The 21st International Hypoxia Symposium
meeting to advance the science of Hypoxia every two years since 1979

19-24 February 2019
Chateau Lake Louise
Lake Louise, Alberta, Canada
The 21st International Hypoxia Symposium

Chairs
Robert Roach
Peter Hackett

Advisory Board
Phil Ainslie, Peter Bärtsch, Beth Beidleman, Marc Berger, Analisa Cogo, Jerry Dempsey, Holger Eltzschig, Max Gassmann, Tom Hornbein, Bengt Kayser, Linda Keyes, Fabiola Leon-Velarde, Denny Levett, Ben Levine, Andrew Luks, Carsten Lundby, Marco Maggiorini, Heimo Mairbäurl, Jim Milledge, Marc Poulin, Frank Powell, Ge Ri Li, Jean-Paul Richalet, Claudio Sartori, Urs Scherrer, Brownie Schoene, Tatum Simonson, Erik Swenson, Francisco Villafuerte, Peter Wagner, John West, Tanna Wuren

Administrative Support
Ann Wislowski and Barbara Lommen

Special Thanks for Support
Centura
Trudell Medical
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 web site (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 Victoria Foyer on Tuesday evening from 1830-2030, on Wednesday morning outside the main meeting room in Heritage Hall from 0730-0830, or any morning thereafter from 0730-0830.

Reception. Join us for a reception in Victoria Foyer 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.

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.
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 2019 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 several 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.

For 2019, please welcome Trudell Medical as our Trainee Award sponsor!
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:

- Peter Bärtsch
- 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
Announcing a high-altitude study for the 21st century by Centura Health and the University of Colorado School of Medicine

“This unique living laboratory brings an unparalleled opportunity to high-altitude research that’s never been done before.” – Marshall Denkinger, MD

SITE  Summit County, Colorado, home to more than 30,000 residents living at high altitude

SCOPE  Participants: 6,000+ local residents

FOCUS  Reducing hypoxia risk and emphasizing whole-person care

Centura Health is the 2019 Hypoxia Symposium’s Platinum Level Sponsor

Please be sure to visit their poster.

Centura’s Sponsorship will be used to underwrite the general costs of the symposium.

Centura Health will also sponsor Dr. Peter Robbins, the 2019 Houston Professor

Dr. Robbins will join the meeting as our distinguished guest and sponsored asker of tough questions. Please join us in welcoming Dr. Robbins.
Trudell Medical International*, maker of the Altimate* is the 2019 Hypoxia Symposium’s Gold Level Sponsor. Please be sure to visit their information table. Trudell’s Sponsorship will be used to underwrite all of the presentation prizes for 2019.
<table>
<thead>
<tr>
<th>Faculty Name</th>
<th>Title</th>
<th>Email Address</th>
</tr>
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<tbody>
<tr>
<td>Benveniste, Helene</td>
<td>The Glympathic System and Its Role in Cerebral Homeostasis</td>
<td><a href="mailto:helene.benveniste@yale.edu">helene.benveniste@yale.edu</a></td>
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<td>Berger, Marc M</td>
<td>The Early Hours in the Pathophysiology of AMS - fishing in the dark?</td>
<td><a href="mailto:ma.berger@salk.at">ma.berger@salk.at</a></td>
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<td>Charles, Andrew</td>
<td>Hypoxia and Headache</td>
<td><a href="mailto:acharles@ucla.edu">acharles@ucla.edu</a></td>
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<td>Dunn, Jeff</td>
<td>The Blood Brain Barrier and Hypoxia</td>
<td><a href="mailto:dunnj@ucalgary.ca">dunnj@ucalgary.ca</a></td>
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<td>Eichstaedt, Christina</td>
<td>Genetics of Pulmonary Hypertension and HAPE</td>
<td><a href="mailto:christina.eichstaedt@med.uni-heidelberg.de">christina.eichstaedt@med.uni-heidelberg.de</a></td>
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<tr>
<td>Grissom, Colin</td>
<td>Ventilation Strategies in Hypoxemic Respiratory Failure</td>
<td><a href="mailto:colin.grissom@imail.org">colin.grissom@imail.org</a></td>
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<tr>
<td>Hindle, Allyson</td>
<td>The Champions of Breath Hold Diving: “Omics” of the Antarctic Weddell Seal</td>
<td><a href="mailto:ahindle@mgh.harvard.edu">ahindle@mgh.harvard.edu</a></td>
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<tr>
<td>Lawley, Justin</td>
<td>HACE-Its Own Entity or End-Stage AMS?</td>
<td><a href="mailto:Justin.Lawley@uibk.ac.at">Justin.Lawley@uibk.ac.at</a></td>
</tr>
</tbody>
</table>
Lewin, Gary
Hypoxia and the Naked Mole Rat
Email: glewin@mdc-berlin.de

Mairbäurl, Heimo
Ethnicity, Age and Sex Impacting Normal Hemoglobin Values
Email: Heimo.Mairbaeurl@med.uni-heidelberg.de

McKenna, Helen
Examining the Evidence for Human Adaptation to Hypoxia in Critical Illness
Email: helen.mckenna.15@ucl.ac.uk

Muckenthaler, Martina
The Impact of Iron on Hemoglobin Values and Anemia
Email: Martina.Muckenthaler@med.uni-heidelberg.de

Naeije, Robert
The Right Heart, Pulmonary Circulation and Critical Illness
Email: rnaeije@ulb.ac.be

Prchal, Joe
Hypoxia, Erythropoiesis and High Altitude Evolutionary Adaptation
Email: josef.prchal@hsc.utah.edu

Reyes, Victor
Perinatal Cardiopulmonary Adaptations Of The Llama To Hypoxia
Email: vicreyes@med.uchile.cl

Schmidt, Walter
Hemoglobin Mass and Blood Volume in Patients Suffering from Chronic Mountain Sickess
Email: walter.schmidt@uni-bayreuth.de

Semenza, Gregg
Acclimation to the Hypoxic Tumor Microenvironment
Email: gsemenza@jhmi.edu

Simonson, Tatum
Genes and High-Altitude Tolerance
Email: tsimonson@ucsd.edu
Swenson, Erik R
The Early Hours in the Pathophysiology of HAPE
Email: Erik.Swenson@va.gov

Evening Speakers

Barry Blanchard
The Mountain, An Arrow Pointing Up

Danika Gilbert
Ascending Afghanistan

Zac Robinson
The Shining Mountains and the Emerald Lake
### Tuesday and Wednesday

**Program At a Glance**

**Tuesday, 19 February 2019**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1830-2030</td>
<td>Registration and Reception with Food, Victoria Foyer</td>
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</table>

**Wednesday, 20 February 2019**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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<tr>
<td>0630-0830</td>
<td>Breakfast, Victoria Dining Room</td>
</tr>
<tr>
<td>0730-0830</td>
<td>Registration, Heritage Hall</td>
</tr>
<tr>
<td>0745-0800</td>
<td>Opening Ceremonies, Mount Temple Ballroom</td>
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<tr>
<td>0800-0930</td>
<td>High Altitude Genetics</td>
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<tr>
<td>0800-0830</td>
<td>Genes and high-altitude tolerance—Tatum Simonson</td>
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<tr>
<td>0830-0900</td>
<td>Genetics of pulmonary hypertension and HAPE—Christina Eichstaedt</td>
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<td>0900-0930</td>
<td>Hypoxia, erythropoiesis and high altitude evolutionary adaptation—Joe Prchal</td>
</tr>
<tr>
<td>0930-1000</td>
<td>Refreshment Break, Heritage Hall</td>
</tr>
<tr>
<td>1000-1130</td>
<td>Hemoglobin</td>
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<tr>
<td>1000-1030</td>
<td>Ethnicity, age and sex impacting normal hemoglobin values—Heimo Mairbäurl</td>
</tr>
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<td>The impact of iron on hemoglobin values and anemia—Martina Muckenthaler</td>
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<td>Hemoglobin mass and blood volume in patients suffering from chronic mountain sickness—Walter Schmidt</td>
</tr>
<tr>
<td>1130-1600</td>
<td>Ski Break</td>
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<tr>
<td>1130-1330</td>
<td>Lunch, Victoria Dining Room</td>
</tr>
<tr>
<td>1600-1830</td>
<td>Poster Session</td>
</tr>
<tr>
<td>1900-2130</td>
<td>Dinner, Victoria Dining Room</td>
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<tr>
<td>2030-2130</td>
<td>Ascending Afghanistan—Danika Gilbert</td>
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<td>0800-0930</td>
<td><strong>Hypoxia: Consequences in Intensive Care Medicine</strong></td>
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<tr>
<td>0800-0830</td>
<td>Examining the evidence for human adaptation to hypoxia in critical illness—Helen McKenna</td>
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<td>0830-0900</td>
<td>The right heart, pulmonary circulation and critical illness—Robert Naeije</td>
</tr>
<tr>
<td>0900-0930</td>
<td>Ventilation strategies in hypoxemic respiratory failure—Colin Grissom</td>
</tr>
<tr>
<td>0930-1000</td>
<td>Refreshment Break, Heritage Hall</td>
</tr>
<tr>
<td>1000-1130</td>
<td><strong>New Lessons from Hypoxic Mammals</strong></td>
</tr>
<tr>
<td>1000-1030</td>
<td>Perinatal cardiopulmonary adaptations of the llama to hypoxia—Victor Reyes</td>
</tr>
<tr>
<td>1030-1100</td>
<td>Hypoxia and the naked mole rat—Gary Lewin</td>
</tr>
<tr>
<td>1100-1130</td>
<td>The Champions of breath hold diving: “omic” analysis of the Antarctic Weddell Seal—Allyson Hindle</td>
</tr>
<tr>
<td>1130-1600</td>
<td>Ski Break</td>
</tr>
<tr>
<td>1130-1330</td>
<td>Lunch, Victoria Dining Room</td>
</tr>
<tr>
<td>1600-1800</td>
<td><strong>Hot Topics in Hypoxia I—Free Communications</strong></td>
</tr>
<tr>
<td>1900-2130</td>
<td>Dinner, Victoria Dining Room</td>
</tr>
<tr>
<td>2030-2130</td>
<td><strong>The Mountain, An Arrow Pointing Up</strong>—Barry Blanchard</td>
</tr>
</tbody>
</table>
**Program At a Glance**

**Friday, 22 February 2019**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>0630-0830</td>
<td>Breakfast, Victoria Dining Room</td>
</tr>
<tr>
<td>0730-0830</td>
<td>Registration, Heritage Hall</td>
</tr>
<tr>
<td>0800-0930</td>
<td><strong>Pathophysiology of High Altitude Diseases</strong></td>
</tr>
<tr>
<td>0800-0830</td>
<td>The early hours in the pathophysiology of HAPE—Erik R. Swenson</td>
</tr>
<tr>
<td>0830-0900</td>
<td>The early hours in the pathophysiology of acute mountain sickness - fishing in the dark?—Marc M Berger</td>
</tr>
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<td>HACE—its own entity or end-stage AMS?—Justin Lawley</td>
</tr>
<tr>
<td>0930-1000</td>
<td>Refreshment Break, Heritage Hall</td>
</tr>
<tr>
<td>1000-1130</td>
<td><strong>Hot Topics in Hypoxia II—Free Communications</strong></td>
</tr>
<tr>
<td>1130-1600</td>
<td>Ski Break</td>
</tr>
<tr>
<td>1130-1330</td>
<td>Lunch, Victoria Dining Room</td>
</tr>
<tr>
<td>1600-1830</td>
<td><strong>Oral 3x3 Poster Session Presentations</strong></td>
</tr>
<tr>
<td>1900-2130</td>
<td>Dinner, Victoria Dining Room</td>
</tr>
<tr>
<td>2030-2130</td>
<td><strong>The Shining Mountains and the Emerald Lake</strong>—Zac Robinson</td>
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</tr>
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<td>0800-0930</td>
<td><strong>Hypoxia and the Brain</strong></td>
</tr>
<tr>
<td>0800-0830</td>
<td>The glymphatic system and its role in cerebral homeostasis—Helene Benveniste</td>
</tr>
<tr>
<td>0830-0900</td>
<td>The blood brain barrier and hypoxia—Jeff Dunn</td>
</tr>
<tr>
<td>0900-0930</td>
<td>Hypoxia and headache—Andrew Charles</td>
</tr>
<tr>
<td>0930-1000</td>
<td>Refreshment Break, Heritage Hall</td>
</tr>
<tr>
<td>1000-1130</td>
<td><strong>Latest Developments in Hypoxia</strong></td>
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<tr>
<td>1000-1100</td>
<td>Hot Topics in Hypoxia III</td>
</tr>
<tr>
<td>1100-1130</td>
<td>Acclimation to the hypoxic tumor microenvironment—Gregg Semenza</td>
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<tr>
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</tr>
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<td>Lunch, Victoria Dining Room</td>
</tr>
<tr>
<td>1600-1830</td>
<td><strong>Hot Topics in Mountain Medicine</strong></td>
</tr>
<tr>
<td>1900-2300</td>
<td>Dinner, Awards, and Dance, Victoria Dining Room</td>
</tr>
<tr>
<td></td>
<td><strong>Presentation of Student Award Winners</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Presentation of Reeves Prize for Presentation Excellence</strong></td>
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<td>2030-2130</td>
<td><strong>Ascending Afghanistan</strong>—Danika Gilbert</td>
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**Wednesday, 20 February**

**0745-0800**
**Welcome and Introductions**  
The Organizers

**0800-0930**
**High Altitude Genetics**  
**Chairs: Tatum Simonson and Joe Prchal**

**0800-0830 Genes and high-altitude tolerance—**Tatum Simonson

Andean, Tibetan, and Ethiopian highlanders exhibit both distinct and similar genetic signals and physiological traits that reflect adaptive and mal-adaptive responses to high altitude. Various regions of the genome containing hypoxia inducible factor (HIF) pathway and non-HIF-related genes have been reported as top candidates for adaptation across these populations. While results gleaned from individual genomic studies suggest limited overlap of adaptation across populations, standardized analyses across datasets suggest convergence in several adaptive signals but not necessarily the variants contained in these regions. The extent to which these factors contribute to notable physiological differences within and across populations is central to understanding mechanisms of adaptation and lack of adaptation to hypoxia. In addition to striking differences in average hemoglobin concentration, breathing patterns vary markedly between highland groups. Our analyses of Andean men and women at 4340 m in Cerro de Pasco, Peru, revealed that blunted hypoxic ventilatory responses characteristic of many individuals in this population are associated with hematocrit, decreased daytime and nadir saturation during sleep. These findings suggest intermittent and likely extended periods of hypoxia during sleep exacerbate “maladaptations” in this population. Additionally, some markers associated with our top genomic targets of selection are further elevated in Andean males with chronic mountain sickness (CMS).

**0830-0900  Genetics of pulmonary hypertension and HAPE—**Christina Eichstaedt

Heritable pulmonary arterial hypertension (HPAH) is an autosomal dominantly inherited disease caused by mutations in the bone morphogenic protein receptor 2 (BMPR2) gene and/or genes of its signalling pathway in about 85% of patients. New PAH genes have been discovered in the last years including mutations in the transcription factor Krüppel-Like Factor 2 (KLF2). A genetic predisposition to high altitude pulmonary edema (HAPE) has long been suspected but no disease causing mutation has been identified up to date. HAPE and PAH are both characterised by increased systolic pulmonary artery pressures (sPAP). In HAPE-susceptibles (HAPE-S) sPAP at rest is within the normal range but elevated during exercise or hypoxia in a similar manner as in healthy BMPR2 mutation carriers. Therefore, similar pathophysiological and genetic mechanisms might act in HAPE and PAH. Hence, we analysed all known PAH genes in a HAPE-S family and in 64 unrelated HAPE-S mountaineers using next generation sequencing for 42 genes on a PAH-specific panel. Two otherwise healthy family members developed re-entry HAPE at 3640 m during childhood. We identified a likely pathogenic variant (missense mutation, c.1198T>G, p.Cys400Gly) in the Janus Kinase 2 (JAK2) gene. One HAPE-S progressed to mild PAH aged 23 years. In two out of the 64 HAPE-S mountaineers one missense mutation in the gene Cytochrome P450 Family 1 (CYP1B1) and a deletion in the Histidine Rich Glycoprotein (HRG) were identified. In 26 further HAPE-S (40%) 31 variants of PAH-genes of unknown significance were detected. This is the first study identifying an inherited JAK2 mutation in a HAPE-S family with progression to mild PAH in the index patient. Additional pathogenic variants in PAH genes suggest HAPE-susceptibility may partly be linked to PAH signaling pathways. Further studies are needed to assess frequency and implication of these genes in HAPE-S.
Hypoxia is sensed and its effect transmitted by the hypoxia inducible transcription factors (HIFs) - dimers of post-transcriptionally oxygen-regulated HIF-α and HIF-β subunits. In normoxia, these subunits are hydroxylated by prolyl hydroxylases (encoded by EGLN genes) and bind to VHL protein, targeting them for rapid destruction in the proteasome. In hypoxia, these HIF-α subunits proteins are stabilized resulting in increased transcription of HIF-regulated genes. Homozygosity of hypomorphic VHL (the cause of Chuvash polycythemia) and heterozygosity for EGLN1 mutated alleles, and also heterozygous gain-of-function mutations of EPAS1 gene, cause congenital polycythemia. Tibetans and Andean Aymaras and Quechuas, long-standing inhabitants of extreme high altitude, developed evolutionary selected genes. Tibetan-specific of EGLN1, EPAS1 genes contribute to the Tibetans' protection from polycythemia at high altitude; however, these genotypes do not explain the entire polycythemia protection. In contrast to Tibetans, Aymaras and Quechuas are not protected from polycythemia. We performed unbiased whole Aymara transcriptome analyses in granulocytes, 2,585 genes were upregulated and 365 genes were downregulated. Many of these modulated genes are involved in inflammatory pathways. We then analyzed differential exon usage in the transcriptome and identified 2,475 genes with alternative splicing events, comprising 1,568 exon skipping, 485 intron retention, 175 alternative 3’ splice sites, 144 alternative 5’ splice sites, and 902 mutually exclusive exons. These alternative spliced genes were also overrepresented in inflammatory pathways. We detected the previously unreported NFKB1 alternate transcripts skipping exon 4 or 5, which lead to the out-of-framed NFKB1 mRNA. NF-κB is transcriptional regulator of plethora of inflammatory genes and also interacts with HIFs. This truncated nonfunctional NF-κB variant peptide correlates with higher hemoglobin, lower leukocytes and suppresses inflammation. These data indicate that NFKB1 SNPs enriched in Aymara are associated with alternative spliced NFKB1 transcripts which contribute to polycythemia in Aymara.
Wednesday, 20 February

1000-1130
Hemoglobin
Chairs: Heimo Mairbäurl and Martina Muckenthaler

1000-1030 Ethnicity, age and sex impacting normal hemoglobin values—Heimo Mairbäurl

Decreased oxygen-availability at high altitude requires adjustments allowing for adequate tissue oxygenation. One mechanism is a slow increase in hemoglobin (Hb) concentration requiring weeks to months to achieve stably elevated values. Approximately 5% of the world’s population lives at altitudes higher than 1500m, and those have elevated Hb concentration, but there seem to be variations with ethnicity such as the less pronounced increase in Hb concentration in Tibetans than in Andeans. A variety of genetic variations found in high altitude residents might favor adaptation to life in a hypoxic environment, some of which correlate e.g. with decreased Hb in the Tibetans. To get a wider picture on differences in Hb concentration between residents living at different altitudes in different regions of the world we extracted Hb concentrations from published literature for meta- and multiple regression analysis. Results show increased Hb concentration in all high altitude residents but variations in the magnitude of increase among regions and among ethnic groups within a region. The highest increase in Hb concentration per altitude-increment was found in Andean residents (1 g/l/1000m), whereas it was smaller in all others (0.6 g/l/1000m). Small differences were even found in the Hb concentration at low altitude, where Tibetans showed the lowest value. Analyses were restricted to adult males and females and indicate that the difference in Hb concentration of approximately 2 g/l persisted with altitude independent of region and ethnicity. Data for infants, children, and pregnant women are incomplete not permitting such analyses. Together our results may indicate different sensitivity of oxygen dependent control of erythropoiesis, but also differences in control in plasma volume, which is another factor controlling Hb concentration. Our results also provide a basis for defining individual reference values for ethnic groups allowing for appropriate diagnosis of anemia in high altitude residents.

1030-1100 The impact of iron on hemoglobin values and anemia—Martina Muckenthaler

Hemoglobin synthesis increases in response to decreased oxygen-availability at high altitude. Oxygen in red blood cells is bound to iron to circulate in the human body. Therefore increased erythropoiesis at high altitude requires high amounts of iron that is supplied by dietary absorption and mobilization from iron stores. The regulatory mechanisms maintaining iron homeostasis are tightly interconnected with those controlling hypoxic responses. These mechanisms include hypoxic sensing, erythropoietin synthesis, the control of iron absorption and regulation of hepcidin, the hormone maintaining systemic iron homeostasis.

In my presentation I will discuss how iron metabolism adapts to high altitude. I will present data from an analysis of 70,000 male conscripts aged 18-22 years, where we observe a significant increase of Hb values for every 300 meters of augmented altitude, even below 1500m. These data imply an immense sensitivity and precision of the oxygen sensing process. In addition, we observe an altitude-dependent increase of ferritin levels, independent of increasing hemoglobin levels, suggesting that iron stores may directly adapt to increasing altitude.
Hemoglobin mass and blood volume in patients suffering from chronic mountain sickness—Walter Schmidt

In patients suffering from chronic mountain sickness (P-CMS) hemoglobin concentration ([Hb]) is tremendously increased. Until now, however, the absolute hemoglobin mass (Hbmass) and blood volume (BV) have not been sufficiently investigated. **Purpose:** To determine (i) absolute Hbmass and BV in P-CMS and (ii) to evaluate first treatment strategies (descending to lower altitude, additional oxygen, acetazolamide). **Methods:** 25 CMS patients living at approx. 4000m (55.6 ±10.5 yrs, 80.7 ±13.3 kg, BMI 30.1 ±4.6) entered the study and were compared with 20 healthy control subjects from the identical altitude (C-A: 44.5 ±12.7 yrs, 76.8 ±10.0 kg, BMI 28.3 ±3.5) and with 15 subjects from sea level (C-SL: 43.9 ±15.9 yrs, 72.2 ±11.8 kg, BMI 25.9 ±4.4). In a pilot study, 6 patients each descended for 3 weeks to lower altitude (1100m), received supplemental oxygen for 12h overnight, or were administered 100mg/day acetazolamide for 3 weeks, respectively. **Results:** [Hb] and Hct were 14.4 ±1.1g (43.2 ±3.5%) in C-SL, 17.1 ±0.8g (52.1 ±2.7%) in C-A, and 22.1 ±1.1g/dl (68.8 ±3.6%) in P-CMS. Absolute and relative Hbmass increased from 726 ±118g (10.2 ±1.5g/kg) in C-SL to 941 ±105g (12.3 ±0.9g/kg) in C-Al and to 1605 ±316g (20.2 ±4.1g/kg) in P-CMS (difference between the groups p<0.001). In P-CMS, PV was slightly decreased while BV was clearly elevated (7935 ±1332ml, 99.8 ±17.5ml/kg) compared to the control groups (C-SL: 5543 ±694ml, 77.8 ±10.0 ml/kg; C-Al: 6067 ±688ml, 79.4 ±6.3ml/kg; p<0.001). Descent to low altitude reduced Hbmass by 245 ±117g (p<0.01), inhalation of additional oxygen by 115 ±16g and administration of acetazolamide by 98 ±68g (both p<0.05). **Conclusion:** In P-CMS, Hbmass tremendously increases which is accompanied by blood volume expansion. Descent to low altitude effectively reduces Hbmass; a slight, but significant effect can also be observed with additional oxygen and acetazolamide. **Funding:** BMBF 01DN14025, Germany.
Poster Session

Poster Viewing:
1600-1830

Location:
Mount Temple Ballroom C

When:
Wednesday, 20 February 2019

Poster session includes many great posters. All posters will be available for viewing from 1600-1830h.

