High Altitude

Tom DeLoughery, MD MACP FAWM
Oregon Health & Sciences University
DISCLOSURE

Relevant Financial Relationship(s)
Speaker Bureau - None
Consultant/Research – none
Overview

• Adapting to high altitude
• High altitude illnesses
  – Acute mountain sickness
  – High altitude cerebral edema
  – High altitude pulmonary edema
High Altitude Medicine

- 30,000,000 people live above 9000 ft
- Unique physiologic changes
MT HOOD
11,234 ft
500 mmHg
IN $O_2$: 13 (65%)
PaO$_2$: 55
85%

DENALI
20,325 ft
340 mmHg
IN $O_2$: 8.5 (42%)
PaO$_2$: 37
65%

EVEREST
29,000 ft
243 mmHg
IN $O_2$: 5.4 (27%)
PaO$_2$: 30
52%
High Altitude

- Decreased oxygen tension
- Decreased barometric pressure
  - Varies with latitude
  - If Everest was in Alaska, pressure = 222 mmHg not 243 mmHg
<table>
<thead>
<tr>
<th>Altitude (ft)</th>
<th>Altitude (m)</th>
<th>Approximate TUC* (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 000</td>
<td>5 486</td>
<td>20–30</td>
</tr>
<tr>
<td>25 000</td>
<td>7 620</td>
<td>3–5</td>
</tr>
<tr>
<td>30 000</td>
<td>9 144</td>
<td>1.5 (90 seconds)</td>
</tr>
<tr>
<td>40 000</td>
<td>12 192</td>
<td>≤0.25 (15 seconds or less)</td>
</tr>
</tbody>
</table>

*Indicates individual tolerance varies.
How do we Adapt to Hypoxia???

Increase oxygen delivery to tissues
Chain of Oxygen

- Lungs
- Blood
- Tissue
Lungs

1. Increase ventilation
   - Starts at pO$_2$ of 60 mmHG
   - With acclimatization increase sensitivity to pCO$_2$

2. Increased pulmonary artery pressure
   - ? Increase blood flow to all portions of lungs
   - ? Decrease V/Q mismatch

3. Decreased oxygen diffusion
Hypoxic Ventilatory Response

- People vary in response to hypoxia
- Genetically determined
- People with greater HVR *tend* to do better at altitude
Fig. 2

Change in the Ventilation

Arterial $O_2$ Saturation

At rest  |  50% $VO_2$max

$(\Delta V_e/\Delta SaO_2) \times 100$ [l/min %]

AMS -   |  AMS +

$p < 0.001$

$SaO_2$ [%]

AMS -   |  AMS +

$p < 0.01$

Exception!

- Increasing data show that climbers who reach extreme altitude have lower HVR
- Greater “ventilatory reserve” at higher altitude?
- Less energy for breathing?
Cardiac

• Decreased cardiac output
  – Decreased stroke volume
    • Decreased plasma volume
    • Decreased heart rate
  – Protects against diffusion limitations?

• No ischemia

• Cardiac output not a limiting factor at altitude
\[ \dot{V}_O_2 = 300 \text{ ml/min} \]
\[ D_{MO_2} = 40 \text{ ml/min/mm Hg} \]
\( V_{O_2} = 250 \text{ ml/min} \)
\( D_{MO_2} = 40 \text{ ml/min/mm Hg} \)

- Inspired
- Alveolar
- Mixed venous
- End-capillary

\( \text{PO}_2 \) (mm Hg)

Time along capillary (sec)
Sea Level \( \text{O}_2 = 147 \text{ torr} \)

- 6300m, air \( \text{O}_2 = 64 \text{ torr} \)
- 6300m, 16% \( \text{O}_2 \) \( \text{O}_2 = 49 \text{ torr} \)
- 6300m, 14% \( \text{O}_2 \) \( \text{O}_2 = 43 \text{ torr} \)

Blood

- Changes in hematocrit
- Changes in oxygen disassociation curve
Hematocrit

- Rises with exposure to high altitude
- 2-phases
  - Dehydration (hours)
    - Drop in plasma volume of 25% in days
  - Increase red cell mass (days)
- Benefits of increased \( O_2 \) delivery by more red cells balance by decreased delivery due to increase viscosity
Plasma

Red Cells

SEA LEVEL  2 DAYS  2 WEEKS
Hematocrit at Heights

• Sea Level
  – 40-45%

• High altitude natives
  – Andes 55-60%
  – Sherpas 50-55%

• AMREE
  – 17,000 ft 50%
  – 21,000 ft 53%
Decreased $P_{50}$ (increased affinity):

