The Human Adaptation to Hypoxia and Altitude

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Outline

Altitude and hypoxia: definitions
Physiological responses to altitude
The brain at altitude
Permanent residence at high altitude
Hypoxia: New therapeutic opportunities?

Altitude, pressure & hypoxia

Reduced barometric pressure
Reduced inspiratory oxygen pressure

<table>
<thead>
<tr>
<th>Altitude (ft)</th>
<th>0 (sea level)</th>
<th>1,000</th>
<th>2,000</th>
<th>3,000</th>
<th>4,000</th>
<th>5,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>$F_O_2$ (mL%)</td>
<td>790</td>
<td>674</td>
<td>596</td>
<td>526</td>
<td>402</td>
<td>231</td>
</tr>
<tr>
<td>$P_O_2$ (mmHg)</td>
<td>159.1</td>
<td>141.1</td>
<td>124.7</td>
<td>110.0</td>
<td>96.7</td>
<td>48.3</td>
</tr>
</tbody>
</table>

Types of altitude exposure
Changes in blood gases at altitude

Changes in blood gases at altitude

Physiological responses to altitude

Cerebral perturbations in hypoxia

Table 2: Arterial Blood Gas measurements and Calculated Values for Pulmonary Gas Exchange from Two Subjects at an Altitude of 8000 ft, Rising Desert 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>PaO₂ (mm Hg)</td>
<td>1</td>
<td>56.3</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>1</td>
<td>52.7</td>
</tr>
<tr>
<td>HbO₂ (index)</td>
<td>1</td>
<td>85.9</td>
</tr>
<tr>
<td>RBC volume (µl/ml)</td>
<td>1</td>
<td>23.5</td>
</tr>
<tr>
<td>Erythrocyte count (x 10⁶/mm³)</td>
<td>1</td>
<td>5.2</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>1</td>
<td>42.5</td>
</tr>
<tr>
<td>Oxygen consumption (mL/min/m²)</td>
<td>1</td>
<td>19.5</td>
</tr>
<tr>
<td>Respiratory exchange factor</td>
<td>1</td>
<td>0.82</td>
</tr>
<tr>
<td>PVCO₂ — — PaCO₂</td>
<td>1</td>
<td>40.9</td>
</tr>
</tbody>
</table>

Luks 2015

Verges et al. 2012

Wilmore and Costill 2005

Grocott et al. 2009
Cerebral responses to high altitude

Cerebral blood flow at high altitude

VALLOT 2011 project
4350 m

Doppler & NIRS sea level / altitude (D5)
MRI ASL sea level / post altitude (D7)

Before altitude (212 m)
97.2 ± 0.5
40.9 ± 4.9
13.8 ± 2.7
61.2 ± 7.7
104.4 ± 6.1

Day 5 at altitude (4,350 m)
87.6 ± 1.3
30.5 ± 3.1
19.2 ± 2.7
77.9 ± 16.1
115.6 ± 8.7

Immediately after altitude (212 m)
97.8 ± 0.7
33.2 ± 4.0
14.9 ± 2.9
63.1 ± 8.2
105.8 ± 8.1

Transcranial Doppler
Arterial Spin Labelling

Hypercapnic responses at 4350 m:
Doppler, NIRS

Rupp et al. 2013

⇒ Reduced cerebrovascular response
⇒ Altered cerebral oxygenation
Cerebrovascular reactivity at high altitude

Hypercapnic responses at 4350 m: MRI - ASL

Villien et al. 2013

Cerebral perturbations in hypoxia

Verges et al. 2012

Cortical excitability and hypoxia

Transcranial magnetic stimulation of the motor cortex

Rupp et al. 2012

Time-dependent effect of hypoxia (FiO₂=12%) on corticospinal excitability
Time-dependent effect of hypoxia on corticospinal inhibition

