Elevated sympathetic activity mediated by both baroreflex impairment and tonic activation of peripheral chemoreflex in cardiorenal anemia syndrome

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(no disclosure)
Sympathetic reflexes and CHF

- Sympathetic nervous system (SNS) is activated in chronic heart failure (CHF), contributes to both initiation, progression and increase in morbidity and mortality

- Elevated sympathetic tone has been attributed to autonomic dysfunction focusing mainly on impairment of inhibitory baroreflex control of cardiovascular function

- In recent years the role of excitatory influences has been underlined (i.e. muscle ergoreceptors and chemoreceptors)

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Impairment of inhibitory reflexes (baroreflex)

Circulating neurohormones (e.g. Angiotensine)

Increase in excitatory reflexes (chemo-, ergo- reflexes)

(Malpas 2010)
SYMPATHETIC REFLEXES INTERACTION

**Hyperoxia (100% O2)**
Peripheral Chemoreflex

Sympathetic decrease

**Hypoxia (10% O2)**
Peripheral Chemoreflex

Sympathetic activation
Renal dysfunction and anemia are frequent complications of CHF (20%). This association increases mortality and morbidity:

- Multivariate-adjusted HRs was 2.22 (CI: 1.64–2.98; P < 0.0001).
- Among patients with renal dysfunction, the adjusted HR for the primary outcome increased by 17% for each 1 g/dL decrease below an Hb value of 13.0 g/dL.

Mechanisms explaining this increased risk are poorly understood, role of the autonomic nervous system?

In patients with CHF and CRA syndrom:

1. Is there an increase in sympathetic activity?

2. What are the mechanisms involved?
15 CHF Patients with CRA Syndrome
  • Estimated Glomerular filtration with MDRD equation
  • WHO definition of Anemia
    o Hb < 13 g/dl in men
    o Hb < 12 g/dl in women

15 matched control CHF patients

Sympathetic activity, hemodynamic parameters and sympathetic reflexes were recorded
MEASUREMENT

MICRONEUROGRAPHY

• SNS activity was analysed using microneurography (MSNA)

*Microelectrodes inserted into peroneal nerve*

*Direct sympathetic nerve activity evaluation.*

*Sympathetic activity is recorded and expressed as bursts/min.*
MEASUREMENT

ARTERIAL SYMPATHETIC BAROREFLEX GAIN

Slope (absolute value) of the regression line between spontaneous DBP levels and SNS activity

(Lambert EA. et al. J. Hypertens 2002)
SYMPATHETIC PERIPHERAL CHEMOREFLEX ACTIVITY (transient hyperoxic method)

A significant decrease in MSNA post hyperoxia reflects tonic chemoreceptor activation.
EXPERIMENTAL PROTOCOL

Randomisation room air or hyperoxia

Baseline

BP, HR, Sat O₂, MSNA

15 min

Room Air

15 min

O₂ 100%

15 min

Baroreflex Assessment

30 min

Room Air

15 min

O₂ 100%

15 min

Baroreflex Assessment

30 min

Baroreflex Assessment

15 min

Baseline
## STUDY POPULATION

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CHF Patients n=15</th>
<th>CRAS Patients n=15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>14/1</td>
<td>13/2</td>
</tr>
<tr>
<td>Age, y</td>
<td>57.2 ± 3.7</td>
<td>66.5 ± 3.1</td>
</tr>
<tr>
<td>NYHA distribution (n)</td>
<td>II (6); III (9)</td>
<td>II (4); III (11)</td>
</tr>
<tr>
<td>Radionuclide LVEF (%)</td>
<td>26.8 ± 2.5</td>
<td>31.0 ± 2.9</td>
</tr>
<tr>
<td>Plasma brain natriuretic peptide (pg/ml)</td>
<td>734 ± 265</td>
<td>951 ± 189</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>14.8 ± 0.2</td>
<td>10.9 ± 0.3</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>77.7 ± 6.3</td>
<td>43.9 ± 3.6</td>
</tr>
</tbody>
</table>

Values are the mean ± SEM. *P<0.0001 vs heart failure patients
RESULTS

CRA Syndrom increases baseline SNS activity by 28%
CRA Syndrom decreases arterial baroreflex gain significantly

<table>
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<tr>
<th>Measurements</th>
<th>CHF Patients</th>
<th>CRAS Patients</th>
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<tbody>
<tr>
<td></td>
<td>n=15</td>
<td>n=15</td>
</tr>
<tr>
<td>Mean systolic blood pressure, mm Hg</td>
<td>107.5 ± 5.2</td>
<td>117.0 ± 4.9</td>
</tr>
<tr>
<td>Mean diastolic blood pressure, mm Hg</td>
<td>67.1 ± 2.6</td>
<td>69.8 ± 3.4</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>70.4 ± 3.9</td>
<td>69.5 ± 3.5</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>95.4 ± 0.1</td>
<td>95.8 ± 0.1</td>
</tr>
<tr>
<td>MSNA (bursts/min)</td>
<td>45.5 ± 2.8</td>
<td>57.2 ± 4.0 *</td>
</tr>
<tr>
<td>MSNA (bursts/100 heart beats)</td>
<td>64.9 ± 2.9</td>
<td>83.1 ± 4.6 *</td>
</tr>
<tr>
<td>Arterial Baroreflex gain (%MSNA/mmHg)</td>
<td>5.25 ± 0.60</td>
<td>2.69 ± 0.44 *</td>
</tr>
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RESULTS

CRA Syndrom in CHF patient is associated with a tonic activation of chemoreflex activity.

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<td>100% O₂</td>
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<tr>
<td>MSNA (bursts/100 heart beats)</td>
<td>65.5 ± 3.1</td>
<td>67.7 ± 3.7</td>
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** NORMOXIA

HYPEROXIA

O₂ 100% 15 min

MSNA

TONIC ELEVATED CHEMOREFLEX ACTIVITY
RESULTS

CRA Syndrom tonic activation of chemoreflexactivity decreases arterial baroreflex gain.

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<td>5.47 ± 0.78</td>
<td>4.44 ± 0.44</td>
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Baroreflex gain in a patient with elevated peripheral chemoreflex activity: effect of chemoreflex deactivation
COMPENSATORY MECHANISMS AND CONSEQUENCES OF CRA IN CHF PATIENTS

Cardio Renal and Anaemia
Heart failure
Tissue hypoxia
Peripheral vasodilation
Blood pressure ↓
Renal blood flow ↓
GFR ↓
Salt and water retention
Extracellular volume ↑
Cardiac work load ↑
LV mass ↑
LV remodelling
LV dysfunction
Elevated SNS activity
Decrease Baroreflex Gain
Increase Chemoreflex Activity
Cardio-renal anaemia syndrome
CONCLUSION

- Autonomic balance is altered in patients with CRA Syndrome

- These findings contribute to explain the morbid association between chronic heart failure (CHF) and CRA Syndrome.

- Perspectives
PERSPECTIVES:
**CHEMOREFLEX A NEW TARGET IN CHF PATIENT?**

(Haque et al. JACC 1996, Paul B. et al. Lung Heart Circ 2008)

O₂

Pharmacological Modulation

Renal Denervation


Baroreflex

Peripheral Chemoreflex

SNS Modulation

(Krum H et al. Lancet 2009)