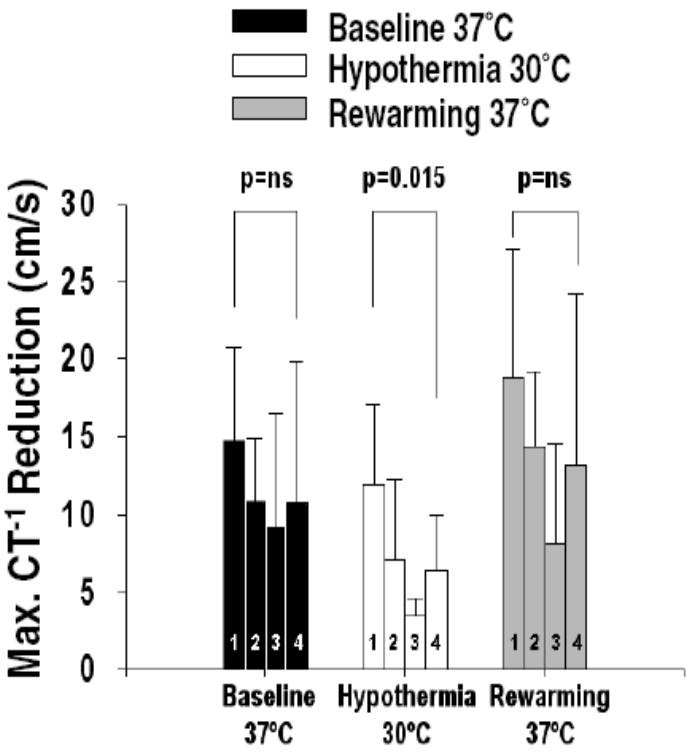
- **When cardiac pacing is necessary in patients undergoing TH**
  - PCL should be carefully determined
  - Placing pacing wire/pulmonary catheter with caution
  - 32-34˚C might be safer than 30˚C



Hsieh YC, et al. Acta Cardial Sin 2014;30:455- 465.

Structural Remodeling During TH in Rabbit Ventricles

Background



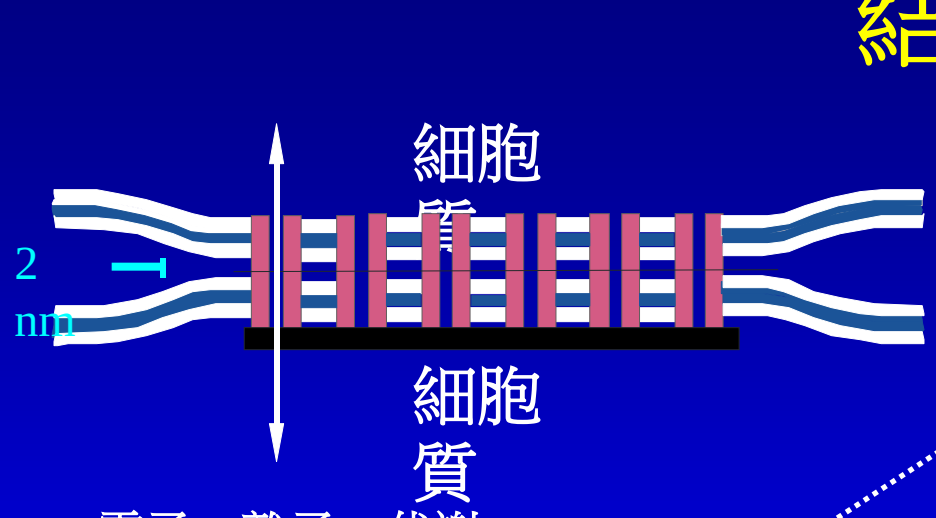
- TH (30ºC) reduces CV and enhances spatial heterogeneity of CV restitution.
- Whether connexin43 (Cx43) gap junctions and spatial heterogeneity of CV are altered during TH remains unclear.

Conduction Velocity and Hypothermia

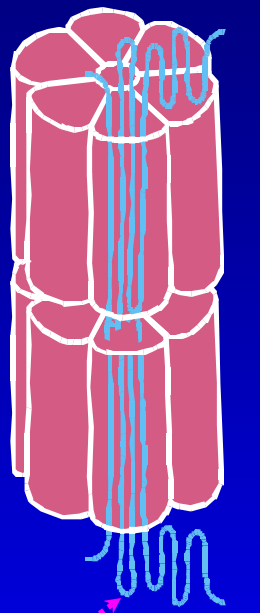
- **Cardiac CV is mainly determined by**
  - Phase 0 Na current
  - Extra-cellular matrix
  - **Gap junction (GJ) coupling**

Pflugers Arch. 1993;423:133-139.

The Gap Junction (隙連結)



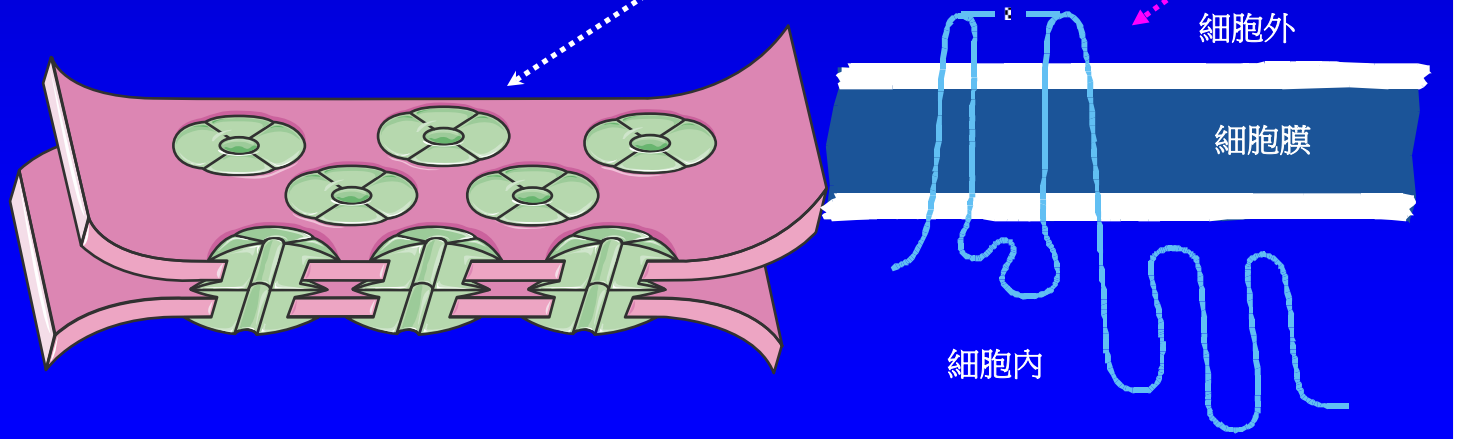
電子，離子，代謝物



Connexon (連接半管)

2 nm

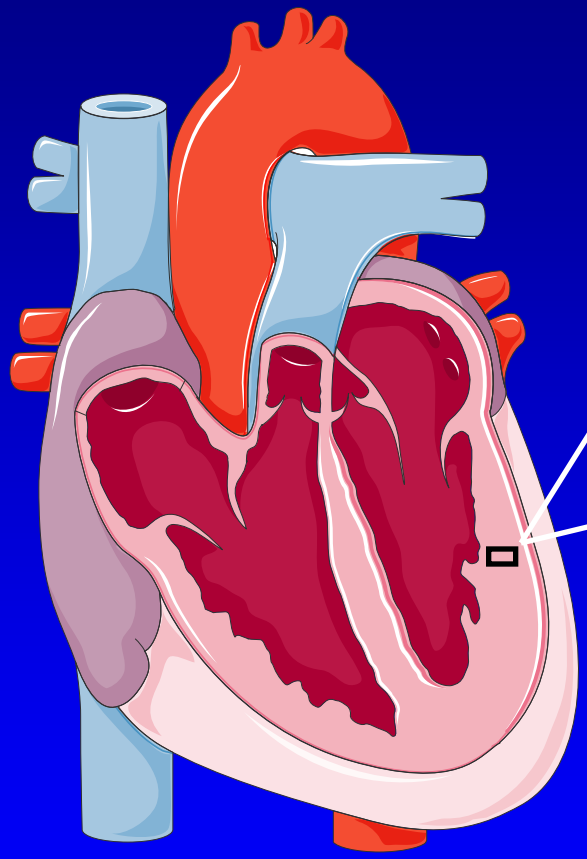
Connexon

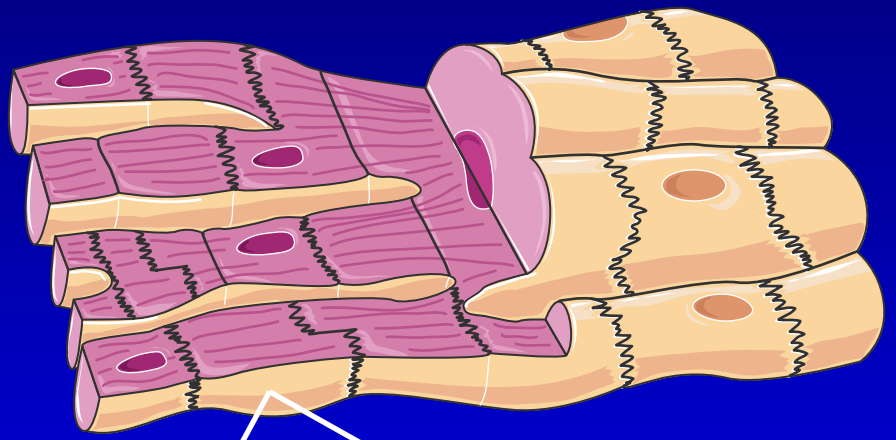


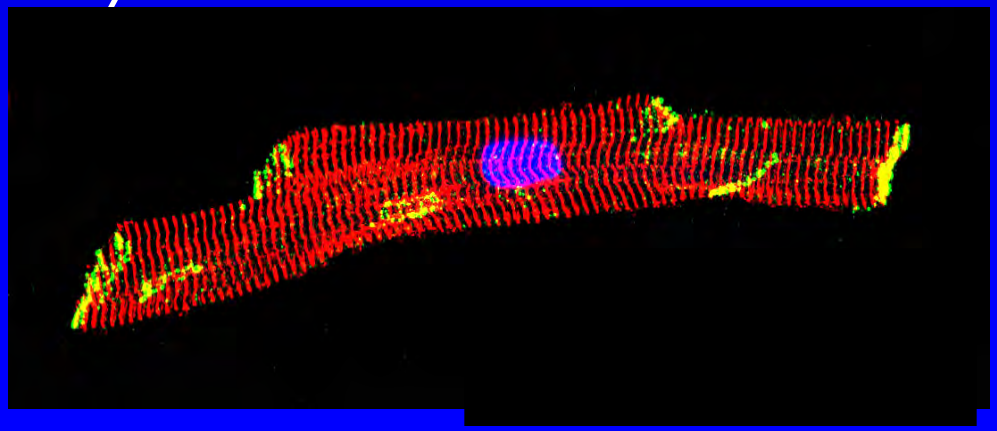
Connexin (連接素)