Anatomical changes

Cerebral perturbations in hypoxia

Hypoxia and cerebral volume

Rupp et al. 2012

Marillier et al. 2017

Verges et al. 2012

Rupp et al. 2014

Verges et al. 2016
Hypoxia, cerebral blood flow and edema

Tight-fit hypothesis

Intracranial pressure

Increased cerebral blood volume or Edema

Cerebral perturbations in hypoxia

Exercise capacity

Cognitive function

Sleep

Mountain sickness
**Exercise-induced central fatigue in hypoxia**

Constant load cycling (80% Wmax) to exhaustion

**Cerebral perturbations in hypoxia**

![Schematic diagram of cerebral perturbations in hypoxia]

Exercise capacity → Cognitive function → Sleep → Mountain sickness

**Sleep at altitude**

Awake, REM sleep, Stages 1 and 2, Stages 3 and 4

First night at 4350 m
Apolo-Hypopnea index = 170 events/h

**Sleep at altitude**

Differences between responders and non-responders

- Subjects with Acute Mountain Sickness
- Subjects without Acute Mountain Sickness

![Graphs comparing sleep parameters at altitude]

**References**

- Goodall et al. 2012
- Verges et al. 2012
- Nespoulet et al. 2012
Types of altitude exposure

- Moderate altitude
- High altitude
- Very high altitude
- Permanent decompression (e.g. highlanders)

Human populations at high altitude

140 millions habitants in the world living at >2500 m

La Rinconada (Peru)
La Paz (Bolivia)
Cerro de Pasco (Peru)
Val Thorens (France)
Font Romeu (France)

Max limit for human permanent life

Human populations at high altitude

Main physiological consequences of living at high altitude:
- Hypoxemia
- Pulmonary hypoxic vasoconstriction
- Increased hemoglobin concentration
- Genetic specificities

Oxygen pressure according to the altitude of residence

West et al. 2017

Azad et al. 2017

La Rinconada (Peru)
Cerro de Pasco (Peru)
Val Thorens (France)
Font Romeu (France)
Highlanders and chronic mountain sickness

- Chronic mountain sickness syndrome (consensus ISMM, 2005): Excessive erythrocytosis + Symptoms (breathlessness/palpitations, sleep disturbances, cyanosis, dilatation of veins, paresthesia, headache, tinnitus)
- 5-20% of high altitude populations (> 2500 m)
- Underlying mechanisms? Inter-individual differences? Morbi-mortality?

From Sahota 2013

LA RINCONADA: THE HIGHEST CITY IN THE WORLD

TRADITIONAL CONCEPT REGARDING EXCESSIVE ERYTHROCYTOSIS AND CHRONIC MOUNTAIN SICKNESS

Excessive erythrocytosis → Increased blood viscosity → Cardiovascular dysfunction → CMS symptoms
### LA RINCONADA: POPULATION CHARACTERISTICS

Clinical data of 1594 highlanders living permanently in La Rinconada (5100-5300m)

| Median (IQR) or n (%) |  
|-----------------------|---
| Age (years)           | 32 (23-39)  
| Sex                   |  
| Female                | 245 (14.7)  
| Male                  | 1359 (85.3)  
| Ethnic group          |  
| Aymara                | 75 (4.7)  
| Quechua               | 1519 (95.3)  
| Residency in La Rinconada (years) | 3 (2-5)  
| Hematocrit (%)        | 60 (54-66)  
| Heart rate (bpm)      | 87 (75-94)  
| Diastolic blood pressure (mmHg) | 70 (60-80)  
| Systolic blood pressure (mmHg) | 100 (100-110)  

Hancco et al. Unpublished results

### TRADITIONAL CONCEPT REGARDING EXCESSIVE ERYTHROCYTOSIS AND CHRONIC MOUNTAIN SICKNESS

Excessive erythrocytosis (Hb > 10-21 g·dl⁻¹)  
Non-excessive erythrocytosis  
Excessive erythrocytosis  
Total chronic mountain sickness (CMS) score ≤5 (no CMS)  
>5 (mild CMS score)  
>10 (moderate-severe CMS score)

Hancco et al. Submitted

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#### With/without Excessive erythrocytosis (EE) (classification 1)

