PHYSIOLOGIC VARIABLES ASSOCIATED WITH THE DEVELOPMENT OF ACUTE MOUNTAIN SICKNESS AT THE SOUTH POLE

Thursday May 16, 2013
Aerospace Medical Association
Chicago, IL

MF Harrison, MD PhD\textsuperscript{1,2}; P Anderson, MD\textsuperscript{1}; A Miller, MSc\textsuperscript{1}; K O’Malley\textsuperscript{1}; M Richert, PhD\textsuperscript{1}; J Johnson, MSc\textsuperscript{1}; BD Johnson, PhD\textsuperscript{1}

\textsuperscript{1}Mayo Clinic, Rochester MN; \textsuperscript{2}Henry Ford Hospital, Detroit MI

Harrison et al, Physiologic variables associated with the development of acute mountain sickness at the south pole. Aviat Space Environ Med 2013; 84(4):426
Disclosure Information
84th Annual AsMA Scientific Meeting
Chicago, IL

MICHAEL HARRISON

I have no financial relationships to disclose.

I will discuss off-label use and/or investigational use in my presentation:
Albumin & Dexamethasone

Dr Bruce Johnson’s Funding:
National Science Foundation, B-179-M
Mayo Clinic Center for Translational Science Activity (CTSA), Clinical Research Unit
Grant Number 1 UL1 RR024150 from the National Center for Research Resources
Overview

• What we know about AMS
• What we don’t know about AMS
• Why our AMS study is different
• What we did
• What we found
• What it means
• Where do we go next
Altitude Illnesses

- Acute Mountain Sickness (AMS)
  - “...unpleasant but self-limiting and benign syndrome...”\(^1\)
  - Most common form of altitude illness\(^2,3\)
    - 1850 – 2750m: 22%
    - >3000m: 42%

- High Altitude Cerebral Edema (HACE)
  - End stage of AMS\(^4\)
  - Highest rate of fatalities amongst altitude illnesses

- High Altitude Pulmonary Edema (HAPE)

\(^1\) Barry & Pollard, 2003; \(^2\) Hultgren, 1979; \(^3\) Honigman et al., 1994; \(^4\) Hackett & Roach, 2001
Can We Identify Who is at Risk for AMS Development?

- “Attempts to predict its development have so far been unsuccessful.”¹
- “...tests undertaken at sea level are disappointingly poor at predicting altitude illness.”²
- “...a complete understanding of related mechanisms remains elusive...”³

¹Austin & Sleigh, 1995; ²Barry & Pollard, 2003; ³Bailey et al, 2004
Factors to Predict AMS?

- Severe gag reflex
- Dizziness with hyperventilation
- Arterial concentrations of epinephrine & norepinephrine
- Mean arterial pressure at sea level
- Fluid retention & redistribution
- Obesity
- Inflammatory response to altitude / hypoxia
- Exaggerated chemoreceptor vasoconstrictive response to hypoxia
- Respiratory rate > 20 after 1h at altitude
- Previous AMS

Consistent “Causes” of AMS

- Travel to elevations >2500m$^{1-4}$
- Commonly identified factors$^{1,2,4,5,6}$:
  - Rate of ascent
  - Altitude attained
    - in particular, the sleeping altitude
  - Individual susceptibility
    - Genetic & environmental interactions?

Previous AMS Publications

• Varying altitudes
• Varying rates of ascent
• Varying methods of ascent
• Varying sample sizes & populations
• Varying diagnostic tools\(^1\)
  – LLSS: 25% at 1900-3000\(\text{m}\)
  – Hackett’s AMS-score: 3.1-9% at 1900-3000\(\text{m}\)
  • Involves a physician examination

\(^1\)Roeggla et al, 1996
Diagnosing AMS

- SUBJECTIVE diagnosis
- There are no physical **SIGNS** that are diagnostic of AMS\(^1,2\)
  - Presence of signs suggests progression to HACE
    - Ataxia, aphasia, abnormal pupillary response, papilloedema, altered level of consciousness, seizures in very late stages etc

\(^1\)Barry & Pollard, 2003; \(^2\)Basnyat & Murdoch, 2003
ASAP Participants

- 2 Summer expeditions 2005-2007
- N=248 (169 M; 79 F)
  - No Acetazolamide w/ complete data, n=90
    - Complete questionnaires
    - 2 blood samples
    - 2 PFT (no significant results found)
  - Two groups:
    - No AMS (n=60)
    - AMS (n=30)
- Acetazolamide available to ANY participant who wanted it
  - NSF mandate
• Acclimatized ~14 d at McMurdo Station
• Travelled by unpressurized airplane to South Pole Station
  – ~4 h flight
  
