The 20th International Hypoxia Symposium
(meeting to advance the science of Hypoxia every two years since 1979)

7-12 February 2017
Chateau Lake Louise
Lake Louise, Alberta, Canada
The 20th International Hypoxia Symposium

Chairs
Robert Roach
Peter Hackett

Advisory Board
Phil Ainslie, Peter Bärtsch, Annalisa Cogo, Jerry Dempsey, Holger Eltzschig, Max Gassmann, Thomas Hornbein, Bengt Kayser, Fabiola Leon-Velarde, Denny Levett, Ben Levine, Andy Luks, Carsten Lundy, Marco Maggiorini, Heimo Mairbäurl, Jim Milledge, Lorna Moore, Annabel Nickol, Marc Poulin, Frank Powell, Ge Ri Li, Jean-Paul Richalet, Claudio Sartori, Urs Scherrer, Robert Schoene, Tatum Simonson, Erik Swenson, Francisco Villafuerte, Peter Wagner, John West and Tanna Wuren

Administrative Support
Jeremy Reitinger and Barbara Lommen

Special Thanks for Support
Altitude Research Center, University of Colorado Denver
Hypoxia Mission Statement

The mission of the International Hypoxia Symposia is to present cutting edge, sophisticated research at the very highest levels into the many effects of hypoxia on humans and animals in health and disease.

Hypoxia is a constant threat to the human body and its vital organs throughout life. There are many situations in which the threat is heightened in health and disease, but mechanisms have evolved to lessen its detrimental effects. The International Hypoxia Symposia was founded in 1979 by Charles Houston, Geoff Coates and John Sutton to enable scientists, clinicians, mountaineers and other interested individuals to share their experiences of the situations associated with oxygen lack and the adaptations that allow us to survive (written by Charles Houston). For more about Charlie, see our website (http://bit.ly/2j1mD9N).

Chronological History

Chaired by: Houston, Coates, and Sutton
1979 Hypoxia 1: (Banff)
1981 Hypoxia 2: Man at Altitude (Banff)
1983 Hypoxia 3: Exercise and Altitude (Banff)
1985 Hypoxia 4: Hypoxia and Cold (Lake Louise)
1987 Hypoxia 5: The Tolerable Limits (Lake Louise)
1989 Hypoxia 6: The Adaptations (Lake Louise)
1991 Hypoxia 7: Hypoxia and Mountain Medicine (Lake Louise)
1993 Hypoxia 8: Hypoxia and Molecular Medicine (Lake Louise)
1995 Hypoxia 9: Hypoxia and the Brain (Lake Louise)
1997 Hypoxia 10: Women at Altitude (Lake Louise)

Chaired by: Roach and Hackett
1999 Hypoxia 11: Hypoxia: Into the Next Millennium (Jasper)
2001 Hypoxia 12: Hypoxia: From Genes to the Bedside (Jasper)
2003 Hypoxia 13: Hypoxia: Through the Life Cycle (Banff)
2005 Hypoxia 14: Hypoxia and Exercise (Lake Louise)
2007 Hypoxia 15: Hypoxia and the Cardiovascular System (Lake Louise)
2009 Hypoxia 16: Hypoxia and Exercise (Lake Louise)
2011 Hypoxia 17: Hypoxia and Cancer (Lake Louise)
2013 Hypoxia 18: Hypoxia (Lake Louise)
2015 Hypoxia 19: Hypoxia (Lake Louise with B. Kayser)
2017 Hypoxia 20: Hypoxia (Lake Louise)
Some Logistical Details

Registration. Register at the Hypoxia Desk in the Alpine Room on Tuesday evening from 1830-2030, on Wednesday morning outside the main meeting room from 0700-0900, or any morning thereafter from 0730-0830.

Reception. Join us for a reception in the Alpine Room on Tuesday evening from 1830 to 2030. This is a great chance to meet old colleagues and new.

Ski Transport. The Cheateau ski bus will leave from the ski bus area in front of the Chateau at 1145 every day. It will return to the Chateau at 1500 and 1530 every day.

Ski Discounts. The Lake Louise Ski Resort kindly offers all Hypoxia delegates and family a 10% discount for half-day (starting at 1130) and full day (for family not attending the conference) lift tickets and rentals. A delegate must be present and show their badge to receive the discount, and all tickets must be purchased at the group sales desk.

Cross Country and Alpine Ski Rentals. Skis are available for rent in the Chateau, at the Lake Louise Ski Resort, and in the village of Lake Louise.

Box Lunches. Chateau guests can sign up the night before each day to reserve a box lunch to take on their next afternoon’s adventures.
Special Meetings During Hypoxia 2017

Wednesday, 8 February 2017

1130-1300  High Altitude Medicine and Biology Editorial Board
            by Invitation Only - Lago Dining Room (in the rear room)

1730-1900  ISMM EC & Kathmandu World Congress Meetings
            by Invitation Only - Saddleback Room

Thursday, 9 February 2017

1300-1600  Chile Interest Group—Marc Poulin
            by Invitation Only - Saddleback Room

Friday, 10 February 2017

1730-1900  STAR Core Group Meetings
            by Invitation Only - Saddleback Room

Saturday, 11 February 2017

0630-0745  International Hypoxia Symposia Advisory Board
            by Invitation Only - Lago Dining Room (in the rear room)

1430-1600  Reeve’s Prize Selection Committee
            by Invitation Only - Plain of Six Glaciers Room

1830-1930  Trainee Awards Selection Committee
            by Invitation Only - Plain of Six Glaciers Room
The Reeves Prize

During the meeting, a panel of judges selected from the Hypoxia Advisory Board will attend every keynote oral presentation to select one winner of the 2017 Reeves Prize for Presentation Excellence. The prize is named after John T. “Jack” Reeves (1928-2004). If you did not have the pleasure of knowing Jack, you may read more about him here (http://bit.ly/2j1tMXt).

The Reeves Prize will be awarded to the speaker judged to present the most outstanding scientific talk, with special emphasis on presentation skills and clarity, characteristics that Jack cherished, practiced, and taught. The judges are asked to make note of those talks that would have thrilled Jack Reeves from a personal and professional perspective. In addition to presentation excellence, he always reminded us to ask:

Is it new, is it true, is it important?

We want to encourage great presenters who do great work.

The prize will be announced at the closing banquet on Saturday.

Awards for Trainees

We give four awards for scientists in training at Hypoxia. Since this is an international meeting and many countries have different definitions for trainee status, we are rather liberal in our categorization. We divide our evaluation of student/fellow awards based on junior and senior status. A junior scientist will most likely be an undergraduate or graduate student. A senior student/fellow will most likely be a postdoctoral fellow or a medically-trained fellow doing a research fellowship.

Award recipients are selected by a panel of judges from the Hypoxia Advisory Board based on the best poster or oral presentations by junior or senior trainees, with awards in each category.

The Trainee Awards will be announced at the closing banquet on Saturday night.
Hypoxia Honorees

Recognizing the contributions of individuals to hypoxia/high altitude research, and their strong relationship with the International Hypoxia Symposia, is a tradition that began in 1979, at the first official Symposia. The tradition continues.

The following luminaries in high altitude and hypoxia research have received Honoree recognition in the first four decades of the meeting:

- Robert F. Grover
- Herb Hultgren
- Tom Hornbein
- Charles S. Houston
- John T. Maher
- Carlos Monge
- Jim Milledge
- L Griffith Pugh
- Hermann Rahn
- John “Jack” T. Reeves
- John Severinghaus
- John Sutton
- John West

Join us in welcoming and celebrating the impressive career of Peter Bärtsch, the International Hypoxia Symposia 2017 Honoree

Presentation Thursday Evening
<table>
<thead>
<tr>
<th><strong>Faculty</strong></th>
<th><strong>20th International Hypoxia Symposium</strong></th>
</tr>
</thead>
</table>
| **Asher, Gad** | Rhythmic Oxygen Levels Reset Circadian Clocks through HIF1α  
Email: gad.asher@weizmann.ac.il |
| **Brauner, Colin** | Beyond Hemoglobin: Red Blood Cell Potentiation of O2 Delivery in Fish…and Other Vertebrates?  
Email: brauner@zoology.ubc.ca |
| **Chang, Andy** | Oxygen Regulation of Breathing Through an Olfactory Receptor Activated by Lactate  
Email: andy.chang@ucsf.edu |
| **Colgan, Sean** | Hypoxia Signaling During Mucosal Inflammation  
Email: sean.colgan@ucdenver.edu |
| **Eltzschig, Holger** | Hypoxia Signaling During Myocardial Ischemia and Reperfusion Injury  
Email: holger.eltzschig@uth.tmc.edu |
| **Fago, Angela** | Functional Roles of Globin Proteins in Hypoxia-Tolerant Vertebrates  
Email: angela.fago@bios.au.dk |
| **Gourine, Alexander** | Functional Oxygen Sensitivity of Astrocytes  
Email: a.gourine@ucl.ac.uk |
| **Kuebler, Wolfgang** | The Alveolar-Capillary Endothelium and Hypoxic Pulmonary Vasoconstriction  
Email: kueblerw@smh.ca |
Lague, Sabine

Birds: Living or Transiting at High Altitude
Email: lague@zoology.ubc.ca

Lundby, Carsten

Blood Volume Kinetics With and After High Altitude Exposure
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Mootha, Vamsi

Hypoxia to Treat Mitochondrial Disease
Email: vamsi_mootha@hms.harvard.edu

Nielsen, Rasmus

Genomics of High Altitude Adaptation
Email: rasmus_nielsen@berkeley.edu

Poulin, Marc

Human Cerebral Blood Flow Control During Hypoxia
Email: poulin@ucalgary.ca

Prchal, Joe

Mechanisms Facilitating Neocytolysis Following Altitude Exposure
Email: josef.prchal@hsc.utah.edu

Robbins, Peter

Iron and Oxygen
Email: peter.robbins@dpag.ox.ac.uk

Sadek, Hesham

Hypoxia-Induced Myocardial Regeneration
Email: hesham.sadek@utsouthwestern.edu

Taylor, Cormac

Prolyl Hydroxylases as Mediators of Inflammatory Responses
Email: cormac.taylor@ucd.ie

Ulrich, Silvia

Hypoxia and Hyperoxia in Exercise Performance in Health and Respiratory Disease
Email: silvia.ulrich@usz.ch
Wagner, Peter  
**Lessons Learned: Operation Everest II 30 Years Later**  
Email: pdwagner@ucsd.edu

Weissmann, Norbert  
**O₂ Sensing and Signal Transduction in Hypoxic Pulmonary Vasoconstriction**  
Email: norbert.weissmann@innere.med.uni-giessen.de

Xia, Yang  
**S1P, The Red Blood Cell and Hypoxia**  
Email: yang.xia@utch.tmc.edu

## Evening Speakers

**Geoff Powter**  
**The Complex Psychology of Adventure**

**Kate Harris**  
**Lands of Lost Borders**

**Kjell Lindgren, MD**  
**A Room With a View: Perspectives on Living and Working in Low Earth Orbit**
<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1830-2030</td>
<td>Registration and Reception with Food, Alpine Room</td>
</tr>
<tr>
<td>0630-0830</td>
<td>Breakfast, Lago Restaurant</td>
</tr>
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<td>0700-0900</td>
<td>Registration, Heritage Hall</td>
</tr>
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<td>0745-0800</td>
<td>Opening Ceremonies, Mount Temple Ballroom</td>
</tr>
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</tr>
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</tr>
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</tr>
<tr>
<td>0930-1000</td>
<td>Refreshment Break, Heritage Hall</td>
</tr>
<tr>
<td>1000-1120</td>
<td><strong>Hypoxia and Inflammation</strong></td>
</tr>
<tr>
<td>1000-1030</td>
<td>Hypoxia Signaling During Mucosal Inflammation — Sean Colgan</td>
</tr>
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<td>Prolyl Hydroxylases as Mediators of Inflammatory Responses — Cormac Taylor</td>
</tr>
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<td>Hypoxia Signaling During Myocardial Ischemia and Reperfusion Injury — Holger Eltzschig</td>
</tr>
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<td><strong>Ski Break</strong></td>
</tr>
<tr>
<td>1130-1330</td>
<td>Lunch, Lago Restaurant</td>
</tr>
<tr>
<td>1600-1630</td>
<td><strong>Hot Topics in Hypoxia I - Selected Abstracts</strong></td>
</tr>
<tr>
<td>1630-1830</td>
<td><strong>Poster Session I</strong></td>
</tr>
<tr>
<td>1900-2130</td>
<td>Dinner, Victoria Dining Room</td>
</tr>
<tr>
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</tr>
</tbody>
</table>
### Thursday, 9 February 2017

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</tr>
</thead>
<tbody>
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<td><strong>Protecting the Brain from Hypoxia</strong></td>
</tr>
<tr>
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<td><em>Functional Oxygen Sensitivity of Astrocytes</em>—Alexander Gourine</td>
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<tr>
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<td><em>Human Cerebral Blood Flow Control During Hypoxia</em>—Marc Poulin</td>
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<td><em>Oxygen Regulation of Breathing Through an Olfactory Receptor Activated</em>—Andy Chang</td>
</tr>
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<td>1000-1130</td>
<td><strong>Novel Strategies for Hypoxia Tolerance</strong></td>
</tr>
<tr>
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<td><em>Beyond Hemoglobin: Red Blood Cell Potentiation of O2 Delivery in Fish...and Other Vertebrates?</em>—Colin Brauner</td>
</tr>
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<td><em>Functional Roles of Globin Proteins in Hypoxia-tolerant Vertebrates</em>—Angela Fago</td>
</tr>
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<td><em>Birds: Living or Transiting at High Altitude</em>—Sabine Lague</td>
</tr>
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</tr>
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<td>Lunch, Lago Restaurant</td>
</tr>
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<td><strong>Hot Topics in Hypoxia II—Selected Abstracts</strong></td>
</tr>
<tr>
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<td>Dinner, Victoria Dining Room</td>
</tr>
<tr>
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<td><strong>Lands of Lost Borders</strong>—Kate Harris</td>
</tr>
</tbody>
</table>
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</tr>
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</tr>
<tr>
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<td><strong>S1P, The Red Blood Cell and Hypoxia</strong>—Yang Xia</td>
</tr>
<tr>
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<td><strong>Mechanisms Facilitating Neocytolysis Following Altitude Exposure</strong>—Joe Prchal</td>
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<tr>
<td>0930-1000</td>
<td>Refreshment Break, Heritage Hall</td>
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<tr>
<td>1000-1130</td>
<td><strong>Hot Topics in Hypoxia III—Selected Abstracts</strong></td>
</tr>
<tr>
<td>1130-1600</td>
<td>Ski Break</td>
</tr>
<tr>
<td>1130-1330</td>
<td>Lunch, Lago Restaurant</td>
</tr>
<tr>
<td>1600-1630</td>
<td><strong>Hot Topics in Hypoxia IV—Selected Abstracts</strong></td>
</tr>
<tr>
<td>1630-1830</td>
<td>Poster Session II</td>
</tr>
<tr>
<td>1900-2130</td>
<td>Dinner, Victoria Dining Room</td>
</tr>
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<td>Event</td>
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</tr>
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</tr>
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</tr>
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</tr>
<tr>
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</tr>
<tr>
<td>0930-1000</td>
<td><strong>Refreshment Break, Heritage Hall</strong></td>
</tr>
<tr>
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<td><strong>Game Changing Concepts about Hypoxia Responses</strong></td>
</tr>
<tr>
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<td>Hypoxia to Treat Mitochondrial Disease—Vamsi Mootha</td>
</tr>
<tr>
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<td>Hypoxia-Induced Myocardial Regeneration—Hesham Sadek</td>
</tr>
<tr>
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<td>Rhythmic Oxygen Levels Reset Circadian Clocks through HIF1α—Gad Asher</td>
</tr>
<tr>
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<td><strong>Ski Break</strong></td>
</tr>
<tr>
<td>1130-1330</td>
<td>Lunch, Lago Restaurant</td>
</tr>
<tr>
<td>1600-1830</td>
<td><strong>Hot Topics in Hypoxia V—Selected Abstracts</strong></td>
</tr>
<tr>
<td>1900-2300</td>
<td>Dinner, Awards, and Dance, Brewster Barn</td>
</tr>
<tr>
<td></td>
<td>Presentation of Student Award Winners</td>
</tr>
<tr>
<td></td>
<td>Presentation of Reeves Prize for Presentation Excellence</td>
</tr>
</tbody>
</table>
Wednesday, 8 February 2017

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0700-0900  Registration, Heritage Hall
0745-0800  Opening Ceremonies, Mount Temple Ballroom

0800-0930  **Updates in Hypoxia**

0800-0830  **Lessons Learned: Operation Everest II 30 Years Later**—Peter Wagner
0830-0900  **Iron and Oxygen**—Peter Robbins
0900-0930  **Genomics of High Altitude Adaptation**—Rasmus Nielsen

0930-1000  **Refreshment Break, Heritage Hall**

1000-1120  **Hypoxia and Inflammation**

1000-1030  **Hypoxia Signaling During Mucosal Inflammation**—Sean Colgan
1030-1100  **Prolyl Hydroxylases as Mediators of Inflammatory Responses**—Cormac Taylor
1100-1130  **Hypoxia Signaling During Myocardial Ischemia and Reperfusion Injury**—Holger Eltzschig

1130-1600  **Ski Break**

1130-1330  Lunch, Lago Restaurant

1600-1630  **Hot Topics in Hypoxia I - Selected Abstracts**
1630-1830  **Poster Session I**
1900-2130  Dinner, Victoria Dining Room
2030-2130  **The Complex Psychology of Adventure**—Geoff Powter
0745-0800
Welcome and Introductions
The Organizers

0800-0830
Updates in Hypoxia
Chairs: Brownie Schoene and Tanna Wuren

0800-0830  Lessons Learned: Operation Everest II 30 Years Later—Peter Wagner

Back in 1978, Peter Habeler and Reinhold Messner performed a feat previously considered impossible—ascending Everest without supplemental \( \text{O}_2 \). Subsequently, Oelz and coworkers assessed their cardiopulmonary function, concluding no advantageous physiological attributes to explain their success. West (High Life: A History of High-Altitude Physiology and Medicine) therefore suggested that grit and determination were more important than cardiopulmonary physiology.

In 1985, Charlie Houston, John Sutton and Al Cymerman hosted a simulated ascent of Everest at the USARIEM. Included in that study were several measurements assessing \( \text{O}_2 \) transport. In particular, mixed venous \( \text{PO}_2 \) was measured at several “altitudes” (sea level, 6100 m and 7620 m) at/near maximal exercise, to provide essential inputs for calculating pulmonary \( \text{O}_2 \) diffusing capacity, but a remarkable, serendipitous observation was made: while both \( \dot{\text{VO}}_{2\text{max}} \) and mixed venous \( \text{PO}_2 \) fell (expected), it was how they fell—in direct proportion—that was remarkable. It later became clear that this reflected diffusion limitation of \( \text{O}_2 \) transport from muscle microvessels to the mitochondria, and that this “forgotten” last step in \( \text{O}_2 \) transport plays a major role in limiting \( \dot{\text{VO}}_{2\text{max}} \). Thus, how Habeler & Messner made it up the hill without bottled \( \text{O}_2 \) and no special cardiopulmonary attributes could be explained if their muscle \( \text{O}_2 \) diffusing capacity, which depends largely on muscle capillarity, was unusually high.

The Oelz paper mentions that muscle capillary density was substantially—40%—above normal, but they did not consider that this accounted for the climbers’ success. It seems likely that high muscle capillarity enhancing diffusive unloading of \( \text{O}_2 \) within the muscles was a major enabling physiological attribute for Habeler & Messner, and that Operation Everest II, by chance, played a key role in bringing this to light.

0830-0830  Iron and Oxygen—Peter Robbins

This presentation will give an overview of the body’s iron stores and the regulation of systemic iron homeostasis by hepcidin and ferroportin. This will be followed by an overview of the regulation of cellular iron content through the iron-response proteins (IRP1 and IRP2) and their effect on the transferrin receptor. There is a tight interplay between iron and oxygen homeostasis for both the systemic and the classical cellular regulatory processes and an overview of this will be given.

Following the introduction to iron homeostasis, a more detailed explanation of our recent findings defining an essential, cell-autonomous role for hepcidin and ferroportin in the regulation of cellular (cardiomyocyte) iron content (1, 2). Again, hypoxia plays a significant regulatory role in this process.

The presentation will finish with some of our recent work defining interactions between hypoxia and iron homeostasis and their effects on systems physiology. It will explore the period over which the administration of intravenous iron continues to affect the pulmonary vascular response to hypoxia (3). Finally, it will examine the influence of iron deficiency in young, otherwise healthy, individuals on the pulmonary vascular response to hypoxia (4) and on cardiac and metabolic function. This
will provide an introduction for some related research findings to be presented at this symposium.


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**0900-0930 Genomics of High Altitude Adaptation**—Rasmus Nielsen

In this talk I will discuss three genomic studies of altitude adaptation in Tibetans, Ethiopians, and Andeans. We have previously identified genes targeted by natural selection in Ethiopians and Tibetans. In Tibetans, genes associated with HIF signaling, in particular *EPAS1* and *EGLN1* show strong signals of selection. We have later shown that *EPAS1* was introgressed into the ancestors of Tibetans from Denisovans, a group of extinct hominins. In Ethiopians a different gene shows the strongest evidence of selection: *BHLHE41*. This gene is a regulator of HIF-1α. In a recent study, we have also scanned the genomes of an Andean population for evidence of natural selection. In contrast to Ethiopians and Tibetans, we do not find strong evidence of selection in genes related to the regulation of erythropoiesis. Instead, selection seems to have targeted various phenotypes that may mitigate potential deleterious effects of polycythemia.

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**0930-1000 Refreshment Break, Heritage Hall**
1000-1130
Hypoxia and Inflammation
Chairs: Heimo Mairbäurl and Tatum Simonson

1000-1030  Hypoxia Signaling during Mucosal Inflammation—Sean Colgan

Sites of inflammation are characterized by significant changes in metabolic activity. Recent studies have implicated a prominent role for oxygen metabolism and hypoxia in inflammation, so called “inflammatory hypoxia”, that results from a combination of recruited inflammatory cells (e.g. neutrophils and monocytes), the local proliferation of multiple cell types and the activation of multiple oxygen consuming enzymes during inflammation. Within the gastrointestinal mucosa, changes in microbial communities (i.e. the microbiota) associated with inflammatory disease can impact homeostatic metabolic mechanisms that influence tissue function. Such changes in energy supply and demand result in localized regions of hypoxia and have revealed a prominent role for the transcription factor hypoxia-inducible factor (HIF) in the regulation of key target genes that promote inflammatory resolution. Analysis of these pathways has provided multiple opportunities for understanding basic mechanisms of inflammation and has defined new targets for intervention. Here, we discuss recent work addressing tissue hypoxia and metabolic control of innate immunity.

1030-1100  Prolyl Hydroxylases as Mediators of Inflammatory Responses—Cormac Taylor

Hypoxia is a common and prominent feature in a range of physiologic and pathophysiologic niches that is now appreciated to play a determining role both in inflammation and immunity. Multiple immune and non-immune cell types display sensitivity to hypoxia. This is mediated through changes in gene expression driven by the hypoxia-inducible factor (HIF) and nuclear factor kappa B (NF-kB). Through these pathways, hypoxia has a profound impact on immunity, inflammation and the course of infection. Here, the mechanisms underpinning the immune response to hypoxia and the implications of this for inflammatory disease progression will be discussed. Furthermore, we will describe the potential for interference with hypoxia-sensitive pathways for the treatment of inflammatory disease.
Hypoxia-inducible factors (HIFs) such as HIF1α or HIF2α are stabilized during adverse inflammatory conditions including inflammatory bowel disease, infections with pathogens, acute lung injury, or during ischemia and reperfusion injury. While the mechanism that initiates HIF stabilization may be different for each condition, the final molecular steps that control HIF stabilization converge on a set of oxygen-sensing prolyl hydroxylases (PHDs). These enzymes mark HIFs for proteasomal degradation. Pharmacologic compounds that function to inhibit PHDs and promote HIF stabilization are available for the treatment of patients. Here, we discuss the functional role of HIF stabilization during myocardial ischemia and reperfusion injury. Several transcriptionally regulated signaling pathways have been implicated in mediating a protective role of HIF stabilization during myocardial injury. As such, purinergic signaling events involving the A2B adenosine receptor and further downstream targets have been implicated in cardio-protection provided by HIF1α. More recent studies also reveal a functional role of HIF2α in cardio-protection during ischemia and reperfusion injury of the heart. These studies suggest that HIF2α expressed in cardiac myocytes mediates cardio-protection via the induction of the HIF2 target gene amphiregulin and signaling events through growth factor receptors. We hope that in the future, these signaling events can be targeted for the prevention or treatment of myocardial ischemia and reperfusion injury. Pharmacologic targeting of PHDs and thereby enhancing HIFs can thus be useful for the treatment of acute inflammatory or ischemic diseases in order to dampen hypoxia-associated inflammation.
**DEVELOPMENTAL PROGRAMMING OF HYPOXIA-INDUCED PULMONARY VASCULAR DYSFUNCTION.**

**Julian, Colleen; Wolfson, Gabriel; Park, Do; Yang, Ivana; Schwartz, David**
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Perinatal exposures alter susceptibility to adult-onset disease. Since developmental processes that are required for efficient pulmonary gas transfer are incomplete at birth, the lung and its pulmonary circulation are particularly vulnerable. Our human studies demonstrate that perinatal hypoxia (PHx) raises the risk of chronic mountain sickness and attendant pulmonary vascular dysfunction (PVD) among male high-altitude residents. **OBJECTIVE:** To utilize a murine model in which the degree and timing of environmental hypoxia could be strictly controlled to directly test the hypothesis that PHx increases susceptibility to hypoxia-induced PVD during adulthood. **METHODS:** Experiments were performed using three groups of C57/BL6 mice distinguished by the timing of normoxic (Nx) or hypoxic (Hx) exposure: Nx controls (C-C), PHx + adult Hx (PHx-Hx) and perinatal Nx + adult Hx (C-Hx). For the perinatal normoxia and Hx (PHx or Hx), pregnant dams were placed in a hyperbaric(760mmHg) or hypobaric chamber (375mmHg) from gestational day 14 through postnatal day 4. All animals were housed in normoxia from postnatal day 5 to 3wks. Adult exposures lasted from 3-8 wks of age. Pulmonary hemodynamic (via echocardiography) and right ventricular systolic pressure (RVSP) measurements were performed in 8wk old offspring. Intracardiac blood samples were used to measure hematocrit. ANOVA with multiple comparisons was used to identify differences between groups. **RESULTS:** PHx reduced pulmonary artery acceleration time and pulmonary valve peak flow velocity, and increased RV wall thickness, RVSP and hematocrit in males only. **CONCLUSIONS:** Our studies demonstrate that PHx increases hypoxia-induced PVD, and that such effects are sex dependent. (Supported by 5 K12 HD057022-07). See poster W20.

**ACUTE XENON INHALATION STIMULATES PROLONGED ERYTHROPOIESIS**

**Lawley, Justin1,2; Gatterer, Hannes3; Howden, Erin1,2; Sarma, Satyam1,2; Cornwell 3rd, William1,2; Hearon Jr, Christopher1,2; Hieda, Michinari1,2; Hendrix, Max3; Piper, Thomas4; Thevis, Mario3; Bruick, Richard2; Levine, Benjamin1,2**
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**OBJECTIVE:** Xenon is an inhalation anesthetic with the potential to increase plasma erythropoietin (EPO). This study aimed to describe the efficacy of three subanesthetic dosages of xenon inhalation to cause erythropoiesis. **METHODS:** On three occasions, 7 (2 female) participants breathed three increasing but subanesthetic concentrations of xenon (Xenon, 30% for 20 min; Xenon, 50% for 5 min; Xenon, 70% for 2 min and oxygen, 21% with balance Nitrogen). Pulse oximetry documented the absence of hypoxemia in all trials (data not shown). EPO was measured in duplicate at rest, during xenon inhalation and then at 1, 3, 6, 24, 72, 192 hours post xenon inhalation. **RESULTS:** The technical error in our EPO measurement was 0.65 mU/mL with an estimated biological variability of 1.5 mU/mL over the three trials separated by at least 6 weeks. In all trials, EPO peaked 6 hours post xenon inhalation (30%, 6.4±2.1 to 10.9±6.8, P=0.10; 50%, 6.9±2.2 to 9.3±2.3, P=0.01; 70%, 6.2±3.0 to 8.4±3.2, mU/mL, P=0.13), thereafter trending downwards, yet remaining above baseline conditions for at least 24 hours post inhalation (24hours, 30%, 6.4±2.1 to 7.8±1.8, P=0.05; 50%, 6.9±2.2 to 8.4±2.3, P=0.01; 70%, 6.2±3.0 to 7.8±2.1, mU/mL P=0.06).
CONCLUSIONS: We show that three sub-anesthetic acute single dosages of xenon cause a small yet highly consistent pattern of erythropoiesis. Thus, despite the absence of hypoxia, xenon appears to stabilize hypoxia inducible factors and therefore has the potential to increase red cell mass and exercise performance. FUNDING: These studies were supported in part by funding from the Partnership for Clean Competition Research Collaborative. The content of this abstract does not necessarily reflect the views or policies of Research Collaborative. See poster F13.
Poster Session I

Poster Viewing:
1630-1830h

Location:
Mount Temple Ballroom C

When:
Wednesday, 8 February 2017

Poster session I includes many great posters. All posters will be available for viewing from 1630-1830h.

All Wednesday posters should be put up for viewing Tuesday evening, and should be taken down by late Wednesday evening.
**Abstract: W01**

**THE MULTI-FUNCTIONAL ROLE OF ERYTHROPOIETIN IN THE CARDIO-VENTILATORY SYSTEM**

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**OBJECTIVE:** Erythropoietin (Epo) has long been considered as a growth factor for erythropoiesis and a determinant factor for acclimatization to chronic hypoxia. However, Epo and its receptors (Epo-R) are expressed in many tissues suggesting other physiological roles than those usually assigned to this protein. Our aim was to elucidate other physiological role of Epo using a unique model of Epo-deficiency. **METHODS:** Experiments were performed in chronic Epo-deficient mice (Epo-TAg\(^b\)) and their control. Epo-TAg\(^b\) mice present a decrease of whole body Epo expression leading to a low plasma and brain Epo concentration, low haemoglobin concentration and low haematocrit. Physiological roles of Epo were highlighted by the use of classic methods of respiratory physiology (plethysmography, indirect calorimetry), immunohistochemistry and molecular biology (western blot, RT-PCR). **RESULTS:** High levels of Epo are not necessary for survival in chronic hypoxia but play a key-regulating role in the neural control of the hypoxic ventilatory response and ventilatory acclimatization to hypoxia. Epo-deficiency leads to cerebral and cardiac angiogenesis, which participate to neuro- and cardio-protection and \(O_2\) supply optimization, limiting the consequences of anemia on cerebral and cardiac cells. However, under both constraints (chronic Epo deficiency and hypoxia), angiogenesis, neuro- and cardio-protective pathways along with a functional LV adaptation failed to occur, showing the limits of these adaptive processes in heart and brain. Furthermore, Epo-deficiency does not alter the chemosensitivity to \(CO_2\). Chemodenervation had no effects on basal ventilatory parameters but abolished hypercapnic ventilatory response independently of Epo-deficiency. **CONCLUSION:** Our studies suggest a key role of Epo on main physiological adaptive functions. Thus, Epo play a key role in neural control of ventilatory acclimatization and response to hypoxia, in cerebral and cardiac angiogenesis and in neuro- as well as cardio-protection.

**Abstract: W02**

**2016 UBC NEPAL EXPEDITION: IRON AND THE PULMONARY VASCULAR RESPONSES DURING ASCENT TO 5050M: SHERPA AND LOWLANDERS COMPARED**

Willie, Christopher\(^1\); Plato, Sawyer\(^2\); Mcbride, Emily\(^2\); Varoli, Giovanfrancesco\(^2\); Stembridge, Mike\(^2\); Eller, Lindsay\(^2\); Hoiand, Ryan L\(^1\); Williams, Alex\(^1\); Gasho, Chris\(^4\); Subedi, Prajan\(^4\); Anholm, James\(^4\); Ainslie, Philip\(^1\)

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**INTRODUCTION:** People of Tibetan descent possess variants of genes that regulate the Hypoxia Inducible Factor (HIF) transcription system. As an obligate cofactor in the degradation of HIF mRNA, iron affects the sensitivity of the HIF system to hypoxia, which is the probable mechanism for the inverse relationship between iron status and hypoxic pulmonary vasoconstriction; indeed, progressively decreased iron status and increased pulmonary arterial systolic pressure (PASP) are hallmarks of ascent to high-altitude. **METHODS:** To determine the phenotypic differences in PASP responses and iron status between Sherpa and lowlanders during ascent to high-altitude, 21 lowlanders (BMI=23±2kg/m\(^2\)) and 12 Sherpa (BMI=24±4kg/m\(^2\)) were assessed prior to and during ascent to 5050m. Sherpa were de-acclimatized to 1400m over 5-15 days before both groups ascended over 10 days with measurements taken at 1400m, 3440m, 4371m and 5050m. Arterial and venous blood, blood pressure, heart rate, and PASP (echocardiography) were collected at each elevation. **RESULTS:** Blood pressure was greater in Sherpa until 5050m and remained unchanged during ascent, whereas in lowlanders it increased during ascent (P<0.05). Arterial pH was higher in lowlanders across all elevations; and, serum iron, total iron binding capacity (TIBC), transferrin saturation, and ferritin decreased during ascent (main effect, P<0.05). Ferritin was higher in Sherpa at each elevation (P<0.05),
whereas serum iron and transferrin saturation were higher in Sherpa at baseline and 3440m. Soluble transferrin receptor increased with ascent but did not differ between ethnicities. PASP increased during ascent in both groups and was lower in Sherpa at 3440m (P<0.05). CONCLUSION: Indices of iron status were greater, and PASP lower in Sherpa than lowlanders at baseline and 3440m suggesting an iron-pulmonary vascular relationship during acclimatization.

Abstract: W03

PHARMACOLOGICAL BUT NOT GENETIC ALTERATION OF NEURAL EPO MODIFIES CO2/H+ CENTRAL CHEMOSENSITIVITY IN POSTNATAL MICE AT BIRTH

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OBJECTIVE: The central chemosensitivity to CO2/H+ is considered essential for breathing during the maturation of the mammalian respiratory network. Besides, the neural erythropoietin (Epo) plays a crucial role in the mammalian brain maturation, and stimulates the hypoxic ventilatory response from the early ages by interacting with brainstem respiratory areas. Despite these evidences, we previously reported that neural Epo does not affect the CO2/H+ central chemosensitivity in mice after 10 postnatal days (P10). Such effect was observed in adult transgenic mice overexpressing Epo in brain only, and also in control juvenile (P10) and adult mice receiving an intra-cisternal injection of soluble Epo receptor (sEpoR, the endogenous antagonist of Epo). However, keeping in mind that the central sensitivity to CO2/pH during the mammalian respiratory network maturation is age-dependent, we wanted to test the hypothesis that at birth, the neural Epo is involved in the stimulation of breathing induced by the activation of central CO2/pH chemoreceptors.

METHODS: To this aim, we used transgenic mice that over- and under-express Epo in brain (Tg21 and Epo-TAg respectively) and their control. Ex vivo brainstem-spinal cord preparations isolated from newborn mice (P0-P4) were used and fictive breathing response to CO2-induced acidosis or metabolic acidosis was analyzed. RESULTS: There was no difference in the response to hypercapnia between preparations from control and transgenic mice. However, when the brainstem-spinal cord preparations of Tg21 mice were incubated with sEpoR or with ERK/Akt inhibitors (that block the activation of the Epo pathway), the chemosensitivity was blunted. CONCLUSIONS: We conclude that pharmacological but not genetically alteration of neural Epo signalization modifies the CO2/H+ central chemosensitivity in postnatal mice and that variation of the Epo/sEpoR ratio is crucial in the modulation of breathing. ACKNOWLEDGEMENTS: Univ Laval, Univ Paris 13, Labex GR-Ex and Legs Poix, Chancellerie des Univ Paris (Legs 1504, 1022).

Abstract: W04

SPINAL OXYGEN SENSORS (SOS): COUNTERING HYPOXIA AND SURVIVING SIDS.

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BACKGROUND: Hypoxia associated with cardiorespiratory crisis initiates vigorous respiratory and sympathetic “fight/flight” responses. The carotid bodies are the main respiratory oxygen sensors but sympathetic responses persist after denervation, suggesting a cardiovascular-specific oxygen chemoreceptor. Recently, in an anesthetized artificially ventilated, vagotomized, cardiac depressor nerve cut and carotid body denervated in vivo rat preparation, we discovered that thoracic preganglionic sympathetic neurons in the intermediolateral (IML) nucleus of the thoracic spinal cord, are highly responsive to oxygen without descending input from the brainstem. To eliminate the possibility that responses to hypoxia were triggered by circulating neuromodulators, we developed an artificially-perfused thoracic spinal cord preparation consisting of the dorsal sections of the ribs, descending aorta and spine (heart, lungs, brainstem, cervical and lumbar spinal cord were removed). Sympathetic (splanchnic) activity retained exquisite oxygen sensitivity. The spinal oxygen sensors (SOS) appear more sensitive than the carotid body in the hypoxic range; only when hypoxia is severe is the sensitivity of carotid bodies greater. Since 70% of SIDS cases have
anatomical abnormalities in the IML, we hypothesized that SOS are important in preventing SIDS. **METHOD:** We developed a neonatal artificially-perfused thoracic spinal cord preparation and tested the sympathetic response to changes in perfusion PO2 (5 min bouts of 400, 300, 200, 100, 60 PO2; returning to 560 Torr PO2 between bouts). **RESULTS:** Splanchnic activity increased as perfuse PO2 decreased. Responses were detectable at 300 Torr and increased to 60 Torr. **CONCLUSIONS:** SOS are present in neonates. As sympathetic-mediated responses are likely to be critical in protecting vital organs during asphyxia, we conclude that the SOS likely play an important role in preventing neonatal death. Consequently, a dysfunctional SOS system may increase the likelihood of SIDS.

**Abstract: W05**

**CAROTID CHEMORECEPTOR CONTROL OF CARDIOVASCULAR FUNCTION AT REST IN COPD**

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**INTRODUCTION:** COPD patients have increased sympathetic nerve activity (SNA) and central arterial stiffness, both of which are linked to cardiovascular (CV) deterioration, and increased mortality. We have recently demonstrated enhanced activity/sensitivity of the carotid chemoreceptor (CC) in COPD which contributes to increased SNA and peripheral arterial stiffness. Thus, the CC may play an important role in CV regulation in COPD. We hypothesized that CC inhibition would reduce central arterial stiffness and improve CV function in COPD. **METHODS:** Twelve non-hypoxemic mild-moderate COPD patients (mean FEV1±SD: 84±13% predicted) and six risk-matched controls completed 1) cardiopulmonary exercise test, 2) basal CC activity/sensitivity assessment and 3) resting CV function measurements with either intravenous (I. V.) saline or low dose I. V. dopamine (2 mg/kg/min) while breathing normoxia or 100% O2. Ventilation was evaluated by expired gas data and central arterial stiffness was determined by pulse wave velocity (PWV). Brachial blood flow was determined using Doppler ultrasound, cardiac output (Q) was estimated by impedance cardiography, and vascular conductance was calculated as flow/mean arterial pressure (MAP). **RESULTS:** CC inhibition using either hyperoxia or dopamine decreased ventilation (p<0.05) in COPD, while no change was observed in controls. MAP was reduced with dopamine in COPD (p<0.05), but not with hyperoxia. No change in MAP was observed in controls between conditions. Central PWV was not different between conditions within either group. Brachial and total vascular conductance were increased with dopamine in COPD (p<0.05) secondary to a reduction in blood pressure (p<0.05), while no change was observed in controls. Hyperoxia had no effect on conductance or blood pressure in either group. **CONCLUSION:** CC inhibition with dopamine improved conductance in COPD, suggesting that the CC is active at rest in COPD and contributes to tonic vasoconstrictor outflow.

**Abstract: W06**

**EXERCISE INTOLERANCE AT EXTREME ALTITUDE**

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**INTRODUCTION:** The factors limiting exercise tolerance at extreme altitude remain controversial. Breath by breath incremental exercise tests to the limit of tolerance allow the objective determination of exercise capacity. They also provide insight into the cause of exercise intolerance. We set out to interrogate the exercise response at extreme altitude for evidence of ventilatory or cardiac limitation. **METHODS:** Fourteen healthy climbers performed incremental exercise tests to the limit of tolerance in London, Pheriche (4200m), Everest Base Camp (EBC) (5300m) the Western Cwm (6400m) and in a subgroup of 5 at the South Col (7950m)(Metamax 3B, Cortex, Germany). They followed an identical ascent profile and took no propylactic medication. Spirometry was performed and MVV was measured directly using an ultrasonic flowmeter which has been validated at altitude (Easy-One™, USA). **RESULTS:** The LaT and VO2 peak both progressively decreased with altitude. The VO2 peak was fell more than the LaT and this difference was more pronounced at higher altitudes: 32.5 vs 27.2% reduction at 5300m and 56 vs 46% at 8000m for VO2 peak and LaT respectively. After prolonged altitude exposure (2 months >/= 5300m), the LaT improved by 1ml/kg and the work rate at LaT was preserved but there was no improvement in VO2 peak and the peak work rate decreased. There was no evidence of ventilatory limitation at altitudes up to 8000m. In two of 5 individuals at
8000 metres the oxygen pulse flattened with a compensatory tachycardia towards peak exercise suggesting either stroke volume limitation or oxygen extraction limitation. **CONCLUSIONS:** The lactate threshold was preserved relative to \( \text{VO}_2\text{peak} \) at extreme altitude. There was a suggestion of cardiac limitation at peak exercise at 8000m in 2 of 5 subjects. There was no evidence of reduced breathing reserve as a cause of exercise intolerance at extreme altitude.

**Abstract: W07**

**CHANGES IN THE LACTATE THRESHOLD ESTIMATED FROM PULMONARY GAS EXCHANGE INDICES AT ALTITUDE**

Levett, Denny Zh; Leury, Helen; Morgan, Gwen; Martin, Daniel S; Mitchell, Kay; Ward, Susan A; Grocott, Michael Pw; Caudwell Xtreme Everest, Research Group

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**INTRODUCTION:** There is marked inter-individual variability in performance at altitude. Assessment of lactate threshold (LaT) permits partitioning of exercise between moderate and heavy intensity domains. Exercise below LaT is sustainable and thus preservation of the LaT might be expected to preserve sustainable performance. Changes in LaT at altitude have not been widely investigated and report conflicting results. We evaluated changes in LaT and maximum exercise capacity in a large group of healthy volunteers with a standardized ascent profile to 5300m. **METHODS:** 198 healthy volunteers underwent maximal incremental exercise testing (Metamax 3B, Cortex, Germany) in London, Namche 3500m and Everest Base Camp (EBC) 5300m. All subjects followed an identical 11-day ascent profile. LaT was identified from expired gas analysis using the modified V-Slope method and confirmed from profiles of ventilatory equivalents and end tidal oxygen response. **RESULTS:** 182 subjects reached EBC. This analysis was performed on the 148 subjects tested at all altitudes. LaT and \( \text{VO}_2\text{peak} \) progressively decreased to -27.2% (12) and -32.5% (9.1) respectively at 5300m when compared to sea level values (repeated measures ANOVA p<0.001). There was variability in the decrements in both LaT (range 5.3-59%) and \( \text{VO}_2\text{peak} \) (range 12.7-55%). At 3500m and 5300m the \( \text{VO}_2\text{peak} \) decreased more than the LaT. LaT occurred at 60.2% of \( \text{VO}_2\text{peak} \) at sea level, 61.1% of \( \text{VO}_2\text{peak} \) at 3500m and 64.5% of \( \text{VO}_2\text{peak} \) at 5300m resulting in a reduction in Delta (the difference between and LaT) at altitude (repeated measures ANOVA p<0.001). There were no gender difference in the changes observed. **CONCLUSIONS:** There is variability in the decrement in exercise capacity observed at altitude. The LaT is better preserved than \( \text{VO}_2\text{peak} \) above 5300m. This may explain some of the variability in exercise performance above 5300m.

**Abstract: W08**

**ESTIMATING THE ARTERIAL LACTATE THRESHOLD DURING EXERCISE AT ALTITUDE USING PULMONARY GAS EXCHANGE INDICES**

Levett, Denny Zh; Martin, Dan S; Duncan, Polly; Montgomery, Hugh E; Ward, Susan A; Grocott, Mike Pw; Caudwell Xtreme Everest, Research Group

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**INTRODUCTION:** Arterial lactate threshold (LaT) can be measured directly from the \([\text{lactate}]\)-response or reliably estimated (at sea-level) using expired gas analysis. This technique has not been validated at altitude and may be inaccurate. We evaluated the relationship between directly measured LaT and estimated LaT from pulmonary gas exchange (LaTge) at sea level and 5300m. **METHODS:** Five healthy volunteers performed incremental ramp tests at sea level, and after 24 hours and 59 days at 5300m (Metamax 3B, Cortex, Germany). Radial arterial blood samples were taken every minute during unloading cycling and every 15 seconds during the incremental ramp and analysed using a calibrated and validated hand-held lactate monitor (Lactate Scout, SensLab, Germany). LaTge was identified using the V-slope method and confirmed using ventilatory equivalents (VE) for \( \text{O}_2 \) and \( \text{CO}_2 \). Directly-measured LaT was determined from the log arterial \([\text{lactate}]\)-log transformation as the point of the departure from baseline arterial \([\text{La}]\) values occurring with a systematic increase in arterial \([\text{La}]\). **RESULTS:** LaT estimation the using the v-slope method discriminated in all subjects at sea level and altitude. The VE method identified a threshold that agreed with the v-slope method in all subjects at sea level but did not identify a threshold in 5 of 10 tests at altitude. ATgge was determined using the v-slope and VE when there was agreement between the methods, otherwise the v-slope was used alone. There was good agreement between LaT and ATgge at sea-level (mean difference 28ml; SD difference 73ml) and at 5300m (mean difference 34ml; SD difference 117ml). **CONCLUSIONS:** Expired gas analysis provides a valid non-invasive estimate of the arterial lactate threshold at altitude. The v-slope method of LaT determination provides a more accurate estimate than the ventilatory equivalents method.
Abstract: W09

DYNAMIC PULMONARY FUNCTION TESTS AS A PREDICTOR OF ACUTE MOUNTAIN SICKNESS

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BACKGROUND: The flow and volume metrics of pulmonary function have been found to vary with ascent to high altitude and acute mountain sickness (AMS). This study aimed to corroborate prior findings and determine whether the pathophysiological changes associated with acute AMS were reflected in pulmonary function tests (PFT).

METHODS: The study was conducted as part of a randomized controlled trial comparing budesonide to acetazolamide to placebo for the prevention of AMS in August 2016. Healthy adults were enrolled at 1,240 m (4,100 ft), drove to 3,545 m (11,700 ft), then hiked to and slept at 3,810 m (12,500 ft). PFTs were measured using standard techniques with a portable pneumotachometer at low altitude and again at sleeping altitude the evening of and morning after ascent. The device was calibrated before each round of measurements.

