Pulmonary hypertension at high altitude
Pulmonary hypertension (PH) at high altitude (HA):

1) Going to high altitude with PH (already present at sea level)?

Absolute contraindication:
- marked PH (PAPm > 30 mmHg) and/or
- classe >II and/or
- markers of poor prognosis

Rimoldi et al, Progress in cardiovasc Disease 2010
Pulmonary hypertension (PH) at high altitude (HA):

1) Going to high altitude with PH (already present at sea level)??
   Absolute contraindication

2) PH in HA dwellers
   - **Chronic Montain Sickness, CMS**
     Excessive erythrocytosis, severe hypoxemia +/-PH +/-HF
   - **High Altitude Pulmonary Hypertension**
     PaPm > 30mmHg, Rv hypertrophy, heart failure, moderate hypoxemia, no erythrocytosis

*Consensus statement chronic High Altitude disease, 2005*
Pulmonary hypertension (PH) at high altitude (HA):

1) Going to high altitude with PH (*already present at sea level*)??
   Absolute contraindication

2) PH in HA dwellers

3) PH at HA after acute exposure
Acute exposure at HA

Enormous interindvidual variability of these responses

Fig 2. Range of systolic pulmonary artery pressure, sympathetic nerve activity, and systolic blood pressure during the first 2 and half days of high-altitude exposure (4500 m) in normal subjects. Note that there is enormous interindividual variability of these responses.

HAPE is associated with exaggerated pulmonary hypertension

Pulmonary artery pressure (mmHg)

Incidence of HAPE (%)

HAPE-Prone
Controls

HAPE-Prone
Controls

Exaggerated hypoxic pulmonary hypertension

**Defective NO synthesis**  
Scherrer et al., NEJM 1996;334:624-8  
Duplain et al., Am J Respir Crit Care Med

**Sympathetic overactivity**  
Duplain et al., Circulation 1999;99:2665-8

**Exaggerated ET-1 synthesis**  
Sartori et al., Circulation 1999;99:1713-8

=> Inhomogeneous hypoxic pulmonary vasoconstriction  
+ hypoxia-induced constriction of pulmonary veins  
=> overperfusion of capillaries  
=> high permeability oedema
Fig 3. Schematic representation of the central role of defective NO synthesis (and/or bioavailability) in the pathogenesis of exaggerated hypoxic pulmonary hypertension and HAPE.
Vascular dysfunction later in life

Premature cardiovascular diseases
Exaggerated hypoxic pulmonary hypertension, frequent?
HAPE frequent among Exaggerated hypoxic pulmonary hypertension?

HAPE/30 HPV+ = 13\% = PPV of hypoxic test
0 HAPE/24 HPV- = 100\% = NPV of hypoxic test
No HAPE = 26/30 HPV+ = FP

Exaggerated hypoxic pulmonary vasoconstriction without susceptibility to high altitude pulmonary edema.

Dehnert C\textsuperscript{1}, Maggiorini M, et al, High Alt Med Biol, 2015 Mar;16(1)
Exaggerated hypoxic pulmonary hypertension => HAPE??

Fig 4. Pulmonary-artery pressure and incidence of HAPE in 18 HAPE-prone mountaineers, 10 healthy young adults with a history of transient perinatal pulmonary hypertension, and 17 HAPE-resistant control subjects at 4559 m (adapted from Sartori et al^{46,47}).
Defective alveolar transepithelial sodium transport

Pulmonary edema

Alveolar fluid flooding

Alveolar fluid clearance

HAPE

Genetic
- Sympathetic overactivity
- PFO
- Endothelial dysfunction
- Impairment of alveolar fluid clearance

Acquired
- Exaggerated hypoxic pulmonary hypertension
- Augmented alveolar fluid flooding

