
# 22nd International Hypoxia Symposium

**meeting to advance the science of Hypoxia every two years since 1979**

7-12 February 2023 Chateau Lake Louise
Lake Louise, Alberta, Canada

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# 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).

**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)
2017 Hypoxia 20: Hypoxia (Lake Louise)
2019 Hypoxia 21: Hypoxia (Lake Louise)

Our 44th year!
2023 Hypoxia 22: Hypoxia (Lake Louise) (Ainslie, Luks, Hackett, Roach)

# 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.

*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.

*Meals:* All meals are for Chateau guests or those who buy meals tickets at the front desk. All meals in the Victoria Dining Room. Breakfast at 0630 to 0830, lunch from 1130 to 1330, and dinner starts at 1900 Wednesday through Friday, and 1930 on Saturday.

*Sunday morning breakfast:* Breakfast Sunday will be from 0730 until 0930 in the Lago Dining Room, downstairs, toward the Mt Temple wing of hotel. If you are leaving early on Sunday, ask the organizers on Saturday for a breakfast voucher good for redemption at the Guide's Pantry (other side of hotel past the main lobby on mountain (not lake) side of hotel.

*Ski Transport.* The Chateau 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.

## Ex-Curricular Meetings

- HAMB Editorial Board meeting, Thursday 0645, Sunroom (behind Victoria dining room)
- EURAC Everest Project planning meeting--Friday at 1430, Mollison Room, downstairs from Mt Temple
- Hypoxia Advisory Committee Saturday morning at 0645, Sunroom (behind Victoria dining room)

**International Hypoxia Symposium**
**Recommendations for Preventing the Spread of COVID-19**

We are excited to return to in-person conferences and offer the first International Hypoxia Symposium since 2019. While much of life has returned to normal, SARS-CoV-2 and other respiratory viruses continue to circulate in our communities and cause illness and sometimes hospitalization and even death. Because of this, we must depend on conference participants to do their part to protect each other. We offer the following recommendations to ensure a safe experience for everyone.

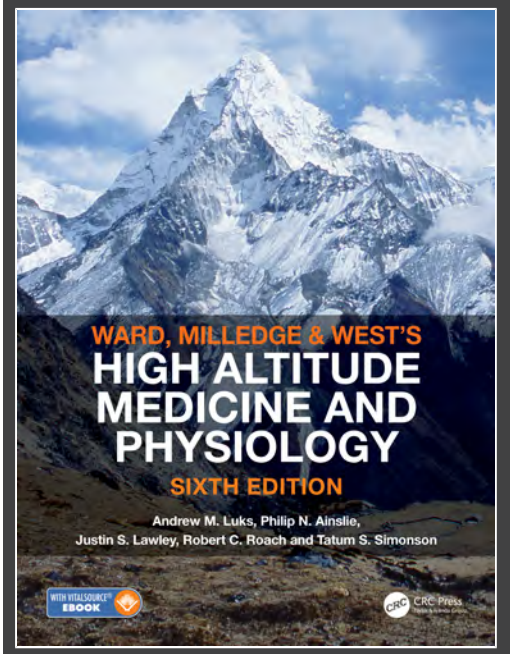
## Ahead of the Conference

- In the one to two weeks before the meeting, do your best to limit exposure to situations where you could contract a viral respiratory illness
- We strongly advise that all attendees are up to date on COVID-19 vaccination, including completion of a primary series and the most recent booster
- Do not travel to the conference if you have symptomatic illness due to COVID-19, influenza, RSV or other seasonal viruses
- Obtain a supply of masks to use at the conference in the event you develop illness
- Obtain a supply of at-home COVID-19 tests to use at the conference. The conference organizers will have a limited supply of tests, but this will not be sufficient for all who attend
- Travel with a personal supply of hand sanitizer

## At the Conference

- Wash your hands frequently and make liberal use of available hand sanitizer
- Consider wearing a mask in communal gatherings and during presentations except when eating or drinking
- If you develop cough, fever, muscle aches, runny nose or other symptoms of a viral upper respiratory tract infection, please test (PCR or antigen) for COVID-19 before going to any group meals or conference sessions. If you have a negative antigen test, please do a second antigen test the next day and do not attend any group activities until that second test is negative.
- If you are positive for COVID-19, do not attend any communal meals or conference sessions
- If you are COVID-negative but still have symptoms, we strongly encourage you to refrain from attending conference sessions. If you opt to attend conference sessions, you should wear a mask.

The conference organizers are available to answer questions that may arise over the course of the conference. We realize these recommendations impose some constraints not seen at prior meetings but we feel they are important for ensuring a safe, enjoyable experience for all.

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**The following people and organizations made major financial or in-kind contributions to the 2023 Hypoxia Symposium.**

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Altitude Research Center
Department of Medicine
Division of Pulmonary Sciences
University of Colorado

at Anschutz Medical Center, Aurora, Colorado (Rob Roach)

Centre for Heart, Lung & Vascular Health

at University of British Columbia Kelowna (Phil Ainslie)

UBC a place of mind THE UNIVERSITY OF BRITISH COLUMBIA

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## The Reeves Prize

During the meeting, a panel of judges selected by the Hypoxia Symposia Advisory Board from the keynote oral presentations to select a winner of the 2023 Reeves Prize for Presentation Excellence. The prize is named after John T. "Jack" Reeves (1928-2004). From the beginning in the 1980s, Jack was a leading figure and stalwart of the Symposia. An accomplished physician, scientist and educator, he enlightened and mentored many of today's high altitude and hypoxia researchers. Many of the current participants will remember Jack's incisive analyses of presentations as well as his own inspiring talks. The Reeves prize is to recognize a speaker at the biannual Symposia who embodies Jack's passion for excellence in science, communication and education.

## New for Hypoxia 2023: The John B West Prize in High Altitude Physiology and Medicine

The awards committee will also select a recipient to receive the inaugural John West prize for groundbreaking hypoxia research. This award will be selected from all 2023 oral presentations in honor of Dr John West, a pioneer in respiratory and high altitude medicine and physiology. John has been a steadfast supporter of the International Hypoxia Symposia. This one-time award that will be altered in 2025 onwards to become the John West Lectureship.

## Trainee Awards

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 pragmatic with our categorization. We divide our evaluation of trainee 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 based on the best poster or oral presentations by junior or senior trainees, with awards in each category.

**The judges for the Trainee, Reeves and West prizes include:** Phil Ainslie, Nanna Arngrim, Beth Beidleman, Trevor Day , Jerry Dempsey, Peter Hackett (Reeves/West Chair), Erica Heinrich, Linda Keyes, Trish Kritek, Justin Lawley, Andrew Luks, Barbara Morgan, Barbara Morgan, Rob Roach, Brownie Schoene, Mary Slingo, Michael Stembridge (Trainee Chair), Erik Swenson, and Silvia Ulrich.

**The Prizes and Awards will be announced at the closing banquet on Saturday night.**

## Equality, Inclusion and Diversity

The International Hypoxia Symposia values equity, diversity and inclusion. Embracing diversity means recognizing bias and cultural stereotypes and working to change mindsets. We appreciate, value and seek the different dimensions that age, race, ethnicity, sex, sexual orientation, gender identity, socio-economic status, religious beliefs, experiences, perspectives, lifestyles, geographic regions and cultures have to offer. The Symposia strives to provide a safe and inclusive environment for all individuals. Attendees of the conference are called upon to uphold these values within all professional settings by treating others with respect at all times. The panel of judges incorporates equity, inclusion and diversity into the Hypoxia award process.

international HYPOXIA SYMPOSIA

**22nd International Hypoxia Symposium**
**7-12 February 2023**
**Chateau Lake Louise (www.hypoxia.net)**
**Hypoxia 2023: Program**

## Wednesday

*Morning I* — **From Mountain Tops To Sea Depths: Hypoxia-Tolerant Species**
— Genomics of adaptation in the world's highest-dwelling mammal—Jay Storz
— Carbon monoxide (CO) in hypoxia tolerant species— Michael Tift
— Genes, the environment and the control of breathing—Catherine Ivy

*Morning II* — **Mountain Medicine I: Research Landscape Around The World**
— La Rinconada: The limits of human adaptation to chronic hypoxia—Sam Verges
— USARIEM: Humans at high altitude—Beth Beidleman
— EURAC: Humans at simulated high altitude—Giacomo Strapazzon

*Afternoon* — **Poster Session I and Poster 3x3**

*Evening* — **Elder Chiniki First Nation Blessing**—Henry Holloway
**Climate Extremes and Exploration Science**—Kimberley Miner

## Thursday

*Morning I* — **Mountain Medicine II: Birth and patients at high altitude**
— Surviving birth at high altitude—Alexandra Heath
— Altitude travel with COPD—Michael Furian
— Altitude travel with pulmonary vascular disease—Silvia Ulrich

*Morning II* — **Advances in Hypoxia Research I**
— Hypoxemia in the COVID ICU – mechanisms and reflections—Trish Kritek
— Advances in hypoxia signaling—Gregg Semenza

*Afternoon* — **Hot Topics in Hypoxia I**—Free Communications

*Evening* — **Life In Space, and Life On Earth**—Kjell and Kristi Lindgren

## Friday

*Morning I* — **Hypoxia and the Brain**
— Brain tissue hypoxia in humans after cardiac arrest—Mypinder Sekhon
— Migraine induced by hypoxia—Nanna Arngrim
— Sensing brain hypoxia by glial cells and regulation of CBF—Alex Gourine

*Morning II* — **Intravascular Volume Changes At Altitude: Causes And Consequences**
— Mechanisms underlying the increase in hemoglobin concentration at high altitude—Christoph Siebenmann
— Blood volume control of blood pressure at altitude—Lydia Simpson
— A change of heart: cardiac adaptation to hypoxia—Mike Stembridge

*Afternoon* — **Hot Topics in Mountain Medicine**

*Evening* — **A Mountaineer's View Of Climate Change**—Gordon Wiltsie

## Saturday

*Morning I* — **Oxygen sensing in the lungs**
— Sensing oxygen in the pulmonary circulation—Mary Slingo
— O2, CO2 and Breathing...What's the Controversy?!—Jerry Dempsey

*Morning II* — **Latest Developments in Hypoxia Research II**
Targeting Hypoxia Signaling for ARDS Treatment—Holger Eltzschig
HIF2 and the carotid body—Peter Ratcliffe

*Afternoon* — **Hot Topics in Hypoxia II**—Free Communications

*Evening* — **Awards, Banquet and Dance at Chateau Lake Louise**

## 0800-0930 From Mountain Tops to Sea Depths: Hypoxia-Tolerant Species

### 0800-0830 Genomics of adaptation in the world's highest-dwelling mammal—Jay Storz

During the past three years we have conducted mountaineering mammal surveys in the Central Andes that have yielded live-trapping records of multiple species of mice living at extraordinarily high elevations (5800-6740 m [=~19,000'-22,100']), far exceeding all previous specimen-based records for mammals. In addition to these surprising live-trapping records, we also discovered the mysterious phenomenon of mouse graveyards (collections of desiccated cadavers and skeletal remains) on the summits of multiple >6000 m volcanoes in the Puna de Atacama (Chile-Argentina). Here we report results of a population genomic analysis to identify mechanisms of hypoxia adaptation in high-altitude Andean leaf-eared mice (*Phyllotis vaccarum*). This species holds the record as the highest-dwelling mammal in the world and lives at altitudes (>6700 m [>22,000']) that were previously considered to be completely uninhabitable by mammals. Results of population genomic analyses revealed evidence for altitude-related selection on numerous genes that play key roles in the maintenance of acid-base homeostasis, fluid balance, and circulatory oxygen transport. These preliminary results demonstrate the utility of using altitudinal patterns of genomic differentiation to identify candidate genes for hypoxia adaptation.

### 0830-0900 Carbon monoxide (CO) in hypoxia tolerant species— Michael Tift

Carbon monoxide (CO) is known by many as 'The Silent Killer', due to the colorless, odorless, and tasteless gas having a high affinity for heme, the primary oxygen binding site of many hemoproteins. While many sources of CO exposure are exogenous (e.g., cigarette smoke and vehicle exhaust), the gas is also produced endogenously in most organisms on the planet as a byproduct of heme degradation. For every mole of heme degraded by heme oxygenase enzymes, there is an equimolar amount of CO produced. Surprisingly, exposure to low or moderate concentrations of CO can have potent cytoprotective effects for tissues, especially those that have experienced injuries from severe hypoxia and/or ischemia-reperfusion events. Certain high altitude human populations in Tibet experience positive selection for heme oxygenase-2 and recent research from our group has highlighted that some species of deep-diving mammals have levels of CO in their blood that resemble those seen in chronic cigarette smokers. We have also discovered certain hypoxia-tolerant mammals have quantities of CO in their tissues that are higher than those found in humans that suffered fatalities from either fires or CO asphyxiation. Here, I will discuss the variability of CO in several tissues from over 40 species of animals, the importance of CO in terms of hypoxia tolerance, and provide new information on the variability of the heme oxygenase/CO pathway in species exposed to variable levels of hypoxia.

**0900-0930 The role of genes and the environment on the control of breathing—Catherine Ivy**

Many genes have experienced a history of natural selection in a variety of high-altitude taxa, but the functional role of these variants/mutations are poorly understood. My research is focused on understanding how animals at high altitude maintain oxygen uptake through the control of breathing, and whether there are associated genetic mechanisms. I have shown that high-altitude deer mice breathe more effectively to enhance oxygen uptake in hypoxia, through slower deeper breaths, compared to lowlanders. Additionally, highlanders do not exhibit phenotypic plasticity in breathing pattern or carotid body morphology when exposed to chronic hypoxia, in contrast to the hypertrophy of the carotid body observed in lowlanders. To investigate the genetic mechanisms that may be involved with these findings, I used hybrid high- and low-altitude deer mice to create an admixed genomic background. My findings show that these differences in the control of breathing are associated with the high-altitude variants of alpha haemoglobin and *Epas1*, genes that are under strong directional selection in our high-altitude deer mouse population. Currently, I am investigating whether there are similar changes in the control of breathing in songbirds that encounter hypoxia during migratory flight.

*0930-1000 Refreshment Break, Heritage Hall*

## 1000-1130 Mountain Medicine I: Research Landscape Around the World

**1000-1030 La Rinconada: The limits of human adaptation to chronic hypoxia—Sam Verges**

La Rinconada is known as the highest city in the World, located in South Peru at 5100-5300 m. More than 50 000 dwellers live permanently in this gold mining city with an inspiratory oxygen partial pressure reduced by 50% compared to sea level. Living permanently in La Rinconada imposes a tough combination of chronic severe hypoxia, harsh weather and living conditions. In 2019, our group has initiated a biomedical research program to explore the physiological adaptations and health issues of this unique population. The results collected over the past four years indicate that these Quechua highlanders exhibit very high hemoglobin concentration, about half of them above the thresholds used to define excessive erythrocytosis. Hemoglobin mass and blood volume are about twice larger than normal values observed at sea level. This considerable erythrocytosis is associated with substantial increase in blood viscosity and leads to important cardiovascular constraints. Despite normal systemic blood pressure, pulmonary arterial blood pressure is excessively high and both the right and left heart shows profound remodeling. Macro- and micro-vascular function is also affected by the large blood changes as well as by some degree of systemic inflammation. Symptoms of chronic mountain sickness are frequent in this population although the observations challenge both the definition and the classical understanding of this syndrome. Although the clinical management of these symptoms remains challenging, these highlanders may benefit from some pharmacological interventions such as acetazolamide that can reduce their hematocrit. Sleep and exercise responses are also impaired especially in highlanders with chronic mountain sickness. Permanent residency in La Rinconada is a unique model to explore the limits of human tolerance to chronic hypoxia. It also raises important public health issues for millions of families living at very high altitude in the Andes and throughout the World.

**1030-1100 USARIEM: Humans at high altitude—Beth Beidleman**

The US Army Research Institute of Environmental Medicine (USARIEM) is the premier Department of Defense Research Institute for altitude research. USARIEM has conducted numerous landmark studies over the past 60 years to optimize health and performance of Soldiers operating in mountainous environments. This talk will review the unique facilities operated by USARIEM, including the hypobaric chamber where the famous Operation Everest II was conducted and the John Maher Pikes Peak laboratory in Colorado Springs, CO. In addition, significant findings based on comparisons between the use of intermittent hypobaric hypoxia, staged ascent, and moderate altitude residence for facilitating rapid altitude acclimatization will be presented. Current research on both population and individualized predictions of Acute Mountain Sickness (AMS) using the Altitude Readiness Management System and patent-pending AMS alert algorithm will be discussed. Limited results from the largest USARIEM altitude study ever conducted over the past two summers in Taos, NM (3600m) will be presented. Future research involving genomic predictions of AMS prior to ascending to altitude will be highlighted. Authors' views not official U.S. Army or DoD policy. Funding: USAMRDC

**1100-1130 EURAC: Humans at simulated high altitude—Giacomo Strapazzon**

Field-based scientific investigations in extreme environments represent a major challenge. Complex combinations of multiple environmental parameters can prove highly difficult to mitigate against, thus making it difficult to standardise data collection and manage the logistics necessary to enable detailed assessment of individual response. The design and realisation of the terraXcube research facility, run by Eurac Research in Bolzano, Italy, is a unique technological advancement in environmental research. The terraXcube is a comprehensive unit with two hypobaric climate simulation facilities, medical support services and research expertise. The terraXcube enable the simultaneous control of multiple climatic parameters: barometric pressure, oxygen concentration, temperature, humidity, wind, precipitation (rain and snowfall), as well as light (day and night cycles). Several experimental human short and long-term studies up to 30 days with hypobaric exposure up to 7700 m have been performed since its opening in 2019, some of them in combination with multiple climatic parameters. Exemplarily we present a series of in-field and chamber studies with the aim to evaluate, under replicable, blinded and standardised conditions, the effect of acute exposure to hypobaric hypoxia on physiological parameters and selected cognitive domains, and the effect of supplemental oxygen administration during exposure. Our data showed signs of cognitive impairment above 5000 m that were not perceived by the participants and can be reversed by the administration of supplemental oxygen. Our data also showed a time-dependent decrease in cardiopulmonary resuscitation quality above 3000 m. The results advise caution when traveling to high altitude and will help to establish evidence-based guidelines for the equipment and safety operating procedures of helicopter emergency medical services and search and rescue personnel operating at high altitude.

*1130-1600, Ski Break* and *1130-1330, Lunch, Victoria Dining Room*

**1600-1830 Poster Session I and Poster 3x3, Mount Temple** (see next pages)

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

2030-2130 **Elder Chiniki First Nation Blessing**—Henry Holloway

We are honored to receive a blessing from Elder Holloway from the Chiniki First Nation for our conference to take place on their land.

The Stoney Nakoda are the original "peoples of the mountains" known in the Nakoda language as the Iyarhe Nakoda. They have continuously used, occupied, and possessed their traditional lands since well before contact with the Europeans. Their traditional territory ranged from the Great Plains where they hunted buffalo to the Rocky Mountain foothills and watersheds where they harvested, fished and hunted big game, and over the mountain passes to the British Columbia interior. The Stoney Nakoda Nations are comprised of the Bearspaw First Nation, Chiniki First Nation and Goodstoney First Nation and were signatories to Treaty No. 7 made on September 22, 1877 at Blackfoot Crossing. The Stoney Nakoda language is their mother tongue and continues to be spoken at meetings of Chief and Council, community meetings, special events and ceremonies.

**Climate Extremes and Exploration Science**—Kimberley Miner

## Poster #: 1 .CARDIAC RESPONSE TO VOLITIONAL APNEA IN UNTREATED OBSTRUCTIVE SLEEP APNEA: A PROSPECTIVE OBSERVATIONAL STUDY.

Sana Ayesha1, Emily C King2, Sean Van Diepen2, Carlos F Mir2, Craig D Steinback1. 1Neurovascular Health Lab, Faculty of Kinesiology, Sport, and Recreation, University of Alberta, Edmonton, Canada, 2Faculty of Medicine and Dentistry, University of Alberta

Introduction: We have previously shown that voluntary apnea during periods of chemosensitization (e.g., altitude) elicits bradyarrhythmias in healthy individuals. Obstructive sleep apnea (OSA) is also associated with chemoreflex hyperactivity and OSA patients have an increased risk of arrhythmias during sleep.Objective: We sought to evaluate whether volitional apnea may elicit bradyarrhythmia in individuals with OSA.Methods: A prospective observational cohort included 8 (5M/3F) untreated OSA patients and 4 (3M/1F) healthy controls matched for age, sex, and, BMI. The mean AHI for the OSA group was 12 ±6 and <5 in the Control group.Results: No differences were observed in baseline Heart Rate (HR) (69±12 beats per minute (bpm) in OSA vs 61±12 bpm in controls, P=0.35) or mean blood pressure (BP) (96±13 mmHg in OSA and 93±3 mmHg in controls, P= 0.65) between groups. The average apnea duration was 23±8 seconds in OSA patients and 32±7 seconds in Controls. During apnea, HR dropped -12±15 bpm in OSA and -16±9bpm in Controls; however, this was not different between groups, (P= 0.60). There were no incidences of arrhythmia in either group during or immediately following apnea. During Voluntary Apnea mean BP increased (+10 ±7mmHg in OSA and +12±5mmHg in Controls), and this increase was not different between groups (P=0.753). Conclusions: Our data suggest no differences in the incidence of bradyarrhythmias during volitional apnea among individuals with untreated OSA versus matched controls. Further participant recruitment may improve the power to detect a clinically important difference in the potentiation of bradyarrhythmia between the OSA group and the control group. Funding: This study is being Funded by NSERC

## Poster #: 2 .Vagal Block Attenuates Bradycardia and Arrhythmias During Apnea at High Altitude.

Lindsey Berthelsen1, 2, Emily Vanden Berg2, Lauren Maier2, Lydia Simpson3, Michiel Ewalts4, Connor Howe5, Sean van Diepen6, Phil Ainslie5, James Anholm7, Jonathan Moore4, Michael Stembridge8, Craig Steinback2. 1University of Calgary, 2Faculty of Kinesiology, Sport, and Recreation; University of Alberta, 3University of Innsbruk, 4Bangor University, 5University of British Columbia Okanagan, 6Faculty of Medicine and Dentistry; University of Alberta, 7Loma Linda University, 8Cardiff Metropolitan University

Background. Voluntary apnea at high-altitude elicits bradycardia and cardiac arrhythmias which are not seen during similar maneuvers at low-altitude. This may be related to hypoxia induced increases in chemoreceptor sensitivity and concomitantly augmented autonomic outflow. While parasympathetic cardiac activity is masked at high-altitude by augmented ventilation, apnea (via the dive reflex) provides a model to mechanistically investigate the effect of high altitude on vagal tone. To isolate the potential influences of hypoxia, chemoreflex sensitivity and/or parasympathetic drive on cardiac conduction, we investigated the heart rate and rhythm response to apnea in 9 (3 female) participants following 6-9 days of high-altitude exposure (3800m) under 1) control conditions (CON); 2), peripheral chemoreceptor blockade using low dose dopamine (DOPA); 3), following vagal block using glycopyrrolate (GLY). Methods. Participants performed a single apnea during each condition. 1 minute of baseline was analyzed

prior to apnea in each condition to obtain resting heart rate and blood pressure. The heart rate and rhythm response were assessed individually for each apnea, with the bradycardic response being evaluated as the drop in heart rate (nadir) minus the preceding baseline. Comparisons across condition were performed using a one-way ANOVA. Results. Dopamine decreased ventilation (L/min) by 58% (CON, 27 ± L/min; DOPA, 15 ± 3L/min; p=0.01), demonstrating a significant peripheral chemoreceptor block. The bradycardic response to apnea was similar between CON and DOPA conditions (-31 ± 18bpm and -33 ± 11bpm), whereas heart rate increased during GLY apneas (+10 ± 4bpm; effect of condition, p<0.001). Interestingly, the incidence of arrhythmia was similar between CON and DOPA conditions, but arrhythmias were attenuated following GLY. Conclusion. Vagal block attenuates bradycardia and arrhythmias during apnea at high-altitude; however, peripheral chemoreceptor inhibition did not alter the heart rate or rhythm response to apnea, suggesting an alternative mechanism underlying heightened vagal tone. Funded by NSERC.

**Poster #: 3 .RELATIONSHIP OF NOCTURNAL OXYGEN SATURATION TO BLOOD PRESSURE AT HIGH ALTITUDE.** Diana Biggs1, Andrew Burns1, Greta Carlson1, Ilaria Ferrari1, Lukas Sloan1, Linda E. Keyes1. 1University of Colorado

Objective: We evaluated the hypothesis that nocturnal hypoxia at high elevation would cause nocturnal and diurnal elevations in 24h ambulatory blood pressure (ABP).Methods: This prospective observational cohort study of adult lowlanders compared 24h ABP and nocturnal SpO2 during participants' first 24h at high altitude (2470-2700m). ABP was measured hourly 7am-10pm and every 30 minutes 10pm-7am using Welch-Allyn 6100 ABP monitors. SpO2 was measured continuously overnight using Nonin WristOx.Results: We report preliminary data on 9 participants, (mean age = 46 yo, female = 6). Mean basal nocSpO2 was 87%, 95% CI [85-89], mean minimum nocSpO2 75%, 95% CI [70-80]. The mean nocturnal SBP was 121, 95% CI [107-135], mean diurnal SBP 136, 95% CI [124-148], mean nocturnal DBP 67, 95% CI [59-75], and mean diurnal DBP 79, 95% CI [71-87]. Lower minimum nocSpO2 was weakly associated with higher mean diurnal SBP (R2=0.4), but not with mean nocturnal SBP (R2=0.1) nor the measured SBP at the time of minimum SpO2 (R2=0.2). Higher oxygen desaturation index was weakly associated with higher mean diurnal SBP (R2=0.4), but not with nocSBP (R2=0.1). Greater percent of nocturnal time < SpO2 88% was weakly correlated with higher mean nocSPB (R2=0.3), but not with diurnal SBP (R2=0.2). We found no associations between DBP and nocSpO2 parameters. In those with normal nocturnal BP dipping (n=4), the mean percent time <88% SpO2 was 34% versus 60% for non-dippers (n=4).Conclusion: Lower nocturnal SpO2 was associated with higher diurnal but not nocturnal SBP at high altitude. In contrast, DBP was not associated with nocturnal SpO2. Our preliminary results suggest that nocturnal hypoxia plays a role in the elevation of diurnal SBP observed at high altitude.Funding: Wilderness Medical Society Hultgren grant.

**Poster #: 4 .RELATIONSHIP OF NOCTURNAL OXYGEN SATURATION TO SLEEP QUALITY AT HIGH ALTITUDE.** Diana Biggs1, Andrew Burns1, Greta Carlson1, Ilaria Ferrari1, Lukas Sloan1, Linda E. Keyes1. 1University of Colorado

Objective: Few studies have investigated sleep quality vs. nocturnal SpO2, but rather have compared sleep fragmentation and nocturnal wakening to sleep quality. We evaluated the hypothesis that nocturnal hypoxia at high elevation would lead to poorer sleep quality.Methods: This prospective observational cohort study of adult lowlanders compared sleep quality measured by the Groningen Sleep Quality Scale (GSQ) and nocturnal SpO2 during participants' first 24h at high altitude (2470-2700m). SpO2 was measured continuously overnight using the Nonin WristOx.Results: We report preliminary data on 9 participants, (mean age = 46 yo, female = 6), none with a history of OSA. Mean basal nocSpO2 was 87%, 95% CI [85-89], mean minimum nocSpO2 75%, 95% CI [70-80] and mean percent time SpO2<88% 51%, 95% CI [27-75]. Mean GSQ was 7, 95% CI [4-10]. GSQ scores were not associated with minimum nocSpO2 (R2 = 0.0) or percent of time SpO2<88% (R2 =0.0). Lower mean nocSpO2 was associated with better perceived sleep quality (lower GSQ) (R2=0.6).Conclusion: Contrary to our hypothesis, despite participants reporting poor sleep quality the first night after arrival to high altitude, lower nocturnal SpO2 was not associated with worse sleep quality. We are unsure why higher mean nocturnal SpO2 was associated with worse sleep quality but suspect other unmeasured variables affect sleep quality.Funding: This work was supported by a Wilderness Medical Society Hultgren grant.

**Poster #: 5 .INVESTIGATING SEX-RELATED DIFFERENCES IN PERIPHERAL FATIGABILITY AT HIGH ALTITUDE IN HUMANS.** Christina D Bruce1, Sianna PC Tomich1, Travis D Gibbons1, Philip N Ainslie1, Chris J McNeil1. 1University of British Columbia Okanagan, Canada

Objective: Whole muscle intrinsic fatigability (i.e., peripheral fatigability) is exacerbated when male lowlanders become acutely hypoxic, which acclimatization to high altitude (HA) restores. It is currently unknown if peripheral fatigability of females is altered when oxygen availability is reduced. Therefore, we investigated the hypothesis that peripheral fatigability would be greater in females than males when acutely exposed to HA and that both groups would fatigue similarly following 14 days of residing at HA. Methods: The knee extensors of the dominant leg were fatigued via 144 electrically evoked contractions (7 pulses at 10Hz; 1.25s between trains of stimuli) in 10 females and 9 males at sea level (SL; 344m), and again after 2 and 14 days of residing at 3800m (HA1 and HA2, respectively). Initial peak force of the evoked contractions was ~25% of maximal voluntary force. To quantify fatigability, mean peak force of the last 8 contractions was expressed relative to the mean of the first 8 contractions. Results: By the end of the fatigue protocol at SL, peak force was more impaired for females (21.9%) than males (10.5%; P=0.035). At HA1 (22.8%) and HA2 (25.5%), force loss was greater for males compared to SL, whereas the fatigability of females did not change from SL (26.4 and 23.0% at HA1 and HA2, respectively). In other words, females and males experienced similar levels of fatigue while residing at altitude, but when considering changes from SL, only the fatigability of males was impaired by HA. Conclusion: Contrary to our hypothesis, female skeletal muscle fatigability was not more impaired at HA than males. These findings are relevant for determining how sex-

related differences in skeletal muscle could affect fatigability when oxygen availability is impaired. Funding: NSERC and CFI/BCKDF

**Poster #: 6 .EXPEDITION 5300: CEREBRAL HOMEOSTASIS AND ORTHOSTATIC RESPONSES IN RESIDENTS OF THE HIGHEST CITY IN THE WORLD.** Julien Brugniaux1, Michael Furian1, Mathilde Ulliel-Roche1, Connor A Howe2, Fanny Zerizer1, Mathieu Marillier1, Anne-Catherine Bernard1, Ivan Hancco1, Benoit Champigneulle1, Sébastien Baillieul1, Emeric Stauffer3, Philip N Ainslie2, Aurélien P Pichon4, Stéphane Doutreleau1, Samuel Vergès1. 1Université Grenoble Alpes, France, 2University of British Columbia, Kelowna, British Columbia, Canada, 3Université Claude Bernard Lyon 1, France, 4Université de Poitiers, France

Background. Permanent residence at high-altitude and chronic mountain sickness (CMS) may alter the cerebrovascular homeostasis and orthostatic responses. Methods. 15/13/17 healthy participants living at sea-level (LL), 3,800m (HL3800m) and 5,100m (HL5100m), respectively, and 31 additional highlanders with CMS living at 5,100m were recruited. Middle cerebral artery mean blood velocity (MCAv-transcranial Doppler ultrasound), cerebral oxygen delivery (CDO2), mean blood pressure (MAP-finger plethysmography), heart rate variability (low/high frequency – LF/HF, respectively) and baroreflex sensitivity (BRS) were assessed during 3 phases of a tilt test; while sitting, during standing-up and while standing for 3min. Cerebral autoregulation index (ARI) was estimated (ΔMCAv%baseline)/ΔMAP%baseline) in response to standing-up. Results. Altitude and CMS were associated with hypoxemia and elevated hemoglobin concentration. While sitting, MAP increased, MCAv and LFpower decreased with altitude but were not further affected by CMS and CDO2 was preserved. BRS was comparable across all altitudes, but reduced with CMS. With standing-up, altitude and CMS were associated with a lesser reduction in MAP; ARI was unaffected by either altitude or CMS. Compared to sitting in lowlanders, standing was associated with preserved MCAv, CDO2 and BRS across all altitudes. The LF/HF ratio increased in HL5100m compared to LL and HL3800m from sitting to standing. Likewise, in CMS while standing, MCAv was reduced but CDO2 remained unaffected; however, CMS showed blunted LFpower, HFpower and LF/HF ratio responses to standing compared to sitting. Conclusions. Despite altitude- and CMS-associated hypoxemia, erythrocytosis and impaired blood pressure regulation (CMS only), cerebral homeostasis while sitting, standing-up and standing was overall preserved. The origin of CMS-related neurological symptoms remains to be established.

**Poster #: 7 .Loop Gain Response to Increased Cerebral Blood Flow at High-Altitude. .** Andrew Burgess1, Gareth Andrews2, Katie Colby2, Samuel Lucas3, Kate Sprecher2, Joseph Donnelly4, Philip Ainslie5, Aparna Basnet6, Keith Burgess7. 1Canberra Sleep Clinic, 2Peninsula Sleep Clinic, 3University of Birmingham, 4University of Auckland, 5University of British Columbia, 6Banner University Medical Centre, 7Macquarie University

Background: Loop gain (LG) describes the stability of a negative-feedback control system; defined by magnitude of response to a disturbance, e.g. hyperpnea to an apnea in central sleep apnea (CSA). The lower the value the more stable the system. Objective: To compare LG before and during pharmacological increases in CBF at high altitude (HA). Methods:

Polysomnography (PSG) was performed on 11 volunteers after administration of I.V. Acetazolamide (ACZ-10mg/kg) + Dobutamine (DOB-2-5 μg/kg/min) to increase CBF. CBF measured by duplex doppler. CSA was measured during NREM sleep. The LG was calculated (LG=2π/(2πDR-sin2πDR) using duty ratio (DR)(hyperpnea/hyperpnea+apnea). Results: Compared to placebo-control, ACZ/DOB showed a reduction in LG (1.29±0.35 vs 1.90±0.23, p=0.0004) and a significant increase in the DR (0.79±0.21 vs 0.52±0.03, P=0.002) while ACZ/DOB increased CBF (718±120 vs 526±110ml/min, P<0.001). There was no significant change in arterial blood gases, minute ventilation (VE), or hypoxic ventilatory response (HVR), however there was a 29% reduction of hypercapnic ventilatory response (HCVR) (4.2±2.8 vs 5.9±2.7 L/min, P=0.1). Conclusion: Pharmacological elevation in CBF significantly reduced LG and severity of CSA. We speculate the effect was on HCVR "Controller Gain", rather than "Plant-Gain", because PaCO2 and VE were unchanged. An effect via reduced circulation time is unlikely, because the respiratory-cycle length was unchanged.