All posters should be put up for viewing Tuesday evening, and should be taken down by late Wednesday evening.
Poster Session Wednesday Afternoon, 20 February

Poster: 1

METAZOAN EVOLUTION OF THE OXYGEN-SENSING PATHWAY INVOLVED CONSERVED DIVERGENCE OF VHL AFFINITY FOR HIF1A AND HIF2A
Daniel Tarade1, Jeffrey E Lee1, Michael Ohh1,2
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Objective: To dissect how hypoxia-inducible factor (HIF)1α and HIF2α bind to von Hippel-Lindau (VHL) and test whether evolutionarily conserved differences impact binding affinity. Methods: Steady-state and kinetic binding experiments were employed to probe HIFα/VHL complex stability. The structure of HIF2α peptide bound to VHL was determined via protein crystallography. Alignment of annotated HIF1α, HIF2α, and VHL sequences was used to assess evolutionary conservation of key amino acid residues. Results: We observed that HIF1α binds more tightly than HIF2α to VHL in steady-state and kinetic binding experiments. A mutation screen revealed that the key determinant of differential HIFα-VHL complex stability is the amino acid three residues N-terminal of the primary hydroxylation site recognized by VHL (i.e. HIF1α Metn-3 versus HIF2α Thrn-3). Analysis of HIFα-VHL co-crystal structures revealed that both residues pack against VHL Phe91, providing a structural basis for the increased binding of HIF1α to VHL as the Met-aromatic interaction is favourable. Notably, HIF1α Metn-3 is invariant in the vertebrate lineage but variable in invertebrate species, which possess only a single copy of HIFα. Similarly, VHL Phe91 is also invariant in vertebrate species whereas a tyrosine substitution is prevalent among invertebrates, which confers decreased binding affinity to both HIF1α and HIF2α. These findings support the notion that the evolution of the vertebrate lineage included a more complex hypoxia response involving a fine-tuned divergence of VHL affinity for HIF1α and HIF2α. Summary: Our biophysical, structural, and phylogenetic studies support the notion that metazoan evolution coincided with precise divergence of VHL affinity for HIF1α and HIF2α upon duplication of the ancestral HIFα. Funding: Research was supported by funds from the Canadian Institutes of Health Research.

Poster: 2

SILDENAFIL DOES NOT IMPROVE EXERCISE PERFORMANCE IN HYPOXIA – A META-ANALYSIS
Eric A Carter1, Keith Lohse2, A William Sheel1, Michael S Koehle1
1University of British Columbia, Canada; 2University of Utah, USA; ecarter1@interchange.ubc.ca

Objective: To explore the use of the pulmonary vasodilator sildenafil to reduce the decrement in endurance performance in moderate hypoxia. Methods: We assessed efficacy of sildenafil to improve performance in hypoxia by systematically searching electronic databases (until August 2018) for randomized trials comparing sildenafil with placebo. We also examined the effect of sildenafil on pulmonary artery pressure (PAP), cardiac output (CO), and pulse oxygen saturation (SPO2) compared to placebo in hypoxia. Fourteen studies were included; 210 subjects received sildenafil 40, 50, or 100 mg/day. Results: Sildenafil showed a large effect for decreasing PAP during exercise and at rest, a small effect for increasing CO during exercise and a moderate effect at rest, a moderate effect for increasing SPO2, and a small effect for improving performance. In a subgroup analysis, there was not a statistically significant difference between 100 and 50 mg sildenafil dose on SPO2. Sildenafil had a moderate effect on increasing SPO2 and performance at terrestrial altitude but a small effect in normobaric hypoxia. Regression analysis showed that hypoxic dose (PO2) and metabolic rate do not account for a significant portion of the variance in effect size for sildenafil on PAP, CO, SPO2, and performance. Summary: This meta-analysis indicates that sildenafil is effective in reducing PAP, has a moderate to small effect on CO and SPO2, and no effect on performance in hypoxia.

Poster: 3

SILDENAFIL DOES NOT INCREASE IPAVA RECRUITMENT IN HYPOXIA
Eric A Carter1, Sarah Koch1, James O’Donovan1,2, A William Sheel1, William K Milsom3, Michael S Koehle1
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Introduction: Sildenafil is a pulmonary vasodilator that has been previously shown to improve oxygen saturation (SPO2) and endurance performance in moderate hypoxia. Intrapulmonary arteriovenous anastomoses (IPAVA) open during exercise and in hypoxia, and result in venous admixture, reducing SPO2. Objective: The purpose of this study was to determine if 50mg sildenafil would reduce IPAVA opening and if the reduction in maximal exercise capacity in hypoxia
is related to opening of IPAVA. We hypothesized that during progressive levels of hypoxia at rest ($F_{O_2} = 0.21, 0.14, 0.12$), sildenafil would increase $S_P{O_2}$ and reduce shunt score (an estimate of IPAVA opening) compared to placebo, and that the reduction in maximal exercise capacity in hypoxia would be positively correlated with shunt score in hypoxia. **Methods:** Fourteen endurance-trained men performed a maximal exercise test at sea-level and at a simulated altitude of 3000m followed by two experimental visits where, after randomly ingesting sildenafil or placebo, they underwent measurement of shunt score using agitated saline contrast echocardiography during progressive levels of hypoxia. **Results:** All subjects experienced a decline in maximal exercise capacity in hypoxia that ranged from 10% to 19% of sea-level values. Shunt score increased significantly in hypoxia with no effect of sildenafil. At increasing levels of hypoxia, the inverse relationship between $S_P{O_2}$ and shunt score became stronger. The decrement in performance was unrelated to IPAVA recruitment in resting hypoxia. We identified a critical threshold $S_P{O_2}$ of 87%, below which all subjects displayed recruitment of IPAVA; however, several subjects had IPAVA shunting in room air, indicating that arterial hypoxemia may not be the sole trigger. **Conclusions:** These results indicate that recruitment of IPAVA is not related to endurance performance in hypoxia and that athletes would not benefit from the use of 50mg sildenafil to affect the recruitment of IPAVA.

**Poster:** 4

**STAR – THE UTSTEIN STYLE FOR CLINICAL HIGH ALTITUDE RESEARCH**

Rachel Turner¹, Monika Brodmann Maeder¹, Hermann Brugger², Matiram Pun¹, Giacomo Strapazzon¹, Tomas Dal Capello¹, Marco Maggiorini³, Peter H Hackett¹, Peter Bärtsch⁵, Erik R Swenson⁶⁷, Ken Zafren⁸

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**Objective:** The STAR initiative aimed to improve the quality and reproducibility of study results in clinical high altitude (HA) research by developing guidelines for data reporting. **Methods:** A core group of experts in HA research convened an international group of 42 experts to participate in a Delphi process to define core parameters mandatory for research proposals and reports of clinical HA research. **Results:** The Delphi experts carried out two rounds of electronic questionnaires and defined 42 core parameters for HA research, grouped under five headings: i. Setting (study location, setting, altitude, starting point of the ascent, maximum altitude reached, mode of ascent); ii. Individual factors (age, sex, preexisting altitude exposure, preacclimatization, HA native, altitude of residence, preexisting health conditions, history of prior AMS/HACE/HAPE); iii. AMS and HACE (headache, gastrointestinal symptoms, fatigue/weakness, dizziness/light-headedness, ataxia, change in mental status, AVPU, SpO₂, time of AMS/HACE definition, revised Lake Louise AMS Score); iv. HAPE (weakness/decreased exercise performance, dyspnea at rest, cough, tachypnea, orthopnea, pink frothy sputum, respiratory rate, heart rate, SpO₂, rales and wheezing, time of HAPE definition), and v. Therapy (list of drugs used, supplemental oxygen, hyperbaric bag, descent). The guidelines additionally provide definitions of each core parameter. An additional 47 parameters were defined as supplemental, meaning that they should be mentioned depending on the nature of the research. **Conclusion:** Reproducibility of data is one of the most concerning issues in natural and medical sciences. Developing guidelines for study report in clinical HA medicine is important because the number of studies is increasing rapidly. Using the 42 core parameters defined by the STAR initiative should help to standardize evidence for prevention, diagnosis and treatment of altitude illnesses. We anticipate regular update of these guidelines as the field of clinical HA research is dynamic.
THE EFFECT OF AN EXPIRATORY RESISTANCE MASK WITH DEAD SPACE ON SLEEP, ACUTE MOUNTAIN SICKNESS, COGNITION AND VENTILATORY ACCLIMATIZATION IN NORMOBARIC HYPOXIA

Alexander Patrician, Michael M Tymko, Hannah G Caldwell, Connor A Howe, Geoff B Coombs, Rachel Stone, Allison Hamilton, Ryan L Hoiland, Philip N Ainslie
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Objective: We examined the hypothesis that an expiratory resistance mask containing a small amount of dead-space (ER/DS) would reduce the apnea-hypopnea index (AHI) during sleep, attenuate the severity of acute mountain sickness (AMS), and offset decrements in cognitive function compared to a sham mask. Methods: In a double-blinded, randomized, sham-controlled, cross-over design, 19 volunteers were exposed to two nights of normobaric hypoxia (FIO2 = 0.125), using an ER/DS mask (3.5 mm restrictive expiratory orifice; 125 mL dead-space volume) and sham mask (zero-flow resistance; 50 mL dead-space volume). Cognitive function, AMS, and ventilatory acclimatization were assessed before and after the 12-hour normobaric hypoxia exposure. Polysomnography was conducted during sleep. Results: AHI was reduced using the ER/DS sleep mask compared to the sham (30.1 ± 23.9 events·hr⁻¹ vs. 58.9 ± 34.4 events·hr⁻¹, respectively; p=0.01). Likewise, oxygen desaturation index and headache severity were reduced (both p<0.05). There were also benefits on limiting the hypoxia-induced reductions in select measures of reaction speed and attention (p<0.05). Conclusion: Our study indicates that a simple non-invasive and portable ER/DS mask resulted in reductions (49%) in AHI, and reduced headache severity and aspects of cognitive decline. The field applications of this ER/DS mask should be investigated further before recommendations can be made to support its benefit for travel to high altitude. Funding: The study was sponsored by Trudell Medical International.

CORONARY VASOCONSTRICTION DURING METABOREFLEX AT HIGH ALTITUDE

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Introduction: Muscle metaboreflex activation (MMA) leads to conflicting coronary vasomotor signals (i.e. α-adrenergic vasoconstriction vs. metabolic vasodilation). At altitude, reduced PO₂ augments sympathetic vasomotor activity and MMA may become potentiated. We hypothesized that greater MMA at altitude constrains metabolic coronary vasodilation. Objective: To measure coronary vasomotor activity during MMA at high altitude. Methods: Participants (n=6) performed two-minutes of isometric handgrip exercise (30% of maximum voluntary contraction [MVC]) followed by 3-minutes of post-exercise circulatory occlusion (PECO) to activate the muscle metaboreflex at sea level and high altitude (3800 m). Measurements at baseline and during PECO included mean blood velocity of the left anterior descending coronary artery (LADVmean; transthoracic Doppler echocardiography), left ventricular volumes at end-systole and end-diastole, heart rate (HR; ECG), mean arterial blood pressure (MAP; photoplethysmography) and coronary vascular resistance index (CVR; MAP/LADVmean). Left ventricular mechanical energy (MELV) and rate-pressure product (RPP) served as indices of myocardial oxygen demand. Results: Compared with sea level, baseline LADVmean, RPP, ME, and HR were significantly elevated while CVR, Pₐ[O₂] and Pₐ[CO₂] were significantly reduced (P<0.05). PECO resulted in a 6.7 ± 4.2% increase in LADVmean at sea level, but a 25.7 ± 11.0% reduction at high altitude (P<0.001). The change in MAP (Δ13.0 ± 4.3 mmHg vs. Δ14.0 ± 3.1 mmHg), HR (Δ1.5 ± 1.3 bpm vs. Δ0.2 ± 2.5 bpm), ME (Δ9.4 ± 3.2 % vs. Δ16.2 ± 2.5 %) and RPP (Δ12.7 ± 1.7 % vs. Δ20.3 ± 5.1 %) induced by PECO were not different between sea level and high altitude. CVR during PECO did not change from baseline at sea level (4.2 ± 0.3 mmHg/cm/s, to 4.5 ± 0.3 mmHg/cm/s, P=0.5) but increased by 40 ± 9.7% during PECO at altitude (P=0.02). Conclusion: We conclude that forearm MMA leads to coronary vasoconstriction during acute high-altitude exposure possibly due to a synergistic interaction between the chemoreflex and metaboreflex.
GLOBAL REACH EXPEDITION: INCREASED BASAL α-ADRENERGIC VASOCONSTRICTION AND IMPAIRED α-ADRENERGIC RESPONSIVENESS IN ANDEANS WITH CHRONIC MOUNTAIN SICKNESS

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Introduction: Exposure to chronic hypoxia induces several autonomic related adaptations that facilitate acclimatization. While many lifelong residents acclimatize normally, some develop chronic mountain sickness (CMS) characterized by erythrocytosis, exaggerated plasma catecholamine levels, and impaired vascular function. However, the mechanisms of impaired sympathetic vascular regulation in individuals with CMS are unclear. Purpose: To test the hypothesis that Andeans with CMS (CMS+) would have greater baseline α-adrenergic vasoconstrictor tone, and reduced α-adrenergic responsiveness, compared to healthy Andeans (CMS-).

Methods: We studied CMS+ (n=7) and CMS- (n=9) (CMS: Hb=22.2±1.4 vs. HA: Hb=19.1±1.6; p<0.01) living at ~4350m. We measured forearm blood flow (Doppler ultrasound), mean arterial pressure (MAP, intra-arterial catheter), heart rate (ECG) and calculated changes in forearm vascular conductance (∆FVC) at rest, after local α-adrenoceptor blockade (phentolamine; PHT) and in response to three doses of a direct α1-adrenergic agonist (phenylephrine; PE: 0.0625, 0.125, and 0.250 µg/dl forearm volume/min).

Results: During baseline, there was no difference in FVC between CMS+ and CMS- (FVC: CMS+: 47.6±18.9 vs. CMS-: 40.8±20.8 ml/100mmHg/min; p=0.51). Local α-adrenoceptor blockade increased FVC more in CMS+ compared to CMS- (∆FVC: CMS+: 131.4±57.2 vs. CMS-: 73.5±38.2 ∆ml/100mmHg/min; p=0.03) indicative of greater resting α-adrenergic vasoconstrictor tone. Further, the vasoconstrictor response to the lowest dose of the direct α1-adrenergic agonist PE was significantly attenuated in CMS+ patients (∆FVC: CMS+: -1.5±9.6 vs. CMS-: -7.8±6.7 ml/100mmHg/min; p=0.02). However, there was no difference between groups in response to the medium (∆FVC: CMS+: -18.4±12.1 vs. CMS-: -16.8±6.7 ml/100mmHg/min; p=0.24) and higher (∆FVC: CMS+: -24.5±11.9 vs. CMS-: -19.5±7.5 ∆ml/100mmHg/min; p=0.55) PE doses. Conclusions: CMS+ patients have greater resting α-adrenergic vasoconstrictor tone, and reduced α1-adrenergic responsiveness compared to CMS-. These findings are consistent with increased sympathetic activity and impaired sympathetic regulation of vascular tone. These changes in autonomic vascular regulation may contribute to the progression and pathophysiology of CMS+.

INFLUENCE OF ANGIOTENSIN-II, TYPE-I RECEPTOR BLOCKADE ON CARDIO-RESPIRATORY CONTROL AND HYPOXIA INDUCED SLEEP APNEA

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Introduction: Renin-angiotensin systems local to the carotid body (CB) may contribute to heightened chemosensitivity and central sleep apnea (CSA) induced by hypoxia. In rodents, angiotensin-II increases CB activity which is abolished by losartan, an angiotensin-II type-I receptor (AT1R) antagonist. Objective: The purpose of this study was to examine the influence of losartan on chemosensitization and hypoxia-induced CSA. We hypothesized that losartan would attenuate heightened chemosensitivity following 8-hours of nocturnal hypoxia and reduce CSA severity.

Methods: Fourteen participants were administered losartan (50 mg) or placebo every 8-hours. Chemosensitivity was assessed during hypoxic (P O2=50 mmHg) and hyperoxic (P O2=350 mmHg) hypercapnic (P CO2=3-min each at +2, +4, +6 mmHg above baseline) ventilatory response (HCVR) tests and during 6-20s hypoxic apneas before and after 8-hours of normobaric hypoxia (F O2=0.135). Loop gain was assessed from a ventilatory control model fitted to the ventilatory pattern of CSA measured by polysomnography. Results: Plasma renin activity was higher on
losartan than placebo (0.83±0.12 and 0.27±0.12 ng/l/s; P<0.001) suggesting functional AT1R blockade. Prior to nocturnal hypoxia, losartan did not affect the hyperoxic (losartan: 3.6±1.1, placebo: 4.0±0.6 l/min/mmHg; P>0.05) or hypoxic HCVR (losartan: 5.3±1.4, placebo: 5.7±0.68 l/min/mmHg; P>0.05). Likewise, both the hyperoxic (losartan: 4.2±1.3, placebo: 3.8±1.1 l/min/mmHg; P>0.05) and hypoxic HCVR (losartan: 6.6±1.8, placebo: 6.3±1.5 l/min/mmHg; P>0.05) were not influenced by losartan following hypoxic exposure. The cardiorespiratory responses to apnea followed similar trends. The apnea hypopnea index was similar between placebo and losartan (73±15 vs 75±14 events/hr; P=0.9). Loop gain correlated with CSA severity (r = 0.94, P<0.001) and was similar between treatments (P>0.05). **Conclusions:** In summary, loop gain is strongly associated with CSA severity at high altitude and AT1R activation does not contribute to chemosensitivity or cardiorespiratory responses to apnea before or after acute poikilocapnic hypoxia in young healthy men. **Funding:** NSERC, HSFC, MSFHR & CFI.

**Poster:** 9

**SEX DIFFERENCES IN CARDIAC STRUCTURE AND TOTAL BLOOD VOLUME IN ANDEANS NATIVE TO 4300M**

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**Introduction:** High-altitude populations experience multi-generational cardiovascular adaptations to hypobaric hypoxia that aid convective oxygen delivery. To date, studies in highlander natives have almost exclusively examined males, leaving a major gap in our knowledge of how sex influences long-term cardiovascular adaptations to high-altitude. Recent reports have identified that resting heart rate and hemoglobin concentration ([Hb]) are correlated with reproductive success in highlander females, further highlighting the importance of understanding sex differences in cardiac physiology and oxygen delivery that may ultimately underpin long-term population survival. **Objective:** This investigation therefore compared cardiac structure and function, total blood volume (Vblood), hemoglobin [Hb] and hematocrit ([Hct]) in Andean males and females. **Methods:** Males (n=10, 25.7±4.6yr, 62.1±8.8kg, four with chronic mountain sickness) and females (n=10, 25.2±3.2yr, 54.3±4.1kg, none with chronic mountain sickness) were recruited locally in Cerro de Pasco, Peru (~4330m). Cardiac structure and function were assessed at rest using two-dimensional echocardiography. Vblood was determined with the modified carbon-monoxide rebreathe technique. **Results:** Females had lower [Hb] (17.3±1.5g/dl vs. males:21.3±2.1g/dl, p<0.001), [Hct] (50.7±2.8% vs. males:61.9±6.9%, p<0.001) and Vblood (4.61±1.26L vs. males:6.07±1.65L, p<0.001), though indexed Vblood did not differ between the sexes (females:85±22ml/kg, males:97±14ml/kg). In addition, females had smaller indexed left ventricular (LV) stroke volume (22.8±2.9ml/m² vs. males:25.7±3.4ml/m², p=0.048) and a trend of smaller indexed LV end-diastolic volume (38.5±4.8ml/m³ vs. males:50.0±5.4ml/m³, p=0.065) but there were no sex-differences in ejection fraction. While LVmax index was lower in females (67±10g/m² vs. males:79±8g/m², p=0.008), there were no sex-differences in relative wall thickness. Regression analyses revealed a significant positive relationship between Vblood and LVmax in males (r²=0.62, p=0.01) but not in females. **Conclusions:** For the first time, this work has characterized key sex-related differences in cardiac structure, function and blood volume in high-altitude natives, and provided novel insight to contrasting relationships between cardiac structure and blood volume amongst highlander males and females.
**Poster Session**

**Wednesday Afternoon, 20 February**

**Poster: 10**

**EFFECTS OF HYPOXIC VENTILATORY RESPONSE AND PULMONARY ARTERY RESPONSE TO ARTERIAL OXYGEN SATURATION UNDER HYPOBARIC HYPOXIA**

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**Objective:** This study aimed to investigate the effects of hypoxic ventilatory response (HVR) and pulmonary artery response on arterial oxygen saturation (SpO2) under hypobaric hypoxia. **Methods:** The subjects were healthy adults: 7 men and 1 woman. The HVR of all subjects was measured under normoxia by using the progressive hypoxia method before exposure to hypobaric hypoxia. The pulmonary artery systolic pressure (PASP) of the subjects was measured in hypobaric hypoxic environments at 1400 m (856 hPa), 2400 m (756 hPa), 3400 m (666 hPa), and 4400 m equivalents (585 hPa). For PASP, noninvasive assessment by Doppler echocardiography was used. SpO2 was measured simultaneously using a pulse oximeter. A hypobaric chamber was used to create hypobaric hypoxic environments. **Results:** Because barometric pressure declined (with altitude increase), SpO2 significantly declined, and PASP significantly increased. Significant correlation was found between PASP and SpO2. No significant correlation was found between SpO2 and HVR at any of hypobaric hypoxic environments. Pulmonary hyperinflation findings were confirmed in three subjects, one at an altitude of 3400 m equivalent and two at an altitude of 4400 m equivalent. **Conclusions:** The rise in PASP, accompanying barometric pressure reductions, is gradual until a sudden dramatic increase in altitude from 3,000 m to 4,000 m. We learned that there are large individual subject differences in changes in PASP with respect to changes in barometric pressure. HVR was suggested to be slightly involved in the SpO2 acute response. Therefore, we consider that oxidation levels in the body during acute responses to high-altitude environments are primarily dependent on pulmonary vascular response to hypoxia. **Funding:** This work was supported by JSPS KAKENHI Grant Number JP15K01585.

**Poster: 11**

**ENHANCED DE-NOVO PROLINE BIOSYNTHESIS AS A METABOLIC FEATURE IN THE HYPOXIA-TOLERANT SPALAX**

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**Introduction:** Spalax carmeli (Spalax) is a fossorial, solitary, long-living species inhabiting sealed underground burrows under extreme fluctuations in O2/CO2 levels. Spalax is tolerant to hypoxia, hypercapnia and oxidative stress. **Methods:** Here, the role of Glc and glutamine (Gln) was addressed in Spalax (SFb) and rat (RFb) skin fibroblasts by tracking the fate of 13C-labeled Glc and Gln in normoxia (20% O2) and hypoxia (1% O2) for 24 hours. Spalax fibroblasts were characterized by intensive production of high molecular mass hyaluronic acid, suggesting massive glucose (Glc) redirection to hexosamine pathway, and affecting the formation of glycolysis-derived pyruvate for the tricarboxylic acid cycle (TCA). Contrariwise, Spalax cells express higher levels of HIF-1α under normoxia and hypoxia which proposes a switch of energy production from oxidative to the glycolytic pathway. **Results:** The ratios of labeled Gln over the corresponding isotopologue of proline (Pro); and glutamate (Glu) over Pro in SFb extracts were lower than in RFb, demonstrating significantly greater production of Gln-derived Pro than RFb. Spalax cells forwarded 46% of the consumed Gln to de-novo Pro biosynthesis in normoxia and 64% in hypoxia (6 and 3% for RFb). Moreover, Spalax cells switched the flow of Gln-derived carbons from the direct Gln-α-Ketoglutarate (αKG) axis to Pro biosynthesis in normoxia (the ratio of Glu over αKG was 7 times more in SFb than in RFb). This ratio was, however, lower in hypoxia (1.2). **Conclusion:** This data suggests that pronounced proline metabolic axis serves as a part of metabolic adaptation scaffold in Spalax. **Funding:** This work is supported by the Israel Science Foundation (grant # 1935/17).
INDUCTION OF VENTILATORY LONG-TERM FACILITATION IN HUMANS BY HIGH FREQUENCY INTERMITTENT HYPERCAPNIC HYPOXIA

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Introduction: Ventilatory long-term facilitation (vLTF) is a form of respiratory neuroplasticity developed following exposure to intermittent hypoxia. vLTF manifests as an increase in ventilation during normoxic breathing for up to 60-minutes following the removal of intermittent hypoxia. However, vLTF has been inconsistently demonstrated in humans often requiring a background of hypercapnia throughout intermittent hypoxia and recovery period to elicit a response. Objective: The purpose of this study was to (1) determine whether 40-minutes of high frequency intermittent hypercapnic hypoxia (IH) induces vLTF in healthy humans and (2) determine if tonic peripheral chemoreceptor drive is a contributing factor. Methods: In seven men (21 ± 1 years), minute ventilation (V̇I), end-tidal gases (PEtCO2 and PEtO2), oxyhemoglobin saturation (SpO2) and arterial blood pressure (finger plethysmography) were measured throughout baseline, 40-minutes of IH, and 50-minutes of recovery. During baseline and recovery, dynamic end-tidal forcing was used to control end-tidal gases at resting levels and 1-minute bouts of hyperoxia (PEtO2: 368 ± 4 mmHg; mean ± SEM) were administered at 5-minute intervals to assess peripheral chemoreceptor contribution to vLTF. IH involved 1-minute cycles of 40-seconds hypoxia (nadir SpO2: 83 ± 1%) with concomitant hypercapnia (PETO2: +3.3 ± 0.3 mmHg from baseline) followed by 20-seconds of isocapnic euoxia. Results: Compared with baseline, V̇I was increased by +5.6 ± 0.4 l/min (P < 0.05) throughout recovery suggesting vLTF. Hyperoxia did not depress V̇I (P = 0.53) during baseline or recovery. Mean (+5.8 ± 0.4 mmHg, P < 0.05) and diastolic (+6.0 ± 0.4 mmHg, P < 0.05) blood pressure were increased from baseline following IH, but not systolic blood pressure. Conclusions: These results suggest that 40-minutes of intermittent hypercapnic hypoxia is sufficient to induce vLTF and augment blood pressure through a mechanism independent of peripheral chemoreceptor drive in healthy males. Funding: CFI, NSERC & MSFHR.