- Excessive erythrocytosis
- Non-excessive erythrocytosis

= Lower frequency of CMS symptoms in subjects with EE

#### With/without Excessive erythrocytosis (EE) (classification 2)

- Excessive erythrocytosis
- Non-excessive erythrocytosis

= Lower frequency of CMS symptoms in subjects with EE

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**08/04/2019**
Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Lowlanders</th>
<th>Highlanders at SL (n = 10)</th>
<th>Highlanders at 3,800 m (n = 13)</th>
<th>Highlanders at 5,100 m (n = 15)</th>
<th>Highlanders with CMS at 5,100 m (n = 13)</th>
<th>Highlanders with CMS+ at 5,100 m (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32.8 ± 7.2</td>
<td>28.8 ± 11.4</td>
<td>37.9 ± 12.7</td>
<td>35.1 ± 8.1</td>
<td>40.8 ± 7.0</td>
<td>40.8 ± 7.0</td>
</tr>
<tr>
<td>Duration of stay (yrs)</td>
<td>-</td>
<td>-</td>
<td>11.6 ± 8.9</td>
<td>7.3 ± 6.9</td>
<td>10.3 ± 6.3</td>
<td>10.3 ± 6.3</td>
</tr>
<tr>
<td>BMI (kg∙m⁻²)</td>
<td>22.8 ± 1.7</td>
<td>26.5 ± 3.2</td>
<td>25.9 ± 3.1</td>
<td>25.6 ± 3.1</td>
<td>26.3 ± 2.9</td>
<td>26.3 ± 2.9</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>41.9 ± 2.5</td>
<td>57.0 ± 4.7</td>
<td>58.2 ± 4.9</td>
<td>58.8 ± 5.0</td>
<td>70.1 ± 7.8</td>
<td>70.1 ± 7.8</td>
</tr>
<tr>
<td>[Hb] (g·dL⁻¹)</td>
<td>98.1 ± 1.0</td>
<td>96.6 ± 1.4</td>
<td>83.8 ± 6.5</td>
<td>83.1 ± 5.6</td>
<td>86.1 ± 3.5</td>
<td>86.1 ± 3.5</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>65.2 ± 13.0</td>
<td>71.3 ± 11.8</td>
<td>80.2 ± 6.6</td>
<td>81.3 ± 11.5</td>
<td>85.8 ± 9.5</td>
<td>85.8 ± 9.5</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>120.3 ± 9.2</td>
<td>120.6 ± 10.7</td>
<td>126.0 ± 10.7</td>
<td>126.5 ± 10.7</td>
<td>134.5 ± 11.3</td>
<td>134.5 ± 11.3</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>70.4 ± 8.2</td>
<td>72.3 ± 8.7</td>
<td>81.5 ± 6.0</td>
<td>76.5 ± 9.8</td>
<td>76.2 ± 8.5</td>
<td>76.2 ± 8.5</td>
</tr>
</tbody>
</table>

Results are mean ± SD. BP, blood pressure; BMI, body mass index; CMS, chronic mountain sickness; EE, excessive erythrocytosis; [Hb], haemoglobin concentration; SL, sea level. * significantly different compared to lowlanders, ǂ significantly different compared to highlanders at 3,800 m, + significantly different compared to highlanders without EE, # significantly different compared to EE CMS–.
TRADITIONAL CONCEPT REGARDING EXCESSIVE ERYTHROCYTOSIS AND CHRONIC MOUNTAIN SICKNESS

Excessive erythrocytosis
Increased blood viscosity
Cardiovascular dysfunction
CMS symptoms

