TONIC CHEMOREFLEX ACTIVATION CONTRIBUTES TO INCREASED SYMPATHETIC NERVE ACTIVITY IN HEART FAILURE RELATED ANEMIA

Nicolas Franchitto*, Fabien Despas *, Marc Labrunée, Jérome Roncalli, Serge Boveda, Michel Galinier, Jean-Michel Senard, Atul Pathak
C.H.U RANGUEIL – Toulouse - FRANCE
INTRODUCTION

- Sympathetic nervous system (SNS) is activated in chronic heart failure (CHF).

- SNS overactivity is known to increase morbidity and mortality in patients with CHF.

- Mechanisms leading to increased sympathetic tone are well known (among them modification of baroreflex sensitivity, chemoreflex modulation but also involvement of metabo- or mecano- reflexes).
ANEMIA AND CHF

- Increasing epidemiological evidence shows a frequent association of anemia with heart failure with a prevalence ranging from 4 to 61%.

- Anemia is an independant factor associated with an increased risk of mortality, hospitalization and arrhythmias in CHF patients.

- Mechanisms explaining this increased risk are poorly understood.

- Heart failure comorbidities increase SNS activity
AIM

In patients with CHF and anemia

- Does anemia increase sympathetic activity as seen with other comorbidities?
- Is this effect mediated by peripheral chemoreflex activation?
METHODS

- 18 CHF Patients with anemia (WHO definition)
  - Hb < 13 g/dl in men
  - Hb < 12 g/dl in women
- 18 matched CHF patients without anemia.

- Sympathetic activity and hemodynamic parameters were recorded.

- Study of periphereral chemoreflex activity:
  - Double blind,
  - randomized,
  - control design versus placebo.
METHODS AND PROTOCOL

- SNS activity was analysed using microneurography

  - Microelectrodes inserted into peroneal nerve

  - Direct sympathetic nerve activity evaluation.

  - Sympathetic activity is recorded and expressed as bursts/min.
## STUDY POPULATION

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CHF Patients</th>
<th>CHF-A Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=18</td>
<td>n=18</td>
</tr>
<tr>
<td>Male/Female</td>
<td>15/3</td>
<td>15/3</td>
</tr>
<tr>
<td>Age, y</td>
<td>58.8 ± 2.3</td>
<td>63.4 ± 2.6</td>
</tr>
<tr>
<td>NYHA distribution (n)</td>
<td>II (9); III (9)</td>
<td>II (12); III (6)</td>
</tr>
<tr>
<td>Radionuclide LVEF( %)</td>
<td>28.7 ± 1.8</td>
<td>29.9 ± 2.1</td>
</tr>
<tr>
<td>Plasma brain natriuretic peptide (pg/ml)</td>
<td>415 ± 79</td>
<td>573 ± 134</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>14.6 ± 0.2</td>
<td>11.2 ± 0.3</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>82.1 ± 4.0</td>
<td>75.5 ± 4.1</td>
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</tbody>
</table>

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

*Franchitto N et al. Hypertension. 2010;55:1012-7*
RESULTS

Anemia increases SNS activity in CHF patients

<table>
<thead>
<tr>
<th>Measurements</th>
<th>CHF Patients</th>
<th>CHF-A Patients</th>
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<tbody>
<tr>
<td></td>
<td>n=18</td>
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</tr>
<tr>
<td>Mean systolic blood pressure, mm Hg</td>
<td>109.4 ± 3.8</td>
<td>111.3 ± 6.3</td>
</tr>
<tr>
<td>Mean diastolic blood pressure, mm Hg</td>
<td>67.2 ± 2.6</td>
<td>64.1 ± 3.1</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>67.9 ± 3.3</td>
<td>71.7 ± 3.2</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>95.3 ± 0.4</td>
<td>95.8 ± 0.7</td>
</tr>
<tr>
<td>MSNA (bursts/min)</td>
<td>45.5 ± 3.1</td>
<td>56.0 ± 3.2*</td>
</tr>
<tr>
<td>MSNA (bursts/100 heart beats)</td>
<td>67.3 ± 2.8</td>
<td>79.0 ± 4.6*</td>
</tr>
</tbody>
</table>

RESULTS

SNS activity increases with anemia severity

RESULTS

SNS activation is mediated by peripheral tonic chemoreflex activation

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<tr>
<td></td>
<td>Placebo</td>
<td>100% O₂</td>
</tr>
<tr>
<td>MSNA (bursts/min)</td>
<td>45.9 ± 3.2</td>
<td>47.3 ± 3.4</td>
</tr>
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Tonic chemoreflex deactivation under 100% Oxygen

DISCUSSION

What are the mechanisms of Chemoreflex activation in CHF patients with anemia?

- Oxygen saturation and arterial oxygen contents were not different between groups.

- We propose that chemoreflex activation could be mediated through:
  - Tissular hypoxemia, at level of carotid body by lack of oxygen extraction;
  - Carotid body ischemia;
  - Baroreflex impairement.

DISCUSSION

- Hyperoxia does not result in normalization of sympathetic traffic

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- Other mechanisms than tonic activation of peripheral chemoreflex could be involved in anemia-mediated SNS activation:
  - Volume overload
  - Kidney Dysfunction
  - Inflammation
  - Bone Marrow Dysfunction
  …….
CONCLUSION

- In chronic heart failure (CHF) patients, anemia increases sympathetic nervous system (SNS) activity.

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

- Perspectives