**Poster #: 8 .MAXIMAL FAT OXIDATION AND TOTAL ENERGY EXPENDITURE ARE LOWER DURING SUBMAXIMAL STEADY-STATE CYCLING EXERCISE AT 3,800 M.** Hannah Caldwell1, Jack Talbot2, Elliott Jenkins2, Connor Howe1, Jonathan Little1, Michael Stembridge2, Philip Ainslie1, Travis Gibbons1. 1Centre for Heart, Lung and Vascular Health, School of Health and Exercise Sciences, University of British Columbia Okanagan, Kelowna, BC, Canada, V1V 1V7, 2Cardiff School of Sport and Health Sciences, Cardiff Metropolitan University, Cardiff, UK

Objective: This study investigated substrate oxidation and energy expenditure during exercise at an intensity that elicits maximal fat oxidation at sea level (SL) and following 3-8 days at 3,800 m (HA). Methods: Healthy adults (SL: n=16, 9/7 females/males; HA: n=15, 7/8 females/males) completed the following protocols at SL and HA: resting metabolic rate, steady-state incremental submaximal exercise to determine maximal fat oxidation (FATmax) and peak oxygen uptake (VO2peak) tests on a semi-recumbent cycle ergometer. Thereafter, 60 minutes of steady-state cycling at FATmax was performed. Results: There was no difference between the absolute exercise intensity where FATmax was achieved between HA and SL (HA: 47 W, 95% CI: 39 to 56 vs. SL: 54 W, 95% CI: 45 to 64; P=0.081). The FATmax exercise intensity relative to maximal VO2peak wattage was also not different between altitudes (HA: 22 % VO2peak, 95% CI: 19 to 25 vs. SL: 23 % VO2peak, 95% CI: 21 to 26; P=0.529). Maximal fat oxidation achieved during the FATmax test was 26.9 % lower at HA versus SL (HA: 0.28 grams/min, 95% CI: 0.23 to 0.33 vs. SL: 0.38 grams/min, 95% CI: 0.32 to 0.45; P=0.002) which was likely attributable to the 24.4 % reduction in relative contribution of fats to total energy expenditure at rest at HA (HA: 34 % fats, 95% CI: 26 to 42 vs. SL: 45% fats, 95% CI: 36 to 53; P=0.048). Further, as there were no differences between the relative contribution of carbohydrates to total energy expenditure at rest (HA vs. SL: P=0.105) or maximal carbohydrate oxidation during submaximal steady-state exercise (HA vs. SL: P=0.058), total energy expenditure was 17.0 % lower during 60 minutes of steady-state cycling exercise at altitude-specific FATmax exercise intensity (HA: 263 kcal, 95% CI: 227 to 298 vs. SL: 316 kcal, 95% CI: 281 to 351; P=0.004). Conclusions: Reductions in the relative contribution of fats to resting energy expenditure and lower maximal fat oxidation during submaximal cycling exercise explains, in part, the attenuated total energy expenditure during 60 minutes of low intensity

cycling at high-altitude. The implications of these findings on optimizing energy requirements during prolonged submaximal exercise warrants further research.

**Poster #: 9 .THE IMPACT OF ACUTE MILD CARBON MONOXIDE EXPOSURE ON FLOW-MEDIATED DILATION.** Nicholas Cheung1, Scott Thrall2, Sean Van Diepen3, Craig Steinback1. 1University of Alberta, Faculty of Kinesiology, Sport and Recreation, 2University of British Columbia Okanagan, 3University of Alberta, Faculty of Medicine and Dentistry

Objective: Endogenous carbon monoxide (CO) is vasoactive, influencing endothelial dependent and independent pathways. Exogenous CO has also been shown to have vasoactive effects following prolonged exposure. We examined endothelial function, measured via flow-mediated dilation (FMD), following mild, acute carbon monoxide (CO) exposure in 19 healthy non-smoking participants (n=10 females). Methods: Participants were assessed prior to and following a room air (SHAM), or CO rebreathe exposure on two consecutive days in a randomized single-blinded crossover design. The Schmidt-Prommer rebreathe method for the measurement of Hb mass was used for the CO exposure. We hypothesized CO would increase endothelial-dependent vasodilation in vascular smooth muscle.Results: Baseline brachial artery diameter was not different between sham (3.84±0.75mm) and CO rebreathe (3.77±0.81mm, p=0.344). Baseline arterial bulk flow was also not different between SHAM (34.48± 36.90ml/min) and CO rebreathe (31.73±19.29, p=0.932) Baseline forearm vascular conductance was not significantly different between the two days (SHAM=0.50±0.32, CO=0.63±0.52, p=0.865).Carboxyhemoglobin was elevated following the CO (5.6±1.2%, Mean ± SD) compared to SHAM (1.5 ± 0.3%) rebreathe (p<0.001)No changes in absolute FMD (SHAM = 0.23±0.20mm, CO = 0.24±0.22mm, interaction p=0.690), FMD% (SHAM = 6.69±6.36, CO = 6.46±5.89, interaction p=0.840), or FMD:ssAUC (SHAM = 2.61x10–-5 ± 1.94x10-5, CO = 2.82x10-5 ± 3.55x10-5, interaction p=0.200) were observed.Conclusion: Mild elevation of Carboxyhemoglobin (COHb%) and resulting hypoxemia does not impact resting arterial diameter, flow, or endothelial function in a healthy, non-smoking population. The Schmidt-Prommer rebreathe protocol for the measurement of Hb mass does not impact vascular endothelial function.

**Poster #: 10 .A COMPARISON OF METHODS OF ASSESSING PATIENT OXYGENATION DURING GENERAL ANAESTHESIA AS PART OF A LARGER RANDOMISED CONTROLLED TRIAL (PULSE Ox) .** Andrew Cumpstey1, Anna Clark1, Magdalena Minnion1, Helen Moyses1, Daniel Martin2, Mark Edwards1, Martin Feelisch1, Michael Grocott1. 1University of Southampton, 2University of Plymouth

Background: Anaesthetists routinely use oxygen saturations to monitor patients' oxygenation during general anaesthesia, but the constraints of this scale (maximum of 100%) means that hyperoxaemia may remain undetected for extended periods of time during surgery. The Oxygen Reserve Index ('ORi') is a novel continuous and non-invasive measure of oxygenation status, which may allow better detection of perioperative hyperoxaemia.Objective: This study aimed to compare the ORi to other routine methods of assessing oxygenation status during general anaesthesia.Methods: Twenty-eight adult patients undergoing major (defined as needing

a central venous catheter) abdominal surgery for cancer resection received either 30%, 55% or 80% oxygen throughout anaesthesia. Patients and research staff remained blinded to the allocated intervention. Partial arterial pressures of oxygen (PaO2), peripheral oxygen saturation (SpO2) and ORi were measured and compared throughout each case.Results: The correct targets were achieved with good group separation (mean[SD] FiO2: 33.2[4.3]%/55.1[3.6]%/79.8[3.3]% for 30%/55%/80% groups respectively, $p < 0.001$). Mean SpO2 readings were not different between groups (98.0[1.3]%/98.8[1.1]%/99.3[0.4]%, $p = 0.22$). Hypoxaemia (SpO2 <90%) was rare (median(IQR): 0.11(0.03-0.44)%/0.00(0.00-0.30)%/0.00(0.00-0.01)% of total anaesthetic duration, $p = 0.03$). PaO2 increased significantly with higher FiO2 (18.1[3.9]/27.7[7.0]/46.4[9.1]kPa, $p < 0.001$) but required arterial sampling, distant processing and only allowed intermittent monitoring. ORi also increased significantly with higher FiO2 (0.13[0.18]/0.51[0.32]/0.72[0.25], $p < 0.001$), and this point-of-care test could be measured continuously in a non-invasive fashion.Conclusion: ORi allows a convenient, simple and non-invasive way of continuously monitoring for hyperoxaemia in anaesthetized patients and could have clinical application in helping anaesthetists avoid hyperoxaemia during general anaesthesia.Funding: Doctoral Fellowship (Southampton NIHR Biomedical Research Centre). Equipment loaned by Masimo for this study.

**Poster #: 11 .INTRAOPERATIVE OXYGEN CONCENTRATIONS INCREASE PERIOPERATIVE OXIDATIVE STRESS IN A DOSE-DEPENDENT MANNER – A RANDOMISED CONTROLLED TRIAL (PULSE Ox) .** Andrew Cumpstey1, Anna Clark1, Magdalena Minnion1, Renato Nogueira2, Helen Moyses1, Daniel Martin3, Jose Tanus-Santos2, Mark Edwards1, Michael Grocott1, Martin Feelisch1. 1University of Southampton, 2University of São Paulo, 3University of Plymouth

Background: The World Health Organization (WHO) recommends all anaesthetised patients receive 80% oxygen during surgery to reduce the risk of surgical site infection (SSI). Results from the PROXI trial (no difference in SSI rates between 30% and 80% oxygen but possibly worse postoperative outcomes with 80% oxygen) would caution against this but were considered 'mechanistically implausible' (WHO).Objective: To investigate whether administering higher inspired oxygen concentrations during anaesthesia might increase systemic oxidative stress (and therefore predispose to adverse outcomes).Methods: Twenty-eight adult patients undergoing major (central venous catheter required) abdominal surgery were randomly allocated to receive 30%, 55% or 80% oxygen throughout anaesthesia. Paired arterial and central venous blood gases (to measure oxygen extraction) and samples were collected 2-hourly. Total nitroso species (RxNO) and Nitric Oxide (NO) scavenging were quantified using gas phase chemiluminescence. Total free thiols (TFTs) and ferric reducing ability of plasma (FRAP) were measured colorimetrically.Results: Higher oxygen was associated with higher RxNO concentrations (Mean[SD] 52.6[19.1]/100.2[36.1]/91.2[34.4] nM for 30/55/80% respectively, $p = 0.05$) & reduced NO scavenging (4.4[0.7]/3.5[0.4]/3.6[0.6]uM, $p = 0.02$) at the end of surgery. Normalized TFTs increased throughout surgery but with no difference between groups (4.5[0.3]/4.1[0.3]/4.2[0.4], $p = 0.26$). FRAP concentrations did not change overall (866.5[52.0]/908.1[37.1]/810.6[57.4], $p = 0.42$) but decreased markedly in some patients. Why inter-individual perioperative oxygen sensitivity differs merits further investigation. Tissue oxygen extraction reduced significantly with 80% oxygen (0.28[0.10]/0.23[0.08]/0.20[0.06], $p < 0.001$), supporting previous data in critically ill patients.Conclusion: Higher intraoperative

oxygen concentrations significantly increase markers of oxidative stress, lower systemic antioxidant capacity and decrease oxygen extraction during surgery in a dose-dependent fashion.Funding: Doctoral Fellowship (Southampton NIHR Biomedical Research Centre)

**Poster #: 12 .MAPPING RESTING CEREBRAL BLOOD FLOW DISTRIBUTION USING MAGNETIC RESONANCE IMAGING DURING A STEP CHANGE IN OXYGEN TENSION .** James Duffin1, Ece Su Sayin1, Olivia Sobczyk1, Julien Poublanc2, Harrison Levine1, David Mikulis2, Joseph Fisher 1. 1University of Toronto, Canada, , 2University Health Network, Toronto, Canada.

Mapping RESTING cerebral blood flow DISTRIBUTION using magnetic resonance imaging DURING a step change in oxygen tension James Duffin, Ece Su Sayin, Olivia Sobczyk, Julien Poublanc, Harrison T. Levine, David J. Mikulis, Joseph A. Fisher University of Toronto, Canada, j.duffin@utoronto.caObjective: We examined the premise that a step change in lung oxygen tension generates a step change in arterial deoxyhemoglobin concentration, which, acting as a susceptibility contrast agent during magnetic resonance imaging (MRI), enables the calculation of resting cerebral perfusion measures.Methods: In 24 volunteers we precisely controlled inspired oxygen tensions to deoxygenate their arterial blood to target PO2 of 40 mmHg for 2 consecutive 60 s intervals. Each interval concluded with a rapid step reoxygenation accomplished during a single inspiration. The step reoxygenation produced a step decrease in deoxyhemoglobin and its susceptibility effect as it passed though the cerebral vasculature and was detected as an increase in the blood oxygen level dependent (BOLD) signal with MRI. These BOLD signal changes were assumed to result from a step input function and analysed to calculate voxel wise hemodynamic measures. Anatomical maps of these measures for the 24 volunteers were combined to calculate average measures maps. In addition, example maps from a healthy control and a patient were compared with maps calculated with a conventional deconvolution-based method that requires an arterial input function. Results: All the maps from the step analysis showed similar regional differences to those seen in published maps using deconvolution-based methods requiring the identification of an arterial input function. The patient example maps showed regional areas corresponding to the patient's known pathology. Conclusion: A step change in oxygen tension can be used with magnetic resonance as a non-invasive means of imaging and calculating resting cerebral perfusion measures.

**Poster #: 13 .CHARACTERIZING THE CARDIOVASCULAR COMPENSATORY RESPONSES TO ORTHOSTATIC STRESS AT SEA-LEVEL AND HIGH-ALTITUDE.** Jennifer S Duffy1, Travis D Gibbons1, Liisa Wainman1, Elliott Jenkins2, Jennavieve R Crockett3, Philip N Ainslie1, Christopher R West1, Alexandra M Williams1. 1Centre for Heart, Lung and Vascular Health, University of British Columbia, Kelowna, BC, Canada, 2Cardiff Centre for Exercise & Health, Cardiff Metropolitan University, Cardiff, United Kingdom., 3Kelowna Secondary School, Kelowna, BC, Canada

OBJECTIVE: To determine the relative contributions of cardiac output (Q) and total peripheral resistance (TPR) in maintaining blood pressure during orthostatic stress at sea-level and high-altitude. We further interrogated how changes in leg arterial vascular conductance and leg venous compliance might contribute to these responses. METHODS: Seventeen young healthy

humans (27 ±4 years, 9F) completed a head-up-tilt (HUT) comprising four 5-minute stages of 0°, 20°, 40°, and 60° at sea-level (Kelowna, 355m) and high-altitude (days 3-5 at Barcroft Field Station, 3800m). At 2-5 minutes into each stage, superficial femoral artery blood flow was measured via duplex ultrasound and mean arterial blood pressure (MAP), stroke volume (SV) and heart rate (HR) were assessed via automated sphygmomanometry, echocardiography and electrocardiogram, respectively. Venous compliance was estimated via great saphenous vein pressure (direct catheterization) and calf volume (air plethysmography). RESULTS: Symptoms of orthostatic intolerance prematurely terminated the study in 2 and 4 individuals at sea-level and high-altitude, respectively. MAP was 9 ±7 mmHg higher at high-altitude ($p<0.0001$), driven by a tachycardia-mediated (+11 ±9 bpm, $p=0.0002$) increase in Q (0.5 ±0.2 L/min, $p=0.0025$). SV was unchanged at high-altitude ($p=0.2478$) despite a 9 ±7% reduction in blood volume ($p=0.0002$) and no change in arterial conductance, venous capacitance or compliance (all $p>0.1425$). Irrespective of altitude, upon HUT to 60° (or last completed stage) MAP increased by 4 ±5 mmHg ($p=0.0101$); mediated via increased TPR (3.0 ±2.9 mmHg/L·min-1, $p=0.0013$) that compensated for decreases in SV (-29.1 ±9.3 mL, $p<0.0001$) and Q (-0.5 ±0.5 L/min, $p=0.0025$). Arterial conductance and venous compliance decreased linearly with HUT, independent of altitude (both $p\leq0.0006$). CONCLUSION: MAP is maintained or enhanced with tilt at both altitudes owing primarily to increases in TPR, reflected by decreases in venous compliance and arterial conductance.

## Poster #: 14 .ACTIVE ASCENT ACCELERATES THE TIME COURSE OF ACUTE MOUNTAIN SICKNESS (AMS) IN AMS-SUSCEPTIBLE INDIVIDUALS AT 3600M

**.** Peter Figueiredo1, Steven Landspurg1, Jon Femling2, Jason Williams2, Mark Buller1, J Philip Karl1, Janet Staab1, Reed Hoyt1, Aaron Reilly2, Trevor Mayschak2, Emma Atkinson1, Tim Mesite1, Beth Beidleman1. 1US Army Research Institute of Environmental Medicine, 2University of New Mexico

Objective: Acute mountain sickness (AMS) typically peaks following the first night at high altitude (HA) and resolves over the next 2-3 days but the impact of active ascent on the time course of AMS is debated. Methods: To determine the impact of ascent conditions on the incidence, severity, and time course of AMS, 78 healthy Soldiers (mean±SD; age=26±5yr) were tested at baseline residence, transported to Taos, NM (2845m), then hiked (n=39) or were driven (n=39) to HA (3600m), and stayed for 4 days. AMS Cerebral Factor Score (AMS-C) was assessed using the Environmental Symptoms Questionnaire at HA twice on day 1 (HA1), five times on days 2 and 3 (HA2 and HA3) and once on day 4 (HA4). If AMS-C was ≥0.7 on any assessment, individuals were categorized as AMS-susceptible (AMS+; n=33); others were non-susceptible (AMS-; n=45). The peak AMS incidence and severity were recorded daily and used for analyses. Results: The AMS- group demonstrated no difference in AMS incidence or severity between active and passive ascent at 3600m. The AMS+ group, however, demonstrated a higher AMS incidence in the active vs. passive group on HA1 (93 vs. 56%, $p=0.001$), similar incidence on HA2 (60 vs. 78%, $p=0.10$), lower incidence on HA3 (33 vs. 67%, $p=0.003$), and similar incidence on HA4 (13 vs. 28%, $p=0.12$). The AMS+ group also demonstrated a higher AMS severity score in the active vs. passive group on HA1 (1.35±0.97 vs. 0.90±0.70, $p=0.02$), similar score on HA2 (1.00±0.97 vs. 1.34±0.70, $p=0.08$), and lower score on HA3 (0.56±0.55 vs. 1.02±0.75, $p=0.005$) and HA4 (0.32±0.41 vs. 0.60±0.72, $p=0.05$). Conclusion: Active compared to passive ascent accelerated the AMS time course in AMS+ individuals with more

individuals sick on HA1 and less individuals sick on HA3 and HA4. Authors' views not official U.S. Army or DoD policy. Funding: USAMRDC

**Poster #: 15 .EFFECTS OF NALTREXONE ON SLEEP QUALITY AND PERIODIC BREATHING AT HIGH ALTITUDE.** Katharine Foster1, James Anholm2, Gary Foster3, Prajan Subedi2. 1Emergency Medicine, Loma Linda University School of Medicine, Loma Linda, CA 92354, 2Pulmonary & Critical Care, VA Loma Linda Healthcare System & Department of Medicine, Loma Linda University School of Medicine Loma Linda, CA 92357, 3Cardiology, St. Charles Health System, Bend, OR 97701

Objective: This study examined the role of the Mu-opioid receptor (MOR) on breathing and sleep at high altitude (HA). We hypothesized that MOR blockade with naltrexone would result in higher nocturnal oxygen saturations, fewer apneas and improved sleep at high altitude.Methods: This double blind, placebo-controlled, crossover study included 9 healthy subjects aged, 27.9 ± 4.6 years. Two overnight trips spaced at least two weeks apart occurred from Loma Linda, CA (355m) to Barcroft Laboratory, CA (3810m) for each arm. Subjects took either 50 mg naltrexone or matching placebo at bedtime. Sleep metrics were recorded using WatchPATTM device (Itamar Medical Ltd.). Subjective data was measured with the Groningen Sleep Quality Scale, Stanford Sleepiness Scale and Lake Louise Score (LLS) for acute mountain sickness (AMS).Results: Mean overnight SpO2 was lower after taking naltrexone, 81 ± 6% vs. 83 ± 4% (mean difference 1.9 ± 2.1%), 95%CI=0.1–3.6, p=0.04). Minimum overnight SpO2 was lower on naltrexone 70 ± 6% vs. 74 ± 4% (dif. 4.6% ± 4.3%) CI=1.0–8.2, p=0.02). Total sleep time and total apnea-hypopnea index(AHI) were not different. Subjective sleep quality was significantly worse on naltrexone measured via Groningen ($p<0.03$) and Stanford Sleepiness Scale ($p<0.03$). AMS measure via the LLS was significantly worse while taking naltrexone ($p<0.03$).Conclusion: In contrast to our hypothesis, this study demonstrated a significant decrease in oxygen saturation and sleep quality with no change in sleep time or AHI. AMS scores were significantly worse after taking naltrexone. To our knowledge this is the first study to test physiologic effects of MOR blockade in humans at altitude. Further characterization of the MOR's vasoactive and sympathetic modulation and its effects on regulation of cerebral blood flow are needed to further interpret these results.

**Poster #: 16 .Effects of Pentoxifylline on Sleep and Periodic Breathing at High Altitude.** Katharine Foster1, Craig Steinback2, Travis Gibbons3, Connor Howe3, Andrew Steele3, Joshua Tremblay4, Philip Ainslie3, James Anholm5, Prajan Subedi5. 1Emergency Medicine, Loma Linda University School of Medicine, Loma Linda, CA 92354, fostkath@gmail.com, 2University of Alberta, Edmonton, Alberta, Canada, 3University British Columbia Okanagan, Kelowna, BC, Canada, 4School of Sport and Health Sciences, Cardiff Metropolitan University, Cardiff, UK, 5Pulmonary & Critical Care, VA Loma Linda Healthcare System & Department of Medicine, Loma Linda University School of Medicine Loma Linda, CA 92357

Objective: This study examined the effect of pentoxifylline on sleep at altitude with the hypothesis that pentoxifylline would improve arterial oxygen saturation during sleep and reduce the amount of periodic breathing during sleep when compared to placebo.Methods: Of 16

participants, 13 had usable sleep data (6M/7F, age = 26 ± 4 years) in this double blinded, randomized, placebo-controlled crossover trial. After residing at 3810m altitude for approximately one- and one-half weeks, participants received either pentoxifylline ER 400mg or matching placebo at bedtime followed by the alternate pill two nights later. The order of medication vs. placebo was randomized. Sleep data was recorded with WatchPAT® (Itamar Medical Ltd.) device.Results: Total sleep time was decreased on pentoxifylline compared to placebo (366 ± 90 min vs. 420 ± 71 min, p=0.02). Time spent sleeping in the supine position, but not in the prone position, was also reduced with pentoxifylline (228 ± 112 min vs. 178 ± 125 min, p=0.01). Cumulative time spent with SpO2 < 88% was lower on pentoxifylline (258 ± 80 min vs. 338 ± 108, p=0.03). The Respiratory Disturbance Index (RDI) and Apnea-Hypopnea Index (AHI) were reduced in the prone position with pentoxifylline compared to placebo: RDI (63.4 ± 34.4 vs. 82.2± 31.1, p=0.01), AHI (63.1 ± 34.8 vs. 81.6 ± 31.0, p=0.01). There were no significant differences in overnight mean arterial oxygen saturation or total number of oxygen desaturations.Conclusion: These results indicate that pentoxifylline reduced overall sleep time and periodic breathing in the prone position with no change in overall nocturnal oxygen saturation. Further study with more prolonged use of pentoxifylline at higher altitude will be needed to extend these findings.

**Poster #: 17 .ACUTE MOUNTAIN SICKNESS IS ASSOCIATED WITH REDUCED REACTION TIME FOLLOWING BOTH ACTIVE AND PASSIVE ASCENT TO 3600M.** Karl Friedl1, Steven Landspurg1, Peter Figueiredo1, Janet Staab1, Mark Buller1, J Philip Karl1, Reed Hoyt1, Jon Femling2, Jason Williams2, Aaron Reilly2, Trevor Mayschak2, Emma Atkinson1, Tim Mesite1, Beth Beidleman1. 1US Army Research Institute of Environmental Medicine, 2University of New Mexico

Objective: Cognitive performance is known to decrease following acute exposure to high altitude (HA) (>3500m) but it is unknown whether acute mountain sickness (AMS) and active ascent affects the cognitive decline. Methods: To determine whether reaction time is differentially impacted at HA by the presence of AMS and ascent conditions, 78 healthy Soldiers (mean±SD; age=26±5yr) were tested at baseline residence (BLR), transported to Taos, NM (2845m), then hiked (n=39) or were driven (n=39) to a HA facility at 3600m and stayed for four days. AMS-Cerebral Factor Score (AMS-C) was assessed using the Environmental Symptoms Questionnaire at HA twice on day one (HA1), and five times on days two (HA2) and three (HA3). If AMS-C was ≥0.7 at any assessment, individuals were categorized as AMS-susceptible (AMS+; n=33); others were non-susceptible (AMS-; n=45). Simple reaction time (SRT), fatigued reaction time (FRT) and go-no-go choice reaction time (GNG) were measured using the Automated Neuropsychological Assessment Metrics (ANAM) in the mornings on BLR, HA2, and HA3. Results: Ascent conditions did not differentially impact reaction times. The percent change (%) in SRT from BLR was more negative in AMS+ vs. AMS- groups on HA2 (-10.8±17.3 vs. -3.8±13.8, p=) but not HA3 (-4.7±13.1; 0.0±12.0, p=). Similarly, the percent change (%) in FRT from BLR was more negative in the AMS+ group on HA2 (-13.2±19.5 vs. -5.6±20.9) but not HA3 (-2.6±14.7; -4.3±18.4). There were no changes in GNG from SL to HA1 or HA2. AMS-C was also negatively correlated with SRT and FRT, respectively, at both HA2 (r=-0.32, p=0.004; r=-0.29, p=0.01) and HA3(r=-0.38, p=0.001; r=-0.23, p=0.04) but GNG was only negatively correlated at HA2 (r=-0.35, p=0.004). Conclusion: Symptoms of AMS were

associated with greater decrements in reaction time, regardless of ascent conditions. Authors' views not official U.S. Army or DoD policy. Funding: USAMRDC

**Poster #: 18 .PARTIAL PRESSURE OF ARTERIAL OXYGEN IN HEALTHY AT ALTITUDE. A META-ANALYSIS USING INDIVIDUAL PATIENT DATA .** Aglaia Forrer1, Thomas Gaisl1, Ahmet Sevik1, Michelle Meyer1, Luzi Senteler1, Mona Lichtblau1, Konrad E Bloch1, Silvia Ulrich1, Michael Furian1, 2. 1Department of Respiratory Medicine, University Hospital of Zurich, Zurich, Switzerland, 2Research Department, Swiss University of Traditional Chinese Medicine, Bad Zurzach, Switzerland

Importance With increasing altitude, the partial pressure of inspired oxygen falls and consequently the arterial partial pressure of oxygen (PaO2) decreases. Even though this phenomenon is well known to occur in healthy people, the extent of the reduction as a function of altitude remains unknown.Objective The aim of this study was to present an effect size for the decrease in PaO2 that comes with each kilometre vertical gain and to identify factors influencing PaO2 at altitude. The study is registered at www.crd.york.ac.uk/prospero:CRD42021283236.Data Sources and Study Selection A systematic search of PubMed and Embase was performed from database inception to March 04, 2022. Peer-reviewed, prospective studies in healthy adults providing arterial blood gas analysis at low altitude (<1500m) and within the first 3 days at the target altitude (≥1500m) were analysed. Language was restricted to English, French and German.Data Extraction and Synthesis Main and secondary outcomes as well as study characteristics were extracted from the included studies and if possible the individual patient data was obtained. Estimates were pooled using a random-effects DerSimonian–Laird model for the meta-analysis.Main Outcomes and Measures Mean estimates and 95% confidence intervals of the association between PaO2 and altitude in healthy adults.Results 53 studies (777 individuals, 34.4% female) reporting 171 group ascents including an altitude range from 1524m to 8730m were included in the qualitative and 13 studies (305 individuals, 45.1% female) reporting 29 ascents were included in the quantitative analysis. The estimated effect size PaO2 was -1.60kPa [-1.73 to -1.47kPa] for each 1000m of altitude gain.Conclusions and Relevance This systematic review and meta-analysis provides estimates of altitude-related reductions in PaO2 in healthy individuals above 1500m. This effect estimate of 1.60kPa/1000m vertical gain for healthy people will contribute to a better understanding of hypobaric hypoxia and provide a basis for investigation in chronically ill people.

**Poster #: 19 .SELF-MONITORING TO DETECT EARLY SIGNS OF ALTITUDE ILLNESS IN COPD. A DIAGNOSTIC ACCURACY STUDY.** Michael Furian1, Aurelia Reiser1, Maamed Mademilov2, Konstantinos Bitos1, Simone Buenzli1, Ainura Abdraeva2, Benoit Champigneulle3, Arcangelo Carta1, Meret Bauer1, Tanja Ulrich1, Philipp Scheiwiller1, Julian Mueller1, Ahmet Sevik1, Stefanie Ulrich1, Laura Mayer1, Mirjam Grimm1, Simon R Schneider1, Ulan Sheraliev2, Aichurok Alymbekova2, Nurdin Shakiev2, Aijan Taalaibekova2, Aigul K Ozonova2, Kamilla Magdieva2, Gulzada Mirzalieva2, Azamat Akylbekov2, Saltanat Shabykeeva2, Talant M Sooronbaev2, Silvia Ulrich1, Konrad E Bloch1. 1Department of Respiratory Medicine, University Hospital of Zurich, Zurich, Switzerland, 2Department of Respiratory Medicine, National Center for Cardiology and Internal Medicine, Bishkek, Kyrgyz Republic, 3HP2 laboratory, Université Grenoble Alpes, Inserm (U1300), CHU Grenoble Alpes, Grenoble, 38000, France

BackgroundThere are no reliable means to identify patients with COPD at risk of altitude-related adverse health effects (ARAHE) during altitude travel. Therefore, diagnostic tests that predict ARAHE in COPD would be desirable.MethodsThis prospective diagnostic accuracy study included patients with COPD (FEV1 40-80%pred.), pulse oximetry (SpO2) ≥92% and PaCO2 <6kPa at low altitude. After baseline evaluation at 760m, patients traveled by bus to a clinic at 3100m and stayed there for 2 days. During this period, they performed structured self-monitoring (SSM) using a symptom checklist and pulse oximetry. They reported occurrence of at least moderate symptoms of acute mountain sickness (AMS) and/or SpO2 <85% (=positive index test). Patients remained at 3100m to observe whether ARAHE (=positive reference test), i.e. severe AMS symptoms, SpO2 <80% for >30min or any condition requiring medical intervention subsequently developed or not. ClinicalTrials.gov NCT03957759.Results158 COPD patients (80 women), mean±SD age 57±9yrs, participated. At 3100m, 98(62%) remained SSM negative, 55(35%) became SSM positive; ARAHE occurred in 112 of 153 (73%), ARAHE was indeterminate in 5(3%) participants. Most common ARAHE were severe hypoxemia 85(56%) and AMS 17(11%). Diagnostic accuracy of SSM quantified by C-statistic (95%CI) was 0.66 (0.59 to 0.73), sensitivity 45%, specificity 88% and positive and negative predictive value 91% and 37%, respectively.ConclusionIn lowlanders with moderate to severe COPD ascending to 3100m, ARAHE are common. SSM of symptoms and pulse oximetry is highly positive predictive of imminent ARAHE. Therefore, COPD patients testing positive in SSM may timely descend or take preventive treatment to reduce the risk of ARAHE.

**Poster #: 20 .SLEEP AND BLOOD PRESSURE DURING A 12-MONTH STAY AT CONCORDIA STATION (3233 M), ANTARCTICA.** Michael Furian1, Paul Robach2, Stijn Thoolen3, Sarah Rommel3, Sebastien Baillieul1, Stephane Doutreleau1, Pierrick J Arnal4, Samuel Verges1. 1HP2 laboratory, Université Grenoble Alpes, Inserm (U1300), CHU Grenoble Alpes, Grenoble, 38000, France, 2Ecole Nationale des Sports de Montagne, 74400 Chamonix, France, 3French Polar Institute Paul-Émile Victor, Brest, 4Dreem, Paris, France

IntroductionSleep architecture remains impaired when staying at the Concordia Station (3233m), Antarctica. The purpose of this study was to investigate sleep and blood pressure, and the pathophysiological role of hypoxia.MethodProspective cohort study in 23 subjects staying for 12 months at 3233m (N=11, mean±SD age 36±10y, BMI 24.3±3.1kg/m2) or in Dumont d'Urville, 20m (N=12, age 31±12y, BMI 22.3±3.1kg/m2), Antarctica. Before departure (BL) and

in the 1st and 12th month at the Stations, sleep assessment (DREEM) and 24h ambulatory blood pressure (BP) monitoring was performed.ResultAt 3233m, subjects had less stage 3 sleep (%total sleep time, TST) in the 1st (mean±SE 18±2%TST) and 12th (18±2%TST) month vs BL (24±3%TST, both P<0.05). In contrast, proportion of stage 2 sleep and micro-arousals were higher in the 1st (50±2%TST, 10.1±1.0/h) and 12th (51±2%TST, 11.5±1.0/h) month vs BL (43±3%TST, 7.1±1.2/h, both P<0.05). At 20m, no changes occurred. At 3233m, nocturnal mean BP was higher in the 1st (85±2mmHg) and 12th (80±2mmHg) month vs BL (76±2mmHg, both P<0.05). The higher nocturnal BP was caused by a higher proportion of non-dipping defined by <10% Δnight-day BP, which was 0% at BL, 45% in 1st and 27% in 12th month at 3233m (P<0.05, 1st month vs BL). At 20m, no changes occurred. ConclusionA 12-month stay at the Concordia Station at 3233m was associated with worse sleep and nocturnal BP compared to pre-departure. Since these impairments were not observed at Dumont d'Urville, preventive measures against hypoxia might be considered to improve outcomes in these crewmembers.

**Poster #: 21 .PRELIMINARY OBSERVATIONS ON THE EFFECT OF ACUTE INTERMITTENT HYPOXIA ON POSTPRANDIAL PLASMA LIPID LEVELS IN PREMENOPAUSAL WOMEN.** Nicholas Goulet1, Caroline Marcoux1, Vincent Bourgon2, Jean-François Mauger1, Ruwan Amaratunga3, Pascal Imbeault1, 3. 1University of Ottawa, Canada, 2Université du Québec en Outaouais, Canada, 3Institut du Savoir Montfort, Canada

Introduction: Hypoxia impairs lipid metabolism in multiple tissues, resulting in increased circulating blood lipid levels. Despite well-characterized differences in lipid metabolism between men and women, research into the relationship between hypoxia and lipid metabolism has been conducted almost exclusively in men thus far. Therefore, we investigated whether acute moderate intermittent hypoxia, previously demonstrated to increase postprandial blood lipid levels in men, has similar effects in women. Methods: Using a randomized crossover design, six young women (mean age [SD], 21.5 years [3.6]) were exposed to 6 hours of normoxia (~98% SpO2) and intermittent hypoxia (~15 hypoxic cycles per hour: 100% nitrogen, ~85% SpO2) following the consumption of a high-fat meal (59% fat) during the early follicular phase. Plasma levels of total triglycerides (TG), buoyant triglyceride-rich lipoprotein TG (TRL-TG), denser TRL-TG, and non-esterified fatty acids (NEFA) were analyzed using colorimetric assays at 0, 30, 60, 90, 120, 180, 240, 300, and 360 minutes after meal ingestion. Oxyhemoglobin saturation (SpO2) was monitored continuously with pulse oximetry. Results: Mean SpO2 was lower during intermittent hypoxia compared to normoxia ($p = 0.045$). Plasma levels of total TG, buoyant TG, and denser TG increased similarly over time in both conditions (time: $p \leq 0.047$, $\eta p2 \geq 363$; time x condition: $p \geq 0.365$). Across time, plasma NEFA levels were higher during intermittent hypoxia, however, this fell short of statistical significance (time x condition: $p = 0.057$, $\eta p2 = 0.352$). Conclusion: While not definitive, our findings indicate that acute intermittent hypoxia does not alter the postprandial TG response in premenopausal women. Funding: Natural Sciences and Engineering Research Council of Canada, and Association Médicale Universitaire de l'Hôpital Montfort.