GLOBAL REACH 2018: HIGH ALTITUDE ACCLIMITIZATION IMPROVES NEURO-VASCULAR FUNCTION

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Introduction: Neurovascular coupling (NVC) is responsible for the close temporal and regional linkage of cerebral blood supply to local cerebral metabolic requirements. Objective: The present study sought to examine the influence of simulated high altitude (SHA) and high altitude acclimatization (HAA) on NVC in seven healthy male lowlanders (aged 28±8 years). Methods: NVC was assessed at three time points: sea level (344m); after 30 minutes of dynamic end-tidal forcing to simulate an equivalent altitude of 4,340m (SHA) and after two weeks acclimatization to the same altitude (HAA, Cerro de Pasco, Peru). Posterior cerebral artery blood velocity (PCAv) was assessed using transcranial Doppler ultrasound during five consecutive trials of 30s of eyes open with standardised visual stimulation (flashing checkerboard), followed by 30s of eyes closed. The NVC response was characterised as the percent peak and average increase (relative to eyes closed) in PCAv during 25s of visual stimulation, averaged across the five trials. Distribution normality was confirmed by Shapiro Wilks W tests and data analysed using a repeated measures ANOVA. Significance was set at P<0.05. Results: SHA attenuated both peak (10 ± 2% vs. 18 ± 4%, P = 0.021) and average percent increases PCAv (3 ± 2% vs. 8 ± 3%, P = 0.015) compared to sea level. Despite matched reductions in arterial oxygen saturation and partial pressures of oxygen and carbon dioxide, HAA increased both peak (25 ± 7% vs. 18 ± 4%, P = 0.016) and average (13 ± 5% vs. 8 ± 3%, P = 0.045) percent increases in PCAv during visual stimulation, when compared to sea level. Conclusions: The differential response of NVC to SHA and HAA (reduction and increase, respectively) may reflect influences of acid base status and nitric oxide availability, considering their differences between conditions.
Introduction: Low-O2 partial pressure results in decreased ATP levels via reduction in oxidative phosphorylation – which is most acutely experienced in organs with high metabolic demand. Zebrafish embryos maintain function and homeostasis under low-O2 by transitioning into a hypometabolic state, which is manifested by an arrest or a delay in development. Remarkably, zebrafish embryos can survive up to 50 hours in this hypometabolic state in complete absence of O2 (anoxia). Currently, the molecular mechanisms that initiate and maintain the hypometabolic state in zebrafish are unknown. A mass-spectrometry study examining metabolites whose levels change in anoxic conditions revealed a significant increase in the concentration of lactate – a molecule which was recently shown to bind to N-myc downstream-regulated gene (NDRG) to promote proliferation in hypoxic cancer cells, suggesting a signaling role of lactate in cellular adaptation to low-O2. Objective: Given these findings, we hypothesize that a lactate mediated signaling via NDRG under low-O2 may be present in zebrafish embryos. Methods/Results: To test whether lactate functions in an NDRG-dependent manner to promote low-O2 tolerance in the zebrafish embryo, we examined in situ and immunofluorescence data of family members of NDRG. In situ and immunofluorescence expression revealed NDRG1 is enriched in the kidney and mucous cells. Next, we tested whether NDRG1 is sensitive to low-O2 using western blot analysis. The analysis revealed stabilization of NDRG1 in anoxia-treated embryos relative to normoxic control embryos. Next, to test the requirement of NDRG1 for low-O2 tolerance, loss of function studies were performed using NDRG1 morpholino and CRISPR mutants. In addition, we will verify lactate binding of NDRG1 under anoxia using an in vitro binding assay for WT and lactate binding site mutant NDRG1 protein. Conclusions: Together, these studies investigate a novel role for lactate as a putative low-O2 proximal signal for NDRG1 that promotes low-O2 tolerance in zebrafish embryos.

THE EFFECT OF PERIOPERATIVE OXYGEN ON OXIDATIVE STRESS AND INFLAMMATION IN SURGICAL PATIENTS: A SYSTEMATIC REVIEW
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Introduction: The fraction of inspired oxygen concentration (FiO2) administered during general anaesthesia in the UK and USA varies widely (<30% to >80% FiO2) but WHO guidelines recommend using 80% FiO2 to reduce surgical site infections (SSIs). However systematic reviews conclude insufficient data exists to support routinely using high FiO2 (>60%) to reduce SSIs, and doing so might increase patient harm through oxidative stress. Objective: We set out to address this uncertainty through systematic review of the available clinical literature. Methods: EMBASE, MEDLINE, and Cochrane databases were searched up to October 2018 for randomised controlled trials (RCTs) quantifying oxidative stress levels in adults undergoing non-cardiac surgery & receiving either high or low FiO2 (>60% vs <40%, or >20% between groups). All results were independently screened for eligibility by two reviewers and references systematically hand-searched. Results: From 17,056 initial results, 118 RCTs were assessed, representing 28,891 patients. Four trials (n=378) reporting on biomarkers of oxidative stress/inflammation were included. One study focussed on maternal and neonatal markers of oxidative stress in elective C-sections (n=44). One reported on serum and pulmonary markers of oxidative stress in low risk surgical patients (n=40), and two manuscripts reported inflammatory mediators during laparoscopic surgery (n=294). Patients receiving low FiO2 demonstrated increased neutrophil elastase, IL-1, IL-6, and CRP, and reduced HLA-DR monocyte antigens in comparison to patients administered high FiO2. High FiO2 was associated with greater lactate, malondialdehyde (MDA), 8-isoprostane and organic hydroperoxide levels; together with reduced antioxidant markers such as superoxide dismutase activity and sulfhydryl expression. In neonatal blood, high FiO2 also led to increased lipid peroxidation markers; 8-isoprostane, MDA and organic hydroperoxides. Summary: Higher perioperative FiO2 values may be associated with more oxidative stress during surgery, but studies specifically looking at biomarkers of oxygenation are currently limited in number and quality. Further research is warranted.
GLOBAL REACH EXPEDITION: NORMAL EXERCISE CAPACITY AND EXERCISE PRESSOR RESPONSE IN MALE ANDEANS WITH CHRONIC MOUNTAIN SICKNESS.

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Introduction: Chronic Mountain Sickness (CMS) is characterized by excessive erythrocytosis. However, the influence greater blood viscosity has on exercise tolerance and the hemodynamic response to exercise is unclear. **Objective:** To evaluate cardiorespiratory fitness, convective oxygen transport and the pressor response to exercise in persons with (CMS+) and without (CMS-) chronic mountain sickness. **Methods:** CMS+ (n=7, Qinghai Score=7±3, Hb=22±2g/dL, Hct=68±5%) and CMS- (n=9, Qinghai Score=2±1, Hb=19±2g/dL Hct=58±5%, all p≤0.05) performed a semi recumbent graded cardiopulmonary exercise test on a cycle ergometer. On a separate day, participants cycled at three metabolic equivalents, and 30% and 60% peak power output (PPO) for five minutes. Arterial pressure (brachial artery catheter), heart rate (ECG), oxygen saturation (forehead oximeter) and arterial pressure of oxygen were measured at each stage. Stroke volume was estimated using the model flow method from the brachial arterial pressure waveform and cardiac output, total peripheral resistance, arterial oxygen content and oxygen dispatch (cardiac output*arterial oxygen content) were calculated. **Results:** Cardiorespiratory fitness was similar between CMS+ and CMS- (28±12 vs 31±6, mL/kg/min, p=0.61). Indeed, despite the higher resting arterial oxygen content (CMS+, 24±1 vs CMS-, 21±1, mL/dL, p=0.001) the increase in oxygen dispatch was similar between groups at all exercise intensities (e.g. 60% PPO CMS+, Δ738±462 vs CMS-, Δ773±396, mL/min, p=0.87). The increase in mean and systolic arterial blood pressure were similar between groups at all exercise intensities (all p≤0.05). However, at 60% PPO, diastolic blood pressure was slightly higher in CMS+ (CMS+, Δ19±5 vs CMS-, Δ13±6, mmHg, p=0.09), alongside an attenuated fall in total peripheral resistance (CMS+, Δ-7±4 vs CMS-, Δ-11±4, mmHg.min /L, p=0.04). **Conclusion:** These results indicate that despite high hematocrits, persons with mild CMS have a normal exercise capacity. Moreover, the exercise pressor response is well maintained despite a slightly augmented peripheral vascular response to higher intensity workloads.

SHERPAS DISPLAY A BLUNTED HYPOXIC VENTILATORY RESPONSE COMPARED TO LOWLANDERS AT AN ALTITUDE OF 5300M

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**Background:** The hypoxic ventilatory response (HVR), i.e. the increase in ventilation (V_e) during acute isocapnic hypoxia expressed relative to the associated decrease in end-tidal PO_2 or arterial O_2 saturation (SaO_2), has been reported to be blunted in some [1] but not all [2] Sherpas relative to lowlanders at altitudes up to 4800m. We aimed to explore this issue in a large cohort at higher altitude. **Methods:** As part of the Xtreme Everest 2 Expedition, native Sherpas and lowlanders performed isocapnic rebreathing tests [3] at baseline altitude (lowlanders/Sherpas in London[75m]/Kathmandu[1300m]) and after an 11-day trek from Lukla (2800m) to Everest Base Camp (EBC 5300m). End-tidal PCO_2 was maintained within 2mmHg of resting levels by appropriate diversion of the exhaled gas stream through a soda-lime scrubber. HVR was estimated as the slope (m) of the V_e-SaO_2 relationship:V_e = -m × SaO_2 + V_e(0),whereV_e(0) is the asymptotic V_e at infinitely high SaO_2.[3] Significance was assumed when p < 0.05 (paired/unpaired t-tests). **Results:** 47 Sherpas (21 female, 25 male; age 28.3 ± 8.5yr) and 27 lowlanders (17 female, 10 male; age 44.1 ± 12.5yr) participated; 5 (4 Sherpa, 1 lowlander) were unable to complete testing at EBC. There was no significant difference between HVR in Sherpas and lowlanders at baseline altitudes (0.57 ± 0.33 vs 0.44 ± 0.26 l/min/% respectively, p = 0.07). At EBC, HVR was significantly higher than baseline in Sherpas and lowlanders (p < 0.0001), but significantly lower in Sherpas than lowlanders (0.89 ± 0.56vs 1.50 ± 0.95 l/min/% respectively, p = 0.0013).
Conclusions: In this large-cohort study, Sherpas displayed a blunted HVR at 5300m compared to lowlanders, in agreement with Milledge and Lahiri [1] but not Hackett et al [2]. The reasons for these discrepant findings are not clear, but we feel confident in ruling out technical factors such as poor maintenance of isocapnia throughout tests.

Poster: 18
EXERCISE PERFORMANCE IN PATIENTS WITH COPD AT HIGH ALTITUDE. RANDOMIZED PLACEBO-CONTROLLED TRIAL EVALUATING EFFECTS OF ACETAZOLAMIDE
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Objective: Acetazolamide is used to prevent altitude-related illness but its effect on exercise performance has been debated. The current randomized, placebo-controlled, double-blind trial investigates effects of preventive treatment with acetazolamide on exercise performance in patients with chronic obstructive pulmonary disease (COPD) ascending to high altitude. Methods: COPD patients, FEV1 ≥40 to <80% predicted, living below 800m, were randomized to acetazolamide (125-0-250mg/day) or placebo, starting 24h before ascent to and while staying at 3100m for 48 hours. Patients performed progressive cycling exercise to exhaustion at 760m, before taking the study drug, and within 4 hours after arrival at 3100m. Ventilation, gas exchange, heart rate and arterial blood gases were measured (www.ClinicalTrials.gov NCT03177837). Results: Of 176 randomized patients, 1 using acetazolamide and 9 using placebo (P<0.001) could not perform exercise because of altitude-related illness. Per protocol analysis revealed: In 53 patients receiving acetazolamide, maximal work rate (Wmax) and oxygen uptake (V'O2max) at 760m and 3100m were 105±40 and 91±40 watts, and 18.0±6.8 and 15.5±6.8 ml/min/kg (P<0.001, both instances). Corresponding Wmax and V'O2max in 50 patients receiving placebo were 107±41 and 97±41 watts, and 18.9±7.0 and 17.2±7.0 ml/min/kg (P<0.001, both instances). Between-group differences (95%CI) in altitude-induced changes (acetazolamide vs. placebo-group) in Wmax were -3 watts (-9 to +3, P=0.305) and in V'O2max -0.8 ml/min/kg (-2.1 to +0.5, P=0.213). At end-exercise, acetazolamide mitigated altitude-induced reductions of PaO2 by 0.8 kPa (0.13 to 1.3, P=0.016), reduced pH by 0.04 (0.02 to 0.06, P<0.001) and reduced serum lactic acid by 1.6 mmol/l (0.8 to 2.4, P<0.001). Conclusions: Lowlanders with moderate to severe COPD travelling to 3100m experienced an altitude-induced reduction in maximal exercise performance by about 10%. Preventive acetazolamide treatment improved hypoxemia at 3100m but did not alter performance. Funding: Swiss National Science Foundation, Lunge Zurich.

Poster: 19
EFFECT OF PREVENTIVE ACETAZOLAMIDE TREATMENT ON VISUO-MOTOR LEARNING PERFORMANCE IN LOWLANDERS WITH COPD STAYING AT HIGH ALTITUDE. RCT.
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Introduction: Hypoxia may impair visuo-motor learning of healthy individuals (Stadelmann, Physiol. Behav. 2015). Objective: The current randomized, placebo-controlled, double-blind trial evaluated whether such impairments occurred in lowlanders with chronic obstructive pulmonary disease (COPD) staying at high altitude and whether this was prevented by acetazolamide treatment. Methods: 46 Patients with COPD, FEV1 ≥40 to <80 %predicted, living <800m, were randomized to acetazolamide (n=23, 125-0-250mg/day) or placebo starting 24h before ascending to and while staying at 3100m for 48h. During 30min Motor Task Manager tests (MTMT), patients had to operate a mouse in order to let a pointer hit moving targets displayed repeatedly at variable positions on a computer screen. After evening practice sessions, the immediate (within 10min) and delayed performance (in the morning after overnight sleep) were quantified by the directional error of pointer vs. target trajectories as indices of visuo-motor memory retrieval.
ClinicalTrials.gov NCT03156231. **Results:** Multivariable regression analyses of data from 23 patients using placebo and 23 using acetazolamide revealed an increase in mean directional error during immediate and post-sleep MTMT at 3100m vs. 760m of 3° (95% confidence interval 2 to 4), both instances. Acetazolamide improved directional errors in immediate MTMT by 3° (95%CI 2 to 4) and post-sleep MTMT by 4° (95%CI 2 to 5), P<0.001, both changes. **Conclusions:** During sojourns at 3100m, lowlanders with moderate to severe COPD experienced impairments in immediate and post-sleep MTMT performance that were significantly mitigated by acetazolamide. The results suggest beneficial effects of preventive acetazolamide treatment on visual-motor learning performance in COPD patients exposed to hypobaric hypoxia. **Funding:** Swiss National Science Foundation, Swiss Lung Foundation, Lunge Zurich.

**Poster: 20**

EFFECT OF PREVENTIVE ACETAZOLAMIDE TREATMENT ON SLEEP-RELATED BREATHING DISTURBANCES IN PATIENTS WITH COPD STAYING AT HIGH ALTITUDE. RANDOMIZED TRIAL.

**Objective:** The current randomized, placebo-controlled, double-blind trial evaluates whether preventive treatment with acetazolamide reduces nocturnal hypoxemia and breathing disturbances in lowlanders with chronic obstructive pulmonary disease (COPD) sleeping at high altitude. **Methods:** 176 COPD patients, median age 58y, FEV1 64%predicted (range ≥40 to <80%predicted), living below 800m, underwent baseline assessments at 760m and were randomized to receive acetazolamide (125-250mg/day) or placebo starting 24 hours before ascending to and while staying at 3100m for 2 nights. Co-primary outcomes were mean nocturnal SpO2 and the oxygen desaturation index (ODI, SpO2 dips >3%) recorded during respiratory sleep studies at 3100m (www.ClinicalTrials.gov NCT03177850). **Results:** Over the course of 2 days at 3100m, 10 patients (12%) randomized to acetazolamide and 43 patients (48%) randomized to placebo (P<0.001 vs. acetazolamide) experienced severe hypoxemia (SpO2 <80% for >30min) requiring oxygen therapy according to predefined rules. In 70 patients receiving acetazolamide, mean±SD SpO2 at 760m and 3100m, night 1, was 91±2 and 86±2%; ODI was 6.0±6.5 and 13.8±14.4/h (P<0.001 vs. 760m, both instances). In 69 patients receiving placebo, SpO2 at 760m and 3100m, night 1, were 91±2 and 84±2%, ODI 5.9±8.4 and 26.3±26.6/h (P<0.001, both instances). Mean differences (95% confidence interval) in altitude-induced changes with acetazolamide vs. placebo were SpO2 +2% (1 to 2, P<0.001), ODI -11.7/h (-16.9 to -6.5, P<0.001). **Conclusion:** In unacclimatized lowlanders with moderate to severe COPD sleeping for 2 nights at 3100m, preventive acetazolamide treatment reduced the incidence of severe nocturnal hypoxemia and altitude-related periodic breathing. **Funding:** Swiss National Science Foundation, Lunge, Zurich.
**Poster: 21**

**EFFECTS OF LIVING AT MODERATE ALTITUDE ON PULMONARY VASCULAR FUNCTION AND EXERCISE CAPACITY IN MICE WITH SICKLE CELL ANEMIA**

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**Introduction:** Exposure to high altitude worsens symptoms and crises in patients with sickle cell disease (SCD). However, it remains unclear if prolonged exposure to low barometric pressures exacerbates SCD etiologies or impairs quality of life. **Objective:** We tested the hypothesis that, relative to wild-type (WT) mice, Berkeley sickle cell mice (BERK-SS) residing at sea level, mild (1609 m) and moderate (2438 m) altitude would have a higher rate of hemolysis, impaired cardiac function, and reduced exercise tolerance and that the level of altitude would worsen these decrements. **Methods:** Following 3 months of altitude exposure, right ventricular systolic pressures (RVSP) were measured (solid-state transducer). In addition, the adaptive balance between pulmonary vascular endothelial nitric oxide synthase and endothelin was assessed in lung tissue to determine differences in pulmonary vascular adaptation and the speed/duration relationship (critical speed, CS) was used to evaluate treadmill exercise tolerance. **Results:** At all altitudes, BERK-SS mice had a significantly lower %Hct and higher total bilirubin and free hemoglobin concentration (P<0.05 for all). RVSPs in BERK-SS were higher than WT at moderate altitude and when compared to BERK-SS at sea level (P<0.05, for both). CS was significantly lower in BERK-SS at mild and moderate altitude (P<0.05). BERK-SS demonstrated exacerbated SCD complications and reduced exercise capacity associated with an increase in altitude. **Conclusion:** These results suggest that exposure to mild and moderate altitude enhances the progression of SCD in BERK-SS mice compared to healthy WT cohorts and BERK-SS mice at sea level and provides crucial information for the clinical counseling of SCD patients. **Funding:** This study was supported by the National Heart, Lung and Blood Institute Grants 1R01HL125642-01A1 (Irwin DC), 1R01HL086680-07 (Nozik-Grayck E), 5P01HL014985-38 (Stenmark KR), and T32-HL007171 (Stenmark KR), Colorado Sickle Cell Treatment and Research Center (Hassell K and Nuss R).

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**Poster: 22**

**SUPPLEMENTAL OXYGEN DOES NOT INFLUENCE SELF-SELECTED WORK RATE AT MODERATE ALTITUDE**

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**Introduction:** It is well known that supplemental oxygen can increase aerobic power output during high-intensity and/or maximal efforts at moderate altitude, yet the effects on self-selected work rate during lower-intensity, submaximal exercise are unknown. **Objective:** To determine if supplemental oxygen given at moderate altitude would increase average power output during exercise performed at self-selected work rates corresponding to rate of perceived exertion (RPE) 9 (very light) and 13 (somewhat hard). **Methods:** Twenty-three subjects (17 males, 6 females) completed one familiarization (fraction of inspired O₂ (FIO₂)=0.209) and two blinded, experimental trials (FIO₂=0.209 and FIO₂=0.267). In each trial, subjects self-regulated their work rate on a cycle ergometer to maintain RPE 9 for 5 min and RPE 13 for 10 min, before performing an incremental step test to exhaustion (25 W/min). Oxygen consumption (VO₂) and SaO₂ via pulse oximetry (SpO₂) were continuously monitored. Subjects were asked to guess the experimental condition after each stage of the protocol. **Results:** Supplemental oxygen increased SpO₂ throughout exercise (~4%; P<0.001) and was associated with greater peak power output (4±4%; P<0.001) and VO₂ (5±10%; P=0.010) during the incremental test, but did not increase average power output selected during exercise at RPE 9 (P=0.235) or 13 (P=0.992). Subjects were unable to perceive the difference in FIO₂ at any stage (P>0.14). **Summary:** Small increases in inspired oxygen concentration at moderate altitude are imperceptible and do not appear to influence selection of submaximal work rates at RPE ≤ 13.
NOVEL DAY OF ASCENT DOSING OF ACETAZOLAMIDE FOR PREVENTION OF ACUTE MOUNTAIN SICKNESS

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Objective: The objective of our study was to evaluate efficacy of acetazolamide started day of ascent for prevention of AMS. Methods: Double blind, randomized, controlled non-inferiority trial of acetazolamide 125mg twice daily, started on the night prior to ascent (TRAD) or on the morning of ascent (NOVEL) to high altitude. Healthy low altitude dwelling adults ascended from 1,240m to 3,810m in the summer of 2018 on White Mountain, California. Primary outcome was AMS incidence (headache and Lake Louise Questionnaire [LLQ] > 3). Results: 104 participants completed the study, with well-matched characteristics (p > 0.09). There were 54 (52%) participants randomized to TRAD and 50 (48%) to NOVEL acetazolamide, with 95 (91%) fully compliant. Intent-to-treat (ITT) analysis showed NOVEL AMS incidence was 9% greater than TRAD, just surpassing predetermined 26% noninferiority margin (48.0% vs. 39.5%, 95% CI: -12% to 30%). Incidence of severe AMS was non-inferior between groups but lower with NOVEL vs TRAD [5(10%) vs 12(22%), 95% CI -28 to 3.6], as were symptom severity [3.1 vs 3.5, 95% CI -0.6 to 1.3], 2018 AMS [19(38%) vs 28(52%), 95% CI -34.7 to 7], and severe 2018 AMS [5(10%) vs 6(12%), 95% CI -17.1 to 11.2]. Combined AMS incidence was 45 (43%, 95% CI 33.7 to 53.3) compared to 2018 AMS criteria of 47 (46%, 95% CI 35.5 to 55.2). All ITT outcomes were similar to compliant groups. Conclusion: Day of ascent acetazolamide did not demonstrate non-inferiority of AMS prevention when compared to traditional dosing by a very small margin. As all secondary outcomes were similar between groups, potential improved convenience and compliance of day-of ascent dosing may support high-risk day of ascent use. Funding: WMS Herbert N. Hultgren Grant, Academy of Wilderness Medicine,® Institute for Altitude Medicine, U.S. Army Research Institute of Environmental Medicine.