RESULTS: 103 participants were enrolled with well-matched baseline demographics (p > 0.09) with no significant differences between the drugs and control groups at both baseline and change on ascent for incidence of AMS (p > 0.05). Total AMS incidence was 73%. Examining the entire cohort as a single group, there were no significant changes in peak expiratory flow (PEF), forced expiratory volume in one second (FEV1), or forced vital capacity (FVC) on ascent or in those diagnosed with AMS. Predictive ensemble methods had a 68–72% accuracy overall for predicting AMS from low altitude baseline, with PEF the most important variable (ROC = 0.65).

CONCLUSION: Rapid ascent to high altitude did not impact dynamic pulmonary function within the first 24 hours of exposure. Pulmonary function testing overall had a weak prediction for the development of AMS, with peak expiratory flow being the most predictive variable that showed promising accuracy using an ensemble learning approach.

FUNDING SOURCES: American Alpine Club, Institute for Altitude Medicine, WMS Herbert N. Hultgren Grant.

Abstract: W10

PRESENCE OF COMET TAILS DURING ACTIVE ACCLIMATIZATION TO HIGH ALTITUDE

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Comet tails have been used clinically and at altitude as an index of increases in extravascular lung water (EVLW). Previous studies have suggested that mild increases in EVLW may be common with altitude. However, our work has suggested that EVLW more typically remains unchanged or decreases with normobaric and hypobaric hypoxia. We aimed to determine how the presence of comet tails changed throughout acclimatization to high-altitude and the relationship with other symptoms. 14 younger (6F; 32±6y) and 12 older (4F; 58±5y) individuals climbed Mount Kilimanjaro over 11 days. Testing was performed pre-trek, day 0 (Moshi; 950m), day 3/4 (Shira; 3505m), day 8/9 (Barafu; 4837m), and post-trek, day 12/13 (Moshi). Comet tails (CT) were counted in 28 echocardiographic windows using a Philips Lumify linear probe and totaled. Participants were grouped into those with (≥5) or without (<5) CT for each test. Resting pulmonary pressures, PETCO2, SaO2, lung function, and AMS were also collected. Older individuals tended to have more CT than younger individuals at altitude; this nearly reached statistical significance at Barafu (young 21% vs. old 44%, p=0.058). However, >15 CT, indicative of at least moderate EVLW, was only observed twice. Additionally, those individuals who had CT was inconsistent throughout the climb; while 12 participants showed CT at some point, only 4 showed CT at two camps and 2 showed CT at three camps. Furthermore, the CT were not related to pulmonary pressures, PETCO2, SaO2, lung function, or AMS at any camp. In conclusion, while older adults may develop more CT at altitude, there is minimal evidence of increases in EVLW in acclimatizing adults. Furthermore, the presence of CT does not coincide with altitude-related physiological changes or symptoms, including increased pulmonary pressures, decreased saturation, worsened lung function, or AMS. This study was funded by Thorne Research, Philips, and The North Face.
Abstract: W11

**MEDEX 2015: POSITIVE EXPIRATORY PRESSURE IMPROVES OXYGENATION AND SYMPTOMS AT HIGH ALTITUDE**

**INTRODUCTION:** Breathing with a positive expiratory pressure (PEP) has been shown to increase arterial oxygenation during acute hypoxic exposure but the underlying mechanisms and consequences on symptoms during prolonged sojourn at high altitude remain to be elucidated. **METHODS:** Twenty four males (mean(SD): age 41(6) yrs) were investigated twice: i) at sea level, and ii) the day after arrival at 5100 m after trekking for 10 days from 500 m. Participants layed down for 90 min, while breathing through a face mask with PEP=0 cmH₂O (PEP₀, 0-45 min) and with PEP=10 cmH₂O (PEP₁₀, 46-90 min). During PEP₀ and PEP₁₀, arterial (SpO₂, pulse oximetry), quadriceps and prefrontal (near infrared spectroscopy) oxygenation, middle cerebral artery blood velocity (MCAv, transcranial Doppler), cardiac function (2D-echocardiography), extravascular lung water accumulation (UsLC, thoracic ultrasound lung comets) and symptoms of acute mountain sickness (Lake Louise score) were assessed.

**RESULTS:** At 5100 m with PEP₀, SpO₂ was 78(4)%%, UsLC was 8(5) and the Lake Louise score was 2.3(1.7) points (all p<0.05 versus sea level). At high altitude, PEP₁₀ increased SpO₂ (+9(5)%%, quadriceps (+3(1)%%) and prefrontal cortex (+1(2)%%) oxygenation (all p<0.05), but decreased mean MCAv (-16±14 cm. s⁻¹, p<0.001) and reduced cardiac output (-0.7(1.2) L. min⁻¹, p=0.01) due to a decreased stroke volume (-9(15) mL, p=0.01). The number of UsLC was slightly decreased (-1(3), p=0.08) while Lake Louise score decreased significantly (-0.5(1.3) points, p=0.04), with the incidence of acute mountain sickness (Lake Louise score ≥3 points) being 42% with PEP₀ (10/24) and 25% with PEP₁₀ (6/24). **CONCLUSION:** PEP breathing improved arterial and tissue oxygenation and decreased symptoms of acute mountain sickness after prolonged exposure to high altitude, together with cerebral perfusion and cardiac performance alterations. The PEP₁₀-induced improvement in SpO₂ corresponds to an altitude drop of ~1500 m.

Abstract: W12

**IS THERE EVIDENCE OF PRECAPILLARY PULMONARY GAS EXCHANGE?**

**INTRODUCTION:** Pulmonary gas exchange is hypothesized to occur proximal to the pulmonary capillary. We used the multiple inert gas elimination technique (MIGET) and blood gas measurements to simultaneously compare inert gas (IG) and O₂ exchange in the distal pulmonary artery. **METHODS:** In steady-state, simultaneous blood samples were obtained from five anaesthetized, ventilated dogs from a: 1) femoral arterial catheter, ARTERIAL, 2) 7 Fr. Swan-Ganz catheter advanced 3-5 cm into the main pulmonary artery, PROXIMAL, and 3) separate 5 Fr. Swan-Ganz catheter advanced to the wedged position and then retracted 1cm, DISTAL. Inert gas concentrations within each sample were normalized to PROXIMAL, which represents mixed venous blood entering the pulmonary artery. DISTAL samples showing inert gas concentrations below that of ARTERIAL, suggesting retrograde flow and capillary blood sampling, were not analyzed. **RESULTS:** As expected, ARTERIAL blood showed little retention of the low-solubility inert gases, with 2.9% of SF6 and 18.7% of ethane retained. DISTAL concentrations, while much higher, were significantly less than PROXIMAL, by 17.6% (SF6) and 18.1% (ethane), indicating either some excretion of inert gas across small pulmonary arteries, or aspiration of some capillarized blood. Similarly, hemoglobin O₂ saturation (SO₂) obtained from DISTAL (SO₂ = 76.0%) was higher than from PROXIMAL (70.9%). The relative changes in [IG] and SO₂ from PROXIMAL to DISTAL were similar, suggesting that pre-capillary gas exchange, if occurring, affected IG and O₂ similarly. In addition, ARTERIAL O₂ concentration predicted by MIGET was not significantly different than measured. **CONCLUSION:** These results suggest that either there is inert gas excretion and O₂ exchange across small pulmonary arteries proximal to the pulmonary capillary or that the sampling procedure aspirated some capillarized blood. In either case, gas exchange across the lung for O₂ and IG are similarly affected.
INTRODUCTION: Pre-term birth can induce lifelong pulmonary system sequelae and compromise ventilatory control. While blunted hypoxic ventilatory response (HVR) is consistently reported in pre-term infants, it remains unclear if HVR impairment persists with aging. We investigated potential differences in HVR responses during both rest and exercise between pre-term born adults and their age matched full-term controls. METHODS: Twenty-one pre-term (age = 21 ± 2 yrs.; gestational age = 29 ± 3 weeks (mean ± SD)) and 14 full-term born individuals (age = 21 ± 2 yrs.; gestational age = 39 ± 1 weeks) underwent the Richalet hypoxia sensitivity test. The protocol comprised of the following four phases, each lasting 4-minutes: rest in normoxia, rest in normobaric hypoxia (FiO\textsubscript{2} = 0.11; P\textsubscript{O\textsubscript{2}} = 77 mmHg), exercise in hypoxia, and exercise in normoxia. During the exercise phases, the mechanical power of the cycle ergometer was adjusted at the start of the hypoxic cycling phase to attain the heart rate of 120 -130 bpm and was then kept constant. The changes in ventilation and capillary oxygen saturation between the resting and exercise phases were used to calculate the resting (HVR\textsubscript{r}) and exercise (HVR\textsubscript{e}) ventilatory responses. RESULTS: Lower HVR\textsubscript{r} was observed in pre-term (0.21 ± 0.21 L·min\textsuperscript{-1}·kg\textsuperscript{-1}) as compared to full-term born individuals (0.47 ± 0.23 L·min\textsuperscript{-1}·kg\textsuperscript{-1}; p < 0.05). Conversely, no differences were noted in the HVR\textsubscript{e} between the two cohorts (Pre-term = 0.62 ± 0.23; Full-term: = 0.70 ± 0.20; p = 0.29). CONCLUSIONS: Our data indicate that in prematurely born individuals, the blunted hypoxic ventilatory response at rest persists into adulthood. Interestingly, reduced ventilatory response to hypoxia is not evident during moderate intensity exercise. ACKNOWLEDGEMENTS: Funded by Slovene Research Agency (Grant Nr-J3-7536) and Ljubljana Univ Medical Centre (Grant Nr-TP20140088).
Abstract: W15

DOES HYPOXIC VENTILATORY RESPONSIVENESS PREDICT ARTERIAL OXYGENATION ON THE SUMMIT OF MOUNT EVEREST?

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A high hypoxic ventilatory response (HVR), which better defends arterial oxygenation (3), may facilitate successful ascent to extreme altitude by lowland mountaineers. Alternatively, an elevated HVR may compromise oxygenation through ventilatory-mechanical limitation and dypnoea (1). Having previously reported arterial blood-gas and acid-base status on the summit ridge of Mount Everest (8,400 m, 27,559 ft) (2), we therefore investigated whether “summit” arterial $\text{PO}_2$ ($\text{PaO}_2$) correlated with sea-level HVR. Arterial blood-gas and acid-base status was measured in 4 high-altitude air-breathing climbers at 8,400 m after summiting. HVR was determined (isocapnic hypoxic rebreathing) in London (75 m) as the ventilation-$\text{O}_2$ saturation (oximetry) response slope ($\Delta V_T/\Delta \text{SaO}_2$) and the curvature constant (A) of the hyperbolic $V_T$-end-tidal $\text{PO}_2$ ($P_{ET\text{O}_2}$) relationship. $\text{PaO}_2$ ranged from 19.1 to 29.5 mm Hg, and A and $\Delta V_T/\Delta \text{SaO}_2$ from 56.9 to 183.0 mm Hg×l×min$^{-1}$ and 0.002 to -1.873 l×min×%$^{-1}$ (i.e. low to high HVR). There was a nonsignificant tendency for HVR to associate with $\text{PaO}_2$: $\text{A} = 8.77 \times \text{PaO}_2 - 68.69$ (R = 0.386); $\Delta V_T/\Delta \text{SaO}_2 = -0.094 \times \text{PaO}_2 +1.03$ (R = -0.576). Our results are cautiously suggestive of a role for HVR in defending $\text{PaO}_2$ at very high altitudes, recognising the limitation imposed by the small sample size and subject to the proviso that sea-level HVR approximates HVR at 8,400 m, which has been reported to be the case at 5,400 m (3).

REFERENCES:

Abstract: W16

VENTILATORY ACCLIMATIZATION IS SUSTAINED DURING REINTRODUCTION TO ALTITUDE FOLLOWING 12 DAYS AT SEA LEVEL

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This study examined whether ventilatory acclimatization can be sustained during re-introduction to altitude (RA) after 12 days at sea level (SL) using intermittent normobaric hypoxia (NH) treatment. Seventeen SL residents (M=11, F=6, age=23±6yrs; mean±SE) completed: 1) 4d of baseline SL (50m) testing, 2) 12d of altitude acclimatization at 4300 m on Pikes Peak (CO), 3) 12d at SL with and without NH treatment and 4) a 24-hour RA (hypobaric chamber; 4300 m). After acclimatization and return to SL, each received either NH (n=9, $\text{FiO}_2=0.122$) or SHAM (n=8; $\text{FiO}_2=0.209$) treatment for 3 hrs/day for 9 of the 12 days. Resting ventilation, as measured by end-tidal carbon dioxide pressure ($P_{ET\text{CO}_2}$) and arterial oxygen saturation ($\text{SaO}_2$), was assessed at SL, on d2, d6 and d11 of acclimatization at 4300 m and after the 20th hour of RA. Since there were no significant differences in ventilatory outcomes between NH and SHAM treatment, data from both groups were combined. $P_{ET\text{CO}_2}$ (mmHg) decreased (P<0.05) from SL (37.2±0.5) to d2 (32.2±0.6), d6 (28.8±0.6) and d11 (27.1±0.4) at 4300 m. $\text{SaO}_2$ (%) decreased (P<0.05) from SL (97±0.3) to d2 (81±1.1) and increased (P<0.05) on d6 (84±0.5) and d11 (87±0.5) at 4300 m. During RA, $P_{ET\text{CO}_2}$ (29.3±0.6) and $\text{SaO}_2$ (87±0.5) were similar to their full acclimatization values on d11 at 4300 m. These results demonstrate that the ventilatory acclimatization achieved after 12 days at 4300 m is retained during RA at 4300 m after 12 days at SL regardless of NH treatment. The views expressed in this abstract are those of the authors and do not reflect the official policy of the Dept Army, Dept Defense, or the U. S. Government.
OLDER SUBJECTS DEMONSTRATE INCREASED VENTILATORY RESPONSES TO EXERCISE AT ALTITUDE

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INTRODUCTION: High altitude exposure results in hypoxia and a hyperventilatory response, particularly during exercise. Recent evidence suggests that older individuals have an augmented hypoxic ventilatory response (HVR) which may help minimise the oxygen desaturation often associated with exercise at high altitude. However, aging is also associated with changes in lung mechanics and gas-exchange surface area which may affect oxygen desaturation. This study investigated the degree of oxygen desaturation during exercise in young and older adults at altitude. We hypothesised that during submaximal exercise, a greater HVR may prevent greater desaturation in older subjects. METHODS: 14 young (YG:31±6yr) and 13 old (OG:58±5 yr) non-acclimated individuals completed a 10-day ascent of Mt Kilimanjaro. Exercise testing (4-minute step test at 60, 90, 120 and 150 steps/minute) with gas-exchange was completed at the following altitudes: (1)850m; (2)3505m; (3)4837m. We measured the HVR from the ratio of the increase in \( \frac{V_e}{\Delta V_e} \) to the decrease in oxygen saturation (\( \Delta S_O_2 \)) with altitude during exercise at the same intensity. RESULTS: The nadir \( S_O_2 \) (%) achieved during exercise was similar for both young and old groups during the ascent (850m, YG:96±2; OG:96±3; 3505m, YG:86±3; OG:83±6; 4837m, YG:76±5, O:77±2). At a fixed exercise intensity, older subjects had a significantly (P<0.01) higher (\( V_e \)) to carbon dioxide (\( CO_2 \)) ratio (\( \frac{V_e}{CO_2} \)) 850m, YG:29.8±2.4, OG:32.6±3.3; 3505m, YG:34.3±2.8, OG:37.8±2.6; 4837m, YG:45.0±3.1, OG:51.3±5.0) and a significantly lower (P<0.01) end tidal carbon dioxide (\( P_{ET,CO_2} \) mmHg, 850m, Y:31.8±3.1; O:30.5±3.0; 3500m: Y:27.9±1.8; O:26.0±2.0; 4840m: Y:21.2±1.3; O:19.0±1.3). HVR was significantly higher (P<0.05) for older (2.0±1.6 L. min\(^{-1}\) kg\(^{-1}\)) compared to the younger (1.1±2.2 L. min\(^{-1}\) kg\(^{-1}\)) subjects. CONCLUSIONS: Whilst older subjects had the same degree of exercise induced desaturation with altitude exposure as younger subjects, they demonstrated a more pronounced ventilatory response. Our results are consistent with the hypothesis that aging is associated with a greater HVR that may help prevent further desaturation at altitude.

BREATH-HOLD DURATION AND CHEMOREFLEX DRIVE DURING HIGH ALTITUDE ASCENT

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INTRODUCTION: Breath-holding duration (BHD) is influenced by cognitive factors, lung stretch and respiratory chemoreceptor activation. Breath-holding stimulates central (\( CO_2 \)) and peripheral (\( O_2 \) and \( CO_2 \)) respiratory chemoreceptors, increasing the chemoreflex drive to breathe. However, the extent that prevailing \( CO_2 \), \( O_2 \) and steady-state chemoreflex drive (SS-CD) determine BHD is unclear. We tested the relationship between an index of SS-CD and BHD during ascent to high altitude. We hypothesized that voluntary BHD would be progressively reduced and negatively correlated with altitude and SS-CD magnitude during ascent, suggesting a role of chemoreceptor activation in determining BHD. METHODS: Nine healthy participants (26.8±8.1yrs) ascended to 4370m over seven days in Nepal. Using a calibrated pneumotachometer, pulse oximeter and capnograph on rest days at 1045m, 3440m, 3860m and 4370m in heated lodges, we measured ventilation (\( V_e \) L/min), peripheral oxygen saturation (\( Sp_O_2 \) %) and the pressure of end-tidal (\( P_{ET,CO_2} \) Torr). An index of resting SS-CD was calculated as \( V_e \) divided by a chemoreceptor stimulus index (SI; \( P_{ET,CO_2}/Sp_O_2 \) Torr/%). A maximal total lung capacity breath-hold was then performed at each altitude. RESULTS: Voluntary BHD was inversely correlated with altitude (\( r=-0.69, P<0.0001 \); Spearman’s Rho) and decreased with ascent: 1045m=54.6±4s; 3440m=39.7±2.1s; 3860m=34.8±1.5s; 4370m=33.1±1.4s (P<0.001; 1F RM ANOVA). SS-CD was positively correlated with altitude (\( r=0.68, P<0.0001 \); Spearman’s Rho) and increased with...
ascent: 1045m=30±1.5L/min/SI; 3440m=55.8±4.8L/min/SI; 3860m=56.7±4.2L/min/SI; 4370m=62.85±4.5L/min/SI (P<0.0001; 1F RM ANOVA). BHD was negatively correlated with SS-CD magnitude during ascent (r=0.59, P<0.001; Pearson r).

CONCLUSIONS: Using a novel method to assess overall steady-state chemoreflex drive, our data suggest that the background chemoreflex drive contributes to BHD during acclimatization to high altitude. This is the first clear demonstration of a role of central and peripheral chemoreceptors in determining breath-hold duration at altitude, where concomitant hypoxia and hypocapnia have competing effects on the chemoreflex control of breathing.

Abstract: W19

NOVEL IMAGE ANALYSIS DETECTS INCREASED ANATOMIC DEAD SPACE IN A MURINE MODEL OF ACUTE LUNG INJURY

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BACKGROUND: Increased physiological dead space is an important prognostic marker in early acute respiratory distress syndrome (ARDS) that correlates with mortality. The cause of increased dead space has been largely attributed to increased alveolar dead space due to ventilation/perfusion mismatching and shunt. We sought to determine if anatomical dead space also contributes to increased physiological dead space. METHODS: Mice received intratracheal LPS or saline and mechanical ventilation (MV) to induce the development of acute lung injury. Four-dimensional computed tomography (4DCT) scans were performed at onset of MV and after 5 h of MV. Detailed measurements of airway volumes and lung tidal volumes were performed using image analysis software. The forced oscillation technique was used to obtain measures of airway resistance ($R_{aw}$), tissue damping ($G$) and tissue elastance ($H$).

RESULTS: The ratio of airway tidal volume to total tidal volume increased significantly in response to mechanical ventilation ($p<0.001$), regardless of LPS exposure. These finding were associated with an increase in tissue elastance ($p= .04$). CONCLUSIONS: Airway tidal volumes increased with the development of increased tissue elastance following acute lung injury. These findings suggest that the increase in physiologic dead space seen in ARDS may be, in part, attributable to increased anatomical dead space. Further research will be needed to dissect the relative contributions of alveolar and anatomic dead space in ARDS and the mechanisms and prognostic value for each.

Abstract: W20

DEVELOPMENTAL PROGRAMMING OF HYPOXIA-INDUCED PULMONARY VASCULAR DYSFUNCTION

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Perinatal exposures alter susceptibility to adult-onset disease. Since developmental processes that are required for efficient pulmonary gas transfer are incomplete at birth, the lung and its pulmonary circulation are particularly vulnerable. Our human studies demonstrate that perinatal hypoxia (PHx) raises the risk of chronic mountain sickness and attendant pulmonary vascular dysfunction (PVD) among male high-altitude residents. OBJECTIVE: To utilize a murine model in which the degree and timing of environmental hypoxia could be strictly controlled to directly test the hypothesis that PHx increases susceptibility to hypoxia-induced PVD during adulthood. METHODS: Experiments were performed using three groups of C57/BL6 mice distinguished by the timing of normoxic (Nx) or hypoxic (Hx) exposure: Nx controls (C-C), PHx + adult Hx (PHx-Hx) and perinatal Nx + adult Hx (C-Hx). For the perinatal normoxia and Hx (PHx or Hx), pregnant dams were placed in a hyperbaric(760mmHg)or hypobaric chamber (375mmHg)fromgestational day 14 through postnatal day 4. All animals were housed in normoxia from postnatal day 5 to 3wks. Adult exposures lasted from 3-8 wks of age. Pulmonary hemodynamic (via echocardiography) and right ventricular systolic pressure (RVSP) measurements were performed in 8wk old offspring. Intracardiac blood samples were used to measure hematocrit. ANOVA with multiple comparisons was used to identify differences between groups. RESULTS: PHx reduced pulmonary artery acceleration time and pulmonary valve peak flow velocity, and increased RV wall thickness, RVSP and hematocrit in males only. CONCLUSIONS: Our studies demonstrate that PHx increases hypoxia-induced PVD, and that such effects are sex dependent. (Supported by 5 K12 HD057022-07).
**Abstract: W21**

**RIGHT HEART FUNCTION AND PULMONARY PRESSURE IN ASTHMA PATIENTS DURING 17 DAYS AT HIGH-ALTITUDE**

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**STUDY OBJECTIVES:** Asthmatics may benefit from the climate and reduced allergens at altitude. But the hypoxic environment may also be associated with adverse health effects, such as right heart strain due to increased pulmonary artery pressure (PAP), especially during the first days. We studied the right ventricular function (RVF) and SpO2 at lowland, immediately after arrival at 3200m and after 17 days at that altitude in asthmatics. **METHODS:** Twenty-two asthmatics (living<800m, mean±SD age 44±12y, FEV1 92±19%predicted) who participated in a three-week rehabilitation program at the Tuja Ashu High Altitude Clinic, 3200m, were assessed before departure in Bishkek (Kyrgyzstan, 760m) and on the 2nd and 18th day at 3200m. The RVF was assessed by several echocardiographic indices: tricuspid annular plane systolic excursion (TAPSE), tricuspid annular systolic velocity (TASV), mean (m) PAP, stroke index (SI), and cardiac index (CI). SpO2 was measured by pulse oximetry. **RESULTS:** The mPAP (mean±SD) was 13.5±5.4mmHg at 760m, 18.5±5.5mmHg after one and 18.2±5.5mmHg after 17 nights at 3200m (p<0.01 vs. 760m, p=ns at altitude). Heart rate was 72±11/min, 75±9/min, 79±9/min (p=0.03 vs. 760m & vs. day 17) and SI 38.5±7.4ml/m2, 34.2±7.1ml/m2 and 34.6±5.6 (p<0.02, p=ns at altitude). There was no difference in CI, TAPSE and TASV between altitudes and days. SpO2 was 96±2.0% at 760m and 89.1±5.5 and 91.2±2.7 on day 1 and 18 at 3200m, P<0.02, all changes. **CONCLUSIONS:** In otherwise healthy asthmatics acute exposure to high altitude induces a significant increase in mPAP and heart rate along with a decrease in SI resulting in an unchanged CI. During the subsequent 17 days at 3200m there is no further change in the studied indices of RVF despite increasing SpO2. Therefore, respiratory acclimatization seems to be more rapid than acclimatization of the pulmonary circulation. Funding: Swiss Lung Foundation, Zurich Lung League and Swiss National Science Foundation.

**Abstract: W22**

**EXTRAVASCULAR LUNG WATER IN HEALTHY LOWLANDERS DURING REPEATED HIGH ALTITUDE EXPOSURE**

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**STUDY OBJECTIVES:** High altitude pulmonary edema (HAPE) is a life-threatening condition associated with increasing extravascular lung water (EVLW). In healthy individuals, we investigated 1) whether EVLW is observed upon acute exposure to very high altitude; 2) changes in EVLW over a one-week stay at altitude; and 3) the effect of re-exposure on EVLW to the same altitude. **METHODS:** EVLW was assessed in twenty-one healthy lowlanders (living< 800m, mean±SD age 25±4 years, FEV1 96±12%predicted) by lung ultrasonography and quantified as lung comets during two consecutive sojourns to the ALMA Observatory (Atacama, Chile). Participants slept at 2900m and drove 45-minutes by car to 5050m on six consecutive days and stayed there for 6-8 hours. Measurement took place at low altitude (LA1; Santiago, 520m), and after the first and the sixth night at 5050m (HA1 and HA6, respectively). This cycle was repeated following an identical protocol, after 7-days rest at LA (i.e., cycle 2). ClinicalTrials.gov [NCT02760186]. **RESULTS:** The median numbers (Q1;Q4) of lung comets in cycle 1 were 0 (0;0), and 1 (0;3.5) and 7 (3;10) in LA, HA1 and HA6 (LA5; HA1 and HA6; HA15; HA6; p<0.01). In cycle 2, lung comets were 1 (0;2), 2 (0;5;3) and 12 (7.5;13) (LA15; HA6; HA15; HA6; both p<0.01). Comparing the two cycles, a difference was found between LA and HA6 (p<0.01). **CONCLUSIONS:** In healthy lowlanders acutely exposed to hypobaric hypoxia, EVLW is increased after the first night, further increases until after the sixth night and is still present after return to low altitude. Repeated exposure after a break at lowland reveals even more pronounced EVLW accumulation. This may have repercussions for individuals who engage in repetitive ascent to altitude for occupational purposes. Funding and Support: NSERC Discovery Grant (MJP; 2014-05554), The Brenda Strafford Foundation Chair in Alzheimer Research (MJP), the ALMA Observatory and the Zurich Lung League.
INTRODUCTION: The sulfonamide acetazolamide (AZ), a carbonic anhydrase inhibitor, is frequently used to prevent acute mountain sickness (AMS). AZ causes a metabolic acidosis without influencing the hypoxic and hypercapnic ventilatory responses (HVR and HCVR). Its more lipophilic analogue, methazolamide (MZ; methylated at the thiadiazole ring), is reported to have fewer side effects but its effect on respiratory control in humans is unknown. METHODS: In a placebo-controlled, double blind, randomized crossover study, participants (n=8, 25±1 yrs) ingested a placebo (tid), AZ (250 mg tid) or MZ (100 mg bid separated by a placebo) for 3 days after which their HCVR (P\textsubscript{ET}CO\textsubscript{2} = +6 mmHg; 5 min) and both isocapnic and hypercapnic HVR (P\textsubscript{ET}O\textsubscript{2} = 65, 57, 47 mmHg; 3 min each) were measured. Ventilation (V\textsubscript{E}) and end-tidal gases were measured continuously. Arterial blood was sampled at baseline, while arterialized venous blood was collected at each stage. RESULTS: Both agents led to a partially compensated metabolic acidosis: pHa 7.43±0.01, PaCO\textsubscript{2} 38.6±1.0 mm Hg, base excess 1.2±0.5 meq.l\textsuperscript{-1} in placebo; 7.38±0.01, 33.8±0.9 and -4.7±0.5 after MZ; 7.33±0.00, 32.5±0.8 and -7.9±0.3 after AZ (all P < 0.05 vs. placebo). HCVR was unaffected by both drugs: 4.3±0.9, 4.3±0.8 and 4.6±1.11.min\textsuperscript{-1}.mmHg\textsuperscript{-1} in placebo, MZ and AZ, respectively. In all treatments, raising the PCO\textsubscript{2} increased HVR (expressed as delta V\textsubscript{E}/delta logPO\textsubscript{2}) to a similar extent: 13.7±5.8, 16.0±2.4 and 13.7±5.81.min\textsuperscript{-1}.mmHg\textsuperscript{-1} in placebo, MZ and AZ, respectively (NS), indicating that neither agent inhibited the O\textsubscript{2}− CO\textsubscript{2} interaction known to partly reside in the carotid bodies. CONCLUSION: We conclude that similar to AZ, MZ does not influence ventilatory control but that due to its longer half-life and fewer side effects it may be an alternative to AZ for the prevention of AMS. Funding: NSERC, CFI.

PREDICTING OXYGEN SATURATION CHANGES IN THE SITTING, SUPINE, AND PRONE POSITIONS AT HIGH ALTITUDE-MEDEX 2015

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INTRODUCTION: Changes in body position alter multiple aspects of pulmonary function, including arterial oxygenation (SpO\textsubscript{2}), in some individuals at high altitude. OBJECTIVES: In a group of healthy individuals we sought to determine the frequency of positional oxygenation changes and whether these changes could be easily predicted from demographics or sitting rest values. METHODS: Twenty-eight healthy subjects were studied at sea level and at 5050m, following gradual ascent over 17-18 days. After 10 minutes (sitting) rest, subjects were each studied for 5 minutes in the sitting, supine and prone positions, with the order of positions randomly assigned for each subject. SpO\textsubscript{2} was measured continuously for each subject in a quiet environment. A linear regression model was developed to predict oxygen desaturation in subjects when moving from the sitting to the supine position. RESULTS: At altitude, 22 out of 28 subjects had a fall in SpO\textsubscript{2} on going from the sitting to the supine position and 7 subjects had a change of greater than 4% or greater change in SpO\textsubscript{2}. SpO\textsubscript{2} was 81.2 ± 4.5 % (mean ± SD) whilst sitting and 78.8 ± 6.0 % in the supine position (p < 0.01). Mean SpO\textsubscript{2} change: 2.4 ± 4.9 % (95% CI: 0.5% to 4.3%). SpO\textsubscript{2} was no different in the supine and prone positions. A regression model for predicting desaturation was developed using sitting rest SpO\textsubscript{2}, age, BMI, the number of days spent at BC before testing, and whether or not subjects had AMS. This regression equation had an R-square value of 0.39, thus accounting for less than 40% of the data variance. CONCLUSIONS: Although more than three fourths of subjects had lower SpO\textsubscript{2} in the supine position, proning these subjects did not improve SpO\textsubscript{2}. Easily obtained demographic and non-invasive variables poorly predict the degree of observed positional desaturation.
EFFECT OF ACUTE AND SUBACUTE EXPOSURE AND RE-EXPOSURE TO HIGH ALTITUDE ON PULMONARY ARTERY PRESSURE IN HEALTHY LOWLANDERS

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OBJECTIVE: To evaluate the effect of acute and subacute exposure to high altitude on pulmonary artery pressure (PAP) in non-acclimatized healthy lowlanders, and to study the response to repeated exposure after a week at lowland. We hypothesized that 1) very high altitude exposure would increase PAP, 2) that PAP would decrease with acclimatization over 6 days, and 3) that repeated exposure would mitigate the initial altitude related PAP increase.

METHODS: 21 healthy lowlanders, age 18-30y were included. Tricuspid pressure gradient (TPG) as a estimate of PAP measured with echocardiography at low altitude (LA, 520m) and the first sojourn to 5050m on day 1 and day 6 (1-HA1 and 1-HA6, respectively) after spending corresponding nights at 2900m. Measurements were repeated after a 1-week break at lowland during a second, identical altitude sojourn (2-HA1 and 2-HA6, respectively). Registration: www.Clinicaltrials.gov: NCT02730156

RESULTS: TPG increased significantly from LA to 1-HA1 from median (IQR) 16.7 (15.2;20.6) mmHg to 31.2 (27;35) mmHg (median change, 95%CI 12.6 (10.2;19.2)). After 6 days at 5050m TPG was 25.6 (22.9;29.8) mmHg (median change, 95%CI vs. 1-HA1 -4.9 (-8.6;-0.8)). During the second altitude sojourn TPG was 31.6 (29.6; 40.2) mmHg on 2-HA1 (median change, 95%CI 10.5 (5.0;12.7)) and 26.6 (20.3;30.5) mmHg on 2-HA6 (median change vs. 2-HA1, 95%CI -5.0 (-11.5;-1.2)). Differences in TPG on corresponding days during the first and second altitude sojourn were statistically nonsignificant. CONCLUSION: In young, healthy lowlanders, schedules of very high altitude exposure similar to that of specialized and technical professionals working at high altitude sites induce major initial increases in PAP which tend to decrease within 6 days of acclimatization. FUNDING AND SUPPORT: NSERC Discovery Grant (MJP; 2014-05554), The Brenda Strafford Foundation Chair in Alzheimer Research, the ALMA Observatory, Lunge Zurich, Swiss Lung Foundation, Swiss National Science Foundation.

DOES DOPAMINE CONTRIBUTE TO PULMONARY CAPILLARY BLOOD VOLUME REGULATION DURING EXERCISE?

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INTRODUCTION: Pulmonary diffusing capacity (DLco) must increase to meet the increased oxygen demand during exercise. Expansion of pulmonary capillary blood volume (Vc) is an important contributor to the increased DLco observed during upright cycle exercise. Recent work shows that circulating dopamine may play an important role in pulmonary vascular regulation and gas exchange. The purpose of this study is to examine the effect of dopamine modulation on Vc, cardiac output (Q), and exercise tolerance.

METHODS: Six young healthy subjects (age means±SE: 29±6yrs, peak oxygen consumption (VO2peak): 45.3±5.3mL/kg/min) performed a graded exercise test to determine VO2peak and peak workload on a cycle ergometer. Over three days, participants were randomly assigned to the following conditions: 1) intravenous (IV) dopamine (2ugen/kg/min) and placebo pill, 2) IV saline and dopamine blockade (20mg oral metoclopramide), or 3) IV saline and placebo. For each condition, hemoglobin-corrected DLco and Vc were measured at rest, 60%, and 85% of VO2peak using the Roughton and Forster (1957) multiple oxygen tension DLco method. Participants then performed a time-to-exhaustion (TTE) trial at 85% of VO2peak and Q was determined by impedance cardiography.

RESULTS: No differences in DLco were observed at rest or exercise between experimental conditions. At 85% VO2peak dopamine increased Vc by 22% compared to placebo (dopamine: 176±45mL, placebo: 144±13mL) and blockade reduced
**Poster Session I**

Wednesday Afternoon, 8 February

Vc by 6% (blockade: 136±20mL, placebo: 144±13mL). TTE was reduced with blockade (blockade: 246±67sec, placebo: 416±152sec), which was not explained by arterial saturation (blockade: 91±1%, placebo: 92±2%), Q (blockade: 24.0±2.7L/min, placebo: 23.3±4.5L/min) or oxygen delivery. **CONCLUSION:** Preliminary findings indicate that IV dopamine increased Vc during exercise, while dopamine blockade appears to reduce Vc. These findings suggest that dopamine is important to the regulation of Vc during heavy exercise. **FUNDING:** Natural Sciences & Engineering Research Council.

**Abstract: W27**

**EFFECT OF REPEATED EXPOSURE TO VERY HIGH ALTITUDE ON LUNG FUNCTION IN HEALTHY LOWLANDERS.**

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**OBJECTIVE** To study the effects of repeated exposure to very high altitude on lung function in lowlanders.

**METHODS:** 21 healthy lowlanders, aged 18-30y, started from 520m to undergo 2 sojourns of 6 days each at the ALMA observatory, Chile (spending 6 hours/day at 5050m, nights at 2900m), separated by a 1-week recovery period at 520m. Pulse oximetry (SpO2), spirometry and sniff nasal inspiratory pressure (SNIP), were assessed.

**RESULTS:** At 520m, and during the first sojourn at 5050m, day 1 and 6, median (quartiles) SpO2(%) was 98(97;98), 79(75;84) and 84(81;85), P<0.05 day 1 at 5050 vs. 520m and vs. day 6, respectively; forced vital capacity (FVC, % predicted) was 95(88;100), 91(84;95) and 91(88;96), P<0.05 day 1 at 5050 vs. 520m and P=NS day 1 vs. day 6 at 5050m; ratio of forced expiratory volume in 1 second to FVC (FEV1/FVC) was 0.85(0.82;0.89), 0.88(0.84;0.92) and 0.89(0.86;0.93), P<0.05 day 1 at 5050 vs. 520m and P=NS day 1 vs. day 6 at 5050m; SNIP (mbar) was 105(87;123), 90(71;102) and 90(66;104), P<0.05 day 1 at 5050 vs. 520m and P=NS day 1 vs. day 6 at 5050m. During the second sojourn, SpO2 was higher but spirometry variables were similar to values during the first sojourn.

**CONCLUSIONS:** Exposure to very high altitude decreased FVC, which may be related to reduced inspiratory muscle strength. Six days of acclimatization at 5050m and re-exposure after a low altitude recovery period did not change spirometry and sniff nasal inspiratory pressure although acclimatization increased SpO2. **FUNDING AND SUPPORT:** NSERC Discovery Grant (MJP; 2014-05554), The Brenda Strafford Foundation Chair in Alzheimer Research, the ALMA Observatory, Swiss Lung Foundation, Lunge Zurich, Swiss National Science Foundation.

**Abstract: W28**

**EFFECT OF DEXAMETHASONE ON NOCTURNAL BREATHING IN LOWLANDERS WITH COPD TRAVELLING TO 3200M. RANDOMIZED PLACEBO-CONTROLLED TRIAL.**

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**INTRODUCTION:** We investigated the effect of preventive dexamethasone treatment on sleep related breathing disturbances in lowlanders with COPD staying at 3200m. **METHODS:** 112 COPD patients, GOLD grade 1-2, living below 800m were randomized to receive dexamethasone (2x4mg/d) or placebo 24hrs before ascent from 760m and while staying at 3200m. Co-primary outcomes assessed at 760m and during 2 nights at 3200m were mean nocturnal oxygen saturation (SpO2) by pulse oximetry and the apnea/hypopnea index (AHI). Registration: www.ClinicalTrial.gov: NCT02450094. **RESULTS:** In 57 patients (median age 57y FEV1 84%pred) randomized to dexamethasone, median (quartiles) SpO2 and AHI at 760m were 92% (91;93), 25.8/h (16.3;37.1). In night 1 and 2 at 3200m, SpO2 and AHI were: 86% (84;88), 24.8/h (12.7;34.8) and 87% (86;89), 21.8/h (13.8;38.7), P<0.05 SpO2 night 1 at 3200m vs. 760m and vs. night 2; P=NS for changes in AHI. In 55 patients (median age 60y, FEV1 94%pred) randomized to placebo, SpO2 and AHI at 760m were 92% (91;93), 21.3/h (11.8;47.7). In night 1 and 2 at 3200m SpO2 and AHI were 84% (82;85), 39.8/h (20.9;63.1) and 85% (84;86), 37.4/h (16.5;59.5), P<0.05 SpO2 and AHI night 1 at 3200m vs. 760m and vs. night 2. During night 1 and 2 at 3200m, the altitude-related changes in SpO2 and AHI were reduced.
HEART RATE AND OXYGEN SATURATION RATIO DURING SLEEP AND EXERTION AS A MARKER OF ALTITUDE ACCLIMATIZATION

**Abstract:** The ratio of heart rate to peripheral oxygen saturation ($HR/SpO_2$) can be a combined measure of the extent of arterial hypoxemia and how the body is responding, where a high value (high HR and a low SpO$_2$) could suggest poor acclimatization and potentially increased susceptibility for AMS. METHODS: Twenty-eight non-acclimatized individuals (females=40%, age=44±15yrs.) wore a pulse oximeter at night, performed a submaximal 4-minute step test at baseline and two camps (Shira:11,500ft/3505m and Barafu:15,870ft/4837m) where HR and SpO$_2$ data were collected and completed a modified LLS questionnaire each morning. With nighttime and controlled exercise HR and SpO$_2$ nadir were lower over the course of the trek in those with AMS. The nighttime HR/SpO$_2$ demonstrated a significant interaction for altitude and AMS incidence (0.74±0.5, 1.10±0.12, 1.16±0.07 vs. 0.62±0.03, 0.66±0.09, 0.81±0.05 Base, Shira, Barafu). The degree of desaturation with exercise at Shira and Barafu tended to be lower in those who experienced AMS. Those with AMS demonstrated a higher ratio with increasing altitude, but the interaction was not significant (1.20±0.05, 1.50±0.06, 1.62±0.07 vs. 1.15±0.05, 1.34±0.05, 1.39±0.06). Neither nighttime SpO$_2$ variables, nor exercise desaturation were different based on age. In contrast, the HR/SpO$_2$ relationship during exercise tended to increase with increasing altitude in younger subjects, whereas it plateaued in older subjects (1.12±0.05, 1.35±0.06, 1.33±0.06 vs. 1.23±0.05, 1.47±0.06, 1.64±0.06, old vs. young respectively). CONCLUSION: From our initial analysis the HR/SpO$_2$ relationship at night and during exercisesuggests it may be a useful marker of assessing how one is acclimatizing to altitude as those who experience AMS demonstrated a higher ratio with increasing altitude.

SYMPATHETIC BAROREFLEX SENSITIVITY IS PRESERVED IN LOWLANDERS SOJOURNING AT 5050 M

**Abstract:** We explored the effect of high altitude (HA) exposure on muscle sympathetic nerve activity (MSNA), arterial blood pressures, and sympathetic baroreflex sensitivity (BRS). METHODS: Blood pressures (photoplethysmography) and MSNA (microneurography) were measured in healthy lowlanders (12 male, 2 female) and 8 Nepalese Sherpa males. Lowlanders were assessed at 344 m. above sea level (SL) and at 5050 m. (Pyramid Laboratory, Nepal). Sherpa were studied at 5050m. Sympathetic BRS was estimated using the modified Oxford method (nitroprusside and phenylephrine). RESULTS: In lowlanders, ascent to HA resulted in elevated resting MSNA burst frequency (30 ± 6 vs. 11 ± 5 bursts min$^{-1}$, $P<0.05$) and burst incidence (50 ± 15 vs. 23 ± 12 bursts 100 heartbeats$^{-1}$,$P<0.05$) compared with SL. In contrast, resting mean arterial blood pressure (MAP) was unaffected by HA compared with SL (81 ± 15 vs. 84 ± 15 mmHg). Sympathetic BRS at HA (2.7 ± 0.5 bursts 100 heartbeats$^{-1}$ mmHg$^{-1}$) was not significantly different from that at SL (2.7 ± 1.0 bursts 100 heartbeats$^{-1}$ mmHg$^{-1}$). Compared with HA values from the lowlander males, Sherpa had lower values for resting MSNA burst frequency (23 ± 11 vs 30 ± 7 bursts min$^{-1}$, $P<0.05$) and burst incidence (30 ± 13 vs 47 ± 15 bursts 100 heartbeats$^{-1}$, $P<0.05$), but resting MAP was not different (80 ± 10 vs 81 ± 9 mmHg). Sympathetic BRS was similar in Sherpa and lowlander males (2.4 ± 1.0 vs. 2.9 ± 1.5 bursts 100 heartbeats$^{-1}$ mmHg$^{-1}$). CONCLUSION: Our data indicates that sympathetic...
baroreflex sensitivity in lowlanders is not confounded by markedly elevated sympathetic vasomotor drive following HA exposure. Preservation of an appropriately sensitive sympathetic baroreflex during HA acclimatization likely balances the opposing effects of local hypoxic vasodilatory mechanisms and sympathoexcitation in response to hypoxaemia. Funded by NSERC (CDS & PNA), Canada Research (PNA), U Alberta, Presidents Grant Scholarship (SAB).

Abstract: W31

MOLECULAR COMPOSITION OF THE MITOCHONDRIAL PERMEABILITY TRANSITION PORE (mPTP).

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Calcium-induced Mitochondrial Permeability Transition Pore (mPTP) is a large non-selective channel located in the mitochondrial inner membrane. It has been established that prolonged opening of mPTP during stress conditions of hypoxia leads to the increase in permeability of the mitochondrial membrane, disruption of energy generation in the form of ATP and eventually to cell death. mPTP opening is the central event leading to tissue damage during stroke. Thus, block of mPTP by pharmacological agents can be highly protective. Molecular composition of the PTP is not well-understood. Previously we demonstrated that mitochondria contain complex of C-subunit of ATP synthase, inorganic polyphosphate (polyP) and polyhydroxybutyrate (PHB) that form channel identical to the native mPTP. Here we demonstrate that amount of this complex in isolated mitochondria is dramatically increased when mPTP is activated by the addition of calcium. Complex formation was inhibited by both: Cyclosporine A - an inhibitor of mPTP and by Ruthenium Red - an inhibitor of the mitochondrial calcium overload. Further, we confirm that similar increase occurs in vivo in brain under conditions of hypoxia induced injury. We propose that molecular mechanism of mPTP activation involves calcium induced formation of the complex made of oligomers of the ATP synthase C-subunit, PHB and polyP. Specifically we suggest that calcium-induced mPTP is associated with de novo assembly of a channel comprising C-subunit, polyP and PHB.

Abstract: W32

PERIPHERAL OXYGEN CHEMORECEPTOR ACTIVATION BY INFLAMMATORY MEDIATOR LYSOPHOSPHATIDIC ACID: A MISSING LINK BETWEEN OBESITY AND HYPERTENSION?