Science 1998

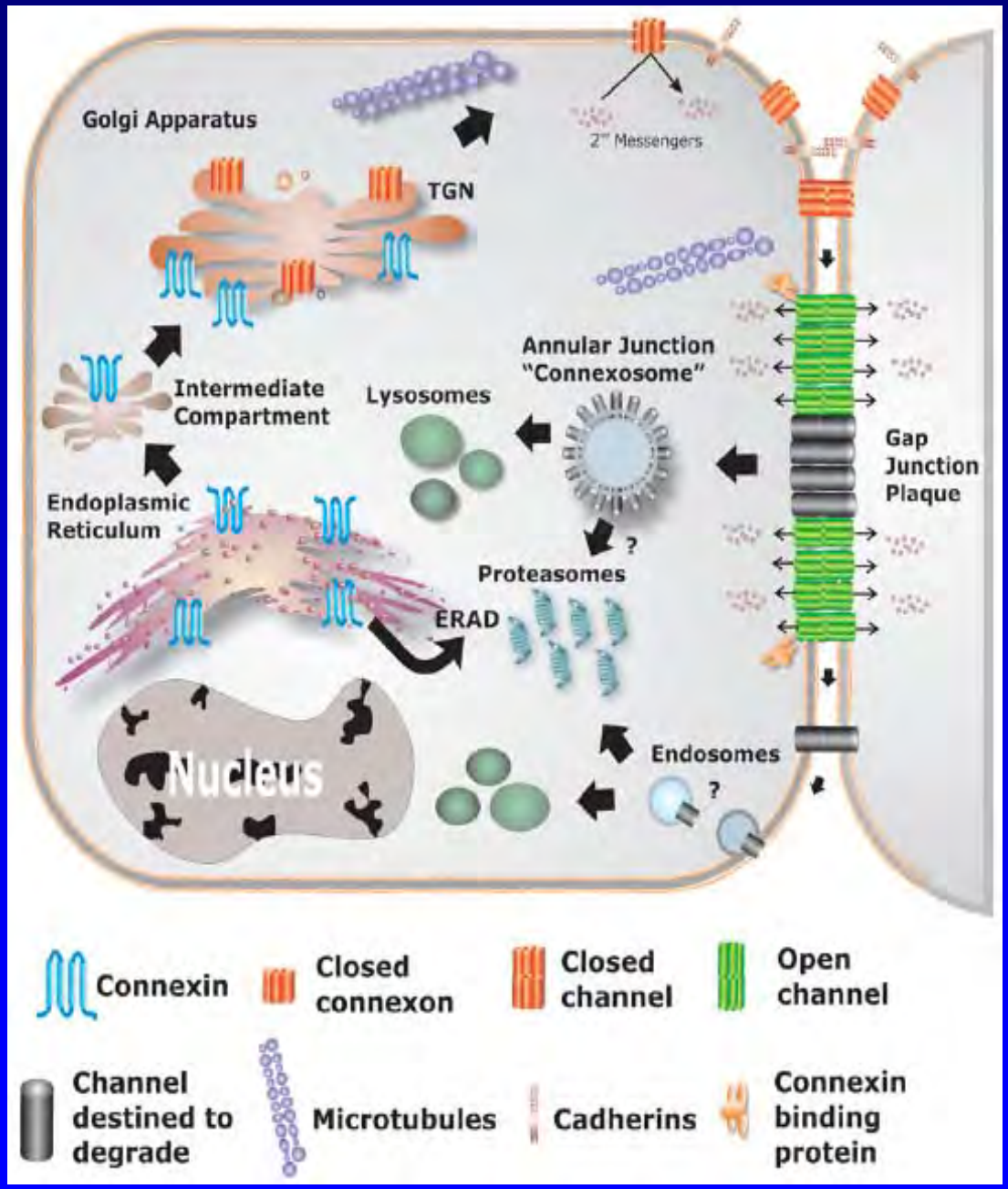
Cardiomyocyte Gap Junction







Life Cycle of GJ



Laird et al. 2006

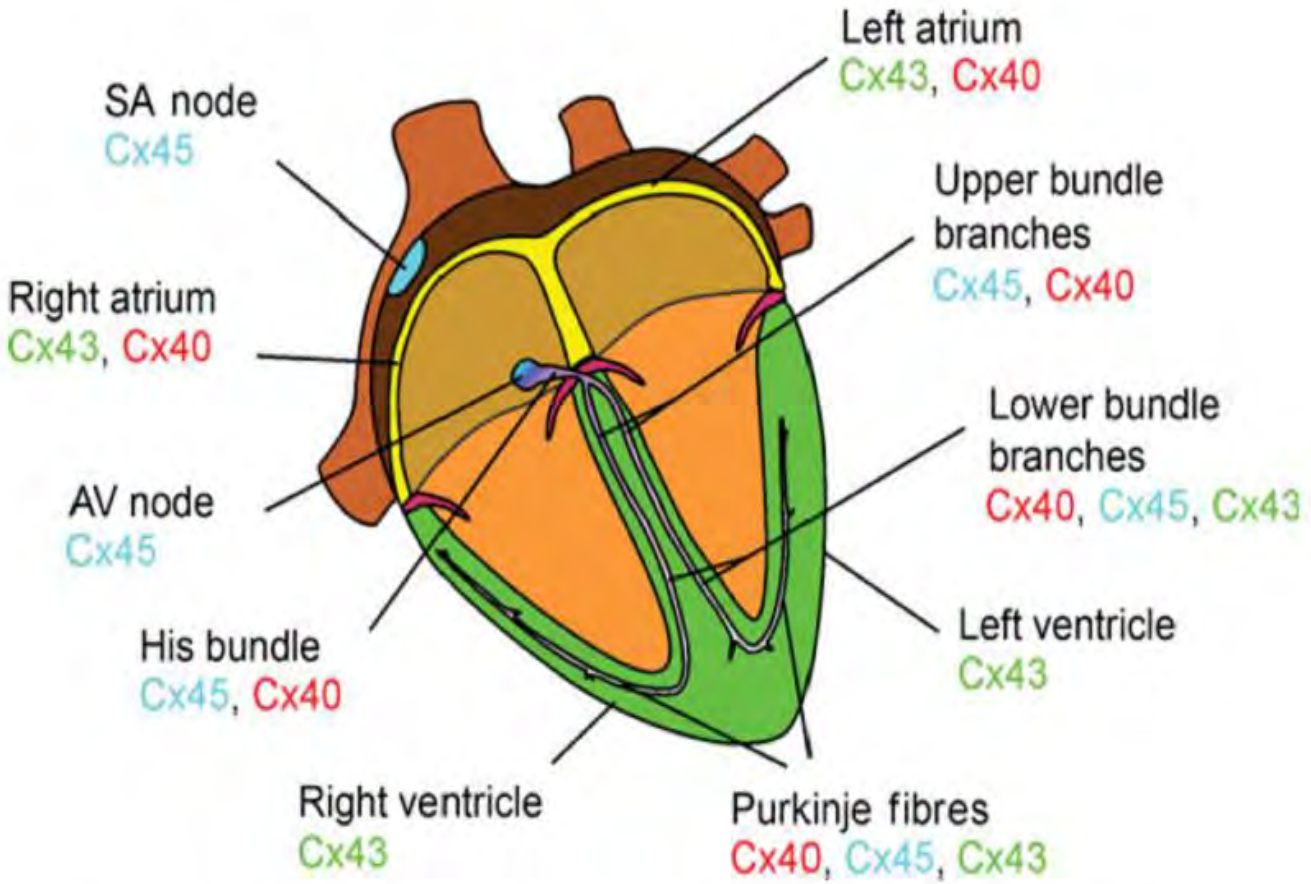
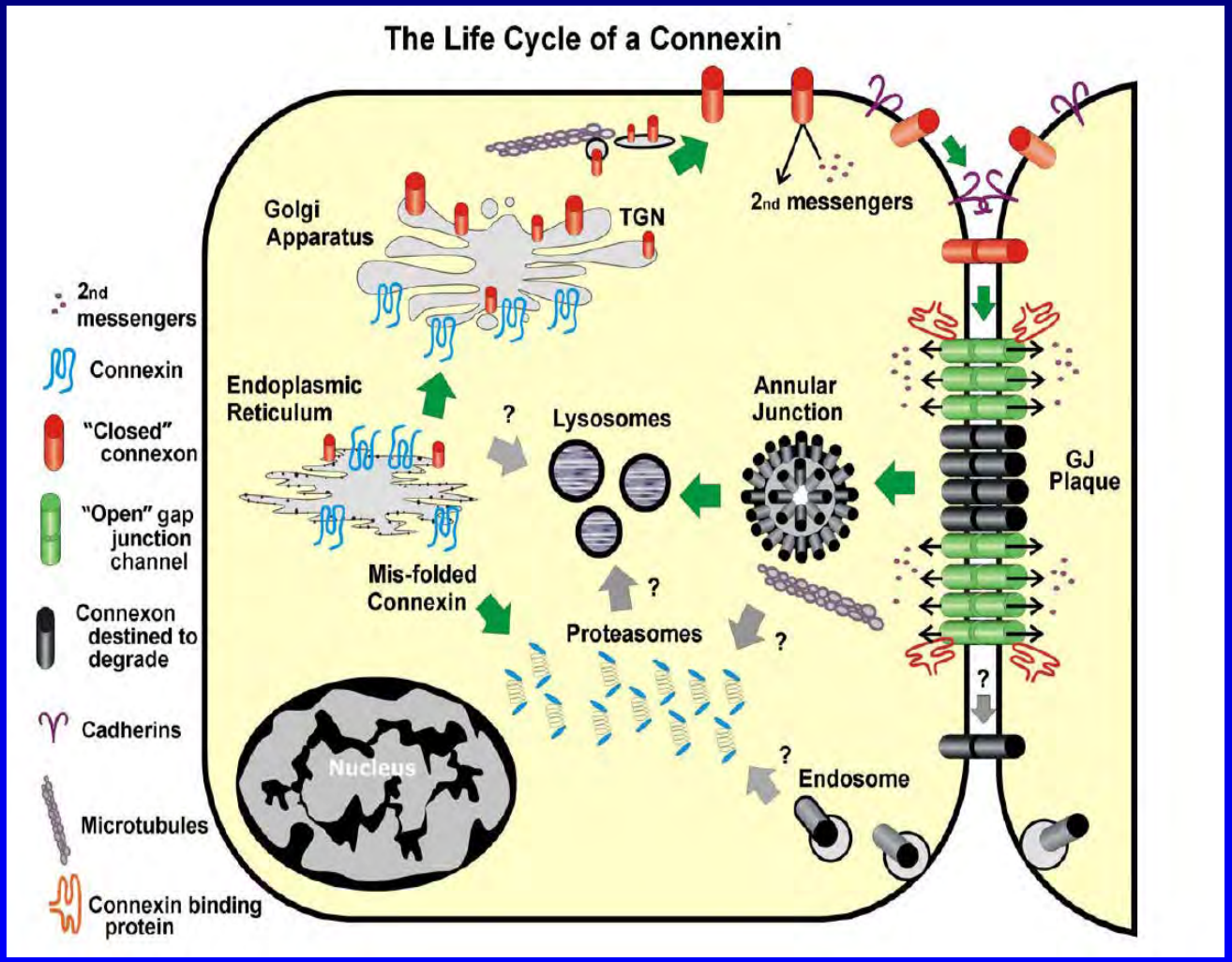
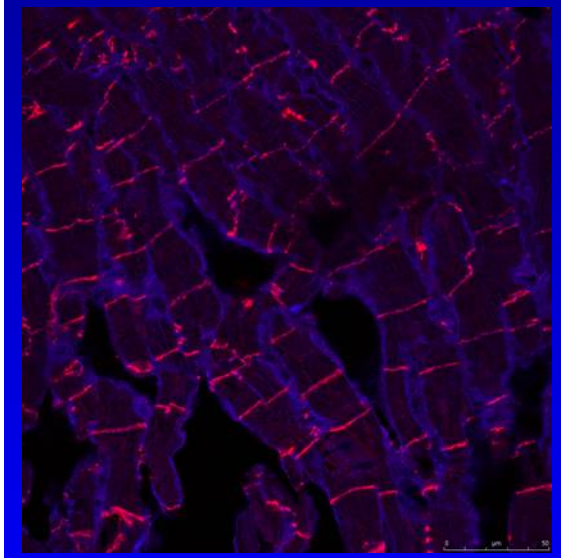


Figure 1 Summary of the typical connexin expression patterns of the mammalian heart.

