Sympathetic Inhibition and Inflammation

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Sympathetic Denervation
Cardiac innervation and left sympathetic cardiac denervation

Effects of unilateral stellate ganglion blockade on the arrhythmias associated with coronary occlusion

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H. Lowell Stone, Ph.D.
Arthur M. Brown, M.D., Ph.D.

Galveston, Texas, and Milano, Italy
Effects of Unilateral Cardiac Sympathetic Denervation on the Ventricular Fibrillation Threshold

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NEAL G SNEBOLD, MA
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Galveston, Texas
Milan, Italy

Effect of unilateral stellectomy and blockade on VF threshold

Ventricular fibrillation threshold (% change from control)

Left
Right
Left stellectomy is accompanied by a reflex increase in cardiac vagal efferent nerve activity.
LCSD reduces the incidence of sudden cardiac death after myocardial infarction.

LCSD: left cardiac sympathetic denervation
Oxyprenolol: a non-selective beta blocker

Treating Electrical Storm
Sympathetic blockade vs. ACLS therapy

Beta blocker

Sympathetic blockade Tx: (n=25)
7 esmolol,
14 propranolol
6 LSGB

Neuraxial Modulation for Refractory Ventricular Arrhythmias

Value of Thoracic Epidural Anesthesia and Surgical Left Cardiac Sympathetic Denervation

Tara Bourke, MD; Marmar Vaseghi, MD; Yoav Michowitz, MD; Vineet Sankhla, MD; Mandar Shah, MD; Nalla Swapna, MD; Noel G. Boyle, MD, PhD; Aman Mahajan, MD, PhD; Calambur Narasimhan, MD, DM; Yash Lokhandwala, MD, DM; Kalyanam Shivkumar, MD, PhD

Figure 2. Effect of TEA. Line graph demonstrating number of VT therapies both before and during TEA infusion.
Renal sympathetic denervation in patients with ICD and electrical storm
Inflammation and arrhythmia

- Myocarditis
  - Injection into footpads: 0.2 ml porcine cardiac myosin (10mg/ml)

- Air pollution

- Acute MI
Myocarditis and arrhythmia

A

Control  Myo  MyoS

B

Control  Myo  MyoS

H&E

Trichrome

C

Survival (%)

Control (n=15)
Myo (n=15), p=0.03 vs. control
MyoS (n=15)

Time (days)

D

Injection into footpads: 0.2 ml porcine cardiac myosin (10mg/ml)

Inflammation (%)

Control  Myo  MyoS

Fibrosis (%)

Control  Myo  MyoS

2 sec

Spontaneous Ca\textsuperscript{2+} release in rat neonatal myocytes treated with TNF-\alpha

A

B

C

Inflammation, oxidative stress and the phosphorylation of Ca$^{2+}$ handling protein in myocarditis

Air pollution increased arrhythmia with APD prolongation: Prevention with TAT-CryAB

Kim, Joung et al. Toxicology and App Pharm 2012

Park, Joung et al. Toxicology and App Pharm 2013
CryAB suppress DEP induced ROS generation and phosphated CaMKII activation

**A**

![Graph showing counts of ROS](image)

**B**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>DEP</th>
<th>DEP + KN92</th>
<th>DEP + KN93</th>
<th>CryAB + DEP</th>
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</table>

**C**

- p-CaMKII
- CaMKII
- β-actin

![Protein level bar graph](image)

* p<0.001

Park, Joung et al. Toxicology and App Pharm 2013:266:267-75
RAGE-mediated signal transduction

- A multi-ligand receptor of the immunoglobulin superfamily.
- Interacts with families of ligands that mediate diverse functions in a broad array of cell types, including activation of pro-inflammatory mechanisms.
- In chronic disease states such as diabetes, immune/inflammatory foci, cardiac ischemic injury and neurodegenerative disorders, upregulation of RAGE was associated with tissue injury.

PEI-DA/siRAGE complex formation

RAGE gene sequence

PEI-DA + sRAGE → PEI-DA/siRAGE complex

Target sequences:

- #1 (S100274904)
  5' - GCCATATGCTGCTGG CTAGGG 3'
- #2 (S100274904)
  5' - GCCATATGCTGCTGG CTAGGG 3'
- #3 (S100274904)
  5' - GCCATATGCTGCTGG CTAGGG 3'
- #4 (S100274904)
  5' - GCCATATGCTGCTGG CTAGGG 3'

Weight ratio (PEI-DA/siRAGE):

0 0.5 1 2 4 8

Relative RAGE expression level

Vehicle PEI-DA/PEI-DA/siRAGE

Park H et al. / J Control Release 2015;217:315–26
RAGE silencing improved CV and VT/VF induction threshold

Restitution kinetics of APD$_{90}$, CV, CV map

CV was decreased in IR model, but not in IR/siRAGE.