- $\downarrow$ Temperature
- $\downarrow$ $P_{CO_2}$
- $\downarrow$ 2,3-DPG
- $\uparrow$ pH

Increased $P_{50}$ (decreased affinity):

- $\uparrow$ Temperature
- $\uparrow$ $P_{CO_2}$
- $\uparrow$ 2,3-DPG
- $\downarrow$ pH

Hemoglobin saturation (%) vs. Oxygen partial pressure (mm Hg)
Modest Altitude (~ 10,000 ft)

More $O_2$ Unloading
Higher Altitude (~20,000 ft)
Extreme Altitude (~ 30,000 ft)
Evidence Increase $O_2$ Affinity is Beneficial

- High altitude animals
  - Sheep with high affinity polymorphism
- Human studies
- “Human llamas” study
Human Llamas

- High affinity hemoglobin
- At altitude (14,000ft)
  - No change in EPO
  - No decrease in exercise ability

Tibetans

• Evolved in high altitudes
• Tibetans
  – Less erythrocytosis
  – Lower P50
  – Altitude adaptation legendary
Tissues

• Increase capillary density
• Decrease muscle mass
Table 2. Arterial Blood Gas Measurements and Calculated Values for Pulmonary Gas Exchange from Four Subjects at an Altitude of 8400 m, during Descent from the Summit of Mount Everest.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subject No.</th>
<th>Group Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>pH</td>
<td>7.55</td>
<td>7.45</td>
</tr>
<tr>
<td>(\text{PaO}_2) (mm Hg) (\uparrow)</td>
<td>29.5</td>
<td>19.1</td>
</tr>
<tr>
<td>(\text{PaCO}_2) (mm Hg) (\uparrow)</td>
<td>12.3</td>
<td>15.7</td>
</tr>
<tr>
<td>Bicarbonate (mmol/liter) (\downarrow)</td>
<td>10.5</td>
<td>10.67</td>
</tr>
<tr>
<td>Base excess of blood (\downarrow)</td>
<td>-6.3</td>
<td>-9.16</td>
</tr>
<tr>
<td>Lactate concentration (mmol/liter)</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>(\text{SaO}_2) (%) (\downarrow)</td>
<td>68.1</td>
<td>34.4</td>
</tr>
<tr>
<td>Hemoglobin (g/dl) (\downarrow)</td>
<td>20.2</td>
<td>18.7</td>
</tr>
<tr>
<td>Respiratory exchange ratio (\downarrow)</td>
<td>0.81</td>
<td>0.74 (\uparrow)</td>
</tr>
<tr>
<td>(\text{PaO}_2) — mm Hg (\downarrow) (\ast\ast)</td>
<td>32.4</td>
<td>26.9</td>
</tr>
<tr>
<td>Alveolar–arterial oxygen difference — mm Hg (\uparrow)</td>
<td>2.89</td>
<td>7.81</td>
</tr>
</tbody>
</table>

* \(\text{PaCO}_2\) denotes partial pressure of arterial carbon dioxide, \(\text{PaO}_2\) partial pressure of alveolar oxygen, \(\text{PaO}_2\) partial pressure of arterial oxygen, and \(\text{SaO}_2\) calculated arterial oxygen saturation.

† To convert the values for \(\text{PaO}_2\), \(\text{PaCO}_2\), \(\text{PaO}_2\), and the alveolar–arterial oxygen difference to kilopascals, multiply by 0.1333.

‡ These values were calculated with the use of the algorithms currently approved by the Clinical Laboratory Standards Institute.\(^10\)

§ The values for hemoglobin are the mean values of measurements obtained at 5300 m (17,388 ft) 9 days before and 8 days after the arterial blood sampling.

¶ The respiratory exchange ratio was measured at an elevation of 7950 m while the subject was resting.

‖ No measured respiratory exchange ratio was available for this subject; the value was derived from the mean values for the other three subjects.