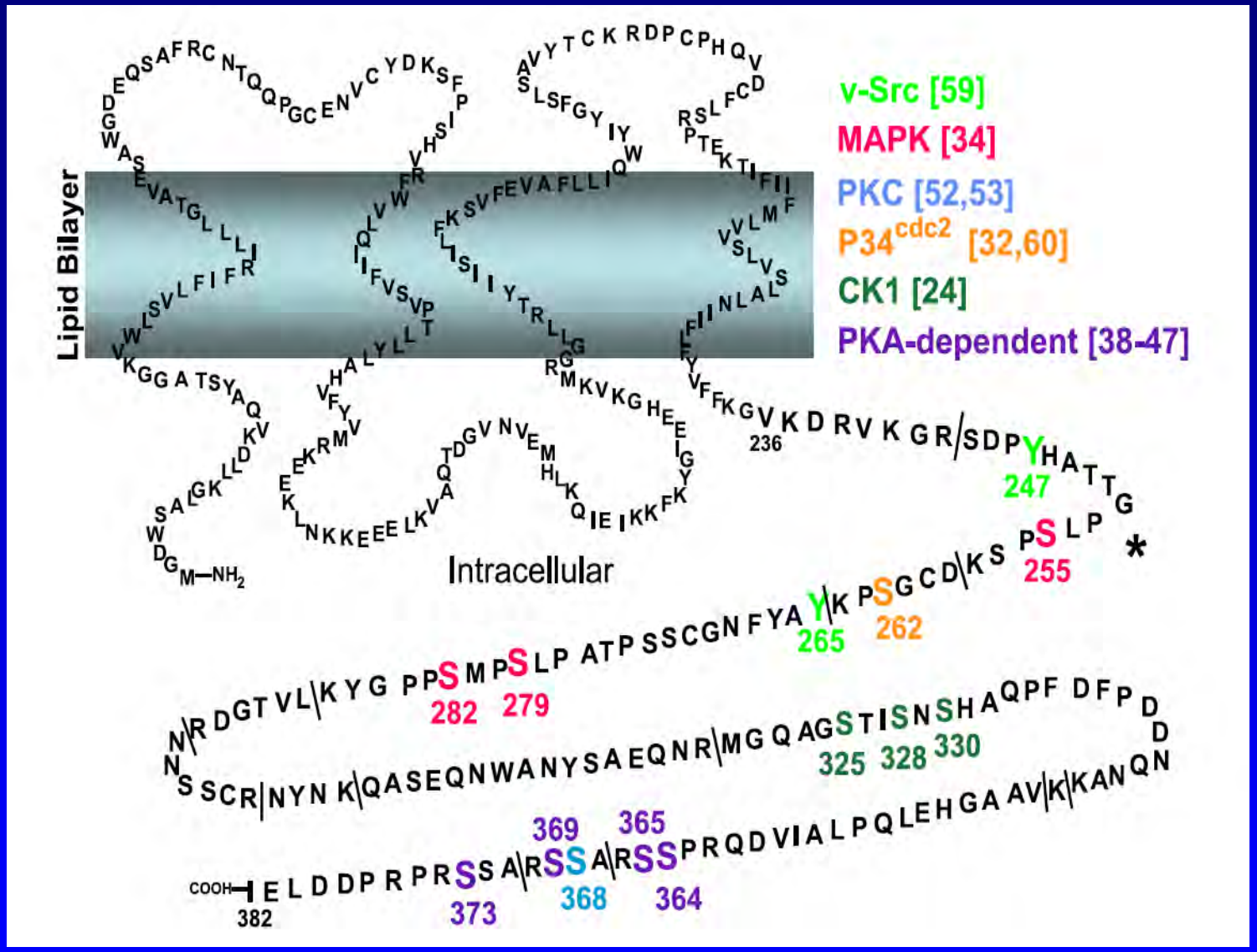
Cardiovasc Res. 2008;80:9-19.



Normal Ventricles



Taichung VGH data



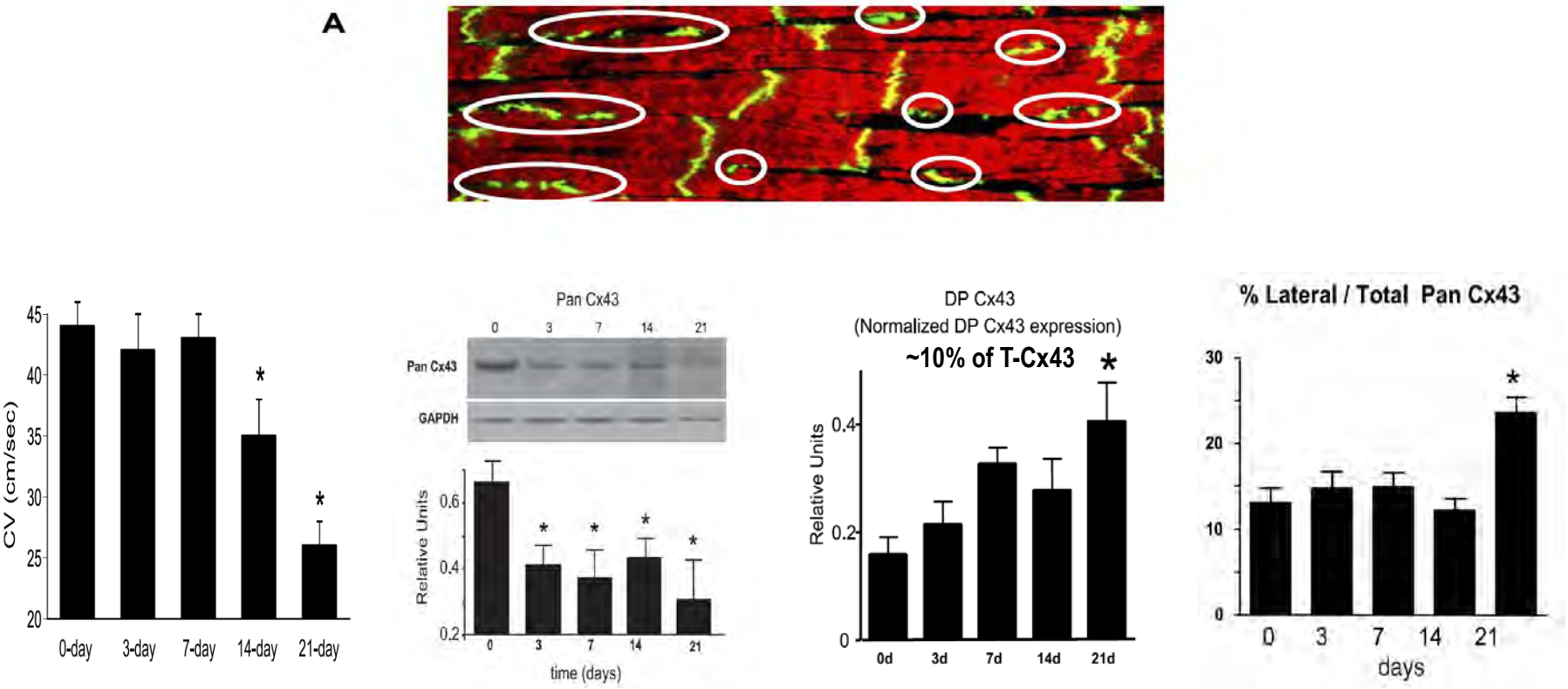
Biochimica et Biophysica Acta 1711 (2005) 154–163

Dynamic changes in conduction velocity and gap junction properties during development of pacing-induced heart failure

Fadi G. Akar, Robert D. Nass, Samuel Hahn, Eugenio Cingolani, Manish Shah, Geoffrey G. Hesketh, Deborah DiSilvestre, Richard S. Tunin, David A. Kass, and Gordon F. Tomaselli

Division of Cardiology and Institute for Computational Medicine, Johns Hopkins University, Baltimore, Maryland

Submitted 18 January 2007; accepted in final form 12 April 2007

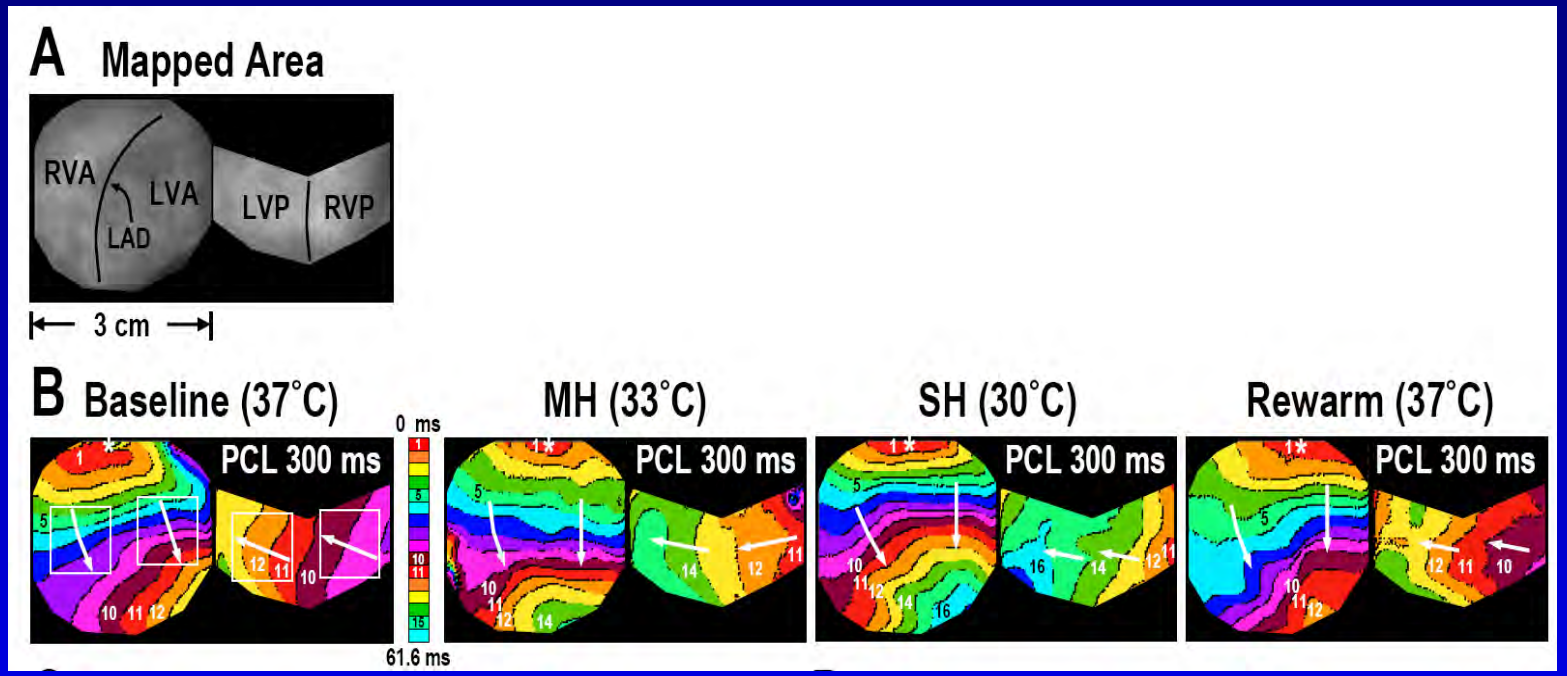


Am J Physiol Heart Circ Physiol. 2007;293:H1223-30.