**Poster #: 22 .ACUTE INTERMITTENT HYPOXIA IS NOT ASSOCIATED WITH CHANGES IN PLASMA BIOMARKERS OF ACUTE KIDNEY INJURY IN HEALTHY YOUNG ADULTS AND INDIVIDUALS WITH OBSTRUCTIVE SLEEP APNEA.** Nicholas Goulet1, Emily J. Tetzlaff1, Renée Morin1, Jean-François Mauger1, Ruwan Amaratunga2, Glen P. Kenny1, Pascal Imbeault1, 2. 1University of Ottawa, Canada, 2Institut du Savoir Montfort, Canada

Introduction: It is currently proposed that obstructive sleep apnea (OSA) can induce kidney dysfunction by causing ischemia-reperfusion injury in proximal tubular cells. However, it remains unclear whether a single exposure to intermittent hypoxia can increase circulating biomarkers of acute kidney injury (AKI). Therefore, we conducted an exploratory study aimed at evaluating the relationship between intermittent hypoxia and AKI. Methods: Using a randomized crossover design, 24 healthy young adults (18 men, 6 women; mean age [SD], 22 years [3]) and 7 middle-aged adults with OSA (6 men, 1 woman; 54 years [6]) were exposed to normoxia (~98% oxyhemoglobin saturation (SpO2)) and intermittent hypoxia (~15 hypoxic cycles per hour: 100% nitrogen, ~85% SpO2) for 6 hours following a meal. Plasma concentrations of neutrophil gelatinase-associated lipocalin (NGAL), interleukin 18 (IL-18), liver-type fatty acid-binding proteins (L-FABP), and kidney injury molecule-1 (KIM-1) were measured at baseline, and after 3 and 6 hours of exposure. SpO2 was monitored continuously. Results: Mean SpO2 (%) and time spent under 90%, 85%, and 80% were lower during intermittent hypoxia compared to normoxia ($p < 0.001$, $\eta p2 \geq 771$). No differences in plasma concentrations of NGAL and KIM-1 were observed. Irrespective of group, plasma IL-18 concentrations increased over time during normoxia (time x condition: $p = 0.033$, $\eta p2 = 0.122$) and plasma L-FABP concentrations transiently decreased after 3 hours in both conditions (time: $p = 0.008$, $\eta p2 = 0.152$). Conclusion: We did not observe a clear relationship between intermittent hypoxia and biomarkers indicative of AKI. Further studies looking at intensity-dependent effects are needed to elucidate the mechanisms underlying this relationship. Funding: Natural Sciences and Engineering Research Council of Canada, Association Médicale Universitaire de l'Hôpital Montfort.

**Poster #: 23 .CHARACTERIZING THE RESPONSE TO INTERMITTENT HYPOXIA DURING THE POSTPRANDIAL STATE IN IMMUNE CELLS FROM YOUNG ADULTS.** Nicholas Goulet1, Vincent Bourgon2, Caroline Marcoux1, Jean-François Mauger1, James J. McCormick1, Ruwan Amaratunga3, Glen P. Kenny1, Pascal Imbeault1, 3. 1University of Ottawa, Canada, 2Université du Québec en Outaouais, Canada, 3Institut du Savoir Montfort, Canada

Introduction: Growing evidence shows that postprandial inflammation occurs in immune cells following a high-fat meal. However, little is known about how inflammatory responses are modulated by intermittent hypoxia during the postprandial state, which is important considering that individuals with obstructive sleep apnea are exposed to chronic intermittent hypoxia. Additionally, it remains unclear if postprandial inflammation occurs synchronously with changes in autophagy, an important component of the cytoprotective responses. Methods: Four young adults (2 men, 2 women; mean age [SD], 22 years [5]) were randomly exposed to normoxia (~98% SpO2) and intermittent hypoxia (~15 hypoxic cycles per hour, 100% nitrogen, ~85% SpO2) for 6 hours following a high-fat meal (59% fat). Plasma non-esterified fatty acid (NEFA)

concentrations were measured using colorimetric assays, and proteins associated with autophagy (microtubule-associated protein 1 light chain 3 [LC3]-II) and inflammation (interleukin-6 [IL-6]) were assessed in peripheral blood mononuclear cells at baseline, and after 3 and 6 hours of exposure via Western blot (data presented as a relative quantity (RQ) to the respective baseline). Results: NEFA changed over time, decreasing after 3 hours, but increasing above baseline after 6 hours ($p = 0.012$, $\eta p2 = 0.891$), with higher elevations observed during intermittent hypoxia ($p = 0.036$, $\eta p2 = 0.819$). During normoxia only, IL-6 increased after 3 hours (1.5RQ [0.4], $p = 0.046$). When comparing between conditions, a trend towards higher LC3-II during normoxia was observed relative to intermittent hypoxia ($p = 0.063$, $\eta p2 = 0.735$). Conclusion: Due to a small sample size, our preliminary observations remain inconclusive with the additional caveat that complex cellular processes cannot be assessed with a single biomarker, highlighting the need for larger studies. Funding: Natural Sciences and Engineering Research Council of Canada, Association Médicale Universitaire de l'Hôpital Montfort.

**Poster #: 24 .CHARACTERIZATION OF THE INFLAMMATORY RESPONSE TRIGGERED BY NORMOBARIC HYPOXIA.** Sonja Hersel1, Frank Splettstoesser1, Katrin Reiners2, Sarah Zaffarana2, Laura de Boni3, Henning Weis3, 4, Fabian Hoffmann3, 5, Jan-Niklas Hoenemann3, 5, Jens Jordan3, Ulrich Limper3, Jens Tank3, Stilla Frede1. 1Department of Anesthesiology and Intensive Care Medicine, University Hospital Bonn, Germany, 2Institute of Clinical Chemistry and Clinical Pharmacology, University Hospital Bonn, Germany, 3Department of Cardiovascular Aerospace Medicine, Institute for Aerospace Medicine, German Aerospace Center, Cologne, Germany, 4Department of Nuclear Medicine, University of Cologne, Germany, 5Department of Internal Medicine III, Division Cardiology, Pneumology, Angiology and Intensive Care, University of Cologne, Germany

Objective: Hypoxia and inflammation share interlinked cellular pathways. We investigated the hypothesis that exposure to normobaric hypoxia is sufficient to trigger pro-inflammatory processes in human immune and endothelial cells, which could be involved in inflammatory signaling. Methods: White blood cells (WBCs) were collected from normoxic healthy donors. Primary human pulmonary microvascular endothelial cells (HPMECs) were purchased from PromoCell. Cells were incubated for up to 24h under normoxic or hypoxic conditions with 10% or 1% oxygen (O2). Regulation of pro-inflammatory and hypoxia-inducible genes and proteins was evaluated by RT-PCR and ELISA. Blood samples were taken from participants of the MyoCardioGen 3 (MCG3) study who were exposed to sustained severe normobaric hypoxia (30 days, lowest O2 concentration 9.5%). Plasma from the MCG3 participants was analyzed by Luminex assay and ELISA. In addition, extracellular vesicles (EVs) were investigated using nanoparticle tracking analysis (NTA). Results: WBCs and HPMECs exposed to 1% O2 showed an increased expression of tested pro-inflammatory cytokines, which was absent under normoxic or 10% hypoxic conditions. However, the concentrations of pro-inflammatory cytokines were undetectable or unchanged in cell supernatants under both hypoxic conditions. ELISA results showed a trend towards increased IL-8 concentrations in plasma of MCG participants and HPMEC supernatants under comparable oxygen concentrations. NTA analysis confirmed a change in EV numbers in in vitro and in vivo hypoxia experiments. Conclusion: Our study indicates that normobaric hypoxia is unable to induce a pro-inflammatory state in WBCs and HPMECs. Since regulation of chemokines and EVs was observed in donors exposed to

sustained hypoxia, we conclude that hypoxia most likely affects immune priming in vivo. The role of cell-cell communication via unidentified humoral factors or EVs needs further investigation. Funding: No external funding.

**Poster #: 25 .Measuring the effects of supplemental oxygen on inspired oxygen fraction at extreme simulated altitude..** Matthew M. Howrey1, Denis J. Wakeham1, 2, Peter Hackett3, Murugappan Ramanathan1, Marcus Payne1, Dean Palmer1, Renie Guilliod1, 2, James Berry1, 2, Tony G. Babb1, 2, Benjamin D. Levine1, 2, Christopher M. Hearon Jr.1, 2, Andrew R. Tomlinson1, 2. 1Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital Dallas, Dallas, Texas, USA, 2The University of Texas Southwestern Medical Center, Dallas, Texas, USA, 3Altitude Research Center, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA

Most extreme altitude climbers use supplemental oxygen when climbing above 8000m. Despite its common use, the fraction of inspired oxygen (FiO2) delivered and its effects on oxygen saturation (SpO2) during extreme hypobaric hypoxia are unknown.Therefore, we measured gas fractions (via mass spectrometry) in six unacclimatized or partially acclimatized individuals using a capillary within the Summit Oxygen mask. Continuous measurements of gas fractions were made during 4-minute exposures at nominal flows of 6, 4, 2, 1 and 0 L/min. Measurements were made at rest and during cycling at 60 and 120 Watts at extreme simulated altitude (282 mmHg; 8100m), as well as at rest at 253 mmHg (8848m). Dynamic mixing of ambient air with supplemental oxygen within the mask as well as a reservoir effect produced distinct patterns of oxygen fractions that were not amenable to standard assessments of FiO2. Thus, we quantified the time-averaged mean oxygen fraction during inspiration (TA-mean) and the end-tidal (alveolar) oxygen fraction (taken as the end-expiratory plateau) and performed exploratory regression analyses between these oxygen fractions and SpO2 to assess their physiological relevance and utility in this setting.With decreasing supplemental oxygen flow (6, 4, 2, 1 and 0 L/min) during rest at 282 mmHg, there were stepwise decreases in TA-mean oxygen fraction (0.659, 0.425, 0.405, 0.272, 0.215, P=0.004) and end-tidal oxygen fraction (0.697, 0.489, 0.391, 0.276, 0.153, P=0.0004). Similar stepwise decreases were observed during exercise and at 253 mmHg. There were exponential relationships between both TA-mean and end-tidal oxygen with SpO2 (R2=0.67 and R2=0.78, respectively) across all conditions.These data provide the first assessments of oxygen fractions at extreme simulated altitude when using supplemental oxygen. Based upon our results, TA-mean and end-tidal oxygen can provide insight into oxygen fractions when assessments of FiO2 are not possible during studies delivering supplemental oxygen via a mask.

**Poster #: 26 .ACTIVE ASCENT INDUCES PLASMA VOLUME RETENTION THAT LIKELY EXACERBATES ACUTE MOUNTAIN SICKNESS AT 3600M.** Reed Hoyt1, Janet Staab1, Peter Figueiredo1, Steven Landspurg1, Jon Femling2, Jason Williams2, Aaron Reilly2, Trevor Mayschak2, Mark Buller1, J Philip Karl1, Emma Atkinson1, Tim Mesite1, Beth Beidleman1. 1US Army Research Institute of Environmental Medicine, 2University of New Mexico

Objective: Plasma volume (PV) typically decreases following passive ascent to high altitude (HA), but strenuous exercise may alter this response due to greater arterial desaturation with exercise. Methods: To determine the impact of active versus passive ascent on PV changes at HA, 78 healthy Soldiers (mean±SD; age=26±5yr) were tested at baseline residence (BLR), transported to Taos, NM (2845m), then hiked (n=39) or were driven (n=39) to HA (3600m), and stayed for 4 days. AMS-Cerebral factor score (AMS-C) was assessed using the Environmental Symptoms Questionnaire (ESQ) at HA twice on day 1 (HA1), five times on days 2 and 3 (HA2 and HA3) and once on day 4 (HA4). Pulse arterial oxygen saturation (SpO2) was measured immediately after the ESQ. If AMS-C was ≥0.7 at any assessment, individuals were categorized as AMS-susceptible (AMS+; n=33); others were non-susceptible (AMS−; n=45). Hemoglobin and hematocrit were measured in the morning at BLR, HA2, HA3 and HA4 and at 18:00 on HA1 to calculate PV changes. Results: The SpO2 did not differ between active and passive ascent cohorts in the AMS- group at any HA time point. SpO2 (%), however, was lower in the active vs. passive ascent cohort in the AMS+ group, on HA1 (85.0±7.9 vs. 87.9±7.9, p=0.04) and HA4 (87.8±4.6 vs. 89.0±3.1, p=0.03). In the passive ascent cohort, PV changes were similar in the AMS+ and AMS− groups at all HA time points. In the active ascent cohort, PV changes (%) were lower in the AMS+ vs. AMS− group at HA1 (+1.7±6.5 vs. −4.3±6.0, p=0.04) and HA4 (−1.3±5.1 vs. −7.3±7.8, p=0.04). The PV changes were positively correlated with AMS-C scores at HA1 (r=0.22, p=0.05) and HA2 (r=0.21, p=0.04). Conclusion: Active ascent induced a retention of plasma volume in AMS+ individuals early in the exposure likely due to a reduction in blood oxygen saturation and associated antidiuresis. Authors' views not official U.S. Army or DoD policy. Funding: USAMRDC

**Poster #: 27 .AMBULATORY BLOOD PRESSURE IN OLDER ADULTS AT LOW VERSUS HIGH ALTITUDE: THE COLORADO HIGH ALTITUDE MONITORING BLOOD PRESSURE STUDY (CHAMPS) .** Greta Kreider-Carlson 1, Andrew C Burns2, Ilaria Ferrari2, Cameron Niswander2, Linda E Keyes3. 1Hennepin, 2University of Colorado School of Medicine, 3University of Colorado, Anchutz Campus

Introduction: Blood pressure (BP) after acute high altitude exposure varies between individuals and is most accurately measured by 24-hour ambulatory BP (ABP) monitoring. Understanding impacts of altitude on BP is essential in the creation of evidence-based travel guidelines.Objective: Compare 24-hour ABP at low versus high altitude in participants with and without preexisting hypertension.Methods: This was a prospective observational cohort study of adult lowlanders, comparing 24-hour ABP at low (<1,000 m) versus high altitude (2,800-3,000 m). BP was monitored every 30 minutes while awake and hourly overnight for 24 hours using Welch-Allyn 6100 ABP monitors.Results: 19 participants completed the high altitude study (mean age 64, 11 with underlying hypertension). 12 participants completed low and high altitude measurements. We found no difference in average 24-hour mean arterial pressure (MAP) between low and high altitude in all-comers, mean diff 4 mmHg, [95% CI:-4-11 mmHg], p=0.3. Participants without preexisting hypertension had a greater increase in 24-hour MAP from low to high altitude on average versus those with preexisting hypertension (average change +11 mmHg vs -2 mmHg, respectively, p=0.042). Asymptomatic severely elevated BP was common at both altitudes.Conclusions: In these older adults, BP was similar at low and high altitude, with high individual variation. Our data suggest that BP is more likely to increase at

high altitude in those without underlying hypertension, and to stay the same or decrease in those with hypertension.

**Poster #: 28 .ACUTE MOUNTAIN SICKNESS DOES NOT IMPACT VENTILATORY ACCLIMATIZATION FOLLOWING ACTIVE AND PASSIVE ASCENT TO 3600M.** Steven Landspurg1, Peter Figueiredo1, Emma Atkinson1, Janet Staab1, Mark Buller1, Reed Hoyt1, Philip Karl1, Tim Mesite1, Beth Beidleman1, Jon Femling2, Jason Williams2, Aaron Reilly2, Trevor Mayschak2. 1US Army Research Institute of Environmental Medicine, 2University of New Mexico Health Sciences Center

Introduction: Whether acute mountain sickness (AMS) differentially impacts the magnitude or time course of ventilatory acclimatization at high altitude (HA) remains controversial. Methods: To determine whether AMS impacts ventilatory acclimatization following both passive and active ascent to HA, 78 healthy Soldiers (mean±SD; age=26±5yr) were tested at baseline residence (BLR), transported to Taos, NM (2845m), then hiked (n=39) or were driven (n=39) to 3600m, and stayed for four days. AMS-C was assessed using the Environmental Symptoms Questionnaire at HA twice on day 1 (HA1), five times on days 2 (HA2) and 3 (HA3) and once on day 4 (HA4). If AMS-C was ≥0.7 at any timepoint, individuals were categorized as AMS-susceptible (AMS+, n=33); others were categorized as non-susceptible (AMS-, n=45). Portable real-time capnography was used to measure resting partial pressure of end-tidal carbon dioxide (PETCO2 mmHg) at ~09:00 at BLR, and after 19h (HA2), 43h (HA3), and 67h (HA4) at HA. Resting pulse arterial oxygen saturation (SpO2, %) was measured immediately after PETCO2. Results: Ascent conditions did not differentially impact ventilatory responses. PETCO2 and SpO2 did not differ between AMS+ and AMS- groups at BLR or any time point at HA. The PETCO2(mmHg) in AMS+ vs. AMS- groups, decreased($p<0.05$) from BLR (37.2±3.6 vs. 36.9±3.1) on HA2 (33.5±4.1 vs. 33.7±4.0), remained stable from HA2 to HA3 (33.4±4.1 vs. 33.8±3.9) and decreased($p<0.05$) from HA3 to HA4 (31.8±4.4 vs. 31.4±4.1). SpO2(%) decreased($p<0.05$) in both AMS+ and AMS-, from BLR (97.3±1.5 vs. 96.9±1.5) on HA2 (87.9±3.1 vs. 88.8±2.9) and remained stable from HA2 to HA3 (88.8±3.1 vs. 89.1±2.9) and HA4 (88.9±3.1 vs. 89.6±2.1). Conclusions: Ventilatory acclimatization occurred at HA, but AMS-susceptibility did not impact the magnitude or time course of acclimatization following active or passive ascent to 3600m. Authors' views not official U.S. Army or DoD policy. Funding: USAMRDC

**Poster #: 29 .VENTILATORY ACCLIMATIZATION OBTAINED AT MODERATE ALTITUDE (1190M) DOES NOT CARRY OVER FOLLOWING ACTIVE OR PASSIVE ASCENT TO A HIGHER ALTITUDE (3600M) .** Steven Landspurg1, Peter Figueiredo1, Emma Atkinson1, Janet Staab1, Mark Buller1, Reed Hoyt1, Philip Karl1, Tim Mesite1, Beth Beidleman1, Jon Femling2, Jason Williams2, Aaron Reilly2, Trevor Mayschak2. 1US Army Research Institute of Environmental Medicine, 2University of New Mexico Health Sciences Center

Introduction: Previous research has demonstrated that ventilatory acclimatization obtained at moderate altitude (1800-2200m) carries over following ascent to a higher altitude, but whether a lower altitude threshold (1190m) is also effective at inducing ventilatory acclimatization

following ascent to a high altitude (HA) is unknown. Methods: To determine the impact of moderate- versus low-altitude residence (MAR vs. LAR) and ascent conditions on ventilatory acclimatization following ascent to HA, 78 healthy Soldiers (mean±SD; age=26±5yr) were tested at baseline residence (BLR) at 331m (LAR; n=41) or 1190m (MAR; n=37), transported to Taos, NM (2845m), then hiked (n=39) or were driven (n=39) to HA (3600m), and stayed for four days. Portable real-time capnography was used to measure resting partial pressure of end-tidal carbon dioxide (PETCO2, mmHg) at ~09:00 on BLR, and after 19h (HA2), 43h (HA3), and 67h (HA4) at HA. Resting pulse arterial oxygen saturation (SpO2, %) was measured immediately after the PETCO2 assessment. Results: Ascent conditions did not differentially impact ventilatory responses. PETCO2 (mmHg) did not differ between MAR versus LAR, at any time point but decreased($p<0.05$) from BLR (36.6±3.2 vs. 37.5±3.3) on HA2 (34.1±3.7 vs. 33.3±3.7), remained stable from HA2 to HA3 (34.1±4.4; 33.3±3.7) and decreased($p<0.05$) from HA3 to HA4 (32.4±4.3 vs. 31.1±4.2). SpO2 (%) was lower in MAR versus LAR, at BLR (96.5±1.1 vs. 97.6±1.2, $p=0.001$) but did not differ between groups at HA2, HA3 or HA4. SpO2(%) decreased($p<0.05$) in both MAR and LAR, from BLR on HA2 (89.1±3.2; 87.9±3) and remained stable from HA2 to HA3 (89.4±3.7; 88.7±3.1) and HA4 (89.6±3.3; 89.1±3.0). Conclusion: Ventilatory acclimatization occurred in both LAR and MAR at 3600m, but the magnitude and time course did not differ between altitude-residence groups or ascent conditions. Authors' views not official U.S. Army or DoD policy. Funding: USAMRDC

**Poster #: 30 .ACCURACY OF WRIST WORN OXYGEN SATURATION MONITORS IN HYPOXIC AND HYPOXIC AND COLD CONDITIONS. .** Floris Paalman1, Carmen Possnig1, Hendrik Mugele1, Justin Lawley1, 2. 1Department of Sport Science, Division of Performance Physiology and Prevention, University of Innsbruck, 2Institute of Mountain Emergency Medicine, Eurac Research, Bolzano, Italy

Introduction: Wrist-worn oxygen saturation (SpO2) monitors could provide valuable information if accurate, especially in comparison to fingertip devices in cold environments where a reduction in finger cutaneous blood flow impairs signal quality. Methods: Study 1: Seven participants were exposed to a simulated altitude of 4500m, and then SpO2 was clamped at 85%, 90% & 95% based on a clinical Nellcor N600x monitor with a forehead sensor. SpO2 was simultaneously recorded on a Nonin 9590 finger sensor, the Apple Watch 6 and the Garmin Venu 2S. Study 2: Nineteen participants were exposed to a simulated altitude of 4500m for 2 hours, and on a separate occasion combined with whole body cooling to a target skin temperate of 27°C. SpO2 was recorded with the Nellcor N600x, Nellcor 9590 fingertip sensor and the Apple Watch 6. Results: Study 1: The Apple Watch 6 showed good validity (typical error of the estimate (TEE) = 2.4%, $r=0.82$, $p<0.0001$, CV=3.3%, Bias -0.33) compared to the clinical forehead sensor, which was similar to the Nonin fingertip sensor (data not shown). The validity of the Garmin Venu 2S was inferior (TEE = 3.8%, $r=0.66$, $p<0.0001$, CV =4.6%, Bias 1.92). Study 2: The Apple Watch 6 showed acceptable validity when free breathing (TEE = 3.01%, $r=0.75$, $p<0.0001$, CV =3.8%) over a SpO2 range of 75 to 95%. In the cold, the validity was reduced on the Apple watch (TEE = 4.34%, $r=0.71$, $p<0.0001$, CV =5.6%) similar to the Nonin fingertip sensor (TEE = 3.68%, $r=0.80$, $p<0.0001$, CV =4.6%). Conclusion: SpO2 can be obtained by a wrist-worn monitor with similar validity to a clinical SpO2 forehead monitor in hypoxic conditions. However, its validity is reduced during cold exposure like a fingertip sensor.

## Poster #: 31 .HIGH-ALTITUDE PULMONARY EDEMA IN COLORADO CHILDREN: A CROSS-SECTIONAL SURVEY AND RETROSPECTIVE REVIEW.

Timothy Kelly1, Maxene Meier2, Jason Weinman2, Dunbar Ivy2, John Brinton2, Deborah Liptzin2. 1University of Indiana, 2University of Colorado

Introduction: Few studies of high-altitude pulmonary edema (HAPE) are specific to the pediatric population. The purpose of this investigation was to further characterize the radiographic patterns of pediatric HAPE, and to better understand ongoing risk following an initial pediatric HAPE episode.Methods: This study uses both a retrospective chart review and cross-sectional survey. Pediatric patients with HAPE at a single quaternary referral center in the Rocky Mountain Region were identified between the years 2013 and 2020. Patients were eligible if they presented with a clinical diagnosis of HAPE and had a viewable chest radiograph (CXR). Surveys were sent to eligible patients/families to gather additional information relating to family history, puberty, and HAPE recurrence.Results: Forty-two individuals met criteria for clinical diagnosis of HAPE with a viewable CXR. A majority of CXRs (24/42, 57.1%) demonstrated predominant right-sided involvement. Similarly, 24 CXRs (24/42, 57.1%) demonstrated predominant upper lobe involvement. Twenty-one (21/42, 50%) surveys were completed. Many children went on to experience at least one other HAPE episode (8/19, 42.1%).Conclusion: The most common radiographic pattern seen in pediatric HAPE is pulmonary edema that favors the right lung and upper lobes. After an initial HAPE presentation, over 1/3 of children will experience additional HAPE episodes. One family reported "We have not been back to higher altitudes in fear of this [HAPE] happening again;" clearly, pediatric HAPE is an anxiety provoking, and potentially deadly disease that requires ongoing efforts to better understand pediatric HAPE physiology, treatment, and recurrence risk. Funding: DI is supported by NIH/NCATS Colorado CTSA Grant Number UL1 TR002535. DRL is supported by NIH/ECHO UG1OD024952. Contents are the authors' sole responsibility and do not necessarily represent official NIH views.

## Poster #: 32 .ASSESSING LOOP GAIN VIA VOLUNTARY END-EXPIRATORY BREATH HOLDS IN STEADY-STATE HYPOXIA: A METHODOLOGICAL CHARACTERIZATION.

Benjamin Mackenzie1, Courtney Taylor1, Anthony Marullo1, Jordan Bird1, Scott Thrall1, Alexandra Skalk1, Britta Byman1, Brandon Pentz1, Trevor Day1. 1Mount Royal University

Introduction: Central sleep apnea (CSA) occurs in 50-60% of heart failure (HF) patients, and is universal with high altitude (HA) ascent. HF patients with CSA have higher peripheral chemoreflex (PCR) gain than those without CSA. Hypoxic exposure during HA ascent increases PCR gain via carotid body sensitization. Loop gain (LG) is defined as the responsiveness of the chemoreflex feedback loop. In sleep studies, LG is quantified as the ratio of the ventilatory response following a ventilatory disturbance, with values over 1.0 representing susceptibility to ventilatory instability during sleep and CSA. We aimed to characterize a novel method to quantify LG using a standardized series of short, voluntary, end-expiratory breath holds (EEBH) in a background of steady-state hypoxia, to simulate CSA. We hypothesized that LG would be similar in magnitude to that quantified during sleep studies

(Range:0.2-2.0).Methods: Fifteen heathy participants (6F) were instrumented with a calibrated pneumotachometer to measure breath-by-breath ventilation and underwent a baseline period of 10-min under steady-state hypoxia (FIO2≈0.145, PO2≈96mmHg), followed by five consecutive ~15-sec EEBHs separated by ~1-min recovery. LG was quantified as the ventilatory response immediately following EEBH breakpoint, indexed against the ventilatory disturbance, taken as the absolute reduction in ventilation to apnea from baseline values. LG was then quantified using either (a) the 1st, (b) an average of the 1st+2nd and (c) an average of the 1st+2nd+3rd breaths following EEBH, with the five LG calculations averaged to obtain a representative within-individual value.Results: Mean LG ratios were 1.77±0.70 (1st), 1.31±0.56 (1st+2nd), and 0.96±0.46 (1st+2nd+3rd; P<0.00001). These three LG calculations were well-correlated, within-individual (r>0.99, P<0.00001).Conclusions: We suggest that this simple voluntary EEBH protocol can be used to quantify LG in those susceptible to CSA, as a predictor of CSA severity in contexts such as HF or HA ascent. Funding: NSERC Discovery

**Poster #: 33 .VASCULAR REACTIVITY TO RHYTHMIC HANDGRIP AT ALTITUDE.** Lauren Maier1, Emily Vanden Berg1, Lydia Simpson2, Michiel Ewalts3, Jenna Wowdzia1, 4, Travis Gibbons5, Katharine Foster6, Jared Baylis7, Christopher Gasho6, David Macleod8, Sean van Diepen9, Philip Ainslie5, James Anholm6, Michael Stembridge10, Jonathan Moore3, Craig Steinback1. 1Neurovascular Health Laboratory, Faculty of Kinesiology, Sport, and Recreation, University of Alberta, 2University of Innsbruck, 3Bangor University, 4Program for Pregnancy and Postpartum Health, Faculty of Kinesiology, Sport, and Recreation, University of Alberta, 5University of British Columbia - Okanagan, 6Loma Linda University, 7Southern Medical Program, University of British Columbia, 8Duke University, 9Faculty of Medicine and Dentistry, University of Alberta, 10Cardiff Metropolitan University

Objectives: We aimed to examine sympathetic reactivity of the vasculature to handgrip exercise at altitude, determine the direct contribution of adrenergic receptors to the exercise response, and explore any sex-based differences.Methods: 8 young, healthy participants (4M/4F) were tested at low (Kelowna, BC; 344m) and high (Barcroft Station, White Mountain 3800m) altitude (days 3-12). Participants performed 3 minutes of rhythmic handgrip exercise at 25% of their maximal voluntary contraction during local infusions of saline, propranolol (beta-blockade), and propranolol plus phentolamine (combined alpha- and beta-blockade). Doppler ultrasound was used to examine brachial artery blood flow (FBF) and calculate forearm vascular conductance (FVC).Results: There was a main effect of blockade on resting FVC (p<0.001), but it was not different between low- and high-altitude (main effect p=0.606). The FVC response to rhythmic handgrip was also different between conditions [low-altitude (control, +10.1±6.5 a.u.; beta-blockade, +13.9±3.4 a.u.; alpha-beta-blockade, +3.1±5.1 a.u.); and high-altitude (control, +11.0±3.8 a.u.; beta-blockade, +13.0±4.8 a.u.; alpha-beta-blockade, +2.9±6.8 a.u.) p=0.009], but was not different between locations (p=0.989). There was a main effect of blockade on FBF during exercise [low-altitude (control, 17.8±5.7 mL/min/100mLx102; beta-blockade, 20.7±7.2 mL/min/100mLx102; alpha-beta-blockade, 25.9±5.3 mL/min/100mLx102); and high-altitude (control, 16.4±4.5 mL/min/100mLx102; beta-blockade, 27.3±6.1 mL/min/100mLx102; alpha-beta-blockade, 31.2±6.9 mL/min/100mLx102) p=0.0007], but it was not different between locations (p=0.095). No differences between males and females existed in baseline FVC or response to handgrip exercise at low- or high-altitude.Conclusions: This evidence supports that there is alpha-mediated restraint of exercising blood flow in the vasculature. However, it does

not differ between low- and high-altitude, suggesting the response to low to moderate-intensity exercise is preserved at altitude. Despite evidence indicating females have differing control of the vasculature due to beta-receptor sensitivity, these results suggest no difference in resting conductance or response to rhythmic exercise at altitude.Funding: NSERC

**Poster #: 34 .Pulsatile cerebrovascular hemodynamics in response to pharmacologically altered cerebral perfusion following acclimation to high altitude.**

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Background: Cerebral blood flow (CBF) at high altitude (HA) increases to maintain oxygen($O_2$) delivery; however, since HA also increases systemic hemodynamic factors (i.e., blood pressure [BP] and heart rate [HR]) we aimed to characterize the impact of HA cerebral perfusion on cerebral hemodynamic pulsatilities (PI) and damping (DF = PIICA / PIMCAv), both of which are considered indexes of cerebrovascular compliance. Because the brain acts as a high pass filter, we hypothesized that acute pharmacologically-induced elevations and reductions in PI and CBF would elicit robust increases and decreases in DF, respectively.Methods: Six males were studies following 2-weeks acclimatization to 5050m. Extracranial hemodynamics (velocity, diameter, flow, PI) were measured proximally in the internal carotid artery (ICA), while velocity (MCAv) and pulsatility (PIMCAv) were measured in the distal middle cerebral artery using ultrasound. DF was calculated using proximal and distal PI's. BP, HR, and arterial blood gases were also measured. Dobutamine (DOB-2-5 μg/kg/min + acetazolamide (ACZ-10mg/kg) and indomethacin (INDO 1.45 mg/kg) trials were randomized. Results: DOB+ACZ significantly increased HR (78±14bpm vs 83±14bpm), MCAv (74±15cm.s-1 vs 91±17cm.s-1), ICAdiameter (5.0±0.02 mm vs 5.3±0.03 mm), ICAflow (271±115ml.min-1 vs 360±68.9ml.min-1), and PIICA(1.0±0.28a.u. vs 1.2±0.29a.u), but did not alter DF. In contrast, INDO decreased ($p<0.05$) ICAflow (225±66ml.min-1 vs 184±55ml.min1) and DF (1.9±0.59a.u vs 1.38±0.29a.u), but increased PIMCAv (0.65±0.11a.u vs 0.83±0.11a.u; $p<0.05$). Neither drug altered BP or arterial blood gases.Conclusion: Our findings indicate that a compliant cerebral vasculature may be protected from enhanced hemodynamic pulsatile stress (i.e., preserved DF) when perfusion is pharmacologically increased at HA. This protective benefit appears to be diminished (reduced DF) when perfusion is pharmacologically reduced. Future studies exploring whether these cerebrovascular compliance mechanisms underlie the etiology of altitude-related illness are required.