Park H et al. / J Control Release 2015;217:315–26
Sympathetic Inhibition and Inflammation

Anti-inflammatory effect of sympathetic nerve denervation: Splenic JAK2-STAT3 pathway

Hyelim Park, Boyoung Joung
Methods

Left Stellate Ganglion Block (NB)

Animal groups

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<tr>
<th>Days</th>
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<th>7</th>
<th>14</th>
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<td>NB (n=7)</td>
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Myocarditis model (Myo)

Injection into footpads:
0.2 ml porcine cardiac myosin (10mg/ml)

Left SGB improved survival and cardiac function in EAM.

Left SGB suppressed arrhythmias in EAM.

- Myo group showed lower survival rate, QT prolongation and VT episodes.
- Left SGB prevented these effects of myocarditis.

Left SGB improved conduction time and APD prolongation in EAM

Left SGB decreased oxidative stress and inflammation in EAM

**A**

- **TNF-α (pg/ml)**
- **IL-6 (pg/ml)**
- **HMGB1 (ng/ml)**

Control, Myo, MyoNB

* p<0.05

**B**

- **TNF-α**
- **IL-6**
- **HMGB1**

GAPDH

Relative to Control (normalized to GAPDH)

Control, Myo, MyoNB

* p<0.05

Inflammation: A nervous connection

Figure 1 The inflammatory response to microorganisms, and ways of controlling it. Clockwise

Immune-to-brain Communication

The Cholinergic Anti-Inflammatory Pathway

The central level of norepinephrine, epinephrine, and acetylcholine

- The left SGB significantly reduced the level of norepinephrine, epinephrine in serum as compared with the Myo group. (p<0.05)

The findings of autonomic balance of LF and HF components of power.

A

**Control**

Power (ms²/Hz) vs. Frequency (Hz)

**Myo**

Power (ms²/Hz) vs. Frequency (Hz)

**MyoNB**

Power (ms²/Hz) vs. Frequency (Hz)

**NB**

Power (ms²/Hz) vs. Frequency (Hz)

B

**HF Peak**

Control, Myo, MyoNB, NB

**LF/HF Ratio**

Control, Myo, MyoNB, NB

* P<0.05
Left stelllectomy activates STAT3 in spleen

α7nAch R
DAPI

p-STAT3
DAPI

STAT3
DAPI

Left stellectomy activates STAT3 and JAK2 in spleen, kidney, liver and heart

A

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<th>Kidney</th>
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<td>MyoNB</td>
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</tbody>
</table>

B

Relative to Control (normalized to GAPDH)

- **Spleen**
  - p-STAT3
  - p-JAK2
  - α7AChR
  - NF-κB
  - * P<0.05
- **Liver**
  - p-STAT3
  - p-JAK2
  - α7AChR
  - NF-κB
  - *
- **Kidney**
  - p-STAT3
  - p-JAK2
  - α7AChR
  - NF-κB
  - *

- **Heart**
  - p-STAT3
  - p-JAK2
  - α7AChR
  - NF-κB
  - **

Left stelllectomy

- Cholinergic anti-inflammatory pathway and heart -
Q1. Transient sympathetic N block with bupivacaine
Q2. Beta blocker
Take-Home Message

- Sympathetic nerve block suppress inflammation and arrhythmia via the activation of cholinergic anti-inflammatory pathway (splenic JAK2-STAT3 activation) in rat myocardial model.
- Transient nerve block or beta blocker were also related with the suppression of arrhythmia.
- The modulation of cholinergic anti-inflammatory pathway might be an important treatment modality in many cardiac disease.
Thank you for your attention!

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Kyu Kim, MD
Daehoon Kim, MD
Hyn-Sun Bak
Hyun-mi Kwon
Chae-hee Lee
Inflammation and arrhythmia

Myocarditis

Air pollution

Acute MI

Injection into footpads: 0.2 ml porcine cardiac myosin (10mg/ml)