  UNIQUE → everyone got to same place in the same way

• Altitude at South Pole: 2835m
  – Physiologic altitude at South Pole: ~3200m

\(^1\)Schoene, 2008
Lake Louise Symptom Score (LLSS)

- Repeated LLSS
- 9 in total
- Baseline / Sea Level; Plane; Days 1-7 in AM

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td>No headache</td>
<td>0</td>
</tr>
<tr>
<td>Mild headache</td>
<td>1</td>
</tr>
<tr>
<td>Moderate headache</td>
<td>2</td>
</tr>
<tr>
<td>Severe headache, incapacitating</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Poor appetite or nausea</td>
<td>1</td>
</tr>
<tr>
<td>Moderate nausea &amp;/or vomiting</td>
<td>2</td>
</tr>
<tr>
<td>Severe nausea &amp;/or vomiting</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue &amp;/or weakness</td>
<td></td>
</tr>
<tr>
<td>Not tired or weak</td>
<td>0</td>
</tr>
<tr>
<td>Mild fatigue/ weakness</td>
<td>1</td>
</tr>
<tr>
<td>Moderate fatigue/ weakness</td>
<td>2</td>
</tr>
<tr>
<td>Severe fatigue/ weakness</td>
<td>3</td>
</tr>
<tr>
<td>Dizziness/lightheadedness</td>
<td></td>
</tr>
<tr>
<td>Not dizzy</td>
<td>0</td>
</tr>
<tr>
<td>Mild dizziness</td>
<td>1</td>
</tr>
<tr>
<td>Moderate dizziness</td>
<td>2</td>
</tr>
<tr>
<td>Severe dizziness, incapacitating</td>
<td>3</td>
</tr>
<tr>
<td>Difficulty sleeping</td>
<td></td>
</tr>
<tr>
<td>Slept as well as usual</td>
<td>0</td>
</tr>
<tr>
<td>Did not sleep as well as usual</td>
<td>1</td>
</tr>
<tr>
<td>Woke many times, poor sleep</td>
<td>2</td>
</tr>
<tr>
<td>Could not sleep at all</td>
<td>3</td>
</tr>
</tbody>
</table>

TOTAL SCORE:
ASAP Data Collection Tools

• Vital signs
• Anthropometrics
• Lifestyle questionnaires
  – Residence altitude
  – Exercise
  – Smoking / EtOH
• Health hx questionnaires

• Repeated blood samples
  – Hematology
  – Serum electrolytes
  – Catecholamine levels
  – Endocrinology
• Urinalysis
• Electrocardiogram (ECG)
• Repeated Pulmonary Function Tests (PFT)
Blood Samples

• **Hematology**
  - RBC, WBC, Hb, Hct, Plt, RDW
  - MCV, MCH, MCHC
  - Iron studies
    - [Iron], Iron Sat, TIBC, UIBC
  - Estimated plasma volumes