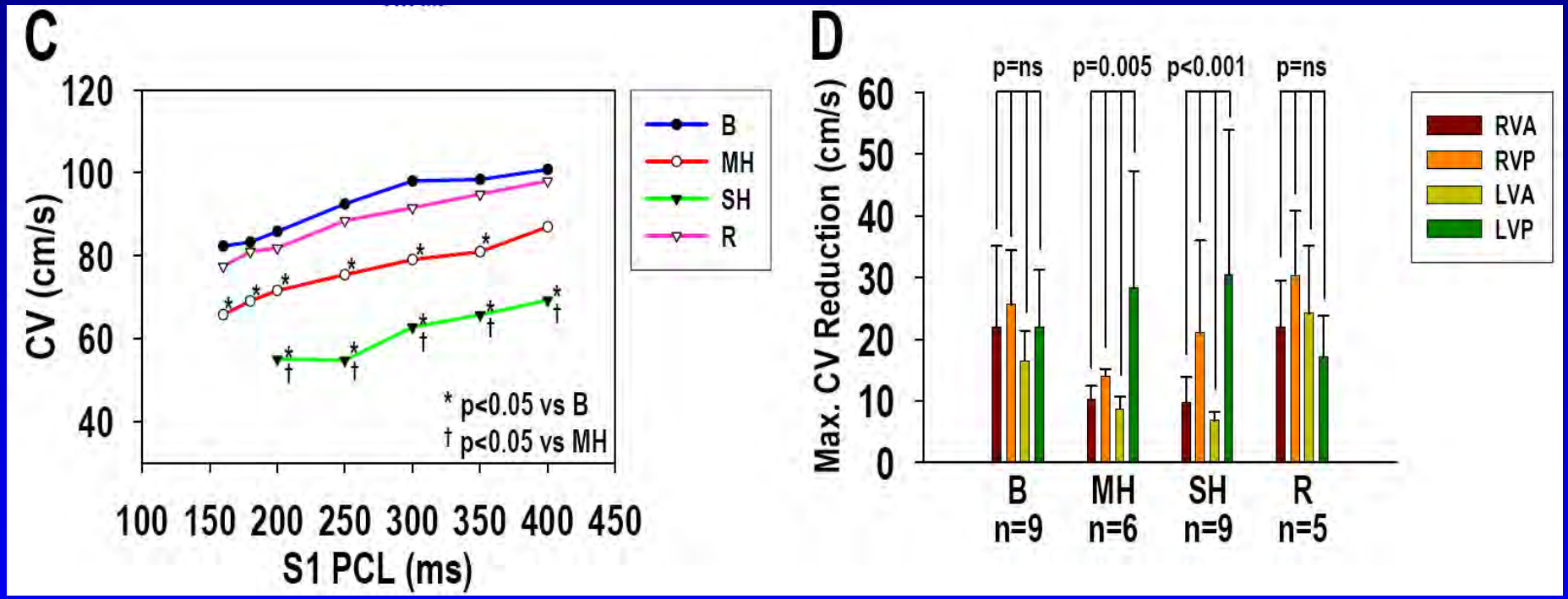
Method

- Epicardial CV of ventricles was evaluated by S1 pacing in Langendorff-perfused isolated rabbit hearts
  - Baseline (37˚C, 9 hearts)
  - After 30-min moderate hypothermia (MH, 33˚C, 6 hearts)
  - After 30-min severe hypothermia (SH, 30˚C, 9 hearts)
  - Rewarming (30-min SH+ 30 min 37˚C, n=5)

Immunoblotting and Histopathological study

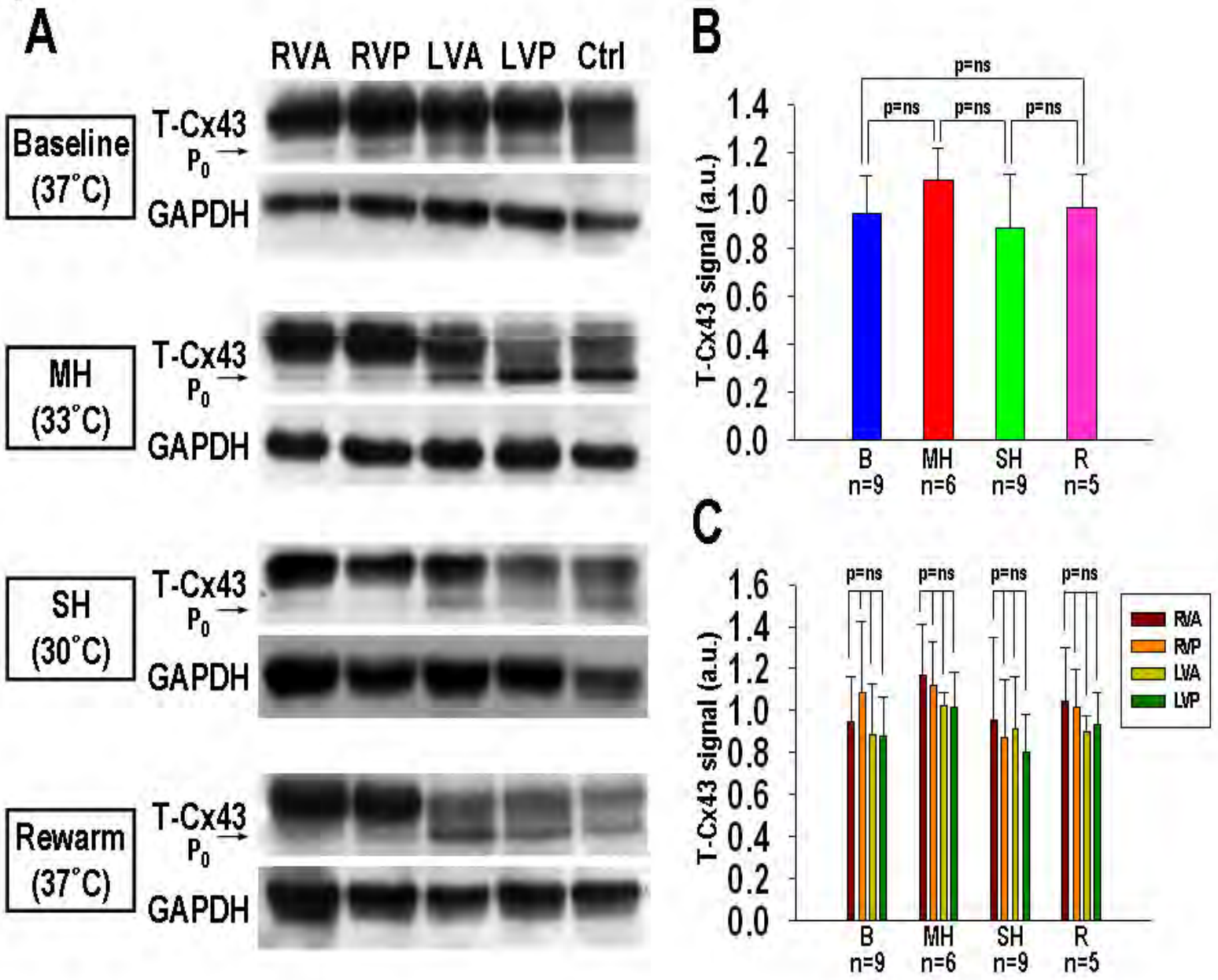


- CV was determined at anterior and posterior aspects of RV and LV.
- Tissue samples were collected to measure the level and distribution of the non-phosphorylated (NP-Cx43) and total (T-Cx43) forms Cx43 by Western blotting and immunoconfocal microscopy.



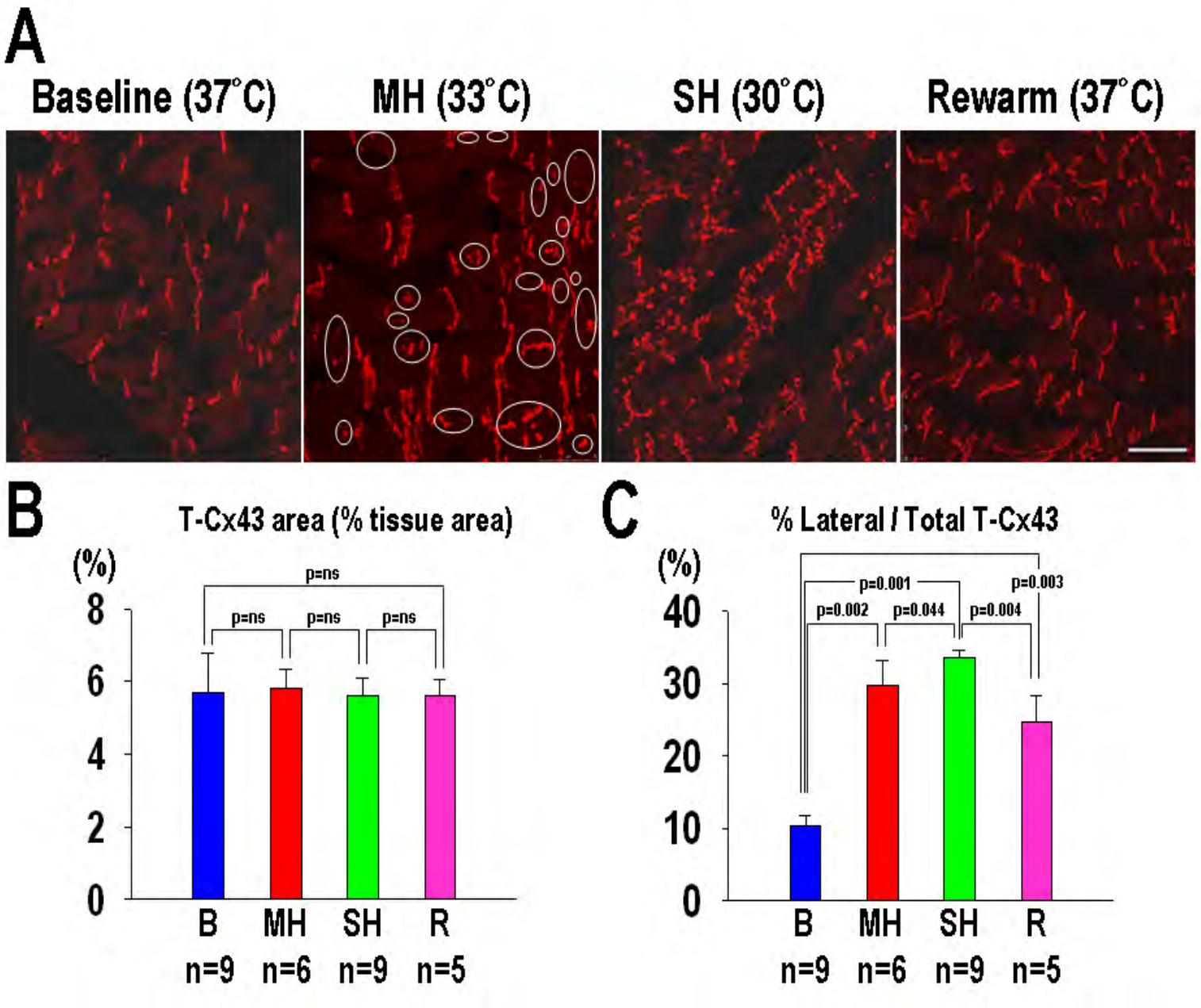
Hsieh et al. Circ J. 2011;75:1706-16.