**Poster #: 35 .DIFFERENTIAL CLAMPING OF HYPOXIA INDUCES DISTINCT CHANGES IN INTRACORTICAL AND SPINAL NEURAL NETWORKS.** Daniel McKeown1, 2, 3, Glenn Stewart2, 3, Justin Kavanagh1, 2, 3. 1Neural Control of Movement Laboratory, 2Menzies Health Insitute Queensland, 3Griffith University

The purpose of this study was to examine how two common methods of continuous hypoxia impact the activity of intracortical circuits responsible for inhibition and facilitation of motor output, and spinal excitability. Ten participants were exposed to 2 hr of hypoxia at 0.13 fraction of inspired oxygen (FIO2 clamped protocol) and 80% of peripheral capillary oxygen saturation (SpO2 clamped protocol) using a simulating high-altitude device on two visits separated by a week. Using transcranial magnetic and peripheral nerve stimulation, unconditioned motor evoked potential (MEP) area, short intracortical inhibition (SICI) and facilitation (ICF), and F-wave persistence and area, were assessed in the first dorsal interosseous muscle before titration, 1 and 2 hr of hypoxia, and at reoxygenation. The clamped protocols resulted in differing reductions in SpO2 by 2 hr (FIO2 clamped protocol: 90.6 ± 2.5%, SpO2 clamped protocol: 81.9 ± 1.3%). Although unconditioned MEP area did not differ between the protocols, SICI was significantly lower at 2 hr ($P < 0.001$) and ICF was higher throughout ($P = 0.005$) the FIO2 clamped protocol compared to the SpO2 clamped protocol. Furthermore, a negative correlation between SICI and SpO2 ($r = 0.31$) and a positive correlation between ICF and SpO2 ($r = 0.30$) were determined, where greater reductions in SpO2 resulted in less inhibition and less facilitation of MEP responses. Although F-wave area progressively increased similarly throughout the protocols ($P = 0.036$), persistence of responses was reduced at 2 hr and reoxygenation ($Ps < 0.01$) during the SpO2 clamped protocol compared to the FIO2 clamped protocol. This study demonstrates that activity in intracortical networks responsible for facilitating and inhibiting motor output from the motor cortex, and activity of spinal motoneurones, are dependent on the degree of hypoxia, where greater severities of exposure lead to reduced excitability of these networks.

**Poster #: 36 .DIFFERENCES IN DNA METHYLATION BETWEEN ALTITUDE EXPERIENCED AND ALTITUDE NAÏVE HEALTHY VOLUNTEERS ON EXPOSURE TO HYPOBARIC HYPOXIA.** Kay Mitchell1, Emma Garratt1, Michael Natoli2, Elie Antoun1, Matthew Hewitt1, Negusse Kitaba1, Andrew Cumpstey1, Thomas Smedley1, Nelson Diamond2, Timothy Beck2, Denny Levett1, Michael Mythen3, Andrew Murray4, Hugh Montgomery3, Daniel Martin5, Keith M Godfrey1, Richard Moon2, Karen Lillycrop1, Michael Grocott1. 1University of Southampton, 2Duke University, 3University College London, 4University of Cambridge, 5University of Plymouth

Objectives: We investigated skeletal myocyte DNA methylation patterns in altitude experienced (AE) and altitude naïve (AN) lowlander volunteers on exposure to hypobaric hypoxia and subsequent return to normoxia. Methods: Twenty-one healthy male volunteers were exposed to environmental hypoxia over 3 days in a hypobaric chamber (maximum altitude equivalent to 3500m, PaO2 8 kPa). Vastas lateralis skeletal muscle biopsies were taken at baseline, at the end of hypoxia, and 3 hours after return to normoxia. Following quality control and normalisation procedures methylation levels of cytosine-guanine sequences (CpGs), generated using an Illumina HumanMethyaltion EPIC bead array, were compared between baseline and hypoxia, and between hypoxia and subsequent normoxia using paired t-tests.

Associations between sites of methylation change and all known biological pathways were sought. Results: Methylation patterns altered in response to hypoxia in all participants, with further changes following return to normoxia. The number of differentially methylated CpGs (dmCpGs) was greater in AE than AN participants following exposure to hypoxia (ratio 2.06:1, $p<0.001$), and subsequent return to normoxia (ratio 4.14:1, $p<0.001$), and differed between them. DmCpGs were enriched in MAPK and PI3K-Akt signalling pathways following exposure to hypoxia, and subsequent return to normoxia. Conclusions: Altered DNA methylation patterns were associated with hypoxic exposure and subsequent return to normoxia in healthy humans with differences in methylation patterns between AE and AN individuals. Methylation changes were associated with signalling pathways that may underpin the skeletal muscle response to hypoxia.

**Poster #: 37 .HEMORHEOLOGY DURING ACCLIMATIZATION TO HIGH ALTITUDE (3800 m).** Justin A Monteleone1, Andrew R Steele1, Connor A Howe1, Katharine Foster2, Hannah G Caldwell1, L Madden Brewster1, Jennifer Duffy1, Prajan Subedi2, James D Anholm2, Philip N Ainslie1, Joshua C Tremblay3. 1University of British Columbia Okanagan, 2Loma Linda University School of Medicine, 3Cardiff Metropolitan University

OBJECTIVE: High altitude causes numerous hematological changes to maintain oxygen delivery to tissues. Hemoconcentration occurs at high altitude causing a substantial increase in whole blood viscosity. However, it remains unresolved if changes in specific red blood cell properties – red blood cell deformability and aggregation – contribute to these hematological changes. Therefore, we aimed to characterize hemorheology at baseline (BL) (344m), during EARLY (days 1-2) and LATE (days 11-14) acclimatization to high altitude (Barcroft Field Station, 3800m). METHODS: Participants (9M/10F; age = 27±4 years) arrived in the lab fasted, where blood was taken from the antecubital vein to assess hemorheology (whole blood viscosity, plasma viscosity, hematocrit, red blood cell deformability and aggregation). Viscosity was determined using a temperature-controlled cone/plate viscometer at a physiological shear rate of 225 s-1, hematocrit using a microcentrifuge and red blood cell deformability and aggregation using a laser-optical rotational red cell analyzer. RESULTS: Whole blood viscosity and hematocrit were elevated during EARLY (4.87±0.3 cP $p < 0.01$ and 48.0±3.6 % $p = 0.03$) and remained elevated during LATE (4.87±0.8 cP $p < 0.01$ and 48.5±3.6 % $p < 0.01$) compared to BL (4.07±0.3 cP and 46.4±3.0 %). Plasma viscosity was not different between BL (1.45±0.2 cP) and EARLY (1.44±0.07 cP $p = 0.93$); however, plasma viscosity was higher at LATE compared to EARLY (1.51±0.10 $p = 0.02$), but not when compared to BL ($p = 0.17$). Red blood cell deformability and aggregation were unchanged across all conditions. CONCLUSION: Hypoxic mediated hyperviscosity is caused by rapid increases in hematocrit without changes in red blood cell properties. Plasma viscosity may also contribute to this increase after 11-14 days of acclimatization. The mechanisms and implications of changing plasma viscosity remains to be established.Funding: This work was funded by an NSERC Discovery grant and University Research Chair to PNA.

**Poster #: 38 .Heart Rate Responses to End-Expiratory Apneas During Simultaneous Hypercapnia and Hypoxia.** Ben O'Croinin1, Desmond Young1, Lauren Maier1, Trevor Day2, Craig Steinback1. 1Faculty of Kinesioloyg, Sport, and Recreation; University of Alberta, 2Mount Royal University

Objective: We have previous observed bradyarrythmias during voluntary apneas during hypoxia (HX). We sought to examine the influence of concurrent hypercapnia on apnea induced bradycardia during hypoxia. We hypothesized that there would be a greater bradycardic response to apneas during apneas in concurrent hypoxic hypercapnia (HCHX) when compared to HX or hypercapnia (HC) alone. Methods: 13 participants (10M/3F) were exposed to three gas conditions: HC (+5 mmHg above baseline end tidal partial pressure of CO2), HX (decrease to 50 mmHg end tidal partial pressure of O2), and HCHX (combination of HC and HX gas exposures), control apneas were performed during interspaced periods of normoxic normocapnia (NX). Heart rate and rhythm (3-lead ECG), blood pressure, gas concentrations, and oxygen saturation were measured continuously. Results: Apneas during concurrent HCHX (-17.2 ± 18.9 bpm; p=0.015) and HX (-17.9 ± 16.4 bpm; p=0.004) elicited a significantly larger bradycardia than NX apneas (-11.0 ± 15.3 bpm).Although HC apneas (-15.7 ± 12.6 bpm) did not show a significantly larger bradycardic response compared to NX apneas (p=0.069), there were no significant differences between the HX, HC, and HCHX responses (main effect p=0.892). A comparison between the arithmetic sum of the bradycardic responses to apneas during HX and HC (-33.6 ± 28.0 bpm) was larger than the actual HCHX response (p=0.0016) demonstrating a hypoadditive influence on heart rate during the combined condition. Conclusion: Our data suggests that a combination of HC and HX produces a non-additive heart rate response during apneic conditions. The apnea response to the HC stimulus was similar to that during HCHX and HX are greater. The application of this research is primarily to sleep apnea which is characterized by concurrent HC, HX, and apneas.Funding: NSERC

**Poster #: 39 .MODERATE- AND LOW-ALTITUDE RESIDENTS EXPIENCE SIMILAR DECREMENTS IN PLASMA VOLUME FOLLOWING PASSIVE BUT NOT ACTIVE ASCENT TO 3600M .** Stefan Pasiakos1, Reed Hoyt1, Janet Staab1, Peter Figueiredo1, Steven Landspurg1, Jon Femling2, Jason Williams2, Aaron Reilly2, Trevor Mayschak2, Mark Buller1, J Philip Karl1, Emma Atkinson1, Tim Mesite1, Beth Beidleman1. 1US Army Research Institute of Environmental Medicine, 2University of New Mexico

Objective: Previous research has demonstrated both similar and smaller decrements in plasma volume (PV) in moderate (>1500m) compared to low-altitude residents (MAR vs. LAR) following ascent to high altitude (HA) due to previously acquired hematologic acclimatization. Whether a lower altitude threshold (1190m) induces a similar response following active versus passive ascent to HA is unknown. Methods: To determine the impact of MAR versus LAR and ascent conditions on PV changes following ascent to HA, 78 healthy Soldiers (mean±SD; age=26±5yr) were tested at baseline residence (BLR) at 331m (LAR; n=41) or 1190m (MAR; n=37), transported to Taos, NM (2845m), then hiked (n=39) or were driven (n=39) to HA (3600m), and stayed for four days. AMS-Cerebral factor score (AMS-C) was assessed using the Environmental Symptoms Questionnaire at HA twice on day 1 (HA1), five times on days 2 and 3 (HA2 and HA3) and once on day 4 (HA4). Hemoglobin and hematocrit were measured at 07:00 at BLR, HA2, HA3 and HA4 and 18:00 on HA1 to calculate changes in PV. Results: In the

passive ascent group, there were no differences in PV changes at HA between MAR and LAR. In the active ascent group, PV changes (%) were different in MAR versus LAR, respectively, on HA1 (-4.8±7.5 vs. +5.2±6.8, p=0.001), HA2 (-5.3±10.0 vs. -0.05±6.5, p=0.04), HA3 (-6.5±9.2 vs -0.47±7.2, p=0.02) and HA4 (-6.7±6.6 vs. 0.64±8.5, p=0.01). PV changes (%) were positively correlated with AMS-C scores on HA1 (r=0.22; p=0.05) and HA2 (r=0.21; p=0.04). Conclusion: Our data suggest that residents living at a lower altitude threshold (1190m) demonstrate similar changes in PV as LAR following passive ascent to 3600m. More importantly, active ascent in LAR compared to MAR induced retention of PV at 3600m which may have resulted in more AMS. Authors' views not official U.S. Army or DoD policy. Funding: USAMRDC

**Poster #: 40 .MANIPULATION OF IRON STATUS ON CEREBRAL BLOOD FLOW AT HIGH ALTITUDE IN LOWLANDERS AND ADAPTED HIGHLANDERS .** Alexander Patrician1, Christopher Willie1, Ryan Hoiland2, Christopher Gasho3, Prajan Subedi3, James Anholm3, Michael Tymko1, Philip Ainslie1. 1Centre for Heart, Lung & Vascular Health, University of British Columbia Okanagan, 2Department of Anesthesiology, University of British Columbia, 3Pulmonary/Critical Care, Loma Linda University

Objective: Cerebral blood flow (CBF) increases during hypoxia to counteract the reduction in arterial oxygen content. The onset of tissue hypoxemia coincides with the stabilization of hypoxia-inducible factor (HIF) and transcription of downstream HIF-mediated processes. It has yet to be determined, whether HIF down- or upregulation can modulate hypoxic vasodilation of the cerebral vasculature. Therefore, we examined whether: 1) CBF would increase with iron depletion (via chelation) and decrease with repletion (via iron infusion) at high-altitude, and 2) explore whether genotypic advantages of highlanders extend to HIF-mediated regulation of CBF. Methods: In a double-blinded and block-randomized design, CBF was assessed in 82 healthy participants (38 lowlanders, 20 Sherpas and 24 Andeans), before and after the infusion of either: iron(III)-hydroxide sucrose, desferrioxamine or saline. Results: Across both lowlanders and highlanders, baseline iron levels contributed to the variability in cerebral hypoxic reactivity at high altitude ($R^2$=0.174, P<0.001). At 5,050 m, CBF in lowlanders and Sherpa were unaltered by desferrioxamine or iron. At 4,300m, iron infusion led to 4±10% reduction in CBF (main effect of time p=0.043) in lowlanders and Andeans. Conclusion: Iron status may provide a novel, albeit subtle, influence on CBF that is potentially dependent on the severity and length-of-stay at high altitude. Funding: The 2016 UBC Mt Everest Expedition and the 2018 Global REACH expedition to Peru was funded as a whole, by a Canada Research Chair (CRC) and the Natural Sciences and Engineering Research Council (NSERC) Discovery Grant and the Canadian Foundation for Innovation to P.N.A. A.P., M.M.T., R.L.H., were supported by an NSERC Doctoral Grants.

## Poster #: 41 .HIGH-ALTITUDE EXPOSURE INDUCES UPREGULATION OF KEY PROINFLAMMATORY IMMUNE CELL MOBILIZATION FACTORS THAT ARE POTENTIALLY LINKED TO PHYSIOLOGICAL RESPONSES TO HYPOXIA.

Kathy Pham1, Shyleen Frost1, Erica Heinrich1. 1University of California, Riverside

Objective: We hypothesize that proinflammatory gene expression increases in response to high-altitude hypoxia, and exacerbates high-altitude pathologies. Methods: We compared the inflammatory profile in whole blood samples collected in the morning during fasting at sea level and after one and three nights at high altitude (3800m elevation). Basic physiological measurements (oxygen saturation, blood pressure, Acute Mountain Sickness (AMS) Scores) were taken every night at high altitude. RNA samples were collected in 15 healthy sojourners. RNA sequencing was coupled with a nanoString Human Inflammatory Panel. In a separate expedition, plasma was isolated from fasting whole blood in 20 healthy sojourners. A bead-based immunoassay was used to quantify inflammatory cytokines and chemokines (LEGENDPlex Inflammatory Panel 1). Results: Previously, we have identified upregulation of key components of the innate immune toll like receptor 4 pathway (TLR4) following acute high-altitude exposure. Several chemotactic factors were found to be significantly differentially expressed in plasma collected at high altitude. This includes IL-8, a chemotactic cytokine responsible for neutrophil mobilization ($p<0.05$) and IL-18, a cytokine involved in regulation of T cell populations ($p<0.05$). Conclusions: Our study indicates that, even in the absence of a pathogen infection, high-altitude hypoxia alone is enough to stimulate proinflammatory immune cell mobilization in healthy unacclimatized sojourners. This may have consequential implications in the development of high-altitude pathologies, where individuals who have a chronic inflammatory profile may have an exacerbated response to subsequent inflammatory stimuli. Funding: The study was supported by WMRC Mini-Grant 2022 and Mildred E. Mathias Grant.

## Poster #: 42 .EXPEDITION 5300 : EXCESSIVE ERYTHROCYTOSIS IS NOT ASSOCIATED WITH ALTERED IRON HOMEOSTASIS IN MEN FROM THE WORLD'S HIGHEST CITY .

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Objective: Despite continuously high erythropoiesis and iron demand, high-altitude residents appear to keep iron stores within the normal range. However, the mechanisms enabling iron

stores to be maintained have not been described. This study explores how iron homeostasis adapts in polycythemic residents from the world's highest city (5,100 m), with and without chronic mountain sickness (CMS). Methods: This study involved 100 male participants: 57 were permanent residents in La Rinconada (5,100 m) with no CMS, mild CMS or moderate-to-severe CMS; 26 were permanent residents in Puno (3,800 m), with no CMS, mild CMS or moderate-to-severe CMS; and 17 were healthy residents from Lima (sea level). Total hemoglobin mass (Hbmass) was assessed by carbon-monoxide rebreathing. Erythropoiesis and iron homeostasis were examined from serum samples. Results:Hbmass progressively increased with altitude, reaching extremely high values at 5,100 m. Excessive erythrocytosis was accompanied by increased erythropoietin and soluble transferrin receptor (sTfR) levels. However, healthy residents at 5,100 m did not modify iron metabolism, as erythroferrone and hepcidin concentrations remained similar to those in sea-level residents. Furthermore, iron deficiency was absent as indicated by unaltered transferrin saturation and ferritin, while ceruloplasmin was found increased. Similar high levels of Hbmass and erythropoietin were found in CMS patients and healthy individuals at 5,100 m, although moderate-to-severe CMS patients displayed trends toward even higher levels, suggesting a stronger erythropoietic response, substantiated by higher sTfR levels. In this subpopulation, excessive erythrocytosis was accompanied by erythroferrone induction and hepcidin inhibition, however without reduction in iron stores. Conclusion: Male residents from the world's highest city experience excessive erythrocytosis and massive Hbmass expansion without concomitant iron deficiency, presumably since iron regulation reaches equilibrium at a different level of erythropoiesis, through optimization of iron transport mechanisms not involving the erythroferrone/hepcidin axis.Funding: The study was sponsored by Grenoble Alpes University foundation and the French National Research Agency

**Poster #: 43 .Feasibility of polysomnography sleep study among high altitude acclimatized shift workers in an industrial setting at 5050 m.** Matiram Pun1, Bradley Hansen1, Ivan Lopez2, Marc Poulin3. 11. Department of Physiology & Pharmacology, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada 2. Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada, 2Safety Group, Atacama Large Millimeter Submillimeter Array (ALMA), Calama, Chile, 31. Department of Physiology & Pharmacology, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada 2. Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada 3. O'Brien Institute for Public Health, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada 4. Faculty of Kinesiology, University of Calgary, Calgary, Alberta, Canada 5. Libin Cardiovascular Institute of Alberta, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada.

Feasibility of polysomnography sleep study among high altitude acclimatized shift workers in an industrial setting at 5050 m Matiram Pun1,2, Bradley Hansen1,2, Ivan Lopez3, Marc Poulin1,2,4,5,6 1Department of Physiology & Pharmacology, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada2Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada3Safety Group, Atacama Large Millimeter Submillimeter Array (ALMA), Calama, Chile4O'Brien Institute for Public Health, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada5Faculty of Kinesiology, University of Calgary, Calgary, Alberta, Canada6Libin Cardiovascular Institute of

Alberta, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada. Corresponding author:Marc J. Poulin, PhD, DPhilProfessor and Brenda Strafford Foundation Chair in Alzheimer ResearchDepartment of Physiology & Pharmacology, Hotchkiss Brain Institute, Cumming School of Medicine, University of CalgaryHeritage Medical Research Building Room 210, University of Calgary3330 Hospital Drive NW, Calgary Alberta, T2N 4N1, CanadaTel.: +1 403-220-8372, Fax: +1 403-210-8420 Email: poulin@ucalgary.ca
AbstractObjective: Very few studies have exploited the use of full overnight polysomnography (PSG) for high-altitude sleep studies. Published studies have been limited by small sample sizes, lower sleeping altitudes and lack of data from high-altitude workers. Here, we investigate the feasibility of using full PSG sleep studies among high-altitude acclimatized shift workers from an astronomical observatory, the Atacama Large Millimeter Array (ALMA) in the Atacama Desert in Northern Chile.Methods: High-altitude acclimatized workers at ALMA Array Operations Site (AOS, 5050 m) typically spend a week of high-altitude shift work followed by another week of rest at or near sea level (~500 m). During the week of high-altitude shift work, workers sleep at the ALMA Operation Support Facility (OSF, 2900 m) and go to work at the AOS during the day. AOS workers were recruited for a full PSG assessment during their week of shift work at high-altitude. The sleep data were analysed using Michele Sleep Scoring System (MSS).Results: We have successfully recruited a total of fifty-three high-altitude acclimatized workers (36.5±10.6 years old, male/female=36/17, body mass index=27.3±3.8kg/m2). Traditional sleep parameters such as total sleep time (TST), sleep efficiency (SE), wake after sleep onset (WASO), sleep onset latency (SOL), awakenings and periodic limb movement index were assessed and will be presented. Similarly, we will present results for sleep apnea indices (apnea-hypopnea index (AHI), central and obstructive sleep apnea indices (CSA, OSA), hypoxia burden (oxygen desaturation index (ODI) and TST below blood oxygen saturation 90% (TST90)) and sleep depth parameters (deep sleep, transitional sleep, drowsy awake and full wakefulness).Conclusion: Gold-standard sleep assessments using full PSG are feasible in industrial settings at high-altitude. Preliminary analyses show that the sleep data from high-altitude are as high quality as in-home PSG and in-hospital PSG studies at lower altitude.
Acknowledgements: We acknowledge support from ALMA, Alberta Innovates (MP), Canadian Institutes of Health Research (MJP, MP), NSERC CREATE (BRAIN CREATE; MJP, MP) and DISCOVERY (MJP) programs, and the Brenda Strafford Chair in Alzheimer Research (MJP).

**Poster #: 44 .THE RELATIONSHIP BETWEEN SLEEP DURING THE FIRST NIGHT OF EXPOSURE TO 3600M ON ACUTE MOUNTAIN SICKNESS THE NEXT MORNING.** Bradley Ritland1, Peter Figueiredo1, Steven Landspurg1, Jon Femling2, Jason Williams2, Janet Staab1, Reed Hoyt1, Mark Buller1, J Philip Karl1, Aaron Reilly2, Trevor Mayschak2, Emma Atkinson1, Tim Mesite1, Beth Beidleman1. 1US Army Research Institute of Environmental Medicine, 2University of New Mexico

Objective: Sleep disturbances are common at high altitude (HA) (> 3500m), but the relationship between sleep and the incidence and severity of acute mountain sickness (AMS) is debated. The objective was to investigate whether sleep on the first night at HA was associated with AMS the next morning following active and passive ascent to 3600m. Methods: 78 healthy Soldiers (mean±SD; age=26±5yr) were transported from their baseline residence (BLR) to Taos, NM (2845m), where they hiked (n=39) or were driven (n=39) to HA (3600m) and assessed for two days (HA1 and HA2). Sleep was measured via actigraphy on the first night of

sleep at HA (HA1) and used to calculate sleep awakenings (events/hr), duration (min), onset latency (min), wakefulness after sleep onset (WASO, min), and sleep efficiency (%). Mean pulse oxygen saturation (SpO2) was measured using pulse oximetry during sleep. AMS-Cerebral factor score (AMS-C) was assessed using the Environmental Symptoms Questionnaire on day 2 at HA (HA2). If AMS-C values were ≥0.7 on HA2, individuals were classified as AMS-susceptible (AMS+, n=23); others as non-susceptible (AMS-, n=55). Results: Ascent conditions did not differentially impact sleep measurements. There were no differences in sleep awakenings, onset latency, WASO, or sleep efficiency between the AMS+ and AMS- groups. In the AMS+ group compared to the AMS- group, sleep duration (min) was lower (392±57 vs. 433±63, p=0.009) and mean SpO2 (%) was lower (79.7±6.1 vs 82.0±3.9, p=0.05). Sleep duration (r=-0.32, p=0.004) and mean SpO2 (r=-0.32, p=0.005) values on the first night at HA were negatively correlated with AMS-C values the following morning on HA2. Conclusion: When Soldiers passively or actively ascend to high altitude (3600m), sleep duration and arterial oxygen saturation during the first night at HA is associated with AMS the next morning. Authors' views not official U.S. Army or DoD policy. Funding: USAMRDC

**Poster #: 45 .SEX, BLOOD PRESSURE, AND ALTITUDE: A PROSPECTIVE OBSERVATIONAL COHORT STUDY.** T Douglas Sallade1, Charles Duke2, Jennifer Starling3, 4, Alison Sheets5, Sushil Pant6, David Young7, David Twillman4, Nirajan Regmi8, Benoit Phelan9, Purshotam Paudel10, Matthew McElwee11, Luke Mather12, 13, Devlin Cole14, Theodore McConnell15, Buddha Basnyat16, 17, Linda Keyes4, 5. 1Geisinger Lewistown Hospital, Lewistown, Pennsylvania, 2Department of Emergency Medicine, Yale School of Medicine, New Haven, Connecticut, 3Colorado Permanente Medical Group, Saint Joseph Hospital, Denver, Colorado, 4Department of Emergency Medicine, University of Colorado, Aurora, Colorado, 5Longmont United Hospital, Longmont, Colorado, 6Mountain Medicine Society of Nepal and Kunde Hospital, Kathmandu, Nepal, 7Department of Emergency Medicine, Rush University Medical Center, Chicago, Illinois, 8Mountain Medicine Society of Nepal, Kathmandu, Nepal, 9Saint John Regional Hospital, Saint John, Canada, 10Mountain Medicine Society of Nepal and District Hospital, Dhading, Nepal, 11Department of Medicine, University of Minnesota, Minneapolis, Minnesota, 12Family Medicine Residency of Idaho, Boise, Idaho, 13University of Washington School of Medicine, Seattle, Washington, 14Kapiolani Women and Children's Hospital, Honolulu, Hawaii, 15McGill University, Montreal, Canada, 16Oxford University Clinical Research Unit - Nepal, Nepal, 17Nepal International Clinic, Kathmandu, Nepal

Objective: A recent study found blood pressure (BP) increased more in men than women upon acute high altitude exposure. We sought to confirm these sex differences in a cohort of Himalayan trekkers.Methods: We reanalyzed data from our previously published cohort comparing mean BP and change in BP in male (M) versus female (F) trekkers ascending from 2860 m to 3400 m and 4300 m.Results: We analyzed 658 trekkers, 60 with preexisting hypertension (M=387, F=271). In those without preexisting hypertension, systolic BP (mean (mmHg), 95% CI) was greater in men than women at 2860 m (M:130, 128.7-131.7; F:122, 120.4-124.2) and 3400 m (M:129, 127.4-130.9; F:124, 122.2-126.6), but not 4300 m (M:129, 127.2-131.2; F:126, 123.6-128.6). In men and women with preexisting hypertension, BP was similar at 2860 m (M:150, 144.0-155.7; F:153, 141.4-163.6), 3400 m (M:150, 141.8-157.3; F:153, 139.8-165.6) and 4300 m (M:143, 134.1-152.8; F:139, 122.0-156.0). From 2860 m to 3400 m the

proportion of trekkers without preexisting hypertension whose BP increased (F=25%, M=18%), decreased (F=17 %, M=21%) or did not change >10 mmHg (F=58%, M=61%) was similar between sexes (p=0.2). Similar results were found among those with preexisting hypertension and between 3400 m to 4300 m (data not shown).Conclusion: Normotensive men had higher BP than women at 2860 m and 3400 m. BP changed little with altitude and changes did not differ by sex. Our study is limited by the lack of a low altitude measurement. Funding: Nepal International Clinic, Wilderness Medicine Society.

**Poster #: 46 .TRANSIENT HYPOXIA-INDUCED DEOXYHEMOGLOBIN FORMATION SERVES AS AN MRI CONTRAST FOR PERFUSION IMAGING IN PATIENTS WITH STENO-OCCLUSIVE DISEASE.** Ece Su Sayin1, 2, Vittorio Stumpo3, 4, Jacopo Bellomo3, 4, Julien Poublanc2, Marco Piccirelli3, 4, James Duffin1, Vepeson Wijeya2, Athina Pangalu 3, 4, Andrea Bink3, 4, Bence Nemeth3, 4, Zsolt Kulcsar3, 4, David Mikulis1, 2, Olivia Sobczyk2, Jorn Fierstra3, 4, Joseph Fisher1, 2. 1University of Toronto, 2University Health Network, 3University Hospital Zurich, 4University of Zurich

Background: Susceptibility agents are required to generate contrast for calculating resting perfusion measures (such as mean transit time, cerebral blood volume, and cerebral blood flow) using dynamic susceptibility contrast (DSC) MR perfusion. Currently this requires the intravascular injection of gadolinium (Gd), engendering medical risks, cost, along with image, and environmental drawbacks. Hypoxia-induced deoxyhemoglobin (dOHb) is intrinsic, reversibly paramagnetic, and relatively low-cost.Objective: Here we use hypoxia-induced dOHb as a suitable agent for DSC perfusion and validate against a clinical standard, Gd, in patients with steno-occlusive disease (SOD).Methods: We studied 10 patients between the ages of 39 and 74 (8 M) with known steno occlusive disease in a 3-Tesla scanner running-BOLD acquisition sequences. Transient hypoxia was induced via an automated gas blender running feed-forward gas algorithm targeting 2 consecutive reductions of pulmonary PO2 from 95 mmHg to 40 ± 3 mmHg followed by full reoxygenation within a single inhalation. A second BOLD sequence was acquired following an intravenous injection of 5 ml of Gd. All images were analyzed, and resting perfusion measures were calculated using a standard tracer kinetic model.Results: The calculated perfusion measures and their distribution showed similar voxel-wise proportional changes in BOLD signal throughout the brain. Bland-Altman analysis indicated little bias or difference in hemodynamic measures between methods.Conclusions: The resting perfusion measures obtained from brief transient hypoxia are spatially and quantitatively comparable to those obtained using Gd in the same patients with varying patterns of SOD. The main advantages of transient hypoxia as a contrast agent include it being non invasive; reduced risk of allergy, renal or fetal toxicity; no accumulation in organs, and no environmental damage, making it a suitable contrast for DSC perfusion imaging.Funding: Dr Joseph Fisher Critical Care Research Fund

**Poster #: 47 .Hyperoxia improves exercise capacity in cardiopulmonary disease. A series of RCT's.** Julian Müller1, Mona Lichtblau1, Saxer Stéphanie1, Simon Raphael Schneider1, Paula Appenzeller1, Bauer Meret1, Elisabeth Hasler1, Esther Irene Schwarz1, Konrad Ernst Bloch1, Silvia Ulrich1. 1Department of Pulmonology, University Hospital Zurich, Zurich, Switzerland ; University of Zurich, Zurich, Switzerland

Background: To study the overall and differential effect of breathing hyperoxia (FiO2 0.5) vs. placebo (ambient air, FiO2 0.21) to enhance exercise performance in healthy people, patients with pulmonary vascular disease (PVD) with precapillary pulmonary hypertension (PH), chronic obstructive pulmonary disease (COPD), PH due to heart failure with preserved ejection fraction (HFpEF) and cyanotic congenital heart disease (CHD) using data of five RCTs performed with identical protocols.Methods: 91 subjects (32 healthy, 22 PVD with pulmonary arterial or distal chronic thromboembolic PH, 20 with COPD, 10 with PH in HFpEF and 7 with CHD) performed 2 cycle incremental (IET) and 2 constant work-rate exercise tests (CWRET) at 75% of maximal load (Wmax), each with ambient air and hyperoxia in single blinded, randomized-controlled cross-over trials. The main outcomes were differences in Wmax (IET) respectively cycling time (CWRET) with hyperoxia vs ambient air.Results: Overall, hyperoxia increased Wmax by +12 W (95%CI: 9 to 16, p<0.001) and cycling time by +6:13 min (4:50 to 7:35, p<0.001), with improvements being highest in patients with PVD: (Wmax/min: +18%/+118% vs. COPD: +8%/+60%, healthy: +5%/+44%, HFpEF: +6%/+28%, CHD: +9%/+14%).Conclusion: This large collective of healthy and patients with various cardiopulmonary disease confirms that hyperoxia significantly prolongs cycling exercise with improvements being highest in endurance CWRET and patients with PVD. These results call for studies investigating optimal oxygen levels to prolong exercise time and effects on training.

**Poster #: 48 .ACUTE HYPOXIA ELICITS LASTING REDUCTIONS IN THE SYMPATHETIC ACTION POTENTIAL TRANSDUCTION OF ARTERIAL BLOOD PRESSURE IN MALES. .** Brooke Shafer1, Massimo Nardone2, Anthony Incognito 2, Tyler Vermeulen1, Andre Teixeira2, Philip Millar2, William Sheel1, Christopher West1, Najib Ayas1, Glen Foster1. 1University of British Columbia, 2University of Guelph

Objective: Acute hypoxia leads to lasting sympathoexcitation without corresponding changes in vascular tone, suggesting reduced sympathetic transduction. We hypothesized that (1) changes in mean arterial pressure (MAP) evoked by sympathetic action potential (AP) activity would be blunted during acute hypoxia but restored in recovery and (2) that asynchronous APs would elicit a smaller change in MAP compared with synchronous APs. Methods: Seven healthy males (age: 24 (3) yrs; BMI: 25 (3) kg/m2) underwent 20-min isocapnic hypoxia (PETO2: 47 (2) mmHg) and 30-min recovery. MAP (photoplethysmography) and muscle sympathetic nerve activity (MSNA; fibular microneurography) were acquired during baseline, hypoxia, early (first 7-min) and late recovery (last 7-min). A continuous wavelet transform with matched mother wavelet was used to detect sympathetic APs. AP groups were classified as cardiac cycles associated with synchronous (APs with MSNA burst), asynchronous (APs outside MSNA burst), and no sympathetic AP activity. Sympathetic transduction of MAP was quantified using signal-averaging and DMAP was tracked following AP group activity. Results: Following synchronous APs, DMAP was reduced in hypoxia (+1.8 (0.9) mmHg, P = 0.041) and early recovery (+1.5 (0.7) mmHg, P = 0.009) compared with baseline (+3.1 (2.2) mmHg). At rest, MAP reductions

following asynchronous APs was attenuated compared with no AP activity (-0.4 (1.1) vs. -2.2 (1.2) mmHg, respectively; P = 0.003) but did not differ between AP groups in hypoxia, early, or late recovery. Conclusion: Sympathetic transduction of MAP is blunted in hypoxia and early recovery. At rest, asynchronous sympathetic APs contribute to neural regulation of MAP by attenuating nadir pressure responses. Funding: NSERC, HSFC

**Poster #: 49 .THE EFFECTS OF ACUTE INTERMITTENT HYPERCAPNIA ON VENTILATORY LONG-TERM DEPRESSION AND CARDIOVASCULAR FUNCTION.** Conan Shing1, Scott Thrall1, Megan Lance1, Jordan Bird1, Brooke Shafer1, Mohammad Soltani1, Glen Foster1. 1Centre for Heart, Lung, and Vascular Health, School of Health and Exercise Sciences, University of British Columbia, Kelowna, British Columbia, Canada

The ventilatory and cardiovascular effects of intermittent hypercapnia (IHc) in the absence of hypoxia is unknown. This study investigated if IHc led to long-lasting effects on ventilation, blood pressure, and vascular conductance. Thirteen healthy participants (age: 23±4 years; BMI: 22±2 kg/m2) underwent a 10-minute baseline, 40-minutes of IHc (40 seconds end-tidal PCO2 +5 mmHg from baseline and 20 seconds of normocapnia), followed by 30-minutes of room-air recovery. Ventilation and mean arterial pressure (MAP) were measured continuously, while arm and leg blood flow were measured via strain gauge plethysmography at the end of baseline and every 10 minutes throughout recovery. Limb vascular conductance was calculated as the sum of arm and leg blood flow multiplied by two and divided by MAP. Data were compared statistically (P<0.05) using mixed effects linear modeling with time (baseline, 10-, 20-, and 30-minutes recovery) as a fixed factor and participants as a random factor. Ventilation (P=0.05) and tidal volume (P=0.06) tended to be reduced throughout recovery while breathing frequency (P=0.2) was unchanged. There was a time effect for MAP (P<0.001) and post hoc analysis indicated that MAP was increased at 10-minutes (7.2 mmHg, CI95%: 3.7 – 10.7, P<0.001), 20-minutes (7.7 mmHg, CI95%: 4.2 – 11.2, P<0.001), and 30-minutes (8.6 mmHg, CI95%: 5.1 – 12.1, P<0.001) following IHc. There was a time effect for limb vascular conductance (P=0.001) and post-hoc analysis found conductance was reduced throughout recovery (0.03 ml/min/100ml/mmHg, CI95%: -0.05 – -0.01, P<0.01) following IHc. In conclusion, IHc attenuated minute ventilation and limb vascular conductance and led to long-lasting increases in arterial pressure. This suggests IHc may contribute to the long-lasting sympathoexcitatory effects of intermittent hypoxia in obstructive sleep apnea.Funding Sources: American Physiological Society, Natural Sciences and Engineering Research Council of Canada.