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BACKGROUND: The carotid bodies (primary peripheral oxygen chemoreceptors) are activated in, and contribute significantly to obesity-associated cardiorespiratory and metabolic disease. Lysophosphatidic acid (LPA) is produced by an enzyme released into blood by abdominal adipose tissue. LPA activates cells via excitatory TRPV1 and LPA-specific G-protein coupled receptors (LPAr). Recently, we demonstrated that the carotid bodies express TRPV1. Given that the carotid bodies play an important role in cardiorespiratory diseases associated with obesity and contains TRPV1, we hypothesize that LPA-mediated activation of carotid bodies contributes to neurogenic hypertension in obesity. METHOD: We evaluated the effects of LPA on (a) chemosensory afferent activity using a perfused en bloc rat carotid body preparation (LPA delivered via the common carotid artery) and (b) sympathetic activity in a urethane anesthetized in vivo rat preparation (LPA delivered via the jugular vein). Blood pressure was measured from the femoral artery and sympathetic activity was recorded from the splanchnic nerve. qPCR determined the expression of LPAr in the carotid bodies and petrosal ganglia (expression in superior cervical ganglia and thymus gland served as positive controls). RESULTS: 10µM LPA increased carotid sinus nerve activity in the en bloc carotid body preparation. LPA-induced activity was partially blocked by TRPV1 antagonist, AMG9810. In carotid body intact in vivo preparations, LPA triggered a significant rise in splanchnic nerve activity after LPA infusion (p<0.05). However, LPA had no effect in carotid body denervated preparations. qPCR revealed expression of LPAr 1, 3, 4 and 6 in the carotid body, and LPAr 1, 3, 4 and 5 in the petrosal ganglia. CONCLUSION: Our data suggest that the carotid bodies are sensitive to LPA via TRPV1 and LPAr. We therefore postulate that carotid body sensing of LPA is involved in the development of heightened sympathetic nervous system activity, and consequently neurogenic hypertension associated with obesity.
TRANSSCRIPTION FACTOR MRNA LEVELS IN HUMAN BLOOD DURING SUB-ACUTE ACCLIMATIZATION TO HYPOBARIC HYPOXIA

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INTRODUCTION: An adequate supply of oxygen is crucial for life of all aerobic organisms, including humans. It is well known that Hypoxia Inducible Factors (HIFs), as well as Nuclear Factor κB (NFκB) and the Nuclear Factor Erythroid 2L2 (NFE2L2), are considered key factors involved in the molecular response and adaptation to hypoxia.

OBJECTIVE: To investigate HIF-1α, HIF-2α, NFκB and NFE2L2 mRNA levels in blood samples collected from 16 lowlanders during the early phase of acclimatization to high altitude. METHODS: Blood samples were collected at baseline and after rapid, passive ascent to 3830m (24h, 72h, and 7 days). RNA was extracted by PAXgene Blood RNA method, and gene expression was assessed by qPCR. Paired samples t-test was used for the analysis of the change in mRNA levels over time. RESULTS: We observed that hypoxia slightly enhanced HIF-1α mRNA levels over time during exposure to hypobaric hypoxia reaching a peak after 24h (+46%; p=0.09), with a return to baseline after 72h (-22%; p=0.16). In contrast, compared to baseline, HIF-2α expression showed a significant increase of 33% after 72h of exposure (p<1x10^-4), and reached the highest expression level after 7 days (+111%, p<1x10^-4). NFE2L2 showed an increase and reached a peak after 72h of exposure (+97%, p<1x10^-4). Finally NFκB expression showed a slight increase, reaching a peak after seven days (+79%, p=0.06). CONCLUSION: To our knowledge, this 8-day hypoxic exposure is the first field study in Caucasian lowlanders to investigate in vivo regulation of key transcription factors during sub-acute acclimatization to hypoxia. Results show different effects over time on gene expression of all four transcription factors investigated. In particular, the expression pattern comparison of HIF-1α, HIF-2α, NFκB and NFE2L2 suggests an induction of different time dependent molecular pathways.

ACUTE EFFECT OF HIGH ALTITUDE EXPOSURE ON TOTAL BODY WATER STATUS AND NT-PROBNP

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INTRODUCTION: The role of body water status (hypo- and hyper-hydration) in acute altitude illnesses remains unclear. However, the cardiac hormone B-type Natriuretic Peptide (BNP), which is involved in vasodilation, diuresis and fluid balance, is reportedly elevated at altitude. Here, we report total body water (TBW) dynamics during acute altitude exposure using bioelectrical impedance vector analysis (BIVA) and N-Terminal pro-BNP (NT-proBNP), a stable metabolite of BNP.

METHODS: Data from eleven healthy lowlanders transported to 3830m via helicopter were analyzed. BIVA measurements were assessed at baseline 262m (BL) and 9h, 24h, 48h, 72h and post 8 d. Blood and urine samples were taken at identical time points; excluding 48h. TBW status was estimated via impedance vector, derived from bivariate analysis of the Resistance-Reactance graph (R-Xc). NT-proBNP was quantified from peripheral venous blood.

RESULTS: Vector lengths at 9h, 48h and 72h were significantly lengthened (p<0.05, dehydrated) but there was no difference at 24h from baseline. The vector length seemed to shorten (i.e. demonstrated a fluid gain) from 9h to 24h (p=0.097). NT-proBNP was elevated at altitude (reaching maximum at 24h), but not statistically significant from the baseline (p>0.05). There was no significant correlation between changes in vector length and changes in NT-proBNP (r = -0.165, p>0.05). The blood and urine osmolality did not differ significantly over different time points and changes were not correlated with changes in BIVA impedance vector length. The subjects remained desaturated throughout altitude exposure (p<0.05).

CONCLUSIONS: The subjects remained dehydrated during high altitude exposure over 72h, which trended towards euhydration only from 9h to 24h. The changes in BIVA impedance vector length were not correlated with changes in NT-proBNP, plasma and urine osmolality.
Abstract: W35
THE EFFECT OF ACUTE EXPOSURE TO NORMOBARIC HYPOXIA ON POSTPRANDIAL TRIGLYCERIDE LEVELS
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INTRODUCTION: The effect of altitude exposure on circulating triglyceride (TG) levels still remains controversial in humans. Indeed, some studies show an increase while others report a decrease in TG levels upon altitude exposure. We examined the effect of acute exposure to normobaric hypoxia on key parameters involved in the production and disposal of TG levels in men. METHODS: Energy expenditure, substrate oxidation rate, TG and NEFA levels were measured postprandially on seven healthy young men (1.81(0.02) m; 79.2(8.5) kg; 25(5) y) exposed for 6h to either a control (FiO2=0.2093) or hypoxic (FiO2=0.1200) condition in a randomized crossover fashion. RESULTS: There was no statistical difference in energy expenditure or substrate oxidation rate measured through indirect calorimetry for 6h between control and hypoxia sessions. Exposure to acute hypoxia led to a close to significant (p= .06) increase in postprandial plasmatic TG levels as well as a significant increase in postprandial NEFA levels (p<0.05) as compared to control. CONCLUSION: Acute hypoxia in healthy men tends to negatively affect postprandial TG levels. These results lend support to the increased blood lipid levels reported in individuals exposed to lower partial pressure of oxygen during sojourn at high altitude. ACKNOWLEDGEMENTS: This study was supported by a NSERC Discovery grant and in part by a Research Chair in Physical and Mental Comorbidities awarded to P. Imbeault by the Institut du savoir Montfort. É. Chassé received a scholarship from the Institut du savoir Montfort.

Abstract: W36
PHYSIOLOGICAL MICROCIRCULATORY RESERVE IS PRESERVED DURING ASCENT TO 7042 M
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INTRODUCTION: Assessment of microcirculatory alterations play an increasing role in the hemodynamic monitoring in states of compromised tissue oxygenation. Physiological microcirculatory reserve – the recruitment of capillary microcirculatory diffusion and convection reserve in response to sublingual topical application of acetylcholine (ACH) and nitroglycerin (NG) – has been suggested as a functional measurement parameter of the microcirculation. Altitude exposure to 5364m at Everest Base Camp has previously been demonstrated to decrease capillary flow velocity, as well as increase total vessel density (TVD) during subacute exposure, however its influence on functional microcirculatory parameters remains unknown. Our hypothesis is that the physiological microcirculatory reserve as a functional microcirculatory parameter is impaired during subacute exposure to hypoxia. METHODS: In 41 healthy subjects (age 45.8±1.9 years, 54% male) sublingual capillary microscopy was performed in normoxia and during ascent to 7042m within 21 days as part of the Swiss High Altitude Medical Research Expedition Himlung Himal 2013. Total vessel density (TVD) and average perfused speed indicator (APSI) were assessed before and after topical application of ACH and NG using a handheld incident dark field digital video microscope (Cytocam, Braedius Medical, Huizen, The Netherlands). The data were analyzed using computerized image processing (Cytocam Tools 1.7.12). RESULTS: 36 subjects reached 6022m and 10 subjects reached 7042m. TVD was increased from (mean±SEM) 15.97±0.49mm/mm2 at low altitude normoxia to 17.80±0.46mm/mm2 at 6022m and 18.24 ±0.51mm/mm2 at 7042m (p<0.0001). The topical application of NG led to an similar increase in TVD (from 2.12±0.52mm/mm2 to 1.23±1.16mm/mm2) and APSI (from 0.31±0.12 to 0.18±0.21) at low and high altitude. The topical application of ACH affected neither TVD nor APSI. CONCLUSIONS: The sublingual physiological microcirculatory reserve as assessed non-invasively by topical application of nitroglycerin is preserved throughout subacute hypoxic exposure to 7042 m despite an increase in microcirculatory total vessel density.
**PERIPHERAL ENDOTHELIAL FUNCTION AND HEMODYNAMICS ON ASCENT TO 5050M: A BETWEEN-LIMB COMPARISON IN LOWLANDERS AND SHERPA**

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**Abstract:** The study of endothelial adaptation to hypoxia has been restricted to the upper limb, and comparisons to highlanders are also confounded by differences in altitude exposure, exercise, and unknown levels of blood viscosity. **METHODS:** Healthy lowlanders (n=22, 28±6 years [mean±SD], BMI=23±2 kg m⁻²) and Sherpa (n=12, 34±11 years, BMI=24±4 kg m⁻²) were tested. Sherpa were partially de-acclimatized to 1400m over 5-15 days following which both groups ascended over 10 days with measurements taken at 1400m, 3440m (day 4), 4371m (day 7), and 5050m (day 10) without pharmaceutical altitude sickness prevention. Resting hemodynamic shear patterns and endothelial function (reactive hyperemia flow-mediated dilation; FMD) were acquired via duplex ultrasound in the brachial (BA; atherosclerotic-resistant) and superficial femoral (SFA; atherosclerotic-prone) arteries. Venous blood viscosity was acquired at each location. The relevant shear stress stimulus to evoke FMD was calculated as the shear stress area under the curve (shear rate x viscosity; SSAUC) from cuff deflation to peak diameter. **RESULTS:** In lowlanders, viscosity rose by 29±16% (P<0.001), and resting mean shear stress decreased and retrograde shear stress increased in both limbs on ascent to 5050m. Although BA FMD decreased from 6.5±3.8% to 4.5±2.2% on progressive ascent to 5050m (P<0.05) without any change in SSAUC, SFA FMD was preserved. In contrast, in the Sherpa, neither viscosity, retrograde shear stress, BA nor SFA SSAUC or FMD were changed upon ascent to 5050m. **CONCLUSION:** Our findings indicate that endothelial function is protected in Sherpa upon ascent to high altitude. In lowlanders, although FMD in the SFA is persevered, there is a selective impairment in the BA. While the ascent-related exercise may favorably influence endothelial function in the active limb (SFA), the impairment in FMD in the normally atherosclerotic-resistant BA might be mediated via the low mean or high retrograde shear stress during ascent in lowlanders.

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**ONE SESSION OF REMOTE ISCHEMIC PRECONDITIONING DOES NOT IMPROVE VASCULAR FUNCTION IN ACUTE AND CHRONIC HYPOXIA**

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The application of repeated short duration bouts of ischemia, termed remote ischemic preconditioning (RIPC), is a novel technique that may have protective effects on vascular functioning during hypoxic exposures. We determined the effects of RIPC on pulmonary, peripheral, and cerebral vascular function during acute and chronic hypoxia. At sea-level (SL; n=16) and after 8-12 days at high-altitude (HA; n=12; White Mountain, CA; 3800m), participants underwent either a sham protocol or one single session of 4x5 minutes of dual-thigh cuff occlusion with 5-minutes recovery. Brachial artery flow-mediated dilation (FMD; duplex ultrasound), pulmonary artery systolic pressure (PASP; echocardiography), and internal carotid artery (ICA) flow were measured at SL in normoxia and isocapnic hypoxia [partial pressure of end-tidal O₂ (PETO₂) clamped to 50mmHg], and during room air breathing at HA. The hypoxic ventilatory response (HVR) was calculated using the change in resting ventilation to peak ventilation upon the transition from normoxia to hypoxia at both SL (PETO₂=50mmHg) and HA (PETO₂=45mmHg). All measures at SL and HA were obtained at baseline (BL), and 1 hour, 24 hours, and 48 hours post RIPC or sham. At SL, RIPC produced no changes in FMD, PASP, ICA flow, end-tidal gases or HVR. At HA, although HVR increased 24 hours post RIPC compared to BL (2.40 vs. 1.50 L min⁻¹ %SpO₂⁻¹, p<0.01), there were no significant differences in FMD, PASP, ICA flow, resting end-tidal gases, or SpO₂. Our findings suggest that a single session of RIPC is insufficient to evoke changes in peripheral, pulmonary, and cerebral vasculature. Although hypoxic chemosensitivity may increase following RIPC at HA, this did not confer any vascular benefits; therefore, the utility of a single RIPC session seems unremarkable during acute and chronic hypoxia.
Abstract: W39

CEREBROVASCULAR AND CARDIOVASCULAR RESPONSES TO HYPOXIA FOLLOWING INTERMITTENT HYPOXIA EXPOSURE DURING SLEEP
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INTRODUCTION: A limitation of most human experimental models of intermittent hypoxia (IH) that tempts extrapolation of findings to obstructive sleep apnea is that IH is administered during wakefulness. Thus, whether IH during sleep impacts vascular regulation remains poorly understood. Using a human experimental IH model this study assessed the impact of IH during sleep on vascular responses to hypoxia during wakefulness. METHODS: In a randomized, counterbalanced experimental design, 8 healthy males underwent overnight polysomnography (PSG) twice, separated by ≥4 days. One PSG was performed in room-air (normoxia) and the other was accompanied by isocapnic-IH. In addition to PSG, participants were instrumented for continuous measurements of cerebral blood flow (CBF; transcranial Doppler ultrasound), mean arterial blood pressure (MAP; finger photoplethysmography) and heart rate (HR; 3-lead ECG). On both nights, awake CBF, MAP and HR responses to hypoxia were assessed before going to sleep and following ~6 hours of sleep. Comparisons were performed using a 2-by-2 RM-ANOVA (exposure: normoxia, IH; time: pre- and post-sleep).

RESULTS: Mean awake CBF, MAP and HR hypoxic responses were similar between the normoxic and IH nights (p≥0.058). Sleep, regardless of exposure, did not impact the awake CBF and HR hypoxic responses (p≥0.521). However, the morning MAP response to hypoxia was lower within both conditions (p=0.019). Lastly, the exposure-by-time interaction was significant for only the HR hypoxic response (p=0.001) as the response was decreased following normoxic sleep (p<0.001), but maintained following sleep accompanied by IH (p=0.604); resulting in the post-sleep HR response being lower following normoxic sleep compared to IH sleep (p=0.008). CONCLUSION: These data indicate that the CBF and MAP responses to hypoxia are not impacted by IH during sleep, but 6 hours of IH is sufficient to abrogate the decrease in the HR response to hypoxia that occurs during sleep in normoxia. Funded by the CIHR, HSFC, AIHS, and NSERC.

Abstract: W40

CEREBROVASCULAR AND RESPIRATORY RESPONSES TO ACUTE HYPOXIA IN CHILDREN AND ADULTS
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The physiological response to high altitude in children is incompletely understood. We aimed to characterize cerebrovascular and respiratory responses to normobaric hypoxia in girls and their mothers. METHODS: Eight healthy girls (9.9 ± 1.89 y; mean ± SD; Tanner stage 1 and 2) and their biological mothers (43.0 ± 3.38 y) participated. Velocity, diameter and flow (duplex ultrasound) of the internal carotid (ICA) and vertebral artery (VA) was recorded before and after 1h of hypoxic exposure in a normobaric chamber simulating 3,800m altitude. Ventilation (VE), end-tidal carbon-dioxide (PETCO2) and the drive to breathe (VT/Ti) were collected at baseline (BL) and 5, 30 and 60 minutes in the chamber (5/30/60HP). Heart rate (HR), arterial blood pressure (BP) and oxygen saturation (SpO2) were also taken at 5/30/60HP.

RESULTS: SpO2 declined from 97% at BL to 81% 60HP in the children and from 96% at BL to 83% at 60HP in the adults. Repeated measures ANOVA showed that VA flow increased by 28% and 37% in children and adults respectively (P < .01) at 60HP, accompanied by increases in diameter (P < .01). ICA flow also increased following hypoxic exposure (children 29%, adults 14%), but this failed to reach significance (P=.068). VE increased with increasing hypoxic exposure in children (P<.05), peaking at 30HP (BL-249 ml. kg.min⁻¹; 30HP-314 ml. kg.min⁻¹). Mean increases in VE were not significant in adults (BL-125 ml. kg.min⁻¹; 30HP-139 ml. kg.min⁻¹). Hypoxic exposure resulted in an age-specific change in respiratory drive (VT/Ti; P<.05). In children, VT/Ti increased by 30% at 5HP and remained at this level at 30 and 60HP. In adults VT/Ti increased by 15% at 5HP, but returned to baseline at 30 and 60HP. CONCLUSION: VA artery diameter and flow responses to acute hypoxic exposure are similar in children and adults, but respiratory responses differ by age implying developmental differences.
Abstract: W41

THE EFFECT OF ALPHA1-ADRENERGIC BLOCKADE ON POST-EXERCISE BRACHIAL ARTERY FLOW-MEDIATED DILATATION AT SEA-LEVEL AND HIGH-ALTITUDE

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We examined the hypotheses that 1) at rest, endothelial function would be impaired at high-altitude compared to sea-level, 2) endothelial function would be reduced to a greater extent at sea-level compared to high-altitude after maximal exercise, and 3) reductions in endothelial function following moderate-intensity exercise at both sea-level and high-altitude are mediated via an alpha1-adrenergic pathway. In a double-blinded, counter-balanced, randomized and placebo-controlled design, nine healthy participants performed a maximal-exercise test, and two 30-minute sessions of semi-recumbent cycling exercise at 50% peak Watt following either placebo or alpha1-adrenergic blockade (prazosin; 0.05mg/kg). These experiments were completed at both sea-level (Kelowna, British Columbia; 344m) and high-altitude (White Mountain, California; 3800m). Blood pressure (finger photoplethysmography), heart rate (electrocardiogram), oxygen saturation (pulse oximetry), and brachial artery blood flow and shear rate (ultrasound) were recorded prior to, during, and following exercise. Endothelial function assessed by brachial artery flow-mediated dilatation (FMD) was measured prior to, immediately following, and 60-minutes post-exercise. Our findings were: 1) at rest, FMD remained unchanged between sea-level and high-altitude (placebo P=0.287; prazosin: P=0.110); 2) FMD remained unchanged after maximal exercise at sea-level and high-altitude (P=0.244); 3) the 2.9±0.8% (P=0.043) reduction in FMD immediately after moderate-intensity exercise at sea-level was abolished via alpha1-adrenergic blockade. Conversely, at high-altitude, FMD was unaltered following moderate-intensity exercise, and administration of alpha1-adrenergic blockade elevated FMD (P=0.032). Our results suggest endothelial function is differentially affected by exercise when exposed to hypobaric hypoxia. These findings have implications for understanding the chronic impacts of hypoxemia on exercise, and the interactions between the alpha1-adrenergic pathway and endothelial function. FUNDING: This study was supported by the Natural Sciences and Engineering Research Council of Canada (PNA and MMT), the Canadian Foundation for Innovation (PNA), and a Canada Research Chair (PNA).

Abstract: W42

EFFECT OF ACUTE, SUBACUTE AND REPEATED HIGH ALTITUDE EXPOSURE ON PSYCHOMOTOR VIGILANCE

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OBJECTIVE: Poor sleep at altitude may affect daytime performance. The speed of response to light stimuli in the psychomotor vigilance test (PVT-RS) is slower following sleep deprivation. We investigated 1) the effect of very high altitude exposure, acclimatization, and re-exposure on PVT-RS and 2) assess relationships between PVT-RS, sleep parameters, and AMS. METHODS: 21 altitude-naive individuals (25±4 yrs [mean±SD]; 8M/13F) completed 2 cycles of altitude exposure; each cycle separated by 7 days at low altitude (LA, 520m). Participants slept at 2900m (7-nights) and spent the daytime at HA (5050m). The effect of acute altitude (LA vs. HA1) and acclimatization (HA1 vs. HA6) were studied. Sustained attention was assessed for 10-min using the PVT-RS. Acute mountain sickness was assessed using the Environmental Symptoms Questionnaire cerebrospinal score (AMS; score >0.7 identifies AMS). Sleep parameters were assessed using actigraphy. ClinicalTrials.gov NCT02731456. RESULTS: In cycle 1, PVT-RS was slower at HA1 compared to LA (HA1: 4.1±0.8; LA: 4.5±0.6 s1;P≤0.05), but not at HA6 (4.6±0.7; P>0.05). In cycle 2, PVT-RS at HA1 and HA6 was not different from LA (P>0.05). In both cycles, AMS scores were higher at HA1 than at HA6 (P≤0.05). At HA1, subjects who reported higher AMS scores exhibited slower PVT-RS (r=−0.56; p<0.01). Sleep parameters (sleep efficiency, awakenings, and sleep latency) were unaffected by altitude. CONCLUSIONS: PVT-RS is reduced with acute exposure to HA and normalized with acclimatization over 6 days.
Acclimatization effects are retained upon re-exposure to altitude. These results have implications for individuals engaging in activities at altitude requiring high daytime attentiveness such as mining, astronomical observation and athletics.

**FUNDING:** NSERC Discovery Grant (MJP; 2014-05554), The Brenda Strafford Foundation Chair in Alzheimer Research (MJP), the Alma Observatory, Swiss Lung Foundation, Lunge Zurich, Swiss National Science Foundation.

**Poster Session I Wednesday Afternoon, 8 February**

**Abstract: W44**

**MEASURING CEREBROVASCULAR REACTIVITY IN TERMS OF RESISTANCE**

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**INTRODUCTION:** The cerebral blood flow (CBF) response to a ramp increase in the end-tidal partial pressure of CO₂ (PetCO₂) may differ between brain regions, but is balanced in health such that CBF increases in all regions with rising PetCO₂. However, this balance is precarious; determined not only by local changes in vascular resistance, but also by changes in local perfusion pressure induced by resistance changes in other brain regions, which result from competition for inflow from a common blood supply. **PURPOSE:** Introduce a method to measure the vascular resistance responses to a vasoactive stimulus by vessels in a single voxel, ROI, or hemisphere in health and with cerebrovascular disease. **METHODS:** We use a ramping PetCO₂ as the stimulus and BOLD signals as a surrogate of CBF. We developed a simple, fractally-scaled model, to convert BOLD responses into voxel-wise regional resistance parameters. The basis for the model is a flow competition between two vessels, each with their own resistance profile, that compete for a limited blood supply from a common perfusing artery. As changes in resistance over a range of PetCO₂ must be sigmoidal in shape, the vessel resistance response can be analyzed in the terms of sigmoidal characteristics of amplitude, midpoint, and range. By assigning an interrogated branch of the model to compete with a standard reference vessel resistance having a fixed sigmoidal profile, we derive a relative resistance profile for the interrogated voxel. **RESULTS:** The model generated resistance sigmoidal curves with high r-squared fitting values (>0.8) for the majority of voxels in scans from healthy subjects and from patients with intra- and extra-cranial steno-occlusive disease. Anatomical maps of these sigmoidal parameters provided physiological insight. **DISCUSSION AND CONCLUSION:** This is the first report of an imaging-based localized measure of underlying vascular physiology in the brain.

**THE SMELL OF HYPOXIA: THE USE OF AN ELECTRONIC NOSE AT HIGH ALTITUDE**

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**BACKGROUND:** Electronic nose (e-nose) devices can be used to identify volatile organic compounds (VOCs) in exhaled breath. VOCs generated via metabolic processes are candidate biomarkers of (patho)physiological pathways. We explored the feasibility of using an e-nose to generate human “breathprints” at high altitude. Furthermore, we explored the hypothesis that pathophysiological processes involved in the development of acute mountain sickness (AMS) would manifest as altered VOC profiles. **METHODS:** Breath analysis was performed using the handheld Cyranose 320 (Sensigent, USA). Exhaled breath was collected and analysed from adult Sherpa and lowlander trekkers at high altitude (3500m) on an 11 day ascent to Everest base camp (5300m). To minimise contamination by ambient VOCs, participants underwent five minutes tidal breathing of VOC free air, using a VOC filter. A daily self-reported Lake Louise score (LLS) was used to diagnose AMS. Raw data were reduced by principal component (PC) analysis (PCA). Cross validated linear discriminant analysis (CV-LDA) and receiver operating characteristic area under curve (ROC-AUC) assessed discriminative function. **RESULTS:** Breathprints suitable for analysis were obtained from 58% (37/64) of participant samples. The 37 participants were comprised of 18 Sherpas and 19 lowlanders. PCA showed significant differences between breathprints from participants with, and without, AMS; CV-LDA showed correct classification of 83.8%, ROC-AUC 0.86; PC 1 correlated with AMS severity. There were significant differences between breathprints of participants who remained AMS negative and those whom later developed AMS (CV-LDA 68.8%, ROC-AUC 0.76). PCA was also able to successfully discriminate between Sherpas and lowlanders (CV-LDA 89.2%, ROC-AUC 0.936). **CONCLUSIONS:** This study demonstrated the feasibility of breath analysis for VOCs using an e-nose at high altitude. Furthermore, it provided proof-of-concept data supporting the Cyranose 320 e-nose has the potential to objectively diagnose and predict AMS at altitude.
THE EFFECTS OF HIGH ALTITUDE ON TASTE AND SMELL
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INTRODUCTION: Anecdotally loss of appetite and weight occur at altitude. Investigation of the role of taste and smell in this loss was undertaken. METHODS: During the Caudwell Extreme Everest 2007 expedition, evaluation of smell and taste was undertaken at sea level and Everest Base Camp (EBC) (5300m) in healthy volunteers. Smell was assessed with a 40-item Univ Pennsylvania Smell Identification test (UPSIT) and crude taste by standardized application of concentrated aqueous solutions of salty (saline), sour (citric acid), bitter (quinine), sweet (sucrose) and savoury (soy) to the tongue. RESULTS: Sixty-two subjects were tested. Statistical evaluation showed no difference in the group between sea level and EBC for both smell and taste. CONCLUSION: The potential causes of loss of appetite and weight at high altitude are multi-factorial. In this study ascending to a height of 5300m did not result in loss of taste and smell suggesting that these are not important factors in loss of appetite and weight.

REMOTE ISCHEMIC PRECONDITIONING DOES NOT ATTENUATE ACUTE MOUNTAIN SICKNESS AND HIGH-ALTITUDE-INDUCED PULMONARY HYPERTENSION AT 3450 M
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INTRODUCTION: Remote ischemic preconditioning (RIPC) has been shown to protect organs such as brain and lung remote from the preconditioned site against damage induced by subsequent hypoxia or ischemia. Acute mountain sickness (AMS) and high-altitude pulmonary edema (HAPE) represent the cerebral and the pulmonary form of high-altitude diseases. Activation of the trigeminovascular system and an exaggerated hypoxic pulmonary vasoconstriction are considered to play a pivotal role in AMS and HAPE, respectively. We hypothesized that RIPC protects the brain from AMS through reduction of reactive oxygen species and the lung from an exaggerated hypoxic pulmonary vasoconstriction are considered to play a pivotal role in AMS and HAPE, respectively. We hypothesized that RIPC protects the brain from AMS through reduction of reactive oxygen species and the lung from an exaggerated rise in pulmonary artery systolic pressure (PASP) at 3450 m. METHODS: Forty non-acclimatized volunteers were randomized into 2 groups. At low altitude (750 m) the RIPC group underwent 4 cycles of lower limb ischemia, induced by inflation of 2 thigh cuffs to 200 mmHg for 5 min, followed by 5 min of reperfusion. In the control group cuffs were inflated to only 20 mmHg. Thereafter, participants were transported by railway over 2 h to 3450 m. AMS was evaluated by the Lake Louise score (LLS) and the AMS-C score after 5 h, 10 h, 24 h, 29 h, 34 h and 48 h at high-altitude. PASP was assessed by transthoracic echocardiography. RESULTS: RIPC had no effect on the incidence (RIPC: 35%, control: 35%) and severity of AMS. Mean±SD of LLS scores after 24 h at high-altitude were: RIPC 4.6±4.1, control 3.0±1.8, P=0.47; corresponding AMS-C scores were: 0.69±0.9 and 0.37±0.08, P=0.25. There was also no difference in PASP between both groups (maximum after 10 h at high-altitude; RIPC: 33±8, controls: 37±7 mmHg; P=0.19). CONCLUSION: This study indicates that RIPC, performed immediately before passive ascent to 3450m, does not attenuate AMS and the degree of high-altitude pulmonary hypertension. Thus, RIPC cannot be recommended for prevention of high-altitude diseases.
Poster Session I Wednesday Afternoon, 8 February

Abstract: W47

TIJEBAN ENRICHED PKLR VARIANT FACILITATES IMPROVED OXYGEN DELIVERY IN HIGH ALTITUDE.

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Tibetans have been living at altitudes over 3500m for ~20,000 years and developed number of beneficial evolutionary adaptations. Two Tibetan specific EPAS1 (encoding hypoxia-inducible factor alpha [HIF2α], a transcription factor that mediates the hypoxic response), and EGLN1 (encoding prolyl hydroxylase 2 [PHD2], a principal negative regulator of HIF stability) haplotypes were identified and are present in most Tibetans and the presence of these two haplotypes correlates with lower hemoglobin levels in Tibetans. However, these do not fully explain the entire Tibetan polycythemia protection. We identified a Tibetan enriched haplotype of a gene in the glycolytic pathway, PKLR, encoding the red cell and liver specific pyruvate kinase (PK). We hypothesized that different PKLR haplotypes improve hemoglobin oxygen delivery associated with PK enzyme activity. This haplotype is not unique to Tibetans; however, it has the highest frequency in Tibetans (89%), with a lower prevalence in Chinese and Mongolians (~77%) and a much lower frequency in Caucasians (11%), perhaps explaining the individual and ethnic/racial heterogeneity of responses to hypoxia. We found that PKLR transcript levels in reticulocytes (RNA containing subpopulations of red cells) progressively decreases with increasing altitudes in controls and even more in PKLR with Tibetans enriched haplotype. It is known that the decreased PK activity leads to accumulation of proximal glycolytic intermediates 2,3 diphosphoglycerate (DPG). Our findings suggest that the majority of Tibetans have progressively lower PK levels with increasing altitudes, and their higher 2,3 DPG shifts the hemoglobin dissociation curve to right, decreases affinity of the hemoglobin for oxygen, which improve tissue oxygen delivery. Here, we suggest that Tibetan enriched PKLR haplotype might improve oxygen delivery to tissue contributing to high altitude adaptation resulting in their partial protection from polycythemia.

Abstract: W48

SYMPATHETIC NERVE ACTIVITY AND VASCULAR TRANSDUCTION IN LOWLANDERS AND SHERPA AT 5050M

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INTRODUCTION: Previous data suggest resting muscle sympathetic activity (SNA) is elevated in lowlanders at altitude. Our study examined how this influences vascular function and whether highland natives exhibit similar sympathetic hyperactivity at altitude. METHODS: SNA (microneurography) was assessed in lowland dwellers (n=14; age=27±6yrs) and locally recruited Nepalese Sherpa (n=9; age=32±11yrs) at both low altitude (Kelowna, Canada, 344m; Kathmandu, Nepal, 1400m) and following a 9 day ascent to the Ev-K2-CNR research facility (Khumbu Region, Nepal, 5050m). Burst frequency (bursts/min), incidence (bursts/100 heart-beats), and total SNA (frequency*amplitude) data was collected during a 10 minute period of supine rest. Transduction was assessed through the relationship between resting burst frequency, mean arterial pressure (MAP), and total peripheral resistance (TPR). T-tests adjusted for multiple comparisons assessed differences between Sherpa and lowlanders at different altitudes. RESULTS: Resting burst frequency (11±5 vs 30±6 burst/min), burst incidence (23±12 vs 50±15 bursts/100hb) and total SNA (563.6±276.2 vs 1563.5±421.1 au) were all elevated (p<0.001) in lowlanders at 5050m. Similar non-significant responses were observed in Sherpa (14±2 vs 23±11 bursts/min; 23±5 vs 44±20 bursts/100hb; 710.0±173.0 vs 1193.7±546.4 au; P>0.05). There were no SNA differences between groups at low altitude. However, lowlanders had higher burst frequency (P<0.05), incidence (P<0.01), and a trend for higher total SNA (P<0.05) at 5050m compared to Sherpa. Vascular transduction (MAP/burst/min) was reduced in both lowlanders and Sherpa (P<0.05) at 5050m though no differences were observed between groups at either low (P>0.05) or high (P>0.05) altitude. CONCLUSION: Our data shows elevated SNA in both high altitude natives and lowland dwellers at high altitude. However, sympathetic hyperactivity is offset by reduced vascular responsiveness or competing dilatory mechanisms. Furthermore, sympathetic hyperactivity observed in Sherpa appears to be specific to high altitude exposure as it was reduced at lower elevations despite permanent residence at altitude. ACKNOWLEDGEMENTS: This study was supported by NSERC and the President’s Grant for the Creative Performing Arts - Human Performance Scholarship (U-Alberta).
Abstract: W49

CHANGES IN HUMAN CORONARY PERFUSION FOLLOWING ACUTE AND PROLONGED HIGH ALTITUDE EXPOSURE.
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INTRODUCTION: Previously, in a small group of participants (n=3), coronary blood flow was shown to decrease below sea level values when measured invasively following 10 days of acclimatization to high altitude (HA; 3100m). This phenomenon was attributed to an increase in O2 extraction rather than changes in O2 delivery or cardiac function. To extend these findings, we employed noninvasive measurements in a larger subject pool to compare changes in coronary blood velocity (CBV) and myocardial workload (RPP; systolic blood pressure*heart rate) at sea level (SL), and with acute and prolonged HA. We hypothesized that (1) CBV would increase acutely in relation to changes in RPP and end-tidal gases and (2) decrease below SL with prolonged HA exposure despite elevated RPP.

METHODS: Resting mean blood velocity of the left anterior descending artery (LADVmean) was assessed, using Doppler echocardiography, in male participants (n=7; 27.6±2 yrs; mean±SE) at SL (344 m) and following acute (80-150 min) and prolonged (5-11 days) exposure to HA (3800 m). Heart rate, blood pressure, end-tidal gases, and O2 saturation (SpO2) were recorded at each time point.

RESULTS: SpO2 decreased from SL values (97±0.7 %) during acute HA (85±1.3 %; P<0.01) and improved significantly during prolonged HA (88±0.6 %; P<0.01). With acute HA both LADVmean and RPP increased significantly compared to SL (SL: 20.7±1 cm/s, 5960 ± 226 beats/min•mmHg; Acute HA: 31.2±2 cm/s, 8059±1214 bpm•mmHg; P<0.01). However, with prolonged HA exposure LADVmean was restored to sea level values (19.3±1 cm/s; P=0.70) while RPP remained elevated (8439.7±1947 bpm•mmHg, P<0.01 compared to SL).

CONCLUSION: In summary, acute HA exposure increases both LADVmean and RPP compared to SL, while prolonged HA exposure reestablished SL LADVmean values despite persistently elevated RPP. These findings suggest that changes in coronary perfusion during prolonged HA exposure is likely influenced by both improved O2 delivery and extraction.

Abstract: W50

EFFECT OF NORMOBARIC HYPOXIA TREATMENT ON PLASMA VOLUME ACCLIMATIZATION UPON REINTRODUCTION TO ALTITUDE FOLLOWING 12 DAYS AT SEA LEVEL
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INTRODUCTION: Plasma volume (PV) is reduced in sea-level (SL) residents during altitude acclimatization (ACC). Following return to SL, data are limited on PV restoration rate and whether PV restoration rate is affected by normobaric hypoxia (NH) treatment. This study determined if daily NH exposures affect PV restoration rate at SL after ACC and if the ACC-induced PV reduction can be sustained during re-exposure to the same altitude (RA) with and without NH treatment. METHODS: Seventeen healthy SL residents (age=23±6years) underwent: 1) 4d at SL (baseline); 2) 12d of ACC (4300m; Pb=460 torr); 3) 12d at SL, with 9d (3h/day) exposed to either NH (n=9; FiO2=0.122) or “sham” (n=8; FiO2=0.209) treatment; and 4) a 24-hour RA (hypobaric chamber, Pb=460 torr). Change in PV from baseline (∆PV) was calculated from hemoglobin and hematocrit measured at SL, during ACC (ACC2 and 11), at SL following ACC (NH1, 5, and 9), pre-RA at SL, and at hour 17 of RA (Dill and Costill, 1974).

RESULTS: There was no difference between groups on any test day so data were combined (p>0.05). From baseline to ACC2 and ACC11, ∆PV was -13.4 ± 7.5% and -21.7 ± 9.2%, respectively. At SL following ACC, ∆PV was -7.5 ± 9.0% on NH1 (p<0.05); but did not differ from baseline on any other SL day (P>0.05). During RA, ∆PV (-14.7 ± 10.1%) was similar to ACC2 (-13.4 ± 7.5%, p>0.05) but different compared to ACC11 (-21.7 ± 9.2%, p<0.05).

CONCLUSION: These results suggest that following ACC: 1) PV returns to baseline levels within 5 days at SL; 2) NH treatment while living at SL for 12 days following ACC does not influence PV restoration rate; and 3)the ACC-induced reduction in PV following 12 days of exposure to 4300m was not retained upon RA regardless of treatment.
INTRODUCTION: We examined the influence of myocardial workload on the coronary vascular response to poikilocapnic, isocapnic, and hypercapnic hypoxia in humans. We hypothesized that cardiac-specific $\beta_1$-receptor blockade would attenuate the coronary artery blood velocity response to $\text{PO}_2$ and $\text{PCO}_2$ manipulations due to a reduced myocardial workload index. METHODS: Participants (n=11, 25±3 years) received an intravenous bolus (500 µg/kg) of Esmolol ($\beta_1$-adrenergic antagonist) followed by a continuous infusion at 150 µg/kg/min volume-matched saline (placebo) administered in a double-blind, randomized order. Participants were then exposed to poikilocapnic hypoxia ($P_{ET, O_2} = 45 \text{mmHg}$), isocapnic hypoxia ($P_{ET, CO_2} = 45 \text{mmHg}$, $P_{ET, CO_2} = \text{baseline}$) and hypercapnic hypoxia ($P_{ET, CO_2} = 45 \text{mmHg}$, $P_{ET, CO_2} = +3 \text{mmHg}$ from baseline) using end-tidal forcing. Data were obtained at baseline and following 5-min of steady state at each gas manipulation, and included measures of left anterior descending coronary blood velocity (LAD$_{Vmean}$; transthoracic Doppler echocardiography), heart rate (HR; ECG) and arterial blood pressure (photoplethysmography). Rate pressure product [RPP; systolic blood pressure ($\text{SBP}$*$\text{HR}$)] was calculated as an index of myocardial workload. Coronary vascular resistance (CVR; mean arterial pressure/LAD$_{Vmean}$) was estimated to account for changing perfusion pressure. RESULTS: Both RPP and SBP increased from baseline during all gas manipulations (main effects; p<0.05) and RPP was attenuated by 11.2±26.2% (mean±SEM) following $\beta_1$-blockade across all gas manipulations (main effect; p<0.05). $\beta_1$-blockade did not influence the LAD$_{Vmean}$ response (p=0.8) which increased 7.8±1.4cm/s in poikilocapnic hypoxia (p<0.01), 9.3±1.3cm/s in isocapnic hypoxia (p<0.01), and 10.5±1.6cm/s in hypercapnic hypoxia (p<0.01) from baseline. CVR was reduced across all gas manipulations (main effect; p<0.01) and was not influenced by $\beta_1$-blockade (p=0.3). CONCLUSION: Our data suggest, over the blood gas range studied, the coronary vascular response to $O_2$ and $CO_2$ was conserved despite significant reductions in myocardial workload. Funding: NSERC, CFI.

Abstract: W52

MYOCARDIAL ADAPTATIONS DURING GRADED ALTITUDE EXPOSURE: DOES AGE MATTER?

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INTRODUCTION: Healthy individuals ascending to high-altitude experience hypoxia-induced cardiopulmonary perturbations. However, it is unclear if decrements in cardiac function observed with advancing age exacerbate cardiopulmonary disturbances at altitude. Accordingly, this study investigated the influence of age on myocardial adaptations during graded altitude exposure. METHODS: Echocardiography was used to assess left (LV) and right (RV) ventricular function in 27 individuals (16men; Age: 23-64yr) during 11 days of graded altitude exposure (Day0: 850m; Day3: 3505m; Day8: 4837m; Day11/post-climb: 850m) whist summiting Mount Kilimanjaro (5895m).

RESULTS: Baseline RV function (e.g., RV EDA, TAPSE) was similar across the cohort, while typical changes in LV function (e.g., decreased LV EDV, E/A; increased E/E') were observed in older subjects. During the ascent RV systolic pressure progressively increased from Day0 (19±4mmHg) to Day3 (27±8mmHg, p<0.01) and Day8 (33±8mmHg, p<0.01), while LV filling pressures decreased from Day0 (5.6±0.9) to Day3 (5.1±0.8, p<0.01) and Day8 (4.7±1.0, p<0.01). RV systolic pressure and LV filling pressures returned to baseline post-climb (p>0.05). RV end-diastolic (Day0: 20.8±4.3cm; Day3: 22.0±4.8cm; Day8: 22.3±4.5cm, p<0.01) and end-systolic (Day0: 11.5±2.7cm; Day3: 13.2±3.3cm; Day8: 13.4±3.1cm, p<0.01) areas increased during the ascent, while LV end-diastolic (Day0: 135±28ml; Day3: 122±28ml; Day8: 120±29ml, p<0.01) and end-systolic (Day0: 64±21ml; Day3: 57±18ml; Day8: 56±17ml, p<0.01) volumes decreased. RV areas and LV volumes were similar on Day3 and Day8 (p>0.05) and returned to baseline post-
climb (p>0.05). While age-dependent differences in LV function were evident at all altitudes, relative perturbations during graded altitude exposure were independent of age. CONCLUSIONS: Altitude-induced myocardial adaptations are chamber specific, secondary to hypoxia-induced hemodynamic changes. Despite progressive hemodynamic perturbations during graded altitude exposure, LV and RV functional changes plateaued, suggesting myocardial adaptation. Myocardial adaptations were similar across the cohort, despite diminished LV diastolic function in older individuals. Future studies should interrogate if age-dependent differences at rest are exacerbated by exercise at high-altitude.

Abstract: W53

NORMOBARIC HYPOXIA PROVOKES SIMILAR DECREASE IN EXERCISE PERFORMANCE IN PRE-TERM AND FULL-TERM BORN ADULTS

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INTRODUCTION: Reduced exercise capacity is often reported in individuals born prematurely. However, the potential influence of hypoxia on exercise performance in pre-term born individuals is currently unresolved. We aimed to compare the effects of hypoxia on maximal aerobic power (MAP) between pre-term born adults and their age and peak oxygen uptake matched controls born at full-term. METHODS: Thirty-five healthy adults (Pre-term group, n=21, gestational age=29±3 weeks (mean ± SD)); Full-term group, n=14, gestational age=39±1 weeks) performed two graded exercise tests to volitional exhaustion in a randomized manner. Tests were performed on a cycle ergometer in normoxia (Nor; FO2 =0.21; PO2 =147 mmHg) and normobaric hypoxia (Hyp; FO2 =0.13; PO2 =91 mmHg). MAP was calculated based on the completed workloads. Minute ventilation and the first ventilatory threshold (VT), calculated with the respiratory equivalent, were derived from continuous pneumotachograph measurements. RESULTS: Absolute MAP was lower in pre-term compared to full-term individuals in both, normoxia (Pre-term = 272±39 W; Full-term = 322±33 W; p<0.01) and hypoxia (Pre-term = 234±36 W; Full-term = 273±28 W; p<0.01). However, hypoxia-induced reduction of MAP was similar between the two groups (Pre-term = -8.6±0.4%; Full-term = -8.5±0.5%; p=0.31). Power outputs at VT were lower in pre-term than full-term group during normoxic (Pre-term = 172±43; Full-term = 223±34 W; p<0.01) and hypoxic (Pre-term = 156±34 W; Full-term = 183±27 W; p<0.05) exercise. No differences were noted between the groups in ventilation at VT in both conditions. CONCLUSIONS: Hypoxia provokes similar relative reduction in maximal aerobic power and submaximal ventilatory threshold in healthy pre-term and full-term born adults with comparable peak oxygen consumption levels. These data suggest that exercising in normobaric hypoxia does not exert higher ventilatory and metabolic load in otherwise healthy individuals born prematurely.

ACKNOWLEDGEMENTS: This work was funded by Slovene Research Agency (Grant No. J3-7536) and Ljubljana Univ Medical Centre (Grant Nr-TP20140088).

Abstract: W54

ASSESSING PHYSIOLOGICAL FUNCTION DURING A HIGH-ALTITUDE HIKE USING REAL-TIME MONITORING

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Assessing the physiological responses to exercise at high altitude in real time or using cloud-based data storage has important implications for remote monitoring of human health and well-being in challenging environments. PURPOSE: To determine the feasibility of using real-time monitoring to assess the cardiovascular responses to a simulated climb for military operations. METHODS: Seventy-four male sea level (SL) residents participated in this study after completing the Army Physical Fitness Test. Subjects were flown from SL to high altitude (HA) and completed a timed 5.9-km hike with a 35-pound rucksack from 3239 m to 3840 m the morning after arrival at HA. Heart rate (from ECG) and step count (cadence) were assessed using a shirt with built-in sensors (Carre Technologies inc., Hexoskin). For analysis, the 5.9 km course was divided into four equal segments based on step count. Elevation gain for each of the segments was determined from topographical maps (Segment 1 = 123 m, 2 = 178, 3 = 142 m, and 4 = 262 m). Average and maximal heart rates were calculated for each of the segments. RESULTS: Average heart rates for the four segments corresponding to 74.5%, 86.1%, 84.6%, and 85.9% of estimated heart rate max. Heart rate reflected the elevation gain except for Segment 4 which had the greatest elevation gain but similar heart rates to Segment 3. Further analysis indicated
that subjects had more stops during this segment (73% of all stops occurred in Segment 4) which resulted in an overall lower average. CONCLUSIONS: These results suggest that real-time monitoring for multiple variables simultaneously (heart rate, ECG, step count) in the field is a viable means of assessing physiological function and simulating a military operation with a 610 m elevation gain results in relatively high heart rates that generally reflect elevation gained.