\(\ast\ast\) \(\text{PaO}_2\) was calculated with the use of the full alveolar gas equation.
Diseases of High Altitude

- Acute mountain sickness (AMS)
- High altitude pulmonary edema (HAPE)
- High altitude cerebral edema (HACE)
<table>
<thead>
<tr>
<th>Group</th>
<th>Sleep</th>
<th>Max</th>
<th>Time</th>
<th>AMS</th>
<th>HAPE</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skiers</td>
<td>8,-</td>
<td>11,000</td>
<td>1-2</td>
<td>15-40%</td>
<td>0.1</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>10,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trekker</td>
<td>10,-</td>
<td>18,000</td>
<td>1-2</td>
<td>47%</td>
<td>1.6</td>
<td>1:2500</td>
</tr>
<tr>
<td></td>
<td>17,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trekker</td>
<td>10,-</td>
<td>18,000</td>
<td>10</td>
<td>23%</td>
<td>0.05</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>17,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denali</td>
<td>10,-</td>
<td>20,325</td>
<td>1-3</td>
<td>50%</td>
<td>2-3</td>
<td>1:625</td>
</tr>
<tr>
<td></td>
<td>18,000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rainier</td>
<td>10,000</td>
<td>14,409</td>
<td>1-2</td>
<td>67%</td>
<td>0.1</td>
<td>1:10,000</td>
</tr>
</tbody>
</table>
Acute Mountain Sickness

- Occurs in 6 - 24 hours of altitude
- Most common altitude problem
- Annoying, debilitating, and precursor of fatal syndromes
<table>
<thead>
<tr>
<th>Height</th>
<th>%AMS</th>
<th>avg score</th>
</tr>
</thead>
<tbody>
<tr>
<td>2850m (9350ft)</td>
<td>9%</td>
<td>0.85</td>
</tr>
<tr>
<td>3050m (10,000ft)</td>
<td>13%</td>
<td>1.03</td>
</tr>
<tr>
<td>3650m (12,000ft)</td>
<td>34%</td>
<td>2.11</td>
</tr>
<tr>
<td>4559m (14,950ft)</td>
<td>52%</td>
<td>3.28</td>
</tr>
</tbody>
</table>
AMS: Symptoms

- Headache:
  - Key symptom
  - Throbbing
  - Worse with valsalva
- Dizziness
- Lassitude
- Nausea/Vomiting
- Decreased urine output
Grading of AMS

• Lake Louise criteria
  – Headache (0-3)*
  – GI symptoms (0-3)*
  – Fatigue (0-3)*
  – Dizziness (0-3)*
  – Sleep difficulty (0-3)*
  – Change in mental status
  – Ataxia (0-4)
  – Peripheral edema (0-2)

AMS:
Headache plus:
Self-reported \( \geq 4 \)
Total \( > 5 \)
Therapy

- No further ascent
- Descent or oxygen
- Time
  - Resolves 1-3 days
- Acetazolamide
  - 125 - 250 mg bid
- Dexamethasone
  - Rebound
Acetazolamide

- Carbonic anhydrase inhibitor
  - Increases ventilation
  - Diuresis
- Speeds acclimatization
- Maintains oxygenation
- Treatment/prophylaxis
AMS: Prevention

- Slow ascents
  - > 3000m no increase sleeping elevation by >500m
  - Rest day every 3-4 days
- Acetazolamide
- Dexamethasone
Acetazolamide

- Standard pharmacological therapy of AMS
- Two RCT show 125 mg BID effective for preventing AMS by 50-60% – Reduced incidence of headache
  – Reduced incidence of severe AMS
Acetazolamide

- RCT
- 3440-->4300-->4928m

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>125 mg BID</th>
<th>375 BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMS</td>
<td>51%</td>
<td>24%</td>
<td>21%</td>
</tr>
<tr>
<td>O₂Sat</td>
<td>80.7%</td>
<td>82%</td>
<td>82.8%</td>
</tr>
</tbody>
</table>

RADICAL Trial

- 125 mg BID vs 62.5 mg BID
- N = 73

<table>
<thead>
<tr>
<th></th>
<th>62.5 mg BID</th>
<th>125 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMS (%)</td>
<td>55.3</td>
<td>60.0</td>
</tr>
<tr>
<td>Daily incidence</td>
<td>6.7%</td>
<td>8.9%</td>
</tr>
<tr>
<td>LLS</td>
<td>1.102</td>
<td>0.097</td>
</tr>
</tbody>
</table>

- WEM 30:12-21, 2019
Dexamethasone

• Effective for treating AMS but does not speed up acclimatization – “Rebound”
• May be useful adjunct with acetazolamide for prevention of severe AMS
AMS: Prediction

• No good tool for predicting who will get AMS except history
• People with good HVR and good sats tend not to get AMS
Sleep Disturbances

- Poor sleep common
- Disrupted sleep
  - Cheyne-Stokes breathing
- More common with high HVR
- TX: acetazolamide or zolpidem
High Altitude Cerebral Edema

- AMS with
  - Ataxia
  - Altered mental status
  - Seizures
  - Photophobia
- Rate: 1-3%
- Rapidly evolves to coma and death
  - Once coma ensures 60% fatality rate
HACE:

- Vasogenic cerebral edema
  - microbleeds
- Late stages: thrombosis
HACE: Therapy

- Descent!!!
- Dexamethasone
- Portable hyperbaric chamber
- Prevention:
  - Same as AMS
  - Early recognition
AMS: Pathogenesis

- Hypoxia
  - Poor HVR
- Fluid retention
- Unpredictable
- Individual susceptibility
Disorder of Fluid Regulation?