**Poster #: 50 .24-HOUR AMBULATORY BLOOD PRESSURE AT LOW VERSUS HIGH ALTITUDE BEFORE AND AFTER PARTIAL ACCLIMATIZATION: THE COLORADO HIGH ALTITUDE MONITORING PRESSURE STUDY (CHAMPS). .**
Lukas Sloan1, Andrew Burns1, Greta Carlson1, Ilaria Ferrari1, Diana Biggs1, Linda Keyes1. 1University of Colorado School of Medicine

Andrew C. Burns; Greta Kreider-Carlson MD; Ilaria Ferrari BS; Lukas Sloan BS; Diana Biggs MD; Linda E. Keyes MD; University of Colorado School of Medicine Aurora, Colorado; andrew.c.burns@colorado.edu24-HOUR AMBULATORY BLOOD PRESSURE AT LOW VERSUS HIGH ALTITUDE BEFORE AND AFTER PARTIAL ACCLIMATIZATION: THE COLORADO HIGH ALTITUDE MONITORING PRESSURE STUDY (CHAMPS).Abstract:Objective: Acute high altitude exposure may increase 24-hour ambulatory blood pressure (ABP), but change in blood pressure with acclimatization is poorly understood. [LK1] We compare 24-hour ABP at low altitude versus the first 24 hours at high altitude and after 72 hours.Methods: This is a prospective observational cohort study of adult lowlanders, comparing 24-hour ABP at low (<1,000m) versus high-altitude (2,500-2,800m). BP was monitored every 30 minutes while awake and every hour overnight for 24 hours using Welch-Allyn6100 ABP monitors. High altitude data was collected during the first and third days at high altitude.Results: We present preliminary data on 8 participants (f=5, m=3) with complete matched data for all three time points (mean age 48 (range 34-70), 2 [LK2] with underlying hypertension). We found an increase in average 24-hour SBP between low and high altitude (121 [91-150] mmHg vs 132 [96-169] mmHg, respectively), with a mean SBP increase of 12 [-16-40] mmHg, p=0.049. Diurnal SBP was greater at high altitude (123 [94-151] vs 136 [100-172], p=0.02), but nocturnal SBP did not differ (112 [72-151] vs 121[79-163], p=NS). Results were similar for DBP. Comparing the first 24h versus 72h at high altitude, we found no differences in average 24-hour (132 [96-169] mmHg vs 132 [92-172] mmHg, p=NS), diurnal SBP (136 [100-172]) mmHg vs 136 [95-177] mmHg, p=NS) or nocturnal SBP (121 [79-163] mmHg vs 113 [84-142] mmHg.Conclusions: In our cohort, BP was elevated at high altitude compared to low altitude due to increases in diurnal BP, and remained so after 72-hours of acclimatization. The clinical importance and the long-term effects of elevated BP during high altitude sojourns remain to be determined.Funding: Wilderness Medical Society Hultgren Grant.

**Poster #: 51 .SLEEP QUALITY, AMBULATORY BLOOD PRESSURE AND ACUTE MOUNTAIN SICKNESS.** Lukas Sloan1, Diana Biggs1, Andrew Burns1, Greta Carlson1, Ilaria Ferrari1, Linda Keys1. 1University of Colorado School of Medicine

SLEEP QUALITY, AMBULATORY BLOOD PRESSURE AND ACUTE MOUNTAIN SICKNESSLukas Sloan, Diana Biggs, Andrew Burns, Greta Carlson, Ilaria Ferrari, and Linda E. KeyesObjectiveHigh altitude may negatively affect sleep quality, but the association between poor sleep and acute mountain sickness (AMS) is controversial. BP measured at the time of altitude-related symptoms has no association with AMS, but nocturnal BP might. Thus, we compared sleep quality and 24h-ambulatory blood pressure (ABP) in high altitude travelers with and without AMS.MethodsThis is a prospective observational cohort study of lowlanders visiting 2500-2800m during their first 24h at high altitude, and at 72h. We measured sleep quality with the Groningen Sleep Quality Scale (GSQ), AMS by the 2019 Lake Louise Questionnaire (LLS) and 24-hour ABP with Welch-Allyn 6100 ABPM. ResultsWe enrolled 28

participants (mean age 58, range 32-77, m=18, f= 10), 3 with AMS and 23 without AMS (missing data, n=2)). Baseline GSQ did not differ in AMS+ vs AMS- (p=NS), however, AMS+ had higher 24-h GSQ scores, (ie, worse sleep quality) vs AMS- (mean GSQ AMS+= 10.7 [95%CI:8.88-12.4] vs AMS-= 5.5 [95%CI:3.89-7.16], p=0.04). In a subset (n=8), baseline GSQ did not differ versus 24-h GSQs or 72-h scores (p=NS); however, sleep quality was worse on the first night vs the third (GSQ 6.9 vs 1.9, p=0.02). Mean 24-hour SBP (129 mmHg vs 140 mmHg) and mean daytime SBP (136 mmHg vs 150 mmHg) did not differ by AMS status (p=NS), however, AMS+ had lower mean nocturnal SBP versus AMS- (96 mmHg vs 127 mmHg, p=0.01).ConclusionThose with AMS had worse sleep quality, supporting the inclusion of a sleep quality question in the LLS. Sleep quality improved after time at high altitude. Surprisingly, mean nocturnal SBP was lower in those who develop AMS. We need more participants to validate this finding.Funding: Wilderness Medical Society Hultgren Grant

**Poster #: 52 .Effect of Aymara Enriched Genetic Variants in Austrians Exposed to Acute Hypoxia..** Jihyun Song1, Martin Burtscher2, Ricardo Amaru3, Maria Wille2, Soo Jin Kim1, Josef T. Prchal1. 1Division of Hematology and Hematologic Malignancies, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA, 2Dept. of Sport Science of the University of Innsbruck, A-6020 Innsbruck, Austria, 3Cell Biology Unit, School of Medicine, San Andres University, La Paz, Bolivia

Objective: The evolutionary adaptation to the high-altitude hypoxia is best defined in Tibetans and Andean natives. We reported evolutionary selected genetic variants of Andean Aymaras identified by whole genome analysis (Crawford, AJHG, 2017, Sundar, Blood, 2022). These variants are not unique to Aymaras and are present also in other populations, but at lower frequencies. We postulated that they likely modify hypoxic responses in non-Aymaras, and we attempted to define their functional consequences in non-Aymara population upon acute hypoxia exposure.Methods: We genotyped 6 Aymara enriched single nucleotide polymorphisms (SNPs) - BRINP3(rs11578671), NOS2(rs34913975), SH2B1(rs12448902), TBX5(rs487105), PYGM(rs487105), and NFKB1(rs230511) in 74 fit Austrians. Physiological parameters including SpO2, PaCO2, PaO2, SaO2, blood pressure (BP), heart rate (HR), lactate, and Lake Louis Score (LLS) were measured at 0, 3, and 6 hours of hypoxic exposure (~4500m). Hemoglobin was measured before hypoxic exposure. We interrogated associations of these genotypes with these physiological responses to acute hypoxia.Results: 6 hours-hypoxic exposure decreased SpO2, PaCO2, PaO2, SaO2, systolic and diastolic BP, while increased HR, but did not alter lactate.Heterozygotes for NOS2 SNP and SH2B1 SNP had lower SpO2 while homozygotes for NFKB1 SNP had higher SpO2. Systolic and diastolic BP were more decreased in homozygotes for NOS2 SNP and heterozygotes for PYGM SNP. After hypoxia, the BP was the highest in NFKB1 SNP heterozygotes. HR was highest in NOS2 SNP heterozygotes but negatively correlated with PYGM SNP. BRINP3 SNP heterozygotes had lower lactate compared to wild type after hypoxia. LLS at 3 hour-hypoxia was lower in SH2B1 SNP heterozygotes. NFKB1 SNP homozygotes had the lowest LLS at 6 hour-hypoxia, while hemoglobin measured before hypoxia positively correlated with NFKB1 SNP in females. Only NFKB1 SNP negatively correlated with severity of AMS.Conclusion: We report that these genetic variants enriched in Aymaras modify hypoxic responses also in Europeans.

**Poster #: 53 .Expedition 5300 - Reduced red blood cell deformability is associated with excessive erythrocytosis in the highest city of the world .** Emeric STAUFFER1, 2, Aurélien PICHON3, Benoit CHAMPIGNEUL4, Michaël Furian5, Lars KARSTNER6, 7, Ivan HANCCO4, Paul ROBACH4, 8, Julien V. BRUGNIAUX4, Mélanie ROBERT1, Elie NADER1, Philippe CONNES1, Samuel VERGES4. 1Laboratoire Interuniversitaire de Biologie de la Motricité (LIBM) EA7424, Team « Vascular Biology and Red Blood Cell », Université Claude Bernard Lyon 1, Université de Lyon, France, 2Explorations Fonctionnelles Respiratoires, Médecine du sport et de l'Activité Physique, Hospices Civils de Lyon, Hôpital Croix Rousse, Lyon, France, 3Université de Poitiers, Laboratoire MOVE, Poitiers, France , 4Univ. Grenoble Alpes, Inserm, CHU Grenoble Alpes, HP2, 38000 Grenoble, France, 5Pulmonary Division, University Hospital Zurich, 8092 Zurich, Switzerland, 6Theoretical Medicine and Biosciences, Saarland University, Homburg, Germany., 7Experimental Physics, Saarland University, Saarbrücken, Germany, 8National School for Mountain Sports, Site of the National School for Skiing and Mountaineering (ENSA), Chamonix, France

Introduction: Excessive erythrocytosis (EE) is a frequent condition observed in highlanders leading to blood hyperviscosity, which can favour the onset of clinical complications. Blood viscosity is highly dependent on haematocrit (and haemoglobin concentration) but also on red blood cell rheological properties. However, very few studies investigated RBC rheological properties in individuals residing at high altitude and suffering from EE. The present study investigated blood viscosity and RBC rheological parameters in residents of the highest city in the world (La Rinconada, Peru, 5,100 m) with (EE group) and without EE (non-EE group).Methods: Seventy-two Andean highlanders living at 5,100 m were included in this study (38 with EE and 24 without). Blood viscosity at native haematocrit, RBC deformability and aggregation, reticulocytes count and free haemoglobin were measured.Results: EE group exhibited lower arterial oxygen pressure ($p=0.01$) and higher percentage of reticulocytes ($3.37\pm1.6\%$ vs $2.64\pm1.1\%$; $p=0.02$) than subjects without EE. Blood viscosity at 22.5 s-1 shear rate at native haematocrit was higher in the EE group than in non-EE group ($38.3 \pm 1.7$ vs $27.43 \pm 1.1$ cP; $p <0.001$). RBC deformability was lower in EE subjects ($p<0.01$). Free haemoglobin concentration was higher in subjects suffering from EE ($24.35\pm13.41$mg/dL vs $12.13\pm4.32$ mg/dL; $p<0.001$). No difference was observed for RBC aggregation.Conclusion: The lower arterial oxygen pressure in EE subjects resulted in increased erythropoietic activity, marked by higher percentage of reticulocytes. Reticulocytes are immature RBCs that are less deformable than mature RBCs that could explain why the EE group had a lower RBC deformability. Indeed, both the higher haematocrit and the lower RBC deformability could be at the origin of the greater blood viscosity in EE individuals. The greater amount of less deformable RBCs in the EE group could have increased haemolysis and accumulation of free haemoglobin.

**Poster #: 54 .THE INFLUENCE OF PENTOXIFYLLINE ON HEMORHEOLOGY AND PULMONARY ARTERY PRESSURE AT 3800M.** Andrew R Steele1, Connor A Howe1, Katharine Foster2, Alexandra M Williams3, Hannah G Caldwell1, L Madden Brewster1, Jennifer Duffy1, Justin A Monteleone1, Prajan Subedi2, James D Anholm2, Philip N Ainslie1, Joshua C Tremblay4. 1University of British Columbia Okanagan, 2Loma Linda University School of Medicine, 3University of British Columbia, 4Cardiff Metropolitan University

OBJECTIVE: Pentoxifylline, a non-selective phosphodiesterase inhibitor, reduces blood viscosity and directly vasodilates and is used for the treatment of peripheral vascular disease. High altitude pathologies relate to rises in blood viscosity and pulmonary artery pressure. METHODS: We conducted a double-blinded, placebo-controlled study to test the hypothesis that pentoxifylline would reduce blood viscosity and pulmonary pressure in lowlanders after 11-14 days at Barcroft Field Station (3800m). Participants (6M/10F; age = 27 ± 4) were administered placebo or 400 mg of pentoxifylline orally the preceding night and the two hours before testing. An arterial blood sample was acquired to assess blood gases and venous sample for hemorheology (viscosity, hematocrit, plasma viscosity, red blood cell deformability and aggregation). Pulmonary artery systolic pressure (PASP) was estimated using echocardiography during room air breathing and following 8-10 minutes of isocapnic hypoxia (end tidal partial pressure of oxygen: 40 mmHg). RESULTS: Pentoxifylline did not alter arterial blood gases, red blood cell deformability or aggregation compared to placebo. Blood viscosity was reduced at high shear rates (>150 s-1) in males (Cohen's d = 1.41-1.83, P= 0.02-0.008) but not females. Plasma viscosity (d = 2.06, P = 0.01) and hematocrit (d = 2.43, P = 0.002) were also reduced in males. PASP conversely, was reduced with pentoxifylline in females during room air (d = 1.05, p = 0.02) and isocapnic hypoxia (d = 0.971, p = 0.03), but not in males. CONCLUSION: Therefore, acute pentoxifylline administration appears to influence both hemorheological properties and PASP in lowlanders without high altitude-related illnesses at 3800m; however, these effects may be sex specific. Pentoxifylline may be useful for the prevention or treatment of high altitude-related illnesses and merits further investigation in individuals susceptible for high altitude pulmonary edema and with excessive erythrocytosis.Funding: This work was funded by NSERC.

**Poster #: 55 .MECHANISTIC INSIGHTS INTO NORMOTHERMIC REGIONAL PERFUSION (NRP) FOR THE TREATMENT OF HYPOXIA INDUCED LIVER DAMAGE PRIOR TO TRANSPLANTATION..** Andrew Sutherland1, Bansal Sukhchain 2, Carolyn Cairns1, Brian Conway1, Emma Morrison1, Chris Watson3, James Dear1, Gabriel Oniscu1. 1University of Edinburgh, 2University of Birmingham, 3University of Cambridge

Introduction: Normothermic regional perfusion (NRP) is a transplant procurement technique that can reverse the deleterious effects of hypoxia associated with donors after circulatory death (DCD). A number of studies have demonstrated NRP improves clinical outcomes and organ utilization. However, little is known about the mechanism of action. We hypothesised that DCD livers are preconditioned during the initial period of hypoxia and then reconditioned during NRP. Furtherrmore NRP provides a period of organ assessment prior to transplantation.Methods: NRP was commenced following cardiac arrest in DCD donors for 2 hours and liver biopsies and serum samples were taken at 0 and 120 minutes. mRNA expression of 6 common HIF target genes; erythropoietin (EPO), haemoxygenase-1 (HMOX-1),

pyruvate dehydrogenase kinase-1 (PDK1), glucose transporter-1 (SLC2A1) , vascular endothelial growth factor (VEGFA), and VEGF receptor (FLT-1) was assessed. ADP/ATP ratio was assessed using bioluminescence and serum miR-122 concentration (a marker of liver injury) was determined by quantitative real time RT-PCR. Two-sample t tests were run to compare groups.Results: HIF target genes were up-regulated following 2 hours NRP (NRP2) compared to the start of NRP (NRP0). The mean up-regulation ranged from 1.3 fold (EPO) to 2.4 fold (FLT-1). The up-regulation of 4 genes reached significance ($p<0.05$). At the end of NRP serum miR-122 was significantly lower in the donors whose livers were successfully transplanted compared to those deemed not suitable. ATP/ADP ratio was restored and lactate reduced.Conclusions: Upregulation of HIF target genes suggests that hypoxic preconditioning may play a role in the mechanism of NRP. Reconditioning likely occurs through replenishment of `ATP and normalization of lactate. miR-122 is a sensitive and specific marker of liver injury that was able to differentiate transplantable from non-transplantable livers.

**Poster #: 56 .A PILOT STUDY INVESTIGATING THE EFFECT OF POSITIVE PRESSURE VENTILATION ON OXYGEN SATURATION AT ALTITUDE DURING RECREATIONAL AVIATION.** Jenna L Taylor1, J. Hunter Downs III1, Joshua D Donkor1, Jessica I Johnston1, Aidan K Downs1, Crystal L Marshall2, Elias Smirlis2, Alex R Carlson1, Douglas Rozendaal3, Peter Larsen2, Bruce D Johnson1, Douglas T Summerfield2. 1Mayo Clinic Rochester, 2MercyOne North Iowa Medical Center, 3None

Objective: We investigated whether positive pressure ventilation (PPV), using a commercial bilevel positive airway pressure (BIPAP) device, would improve oxygen saturation during recreational aviation up to 12500ft without supplemental oxygen. Methods: In this pilot study, ten healthy adults with recreational flight experience (age:47±14; female=5; flight hours=1450±2105) completed a standardized flight profile in an unpressurized aircraft, involving randomized crossover design at 8000ft and 12500ft with BIPAP or control. Peripheral oxygen saturation (SpO2), middle cerebral artery velocity (MCAv), and mean arterial pressure (MAP) were measured continuously on the ground and during flight. Subjects completed a 3-min psychomotor vigilance test (PVT) during flight taxi and halfway through each 15-min altitude period. Data were analyzed for the effect of altitude or BIPAP using two-tailed paired t-tests. Results: There was a large significant effect of altitude on mean SpO2 [ground:97±1%; 8000ft:92±1%; 12500ft:86±4%; mean difference (MD)=-8±2%; $p<0.001$; effect size (ES)=3.3], SpO2 nadir [ground:95±2%; 8000ft:87±3%; 12500ft:78±3%; MD=-12±3%; $p<0.001$; ES=4.0], and MCAv [ground:57±9cm/s; 8000ft:53±9cm/s; 12500ft:52±9cm/s; MD=-5±5cm/s; $p=0.01$; ES=1.0]. There was no effect of altitude ($p>0.05$) on MAP or PVT reaction time. There was a large significant effect of BIPAP on mean SpO2 at 8000ft [Control:92±1%; BIPAP:94±2%; MD=2±1; $p=0.003$; ES=1.3] and 12500ft [Control:86±4%; BIPAP:89±4%; MD=2±3%; $p=0.03$; ES=0.8]. There was also a large significant effect of BIPAP on MCAv at 8000ft [Control:53±9%; BIPAP:50±9cm/s; MD=-4±3cm/s; $p=0.005$; ES=1.4] but not 12500ft ($p>0.05$). There was no effect of BIPAP ($p>0.05$) on SpO2 nadir, MAP, or PVT reaction time. Conclusion: This small pilot study provides preliminary results that BIPAP may improve mean oxygen saturation for recreational aviators up to 12500ft without supplemental oxygen. BIPAP appears to reduce MCAv, however, reaction time was unaffected. Future adequately powered studies are needed to further investigate the potential utility of PPV to optimize oxygen saturation and cognition in recreational aviation.Funding: Mayo Clinic and MercyOne North Iowa Medical Center

**Poster #: 57 .ACUTE MOUNTAIN SICKNESS NEGATIVELY IMPACTS MOOD STATE FOLLOWING BOTH ACTIVE AND PASSIVE ASCENT TO 3600M.** William Tharion1, Peter Figueiredo1, Steven Landspurg1, Janet Staab1, Mark Buller1, J Philip Karl1, Reed Hoyt1, Jon Femling2, Jason Williams2, Aaron Reilly2, Trevor Mayschak2, Emma Atkinson1, Tim Mesite1, Beth Beidleman1. 1US Army Research Institute of Environmental Medicine, 2University of New Mexico

Objective: Mood state is known to change following acute exposure to high altitude (HA) but it is unknown whether acute mountain sickness (AMS) and ascent conditions exacerbate this response. Methods: To determine if AMS impacts mood state following active and passive ascent to HA, 78 healthy Soldiers (mean±SD; age=26±5yr) were tested at baseline residence (BLR), transported to Taos, NM (2845m), then hiked (n=39) or were driven (n=39) to HA (3600m), and stayed for four days. AMS-Cerebral factor score (AMS-C) was assessed using the Environmental Symptoms Questionnaire at HA twice on day 1 (HA1) and five times on days 2 and 3 (HA2 and HA3). If AMS-C was ≥0.7 on any assessment, individuals were categorized as AMS-susceptible (AMS+, n=33); others were non-susceptible (AMS-, n=45). Seven mood states (anger, anxiety, depression, fatigue, happiness, vigor, and restlessness) were assessed using the Automated Neuropsychological Assessment Metrics at BLR, and after 19h (HA2) and 43h (HA3) at HA. Results: Ascent conditions did not differentially impact mood state. In the AMS- group, none of the mood states changed from BLR to HA. In the AMS+ group, however, anger and anxiety increased ($p<0.05$), respectively, from BLR (0.07±0.15; 0.06±0.17) to HA2 (0.51±0.80; 0.39±0.59) and decreased ($p<0.05$) from HA2 to HA3 (0.39±0.69; 0.21±0.61). Depression and fatigue increased ($p<0.05$), respectively, from BLR (0.02±0.08; 0.50±0.67) to HA2 (0.41±0.67; 1.89±1.20) and decreased ($p<0.05$) from HA2 to HA3 (0.18±0.57; 1.25±1.17). Happiness and vigor decreased ($p<0.05$), respectively, from BLR (3.27±1.62; 2.14±1.53) to HA2 (2.27±1.64; 1.48±1.24) and remained unchanged from HA2 to HA3 (2.54±1.70; 1.66±1.50). Restlessness increased ($p<0.05$) from BLR (0.19±0.36) to HA2 (0.85±1.02) and decreased ($p<0.05$) from HA2 to HA3 (0.46±0.20). All mood states (both positive and negative) remained different at HA3 compared to BLR. Conclusions: Mood was negatively impacted by rapid ascent to 3600m in AMS-susceptible individuals for the first three days at HA which may negatively impact operational effectiveness. Authors' views not official U.S. Army or DoD policy. Funding: USAMRDC

**Poster #: 58 .ACUTE INTERMITTENT HYPERCAPNIC HYPOXIA AUGMENTS LEFT VENTRICULAR END-SYSTOLIC ELASTANCE.** Scott Thrall1, Alexandra Williams2, Philip Millar3, Megan Lance1, Brooke Shafer1, Conan Shing1, Jordan Bird1, Christopher West2, Glen Foster1. 1University of British Columbia Okanagan, 2University of British Columbia, 3University of Guelph

Objective: Acute intermittent hypercapnic hypoxia (IHH) elicits persistent increases in peripheral sympathetic activity – termed sympathetic long-term facilitation (sLTF) – leading to high blood pressure without affecting heart rate. Whether sLTF signals the myocardium to augment left ventricular contractility is unknown. We hypothesized that IHH would augment load-independent metrics of cardiac contractility, improving left ventricular systolic function.

Methods: 15 healthy participants (4F; age: 25±4 yrs; BMI: 23±2 kg/m2) underwent 40 consecutive 1-min bouts of 40-sec hypercapnic hypoxia (PETO2: 45 mmHg; PETCO2: +4 mmHg) and 20-sec normocapnic normoxia. Ventilation, end-tidal gases, blood pressure, heart rate, muscle sympathetic nerve activity (fibular nerve), end-systolic and end-diastolic volumes, and isovolumic contraction time were measured at rest and during conditions of heightened sympathoexcitation using 5-min stages of progressive lower body negative pressure (LBNP; -15, -30, and -45 mmHg) before and after IHH. End-systolic elastance was estimated noninvasively according to validated standards using echocardiography-derived parameters of ventricular volumes, contraction timings, and arterial pressure as an assessment of load-independent left ventricular contractile performance. Results: As expected, IHH elicited sustained increases in ventilation, mean and diastolic blood pressure both at rest (all $P < 0.01$) and across progressive LBNP (all $P < 0.001$). End-systolic elastance at rest was similar before and after IHH (+0.11 [-0.10, 0.31] mmHg/mL, $P = 0.301$) but tended to be greater across all stages of LBNP following IHH (+0.11 [0.00, 0.21] mmHg/mL, $P = 0.055$) irrespective of cardiac loading, with LBNP-mediated reductions in end-diastolic volume unchanged between conditions (-0.4 [-4.4, 3.6] ml, $P = 0.841$). Conclusions: In addition to the well-established effects of IHH on ventilation and blood pressure, IHH appears to influence cardiac contractility during orthostatic stress, suggesting sLTF may exert a positive inotropic effect on the left ventricular myocardium.Funding: NSERC; Stober Foundation; APS

**Poster #: 59 .EXPEDITION 5300 – ANDEAN HIGHLANDERS WITH EXCESSIVE ERYTHROCYTOSIS PERMANENTLY LIVING ABOVE 5000M EXHIBIT A HYPOCOAGULABLE PROFILE: A THROMBOELASTOMETRIC STUDY.** Samuel Verges1, François Caton2, Landry Seyve3, Emeric Stauffer4, Aurélien Pichon5, Julien Brugniaux1, Michael Furian1, Ivan Hancco1, Blandine Deschamps1, Lars Kaestner6, Paul Robach1, 7, Philippe Connes4, Pierre Bouzat1, Benoit Polack3, Raphael Marlu3, Benoit Champigneulle1. 1HP2 laboratory, Univ. Grenoble Alpes, INSERM, CHU Grenoble Alpes,Grenoble, France, 2LRP, University Grenoble Alpes, CNRS, Grenoble INP, Grenoble, France, 3Therex, TIMC-IMAG, Univ. Grenoble Alpes, CNRS, CHU Grenoble Alpes, Grenoble, France, 4LIBM, Université de Lyon 1, Hospices Civils de Lyon, Lyon, France, 5Laboratoire MOVE, Université de Poitiers, Poitiers, France, 6Saarland University, Homburg, Germany, 7National School for Mountain Sports, Site of the National School for Skiing and Mountaineering (ENSA), Chamonix, France

Objective: Excessive erythrocytosis (EE, consensually defined as a hemoglobin concentration ([Hb]) ≥ 21 g·dL-1 in men) is highly prevalent in Andean highlanders (HL) chronically exposed to hypobaric hypoxia. How EE impacts the coagulation system remains poorly investigated. We sought to assess the whole-blood coagulation, using a thromboelastometry point-of-care device (ROTEM® delta, Werfen, France), in high-altitude dwellers permanently living in La Rinconada (5100-5300 m, Peru).Methods: A cross-sectional study including 10 lowlanders acclimatized to high-altitude (LL; 80% males; 33±7 years; [Hb], 17.4±1.2 g·dL-1) and 45 HL (100% males; 45±11 years), including 30 HL without EE ([Hb], 19.4±1.2 g·dL-1) and 15 HL with EE ([Hb], 23.5±1.6 g·dL-1). ROTEM® assays (EXTEM, INTEM, FIBTEM, APTEM) were performed at native and at corrected (40%) hematocrit (Hct) by dilution of whole blood samples using autologous platelet-poor plasma (PPP) in the three groups of participants.Results: HL with EE exhibited longer clotting times (CT) as well as lower clot firmness (i.e., smaller clot amplitude at 20 min (A20))

than HL without EE and LL in EXTEM, INTEM and FIBTEM assays (all p-values <0.01) at native Hct. No hyperfibrinolysis was highlighted by APTEM assay. At corrected Hct, no significant difference persisted regarding CT in EXTEM, INTEM and FIBTEM assays between the 3 groups of participants (all p-values >0.05). Significant differences between groups in A20 persisted at corrected Hct (all p-values <0.01) in EXTEM and INTEM assays but not in FIBTEM assay (p-value >0.05).Conclusion: Compared to acclimatized LL and HL without EE, HL with EE exhibited significant delayed clot initiation (CT) and weaker clot stiffness (A20), partially corrected after hemodilution with PPP. These findings indicate a hypocoagulable profile in EE Andeans highlanders permanently living at extreme altitude.

**Poster #: 60 .RETINAL VASCULAR CHANGES AT HIGH ALTITUDE.** Jessica Westwood1, 2, Ciaran Simpkins1, 2, India Mayhook-Walker1, 3, Andrew Darby-Smith1, Eduardo Normando1, Daniel Morris4. 1Imperial College London, 2University of Birmingham, 3University of Sheffield, 4University Hospital of Wales

Objective: This study aimed to evaluate retinal vascular changes throughout an expedition to 4167 metres. Methods: 10 healthy participants summitted Mount Toubkal, Morocco. Fundus images were taken on a handheld camera pre-departure, daily throughout the expedition, and one-month post-return. Diameter and tortuosity of four vessels was assessed, in addition to vessel density and the presence of HAR. Results: Significant ($p \leq 0.05$) increases in tortuosity and diameter were observed in some vessels on high-altitude exposure days. There was a significant increase in vessel density on summit day only. This is the first study to report no evidence of high-altitude retinopathy. Conclusion: This is the first study to report increased vessel density and no incidence of HAR. These results are likely attributable to relatively low altitude exposure, a conservative ascent profile, and the young, healthy demographic profile of participants. However, the study is limited by its small sample size, environmental confounding factors and semi-subjective diameter measurements. Physiological but not pathological changes were seen in this cohort, which gives insight to the state of the cerebral vasculature throughout this expedition and builds on current understanding of retinal vascular changes in hypoxia. Future work must include daily retinal images of larger sample sizes at higher altitude and take steps to mitigate against environmental confounders. This work is relevant to altitude tourists, patients with diabetic retinopathy or retinal vein occlusion, and critically ill patients at sea level.

**Poster #: 61 .SEX DIFFERENCES IN THE LEFT VENTRICULAR RESPONSES TO ORTHOSTATIC STRESS AT 3800 M.** Alexandra M Williams1, 2, Jennifer S Duffy2, 3, Liisa Wainman2, 3, Travis D Gibbons4, Mike Stembridge5, Elliot Jenkins5, Philip N Ainslie4, Christopher R West1, 2, 3. 1Cellular & Physiological Sciences, Faculty of Medicine, University of British Columbia, Canada, 2International Collaboration on Repair Discoveries, University of British Columbia, Canada, 3Centre for Chronic Disease Prevention & Management, Faculty of Medicine, University of British Columbia, Canada, 4Centre for Heart, Lung and Vascular Health, School of Health and Exercise Science, University of British Columbia, Canada, 5Cardiff School of Sport and Health Sciences, Cardiff Metropolitan University, Cardiff, United Kingdom

Objective. While the left ventricular (LV) responses to reductions in preload are known to differ between males and females, any potential impacts of hypoxia on sex-related differences in

LV function have not been examined. Methods. 9 females (28±4yrs) and 8 males (29±4yrs) were tested near sea level (SL) and following 3-5 days arrival at 3800m (high-altitude, HA). In both settings, participants were assessed while resting supine, then during sequential levels of head-up tilt (HUT; 20°, 40° and 60°). LV volumes and hemodynamics (i.e. end-diastolic volume, EDV; stroke volume, SV; ejection fraction, EF; cardiac output, Q), mean arterial blood pressure (MAP) and heart rate (HR) were assessed with 2-dimensional echocardiography, automated brachial pressure cuff and electrocardiogram, respectively. Results. At HA, MAP and HR were elevated at baseline compared to SL baseline in both sexes ($p<0.05$ for all). Overall, HA led to shifts in EDV, SV and Q (main effects $p<0.01$), and the profile of LV hemodynamic adjustments to altitude differed between the sexes. First, baseline EDV was reduced ($p=0.012$) and Q was augmented ($p=0.003$) in males at HA, while baseline SV was reduced in females (HA:42±9ml vs. SL:50±7ml, $p=0.01$). Next, sex x HUT interactions were not detected for EDV, SV, Q or EF at SL; however, significant sex x HUT interactions were detected for EDV ($p=0.005$) and SV ($p=0.031$) at HA. Specifically, males had greater reductions to EDV (males:-37±7ml vs. females:-20±11ml, $p=0.004$) and SV (males:-24±6ml vs. females:-12±7ml, $p=0.006$) from baseline to 60° HUT. Nonetheless, both males and females were able to maintain EF, Q and MAP during HUT at HA. Conclusion. Males and females appear to have distinct LV hemodynamic adjustments to hypoxic environments, both at rest and during orthostatic challenges. The specific physiological factors contributing to such sex differences (e.g. cardiac autonomic control) remain to be determined.