Abstract: W55
FACTORS PREDICTING PERFORMANCE DURING A HIGH ALTITUDE HIKE
Brown, Allison; Deel, Nicole; Davis, John; Achatz, Eric; Miller, Michael; Reitinger, Jeremy; Reno, Elaine; Yeager, Luke; Wislowski, Ann; Subudhi, Andrew; Roach, Robert
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INTRODUCTION: Civilian and military personnel often endure heavy exercise loads at high altitude. To improve performance at altitude, it is important to understand what factors predict human performance at high altitude. PURPOSE: To assess whether a physical fitness test at sea-level can be used to predict exercise performance at high altitude. METHODS: Subjects were recruited from mid-Michigan (sea level) and were required to achieve a high score on the Army Physical Fitness Test (APFT). The APFT performance trial consisted of a pushup test (maximum number of pushups in 2 min), a sit-up test (maximum number of sit-ups in 2 min), and a timed two-mile run. Ninety-nine subjects completed APFT testing at sea-level before being transported to Breckenridge, Colorado (2766 m) to undergo APFT testing immediately upon arrival. On day two in Colorado, subjects wore a 35-pound rucksack during a timed, 3.7-mile uphill hike from 3239 m to 3840 m. Multivariable regression analysis was performed to predict which variable(s) (height, weight, pushup score on APFT, sit-up score on APFT, 2 mile run time at the performance trial and at altitude) were most important in determining hike time. RESULTS: One multi-variable linear regression model indicated a significant correlation ($p < 0.05$) between subject’s weight and two-mile run time at the APFT performance trial at sea level relative to hike time ($r^2 = .33$). These findings indicate that as body weight increases hike time was slower, and that a faster 2-mile run time resulted in a faster hike time. A second multi-variable linear regression analysis indicated a significant relationship between the 2-mile run time, sit-ups, and push-ups at high altitude, and subject’s weight relative to hike time ($r^2 = .52$). CONCLUSIONS: Overall, the APFT high-altitude trial was a better predictor of performance given that the model accounted for 52% of the variance relative to hike performance.

Abstract: W56
MUSCLE PERFUSION AND DEOXYGENATION DURING SUBMAXIMAL LEG- vs. ARM-CYCLING WITH BLOOD FLOW RESTRICTION AND HYPOXIA
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INTRODUCTION: Exercise combined with blood flow restriction (BFR) induces local accumulation of metabolites, muscle deoxygenation, and ischemia (Scott, et al., 2014), whereas normobaric hypoxia (NH; decreased oxygen fraction of ambient air) leads to compensatory vasodilation (Hultgren, 1996) and muscle deoxygenation. Our aim was to compare muscle perfusion and deoxygenation during submaximal leg- vs. arm-cycling in combined BFR and NH conditions. METHODS: Subjects ($n=11$ legs; $n=14$ arms) performed a 6-min submaximal cycling bout (1.5 W/kg legs, 1 W/kg arms) in four randomized conditions (normoxia and 3800m (NH)), each at 0% and 45% BFR). BFR was normalized as a percentage of the pulse elimination pressure. Blood flow (ml/min) and diameter (mm) were measured pre- and post-exercise with Doppler ultrasound, while total hemoglobin (tHb, arbitrary unit) and tissue saturation index (%) were averaged over the last minute (PortaMon-Artinis). RESULTS: Blood flow increased post-exercise (54% legs, 101% arms, $p<0.01$, respectively) and decreased with BFR (32% arms, $p<0.001$; 6% legs, NS). Diameter increased with NH (4% legs, 5% arms, $p<0.05$, respectively) and also increased post-exercise (7% arms, $p<0.01$; 0.5% legs, NS). BFR increased tHb (90% legs, $p<0.01$; 146% arms, $p<0.05$, respectively). NH decreased TSI (8% legs, 10% arms, $p<0.001$, respectively). CONCLUSION: Occlusion conditions resulted in decreased limb blood flow. Additionally, BFR altered tHb likely from an increased tissue blood volume, and thus blood perfusion was altered in legs and arms. Limb differences may be influenced by oxygen utilization due to fiber type, muscle mass, and location. Hypoxia clearly demonstrated a hypoxia-induced-vasodilation in the femoral/brachial arteries, and a corresponding decrease in the percentage of oxygenated tissue. REFERENCES: Scott BR, Slattery KM, Sculley DV, Dascombe BJ. Hypoxia and resistance exercise: a comparison of localized and systemic methods. Sports Med 44: 1037-1054, 2014. Hultgren HN. High-altitude pulmonary edema: current concepts. Ann Rev Med 47: 267–284, 1996.
Abstract: W57
THERMOREGULATORY RESPONSES TO COMBINED HEAT AND HYPOXIA DURING EXERCISE
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Heat and high altitude acclimation strategies are proven to improve performance in extreme environments. Evidence exists to indicate that some degree of cross-acclimation might occur in response to heat and hypoxic stress; however, thermoregulatory responses to heat stress in a hypoxic environment have not been thoroughly evaluated. This study therefore sought to determine the independent influence of hypoxia (13% O2) on thermoregulatory responses to exercise in uncompensable hot conditions. Eight participants [1.75(0.06) m; 70.2(6.8) kg; 25(4) y; 3.78(0.67) L/min] performed two experimental trials at a fixed heat production (Hprod): one in normoxia (NORM) and one in normobaric hypoxia (HYP). The protocol comprised 90 min of cycling; 45 min were performed at 34(0.2) ºC, 45.9(2.8)% RH to achieve steady-state esophageal temperature prior to beginning an incremental humidity protocol (34 ºC, +4% RH every 7.5 min) for the remaining 45 min of exercise. Mean Hprod was not different between NORM and HYP [480(38) vs. 499(37) W; P=0.24], and as a result, neither mean local sweat rates [1.46(0.15) vs. 1.41(0.16) mg/cm2/min; P=0.93] nor whole-body sweat losses [1029(137) vs. 1025(150) g; P=0.95] were different between trials. Mean laser-Doppler flux values (LDF; arbitrary units) were not different between NORM and HYP [80(29) vs. 81(17); P=0.49]; however, when normalized as a percentage of maximum, LDF values were higher in HYP compared to NORM [38.5(11.5) vs. 28.5(6.5)%LDFmax; P<0.01]. Despite potentially greater skin blood flow in hypoxia by ~30%, there was no difference in the critical ambient vapour pressure (Pcrit) at the inflection of esophageal temperature [NORM: 3.67(0.35) kPa; HYP: 3.46(0.39) kPa; P=0.22]. Thus, our data suggest that (i) there is no independent effect of hypoxia on the core temperature or sweating responses to exercise in very hot-humid conditions, and (ii) maximum heat loss is unaffected by exposure to normobaric hypoxia.

Abstract: W58
A PREDICTIVE TOOL FOR LIFE-THREATENING ILLNESS AT HIGH ALTITUDE: PILOT DATA AND RECOMMENDATIONS
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INTRODUCTION: Death from acute altitude illness is rare but theoretically avoidable with early detection. There is an unmet need for a simple, predictive tool to identify individuals at high risk of death. We conducted a pilot of a draft Altitude Risk Prediction Score (ARP), a broad questionnaire designed by consensus and intended to be evaluated subsequently in large prospective studies. We evaluated the utility and clarity of the draft ARP for laypeople in a field environment. METHODS: Subjects (n = 28) travelled from sea level (~50m) to 3700m, spending 4 days there before ascending to 5200m for 7 days. The ARP was administered once daily and twice on the day subjects ascended to 5200m. The primary outcomes related to appraisal of the questionnaire itself, while secondary outcomes examining the questionnaires ability to detect altitude illness were unplanned descent & severe AMS (LLS >7). RESULTS: The questionnaires were completed with minimal logistical complications. The external observation section required further explanation but all symptom questions were completed adequately. Some of the more burdensome components of the questionnaire were found to be redundant and could hence be removed from the evaluation version. CONCLUSIONS: Clarifying the question related to unsteadiness and removing the external observer report and outcome assessment would increase the accessibility to laypersons. Once refined, we propose a large scale, multi-centre study to quantify the utility of each component of the ARP for predicting severe acute altitude illness. Such a study would derive a short, simple questionnaire that high-altitude sojourners without medical training could use to identify those who should be evacuated from altitude. FUNDING: Apex, The Univ Edinburgh, The Wilderness Medicine Society, The Carnegie Trust, The Scottish Mountaineering Trust, The Royal College of Physicians of Edinburgh & the Mount Everest Foundation.
Abstract: W59

HYPOXIA IN AUSTERE ENVIRONMENTS

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OBJECTIVE: To inform healthcare professionals that international grants can be used to gain firsthand experience in high altitude environments which would be useful for endeavors that might require skills obtained from serving in hypoxic conditions. ABSTRACT: The Mayo International Health Program is a grant that serves to provide medical residents and fellows with an opportunity to serve and learn from varying international health organizations in resource-scarce areas. Likewise, there are many other programs available to all providers who wish to gain competency with hypoxic medicine and altitude pursuits. Many missions, other than Medecins Sans Frontieres (MSF), provide healthcare professionals with an opportunity to serve abroad and a short list is provided herein. I received a grant to travel to Kathmandu, Nepal in November of 2015 to learn from the local physicians about the unique challenges of delivering an anesthetic at an altitude of 4600 feet. In addition to the hypoxic physiologic challenges, they face adversity from resource scarcity, cleanliness, facility limitations, and even cultural issues. Because of this, endotracheal tubes sometimes had to be reused, capnography was not routine for surgical procedures, oxygen pipelines were malfunctioning, and patients routinely had to purchase their own medications at an outside pharmacy and bring a “shopping list” into the hospital for their admission. To that end, careful attention should be paid to the resources of the intended destination through communication with the host institution to help alleviate the resource vacuum when visiting. In certain instances, technology companies could help to provide demonstration units for certain duration or donation to the host facilities in need. These grants are not always the length of a typical MSF contract lasting two months to two years and serve as great primer in the quest of vertical pursuits to come.

Abstract: W60

THE INFLUENCE OF EXERCISE WITH AND WITHOUT ARTERIAL OCCLUSION ON THE DISTRIBUTION OF NO2 AND NO3 IN THE BLOOD

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METHODS: After warming up for 10 min with 50% of the maximum load reached in an incremental test 10 male subjects performed maximal hand grip exercise bouts to exhaustion (Wingate test, WT). Exercise was followed by 45 min of recovery. The WT was performed twice, with (O) and without (F) arterial occlusion. Blood was taken from a heated hand vein and from a cubital vein draining the working muscles. Voluntary EMG and M-waves were recorded from the flexor muscles. In plasma [nitrate] and [nitrite] were determined by GC-MS. [Lac] in plasma was determined by means of an enzyme electrode (Biosen 5030, EKF). [K+], [Na+], [Cl-], pH and blood gases were analyzed by conventional methods (ABL 505, Radiometer). Additionally HBO2, HCT, plasma protein concentration, inorganic phosphate ([Pi]), and [NH3] were measured. Forearm blood flow was determined by venous occlusion plethysmography. For statistical evaluation two-way-ANOVA with repeated measurements was used. RESULTS AND DISCUSSION: Performance times F: 44.35±8.3 min and O: 39.83±7.94 min were not significantly different. The same held true for Power and contraction frequency. EMGrms and the m-waves were not different as well. The electrolytes, lactate, NH3, Pi did not show any influence of the occlusion. Blood flow was not different after exercise. Under both conditions [NO3]ery seems not to be influenced neither by exercise nor by occlusion. [NO3]pl seems to reflect water shifts out of the plasma, only. However, [NO2]ery increases by about 110% (p<0.001) whereas [NO2]pl decreases by about 10% (p<0.001). A shift of NO2 from plasma to the red cells is not sufficient to explain the increase inside the cells.
Altitude acclimatization (ACC) improves some physiologic responses (e.g., increased oxygen saturation) during submaximal exercise in sea level (SL) residents sojourning at altitude. ACC is slowly lost after descent to SL. This study determined if normobaric hypoxia (NH) treatment following ACC could retain ACC-induced improvements during early re-exposure to altitude (RA). Seventeen SL residents (23 ± 6 yrs) were tested in the following order: 1) SL baseline (Pb=755 Torr); 2) 12 days of ACC (4300m; Pb=460 Torr); 3) 12d at SL with 9d (3 hrs/d) under conditions of either NH (n=9, FiO₂=0.122) or “SHAM” (n=8, FiO₂=0.209) treatment; and 4) 1d of RA (hypobaric chamber, Pb=460 Torr). Steady-state values for ventilatory equivalent (Ve/O₂), heart rate (HR), and percent oxygen saturation (%SaO₂) were collected during 10 mins of treadmill walking at 40% of SL peak oxygen uptake at SL, days 2 & 11 of ACC, and during the 20thour of RA. There were no differences between treatment groups for any measure on any of the test days (P>0.05), so all data were combined. From SL to ACC2, Ve/O₂ (26.3 ± 2.7 vs 36.2 ± 4.5) and HR (112 ± 8 vs 140 ± 14 bpm) increased (P<0.05) respectively, while %SaO₂ decreased (97 ± 2 vs 75 ± 5%, P<0.05). By ACC11, Ve/O₂ (39.3 ± 4.5) and %SaO₂ (79 ± 4%) were higher (P<0.05) while HR was lower (129 ± 12 bpm, P<0.05) when compared to ACC2. On RA, there were no differences (P>0.05) from ACC11 for Ve/O₂ (41.5 ± 4.6), %SaO₂ (79 ± 4%), or HR (135 ± 15 bpm). We conclude that ACC-induced improvements in Ve/O₂, %SaO₂, and HR during submaximal exercise were preserved during RA following 12 d at SL and that NH treatment was inconsequential. Author views not official Army or DoD policy.

INTRODUCTION: Highland populations have persisted at altitude for many generations despite the chronic, unavoidable stress of hypoxia. Several hypoxia-related candidate genes have been identified as targets of natural selection in these populations, and some variants within these genes are associated with the relatively lower (sea-level) hemoglobin concentration ([Hb]) exhibited by many Tibetans at high altitude. Our previous studies identified the heme oxygenase 2/NmrA-like family domain-containing protein 1 (HMOX2/NMRAL1) gene region as a top candidate for adaptation to altitude in two geographically distinct Tibetan populations. Heme oxygenase is involved in the break down of heme leading to production of carbon monoxide; NmrA-like family domain-containing protein 1 plays a role in nitric oxide production. METHODS: To determine whether variants tagging the putatively adaptive HMOX2/NMRAL1 gene region in Tibetans are associated with oxygen transport in a Tibetan population at 4200m, we compared the number of putatively adaptive haplotype copies, based on single nucleotide polymorphism (SNP) genotypes, to measurements of peak VO₂, ventilation, lung diffusional conductance, cardiac output, and muscle O₂ diffusion conductance in 21 Tibetan males at peak exercise on a cycle ergometer. RESULTS: The HMOX2/NMRAL1 adaptive haplotype showed a significant positive relationship with VO₂/kg (p<0.05) and was further associated with cardiac output/kg (p < 0.05) but not [Hb], ventilation, nor diffusion capacity in lung or muscle. CONCLUSION: These findings suggest that specific genetic variations at the adaptive HMOX2/NMRAL1 locus likely convey an advantage for oxygen transport at altitude in Tibetans. Our previous physiological analyses revealed associations between relatively lower [Hb] and higher cardiac output, ventilation, and muscle diffusion capacity in this population, suggesting further interplay among these key oxygen transport components and adaptive genetic factors. FUNDING: National Institutes of Health - R00 HL118215.
**Thursday, 9 February 2017**

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<th>Time</th>
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<tr>
<td>0630-0830</td>
<td>Breakfast, Lago Restaurant</td>
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<td>0700-0800</td>
<td>Registration, Heritage Hall</td>
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<tr>
<td>0800-0930</td>
<td><strong>Protecting the Brain from Hypoxia</strong></td>
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<td>0800-0830</td>
<td>Functional Oxygen Sensitivity of Astrocytes—Alexander Gourine</td>
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<td>0830-0900</td>
<td>Human Cerebral Blood Flow Control During Hypoxia—Marc Poulin</td>
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<td>0900-0930</td>
<td>Oxygen Regulation of Breathing Through an Olfactory Receptor Activated by Lactate—Andy Chang</td>
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<td>0930-1000</td>
<td><strong>Refreshment Break, Heritage Hall</strong></td>
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<tr>
<td>1000-1130</td>
<td><strong>Novel Strategies for Hypoxia Tolerance</strong></td>
</tr>
<tr>
<td>1000-1030</td>
<td>Beyond Hemoglobin: Red Blood Cell Potentiation of O2 Delivery in Fish…and Other Vertebrates?—Colin Brauner</td>
</tr>
<tr>
<td>1030-1100</td>
<td>Functional Roles of Globin Proteins in Hypoxia-tolerant Vertebrates—Angela Fago</td>
</tr>
<tr>
<td>1100-1130</td>
<td>Birds: Living or Transiting at High Altitude—Sabine Lague</td>
</tr>
<tr>
<td>1130-1600</td>
<td><strong>Ski Break</strong></td>
</tr>
<tr>
<td>1130-1330</td>
<td>Lunch, Lago Restaurant</td>
</tr>
<tr>
<td>1600-1830</td>
<td><strong>Hot Topics in Hypoxia II—Selected Abstracts</strong></td>
</tr>
<tr>
<td>1900-2130</td>
<td>Dinner, Victoria Dining Room</td>
</tr>
<tr>
<td>2030-2130</td>
<td><strong>Lands of Lost Borders</strong>—Kate Harris</td>
</tr>
</tbody>
</table>
Thursday, 9 February

0800-0930
Protecting the Brain from Hypoxia
Chairs: Marc Poulin and Denny Levett

0800-0830 Functional Oxygen Sensitivity of Astrocytes—Alexander Gourine

In terrestrial mammals the oxygen storage capacity of the central nervous system is limited and neuronal function is rapidly impaired if oxygen supply is interrupted even for a short period of time. However, oxygen tension (PO$_2$) at the level of the peripheral (arterial) chemoreceptor is not sensitive to regional CNS differences in oxygen demands that reflect variable activity levels or local tissue hypoxia, pointing to the necessity of a functional brain oxygen sensor. We now show that astrocytes, the most numerous brain glial cells, are highly sensitive to physiological changes in PO$_2$. Astrocytes respond to decreases in PO$_2$ a few mmHg below normal brain oxygenation with elevations in intracellular calcium. The hypoxia sensor of astrocytes resides in the mitochondria where oxygen is consumed. Physiological decrease in PO$_2$ inhibits astroglial mitochondrial respiration, leading to mitochondrial depolarization, production of free radicals, lipid peroxidation, activation of phospholipase C, IP$_3$ receptors and recruitment of Ca$^{2+}$ from the intracellular stores. Hypoxia-induced [Ca$^{2+}$]i increases in astrocytes trigger fusion of vesicular compartments containing ATP. Blockade of astrocytic signaling by overexpression of ATP-degrading enzymes or targeted astrocyte-specific expression of tetanus toxin (to interfere with vesicular release mechanisms) within the respiratory rhythm-generating circuits of the brainstem reveals the fundamental physiological role of astroglial oxygen sensitivity - in low oxygen conditions (environmental hypoxia) this mechanism maintains enhanced breathing even in the absence of peripheral chemoreceptor oxygen sensing. These results demonstrate that astrocytes are functionally specialized CNS oxygen sensors tuned for rapid detection of physiological changes in brain oxygenation.

0830-0830 Human Cerebral Blood Flow Control During Hypoxia—Marc Poulin

The brain is a vital organ that relies on a constant and adequate blood flow to match oxygen and glucose delivery with the local metabolic demands of active neurons. Thus, exquisite regulation of cerebral blood flow (CBF) is particularly important under hypoxic conditions to prevent a detrimental decrease in the partial pressure of oxygen within the brain tissues. Cerebrovascular sensitivity to hypoxia, assessed as the change in CBF during a hypoxic challenge, represents the capacity of cerebral vessels to respond to, and compensate for, a reduced oxygen supply, and has been shown to be impaired or blunted in a number of conditions. For instance, this is observed with aging, and in clinical conditions such as untreated obstructive sleep apnea (OSA) and in healthy humans exposed to intermittent hypoxia. Further, alterations in arterial blood gases, which occur with the hypoxia of high altitude, are associated with impairment of cognitive functions, potentially via a disruption of neurovascular coupling.

Studies from clinical and healthy populations will be presented, using a translational physiology approach, to investigate human CBF control during hypoxia. First, results from studies in patients with OSA and chronic obstructive pulmonary disease will be presented to identify the effects of aging and the disease processes on cerebrovascular sensitivity to hypoxia. Second, data emerging from experimental human models of intermittent hypoxia, during wakefulness and during sleep, will be reviewed to highlight the effects of intermittent hypoxia on the brain.

Further, results from a number of pharmacological interventions will be presented, which have helped better elucidate the basic mechanisms of cerebrovascular regulation in humans. Finally, new data from studies on the effects of intermittent exposure to very high altitudes in altitude-naïve volunteers and workers will be introduced. Implications for healthy volunteers, workers and selected patient populations traveling to very high altitudes will be discussed.
Animals have evolved homeostatic responses to changes in oxygen availability that act on different time scales. On the acute time scale, the carotid body (CB) is the major sensor of arterial blood oxygen that stimulates ventilation within seconds of hypoxia. Even 90 years after its description as an oxygen sensor, the molecular mechanism of oxygen sensing in the CB is not well understood.

We took a genomic approach to identify putative oxygen sensors in the CB by comparing gene expression of the CB and adrenal medulla (AM) from wild-type adult mice. Looking for genes encoding fast signaling molecules, we found an olfactory receptor (Olfr78) expressed at higher levels in the CB versus AM. Using transgenic mice, we showed that Olfr78 is highly and selectively expressed in oxygen-sensitive glomus cells of the CB, and we observed that Olfr78 null mice failed to increase ventilation in hypoxia while responding normally to hypercapnia. Glomus cells were present in normal numbers and appear structurally intact in Olfr78 mutant CBs. However, nerve output from the CB in hypoxia was reduced by half in Olfr78 mutant preparations. Lactate, a metabolite that rapidly accumulates in hypoxia and induces hyperventilation, activated Olfr78 in heterologous expression experiments in a luciferase assay. In the CB, lactate induced calcium transients in glomus cells and stimulated nerve output through Olfr78.

We propose a model for CB oxygen sensing in which Olfr78 acts as a hypoxia sensor by detecting lactate produced when oxygen levels decline.
The Root effect is a pH-dependent reduction in haemoglobin-O\(_2\) carrying capacity unique to teleost fishes which represent half of all vertebrates. The Root effect has been ascribed specialised roles in retinal oxygenation and swimbladder inflation; however, we propose it may also be associated with greatly enhanced O\(_2\) delivery to other tissues such as muscle. During a generalized acidosis, catecholamines are released into the blood, activating red blood cell (RBC) Na\(^+\)/H\(^+\) exchange (NHE), thus protecting RBC pH and subsequent O\(_2\) binding at the gill. However, plasma-accessible carbonic anhydrase (CA) at the tissues (and absence at the gills) may result in selective short-circuiting of RBC NHE pH regulation within the circulation resulting in a large arterial-venous pH shift within the RBC. When rainbow trout are exposed to elevated water CO\(_2\), (1.5% CO\(_2\)) red muscle PO\(_2\) increases by 65%, which we estimate could double O\(_2\) delivery with no change in perfusion. Inhibiting plasma accessible CA abolished this effect illustrating its importance to this process. We calculate that selective short-circuiting of RBC NHE may double O\(_2\) delivery during exercise and even triple O\(_2\) delivery during some levels of hypoxia with no change in perfusion. Thus, the Root effect in teleosts is associated with greatly enhance O\(_2\) delivery to tissues other than the eye and swim-bladder, which may represent important selection pressures for the evolution of the Root effect. The potential for such a system to operate in other vertebrates will be discussed.

Globins are heme-containing proteins ubiquitously expressed in vertebrates, where they serve a broad range of biological functions, directly or indirectly related to the tight control of oxygen levels and its toxic products in vivo. Perhaps the most investigated of all proteins, hemoglobin and myoglobin are primarily involved in oxygen transport and storage, but also in facilitating arterial vasodilation, suppressing mitochondrial respiration and preventing tissue oxidative damage via accessory redox enzymatic activities during hypoxia. By contrast, the more recently discovered neuroglobin and cytoglobin do not seem to function as reversible oxygen carriers and are more prone to redox activities, although their exact biological roles remain to be clarified. In this context, hypoxia-tolerant ectotherms, such as goldfish and freshwater turtles that survive winter in extreme hypoxia, have proven as excellent models to appreciate the diversity of biological functions of globin proteins. Unraveling physiological roles of globin proteins in these extreme animals will clarify an important part of the adaptive mechanisms for surviving extreme fluctuations of oxygen availability that are prohibitive to mammals.
High altitude (HA) is physiologically challenging for most vertebrates because of hypoxia; however, many birds thrive at altitude. This talk will explore the physiological responses of HA waterfowl (geese and ducks), comparing the strategies of lifelong residents to those of transient sojourners, providing insight into how birds champion HA life.

To compare physiological strategies for maintaining oxygen supply in hypoxia, birds were cannulated (brachial artery and vein) and exposed at rest to 25-minute decreases in the equivalent fractional composition of inspired oxygen (0.12, 0.09, 0.07 and 0.05), and recovered to ambient conditions. Metabolic, respiratory (breathing frequency, tidal volume), cardiovascular (heart rate, stroke volume), and hematologic (hematocrit, haemoglobin concentration) variables were measured.

Bar-headed geese (BHG; Anser indicus) migrate biannually across the Himalayan mountains (>5,500m). While the physiology of bar-headed geese born and raised at sea level is well documented, the extent to which it might differ in HA BHG was unknown. We compared the hypoxic responses of sea level BHG and HA BHG (3,200m). The HA BHG exhibited lower oxygen consumption rates and significantly increased oxygen uptake.

Interested in whether HA waterfowl use similar strategies to maintain oxygen supply, we compared the physiological responses of HA BHG to those of Andean geese (AG; Chloephaga melanoptera), lifelong residents of the Andes (4,000-5,500m). Experiments were conducted at 3,200m in Tibet and Peru, respectively. BHG and AG used dramatically different strategies. BHG responded to hypoxia by increasing ventilation and heart rate, whereas AG increased lung oxygen extraction and stroke volume. Interestingly, several of these divergent avian responses share similarities with those of HA Tibetan and Andean humans.

We propose that transient HA performance in birds has favoured convective oxygen transport recruitment in hypoxia, whereas lifelong HA residency has favoured structural enhancements to the lungs and heart that increase lung oxygen diffusion and stroke volume.
EFFECT OF DEXAMETHASONE ON NOCTURNAL BREATHING IN LOWLANDERS WITH COPD TRAVELLING TO 3200M. RANDOMIZED PLACEBO-CONTROLLED TRIAL.

Furian, Michael; Lichtblau, Mona; Estebesova, Bermet; Aeschbacher, Sayaka S.; Osmonov, Batyr; Bisang, Maya; Nikiforov, Alexey; Knapp, Hannes; Latshang, Tsogyal D.; Ulrich, Silvia; Sooronbaev, Talant; Bloch, Konrad E.

1: Pulmonary Division and Sleep Disorders Center, Univ Hospital of Zurich, Zurich, Switzerland; 2: National Center for Cardiology and Internal Medicine, Bishkek, Kyrgyzstan. Email: michael.furian@usz.ch.

INTRODUCTION: We investigated the effect of preventive dexamethasone treatment on sleep related breathing disturbances in lowlanders with COPD staying at 3200m. METHODS: 112 COPD patients, GOLD grade 1-2, living below 800m were randomized to receive dexamethasone (2x4mg/d) or placebo 24hrs before ascent from 760m and while staying at 3200m. Co-primary outcomes assessed at 760m and during 2 nights at 3200m were mean nocturnal oxygen saturation (SpO2) by pulse oximetry and the apnea/hypopnea index (AHI). Registration: www.ClinicalTrial.gov: NCT02450994. RESULTS: In 57 patients (median age 57y, FEV1 84%pred) randomized to dexamethasone, median (quartiles) SpO2 and AHI at 760m were 92%(91;93), 25.8/h(16.3;37.1). In night 1 and 2 at 3200m, SpO2 and AHI were: 86%/84;88), 24.8/h(12.7;34.8) and 87%/86;89), 21.8/h(13.8;38.7), P<0.05 SpO2 night 1 at 3200m vs. 760m and vs. night 2; P=NS for changes in AHI. In 55 patients (median age 60y, FEV1 94%pred) randomized to placebo, SpO2 and AHI at 760m were 92%(91;93), 21.3/h(11.8;47.7). In night 1 and 2 at 3200m SpO2 and AHI were 84%/82;85), 39.8/h(20.9;63.1) and 85%/84;86), 37.4/h(16.5;59.5), P<0.05 SpO2 and AHI night 1 at 3200m vs. 760m and vs. night 2. During night 1 and 2 at 3200m, the altitude-related changes in SpO2 and AHI were reduced with dexamethasone compared to placebo: median difference(95%CI) SpO2 3%(2 to 4) and 3%(2 to 3); and median difference in AHI -15/h(-22 to -9) and -13/h(-21 to -8). CONCLUSIONS: In lowlanders with COPD travelling to high altitude preventive dexamethasone treatment improves nocturnal arterial oxygen saturation and reduces sleep related breathing disturbances.

GRANT SUPPORT: Swiss Lung Foundation, Lunge Zurich, Swiss National Science Foundation. See poster W28.

ALTITUDE RELATED ILLNESS IN LOWLANDERS WITH COPD TRAVELLING TO 3200M. RANDOMIZED TRIAL OF DEXAMETHASONE PROPHYLAXIS.

Furian, Michael; Lichtblau, Mona; Estebesova, Bermet; Aeschbacher, Sayaka S.; Osmonov, Batyr; Bisang, Maya; Knapp, Hannes; Latshang, Tsogyal D.; Ulrich, Silvia; Sooronbaev, Talant; Bloch, Konrad E.

1: Pulmonary Division and Sleep Disorders Center, Univ Hospital of Zurich, Zurich, Switzerland; 2: National Center for Cardiology and Internal Medicine, Bishkek, Kyrgyzstan. Email: michael.furian@usz.ch.

INTRODUCTION: We studied altitude related adverse health effects in lowlanders with COPD travelling to 3200m, and whether dexamethasone could prevent them. METHODS: 112 COPD patients, GOLD grade 1-2, living below 800m were randomized to receive dexamethasone (2x4mg/d) or placebo 24 hours before ascent from 760m and while staying at 3200m. Primary outcome assessed during 3 days at 3200m was the cumulative incidence of acute mountain sickness (AMSc score ≥0.7), severe hypoxemia (SpO2 <75% for >30min), and discomfort requiring descent or oxygen therapy. Secondary outcomes were arterial blood gases. www.ClinicalTrials.gov NCT02450968. RESULTS: 57 patients (median age 57y, FEV1 84%pred) were randomized to dexamethasone, 55 (median age 60y, FEV1 94%pred) to placebo. During 3 days at 3200m, 10 (18%) patients receiving dexamethasone, 11 (20%) receiving placebo had an altitude-related adverse effect (P=0.739). Within the first 24 hours at 3200m, 2 (4%) patients using dexamethasone and 8 (15%) using placebo had severe hypoxemia (P=0.04) and discomfort requiring descent or oxygen therapy. Secondary outcomes were arterial blood gases. www.ClinicalTrials.gov NCT02450968. With ascent from 760 to 3200m (day 2), PaO2 decreased from median (quartiles) 9.6kPa(9.2;10.0) to 8.2kPa(7.9;8.6) in the dexamethasone group and from 10.0kPa(9.1;10.5) to 8.0kPa(7.5;8.4) in the placebo group (altitude-related change...
with dexamethasone compared to placebo: median difference (95%CI) PaO2 0.4kPa (0.0;0.8, P<0.05) and PaCO2 -0.3kPa (-0.4; -0.1). **CONCLUSIONS:** In lowlanders with COPD, GOLD grade 1-2, staying 3 days at 3200m, the cumulative incidence of clinically relevant adverse health effects was 20% in participants using placebo. This was not altered by preventive dexamethasone therapy although dexamethasone improved hypoxemia at 3200m.

**GRANT SUPPORT:** Swiss Lung Foundation, Lunge Zurich, Swiss National Science Foundation. See poster F07.

**DEXTAMETHASONE REDUCES PULMONARY ARTERY PRESSURE IN LOWLANDERS WITH COPD TRAVELLING TO 3200M. RANDOMIZED, PLACEBO-CONTROLLED TRIAL**

**Lichtblau, Mona1; Furian, Michael1; Aeschbacher, Sayaka S1; Osmonov, Batyr2; Bisang, Maya1; Ulrich, Stefanie1; Knapp, Hannes1; Latshaw, Tsogyal D1; Mirrakhimov, Erkin2; Sooronbaev, Talant2; Bloch, Konrad E1; Ulrich, Silvia1**

1: Pulmonary Division and Sleep Disorders Center, Univ Hospital of Zurich, Zurich, Switzerland; 2: National Centers for Cardiology and Internal Medicine, Bishkek, Kyrgyzstan. Email: mona.lichtblau@usz.ch.

**BACKGROUND:** COPD is associated with increased pulmonary artery pressure (PAP) at lowlands which rises the risk of symptomatic pulmonary hypertension at altitude. Since dexamethasone reduces excessive PAP-increase and prevents pulmonary edema in susceptibles at high altitude we performed a randomized, placebo-controlled trial evaluating the hypothesis that preventive dexamethasone mitigates the altitude-induced PAP increase in COPD-patients. **METHODS:** Consecutive stable COPD-patients Gold 1-2 living <800m, SpO2>93% were randomized to dexamethasone (4mg tablets, bid) or placebo one day prior to ascent from Bishkek (760m) and during a 3-day sojourn at Tuja Ashu (3200m), Kyrgyz Republic. Echocardiography was performed at 760m and after the first night at 3200m. The main outcome was the tricuspid pressure gradient (TPG) as surrogate for PAP. Registration: clinicaltrials.gov: NCT02450968. **RESULTS:** 109 patients were randomized (mean±SD age 56±9y, BMI 26±4kg/m², FEV1 89±21%pred, SpO2 95±2%). The TPG increased from 760 to 3200m (placebo mean ± SD: 19.6±4.2 to 31.3±9.5 mmHg, p<0.0001) and dexamethasone (18.6±4.6 to 25.5±6.6 mmHg, p<0.0001), dexamethasone mitigated the altitude-induced increase in TPG vs. placebo (Δmean (95%CI) -4.76 (-7.69 to -1.83), p=0.0017) while the increase in cardiac output mediated by both a higher heart rate and stroke volume was similar with dexamethasone and placebo (placebo 4.92±0.70 to 5.69±1.09 l/min* and dexamethasone 4.71±0.88 to 5.65 ± 1.05 l/min*, Δmean (95%CI) 0.13 (-0.31; 0.57)). The more moderate increase in TPG with dexamethasone was associated with a higher SpO2 at peak walk test. Regression analysis confirmed that dexamethasone was associated with a reduced altitude-induced increase in TPG even when controlled for age and COPD-severity reflected by FEV1%pred (R²=0.3, P<0.0001). **CONCLUSION:** In lowlanders with COPD, GOLD grade 1-2, travelling to 3200m induces mild pulmonary hypertension. Dexamethasone mitigates this altitude-induced increase in PAP while maintaining cardiac output and with a favorable effect on oxygenation during exercise. See poster F57.

**EFFECT OF DEXAMETHASONE ON CEREBROVASCULAR HEMODYNAMICS IN LOWLANDERS WITH COPD TRAVELLING TO 3200M: RANDOMIZED PLACEBO-CONTROLLED TRIAL**

**Hartmann, Sara E1; Furian, Michael1; Lichtblau, Mona1; Aeschbacher, Sayaka S1; Bisang, Maya2; Ulrich, Stefanie1; Mirrakhimov, Erkin2; Sooronbaev, Talant1; Ulrich, Silvia1; Poulin, Marc J1; Bloch, Konrad E2**

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**INTRODUCTION:** Dexamethasone is used to treat cerebral edema at altitude. However, effects of dexamethasone at altitude on cerebrovascular regulation are unknown. **METHODS:** 82 patients with COPD, GOLD 1-2, (mean±SD; 56±9yrs, FEV1 90±19%predicted) were randomized to placebo or dexamethasone (2x4mg/day) one-day prior to and during an altitude sojourn. Middle cerebral artery blood flow velocity (MCAv; transcranial Doppler ultrasound) and mean blood pressure (MBP) were monitored at rest and during hyperventilation and isometric handgrip exercise to fatigue (60%maximal strength) at lowland (760m, Bishkek, Kyrgyzstan) and altitude (3200m, Tuja Ashu). **RESULTS:** In 44 patients receiving dexamethasone there was no altitude-induced increase in MCAv (48.6±8.8 vs. 49.4±10.5cm·s⁻¹) or MBP (93±9 vs. 94±9mmHg) with ascent to 3200m; both P>0.05. In 38 patients receiving placebo, ascent to 3200m increased MCAv and MBP from 47.7±10.0 to 52.2±10.4cm·s⁻¹ and 91±12 to 97±12mmHg, respectively; both P<0.01. Treatment effect (difference of means [95%CI]) was -3.8cm·s⁻¹ [-7.3; -0.2] and -5mmHg [-9; -1] for MCAv and MBP; both
**Thursday, 9 February**

P<0.05. The change in MCAv during hyperventilation-induced hypocapnia at 3200m was similar between treatments (2.5±0.5% mm Hg; 2.6±1.0% mm Hg; P>0.05). During handgrip at 3200m, dexamethasone blunted MCAv increase (28±14 vs. 21±13%; P≤0.01), despite a similar increase in MBP (46±22 vs. 48±26%; P>0.05). With placebo, the MCAv and MBP during handgrip were similar between 760m and 3200m (MCAv: 30±14 vs. 28±11%; MBP: 47±27 vs. 45±20%); both P>0.05. The treatment effect was 6%[-11;0] P<0.05 and 4%[-7;15] P>0.05) for MCAv and MBP, respectively. **CONCLUSIONS:** In mild-moderate COPD dexamethasone attenuated the altitude-related increase in MCAv and MBP, suggesting that dexamethasone modulates the vasopressor but not the metabolic response to hypobaric hypoxia, thereby perhaps allowing for a protective role in regulating cerebral perfusion pressure. See poster F49.

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**1645-1700 Hot Topics in Hypoxia II**

**EFFECTS OF HYPOTHERMIA, HYPOXIA AND HYPERCAPNIA ON BRAIN OXYGENATION: A PROSPECTIVE PORCINE STUDY**

*Strapazzon, Giacomo*; *Putzer, Gabriel*; *Dal Mulino, Miriam*; *Braun, Patrick*; *Dal Cappello, Tomas*; *Paal, Peter*; *Helbok, Raimund*; *Falk, Markus*; *Mair, Peter*; *Brugger, Hermann*

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**INTRODUCTION:** Limited data are available regarding the combined effects of hypoxia, hypercapnia and hypothermia on cerebral oxygenation. The aim of this study was to evaluate the influence of hypothermia, hypoxia and hypercapnia on brain oxygenation in a porcine model. **METHODS:** Nine anaesthetized pigs were surface-cooled to a core temperature of 28°C and underwent a period (20 min) of hypoxia (FiO₂ 17%) before hypercapnia was induced. Endpoint was considered onset of haemodynamic instability, i. e. 30% decrease in MAP, or 60 min post hypercapnia induction. Pigs were ventilated volume-controlled (20 ventilations/min, V₆ 6–8 ml/kg). Brain oxygenation measurements, including ICP (intracranial pressure), cerebral perfusion pressure (CPP) and cerebral venous oxygen saturation (ScvO₂, a marker for global cerebral oxygen extraction) were monitored. The care and handling of the animals complied with the American Physiological Society, institutional and Utstein-style guidelines. ANOVA for repeated measures was used to compare values across phases (hypothermia, hypoxia and hypercapnia) for ICP, CPP and ScvO₂. Pairwise comparisons were analyzed by means of Student’s t-test with Bonferroni correction. **RESULTS:** ICP did not show significant changes during the hypothermia (p>0.05) and hypoxia phases (p>0.05), but significantly increased during hypercapnia (p<0.05). Despite a progressive and significant decrease of CPP in all three phases (p<0.05), the decrease in CPP had clinically relevant modification only during the hypothermia and hypercapnia phases. ScvO₂ increased significantly during the hypothermia induction (p<0.05), did not show significant changes during the hypoxia phase (p>0.05), and decreased significantly during the hypercapnia phase (p<0.05). **CONCLUSION:** Our results demonstrate that hypercapnia increases ICP in a hypothermic, hypoxic pig to such a degree that CPP is impaired causing cerebral hypoxia, despite a reduced oxygen demand due to a severe hypothermic status (i. e. core temperature of 28°C). See poster F53.

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**1700-1715 Hot Topics in Hypoxia II**

**TIME COURSE AND PROGNOSTIC SIGNIFICANCE OF PULMONARY ARTERY PRESSURE IN HIGHLANDERS**

*Sooronbaev, Talant M.*; *Mademilov, Maamed*; *Emilov, Berik*; *Osmonov, Batyr*; *Tabysheva, Aijamal*; *Marajapov, Nuriddin*; *Seraliev, Ulan*; *Furian, Michael*; *Ulrich, Silvia*; *Bloch, Konrad E.*

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**BACKGROUND:** In a prospective cohort of Kyrgyz highlanders we evaluated mean pulmonary artery pressure (mPAP), its change over time and clinical outcome. **METHODS:** Life-long residents in the Aksay high altitude plateau (Kyrgyzstan, altitude 3000-4000 msl) free of overt lung or cardiovascular disease and non-polycythemic were invited to undergo yearly echocardiography, clinical examinations and spirometry. Deaths were recorded. **RESULTS:** In 2012, 90 highlanders (37 women, 53 men, mean±SD age, 44.8±12.0, range 21-75 yrs) were included. Until
2016, 5 highlanders, all male (6% of all participants), had died. In Cox regression analysis mPAP was a significant predictor of death in all participants (hazard ratio 1.14, 95%CI 1.02 to 1.27, P=0.019) when controlled for age. In Cox regression analysis restricted to men, mPAP tended to be an independent predictor of death (hazard ratio 1.21, 95%CI 1.00 to 1.46, P=0.050) when controlled for age, i.e., in men, the risk of death increased by a factor of 6.5 per 10 mmHg increase in mPAP. In 2012, mPAP was 26.9±7.4 mmHg Multiple regression analysis revealed a mean yearly increase in mPAP of 1.39 mmHg (95%CI 1.05 to 1.74, P=0.0001) when controlled for baseline mPAP, age and gender (R²=0.3689, P<0.001). The prevalence of individuals with mPAP >30 mmHg (corresponding to high altitude pulmonary hypertension) was 40% in 2012 and 63% in 2016 (p<0.05, chi square test). CONCLUSIONS: In the current cohort of highlanders, mPAP was higher than values reported for healthy lowlanders and the prevalence of high altitude pulmonary hypertension was 40% at baseline. The observed rapid increase in mPAP of 1.39 mmHg/year suggests that prolonged high altitude exposure may predispose to high altitude pulmonary hypertension. Further studies are required to investigate the mechanisms linking higher values of mPAP with a greater risk of death. Grant support: OPO foundation, Zurich Lung League, Swiss Lung Foundation. See poster F60.

ATTENUATION OF HYPOXIC PULMONARY VASOCONSTRICTION BY ACETAZOLAMIDE AND METHAZOLAMIDE IN HUMANS.

Boulet, Lindsey M1; Teppema, Luc J2; Hackett, Heather K1; Dominelli, Paolo B3; Nguyen, Trang Anh3; Cheyne, WS1; Dominelli, Giulio S3; Swenson, Erik R4; Foster, Glen E1

1: Centre for Heart, Lung, and Vascular Health, School of Health and Exercise Science, Univ British Columbia, Kelowna, Canada; 2: Dept Anaesthesiology, Leiden Univ Medical Center, Leiden, the Netherlands; 3: Dept Biomedical Engineering, International Univ, VNU – HCMC, Vietnam; 4: School of Kinesiology, Univ British Columbia, Vancouver, British Columbia, Canada.; 5: Faculty of Medicine, Univ British Columbia, Vancouver; 6: Division of Pulmonary & Critical Care Medicine, Univ Washington, Seattle, WA, USA Email: lindseyboulet@gmail.com.

INTRODUCTION: Acetazolamide (AZ) attenuates hypoxic pulmonary vasoconstriction (HPV) in humans and animals. Methazolamide (MZ), a carbonic anhydrase inhibiting sulfonamide analog of AZ, is methylated on the thiadiazole ring and reduces HPV in canines. It is unknown if MZ reduces HPV in humans. Accordingly, we aimed to determine MZ effectiveness in reducing HPV in humans. We hypothesized that HPV would be similarly attenuated between treatments, METHODS: In a double blind, placebo-controlled, randomized cross-over study, male participants (n=11, 25±1 yr) ingested a placebo (3 times/day), AZ (250 mg; 3 times/day) or MZ (100 mg; 2 times/day separated by a placebo) for 2 days and were exposed to poikilocapnic hypoxia (ḞO₂=0.12) for 1 h. Respiratory (ṖĖO₂, ṖĖCO₂, V̇I, SpO₂) and cardiovascular variables (HR, MAP) were recorded continuously, while pulmonary artery systolic pressure (PASP, tricuspid regurgitation) and cardiac output (Q, aortic velocity time integral) were measured at baseline and the last 5 minutes of hypoxia. Arterial blood was collected at baseline while arterialized capillary blood was collected in hypoxia and analyzed for PaO₂, PaCO₂, pH, and [HCO₃⁻]. RESULTS: In hypoxia, AZ and MZ both improved PaO₂ by 7±2 mmHg (p<0.05). PASP increased by 74.5±7.7 % (p<0.01) in response to hypoxia in the control condition and was attenuated similarly between AZ (-7.3 mmHg/treatment) and MZ (-5.7 mmHg/treatment). CONCLUSION: In summary, both AZ and MZ attenuate HPV similarly while improving arterial PO₂. MZ may be a suitable alternative to AZ for acute mountain sickness prophylaxis and reducing HPV possibly preventing high altitude pulmonary edema. FUNDING: NSERC & CFI. See poster F61.
DEOXYHEMOGLOBIN REGULATES CEREBRAL VASODILATION IN HYPOXIA

Hoiland, Ryan1; Macleod, David2; Flück, Daniela1; Willie, Chris1; Tymko, Michael1; Tremblay, Joshua1; Howe, Connor1; Donnelly, Joseph1; Stembridge, Mike3; Patrician, Alexander4; Rieger, Matt1; Hansen, Alex1; Santoro, Antoinette1; Ainslie, Philip1

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INTRODUCTION: We examined the hypothesis that deoxyhemoglobin regulates hypoxic cerebral vasodilation in an in vivo human model. METHODS: Ten healthy males (age: 30±8years, height: 176±4cm, weight: 72±4kg) completed three consecutive isocapnic hypoxia trials: 1) hypoxemia (\(\downarrow\)PaO\(_2\)); 2) isovolumic hemodilution (\(\downarrow\)\([\text{Hb}]\)); and 3) combined hemodilution and hypoxemia. During the last minute of each trial, radial arterial-jugular venous differences and volumetric blood flow in the internal carotid and vertebral arteries (duplex ultrasound) were measured to calculate global cerebral blood flow (gCBF) and metabolic rate (CMRO\(_2\)). RESULTS: In the hypoxemia trial, arterial oxygen content (CaO\(_2\)) decreased from 19.3±1.1mL\(\times\)dL\(^{-1}\) by ~7% and ~14% in sequential stages (PaO\(_2\)=93.3±4.0 vs. 59.2±1.7 vs. 46.8±1.8mmHg). The hemodilution trial involved two equal steps of blood removal and replacement with 5% human serum albumin, resulting in a ~10% and ~20% reduction in CaO\(_2\) ([Hb]=14.2±0.9 vs. 12.7±0.6 vs. 11.3±0.5\(\times\)dL\(^{-1}\)). The final hypoxic trial was repeated in hemodiluted subjects, reducing CaO\(_2\) from 15.7±0.7mL\(\times\)dL\(^{-1}\) by ~8% and ~15% (PaO\(_2\)=95.9±7.2 vs. 58.1±2.4 vs. 45.8±2.3mmHg). Each intervention increased gCBF; however, cerebral reactivity (%change in gCBF per unit reduction in CaO\(_2\)) was ~53% lower in the hemodilution trial compared to hypoxemia (0.9±0.3 vs. 2.0±0.5 \(\Delta\text{CBF}\times\)mL\(\times\)dL\(^{-1}\); P<0.05). In contrast, reactivity was ~43% greater in the combined hypoxemia and hemodilution trial (2.9±0.7 vs. 2.0±0.5 \(\Delta\text{CBF}\times\)mL\(\times\)dL\(^{-1}\); P<0.05). Across all trials, CMRO\(_2\) was unchanged (main effect, P=0.34) despite a lower cerebral O\(_2\) delivery in the hemodilution compared to hypoxic trials (P<0.05 vs. both). This difference was due to a 5% reduction in cerebral O\(_2\) delivery during hemodilution (P<0.05). CONCLUSION: By utilizing both hypoxemia and hemodilution, we have isolated the role of hemoglobin, and determined that (deoxy)hemoglobin may account for up to 50% of hypoxic cerebral vasodilation in humans. Combined hypoxemia and hemodilution mediates hypoxic cerebral vasodilation in an additive manner. See poster F50.
provided insight into the basis for this difference. **CONCLUSIONS:** These findings indicate that having greater iron stores prior to ascent to extreme altitude is associated with significantly different trends in indices of iron homeostasis, and severity of hypoxaemia, during exposure to hypobaric hypoxia. Differences in left and right heart function may underline this latter association, and future studies should aim to elucidate the mechanisms more clearly. See poster F15.