Figure 2



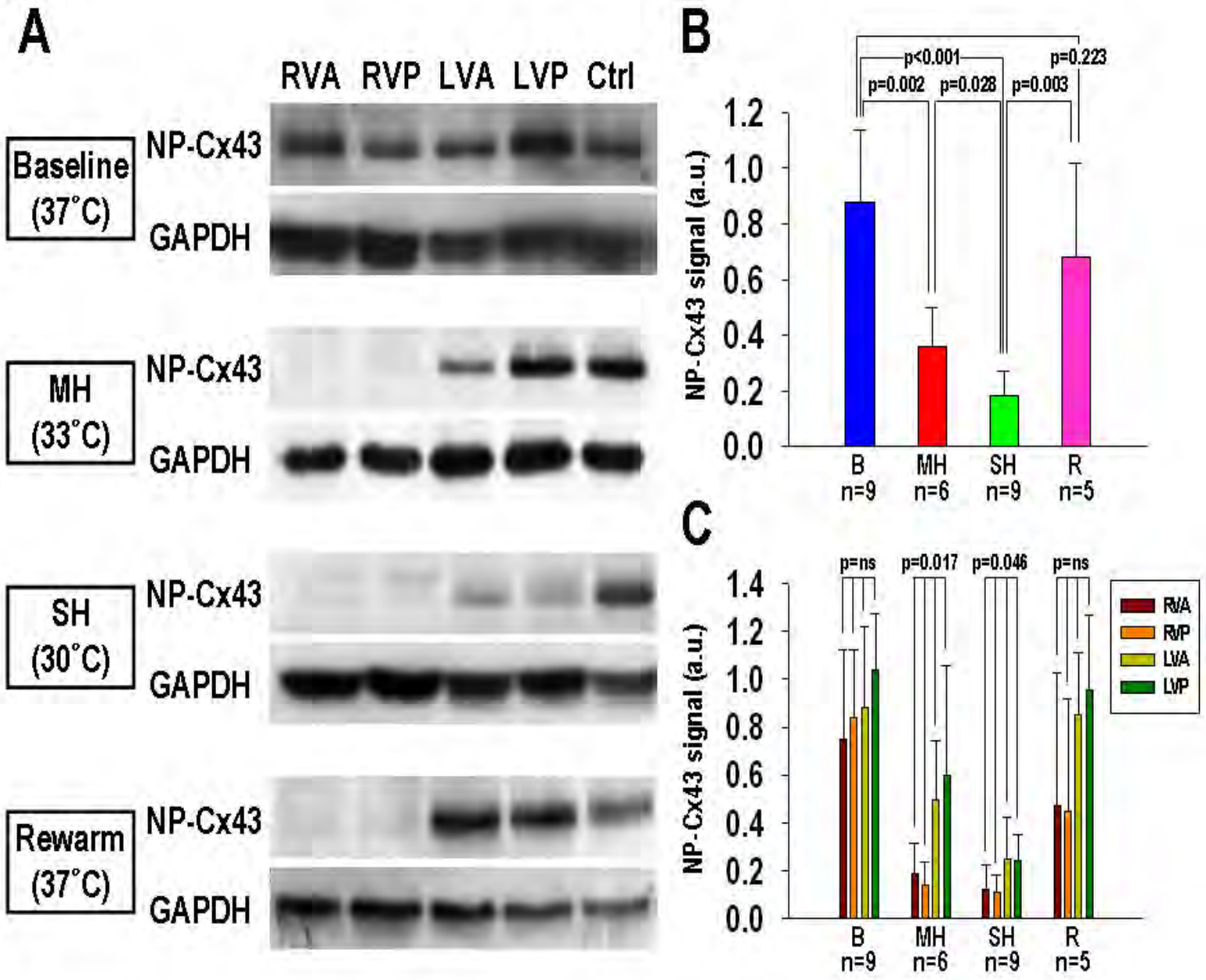
Hsieh et al. Circ J. 2011;75:1706-16.

Figure 3



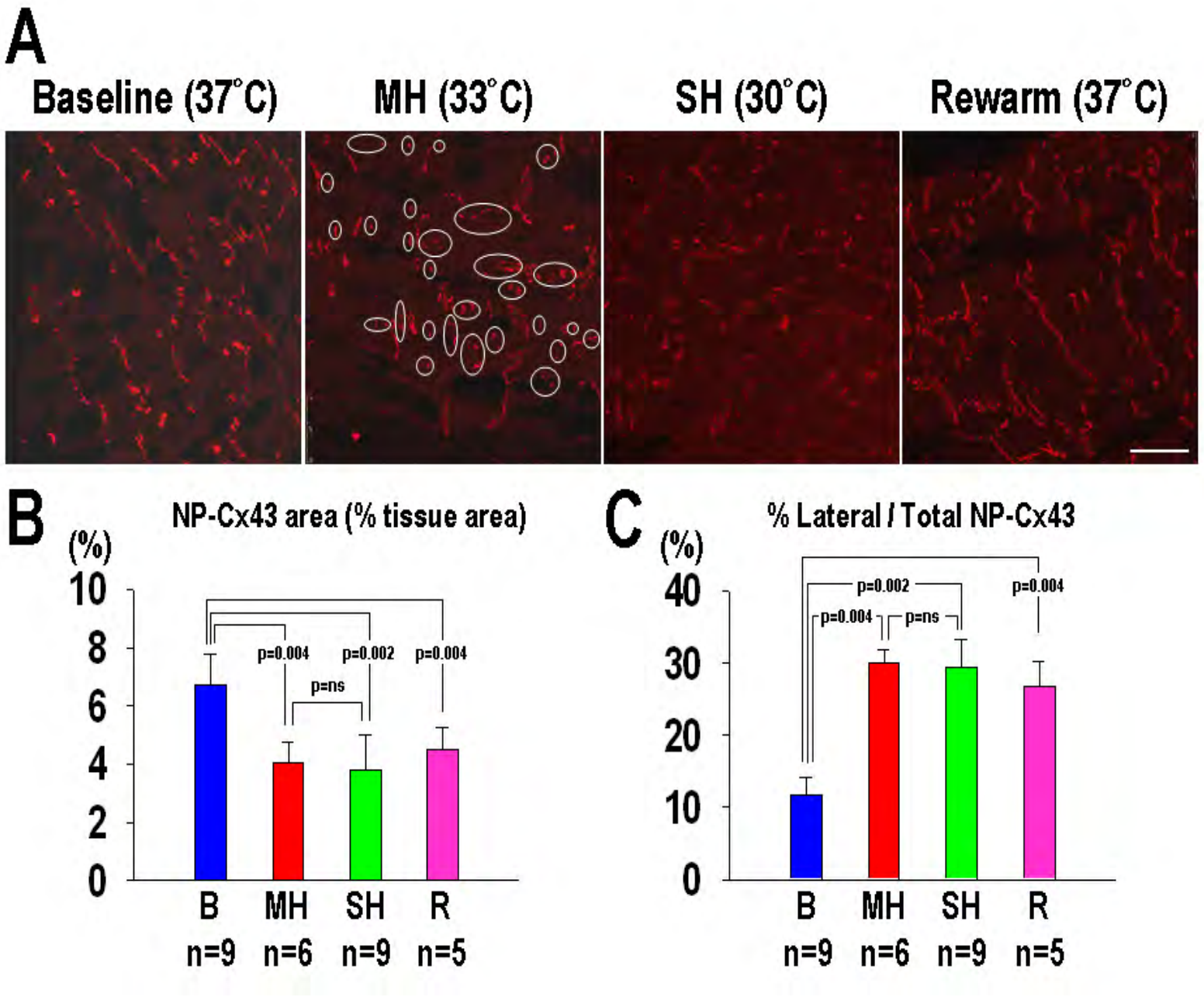
Hsieh et al. Circ J. 2011;75:1706-16.

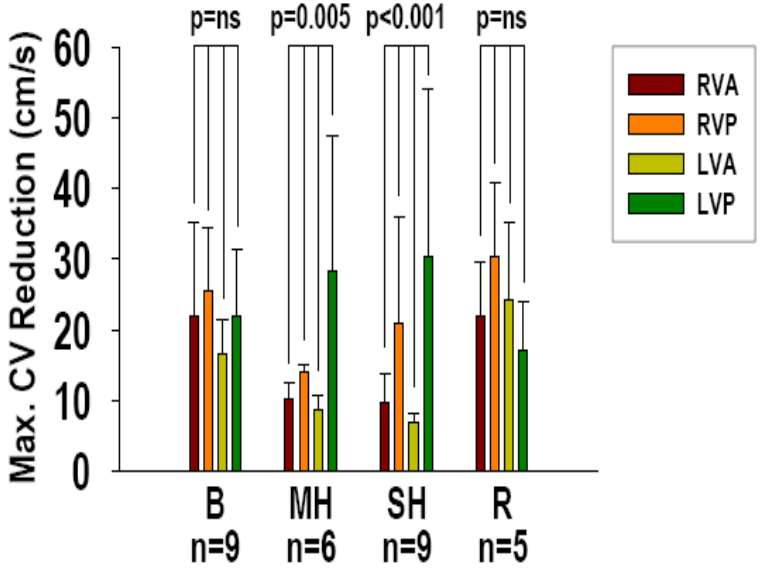
Figure 4

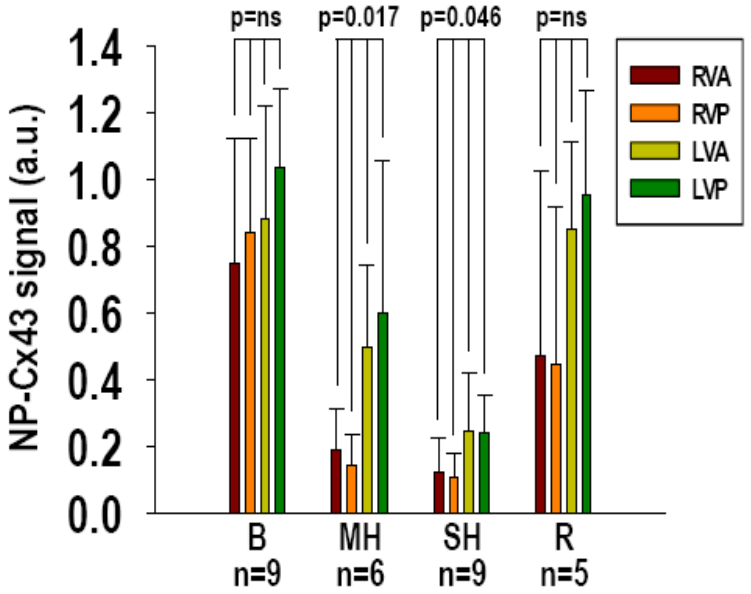


Hsieh et al. Circ J. 2011;75:1706-16.

