DETECTION OF HIGH ALTITUDE PULMONARY EDEMA – SUSCEPTIBLE (HAPE-S) SUBJECTS BY DOPPLER ASSESSMENT OF PULMONARY CIRCULATION

CAILLOT N. and COUDERT J.

Laboratoire de Physiologie – Biologie du Sport
Faculté de Médecine – Université d’Auvergne
CLERMONT-FERRAND, FRANCE
Incidence of HAPE > 60% in vulnerable subjects

Role++ of Hypoxia – induced Pulmonary Arterial Hypertension (PAH)

Possibility to prevent PAH, in HAPE-S subjects using, for example, calcium channel blockers (Bärtsch et al, 1991) or nitric oxide (Anand IS et al, circulation, 1998)
AIM OF STUDY

Testing the hypothesis that combined effects of hypoxia and mild exercise on pulmonary circulation, could be a valuable method to detect HAPE-S subjects
MATERIALS and METHODS

SUBJECTS:

16 healthy volunteer subjects
Age: 24 < < 60 years

- 8 HAPE-S (2 women, 6 men)
- 8 Cont (2 women, 6 men)
## CHARACTERISTICS OF THE GROUPS

<table>
<thead>
<tr>
<th>GROUP</th>
<th>HAPE-S</th>
<th>CONT</th>
<th>(p)-value (\S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>8</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>Age range (years)</td>
<td>24 - 60</td>
<td>41 - 60</td>
<td>-</td>
</tr>
<tr>
<td>Age (years)</td>
<td>49.4 (\pm) 6.1</td>
<td>35.0 (\pm) 14.0</td>
<td>(\ast 0.024)</td>
</tr>
<tr>
<td>Gender</td>
<td>2 women, 6 men</td>
<td>2 women, 6 men</td>
<td>-</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173.0 (\pm) 8.5</td>
<td>173.2(\pm) 10.1</td>
<td>0.958</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72.5(\pm) 10.9</td>
<td>67.5(\pm) 10.9</td>
<td>0.374</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>24.1 (\pm) 2.4</td>
<td>22.4 (\pm) 2.7</td>
<td>0.202</td>
</tr>
</tbody>
</table>
Doppler Echocardiography and ventilatory measurements

PROTOCOL

(CLERMONT-FERRAND, 320m, P_B = 730 mmHg)

Time (min)

NR : Rest

HR : Hypoxia

HE : Exercise

NE : Exercise
Assessment of the peak tricuspid regurgitation jet velocity by continuous-wave doppler, guided by two-dimensional echocardiography.

Estimation of PASP by mean of simplified Bernouilli equation (assumed right atrial pressure = 5 mmHg).

Analysis of recording by two blind reviewers.
VENTILATORY PARAMETERS MEASUREMENTS

Pulmonary gas exchange, measured on a breath-by-breath Spirometry:

- $\dot{V}E$
- $\dot{V}O_2$
- $\dot{V}CO_2$
- $RQ$
- Monitoring of $SaO_2$ (pulsed oxymeter)
Student unpaired t-test for evaluation of significance between groups.

Student paired t-test for comparing normoxia versus hypoxia and exercise versus rest.
## CARDIAC RESPONSES

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Rest Normoxia</th>
<th>Rest Hypoxia</th>
<th>Exercise Hypoxia</th>
<th>Exercise Normoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>CONT</td>
<td>CONT</td>
<td>CONT</td>
<td>CONT</td>
</tr>
<tr>
<td></td>
<td>68 ± 7</td>
<td>71 ± 12</td>
<td>78 ± 11</td>
<td>131 ± 11</td>
</tr>
<tr>
<td></td>
<td>131 ± 14</td>
<td>114 ± 9</td>
<td>131 ± 14</td>
<td>115 ± 10</td>
</tr>
<tr>
<td>CO (L.min⁻¹)</td>
<td>CONTENT</td>
<td>HAPE-S</td>
<td>CONTENT</td>
<td>HAPE-S</td>
</tr>
<tr>
<td></td>
<td>4.91 ± 0.63</td>
<td>5.24 ± 1.01</td>
<td>5.16 ± 0.86</td>
<td>6.18 ± 1.17</td>
</tr>
<tr>
<td></td>
<td>11.19 ± 1.52</td>
<td>11.29 ± 1.86</td>
<td>9.00 ± 1.19</td>
<td>10.09 ± 1.23</td>
</tr>
</tbody>
</table>
### CARDIO-VASCULAR MEASUREMENTS

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Rest &amp; Hypoxia</th>
<th>Exercise &amp; Hypoxia</th>
<th>Exercise &amp; Normoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PASP (mmHg)</td>
<td>PASP (mmHg)</td>
<td>Variation (mmHg)</td>
<td>PASP (mmHg)</td>
</tr>
<tr>
<td>HAPE-S</td>
<td>16.6±5.9</td>
<td>23.6±11.2</td>
<td>7.1±5.7</td>
<td>39.3±9.8</td>
</tr>
<tr>
<td>CONT</td>
<td>13.8±3.0</td>
<td>18.9±5.7</td>
<td>5.2±3.3</td>
<td>29.7±4.7</td>
</tr>
<tr>
<td>p-values</td>
<td>0.256</td>
<td>0.316</td>
<td>0.437</td>
<td>0.031</td>
</tr>
<tr>
<td></td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>*</td>
</tr>
</tbody>
</table>
HVR = \frac{\Delta \dot{V}E}{\Delta SaO_2}

![Graph showing Hypoxic Ventilatory Response at rest and exercise for CONT and HAPE-S groups.](image)

**GROUP**
- CONT
- HAPE-S

**HVR**
- REST
- EXERCISE
I- HVR, as relevant predictive factor:


3) In our study, HVR are not a relevant predictive factor

II- PAP as relevant predictive factor

1) Studies by invasive method

2) Studies by non invasive method


Problem of PASP in relation to age :


Readjustment of our PASP values (mmHg)

During RN = [(50 – Age) * 0.1] + PASP RN
During EH = [(50 – Age) * 0.1] + PASP EH

Differences between our two groups remained significant : p < 0.002

Conclusion : Age could not be considered as a confounding parameter
CONCLUSION

1) Individual increases of PASP during hypoxic exercise from basal resting normoxic values may be considered as a relevant predictive factor to the susceptibility of HAPE.

2) Recommendations of use of doppler echocardiography in measuring PAP during hypoxic test in order to predict this susceptibility.

3) A low HVR has to be considered as an eventual worsening factor of the risk.
Complementary studies of cellular and molecular characteristics of the subjects

1) In leucocytes, expression (quantitative RT-PCR) of HIF1α and aHIF (HIF1 α, natural antisense) and traduction of HIF1 protein (westernblot)

2) In the blood:
   - Dosage of nitrite and nitrate concentrations, indicators of NO production
   - Prooxydant – antioxydant balance
   - Dosage of proteins induced by HIF1α (VGEF…)

NB : Samples before and after hypoxia
EXPECTED RESULTS

1) Decrease of expression and/or traduction of HIF1

2) Decrease of nitrite and nitrate concentrations, important signaling molecules and regulators of gene expression, and NO biology (Bryan N.S. et al, Nature chemical biology, 2005)

3) Prooxydant – antioxydant imbalance

It is planned to do the same studies in pathological (COLD) and physiological (Highlanders) hypoxia. [See Alpha Project]
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