**1800-1815 Hot Topics in Hypoxia II**

**TIBETAN ENRICHED PKLR VARIANT FACILITATES IMPROVED OXYGEN DELIVERY IN HIGH ALTITUDE.**

Song, Jihyun¹; Huerta, Emilia²; Neilson, Rasmus²; Prchal, Josef¹

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Tibetans have been living at altitudes over 3500m for ~20,000 years and developed number of beneficial evolutionary adaptions. Two Tibetan specific *EPAS1* (encoding hypoxia-inducible factor alpha [HIF2α], a transcription factor that mediates the hypoxic response), and *EGLN1* (encoding prolyl hydroxylase 2 [PHD2], a principal negative regulator of HIF stability) haplotypes were identified and are present in most Tibetans and the presence of these two haplotypes correlates with lower hemoglobin levels in Tibetans. However, these do not fully explain the entire Tibetan polycythemia protection. We identified a Tibetan enriched haplotype of a gene in the glycolytic pathway, *PKLR*, encoding the red cell and liver specific pyruvate kinase (PK). We hypothesized that different *PKLR* haplotypes improve hemoglobin oxygen delivery associated with PK enzyme activity. This haplotype is not unique to Tibetans; however, it has the highest frequency in Tibetans (89%), with a lower prevalence in Chinese and Mongolians (~77%) and a much lower frequency in Caucasians (11%), perhaps explaining the individual and ethnic/racial heterogeneity of responses to hypoxia. We found that *PKLR* transcript levels in reticulocytes (RNA containing subpopulations of red cells) progressively decreases with increasing altitudes in controls and even more in *PKLR* with Tibetans enriched haplotype. It is known that the decreased PK activity leads to accumulation of proximal glycolytic intermediates 2,3 diphosphoglycerate (DPG). Our findings suggest that the majority of Tibetans have progressively lower PK levels with increasing altitudes, and their higher 2,3 DPG shifts the hemoglobin dissociation curve to right, decreases affinity of the hemoglobin for oxygen, which improve tissue oxygen delivery. Here, we suggest that Tibetan enriched *PKLR* haplotype might improve oxygen delivery to tissue contributing to high altitude adaptation resulting in their partial protection from polycythemia. See poster W47.
**REDUCTIONS IN ACUTE MOUNTAIN SICKNESS FOLLOWING ACCLIMATIZATION ARE SUSTAINED DURING REINTRODUCTION: TO ALTITUDE FOLLOWING 12 DAYS AT SEA LEVEL**

Beidleman, Beth A; Fulco, Charles S; Cadarette, Bruce S; Cymerman, Allen; Buller, Mark H; Salgado, Roy M; Staab, Janet E; Posch, Alexander M; Yurkevicius, Beau R; Sils, Ingrid V; Luippold, Adam J; Muza, Stephen R

US Army Research Institute of Environmental Medicine, USA  Email: beth.a.beidleman.civ@mail.mil.

This study examined whether reductions in the prevalence and severity of acute mountain sickness (AMS) induced by acclimatization can be sustained during re-introduction to altitude (RA) after 12 days at SL using normobaric hypoxia (NH) treatment. Seventeen sea level (SL) residents (M=11, F=6, age=23±6yrs; mean±SE) completed: 1) 4d of baseline SL testing, 2) 12d at 4300m on Pikes Peak, 3) 12d at SL with and without NH treatment and 4) a 24-hour RA (hypobaric chamber; 4300m). At SL after acclimatization, each received either NH (n=9, FiO\textsubscript{2} =0.122) or SHAM (n=8; FiO\textsubscript{2} =0.209) treatment for 3 hrs/day for 9 of the 12 days. AMS-Cerebral factor score, heart rate (HR), and arterial oxygen saturation (SaO\textsubscript{2}) were assessed in the morning at SL, on d2 and d11 of acclimatization, and in the 20\textsuperscript{th} hour on d2 of RA. There were no differences between NH and SHAM treatment so data were combined. AMS prevalence and severity, respectively, increased (P<0.05) from SL (0%;0.03±0.02) to d2 at 4300 m (76%;1.30±0.26) and then decreased by d11 at 4300 m (0%;0.11±0.06). AMS prevalence and severity during RA (17%; 0.25±0.09) remained the same as d11 at 4300 m. HR (bpm) increased (P<0.05) from SL (69±2) to d2 (107±3) at 4300 m and then decreased (P<0.05) from d2 to d11 (92±4) at 4300 m. During RA, HR (83±3) remained the same as d11 at 4300 m. SaO\textsubscript{2} (%) decreased (P<0.05) from SL (99±1) to d2 (85±1) at 4300 m and then increased (P<0.05) on d11 (89±1) at 4300 m. During RA, SaO\textsubscript{2} (88±1) remained the same as d11 at 4300 m. These results demonstrate that reductions in the prevalence and severity of AMS following 12 days acclimatization are retained during RA after 12 days at SL whether or not NH treatment is utilized. Author’s views not official U. S. Army or DoD policy. See poster F10.
### Friday, 10 February 2017

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<tbody>
<tr>
<td>0630-0830</td>
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<td>0700-0800</td>
<td>Registration, Heritage Hall</td>
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<td>0800-0930</td>
<td><strong>Regulation of Erythropoiesis in Hypoxia</strong></td>
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<td>0830-0900</td>
<td>S1P, The Red Blood Cell and Hypoxia—Yang Xia</td>
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<td>0900-0930</td>
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<td>Refreshment Break, Heritage Hall</td>
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<td>1000-1130</td>
<td><strong>Hot Topics in Hypoxia III—Selected Abstracts</strong></td>
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<td>Ski Break</td>
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<tr>
<td>1130-1330</td>
<td>Lunch, Lago Restaurant</td>
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<tr>
<td>1600-1630</td>
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<td>1630-1830</td>
<td><strong>Poster Session II</strong></td>
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<td>Dinner, Victoria Dining Room</td>
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<td>2030-2130</td>
<td><strong>A Room With a View: Perspectives on Living and Working in Low Earth Orbit</strong>—Kjell Lindgren, MD</td>
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With increasing altitude humans experience a progressive reduction in alveolar $\text{PO}_2$ and hence also in $\text{SaO}_2$ and $\text{CaO}_2$. A reduction (>10%) in plasma volume (PV) within the first 24 hours at high altitude (HA) constitutes a rapid and efficient way to increase [Hb] and restores the reduction in $\text{CaO}_2$. Even after 3 weeks of HA exposure, where ventilatory acclimatization increases $\text{SaO}_2$ and red blood cell volume (RBCV) becomes elevated the reduction in PV remains the main mechanism increasing $\text{CaO}_2$ compared to acute exposure. A mismatch between water uptake and water loss is at least partially responsible for the decrease in PV at HA. Summarizing the literature the renin – angiotensin – aldosterone system presumably plays a role in the regulation of HA diuresis if sufficient time for acclimatization is provided. Atrial natriuretic peptide (ANP) expression has been observed to increase in humans during acute hypoxia and may also be involved in the regulation of HA diuresis. Recent studies have indicated that the increase in RBCV expansion follows a sigmoidal shape, with a notable onset after 12 days and a strong tendency for a plateau after 20–24 days. The delayed onset most likely reflects the time required for the formation of new erythrocytes in the bone marrow in response to the erythropoietic stimulus. The maximal rate of expansion seems to occur after ~15 days at HA and correspond to ~12 ml d⁻¹ of RCV. A meta-analysis yielded that the average increase in RCV at HA is about 50±240 ml week⁻¹. Upon return to sea level PV is rapidly restored and RCBV is normalized within 14 days at SL. In this talk methods used to determine blood volumes will be addressed briefly where after mechanisms facilitating blood volume changes and their consequences will be discussed. Differences between human and animal studies will be highlighted.

Hypoxia is a common and dangerous physiological and pathological condition. Adaptation to hypoxia is essential for survival and involves complex cellular and signaling networks with various levels of interaction and feedback. Improved and faster acclimatization to high altitude upon re-ascent is seen in humans. However, molecular basis for initial acclimatization and retention upon re-ascent to high altitude remains largely unknown. Here we reported that plasma adenosine levels are induced by high altitude and retained at higher levels upon re-ascent in health lowlanders and that its elevation is positively associated with quicker acclimatization upon re-ascent. Unexpectedly, we found that the erythrocyte equilibrative nucleoside transporter 1 (eENT1) protein level is downregulated in both humans at high altitude and mice under hypoxia. Deletion of eENT1 allows rapid accumulation of plasma adenosine to offset hypoxic tissue damage in mice. Further mechanistic studies revealed that plasma adenosine signaling via erythrocyte specific ADORA2B induces PKA phosphorylation, ubiquitination and proteasomal degradation of ENT1 and its reduced levels maintained upon re-ascent in humans or re-exposure to hypoxia in mice. Thus, the reduced eENT1 resulting from the initial hypoxia establishes erythrocyte “hypoxic purinergic memory” to promote quicker and higher accumulation of plasma adenosine and faster acclimatization upon re-ascent.

Overall, we defined that proteasomal-mediated degradation of ENT1 on erythrocytes, the most abundant circulating cells, is a major cellular purinergic signaling regulatory component underlying initial hypoxia-induced adenosine response and that erythrocytes retain a “hypoxic purinergic memory” for quicker adaptation to 2nd hypoxia. Our findings immediately suggest that targeting this newly identified purinergic signaling network will likely enhance adenosine hypoxic response and prolong the “hypoxic purinergic memory” to rapidly offset hypoxia.
During hypoxia, red cell mass is increased by erythropoietin (EPO), which is regulated by hypoxia-inducible transcription factors (HIFs). Neocytolysis is a pathophysiologic mechanism that overcorrects the high RBC mass generated during chronic sustained hypoxemia by preferential destruction of young RBCs after normoxia is restored. We recently showed that neocytolysis is caused by excessive mitochondrial-derived reactive oxygen species (ROS) in reticulocytes mediated by down-regulation of HIF-controlled BNIP3L regulated mitophagy and a decrease in the RBC antioxidant, catalase (CAT) in hypoxia-increased erythron. Decreased CAT results from hypoxia-induced miR-21 that downregulates CAT.

Obstructive sleep apnea (OSA) is associated with cardiovascular and endocrine comorbidities, as well as increased cancer risk and neurocognitive impairment. It has not been determined if OSA is accompanied by any hematological abnormalities. Although chronic intermittent hypoxia (CIH) is a unifying feature of OSA, the prevalence of polycythemia in OSA has not been ascertained. We found that of 527 OSA patients studied, only 9 (1.7%) had polycythemia and we hypothesized that transitions from hypoxia to normoxia prevents polycythemia by neocytolysis.

We studied 31 OSA patients before and after 3 months of CPAP. Sleep studies showed an average of 92.2 minutes spent with oxygen saturations of <89%, with a 4% oxygen desaturation index of 23/hour. In 6/8 patients we demonstrated hemolysis by increased CO in exhaled air. Those with severe OSA had higher EPO levels, EPO decreased after CPAP indicating that uncorrected OSA augments erythropoiesis in spite of normal hematocrits. ROS increased during OSA in B-cells, T-cells, monocytes, granulocytes, and mature RBCs, but not in platelets, and corrected after CPAP treatment. CAT levels in granulocytes, platelets and reticulocytes were lower in uncorrected OSA and corrected after CPAP treatment, with an inverse correlation with miR-21. Increased ROS in reticulocytes accompanied increased mitochondrial mass, concomitantly with decreased BNIP3L transcript. We found that inflammatory genes transcript levels increased in OSA and corrected after CPAP treatment, suggesting that increase of inflammation might also suppress erythropoiesis by increase hepcidin.
EFFECT OF REPEATED ALTITUDE EXPOSURE ON NOCTURNAL BREATHING DISTURBANCES IN LOWLANDERS.
Furian, Michael1, Hartmann, Sara E.2,3; Muralt, Lara1; Lichtblau, Mona1; Bader, Patrick R.1; Rawling, Jean M.1,2,3; Ulrich, Silvia1; Poulin, Marc J.2,3; Bloch, Konrad E.1
1: Pulmonary Division and Sleep Disorders Center, Univ Hospital of Zurich, Zurich, Switzerland; 2: Dept of Physiology & Pharmacology and Hotchkiss Brain Institute, Cumming School of Medicine, Univ Calgary, Calgary, Canada; 3: Dept of Family Medicine, Cumming School of Medicine, Univ Calgary, Calgary, Canada Email: michael.furian@usz.ch

OBJECTIVE: To evaluate the effect of acute exposure, acclimatization and re-exposure to very high altitude on nocturnal breathing and subjective sleep quality in lowlanders. METHODS: 21 healthy lowlanders, aged 18-30y, underwent two 6-day sojourns at the ALMA observatory, Chile (6hrs/day spent at 5050m, nights at 2900m), separated by a 1-week recovery period at 520m. Subjective sleep quality (SSQ, visual analog scale 0-100 with increasing quality) and respiratory sleep studies were assessed at 520m before ascent (LA1) and in the recovery period (LA2), and at 2900m during the first and second sojourn, on days 1 and 6 (sojourn 1: 1-HA1 and 1-HA6; sojourn 2: 2-HA1 and 2-HA6). www.ClinicalTrials.gov NCT02730143. RESULTS: Mean nocturnal oxygen saturation (SpO2), oxygen desaturation index (ODI, >3%) and SSQ were, respectively; medians(quartiles): LA1 95%(94;95), 2.2/h(1.5;3.0), 60(48;72); 1-HA1 86%(85;98), 13.1/h(9.6;33.6), 35(26;56); 1-HA6 90%(89;90), 5.8/h(4.5;7.9), 60(46;65) (P<0.05 LA1 vs. 1-HA1 and 1-HA6 vs. 1-HA1, all comparisons). Compared to values in the first sojourn (LA1, 1-HA1 and 1-HA6), during the second sojourn (LA2, 2-HA1 and 2-HA6), SpO2 and ODI, respectively, changed by medians(95%CI) LA2 -2%(-4%,-1%), -0.7/h(-1.2,-0.2); 2-HA1 +1%(0;2), -4.7/h(-19.7,-1.4); 2-HA6 0%(0;1), -1.1/h(-2.7;0.2). SSQ was not different between first and second sojourn. CONCLUSIONS: In healthy subjects, acclimatization over 6 nights at 2900m, with daily 6hrs exposures to 5050m, improved SpO2 and ODI compared to the first night at 2900m. After 1-week at lowland, re-exposure to 2900m and 5050m had a milder effect on SpO2 and ODI, suggesting some retention of physiologic acclimatization from the previous altitude exposure although no changes in subjective sleep quality were perceived. FUNDING AND SUPPORT: NSERC Discovery Grant (MJP; 2014-05554), The Brenda Strafford Foundation Chair in Alzheimer Research, the ALMA Observatory, Swiss Lung Foundation, Lunge Zurich, Swiss National Science Foundation. See poster F08.

EFFECT OF ACUTE, SUBACUTE AND REPEATED HIGH ALTITUDE EXPOSURE ON PSYCHOMOTOR VIGILANCE
Hartmann, Sara E.1,2,3; Furian, Michael1; Dyck, Adrienna M.1,2,3; Muralt, Lara1; Lichtblau, Mona1; Bader, Patrick R.1; Drogos, Lauren L.1,2,3; Rawling, Jean M.1,2,3; Ulrich, Silvia1; Bloch, Konrad E1; Poulin, Marc J.1,2,3
1: Dept Physiology and Pharmacology; 2: Hotchkiss Brain Institute; 3: Cumming School of Medicine; 4: Family Medicine, Univ Calgary, Alberta, Canada; 5: Dept Respiratory Medicine, Univ Hospital Zurich, Switzerland Email: shartma@ucalgary.ca

OBJECTIVE: Poor sleep at altitude may affect daytime performance. The speed of response to light stimuli in the psychomotor vigilance test (PVT-RS) is slower following sleep deprivation. We investigated 1) the effect of very high altitude exposure, acclimatization, and re-exposure on PVT-RS and 2) assess relationships between PVT-RS, sleep parameters, and AMS. METHODS: 21 altitude-naive individuals (25±4 yrs [mean±SD]; 8M/13F) completed 2 cycles of altitude exposure; each cycle separated by 7 days at low altitude (LA, 520m). Participants slept at 2900m (7-nights) and spent the daytime at HA (5050m). The effect of acute altitude (LA vs. HA1) and acclimatization (HA1 vs. HA6) were studied. Sustained attention was assessed for 10-min using the PVT-RS. Acute mountain sickness was assessed using the Environmental Symptoms Questionnaire cerebral score (AMSc; score >0.7 identifies AMS). Sleep parameters were assessed using actigraphy. www.ClinicalTrials.gov NCT02731456. RESULTS: In cycle 1, PVT-RS was slower at HA1 compared to LA (HA1: 4.1±0.8; LA: 4.5±0.6 s1,P<0.05), but not at HA6 (4.6±0.7; P>0.05). In cycle 2, PVT-RS at HA1 and HA6 was not different from LA (P>0.05). In both cycles, AMSc scores were higher at HA1 than at HA6 (P≤0.05). At HA1, subjects who reported higher AMSc scores exhibited slower PVT-RS (r=-0.56; p<0.01). Sleep parameters (sleep efficiency, awakenings, and sleep latency) were unaffected by altitude. CONCLUSIONS: PVT-RS is reduced with acute exposure to HA and normalized with acclimatization over 6 days. Acclimatization effects are
retained upon re-exposure to altitude. These results have implications for individuals engaging in activities at altitude requiring high daytime attentiveness such as mining, astronomical observation and athletics. **FUNDING:** NSERC Discovery Grant (MJP; 2014-05554), The Brenda Strafford Foundation Chair in Alzheimer Research (MJP), the Alma Observatory, Swiss Lung Foundation, Lunge Zurich, Swiss National Science Foundation.  See poster W42.

**TRACKING ALTITUDE-RELATED CHANGES IN PROCESSING CAPACITY WITH BRAIN SIGNAL VARIABILITY.**
Heard, Alison W; Hart, Jessie M; Burles, Ford; Hartmann, Sara E; Furian, Michael; Lichblau, Mona; Muralt, Lara; Bader, Patrick R; Ulrich, Silvia; Bloch, Konrad E; Rawling, Jean M; Pexman, Penny M; Poulin, Marc F; Protzner, Andrea B.
1: Dept Psychology, Univ Calgary, Canada; 2: Dept Physiology and Pharmacology, Univ Calgary, Canada; 3: Dept Respiratory Medicine, Univ Hospital of Zurich, Switzerland; 4: Dept of Family Medicine, Cumming School of Medicine, Univ Calgary, Canada; 5: Hotchkiss Brain Institute, Canada; 6: Cumming School of Medicine, Univ Calgary, Canada
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**INTRODUCTION:** Cognitive decline at high altitude is well documented, however brain changes associated with this decline are understudied. Increasing evidence suggests that brain signal variability (BSV) is an important marker of information processing capacity (McIntosh et al., 2010). Changes in BSV track individual differences in processing capacity (Protzner et al., 2013), and also relate to task performance. For example, Wang et al. (2016) found that increased BSV during resting state correlated with faster reaction time and better accuracy during a subsequent task.

**METHODS:** In the present study we examined changes in BSV from high (5050m) to low (520m) altitude with multiscale entropy, a measure sensitive to linear and nonlinear variability (Costa et al., 2005). We collected electroencephalography (EEG) in 14 young adults (9 females) during resting state, and related BSC changes to performance during a visual word/non-word decision task. Each participant was tested: on their first day at high altitude (5050m), following 5 days of 6 hours/day exposure to 5050m while sleeping at moderate altitude (2900m), and during the first day returning to low altitude (520m). **RESULTS:** BSV was reduced on the first day at high altitude compared to the 6th day at high altitude and the first day back at low altitude (**p<0.001**). Across all days, individual differences in BSV during resting state predicted performance, such that greater variability was associated with reduced word/non-word decision reaction times (**p<0.001**). **CONCLUSION:** Our results suggest that altitude-related changes in resting-state BSV have consequences for information processing capacity, and may have implications for workers at high altitude. Funding sources and support: Natural Sciences and Engineering Research Council (NSERC) Discovery Grants (MJP, 2014-05554; ABP, 418454-2013; PMP, 217309-2013), the Brenda Strafford Foundation Chair in Alzheimer Research (MJP), ALMA Observatory, Swiss Lung Foundation, Lunge Zurich, Swiss National Science Foundation.  See poster F52.
PULMONARY CAPILLARY BLOOD VOLUME RESPONSE TO EXERCISE IS BLUNTED IN MILD COPD
Tedjasaputra, Vincent1,2; Michaelchuk, Wade W.1,2; Phillips, Devin P.1,2; Bryan, Tracey L.1; Bhutani, Mohit1; Stickland, Michael K.1,3
1: Division of Pulmonary Medicine, Faculty of Medicine and Dentistry, Univ Alberta; 2: Faculty of Physical Education and Recreation, Univ Alberta; 3: G. F. MacDonald Centre for Lung Health, Covenant Health, Edmonton, Alberta, Canada
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INTRODUCTION: Diffusing capacity (DLCO) must increase to meet the metabolic demand of exercise. This increase in DLCO is due to increases in pulmonary capillary blood volume (Vc) and membrane diffusing capacity (Dm). Previous work suggests that mild COPD patients show greater airway dysfunction than previously appreciated, and a reduction in resting DLCO. It is unknown if Vc and Dm responses to exercise are diminished in mild COPD. We hypothesized that the DLCO, Vc, and Dm response to exercise would be blunted in mild COPD compared to healthy controls.

METHODS: Thirteen mild COPD patients (FEV1/FVC mean±SD: 64±3%, FEV1 = 93±13% pred) and 14 age- and sex-matched controls were recruited. Hemoglobin-corrected DLCO, Vc, and Dm were determined using the Roughton and Forster (1957) multiple-FIO2 DLCO method at baseline and during cycling exercise at 40W, 50% and 80% of VO2peak. RESULTS: VO2peak was not different between mild COPD (1.75±0.65 L/min) and control (2.03±0.61 L/min, p=0.28). Peak exercise SpO2 was lower in COPD (94.9±2.8%) compared to control (97.1±1.4%, p=0.02). Baseline DLCO was lower in COPD (17.9±5.1 mL/min/mmHg) compared to control (23.0±4.0 mL/min/mmHg), due to a 24% lower Vc in COPD. During exercise, both groups increased DLCO, Dm, and Vc with exercise intensity; however, COPD had lower DLCO and Vc at 50%, and 80% of VO2peak, but Dm was not significantly different between groups at baseline or during exercise. CONCLUSIONS: Mild COPD patients appear to have impaired DLCO responses at rest and during exercise, secondary to reductions in Vc but not Dm. Despite the relatively minor impairment in airflow obstruction, the pulmonary microvascular response to exercise is blunted in mild COPD patients, which may impact pulmonary gas exchange. FUNDING: Canadian Respiratory Research Network, Lung Association of Alberta, Univ Hospital Foundation. See poster F59.

DIETARY NITRATE SUPPLEMENTATION INCREASES ACUTE MOUNTAIN SICKNESS SEVERITY AND SENSE OF EFFORT DURING SUBMAXIMAL EXERCISE IN HYPOXIA
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INTRODUCTION: Dietary nitrate supplementation enhances performance at sea level and may alleviate hypoxia at high altitude. However, nitrate may exacerbate altitude headache. This study investigated the effect of chronic nitrate supplementation on acute mountain sickness (AMS) and exercise performance in hypoxia. METHODS: Sixteen recreationally-active men (mean(SD): age 22(4) years, VO2max 51(6) mL min-1 kg-1) completed this double-blinded placebo-controlled crossover study. Participants first completed assessments of maximal aerobic capacity in normoxia (FIO2 = 0.209) and hypoxia (FIO2 = 0.141). Participants then completed two six-day supplementation interventions: nitrate (70 mL beetroot juice shot containing ~7 mmol NO3- daily) and placebo (70 mL beetroot juice shot containing ~0.003 mmol NO3- daily). The interventions were separated by a ten-day washout and their order was randomly assigned. On day five of each intervention, participants completed a prolonged hypoxic exposure (six hours, FIO2 = 0.124) to assess AMS (Lake Louise Score (LLS)); high altitude headache (0 to 100 mm visual analogue scale (VAS)); and perceptual response to submaximal exercise (verbal expressions/0 to 100 rating of perceived exertion scale). On day six, participants completed an acute hypoxic exposure (FIO2 = 0.124) to assess AMS (Lake Louise Score (LLS)); high altitude headache (0 to 100 mm visual analogue scale (VAS)); and perceptual response to submaximal exercise (verbal expressions/0 to 100 rating of perceived exertion scale). RESULTS: During prolonged hypoxia nitrate increased AMS severity compared to placebo (LLS: placebo=1.1(1.2); nitrate=2.1(2.4); 95%CI: -0.3, 2.5), which was largely due to elevated high altitude headache (VAS: placebo=19(21); nitrate=33(35) mm; 95%CI: 1, 32 mm). Furthermore, nitrate increased
rating of perceived exertion during submaximal exercise from “moderate” (placebo=26(12)) to “somewhat strong” (nitrate=32(20); 95%CI: -4, 17). During acute hypoxia, nitrate had no effect on maximal exercise performance (TTE: placebo=650(191); nitrate=636(211) s; 95%CI: -102, 74 s). **CONCLUSION:** Chronic dietary nitrate supplementation increases AMS severity, high altitude headache, and sense of effort during exercise in hypoxia. See poster F05.

### 1115-1130 Hot Topics in Hypoxia III

**NOVEL NON-INVASIVE METHOD FOR MEASURING SYMPATHETIC ACTIVITY IN HUMANS USING OPTICAL COHERENCE TOMOGRAPHY IMAGING OF THE RETINA AND CHOROID**

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**BACKGROUND:** Heightened sympathetic nervous system (SNS) activity is associated with prevalent and serious respiratory, cardiovascular and metabolic diseases. Current methods to measure SNS in humans are technical difficulty and invasive (microneurography), give poor temporal resolution ([plasma norepinephrine]) and/or have questionable accuracy (i.e., heart rate variability). Consequently, sympathetic activity is rarely assessed in the clinic and under investigated in human disease and drug discovery.

**AIM:** The choroid blood vessels, which encase the back of the retina, receive strong sympathetic innervation and can be imaged non-invasively with spectral domain optical coherence tomography (OCT). Here we test whether OCT imaging of choroid vascular perfusion density (CVPD) can be used to assess sympathetic activity.

**METHODS:** OCT images were compared with muscle sympathetic activity (MSNA) determined with microneurography during periods of induced hypoxia, hyperoxia, hyperoxic-hypercapnia, hyperventilation, end-expiratory breath-hold and a cold-pressor test in 6 healthy males age 26±3y. **RESULTS:** CVPD and integrated total MSNA were inversely correlated (R= -0.989; p<0.05) over the 6 provocation manoeuvres. The intra-subject correlation between change in MSNA and change in CVPD across SNS provocations were also strongly and inversely related (R= -0.78 ± 0.06). However, macular thickness, measured from the internal limiting membrane to the retinal pigment epithelium remained constant during all sympathetic provocations (p>0.05). The coefficient of variation from repeat measures of CVPD and retinal thickness were 1.5 ± 8.44 and 0.38 ± 2.1, respectively. **CONCLUSION:** These data demonstrate vascular regulation of ophthalmic tissue between the anterior and posterior circulations of the eye differ. Given the strong relationship between CVPD and MSNA, and relative ease of interrogation, OCT may provide a clinically useful and non-invasive method to reliably assess SNS (re)activity. See poster F24.

### 1130-1600 Ski Break
MEDEX 2015: HEART RATE VARIABILITY PREDICTS THE DEVELOPMENT OF ACUTE MOUNTAIN SICKNESS

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INTRODUCTION: Although pre-ascent prediction of susceptibility to acute mountain sickness (AMS) would be a useful tool to prevent subsequent harm, a diagnostic test for AMS susceptibility remains elusive. Heart rate variability (HRV) has shown promise in the early prediction of AMS, but its use pre-expedition has not previously been investigated. This study’s objective was to determine whether pre- and intra-expedition HRV assessment could predict susceptibility to AMS at high altitude with better diagnostic accuracy than peripheral oxygen desaturation (SpO₂) during hypoxic exposure.

METHODS: 44 volunteers (age range 24-62 years; 26 male) undertook an expedition in the Nepali Himalaya to 5085 m. One month prior to the expedition HRV parameters and SpO₂ were recorded over a 15 minute period at rest in normoxia (FiO₂ = 0.209) and in a normobaric hypoxic chamber (FiO₂ = 0.115). On the expedition HRV parameters and SpO₂ were collected again at 3841 m. A daily Lake Louise Score was obtained to assess AMS symptomology.

RESULTS: The ratio of the low frequency (LF) to high frequency (HF) component of the HRV spectrum in normoxia and LF following 15 minutes of exposure to normobaric hypoxia had moderate (area under the curve ≥ 0.8) diagnostic accuracy. LF/HF ratio in normoxia (cutpoint ≤ 2.28 a. u) had the highest sensitivity (85%) and specificity (88%) for predicting AMS during the expedition. In contrast pre- and intra-expedition SpO₂ measurements had poor (area under the curve < 0.7) diagnostic accuracy and inferior sensitivity and specificity. CONCLUSION: Pre-ascent measurement of HRV in normoxia was found to be of better diagnostic accuracy for AMS prediction than all measures of HRV in hypoxia, and better than peripheral SpO₂ monitoring. With refinement of the hardware to allow immediate point of care reporting, HRV has the potential to be a simple pre-expedition tool to predict AMS susceptibility. See poster F06.
ALTITUDE SCIENCE FROM BERT TO PULSE OXIMETERS
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In 1875 Paul Bert was the first to understand the role of partial pressure of oxygen on mammalian life at high altitude when 2 balloonists died euphorically at nearly Everest’s altitude. In World War One, fatal crashes of fighter pilots at high altitude led to failed efforts to use oximetry to warn pilots. In the century after Bert, respiratory physiology, often studied at high altitude, revealed the now well-known mechanisms of mammals in responding to hypoxia. In 1940, English physiologist-physician John R. Squire found that the log of the ratio of ratios of 4 values, two wavelengths (red and infrared) of light passing through human tissue during both blanched and perfused tissue, was sufficient to compute oxygen saturation of the blood. In 1970, Japanese electrical engineer Takuo Aoyagi invented pulse oximetry by carefully reading Squire’s 1940 report from which he suddenly realized how to measure arterial blood oxygen saturation using arterial pulsations in tissue. The author here reports some of his own UCSF lab work contributing to this field. See poster F09.

1700-1830 Poster Session II

1900-2130 Dinner, Victoria Dining Room

2030-2130 A Room With a View: Perspectives on Living and Working in Low Earth Orbit—Kjell Lindgren, MD
Poster Session II

Poster Viewing
1630-1830h

Location:
Mount Temple Ballroom C

When:
Friday, 10 February 2017

Poster session II includes many great posters.
All posters will be available for viewing from 1630-1830h.

All Friday posters should be put up for viewing Thursday evening, and should be taken down by late Friday evening.
Abstract: F01

PHYSIOLOGICAL RESPONSES DURING ASCENT TO HIGH ALTITUDE AND THE INCIDENCE OF ACUTE MOUNTAIN SICKNESS: A PROSPECTIVE OBSERVATIONAL COHORT STUDY

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INTRODUCTION: Ascent to high altitude can result in acute mountain sickness (AMS). Its pathophysiology remains unclear and controversy surrounds the identification of reliable predictors of AMS. The aim of this study was to describe the relationship between a number of physiological variables, measured before and after a standardised exercise protocol, and the occurrence of AMS during ascent to 5300m.

METHODS: 332 healthy volunteers ascended to Everest base camp (5300m) over 11 days, following an identical ascent profile on staggered treks. Self-reported symptoms of AMS were recorded daily using the Lake Louise (LL) score, along with measurements of heart rate (HR), respiratory rate (RR) and peripheral oxygen saturation (SpO₂), before and after a standardised 2 minute Xtreme Everest Step-Test (XEST) protocol. Blood pressure (BP) was also measured prior to exercise. “Mild” AMS was defined as a LL score of ≥3 and “severe” AMS as a LL score of ≥5. XEST values at 3500m were used to predict AMS during the trek.

RESULTS: The overall incidence of AMS during ascent was 73.5%. Compared to no AMS, mild AMS was associated with lower resting SpO₂ (89.7 vs 88.8%) and end-exercise SpO₂ (83.9 vs 81.7%), higher delta SpO₂ (rest minus end-exercise) (-5.8 vs -7.1%), and lower resting RR (14.2 vs 13.2) and end-exercise RR (21.4 vs 19.7) at 3500m. Compared to no AMS, severe AMS was associated with lower resting SpO₂ (89.5 vs 88.5%) and end-exercise SpO₂ (83.0 vs 81.5%) at 3500m. In a multi-variable model, lower end-exercise SpO₂ at 3500m and no previous exposure to altitude >5000m were the only predictors of subsequent mild and severe AMS during the trek.

CONCLUSIONS: Post-exercise SpO₂ at 3500m predicts the subsequent occurrence of AMS. The XEST offers a simple, reproducible and useful field test to help predict AMS in people ascending to high altitude.

Abstract: F02

ALTITUDE READINESS MANAGEMENT SYSTEM (ARMS): A MOBILE APPLICATION FOR PREDICTION OF ACUTE MOUNTAIN SICKNESS, WORK PERFORMANCE, AND ALTITUDE ACCLIMATIZATION

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Rapid deployment of unacclimatized Soldiers to altitudes above 2000 m causes debilitating effects on Soldier health and performance. Mission planners and leaders need accurate estimates of acute mountain sickness (AMS), work performance, and acclimatization status at altitudes from 2000-4500 m to minimize risks to the Soldier and maximize operational effectiveness. The USARIEM has developed predictive models of AMS, work performance and altitude acclimatization using inputs of target altitude, time at altitude, sex, work rate and body mass index. USARIEM collaborated with MIT - Lincoln Laboratory to integrate these predictive models into an Altitude Readiness Management System (ARMS) decision aid software application that provides easy-to-use screens for entering relevant mission parameters and displaying estimates of AMS, work performance and altitude acclimatization status in both text and graphic formats. The application functions on an Android-based mobile device. Limited military user testing was conducted on the ARMS app in collaboration with the Army Mountain Warfare School, Jericho, VT. Questionnaires were developed by USARIEM with 26 questions encompassing the ease of use of the app, as well as its potential usefulness in comparison with current practice. Responses to questions were scaled from “very difficult to very easy”, or “strongly disagree to strongly agree”. Forty-one volunteers completed the ARMS app evaluation. Overall, the ARMS app functionality received ~80% positive responses and ~6% negative responses with ~14% neutral. Approximately 85% said the ARMS app is a better tool than any other tool they currently have available, and 72% said they would use the ARMS app for mission planning. In conclusion, the ARMS decision aid is functional and useful and will support a wide range of military users. Author views not official US Army or DoD policy.
INTRODUCTION: Inhaled budesonide is a potential novel preventative medication for acute mountain sickness (AMS), this study tests its efficacy compared to the standard AMS prophylactic acetazolamide. METHODS: This was a double blind, randomized, placebo controlled trial comparing inhaled budesonide (180mcg bid) to oral acetazolamide (125mg bid) to placebo started the morning of ascent. Healthy adults ascended from 1,240m (4,100ft) to overnight at 3,810m (12,570ft) during August 2016 on White Mountain, California. The primary outcome was AMS incidence (headache + LLQ>=3), with secondary outcomes of AMS severity (LLQ>=5), SpO2, and EtCO2.

RESULTS: 103 participants enrolled and completed the study; 33 (32%) received budesonide, 35 (34%) acetazolamide, 35 (34%) placebo. No differences in demographics between groups. Total AMS incidence 73%. Fewer participants in the acetazolamide group 15 (43%) developed AMS compared to both budesonide 24 (73%) (p<0.05; OR=3.5, 95% CI 1.3 to 10.1) and placebo 22 (63%) (p=0.08; OR=0.5, 95% CI 0.2 to 1.2), NNT of 5. Acetazolamide had less severe AMS 11 (31%) compared with both budesonide 18 (55%) (p=0.05; OR=2.6, 95% CI 1 to 7.2), and placebo 19 (54%) (p<0.05; OR = 0.04, 95% CI 0.1 to 1), NNT of 4. AMS severity was higher in the budesonide group (4.5 [SD 2.6]) and placebo (4.6 [SD 3.5]) than acetazolamide (3.4 [SD 3.1]) [mean difference -1.1%; 95% CI -2.4 to 0.3]. Smaller ventilation increases were associated with greater severity AMS, with EtCO2 a better predictor of AMS than SpO2 (r = - 0.26, p=0.01 versus r = - 0.19, p=0.05).

CONCLUSION: Budesonide was ineffective prophylaxis of AMS compared to acetazolamide. Acetazolamide was protective of severe AMS. FUNDING: American Alpine Club Research Grant, Wilderness Medical Society’s Herbert N. Hultgren Grant, the Institute for Altitude Medicine at Telluride Email: davetpomeranz@gmail.com.

INTRODUCTION: Recent data on slow ascent (5 days) to 3900m suggest a protective effect of inhaled budesonide against acute mountain sickness (AMS), pointing to a role of the lung in the pathophysiology of AMS. We tested whether budesonide protects against AMS after rapid ascent to 4559m. METHODS: This prospective, randomized, double blind and placebo controlled trial, randomized 51 subjects to receive placebo, or 200 or 800µg of budesonide twice/day. Inhalation started 1 day prior to ascending from 1,130m to 4559m within ~20 hours, with an overnight stay at 3611m. Individuals were considered AMS-positive with a Lake Louise score (LLS) ≥5 and an AMS-C score ≥0.70 to at least one time point during the stay. Plasma and 24h-urine concentrations of cortisol were measured to evaluate potential systemic effects of inhaled budesonide. Oxygenation was assessed by capillary blood gas analysis. Pulmonary artery systolic pressure (PASP) was assessed by transthoracic echocardiography. RESULTS: The incidence of AMS at 4559m was not different between groups (placebo: 44%, budesonide 200µg: 50%, and 800µg: 63%). The corresponding LLS were 6.4±4.0, 6.6±2.8, and 8.2±3.5, and AMS-C scores were 0.8±0.8, 1.0±0.9, and 1.3±1.1 after the first night at 4559m. Capillary PO2 decreased from 84±7 to 47±5mmHg (all data combined; P<0.001) and was significantly lower in the AMS-positive than in healthy individuals in placebo and 200µg budesonide groups. Capillary PO2 was, however, not different between those with and without AMS in the 800µg group, indicating that preventing the slight decrease of PO2 compared with healthy individuals does not prevent AMS. PASP increased ~2-fold and was not affected by budesonide (P>0.25). Cortisol was not different between groups (P>0.41) demonstrating no detectable systemic effect on endogenous cortisol levels by inhaled budesonide. CONCLUSION: Prophylactic inhalation of budesonide does not improve AMS after rapid ascent to 4559m. Therefore, budesonide cannot be recommended of prevention of AMS.
**Abstract: F05**

**DIETARY NITRATE SUPPLEMENTATION INCREASES ACUTE MOUNTAIN SICKNESS SEVERITY AND SENSE OF EFFORT DURING SUBMAXIMAL EXERCISE IN HYPOXIA**

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**INTRODUCTION:** Dietary nitrate supplementation enhances performance at sea level and may alleviate hypoxia at high altitude. However, nitrate may exacerbate high altitude headache. This study investigated the effect of chronic nitrate supplementation on acute mountain sickness (AMS) and exercise performance in hypoxia. 

**METHODS:** Sixteen recreationally-active men (mean(SD): age 22(4) years, VO_{max} 51(6) mL·min^{-1}·kg^{-1}) completed this double-blinded placebo-controlled crossover study. Participants first completed assessments of maximal aerobic capacity in normoxia (F_{O_2} =0.209) and hypoxia (F_{O_2} =0.141). Participants then completed two six-day supplementation interventions: nitrate (70 mL beetroot juice shot containing ~7 mmol NO_{3}^{-} daily) and placebo (70 mL beetroot juice shot containing ~0.003 mmol NO_{3}^{-} daily). The interventions were separated by a ten-day washout and their order was randomly assigned.

On day five of each intervention, participants completed a prolonged hypoxic exposure (six hours, F_{O_2} =0.124) to assess AMS (Lake Louise Score (LLS)); high altitude headache (0 to 100 mm visual analogue scale (VAS)); and perceptual response to submaximal exercise (verbal expressions/0 to 100 rating of perceived exertion scale). On day six, participants completed an acute hypoxic exposure (F_{O_2} =0.141) to determine maximal exercise performance (time to exhaustion (TTE) at 80% of their maximal aerobic capacity). 

**RESULTS:** During prolonged hypoxia nitrate increased AMS severity compared to placebo (LLS: placebo=1.1(1.2); nitrate=2.1(2.4); 95%CI: 0.3, 2.5), which was largely due to elevated high altitude headache (VAS: placebo=19(21); nitrate=33(35) mm; 95%CI: 1, 32 mm). Furthermore, nitrate increased rating of perceived exertion during submaximal exercise from “moderate” (placebo=26(12)) to “somewhat strong” (nitrate=32(20); 95%CI: -4, 17). During acute hypoxia, nitrate had no effect on maximal exercise performance (TTE: placebo=650(191); nitrate=636(211) s; 95%CI: -102, 74 s).

**CONCLUSION:** Chronic dietary nitrate supplementation increases AMS severity, high altitude headache, and sense of effort during exercise in hypoxia.

**Abstract: F06**

**MEDEX 2015: HEART RATE VARIABILITY PREDICTS THE DEVELOPMENT OF ACUTE MOUNTAIN SICKNESS**

Sutherland, Angus; Free, Joseph; Evans, Laura Ruth; Dolci, Alberto; Crotti, Matteo; Macdonald, Jamie Hugo

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**INTRODUCTION:** Although pre-ascent prediction of susceptibility to acute mountain sickness (AMS) would be a useful tool to prevent subsequent harm, a diagnostic test for AMS susceptibility remains elusive. Heart rate variability (HRV) has shown promise in the early prediction of AMS and exercise performance in hypoxia. 

**METHODS:** Forty-four volunteers (age range 24-62 years; 26 male) undertook an expedition in the Nepali Himalaya to 5085 m. One month prior to the expedition HRV parameters and SpO_{2} were recorded over a 15 minute period at rest in normoxia (F_{O_2} =0.209) and in a normobaric hypoxic chamber (F_{O_2} = 0.115). On the expedition HRV parameters and SpO_{2} were collected again at 3841 m. A daily Lake Louise Score was obtained to assess AMS symptomology. 

**RESULTS:** The ratio of the low frequency (LF) to high frequency (HF) component of the HRV spectrum in normoxia and LF following 15 minutes of exposure to normobaric hypoxia had moderate (area under the curve ≥ 0.8) diagnostic accuracy. LF/HF ratio in normoxia (cutoffpoint ≤ 2.28 a. u) had the highest sensitivity (85%) and specificity (88%) for predicting AMS during the expedition. In contrast pre- and intra-expedition SpO_{2} measurements had poor (area under the curve < 0.7) diagnostic accuracy and inferior sensitivity and specificity. 

**CONCLUSION:** Pre-ascent measurement of HRV in normoxia was found to be of better diagnostic accuracy for AMS prediction than all measures of HRV in hypoxia, and better than peripheral SpO_{2} monitoring. With refinement of the hardware to allow immediate point of care reporting, HRV has the potential to be a simple pre-expedition tool to predict AMS susceptibility.
INTRODUCTION: We studied altitude related adverse health effects in lowlanders with COPD travelling to 3200m, and whether dexamethasone could prevent them. METHODS: 112 COPD patients, GOLD grade 1-2, living below 800m were randomized to receive dexamethasone (2x4mg/d) or placebo 24 hours before ascent from 760m and while staying at 3200m. Primary outcome assessed during 3 days at 3200m was the cumulative incidence of acute mountain sickness (AMS score ≥0.7), severe hypoxemia (SpO2 <75% for >30min), and discomfort requiring descent or oxygen therapy. Secondary outcomes were arterial blood gases. www.ClinicalTrials.gov NCT02450968.

RESULTS: 57 patients (median age 57y, FEV1 84%pred) were randomized to dexamethasone, 55 (median age 60y, FEV1 94%pred) to placebo. During 3 days at 3200m, 10 (18%) patients receiving dexamethasone, 11 (20%) receiving placebo had an altitude-related adverse effect (P=0.739). Within the first 24 hours at 3200m, 2 (4%) patients using dexamethasone and 8 (15%) using placebo (p=0.04) had severe hypoxemia or discomfort without AMS (AMS<0.7). With ascent from 760 to 3200m (day 2), PaO2 decreased from median (quartiles) 9.6kPa(9.2;10.0) to 8.2kPa(7.9;8.6) in the dexamethasone group and from 10.0kPa(9.1;10.5) to 8.0kPa(7.5;8.4) in the placebo group (altitude-related change with dexamethasone compared to placebo: median difference(95%CI) PaO2 0.4kPa(0.0;0.8, P<0.05) and PaCO2 -0.3kPa(-0.4;-0.1)). CONCLUSIONS: In lowlanders with COPD, GOLD grade 1-2, staying 3 days at 3200m, the cumulative incidence of clinically relevant adverse health effects was 20% in participants using placebo. This was not altered by preventive dexamethasone therapy although dexamethasone improved hypoxemia at 3200m. GRANT SUPPORT: Swiss Lung Foundation, Lunge Zurich, Swiss National Science Foundation.