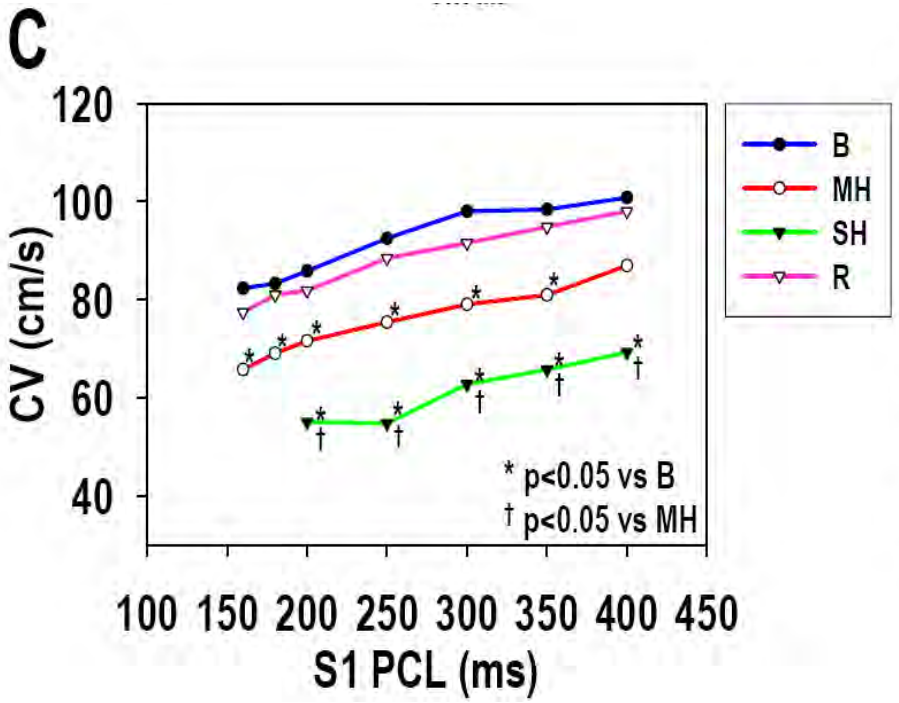
Figure 5

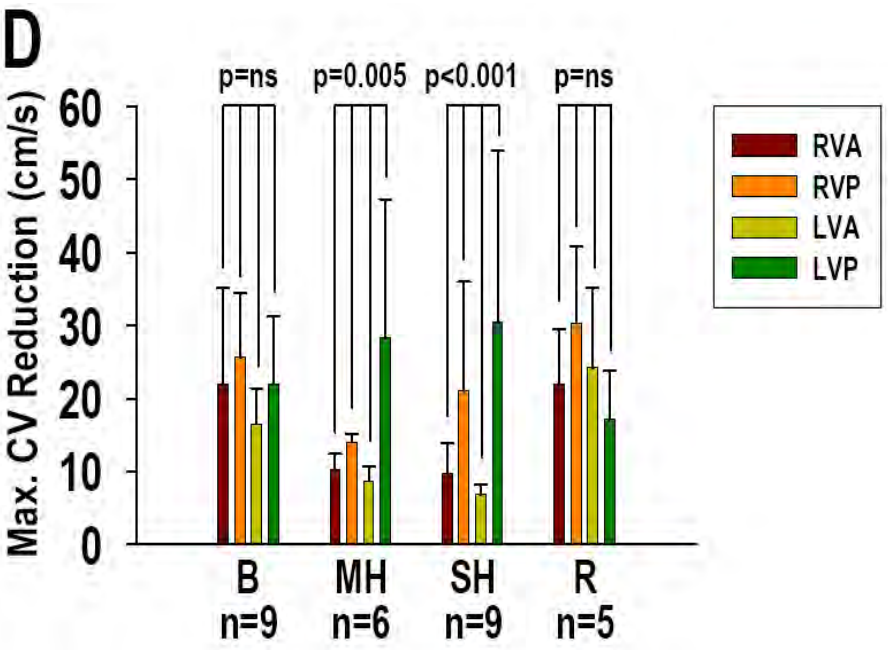

A
Baseline (37˚C)
MH (33˚C)
SH (30˚C)
Rewarm (37˚C)
B
NP-Cx43 area (% tissue area)
(%)
10
8
6
4
2
0
p=0.004
p=0.002
p=0.004
p=ns
B
MH
SH
R
n=9
n=6
n=9
n=5
C
% Lateral / Total NP-Cx43
(%)
40
30
20
10
0
p=0.002
p=0.004
p=ns
p=0.004
B
MH
SH
R
n=9
n=6
n=9
n=5

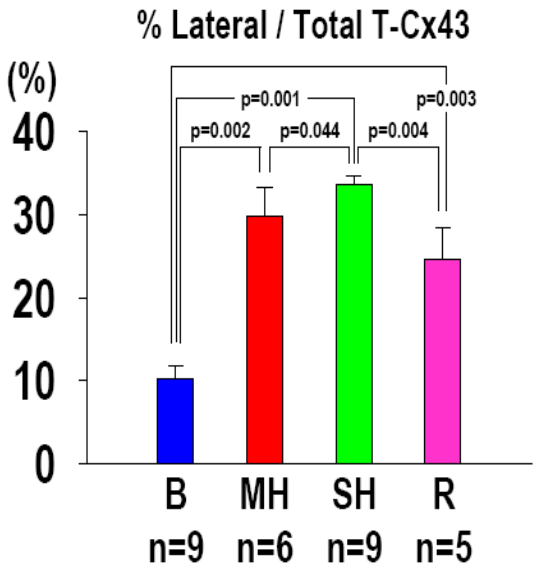


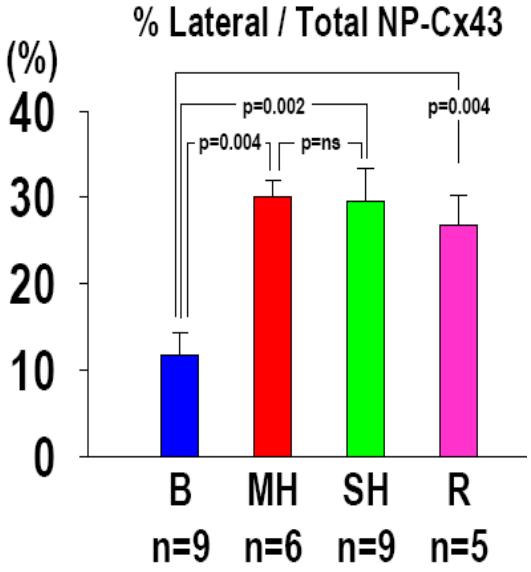


Remodeling of Cx43 gap junctions may contribute to the demonstrated conduction disturbance during hypothermia !?


C
CV (cm/s)
120
100
80
60
40
100 150 200 250 300 350 400 450
S1 PCL (ms)
B
MH
SH
R
* p<0.05 vs B
† p<0.05 vs MH


D
Max. CV Reduction (cm/s)
60
50
40
30
20
10
0
p=ns
p=0.005
p<0.001
p=ns
RVA
RVP
LVA
LVP
B
n=9
MH
n=6
SH
n=9
R
n=5


% Lateral / Total T-Cx43
(%)
40
30
20
10
0
p=0.001
p=0.003
p=0.002
p=0.044
p=0.004
B
n=9
MH
n=6
SH
n=9
R
n=5


% Lateral / Total NP-Cx43
(%)
40
30
20
10
0
p=0.002
p=0.004
p=0.004
p=ns
B
n=9
MH
n=6
SH
n=9
R
n=5

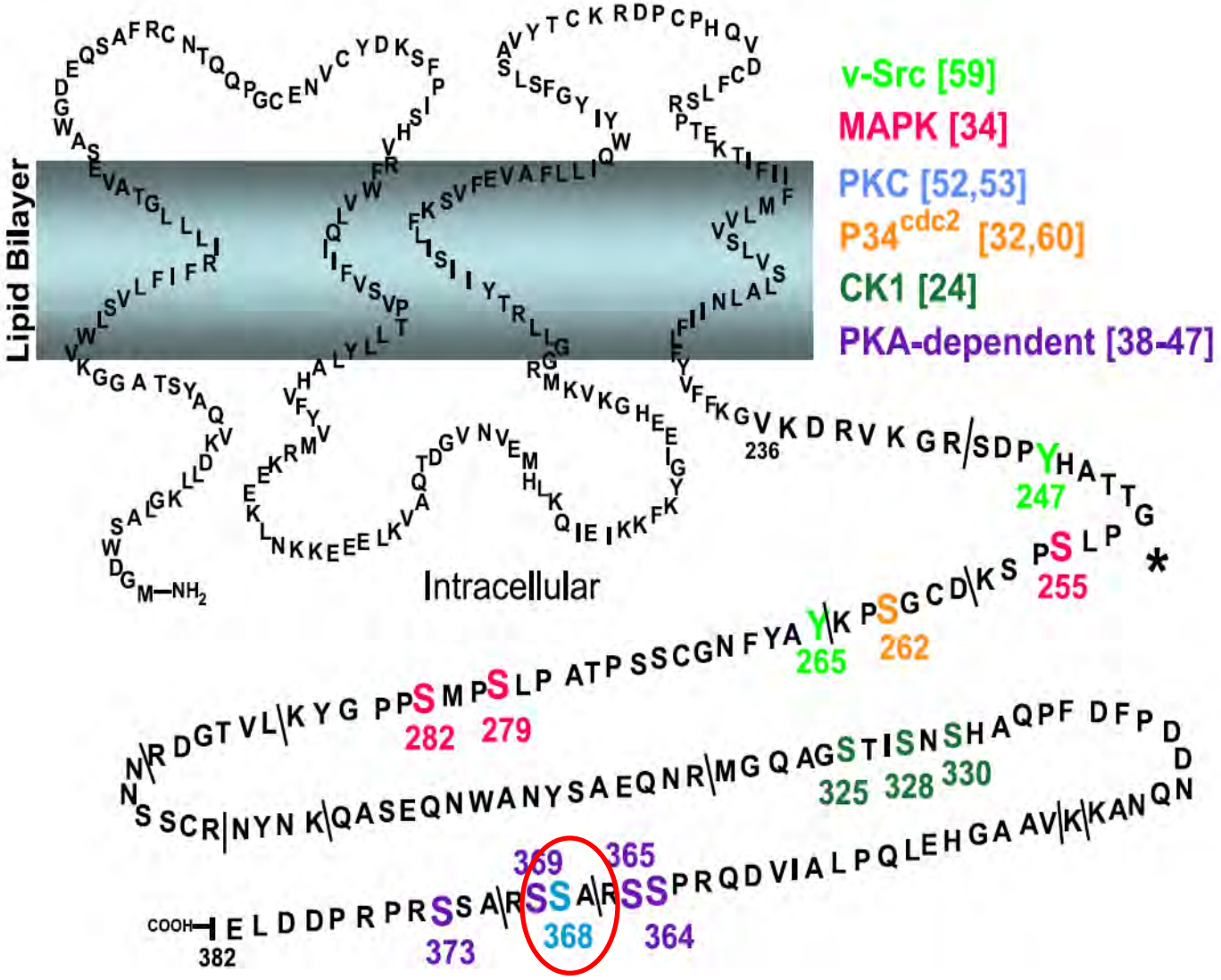
Possible Explanation

- NP- and T-Cx43 lateralization might not play a major role in CV slowing during TH in this acute model.
- Tansey et al. also reported that 30-minute global ischemia in isolated rabbit heart caused significant T-Cx43 lateralization, while CV was not changed, which was similar to our findings.