**Poster #: 62 .DYNAMICS OF THE CEREBRAL BLOOD FLOW RESPONSE TO HYPOXIA .** Harrison T. Levine1, 2, Ece Su Sayin1, 2, Olivia Sobczyk3, 4, Julien Poublanc4, David J. Mikulis4, James Duffin1, 3, Joseph A. Fisher1, 3. 1Department of Physiology, University of Toronto, Toronto, Canada, 2Joint Department of Medical Imaging and the Functional Neuroimaging Lab, University Health Network, Toronto, ON, Canada, 3Department of Anaesthesia and Pain Management, University Health Network, Toronto, Canada , 4Joint Department of Medical Imaging and the Functional Neuroimaging Lab, University Health Network, Toronto, Canada

DYNAMICS OF THE CEREBRAL BLOOD FLOW RESPONSE TO HYPOXIA Harrison T. Levine, Ece Su Sayin, Olivia Sobczyk, Julien Poublanc, David J. Mikulis, James Duffin, Joseph A. Fisher University of Toronto, Toronto, Ontario, Canada, harrison.levine@mail.utoronto.caIntroduction: While steady-state measurements have determined the extent of the increase in cerebral blood flow during hypoxia, how fast the changes occur is unknown. Objective: To quantify the dynamic changes in cerebral blood flow on exposure to hypoxia. Methods: In 21 healthy volunteers we precisely controlled arterial oxygen tensions in a 3 min square wave pattern of 85 - 40 - 85 mmHg while maintaining resting isocapnia. We recorded trans-cranial Doppler (TCD) measurements of cerebral blood flow velocities in the middle cerebral artery (MCAv) and the posterior cerebral artery (PCAv). Beat-by-beat heart rate (HR) was calculated from these recordings, and mean arterial blood pressure (MAP) was recorded in 9 subjects. Results: The cerebral blood flow increase with hypoxia varied considerably among the volunteers (mean (SD) range (%) 22.6 (10.2) 9.4 - 41.4 MCAv; 27.7 (13.8) 0 – 50.9 PCAv). The increase in MCAv was fitted with an exponential rise in 11 volunteers; mean (SD) cm/s 26.45 (9.25), and for PCAv in 9 volunteers; mean (SD) cm/s 34.14 (10.92). Increases in HR and MAP also occurred. Discussion: The exponential time constants

characterizing the speed of the cerebral blood flow velocity changes in response to hypoxia were much smaller than previously published values. Although the resting MCAv and PCAv differ, the dynamic responses to hypoxia do not, suggesting similar vessel wall characteristics. Finally, TCD responses during hypoxia may be affected by HR and MAP changes and possibly those of vessel diameter during hypoxia. Conclusion: The amplitude and speed of MCAv and PCAv responses to hypoxia vary widely between people, with rates of response considerably faster than previously thought.

**Poster #: 63 .HIMALAYA AIR QUALITY IMPACTS FROM COVID-19 LOCKDOWN ACROSS THE INDO-GANGETIC PLAIN.** G.W.K. Moore1, John Semple1. 1University of Toronto

Objective: The COVID-19 lockdown within the heavily polluted Indo-Gangetic Plain (IGP) provided a unique opportunity to assess the impact and the path of pollution from this region into the Himalaya. Unique communities in high-altitude regions, such as those in the Himalaya, are unexpectedly exposed to pollution levels that approximate those reported in industrialized cities and other polluted environments. Little is known about the source of this pollution and its cross-border pathways. Methods: To characterize the impact of the lockdown on the spatial and temporal variability in air quality across the IGP and the Himalaya, we use daily tropospheric NO2 column retrievals from the OMI instrument on NASA's Aura satellite as well as higher spatial resolution data from the TROPOMI instrument on ESA's Sentinel 5P satellite. Mass-weighted wind data from the European Centre for Medium-Range Weather Forecasts' ERA5 Reanalysis were used to characterize the atmospheric circulation during April 2020. Results: In-situ and satellite observations show that there was a step function decrease in two key indicators of air quality, nitrogen dioxide and airborne particulates, in locations within the Indo-Gangetic Plan (IGP) secondary to the Spring 2020 lockdown. Based on anomaly patterns, we find a dipole response with a statistically significant reduction in air pollution along the western IGP and Himalaya and an increase in air pollution in the eastern IGP and Himalaya. We show that spatial variability in the reductions in economic activity across northern India and the adjoining countries of Nepal, Pakistan and Bangladesh contributed to this dipole as did a persistent atmospheric circulation anomaly across the region during the lockdown. Conclusions: The COVID-19 lockdown within the heavily polluted IGP provided a unique opportunity to assess the impact of pollution from this region on the Himalaya.

**Poster #: 64.** CAN CURRENT WEARABLES' HEART RATE VARIABILITY (HRV) INDICES PREDICT HIGH ALTITUDE CLIMB READINESS AND ACUTE MOUNTAIN SICKNESS?

Christian Dean, DO, MS. Community Medical Center, Missoula, MT.

Objective: There currently is no great, non-invasive, easily reproducible objective ability to predict climb readiness or estimation of risk of developing acute mountain sickness (AMS). HRV has been linked to predicting AMS in several studies, but not using the new generation of wearables. The purpose of this study was to ascertain in a pilot, n=1 observational case study using HRV data collected on a non-externally-validated current generation wearable, which could provide a low cost, non-invasive way to predict climb readiness. Methods: The lake louise score (LLS) and HRV value were collected. The HRV value is a proprietary consumer accessible scores on the Coros brand Vertix 2 watch. The study was in two phases. The first phase was the traditional trekking route involving flying to Lukla from Kathmandu and then trekking to Everest Base Camp (EBC) through Phakding, Namche, Tengboche, Dingboche, Lobuche, and then to EBC. Correlation and factor analysis was used to determine the statistical significance. Results: The results were tabulated in a spreadsheet during the data collection period in April and May 2022. The VERTIX 2 watch applies the root mean square of successive differences (rMSSD) method to get an accurate HRV measurement which is then input into Coros' unique HRV Index algorithm to provide a personalized and easy-to-understand metric on the watch display using the status of the body's response to external factors. This proprietary algorithm is not known to the researcher or consumer and the underlying data is not externally validated, unlike some other wearables on the market currently. Using the statistical analyses, it was determined that the HRV index and the chronological elevation profile do not predict AMS or climb readiness statistical significance as determined by LLS reporting. Funding sources: Coros gave Christian Dean a 20% off voucher for the Coros brand watch. The pilot study was done independently from an expedition that I was already paid to be on in the capacity of expedition physician.

**Poster #: 65. Hyperoxia improves exercise capacity in cardiopulmonary disease A series of RCT's.**

Julian Müller1,2,; MSc, Mona Lichtblau1,2,; MD, Stéphanie Saxer1; PhD, Simon R. Schneider1,2; MSc, Paula Appenzeller1; MD, Meret Bauer1; MD, Elisabeth D. Hasler1; MD, Esther I. Schwarz1,2; MD, Konrad E. Bloch1,2; Prof, Silvia Ulrich1,2; Prof 1 Department of Pulmonology, University Hospital Zurich, Zurich, Switzerland 2 University of Zurich, Zurich, Switzerland.

**Background:** To study the overall and differential effect of breathing hyperoxia (FiO2 0.5) vs. placebo (ambient air, FiO2 0.21) to enhance exercise performance in healthy people, patients with pulmonary vascular disease (PVD) with precapillary pulmonary hypertension (PH), chronic obstructive pulmonary disease (COPD), PH due to heart failure with preserved ejection fraction (HFpEF) and cyanotic congenital heart disease (CHD) using data of five RCTs performed with identical protocols. **Methods:** 91 subjects (32 healthy, 22 PVD with pulmonary arterial or distal chronic thromboembolic PH, 20 with COPD, 10 with PH in HFpEF and 7 with CHD) performed 2 cycle incremental (IET) and 2 constant work-rate exercise tests (CWRET) at 75% of maximal load (Wmax), each with ambient air and hyperoxia in single blinded, randomized-controlled cross-over trials. The main outcomes were differences in Wmax (IET) respectively cycling time (CWRET) with hyperoxia vs ambient air. **Results:** Overall, hyperoxia

increased Wmax by +12 W (95%CI: 9 to 16, p<0.001) and cycling time by +6:13 min (4:50 to 7:35, p<0.001), with improvements being highest in patients with PVD: (Wmax/min: +18%/+118% vs. COPD: +8%/+60%, healthy: +5%/+44%, HFpEF: +6%/+28%, CHD: +9%/+14%). **Conclusion:** This large collective of healthy and patients with various cardiopulmonary disease confirms that hyperoxia significantly prolongs cycling exercise with improvements being highest in endurance CWRET and patients with PVD. These results call for studies investigating optimal oxygen levels to prolong exercise time and effects on training.

## Poster #: 66. THE EFFECTS OF CAFFEINE ON BLOOD PRESSURE, SLEEP AND COGNITIVE PERFORMANCE IN HYPOXIC CONDITIONS

Christopher Jung1, Richard Wehling1, Suman Acharya2, Trina Musliu 2, Santosh Baniya 2
1 University of Alaska Anchorage, 2 2. Mountain Medicine Society of Nepal.

Objective: High altitude (HA) exposure can lead to sleep disruption, impaired cognitive performance, elevated blood pressure (BP) and an increase in cardiovascular events in healthy people. Because caffeine can also have similar effects such as increases BP and sleep disruptions, caffeine might have additive and detrimental impacts to the effects of HA. Therefore, the aim of the current study was to examine the effects of caffeine on cardiovascular, sleep and cognitive variables at HA. Methods: We conducted a non-randomized, single-blind, mixed model design at 4,300 m (Nepal). Thirty-three trekkers (nine females), aged 29.510.4 (meanSD), ingested a placebo or 200 mg of caffeine 1.5 hours after awakening. BP and cognitive performance (Stroop Task). Cognitive function was tested using the Stroop task before and after the pill administration and sleep was measured the night following the pill administration. Results: Caffeine did not have any major effect on BP. Caffeine improved cognitive performance when compared to the pretreatment measurement but was worse in the caffeine group prior to the pill administration when compared to the placebo group. Finally, caffeine significantly decreased self-selected total sleep duration (p<0.05), however other sleep quality metrics were not significantly different. Conclusion: Caffeine does not appear to have an additive effect in increasing BP with HA. Additionally, the shorter sleep duration with caffeine use might be a reason for worse cognitive performance prior to the caffeine pill administration in the chronic caffeine users. Alternatively, caffeine users might be more dependent on caffeine to perform optimally at HA. Based off these data, caffeine users should consider abstaining from caffeine prior to exposure to HA to improve sleep duration and mitigate the poor cognitive function prior to caffeine consumption. Funding: UAA IDeA Network of Biomedical Research Excellence, UAA BUILD EXITO.

## Poster #: 67. EFFECT OF ELECTRICAL MUSCLE STIMULATION IN HYPOXIA ON SKELETAL MUSCLE MORPHOLOGY AND STRENGTH

Jin Uchimaru[1], Da-Li Son[2] [1]Sendai University, Faculty of Sports Science, [2] Sendai University Graduate School of Sports Science

**Purpose:** This study was to examine the effects of Electrical Muscle Stimulation (EMS) in normobaric hypoxia for 4 weeks on the morphology and strength of skeletal muscles. **Methods:** Seventeen college age students were randomly divided into EMS in normoxia (20.9%$O_2$) group; (N, n=9) and in normobaric hypoxia (14.5%$O_2$) group (H, n=8). They completed EMS training for 4 weeks (two times per weeks). EMS training consisted of 60 repetitions of tetanus while a relax seated position with their legs extended. EMS was applied to the quadriceps muscle with the stimulator. The stimulator current waveform was set at a frequency of 80 Hz with a pulse width of 250 μs. Also, the stimulation intensity was set to the maximum intensity (20 to 41 mA) that they could tolerate for each session. We measured knee extension isometric strength, rectus femoris and vastus lateralis muscle thickness and thigh circumference before and after 4 weeks of training. Each parameter was statistical analyzed by two-way ANOVA were completed to identify any significant ($p<0.05$). **Results:** Knee extension maximal isometric strength of both group were significantly increase after training period (H and N group; 12%, $p<0.05$). In H group, rectus femoris muscle thickness was significantly increase from 23.9±2.4mm to 26.9±3.8mm ($p<0.05$) and vastus lateralis muscle thickness tended to increase after training. **Conclusion:** These results suggest that 4 weeks of EMS training in hypoxia would be induce increased isometric muscle strength and induce muscle hypertrophy. The increase in muscle strength is considered to be greatly influenced by the improvement of neurological factors. **Funding:** This study supported by Grant from Sendai University.

**Time: 1730-1736**

**Poster #: 11 .INTRAOPERATIVE OXYGEN CONCENTRATIONS INCREASE PERIOPERATIVE OXIDATIVE STRESS IN A DOSE-DEPENDENT MANNER – A RANDOMISED CONTROLLED TRIAL (PULSE Ox) .** Andrew Cumpstey1, Anna Clark1, Magdalena Minnion1, Renato Nogueira2, Helen Moyses1, Daniel Martin3, Jose Tanus-Santos2, Mark Edwards1, Michael Grocott1, Martin Feelisch1. 1University of Southampton, 2University of São Paulo, 3University of Plymouth

Background: The World Health Organization (WHO) recommends all anaesthetised patients receive 80% oxygen during surgery to reduce the risk of surgical site infection (SSI). Results from the PROXI trial (no difference in SSI rates between 30% and 80% oxygen but possibly worse postoperative outcomes with 80% oxygen) would caution against this but were considered 'mechanistically implausible' (WHO).Objective: To investigate whether administering higher inspired oxygen concentrations during anaesthesia might increase systemic oxidative stress (and therefore predispose to adverse outcomes).Methods: Twenty-eight adult patients undergoing major (central venous catheter required) abdominal surgery were randomly allocated to receive 30%, 55% or 80% oxygen throughout anaesthesia. Paired arterial and central venous blood gases (to measure oxygen extraction) and samples were collected 2-hourly. Total nitroso species (RxNO) and Nitric Oxide (NO) scavenging were quantified using gas phase chemiluminescence. Total free thiols (TFTs) and ferric reducing ability of plasma (FRAP) were measured colorimetrically.Results: Higher oxygen was associated with higher RxNO concentrations (Mean[SD] 52.6[19.1]/100.2[36.1]/91.2[34.4] nM for 30/55/80% respectively, $p = 0.05$) & reduced NO scavenging (4.4[0.7]/3.5[0.4]/3.6[0.6]uM, $p = 0.02$) at the end of surgery. Normalized TFTs increased throughout surgery but with no difference between groups (4.5[0.3]/4.1[0.3]/4.2[0.4], $p = 0.26$). FRAP concentrations did not change overall (866.5[52.0]/908.1[37.1]/810.6[57.4], $p = 0.42$) but decreased markedly in some patients. Why inter-individual perioperative oxygen sensitivity differs merits further investigation. Tissue oxygen extraction reduced significantly with 80% oxygen (0.28[0.10]/0.23[0.08]/0.20[0.06], $p < 0.001$), supporting previous data in critically ill patients.Conclusion: Higher intraoperative oxygen concentrations significantly increase markers of oxidative stress, lower systemic antioxidant capacity and decrease oxygen extraction during surgery in a dose-dependent fashion.Funding: Doctoral Fellowship (Southampton NIHR Biomedical Research Centre)

**Time: 1736-1742**

**Poster #: 15 .EFFECTS OF NALTREXONE ON SLEEP QUALITY AND PERIODIC BREATHING AT HIGH ALTITUDE.** Katharine Foster1, James Anholm2, Gary Foster3, Prajan Subedi2. 1Emergency Medicine, Loma Linda University School of Medicine, Loma Linda, CA 92354, 2Pulmonary & Critical Care, VA Loma Linda Healthcare System & Department of Medicine, Loma Linda University School of Medicine Loma Linda, CA 92357, 3Cardiology, St. Charles Health System, Bend, OR 97701

Objective: This study examined the role of the Mu-opioid receptor (MOR) on breathing and sleep at high altitude (HA). We hypothesized that MOR blockade with naltrexone would result in higher nocturnal oxygen saturations, fewer apneas and improved sleep at high altitude.Methods: This double blind, placebo-controlled, crossover study included 9 healthy subjects aged, 27.9 ± 4.6 years. Two overnight trips spaced at least two weeks apart occurred from Loma Linda, CA (355m) to Barcroft Laboratory, CA (3810m) for each arm. Subjects took either 50 mg naltrexone or matching placebo at bedtime. Sleep metrics were recorded using WatchPATTM device (Itamar Medical Ltd.). Subjective data was measured with the Groningen Sleep Quality Scale, Stanford Sleepiness Scale and Lake Louise Score (LLS) for acute mountain sickness (AMS).Results: Mean overnight SpO2 was lower after taking naltrexone, 81 ± 6% vs. 83 ± 4% (mean difference 1.9 ± 2.1%), 95%CI=0.1–3.6, p=0.04). Minimum overnight SpO2 was lower on naltrexone 70 ± 6% vs. 74 ± 4% (dif. 4.6% ± 4.3%) CI=1.0–8.2, p=0.02). Total sleep time and total apnea-hypopnea index(AHI) were not different. Subjective sleep quality was significantly worse on naltrexone measured via Groningen ($p<0.03$) and Stanford Sleepiness Scale ($p<0.03$). AMS measure via the LLS was significantly worse while taking naltrexone ($p<0.03$).Conclusion: In contrast to our hypothesis, this study demonstrated a significant decrease in oxygen saturation and sleep quality with no change in sleep time or AHI. AMS scores were significantly worse after taking naltrexone. To our knowledge this is the first study to test physiologic effects of MOR blockade in humans at altitude. Further characterization of the MOR's vasoactive and sympathetic modulation and its effects on regulation of cerebral blood flow are needed to further interpret these results.

**Time: 1742-1748**

**Poster #: 20 .SLEEP AND BLOOD PRESSURE DURING A 12-MONTH STAY AT CONCORDIA STATION (3233 M), ANTARCTICA.** Michael Furian1, Paul Robach2, Stijn Thoolen3, Sarah Rommel3, Sebastien Baillieul1, Stephane Doutreleau1, Pierrick J Arnal4, Samuel Verges1. 1HP2 laboratory, Université Grenoble Alpes, Inserm (U1300), CHU Grenoble Alpes, Grenoble, 38000, France, 2Ecole Nationale des Sports de Montagne, 74400 Chamonix, France, 3French Polar Institute Paul-Émile Victor, Brest, 4Dreem, Paris, France

Introduction. Sleep architecture remains impaired when staying at the Concordia Station (3233m), Antarctica. The purpose of this study was to investigate sleep and blood pressure, and the pathophysiological role of hypoxia.MethodProspective cohort study in 23 subjects staying for 12 months at 3233m (N=11, mean±SD age 36±10y, BMI 24.3±3.1kg/m2) or in Dumont d'Urville, 20m (N=12, age 31±12y, BMI 22.3±3.1kg/m2), Antarctica. Before departure (BL) and in the 1st and 12th month at the Stations, sleep assessment (DREEM) and 24h ambulatory blood pressure (BP) monitoring was performed.ResultAt 3233m, subjects had less stage 3 sleep (%total sleep time, TST) in the 1st (mean±SE 18±2%TST) and 12th (18±2%TST) month vs BL (24±3%TST, both P<0.05). In contrast, proportion of stage 2 sleep and micro-arousals were higher in the 1st (50±2%TST, 10.1±1.0/h) and 12th (51±2%TST, 11.5±1.0/h) month vs BL (43±3%TST, 7.1±1.2/h, both P<0.05). At 20m, no changes occurred. At 3233m, nocturnal mean BP was higher in the 1st (85±2mmHg) and 12th (80±2mmHg) month vs BL (76±2mmHg, both P<0.05). The higher nocturnal BP was caused by a higher proportion of non-dipping defined by <10% Δnight-day BP, which was 0% at BL, 45% in 1st and 27% in 12th month at 3233m (P<0.05, 1st month vs BL). At 20m, no changes occurred. Conclusion. A 12-month stay at the Concordia Station at 3233m was associated with worse sleep and nocturnal BP compared to pre-departure. Since these impairments were not observed at Dumont d'Urville, preventive measures against hypoxia might be considered to improve outcomes in these crewmembers.

**Time: 1748-1754**

**Poster #: 36 .DIFFERENCES IN DNA METHYLATION BETWEEN ALTITUDE EXPERIENCED AND ALTITUDE NAÏVE HEALTHY VOLUNTEERS ON EXPOSURE TO HYPOBARIC HYPOXIA.**

Kay Mitchell1, Emma Garratt1, Michael Natoli2, Elie Antoun1, Matthew Hewitt1, Negusse Kitaba1, Andrew Cumpstey1, Thomas Smedley1, Nelson Diamond2, Timothy Beck2, Denny Levett1, Michael Mythen3, Andrew Murray4, Hugh Montgomery3, Daniel Martin5, Keith M Godfrey1, Richard Moon2, Karen Lillycrop1, Michael Grocott1. 1University of Southampton, 2Duke University, 3University College London, 4University of Cambridge, 5University of Plymouth

Objectives: We investigated skeletal myocyte DNA methylation patterns in altitude experienced (AE) and altitude naïve (AN) lowlander volunteers on exposure to hypobaric hypoxia and subsequent return to normoxia. Methods: Twenty-one healthy male volunteers were exposed to environmental hypoxia over 3 days in a hypobaric chamber (maximum altitude equivalent to 3500m, PaO2 8 kPa). Vastas lateralis skeletal muscle biopsies were taken at baseline, at the end of hypoxia, and 3 hours after return to normoxia. Following quality control and normalisation procedures methylation levels of cytosine-guanine sequences (CpGs), generated using an Illumina HumanMethyaltion EPIC bead array, were compared between baseline and hypoxia, and between hypoxia and subsequent normoxia using paired t-tests. Associations between sites of methylation change and all known biological pathways were sought. Results: Methylation patterns altered in response to hypoxia in all participants, with further changes following return to normoxia. The number of differentially methylated CpGs (dmCpGs) was greater in AE than AN participants following exposure to hypoxia (ratio 2.06:1, $p<0.001$), and subsequent return to normoxia (ratio 4.14:1, $p<0.001$), and differed between them. DmCpGs were enriched in MAPK and PI3K-Akt signalling pathways following exposure to hypoxia, and subsequent return to normoxia. Conclusions: Altered DNA methylation patterns were associated with hypoxic exposure and subsequent return to normoxia in healthy humans with differences in methylation patterns between AE and AN individuals. Methylation changes were associated with signalling pathways that may underpin the skeletal muscle response to hypoxia.

**Time: 1754-1800**
**Poster #: 28 .ACUTE MOUNTAIN SICKNESS DOES NOT IMPACT VENTILATORY ACCLIMATIZATION FOLLOWING ACTIVE AND PASSIVE ASCENT TO 3600M.** Steven Landspurg1, Peter Figueiredo1, Emma Atkinson1, Janet Staab1, Mark Buller1, Reed Hoyt1, Philip Karl1, Tim Mesite1, Beth Beidleman1, Jon Femling2, Jason Williams2, Aaron Reilly2, Trevor Mayschak2. 1US Army Research Institute of Environmental Medicine, 2University of New Mexico Health Sciences Center

Introduction: Whether acute mountain sickness (AMS) differentially impacts the magnitude or time course of ventilatory acclimatization at high altitude (HA) remains controversial. Methods: To determine whether AMS impacts ventilatory acclimatization following both passive and active ascent to HA, 78 healthy Soldiers (mean±SD; age=26±5yr) were tested at baseline residence (BLR), transported to Taos, NM (2845m), then hiked (n=39) or were driven (n=39) to 3600m, and stayed for four days. AMS-C was assessed using the Environmental Symptoms Questionnaire at HA twice on day 1 (HA1), five times on days 2 (HA2) and 3 (HA3) and once on day 4 (HA4). If AMS-C was ≥0.7 at any timepoint, individuals were categorized as AMS-susceptible (AMS+, n=33); others were categorized as non-susceptible (AMS-, n=45). Portable real-time capnography was used to measure resting partial pressure of end-tidal carbon dioxide (PETCO2 mmHg) at ~09:00 at BLR, and after 19h (HA2), 43h (HA3), and 67h (HA4) at HA. Resting pulse arterial oxygen saturation (SpO2, %) was measured immediately after PETCO2. Results: Ascent conditions did not differentially impact ventilatory responses. PETCO2 and SpO2 did not differ between AMS+ and AMS- groups at BLR or any time point at HA. The PETCO2(mmHg) in AMS+ vs. AMS- groups, decreased($p<0.05$) from BLR (37.2±3.6 vs. 36.9±3.1) on HA2 (33.5±4.1 vs. 33.7±4.0), remained stable from HA2 to HA3 (33.4±4.1 vs. 33.8±3.9) and decreased($p<0.05$) from HA3 to HA4 (31.8±4.4 vs. 31.4±4.1). SpO2(%) decreased($p<0.05$) in both AMS+ and AMS-, from BLR (97.3±1.5 vs. 96.9±1.5) on HA2 (87.9±3.1 vs. 88.8±2.9) and remained stable from HA2 to HA3 (88.8±3.1 vs. 89.1±2.9) and HA4 (88.9±3.1 vs. 89.6±2.1). Conclusions: Ventilatory acclimatization occurred at HA, but AMS-susceptibility did not impact the magnitude or time course of acclimatization following active or passive ascent to 3600m. Authors' views not official U.S. Army or DoD policy. Funding: USAMRDC

**Time: 1800-1806**

**Poster #: 4 .RELATIONSHIP OF NOCTURNAL OXYGEN SATURATION TO SLEEP QUALITY AT HIGH ALTITUDE.** Diana Biggs1, Andrew Burns1, Greta Carlson1, Ilaria Ferrari1, Lukas Sloan1, Linda E. Keyes1. 1University of Colorado

Objective: Few studies have investigated sleep quality vs. nocturnal SpO2, but rather have compared sleep fragmentation and nocturnal wakening to sleep quality. We evaluated the hypothesis that nocturnal hypoxia at high elevation would lead to poorer sleep quality.Methods: This prospective observational cohort study of adult lowlanders compared sleep quality measured by the Groningen Sleep Quality Scale (GSQ) and nocturnal SpO2 during participants' first 24h at high altitude (2470-2700m). SpO2 was measured continuously overnight using the Nonin WristOx.Results: We report preliminary data on 9 participants, (mean age = 46 yo, female = 6), none with a history of OSA. Mean basal nocSpO2 was 87%, 95% CI [85-89], mean minimum nocSpO2 75%, 95% CI [70-80] and mean percent time SpO2<88% 51%, 95% CI [27-75]. Mean GSQ was 7, 95% CI [4-10]. GSQ scores were not associated with minimum nocSpO2 (R2 = 0.0) or percent of time SpO2<88% (R2 =0.0). Lower mean nocSpO2 was associated with better perceived sleep quality (lower GSQ) (R2=0.6).Conclusion: Contrary to our hypothesis, despite participants reporting poor sleep quality the first night after arrival to high altitude, lower nocturnal SpO2 was not associated with worse sleep quality. We are unsure why higher mean nocturnal SpO2 was associated with worse sleep quality but suspect other unmeasured variables affect sleep quality.Funding: This work was supported by a Wilderness Medical Society Hultgren grant.

**Time: 1806-1812**

**Poster #: 44 .THE RELATIONSHIP BETWEEN SLEEP DURING THE FIRST NIGHT OF EXPOSURE TO 3600M ON ACUTE MOUNTAIN SICKNESS THE NEXT MORNING.** Bradley Ritland1, Peter Figueiredo1, Steven Landspurg1, Jon Femling2, Jason Williams2, Janet Staab1, Reed Hoyt1, Mark Buller1, J Philip Karl1, Aaron Reilly2, Trevor Mayschak2, Emma Atkinson1, Tim Mesite1, Beth Beidleman1. 1US Army Research Institute of Environmental Medicine, 2University of New Mexico

Objective: Sleep disturbances are common at high altitude (HA) (> 3500m), but the relationship between sleep and the incidence and severity of acute mountain sickness (AMS) is debated. The objective was to investigate whether sleep on the first night at HA was associated with AMS the next morning following active and passive ascent to 3600m. Methods: 78 healthy Soldiers (mean±SD; age=26±5yr) were transported from their baseline residence (BLR) to Taos, NM (2845m), where they hiked (n=39) or were driven (n=39) to HA (3600m) and assessed for two days (HA1 and HA2). Sleep was measured via actigraphy on the first night of sleep at HA (HA1) and used to calculate sleep awakenings (events/hr), duration (min), onset latency (min), wakefulness after sleep onset (WASO, min), and sleep efficiency (%). Mean pulse oxygen saturation (SpO2) was measured using pulse oximetry during sleep. AMS-Cerebral factor score (AMS-C) was assessed using the Environmental Symptoms Questionnaire on day 2 at HA (HA2). If AMS-C values were ≥0.7 on HA2, individuals were classified as AMS-susceptible (AMS+, n=23); others as non-susceptible (AMS-, n=55). Results: Ascent conditions did not differentially impact sleep measurements. There were no differences in sleep awakenings, onset latency, WASO, or sleep efficiency between the AMS+ and AMS- groups. In the AMS+ group compared to the AMS- group, sleep duration (min) was lower (392±57 vs. 433±63, p=0.009) and mean SpO2 (%) was lower (79.7±6.1 vs 82.0±3.9, p=0.05). Sleep duration (r=-0.32, p=0.004) and mean SpO2 (r=-0.32, p=0.005) values on the first night at HA were negatively correlated with AMS-C values the following morning on HA2. Conclusion: When Soldiers passively or actively ascend to high altitude (3600m), sleep duration and arterial oxygen saturation during the first night at HA is associated with AMS the next morning. Authors' views not official U.S. Army or DoD policy. Funding: USAMRDC

**Time: 1812-1818**

**Poster #: 24 .CHARACTERIZATION OF THE INFLAMMATORY RESPONSE TRIGGERED BY NORMOBARIC HYPOXIA.** Sonja Hersel1, Frank Splettstoesser1, Katrin Reiners2, Sarah Zaffarana2, Laura de Boni3, Henning Weis3, 4, Fabian Hoffmann3, 5, Jan-Niklas Hoenemann3, 5, Jens Jordan3, Ulrich Limper3, Jens Tank3, Stilla Frede1. 1Department of Anesthesiology and Intensive Care Medicine, University Hospital Bonn, Germany, 2Institute of Clinical Chemistry and Clinical Pharmacology, University Hospital Bonn, Germany, 3Department of Cardiovascular Aerospace Medicine, Institute for Aerospace Medicine, German Aerospace Center, Cologne, Germany, 4Department of Nuclear Medicine, University of Cologne, Germany, 5Department of Internal Medicine III, Division Cardiology, Pneumology, Angiology and Intensive Care, University of Cologne, Germany

Objective: Hypoxia and inflammation share interlinked cellular pathways. We investigated the hypothesis that exposure to hypoxia is sufficient to trigger pro-inflammatory processes in human immune and endothelial cells, which could be involved in inflammatory signaling at high altitudes. Methods: White blood cells (WBCs) were collected from normoxic healthy donors. Primary human pulmonary microvascular endothelial cells (HPMECs) were purchased from PromoCell. Cells were incubated for up to 24h under normoxic or hypoxic conditions with 10% or 1% oxygen (O2). Regulation of pro-inflammatory and hypoxia-inducible genes and proteins was evaluated by RT-PCR, ELISA and immunoblot (HIF-2α stabilization). Plasma samples were taken from participants of the MyoCardioGen 3 (MCG3) study who were exposed to sustained severe hypoxia (35 days, lowest O2 concentration 9.5%). The study included three participants who had suffered myocardial infarction and one healthy subject. Plasma from the MCG3 participants was analyzed by Luminex assay. In addition, extracellular vesicles (EVs) were investigated using nanoparticle tracking analysis (NTA). Results: WBCs and HPMECs exposed to 1% O2 showed a slight elevation of tested pro-inflammatory cytokines, which was absent under normoxic or 10% hypoxic conditions. A cellular response to hypoxia could be proven in all in vitro experiments. Luminex results showed changes in pro-inflammatory cytokine concentrations in plasma of MCG3 study participants. NTA analysis confirmed a change in EV numbers in in vitro and in vivo hypoxia experiments. Conclusion: Our study indicates that 1% O2 slightly increases the pro-inflammatory state in WBCs and HPMECs. Since donors exposed to sustained hypoxia showed a more pronounced regulation of inflammatory cytokines, we conclude that inflammatory processes in vivo are influenced by communication between different cell types. Unidentified humoral factors or EVs secreted by cells under hypoxic stress may represent a possible connection.Funding: No external funding.

**Time: 1818-1824**

**Poster #: 40 .MANIPULATION OF IRON STATUS ON CEREBRAL BLOOD FLOW AT HIGH ALTITUDE IN LOWLANDERS AND ADAPTED HIGHLANDERS .** Alexander Patrician1, Christopher Willie1, Ryan Hoiland2, Christopher Gasho3, Prajan Subedi3, James Anholm3, Michael Tymko1, Philip Ainslie1. 1Centre for Heart, Lung & Vascular Health, University of British Columbia Okanagan, 2Department of Anesthesiology, University of British Columbia, 3Pulmonary/Critical Care, Loma Linda University

Objective: Cerebral blood flow (CBF) increases during hypoxia to counteract the reduction in arterial oxygen content. The onset of tissue hypoxemia coincides with the stabilization of hypoxia-inducible factor (HIF) and transcription of downstream HIF-mediated processes. It has yet to be determined, whether HIF down- or upregulation can modulate hypoxic vasodilation of the cerebral vasculature. Therefore, we examined whether: 1) CBF would increase with iron depletion (via chelation) and decrease with repletion (via iron infusion) at high-altitude, and 2) explore whether genotypic advantages of highlanders extend to HIF-mediated regulation of CBF. Methods: In a double-blinded and block-randomized design, CBF was assessed in 82 healthy participants (38 lowlanders, 20 Sherpas and 24 Andeans), before and after the infusion of either: iron(III)-hydroxide sucrose, desferrioxamine or saline. Results: Across both lowlanders and highlanders, baseline iron levels contributed to the variability in cerebral hypoxic reactivity at high altitude ($R2=0.174$, $P<0.001$). At 5,050 m, CBF in lowlanders and Sherpa were unaltered by desferrioxamine or iron. At 4,300m, iron infusion led to 4±10% reduction in CBF (main effect of time $p=0.043$) in lowlanders and Andeans. Conclusion: Iron status may provide a novel, albeit subtle, influence on CBF that is potentially dependent on the severity and length-of-stay at high altitude. Funding: The 2016 UBC Mt Everest Expedition and the 2018 Global REACH expedition to Peru was funded as a whole, by a Canada Research Chair (CRC) and the Natural Sciences and Engineering Research Council (NSERC) Discovery Grant and the Canadian Foundation for Innovation to P.N.A. A.P., M.M.T., R.L.H., were supported by an NSERC Doctoral Grants.