OBJECTIVE: To evaluate the effect of acute exposure, acclimatization and re-exposure to very high altitude on nocturnal breathing and subjective sleep quality in lowlanders. METHODS: 21 healthy lowlanders, aged 18-30y, underwent two 6-day sojourns at the ALMA observatory, Chile (6hrs/day spent at 5050m, nights at 2900m), separated by a 1-week recovery period at 520m. Subjective sleep quality (SSQ, visual analog scale 0-100 with increasing quality) and respiratory sleep studies were assessed at 520m before ascent (LA1) and in the recovery period (LA2), and at 2900m during the first and second sojourn, on days 1 and 6 (sojourn 1: 1-HA1 and 1-HA6; sojourn 2: 2-HA1 and 2-HA6). www.ClinicalTrials.gov NCT02730143. RESULTS: Mean nocturnal oxygen saturation (SpO2), oxygen desaturation index (ODI, >3%) and SSQ were, respectively; medians(quartiles): LA1 95%(94;95), 2.2/h(1.5;3.0), 60(48;72); 1-HA1 86%(85;88), 13.1/h(9.6;33.6), 35(26;56); 1-HA6 90%(89;90), 5.8/h(4.5;7.9), 60(46;65) (P<0.05 LA1 vs. 1-HA1 and 1-HA6 vs. 1-HA1, all comparisons). Compared to values in the first sojourn (LA1, 1-HA1 and 1-HA6), during the second sojourn (LA2, 2-HA1 and 2-HA6), SpO2 and ODI, respectively, changed by medians(95%CI) LA2 +1%(0;2), -0.7/h(-1.2;-0.2); 2-HA1 +1%(0;2), -4.7/h(-19.7;-1.4); 2-HA6 0%(0;1), -1.1/h(-2.7;0.2). SSQ was not different between first and second sojourn. CONCLUSIONS: In healthy subjects, acclimatization over 6 nights at 2900m, with daily 6hrs exposures to 5050m, improved SpO2 and ODI compared to the first night at 2900m. After 1-week at lowland, re-exposure to 2900m and 5050m had a milder effect on SpO2 and ODI, suggesting some retention of physiologic acclimatization from the previous altitude exposure although no changes in subjective sleep quality were perceived. FUNDING AND SUPPORT: NSERC Discovery Grant (MJP; 2014-05554), The Brenda Strafford Foundation Chair in Alzheimer Research, the ALMA Observatory, Swiss Lung Foundation, Lunge Zurich, Swiss National Science Foundation.
ALTITUDE SCIENCE FROM BERT TO PULSE OXIMETERS
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In 1875 Paul Bert was the first to understand the role of partial pressure of oxygen on mammalian life at high altitude when 2 balloonists died euphorically at nearly Everest’s altitude. In World War One, fatal crashes of fighter pilots at high altitude led to failed efforts to use oximetry to warn pilots. In the century after Bert, respiratory physiology, often studied at high altitude, revealed the now well-known mechanisms of mammals in responding to hypoxia. In 1940, English physiologist-physician John R. Squire found that the log of the ratio of ratios of 4 values, two wavelengths (red and infra red) of light passing through human tissue during both blanched and perfused tissue, was sufficient to compute oxygen saturation of the blood. In 1970, Japanese electrical engineer Takuo Aoyagi invented pulse oximetry by carefully reading Squire’s 1940 report from which he suddenly realized how to measure arterial blood oxygen saturation using arterial pulsations in tissue. The author here reports some of his own UCSF lab work contributing to this field.

REDUCTIONS IN ACUTE MOUNTAIN SICKNESS FOLLOWING ACCLIMATIZATION ARE SUSTAINED DURING REINTRODUCTION: TO ALTITUDE FOLLOWING 12 DAYS AT SEA LEVEL
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This study examined whether reductions in the prevalence and severity of acute mountain sickness (AMS) induced by acclimatization can be sustained during re-introduction to altitude (RA) after 12 days at SL using normobaric hypoxia (NH) treatment. Seventeen sea level (SL) residents (M=11, F=6, age=23±6yrs; mean±SE) completed: 1) 4d of baseline SL testing, 2) 12d at 4300m on Pikes Peak, 3) 12d at SL with and without NH treatment and 4) a 24-hour RA (hypobaric chamber; 4300m). At SL after acclimatization, each received either NH (n=9, FiO₂=0.122) or SHAM (n=8; FiO₂=0.209) treatment for 3 hrs/day for 9 of the 12 days. AMS-Cerebral factor score, heart rate (HR), and arterial oxygen saturation (SaO₂) were assessed in the morning at SL, on d2 and d11 of acclimatization, and in the 20th hour on d2 of RA. There were no differences between NH and SHAM treatment so data were combined. AMS prevalence and severity, respectively, increased (P<0.05) from SL (0%;0.03±0.02) to d2 at 4300 m (76%;1.30±0.26) and then decreased by d11 at 4300 m (0%;0.11±0.06). AMS prevalence and severity during RA (17%; 0.25±0.09) remained the same as d11 at 4300 m. HR (bpm) increased (P<0.05) from SL (69±2) to d2 (107±3) at 4300 m and then decreased (P<0.05) from d2 to d11 (92±4) at 4300 m. During RA, HR (83±3) remained the same as d11 at 4300 m. SaO₂ (%) decreased (P<0.05) from SL (99±1) to d2 (85±1) at 4300 m and then increased (P<0.05) on d11 (89±1) at 4300 m. During RA, SaO₂ (88±1) remained the same as d11 at 4300 m. These results demonstrate that reductions in the prevalence and severity of AMS following 12 days acclimatization are retained during RA after 12 days at SL whether or not NH treatment is utilized. Author’s views not official U. S. Army or DoD policy.
Abstract: F11

MAXIMUM OXYGEN CONSUMPTION RETURNS TO SEA LEVEL VALUES AFTER TWO WEEKS OF ALTITUDE ACCLIMATIZATION IN A LARGE MULTI-YEAR STUDY

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While it is generally agreed that maximum oxygen consumption ($\dot{VO}_2^{\text{max}}$) declines upon acute ascent to altitude, there has been some disagreement about the effects of acclimatization on $\dot{VO}_2^{\text{max}}$. Some of this disagreement reflects a small sample size and lack of control of physical activity during the stay at altitude. PURPOSE: Therefore, the purpose of this study was to determine the effect of moderate altitude exposure on maximum oxygen consumption acutely, after acclimatization, and upon return to sea level. METHODS: Over the course of a 6-year period, eighty-eight active subjects (age = 23.3 ± 3.5 yrs, weight = 78.5 ± 17.5 kg, $\dot{VO}_2^{\text{max}} = 42.4 ± 5.7$ ml/kg/min) completed a graded-exercise test on a cycle ergometer at sea level (SL1), upon acute exposure to 3417 m (ALT1), two weeks following acclimatization at 3417 m (ALT2), and upon return to sea level (SL2). Workloads were increased every two minutes following a two-minute warmup until volitional fatigue. Maximum oxygen consumption was measured using a Parvo TruOne 2400 Metabolic cart. Subject’s activity levels were assessed during the 2-week period and were unchanged relative to sea level. RESULTS: Maximum oxygen consumption significantly declined (P<0.05) from SL1 to ALT1 (3.48 ± 0.39 l/min vs. 3.04 ± 0.32 l/min). However, by ALT2 $\dot{VO}_2^{\text{max}}$ was not different from SL1 (3.48 ± 0.39 l/min vs. 3.31 ± 0.51 l/min). Maximum oxygen consumption was slightly, but not significantly higher upon return to sea level (SL2 = 3.65 ± 0.66 l/min). While body weight changes occurred in some subjects, overall there was no difference in average body weight between any of the testing points. CONCLUSIONS: These data suggest that exposure to acute altitude results in a reduction in maximum oxygen consumption. However, after two weeks of acclimatization maximum oxygen consumption returns to pre-sea level values in a large multi-year study.

Abstract: F12

FAILURE OF PHARMACOLOGIC INTERVENTIONS TO IMPROVE EXERCISE PERFORMANCE AT HIGH ALTITUDE

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The purpose of this study was to test the efficacy of four medications to offset the expected decrement in performance during a simulated rapid deployment at altitude. In this double blind, placebo controlled, matched cohort design study, subjects (N = 102) participated in a three-day trip to high altitude (10,000-13,000 feet) that simulated a military deployment. Subjects were assigned to one of 5 groups (placebo control, metformin, quercetin, nifedipine + methazolamide, oral nitrate). Over the course of 6 hours, subjects were transported from Michigan to Breckenridge, Colorado. Subjects completed the Army Physical Fitness Test (APFT) 3 times: twice (screening, performance) at sea level and once at altitude (9075 feet) in Breckenridge. In order to participate in the study, subjects needed to score high on the APFT test (>200). The APFT consisted of a two mile run, timed sit-ups (2 min), and timed push-ups (2 minutes). Subjects were matched based on the average of the screening and performance APFT trials. A one-way ANOVA with planned comparisons was used to determine if participants in each of the treatment groups performed better than those in the placebo group at altitude. A comparison was also made between the performance trial and the altitude trial for each of the groups. Two mile run time was significantly slower (p<0.05) in the nifedipine + methazolamide group relative to the placebo group (1066 ± 134 sec vs. 940 ± 113 sec). Furthermore, the nifedipine + methazolamide group performed significantly fewer sit-ups compared to the placebo group at altitude relative to the performance trial (-8.8 ± 10.6 vs. 1.0 ± 13.1). However, there were no differences between the placebo group and the metformin, quercetin, or oral nitrate groups for any of the APFT measurements. In summary, metformin, quercetin, and oral nitrate were not effective at improving exercise performance at altitude. Moreover, nifedipine and methazolamide taken together adversely affected physical performance.
ACUTE XENON INHALATION STIMULATES PROLONGED ERYTHROPOIESIS

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OBJECTIVE: Xenon is an inhalation anesthetic with the potential to increase plasma erythropoietin (EPO). This study aimed to describe the efficacy of three subanesthetic dosages of xenon inhalation to cause erythropoiesis.

METHODS: On three occasions, 7 (2 female) participants breathed three increasing but subanesthetic concentrations of xenon (Xenon, 30% for 20 min; Xenon, 50% for 5 min; Xenon, 70% for 2 min and oxygen, 21% with balance Nitrogen). Pulse oximetry documented the absence of hypoxemia in all trials (data not shown). EPO was measured in duplicate at rest, during xenon inhalation and then at 1, 3, 6, 24, 72, 192 hours post xenon inhalation.

RESULTS: The technical error in our EPO measurement was 0.65 mU/mL with an estimated biological variability of 1.5 mU/mL over the three trials separated by at least 6 weeks. In all trials, EPO peaked 6 hours post Xenon inhalation (30%, 6.4±2.1 to 10.9±6.8, P=0.10; 50%, 6.9±2.2 to 9.3±2.3, P=0.01; 70%, 6.2±3.0 to 8.4±3.2, mU/mL P=0.13), thereafter trending downwards, yet remaining above baseline conditions for at least 24 hours post inhalation (24hours, 30%, 6.4±2.1 to 7.8±1.8, P=0.05; 50%, 6.9±2.2 to 8.4±2.3, P=0.01; 70%, 6.2±3.0 to 7.8±2.1, mU/mL P=0.06).

CONCLUSIONS: We show that three sub-anesthetic acute single dosages of xenon cause a small yet highly consistent pattern of erythropoiesis. Thus, despite the absence of hypoxia, xenon appears to stabilize hypoxia inducible factors and therefore has the potential to increase red cell mass and exercise performance.

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2016 UBC NEPAL EXPEDITION: IRON INFUSION REDUCES PULMONARY ARTERIAL SYSTOLIC PRESSURE AT HIGH ALTITUDE IN LOWLANDERS BUT NOT SHERPA

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INTRODUCTION: An obligate cofactor in the regulation of the hypoxia inducible factor (HIF) system, iron decreases the sensitivity of the HIF system to hypoxia, the probable mechanism for the inverse relationship between iron status and hypoxic pulmonary vasoconstriction. People of Tibetan descent possess variants of the genes regulating HIF and show blunted pulmonary arterial vasoconstriction in response to acute and chronic hypoxia; however, it remains unknown how iron manipulation may differentially effect pulmonary vascular responses to sustained hypoxia between Tibetan descendants and lowlanders. We hypothesized that in lowlanders iron supplementation would attenuate, and iron chelation exacerbate pulmonary arterial systolic pressures (PASP; echocardiography) but that neither would affect PASP in Sherpa.

METHODS: Following 4-10 days at 5050m, 20 Sherpa (BMI 22.2 ± 4.3 kg/m2) and 18 lowlanders (BMI=23±2kg/m2) were randomized to receive intravenous iron sucrose (200mg; IRON) or desferrioxamine (~4g; DFO). Echocardiographic metrics, arterial and venous blood, blood pressure and ventilation were collected before and after infusions.

RESULTS: Across both groups, IRON increased serum [iron] by 40.4 ± 22 umol/L (P < 0.05) whereas DFO decreased serum [iron] by 7.4 ± 6 umol/L to below the detectable range (P < 0.05), but neither affected serum ferritin. Total iron binding capacity increased with DFO but remained stable following IRON. Soluble transferrin receptor was decreased by IRON in both Sherpa and lowlanders (P<0.05) but was unaffected by DFO. In lowlanders, DFO increased cardiac output (+20±11%)
and stroke volume (+25.5±14%), and IRON decreased PASP (-4.3 ± 5 mmHg) and pulmonary vascular resistance (P<0.05). Sherpa PASP were unaffected by either IRON or DFO. CONCLUSION: There were no clear physiological changes following iron manipulation in Sherpa, whereas in lowlanders IRON reduced PASP at rest, suggesting lower sensitivity to iron in Sherpa at high altitude, and a possible prophylactic effect of iron for high altitude sojourners.

Abstract: F17
ERYTHROPOIESIS AND IRON HOMEOSTASIS AT HIGH ALTITUDE IN WORKERS AT THE ALMA OBSERVATORY IN CHILE
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INTRODUCTION: Ascent to high altitude has well-characterised effects on erythropoiesis and iron homeostasis in sea-level residents. These are less studied in individuals working intermittently under conditions of hypobaric hypoxia. This study explored iron biology and erythropoiesis in Chilean high-altitude shift workers. METHODS: Nineteen male workers at the ALMA Operations Support Facility provided venous blood samples at an altitude of 2,900 m at two time points, prior to and immediately following a period of several days commuting to 5,050 m. Workers spent 6-8 hours daily at the higher altitude and slept at 2,900 m. Haemoglobin concentration ([Hb]) was measured using a near-patient testing device. Samples of serum and plasma were frozen for subsequent analysis of indices including concentrations of erythropoietin (Epo), soluble transferrin receptor (sTfR) and hepcidin. RESULTS: Mean participant age was 40 years (range 28-60). There was no significant change between time points in [Hb] (median 16.9 vs 16.9 g/dL; P = 0.16), [sTfR] (mean 20.7 vs 20.9 nmol/L; P = 0.78), [Epo] (mean 13.4 vs 17.9 mIU/mL; P = 0.08) or [hepcidin] (mean 31.1 vs 29.8 pg/L; P = 0.69). However, individual responses were highly variable. Further analysis indicated a significant negative relationship between changes in Epo and hepcidin concentrations over time in a given individual (Pearson’s correlation coefficient -0.49; P = 0.035). CONCLUSION: These data indicate that in males habituated to high-altitude shift work, changes in markers of iron homeostasis occur after a period at very high altitude.
Abstract: F18

MUSCULAR EFFICIENCY AT ALTITUDE
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INTRODUCTION: The dissociation between aerobic exercise capacity and systemic oxygen delivery after chronic exposure to altitude may reflect changes in tissue oxygen utilization secondary to metabolic adaptation. Muscular efficiency is defined as the ratio of work accomplished to energy expended. It encompasses significant unmeasured work, including for example, the work of breathing. In the context of hypoxic adaptation, the efficiency of the unmeasured components of work itself are of interest as these reflect the efficiency of oxygen utilisation for the whole body. Gross efficiency (GE) evaluates “whole body” or metabolic efficiency, whereas delta efficiency (DE) provides the most specific evaluation of the efficiency of muscle force transduction. Efficiency changes in hypoxia remain controversial. We evaluated changes in muscular efficiency during a standardized ascent to 5300m.

METHODS: 118 healthy volunteers performed three ten-minute cycle ergometry constant work rate tests at sub anaerobic threshold work rates (Metamax 3B, Cortex) in London, Namche 3500m and Everest Base Camp (EBC) 5300m. All subjects followed an identical 11-day ascent profile. Seat height was standardized for each individual for all tests and pedalling cadence was fixed at 60rpm. RESULTS: There was a small (0.5%) but statistically significant increase in GE at 20 watts (8.5%-9% - repeated measures ANOVA p=0.001) and 40 watts (13-15.5% repeated measures ANOVA p=0.001). At 60 watts this increase did not reach statistical significance. There was no change in DE on exposure to altitude (26.9%,26.4%,26.3%). Gender had a significant effect on GE at sea level and at altitude (repeated measures ANOVA p<0.001), with women demonstrating higher GE, reflecting their lower VO2. However there was no interaction between gender and altitude. CONCLUSIONS: There is a small increase in GE at altitude which may primarily reflect non muscular components of oxygen uptake during exercise given that DE is unchanged.

Abstract: F19

VALIDATION OF THE GAS ANALYSERS OF A PORTABLE BREATH BY BREATH CARDIOPULMONARY EXERCISE TESTING SYSTEM (CPET) AT ALTITUDE (METAMAX 3B)
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INTRODUCTION: Gas concentration sensor performance in contemporary CPET systems may be affected (sensitivity or gain) when ambient operating conditions are changed. Consequently, the validity of CPET systems should be established in the environmental conditions in which they will be used. There is limited reporting of commercial CPET systems performance at altitude. We evaluated the validity of the Metamax 3B (M3B)(Cortex, Leipzig, Germany) gas analysers in a hypobaric chamber at simulated altitudes of up to approximately 9400m Model Atmosphere Equivalent (MAE).

METHODS: The M3B was decompressed in 10 KPa increments in a hypobaric chamber from 102 KPa (sea level) to 31kPa (234 Torr; 9400m MAE). At each altitude, a two-point gas calibration was performed. The M3B was then presented with two gases, one approximating ambient air (21% O2, 0.03% CO2, balance nitrogen) and the other approximating expired air (15% O2, 5% CO2, balance nitrogen). After decompressing to 234 Torr, the chamber was re-pressurised and the protocol repeated. M3B recorded and concentrations were compared with true gas concentrations calculated from the chamber pressure verified using an independent barometer (accuracy ± 0.1KPa). RESULTS: Inter-trial differences in recorded values were minimal indicating high levels of precision. Both analysers were negatively biased. The absolute error in measurement was 0-0.14% for the oxygen cell and 0-0.03% for the CO2 cell. Relative percentage error was 0-0.5% for the oxygen cell and 0-0.4% for the CO2 cell. CONCLUSION: M3B gas analysers performed within ATS guideline criteria for accuracy (1) of ± 1% at ambient pressures from sea level to ~ 9500m MAE. REFERENCES: 1. ATS/ACCP Statement on cardiopulmonary exercise testing. American Journal of Respiratory and Critical Care Medicine 167: 211-277, 2003.
Abstract: F20

REDUCED BREATHING RESERVE DOES NOT LIMIT EXERCISE CAPACITY AT ALTITUDES UP TO 5300M

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INTRODUCTION: The factors limiting VO2peak at altitude remain a source of controversy. It has been suggested that ventilation may become limiting at altitude because of reduced breathing reserve (1). However maximal voluntary ventilation (MVV) has not been directly measured but inferred from the FEV1 using predictive equations that have not been validated at altitude. We evaluated changes in breathing reserve during a standardized ascent to 5300m to test the hypothesis that breathing reserve limits exercise tolerance at altitude.

METHODS: 198 healthy volunteers underwent maximal incremental exercise testing (Metamax 3B, Cortex) in London, Namche 3500m and Everest Base Camp (EBC) 5300m. All subjects followed an identical 11-day ascent profile. Spirometry was performed and MVV was measured directly using an ultrasonic flowmeter which has been validated at altitude (Easy-One®, MA, USA).

RESULTS: 182 subjects reached EBC. This analysis was performed on the 148 subjects tested at all altitudes. LaT and VO2peak progressively decreased by 27.2% and 32.5% respectively at 5300m (repeated measures ANOVA p<0.001). MVV increased from 149 L/min at sea level to 177 L/min at EBC (5300m) (Repeated measures ANOVA p<0.001). VEpeak also increased (Repeated measures ANOVA p<0.001) but by less than the MVV resulting in an increase in breathing reserve (BR) at EBC (repeated measures ANOVA p<0.001). There was no association between exercise capacity and breathing reserve at any altitude. VEpeak did not encroach upon MVV in any tests. There was no change in FEV1 at altitude, consequently sea level equations inferring MVV were not accurate.

CONCLUSIONS: Reduced breathing reserve does not limit exercise capacity at 5300m. FEV1 is unchanged at altitude.


Abstract: F21

DOES HYSTERESIS IN CARDIORESPIRATORY VARIABLES DURING HIGH ALTITUDE ASCENT AND DESCENT QUANTIFY THE MAGNITUDE OF ACCLIMATIZATION?

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Acute mountain sickness (AMS) is common during ascent to high altitude. However, large variation exists between individuals and prediction of AMS severity before ascent is difficult. There is currently no metric associated with the magnitude of acclimatization. The purpose of this study was to assess and quantify ventilatory acclimatization in the context of high altitude hypoxia by comparing ascent and descent values in oxygen saturation (SpO2) and end-tidal CO2 (PETCO2).

We hypothesized (1) the area formed by differential cardiorespiratory values during ascent and descent (i.e., hysteresis) would quantify the magnitude of acclimatization, (2) prolonged stays above 5000m would lead to larger areas compared with shorter stays, and (3) larger hysteresis areas would be correlated with lower AMS symptoms (Lake Louise score). In 2012 a single male participant (P1) ascended to 5050m in Nepal and stayed approximately three weeks, with SpO2 measures obtained during ascent and descent. P1 returned in 2016 as a part of a group of 20 participants (P20), where the group ascended over nine days and stayed only one night above 5000m before descending. In P1, the calculated SpO2 hysteresis area in 2016 was 72% smaller than in 2012, likely due to a shorter stay above 5000m. In P20, there was a weak positive correlation between SpO2 and PETCO2 hysteresis areas (r=0.43, P=0.06), but these values were not correlated with AMS severity when arriving above 5000m (r=0.06, P=0.8; r=0.3, P=0.2, respectively), likely because of limited acclimatization time. We conclude that calculation of hysteresis in cardiorespiratory variables measured during ascent and descent may hold promise as a simple method to quantify the magnitude of ventilatory acclimatization for prolonged stays at altitude.
Abstract: F22

CARDIORESPIRATORY RESPONSES DURING HIGH ALTITUDE ASCENT TO 5160M IN NEPAL: RELATIONSHIPS TO SELF-REPORTED AMS

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INTRODUCTION: Individuals ascending to high altitude risk developing acute mountain sickness (AMS). The Lake Louise AMS scoring system is a self-reporting tool without quantitative physiological metrics. Large variability exists in the severity of AMS symptoms, which are difficult to predict in advance. We aimed to assess cardiorespiratory acclimatization and AMS severity during an ascent to 5160m in the Nepal Himalaya. We hypothesized that AMS symptoms would be correlated with a battery of measured cardiorespiratory variables during ascent.

METHODS: A group of 20 participants started in Kathmandu (1400m) and trekked from Lukla (2840m) to the village of Gorak Shep (5160m) near Everest Base Camp over nine days, using prophylactic oral acetazolamide (125mg BID) and a standard ascent profile. Cardiorespiratory variables were measured in seated position every morning following one night sleep at each altitude. Variables included oxygen saturation (SpO2 (%), heart rate (HR; min-1), pressure of end-tidal PET CO2 (Torr) and respiratory rate (RR; min-1). Measures were made at the following altitudes (m): 1400, 2840, 3440, 3860, 4370, 4910, 5160. These measures were correlated with AMS scores within-individuals using Spearman’s Rho statistics (n=140).

RESULTS: AMS vs. SpO2, significant, weak negative correlation (r=-0.2, P=0.03); AMS vs. HR, significant, moderate positive correlation (r=0.4, P<0.0001); AMS vs. PET CO2, significant, weak negative correlation (r=-0.3, P<0.0001); AMS vs. RR, no significant correlation (r=0.2, P=0.07). CONCLUSIONS: Self-reported AMS scores were only weakly reflected in measured cardiorespiratory variables during ascent to altitude. Our data add a quantitative component to assessing AMS symptoms, compared to qualitative self-reporting alone. Portable pulse oximetry and capnography may contribute additional monitoring utility to assess the relative risk of developing AMS during incremental ascent to high altitude.

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Abstract: F23

THERMODILUTION CARDIAC OUTPUT IS INACCURATE DURING VENOVENOUS EXTRACORPOREAL MEMBRANE OXYGENATION THERAPY FOR HYPOXEMIC LUNG FAILURE IN PIGS

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INTRODUCTION: Veno-venous extracorporeal membrane oxygenation (vvECMO) is a lifesaving intervention in acute respiratory distress syndrome (ARDS). The relationship of ECMO blood flow to cardiac output (CO) determines the contribution of vvECMO to systemic oxygen delivery. Recirculation of blood from the superior to the inferior vena cava may limit the oxygen delivery efficiency and influence thermodilution based measurements of CO. We investigated the effect of vvECMO blood flow on thermodilution-based CO measurements in a porcine model of acute hypoxemic lung injury (ALI).

METHODS: Anesthetized pigs (n=6) were cannulated for vvECMO (bifemoral/jugular configuration). CO was measured with an ultrasound flow probe placed around the ascending aorta. ECMO blood flow was set at 25, 50, 75, 100, 125 % of CO. Cardiac output was also measured at each ECMO flow setting by the thermodilution technique using a pulmonary artery catheter (PAC) in conjunction with measurements of blood recirculation volume. All experiments were performed in healthy pigs and repeated after induction of acute lung injury (ALI) by sequential whole lung saline lavages. Data were analyzed using Bland-Altman plots.

RESULTS: PAC measurements overestimated CO at all ECMO blood flow settings (mean difference = 2 l/min) both in healthy and lung injured pigs. The difference between CO as measured by the PAC and blood flow measured at the ascending aorta increased when results were analyzed for low
ECMO blood flows (mean difference between measurements: 1.3 l/min) vs. high ECMO blood flows (mean difference 3 l/min). Overestimation of CO by thermodilution was highest when high ECMO blood flow resulted in relevant recirculation of ECMO blood flow. **CONCLUSION:** Thermodilution-based measurements overestimate cardiac output during veno-venous ECMO therapy in healthy and lung injured pigs. Overestimation of CO by thermodilution is depending on the proportion of ECMO blood flow to cardiac output and on the amount of recirculating blood volume.

**Abstract: F24**

**NOVEL NON-INVASIVE METHOD FOR MEASURING SYMPATHETIC ACTIVITY IN HUMANS USING OPTICAL COHERENCE TOMOGRAPHY IMAGING OF THE RETINA AND CHOROID**

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**BACKGROUND:** Heightened sympathetic nervous system (SNS) activity is associated with prevalent and serious respiratory, cardiovascular and metabolic diseases. Current methods to measure SNS in humans are technical difficulty and invasive (microneurography), give poor temporal resolution ([plasma norepinephrine]) and/or have questionable accuracy (i.e. heart rate variability). Consequently, sympathetic activity is rarely assessed in the clinic and under investigated in human disease and drug discovery. **AIM:** The choroid blood vessels, which encase the back of the retina, receive strong sympathetic innervation and can be imaged non-invasively with spectral domain optical coherence tomography (OCT). Here we test whether OCT imaging of choroid vascular perfusion density (CVPD) can be used to assess sympathetic activity. **METHODS:** OCT images were compared with muscle sympathetic activity (MSNA) determined with microneurography during periods of induced hypoxia, hyperoxia, hyperoxic-hypercapnia, hyperventilation, end-expiratory breath-hold and, a cold-pressor test in 6 healthy males age 26±3y. **RESULTS:** CVPD and integrated total MSNA were inversely correlated (R= -0.989; p<0.05) over the 6 provocation manoeuvers. The intra-subject correlation between change in MSNA and change in CVPD across SNS provocations were also strongly and inversely related (R= -0.78 ± 0.06). However, macular thickness, measured from the internal limiting membrane to the retinal pigment epithelium remained constant during all sympathetic provocations (p>0.05). The coefficient of variation from repeat measures of CVPD and retinal thickness were 1.5 ± 8.44 and 0.38 ± 2.1, respectively. **CONCLUSION:** These data demonstrate vascular regulation of ophthalmic tissue between the anterior and posterior circulations of the eye differ. Given the strong relationship between CVPD and MSNA, and relative ease of interrogation, OCT may provide a clinically useful and non-invasive method to reliably assess SNS (re)activity.
RESPIRATORY SINUS ARRHYTHMIA REACTIVITY DURING HIGH ALTITUDE ACCLIMATIZATION: EFFECTS ON OXYGENATION

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Respiratory sinus arrhythmia (RSA) is the transient fluctuation in heart rate (HR) in phase with the respiratory cycle. There is controversy regarding the underlying mechanisms and possible utility of RSA. Hypoxia activates the sympathetic nervous system (SNS), potentially decreasing RSA magnitude. However, deep breathing increases RSA magnitude and may improve ventilation/perfusion (V/Q) matching, possibly preventing oxygen desaturation. We aimed to investigate the relationship between RSA magnitude and peripheral oxygen saturation (SpO₂) during incremental ascent to altitude. We hypothesized that (a) RSA reactivity to increases in inspiratory tidal volume (V₁₁) would be blunted with ascent as a result of SNS activation and (b) individuals with larger RSA magnitudes would have higher SpO₂ through improved V/Q matching. Measurements were conducted over eleven days at 1045m (baseline, day 1), 3440m (day 7), 3860m (day 9), and 4370m (day 11) during a trek to altitude in the Nepal Himalaya. Participants (26±2.1 years; BMI 23.8±1.1 kg/m²; n=12) were instrumented with ECG, pneumotachometer, and finger pulse oximeter and tested on rest days after one night at each altitude. Participants breathed 30, 40, and 50% of their previously-determined forced vital capacity (FVC). Five consecutive targeted breaths were averaged to determine RSA magnitude and SpO₂. RSA linearly increased with targeted increases in V₁₁ at each altitude (R²≥0.96). However, there were no differences in RSA reactivity with high altitude ascent (P=0.64). Individuals with larger RSA magnitudes during 50%FVC did not show larger improvements in SpO₂ from baseline breathing at 4370m (r=0.02, P=0.95). Our data suggests that slow ascent to high altitude does not decrease RSA magnitude. In addition, individuals with larger RSA magnitudes do not have improved SpO₂, suggesting that V/Q matching is likely not improved by RSA magnitude. Acknowledgments: NSERC (USRA and Discovery), AIHS, Government of Alberta STEP funding.
CHEMOREFLEX MEDIATED BRADYCARDIA AND ARRHYTHMIA DURING APNEA AT ALTITUDE IN LOWLANDERS BUT NOT SHERPA

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INTRODUCTION: There is increased risk of bradycardic arrhythmia at altitude. We investigated if a) bradycardia or conduction abnormalities occur in apnea, b) this occurs in high altitude natives and c) the chemoreflex plays a role. METHODS: Electrocardiograms (ECG; lead II) were collected in lowlanders (LL; n=14; age=27±6yrs) and Nepalese Sherpa (SH; n=9; age=32±11yrs). LL were assessed at 344m and 5050m (Pyramid Laboratory); SH were assessed at 5050m. ECG rhythm and heart rate (HR) were assessed during rest and end-expiratory apnea. The contribution of the peripheral chemoreflex to the genesis of arrhythmia was assessed in LL (n=9) at altitude after 100% oxygen. RESULTS: In LL, resting HR was higher at altitude (55.4±10.1 vs 64.9±13.5 bpm; P<0.01) but not different to SH (73.8±5.9 bpm). Sea-level apnea did not elicit significant bradycardias in LL (nadir -2.8±12.9 bpm; -6.2±23.5% from baseline) or conduction abnormalities. In contrast, high-altitude apnea caused marked bradycardia in LL (nadir -31.4±17.7 bpm; -47.4±21.4% from baseline; P<0.001) and conduction abnormalities in 8/14 participants (junctional rhythm, 3º atrio-ventricular block, sinus pause). Although apnea decreased HR modestly in SH (nadir -9.2±9.2 bpm; -12.3±12.3% from baseline; P<0.05), there were no conduction abnormalities. Bradycardia was more pronounced in LL versus SH (P<0.001). Hyperoxia at altitude did not affect HR in LL (64.9±13.5 vs 69.2±13.8 bpm); however, bradycardia (nadir -14.3±20bpm; -17.7±26.8% from baseline) was less pronounced (P<0.001 compared to hypoxic state) and conduction abnormalities occurred inonly 1/9 LL (junctional rhythm). CONCLUSION: At altitude, there is increased risk of bradycardia and conduction abnormalities associated with apnea in LL, but not Sherpa. Reduced magnitude of apnea-induced bradycardia and incidence of conduction abnormalities during hyperoxia indicates an important role of the peripheral chemoreflex. Funded by NSERC (CS & PNA), President’s Grant for the Creative Performing Arts - Human Performance Scholarship (CS) and a Canada Research Chair (PNA).

IMPOSED OSCILLATORY SHEAR STRESS IN ACUTE AND CHRONIC HYPOXIA: IMPACT ON ENDOTHELIAL FUNCTION

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INTRODUCTION: Experimentally-induced oscillatory shear stress and hypoxia independently impair endothelial function in humans. The endothelium appears to be especially sensitive to imposed-oscillatory shear stress, both at rest and following 24-48 hours of hypoxic exposure; whether this manifests acutely or is sustained with chronic hypoxia is unknown. METHODS: Healthy lowlanders (n=15, 30±6 years [mean±SD], BMI=23±2 kg m²) participated in three oscillatory shear stress interventions; twice at sea level (normoxia [NX] and following 20-minutes of normobaric hypoxia [HX, 11% O₂]) and once 5-7 days after a 9-day ascent to 5050m (HA). Oscillatory shear stress was provoked in the brachial artery using a 30-minute distal cuff inflation (75-mmHg). Venous blood viscosity was measured at a shear rate of 225 s⁻¹ prior to each intervention. Endothelial function was assessed before and after each intervention by reactive hyperemia flow-mediated dilation (FMD). Shear patterns were obtained via duplex ultrasound. The stimulus for FMD was calculated as the shear stress area under the curve (shear rate x viscosity; SSAUC) from cuff deflation to peak vasodilation. RESULTS: The oscillatory shear index was greater during HX and HA compared to NX (P=0.002, 0.042). Distal cuff inflation increased retrograde shear stress and the oscillatory shear index during each condition. Following the distal cuff inflation, FMD decreased during NX (-36±41%; P<0.001) without any effect during HX and HA. The SSAUC decreased after distal cuff inflation during HX and HA (P=0.043 and P<0.001), but was unchanged during NX. CONCLUSION: A 30-minute exposure to an oscillatory shear stress pattern impaired FMD during NX, a condition with an unchallenged, healthy endothelium; however, acute exposure to oscillatory shear stress does not appear to worsen endothelial function during acute or chronic hypoxia. The existence of disturbed shear stress patterns at baseline in hypoxia may contribute to the insensitivity to further acute augmentation of retrograde shear stress.
**Poster Session II**

**Abstract: F29**

**ACUTE HYPOXEMIA CAN REDUCE VASCULAR FUNCTION IN HEALTHY HUMANS**

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**INTRODUCTION:** Vascular function is impaired at high altitude and following one hour of comparably severe normobaric hypoxia (~F\textsubscript{1}O\textsubscript{2} =0.11). Whether vascular function is impaired during milder hypoxia is unknown. We examined the hypothesis that vascular function would be impaired following acute exposure to both mild (74 ± 2 mmHg P\textsubscript{ET}O\textsubscript{2}) and moderate (50 ± 3 mmHg P\textsubscript{ET}O\textsubscript{2}) normobaric hypoxia. METHODS: Brachial endothelium-dependent flow mediated dilation (FMD) was assessed at baseline and following 30-minutes of hypoxia (n=12). Endothelium-independent dilation (via glyceryl trinitrate; GTN) was assessed following the FMD test, and in normoxia on a separate control day (n=8). RESULTS: Independent of the magnitude of hypoxia, there was a decline in baseline blood flow (~39%; P=0.01), anterograde shear rate ([SR]) (~21%; P=0.01) and an increase retrograde SR (~48%; P<0.01), compared to normoxic baseline. Compared to normoxic baseline, both FMD and GTN-induced dilation were reduced following mild hypoxia (FMD: 6.9 ± 0.9 vs. 4.8 ± 1.7%; P<0.001; GTN: 16.8 ± 5.7 vs. 14.6 ± 4.9%; P=0.01) and even more during moderate hypoxia (FMD: 6.9 ± 0.9 vs. 3.1 ± 1.7%; P<0.01; GTN: 16.8 ± 5.7 vs. 12.7 ± 4.0%; P=0.01). Independent of the hypoxic stimulus, FMD SR area under the curve was reduced during hypoxia by (~30%, P<0.01); when this metric was used as a covariate for the analyses, FMD was attenuated in the both hypoxic trials by ~9%. CONCLUSION: Adverse shear patterns and an impairment in the NO-vasodilator system is evident in healthy individuals following an acute bout of mild and moderate isocapnic hypoxia. These findings have important implications for individuals with pre-existing medical conditions, especially those who are acutely and rapidly exposed to acute hypoxia.

**Abstract: F30**

**HIF/RAGE AXIS MEDIATED GENE EXPRESSION AND PATHOLOGICAL IMPACT IN CIGARETTE SMOKING**

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Cigarette smoking (CS) results in an inflammatory and pro-oxidant alveolar environment. Our previous studies demonstrated that whole body CS exposure increases expression of genes regulated by a variety of transcription factors involved in inflammation, oxidant and ER stress by a RAGE (receptor of advanced glycation end products)-mediated effect. RAGE is a multi-ligand receptor that belong to the immunoglobulin superfamily of transmembrane proteins. As HIF-mediated signaling also regulates genes integral to inflammation and responses to oxidant stress, we hypothesized that 1) HIF is involved in the pathogenesis of alveolar injury due to CS exposure and 2) RAGE is necessary for CS-mediated HIF signaling. To address these hypotheses, we exposed C57BL/6 wild type (WT) and RAGE null mice to 7 days of whole-body CS, assessed alveolar macrophage (AM) gene expression using RNA sequencing, and measured oxidative stress proteins in lung tissue. In WT mice, CS exposure increased 68 HIF-regulated genes in AM including EPAS1, HMOX1, PDK4, CXCR2 lingadsand VEGF. In contrast, many of these genes were not increased in RAGE null AM; results were verified using quantitative RT-PCR. Lung tissue from WT mice showed evidence of increased protein modification by oxidant stress due to CS; no increase in oxidative stress proteins in RAGE null mice was seen. We conclude that the HIF signaling pathway plays an important role in CS-induced cellular stress and that CS alters the HIF-regulated gene expression pattern in WT, but not in RAGE null mice. Our findings highlight a novel mechanism by which an extracellular signal initiated by the RAGE/HIF axis is integral to CS-caused stress response.
Abstract: F31

NO EVIDENCE OF ANAPYREXIA DURING ACUTE AND LONG-TERM EXPOSURE TO NORMOBARIC HYPOXIA
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INTRODUCTION: A regulated decrease of body temperature, known as anapyrexia, represents an important compensatory response of mammals to environmental hypoxia. Recent investigations suggest that acute hypoxia also provokes a measurable anapyrexic effect in humans. We sought to establish whether anapyrexia can also be observed in healthy humans during acute and long-term normobaric hypoxic exposures. METHODS: The data were collated from three separate projects investigating the effect of anticipated environmental conditions within the Lunar and Mars habitats on different physiological systems. Given that internal environment of the habitats will be hypoxic, the astronauts will be concomitantly exposed to hypoxia and reduced gravity. Horizontal bed rest was employed to simulate reduced gravity. These studies were designed to assess the separate and combined effects of unloading/inactivity and hypoxia on physiological systems. Healthy young male (LunHab, N=11, 10-day exposure; PlanHab, N=11, 21-day exposure) and female (FemHab, N=9, 10-day exposure) participants underwent the following three campaigns in a randomised manner: 1) Normobaric Hypoxic Ambulatory confinement (HAMB; PO₂=90.0mmHg, ~4,000m); 2) Normobaric Hypoxic Bed Rest (HBR; PO₂=90mmHg, ~4,000m) and 3) Normoxic Bed Rest (NBR; PO₂=133mmHg, ~940m). Tympanic temperature was measured before (2-days prior (Pre)) and daily throughout the initial two days of either the HAMB, HBR or NBR campaigns in both males and females. Similarly, no evidence of anapyrexia was noted during the latter stages of each hypoxic exposure irrespective of sex and activity. CONCLUSIONS: These data suggest that both, acute and long-term hypoxic exposure (~4,000m simulated altitude) does not alter tympanic temperature in healthy individuals. ACKNOWLEDGEMENTS: Supported by the European Union FP7 (PlanHab; Grant no. 284438) and the European Space Agency (ESTEC/Contract 40001043721/11/NL/KML).

Abstract: F32

STRENGTHENING HIGH ALTITUDE RESEARCH (STAR): DEVELOPING A GUIDELINE FOR HIGH ALTITUDE RESEARCH
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BACKGROUND: In recent decades research on high altitude medicine has substantially increased. However, data reporting is still inconsistent due to the lack of standardization. The STrengthening Altitude Research (STAR) project is an initiative to involve a large group of internationally renowned experts in high altitude research in order to produce a standardized and uniform data reporting protocol based on their broad consensus. METHODS: A core group of experts devised a register of key parameters for consideration, based on fundamental publications. This dataset underwent the Delphi technique, i.e. a structured, deliberative process that uses a series of rounds within a group of experts who collaborate anonymously. The experts rate the parameters as being either core or supplementary, provide comments and can suggest additional parameters. The overall aim is to progress an approved consensus, culminating in the production of a set of parameters and guidelines to standardize data reporting for clinical high altitude research. RESULTS: Based on their scientific credentials in high altitude research, 51 worldwide experts were selected and invited to participate in the STAR Delphi process. 42 experts agreed, and 32 completed the first round whereby 46 of 162 parameters reached consensus as being core parameters. The feedback from the experts resulted in major changes for the second round: The list of parameters was substantially shortened and underwent a third round of discussion to eventually be integrated into a uniform data reporting protocol. CONCLUSIONS: The Delphi process is an established tool to find consensus among a large group of experts and is particularly suitable for clinical high altitude research. With the help of the experts' feedback, the essential core and supplementary parameters for high altitude research will be identified and a uniform data reporting protocol established.
INTRODUCTION: High altitude provides a challenging environmental condition to ensure proper visual function. The aim of this study was to investigate a deterioration of visual acuity and contrast sensitivity function during high altitude exposure in healthy subjects due to the effects of hypobaric hypoxia. This study is related to the Tübingen High Altitude Ophthalmology (THAO) study. METHODS: Visual acuity and contrast sensitivity function were tested using the Freiburger Visual Acuity and Contrast Test (FrACT) under standardized conditions in 14 healthy subjects at high altitude at the Capanna Margherita (CM; 4559m, Italy) and compared to baseline measurements in Tübingen (341 m, Germany). Intra-individual differences between baseline and follow-up examinations were calculated by multivariate analysis of variance for repeated measures (MANOVA; P=0.05). Clinical parameters of peripheral oxygen saturation (SpO₂) using a finger pulse oximeter and heart rate (HR) were correlated to psychophysical tests by Pearson’s correlation coefficient. RESULTS: Upon arrival at CM, a significant decrease of contrast sensitivity function on all days tested was noted (day1 = -0.16 ± 0.22, day2 = -0.10 ± 0.2, day3 = -0.12 ± 0.19; P < 0.05) compared to baseline. Visual acuity remained unchanged upon high altitude exposure. Contrast sensitivity function correlated with SpO₂ (r = 0.53, P = 0.05) but not with HR (r = -0.16, P = 0.59). Comparisons of right and left eyes showed no statistically significant difference on any day measured. CONCLUSION: High altitude exposure leads to an altered contrast sensitivity function. These changes are fully reversible after return to low altitude. This finding is of clinical importance to trekkers and mountaineers exposed to high altitude as visual processing in particular under mesopic conditions at dusk and dawn is altered.

INTRODUCTION: Nasal mucociliary clearance (NMCC) was investigated to consider if this aspect of Sherpa physiology differed from lowlanders. METHOD: During Caudwell Extreme Everest 2007 and Xtreme Everest 2013 expeditions, evaluation of NMCC was undertaken by placing a dried granule of saccharin on the inferior turbinate under endoscopic control and time to tasting sweetness measured with an upper time limit of 90 mins. Rigid endoscopic photography of the nose and oropharynx was performed to improve accuracy. Testing was performed in healthy lowlanders at sea level in London and at Everest Base Camp (EBC) (5300m). A group of Sherpas who had not been to altitude in the previous year were also studied on the 2013 expedition with baseline testing in Kathmandu (1300m) and after an identical ascent profile to EBC. RESULTS: In 31 lowlanders, NMCC range at sea level was 6-30 mins, mean 16.3 mins. At arrival at EBC, 12 (39%) had abnormal saccharin times, 10 > 45 minutes (range 6-90mins, mean 37.5mins). Prolonged NMCC correlated with notable changes on endoscopy with significant degrees of dried mucus and crusting. All 13 Sherpas had normal saccharin times at Kathmandu (mean 10mins, range 6-25mins) and EBC (mean 10 mins, range 7-21mins) without any notable endoscopic abnormalities. CONCLUSION: NMCC is one of the most important defense mechanisms of the respiratory tract. In contrast to lowlanders, all 13 Sherpas had normal saccharin times at EBC, without the endoscopic changes seen in lowlanders. This is the first time that intranasal endoscopic images have been taken at high altitude, directly demonstrating the profound changes which can occur. The nasal saccharin test provides an in vivo measurement of the effectiveness of both mucus and ciliated nasal epithelium. The study indicates that the Sherpa’s upper respiratory tract mucociliary system is another example of their physiological adaptation to high altitude.
Abstract: F36

PHYSIOLOGICAL RESPONSES TO TWO HYPOXIC CONDITIONING STRATEGIES IN HEALTHY SUBJECTS

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OBJECTIVE: Hypoxic exposure can be used as a therapeutic tool by inducing various cardiovascular, neuromuscular and metabolic adaptations. Hypoxic conditioning strategies have been evaluated using either sustained (SH) or intermittent (IH) hypoxic sessions. Whether hypoxic conditioning via SH or IH may induce different physiological responses remains to be elucidated. METHODS: Fourteen healthy active subjects performed two interventions in a single blind, randomized cross-over design, starting with either 3x SH (48 h apart), or 3x IH (48 h apart), separated by a 2 week washout period. SH sessions consisted of breathing a gas mixture with reduced inspiratory oxygen fraction (FiO₂), continuously adjusted to reach arterial oxygen saturations (SpO₂) of 70-80% for 1 hour. IH sessions consisted of 5 min with reduced FiO₂ (SpO₂ = 70-80%), followed by 3-min normoxia, repeated 7 times. During the first (S1) and third (S3) sessions of each hypoxic intervention, cardiorespiratory parameters, and muscle and pre-frontal cortex oxygenation (near infrared spectroscopy) were assessed continuously. RESULTS: Minute ventilation increased significantly during IH sessions while heart rate increased during both SH and IH sessions. Arterial blood pressure increased during all hypoxic sessions, although baseline normoxic systolic blood pressure was reduced from S1 to S3 in IH only. Muscle oxygenation decreased significantly during S3 but not S1, for both hypoxic interventions; pre-frontal oxygenation decreased in S1 and S3, and to a greater extent in SH versus IH. Heart rate variability indices indicated a significantly larger increase in sympathetic activity in SH versus IH. From S1 to S3, further reduction in heart rate variability was observed in SH while heart rate variability increased in IH. CONCLUSIONS: These results showed significant differences in heart rate variability, blood pressure and tissue oxygenation changes during short-term SH versus IH conditioning. Heart rate variability may provide useful information about the early adaptations induced by such intervention.