Pathogenesis of HAPE, adapted from New Insights in the Pathogenesis of HAPE, Scherrer/Sartori 2010
<table>
<thead>
<tr>
<th>Condition</th>
<th>Mechanism representing potential therapeutic target</th>
<th>Prevention</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exaggerated sympathetic nerve activity [Duplain et al, 1999]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased endothelin-1 bioavailability [Sartori et al, 1999]</td>
<td></td>
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<tr>
<td></td>
<td>PFO [Allemann et al, 2006]</td>
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<tr>
<td></td>
<td>Increased oxidative stress (related to gene dosage)</td>
<td></td>
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<tr>
<td>Trisomy 21</td>
<td>Epigenetic</td>
<td>PFO closure ?</td>
<td></td>
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<tr>
<td>Durmowicz, 2011</td>
<td></td>
<td>Nifedipine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tadalafil</td>
<td></td>
</tr>
<tr>
<td>ART [Scherrer et al, 2012]</td>
<td></td>
<td>Antioxidants</td>
<td></td>
</tr>
<tr>
<td>Perinatal hypoxia</td>
<td>Epigenetic ?</td>
<td></td>
<td>Deacetylase inhibitors ?</td>
</tr>
<tr>
<td>[Sartori et al, 1999]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preeclampsia ?</td>
<td>Epigenetic</td>
<td></td>
<td></td>
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</table>
Résumé du niveau d'évidence des mesures de prévention et de traitement des maladies liées à l'altitude.

**Prévention**

<table>
<thead>
<tr>
<th></th>
<th>AMS</th>
<th>HACE</th>
<th>HAPE</th>
<th>Dosage</th>
<th>But</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascension progressive</td>
<td>1B</td>
<td>1B</td>
<td>1B</td>
<td>300–400 m/j en dessus de 2500 m</td>
<td>Favoriser l'acclimatation</td>
</tr>
<tr>
<td>Acetazolamid</td>
<td>1A</td>
<td>1A</td>
<td>2C</td>
<td>2 × 125 mg/j PO pendant 5 jours</td>
<td>Stimuler la ventilation</td>
</tr>
<tr>
<td>Dexaméthasone</td>
<td>1A</td>
<td>1A</td>
<td>1C</td>
<td>4 × 2 mg/j PO pendant max. 10 jours</td>
<td>Diminuer l’activation sympathique?</td>
</tr>
<tr>
<td>Nifédipine</td>
<td>–</td>
<td>–</td>
<td>1A</td>
<td>2 × 30 mg SR/j (J3 au J0) puis 3 × 30 mg SR/j pendant 5–7 jours PO</td>
<td>Diminuer la pression artérielle pulmonaire</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>–</td>
<td>–</td>
<td>1C</td>
<td>2 × 10 mg/j PO</td>
<td>Diminuer la pression artérielle pulmonaire</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>–</td>
<td>–</td>
<td>2C</td>
<td>2 × 125 µg/j inhalation de J1</td>
<td>Stimuler la clairance alvéolaire liquidienne</td>
</tr>
</tbody>
</table>

**Traitement**

<table>
<thead>
<tr>
<th></th>
<th>AMS</th>
<th>HACE</th>
<th>HAPE</th>
<th>Dosage</th>
<th>But</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descente</td>
<td>1A</td>
<td>1A</td>
<td>1A</td>
<td>300–1000 m</td>
<td>Réoxygenation</td>
</tr>
<tr>
<td>Oxygène</td>
<td>1C</td>
<td>1C</td>
<td>1B</td>
<td>Pour une saturation &gt;90%</td>
<td>Réoxygenation</td>
</tr>
<tr>
<td>Caisson hyperbare</td>
<td>1B</td>
<td>1B</td>
<td>1B</td>
<td></td>
<td>Réoxygenation</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>1B</td>
<td>–</td>
<td>–</td>
<td>3 × 250 mg/j</td>
<td>Stimuler la ventilation</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>1B</td>
<td>1C</td>
<td>–</td>
<td>AMS: 4 × 4 mg/j</td>
<td>Diminuer l’activation sympathique?</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HACE: 4 × 8 mg/j PO, IV ou IM</td>
<td></td>
</tr>
<tr>
<td>Nifédipine</td>
<td>–</td>
<td>–</td>
<td>1C</td>
<td>3 × 30 mg SR/j PO</td>
<td>Diminuer la pression artérielle pulmonaire</td>
</tr>
</tbody>
</table>
Effects of Iron Supplementation and Depletion on Hypoxic Pulmonary Hypertension
Two Randomized Controlled Trials

Sea Level Protocol

Iron infusion: ↓ 6mmHg
Placebo: ↓ 2mmHg
Conclusion:

- High Altitude, An exciting natural research laboratory
- Exaggerated pulmonary hypertension is a hallmark but not sufficient to trigger HAPE
- Hypoxic condition detect pulmonary and systemic vascular dysfunction
- Prevention and treatment of PHHA/HAPE is based on the pathophysiological mechanisms