Disclosures

• Sorrento Therapeutics Inc. grant recipient
The Vicious Cycle of Heart Failure

Heart Failure

- Myocardial Cell Death
- Myocardial Energy Expenditure
- Afterload
- Preload
- Venous return
- LVEDP
- Lung edema

Circulation

- Vasoconstriction
- Myocardial Growth
- Inotropy / Lusitropy
- Arrhythmias, Sudden Death

Heart

- Cytosolic Ca²⁺
- Myocardial Growth

Net Result: Heart Failure
Sympathetic Nerve Activity in Heart Failure


Reflex Control in Heart Failure

Afferent
- Arterial Baroreflex (-)
- Arterial Chemoreflex (+)
- Atrial Reflex (-)
- Ventricular Vagal Mechano Reflex (-)
- Chemosensitive Reflex (+)

Efferent
- Cardiac Sympathetic Afferent Reflex

(+)

Reflex Control in Heart Failure
The Baroreflex

Vagal Nerve Stimulation

A

Left ventricular volume indexes

Baseline 3 months 6 months

LVESVI, P = 0.35

LVEDVI, P = 0.44

P = 0.02

P = 0.35

P = 0.69

B

Left ventricular ejection fraction

Baseline 3 months 6 months

P < 0.001

P = 0.01

P = 0.78

P = 0.003

De Ferrari, G. Europ. Heart J. 2011
Chemoreflex Sensitivity

Carotid Body Denervation

A. Effects of carotid body denervation (CBD) on hypoxia-induced changes in respiration and arterial blood pressure.

B. Changes in RSNA (mV) and iSNA (mV/s) in sham-sham and CHF-sham groups.

C. Changes in RSNA (mV) and iSNA (mV/s) in sham-sham and CHF-CBD groups.

D. Changes in arterial blood pressure and heart rate in sham-sham and CHF-CBD groups.

Marcus, N et al. J. Physiol. 2014
Cardiac Sympathetic Afferents in Heart Failure: It's not just about the pain
Visceral afferent structure

Stimuli for Cardiac Sympathetic Afferents

- Hydrogen ion
- Oxygen radicals
- Potassium
- Lactate
- ATP
- Prostaglandins and other AA metabolites
- Bradykinin
- Substance P
- Capsaicin
CARDIAC SYMPATHETIC AFFERENT REFLEX IN HEART FAILURE

A

Arterial Pressure (mm Hg)

Renal Nerve Activity

10 Seconds  Bradykinin

B

Bradykinin

Change in RSNA (% of Ctrl)

5 ug

50 ug

Wang W and Zucker IH, Am. J. Physiol. 1996
Epicardial lidocaine reduces SNA in heart failure

Capsaicin (10 µg/kg, LA)

Pre-Cap. vs Post Cap.

Discharge Rate (spikes/sec)

Change in MAP (mm Hg)

Change in RNA (% of Ctrl)

Change in HR (BPM)

Zucker et al. In: Spinale FG. Pathophysiology of Tachycardia-Induced Heart Failure, 1996
TRPV1
Euphorbia resinifera
16 Billion Scoville Units

Resineferitoxin (RTX)
*P<0.05 vs. sham+vehicle; †, P<0.05 vs. CHF+vehicle.

Wang et al. Hypertension, 2014
Hemodynamic and morphological data in sham and CHF rats treated with vehicle or RTX

<table>
<thead>
<tr>
<th></th>
<th>Sham+Vehicle (n=21)</th>
<th>Sham + RTX (n=20)</th>
<th>CHF+Vehicle (n=23)</th>
<th>CHF + RTX (n=25)</th>
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</thead>
<tbody>
<tr>
<td>Body weight, g</td>
<td>429 ± 7</td>
<td>430 ± 7</td>
<td>452 ±8</td>
<td>440 ± 8</td>
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<tr>
<td>Heart weight, mg</td>
<td>1438 ± 28</td>
<td>1430 ± 30</td>
<td>2239 ± 61*</td>
<td>1650 ± 49*†</td>
</tr>
<tr>
<td>HW/BW, mg/g</td>
<td>3.4± 0.1</td>
<td>3.3 ± 0.1</td>
<td>5.0 ± 0.1 *</td>
<td>3.8 ± 0.1*†</td>
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<tr>
<td>WLW/BW, mg/g</td>
<td>4.4± 0.1</td>
<td>4.5 ± 0.1</td>
<td>8.7 ± 0.3 *</td>
<td>5.1 ± 0.2*†</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>103.5 ± 2.4</td>
<td>105.0 ± 3.1</td>
<td>96.7 ± 2.0*</td>
<td>101.3 ± 2.1</td>
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<td>LVEDP mmHg</td>
<td>5.0± 0.4</td>
<td>4.8± 0.4</td>
<td>21.3± 1.0*</td>
<td>8.3± 0.7*†</td>
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<tr>
<td>HR, bpm</td>
<td>357.3 ± 6.1</td>
<td>362.0 ± 6.8</td>
<td>368.9 ± 5.1</td>
<td>348.3± 5.5†</td>
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<td>dp/dt&lt;sub&gt;max&lt;/sub&gt;</td>
<td>9108±324</td>
<td>8601±224</td>
<td>5137 ± 180 *</td>
<td>5446 ± 173*</td>
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<td>dp/dt&lt;sub&gt;min&lt;/sub&gt;</td>
<td>-8458±235</td>
<td>-8088±196</td>
<td>-3452±113*</td>
<td>-4643±149*†</td>
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<tr>
<td>Infarct size, %</td>
<td>0</td>
<td>0</td>
<td>42.5± 1.4 *</td>
<td>39.1 ± 1.2 *</td>
</tr>
</tbody>
</table>