• **Electrolytes**
  - Na⁺, K⁺, Cl⁻, Ca⁺⁺

• **Liver function**
  - ALT, AST, AlkPhos

• **Catecholamines**
  - Epi, Norepi, Dopa

• **Endocrine**
  - Progesterone, TSH, EPO, ANP, AngII, Leptin, VEGF, TNF-α

\(^{1}\text{Dill & Costill, 1974} \)
ASAP Statistics

• SPSS V20 (IBM Inc, Armonk NY)
• Visual inspection for outliers
  – > 3SD from mean; removed on case-by-case basis
• Groups:
  – No AMS: LLSS ≤ 2;
  – AMS: LLSS ≥ 3 + headache
• Appropriate statistical analyses between and within groups (p ≤ 0.05)
  – Independent samples t-test
  – Forward, stepwise binary logistic regression
Table 1 – Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>No AMS (n=60)</th>
<th>AMS (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M, F)</td>
<td>37M, 23F</td>
<td>18M, 12F</td>
</tr>
<tr>
<td>Age (y)</td>
<td>36.2 ± 9.4</td>
<td>33.8 ± 9.2</td>
</tr>
<tr>
<td>Residence Altitude (m)</td>
<td>695.6 ± 785.8</td>
<td>818.3 ± 802.8</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.8 ± 0.1</td>
<td>1.7 ± 0.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Sea Level</td>
<td>78.3 ± 14.8</td>
<td>70.2 ± 15.4</td>
</tr>
<tr>
<td>• Altitude</td>
<td>78.3 ± 14.3</td>
<td>71.2 ± 14.1</td>
</tr>
<tr>
<td>Body Mass Index (Wt/ht²)</td>
<td>26.1 ± 4.1</td>
<td>24.1 ± 2.5</td>
</tr>
<tr>
<td>Heart Rate (beats*min⁻¹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Sea Level</td>
<td>73.3 ± 12.2*</td>
<td>67.4 ± 10.0*</td>
</tr>
<tr>
<td>• Altitude</td>
<td>83.6 ± 12.4</td>
<td>80.5 ± 13.7</td>
</tr>
<tr>
<td>Blood Pressure (seated)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Sea Level</td>
<td>111.2 ± 13.3*</td>
<td>109.2 ± 9.9*</td>
</tr>
<tr>
<td>• Altitude</td>
<td>106.1 ± 12.7</td>
<td>101.1 ± 12.6</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Sea Level</td>
<td>70.3 ± 10.4*</td>
<td>67.0 ± 9.2*</td>
</tr>
<tr>
<td>• Altitude</td>
<td>69.1 ± 9.0</td>
<td>63.3 ± 7.1</td>
</tr>
<tr>
<td>Oxygen Saturation (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Sea Level</td>
<td>97.7 ± 1.2</td>
<td>97.5 ± 0.9</td>
</tr>
<tr>
<td>• Altitude</td>
<td>88.8 ± 3.9</td>
<td>89.3 ± 3.0</td>
</tr>
<tr>
<td>Post-Breath Hold</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Sea Level</td>
<td>93.5 ± 4.7</td>
<td>94.9 ± 3.3</td>
</tr>
<tr>
<td>• Altitude</td>
<td>82.7 ± 5.4</td>
<td>84.9 ± 4.6</td>
</tr>
<tr>
<td>Neck Circumference (cm)</td>
<td>35.9 ± 3.5</td>
<td>35.4 ± 3.2</td>
</tr>
<tr>
<td>Waist Circumference (cm)</td>
<td>88.0 ± 12.5</td>
<td>83.3 ± 10.5</td>
</tr>
<tr>
<td>Waist-to-Hip Ratio</td>
<td>0.9 ± 0.1</td>
<td>0.8 ± 0.1</td>
</tr>
</tbody>
</table>

* significant difference between the AMS and No AMS groups, p<0.05
<table>
<thead>
<tr>
<th></th>
<th>No AMS (n=60)</th>
<th>AMS (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mEq • L⁻¹)</td>
<td>139.4 ± 1.6*</td>
<td>138.5 ± 1.8*</td>
</tr>
<tr>
<td>Leukocytes (10³ • μL⁻¹)</td>
<td>5.8 ± 1.4</td>
<td>6.1 ± 1.9</td>
</tr>
<tr>
<td>Eosinophils (10² • μL⁻¹)</td>
<td>1.9 ± 1.6*</td>
<td>2.7 ± 2.0*</td>
</tr>
<tr>
<td>Hemoglobin (g • dL⁻¹)</td>
<td>14.8 ± 1.4</td>
<td>15.1 ± 0.9</td>
</tr>
<tr>
<td>Estimated ΔPlasma Volume (%)</td>
<td>-2.9 ± 9.4*</td>
<td>-9.4 ± 12.5*</td>
</tr>
<tr>
<td>Iron Studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Iron (μg • dL⁻¹)</td>
<td>113.9 ± 31.8</td>
<td>119.5 ± 42.0</td>
</tr>
<tr>
<td>• Iron Sat (%)</td>
<td>36.5 ± 12.6</td>
<td>37.4 ± 13.0</td>
</tr>
<tr>
<td>• Total Iron Binding Capacity (μg • dL⁻¹)</td>
<td>325.0 ± 47.5</td>
<td>322.1 ± 37.4</td>
</tr>
<tr>
<td>• Unsaturated Iron Binding Capacity (μg • dL⁻¹)</td>
<td>209.5 ± 56.9</td>
<td>202.6 ± 53.9</td>
</tr>
<tr>
<td>Low Density Lipoprotein (mg • dL⁻¹)</td>
<td>105.9 ± 27.6*</td>
<td>97.7 ± 25.4*</td>
</tr>
<tr>
<td>High Density Lipoprotein (mg • dL⁻¹)</td>
<td>60.2 ± 15.8</td>
<td>65.3 ± 17.4</td>
</tr>
<tr>
<td>Very Low Density Lipoprotein (mg • dL⁻¹)</td>
<td>21.6 ± 12.8</td>
<td>20.3 ± 10.4</td>
</tr>
<tr>
<td>Triglycerides (mg • dL⁻¹)</td>
<td>107.2 ± 62.9</td>
<td>101.4 ± 51.8</td>
</tr>
</tbody>
</table>