Abstract: F37

EFFECTS OF HIGH-ALTITUDE EXPOSURE ON SUPRASPINAL FATIGUE AND CORTICOSPINAL EXCITABILITY AND INHIBITION

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INTRODUCTION: While acute hypoxic exposure enhances exercise-induced central fatigue and can alter corticospinal excitability and inhibition, the effect of prolonged hypoxic exposure on these parameters remains to be clarified. We hypothesized that five days of altitude exposure would (i) normalize exercise-induced supraspinal fatigue during isolated muscle exercise to sea level (SL) values and (ii) increase corticospinal excitability and inhibition. METHODS: Eleven healthy male subjects performed intermittent isometric elbow flexions at 50% of maximal voluntary contraction to task failure at SL and after one (D1) and five (D5) days at 4,350 m. Transcranial magnetic stimulation and peripheral electrical stimulation were used to assess supraspinal and peripheral fatigue. Pre-frontal cortex and biceps brachii oxygenation was monitored by near-infrared spectroscopy. RESULTS: Exercise duration was similar between SL (1,095±562 s), D1 (1,132±516 s) and D5 (1,440±689 s). No significant differences were found between the three experimental conditions in maximal voluntary activation declines at task failure (SL: -16.8±9.5%; D1: -25.5±11.2%; D5: -21.8±7.0%; p>0.05). Exercise-induced peripheral fatigue was larger at D5 versus SL (100 Hz doublet at task failure: -58.8±16.6 versus -41.8±20.1%; p<0.05). Corticospinal excitability at 50% maximal voluntary contraction was lower at D5 versus SL (brachioradialis p<0.05, biceps brachii p=0.055). Cortical silent periods were shorter at SL versus D1 and D5 (brachioradialis and biceps brachii, p<0.05). CONCLUSION: The present results show similar pattern of supraspinal fatigue development during isometric elbow flexions at SL and after one and five days at high altitude, despite lowered corticospinal excitability and enhanced intracortical inhibition at altitude.
Abstract: F38

CENTRAL FATIGUE DOES NOT DIFFER BETWEEN LOWLANDERS AND SHERPA AFTER GRADUAL ASCENT TO 5050M

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INTRODUCTION: This study aimed to assess the effect of a sustained submaximal elbow flexion on supraspinal fatigue and corticospinal excitability of lowlanders (LL) and Sherpa (SH), performed after gradual ascent to 5050m.

METHODS: Nine age-matched LL and SH (30.0 ± 1.0 vs. 30.3 ± 1.8 years, respectively) completed a 4-minute submaximal (25% maximal torque, MVC) sustained isometric elbow flexor contraction. At baseline (BL), and each minute during the protocol, motor evoked potentials (MEP) and maximal compound action potentials (Mmax) were elicited by transcranial magnetic stimulation (TMS) of the motor cortex and supramaximal stimulation of the brachial plexus, respectively. Ratings of perceived effort (RPE) were collected using a 0-10 Borg scale. To measure voluntary activation (VA), TMS was also delivered during contractions at 100, 75 and 50% MVC, separated by 3s. This was done at BL and the end of the fatigue protocol.

RESULTS: At BL, MVC torque and VA were significantly greater in LL than SH (79.5 ± 3.6 vs. 50.1 ± 1.3 Nm and 95.4 ± 2.7 vs. 88.2 ± 6.6%, respectively). At the end of the fatigue protocol, MEPs and root mean square of biceps electromyography (EMG) were significantly increased, while MVC and VA were decreased, with no differences between LL and SH (pooled data; MEP: 44.8 ± 21.7% increase; EMG: 53.0 ± 52.5% increase; MVC: 25.7 ± 11.4 decrease; VA: 7.6 ± 7.4% decrease). RPE significantly increased more in LL than SH (final value of 7.9 ± 1.1 vs. 6.0 ± 2.2).

CONCLUSION: Given the deleterious effects of hypoxia on neuromuscular function, it was expected that LL would show more fatigue than SH. RPE data suggest that LL found the task more difficult than SH but the loss of torque was equivalent for both groups. Further, similar decreases in VA and increases in descending drive and corticospinal excitability suggest that a lifetime at altitude did not substantially alter neural control in SH compared to LL. Supported by NSERC, CFI, and BCKDF.

Abstract: F39

CEREBRAL BLOOD FLOW IN SHERPA AND LOWLANDER CHILDREN

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INTRODUCTION: The brain of hypoxia-tolerant vertebrates is known to survive extreme limitations of oxygen in part because of very low rates of energy production and utilization. Developmental cerebral hemodynamic adaptations to chronic high altitude exposure are largely unknown.

METHODS: To assess if adaptations may be involved in the developing human brain, we assessed common carotid (CCA), internal carotid (ICA) and vertebral (VA) volumetric flow and middle cerebral artery (MCA) velocity in 25 (9.6 ± 1.0 yrs, 129±9 cm, 27±8 kg, 14 girls) Sherpa children (3800m, Thame and Khunde, Nepal) and 25 (9.9 ± 0.7 yrs, 143±7 cm, 34±6 kg, 14 girls) age-matched lowlanders (344m, Kelowna, Canada) during supine rest. Resting gas exchange, blood pressure and heart rate were also assessed.

RESULTS: Despite comparable age, height and weight were lower (both p<0.01) in Sherpa compared to lowlander children. Mean arterial pressure, heart rate and ventilation were similar, whereas oxygen saturation (95±2 vs. 99±1%, p<0.01) and end-tidal CO2 (24±3 vs 36±3 mmHg, p<0.01) were lower in Sherpa children. Global cerebral blood flow was ~30% lower in Sherpa compared to lowlander children. These changes were reflected in reductions in ICA flow (283±108 vs. 333±56 ml/min, p=0.05), VA flow (78±26 vs 118±35 ml/min, p<0.05) and MCA velocity (72±14 vs 88±14 cm/s, p<0.01). In contrast, CCA flow was similar between Sherpa and lowlander children (425±92 vs. 441±81 ml/min, p=0.52). Sherpa children showed ~ 30% decreased resting oxygen uptake (233±43 vs 350±66 ml, p<0.01) compared to lowlander children, indicating hypo-metabolism.

DISCUSSION: A lower cerebral blood flow in Sherpa children highlights a developmental cerebral hemodynamic pattern that may be the result of defense adaptation against chronic hypoxia.

FUNDING SOURCES: NSERC Discovery grant, Swiss National Science Foundation.
**Abstract: F40**

**FINDINGS OF COGNITIVE IMPAIRMENT AT HIGH ALTITUDE: RELATIONSHIPS TO ACETAZOLAMIDE USE AND ACUTE MOUNTAIN SICKNESS**

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**OBJECTIVE:** Acute mountain sickness (AMS) is defined by patient-reported symptoms using the Lake Louise Score (LLS), which provides limited insight into any possible underlying central nervous system (CNS) dysfunction. Some evidence suggests AMS might co-exist with altered neural functioning. Cognitive impairment (CI) may go undetected unless a sensitive test is applied. Our hypothesis was that a standardized test for mild CI would provide an OBJECTIVE measure of CNS dysfunction, which may correlate with the symptoms of AMS and so provide a potential new tool to better characterize altitude-related CNS dysfunction. We compared a cognitive screening tool with the LLS to see if it correlated with CNS dysfunction. **METHODS:** Adult native English-speaking subjects visiting Himalayan Rescue Association aid stations in Nepal at 3520m (11,548ft) and 4550m (14,927ft) were recruited. Subjects were administered the LLS and a slightly modified version of the Quick Mild Cognitive Impairment Screen (eQmci). Medication use for altitude illness was recorded. Scores were compared using the Spearman correlation coefficient. Data also included medication use. **RESULTS:** Seventy-nine subjects were enrolled. A cut-off of three or greater was used for the LLS to diagnose AMS and 67 or less for the eQmci to diagnose CI. There were 22 (28%) subjects who met criteria for AMS and 17 (22%) subjects who met criteria for CI. There was a weak correlation ($r^2=0.06$, $p=0.04$) between eQmci score and LLS. In matched subjects with identical LLS, recent acetazolamide use was associated with significantly more CI. **CONCLUSION:** Field assessment of CI using a rapid standardized tool demonstrated that a substantial number of subjects were found to have mild CI following rapid ascent to 3520-4550m (11,548-14,927ft). The weak correlation between the LLS and eQmci suggests that AMS does not result in CI. Use of acetazolamide appears to be associated with CI at all levels of AMS severity.

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**Abstract: F41**

**COGNITIVE EFFECTS OF ACUTE EXPOSURE TO HIGH ALTITUDE IN ALTITUDE-EXPERIENCED WORKERS.**

Drogos, Lauren L.; Pon, Charlotte; Hartmann, Sara E.; Furian, Michael; Dyck, Adrianna M.; Lichtblau, Mona; Bader, Patrick R.; Moraga, Fernando; Soza, Daniel; Lopez, Ivan; Rawling, Jean M.; Ulrich, Silvia; Bloch, Konrad E.; Giesbrecht, Barry; Poulin, Marc J.

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**OBJECTIVE:** We investigated the effect of moderate (2900m–MA) and high (5050m–HA) altitudes on measures of attention (ATT) and executive function (EF) in altitude-veteran workers from the ALMA observatory, Chile. We hypothesized that cognitive performance at HA would be lower than cognitive performance at MA. **METHODS:** Cognitive measures of ATT and EF were measured in 19 male workers (Mean age 40.1±8.5(SD), range 28-60). Testing was conducted in a randomized order at MA and HA over two separate working-shifts. Testing session involved four tests assessing ATT (Attention Switching Task [AST], Reaction Time [RTI], Rapid Visual Processing [RVP]), EF (One Touch Stockings of Cambridge [OTS]) using CANTAB (Cambridge Cognition Ltd). Instruction and testing was administered on iPads using Latin American Spanish. Data were analyzed using repeated measures of covariance. **RESULTS:** Contrary to our hypothesis we did not observe main effects of altitude on RVP, OTS, or AST. There were significant interactions between altitude and order of administration (MA to HA; HA to MA). More specifically, there was a practice effect only when the first administration occurred at MA, but not HA on RVP response latency ($F(1,15)=4.64$, $p=0.048$); latency to correct response on the OTS ($F(1,17)=18.50$, $p=0.001$); latency to response on the AST ($F(1,16)=6.97$, $p=0.018$); and a trend for RVP probability of a correct response ($F(1, 15)=3.68$, $p=0.073$). This pattern was not seen on the RTI task. However, participants had significantly faster movement, but not reaction times at HA on the RTI. **CONCLUSIONS:** This study provides evidence that learning effects on tasks may be diminished at HA. These data suggest that repetition or training should occur at MA, whenever possible. **FUNDING AND SUPPORT:** NSERC Discovery Grant (MJP; 2014-05554), The Brenda Strafford Foundation Chair in Alzheimer Research (MJP), the Alma Observatory, Swiss Lung Foundation, Lunge Zurich, Swiss National Science Foundation.
INTRODUCTION: High altitude (HA) workers experience a unique exposure to sustained hypoxia. However, the impact of this exposure on cognitive function (CF) is unclear. We investigated the effect of HA (5050m) on CF with acute, subacute, and repeated exposures to HA in altitude-naïve healthy young adults, using a pattern of HA exposure common at HA worksites in Chile. METHODS: CF was tested in 21 adults (24.8±3.7 years, 14 females) during two 7-day sojourns to HA, each sojourn including 6-8 hours/day at HA, with the remaining time spent at 2900m to reflect the pattern of HA exposure experienced by workers at the Alma observatory. The sojourns were separated by 7-days rest at low altitude (LA; 520m). Testing was conducted at LA before and after HA and on days one and six at HA. The CF test battery consisted of four tasks focused in domains of attention [Reaction Time; Attention Switching Task (AST); and Rapid Visual Processing (RVP)] and executive function [One Touch Stockings of Cambridge]. Testing was conducted on an iPad using CANTAB (Cambridge Cognition). Statistical significance was determined with repeated measures analysis of covariance. ClinicalTrial.gov NCT02738307. RESULTS: AST performance improved with acclimatization as there was decreased response latency (first vs. second sojourn; $F(1,14)=5.85, p=0.033$) and greater variability in reaction time by the mean standard deviation during the first sojourn ($F(1,14)=4.86, p=0.043$). The latency to correct response (i.e., time to a correct decision; RVP) improved in the second sojourn, compared to the first ($F(1,14)=8.62, p=0.011$). CONCLUSIONS: Reduced CF is observed with acute exposure to HA on cognitive tasks of attention, but not executive function, and is partially reversed after repeated 7-day exposure to HA, likely due to acclimatization. FUNDING AND SUPPORT: NSERC (2014-05554), Brenda Strafford Foundation Chair in Alzheimer Research, Alma Observatory, Swiss Lung Foundation, Lunge Zurich, Swiss National Science Foundation.
Abstract: F44

**ACUTE EFFECTS OF HIGH-ALTITUDE TRAVEL ON COGNITION AND MOOD: COMPARISONS FOLLOWING SLEEP AT SEA LEVEL VERSUS 3800M**

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Hypoxia influences cognitive function and mood. However, most investigations of mood are completed under conditions of simulated altitude. We hypothesized cognitive function and mood would be impaired following short-term high-altitude exposure. Seventeen subjects were studied at the Univ California White Mountain Research Center, Barcroft Station (3800m). At altitude, subjects slept with adaptive servo ventilation, supplemental oxygen (SpO₂ > 95%), or no-treatment (NT) randomized across three consecutive nights. Subjects completed baseline (B) measurements with no treatment at the UC San Diego Clinical Sleep Laboratory (sea level). Sleep quality was evaluated with polysomnography. The following battery of cognitive tests were completed each morning: Psychomotor Vigilance Test, Attentional Network Test, Emotion Recognition Test, Balloon Analog Risk Task, Trail Making Test, Digit Span Test, Corsi Block-Tapping Test, Verbal Paired Associates, along with self-reported mood and sleep questionnaires (i.e., Pittsburgh Sleep Quality Index, Brunel Mood Scale, and Stanford Sleepiness Scale). Data analyzed from 12 subjects revealed that sleep at sea level was associated with more accurate identification of happiness (NT: 7.08, B: 7.77, p<0.04) while no-treatment sleep at 3800m was associated with higher misattribution of happiness (NT: 0.92, B:0.23, p<0.04). Subjects also reported being more confused, worn out, annoyed, exhausted, mixed-up, muddled, bad-tempered, and uncertain at 3800m. There was no other significant difference between measured cognition at altitude versus baseline, which may reflect our randomized treatment design and variability in subject acclimatization on assigned NT day. We conclude high-altitude travel increases incidence of negative mood and decreases accuracy of identifying happiness in others. Further analyses will determine whether high-altitude sleep quality influences cognitive test performance and elucidate the effectiveness of different sleep treatments on daytime mood and cognition. Funding was provided by the Ledell Family Award.

Abstract: F45

**ENHANCED NEURONAL SYNCHRONY DURING SKILLED REACHING AT HIGH ALTITUDE**

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**OBJECTIVE:** To establish a method of measuring and characterizing task-related neuronal activity during a high altitude ascent.  
**METHODS:** We implemented cortical electroencephalography (EEG) on two healthy, right-handed subjects during a self-paced skilled reaching task over a seven-day ascent to Annapurna Base Camp in the north-central region of Nepal.  
**RESULTS:** We correlated task-centered sensorimotor oscillatory activity of five physiologically relevant EEG bands (Delta: 0.5-3.5 Hz; Theta: 4-8 Hz; Alpha: 7.5-12.5 Hz; Beta: 13-30 Hz; Gamma: 30-100 Hz) with daily measures of altitude, ascent, and blood oxygen saturation (SpO2). Our data reveal a significant positive correlation between sensorimotor delta phase-amplitude synchrony and altitude.  
**CONCLUSIONS:** Our method represents a novel approach to studying the brain at high altitude and revealed task-related neuronal adaptations. Although we experienced significant changes in SpO2 at altitude, our task performance remained unchanged. This suggests that the enhanced delta phase and amplitude characteristics of our EEG activity at high altitude likely represent the recruitment of additional sensorimotor resources to maintain task coordination. We hypothesize the homeostatic delta oscillations represent a separate oscillatory system that is driving task-related, cortical-level compensation. While healthy individuals may have relatively robust compensation machinery, it may breakdown in subjects with disease, under abnormal stress, or generally in situations where basic brain functions serving survival are paramount. Therefore, potential countermeasures for high altitude mountaineers may benefit from a dual approach: one for supplementing homeostatic processes and another that enhances cortical-specific pacemaker networks.  
**ACKNOWLEDGEMENTS:** The Harvard Travellers Club financially supported this study. Brain Products, LLC, sponsored all equipment. This study received “non-regulated” status by the Univ Michigan Medical School Institutional Review Board (ID: HUM00119637).
**Abstract: F46**

**DEVELOPMENT OF A CLINICALLY USEFUL CEREBROVASCULAR STRESS TEST USING CO2 AND BOLD-MRI**

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**BACKGROUND:** Cerebrovascular reactivity (CVR) refers to a hemodynamic response to a vasoactive stimulus. It is used to assess and anatomically map hemodynamic deviations from normality that occur in association with cerebrovascular disease such as vascular stenosis, and as an aid in the risk assessment for stroke and dementia. Regrettably, the literature is replete with a wide array of vasoactive stressors and measures of cerebral blood flow, making it impossible to define abnormal findings in a single patient. **PURPOSE:** To systematically study and develop a standardized CVR test. **METHODS/RESULTS:** We used precise CO₂ targeting as the vasoactive stimulus and BOLD MRI signals as the surrogate for cerebral blood flow. CVR tests were performed over several studies in 150 healthy individuals and 250 patients with stenocclusive disease. Initial experiments identified the optimal amplitude and duration of the stimulus. We then assembled standardized CVR tests from healthy subjects into an atlas that enabled statistical scoring of an individual patient’s CVR relative to the normal range, voxel by voxel, to create CVR z-maps. Similarly, we assembled an atlas of normal test-retest CVR differences (CVR Interval Difference z-maps), which statistically score the probability of a significant change in CVR over time in a single patient. **CONCLUSIONS:** Voxel-wise normalization of CVR measures to reference atlases maximizes the sensitivity of identifying abnormalities within a single patient, between cohorts, and finding significant changes in a single patient over time. It also allows comparison of data between institutions to enable multicenter trials.


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**Abstract: F47**

**A CNS CELL GROUP THAT DETERMINES EXERCISE CAPACITY**

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Breathing is a vital physiological activity that continually adapts to ever-changing behavioural and environmental conditions to maintain constant levels of arterial and brain PO₂, PCO₂ and pH. To match ventilation to the metabolic demands of the body during exercise, respiratory output is controlled by several feed-forward and feedback mechanisms. Descending cortical projections increase ventilation in anticipation of, and during the initial stages of, exercise, while central/peripheral chemoreceptors, and muscle afferents maintain enhanced respiratory activity during continued exercise. Neuronal cell groups residing within the retrotrapezoid nucleus (RTN) and C1 area of the rostral ventrolateral medulla oblongata contribute to the maintenance of resting respiratory activity and the arterial blood pressure, and play an important role in the development of cardiorespiratory responses to metabolic challenges (such as hypercapnia and hypoxia). We hypothesised that RTN and C1 neurones may play an important role in the control of breathing during exercise. In rats, acute silencing of RTN/C1 neurons, transduced to express HM4D (Gi-coupled) receptors was found to dramatically reduce the exercise capacity (by 60%), during intensity controlled forced treadmill running. In a model of simulated exercise (electrical stimulation of the sciatic or femoral nerve in urethane-anaesthetised spontaneously breathing rats) silencing of the RTN/C1 neurones had no effect on cardiovascular changes, but significantly reduced the respiratory response during steady state exercise. These results identify a neuronal cell group (RTN) in the lower brainstem which is critically important for the development of the respiratory response to exercise and, therefore, determines the exercise capacity (supported by The Wellcome Trust and British Heart Foundation).
ABSTRACT: F48

REGIONAL CEREBRAL BLOOD FLOW AND BLOOD GAS CONTENT CHANGES DURING ASCENT TO 5050M: A COMPARISON BETWEEN LOWLANDERS AND SHERPA

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INTRODUCTION: The effect of chronic hypoxia on cerebral blood flow (CBF) in high-altitude natives (Sherpa) and lowlanders during ascent to high-altitude has not been investigated in the absence of prophylactic acetazolamide use.

METHODS: Global CBF, via measurement of internal carotid (ICA) and vertebral artery (VA) blood flow, arterial blood gases, venous blood viscosity and mean arterial pressure (MAP) were measured in 21 lowlanders (BMI=23±2kg/m²) and 12 Sherpa (BMI=24±4kg/m²) prior to and during ascent to 5050m. Sherpa were partially de-acclimatized to 1400m over 5-15 days following which both groups ascended over 10 days with measurements obtained at 1400m, 3440m, 4371m and 5050m.

RESULTS: Across both groups, global CBF initially decreased from baseline at 3440m (Sherpa=-21.71%, lowlanders=-1.88%) but was elevated by 5050m (Sherpa=9.13%, lowlanders=20.08%; P<0.05). Alterations in CBF were mediated via changes in ICA blood flow and, in particular, VA diameter and velocity; these values were higher in lowlanders across all altitudes (main effect, P<0.05). Consequently, cerebral O₂ delivery (CDO₂) was higher in lowlanders above 1400m (P<0.05). Although arterial O₂ content and saturation were similar between groups, arterial PCO₂ was lower in lowlanders above 3440m (P<0.05), and pH was higher across all altitudes (main effect, P<0.05). Venous viscosity, arterial hemoglobin and hematocrit were higher in the Sherpa at baseline (P<0.05); however, these increased in lowlanders throughout ascent reaching similar values to the Sherpa. MAP was higher in the Sherpa until 4371m but remained unchanged throughout ascent; MAP in the lowlanders increased at all altitudes.

CONCLUSION: Despite the lower pH and greater hypertension in the Sherpa, both CBF and CDO₂ were lower compared to lowlanders. Whether this potentially blunted cerebrovascular reactivity is an adaptive or maladaptive response in the Sherpa remains to be established.

ABSTRACT: F49

EFFECT OF DEXAMETHASONE ON CEREBROVASCULAR HEMODYNAMICS IN LOWLANDERS WITH COPD TRAVELLING TO 3200M: RANDOMIZED PLACEBO-CONTROLLED TRIAL

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INTRODUCTION: Dexamethasone is used to treat cerebral edema at altitude. However, effects of dexamethasone at altitude on cerebrovascular regulation are unknown.

METHODS: 82 patients with COPD, GOLD 1-2, (mean±SD; 56±9yrs, FEV₉₀ 90±19%predicted) were randomized to placebo or dexamethasone (2x4mg/day) one-day prior to and during an altitude sojourn. Middle cerebral artery blood flow velocity (MCAv; transcranial Doppler ultrasound) and mean blood pressure (MBP) were monitored at rest and during hyperventilation and isometric handgrip exercise to fatigue (60%maximal strength) at lowland (760m, Bishkek, Kyrgyzstan) and altitude (3200m, Tuja Ashu).

RESULTS: In 44 patients receiving dexamethasone there was no altitude-induced increase in MCAv (48.6±8.8 vs. 49.4±10.5cm·s⁻¹) or MBP (93±9 vs. 94±9mmHg) with ascent to 3200m; both P>0.05. In 38 patients receiving placebo, ascent to 3200m increased MCAv and MBP from 47.7±10.0 to 52.2±10.4cm·s⁻¹ and 91±12 to 97±12mmHg, respectively; both P<0.01. Treatment effect (difference of means[95%CI]) was -3.8cm·s⁻¹ [-7.3;-0.2] and -5mmHg [-9;-1] for MCAv and MBP; both P<0.05. The change in MCAv during hyperventilation-induced hypocapnia at 3200m was similar between treatments (2.5±0.5mmHg [-1.5; 2.6±1.0mmHg]; P>0.05). During handgrip at 3200m, dexamethasone blunted MCAv increase (28±14 vs. 21±13%; P≤0.01), despite a similar increase in MBP (46±22 vs. 48±26%; P>0.05). With
placebo, the MCAv and MBP during handgrip were similar between 760m and 3200m (MCAv: 30±14 vs. 28±11%; MBP: 47±27 vs. 45±20%; both P>0.05). The treatment effect was -6%[-11;0] P<0.05 and 4%[-7;15] P>0.05 for MCAv and MBP, respectively. **CONCLUSIONS:** In mild-moderate COPD dexamethasone attenuated the altitude-related increase in MCAv and MBP, suggesting that dexamethasone modulates the vasopressor but not the metabolic response to hypobaric hypoxia, thereby perhaps allowing for a protective role in regulating cerebral perfusion pressure.

**Abstract: F50**

**DEOXYHEMOGLOBIN REGULATES CEREBRAL BASODILATION IN HYPOXIA**

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**INTRODUCTION:** We examined the hypothesis that deoxyhemoglobin regulates hypoxic cerebral vasodilation in an in vivo human model. **METHODS:** Ten healthy males (age: 30±8 years, height: 176±4cm, weight: 72±4kg) completed three consecutive isocapnic hypoxia trials: 1) hypoxemia (\(\phi PaO_2\)); 2) isovolumic hemodilution (\(\phi[Hb]\)); and 3) combined hemodilution and hypoxemia. During the last minute of each trial, radial arterial-jugular venous differences and volumetric blood flow in the internal carotid and vertebral arteries (duplex ultrasound) were measured to calculate global cerebral blood flow (gCBF) and metabolic rate (CMRO\(_2\)). **RESULTS:** In the hypoxemia trial, arterial oxygen content (CaO\(_2\)) decreased from 19.3±1.1mL\(\times\)dL\(^{-1}\) by ~7% and ~14% in sequential stages (PaO\(_2\)=93.3±4.0 vs. 59.2±1.7 vs. 46.8±1.8mmHg). The hemodilution trial involved two equal steps of blood removal and replacement with 5% human serum albumin, resulting in ~10% and ~20% reduction in CaO\(_2\)([Hb]=14.2±0.9 vs. 12.7±0.6 vs. 11.3±0.5g×dL\(^{-1}\)). The final hypoxic trial was repeated in hemodiluted subjects, reducing CaO\(_2\) from 15.7±0.7mL×dL\(^{-1}\) by ~8% and ~15% (PaO\(_2\)=95.9±7.2 vs. 58.1±2.4 vs. 45.8±2.3mmHg). Each intervention increased gCBF; however, cerebral reactivity (%change in gCBF per unit reduction in CaO\(_2\)) was ~53% lower in the hemodilution trial compared to hypoxemia (0.9±0.3 vs. 2.0±0.5% \(\Delta\text{CBF}×\text{mL}^{-1}×\text{dL}^{-1}\); P<0.05). In contrast, reactivity was ~43% greater in the combined hypoxemia and hemodilution trial (2.9±0.7 vs. 2.0±0.5% \(\Delta\text{CBF}×\text{mL}^{-1}×\text{dL}^{-1}\); P<0.05). Across all trials, CMRO\(_2\) was unchanged (main effect, P=0.34) despite a lower cerebral O\(_2\) delivery in the hemodilution compared to hypoxic trials (P<0.05 vs. both). This difference was due to a 5% reduction in cerebral O\(_2\) delivery during hemodilution (P<0.05). **CONCLUSION:** By utilizing both hypoxemia and hemodilution, we have isolated the role of hemoglobin, and determined that (deoxy)hemoglobin may account for up to 50% of hypoxic cerebral vasodilation in humans. Combined hypoxemia and hemodilution mediates hypoxic cerebral vasodilation in an additive manner.

**Abstract: F51**

**CEREBROVASCULAR AND CARDORESPIRATORY RESPONSES TO HYPOXIA IN OSA PATIENTS FREE OF OVERT CARDIOVASCULAR DISEASE:**

**EFFECTS OF NOCTURNAL OXYGEN AND CPAP THERAPIES**

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**INTRODUCTION:** Obstructive sleep apnea (OSA) patients are reported to have impaired cerebral blood flow (CBF) responses to hypoxia that is corrected by continuous positive airway pressure (CPAP) treatment. Though CPAP removes the intermittent hypoxia (IH) and hypercapnia, negative intrathoracic pressure, sympathetic activation and sleep fragmentation characteristics of OSA, CPAP's beneficial effects on cerebrovascular and cardiorespiratory function are ascribed principally to correction of IH. Whether correction of other ancillary features of OSA contributes to the improved CBF response to hypoxia with CPAP is unknown. Nocturnal oxygen corrects OSA-associated IH, but not the other ancillary features. Therefore, this study examined the independent effects of nocturnal oxygen and CPAP therapies on cerebrovascular and cardiorespiratory responses to hypoxia in OSA. **METHODS:** Hypoxic CBF, cardiovascular and ventilatory responses were assessed in 52 OSA patients free of overt cardiovascular disease at baseline, after 2 weeks of nocturnal oxygen therapy (n=26) or no OSA treatment (n=26), and after ~4 weeks of CPAP (n=40). Twenty-two healthy controls were assessed at baseline and follow-up visits. The impact of oxygen and CPAP...
Therapies was determined using an analysis of co-variance. **RESULTS:** Mean blood pressure during isocapnic-euoxia was decreased by 3.6±1.2mmHg following nocturnal oxygen (p=0.006) and 4.5±1.2mmHg following CPAP (p<0.001) while cerebrovascular conductance was increased following CPAP treatment only (p=0.001). However, the magnitude of these changes was not different from controls. Surprisingly, OSA patients and controls had similar cerebrovascular and cardiorespiratory responses to isocapnic-hypoxia at baseline; neither nocturnal oxygen nor CPAP altered the vascular responses. Conversely, both treatment modalities decreased the hypoxic ventilatory response among patients with the most severe OSA (p<0.013). **CONCLUSIONS:** Neither nocturnal oxygen nor CPAP alter blood pressure or vascular responses to hypoxia in OSA patients free from overt cardiovascular disease, but both modalities improve the hypoxic ventilatory response in patients with severe OSA. Funded by the CIHR, HSFC, AIHS, and NSERC.

**Abstract:** F52

**TRACKING ALTITUDE-RELATED CHANGES IN PROCESSING CAPACITY WITH BRAIN SIGNAL VARIABILITY.**

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**INTRODUCTION:** Cognitive decline at high altitude is well documented, however brain changes associated with this decline are understudied. Increasing evidence suggests that brain signal variability (BSV) is an important marker of information processing capacity (McIntosh et al., 2010). Changes in BSV track individual differences in processing capacity (Protzner et al., 2013), and also relate to task performance. For example, Wang et al. (2016) found that increased BSV during resting state correlated with faster reaction time and better accuracy during a subsequent task. **METHODS:** In the present study we examined changes in BSV from high (5050m) to low (520m) altitude with multiscale entropy, a measure sensitive to linear and nonlinear variability (Costa et al., 2005). We collected electroencephalography (EEG) in 14 young adults (9 females) during resting state, and related BSC changes to performance during a visual word/non-word decision task. Each participant was tested: on their first day at high altitude (5050m), following 5 days of 6 hours/day exposure to 5050m while sleeping at moderate altitude (2900m), and during the first day returning to low altitude (520m). **RESULTS:** BSV was reduced on the first day at high altitude compared to the 6th day at high altitude, and the first day back at low altitude (p<0.001). Across all days, individual differences in BSV during resting state predicted performance, such that greater variability was associated with reduced word/non-word decision reaction times (p<0.001). **CONCLUSION:** Our results suggest that altitude-related changes in resting-state BSV have consequences for information processing capacity, and may have implications for workers at high altitude. Funding sources and support: Natural Sciences and Engineering Research Council (NSERC) Discovery Grants (MJP, 2014-05554; ABP, 418454-2013; PMP, 217309-2013), the Brenda Strafford Foundation Chair in Alzheimer Research (MJP), ALMA Observatory, Swiss Lung Foundation, Lunge Zurich, Swiss National Science Foundation.
**Abstract: F53**

**EFFECTS OF HYPOThERMIA, HYPOXIA AND HYPERCAPNIA ON BRAIN OXYGENATION: A PROSPECTIVE PORCINE STUDY**
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**INTRODUCTION:** Limited data are available regarding the combined effects of hypoxia, hypercapnia and hypothermia on cerebral oxygenation. The aim of this study was to evaluate the influence of hypothermia, hypoxia and hypercapnia on brain oxygenation in a porcine model. METHODS: Nine anaesthetized pigs were surface-cooled to a core temperature of 28°C and underwent a period (20 min) of hypoxia (FiO₂ 17%) before hypercapnia was induced. Endpoint was considered onset of haemodynamic instability, i.e. 30% decrease in MAP, or 60 min post hypercapnia induction. Pigs were ventilated volume-controlled (20 ventilations/min, V₆, 6–8 ml/kg). Brain oxygenation measurements, including ICP (intracranial pressure), cerebral perfusion pressure (CPP) and cerebral venous oxygen saturation (ScvO₂, a marker for global cerebral oxygen extraction) were monitored. The care and handling of the animals complied with the American Physiological Society, institutional and Utstein-style guidelines. ANOVA for repeated measures was used to compare values across phases (hypothermia, hypoxia and hypercapnia) for ICP, CPP and ScvO₂. Pairwise comparisons were analyzed by means of Student’s t-test with Bonferroni correction. RESULTS: ICP did not show significant changes during the hypothermia (p>0.05) and hypoxia phases (p>0.05), but significantly increased during hypercapnia (p<0.05). Despite a progressive and significant decrease of CPP in all three phases (p<0.05), the decrease in CPP had clinically relevant modification only during the hypothermia and hypercapnia phases. ScvO₂ increased significantly during the hypothermia induction (p<0.05), did not show significant changes during the hypoxia phase (p>0.05), and decreased significantly during the hypercapnia phase (p<0.05). CONCLUSION: Our results demonstrate that hypercapnia increases ICP in a hypothermic, hypoxic pig to such a degree that CPP is impaired causing cerebral hypoxia, despite a reduced oxygen demand due to a severe hypothermic status (i.e. core temperature of 28°C).

**Abstract: F54**

**OXIDATIVE STRESS RESPONSE IS NOT ASSOCIATED WITH INDIRECT MEASUREMENT OF INTRACRANIAL PRESSURE POST ACUTE HYPOBARIC HYPOXIC EXPOSURE**
Strapazzon, Giacomo; Malacrida, Sandro; Vezzoli, Alessandra; Dal Cappello, Tomas; Falla, Marika; Lochner, Piergiorgio; Turner, Rachel; Moretti, Sarah; Brugger, Hermann; Mrakic-Sposta, Simona

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**INTRODUCTION:** Ultrasonography studies have shown that optic nerve sheath diameter (ONSD) correlates with intracranial pressure (ICP) in critical care patients. ONSD changes were also previously associated with AMS and HACE, plus recent studies report elevated ONSD values in individuals exposed to hypobaric hypoxia (HH). However, the assumption that ONSD reflects changes in ICP, the pathophysiological significance of increased ONSD in individuals exposed to HH remains unclear. The aim of this study was to investigate the association between changes in ONSD and oxidative-stress (OxS) biomarkers. METHODS: Clinical signs and symptoms of AMS and HACE, plus ultrasonography of ONSD and biological samples, were assessed at baseline and post passive ascent to 3830m (9, 24 and 72h) in 16 healthy lowlanders. ROS production rate was determined via Electron Paramagnetic Resonance. OxS biomarkers were assessed via immune and/or enzymatic methods. ROS production and OxS biomarkers were correlated with ONSD, as were signs and symptoms of AMS and HACE by means of a model including subject as a random effect; first without time and then adding time as fixed effect. A multivariate analysis of factors associated with ONSD was performed by means of generalized estimating equations for all measurements up to 24h. RESULTS: ROS production and OxS biomarkers were correlated with ONSD (p<0.001 for all tests) only if time was not added to the model. The regression analysis did not show a significant influence of ROS production and OxS biomarkers on ONSD. CONCLUSION: A multivariate analysis did not infer a causal relationship between ROS production, OxS biomarkers and changes in ONSD. Further studies with neuroimaging techniques are necessary to better elucidate the clinical significance of increased OxS biomarkers and ONSD during exposure to acute HH.
Abstract: F55

AVALANCHE-INDUCED HYPOXIA: A HUMAN EXPERIMENTAL STUDY ON THE INFLUENCE OF SNOW PHYSICAL PROPERTIES

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INTRODUCTION: Sufficient oxygenation is critical for completely buried avalanche victims to avoid life-threatening consequences during hypoxic exposure. Snow contains a remarkable capacity to maintain air availability; it was suspected that the snow physical properties affect the development of hypoxia and hypercapnia. The aim of this study was to evaluate the influence of different snow physical properties on the development of hypoxia and hypercapnia in subjects breathing into an artificial air pocket in snow. METHODS: Twelve male healthy subjects breathed through an airtight face-mask and 40 cm tube into an artificial air pocket of 4L. Every subject performed three tests on different days with varying snow characteristics. Symptoms, gas and cardiovascular parameters were monitored up to 30 min. Tests were interrupted at \( \text{SpO}_2 < 75\% \) (primary endpoint); or hypercapnia (i.e. \( \text{FiCO}_2 > 8\% \)); or due to subjective symptoms like dyspnea, dizziness, and headache. Snow density was assessed via standard methods and micro-computed tomography (CT) analysis, and permeability and penetration with the snow micro-penetrometer (SMP). A general linear model, with subject as a random factor, was performed to investigate correlation of snow characteristics with changes of \( \text{O}_2 \) and \( \text{CO}_2 \) in the air pocket. RESULTS: In eighteen of 36 (50%) tests, subjects completed the full test duration of 30 min; tests were terminated due to hypoxemia (\( \text{SpO}_2 \leq 75\% \) ) in 13 (36%) cases and due to clinical symptoms in five (14%) cases. Changes of \( \text{O}_2 \) and \( \text{CO}_2 \) in the air pocket were correlated with snow density (\( p < 0.05 \)), but not with permeability and other related measurements (i.e. coefficient of variation and standard deviation of penetration resistance). CONCLUSION: Among different snow physical properties only snow density seems to have direct influence on the respiratory gas concentrations of subjects breathing into an artificial air pocket.

Abstract: F56

RIGHT-TO-LEFT SHUNT IN PATIENTS WITH COPD AT HIGH ALTITUDE: A RANDOMIZED, PLACEBO-CONTROLLED TRIAL WITH DEXAMETHASONE

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OBJECTIVE: To study the prevalence of right-to-left shunts (RLS) in patients with COPD traveling to altitude with and without dexamethasone prophylaxis. We hypothesized that hypobaric hypoxia would increase RLS and dexamethasone would be preventive. METHODS: Lowlanders with COPD, GOLD 1-2, \( \text{SpO}_2 > 93\% \), were randomized to Dexamethasone (4mg, bid) or placebo, starting one day before ascent from 760m and during a 3-day-stay at 3200m, Kyrgyzstan. Resting and saline contrast echocardiography were performed at 760m and after the first night at 3200m. Shunt was defined by visible bubbles in the left atrium and classified as intracardiac (within 3 cardiac cycles) or intrapulmonary. RESULTS: Of 87 patients (84% male, mean±SD age 57.0±8.8, BMI 25.1±4.0 kg/m\(^2\), FEV\(_1\) 88.6±21.5%pred, \( \text{SpO}_2 \) 94.7±2.1%) 39 were assigned to placebo, 48 to dexamethasone. In the placebo group 19/39 patients (49%) had RLS, 11 of these intracardiac; in the dexamethasone group 23/48 patients (48%) had RLS, 13 of these intracardiac (p=NS placebo vs. dexamethasone). 12 patients in the placebo and 17 in the dexamethasone group developed new or changed from intrapulmonary to intracardiac RLS at altitude (760m vs 3200m, \( p = 0.018 \) resp. 0.011, p=NS between groups). The prevalence of RLS at 3200m was 30/39 (77%) in the placebo and 36/48 (75%) in the dexamethasone group (p=NS). Multivariate regression analyses indicated that a higher increase in systolic pulmonary artery pressure (SPAP) but not treatment allocation was an independent predictor of new RLS development at 3200m. Independent predictors of SPAP were altitude, dexamethasone, FEV\(_1\), age and new/changed RLS. CONCLUSION: In lowlanders with mild COPD, travelling to 3200m significantly increases the prevalence of RLS. Dexamethasone treatment does not prevent this. An increase in SPAP may be a cause or a consequence of the development RLS at altitude.
**Abstract: F57**

**DEXAMETHASONE REDUCES PULMONARY ARTERY PRESSURE IN LOWLANDERS WITH COPD TRAVELLING TO 3200M. RANDOMIZED, PLACEBO-CONTROLLED TRIAL**

Lichtblau, Mona; Furian, Michael; Aeschbacher, Sayaka; Osmonov, Batyr; Bisang, Maya; Ulrich, Stefanie; Knapp, Hannes; Latshang, Tsogyal; Mirrakhimov, Erkin; Sooronbaev, Talant; Bloch, Konrad

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**BACKGROUND:** COPD is associated with increased pulmonary artery pressure (PAP) at lowlands which rises the risk of symptomatic pulmonary hypertension at altitude. Since dexamethasone reduces excessive PAP-increase and prevents pulmonary edema in susceptibles at high altitude we performed a randomized, placebo-controlled trial evaluating the hypothesis that preventive dexamethasone mitigates the altitude-induced PAP increase in COPD-patients. **METHODS:** Consecutive stable COPD-patients Gold 1-2 living <800m, SpO\textsubscript{2}>93% were randomized to dexamethasone (4mg tablets, bid) or placebo one day before ascent from Bishkek (760m) and during a 3-day sojourn at Tuja Ashu (3200m), Kyrgyz Republic. Echocardiography was performed at 760m and after the first night at 3200m. The main outcome was the tricuspid pressure gradient (TPG) as surrogate for PAP. Registration: clinicaltrials.gov: NCT02450968. **RESULTS:** 109 patients were randomized (mean±SD age 56±9y, BMI 26±4kg/m\textsuperscript{2}, FEV1 89±21%pred, SpO\textsubscript{2} 95±2%). The TPG increased from 760 to 3200m (placebo [mean ± SD: 19.6±2.4 to 31.3±9.5 mmHg, p<0.0001] and dexamethasone (18.6±4.6 to 25.5±6.6 mmHg, p<0.0001), dexamethasone mitigated the altitude-induced increase in TPG vs. placebo (Δmean [95%CI] -4.76 (-7.69 to -1.83), p=0.0017) while the increase in cardiac output mediated by both a higher heart rate and stroke volume was similar with dexamethasone and placebo (placebo 4.92±0.70 to 5.69±1.09 l/min* and dexamethasone 4.71±0.88 to 5.65 ± 1.05 l/min*, Δmean [95%CI] 0.13 [-0.31; 0.57]). The more moderate increase in TPG with dexamethasone was associated with a higher SpO\textsubscript{2} at peak walk test. Regression analysis confirmed that dexamethasone was associated with a reduced altitude-induced increase in TPG even when controlled for age and COPD-severity reflected by FEV1%pred (R\textsuperscript{2}=0.3, P<0.0001). **CONCLUSION:** In lowlanders with COPD, GOLD grade 1-2, travelling to 3200m induces mild pulmonary hypertension. Dexamethasone mitigates this altitude-induced increase in PAP while maintaining cardiac output and with a favorable effect on oxygenation during exercise.