**Time: 1824-1830**

**Poster #: 46 .TRANSIENT HYPOXIA-INDUCED DEOXYHEMOGLOBIN FORMATION SERVES AS AN MRI CONTRAST FOR PERFUSION IMAGING IN PATIENTS WITH STENO-OCCLUSIVE DISEASE.**

Ece Su Sayin1, 2, Vittorio Stumpo3, 4, Jacopo Bellomo3, 4, Julien Poublanc2, Marco Piccirelli3, 4, James Duffin1, Vepeson Wijeya2, Athina Pangalu 3, 4, Andrea Bink3, 4, Bence Nemeth3, 4, Zsolt Kulcsar3, 4, David Mikulis1, 2, Olivia Sobczyk2, Jorn Fierstra3, 4, Joseph Fisher1, 2. 1University of Toronto, 2University Health Network, 3University Hospital Zurich, 4University of Zurich

Background: Susceptibility agents are required to generate contrast for calculating resting perfusion measures (such as mean transit time, cerebral blood volume, and cerebral blood flow) using dynamic susceptibility contrast (DSC) MR perfusion. Currently this requires the intravascular injection of gadolinium (Gd), engendering medical risks, cost, along with image, and environmental drawbacks. Hypoxia-induced deoxyhemoglobin (dOHb) is intrinsic, reversibly paramagnetic, and relatively low-cost.Objective: Here we use hypoxia-induced dOHb as a suitable agent for DSC perfusion and validate against a clinical standard, Gd, in patients with steno-occlusive disease (SOD).Methods: We studied 10 patients between the ages of 39 and 74 (8 M) with known steno occlusive disease in a 3-Tesla scanner running-BOLD acquisition sequences. Transient hypoxia was induced via an automated gas blender running feed-forward gas algorithm targeting 2 consecutive reductions of pulmonary PO2 from 95 mmHg to 40 ± 3 mmHg followed by full reoxygenation within a single inhalation. A second BOLD sequence was acquired following an intravenous injection of 5 ml of Gd. All images were analyzed, and resting perfusion measures were calculated using a standard tracer kinetic model.Results: The calculated perfusion measures and their distribution showed similar voxel-wise proportional changes in BOLD signal throughout the brain. Bland-Altman analysis indicated little bias or difference in hemodynamic measures between methods.Conclusions: The resting perfusion measures obtained from brief transient hypoxia are spatially and quantitatively comparable to those obtained using Gd in the same patients with varying patterns of SOD. The main advantages of transient hypoxia as a contrast agent include it being non invasive; reduced risk of allergy, renal or fetal toxicity; no accumulation in organs, and no environmental damage, making it a suitable contrast for DSC perfusion imaging.Funding: Dr Joseph Fisher Critical Care Research Fund.

## 0800-0930 Mountain Medicine II: Birth and Patients at High Altitude

### 0800-0830 Surviving birth at high altitude—Alexandra Heath

Chronic hypobaric hypoxia as well as vascular disorders of pregnancy increase susceptibility congenital heart diseases and neonatal pulmonary hypertension in high-altitude populations**.** Preeclampsia and fetal growth restriction (FGR) increase cardiopulmonary disease risk for affected offspring across the lifespan and occur more frequently at high-altitude (≥ 2500 m). Retrospective studies indicate that birth to a preeclamptic woman at high altitude increases pulmonary hypertension (PH) risk in later life. We sought to establish whether preeclampsia with or without FGR exaggerated fetal hypoxia and impaired angiogenesis in the fetal lung, leading to abnormalities in the early neonatal cardiopulmonary circulation and neonatal and/or infantile PH. At the same time, a series of 1000 consecutive newborn babies were scanned with pulse oximetry and echocardiography in a peripheral hospital setting. **Methods and Results:** We studied 79 maternal-infant pairs in Bolivia (≥ 3,600m). Umbilical cord blood erythropoietin and hemoglobin were measured as indices of fetal hypoxia, and umbilical artery and venous blood gases analyzed to detect acute hypoxia at delivery. Maternal and cord plasma angiogenic (VEGF) and antiangiogenic (sFlt1) factor concentrations were determined. Serial postnatal echocardiography studies assessed pulmonary hemodynamics and PH. Preeclampsia augmented fetal hypoxia and increased neonatal, but not infantile, PH. Pulmonary abnormalities were confined to preeclampsia complicated by FGR; angiogenic imbalance may represent an underlying mechanism because maternal and fetal plasma sFlt1 was higher in preeclampsia than controls, and positively associated with PH independent of FGR or gestational age. 4% of the children showed a congenital heart disease and 5,8% needed supplementary oxygen due to pulmonary hypertension. **Conclusion:** The effect of preeclampsia with FGR to increase fetal hypoxia and sFlt1 may impede normal development of the pulmonary circulation at high altitude, leading to adverse neonatal pulmonary vascular outcomes. High altitude newborn showed increased risk of congenital heart disease and prolonged postnatal adaptation process.

### 0830-0900 Altitude travel with COPD—Michael Furian

Due to its high prevalence in the general population, chronic obstructive pulmonary disease (COPD) is also common in mountain tourists and air passengers. Many COPD patients suffer from hypoxemia, impaired pulmonary gas exchange, disturbed breathing control, and pulmonary hypertension, even at sea level. Therefore, they might be particularly susceptible to altitude-induced illnesses. Indeed, our group detected impairments in exercise capacity, cognitive and postural performance, nocturnal breathing stability, and altitude-related adverse health effects (ARAHE) requiring medical intervention and relocation to lower altitudes while staying for two nights at 2590 m. At that time (in 2013), there were no preventive recommendations to counsel patients with COPD planning an altitude trip to prevent altitude-induced maladaptations. Between 2013 and 2022, our group evaluated and discovered several preventive therapies against ARAHE in patients with COPD staying overnight at high altitude. This was achieved by conducting several randomised, placebo-controlled, double-blind trials investigating nocturnal oxygen therapy (NOT), dexamethasone, and acetazolamide as potential preventive treatments to improve functional outcomes in patients with COPD planning an altitude trip. In summary, NOT prevented ARAHE and sleep-disordered breathing but not

exercise intolerance when staying overnight at moderate altitudes. Apart of NOT, these and other functional outcomes were also improved by the pharmacological treatment by preventive acetazolamide (375 mg/day) starting 24 hours before ascent. Therefore, acetazolamide might be considered as a preventative measure when NOT is not available in COPD at high altitude. Recently, we investigated the diagnostic accuracy of structured self-monitoring in COPD patients to detect early signs of severe hypoxemia and AMS when travelling to high altitude. In case of a high diagnostic accuracy, patients rated positive during the structured self-monitoring and being at a high risk for experiencing an ARAHE could take immediate preventive actions, e.g. supplemental oxygen, relocation to lower altitude.

**0900-0930 Risks for altitude travel with pulmonary vascular disease—Silvia Ulrich**

The main pulmonary vascular diseases (PVD) are pulmonary arterial and chronic thromboembolic pulmonary hypertension (PH). PVD are characterized by precapillary PH causing progressive exertional dyspnea and premature death. Advances in therapy improved quality of life rendering PVD to the chronic respiratory diseases. Amongst the millions of travelers which yearly visit easy accessible high-altitude settlements are respiratory patients including PVD. The hypoxic environment at altitude increases the pulmonary artery pressure (PAP), may thus rendering PVD-patients at particular altitude-related health risk. Thus, PH-guidelines discourage patients with symptomatic PVD to join friends and family to altitude visits. We recently showed in 149 PVD-patients assessed by right heart catheterization that normobaric hypoxia (FiO2 15%) did not relevantly increase the AP and PVR, whereas supplemental oxygen improved hemodynamics. In a randomized, single-blinded cross over study in 28 PVD-patients, in accordance with healthy, exercise capacity was significantly decreased whilst breathing FiO2 15 vs. 21%, albeit with a high interindividual variability whereas PAP-increase during exercise was similar under both conditions. We accompanied 28 stable, optimally treated PVD-patients for a daytrip to 2500m. All patients felt subjectively well, but 3/28 experienced predefined altitude-related adverse health effects defined as SpO2 <80% for >30', which were successfully treated with oxygen. Exercise capacity at 2500 vs. 470m was overall reduced but with a high inter-individual variability and a similar PAP-increase. The best predictors at low-altitude for altitude-related adverse effects was the NYHA class and resting SpO2, whereas testing with normobaric hypoxia was of little added value due to high false negative rate. In a first pilot, three-day-two-overnight-study at 2048m, nocturnal hypoxemia and sleep apnea were seen and if severe responded to oxygen therapy. All PVD-patients should be counseled before any high-altitude sojourn by doctors with experience in PVD and high-altitude medicine and have an action plan for any altitude-related conditions.

*0930-1000 Refreshment Break, Heritage Hall*

## 1000-1130 Advances in Hypoxia Research I

### 1000-1045 Novel Therapeutics Targeting Hypoxia-Inducible Factors—Gregg Semenza

Each of the fifty trillion cells in the adult human body require a continuous supply of O2. Hypoxia-inducible factors (HIFs) maintain O2 homeostasis by modulating the expression of thousands of genes in order to match O2 supply and demand. HIFs are heterodimeric transcription factors that consist of an O2-regulated subunit (HIF-1a, HIF-2a or HIF-3a) and a constitutively-expressed subunit (HIF-1b). The HIF-a subunits are subject to O2-dependent modification by prolyl hydroxylase domain proteins (PHDs), leading to binding of the von Hippel-Lindau (VHL) protein and subsequent ubiquitination and degradation. Individuals with hereditary erythrocytosis, which is characterized by excess red blood cells, pulmonary hypertension, and thrombosis, were found to have germline homozygosity for a missense mutation in VHL that reduces but does not eliminate its ability to bind to hydroxylated HIF-a subunits. The residual VHL activity is sufficient to prevent tumor formation but insufficient to regulate HIF activity. In other patients, a mutation in PHD2 or HIF-2a that decreases hydroxylation of the latter by the former have been identified. The prolyl hydroxylases use a-ketoglutarate as a cosubstrate and drugs that compete with a-ketoglutarate for binding to the hydroxylases, such as Daprodustat, increase erythropoietin expression, thereby increasing red blood cell production in patients with anemia due to chronic kidney disease. The VHL syndrome is an autosomal-dominant tumor predisposition syndrome, in which affected individuals have a loss- of-function mutation in one VHL allele and the other allele is inactivated in the tumor tissue leading to cerebellar and retinal hemangioblastoma and clear cell-type renal cell carcinomas due to dysregulated HIF activity. Belzutifan, a drug that binds to HIF-2a and blocks its dimerization with HIF-1b, is a highly effective treatment for RCC and other tumors in patients with VHL syndrome. Many cancers express both HIF-1a and HIF-2a, such that a dual HIF inhibitor might have greater therapeutic efficacy. We identified a small molecule inhibitor of HIF activity that induces the degradation of both HIF-1a and HIF-2a in hepatocellular carcinoma cells and blocks tumor growth and angiogenesis in mouse models of HCC. The inhibitor also alters the tumor immune microenvironment from one favoring immune evasion by cancer cells to one favoring anti-tumor immunity and improved response to anti-PD1 immunotherapy.

### 1045-1100 Andean Aymaras' Enriched Alternatively Spliced NFKB1 Transcripts Increase Inflammation and Hemoglobin—Jihyun Song

Jihyun Song[1], Ricardo Amaru[2], Josef Prchal[1]. [1]Division of Hematology and Hematologic Malignancies, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA, [2]Cell Biology Unit, University of San Andres, National Academy of Sciences, La Paz, Bolivia.

Objective: Andean highlanders (Aymara and Quechua) are evolutionary acclimated to environmental hypoxia and have increased hemoglobin, while Tibetans and Ethiopians have normal hemoglobin at high altitude. We reported Aymara-evolutionary-selected genetic variants from whole genome sequencing (WGS) involved in cardio-pulmonary function and development (Crawford, AJHG, 2017); however, none of these variants correlated with Aymara hemoglobin.Methods: To search for genetic signature to explain Aymara polycythemia, we then analyzed whole transcriptomes of granulocytes from Aymara and Europeans living in La Paz, Bolivia (3,600-4100m).Results: Aymaras had 255 dysregulated genes in inflammatory pathway but without discernable genomic signatures. We then analyzed differential exon usages in this transcriptome. We detected the previously unreported alternatively spiced NFKB1 (an inhibitor

of NF-kB transcriptional machinery) transcripts skipping exons 4 or 5 (AS-NFKB1), both leading to the out-of-frame and loss-of-function NFKB1 mRNA. We then searched for AS-NFKB1 genomic signatures by the integrative analysis of the Aymara transcriptome and our WGS analysis. We identified five single SNPs which were in high linkage disequilibrium with AS-NFKB1 transcript; two SNPs (rs230511 and rs230504) were the most enriched (allele frequency=0.878). This genomic region in Aymaras was genetically differentiated from lowland Native Americans (peak FST = 0.37, peak PBSn1 = 0.31).These SNPs correlated with levels of AS-NFKB1. AS-NFKB1 is inversely correlated with intact NFKB1 transcript and correlated with transcripts of NF-kB regulated inflammatory genes including IFNG and IL6 and their proteins. The hypoxia inducible factors (HIFs) and NF-kB interact, we found a positive correlation of AS-NFKB1 with HIFs' regulated genes. On further analysis AS-NFKB1 transcripts corelated with hemoglobin and leukocyte levels.Conclusion: We report that Aymara-enriched NFKB1 SNPs are associated with AS-NFKB1 which induces inflammation through increased NF-kB activity and that Aymara high hemoglobin level is mediated by upregulated HIFs via AS-NFKB1.

**1100-1130 Hypoxemia in the COVID ICU – mechanisms and reflections—Trish Kritek**

Starting in March of 2020, intensive care units across the world were filled with patients with severe hypoxemia due to SARS CoV-2. The remarkable numbers of patients with acute respiratory distress syndrome (ARDS) and refractory hypoxemia raised multiple questions about pathophysiology and appropriate treatment. For example, did SARS CoV-2 cause a distinct form of lung injury and have unique effects on control of breathing resulting in the observation of "happy hypoxemia." In addition, with concerns about limitations in available resources (e.g., mechanical ventilators), interventions to try to ameliorate hypoxemia were broadened to try to avoid the need for intubation. Over the last three years, we have learned a lot about severe COVID-19 pneumonia and associated ARDS. This talk will discuss the pathophysiologic mechanisms that cause hypoxemia in COVID-19 including theories for why patients present with silent hypoxemia. We will also reflect on what we now know about ARDS secondary to COVID-19. Finally, we will talk about the physiologic rationale for proning (in both intubated and spontaneously breathing patients) as well as the evidence for its use to treat COVID-19.

*1130-1600, Ski Break* **and** *1130-1330, Lunch, Victoria Dining Room*

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| 1600-1830 | **Hot Topics in Hypoxia I**—Free Communications, Mount Temple (see next pages) |
| *1900-2130* | *Dinner, Victoria Dining Room* |
| 2030-2130 | **Life In Space, And Life On Earth**—Kjell and Kristi Lindgren |

**Time: 1600**

**HEMATOLOGICAL RESPONSE DURING APNEA IN ELITE HUMAN FREE-DIVERS AND ELEPHANT SEALS.** Courtney V Brown1, Anthony R Bain2, Joshua C Tremblay3, Alexander Patrician1, Paul J Ponganis4, David B MacLeod5, Philip N Ainslie1. 1Centre for Heart, Lung and Vascular Health, School of Health and Exercise Sciences, University of British Columbia Okanagan, Kelowna, BC, Canada, V1V 1V7, 2Faculty of Human Kinetics, University of Windsor, Windsor, ON, Canada, N9B 3P4, 3School of Sport and Health Sciences, Cardiff Metropolitan University, Cardiff, Wales, CF5 2YB, 4Scripps Institution of Oceanography, University of California San Diego, La Jolla, CA, USA, 92037, 5Department of Anesthesiology, Duke University, Durham, NC, USA, 27710

Objective: To assess if elite human free-divers express similar hematological responses to the highly adapted elephant seals (Mirounga angustirostris) during prolonged apnea. We hypothesized that, despite extensive training in humans, seals would have higher buffering of pH, elevated carboxyhemoglobin (COHb), and lower P50 of hemoglobin (Hb).Methods: Arterial blood samples were collected and analyzed immediately (ABL90 Flex) during eupneic rest (humans; n=14) and eupneic sleep (unanesthetized seals; n=3), and near apnea cessation in humans (1 apnea) and seals (3-5 apneas), respectively. In-vivo P50 values were estimated from individual general additive models calculating oxyhemoglobin saturation over a range of PaO2 values. A linear mixed-effects model interrogated differences between species and time for all variables.Results: Apnea duration (humans: 5-8min, seals: 5-9min) and end apnea PaO2 (human: 40.4±3.0 mmHg, seal: 27.1±5.9 mmHg; p=0.2), and P50 (humans: 29.9±1.5 mmHg, seals: 29.3±0.5 mmHg; p=0.50) were similar between species. There was a main effect of species on [Hb] (seals: 22.4±0.8 g/dl, humans: 14.2±0.4 g/dl; p<0.0001). Compared to baseline, COHb post-apnea was reduced in seals (baseline: 6.1±0.3%, max: 5.6±0.3%; p<0.001), whereas it was slightly elevated in humans (baseline: 0.7±0.1%, max: 0.9±0.1%; p=0.0002). Elevations in PaCO2 from baseline to apnea were similar between humans and seals (15.4±5.8 and 8.3±6.4 mmHg, respectively); however, pH was similar in seals between baseline and apnea cessation (7.39±0.02 and 7.38±0.02 mmHg, respectively; p=0.9), pH was reduced in humans from baseline to end apnea (7.45±0.01 and 7.37±0.01, respectively; p<0.0001).Conclusions: Although P50 was comparable between species, seals may better handle prolonged apnea compared to humans as demonstrated by their ability to buffer changes in pH and protect against ischemia-reperfusion injury via higher levels of carbon monoxide (i.e. COHb levels). Funding: This work was funded by an NSERC Discovery grant and University Research Chair to PNA and an ONR-DURIP grant to T.M. Williams. CB was supported by a NSERC Canada Graduate Doctoral award.

**Time: 1615**

## PERIPHERAL OXYGENATION AND PULMONARY HEMODYNAMICS IN PATIENTS WITH FONTAN CIRCULATION DURING 24 HOURS MODERATE NORMOBARIC HYPOXIA.

Julian Alexander Härtel1, Nicole Müller1, Jan Schmitz2, 3, Iris Rieger2, Darius Gerlach2, Jon von Stritzky2, Anja Bach2, Christopher Hart1, Janina Bros4, Benedikt Seeger4, Emily Zollmann4, Marijke Grau4, Laura De Boni2, Jan-Niklas Hoenemann2, 5, Wilhelm Bloch4, Jens Jordan2, 6, Daniel Aeschbach2, 7, Ulrike Herberg1, Tobias Kratz1, Johannes Breuer1, Jens Tank2. 1Department for Pediatric Cardiology / University Hospital Bonn / Germany, 2Institute of Aerospace Medicine / German Aerospace Center Cologne / Germany, 3Department of Anesthesiology and Intensive Care Medicine / University Hospital of Cologne / Germany, 4Department of Molecular and Cellular Sports Medicine / German Sport University Cologne / Germany, 5Department of Internal Medicine III / Division of Cardiology, Pneumology, Angiology, and Intensive Care / University of Cologne / Germany, 6University of Cologne / Head of Aerospace medicine / Germany, 7Institute of Experimental Epileptology and Cognition Research / University of Bonn Medical Center / Germany

Objectives: In ambient hypoxia, patients with Fontan circulation may experience increased pulmonary vascular resistance and reduced pulmonary blood flow leading to reduced peripheral systemic oxygen saturation (SpO2). The response raises concerns regarding the safety of long-distance flights or stays at altitude in this population. Therefore, we assessed hemodynamic responses to >24 hours normobaric hypoxia in patients with Fontan circulation.Methods: Eighteen patients with Fontan circulation (16-39 years, 9 females) spent three nights and 3.5 days at the DLR :envihab research facility. We obtained baseline measurements after two nights in normoxia including heart rate, blood pressure, respiration, central venous pressure (PICC line, n=14), pulmonary blood flow (real time cardiac MRI), SpO2 during night time sleep (polysomnography) and during the day. We repeated measurements during and after the night spent in normobaric hypoxia (15.2% oxygen, equivalent to ~2440 m altitude, typically experienced in-flight).Results: In resting state during hypoxia, HR was increased by 4.7±4.6 bpm ($p<0.0001$). Blood pressure did not change and minute ventilation increased by 0.90±1.16L/min ($p<0.004$). SpO2 was significantly reduced during hypoxia at night (85.5±4.1vs.92.0±2.8 %, $p<0.001$) and during the day (supine: 86.2±3.8 vs.92.5±2.8 %, standing: 83.9±4.0 vs.89.8±4.1%, $p<0.0001$). Blood flow (2.93±0.80 vs.2.78±0.59L/min) and central venous pressure (9.8±1.9vs.10.6±1.6 mmHg) did not change significantly. None of the participants experienced severe clinical symptoms during hypoxia.Conclusion: Our data suggest that selected patients with Fontan circulation can tolerate moderate hypoxia during night time sleep as well as during the day.Funding: This research was funded by Stiftung KinderHerz Deutschland gGmbH

**Time: 1630**

## SUSTAINED HYPOXIA ENABLES HUMAN PRIMARY ENDOTHELIAL CELLS TO EXPRESS FACTORS INVOLVED IN PROLIFERATION OF ADULT CARDIOMYOCYTES.

Frank Splettstoesser1, Sonja Hersel1, Jan Kleiner1, Laura de Boni2, Jan-Niklas Hoenemann2, Henning Weis2, 3, Fabian Hoffmann2, 4, Jens Jordan5, Ulrich Limper2, Jens Tank2, Stilla Frede1. 1Department of Anesthesiology and Intensive Care Medicine, University Hospital Bonn, Germany, 2Department of Cardiovascular Aerospace Medicine, Institute of Aerospace Medicine, Aerospace Center Cologne, Germany, 3Department of Nuclear Medicine, University of Cologne, Germany, 4Department of Internal Medicine III, Division of Cardiology, Pneumology, Angiology, and Intensive Care, University of Cologne, Germany, 5Institute of Aerospace Medicine, Aerospace Center Cologne, Germany

Objectives: Adult mammalian hearts have limited ability to generate new cardiomyocytes after myocardial infarction (MI). Thus, proliferation of adult cardiomyocytes or resident cardiac stem cells is a potential source of new cardiomyocytes. Therefore, we aim to elucidate whether hypoxia in circulating immune cells and endothelial cells induces expression and release of factors stimulating the proliferation of cardiomyocytes.Methods: Immune cells and plasma were collected from participants of the MyoCardioGen 3 (MCG3) study having suffered from MI and healthy volunteers under normoxic and hypoxic conditions (as low as 9.5% oxygen). Human cardiomyocytes (Promocell) were co-cultured under hypoxic conditions (7% oxygen) with pulmonary microvascular endothelial cells (HPMECs) or aortic endothelial cells (HAoECs, both Promocell). Cardiomyocyte proliferation was evaluated by CFSE staining. Activation of Hypoxia-inducible factors (HIFs) and release of proliferation factors (EGF, FGF, Periostin) were measured.Results: HIF-2α protein was upregulated in circulating immune cells and Erythropoietin was significantly elevated in plasma of the MCG3 participants below 12% oxygen. An increase of HIF-2α in HPMECs and HAoECs was detected after prolonged exposure to 7% oxygen. Under the latter condition, EGF-1, FGFbasic and Periostin were increased more than 3-fold as measured by ELISA and Luminex assay. Moreover, co-culture of endothelial cells with cardiomyocytes under hypoxic conditions (7% oxygen) increased the proliferation rate of cardiomyocytes in vitro.Conclusion: We confirmed a cellular hypoxic response in the participants of the MCG3 study. We detected a significant upregulation of periostin, EGF and FGF in cultured endothelial cells under similar in vitro hypoxic conditions and showed cardiomyocyte proliferation in the presence of endothelial cells. We conclude, hypoxia-induced endothelial cell derived proliferation factors may facilitate the recovery of cardiac tissue after myocardial infarction.

**Time: 1645**

## TONIC SPLENIC CONTRACTION WITH ACCLIMATIZATION TO HIGH-ALTITUDE IN LOWLANDERS COMPARED TO SHERPA: EFFECT OF HYPEROXIA .

Trevor Day1, Pontus Holmström2, Taylor Harman3, Bethany Steiner3, Ella Hawkins3, Anne Kalker4, Kelsey Jorgensen5, Kimberly Zhu5, Abigail Bigham5, Ajaya Kunwar6, Nilam Kunwar6, Sunil Dhungel7, Tom Brutsaert3. 1Mount Royal University, 2Mid Sweden University, 3Syracuse University, 4Raboud Medical Center , 5University of California, 6Global Hospital, Kathmandu, 7Nepalese Army Institute of Health Sciences

Introduction: The spleen is a storehouse for red blood cells, which can be mobilized into the systemic circulation under stress (e.g., breath-holding, exercise, hypoxia) via splenic contraction, increasing [Hb] and oxygen carrying capacity. We previously demonstrated that the spleen is reduced in volume with incremental ascent to high-altitude (HA) in lowlanders, potentially increasing oxygen carrying capacity early in acclimatization. Whether this reduced spleen volume with ascent is caused by tonic splenic contraction or plasma volume reduction is unclear. We aimed to further characterize this potential altitude-induced tonic contraction in lowlanders compared to Sherpa.Methods: We recruited 14 lowlanders (7F) and 46 Sherpa (23F) acclimatized to an altitude of 4240m (PATM≈460mmHg, PO2≈97mmHg; 2weeks-2years) in the Nepal Himalaya. Resting splenic volume was assessed via ultrasonography, measured before, during and after 5-min of inspired hyperoxic gas (FIO2 0.35).Results: Resting splenic volume of Sherpa (234±63mL) was larger than lowlanders (165±34 mL; $P<0.001$, ES=1.17). Splenic volume was unchanged in response to inspired hyperoxic gas in Sherpa ($P=0.64$), but was increased by 35±5mL ($P<0.001$) in lowlanders, returning to baseline values following 5-min of breathing ambient (i.e., hypoxic) air ($P>0.99$). In addition, resting splenic volume correlated positively with the hyperoxia-induced splenic volume increase in lowlanders ($r=0.98$, $P<0.001$).Conclusion: Our findings demonstrate that lowlanders undergo a transient but reversible splenic volume increase in response to hyperoxia at HA, suggesting that (a) oxygen influences splenic volume bi-directionally, and (b) splenic contraction potentially has a functional role during early acclimatization to HA. In contrast, Sherpa had (a) a larger resting splenic volume at HA and (b) a blunted hyperoxia-induced splenic volume increase, suggesting a reduced tonic contraction at HA and a preserved capacity for splenic contraction during exercise. Funding: National Science Foundation

**Time: 1700**

## A1 ADENOSINE RECEPTOR AVAILABILITY IN THE HUMAN BRAIN DURING NORMOXIA AND ACUTE NORMOBARIC HYPOXIA MEASURED WITH [F-18]CPFPX PET.

Henning Weis1, 2, Manuel Michno3, Jan Schmitz2, 4, Anna L. Foerges3, Simone Beer3, Bernd Neumaier5, Alexander Drzezga1, 3, Daniel Aeschbach2, 6, Andreas Bauer3, Jens Tank2, Eva-Maria Elmenhorst2, David Elmenhorst1, 3. 1Department of Nuclear Medicine, University Cologne, Germany , 2Institute of Aerospace Medicine, German Aerospace Center, Cologne, Germany, 3Institute of Neuroscience and Medicine (INM-2), Forschungszentrum Jülich, 52425 Jülich, Germany, 4Department of Anesthesiology and Intensive Care Medicine, University Hospital of Cologne, Cologne, Germany, 5Institute of Neuroscience and Medicine (INM-5), Forschungszentrum Jülich, 52425 Jülich, Germany, 6Institute of Experimental Epileptology and Cognition Research, University of Bonn Medical Center, Bonn, Germany

Objectives: Hypoxia induces numerous metabolic, vascular, biochemical and electrophysiological changes. The neuromodulator adenosine is released into the interstitial space during hypoxia and may mediate some of these effects. A1 adenosine receptor (A1AR) antagonism or knock-out attenuates this neuronal inhibition in mice. Here we tested the hypothesis that exposure to acute hypoxia compared to normoxia reduces the availability of A1AR in the human brain, which would provide evidence for a hypoxia-induced increase in endogenous adenosine. As exploratory objectives, we tested the hypotheses that psychomotor vigilance is affected during hypoxia and that cerebral blood flow is altered.Methods: Ten healthy volunteers (32 ± 13 years, 3f) completed a 110-min bolus plus constant infusion [F-18]CPFPX PET-MRI hybrid experiment: Subjects spent 60 minutes in normoxia followed by 30 minutes of normobaric hypoxia with peripheral oxygen saturation of 70 - 75 %, followed by 20 minutes of normoxia. Blood samples were used to calculate metabolite-corrected steady-state distribution volumes (VT) of A1AR (i. e., 40 - 100 min after start of [F-18]CPFPX administration). Arterial spin labeling was applied to quantify brain perfusion. A 3-minute psychomotor vigilance test (PVT) was conducted every 10 minutes. Heart rate and peripheral blood oxygen saturation were measured continuously.Results: During hypoxia A1AR availability in the cerebral cortex was reduced by 11 % ($p = 0.033$). Cortical gray matter brain perfusion on the other hand increased by 25 % ($p < 0.001$). Heart rate increased by 22 % ($p < 0.001$). PVT mean reaction time was longer by 7 ms ($p = 0.027$).Conclusions: Acute normobaric hypoxia with blood oxygen saturation lowered to approximately 70 % reduces cerebral A1AR availability, indicating increased adenosine concentration and receptor occupancy. Simultaneously brain perfusion is increased and cognitive performance impaired. Financial support: The work was supported by internal DLR and FZJ funds.

**Time: 1715**

## SAFETY AND FEASIBILITY OF EXPOSING HIGHLY SELECTED PATIENTS AFTER MYOCARDIAL INFARCTION TO 14 DAYS OF SEVERE NORMOBARIC HYPOXIA .

Ulrich Limper1, 2, Henning Weis1, 3, Jan-Niklas Höhnemann1, 4, Darius Gerlach1, Laura DeBoni1, Lukas Kessler5, Fabian Hoffmann1, 4, Simone Beer6, Vlad Zaha7, Leonora Zange3, 6, Sven Kühn8, Sven-Erik Soenksen9, Christian Mühl1, Hannes Reuter10, 11, Marc Hein12, Hesham Sadek13, 14, Matthias Basner15, Ben Levine16, Jens Jordan1, 17, David Elmenhorst6, Christoph Rischpler5, Alexander Drzezga3, 6, Jens Tank1. 1Institute of Aerospace Medicine, German Aerospace Center (DLR), 2Department of Anesthesiology and Intensive Care Medicine, Merheim Medical Center, Hospitals of Cologne, University of Witten/Herdecke, 3Department of Nuclear Medicine, University Cologne, 4Department of Internal Medicine III, Division of Cardiology, Pneumology, Angiology, and Intensive Care, University of Cologne, 5Department of Nuclear Medicine, University Essen, 6Institute of Neuroscience and Medicine (INM-5), Forschungszentrum Jülich, 7The University of Texas Southwestern Medical Center, 8Department of Radiology, Bundeswehr Central Hospital Koblenz, 9Department of Radiology, Bundeswehr Central Hospital Hamburg, 10Department of Internal Medicine III, Division of Cardiology, Pneumology, Angiology, and Intensive Care, 11Department of Internal Medicine and Cardiology, Evangelical Clinic Weyertal, 12Department of Anesthesiology, Medical Faculty, RWTH Aachen University, 13Department of Internal Medicine, University of Texas Southwestern Medical Center, 14Center for Regenerative Science and Medicine, University of Texas Southwestern Medical Center, 15Unit for Experimental Psychiatry/Division of Sleep and Chronobiology, Department of Psychiatry, University of Pennsylvania School of Medicine, 16Division of Cardiology, Department of Internal Medicine, University of Texas Southwestern Medical Center, 17Chair of Aerospace Medicine, Medical Faculty, University of Cologne

Background. In mice with myocardial infarction, extreme normobaric hypoxia induced myocardial regeneration. We conducted a pilot study to test feasibility and safety of translating this approach from animals to patients after myocardial infarction. Methods. We conducted the study in the :envihab facility at DLR in Cologne. Three patients who had experienced an anterior myocardial infarction 10 to 4 years earlier, but were fully revascularized (ejection fraction 41-58%), otherwise healthy, physically fit, and one healthy age-matched control (age 55-64 years) participated. Following slowly progressive hypoxia acclimatization, we maintained FiO2 around 9.8±0.6% for two weeks. We applied echocardiography, cardiac and brain magnetic resonance imaging (MRI), ASL-MRI, and 18F labeled D-glucose positron emission tomography/MRI to assess cardiac and brain structure, function, glucose uptake, and perfusion. We regularly assessed pulmonary and kidney function, blood volume, and cognitive and nervous system function. Results. All participants experienced alveolar hypoxia of about 35 mmHg pO2 without severe acute mountain sickness symptoms and completed the study. During hypoxia, an increase in heart rate did not fully compensate for the loss in stroke volume and cardiac glucose uptake was increased. Participants never experienced angina pectoris and daily 12-lead resting ECG readings were always negative for acute ischemic events. High sensitive troponin remained negative and NTproBNP tended to decrease. ASL-MRI indicated reductions in relative cerebral blood flow. Blood volume and glomerular filtration rate decreased in hypoxia. We observed modest brain volume changes and scattered new cerebral white matter lesions. All participants fully recovered within a few weeks in normoxia. Conclusion. Fourteen days of normobaric hypoxia <10% O2 is feasible in physically fit patients after myocardial infarction following an individualized acclimatization profile. Follow up measurements at 3, 6 and 12

months are ongoing and will provide insight in the potential of sustained hypoxia in inducing myocardial regeneration in adult human beings.

**Time: 1730**

## WOMEN AT ALTITUDE: MENSTRUAL CYCLE PHASE, HORMONAL CONTRACEPTION, AND MENOPAUSE ARE NOT ASSOCIATED WITH THE DEVELOPMENT OF AMS.

Laurel Gardner MD1, Tejaswi Adhikari MBBS2, Caleb Phillips PhD3, Elan Small MD1, James Marvel MD1. 1Department of Emergency Medicine, Stanford University, 2Department of General Practice and Emergency Medicine, Patan Academy of Health Sciences, 3Department of Computational Science, University of Colorado

Study Objective: It has long been theorized that progesterone, a known respiratory stimulant, may be protective against the development of Acute Mountain Sickness (AMS). Theories are split on the role of hormonal contraception (HC), with some suggesting the suppression of ovulation may lower progesterone levels and increase risk of AMS, while others postulate the synthetic progesterone may be protective. The aim of our study was to examine the impact of both menstrual cycle phase and the use of HC on the risk developing AMS. Methods: In a prospective observational convenience study conducted in Lobuje (4940m) and Manang (3519m) Nepal, 949 pre-menopausal female participants were surveyed from hikers spending their first night at altitude, having not slept higher in the last week. Data was collected on last menstrual period, use of hormonal contraception, and development of AMS, defined by symptoms using the 2018 Lake Louise Questionnaire. Results: Use of HC does not have a significant effect on the development of AMS (23.7% AMS on HC vs 26.5% not on HC, p=0.41). When looking at cycle phase in women not on HC, we did not find a difference between the follicular or luteal phase and the development of AMS (30% AMS in follicular vs 26% in luteal, p=0.46). The apparent lack of effect of hormones on AMS is further supported by the similarity in AMS rates reported between pre- and post-menopausal women (p=0.26). Conclusion: There is no significant impact of menstrual cycle phase, menopausal status, or the use of HC on the development of AMS. This supports previous studies that suggest progesterone does not play a role in the development of AMS. These results suggest that women can safely use any hormonal contraception they prefer when traveling to altitude.