- Increased ADH, aldosterone, decrease urine output
- Increase atrial natruretic factor
  - Increase tissue permeability
- General permeability defect?
“Tight Fit” Theory

- Hypoxia and fluid retention led to brain edema
- People with lack of “space” would suffer increase ICP and symptoms
- Evidence:
  - Vasogenic edema common in AMS/HACE
  - Preliminary evidence that brain volume to intracranial volume higher in people susceptible to AMS
  - Things that reduced edema work in AMS
- However…
“Tight Fit” Theory

- Brain swelling is minimal
  - No difference AMS vs no AMS
- No evidence of ICP
- Evidence of widespread tissue damage
  - High CK's
- Still no consensus on pathogenesis
High Altitude Pulmonary Edema

• High altitude illness that leads to most deaths
• Occurs in 2-3 days
• Tachycardia/tachypnea
• Orthopnea
• Pink froth
• Severe hypoxia
HAPE: Incidence and Risk Groups

• Severe cases: 1-8%
• Increase lung water seen in up to 75% of climbers
• Risk groups
  – Young men
  – Cold
  – Exercise
• Increasing reports of cases at modest altitudes (1400-2400m)
HAPE: Treatment

- Descent
- Oxygen
- Gamow bag
- Nifedipine 10 mg then 30mg SR
- Nitric oxide?
- Phosphodiesterase-5 inhibitors?
- Dexamethasone?
HAPE: Prophylaxis

- Slow ascents
  - Nifedipine 20-30 mg SR q12
  - Inhaled beta-agonists?
  - Phosphodiesterase-5 inhibitors?
  - Dexamethasone?
HAPE: Phosphodiesterase-5 inhibitors

- Effective for pulmonary HTN
- 4559m study:
  - sPaP
    - C: 44+10
    - NO: 32+6
    - S: 33+6
    - NO+S: 28+5
  - No change in systemic blood pressure
  - Studies showed increase oxygenation
  - Appears to be better than Nifedipine
# HAPE: PDE-5 Inhibitor vs Dex

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Tadalafil</th>
<th>Dex</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAPE</td>
<td>7/9 (78%)</td>
<td>1/8 (13%)</td>
<td>0/10 (0)</td>
</tr>
<tr>
<td>AMS</td>
<td>8/9 (89%)</td>
<td>8/10 (80%)</td>
<td>3/10 (30)</td>
</tr>
<tr>
<td>LLS</td>
<td>7</td>
<td>6.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>2</td>
<td>0.5</td>
</tr>
</tbody>
</table>
PDE-5 Inhibitors

• Fading because of cost and concerns about increased AMS incidence
Dexamethasone
Dexamethasone

- Lowers pulmonary artery pressures
- Effective for AMS
- Needs more study
HAPE Pathogenesis

- Increased pulmonary artery pressures
  - Individual susceptibility
  - Hypoxia
- Hydrostatic fluid leak due to stress failure of capillaries
- Then development of inflammation and thrombosis in later stages
High Altitude Retinopathy

- Retinal hemorrhages
- Rarely results in permanent damage
- Incidence
  - Denali: 36% at 14,200
  - Logan: 56% at 17,000
- Etiologies
  - Increased venous pressure
  - No protection from pressure surges
Altitude and Refractive Eye Surgery

- **Radial keratomy:**
  - Changes occur within hours of altitude
  - Usually returns to normal upon descending
- **LASIK**
  - Seems to be better for extreme altitude
  - No consistent changes with altitude
Summary

• Adaptation to Altitude
  – Increase ventilation
  – Increase hematocrit
  – Changes in $O_2$ affinity

• Acute mountain sickness (AMS)
• High altitude pulmonary edema (HAPE)
• High altitude cerebral edema (HACE)
• High altitude retinal disease
Summary

• Adaptation to Altitude
  – Increase ventilation
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  – Changes in $O_2$ affinity

• Acute mountain sickness (AMS)
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