*P<0.05 vs. sham+vehicle; †, P<0.05 vs. CHF+vehicle.

Wang, HJ. et al. Hypertension, 2014
Wang, HJ. et al. Hypertension, 2014
Wang, HJ. et al. Hypertension, 2014
Wang, HJ. et al. Hypertension, 2014
Periperal tissues

Circulation Immune Epithelial

Multiple factors
Proteases Growth factors Peptides Lipids Amines Purines Ions

Pressure

Temperature

Periphery

Peptidergic nociceptor

GPCRs RTKs TRPs

CGRP SP

Arteriolar dilation Plasma extravasation Granulocyte infiltration

Neurogenic inflammation

Dorsal horn, spinal cord

Spinal neuron

Steinhoff MS et al., Physiol Rev. (2014)
Hypothesis: Local CSAR afferent endings containing pro-inflammatory neuropeptides play a critical role in deleterious cardiac remodeling in CHF.
TNFalpha in cardiac content (pg/mg protein)

Sham+Vehicle
Sham+RTX
C+V periinfarct
C+V remote
C+R periinfarct
C+R remote

10-12 week post MI

TNFalpha in cardiac content (pg/mg protein)

IL-1 beta in cardiac tissue (pg/mg)

1 day post MI
1 week post MI

C+V Infarct Area
C+V Perl-infarct Area
C+V Remote Area
C+RTX Infarct Area
C+RTX Perl-infarct Area
C+RTX Remote Area
Survival

Long term survival rate (%)

Weeks

n = 19

n = 20

CHF+Vehicle

CHF+RTX

0 5 10 15 20 25 30
Epidural T1-T4 DRG application of RTX
A - Epicardial application

B - Epidural T1-T4 DRGs

Epicardial application

Long term survival rate (%)

Weeks

-n=19

-CHF+Vehicle

-n=20

-CHF+RTX

Epicardial application

Long term survival rate (%)

Weeks

-n=9

-CHF+Vehicle

-n=10

-CHF+RTX
Myocardium infarction

Cardiac Sympathetic Afferent Reflex (+)

Peripheral SNA

RAS

CSNA

MMP

Infarct scar expansion

Cardiac fibrosis

Cardiac apoptosis

Cardiac hypertrophy

Myocardial matrix remodeling

Cardiac remodeling

Capillary permeability

Plasma extravasation

Monocytes and leukocytes immigrate into cardiac tissue

Myocardial inflammation

TRPV1-expressing Cardiac afferents

RTX

Substance P

CGRP

Other peptides
Future Directions

Animal Models

• Ischemic
• Non-ischemic (cardiomyopathy)
• Diastolic Heart Failure (HFpEF)
• Large animal models (pig, dog)

Proof of Principle strategies

• Modulation of DRG neuronal activity
  • Channel Rhodopsin
  • Halo Rhodopsin
  • Substance P antagonism

Specificity

• Thoracic DRG
• Lumbar DRG
• Epicardial
Therapeutic windows

Mechanisms

• Central pathways mediating sympato-excitation in response to sympathetic afferent activation.
• Molecular regulation of TRPV1 protein in DRG
• Cardiac sympathetic afferent activation and arrhythmogenesis
• Mechanisms of afferent neuropeptide regulation of cardiac remodeling
• Understanding of the “physiological role” of cardiac sympathetic afferents
• Autonomic regulation
• Permeability
• Inflammation
• Blood flow regulation

Clinical Studies
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