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**Abstract: F58**

**PULMONARY VASCULAR RESPONSE TO HYPOBARIC HYPOXIA AND SUPPLEMENTAL OXYGEN DURING GRADUAL ASCENT IN THE HIMALAYAS**

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Several recent studies challenge the traditional view that Tibetans and Sherpas pulmonary vasculature have less hypoxic pulmonary vasoconstriction (HPV) and less response to oxygen than Westerners. We conducted a prospective longitudinal study on healthy subjects (n=30, 19 Westerners and 11 Sherpas) during an 8-10 day ascent to 5050m in Nepal. High altitude acclimatized Sherpas descended and stayed at 1400m for 7-10 days for baseline testing prior to ascent to 5050m. During ascent, echocardiography was performed to measure pulmonary artery systolic pressure (PASP) and pulmonary vascular resistance (PVR); these were obtained at rest on room air (RA) and during supplemental O\textsubscript{2} titrated to increase SpO\textsubscript{2} to ≥ 96% for 30 minutes. PASP in Westerners on RA increased with ascent to 5050m from 20.0 ± 2.5 mmHg (mean ± SD) to 33.4 ± 6.4 mmHg (p<0.0003) and increased (21.4 ± 4.0 mmHg to 26.0 ± 4.8 mmHg in Sherpas (p<0.001). At 5050m, PASP decreased on supplemental O\textsubscript{2} by 8.6 ± 6.0 mmHg, p<0.001 (CI 5.7 to 11.5) in Westerners and 5.1 ± 3.4 mmHg, p=0.05 (CI 2.8 to 7.5) in Sherpas. On RA, PVR in Westerners significantly increased with ascent to 5050m from 1.33 ± 0.18 Wood Units (WU) to 1.94 ± 0.33 WU (p<0.0001) but did not significantly increase in Sherpas [1.59 ± 0.35 WU to 1.77 ± 0.50 WU (p=0.12)]. At 5050m, the decrease in PVR on supplemental O\textsubscript{2} compared to RA was 0.28 ± 0.29 WU, p<0.001 (CI 0.1 to 0.4) in Westerners and 0.16 ± 0.23 WU, p=0.05 (CI 0.00 to 0.32) in Sherpas. Our findings suggest that Westerners showed a greater HPV response compared to Sherpas upon ascent to altitude, but the pulmonary vasculature remains responsive to supplementary O\textsubscript{2} in both groups following 8-10 days of high altitude exposure.
Abstract: F60

TIME COURSE AND PROGNOSTIC SIGNIFICANCE OF PULMONARY ARTERY PRESSURE IN HIGHLANDERS

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BACKGROUND: In a prospective cohort of Kyrgyz highlanders we evaluated mean pulmonary artery pressure (mPAP), its change over time and clinical outcome. METHODS: Life-long residents in the Aksay high altitude plateau (Kyrgyzstan, altitude 3000-4000 msl) free of overt lung or cardiovascular disease and non-polycythemic were invited to undergo yearly echocardiography, clinical examinations and spirometry. Deaths were recorded. RESULTS: In 2012, 90 highlanders (37 women, 53 men, mean±SD age, 44.8±12.0, range 21-75 yrs) were included. Until 2016, 5 highlanders, all male (6% of all participants), had died. In Cox regression analysis mPAP was a significant predictor of death in all participants (hazard ratio 1.4, 95%CI 1.02 to 1.27, P=0.019) when controlled for age. In Cox regression analysis restricted to men, mPAP tended to be an independent predictor of death (hazard ratio 1.21, 95%CI 1.00 to 1.46, P=0.050) when controlled for age, i.e., in men, the risk of death increased by a factor of 6.5 per 10 mmHg increase in mPAP. In 2012, mPAP was 26.9±7.4 mmHg. Multiple regression analysis revealed a mean yearly increase in mPAP of 1.39 mmHg (95%CI 1.05 to 1.74, P=0.0001) when controlled for baseline mPAP, age and gender (R²=0.3689, P<0.001). The prevalence of individuals with mPAP >30 mmHg (corresponding to high altitude pulmonary hypertension) was 40% in 2012 and 63% in 2016 (p<0.05, chi square test). CONCLUSIONS: In the current cohort of highlanders, mPAP was higher than values reported for healthy lowlanders and the prevalence of high altitude pulmonary hypertension was 40% at baseline. The observed rapid increase in mPAP of 1.39 mmHg/year suggests that prolonged high altitude exposure may predispose to high altitude pulmonary hypertension. Further studies are required to investigate the mechanisms linking higher values of mPAP with a greater risk of death. Grant support: OPO foundation, Zurich Lung League, Swiss Lung Foundation.
Abstract: F61
ATTENUATION OF HYPOXIC PULMONARY VASOCONSTRICTION BY ACETAZOLAMIDE AND METHAZOLAMIDE IN HUMANS.
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INTRODUCTION: Acetazolamide (AZ) attenuates hypoxic pulmonary vasoconstriction (HPV) in humans and animals. Methazolamide (MZ), a carbonic anhydrase inhibiting sulfonamide analog of AZ, is methylated on the thiadiazole ring a reduces HPV in canines. It is unknown if MZ reduces HPV in humans. Accordingly, we aimed to determine MZ effectiveness in reducing HPV in humans. We hypothesized that HPV would be similarly attenuated between treatments. METHODS: In a double blind, placebo-controlled, randomized cross-over study, male participants (n=11, 25±1 yr) ingested a placebo (3 times/day), AZ (250 mg; 3 times/day) or MZ (100 mg; 2 times/day separated by a placebo) for 2 days and were exposed to poikilocapnic hypoxia (F O₂=0.12) for 1 h. Respiratory (P E VO₂, P A CO₂, V T, SpO₂) and cardiovascular variables (HR, MAP) were recorded continuously, while pulmonary artery systolic pressure (PASP, tricuspid regurgitation) and cardiac output (Q, aortic velocity time integral) were measured at baseline and the last 5 minutes of hypoxia. Arterial blood was collected at baseline while arterialized capillary blood was collected in hypoxia and analyzed for PaO₂, PaCO₂, pH, and [HCO₃⁻]. RESULTS: In hypoxia, AZ and MZ both improved PaO₂ by 7±2 mmHg (p<0.05). PASP increased by 74.5±7.7 % (p<0.01) in response to hypoxia in the control condition and was attenuated similarly between AZ (47.2±5.2 % above baseline) and MZ (52.3±6.6 % above baseline; p<0.05). Multiple linear regression analysis determined that the PASP response to hypoxia depended upon the degree of desaturation (0.64 mmHg/%desaturation), baseline P E VO₂ (-0.63 mmHg/mmHg P E VO₂) and the use of AZ (-7.3 mmHg/treatment) or MZ (-5.7 mmHg/treatment). CONCLUSION: In summary, both AZ and MZ attenuate HPV similarly while improving arterial PO₂. MZ may be a suitable alternative to AZ for acute mountain sickness prophylaxis and reducing HPV possibly preventing high altitude pulmonary edema. FUNDING: NSERC & CFI

Abstract: F62
ASTHMA REHABILITATION AT HIGH VS. LOW ALTITUDE: RANDOMIZED CONTROLLED PARALLEL-GROUP TRIAL
Ulrich, Silvia 1; Saxer, Stéphanie 1; Schneider, Simon R. 1; Appenzeller, Paula 1; Bader, Patrick R. 1; Lichtblau, Mona 1; Furian, Michael 1; Estebesova, Bermit 2; Emilov, Berik 2; Soorobbaev, Talant 2; Bloch, Konrad E 1
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OBJECTIVE: Environmental conditions at high altitude reduce allergens and pollution. We thus investigated the additive effect of asthma rehabilitation at high altitude (Tuja Ashu, 3200m, HA) compared to the same rehabilitation at low altitude (Bishkek, 760m, LA) on asthma control. METHODS: For this randomized controlled trial adult asthmatics diagnosed according to GINA-guidelines and living in the Bishkek area (<1000m) were recruited. Patients were randomly assigned to a 3-week in-hospital rehabilitation at either LA or HA, comprising patient education, endurance&strength training, breathing exercises and guided walks (5x/week 30-45min). Co-primary outcomes assessed at 760m were changes in peak expiratory flow (PEF)-variability ([day’s highest-day’s lowest]/mean of day’s highest&lowest), and scores in the Asthma Control Questionnaire (ACQ) from baseline to end-rehabilitation and 3 months thereafter between groups. RESULTS: 50 asthmatics (4 non-atopic, 34 females) were randomized [median(quartiles) LA: 47(34;53)years, FEV₁%pred. 74(53;99)%, PEF 311(274;378)L/min vs. HA: 43(33;49)years, FEV₁%pred. 80(74;86)%, PEF 326(261;368)L/min]. In the LA-group, pre-rehabilitation median(quartiles) PEF-variability was 19(14;33)%, ACQ 2.7(1.7;3.2); end-rehabilitation values were reduced by -7.4%(-13.9 to 0, p=0.033) and -1.4(-0.9 to -2.2, p<0.001), and after 3 months by -2.5%(-17.5 to 2.2, p=0.103) and -0.9(-1.3 to -0.3, p=0.002). In the HA-group, pre-rehabilitation PEF-variability was 17(12;32)%, ACQ 1(1.6;3.0); end-rehabilitation values were reduced by -10.4%(-21.3 to -3.4, p=0.004) and -1.1(-1.3 to -0.7, p<0.001), and after 3 months by -8.9%(-10.3 to -2.8, p=0.003) and -0.2(-0.9 to 0.4, p=0.177). The additive effect of HA vs. LA directly after the rehabilitation on PEF-variability was -5.8(-14 to 2)%, on ACQ 0.3(-0.4 to 1.1) and after 3 months -5(-13.6 to 5.0) respectively 0.4(-0.4 to 1.1), all p=NS. CONCLUSIONS: Asthma rehabilitation is highly effective in improving asthma control in terms of PEF-variability and symptoms, both at LA and HA to a similar degree. FUNDING: Zurich Lung League, Swiss National Science Foundation.
Abstract: F63

FAILURE OF FIVE DRUGS TO SUBSTANTIALLY IMPACT INCIDENCE OR SEVERITY OF AMS: RESULTS FROM A FIELD TRIAL OF QUERCETIN, NIFEDIPINE+METHAZOLAMIDE, METFORMIN, AND ORAL NITRITE.

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INTRODUCTION: Acute Mountain Sickness (AMS) poses a significant threat to anyone who travels too high, too quickly to high altitude. New, safe and effective approaches to prevention and treatment of AMS have been lacking. Based on previous animal work (Quercetin, Nifedipine+Methazolamide and Metformin) and positive results in hypoxia for humans with oral Nitrite, we hypothesized that one or more of these drugs would reduce AMS during a field study with rapid ascent to high altitude and vigorous physical activity. METHODS: These five drugs (four compounds, as Nifedipine and Methazolamide were combined into one compound) were tested in a placebo-controlled, double-blind study. Subjects were altitude naïve, male, aerobically fit, sea-level (SL) residents without pre-existing medical conditions or a history of migraines. 103 completed sea level screening and were to 4 groups and placebo based on baseline APFT score, height, and weight. After baseline testing at SL, subjects flew to Denver, then were driven to 2766-3828m for 3 days. The sleeping altitude for 2 nights was 3222m. We report Lake Louise AMS scores, AMS-C scores, and resting SPO2 values (Nellcor N-200). Symptom and SPO2 responses were compared by drug vs. placebo using non-parametric statistics. RESULTS: Group matching was successful. Both Lake Louise AMS scores and AMS-C scores were similar in all drug treatment groups compared to placebo. On the first night at altitude, Lake Louise AMS scores were 2.4±1.9 for placebo, 2.5±1.7 for Quercetin, 1.7±1.8 for Nifedipine+Methazolamide, 3.1±1.8 for Metformin, and 3.3±2.4 for Nitrite. In Nifedipine+Methazolamide, ESQ headache score and an independent headache pain score were both lower, indicating some effect reducing headache. SPO2 values were higher in the Nifedipine+Methazolamide group at all time points at altitude (p<0.01). However, these higher SPO2 values did not result in improved overall AMS scores. CONCLUSION: Although promising preliminary studies in animals (Quercetin, Methazolamide+Nifedipine, Metformin) and humans (Nitrite) pointed to novel mechanisms of action for these compounds, we found each of them had minimal impact on AMS. Funding: US DoD W81XWH-15-C-0095.

Abstract: F64

COGNITIVE DEFICITS IN SICKLE CELL DISEASE; LINKS WITH NOCTURNAL OXYGEN DESATURATION IN ADOLESCENTS, BUT NOT CHILDREN

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OBJECTIVE: Sickle cell disease (SCD) is associated with neurological compromise and cognitive difficulties. Tentative associations between cognitive difficulties and low daytime oxygen saturation (SpO2) are reported, but any effects of nocturnal desaturation are unknown. METHODS: Sixteen children (8-12y, 6F) and twenty-four adolescents (13-18y, 11F) enrolled on the Prevention of Morbidity in Sickle Cell Disease phase-2 trial underwent cognitive assessment, which included the Wechsler Intelligence Scales, the Tower and Sorting tests from the Delis-Kaplan-Executive-Function System (D-KEFS) and the Conners Continuous Performance Test (CPT). Overnight oximetry was conducted within two weeks of assessment. Multiple deprivation indices (MDI) were derived from postcodes. RESULTS: There were no significant differences between groups in any of the cognitive or oximetry measures. In adolescents, after correcting for the effects of MDI, relationships were found between mean nocturnal SpO2 and full-scale IQ (FSIQ; r=0.486, p=0.016), processing speed index (PSI; r=0.350, p=0.094) and working memory index (WMI; r=0.442, p=0.031), between minimum SpO2 and PSI (r=0.432, p=0.035) and tower time-time-per-move ratio (r=0.348, p=0.096), between the number of 3% oxygen dips per hour and the number of correct sorts (r=0.447, p=0.029) and sorting descriptions (r=-0.438, p=0.032), and between the time spent with SpO2<94% and FSIQ (r=-0.549, p=0.005), PSI (r=-0.434, p=0.034), and WMI (r=-0.464, p=0.022). In children the only significant relationship found was in the opposite direction; performance on the tower test was negatively related to mean SpO2 (r=-0.537, p=0.039). Findings were similar for the CPT.

Abstract: F65

NOCTURNAL OXYGEN DESATURATION IN ADOLESCENTS, BUT NOT CHILDREN; LINKS WITH COGNITIVE DEFICITS IN SICKLE CELL DISEASE; EFFECTS OF MULTIPLE DEPRIVATION INDICES

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Abstract: F66

FAILURE OF FIVE DRUGS TO SUBSTANTIALLY IMPACT INCIDENCE OR SEVERITY OF AMS: RESULTS FROM A FIELD TRIAL OF QUERCETIN, NIFEDIPINE+METHAZOLAMIDE, METFORMIN, AND ORAL NITRITE.

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INTRODUCTION: Acute Mountain Sickness (AMS) poses a significant threat to anyone who travels too high, too quickly to high altitude. New, safe and effective approaches to prevention and treatment of AMS have been lacking. Based on previous animal work (Quercetin, Nifedipine+Methazolamide and Metformin) and positive results in hypoxia for humans with oral Nitrite, we hypothesized that one or more of these drugs would reduce AMS during a field study with rapid ascent to high altitude and vigorous physical activity. METHODS: These five drugs (four compounds, as Nifedipine and Methazolamide were combined into one compound) were tested in a placebo-controlled, double-blind study. Subjects were altitude naïve, male, aerobically fit, sea-level (SL) residents without pre-existing medical conditions or a history of migraines. 103 completed sea level screening and were to 4 groups and placebo based on baseline APFT score, height, and weight. After baseline testing at SL, subjects flew to Denver, then were driven to 2766-3828m for 3 days. The sleeping altitude for 2 nights was 3222m. We report Lake Louise AMS scores, AMS-C scores, and resting SPO2 values (Nellcor N-200). Symptom and SPO2 responses were compared by drug vs. placebo using non-parametric statistics. RESULTS: Group matching was successful. Both Lake Louise AMS scores and AMS-C scores were similar in all drug treatment groups compared to placebo. On the first night at altitude, Lake Louise AMS scores were 2.4±1.9 for placebo, 2.5±1.7 for Quercetin, 1.7±1.8 for Nifedipine+Methazolamide, 3.1±1.8 for Metformin, and 3.3±2.4 for Nitrite. In Nifedipine+Methazolamide, ESQ headache score and an independent headache pain score were both lower, indicating some effect reducing headache. SPO2 values were higher in the Nifedipine+Methazolamide group at all time points at altitude (p<0.01). However, these higher SPO2 values did not result in improved overall AMS scores. CONCLUSION: Although promising preliminary studies in animals (Quercetin, Methazolamide+Nifedipine, Metformin) and humans (Nitrite) pointed to novel mechanisms of action for these compounds, we found each of them had minimal impact on AMS. Funding: US DoD W81XWH-15-C-0095.
CONCLUSION: This study demonstrates, for the first time in SCD, links between nocturnal desaturation and difficulties in processing speed and executive function in adolescents but no similar links and a relationship in the opposite direction in children. These preliminary data may indicate that the effects of hypoxia on these domains only emerge over developmental time. Early interventions aimed at reducing hypoxic exposure may hold promise.
Saturday, 11 February 2017

0630-0830  Breakfast, Lago Restaurant
0700-0900  Registration, Heritage Hall
0800-0930  **Hypoxic Pulmonary Hypertension: More Complexity and New Targets**

0800-0830  **The Alveolar-capillary Endothelium and Hypoxic Pulmonary Vasoconstriction** — Wolfgang Kuebler
0830-0900  **O₂ Sensing and Signal Transduction in Hypoxic Pulmonary Vasoconstriction** — Norbert Weissmann
0900-0930  **Hypoxia and Hyperoxia in Exercise Performance in Health and Respiratory Disease** — Silvia Ulrich

0930-1000  **Refreshment Break, Heritage Hall**

1000-1130  **Game Changing Concepts about Hypoxia Responses**
1000-1030  **Hypoxia to Treat Mitochondrial Disease** — Vamsi Mootha
1030-1100  **Hypoxia-Induced Myocardial Regeneration** — Hesham Sadek
1100-1130  **Rhythmic Oxygen Levels Reset Circadian Clocks through HIF1α** — Gad Asher

1130-1600  **Ski Break**
1130-1330  Lunch, Lago Restaurant
1600-1830  **Hot Topics in Hypoxia V—Selected Abstracts**
1900-2300  Dinner, Awards, and Dance, Brewster Barn
         **Presentation of Student Award Winners**
         **Presentation of Reeves Prize in Presentation Excellence**
Hypoxic pulmonary vasoconstriction (HPV) is the physiological response of the pulmonary vasculature to alveolar hypoxia which redistributes pulmonary blood flow from poorly aerated lung regions to better ventilated lung segments by an active process of local vasoconstriction. Impairment of HPV, as seen in a variety of lung diseases including pneumonia, sepsis, or cystic fibrosis, results in submaximal oxygenation of arterial blood and limits oxygen supply to systemic organs. Although a series of regulatory pathways involved in oxygen sensing and HPV have been identified, considerable gaps in our knowledge and understanding remain, and a unifying concept of the underlying signaling pathways and their impairment in various disease states has not yet emerged. Notably, previous concepts of HPV have largely focused on the pulmonary arterial smooth muscle cell as both sensor and transducer of the hypoxic signal and its contractile effector. In contrast, the role of the vascular endothelium was only considered that of a modulating bystander. From a conceptual point, the ideal site for an oxygen sensor in HPV would be located in the actual area of pulmonary gas exchange, i.e. in the alveolar capillaries or in vessels downstream thereof. This concept, however, would necessitate the retrograde propagation of the hypoxic signal along the vascular wall, a communication mechanism that is known in the systemic vasculature as conducted response and mediated via intercellular gap junctions consisting of connexin molecules.

In a series of studies using in vivo measurements of ventilation/perfusion matching, real-time imaging of endothelial cell signaling in isolated perfused lungs, and cell and molecular biology assays in human pulmonary artery endothelial and smooth muscle cells, we have identified a novel critical role for the pulmonary endothelium and connexin 40 in HPV, in that the hypoxic signal is originally sensed at the alveolo-capillary level, from where it is propagated as endothelial membrane depolarization in a connexin 40-dependent manner as conducted response to upstream arterioles. At the arteriolar level, the endothelial response is communicated to the juxtaposed smooth muscle cells via temporally and spatially tightly controlled lipid mediators including epoxyeicosatrienoic acids and sphingolipids, which result in activation and translocation of Ca²⁺ entry channels of the transient receptor potential family in smooth muscle cells, and their subsequent Ca²⁺ mediated contraction. Notably, translocation of transient receptor potential cation channels is dependent on cystic fibrosis transmembrane conductance regulator (CFTR), thus providing a mechanistic explanation for impaired ventilation/perfusion matching in CF patients. Moreover, the rapid downregulation of both CFTR and Cx40 in scenarios of infection and inflammation is prone to underlie the impairment of HPV in clinical conditions such as sepsis and pneumonia. Supported by operating grants from the Canadian Institute of Health Research (CIHR).
Sensing and Signal Transduction in Hypoxic Pulmonary Vasconstriction—Norbert Weissmann

Hypoxic pulmonary vasoconstriction (HPV), also known as the von-Euler-Liljestrand-mechanism, adapts local blood perfusion in the lung to alveolar ventilation. Blood flow to poorly ventilated and thus hypoxic alveolae is reduced and redirected to well ventilated areas of the lung. The reduction in blood flow is achieved by precapillary vasoconstriction. HPV is essential for optimization of pulmonary gas exchange and prevents hypoxemia under conditions of disturbed alveolar ventilation. Decreased HPV, as it can occur during anesthesia, pneumonia, septic events or liver failure can result in life threatening hypoxemia. If alveolar hypoxia, however, is generalized as under conditions of high altitude, HPV induces pulmonary hypertension. From an ontogenetic view HPV can be termed normoxic pulmonary vasodilatation as pulmonary vessels relax after birth when alveolar ventilation is initiated.

Despite intensive research during the last decades, the underlying mechanisms of HPV have not been fully elucidated yet. On the level of the oxygen sensors, reactive oxygen species (ROS) producing systems like mitochondria and NADPH oxidases have been proposed. Two antithetic concepts suggest either an increase or a decrease of reactive oxygen species originating from mitochondria or NADPH oxidases during alveolar hypoxia. Also, the downstream targets of ROS signaling are still under investigation. Among others, voltage-dependent potassium channels (Kv-channels) as well as transient receptor potential channels (TRPC) have been found to be essential.

Deciphering the mechanism underlying HPV is a prerequisite for the development of strategies to prevent hypoxemia under conditions of HPV disturbance or to antagonize acute pulmonary hypertension during generalized hypoxia.

Hypoxia and Hyperoxia in Exercise Performance in Health and Respiratory Disease—Silvia Ulrich

In healthy individuals near sea level and at altitude, exercise performance is determined by oxygen supply to working muscles and vital organs including the brain. Consistently, in healthy volunteers we observed that breathing oxygen enriched air even at low altitude enhances exercise performance. This was related to an increased arterial, muscle and cerebral tissue oxygenation and a lower heart rate and ventilatory equivalent for CO₂ at isoloads suggesting a reduction in sympathetic excitation and an improved gas exchange efficiency.

In patients with chronic respiratory disease exercise performance is reduced even at low altitude due to impairments of ventilatory mechanics, gas exchange and the pulmonary circulation. Thus, patients with pulmonary hypertension or COPD reveal a sympathetic overexcitation, an increased chemosensitivity and an inefficient pulmonary gas exchange in particular during exercise. When travelling to high altitude respiratory patients may experience an exacerbations of symptoms during exercise or even at rest due to further gas exchange impairment induced by the lower barometric pressure und the consecutive increase in pulmonary artery pressure. In studies performed near sea level in patients with pulmonary hypertension or COPD we observed that maximal performance during progressive ramp exercise and endurance of submaximal constant load exercise was substantially improved by breathing oxygen enriched air. Consistent with data in healthy individuals, these improvements were mediated by a better arterial, muscular and cerebral oxygenation along with a reduced sympathetic overexcitation, as signified by the reduced heart rate over all submaximal isoloads, and an improved pulmonary gas exchange efficiency. In conclusion, breathing oxygen enriched air enhances exercise performance in respiratory patients and even in healthy individuals by its effects on control of breathing, on pulmonary gas exchange, and on oxygen delivery to workings muscles and the brain.

Refreshment Break, Heritage Hall
Satuday, 11 February

1000-1130  
Game Changing Concepts about Hypoxia Responses  
Chair: Ben Levine

1000-1030  Hypoxia to Treat Mitochondrial Disease — Vamsi Mootha

Mitochondria are ancient cellular organelles that serve as our cell’s powerhouses by generating the bulk of its ATP. Mitochondrial dysfunction accompanies a number of human conditions, ranging from severe, inborn errors of metabolism to the aging process itself. At present we have no effective therapies for treating mitochondrial disease. In this talk I will present our recent work in which we’ve used a genome-wide CRISPR genetic screen to identify the hypoxia response as strongly protective against mitochondrial disease. We find that in accurate mouse models of mitochondrial neurodegenerative disease, hypoxia has a remarkable effect in preventing disease onset, while hyperoxia exacerbates disease. Our work has implications for understanding the fundamental relationship between mitochondria and oxygen, with potential therapeutic implications for a broad range of human diseases.

1030-1100  Hypoxia-Induced Myocardial Regeneration — Hesham Sadek

The adult mammalian heart is incapable of regeneration following cardiomyocyte loss, which underpins the devastating impact of cardiomyopathy. Recently, it has become clear that the mammalian heart is not a post-mitotic organ. For example, the neonatal heart is capable of regenerating lost myocardium, and the adult heart is capable of modest self-renewal. In both these scenarios, cardiomyocyte renewal occurs through proliferation of pre-existing cardiomyocytes, and is regulated by aerobic respiration-mediated oxidative DNA damage. Therefore, we reasoned that systemic hypoxemia inhibits aerobic respiration and alleviates oxidative DNA damage, thereby inducing cardiomyocyte proliferation in adult mammals. Here we report that gradual exposure to severe systemic hypoxemia, where inspired oxygen is gradually decreased by 1% and maintained at 7% for two weeks, results in inhibition of oxidative metabolism, decreased reactive oxygen species (ROS) production and oxidative DNA damage, and reactivation of cardiomyocyte mitosis. Intriguingly, we found that exposure to hypoxemia 1 week after induction of myocardial infarction induces a robust regenerative response with decreased myocardial fibrosis and improvement of left ventricular systolic function. Finally, genetic fate mapping confirmed that the newly formed myocardium is derived from pre-existing cardiomyocytes. These results demonstrate that the endogenous regenerative properties of the adult mammalian heart can be reactivated by exposure to gradual systemic hypoxemia, and highlight the potential therapeutic role of hypoxia in regenerative medicine.

1100-1130  Rhythmic Oxygen Levels Reset Circadian Clocks through HIF1α — Gad Asher

The mammalian circadian system consists of a master clock in the brain that synchronizes subsidiary oscillators in peripheral tissues. The master clock maintains phase coherence in peripheral cells through systemic cues such as feeding-fasting and temperature cycles. We examined the role of oxygen as a resetting cue for circadian clocks. To this end, we continuously measured oxygen levels in living animals and detected daily rhythms in tissue oxygenation. Oxygen cycles, within the physiological range, were sufficient to synchronize cellular clocks in HIF1α-dependent manner. Furthermore, several clock genes responded to changes in oxygen levels through HIF1α. Finally, we found that a moderate reduction in oxygen levels for a short period accelerates the adaptation of wild type but not of HIF1α-deficient mice to the new time in a jet lag protocol. We conclude that oxygen, via HIF1α activation, is a resetting cue for circadian clocks and propose oxygen modulation as therapy for jet lag.
PULMONARY VASCULAR RESPONSE TO HYPOBARIC HYPOXIA AND SUPPLEMENTAL OXYGEN DURING GRADUAL ASCENT IN THE HIMALAYAS

Subedi, Prajan1; Stembridge, Mike2; Williams, Alex3; Gasho, Christopher1; Willie, Chris3; Ainsle, Philip N3; Anholm, James D1

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Several recent studies challenge the traditional view that Tibetans and Sherpas pulmonary vasculature have less hypoxic pulmonary vasoconstriction (HPV) and less response to oxygen than Westerners. We conducted a prospective longitudinal study on healthy subjects (n=30, 19 Westerners and 11 Sherpas) during an 8-10 day ascent to 5050m in Nepal. High altitude acclimatized Sherpas descended and stayed at 1400m for 7-10 days for baseline testing prior to ascent to 5050m. During ascent, echocardiography was performed to measure pulmonary artery systolic pressure (PASP) and pulmonary vascular resistance (PVR); these were obtained at rest on room air (RA) and during supplemental O2 titrated to increase SpO2 to ≥ 96% for 30 minutes. PASP in Westerners on RA increased with ascent to 5050m from 20.0 ± 2.5 mmHg (mean ± SD) to 33.4 ± 6.4 mmHg (p<0.0003) and increased in Sherpas (21.4 ± 4.0 mmHg to 26.0 ± 4.8 mmHg in Sherpas (p<0.001)). At 5050m, PASP decreased on supplemental O2 by 8.6 ± 6.0 mmHg, p<0.001 (CI 5.7 to 11.5) in Westerners and 5.1 ± 3.4 mmHg, p=0.05 (CI 2.8 to 7.5) in Sherpas. On RA, PVR in Westerners significantly increased with ascent to 5050m from 1.33 ± 0.18 Wood Units (WU) to 1.94 ± 0.33 WU (p<0.0001) but did not significantly increase in Sherpas [1.59 ± 0.35 WU to 1.77 ± 0.50 WU (p=0.12)]. At 5050m, the decrease in PVR on supplemental O2 compared to RA was 0.28 ± 0.29 WU, p<0.001 (CI 0.1 to 0.4) in Westerners and 0.16 ± 0.23 WU, p=0.05 (CI 0.00 to 0.32) in Sherpas. Our findings suggest that Westerners showed a greater HPV response compared to Sherpas upon ascent to altitude, but the pulmonary vasculature remains responsive to supplementary O2 in both groups following 8-10 days of high altitude exposure. See poster F58.

PERIPHERAL ENDOTHELIAL FUNCTION AND HEMODYNAMICS ON ASCENT TO 5050M: A BETWEEN-LIMB COMPARISON IN LOWLANDERS AND SHERPA

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INTRODUCTION: The study of endothelial adaptation to hypoxia has been restricted to the upper limb, and comparisons to highlanders are also confounded by differences in altitude exposure, exercise, and unknown levels of blood viscosity. METHODS: Healthy lowlanders (n=22, 28±6 years [mean±SD], BMI=23±2 kg m⁻²) and Sherpa (n=12, 34±11 years, BMI=24±4 kg m⁻²) were tested. Sherpa were partially de-acclimatized to 1400m over 5-15 days following which both groups ascended over 10 days with measurements taken at 1400m, 3440m (day 4), 4371m (day 7), and 5050m (day 10) without pharmaceutical altitude sickness prevention. Resting hemodynamic shear patterns and endothelial function (reactive hyperemia flow-mediated dilation; FMD) were acquired via duplex ultrasound in the brachial (BA; atherosclerotic-resistant) and superficial femoral (SFA; atherosclerotic-prone) arteries. Venous blood viscosity was acquired at each location. The relevant shear stress stimulus to evoke FMD was calculated as the shear stress area under the curve (shear rate x viscosity; SSAUC) from cuff deflation to peak diameter. RESULTS: In lowlanders, viscosity rose by 29±16% (P<0.001), and resting mean shear stress decreased and retrograde shear stress increased in both limbs on ascent to 5050m. Although BA FMD decreased from 6.5±3.8% to 4.5±2.2% on progressive ascent to 5050m (P<0.05) without any change in SSAUC, SFA FMD was preserved. In contrast, in the Sherpa, neither viscosity,
retrograde shear stress, BA nor SFA SSAUC or FMD were changed upon ascent to 5050m. **CONCLUSION:** Our findings indicate that endothelial function is protected in Sherpa upon ascent to high altitude. In lowlanders, although FMD in the SFA is persevered, there is a selective impairment in the BA. While the ascent-related exercise may favorably influence endothelial function in the active limb (SFA), the impairment in FMD in the normally atherosclerotic-resistant BA might be mediated via the low mean or high retrograde shear stress during ascent in lowlanders. See poster W37.

**REGIONAL CEREBRAL BLOOD FLOW AND BLOOD GAS CONTENT CHANGES DURING ASCENT TO 5050M: A COMPARISON BETWEEN LOWLANDERS AND SHERPA**

**Howe, Connor A**; **Hoiland, Ryan L**; **Tremblay, Joshua C**; **Carter, Howard H**; **Willie, Chris K**; **Donnelly, Joseph**; **Stembridge, Mike**; **Gascho, Chris**; **Ainslie, Philip N**

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**INTRODUCTION:** The effect of chronic hypoxia on cerebral blood flow (CBF) in high-altitude natives (Sherpa) and lowlanders during ascent to high-altitude has not been investigated in the absence of prophylactic acetazolamide use. **METHODS:** Global CBF, via measurement of internal carotid (ICA) and vertebral artery (VA) blood flow, venous blood viscosity and mean arterial pressure (MAP) were measured in 21 lowlanders (BMI=23±2kg/m²) and 12 Sherpa (BMI=24±4kg/m²) prior to and during ascent to 5050m. Sherpa were partially de-acclimatized to 1400m over 5-15 days following which both groups ascended over 10 days with measurements obtained at 1400m, 3440m, 4371m and 5050m. **RESULTS:** Across both groups, global CBF initially decreased from baseline at 3440m (Sherpa=-21.71%, lowlanders=1.88%) but was elevated by 5050m (Sherpa=9.13%, lowlanders=20.08%; P<0.05). Alterations in CBF were mediated via changes in ICA blood flow and, in particular, VA diameter and velocity; these values were higher in lowlanders across all altitudes (main effect, P<0.05). Consequently, cerebral O₂ delivery (CDO₂) was higher in lowlanders above 1400m (P<0.05). Although arterial O₂ content and saturation were similar between groups, arterial PCO₂ was lower in lowlanders above 3440m (P<0.05), and pH was higher across all altitudes (main effect, P<0.05). Venous viscosity, arterial hemoglobin and hematocrit were higher in the Sherpa at baseline (P<0.05); however, these increased in lowlanders throughout ascent reaching similar values to the Sherpa. MAP was higher in the Sherpa until 4371m but remained unchanged throughout ascent; MAP in the lowlanders increased at all altitudes. **CONCLUSION:** Despite the lower pH and greater hypertension in the Sherpa, both CBF and CDO₂ were lower compared to lowlanders. Whether this potentially blunted cerebrovascular reactivity is an adaptive or maladaptive response in the Sherpa remains to be established. See poster F48.

**SYMPATHETIC NERVE ACTIVITY AND VASCULAR TRANSDUCTION IN LOWLANDERS AND SHERPA AT 5050M**

**Busch, Stephen**; **Simpson, Lydia**; **Moore, Jonathan**; **Sobierajski, Frances**; **Riske, Laurel**; **Stembridge, Michael**; **Ainslie, Philip**; **Steinback, Craig**

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**INTRODUCTION:** Previous data suggest resting muscle sympathetic activity (SNA) is elevated in lowlanders at altitude. Our study examined how this influences vascular function and whether highland natives exhibit similar sympathetic hyperactivity at altitude. **METHODS:** SNA (microneurography) was assessed in lowland dwellers (n=14; age=27±6yrs) and locally recruited Nepalese Sherpa (n=9; age=32±11yrs) at both low altitude (Kelowna, Canada, 344m; Kathmandu, Nepal, 1400m) and following a 9 day ascent to the Ev-K2-CNR research facility (Khumbu Region, Nepal, 5050m). Burst frequency (bursts/min), incidence (bursts/100 heart-beats), and total SNA (frequency*amplitude) data was collected during a 10 minute period of supine rest. Transduction was assessed through the relationship between resting burst frequency, mean arterial pressure (MAP), and total peripheral resistance (TPR). T-tests adjusted for multiple comparisons assessed differences between Sherpa and lowlanders at different altitudes. **RESULTS:** Resting burst frequency (11±5 vs 30±6 burst/min), burst incidence (23±12 vs 50±15 bursts/100hb) and total SNA (563.6±276.2 vs 1563.5±421.1 au) were all elevated (p<0.001) in lowlanders at 5050m. Similar non-significant responses were...
observed in Sherpa (14±2 vs 23±11 bursts/min; 23±5 vs 44±20 bursts/100hb; 710.0±17.3 vs 1193.7±54.6 au; P>0.05). There were no SNA differences between groups at low altitude. However, lowlanders had higher burst frequency (P<0.05), incidence (P<0.01), and a trend for higher total SNA (P<0.05) at 5050m compared to Sherpa. Vascular transduction (MAP/burst/min) was reduced in both lowlanders and Sherpa (P<0.05) at 5050m though no differences were observed between groups at either low (P<0.05) or high (P>0.05) altitude. **CONCLUSION:** Our data shows elevated SNA in both high altitude natives and lowland dwellers at high altitude. However, sympathetic hyperactivity is offset by reduced vascular responsiveness or competing dilatory mechanisms. Furthermore, sympathetic hyperactivity observed in Sherpa appears to be specific to high altitude exposure as it was reduced at lower elevations despite permanent residence at altitude. **ACKNOWLEDGEMENTS:** This study was supported by NSERC and the President’s Grant for the Creative Performing Arts - Human Performance Scholarship (U-Alberta). See poster W48.

### 2016 UBC NEPAL EXPEDITION: IRON INFUSION REDUCES PULMONARY ARTERIAL SYSTOLIC PRESSURE AT HIGH ALTITUDE IN LOWLANDERS BUT NOT SHERPA

**Willie, Christopher 1; Hoiland, Ryan L. 1; Stembridge, Mike 2; Williams, Alex 1; Flück, Daniela 1; Gasho, Chris 3; Subedi, Prajan 1; Anholm, James 2; Eller, Lindsay 4; Reimer, Raylene 5; Macleod, David B. 4; Plato, Sawyer 1; Mcbride, Emily 1; Patrician, Alex 1; Rieger, Matt G. 1; Ainslie, Philip 1**

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**INTRODUCTION:** An obligate cofactor in the regulation of the hypoxia inducible factor (HIF) system, iron decreases the sensitivity of the HIF system to hypoxia, the probable mechanism for the inverse relationship between iron status and hypoxic pulmonary vasoconstriction. People of Tibetan descent possess variants of the genes regulating HIF and show blunted pulmonary arterial vasoconstriction in response to acute and chronic hypoxia; however, it remains unknown how iron manipulation may differentially effect pulmonary vascular responses to sustained hypoxia between Tibetan descendants and lowlanders. We hypothesized that in lowlanders iron supplementation would attenuate, and iron chelation exacerbate pulmonary arterial systolic pressures (PASP; echocardiography) but that neither would affect PASP in Sherpa. **METHODS:** Following 4-10 days at 5050m, 20 Sherpa (BMI 22.2 ± 3.4 kg/m²) and 18 lowlanders (BMI=23±2kg/m²) were randomized to receive intravenous iron sucrose (200mg; IRON) or desferrioxamine (~4g; DFO). Echocardiographic metrics, arterial and venous blood, blood pressure and ventilation were collected before and after infusions. **RESULTS:** Across both groups, IRON increased serum [iron] by 40.4 ± 22 umol/L (P < 0.05) whereas DFO decreased serum [iron] by 7.4 ± 6 umol/L to below the detectable range (P < 0.05), but neither affected serum ferritin. Total iron binding capacity increased with DFO but remained stable following IRON. Soluble transferrin receptor was decreased by IRON in both Sherpa and lowlanders (P<0.05) but was unaffected by DFO. In lowlanders, DFO increased cardiac output (+20±11%) and stroke volume (+25.5±14%), and IRON decreased PASP (-4.3 ± 5 mmHg) and pulmonary vascular resistance (P<0.05). Sherpa PASP were unaffected by either IRON or DFO. **CONCLUSION:** There were no clear physiological changes following iron manipulation in Sherpa, whereas in lowlanders IRON reduced PASP at rest, suggesting lower sensitivity to iron in Sherpa at high altitude, and a possible prophylactic effect of iron for high altitude sojourners. See poster F14.
NASAL MUCOCILIARY CLEARANCE DIFFERS AT HIGH ALTITUDE IN LOWLANDERS AND SHERPAS

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INTRODUCTION: Nasal mucociliary clearance (NMCC) was investigated to consider if this aspect of Sherpa physiology differed from lowlanders. METHOD: During Caudwell Extreme Everest 2007 and Xtreme-Everest 2013 expeditions, evaluation of NMCC was undertaken by placing a dyed granule of saccharin on the inferior turbinate under endoscopic control and time to tasting sweetness measured with an upper time limit of 90 mins. Rigid endoscopic photography of the nose and oropharynx was performed to improve accuracy. Testing was performed in healthy lowlanders at sea level in London and at Everest Base Camp (EBC) (5300m). A group of Sherpas who had not been to altitude in the previous year were also studied on the 2013 expedition with baseline testing in Kathmandu (1300m) and after an identical ascent profile to EBC. RESULTS: In 31 lowlanders, NMCC range at sea level was 6-30 mins, mean 16.3 mins. At arrival at EBC, 12 (39%) had abnormal saccharin times, 10 > 45 minutes (range 6-90 mins, mean 37.5 mins). Prolonged NMCC correlated with notable changes on endoscopy with significant degrees of dried mucus and crusting. All 13 Sherpas had normal saccharin times at Kathmandu (mean 10 mins, range 6-25 mins) and EBC (mean 10 mins, range 7-21 mins) without any notable endoscopic abnormalities. CONCLUSION: NMCC is one of the most important defense mechanisms of the respiratory tract. In contrast to lowlanders, all 13 Sherpas had normal saccharin times at EBC, without the endoscopic changes seen in lowlanders. This is the first time that intranasal endoscopic images have been taken at high altitude, directly demonstrating the profound changes which can occur. The nasal saccharin test provides an *in vivo* measurement of the effectiveness of both mucus and ciliated nasal epithelium. The study indicates that the Sherpa’s upper respiratory tract mucociliary system is another example of their physiological adaptation to high altitude. See poster F35.

REMOTE ISCHEMIC PRECONDITIONING DOES NOT ATTENUATE ACUTE MOUNTAIN SICKNESS AND HIGH-ALTITUDE-INDUCED PULMONARY HYPERTENSION AT 3450 M

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INTRODUCTION: Remote ischemic preconditioning (RIPC) has been shown to protect organs such as brain and lung remote from the preconditioned site against damage induced by subsequent hypoxia or ischemia. Acute mountain sickness (AMS) and high-altitude pulmonary edema (HAPE) represent the cerebral and the pulmonary form of high-altitude diseases. Activation of the trigeminovascular system and an exaggerated hypoxic pulmonary vasoconstriction are considered to play a pivotal role in AMS and HAPE, respectively. We hypothesized that RIPC protects the brain from AMS through reduction of reactive oxygen species and the lung from an exaggerated rise in pulmonary artery systolic pressure (PASP) at 3450 m. METHODS: Forty non-acclimatized volunteers were randomized into 2 groups. At low altitude (750 m) the RIPC group underwent 4 cycles of lower limb ischemia, induced by inflation of 2 thigh cuffs to 200 mmHg for 5 min, followed by 5 min of reperfusion. In the control group cuffs were inflated to only 20 mm Hg. Thereafter, participants were transported by railway over 2 h to 3450 m. AMS was evaluated by the Lake Louise score (LLS) and the AMS-C score after 5 h, 10 h, 24 h, 29 h, 34 h and 48 h at high-altitude. PASP was assessed by transthoracic echocardiography. RESULTS: RIPC had no effect on the incidence (RIPC: 35%, control: 35%) and severity of AMS. Mean±SD of LLS...
scores after 24 h at high-altitude were: RIPC 4.6±4.1, control 3.0±1.8, P=0.47; corresponding AMS-C scores were: 0.69±0.9 and 0.37±0.08, P=0.25. There was also no difference in PASP between both groups (maximum after 10 h at high-altitude; RIPC: 33±8, controls: 37±7 mmHg; P=0.19). **CONCLUSION:** This study indicates that RIPC, performed immediately before passive ascent to 3450m, does not attenuate AMS and the degree of high-altitude pulmonary hypertension. Thus, RIPC cannot be recommended for prevention of high-altitude diseases. **See poster F04.**

**1730-1815  Budesonide at Hypoxia 2017: Lessons in Reproducibility in Research**

This is a special session featuring a review of published research, presentation of two new studies selected as Hot Topics for Hypoxia 2017, and a discussion of the emerging crisis in the reproducibility of biomedical research.

**Introduction and Moderator—Rob Roach**

**Background from previously published studies—Erik Swenson**

**Abstract Presentation I: ALTITUDE SICKNESS PREVENTION AND EFFICACY OF COMPARATIVE TREATMENTS (ASPECT): A RANDOMIZED CONTROLLED TRIAL OF BUDESONIDE VERSUS ACETAZOLAMIDE**

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**INTRODUCTION:** Inhaled budesonide is a potential novel preventative medication for acute mountain sickness (AMS), this study tests its efficacy compared to the standard AMS prophylactic acetazolamide. **METHODS:** This was a double blind, randomized, placebo controlled trial comparing inhaled budesonide (180mcg bid) to oral acetazolamide (125mg bid) to placebo started the morning of ascent. Healthy adults ascended from 1,240m (4,100ft) to overnight at 3,810m (12,570ft) during August 2016 on White Mountain, California. The primary outcome was AMS incidence (headache + LLQ>=3), with secondary outcomes of AMS severity (LLQ>=5), SpO2, and EtCO2. **RESULTS:** 103 participants enrolled and completed the study; 33 (32%) received budesonide, 35 (34%) acetazolamide, 35 (34%) placebo. No differences in demographics between groups. Total AMS incidence 73%. Fewer participants in the acetazolamide group 15 (43%) developed AMS compared to both budesonide 24 (73%) (p<0.05; OR=3.5, 95% CI 1.3 to 10.1) and placebo 22 (63%) (p=0.08; OR=0.5, 95% CI 0.2 to 1.2), NNT of 5. Acetazolamide had less severe AMS 11 (31%) compared with both budesonide 18 (55%) (p=0.05; OR=2.6, 95% CI 1 to 7.2), and placebo 19 (54%) (p<0.05; OR = 0.04, 95% CI 0.1 to 1), NNT of 4. AMS severity was higher in the budesonide group (4.5 [SD 2.6]) and placebo (4.6 [SD 3.5]) than acetazolamide (3.4 [SD 3.1]) (mean difference -1.1%; 95% CI -2.4 to 0.3). Smaller ventilation increases were associated with greater severity AMS, with EtCO2 a better predictor of AMS than SpO2 (r = -0.26, p=0.01 versus r = -0.19, p=0.05). **CONCLUSION:** Budesonide was ineffective prophylaxis of AMS compared to acetazolamide. Acetazolamide was protective of severe AMS. **FUNDING:** American Alpine Club Research Grant, Wilderness Medical Society’s Herbert N. Hultgren Grant, the Institute for Altitude Medicine. **See poster F03.**
Abstract Presentation II. INHALED BUDESONIDE DOES NOT IMPROVE INCIDENCE AND SEVERITY OF ACUTE MOUNTAIN SICKNESS
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INTRODUCTION: Recent data on slow ascent (5 days) to 3900m suggest a protective effect of inhaled budesonide against acute mountain sickness (AMS), pointing to a role of the lung in the pathophysiology of AMS. We tested whether budesonide protects against AMS after rapid ascent to 4559m. METHODS: This prospective, randomized, double-blinded and placebo-controlled trial, randomized 51 subjects to receive placebo, or 200 or 800µg of budesonide twice/day. Inhalation started 1 day prior to ascending from 1130m to 4559m within ~20 hours, with an overnight stay at 3611m. Individuals were considered AMS-positive with a Lake Louise score (LLS) ≥5 and an AMS-C score ≥0.70 to at least one time point during the stay. Plasma and 24h-urine concentrations of cortisol were measured to evaluate potential systemic effects of inhaled budesonide. Oxygenation was assessed by capillary blood gas analysis. Pulmonary artery systolic pressure (PASP) was assessed by transthoracic echocardiography. RESULTS: The incidence of AMS at 4559m was not different between groups (placebo: 44%, budesonide 200µg: 50%, and 800µg: 63%). The corresponding LLS were 6.4±4.0, 6.6±2.8, and 8.2±3.5, and AMS-C scores were 0.8±0.8, 1.0±0.9, and 1.3±1.1 after the first night at 4559m. Capillary $PO_2$ decreased from 84±7 to 47±5mmHg (all data combined; P<0.001) and was significantly lower in the AMS-positive than in healthy individuals in placebo and 200µg budesonide groups. Capillary $PO_2$ was, however, not different between those with and without AMS in the 800µg group, indicating that preventing the slight decrease of $PO_2$ compared with healthy individuals does not prevent AMS. PASP increased ~2-fold and was not affected by budesonide (P>0.25). Cortisol was not different between groups (P>0.41) demonstrating no detectable systemic effect on endogenous cortisol levels by inhaled budesonide. CONCLUSION: Prophylactic inhalation of budesonide does not improve AMS after rapid ascent to 4559m. Therefore, budesonide cannot be recommended of prevention of AMS. See poster F04.

The Importance of Reproducibility in Science—Peter Wagner

General discussion: Can we understand the divergent outcomes?

1900-2300 Awards, Banquet, and Dance at Brewster Barn

1900-1930 Sleigh Rides & Drinks to Brewster Barn
(meet at bottom of lake-side steps of Chateau Lake Louise)

1930-2130 Awards, Dinner, and Dancing at Brewster Barn