A NOVEL TELEMEDICINE PLATFORM FOR TREKKERS AND MOUNTAINEERS IN ALPINE ENVIRONMENTS

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Introduction: ALTIDOC Society, comprising French and Swiss mountain medicine physicians, developed a novel telemedicine platform available to alpine recreationalists and mountain guides. It includes pre-trip teleconsultation and a 24-hour emergency hotline, SOS Mal Aigu des Montagnes (SOS MAM). Dr. Emmanuel Cauchy, lead physician for the platform, tragically died in an avalanche on April 2nd, 2018. This analysis was completed posthumously. Methods: Retrospective analysis of the initial two years of platform use. Data included client satisfaction surveys and locations and altitudes of SOS MAM calls, chief complaints, interventions, and outcomes. Data were analyzed for patterns and potential “saves” (i.e. evacuation avoidance) resulting from the emergency teleconsultation. Results: 81 people completed pre-trip teleconsultations via phone or video. Post-consultation, 49 (60%) updated their expedition medical kits, and clients strongly agreed (8/10, range = 3-10) they were likely to modify high altitude behavior. Pre-trip teleconsultation user satisfaction was 9/10 (range = 5-10), with strong internal consistency (Cronbach alpha = 0.62). There were 66 SOS MAM calls, with Kilimanjaro (37, 56%), Peru (9, 13%), and Nepal (7, 11%) the most common locations, and acute mountain sickness (37, 56%) and medical issues (10, 15%) the most common complaints. Average altitude of calls from these 3 locations was 4,390 m. SOS MAM service was rated 10/10 (range = 7-10), and ALTIDOC physicians 10/10 (range = 7-10). The emergency calls resulted in 41 (62%) saves. Clients scored the platform’s ease of use 7/10 (range = 2-10) and perceived security 8/10 (range = 1-10). Summary: ALTIDOC’s telemedicine platform is a novel mountain medicine resource with high user satisfaction. With a large impact on pre-trip planning, high altitude behavior, and potential saves from evacuation, alpine telemedicine is feasible and worthwhile of further development. Funding: none.
**Poster Session**

**Wednesday Afternoon, 20 February**

Poster: 25  
**THE EFFECTS OF CAFFEINE ON SLEEP AT HIGH ALTITUDE**  
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**Introduction:** Worldwide, 140 million people live above 2,400m. High altitude has been reported to cause decrements in sleep, including reductions in total sleep time, sleep efficiency and REM sleep. In addition, caffeine has disruptive effects on sleep in normoxic conditions so consuming caffeine at altitude could have additional adverse effects. Caffeine has been studied extensively in normoxic conditions, however, to our knowledge, the effects of caffeine on sleep have yet to be examined at high altitude. **Objective:** The aim of the current study was to determine the effects of caffeine on sleep at high altitude.  
**Methods:** A single blind, non-randomized, between-subjects study was performed on 25 participants [six females; 28.6±9.7 years old (mean±SD)] at 4,300m in Nepal. Participants were scheduled to ingest the placebo or caffeine pill 1.5 hours after awakening. To control for withdrawal effects of caffeine, participants that self-reported consuming less than 47 mg of caffeine per day received a placebo while those that consumed more than that received 200 mg of caffeine. Participants refrained from ingesting other drinks and food that contained caffeine and drugs that could affect sleep or the effects of caffeine. A wireless sleep recording device was used to quantify sleep metrics the following night.  
**Results:** Caffeine decreased self-selected total sleep duration (p<0.05), however other sleep metrics associated with sleep quality [sleep onset latency, wakefulness after sleep onset, light sleep, deep sleep and REM] were not significantly different between placebo and caffeine.  
**Conclusions:** Based on these data, when sleep is already disrupted due to hypoxic conditions, caffeine does not have an impact on sleep quality when taken in the morning. However, the total self-selected sleep duration was shorter, which could potentially cause cognitive impairments and other sleep related sequela the following day.

Poster: 26  
**GLOBAL REACH: BRADYCARDIC ARRHYTHMIAS OCCUR DURING APNEA IN LOWLANDERS BUT NOT ANDEANS AT 4300M**  
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**Introduction:** Previously we demonstrated profound bradycardia accompanied by conduction abnormalities during volitional apnea at extreme altitude (5050m) in acclimatized Lowlanders, but not high-altitude Sherpa. **Objective:** Here we sought to investigate whether protection against brady-arrhythmic events is also evident in high-altitude Andeans, with and without Chronic Mountain Sickness (CMS).  
**Methods:** Electrocardiograms (ECG; lead II) were recorded in seventeen locally recruited Andeans (9 healthy, 8 CMS patients; 42 ± 12 years) and Lowlanders (n = 13; 28 ± 7 years) following 4-9 days at 4300m (Cerro de Pasco, Peru). ECG rhythm and heart rate were assessed resting supine and during maximal volitional apnea (performed at functional residual capacity).  
**Results:** Lowlanders and healthy Andeans exhibited similar basal HR (77 ± 18 vs. 69 ± 8 beats/min), while basal HR was lower in CMS patients (62 ± 11 beats/min; P<0.05 versus LL). SpO2 was similar across groups at baseline (82 ± 3 vs. 80 ± 5 vs. 82 ± 1%) and immediately post-apnea (79 ± 4 vs. 78 ± 3 vs. 74 ± 5%). Apnea elicited significant bradycardia (nadir -32 ± 15 beats/min; P<0.01) and conduction abnormalities in 8/13 (61.5%) Lowlanders (n=2 junctional rhythm, n=1 3° atrio-ventricular block, n=5 sinus pause). In contrast, bradycardia was absent during apnea for both healthy Andeans (nadir -6 ± 1 beat/min) and CMS patients (1 ±12 beats/min). Only 2/17 Andeans (1 healthy Andean/1 CMS patient) developed conduction abnormalities (premature atrial beats).  
**Conclusion:** Like Sherpa, volitional apnea has little effect on heart rate or rhythm in native Andeans (including healthy and CMS patients). These data further demonstrate adaptation of cardiac function to hypoxia in permanent high altitude populations. Moreover, we highlight once again the risk of bradycardic arrhythmias for Lowlanders during apnea at altitude.  
**Funding:** NSERC (CS).
GLOBAL REACH: RENAL HEMODYNAMICS, RENAL FUNCTION AND ACID-BASE BALANCE IN LOWLANDERS AND ANDEANS

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Introduction: Hypoxic diuresis is important for acclimatization; however, it is less clear how this is affected by chronic exposure. Objective: We characterized renal function in lowlanders (n=24) at low-altitude (334m; LOW) and after seven-days (ALT7) at 4300m. Responses were compared to Andean highlanders with (n=7), and without (n=14), chronic mountain sickness (CMS+ and CMS-, respectively). Methods: Renal blood flow (vascular ultrasound) was measured in lowlanders and glomerular filtration rate (GFR), urine production and arterial blood gases were measured in all groups. Results: Renal blood flow was decreased at ALT7 compared to LOW (384±162 vs 431±254 mL/min, P<0.05), with an associated decrease in GFR (82±18 vs 104±20 mL/min, p<0.05). This was also associated with a lower urine production at ALT7 compared to LOW (57±40 vs 60±32 mL/hour, p<0.05). Both CMS- (91±17 mL/min) and CMS+ (100±24 mL/min) had GFR comparable to LOW, but both CMS- (69.2±31 mL/hour) and CMS+ (86±35 mL/hour) also had higher urine production compared to ALT7 (p<0.05). PaCO₂ was similar between ALT7 (28.2±2.6 mmHg) and CMS- (29.6±3.8 mmHg) whereas CMS+ had similar PCO₂ to LOW (38.8±3.0 mmHg). Bicarbonate was reduced at ALT7 compared to LOW (19.9±2.0 vs 25.8±1.6 mmol/L, p<0.05), normalizing pH (ALT7, 7.45±0.03 vs LOW, 7.43±0.03). Although bicarbonate was similarly reduced in both CMS+ (21.2±3.0) and CMS- (20.0±2.1 mmol/L) versus LOW (both P<0.05), pH was lower in CMS+ (7.40±0.02; P<0.05 compared to ALT7 and CMS- (7.44±0.03), implying an altered acid-base equilibrium in CMS+. Conclusion: Seven days of high-altitude acclimatization exhibits reduced renal hemodynamics, GFR and urine output in lowlanders, concomitant with normalization of pH. Although all Andeans had similar GFR and urine production to LOW, only CMS- had normal pH. In contrast, CMS+ had elevated PCO₂ and reduced pH, although this was not associated with impaired renal function. Funding: NSERC (CS).

SEX DIFFERENCES IN PEDIATRIC HAPE

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Objective: To explore sex differences in pediatric High Altitude Pulmonary Edema (HAPE). Methods: We performed a retrospective chart review in children who presented to Children’s Hospital Colorado from 2004-2014 with a clinical diagnosis consistent with HAPE and a chest radiograph consistent with non-cardiogenic pulmonary edema. Descriptive statistics were used to describe the demographics, presentations, treatment strategies, and follow-up. Results: From 2004 to 2014, 50 children met criteria for HAPE. Median age at presentation was 10.2 years (range 0.6-19 years). Thirty patients had classic HAPE, 19 patients had re-entry HAPE, and one had high altitude resident pulmonary edema. Most (72%) patients were male. This sex difference was most notable in children older than 11 years of age (p = 0.004) and was driven by children with classic HAPE (p = 0.007) rather than re-entry HAPE (p = 0.25). Conclusions: HAPE appears to be more common in post-pubescent males. Further studies should be done to confirm this sex difference, to determine if female sex hormones are protective against HAPE or male sex hormones are a risk factor for HAPE, and to explore underlying mechanisms to better inform treatment.
ADAPTATION TO HYPOXIA INDUCED PULMONARY HYPERTENSION

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Objective: A human feasibility study testing influences of normobaric hypoxia corresponding to >7,000 m altitude on the heart allowed us to follow the evolution of pulmonary hypertension. Methods: After pre-acclimatization, two healthy mountaineers stayed in a hypoxia chamber, where normobaric hypoxia was achieved by nitrogen dilution starting at 13.5% to a minimum of 8% O2 over three weeks. Afterwards, 8.5% during daytime and 8.8% O2 at night was kept for 14 days. Velocity encoded single-plane phase contrast MRI of the pulmonary artery (PA) and echocardiography were performed 1 month before, during and 1 and 3 months after hypoxia for assessment of right ventricular (RV) function, PA pressure, area and distensibility. Results: Systolic PA pressure (PAPsys) was closely related to decreasing oxygen levels. In subject B PAPsys peaked at 67 mmHg, 48 mmHg higher than baseline. PAPsys decreased steadily to 44 mmHg after two weeks while still at 8.55% oxygen. Peak values occurred with clinical symptoms of acute mountain sickness but without signs of cerebral or pulmonary edema. In subject A peak PAPsys was 44 mmHg and remained stable. RV function was preserved in both subjects. In subject B PA-area showed dilation with a maximum relative change in respect to baseline of 50% and an absolute change of 4.03 cm². PA-distensibility decreased with hypoxia by a maximum of 57%. After 30 hours of reconditioning to normoxia, all values went back to baseline levels in both subjects. Conclusion: In healthy humans, severe hypoxia induces pulmonary hypertension with preserved right ventricular function. Pulmonary hypertension may improve over time in some individuals. The findings attest to the physiological reserve of healthy humans allowing for adaptation to increased pulmonary pressure. Funding: The study was funded by internal funds. FH was supported by the University Hospital of Cologne, 50WB1816.

IMPROVEMENTS IN SLEEP QUALITY AND QUANTITY FOLLOWING ALTITUDE ACCLIMATIZATION ARE RETAINED AFTER TWELVE DAYS AT SEA LEVEL WITH OR WITHOUT NORMOBARIC HYPOXIA TREATMENT

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Introduction: Lowlanders rapidly ascending to high altitude experience disturbances in sleep quality and quantity that ameliorate with acclimatization. Objective: This study examined whether 12 days of normobaric hypoxia (NH) is efficacious for sustaining acclimatization-induced improvements in sleep quality and quantity after return to sea level (SL). Methods: 16 SL residents (M=11, F=5, 23±6yrs; mean±SE) completed: 1) 4d at SL, 2) 12d of high altitude (HA) acclimatization at 4300m, 3) 12d at SL post HA (Post), and 4) 24-h re-introduction to 4300m (RA) in a hypobaric chamber (460 Torr). During Post, volunteers received NH (n=9, FiO₂=0.122) or Sham (n=7; FiO₂=0.207) for 3 h/d for 9 of 12d. Sleep was measured one night at SL, HA1, HA11 and RA. Mean arterial oxygen saturation (%SpO₂) and desaturation events per hour (DeSHr) (# of > 6% drop in %SpO₂ for ≥ 8 sec) were measured by pulse oximetry. Sleep awakenings per hour (Awak) and total % sleep duration (% Slp) were measured by sleep watch. NH and Sham treatment data were similar and combined. Results: Awak was higher (p<0.05) and % Slp was lower (p<0.05), respectively, at HA1 (13±1; 69±6) compared to SL (6±1; 93±2) but did not differ from SL at HA11 (6±1; 84±6) or RA (10±1; 81±4). Mean sleep %SpO₂ was lower (p<0.05) at HA1 (75±2) compared to SL (96±1), increased (p<0.05) from HA1 to HA11 (84±1) and was retained at RA (81±1). DeSHr increased (p<0.05) from SL (1±2) to HA1 (47±10) and remained elevated at HA11 (48±11) and RA (66±14) showing no acclimatization effect. Summary: These results demonstrate that acclimatization-induced improvements in sleep quality and quantity are retained
Poster Session  Wednesday Afternoon, 20 February

during RA after 12 days at SL with or without NH treatment. Authors’ views; not official U. S. Army or DoD policy.

Poster: 31
ACUTE HYPOXIA IN A SIMULATED HIGH-ALTITUDE AIRDROP SCENARIO DUE TO OXYGEN SYSTEM FAILURE
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Introduction: High-Altitude High Opening (HAHO) is a military operational procedure in which parachute jumps are performed at high altitude requiring supplemental oxygen, putting personnel at risk of acute hypoxia in the event of oxygen equipment failure. Objective: This study was initiated by the Norwegian Army to evaluate potential outcomes during failure of oxygen supply, and to explore physiology during acute severe hypobaric hypoxia. Methods: A simulated HAHO without supplemental oxygen was carried out in a hypobaric chamber with decompression to 30,000 ft (9,144 m) and then recompression to ground level with a decent rate of 1,000 ft/min (305 m/min). Nine subjects were studied. Repeated arterial blood gas samples were drawn throughout the entire hypoxic exposure. Additionally, pulse oximetry, cerebral oximetry, and hemodynamic variables were monitored. Results: Desaturation evolved rapidly and the arterial oxygen tensions are among the lowest ever reported in volunteers during acute hypoxia. PaO₂ decreased from baseline 18.4 (17.3–19.1) kPa, 138.0 (133.5–143.3) mmHg, to a minimum value of 3.3 (2.9 –3.7) kPa, 24.8 (21.6 –27.8) mmHg, after 180 (60 –210) s, [median (range)], N [1] 9. Hyperventilation with ensuing hypocapnia was associated with both increased arterial oxygen saturation and cerebral oximetry values, and potentially improved tolerance to severe hypoxia. One subject had a sharp drop in heart rate and cardiac index and lost consciousness 4 min into the hypoxic exposure. Conclusion: A simulated high-altitude airdrop scenario without supplemental oxygen results in extreme hypoxemia and may result in loss of consciousness in some individuals.

Poster: 32
THE XANTHINE DERIVATIVE AGAINST APOPTOSIS IN HYPOXIC-INDUCED RAT H9C2 CARDIOMYOCYTES
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Introduction: Recent attention has focused on the activation of nitric oxide (NO)-guanosine 3′, 5′cyclic monophosphate (cGMP)-protein kinase G (PKG) signaling pathway triggered by MAPK family, including JNK, ERK, and p38 in the mechanism of cardiac protection during hypoxia-induced cell-death. KMUP-1 (7-[2-[4-(2-chlorobenzene)piperazinyl][ethyl]-1,3-dimethylxanthine), a synthetic xanthine-based nitric oxide enhancer, has been reported to inhibit activity of phosphodiesterase and degradation of cAMP and cGMP. However, the potential effects of KMUP-1 on hypoxia-induced injury of cardiomyocytes are still unclear. We proposed that KMUP-1 inhibits hypoxia-induced apoptosis in H9c2 cells culture through this pathway. Methods: Rat H9c2 cardiomyocytes were cultured in hypoxia condition with different doses of KMUP-1. Cell viability was assessed using MTT assay and apoptotic evaluation was using DNA ladder assay and Hoechst 33342 staining. The level of intracellular calcium was detected using Fura-2-AM staining, and mitochondrial calcium with Rhod 2-AM staining under confocal laser scan microscopic observation. The expressions of endothelium NO synthase (eNOS), soluble guanylate cyclase a1 (sGCα1), PKG; Bcl-2/Bax protein, ERK1/2, p38, and JNK proteins were measured by western blotting assay. Results: KMUP-1 pretreatment improved cell viability and inhibited hypoxia-induced H9c2 cells. Calcium overload both in the intracellular and mitochondrial sites were attenuated by KMUP-1 pretreatment. Moreover, KMUP-1 increased the expressions of eNOS, sGCα1 and PKG protein. While the effects of hypoxia on cell apoptosis were reversed by KMUP-1. The increased level of Bcl2 and decreased level of Bax resulted in increasing Bcl-2/Bax ratio. Summary: KMUP-1 protected rat H9c2 cardiomyocytes from hypoxia-induced apoptosis might via regulating NO-cGMP-
MAPK signaling pathway. Funding: The Ministry of Science and Technology (MOST 106-2320-B-037-010-MY3).

Poster: 33
ACADEMIC MOUNTAIN MEDICINE IN THE UK – INTO THE WILDERNESS OR ‘ITS COMING HOME’?
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Introduction: The UK has a rich history of scientific and academic activity in mountain medicine, but this area is not recognised as an academic entity or a training sub-specialty. Objective: Using the successes and failures of the university accredited UK Masters course in Mountain Medicine, which ran from 2003 to 2018, this paper explores some of the facilitators and barriers to developing academic training in mountain medicine in the UK. Methods: Methods include descriptive analysis of student aspirations from application forms for the course, student demographics and final outcomes; student and academic feedback; and a narrative of selected student stories illustrating where and why academic aspirations have been met, or where the programme has fallen short. Results: In the 15 years of the course, 360 students enrolled, with most completing the basic qualification (Postgraduate Certificate in Mountain Medicine). Only 32 students (9%) went on to study to postgraduate diploma level, and only 9 students (2.5%) submitted a thesis and were awarded a Masters Degree. Reasons cited for this included poor organisation of this part of the course; lack of academic support, including both institutional support, availability of academic supervisors and support from employers; and a low priority being placed on gaining a higher academic qualification by students. Institutionally the course was seen as ‘high risk’ and did not fit with the core priorities of the University. Conclusion: In conclusion, the academic standing of the course could have been developed had more support been given to students, and more success been obtained in developing the Masters part of the course with the academic awarding body. These experiences may be useful to people developing similar initiatives elsewhere.

Poster: 34
SEVERITY OF CENTRAL SLEEP APNEA DOES NOT PROTECT SLEEPING OXYGEN SATURATION DURING ASCENT TO HIGH ALTITUDE
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Introduction: Central sleep apnea (CSA) is universal at high altitude (>3000m), increasing in severity with ascent and with time spent at high altitude. Chronic hypoxia, hypoxic ventilatory response-mediated hypocapnia and increases in chemoreflex gain via ventilatory acclimatization are likely contributors to the development and severity of CSA. CSA is characterized by intermittent periods of apnea and hyperventilation, with associated fluctuations in oxygen saturation. The extent that the relative intermittent hyperventilation occurring between apneas may improve and/or protect oxygen saturation during sleep is unknown. Objective: To characterize the effects of increasing CSA severity on baseline, mean and nadir nighttime oxygen saturation during incremental ascent to 5160m in the Nepal Himalaya. We hypothesized that those with more severe CSA would better protect oxygen saturation during sleep at high altitude. Methods: In 21 native lowlanders, we assessed CSA severity during incremental ascent to high altitude at 1400m, 3440m, 4240m and 5160m over 10 days/nights. Using ApneaLink portable polysomnographs and associated commercially available scoring software, we assessed apnea-hypopnea index (AHI) and night-time oxygen saturation (SpO2) during sleep at each altitude. Results: AHI increased in severity with ascent to 5160m (37.5±32.8; P<0.001). Baseline (79.1±3.4%), mean (73.5±4.2%) and nadir (63.7±6.6%) SpO2 during sleep all decreased significantly with ascent to 5160m (P<0.001). During sleep at 5160m, there was no correlation between AHI and baseline (r=0.31, P=0.26, n=15), mean (r=-0.04, P=0.88, n=15) or nadir (r=-0.15, P=0.6, n=15) SpO2 during the same sleep analysis periods. Conclusions: Our results suggest that the development of CSA does not appear to play an adaptive role in protecting oxygen saturation when sleeping at altitude. Funding: Alberta Government STEP, Alberta Innovates Health Solutions, Natural Sciences and Engineering Research Council of Canada Discovery grant.
**Poster Session**

**Wednesday Afternoon, 20 February**

**Poster: 35**

**BLOOD GLUCOSE HOMEOSTASIS IS UNCHANGED DURING ACUTE NORMOBARIC HYPOXIA**

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**Introduction:** Normal blood glucose concentration (BGC) is critical to support metabolism, particularly in contexts of metabolic stressors (e.g., exercise, high altitude). Data regarding BGC in hypoxia are scant and inconclusive.

**Objective:** We aimed to characterize glucose homeostasis over 80-min following a standardized glucose beverage (300 ml, 75g) during both normoxia (NX) and acute normobaric hypoxia (HX).

**Methods:** On two separate days, 28 healthy participants (21.8±1.6 years; BMI 22.8±2.5 kg/m²; 16 females) were randomly exposed to either NX (fraction of inspired [F\text{I}_\text{O}_2]0.209) or HX (F\text{I}_\text{O}_20.148) in a normobaric hypoxia chamber after an overnight fast. Following a 10-min baseline in NX and HX, participants consumed the glucose beverage within 5-min, and blood glucose and physiological variables were measured intermittently over 80-min. Blood glucose (mM) was measured from finger capillary samples via glucometer and sterile lancets every 10-min. Heart rate, blood pressure, oxygen saturation (Sp\text{O}_2), pressure of end-tidal (P_{ET})CO\text{2} and F\text{I}_\text{O}_2 were measured during the protocol in the chamber.

**Results:** Initial fasted BGC was not different between trials (NX:4.8±0.1 vs. HX:4.9±0.1 mM; P=0.47). Both F\text{I}_\text{O}_2 and Sp\text{O}_2 were lower at baseline in hypoxia (P<0.001), which was maintained over 80-min, confirming the hypoxic intervention. Absolute BGC changes from baseline (i.e., delta) and percent change from baseline over 80-min were not different between oxygen conditions (P>0.77). In addition, mean and absolute peak BGC during the 80-min were also unchanged between conditions (P>0.14). **Conclusion:** We conclude that glucose homeostasis following an acute glucose load is unchanged with exposure to acute normobaric hypoxia in healthy humans.

**Funding:** Natural Sciences and Engineering Research Council of Canada Discovery grant, MRU Faculty of Science and Technology.

**Poster: 36**

**VISUAL FIELD DEFECTS AT HIGH ALTITUDE**

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**Objective:** This study investigated the effect of high altitude exposure on the visual field in healthy subjects. This work is related to the Tübingen High Altitude Ophthalmology (THAO) study.

**Methods:** Visual field testing was performed under standardized conditions in 14 healthy subjects before and during exposure to high altitude at the Capanna Margherita (CM; 4559m, Italy) using an Octopus 900 perimeter (Haag-Streit, Switzerland) after 24 hours of arrival at high altitude. Blue on yellow perimetry was used to detect early visual field defects. For statistical analysis the Wilcoxon signed-rank test was used to determine level of significance.

**Results:** Upon arrival at CM, a significant decrease in mean sensitivity (difference of mean sensitivity for right eye: 2.16±0.45, p=0.008; left eye: 2.53±0.37, p=0.001) and mean defect (difference of mean defect for right eye: -2.15±0.44, p=0.001; left eye: -2.54±0.36, p=0.001) was noted compared to baseline recordings. Measurements of each eye at baseline before and after high altitude exposure showed no statistically significant difference for the visual field.

**Conclusions:** High altitude exposure leads to temporary defects of the visual field. In this study a significant decrease in mean sensitivity and defect was found at high altitude compared to baseline recordings. This is of clinical importance to trekkers and mountaineers exposed to high altitude since disturbance of vision including contrast and the visual field may be a potential risk factor at high altitude.
HEALTHY SUMMIT: A POPULATION HEALTH SURVEY OF SUMMIT COUNTY, COLORADO

Marshall Denkinger1, Warren Johnson1, Benjamin Honigman2 and Robert Roach2

1Centura Health, 2Altitude Research Center, University of Colorado Anschutz Medical Campus.

Summit County, Colorado is unique as a living laboratory where high altitude adaptation can be studied in the context of an area with a modern health care system. As one of the highest counties in the United States, and home to about 30,000 full time residents, Summit County provides a unique opportunity to study the long-term health effects of residents at moderate altitude. Most residents live in Summit County at altitudes between 8,000 and 10,000 feet (2438 to 3048 meters). A population health survey, generally similar to the Framingham Study, will allow our researchers to develop a broad view of the effects of high altitude on health. This study will create a comprehensive database of high-altitude health information on a broad cross section of the permanent resident population of Summit County from which we can develop further research studies about specific health conditions that may be caused or aggravated by high altitude. Healthy Summit is the first major research activity of the newly formed High Altitude Research Center (HARC), a part of Centura Health, St. Anthony Summit Medical Center and the Altitude Research Center, Division of Pulmonary Sciences and Critical Care Medicine, Department of Medicine, University of Colorado Anschutz Medical Center.