EXPEDITION 5300
January - February 2019

Study design

Penuvian lowlanders
Lima, 80 m
Healthy, n=20

Penuvian highlanders
Puno, 3800 m
Healthy, n=23

Penuvian highlanders
La Rinconada, 5100 m
Healthy CMS, n=17

Caucasian lowlanders, healthy, n=10

Age (yrs)
29.9 ± 9.1
35.6 ± 12.8
41.4 ± 7.7
43.0 ± 7.7
44.5 ± 6.8

Duration of stay (yrs)
32.2 ± 13.9
12.4 ± 8.0
13.6 ± 9.1
13.8 ± 8.0
26.3 ± 3.0

BMI (kg∙m⁻²)
25.0 ± 4.0
25.0 ± 3.8
25.4 ± 2.1
26.3 ± 3.3
26.3 ± 3.1

[Hb] (g∙dL⁻¹)
14.2 ± 2.2
19.1 ± 2.3
22.1 ± 2.4
22.4 ± 1.6
24.0 ± 1.6

Haematocrit (%)
42.6 ± 5.4
56.1 ± 6.1
69.4 ± 7.8
70.1 ± 4.8
75.3 ± 4.8

SpO₂ (%)
97.7 ± 0.9
91.6 ± 3.5
83.7 ± 5.0
83.1 ± 4.2
78.0 ± 6.5

CMS score
2.9 ± 3.6
4.0 ± 1.5
6.1 ± 1.1
12.7 ± 2.0
12.0 ± 3.4

Systolic BP (mmHg)
114.7 ± 9.3
115.0 ± 8.9
115.4 ± 11.6
113.9 ± 9.9
116.0 ± 19.4

Diastolic BP (mmHg)
69.5 ± 8.8
77.2 ± 7.2
78.6 ± 10.3
78.6 ± 8.5
76.0 ± 8.1

EXPEDITION 5300
January - February 2019

Evaluations

Genetics
Biomechanics
Vascular function
Heart function
Exercise testing

Epigenetics
Biology (oxidative and inflammatory status, EPO and iron metabolism...)
Hemorheology
Hematology
Lung function
Sleep recording

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Hypoxia as a pathological mechanism

Deleterious or protective responses to hypoxia?

Hypoxic alterations versus conditioning

Hypoxia as a protective mechanism?

Hypoxia as a protective mechanism?
**Intermittent hypoxia**

![Image of intermittent hypoxia study](image1)

**Hypoxic preconditioning of the heart**

- 4 groups of rats:
  - 4 h severe intermittent hypoxia (IH; 40 s ON, 20 s OFF; FIO₂ = 5%)
  - 4 h moderate intermittent hypoxia (IH; 40 s ON, 20 s OFF; FIO₂ = 10%)
  - 4 h continuous moderate hypoxia (CH, FIO₂ = 10%)
  - Control normoxic condition

![Graph of heart ischemia-reperfusion](image2)

**Hypoxic conditioning of the brain**

Mice exposed to intermittent hypoxia for 2 weeks
Stroke model until 8 weeks after treatment

![Graph of brain ischemia-reperfusion](image3)

**Passive hypoxic conditioning in obese individuals**

Obese patients, prospective, randomized, controlled, single-blind study
24 x 1-hour sustained/intermittent hypoxic conditioning sessions (8 weeks)

![Graph of obese patients response](image4)

*Different from baseline normoxia
$\Delta$ Difference between sessions 1 and 24

**Chacaroun et al., unpublished results**

![Graph of obese patients response](image5)
**Passive hypoxic conditioning in obese individuals**

Obese patients, prospective, randomized, controlled, single-blind study
24 × 1-hour sustained/intermittent hypoxic conditioning sessions (8 weeks)

- Sustained hypoxia
- Intermittent hypoxia
- Placebo

![](image)

→ Reduced normoxic diastolic blood pressure following both hypoxic programs

Chacaroun et al. unpublished results

**Active hypoxic conditioning in obese individuals**

Obese patients, prospective, randomized, controlled, single-blind study
24 × exercise hypoxic training sessions (8 weeks)

- Hypoxic exercise training
- Normoxic exercise training

![](image)

→ Improved maximal aerobic capacity following hypoxic exercise training only

**Hypoxic conditioning**

Hypoxic conditioning: a new therapeutic opportunity?

Verges et al. 2015

Thank you for your attention

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