* significant difference between the AMS and No AMS groups, p<0.05
### Table 3 – Endocrine Results

<table>
<thead>
<tr>
<th></th>
<th>No AMS (n=60)</th>
<th>AMS (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progesterone</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ng • mL⁻¹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sea Level</td>
<td>1.8 ± 3.5</td>
<td>1.5 ± 2.7</td>
</tr>
<tr>
<td>Altitude</td>
<td>1.4 ± 2.6</td>
<td>1.2 ± 1.8</td>
</tr>
<tr>
<td><strong>Erythropoietin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(μIU • mL⁻¹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sea Level</td>
<td>11.0 ± 5.5</td>
<td>10.0 ± 4.7</td>
</tr>
<tr>
<td>Altitude</td>
<td>31.7 ± 20.1</td>
<td>24.3 ± 9.0</td>
</tr>
<tr>
<td><strong>Tumor Necrosis Factor-α</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(pg • mL⁻¹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sea Level</td>
<td>1.3 ± 0.6*</td>
<td>1.4 ± 0.7*</td>
</tr>
<tr>
<td>Altitude</td>
<td>1.3 ± 0.6</td>
<td>1.3 ± 0.6</td>
</tr>
<tr>
<td><strong>Vascular Endothelial Growth Factor</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(pg • mL⁻¹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sea Level</td>
<td>42.4 ± 22.7</td>
<td>43.5 ± 26.1</td>
</tr>
<tr>
<td>Altitude</td>
<td>57.0 ± 37.8*</td>
<td>76.4 ± 42.5*</td>
</tr>
<tr>
<td><strong>Norepinephrine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(pg • mL⁻¹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sea Level</td>
<td>402.4 ± 165.9</td>
<td>357.9 ± 108.8</td>
</tr>
<tr>
<td>Altitude</td>
<td>569.5 ± 227.1</td>
<td>491.5 ± 159.7</td>
</tr>
<tr>
<td><strong>Epinephrine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(pg • mL⁻¹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sea Level</td>
<td>42.0 ± 76.1</td>
<td>29.2 ± 20.9</td>
</tr>
<tr>
<td>Altitude</td>
<td>36.3 ± 25.2</td>
<td>36.1 ± 30.1</td>
</tr>
<tr>
<td><strong>Dopamine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(pg • mL⁻¹)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sea Level</td>
<td>25.1 ± 62.7</td>
<td>13.4 ± 6.0</td>
</tr>
<tr>
<td>Altitude</td>
<td>24.4 ± 16.6*</td>
<td>16.2 ± 14.8*</td>
</tr>
</tbody>
</table>

* significant difference between the AMS and No AMS groups, p<0.05
Logistic Regression Analysis

- No AMS vs AMS by LLSS
  - Excluded objective data from South Pole
- Forward, stepwise binary logistic regression
  - $P<0.25$ for initial inclusion\(^1\)

- Initial Variables
  - Residence Elevation
  - $\text{Cl}^-$
  - AST
  - LDL
  - Eosinophils (%)
  - RDW
  - Leptin
  - Epi

\(^{1}\text{Honigman et al, 1994}\)
Logistic Regression Equation

\[
\text{Prob (AMS)} = (e^{1.593 + (-0.037)(\text{LDL}) + (0.433)(\text{eos})}) \times (1 + e^{1.593 + (-0.037)(\text{LDL}) + (0.433)(\text{eos})})^{-1}
\]

- \(p < 0.01\)
- -2 log-likelihood = 66.5
- Nagelkerke R\(^2\) = 0.278
  - Sensitivity = 26%
  - Specificity = 92%
  - PPV = 56%
  - NPV = 77%
\[
Prob(AMS) = (e^{1.593 + (-0.037)(LDL) + (0.433)(eos)}) \times (1 + e^{1.593 + (-0.037)(LDL) + (0.433)(eos)})^{-1}
\]