GAL3ST1 IS A HIF-RESPONSIVE GENE THAT ENHANCES EVASION OF IMMUNE CELL CYTOTOXICITY BY PROMOTING TUMOUR CELL-PLATELET INTERACTIONS

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Clear cell renal cell carcinoma (ccRCC) is the most common form of renal cancer. It is characterised by inactivation of von Hippel-Lindau tumour suppressor gene, which normally mediates degradation of the alpha subunit of the hypoxia-inducible factor (HIF) transcription factor family. HIF has been implicated in disease progression and the aim of this study was to identify novel HIF target genes that may contribute to ccRCC. GAL3ST1 is a sulfotransferase which catalyzes the sulfonation of the plasma membrane sulfolipid sulfatide. In a tissue microarray, GAL3ST1 was amongst the top 50 upregulated genes in ccRCC tissue relative to matched normal tissue. Expression of GAL3ST1 is increased in primary ccRCC tumours and its upregulation correlates with decreased survival. Our studies reveal that upregulation of GAL3ST1 is a HIF-mediated event that occurs upon VHL loss in kidney cancer cells. Upregulation of GAL3ST1 results in accumulation of its enzymatic product sulfatide. An abundance of sulfatide on the surface of cancer cells may promote cell adhesion. This process is implicated in the metastatic process whereby platelets adhere to cancer cells to assist with cancer cell navigation in the blood stream. In renal cancer cells with GAL3ST1-sulfatide, platelets bind more efficiently than to GAL3ST1-sulfatide negative counterparts. Platelet binding protects ccRCC cells against natural killer cell mediated cytotoxicity, the degree of which is impacted by sulfatide availability. These results suggest GAL3ST1 is a HIF-responsive gene that enhances renal cancer cell-platelet interactions which promotes evasion of immune cell cytotoxicity.

THE MOLECULAR CHARACTERIZATION OF A CRISPR/CAS9 KNOCKOUT LESION OF NDRG1A IN ZEBRAFISH

Lois Jieun Kang, Jong Park, Rachel Brewster

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Zebrafish serve as a crucial model organism well-studied in the scientific community and a system to investigate the mysteries behind anoxia tolerance. For many organisms, the ability to survive without oxygen is a matter of ATP supply and demand management, which relies heavily on oxidative phosphorylation as a key process for ATP production. Without sufficient oxygen, ATP supply does not meet the demands of the cell, ultimately leading to cell death. NDRG1a is a gene suspected to play a crucial role in anoxia tolerance in zebrafish. Under anoxic conditions, NDRG1a protein transports ATP consumer sodium-potassium ATPase from the cell membrane to the cytoplasm, rendering the cell impermeable and triggering metabolic arrest. This investigation attempted to characterize a CRISPR/Cas9 knockout lesion of NDRG1a, produced using three different guide RNA strands targeting exons 2, 3, and 5 of transcript 202. Both RNA and genomic DNA analyses including RT-PCR, PCR amplification, Sanger sequencing, and in situ
hybridization were performed. Given the placement of the g-RNA target sites, it was expected that a several hundred base pair deletion would occur. To the contrary, comparison of PCR amplicons of the mutant lesion to the wild type indicated that the edited region remained relatively similar in size, and Sanger sequencing suggested that a less than 10bp deletion possibly occurred in exon 2. The mechanism by which NDRG1a contributes to anoxia tolerance is not yet well-understood. However, with the support of the U.S. Department of Defense, the findings discussed through this investigation will pave the way for further molecular characterization and functional assaying of NDRG1a.

**Poster: 40**

**UNRAVELING TRANSCRIPTIONAL REGULATION IMPARTED BY N-MYC DOWNSTREAM REGULATED GENE 1A (NDRG1A) UNDER ANOXIA IN ZEBRAFISH**

Timothy Hufford, Nguyet Le, Jong Park, Rachel Brewster

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Among the responses elicited by low oxygen are widespread changes in gene expression, with transcription and translation of most genes being repressed. The N-Myc Downstream Regulated Genes (NDRGs) are known to be transcriptionally upregulated and post-translationally stabilized under low oxygen conditions and have been linked to adaptive responses in hypoxic cancer cells. Our laboratory has demonstrated that NDRG1a is implicated in the physiological adaptation of normal cells to low oxygen, by downregulating ATP-demanding processes in the pronephric duct (embryonic kidney). Ongoing research in the Brewster lab using the zebrafish as a model organism aims to identify candidate genes upregulated under low oxygen that promote cell and organismal survival, establish whether transcriptional outcomes are qualitatively different under hypoxia (3% oxygen) and anoxia (0% oxygen), and determining which hypoxia-responsive genes are regulated in an NDRG1a-dependent manner. To begin addressing these questions we exposed day old wild type to 8 hours of anoxia (0% oxygen) or hypoxia (3% oxygen) and Crispr-Cas9 ndrg1a mutants (ndrg1a -/-) to anoxia and analyzed the transcript levels of candidate genes in these embryos relative to age and stage-matched normoxic controls. We have thus far observed distinct transcriptional responses in wild-type embryos exposed to anoxia and hypoxia. Our study also revealed elevated expression of HIF targets in ndrg1a mutants under prolonged anoxia relative to control groups, and that ndrg3a and ndrg3b are increased in these embryos in an anoxia-independent manner. The responsiveness of ndrg3b to loss of ndrg1a function was quite unexpected given that these genes do not spatially overlap. Overall, these data indicate that NDRG1a participates in the transcriptional response to oxygen deprivation and that its loss alters the expression of NDRG paralogues independently of oxygen levels. This preliminary analysis of long-term anoxic adaptation, funded by NIH, is part of an ongoing whole-transcriptome analysis our lab is undertaking.

**Poster: 41**

**ROLE OF N-MYC DOWNSTREAM REGULATED GENE 1 (NDRG1) IN CELLULAR ARREST UNDER ANOXIA**

Darius Kyle McKoy, Timothy Hufford, Ikenna Okafor, Rachel Brewster

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**Introduction:** Some organisms such as zebrafish have evolved adaptive mechanisms to survive low oxygen by arresting development, thereby preserving ATP. Mediators of this adaptive response may function as oxygen sensors that either directly or indirectly orchestrate the arrest of ATP-demanding processes. Such mediators may lead to novel therapeutic approaches when dealing with hypoxic injury. Literature reporting on human cancer cells revealed that NNRG3, a member of the N-myc Downstream Regulated family of hypoxia-responsive genes, is stabilized by lactate and promotes cellular adaptation to hypoxia (Lee et al., 2015). Ongoing research aims to test the role of NDRG proteins in promoting cell cycle arrest in blastula-stage zebrafish embryo in response to anoxia. Consistent with previous findings (Padilla and Roth, 2010) we have demonstrated that cells in dome stage zebrafish embryos arrest in S/G2 following 4 hours of exposure to anoxia. We hypothesize that NDRG1a and other members of this family are activated under anoxia and promote this response. **Methods:** To test this, we compared mitotic indices in ndrg1a mutants and ndrg1a morpholino-injected embryos raised under anoxia relative to control embryos (WT raised under normoxia and anoxia and NRG1a-depleted embryos raised in normoxia). We predict that if anoxia-activated NDRG1a is essential for cell cycle arrest then mitotic indices will be higher in NDRG1a-depleted embryos exposed to anoxia than in WT embryos raised under similar conditions. **Results:** Preliminary data is consistent with this hypothesis, although the experiment needs to be repeated. **Conclusions:** If we can establish NDRG1a’s role, this novel information could further help decipher a metabolic pathway for cellular arrest. Future studies will entail knocking down additional members of the NDRG family to address potential
BIOINFORMATIC ANALYSIS FOR DYSREGULATED MIRNA IN MYOCARDIUM OF RATS EXPOSED TO HIGH ALTITUDE HYPOBARIC HYPOXIA

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Objectives: To investigate the characteristic expression of miRNAs in the myocardium of rats exposed to high altitude hypobaric hypoxia and to search for candidate biomarkers for the diagnosis of acute mountain sickness. Methods: Male Sprague Dawley rats were randomly assigned to a normoxic group and four hypoxic groups. Rats in the hypoxic groups were bred in a hypobaric hypoxia chamber simulating an altitude of 7000m for 3/7/1/28 days respectively. Cardiac structure and function were detected by echocardiography. Wet/dry ratio, blood gas, and pathological change of heart and cerebrum were observed in each group. Subsequently, miRNAs were extracted from myocardium samples, which were collected from 7day hypoxia and normoxic group rats. Expression of miRNAs was detected by high-throughput next-generation sequencing technology. Sequencing data were analyzed to filter out the differentially expressed miRNAs, and their function was preliminarily investigated by bioinformatics analysis and functional enrichment analysis. Differentially expressed miRNAs were then detected by qRT-PCR. Results: Cardiac systolic and diastolic function of rats decreased most significantly in hypobaric hypoxia 7days. A total of 18 differentially expressed miRNAs were screened out, including 15 upregulated and 3 downregulated. Bioinformatics analysis revealed function of the differentially expressed miRNAs was mainly related to oxidative stress, cell death, and inflammation, which are closely related to acute myocardial injury induced by hypobaric hypoxia. Compared with the normoxic group, the expression of miR-144 in plasma in four hypoxic groups increased significantly (P<0.05). Spearman correlation analysis indicated that the expression of miR-144 in myocardium was negatively correlated with LVEF (r=-0.92, P<0.05) and FS r=-0.88, P<0.05). The expression of miR-144 in plasma was positively correlated with erythrocyte count and hemoglobin (r=0.94, P<0.01). Conclusion: High altitude hypobaric hypoxia may lead to differential expression of miRNA, which provide candidate biomarkers and intervention targets for AMS.

GENE EXPRESSION PROFILING COUPLED WITH CONNECTIVITY MAP DATABASE MINING REVEALS POTENTIAL THERAPEUTIC DRUGS FOR ACUTE MOUNTAIN SICKNESS

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Introduction: Acute mountain sickness (AMS) is a dangerous hypoxic illness that can affect humans who rapidly reach a high altitude above 2500m and may lead to heart injury and sudden death. Objective: The present study aimed to identify potential drugs that could counteract the dysregulated gene function in AMS and could thus be potential novel therapies for AMS. Methods: Male Sprague Dawley rats were randomly assigned to normoxic group or hypobaric hypoxia group (exposed to simulated altitude of 7000m for 7 consecutive days in a hypobaric chamber). Expression profile of mRNA from the rat myocardium was detected through high-throughput next-generation sequencing. Sequencing data were analyzed to filter out the differentially expressed mRNAs, and their function was preliminarily investigated by bioinformatics analysis and function enrichment analysis. Subsequently, Connectivity Map (CMap) was used to query potential drugs for AMS. Results: A total of 457 upregulated genes and 627 downregulated genes related to heart injury induced by hypobaric hypoxia were screened out. Bioinformatics analysis revealed function of the differentially expressed mRNAs was mainly related to inflammation, oxidative stress,
and MAPK signaling pathways. Using the CMap database, five potential protection and treatment AMS drugs were identified that counteract expression levels of many AMS-associated genes. Furthermore, SB203580, one of five potential anti-AMS drugs, showed significantly preventive effects on tissue injury as evidenced by histopathological findings. In addition, SB203580 could alleviate myocardial edema and brain edema in rats exposed to hypobaric hypoxia via regulation of aquaporin (AQP1/AQP4) and miR-144-3p signaling pathway in the heart and cerebrum. **Conclusion:** Our study found 1084 differently expressed genes involved in AMS and five potential drugs to combat it, which might provide insights into AMS pathogenesis and might shed light on potential AMS treatments.
### Thursday, 21 February 2019

<table>
<thead>
<tr>
<th>Time</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0630-0830</td>
<td>Breakfast, Victoria Dining Room</td>
</tr>
<tr>
<td>0730-0830</td>
<td>Registration, Heritage Hall</td>
</tr>
<tr>
<td>0800-0930</td>
<td><strong>Hypoxia: Consequences in Intensive Care Medicine</strong></td>
</tr>
<tr>
<td>0800-0830</td>
<td>Human adaptation to hypoxia in critical illness—Helen McKenna</td>
</tr>
<tr>
<td>0830-0900</td>
<td>The right heart, pulmonary circulation and critical illness—Robert Naeije</td>
</tr>
<tr>
<td>0900-0930</td>
<td>Ventilation strategies in hypoxemic respiratory failure—Colin Grissom</td>
</tr>
<tr>
<td>0930-1000</td>
<td>Refreshment Break, Heritage Hall</td>
</tr>
<tr>
<td>1000-1130</td>
<td><strong>New Lessons from Hypoxic Mammals</strong></td>
</tr>
<tr>
<td>1000-1030</td>
<td>Perinatal adaptations of the llama to hypoxia—Victor Reyes</td>
</tr>
<tr>
<td>1030-1100</td>
<td>Hypoxia and the naked mole rat—Gary Lewin</td>
</tr>
<tr>
<td>1100-1130</td>
<td>The champions of breath hold diving: “omic” analysis of the Antarctic Weddell Seal—Allyson Hindle</td>
</tr>
<tr>
<td>1130-1600</td>
<td>Ski Break</td>
</tr>
<tr>
<td>1130-1330</td>
<td>Lunch, Victoria Dining Room</td>
</tr>
<tr>
<td>1600-1800</td>
<td><strong>Hot Topics in Hypoxia I—Free Communications</strong></td>
</tr>
<tr>
<td>1900-2130</td>
<td>Dinner, Victoria Dining Room</td>
</tr>
<tr>
<td>2030-2130</td>
<td><strong>The Mountain, An Arrow Pointing Up</strong>—Barry Blanchard</td>
</tr>
</tbody>
</table>
The syndrome of critical illness is a complex physiological stressor that can be triggered by diverse pathologies. A key feature is bioenergetic disturbance caused by shifts in the balance of cellular oxygen (and substrate) supply and demand, leading to multiple organ dysfunction. Teleologically, life has evolved to survive in the face of stressors by undergoing a suite of adaptive changes. Adaptation not only comprises alterations in systemic physiology but also involves molecular reprogramming within the cells. The concept of cellular adaptation occurring in critically ill patients is a matter of contention, in part because medical interventions mask underlying physiology, creating the artificial construct of “chronic critical illness”, without which death would be imminent. Thus far, the intensive care armamentarium has not targeted cellular metabolism to preserve a temporary equilibrium, but instead attempts to normalise global oxygen and substrate delivery. Here, we review human (and mammalian) cellular adaptations that have been demonstrated in response to stressors analogous to components of critical illness: including (1) intrauterine low oxygen environment, (2) hypobaric hypoxia of high altitude, (3) flow-limited scenarios, such as ischaemic preconditioning and myocardial hibernation and (4) acute lung injury. Common features include (1) modification of substrate supply through metabolic pathways, (2) changes in mitochondrial electron transfer capacity and (3) altered efficiency of oxidative phosphorylation. The expression of adaptive phenotypes depends upon the interaction of different competing stressors (such as temperature, inflammation, oxygen availability and metabolic demand) as well as their time-course (acute versus chronic). Ultimately, restoration of supply to match normal demand will be required to facilitate healing and function. In the short term, however, innate cellular adaptations to optimise bioenergetic efficiency or induce a hypometabolic state, may facilitate survival in acute critical illness, and have thus far remained untapped by current supportive measures.

Right heart failure (RHF) is a common occurrence in critically ill patients. It is clinically diagnosed by a combination of systemic hypo-perfusion and congestion, and right atrial pressure higher than the pulmonary artery wedge pressure. Bedside echocardiography in RHF shows dilated right heart chambers with increased estimations of pulmonary artery pressure (PAP). RHF occurs after cardiac surgery, in acute or acute-on-chronic respiratory insufficiency, pulmonary embolism and end-stage chronic pulmonary. RHF is a complication of high pressure and high volume mechanical ventilation. Whatever the cause, the RHF in critically ill patients is associated with a decreased survival. RHF is basically caused by a failure of RV systolic function adaptation to increased loading, with RV-PA uncoupling as assessed by a decreased ratio of end-systolic to arterial elastances (Ees/Ea). Thus increased PAP rapidly induces an increased RV contractility (Ees) matching afterload (Ea). Optimal RV-arterial coupling relies on an Ees/Ea ratio of 1.5-2 to ensure flow output at minimal energy expenditure. When the Ees/Ea decreases down to 1 and below, the RV enlarges to preserve flow output (Starling mechanism), at the price of increased filling pressures, negative ventricular interaction and systemic congestion. The most common cause of RHF is PH. Uncoupling of RV systolic function is generally observed with rapid increase of PAP or end-stage severe PH, but also occurs with only mild PH in patients with connective tissue diseases, inflammatory conditions, sepsis and left ventricular failure, all conditions associated with negative inotropic effects. Most RHF patients are not hypoxemic. Acute or chronic hypoxic PH on high altitude (HA) exposure may be a cause of RHF but the
condition is uncommon as human hypoxic vasoconstriction is generally weak and decreased inspired PO2 is not associated with negative inotropic effects. However, rare cases of HARHF have been reported in uncommon patients with severe hypoxic PH.

**0900-0930 Ventilation strategies in hypoxemic respiratory failure—Colin Grissom**

The primary supportive treatment for patients with severe acute hypoxemic respiratory failure in the intensive care unit is positive pressure mechanical ventilation delivered through an endotracheal tube with a mechanical ventilator. This is markedly different than spontaneous ventilation because each breath for the patient is delivered with positive pressure. We have learned over the past decades that although mechanical ventilation for acute hypoxemic respiratory failure can be lifesaving, it can also cause lung injury. This is due to over distention of the lung because of high tidal volumes that lead to volutrauma, which can cause a systemic inflammatory reaction leading to organ injury outside the lung - referred to as biotrauma. Substantial studies clearly indicate that low tidal volume lung protective ventilation targeting a low plateau pressure (distending pressure on the alveoli) prevents over distension of the lung, mitigates volutrauma and biotrauma, and improves survival. The proven therapy of low tidal volume lung protective ventilation is especially important for improving survival in patients with the acute respiratory distress syndrome (ARDS). In patients with acute hypoxemic respiratory failure and severe ARDS, low tidal volume lung protective mechanical ventilation should be combined with a high positive end expiratory pressure (PEEP) in order to recruit collapsed lung, increase functional residual capacity, and mitigate lung injury caused by opening and closing of small airways. The other important target parameter in mechanical ventilation for acute hypoxemic respiratory failure is the level of oxygenation in arterial blood. Targets for optimal oxygenation are less certain. The non-invasive and universally available method for measuring oxygenation in mechanically ventilated patients is the percent saturation of hemoglobin with oxygen measured with a pulse oximeter. Controversy exists about the optimal target for oxygen saturation in patients with acute hypoxemic respiratory failure. Targeting a low oxygen saturation of 88% to 92% raises concerns for inadequate oxygen delivery to the brain and other organs, despite the proven increase in survival using an oxygenation target with a lower threshold of 88% in studies of ARDS patients. Equally concerning is oxygen saturation of greater than 96% causing potential adverse effects on the brain. The optimal strategy for positive pressure mechanical ventilation of patients with ARDS is to use low tidal volumes, limit plateau pressure, increase PEEP to recruit collapsed lung, and avoid over oxygenation.

**0930-1000 Refreshment Break, Heritage Hall**
Thursday, 21 February

1000-1130
New Lessons from Hypoxic Mammals
Chairs: Ben Levine and Tatum Simonson

1000-1030 Perinatal cardiopulmonary adaptations of the llama to hypoxia—Victor Reyes

Most of the mammals have a poor tolerance to hypoxia, and long-term O2 restriction leads to maladaptive responses or organ injury, particularly during the fetal and early postnatal life. Nevertheless, the llama (Lama Glama) has developed very efficient mechanisms to prevent the deleterious effects of acute and chronic perinatal hypoxia. One of the most striking mechanisms is the marked peripheral vasoconstriction of the fetal llama in response to acute hypoxia, that allows an efficient redistribution of cardiac output. This strong peripheral vasoconstrictor tone is highly dependent on a chemoreceptor reflex triggering adrenergic signaling, since α-adrenergic blockade results in cardiovascular collapse and fetal death. Moreover, this enhanced α-adrenergic peripheral vasoconstrictor response persists through the neonatal life, effectively shutting down the blood flow to the carcass during hypoxia. Another relevant adaptation relates to the ability of the llama to protect the fetal brain against hypoxic damage: fetal brain blood flow does not significantly increase, and moreover, brain O2 consumption and temperature selectively decrease during hypoxia, together with a decrease of Na+-K+-ATPase activity and Na+ channels expression, and a lack of seizures or histological evidence of neuron death. This suggests a strong hypometabolic response to preserve fetal brain indemnity during hypoxia. Finally, the newborn llama does not develop pulmonary hypertension in response to perinatal chronic hypoxia. Lowland and highland neonatal llamas have the same pulmonary arterial pressure, and the pulmonary arterial pressor response to acute hypoxia is lower in highland llamas. The ability to prevent hypoxic pulmonary arterial hypertension and contractile hyperreactivity is partly due to increased hemoxygenase- carbon monoxide signaling and decreased Ca2+-sensitization in highland newborn llamas. In summary, increased α-adrenergic peripheral vasoconstrictor response, brain hypometabolism and absence of hypoxic pulmonary hypertension are physiological adaptations of the fetal and neonatal llama to live in low O2 milieu.

1030-1100 Hypoxia and the naked mole rat—Gary Lewin

The African naked mole-rats’ (Heterocephalus glaber) social and subterranean lifestyle in the wild generates a hypoxic niche to which this species is well adapted. Under experimental conditions naked mole-rats tolerate hours of extreme hypoxia and survive 18 minutes of total oxygen deprivation (anoxia) without apparent injury (Park, Reznick et al 2017 Science 356(6335):307-311). We used GS-MS methods to measure changes in metabolites during anoxia and compared metabolic profiles between anoxia exposed mice and naked mole-rats. We noted a large increase in fructose and sucrose levels in naked mole-rat tissues during anoxia. We could show that during anoxia the naked mole-rat switches to anaerobic metabolism fueled by fructose which is actively accumulated and metabolized to lactate in the brain. Global expression of the GLUT5 fructose transporter and high levels of ketohexokinase (KHK) were identified as molecular signatures of fructose metabolism. Fructose-driven glycolytic respiration in naked mole-rat tissues avoids feedback inhibition of glycolysis via phosphofructokinase, supporting viability. It was especially striking that the naked mole-rat heart could be powered just as well by fructose as by glucose. The metabolic rewiring of glycolysis can circumvent the normally lethal effects of oxygen-deprivation a mechanism that could be harnessed to minimize hypoxic damage in human disease.
Thursday, 21 February

1100-1130 The champions of breath hold diving: “omic” analysis of the Antarctic Weddell Seal—Allyson Hindle

Deep-diving Weddell seals tolerate profound hypoxemia during submergence, with vasoconstriction in select tissues creating locally ischemic conditions and exacerbating hypoxic exposure. A clear understanding of cardiovascular regulation and cell-level protective mechanisms that facilitate long duration diving is key to identifying how seals can function as apex predators in their ecosystems. This investigation into “nature’s solutions” and could also facilitate the development of novel treatments for human diseases associated with hypoxia. To investigate the evolutionary adaptations of the Weddell seal, specifically relevant to tolerance of episodic hypoxia, we sequenced and assembled the genome of this species. On the basis of RNA-seq, homology, and ab initio gene prediction, we predicted 23,419 protein-coding loci and 2,649 functional non-coding genes in the Weddell seal. We investigated three signatures of genomewide selection: (1) gene family expansion and contraction, (2) dN/dS ratios and (3) accelerated regions (ARs). Together, these analyses point to evolutionary innovation in the Weddell seal strongly centered around gene regulation (transcription, translation, protein trafficking, and intracellular signaling), with minimal results that illuminate strategies of hypoxia tolerance. However, given the extensive physiological and morphological specializations of this species that were likewise not clearly detected in the genomewide comparative analyses, we tested whether signals of evolutionary selection for hypoxia tolerance could be identified via a targeted analysis. Indeed, we found a significant difference in the p-value distribution of ARs of 84 genes implicated in hypoxia signaling compared to genomewide p-value distributions, suggesting enrichment of seal-specific ARs related to hypoxia. Two genes from this list contained ARs with Weddell seal genomewide significance. Both target genes are key transcription factors, acting as regulators of hypoxia inducible factor (HIF1α). Identified ARs do not overlap with predicted protein-coding sequences for these genes, but each contain at least one known transcription factor binding motif or microRNA binding site.