Ann Thorac Surg 2006;82:1472-9

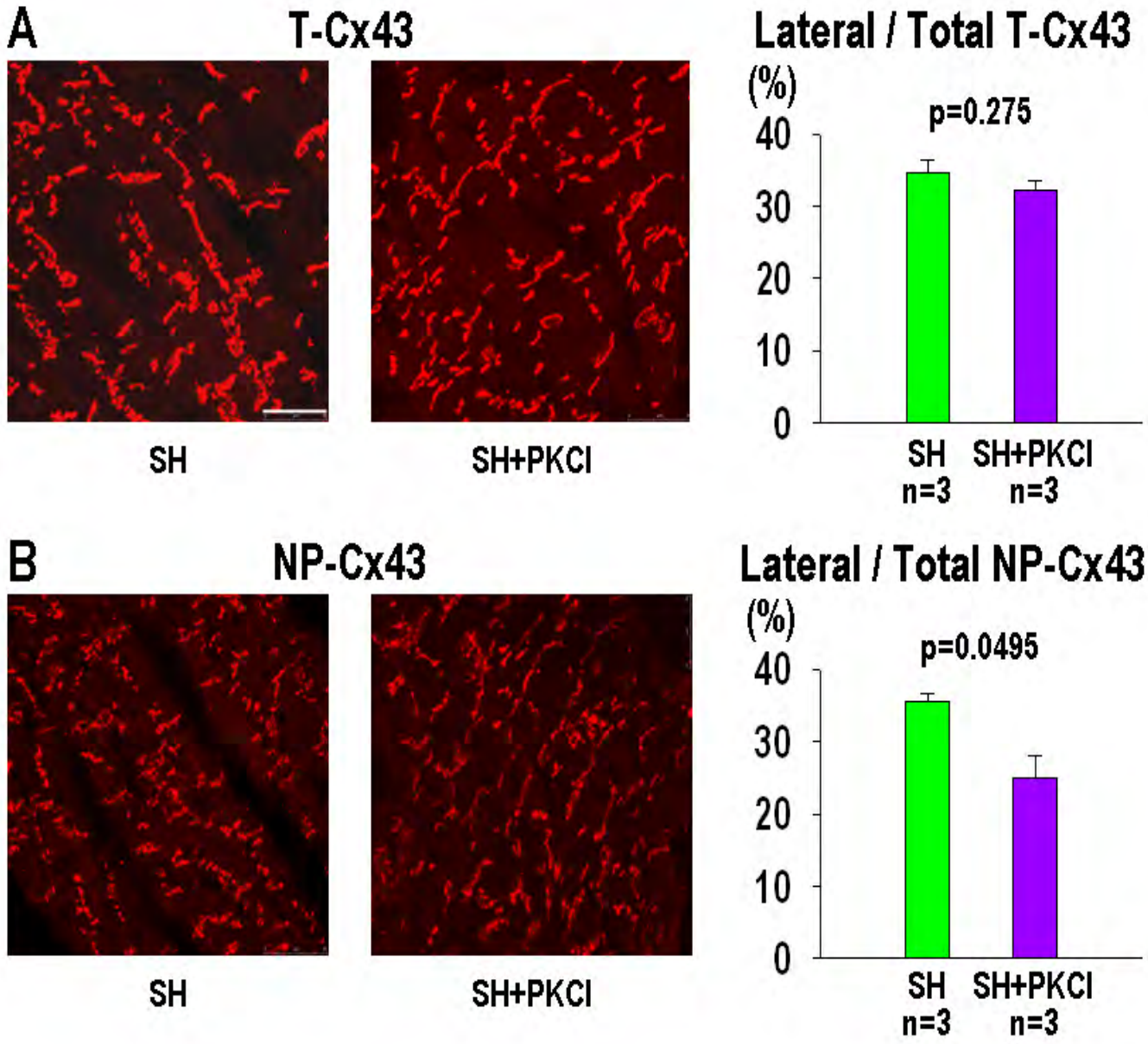
Clinical Implication

- **SH hearts showed a greater extent in**
  - CV slowing
  - NP-Cx43 down-regulation
  - T-Cx43 lateralization
  - Heart numbers with inducible VF, compared to values in MH hearts.
- **33˚C might be a more feasible temperature for patients receiving TH than 30˚C.**



Biochimica et Biophysica Acta 1711 (2005) 154–163

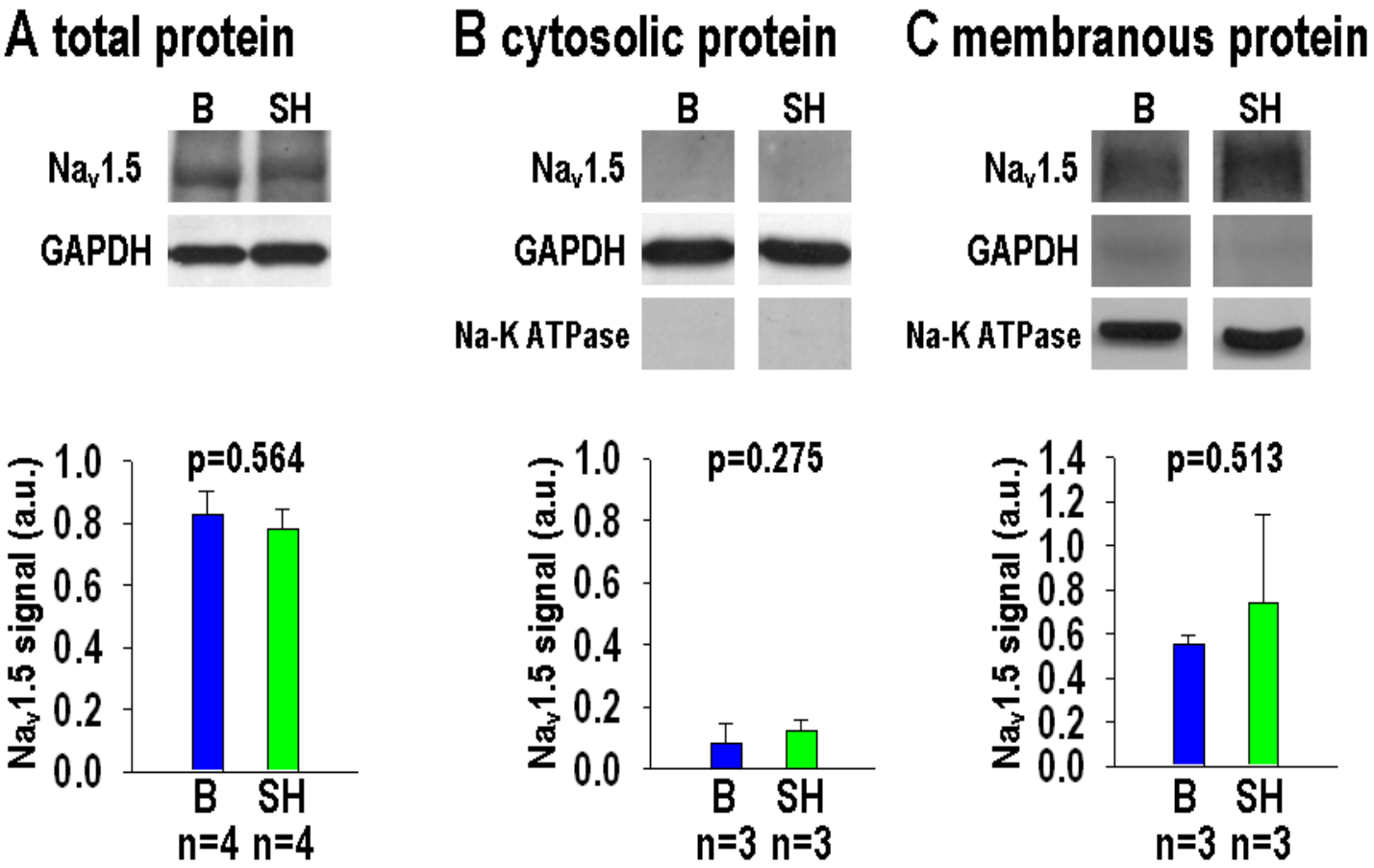
Figure 7


A
T-Cx43
SH
SH+PKCI
Lateral / Total T-Cx43
(%)
p=0.275
40
30
20
10
0
SH
n=3
SH+PKCI
n=3
B
NP-Cx43
SH
SH+PKCI
Lateral / Total NP-Cx43
(%)
p=0.0495
40
30
20
10
0
SH
n=3
SH+PKCI
n=3