- **Na+**
  - Largest component of serum osmolality
    - AMS: 138.5 ± 1.8mEq/L
    - No AMS: 139.4 ± 1.6mEq/L

- **LDL**
  - AMS: 97.7 ± 25.4 mg/dL
  - No AMS: 105.9 ± 27.6 mg/dL
    - Healthy: 70-129 mg/dL
  - Oncotic pressure? Vasogenic edema?
    - ↑↑↑↑ LDL but not HDL in response to nephrotic syndrome\(^1,2\)

- **Δ Plasma Volume**
  - AMS: -9.4 ± 12.5%
  - No AMS: -2.9 ± 9.4%
  - No difference in body weight

- **Eosinophils**
  - AMS: 3.0 ± 2.3%
  - No AMS: 1.9 ± 1.6%
    - Normal: 1-3%
  - Immune mediators
    - Asthma and allergies
      - ↑ risk in asthma sufferers\(^3\)
    - Cytokine production
      - IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-13, TNF-α
    - Prostaglandin & leukotriene production
      - Vascular smooth muscle
      - Gastric smooth muscle
      - Autonomic neurotransmitters

- **VEGF & TNF-α**

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\(^1\)Appel et al, 1985; \(^2\)Haymore et al, 2005; \(^3\)Barry & Pollard, 2003
Hypothesized Pathophysiology of AMS

Figure 1. Proposed Pathophysiological Process of High-Altitude Illness.
At high altitudes hypoxemia can lead to overperfusion, elevated capillary pressure, and leakage from the cerebral and pulmonary microcirculation. Increased sympathetic activity has a central role in this process, and increased permeability of capillaries as a result of endothelial activation (inflammation) may also have a role.

Hackett & Roach, 2001
Oncotic Pressure

- Proportional to proteins in plasma
  - albumin

- Albumin supplement
  - Benefit in healthy population at altitude?
    - In conjunction with corticosteroids / NSAIDS?

Margarson & Soni, 2004

Diagram:
- $P_c$: capillary hydrostatic pressure
- $P_i$: tissue interstitial pressure
- $\pi_c$: capillary plasma oncotic pressure
- $\pi_i$: tissue interstitial oncotic pressure
Correlation between Plasma Oncotic Pressure and Total Plasma Cholesterol Concentration ($r = -0.674$, $P<0.01$).

Appel et al, 1985
Hypoxia & Hypoxemia

Hypoxic tissue becomes inflamed
Inflamed tissue becomes hypoxic

• Specific to AMS\(^1\):
  - ↑ circulating levels of proinflammatory cytokines
    • C-reactive protein (CRP); IL-6; IL-6 receptor
  - ↑ accumulation of inflammatory cells in multiple organs in body
  - ↑ vascular leakage

\(^1\)Eltzschig & Carmeliet, 2011
Further Support for Role of Inflammation

• Glucocorticoids used to treat AMS\(^1\)-\(^4\)
  – ↑ Efficacy as compared to acetazolamide?

• ↑ IL-6 and CRP in high-altitude trekkers who develop AMS & HAPE\(^5\)
  – ↑ IL-6 correlated with ↓ \(\text{SaO}_2\)

• Ibuprofen ↓ AMS incidence vs placebo, 3810m\(^6\)

\(^1\)Hackett & Roach, 2001; \(^2\)Barry & Pollard, 2003; \(^3\)Schoene, 2008; \(^4\)Luks et al, 2010; \(^5\)Bailey et al, 2004; \(^6\)Lipman et al, In Press
Conclusion

• In a population of healthy adults who were rapidly transported to altitude with minimal physical exertion, a comprehensive analysis suggests importance of:
  – Tissue inflammation
  – Oncotic pressures and fluid shifts
Acknowledgements

• We would like to thank:
  – The employees of the US Antarctic Program
  – Crary Lab
  – Jay O’Brien
  – Kent Bailey
  – Josh Mueller

• Funding was provided by
  – National Science Foundation, B-179-M
  – Mayo Clinic Center for Translational Science Activity (CTSA), Clinical Research Unit
  – Grant Number 1 UL1 RR024150 from the National Center for Research Resources
POIN TS OF CONTACT:

MICHAEL HARRISON, MD PHD
MHARRI19@HFHS.ORG
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