1130-1600 Ski Break
Thursday, 21 February

1600-1800
Hot Topics in Hypoxia I—Free Communications
Chairs: Danny Levett and Brownie Schoene

1600-1620 Hot Topics in Hypoxia I. TREATMENT WITH 14% OXYGEN IMPROVES JET-LAG SYMPTOMATOLOGY FOLLOWING RAPID EASTWARD TRAVEL ACROSS EIGHT TIME ZONES

Beth A Beidleman1, Mark J Buller1, Stephen R Muza1, Hannah J Gribble2, Reed W Hoyt1, Joanne L Fallowfield2, Simon K Delves2
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Introduction: In mice, when HIF1-α is stimulated by two hours of 14% oxygen (O2) administration, jet lag recovery is accelerated due to circadian clock reset (Adamovich, 2017). Purpose: To determine if similar treatment accelerates jet-lag recovery in humans, 24 male British military personnel were tested in the UK and after a non-stop 15 h flight to Brunei. Methods: Volunteers arrived around 1600 in Brunei on day one (D1). The morning of day two (D2), half of the group (n=12, 29±3 y, 89±10 kg, mean±SD) received 2 h of 14% O2 treatment; the other half (n=12, 29±4 y, 87±6 kg) received placebo (21% O2) by mask. Volunteers were blinded to treatment. Jet-lag symptoms were evaluated in the UK and on days 2-8 in Brunei using the validated nine question Columbia Jet Lag Questionnaire. Pulse arterial oxygen saturation (SpO2) was recorded every 10 min during treatment. Mean SpO2 (%) in the hypoxia group (88±3) was lower (P<0.05) than the placebo group (96 ±1). Results: Total jet-lag score at baseline in the UK and D2 did not differ between the hypoxia (8±4; 9±5) and placebo (8±5; 12±6) group. However, jet lag scores at D3, D4 and D5 were lower in the hypoxia (10±6, 6±5, 5±4) compared to the placebo group (15±5, 11±5, 11±6). Jet lag scores did not differ between groups at days D6, D7 and D8. Over all time points, the hypoxia group jet lag scores (7±3) were lower (p<0.05) than the placebo group (11±3). Jet-lag symptomatology peaked in both groups at D3 (~48 h after arrival). Conclusions: The most severe jet lag symptoms following an 8-hour phase advance occur following 48 h in the new time zone, and 2 h of 14% O2 administration appears to accelerate recovery from jet lag in humans. Authors’ views; not official U. S. Army, DoD or MoD policy . © Crown Copyright.

1620-1640 Hot Topics in Hypoxia I. GLOBAL REACH 2018: ISOVOLUMIC HEMODILUTION INCREASES CEREBROVASCULAR REACTIVITY IN HIGH-ALTITUDE NATIVE ANDEAN MALES WITH EXCESSIVE ERYTHROCYTOSIS

Ryan L Hoiland1, Michael M Tymko1, David B MacLeod2, Chris Gasho3, Joshua C Tremblay4, Connor A Howe1, Tyler Vermeulen1, Geoff B Coombs1, Benjamin Stacey5, Alexander Patrician1, Tony Dawkins6, Mike Stembridge6, Gustavo A Vizcardo-Galindo7, Romulo J Figueroa-Mujica7, Daniela Bermudez7, Antoinette Santoro2, Francisco C Villafruete7, Damian M Bailey5, Philip N Ainslie1
1Centre for Heart, Lung & Vascular Health, Faculty of Health and Social Development, University of British Columbia Okanagan, Kelowna, British Columbia, Canada; 2Human Pharmacology and Physiology Laboratory, Department of Anesthesiology, Duke University, Durham, NC, USA; 3Division of Pulmonary, Critical Care, Hyperbaric and Sleep Medicine, Loma Linda University School of Medicine, Loma Linda, CA, USA; 4Cardiovascular Stress Response Laboratory, School of Kinesiology and Health Studies, Queen’s University, Kingston, Ontario, Canada; 5Neurovascular Research Laboratory, Faculty of Life Sciences and Education, University of South Wales, Wales, UK; 6Cardiff Centre for Exercise and Health, Cardiff Metropolitan University, Cardiff, UK; 7Laboratorio de Fisiologia Comparada, Departamento de Ciencias Biologicas y Fisicoógicas, Facultad de Ciencias y Filosofía, Universidad Peruana Cayetano Heredia, Lima, Peru; ryanleohoiland@gmail.com

Introduction: Chronic mountain sickness is characterized by pathologically high hemoglobin concentration ([Hb]), termed excessive erythrocytosis, EE that leads to impairments in cardiovascular and cerebrovascular function. Objective: We aimed to determine: 1) the influence of EE on cerebral oxygen delivery (CDO2); 2) the impact of EE on cerebrovascular reactivity to hypoxia and hypercapnia; 3) the mechanistic importance of red blood cell mediated nitric oxide signaling in individuals with EE. Methods: In Cerro de Pasco, Peru (~4300 m), six Andean highlander
males with EE (Age=44±19 years, BMI=25±3 Kg/m2, venous [Hb]=22.8±1.9 g/dL) underwent cerebrovascular testing prior to and following isovolumic hemodilution, where 20±5% of whole blood volume was removed and replaced with an equal volume of 5% human serum albumin. End-tidal forcing was utilized to conduct isocapnic hypoxia and isooxic hypercapnia tests, during which cerebrovascular reactivity was assessed using duplex ultrasound. The radial artery was catheterized to monitor blood pressure and collect blood samples. Arterial plasma nitric oxide bioavailability (nitrite + s-nitrosothiols) was assessed using triiodide reductive ozone based chemiluminescence.

**Results:**
Hemodilution reduced [Hb] by 17% (22.0±1.8 to 18.3±1.1 g/dL; P<0.01) and increased resting global cerebral blood flow (gCBF) by 29% (616±80 vs. 793±165 mL/min; P=0.01); CDO2 was unaltered (140±12 vs 145±13 mL/min; P=0.11). Plasma nitric oxide bioavailability was unaltered pre- to post-hemodilution (52.86±22.90 vs. 48.25±11.24 nM; P=0.74). Cerebrovascular reactivity to hypoxia increased by 135% from -8.15±8.48 to -19.16±6.82 [ΔgCBF (mL/min) / ΔCaO2 (mL/dL)] (P=0.04; effect size=1.12). Similarly, albeit not significantly, cerebrovascular reactivity to hypercapnia increased by 131% from 24.94±14.20 to 57.55±30.40 [ΔgCBF (mL/min) / ΔPaCO2 (mmHg)] (P=0.09; effect size=0.87). Both the change in hypoxic reactivity (r2=0.72; P=0.03) and hypercapnic reactivity (r2=0.88; P<0.01) were correlated to initial [Hb] prior to hemodilution.

**Conclusions:** In Andean highlanders with EE, isovolumic hemodilution increases cerebrovascular reactivity, with increases greatest in those presenting with greater EE.

### 1640-1700 Hot Topics in Hypoxia I. ROLE OF N-MYC DOWNSTREAM REGULATED GENE 1 (NDRG1) IN ADAPTATION OF THE KIDNEY TO LOW OXYGEN

**Afia Sika Osei-Ntansah, Jong Park, Rachel Brewster**
University of Maryland, Baltimore County, MD, USA; afa1@umbc.edu

**Introduction:** Oxygen deprivation, which occurs in pathological conditions such as stroke and congenital heart disease results in irreparable cellular damage. However, a number of organisms, including zebrafish, have evolved adaptive mechanisms to cope with low oxygen. Under anoxia (0% oxygen), zebrafish embryos enter a hypometabolic state characterized by reversible developmental arrest that enables them to conserve cellular energy (ATP) and survive for up to 50 hours. Developmental arrest is manifested by the cessation of most ATP-demanding processes. The molecules that sense low oxygen and orchestrate arrest are for the most part unknown, yet knowledge of such signals would be very beneficial for therapeutic purposes.

**Methods/Results:** In an effort to identify molecules that promote arrest, the Brewster laboratory performed metabolic profiling and found that lactate is one of several metabolites that are up-regulated in embryos exposed to anoxia. Lactate has previously been shown to bind to NDRG3 in hypoxic cancer cells and to promote cell survival, thereby identifying lactate/NDRG as a candidate signal for adaptation to low oxygen. We have further found that NDRGs are expressed in tissues with high metabolic demand in the zebrafish embryo. My research project focuses on NDRG1 that is expressed in the embryonic kidney and ionocytes (which maintain ionic homeostasis). Preliminary data indicate that NDRG1 is localized to the cytosol of ionocytes under normoxia and shifts to the cell cortex under anoxia, where it downregulates the ATP-demanding Na-K-ATPase pump. The goal of my project was to determine whether this change in cellular distribution also occurs in the kidney. To address this, I employed co-immunolabeling using NDRG1 and Na-K-ATPase antibodies and confocal imaging for data acquisition.

**Summary:** My data suggests that NDRG1 subcellular localization changes from the cytoplasm to the cell cortex under low oxygen conditions. This indicates a novel response to low oxygen in the kidney.
Thursday, 21 February

1700-1720 Hot Topics in Hypoxia I. SHORT TERM HYPOXIA PROMOTES CHEMOREFLEX MEDIATED BRADYCARDIA BUT NOT ARRHYTHMIA DURING APNEA

Stephen A Busch¹, Sean Van Diepen², Richard Roberts¹, Andrew R Steele¹, Megan P Smorschok¹, Lindsey Berthelsen¹, Craig D Steinback¹
¹Neurovascular Health Lab, Faculty of Kinesiology, Sport, & Recreation, University of Alberta, Canada; ²Faculty of Medicine & Dentistry, Department of Critical Care and Division of Cardiology, University of Alberta, Canada; craig.steinback@ualberta.ca

Objective: We previously demonstrated significant bradycardia and conduction abnormalities associated with voluntary apnea after 7-10 days acclimatization to altitude (i.e. hypoxia); this was reversed with supplemental oxygen. We hypothesized the development of brady-arrhythmia was caused by chemoreflex sensitization related to acclimatization. Thus, we investigated if bradycardia or conduction abnormalities became apparent in response to apnea during short-term hypoxia.

Methods: Electrocardiograms (ECG; lead II) were collected in twenty-two healthy low altitude residents (F = 12; age=25±5yrs) at 671m. ECG rhythm and heart rate were assessed at rest and during maximal volitional end-expiratory apnea performed at functional residual capacity at baseline, and following 20min (HX20min) and 5hrs (HX5hrs) of normobaric poikilocapnic hypoxia (SpO2 ≈80%).

Results: Resting heart rate was elevated at HX20min (78 ± 10 bpm) and HX5hrs (80 ± 12 bpm) compared to normoxic baseline (68 ± 10bpm; both P <0.001). Voluntary apnea elicited a significant bradycardia responses at HX20min (nadir -17± 14bpm; P<0.001) and HX5hrs (nadir -19± 15bpm; P<0.001), but not during normoxia (nadir -4± 13 bpm). There were no differences in the bradycardia responses between HX20min and HX5hrs. During normoxic conditions, conduction abnormalities were noted during apnea within 5 of 22 participants including premature ventricular contraction (n=2), sinus pause (n=1), junctional rhythm (n=1), and atrial foci (n=1). However the incidence of these abnormalities remained unchanged during at HX20min and HX5hrs (n=1 premature ventricular contraction, n=2 premature atrial contraction, n=1 sinus pause).

Summary: Voluntary apnea is associated with bradycardia during hypoxia (but not normoxia) that is not specific to the duration of hypoxia or acclimatization. However, the incidence of conduction abnormalities during apnea was not increased during acute hypoxia and may only become prevalent under longer-term acclimatization to hypoxia (altitude). Funding: NSERC (CS).

1720-1740 Hot Topics in Hypoxia I. LOWER DIFFUSING CAPACITY OF THE LUNGS FOR CARBON MONOXIDE IN WOMEN WITH A PATENT FORAMEN OVALE

Andrew Thomas Lovering¹, Annalisa Schallerer¹, Julia Phipps Kern¹, Tyler S Mangum¹, Henry Cameron Norris¹, Kara Marie Beasley¹, James Thomas Davis²
¹University of Oregon, Eugene, OR, USA; ²Indiana State University, Terre Haute, IN, USA; lovering@uoregon.edu

Introduction: The diffusing capacity of the lungs for carbon monoxide (DLco) test assumes all cardiac output flows through the pulmonary circuit. Right-to-left blood flow across a patent foramen ovale (PFO) bypasses the pulmonary circuit. Shunted red blood cells not exposed to alveolar gas would not bind carbon monoxide with a DLco test. Objective: We hypothesized that subjects with a PFO (PFO+) would have a lower DLco than subjects without a PFO (PFO-). Methods: We retrospectively analyzed data from 102 PFO+ (Ages:18-79; 46 Female) and 136 PFO-subjects (Ages:18-77; 56 Female). DLco was measured using the single breath, breath hold test per ATS/ERS standards. Percent predicted values and z-scores for DLco, alveolar volume (VA) and the rate of uptake of CO from alveolar gas (Kco) were calculated using global lung initiative equations. Using our previously published scoring system we classified PFO+ subjects as having either a large or a small shunt. Results: The PFO- group had a greater DLco (% predicted, z-score) than the PFO+ group. PFO+ women had a DLco z-score and Kco that was less than PFO- women. PFO- and PFO+ men had similar DLco values. Subjects with large PFO shunts had significantly lower DLco z-scores and women with large PFO shunts had significantly lower Kco. Conclusions: The 0.7 z-score difference in DLco between PFO+ and PFO- subjects and 1.1 z-score difference in DLco between PFO+ and PFO- females is physiologically significant. If PFO-shunted blood resulted in a lower DLco, then a lower DLco in PFO+ men should have been measured, however this was not true. Structural differences in the lung between FO+ and PFO- may explain the lower DLco. Funding: AHA, DoD, ATS/ALA and The Eugene and Clarissa Evonuk Memorial Graduate Fellowship in Environmental Physiology.
**Introduction**: High altitude (HA) exposure presents unique challenges that adversely affect human physiology. A number of compensatory responses occur in the body to cope with changed environment. Intensity of changes depends upon the altitude, duration of stay and ethnicity of the individual. **Objective**: The aim of this study was to evaluate haematological changes in two different ethnic groups, Indian and Kyrgyz, during HA exposure at two different altitudes, i.e. 3200m and 4111m. **Methods**: Data were collected at basal (800m) and at HA-Day 3, 7, 14 & 21 in both groups. **Results**: Indians showed higher blood pressure (sys & dia) as compared to Kyrgyz throughout the study. Heart rate was higher in Indians up to day3 at 3200m and day7 at 4111m; thereafter it was almost equal in both groups. Significant (p<0.001) reduction in peripheral oxygen saturation (SpO2) was observed on day3 of HA exposure; thereafter it started recovering almost similarly in both groups. Significant (p<0.001) increase in haemoglobin levels was observed on HA induction in both groups. The increase was observed up to day7 in Kyrgyz and day14 in Indians at 3200m, whereas at 4111m the increase was observed up to day14 in Kyrgyz and day21 in Indians. Similar trend was followed by MCV, MCH and MCHC in both groups. On HA exposure, increase in erythropoietin was greater in Indians as compared to Kyrgyz. Hepcidin, a central regulator of iron, was significantly decreased in both Indians (p<0.001) and Kyrgyz (p<0.001) as compared to basal levels, but decrease was greater in Indian. Significant (p<0.01) decrease in serum iron was observed at day3 in Indians and day7 in Kyrgyz. **Summary**: Results indicate both groups initially increased haemoglobin for acclimatization but in Kyrgyz there was early decrease in haemoglobin levels, though they maintained their SpO2 levels almost similar to Indians. This may be due to ethnical variation between the groups.

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**1900-2130 Dinner, Victoria Dining Room**

**2030-2130 The Mountain, An Arrow Pointing Up**—Barry Blanchard
# Friday, 22 February 2019

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
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<tbody>
<tr>
<td>0630-0830</td>
<td>Breakfast, Victoria Dining Room</td>
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<td>0730-0830</td>
<td>Registration, Heritage Hall</td>
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<td>0800-0930</td>
<td><strong>Pathophysiology of High Altitude Diseases</strong></td>
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<td>0800-0830</td>
<td>The early hours in the pathophysiology of HAPE—Erik R. Swenson</td>
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<td>0830-0900</td>
<td>The early hours in the pathophysiology of acute mountain sickness - fishing in the dark?—Marc M Berger</td>
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<tr>
<td>0900-0930</td>
<td>HACE—its own entity or end-stage AMS?—Justin Lawley</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 II—Free Communications</strong></td>
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<tr>
<td>1130-1600</td>
<td><strong>Ski Break</strong></td>
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<tr>
<td>1130-1330</td>
<td>Lunch, Victoria Dining Room</td>
</tr>
<tr>
<td>1600-1830</td>
<td><strong>Oral 3x3 Poster Session Presentations</strong></td>
</tr>
<tr>
<td>1900-2130</td>
<td>Dinner, Victoria Dining Room</td>
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<td>2030-2130</td>
<td>The Shining Mountains and the Emerald Lake—Zac Robinson</td>
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Clinically evident HAPE is one of severe cyanosis, dyspnea and alveolar edema. This usually occurs within 1-2 days of ascent often with the additional stresses of any exercise and hypoventilation of sleep. The earliest events in evolving HAPE occur much earlier and progress through clinically silent and then minimally recognized problems. The most important of these events involves an exaggerated elevation of PA pressure in response to the ambient hypoxia. Hypoxic pulmonary vasoconstriction (HPV) is a rapid response with several phases. The first phase in both resistance arterioles and venues occurs within 5-10 minutes. This is followed by a second phase that further raises PA pressure by another 100% over the next 6-12 hours. Combined with vasoconstriction and likely an unevenness in the regional strength of HPV, pressures in some microvascular regions with lesser arterial constriction rise to a level that initiates greater filtration of fluid formation. As pressures continue to rise local lymphatic clearance is exceeded and interstitial fluid begins to accumulate. Beyond elevation of transmural pressure gradients there is a dynamic non-injurious relaxation of microvascular and epithelial cell-cell contacts and an increase in transcellular vesicular transport which accelerate leakage. At some point with further pressure elevation, damage occurs with breaks of the barrier and bleeding into the alveolar space; termed capillary stress failure. Earlier before there is fluid accumulation, alveolar hypoxia and hyperventilation-induced hypocapnia reduce the capacity of the alveolar epithelium to reabsorb sodium and water back into the interstitial space. More modest ascent which slows the rate of rise in PA pressure and allow for adaptive remodeling of the microvasculature, drugs which lower PA pressure, and those that can enhance fluid reabsorption will all forestall the deleterious early rise of microvascular pressures and diminished active alveolar fluid reabsorption that precede and underlie the development of HAPE.

Acute mountain sickness (AMS) is a syndrome of unspecific neurological, gastrointestinal, and respiratory symptoms that develop in unacclimatised individuals in response to a recent gain in altitude. Despite decades of research, the pathophysiology of AMS is incompletely understood, and multiple factors (e.g. impaired gas exchange due to interstitial pulmonary edema, lower ventilatory drive in hypoxia, fluid retention, increased metabolism and sympathetic activity, anatomical variations) have been implicated. However, in all of these factors there is a large individual overlap, and statistically significant differences between individuals with and without AMS are usually only obtained in trials with large study groups. This presentation will discuss the hypothesis that the conglomerate of unspecific symptoms (headache, anorexia, nausea, vomiting, fatigue, dizziness, and sleep disturbances), and the lack of a disease-specific biomarker, may reflect different pathophysiological pathways ultimately leading to the clinical picture of AMS. This hypothesis is supported by the inter-individual variation in the time course of AMS severity and prevalence that is observed under field conditions and in experimental studies. While in some individuals AMS symptoms peak within 3-8 hours after arrival at a new altitude, in others AMS develops after 2 or 3 days. This presentation will discuss current pathophysiological concepts that may explain both the different time course of and the variation in AMS symptoms. Some of our recently obtained findings focusing on the early hours of AMS, including results on heart rate variability and hypoxic ventilatory response, will close the lecture.
Acute mountain sickness and high altitude cerebral edema are both neurological syndromes associated with rapid ascent to high altitude. Symptoms of acute mountain sickness include headache, nausea/vomiting, dizziness and fatigue whereas symptoms of HACE are more serious such as altered consciousness, ataxia and papilledema. Both syndromes are neurological in nature, and individuals with HACE commonly report severe headache and previous symptoms of AMS. Thus, there has long been a speculation that HACE is the end-stage of AMS. However, the exact pathological mechanisms of both disorders remains unclear, which makes identifying divergence or a link between both entities difficult. During the development of AMS, it is well established that hypoxia causes profound cerebral vasodilation due to extracranial and intracranial artery dilation, resulting in an elevation in intracranial blood volume. Over the time course of these experiments, an increase in brain water (edema) has rarely been noteworthy, but fluid shifts interpreted from changes in diffusion indices within white matter are observed consistently. Thus, if extracranial or intracranial artery dilation activates the trigeminal vascular system, known as the ‘vascular hypothesis’, to cause high altitude headache, then a shared common pathology between AMS and HACE is unlikely. However, the increase in intracranial blood volume may predispose the brain to a modest elevation or transient fluctuations in intracranial pressure (causing symptoms of AMS) and the initial fluid shifts within white matter may influence the development vasogenic edema. In this situation, a heamo- and hydrodynamic cascade in the early stages of hypoxia could predispose individuals to HACE and support the continuum between both entities. Ultimately, even if AMS and HACE do not represent the two clinical ends of the exact same pathological spectrum, they likely share common pathological processes that ultimately lead to divergent endpoints.
1000-1020 Hot Topics in Hypoxia II

PULMONARY VASCULAR RESPONSES TO INHALED NITRIC OXIDE IN ANDEANS AND LOWLANDERS AT 4330M

Suman B Thapamagar1, Christopher Gasho1, Michael Stembridge2, Aimee Drane3, Michael M Tymko3, Philip N Ainslie3, James D Anholm1
1Loma Linda University, CA, USA; 2Cardiff Metropolitan University, Cardiff, UK; 3Centre for Heart Lung and Vascular Health, University of British Columbia (Okanagan), Canada; sthapamagar@llu.edu

Introduction: Hypoxic pulmonary vasoconstriction (HPV) from acute altitude exposure is fully reversible with oxygen or inhaled nitric oxide (iNO). During acclimatization to high altitude, pulmonary vascular changes make HPV less responsive to oxygen in both lowlanders and highlanders.

Objective: The responsiveness of HPV to iNO is unclear, and this formed the focus of this investigation.

Methods: We investigated 11 non-Andean lowlanders (three females) 32±9 years old (mean±SD) and 22 Andean highlanders (five females) 38±14 years who were lifelong residents at ~4330m in Peru. Lowlanders were studied 2-4 days following rapid ascent to altitude (Early) and after two weeks of acclimatization (Late). Highlanders were tested on one occasion. Participants underwent standard echocardiography while breathing either room air (RA; PiO2 ~85 mmHg), or RA and ~40 ppm iNO in a randomized crossover design. Echocardiograms were analyzed for pulmonary vascular resistance (PVR) and right ventricular systolic pressure (RVSP).

Results: In lowlanders, although iNO resulted in marked reductions in both RVSP (p=0.0001) and PVR (p=0.0007), these responses were blunted (p=0.02 and p=0.007) following two weeks of acclimatization (RVSP: [D -12mmHg (95% CI -8 to -16) Early vs. D -7 (95% CI -1 to -12) Late; PVR: [D -0.50 (95% CI -0.27 to -0.73) Early vs. D -0.20 (95% CI -0.07 to -0.34) Late]. In contrast, iNO had no influence in the Andeans (RVSP D -2 (95% CI +1 to -5, p=0.2); PVR D -0.01 (95% CI +0.11 to -0.15, p=0.8).

Conclusions: In summary, although iNO reduced HPV in unacclimatized lowlanders, this response was attenuated (but not abolished) following two weeks of acclimatization. In contrast, acclimatized Andeans chronically living at 4330m had no reduction in HPV following iNO. These data indicate a differential influence of iNO on the regulation of HPV-mediated vascular tone with adaptation to high altitude.

1020-1040 Hot Topics in Hypoxia II. EFFECT OF OXYGEN THERAPY ON NOCTURNAL BREATHING AND SLEEP IN PATIENTS WITH COPD TRAVELLING TO HIGH ALTITUDE. RCT.

Michael Furian, Lu Tan, Tsogyal D Latshang, Sayaka S Aeschbacher, Fabienne Huber, Deborah Flueck, Mona Lichtblau, Stefanie Ulrich, Elisabeth D Hasler, Philipp M Scheiwiller, Silvia Ulrich, Konrad E Bloch
University Hospital of Zurich, Department of Respiratory Medicine, Sleep Disorders Center, Zurich, Switzerland; michael.furian@usz.ch

Introduction: Patients with chronic obstructive pulmonary disease (COPD) may deteriorate while sleeping at high altitude (Latshang et al. Sleep 2018). Objective: We evaluated whether oxygen therapy prevented severe deoxygenation, sleep and breathing disturbances in lowlanders with COPD sleeping at 2048m. Methods: 32 patients with COPD, mean±SD FEV1 54±13%predicted, living <800m, participated in this randomized, placebo-controlled, crossover trial. Polysomnographies were performed at 490m and during 2 sojourns at 2048m, one with nocturnal oxygen (3L/min via nasal cannula), the other with placebo (ambient air), in randomized order, with a >2-weeks washout-period in-between. Co-primary outcomes were mean nocturnal oxygen saturation (SpO2) and apnea-hypopnea index (AHI). www.ClinicalTrials.gov NCT02150590. Results: During the stay at 2048m or within 24h after descent, 8 (26%) patients using placebo and 1 (4%, P<0.001) using oxygen had adverse events such as severe hypoxemia (SpO2 <75% >30min, n=4), intolerable dyspnea (n=2), COPD exacerbation (n=2), or non-sustained ventricular tachycardia (n=1). Per protocol analysis in 23 patients revealed at 490m SpO2 92±2%, AHI 19.7±13.9/h, sleep efficiency 81±11%. At 2048m (night 1),
patients using placebo had lower SpO2 (86±3%), higher AHI (36.1±27.9/h), and lower sleep efficiency (72±15%) (all P<0.01 vs. 490m). In patients using nocturnal oxygen, mean differences (95%CI) vs. placebo were: SpO2 +10% (9 to 11), AHI -21.7/h (-29.3 to -14.3), and sleep efficiency +7% (2 to 11). Oxygen therapy improved subjective sleep quality (visual analog scale 0-100%, worst to best) by +9% (0 to 17, P<0.05). **Conclusions:** About one quarter of lowlanders with COPD experienced impaired well-being, pronounced hypoxemia, breathing and sleep disturbances at 2048m. Oxygen treatment significantly mitigated or prevented these adverse effects and can therefore be recommended to tourists with moderate to severe COPD sleeping at high altitude. **Funding:** Swiss National Science Foundation, Lunge, Zurich.