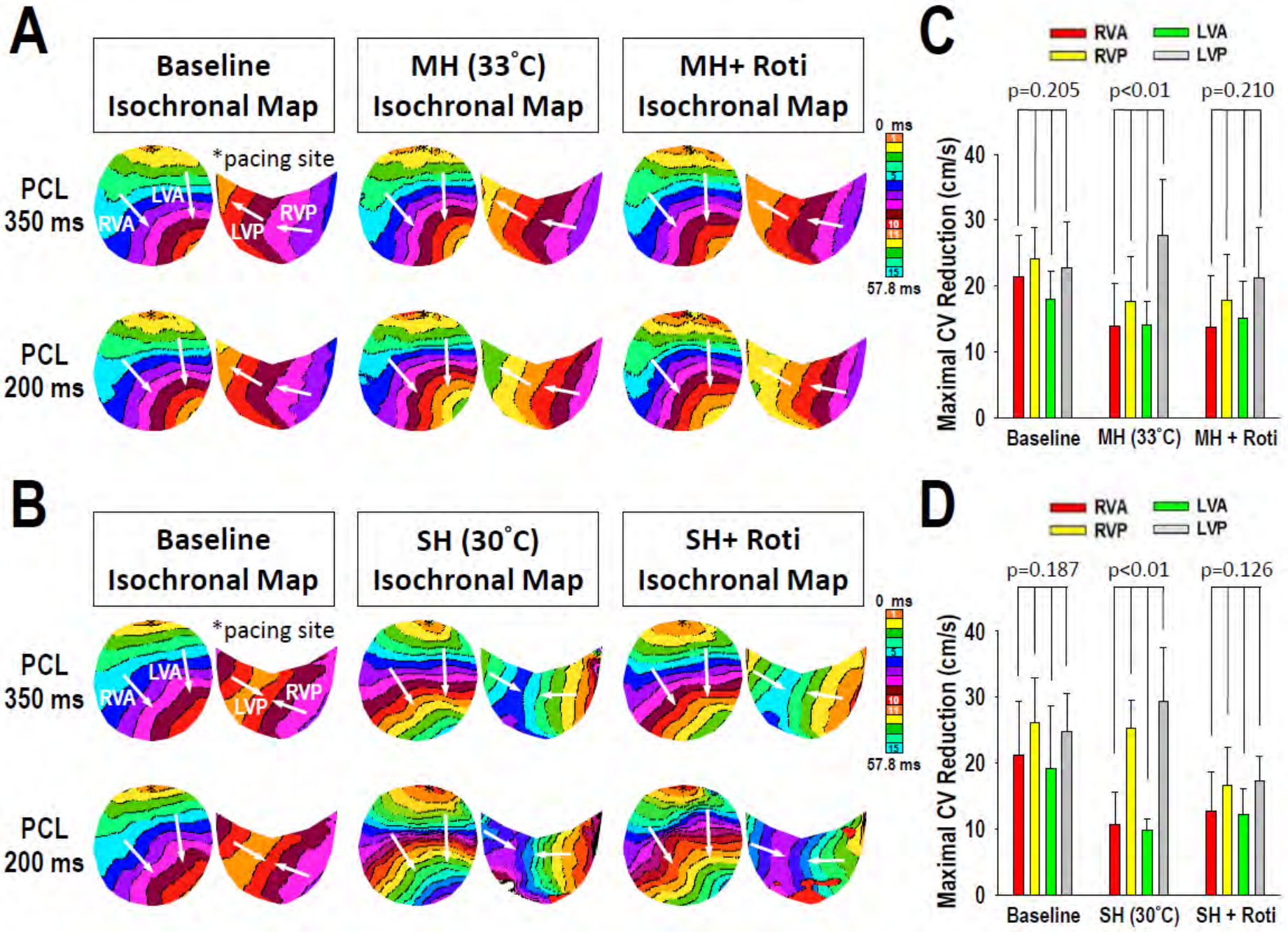
Conclusion

- Short-duration (30 minutes) TH causes a prompt temperature-dependent Cx43 GJ remodeling, in which the PKC pathway is involved.
- However, GJ remodeling alone might not play a major role in the conduction disturbance of this acute model.

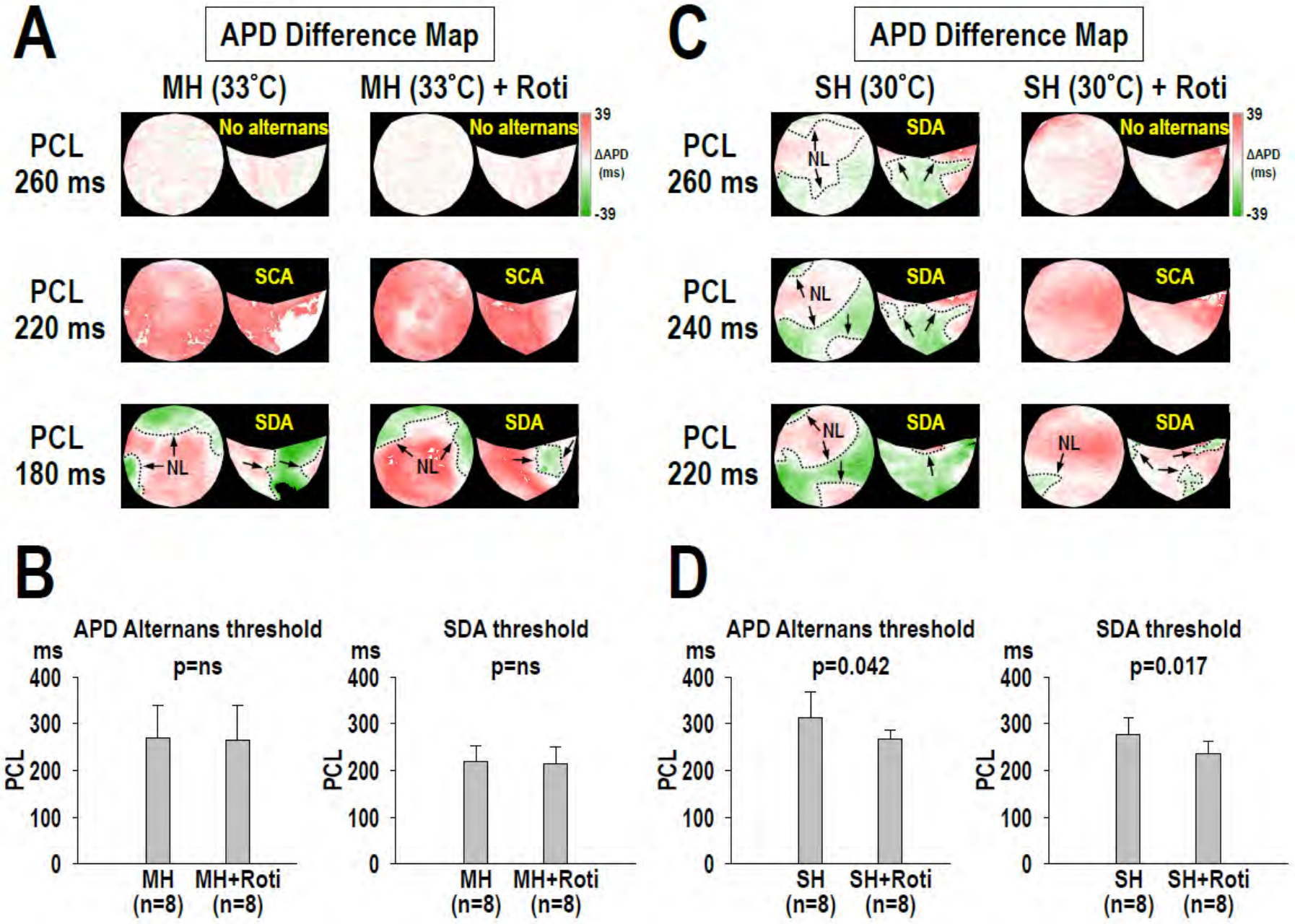
Figure 8



Hsieh et al. Circ J. 2011;75:1706-16.



Hsieh et al. Heart Rhythm 2015 (under revision)



Hsieh et al. Heart Rhythm 2015 (under revision)

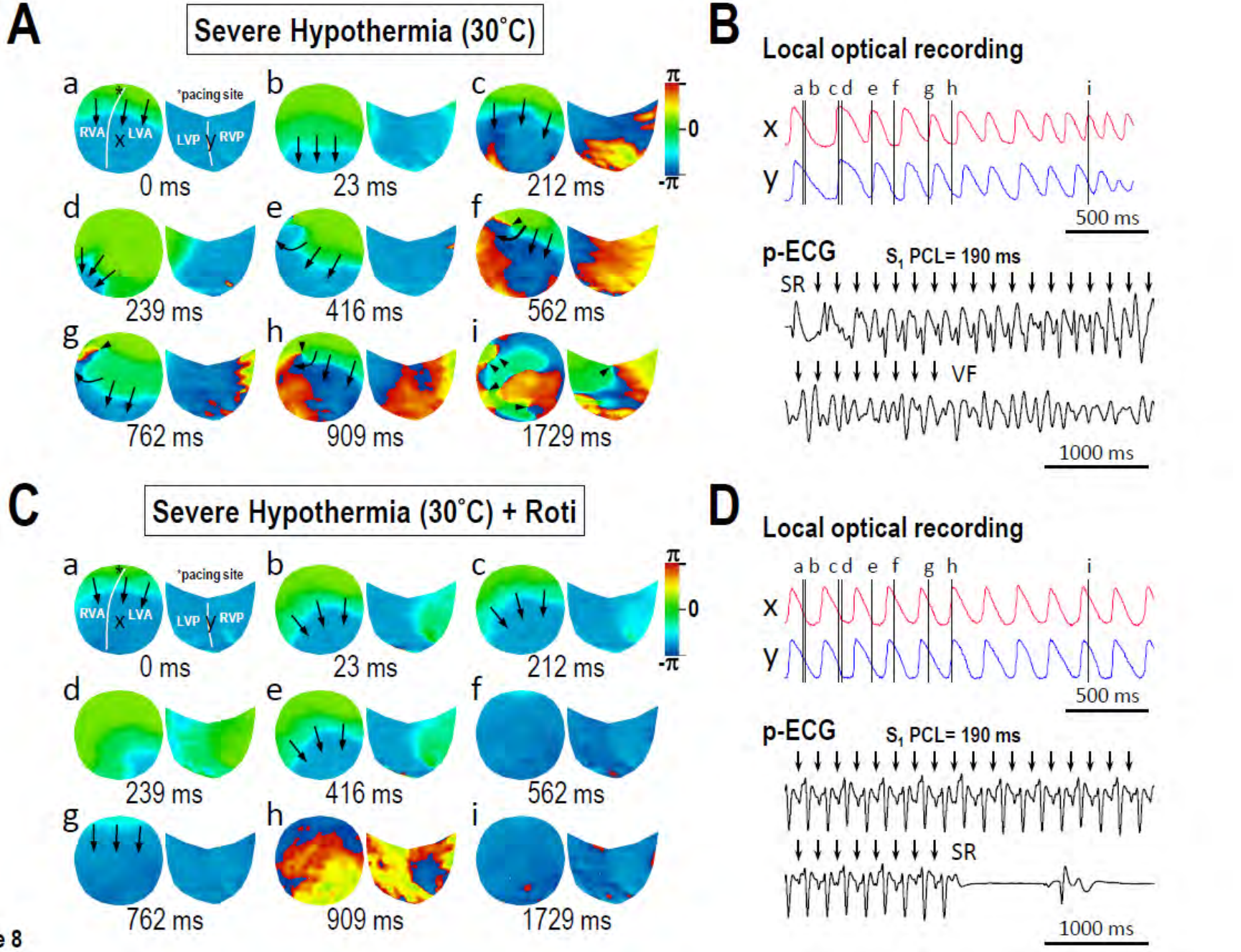


Figure 8

Hsieh et al. Heart Rhythm 2015 (under revision)

Conclusions

- TH (30˚C) increased the vulnerability of VF by enhancing proarrhythmic parameters (SDA).
- Short-duration (30 min) therapeutic hypothermia causes prompt Cx43 GJs remodeling.
- Rewarming abolished hypothermia-induced conduction disturbance, while Cx43 GJs lateralization did not completely recover.
- Rotigaptide protects the hearts against ventricular arrhythmias by increasing ventricular CV and delaying the onset of SDA during TH.
- Enhancing cell-to-cell coupling by rotigaptide might be a novel approach to prevent ventricular arrhythmias during TH.

Thanks For Your Attention !!