**1040-1100 Hot Topics in Hypoxia II. PRESERVED CARDIAC AND CEREBRAL FUNCTION DURING 14 DAYS OF SEVERE NORMOBARIC HYPOXIA (8.5%) - A FEASIBILITY STUDY IN HEALTHY MOUNTAINEERS**

Ulrich Limper1,2, Fabian Hoffmann1,3, Vlad Zaha4, Leonora Zange5,6, Sven Kühn7, Christian Mühl1, Hannes Reuter3, Marc Hein8, Jeanette Schulz-Menger5,6, Hesham Sadek9,10, Mathias Basner11, Benjamin Levine11, Jens Jordan1, Jens Tank1

1Institute of Aerospace Medicine, German Aerospace Center (DLR), Cologne, Germany; 2Department of Anesthesiology and Intensive Care Medicine, Merheim Medical Center, Hospitals of Cologne, University of Witten/Herdecke, Cologne, Germany; 3Department of Internal Medicine III University of Cologne, Germany; 4The University of Texas Southwestern Medical Center, Dallas, TX, USA; 5Working Group on Cardiovascular Magnetic Resonance, Experimental and Clinical Research Center - a joint cooperation between the Charité Medical Faculty and the Max-Delbrück Center for Molecular Medicine, Berlin, Germany; 6Department of Cardiology and Nephrology, HELIOS Hospital Berlin-Buch, Berlin, Germany; 7Center of Aerospace Medicine of the German Air Force, Fürstenfeldbruck, Germany; 8Department of Anesthesiology, Medical Faculty, RWTH Aachen University, Germany; 9Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA; 10Center for Regenerative Science and Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA; 11Division of Cardiology, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA; 12Unit for Experimental Psychiatry/Division of Sleep and Chronobiology, Department of Psychiatry, University of Pennsylvania School of Medicine, PA, USA; ulrich.limper@dlr.de

**Introduction:** In mice with myocardial infarction, two weeks of extreme normobaric hypoxia (7% O2) induced myocardial regeneration, thus, ameliorating cardiac function. **Objective:** We conducted a pilot study to test feasibility and safety of implementing this approach in healthy subjects. **Methods:** The study was conducted in the envihab laboratory at DLR in Cologne. Two healthy professional mountaineers (1 woman 49 yrs., 1 man 56 yrs.) participated. Following 3 weeks of slowly progressive hypoxia acclimatization, we maintained FiO2 around 8.7±0.2% for 2 weeks. We applied magnetic resonance imaging to assess cardiac structure and function and brain tissue morphology before, during, and after hypoxia. We regularly conducted cognitive function testing. **Results:** Left ventricular (-46ml, -50ml) and right ventricular (-44ml, -77ml) end-diastolic volumes decreased during hypoxia compared to baseline in both subjects. End-systolic volumes, remained stable in the left ventricle (+5ml, -7ml) while decreasing in the right ventricle (-15ml, -50ml). During hypoxia, a 20bpm increase in heart rate in both individuals did not compensate for the loss in stroke volume resulting in a small decrease in cardiac output. Left ventricular mass index was lower after hypoxia (-8g/m², -3g/m²). We observed markedly dilated cerebral veins in both subjects and scattered cerebral white matter lesions, yet cognitive function testing remained stable. Both fully recovered within a few weeks in normoxia. **Conclusions:** We conclude that 14 days of normobaric hypoxia between 8 and 9% O2 is feasible in healthy subjects following an individualized acclimatization profile; however, larger studies in healthy subjects are required. Our ultimate goal is to test whether the approach can induce cardiac regeneration in patients after a myocardial infarction.
1100-1120  Hot Topics in Hypoxia II. HAEMOGLOBIN MASS AND CONCENTRATION IN HIGH ALTITUDE SHERPA AND ANDEANS; IMPORTANCE OF PLASMA VOLUME REGULATION AND THE INFLUENCE ON EXERCISE CAPACITY

Michael Stembridge1, Alexandra Williams2, Christopher Gasho3, Francisco Villafuerte4, Rob Shave5, Philip Ainslie5

1Cardiff Metropolitan University, UK; 2University of British Columbia, Canada; 3Loma Linda University, CA, USA; 4Universidad Peruana Cayetano Heredia; 5University of British Columbia Okanagan, Canada; mstembridge@cardiffmet.ac.uk

Introduction: The low haemoglobin concentration in Himalayan vs. Andean high-altitude natives has long been considered a target for natural selection, and it is assumed to be achieved via a blunted erythropoietic response. This is despite previous data in Ethiopian highlanders demonstrating a normal haemoglobin concentration that is achieved via a higher haemoglobin mass and plasma volume. Moreover, haemoglobin concentration is inversely related to exercise capacity, but the importance of haemoglobin mass remains to be determined. Methods: We performed the modified carbon monoxide rebreathing technique in age-matched male lowlanders at sea level (SL, 344 m; n=16), lowlanders at high altitude (HA, 5050 m; n=20), Himalayan Sherpa (5050 m; n=20) and Andean natives (4300 m; n=20). We also explored the relationship between haemoglobin concentration and mass with peak oxygen uptake (VO2 peak). Results: Haemoglobin mass was significantly higher in Sherpa (15.4±3.2 g/kg) and Andeans (18.9±5.4 g/kg) compared to lowlanders at SL (12.0±1.4 g/kg) and HA (12.7±1.5 g/kg). The higher haemoglobin mass was balanced with a larger plasma volume in Sherpa (55.4±13.0 ml/kg) compared to Andeans (43.0±6.7 ml/kg) and lowlanders at SL (47.4±5.6 ml/kg) and HA (44.1±4.4 ml/kg). Consequently, blood volume was larger in Sherpa (99.5±21.8 ml/kg) and Andeans (99.0±18.5 ml/kg) compared to lowlanders at SL (83.1±9.2 ml/kg) and HA (81.5±7.3 ml/kg). We found no significant relationships between VO2 peak and haemoglobin concentrations in any of the four groups (all P>0.5). In contrast, haemoglobin mass was positively related to VO2 peak in lowlanders at SL (r2=0.59, P<0.001) and Sherpa at HA (r2=0.34, P=0.02), but not in acclimatised lowlanders (r2=0.03, P=0.5) or Andean natives (r2=0.01, P=0.8). Conclusions: Collectively, our findings reorientate attention away from haemoglobin concentration and towards a paradigm where a higher haemoglobin mass is a positive adaptation to high altitude, but only when appropriately balanced by plasma volume expansion.

1130-1600  Ski Break
Friday, 22 February

1600-1830
3 x 3 Oral Poster Presentations

Chairs: Beth Beidleman and Max Gassmann

For the abstracts please see The First 18 Abstracts from the Poster Session on Wednesday

All presenters are given these instructions: 3x3 Oral Poster Presentations are six (six) minutes in length, with three (3) minutes for presentation and three (3) minutes for discussion. Don’t try to stuff 10 slides onto three slides by using fancy transitions, multiple layers, etc. The audience will not appreciate you trying to cheat the system. Keep it simple, clear and concise.

1600 3x3-1 TARADE, Daniel, daniel.tarade@mail.utoronto.ca
METAZOAN EVOLUTION OF THE OXYGEN-SENSING PATHWAY INVOLVED CONSERVED DIVERGENCE OF VHL AFFINITY FOR HIF1A AND HIF2A

1606 3x3-2 CARTER, Eric A., ecarter1@interchange.ubc.ca
SILDENAFIL DOES NOT IMPROVE EXERCISE PERFORMANCE IN HYPOXIA – A META-ANALYSIS

1612 3x3-3 TURNER, Rachel, Rachel.Turner@eurac.edu
STAR – THE UTSTEIN STYLE FOR CLINICAL HIGH ALTITUDE RESEARCH

1618 3x3-4 PATRICIAN, mdpatrician@gmail.com
THE EFFECT OF AN EXPIRATORY RESISTANCE MASK WITH DEAD SPACE ON SLEEP, ACUTE MOUNTAIN SICKNESS, COGNITION AND VENTILATORY ACCLIMATIZATION IN NORMOBARIC HYPOXIA

1624 3x3-5 BOULET, Lindsey M., lindseyboulet@gmail.com
CORONARY VASOCONSTRICTION DURING METABOREFLEX AT HIGH ALTITUDE

1630 3x3-6 HANSEN, Alexander B, Alexander.Hansen@uibk.ac.at
GLOBAL REACH EXPEDITION: INCREASED BASAL α-ADRENERGIC VASOCONSTRICTION AND IMPAIRED α-ADRENERGIC RESPONSIVENESS IN ANDEANS WITH CHRONIC MOUNTAIN SICKNESS

1636 3x3-7 BROWN, Courtney V, c.v.brown@live.com
INFLUENCE OF ANGIOTENSIN-II, TYPE-I RECEPTOR BLOCKADE ON CARDIORESPIRATORY CONTROL AND HYPOXIA INDUCED SLEEP APNEA.

1648 3x3-8 WILLIAMS, Alexandra, alex.williams@ubc.ca
SEX DIFFERENCES IN CARDIAC STRUCTURE AND TOTAL BLOOD VOLUME IN ANDEANS NATIVE TO 4300M

1654 3x3-9 MAEGAWA, Taketeru, taketeru@topaz.ocn.ne.jp
EFFECTS OF HYPOXIC VENTILATORY RESPONSE AND PULMONARY ARTERY RESPONSE TO ARTERIAL OXYGEN SATURATION UNDER HYPOBARIC HYPOXIA

1700 Refreshment Break for 30 minutes
Friday, 22 February

1730  3x3-10  MISKEVICH, Dmitry, miskevichd@gmail.com
ENHANCED DE-NOVO PROLINE BIOSYNTHESIS AS A METABOLIC FEATURE IN THE HYPOXIA-TOLERANT SPALAX

1736  3x3-11  VERMEULEN, Tyler D., vermeulen.tyler@gmail.com
INDUCTION OF VENTILATORY LONG-TERM FACILITATION IN HUMANS BY HIGH FREQUENCY INTERMITTENT HYPERCAPNIC HYPOXIA

1742  3x3-12  STACEY, Benjamin, Sbenjamin.stacey@southwales.ac.uk
GLOBAL REACH 2018: HIGH ALTITUDE ACCLIMATIZATION IMPROVES NEUROVASCULAR FUNCTION

1748  3x3-13  PARK, Jong Sung, pjong1@umbc.edu
ROLE OF LACTATE-NDRG1 SIGNALING IN LOW OXYGEN TOLERANCE

1754  3x3-14  CARTER, Eric A., ecarter1@interchange.ubc.ca
SILDENAFIL DOES NOT INCREASE IPAVA RECRUITMENT IN HYPOXIA

1800  3x3-15  OLDMAN, Alex H, alex.oldman@gmail.com
THE EFFECT OF PERIOPERATIVE OXYGEN ON OXIDATIVE STRESS AND INFLAMMATION IN SURGICAL PATIENTS: A SYSTEMATIC REVIEW.

1806  3x3-16  MUGELE, Hendrik, hendrik.mugele@web.de
GLOBAL REACH EXPEDITION: NORMAL EXERCISE CAPACITY AND EXERCISE PRESSOR RESPONSE IN MALE ANDEANS WITH CHRONIC MOUNTAIN SICKNESS.

1812  3x3-17  CUMPSTEY, Andrew F, acumpstey@gmail.com
SHERPAS DISPLAY A BLUNTED HYPOXIC VENTILATORY RESPONSE COMPARED TO LOWLANDERS AT AN ALTITUDE OF 5300M

1818  3x3-18  MAYER, Laura, michael.furian@usz.ch
EXERCISE PERFORMANCE IN PATIENTS WITH COPD AT HIGH ALTITUDE. RANDOMIZED PLACEBO-CONTROLLED TRIAL EVALUATING EFFECTS OF ACETAZOLAMIDE

1900-2130  Dinner, Victoria Dining Room

2030-2130  The Shining Mountain and the Emerals Lake --- Zac Robinson
### Saturday, 11 February 2019

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>0630-0830</td>
<td>Breakfast, Victoria Dining Room</td>
</tr>
<tr>
<td>0730-0830</td>
<td>Registration, Heritage Hall</td>
</tr>
<tr>
<td>0800-0930</td>
<td><strong>Hypoxia and the Brain</strong></td>
</tr>
<tr>
<td>0800-0830</td>
<td>The <em>glymphatic system and its role in cerebral homeostasis</em>—Helene Benveniste</td>
</tr>
<tr>
<td>0830-0900</td>
<td>The <em>blood brain barrier and hypoxia</em>—Jeff Dunn</td>
</tr>
<tr>
<td>0900-0930</td>
<td>Hypoxia and headache—Andrew Charles</td>
</tr>
<tr>
<td>0930-1000</td>
<td>Refreshment Break, Heritage Hall</td>
</tr>
<tr>
<td>1000-1130</td>
<td><strong>Latest Developments in Hypoxia</strong></td>
</tr>
<tr>
<td>1000-1100</td>
<td>Hot Topics in Hypoxia III</td>
</tr>
<tr>
<td>1100-1130</td>
<td>Acclimation to the Hypoxic Tumor Microenvironment—Gregg Semenza</td>
</tr>
<tr>
<td>1130-1600</td>
<td>Ski Break</td>
</tr>
<tr>
<td>1130-1330</td>
<td>Lunch, Victoria Dining Room</td>
</tr>
<tr>
<td>1600-1830</td>
<td><strong>Hot Topics in Mountain Medicine</strong></td>
</tr>
<tr>
<td>1900-2300</td>
<td>Dinner, Awards, and Dance, Victoria Dining Room</td>
</tr>
<tr>
<td></td>
<td>Presentation of Student Award Winners</td>
</tr>
<tr>
<td></td>
<td>Presentation of Reeves Prize in Presentation Excellence</td>
</tr>
</tbody>
</table>
**Saturday, 23 February**

**Hypoxia and the Brain**

**Chairs: Justin Lawley and Jeff Dunn**

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**0800-0830  The glymphatic system and its role in cerebral homeostasis**—Helene Benveniste

The brain is one of the most metabolically active organs in the body. The brain’s high energy demand associated with wakefulness persists during rapid-eye-movement (REM) sleep, and even during non-REM sleep the cerebral O2 consumption is only reduced by 20%. The active bioenergetic state is paralleled by metabolic waste production at a higher rate than in other organs and the lack of lymphatic vasculature in brain parenchyma is therefore a conundrum. A common assumption has been that with the cranium that surrounds and protects the brain; and a tight blood brain barrier restricting solute and large fluid shifts, a lymphatic system is superfluous in the central nervous system (CNS). Cerebrospinal fluid (CSF) flow has long been thought to facilitate CNS tissue detoxification in place of lymphatics. Nonetheless, while CSF production and transport has been studied for decades, the exact processes involved in toxic waste clearance from the brain remain poorly understood. Over the past 5-years, novel data in animals and humans have begun to shed new light on these processes in the form of the “glymphatic system”, a novel brain-wide perivascular transit passageway dedicated to CSF transport and interstitial fluid (ISF) exchange thereby facilitating metabolic waste drainage from the brain. Here we review the key anatomical components and operational drivers of the brain’s glymphatic system with cross-comparison to the lymphatic system present in other body organs. The glymphatic systems’ unique dependence on the state of arousal and functional decline in neurodegenerative states such as cerebral small vessel disease will be discussed. Controversies and gaps in the knowledge of the glymphatic system will also be highlighted, as well as evidence for its existence in the human brain.

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**0830-0900  The blood brain barrier and hypoxia**—Jeff Dunn

The nerves and glia in brain are separated from blood and cerebrospinal fluid by highly regulated barriers comprised of complex multi-cellular structures. In this presentation, I will discuss the impact of hypoxia on the regulation of these barriers. Damage results in edema and often cell death. Abnormal barrier regulation is thought to be a key component of high altitude cerebral edema, and hypoxia is likely a key component of the pathophysiology. Barrier damage also occurs in such diverse conditions as stroke, multiple sclerosis and hydrocephalus. We often think of the blood-brain barrier, for which much is known about the anatomy and physiology. However, we also need to think of the blood-cerebral spinal fluid (or BCSF) barrier. It is the combination of these barriers that regulate the overall movement of water, molecules and cells into the brain (not just the BBB). In the 1950’s, Slobody et. al.1 showed that the rate of radionucleated human serum albumin passage from plasma to CSF was 5-times higher during hypoxic than normoxic conditions in dogs, due to BCSFB disruption. Nathoo et. al.2 reported similar findings by showing that in severe hypobaric (8%) hypoxia, or high dose LPS (1.0 mg/kg) intraperitoneal administration in rats, there was more periventricular leakage of systemically administered contrast material on T1-weighted MRI. This latter paper highlighted the effects of both inflammation and hypoxia. We will discuss the anatomy of the brain barriers and the pathophysiology caused by hypoxia and associated inflammation. 1. Slobody LB, et al. Effect of severe hypoxia on blood-cerebrospinal fluid barrier. The American journal of physiology. 1957;190(2):365-370. 2. Nathoo N, et al. Hypoxia and Inflammation-Induced Disruptions of the Blood-Brain and Blood-Cerebrospinal Fluid Barriers Assessed Using a Novel T1-Based MRI Method. Acta Neurochir Suppl. 2016;121:23-28.
Hypoxia triggers headache, including attacks of migraine with and without aura. Conversely, inhaled oxygen is therapeutic for some types of headache, particularly cluster headache. The mechanisms of these responses remain poorly understood. Animal studies of cortical spreading depolarization (CSD) the brain phenomenon thought to underlie the migraine aura, reveal complex neurovascular changes that may provide some insight into the role of hypoxia in headache. Extreme hypoxia can trigger CSD, and CSD can itself result in local tissue hypoxia related to dramatic and prolonged “neurovascular uncoupling”. I will present multiple video recordings documenting the neurovascular uncoupling caused by CSD. Detailed patient descriptions of migraine aura reveal novel mechanisms of initiation, propagation, and termination of the brain mechanisms underlying migraine aura. I will discuss the potential role of hypoxia in these mechanisms. I will review recent studies regarding the potential role of right to left shunt, including patent foramen ovale, in migraine with aura and its relationship to stroke. Finally, I will review the exciting advances in migraine therapy based upon CGRP as a target, and discuss CGRP as a potential mechanism of hypoxia-induced headache.
Saturday, 23 February

1000-1130
Latest Developments in Hypoxia
Chair: Rob Roach

1000-1100  Hot Topics III

1000-1020  Hot Topics in Hypoxia III. LEAD, CHELATION AND VASCULAR INFLAMMATION IN HYPOXIA

John Schmedtje\textsuperscript{1,2}
\textsuperscript{1}Virginia Circulation Research Center, VA, USA; \textsuperscript{2}Coeurative, Inc., USA; john.schmedtje@roanokeheart.net

\textbf{Introduction}: Lead causes increased accumulation of hypoxia inducible factor HIF-1\textalpha, a transactivator of adaptive responses to hypoxia, and the transactivation factor NF-kB. This effect can be characterized as a pseudohypoxia. Population research on the cardiovascular effects of lead reveals a clear relationship that is inferred to be causal with regard to systemic hypertension and other cardiovascular diseases. Lead also promotes oxidative stress and inflammation, resulting in a reduction of nitric oxide bioavailability, and these mechanisms are believed to play a major role in lead-related endothelial dysfunction. \textbf{Objective}: The Trial to Assess Chelation Therapy (TACT) addressed the concern that chelation use was widespread in the absence of reliable data on safety and efficacy. \textbf{Methods}: The chelation strategy was a combination of up to 40 infusions with intravenous EDTA plus oral multivitamins and multiminerals (OMVM) compared with intravenous and oral placebo over the course of a year in patients with prior myocardial infarction (MI), age 50 or older, otherwise treated with standard evidence-based medical therapy. \textbf{Results}: Chelation led to substantial excretion of lead and a significant reduction in the time to first recurrent cardiovascular event. In the pre-specified subgroup with diabetes the chelation-based strategy reduced the composite primary clinical endpoint (MI, stroke, coronary revascularization, hospitalization for angina, death) by 51\% (HR 0.49, 95\%CI [0.33 0.75]; p<0.001, 5-year NNT 5.5) and total mortality by 43\% (p=0.011, 5-year NNT 12). The Trial to Assess Chelation Therapy 2 (ClinicalTrials.gov Identifier: NCT02733185) is now underway to perform a replication of TACT in patients with diabetes and a prior heart attack. \textbf{Conclusion}: The incidence of major adverse cardiac events associated with hypoxia, such as myocardial infarction, is reduced by the removal of lead from patients that do not manifest overt lead toxicity. This effect is hypothetically linked to a reduction in lead-mediated vascular inflammation and pseudohypoxia.

1020-1040  Hot Topics in Hypoxia III. LACTATE-NDRG1 SIGNALING MEDIATES LOW OXYGEN ADAPTATION IN THE KIDNEY

Jong Park\textsuperscript{1}, Austin Gabel\textsuperscript{1}, Bryanna Canales\textsuperscript{1}, Afia Osei-Ntansah\textsuperscript{1}, Neil Tran\textsuperscript{1}, Ryuji Morizane\textsuperscript{2}, Young-Sam Lee\textsuperscript{3}, Rachel Brewster\textsuperscript{1}
\textsuperscript{1}University of Maryland, Baltimore County, MD, USA; \textsuperscript{2}Harvard Medical School, MA, USA; \textsuperscript{3}Johns Hopkins University, MD, USA; brewster@umbc.edu

\textbf{Introduction}: Hypoxia-tolerant organisms can survive in reduced or absence of oxygen for periods ranging from hours to weeks; however, the underlying mechanisms are not well understood. A prevailing idea is that these organisms sense low oxygen and enter into a hypometabolic state by arresting ATP-demanding processes. To gain insight into such mechanisms we performed metabolic profiling using zebrafish embryos exposed to 1 hour of anoxia (zero oxygen) and found that lactate was one of several metabolites that were significantly up-regulated. A recent study in hypoxic cancer cells revealed that a rise in lactate stabilizes NDRG3, thereby promoting cell survival and proliferation, prompting us to investigate whether lactate-NDRG signaling could also operate under normal physiology to mediate adaptation to low oxygen. In the zebrafish embryo, members of the NDRG family are expressed in ATP-demanding tissues. \textbf{Objective}: We focus here on the role of NDRG1 in kidney and ionocytes. \textbf{Methods/Results}: NDRG1 mutants appear morphologically WT; however, when exposed to prolonged hypoxia followed by a period of re-oxygenation they develop severe pericardial edema, a sign of kidney dysfunction. An important clue about NDRG1’s cellular role came from the observation that NDRG1 expression in kidney cells and ionocytes overlaps with the ATP-demanding Na+-K+ ATPase (NKA). As reported in other anoxia-tolerant organisms, we found that NKA is degraded in zebrafish
embryos exposed to prolonged hypoxia, presumably as a mechanism to preserve ATP. Interestingly, NKA degradation does not occur in NDRG1 mutants. Furthermore, we observed that the subcellular distribution of NDRG1 shifts from the cytosol to the cell cortex under anoxia, where it may interact with NKA. **Conclusions:** Based on these findings, we propose that low oxygen triggers stabilization of NDRG1 in a lactate-dependent manner and its redistribution to the cell periphery, where it signals the degradation of NKA to preserve ATP and promote cell and organismal survival.

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**1020-1040** Hot Topics in Hypoxia III. **CO-CRYSTAL STRUCTURE OF HIF2A-VHL TUMOUR SUPPRESSOR CORE COMPLEX REVEALS A STRUCTURAL BASIS FOR BROAD GENOTYPE-PHENOTYPE CORRELATIONS IN THE EMERGING HIF2A-DRIVEN DISEASE**

Michael Ohh
Department of Laboratory Medicine and Pathobiology, Department of Biochemistry, University of Toronto, Canada; michael.ohh@utoronto.ca

**Introduction:** Mutations in hypoxia-inducible factor (HIF)2α transcription factor have been identified to cause neuroendocrine tumours (class 1 disease) and polycythemia (class 2 disease), leading to the emergence of HIF2α-driven disease. However, the molecular mechanism that underlies genotype-phenotype correlations has remained unclear, and therefore, predicting disease phenotype outcome based solely on genotype has been unreliable. **Methods/Results:** Recently, we solved the structure of HIF2α peptide bound to von Hippel-Lindau tumour suppressor protein (pVHL)-elongin B-elongin C heterotrimeric complex at an atomic resolution of 2.0 Å, which showed a remarkable topographical demarcation of class 1 and 2 mutations affecting residues predicted to differentially impact HIF2α-pVHL interaction interface stability. Notably, class 1 mutations clustered on residues contacting pVHL while class 2 mutations generally localized to a non-contacting ‘kink’ region. Concordantly, class 1 mutations disrupted pVHL binding more adversely than class 2 mutations. These findings suggest that neuroendocrine tumour pathogenesis observed in class 1 disease requires higher HIF2α dose than polycythemia, which appears to only require a mild increase in HIF2α stability as observed with class 2 mutations. **Conclusions:** These biophysical data reveal definitively a structural basis that underlies genotype-phenotype correlations, which can be used to predict de novo HIF2α mutation-driven disease. **Funding:** This work was supported by funds from the Canadian Institutes of Health Research.

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**1100-1130** Acclimation to the Hypoxic Tumor Microenvironment—Gregg Semenza

Topography determines regions of Earth that are not inhabited by humans, with elevation greater than 17,000 feet above sea level resulting in ambient O2 levels of less than 11%, which are not sufficient for long term survival and reproduction. Visitors to Lhasa (12,000 feet; 13% O2) will do well to first acclimate in Xining (7,000 feet; 16% O2). The topography of advanced solid tumors is characterized by a rapid decrease in O2 availability as distance from the nearest blood vessel increases, leading at distances greater than 150 µm to anoxia and cell necrosis. Areas of necrosis are surrounded by cancer cells, which survive despite being subjected to extreme hypoxia. Their hypoxic acclimation endows them with powers that define the lethal cancer phenotype: increased invasive and metastatic properties; cancer stem cell properties; immune evasion/suppression; and resistance to radiation therapy and chemotherapy. Hypoxia-inducible factors (HIFs) activate transcription of hundreds of genes that mediate the acclimation of hypoxic cancer cells. Patients with triple-negative breast cancers (TNBCs), which do not express the estrogen receptor, progesterone receptor or HER2 and are therefore not eligible for targeted therapies, are treated with cytotoxic chemotherapy, which is associated with rapid relapse, metastatic progression, and patient mortality. Exposure of TNBC cells to hypoxia or chemotherapy in vitro or in vivo induces HIF activity leading to the expression of genes encoding proteins that mediate specification of the cancer stem cell and immune evasive phenotypes, which can be blocked by co-administration of a HIF inhibitor, thereby allowing tumor eradication in mouse models of TNBC.
Saturday, 23 February

1600-1830
Hot Topics in Mountain Medicine
Chairs: Linda Keyes and Peter Hackett

1600-1620 HTMM. GLOBAL REACH 2018: BLOOD VISCOSITY CONTRIBUTES TO SHEAR STRESS-ASSOCIATED ENDOTHELIAL DYSFUNCTION IN HIGH ALTITUDE EXCESSIVE ERYTHROCYTOSIS

Joshua C Tremblay¹, Ryan L Hoiland², Connor A Howe², Geoff B Coombs², Gustavo A Vizcardo-Galindo³, Rómulo J Figueroa-Mujica³, Daniela Bermudez³, Travis D Gibbons⁴, Benjamin Stacey⁵, Damian M Bailey⁵, Michael M Tymko², David B MacLeod⁶, Chris Gasho⁷, Francisco C Villafuerte³, Kyra E Pyke¹, Philip N Ainslie²

¹Cardiovascular Stress Response Laboratory, School of Kinesiology and Health Studies, Queen’s University, Kingston, Ontario, Canada; ²Centre for Heart, Lung & Vascular Health, Faculty of Health and Social Development, University of British Columbia – Okanagan, Kelowna, British Columbia, Canada; ³Laboratorio de Fisiología Comparada, Departamento de Ciencias Biológicas y Fisiológicas, Facultad de Ciencias y Filosofía, Universidad Peruana Cayetano Heredia, Lima, Peru; ⁴School of Physical Education, Sport and Exercise Sciences, Division of Sciences, University of Otago, Dunedin, NZ; ⁵Neurovascular Research Laboratory, Faculty of Life Sciences and Education, University of South Wales, Wales, UK; ⁶Human Pharmacology and Physiology Laboratory, Department of Anesthesiology, Duke University Medical Center, Durham, NC, USA; ⁷Division of Pulmonary, Critical Care, Hyperbaric and Sleep Medicine, Loma Linda University School of Medicine, Loma Linda, CA, USA; jtremb01@alumni.uoguelph.ca

Introduction: Excessive erythrocytosis (EE, hemoglobin ≥21 g dl⁻¹ in males) is associated with increased cardiovascular risk in highlander Andeans. Objective: We sought to quantify shear stress and assess endothelial function in male Andeans with [EE(+)] and without [EE(-)] EE. We hypothesized that: 1) EE(+) Andeans would have endothelial dysfunction reflected by impaired flow-mediated dilation (FMD) compared to EE(-) Andeans; and 2) reductions in blood viscosity and hemoglobin would acutely improve FMD.

Methods: Shear stress and endothelial function were assessed in 23 male EE(-) Andeans (age: 40±15 years, hemoglobin: 18.7±1.9 g dl⁻¹ [mean±SD]) and 19 male EE(+) Andeans (age: 43±14 years, hemoglobin: 23.0±1.3 g dl⁻¹) in Cerro de Pasco, Peru (4340m). Shear stress was quantified from Duplex ultrasound measures of shear rate from the brachial artery and viscometer measures of whole blood viscosity. Endothelial function was assessed in the brachial artery via FMD. In a subset of EE(+) participants (n=8), shear stress and FMD were measured before and after isovolemic hemodilution with blood volume replaced with an equal volume of human serum albumin (1063±320mL removed; 17.2±6.6% of total blood volume).

Results: Blood viscosity was 48% higher (P<0.001) and FMD was 31% lower in EE(+) Andeans compared with EE(-) Andeans (P=0.008). Stepwise regression analyses revealed that blood viscosity alone explained 30.3% of the variance in FMD and inclusion of the shear stress stimulus for FMD explained an additional 8.3% (R²=0.385, P<0.001). Isovolemic hemodilution decreased hemoglobin concentration by 14±5% and blood viscosity by 30±10% (both P<0.001) and FMD improved from 2.9±2.2% to 4.1±2.0% (P=0.036); this improvement in FMD persisted after including covariate adjustment for the shear stress stimulus (P=0.022).

Conclusion: Collectively, these findings indicate that the hyperviscosity that accompanies EE contributes to peripheral endothelial dysfunction, thus exposing a potential mechanistic link between EE and increased cardiovascular risk.

Funding: This work was funded by ACSM; WMS; NSERC; Canada Research Chair; Physiological Society.

1620-1640 HTMM. TERRA X CUBE: THE NEXT HI-TECH RESEARCH PLATFORM FOR EXTREME HIGH ALTITUDE CLIMATE SIMULATION

Rachel Turner, Hannes Gatterer, Sandro Malarcida, Anna Vägele, Giacomo Strapazzon, Hermann Brugger
Eurac Research, Institute of Mountain Emergency Medicine, Bolzano, Italy; Rachel.Turner@eurac.edu

Introduction: Field-based scientific investigations in extreme environments represent a major research challenge. Complex combinations of multiple environmental parameters can prove highly difficult to mitigate, thus making it difficult to standardise data collection and manage the logistics necessary to enable detailed assessment of individual response. In an effort to resolve these research concerns and remain reactive to scientific interest in the physiological limitations of human endeavor, institutions worldwide have aimed to develop environmental simulation chambers, as well as accessible research facilities in remote terrestrial habitats. In conjunction with the
ongoing development of next-generation environmental simulation technology and the establishment of dedicated research platforms, interest in investigating specific climate combinations at a high altitude equivalent has fast become an international hot topic. As a result, the design and realisation of the terraXcube research facility, powered by Eurac Research, is a unique example of the latest in technological advancement. A newly emergent EU research infrastructure, the terraXcube is complete with two hypobaric, climate enabled facilities (Large and Small Cube), medical support services and research expertise. The large cube (137 m²), will enable the synchronous control of multiple climatic parameters: barometric pressure (≥ 300mbar), oxygen concentration, temperature (-40°C - +60°C), humidity (10% - 95%), wind (≤ 30m/sec), precipitation (rain and snowfall), as well as light (day and night cycles). In total 15 individuals can be accommodated. Test protocols in the Large Cube test chamber may also include the use of the adjoining hypobaric enabled ambulatory chamber, airlock and toilet. **Objective:** The main objectives of the terraXcube is to enable the controlled, reproducible investigation of both short and long-term exposure to low barometric pressures, specific ascent/descent use cases and potentially invasive or technically complex human physiological assessment under challenging conditions.

**1640-1700 HTMM. EFFECT OF DIETARY NITRATE SUPPLEMENTATION ON MICROVASCULAR PHYSIOLOGY AT 4559M – A RANDOMISED PLACEBO CONTROLLED TRIAL (XTREME ALPS)**

Andrew Cumpstey¹,²,³, Philip Hennis³, Edward Gilbert-Kawai³, Bernadette Fernandez²,⁴, Matthieu Poudevigne², Alexandra Cobb³, Kay Mitchell¹,²,³, Helen Moyses², Helmut Pöhnl⁵, Monty Mythen³, Michael Grocott¹,²,³, Daniel Martin³, Martin Feelisch²,³,⁴, For the Xtreme Alps research group²,³

¹University Hospital Southampton NHS FT, UK; ²University of Southampton, UK; ³Centre for Altitude, Space and Extreme Environment (CASE) Medicine, University College London, UK; ⁴Warwick Medical School, University of Warwick, UK; ⁵AURAPA, Germany;

Contact: acumpstey@gmail.com

**Background:** Native highlanders (e.g. Sherpa) demonstrate remarkable hypoxic tolerance, possibly secondary to higher levels of circulating nitric oxide (NO) and increased microcirculatory blood flow. **Objective:** As part of the Xtreme Alps study (a randomised placebo-controlled trial of dietary nitrate supplementation under field conditions of hypobaric hypoxia at altitude), we investigated whether dietary supplementation with nitrate could improve NO availability and microvascular blood flow in lowlanders. **Methods:** Plasma measurements of nitrate, nitrite and nitroso species were performed together with measurements of sublingual (sidestream dark-field camera) and forearm blood flow (venous occlusion plethysmography) in 28 healthy adult volunteers resident at 4559 m for 1 week; half receiving a beetroot-based high-nitrate supplement and half receiving an identically-tasting low nitrate ‘placebo’. **Results:** Dietary supplementation increased plasma nitrate concentrations 4-fold compared to the placebo group, both at sea level and at high altitude (p < 0.001). Dietary nitrate supplementation also significantly increased both plasma nitrite (p = 0.03) and total nitroso product (p < 0.001) levels both at sea level and at 4559m. However, plasma nitrite concentrations were more than 50% lower at 4559m compared to sea level in both treatment groups. Despite these significant changes, dietary nitrate supplementation had no effect on any measured read-outs of sublingual or forearm blood flow, even when environmental hypoxia was experimentally reversed using supplemental oxygen. **Summary:** Dietary nitrate supplementation does not improve microcirculatory function at 4559m. Whether or not dietary supplementation can improve other measures of performance at altitude remains to be investigated. **Funding:** Friends of University College Hospital NHS Foundation Trust; Smiths Medical Ltd; Deltex Medical Ltd; University of Southampton; MRC; NIHR.
1700-1720 HTMM. PREVENTION OF ALTITUDE-RELATED ILLNESS IN PATIENTS WITH COPD BY ACETAZOLAMIDE. RANDOMIZED, PLACEBO-CONTROLLED TRIAL

Michael Furian1, Aline Buergin1, Philipp M Scheiwiller1, Laura Mayer1, Simon Schneider1, Maamed Mademilov2, Berik Emilov2, Mona Lichtblau1, Bermet Estebesova2, Batyr Osmonov2, Lara Muralt1, Ulan Sheraliev2, Nuriddin H Marazhapov2, Talant M Sooronbaev2, Silvia Ulrich1, Konrad E Bloch1

1University Hospital of Zurich, Department of Respiratory Medicine, Sleep Disorders Center, Zurich, Switzerland; 2National Center for Cardiology and Internal Medicine, Bishkek, Kyrgyz Republic; michael.furian@usz.ch

Introduction: In a recent trial, we found that dexamethasone treatment did not prevent altitude-related illness (ARI) in patients with chronic obstructive pulmonary disease (COPD) (Furian, Chest 2018). Therefore, the current randomized, placebo-controlled, double-blind trial evaluated whether acetazolamide prevented ARI in lowlanders with COPD ascending to high altitude.

Methods: 176 COPD patients, FEV1 ≥40 to <80%predicted, living below 800m, were randomized to acetazolamide (125-0-250mg/day) or placebo starting 24 hours before ascending to and while staying at 3100m for 48 hours. Primary outcome was the incidence of any of the following ARI at 3100m: acute mountain sickness (AMS, Lake Louise score >2 including headache), severe hypoxemia (SpO2 <80%, >30min), or any discomfort requiring medical intervention. Arterial blood gases and other outcomes were also assessed (www.ClinicalTrials.gov NCT03156231).

Results: Of 90 patients (median age 58y, FEV1 64%predicted) randomized to placebo, 64 (71%) experienced ARI; of 86 patients (age 58y, FEV1 64%predicted) randomized to acetazolamide, 35 (41%) experienced ARI, odds ratio 0.28, 95%CI 0.15 to 0.52, P<0.001. Compared to placebo, acetazolamide reduced severe hypoxemia by 77% (incidence 48% vs. 12%, P<0.001) without changing AMS incidence (35% vs. 31%, P=0.579). At 3100m, day 2, acetazolamide decreased PaCO2 by -0.3kPa (-0.1 to -0.5) and increased PaO2 by 0.8kPa (0.5 to 1.1) vs. placebo, P<0.001 both instances. No serious adverse events occurred.

Conclusions: In lowlanders with moderate to severe COPD, staying for 48 hours at 3100m, ARI was common (71% in placebo group). Acetazolamide reduced the incidence of ARI by 42% through prevention of severe hypoxemia while the occurrence of AMS remained unchanged. The results suggest that lowlanders with COPD going to high altitude may benefit from preventive treatment with acetazolamide. Funding: Swiss National Science Foundation, Swiss Lung Foundation, Lung, Zurich.

1720-1740 HTMM. INDIVIDUALS WITH HIGH AFFINITY HEMOGLOBIN HAVE A BLUNTED DECLINE IN VO2MAX IN ACUTE HYPOXIA

Paolo B Dominelli1,2, Chad Wiggins2, Sarah Baker2, John Shepherd2, Shelly Roberts2, Tuhin Roy2, James Hoyer3, Jennifer Oliveira3, Michael Joyner2

1Department of Kinesiology, University of Waterloo, Waterloo ON, Canada; 2Department of Anesthesia & Perioperative Medicine, Mayo Clinic, Rochester MN, USA; 3Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester MN, USA; paolo.dominelli@uwaterloo.ca

Introduction: Current understanding of how hemoglobin affinity influences human exercise responses in acute hypoxia is primarily based on theoretical data. To remedy this, we studied a population with a rare genetic mutation resulting in permanently increased hemoglobin affinity.

Objective: Our objective was to determine if permanently high-affinity hemoglobin (HAH) influenced maximal aerobic capacity (VO2max) in acute hypoxia. We hypothesized those with high-affinity hemoglobin would have an attenuated decrease in VO2max when exercising in acute hypoxia.

Methods: Subjects included those with HAH (n=7, 4 women; 38±4 years; P50=15.9±0.4 mmHg) and healthy controls (n=12, 6 women; 39±3 years; P50=26±0.5 mmHg). Subjects completed one testing day involving a maximal cycle exercise test in normoxia (compressed room-air) and acute hypoxia (15% O2) that were randomized and separated by 1 hr. Temperature corrected arterial blood gases were obtained near the end of each 3 min exercise stage.

Results: Subjects with HAH had marked polycythemia (hemoglobin: 21.2±0.9 vs. 15.9±0.4 mmHg) and hematocrit (65±3 vs. 48±1% for HAH and controls, p<0.05 for both) but were otherwise asymptomatic. VO2max (2.6±0.2 vs. 2.7±0.2 l min-1), minute ventilation (95±6 vs. 98±6 l min-1) and arterial oxygen tension (95±5 vs. 101±4 mmHg) were not different between groups in normoxia; for HAH and controls respectively. The decrease in VO2max during hypoxia was significantly less in the HAH group compared to controls (-7±1 vs. -12±2 %, or 0.18±0.03 vs. 0.34±0.05 l/min, p<0.05 for HAH and controls respectively). During the hypoxia test, despite arterial oxygen tension being similar (55±2 vs. 58±2 mmHg) the control subjects had a significantly greater decrease in oxyhemoglobin saturation (-9.7±0.8
Saturday, 23 February

vs. -4.6±0.5%, for controls and HAH respectively; p<0.05). The change in VO2max from normoxia to hypoxia was significantly related to the change in oxyhemoglobin saturation (r=0.65, p<0.01). **Conclusion:** Our findings suggest that HAH is protective against hypoxia-related decline in maximal exercise capacity. **Funding:** NSERC; NIH-R35.

1740-1800 HTMM. DIFFERENCES BETWEEN ALTITUDE EXPERIENCED AND ALTITUDE NAIÊVE HEALTHY VOLUNTEERS IN MICROCIRCULATORY RESPONSE TO HYPOBARIC HYPOXIA.

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**Objective:** To investigate if the microcirculation phenotype of altitude experienced (AE) individuals differed from altitude naïve (AN) individuals under conditions of sub-acute hypobaric hypoxia. **Methods:** The microcirculation of 6 AE and 6 AN healthy male volunteers aged between 18 and 40 years, matched for level of fitness, was measured in the forearm using Laser Doppler. On Day 1 (D1) participants entered a hypobaric chamber and the pressure was reduced to simulate 2800m altitude exposure. This was further reduced on Day 2 (D2) to simulate 3500m and maintained through Day 3 (D3). On Day 4 (D4) the pressure was increased to baseline (123m). Microcirculation measures were carried out at baseline (D0) and on D2, D3, and D4, using Laser Doppler (Moor Instruments Ltd, UK) and analysed using the manufacturer’s software [Moorsoft]. All participants consumed a diet low in nitrates and nitrates, with no access to caffeine or alcohol in the chamber. Data between groups were compared using a Student t test. One-way ANOVA was used to compare between-day variables within groups. **Results:** There were no differences in baseline values at D0 between AN and AE groups. There were between-day differences in flux and SO2 measurements (D2, D3, D4, vs D0) in the AN group but not in the AE group. D3 and D4 peak post occlusive reactive hyperaemia (PORH) flux (maximum level) was lower than D0 in the AN group but not in the AE group. **Conclusions:** AN individuals exhibited a fall in resting forearm skin blood flow and tissue oxygenation during exposure to hypoxia not observed in AE individuals. There was no effect on dilator capacity in the skin.

1800-1820 HTMM. A Task Force Proposal on Pulmonary Hypertension and Right Heart Failure at High Altitudes. Proposal by Robert Naeije and Urs Scherrer

More than 140 million people worldwide live at high altitude, defined as 2,500 m above sea level or higher. At high altitude, arterial hypoxemia related to decreased barometric pressure leads to a series of physiological responses, including increased pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR). If pronounced, these pulmonary vascular changes may contribute to the increased morbidity and mortality associated with living at high altitude. Accordingly, altitude exposure is traditionally considered as a cause of pulmonary hypertension and right heart failure. In line with this concept, in the expert consensus updated classification of pulmonary hypertension discussed at the 5th World Symposium on Pulmonary Hypertension (WSPH) held in Nice in 2013, altitude is mentioned as a cause of pulmonary hypertension “due to lung diseases and/or hypoxia” (Simonneau et al, JACC 2013;62:D34-D41). The same WSPH confirmed the definition of pulmonary hypertension by an invasive measurement of a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg, with measurements of wedged PAP (PAWP) and calculation of a PVR required to differentiate its pre- and post-capillary categories (Hoeper et al, JACC 2013;62:D42-50). The importance of right ventricular function as main determinant of outcome in patients with pulmonary hypertension was acknowledged and an agreement on a definition of right heart failure was reached, without however definitive cut-off values proposed for invasive (cardiac catheterization) or non-invasive (echocardiography and magnetic resonance imaging) (Vonk Noordegraaf et al, JACC 2013;62:D22-33). European Respiratory Society and European Cardiology society guidelines were recently updated accordingly (Galié et al, Eur Respir J 2015;46:903-75 and Eur Heart J 2016;37;67-119). A 6th WSPH held last year, in 2016, did not alter the classification of pulmonary hypertension or its pathophysiological understanding, but re-defined pulmonary hypertension by mPAP > 20 mmHg combined with a PVR ≥ 3 Wood units (Simonneau G et al, Eur Respir J 2018).

In 2005, a committee of experts of the International Society for Mountain Medicine convened at the 6th World Congress on Mountain Medicine and High Altitude Physiology held in Xining, China, in 2004, and subsequently published a consensus statement about the most common chronic and subacute high altitude diseases (Leon-Velarde et al, High Alt Med Biol 2005;6:147-57). In this document, altitude experts defined
pulmonary hypertension by a mPAP $\geq 30$ mmHg (sPAP $\geq 50$ mmHg), with in addition a correction for viscosity in the presence of excessive polycythemia, but without further specification how to correct for this problem.

In a recent meta-analysis of all published data between 2000 and 2015 on echocardiographic estimates of pulmonary artery pressure in 834 healthy people living at high altitude, meta-analysis revealed a mean resting systolic PAP of 25 mmHg in apparently healthy individuals from the general population living between 3,600 and 5,050 m (Soria et al., J Appl Physiol 2016;121:1151-59). Using the current definition of pulmonary hypertension as a sPAP $>50$ mmHg (high-altitude consensus), the findings of the meta-analysis (systolic PAP of 25 mmHg corresponding to a mPAP of 19.5 mmHg) indicate that in apparently healthy individuals living at high altitude (3,600-4,200 m, i.e., an altitude where the major high-altitude populations live worldwide) pulmonary hypertension appears to be very rare (of the 834 high-altitude dwellers included in the meta-analyzed studies, $<1\%$ had a sPAP $>27.1$ mmHg). It is not sure that the new consensus definition of pulmonary hypertension will significantly alter these figures as a mPAP $> 20$ mmHg has to be combined with a PVR $\geq 3$ Wood units, which implies a very low cardiac output. Furthermore PVR is not easy to measure noninvasively, so that population studies to define the epidemiology of newly of pulmonary hypertension at high altitudes will a challenge.

Taken together, these data call for an urgent revision of the current consensus document definition of high-altitude pulmonary hypertension and for a consensus on how to account for the effects of increased hematocrit on this variable.

In the International Society for Mountain Medicine document, the notion of right heart failure was incorporated into the entities of chronic and subacute mountain sicknesses. Chronic mountain sickness is a syndrome in high-altitude dwellers, of excessive polycythemia due to failing ventilatory adaptation to hypoxia, with actually uncommon viscosity-corrected pulmonary hypertension (Vanderpool, Naeije High Alt Med Biol 2013;14:117-25). Subacute mountain sickness occurs in recent high altitude sojourners and corresponds to clinically diagnosed right heart failure. Acute mountain sickness is not an early form of chronic mountain sickness, nor does it necessarily precede subacute mountain sickness.

Thus the terminology of chronic, subacute and acute mountain sickness is confusing for non-experts. Moreover, and most importantly, an agreement on a definition of right heart failure, the main determinant of outcome in high-altitude dwellers with pulmonary hypertension, needs to be established, with definitive cut-off values for non-invasive (echocardiography) and magnetic resonance imaging?2) and invasive (cardiac catheterization) assessments.

Since the publication of the consensus statement on high altitude diseases (Leon-Velarde et al, High Alt Med Biol 2005;6:147-57), there have been major advances in the methods to assess and the understanding of pulmonary artery pressure and right ventricular function in high altitude dwellers so that a revision is urgently needed. We believe that this should be done within the framework of a Task Force allowing for a constructive dialogue between experts in pulmonary hypertension and high-altitude medicine and assuring optimal visibility.

This Task Force should specifically address the following issues:

1. Diagnosis of pulmonary hypertension. An agreement should be reached on the methods of measurement (invasive vs. noninvasive), cut-off values for sPAP, mPAP, PAWP and PVR, and the method to correct for excessive viscosity.

2. Diagnosis of right heart failure. An agreement should be reached on the optimal use of echocardiography (and magnetic resonance imaging) for clinical diagnosis and invasive hemodynamic approach for unequivocal diagnosis.

Thus, the Task Force we propose aims to redefine pulmonary hypertension and right heart failure in high altitude dwellers, thereby overcoming and eliminating the existing major contradictions in definitions and terminology in the field. The impact is expected to be important. More than 140 million of people permanently live at altitudes between 2500 and 4500 m, and travelling to high altitude for business or recreational reasons is expanding all the time. Providing gold standards for the assessment and the definition of pulmonary hypertension and right heart failure is essential for to epidemiological and therapeutic studies in this rapidly growing field.