**Time: 1745**

## ACUTE HYPOXIC EXERCISE IN HEALTHY SUBJECTS INCREASES RED BLOOD CELL ACYLCARNITINES AND GLYCOLYSIS.

Lindsay Forbes1, Francesca Cendali2, Travis Nemkov2, Angelo D'Alessandro2, Todd Bull1, Tim Lahm1, 3, 4, Robert Roach1, Andrew Subudhi5, William Cornwell6. 1Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado, Aurora, Colorado, United States, 2Department of Medicine, University of Colorado, Aurora, Colorado, United States, 3Division of Pulmonary, Critical Care and Sleep Medicine, National Jewish Health, Denver, Colorado, United States, 4Rocky Mountain Regional Veterans Affairs Medical Center, Aurora, Colorado, United States, 5Department of Human Physiology and Nutrition, University of Colorado, Colorado Springs, Colorado, United States, 6Division of Cardiology, University of Colorado, Aurora, Colorado, United States

Objective: Oxygen delivery to muscle increases during exercise to match metabolic demand. Hypoxic conditions necessitate adaptations to maintain oxygen delivery but also increase red blood cell (RBC) oxidative stress and right ventricular afterload. This study examined the relationship between RBC metabolism and hemodynamic response to acute hypoxic vs normoxic exercise.Methods: Nine healthy subjects (35±10 years, 6 males) exercised on upright cycle ergometer under normoxic conditions (FiO2=0.21) or hypoxia (FiO2=0.12; Patm=623 mmHg). Subjects completed three visits including normoxic and hypoxic maximal exercise tests and invasive exercise test. During invasive exercise test, venous blood was collected during normoxic rest and submaximal exercise (50% normoxic VO2max) and hypoxic rest, submaximal (50% hypoxic VO2max), and maximal exercise. RBC metabolomics were analyzed using ultra-high-performance liquid chromatography coupled to mass spectrometry. Cardiac output was assessed by pressure-volume analysis via conductance (n=5) or Swan-Ganz catheters (n=4).Results: Hypoxic vs normoxic VO2max was reduced (26.2±4.9 vs 41.6±7.4 ml/kg/min; $p<0.05$). During hypoxic exercise, acylcarnitines accumulated in RBCs ($p<0.05$ for AC 8:0, AC 8-OH, AC 10:0, AC 10-OH, AC 12-OH, AC 14:1, AC 14:1-OH, AC 14-OH, AC 16:2, AC 16:1-OH). Glycolytic intermediates decreased but the glycolytic end-product lactate increased ($p<0.05$). Glycolytic intermediate 2-3-bisphosphoglycerate was significantly reduced at maximal hypoxic exercise ($p<0.05$) and varied inversely with lactate ($r=-0.54$, $p<0.05$). Cardiac output augmented similarly from rest to 50% VO2max exercise in normoxia vs hypoxia (5.8 interquartile range [5,4.7.8] to 15.8 [13.9,18.6] L/min [$p<0.05$] vs 6.8 [5.0,7.3] to 14.6 [11.0,18.1] L/min [$p<0.05$]. Conclusion: Exercise in hypoxic conditions is associated with RBC metabolic changes including acylcarnitine accumulation and rapid glycolytic flux. Accumulating acylcarnitines may function to repair RBC membranes damaged in the setting of oxidative stress, and rapid glycolytic flux generates ATP during exercise in acute hypoxia. Funding: NIH/NCATS UL1TR002535

**Time: 1800**

**Hemoglobin and cerebral hypoxic vasodilation in humans: evidence for nitric oxide-dependent and S-nitrosothiol mediated signal transduction .** Jay Carr1, Ryan Hoiland1, 2, 3, 4, David MacLeod5, Benjamin Stacey6, Hannah Caldwell1, Connor Howe1, Daniela Nowak-Flück1, Michael Tymko1, Geoff Coombs1, Alexander Patrician1, Joshua Tremblay1, Michelle Van Mierlo7, Chris Gasho8, Mike Stembridge9, Mypinder Sekhon4, 10, 11, Damian Bailey6, Philip Ainslie1. 1Centre for Heart, Lung, and Vascular Health, School of Health and Exercise Sciences, Faculty of Health and Social Development, University of British Columbia Okanagan, Kelowna, BC, Canada, 2Department of Anesthesiology, Pharmacology and Therapeutics, Vancouver General Hospital, West 12th Avenue, University of British Columbia, Vancouver, BC, Canada, 3Department of Cellular and Physiological Sciences, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada, 4International Collaboration on Repair Discoveries, West 10th Avenue, Vancouver, BC, Canada, 5Human Pharmacology & Physiology Lab, Department of Anesthesiology, Duke University Medical Center, Durham, NC, 27708, USA, 6Neurovascular Research Laboratory, Faculty of Life Sciences and Education, University of South Wales, Pontypridd, UK, CF37 4BB, 7Department of Biomechanical Engineering, University of Twente, Enschede, The Netherlands, 8Department of Medicine, Division of Pulmonary and Critical Care, Loma Linda University School of Medicine, Loma Linda, CA, USA, 9Cardiff School of Sport and Health Sciences, Cardiff Metropolitan University, Cardiff, UK, CF23 6XD, 10Djavad Mowafaghian Centre for Brain Health, Department of Pathology and Laboratory Medicine, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada, 11Division of Critical Care Medicine, Department of Medicine, Vancouver General Hospital, West 12th Avenue, University of British Columbia, Vancouver, BC, Canada

Objective: Cerebral hypoxic vasodilation is poorly understood in humans, which undermines the development of therapeutics to optimize cerebral oxygen delivery. Across four investigations (total n=195) we investigated the role of nitric oxide (NO) and hemoglobin-based S-nitrosothiol (RSNO) and nitrite ($NO_2^-$) signalling in the regulation of cerebral hypoxic vasodilation. Methods: We conducted hemodilution (n=10) and NO synthase inhibition (n=11) experiments as well as hemoglobin oxygen desaturation protocols, wherein we measured cerebral blood flow (CBF), intra-arterial blood pressure, and in subsets of participants, trans-cerebral release/uptake of RSNO and $NO_2^-$. Results: Higher CBF during hypoxia was associated with greater trans-cerebral RSNO release but not $NO_2^-$, while NO synthase inhibition reduced cerebral hypoxic vasodilation. Hemodilution increased the magnitude of cerebral hypoxic vasodilation, while in 134 participants tested under normal conditions, hypoxic cerebral vasodilation was inversely correlated to arterial hemoglobin concentration. These studies were replicated in a sample of polycythemic high-altitude native Andeans suffering from excessive erythrocytosis (n=40), where cerebral hypoxic vasodilation was inversely correlated to hemoglobin concentration, but improved with hemodilution (n=6). Conclusion: Collectively, our data indicate that cerebral hypoxic vasodilation is NO-dependent, associated with trans-cerebral RSNO release, and place hemoglobin-based NO signalling as a central mechanism of cerebral hypoxic vasodilation in humans.Funding: This work was supported by a Heart and Stroke Foundation of Canada Grant in Aid (G-18-0022304) and Canada Research Chair in Cerebrovascular Physiology (PNA).

## 0800-0930 Hypoxia and the Brain

### 0800-0830 Brain tissue hypoxia in humans after cardiac arrest—Mypinder Sekhon

Following resuscitation from cardiac arrest, hypoxic ischemic brain injury (HIBI) is the resultant neurological injury sustained to the brain and is primary determinant of adverse outcome. The pathophysiology of HIBI is characterized as a primary and secondary injury, resulting from cerebral ischemia during cardiac arrest and reperfusion following successful resuscitation. During the secondary injury phase, increased attention has been directed towards the optimization of cerebral oxygen delivery to prevent additive ischemic injury to the brain. Cerebral hemodynamics in HIBI are characterized by early hyperemia following successful resuscitation but followed by a protracted phase of cerebral oligemia termed "no reflow" during which additional ischemic injury to the vulnerable brain is theorized to occur. As such, identification of therapeutic strategies to optimize cerebral delivery of oxygen during the secondary injury phase is at the forefront of critical care research in HIBI. Unfortunately, several studies investigating the manipulation of arterial carbon dioxide tension, mean arterial pressure augmentation, elevated arterial oxygen tension have shown minimal clinical efficacy. The onset of post-resuscitation brain tissue hypoxia is associated with additional injury to the neurovascular unit and worse clinical outcomes. This finding suggests that other pathophysiologic mechanisms are at play. Among these, the innate immune response is noted to play an integral role in inciting additional injury to the neurovascular following cerebral reperfusion. Culprit mechanisms may be attributable to inflammatory cytokine signalling, phagocytic activation and the complement cascade.

### 0830-0900 Migraine induced by hypoxia—Nanna Arngrim

Migraine is a ubiquitous neurological disorder estimated to directly affect more than one billion people worldwide. Approximately one third of individuals with migraine experience aura, either with every attack or with some attacks. Migraine with aura (MA) is defined as transient focal neurological symptoms that usually precede, but sometimes accompany, the headache phase of a migraine attack. Several methods currently exist for experimental provocation of migraine attacks without aura, while no reliable method for triggering migraine with aura has been developed. Here we investigated if experimental hypoxia triggers migraine and aura. Fifteen MA patients were exposed to 180 min of normobaric hypoxia (SaO2 70–75%) and sham and 14 healthy controls were exposed to hypoxia. We measured: glutamate and lactate concentrations in the visual cortex by proton MRI spectroscopy; the circumference of cranial arteries by MRI angiography; the total cerebral blood flow (CBF) by phase-contrast mapping MRI; the blood oxygenation level-dependent (BOLD) functional MRI (fMRI) response to visual stimulation; the BOLD fMRI response during visual aura symptoms in five patients. Hypoxia induced migraine attacks in 53% of MA patients. Aura was induced in three and possible aura in four patients. Hypoxia caused no changes of visual cortex glutamate compared to sham, but increased lactate, total CBF and circumference of the cranial arteries. During hypoxia there was a greater decrease in BOLD response in patients compared to controls. The BOLD response was reduced in patients scanned during aura scotoma and increased in patients with only positive aura symptoms. In conclusion, hypoxia induced migraine attacks with aura. Hypoxia induced a greater decrease in BOLD response in patients, which may represent an increased neuronal excitability or abnormal vascular response to visual stimulation. There is a specific pattern in clinically heterogenous visual aura symptoms and BOLD fMRI changes.

**0900-0930 Sensing brain hypoxia by glial cells and regulation of CBF—Alex Gourine**

In low oxygen conditions, increases in cerebral blood flow maintain brain oxygen delivery but the mechanisms underlying hypoxia-induced dilation of cerebral vasculature are incompletely understood. All penetrating and intraparenchymal cerebral blood vessels are wrapped by the end-feet of astrocytes, - omnipresent multifunctional glial cells that control cerebral vasculature via the release of vasoactive signalling molecules. We studied the potential role of astrocytes in the mechanisms underlying hypoxia-induced increases in cerebral blood flow. The data will be presented suggesting that at rest astrocytes accumulate nitrite and, in response to hypoxia, produce nitric oxide (NO) via mitochondrial reduction of nitrite by a molybdenum-containing enzyme sulfite oxidase. In contrast to NO synthesis by the enzymes of the NO synthase family, generation of vasoactive NO by this mechanism does not require molecular oxygen. This appears to be particularly advantageous in conditions of reduced oxygen supply when rapid signalling by NO is required to increase brain tissue perfusion. We hypothesise that the identified mechanism of NO production by astrocytes dynamically matches regional cerebral perfusion with brain tissue oxygenation and contributes to the increases in global cerebral blood flow that occur during systemic hypoxia.

*0930-1000 Refreshment Break, Heritage Hall*

**1000-1130 Intravascular Volume Changes at Altitude: Causes and Consequences**

**1000-1030 Mechanisms underlying the increase in hemoglobin concentration at high altitude—Christoph Siebenmann**

Acute exposure to high altitude (HA) leads to a reduction in arterial O2 content (CaO2). However, as HA exposure extends, CaO2 progressively returns to normal or even higher levels. The main mechanism underlying the restoration of CaO2 at HA is an increase in arterial hemoglobin concentration. Initially, this hemoconcentration is exclusively the result of a reduction in plasma volume (PV), but expansion of total red blood cell volume (RBCV) progressively contributes if the HA exposure extends over several weeks. The expansion of RBCV at HA is governed by a hypoxia-induced increase in renal erythropoietin release and the resulting acceleration of erythropoiesis, although a contribution of other mechanisms cannot be ruled out. The reduction in PV has classically been attributed to a disbalance between fluid intake and fluid loss, and an increased diuresis was considered the main cause for this disbalance. However, we have recently demonstrated that the diuretic effect of hypoxia is mild, short-lived, and of minimal relevance for PV regulation. Instead, hypoxia-induced PV reduction seems to reflect oncotically driven water redistribution in the face of a preserved total body water. The mechanism underlying this water redistribution remains incompletely understood. It should also be emphasized that during high altitude expeditions limited water supply and/or increased water loss through sweat or feces can reduce total body water and thus PV independently of hypoxia.

**1030-1100 Blood volume control of blood pressure at altitude—Lydia Simpson**

Appropriate regulation of arterial pressure is critical to ensure adequate oxygen delivery to tissues; especially at high altitude (HA), when oxygen availability is reduced. Arterial pressure is determined by several factors including: blood volume, cardiac output, vascular control mechanisms and sympathetic vasomotor activity, which all change to varying degrees with acclimatisation and adaptation to HA hypoxia. Importantly, despite marked alterations in these factors, resting blood pressure (BP) is largely unchanged from sea-level, in both lowland and

highland populations (Nepalese Sherpa and Peruvian Andeans). In lowland natives, despite expansion of erythrocyte volume with acclimatisation, blood volume and stroke volume remain reduced, compared to sea-level, engaging the arterial baroreflex and elevating sympathetic vasomotor activity (MSNA). Profound sympathoexcitation is a feature of altitude acclimatisation and adaptation, with differences in resting MSNA between lowlanders, Sherpa and Andean natives partially explained by differences in stroke volume. Altered sympathetic transduction and vasodilatory signalling play a role in balancing the pressor effects of elevated MSNA at HA, with Andean highlanders exhibiting severely blunted α1-adrenergic responsiveness, the primary mechanism for sympathetic vasoconstriction. Consequently, resting BP in Andeans is comparable to Sherpa and Lowlanders, despite elevated MSNA, haematocrit and total blood volume. The function of the arterial baroreflex, the body's primary beat-by-beat BP controller, is also well preserved at altitude, but reset to operate around a higher level of MSNA and heart rate. However, blunted sympathetic transduction and a reduced sympathetic and heart rate reserve will impair baroreflex-mediated vasoconstriction during severe BP challenges. Although, no impairment in orthostatic tolerance is reported in acclimatised Lowlanders and superior orthostatic tolerance is observed in Andean highlanders at HA, due to their greater red cell mass, blood volume and reliance on non-adrenergic vasoconstrictor mechanisms. Overall, arterial BP during acclimatisation and adaptation HA is well maintained due to the complex integration of several factors.

**1100-1130 A change of heart: cardiac adaptation to hypoxia—Mike Stembridge**

Upon ascent to high altitude, the decrease in intravascular volume is mirrored by a fall in left ventricular end-diastolic and stroke volume. Despite this observation decades ago, early attempts to restore ventricular filling via volume expansion failed to confirm a mechanistic role for plasma volume constriction in driving a decrease in ventricular filling. A series of studies over the last decade have confirmed that changes in intravascular volumes decrease ventricular filling, and highlighted the functional consequences for the heart in response to the decreased venous return. Furthermore, it has become clear that alternative mechanisms also modify ventricular filling and ejection at high altitude, including hypoxic pulmonary vasoconstriction and sympathoexcitation. This session will explore the mechanisms underpinning the adaptive response of the heart as lowlanders acclimatise to high altitude. We will also compare and contrast with different populations of high altitude natives, where in contrast to acclimatised lowlanders, total blood volume is expanded compared to sea level residents. Hypervolemia is achieved by increased plasma volume in Sherpa, but via erythropoiesis in Andean natives resulting in significant haemoconcentration with functional consequences for life at high altitude.

*1130-1600, Ski Break* **and** *1130-1330, Lunch, Victoria Dining Room*

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| **1600-1830** | **Hot Topics in Mountain Medicine—Free Communications (see next pages)** |
| *1900-2130* | *Dinner, Victoria Dining Room* |
| **2030-2130** | **Lessons from a Lifetime of Adventure—Gordon Wiltsie** |

**Hypoxia 2023: Hot Topics in Mountain Medicine, Friday afternoon, 1600-1815, Mount Temple A-B**

**Time: 1600**

**CEREBROVASCULAR FUNCTION UNDER CONDITIONS OF SIMULATED AVALANCHE BURIAL IN HUMANS.** Connor A Howe1, Ryan L Hoiland1, 2, 3, 4, Travis D Gibbons1, Andrew R Steele1, JMJR Carr1, Gustavo A Vizcardo-Galindo1, Michael M Tymko1, Tison Schoenthal5, Valerie C Cates6, Anthony L Marullo6, Trevor A Day6, Mypinder S Sekhon7, Philip N Ainslie1. 1Centre for Heart, Lung, and Vascular Health, School of Health and Exercise Science, University of British Columbia, Kelowna, Canada, 2Department of Anesthesiology, Pharmacology and Therapeutics, University of British Columbia, Vancouver, BC, Canada., 3Department of Cellular and Physiological Sciences, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada., 4International Collaboration on Repair Discoveries, Vancouver, BC, Canada., 5Experimental Medicine, Department of Medicine, University of British Columbia, Vancouver, BC, Canada., 6Department of Biology, Faculty of Science and Technology, Mount Royal University, Calgary, Alberta, Canada., 7Division of Critical Care Medicine, Department of Medicine, University of British Columbia, Vancouver, BC, Canada.

Objective: To investigate the potential cerebrovascular and neuroprotective effects of hypothermia during conditions of simulated avalanche burial. Methods: In 14 participants (6 female), the radial artery and internal jugular bulb were catheterized to measure blood gases and intravascular pressure, collect blood specimens, and quantify cerebral oxygen delivery ($CDO_2$) and metabolic rate of oxygen ($CMRO_2$). Measurements were assessed before and during mild hypothermia (-1.8±0.6°C; esophageal temperature) induced via cold water (7$^0$C) immersion. Progressive hypercapnic-hypoxia was imposed during normothermia and hypothermia using dynamic end-tidal forcing in 2-minute stages (-5mmHg $PaO_2$; +2mmHg $PaCO_2$) to a maximal stimulus of 40mmHg $PaO_2$ and +20mmHg $PaCO_2$, or until volitional tolerance. Duplex ultrasound measurements of the internal carotid and vertebral arteries were used to calculate global cerebral blood flow (gCBF), $CDO_2$ and $CMRO_2$. Serum biomarkers of brain injury and blood brain barrier permeability, Tau, neurofilament light (Nf-L), and glial fibrillary acidic protein (GFAP) were quantified. Results: Hypothermia was associated with increased arterial oxygen content ($CaO_2$; 19±1 vs. 22±2mL/dL; $P<0.01$), mean arterial pressure (90±6 vs 111±10mmHg; $P<0.01$), and ventilation (14±4 vs. 43±10L/min; $P<0.01$); $PaCO_2$ was reduced as a result (43±2 vs 38±3mmHg; $P<0.01$). Conversely, gCBF was lower (840±142 vs. 696±174mL/min; $P<0.01$) and $CDO_2$ unaltered (160±30 vs. 150±39mL/min; $P=0.20$). With hypercapnic-hypoxia, $CaO_2$ was lower during normothermic-hypercapnic-hypoxia versus hypothermic-hypercapnic-hypoxia ($CaO_2$: 16±3 vs. 18±3mL/dL; $P<0.01$), while gCBF and $CDO_2$ were both increased during normothermic-hypercapnic-hypoxia (+78% and +56%, respectively) and hypothermic-hypercapnic-hypoxia (+47% and +28%, respectively). In contrast, $CMRO_2$ was selectively attenuated during hypothermic-hypercapnic-hypoxia compared to normothermic-normocapnic-normoxia (26±8 vs. 43±10mL/min; $P=0.035$). Increases in arterial Tau and GFAP were observed with normothermic-hypercapnic-hypoxia, but not with hypothermic-hypercapnic-hypoxia. Conclusion: Hypothermia decreased gCBF without altering $CDO_2$ or $CMRO_2$. Combined hypothermic-hypercapnic-hypoxia reduced $CMRO_2$, indicating that the combination of these stimuli may provide some form of cerebrovascular protection in the early stages of avalanche burial. Funding: NSERC, CIHR, WMS.

**Time: 1615**

**Mechanisms of adaptation in high-altitude pregnancy: association of genotype with oxygen delivery and placental metabolism.** Katie O'Brien1, Wanjun Gu2, Julie Houck3, Lorenz Holzner1, Jenna Armstrong1, Alice Sowton1, Paula Darwin1, Lilian Toledo-Jaldin 4, Lorna Moore3, Andrew Murray1, Tatum Simonson2. 1University of Cambridge, 2University of California, San Diego, 3University of Colorado, 4Hospital Materno-Infantil, Bolivia

Study objectiveTo determine whether genetic regions exhibiting strong signals of natural selection in the maternal genome of highland Andeans associate with putatively adaptive placental metabolic phenotypes. Further, we aimed to investigate metabolic phenotype in the context of preeclampsia.MethodsA cohort of 79 pregnant Andeans (18-45y, 39 with preeclampsia) living in La Paz, Bolivia (3600 - 4100m) and delivering by unlabored Cesarean section. Maternal genotyping was performed using the 1.8 million SNP Multiethnic Genotyping Array (Illumina). Placental mitochondrial function was assessed in cryopreserved villous biopsies using high-resolution respirometry (Oxygraph-2k, Oroboros). Maternal and umbilical venous plasma was obtained to measure circulating protein levels by ELISA. Using within-population selection tests (iHS) to detect signatures of natural selection, putatively adaptive haplotypes (iHS≥3) were identified; those overlapping with an a priori cellular hypoxic signaling and metabolism gene list were prioritized for association analysis. Linear regression modeling revealed associations between prioritized haplotypes and key outcome measures at an FDR corrected level of p≤0.05.ResultsA haplotype within PTPRD (iHS 3.31) associated with lower placental respiratory capacity (p=0.002). Haplotypes within 200kb of CPT2 (iHS 5.38) and both POMC and DNMT3 (iHS 3.28) associated with lower maternal plasma erythropoietin (p=0.02 and p=0.01, respectively). A haplotype within 200kb of TBX5 associated with lower protein levels of the angiogenic factor VEGF (iHS 3.65, p=0.04) in umbilical venous blood. While greater placental maximal respiratory capacity was associated with lower umbilical venous PO2 in controls (p=0.03), this relationship was absent in preeclampsiaConclusionOur results reveal novel associations between putatively adaptive gene regions and phenotypes linked to oxygen carriage and delivery, as well as placental mitochondrial respiratory capacity. These may act to preserve fetal oxygenation. Examination of these phenotypes in preeclampsia revealed disruption in the relationship between O2 delivery to the fetus and placental O2 consumption.

**Hypoxia 2023: Hot Topics in Mountain Medicine, Friday afternoon, 1600-1815, Mount Temple A-B**

**Time: 1630**

## EXPEDITION 5300 - EARLY EFFECTS OF ACETAZOLAMIDE ON TOTAL HEMOGLOBIN MASS AND PLASMA VOLUME IN CHRONIC MOUNTAIN SICKNESS PATIENTS FROM THE HIGHEST CITY IN THE WORLD.

Aurélien Pichon1, Benoit Champigneulle2, Emeric Stauffer3, Paul Robach4, Stéphane Doutreleau2, Connor A. Howe5, Alessandra Pina6, Alberto A. Salazar-Granara7, Ivan Hancco2, Dorra Guergour8, Julien V. Brugniaux2, Philippe Connes9, Samuel Verges2. 1Université de Poitiers, MOVE UR 20296, STAPS, Poitiers, France, 2HP2 Laboratory, INSERM U1300, Grenoble Alpes University, CHU Grenoble Alpes, Grenoble, France, 3LIBM EA7424, Team "Vascular Biology and Red Blood Cell", Labex GR-EX, Université Claude Bernard Lyon 1, Université de Lyon, Hospices Civils de Lyon, France, 4National School for Mountain Sports, Site of the National School for Skiing and Mountaineering (ENSA), Chamonix, France, 5Centre for Heart, Lung and Vascular Health, School of Health and Exercise Sciences, University of British Columbia - Okanagan, Kelowna, Canada, 6Department of Cardiovascular, Neural and Metabolic Sciences, Istituto Auxologico Italiano, IRCCS, S. Luca Hospital, Milan, Italy, 7University of San Martín de Porres, Peru, 8Biochemistry Laboratory, Grenoble University Hospital, Grenoble, France, 9LIBM, EA7424, Team "Vascular Biology and Red Blood Cell", Labex GR-Ex, Université Claude Bernard Lyon 1, Université de Lyon, France

Objective: Chronic Mountain Sickness (CMS) syndrome, combining excessive erythrocytosis and hyperviscosity symptoms in highlanders, remains a public health issue in high-altitude areas, especially in the Andes, with limited economic and therapeutic approaches. The objectives of this study were to assess in CMS-highlanders permanently living in La Rinconada (5100-5300m, Peru, the highest city in the world), the short-term efficacy of acetazolamide (250mg q.d) and atorvastatin (20mg q.d.) to reduce hematocrit (Hct), as well as the underlying mechanisms focusing on intravascular volumes.Methods: Forty-one males (46±8 years) permanently living in La Rinconada for 15 [10-20] years and suffering from CMS (mild CMS for 90% of them) were included in this randomized, double-blinded, parallel, and placebo-controlled study. Hct (primary endpoint) as well as arterial blood gases, total hemoglobin mass (Hbmass) and intravascular volumes were assessed at baseline and after 19±2 days of treatment with the carbon monoxide rebreathing method.Results: ACZ was effective to improve PaO2 by +13.4% (95% CI: 4.3 to 22.5%, p=0.007) and to decrease Hct by -5.2% (95%CI: -8.3 to -2.2%, p=0.004), whereas no significant early changes in Hct were shown in the placebo and atorvastatin groups. CMS score only significantly decreased in the ACZ group (p=0.03) The decrease in Hct in the ACZ group was explained by an increase in plasma volume of +17.6% (95% CI: 4.9 to 30.3%, p=0.01) without any significant decrease in Hbmass (-2.6%, 95% CI: -5.7 to 0.5%, p=0.09).Conclusions: Short-time ACZ uptake was effective to reduced Hct in CMS-highlanders living at extreme altitude >5000m. The early effect on Hct seems mostly mediated by a restoration of plasma volume rather than a decrease in Hbmass. Atorvastatin uptake had no short-term effect on Hct.Funding: The study was sponsored by Grenoble Alpes University foundation and the French National Research Agency.

**Time: 1645**

**EXPEDITION 5300: MICRO- AND MACROVASCULAR FUNCTION IN THE HIGHEST CITY IN THE WORLD.** Julien V Brugniaux1, Yann Savina1, Aurélien Pichon2, Lucas Lemaire1, Connor A Howe3, Mathilde Ulliel-Roche1, Sarah Skinner4, Elie Nader4, Nicolas Guillot4, Émeric Stauffer4, Mathieu Roustit1, Ivan Hancco1, Paul Robach5, François Esteve1, Vincent Pialoux4, Elisa Perger6, Gianfranco Parati6, Philip N Ainslie3, Stéphane Doutreleau1, Philippe Connes4, Samuel Vergès1. 1Université Grenoble Alpes, France, 2Université de Poitiers, France, 3University of British Columbia, Kelowna, British Columbia, Canada, 4Université Claude Bernard Lyon 1, France, 5National School for Skiing and Mountaineering (ENSA), France, 6Istituto Auxologico Italiano, IRCCS, Sleep Disorders Center & Department of Cardiovascular, Neural and Metabolic Sciences, San Luca Hospital, Italy

Background. Since vascular responses to hypoxia in both healthy high-altitude natives and chronic mountain sickness (a maladaptive high-altitude pathology characterised by excessive erythrocytosis and the presence of a variety of symptoms – CMS) remain unclear, the role of inflammation and oxidative/nitrosative stress on the endothelium-dependent and -independent responses in both the micro- and macrocirculation, in healthy Andeans at different altitudes and in CMS patients, was examined. Methods. 94 men were included: 18 lowlanders (LL), 38 healthy highlanders permanently living at 3,800 m (n=21 – HL-3,800) or in La Rinconada, the highest city in the world (5,100-5,300 m) (n=17 – HL-5,100/No CMS). Moreover, 14 participants with mild (CMS score 6-10 – Mild CMS) and 24 with moderate to severe CMS (CMS score ≥11 – Mod/Sev CMS) were recruited. All undertook two reactivity tests: i) local thermal hyperemia (microcirculation – LTH) and ii) flow-mediated dilation (macrocirculation – FMD). Endothelium-independent function (glyceryl trinitrate – GTN) was also assessed only in La Rinconada. Results. Both conductance and skin blood flow velocity during LTH as well as FMD progressively decreased with altitude (LL>HL-3,800>HL-5,100/No CMS). CMS also induced a decrease in FMD (HL-5,100/No CMS>Mild CMS=Mod/Sev CMS), while GTN restored vascular function. Both oxidative stress and nitric oxide metabolites increased with altitude only. Principal component analysis, used to define inflammatory profiles, revealed that increasing inflammation with altitude was associated with a progressive decline in both micro- and macrovascular function in healthy highlanders. Conclusions. Both micro and macrovascular function are affected by chronic exposure to hypoxia, the latter being further compounded by CMS.

**Time: 1700**

## THE EFFECTS OF STEPWISE REDUCTIONS IN SUPPLEMENTAL OXYGEN ON OXYGEN SATURATION AT REST AND DURING EXERCISE AT EXTREME (SIMULATED) ALTITUDE.

Denis Wakeham1, 2, Andrew Tomlinson1, 2, Peter Hackett3, Matthew Howrey1, Murugappan Ramanathan1, Marcus Payne1, Dean Palmer1, Renie Guilliod1, 2, James Berry1, 2, Tony Babb1, 2, Benjamin Levine1, 2, Christopher Hearon1, 2. 1Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital Dallas, Dallas, Texas, USA, 2The University of Texas Southwestern Medical Center, Dallas, Texas, USA, 3Altitude Research Center, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA

Nearly all (95%) high-altitude mountaineers use supplemental oxygen when climbing peaks at or above 8000m, typically at a flow rate > 4 l/min. Despite its high utilization, the physiological effects and optimal dosing strategies for supplemental oxygen use at extreme altitude are unknown. Therefore, we determined the effects of stepwise reductions in supplemental oxygen flow (nominal: 6, 4, 2, 1 and 0 l/min) using the SUMMIT Oxygen mask during rest and cycling at 60 and 120 Watts (W) at extreme simulated altitude in a hypobaric chamber (282mmHg; 8100m), and during rest at 253mmHg (8848m), in 3 un- and 3 partially acclimatized individuals (age, 34 ± 8 years; 2 females). We recorded oxygen saturation (SpO2) and heart rate (both via photoplethysmography) during 4-minute exposures to each flow rate. During rest at 282 mmHg, SpO2 decreased ($P<0.0001$) with stepwise reductions in supplemental oxygen (6l/min: 99±0%; 4l/min: 96±1%; 2l/min: 91±1%; 1l/min: 83±2%; 0l/min: 70±8%). The reduction in SpO2 led to increases in heart rate (6l/min: 70±1 bpm; 0l/min: 113±13; $P<0.0001$). The pattern of SpO2 and heart rate changes were similar during exercise (60W and 120W) and during rest at 253mmHg. Without supplemental oxygen, 3 participants were able to exercise at 60W; no participant could exercise at 120 Watts. Notably, 1l/min of supplemental oxygen (4-fold lower than standard practice) offset all hypoxemia-related symptoms at rest, whilst during 60W of exercise (ascent rate of ~250-350m/hr) 2l/min maintained participants' SpO2 above 60% (68±2%), below which participants developed hypoxemia-related symptoms. In conclusion, supplemental oxygen flow rates of 1l/min at rest and 2l/min during exercise at extreme simulated altitude were sufficient to maintain oxygen saturation at a level that offsets hypoxemia-related symptoms in un- or partially acclimatized persons.

**Time: 1715**

## ALTITUDE RELATED ADVERSE EFFECT AND THERAPEUTIC BENEFIT OF SUPPLEMENTAL OXYGEN IN PATIENTS WITH PULMONARY VASCULAR DISEASE DURING AN OVERNIGHT STAY AT 2500M.

Simon R Schneider1, Julian Müller1, Meret Bauer1, Laura Mayer1, Lea Lüönd1, Tanja Ulrich1, Michael Furian1, Aglaia Forrer1, Esther I Schwarz1, Konrad Bloch1, Mona Lichtblau1, Silvia Ulrich1. 1University Hospital Zurich, Clinic of Pulmonology, Zurich, Switzerland

Objective: Journeys to high altitude (HA) touristic areas became increasingly popular also among potentially vulnerable groups such as precapillary pulmonary hypertension (PH) due to pulmonary vascular disease (PVD). Scientific evidence to counsel PVD-patients for their upcoming HA trips is scarce. We investigated altitude-related adverse health events (ARAHE) during an overnight stay at 2500m and whether supplemental oxygen reverses the effects of altitude.Methods: In a randomized-sequence, cross-over trial, 27 (44% female) stable patients with pulmonary arterial or distal chronic thromboembolic PH were exposed to 2500m for around 30 hours. ARAHE requiring oxygen therapy was defined as severe hypoxemia ($SpO_2$<80% for >30min) Right heart function by echocardiography, acute mountain sickness (AMS), arterial blood gas and more were assessed the second day at altitude.Results: 10/27 patients experienced severe hypoxemia according to predefined safety criteria and received oxygen, 6 experienced AMS. Only one patient required oxygen the first day, all others during the night. All completed the study according to the protocol.Main significant differences between 470m and 2500m among patients not requiring oxygen were present in tricuspid regurgitation pressure gradient (mean±SD) 40±19 and 61±23; (mean-difference and confidence interval) 21(7 to 35) mmHg, in $PaCO_2$ 4.5±0.4 and 4.2±0.4 kPa; -0.32(-0.6 to -0.04) and in $PaO_2$ 10.4 ± 1.5 and 7.2 ± 0.8; -3.42(-3.97 to -2.87) kPa, however not among patients receiving oxygen at 2500m.Conclusion: During an overnight stay at 2500m, 37% of PVD-patients experienced severe hypoxemia, which was reversed with supplemental oxygen. Significant physiological differences between 470 m and 2500 m in blood gases and right heart function among non-hypoxemic patients were detected but no longer among those receiving oxygen (Clinicaltrial.gov: NCT05107700).Funding: The Swiss National Science Foundation funded the study. Grant number: 32003B_197706

**Time: 1730**

## MODERATE- COMPARED TO LOW-ALTITUDE RESIDENTS ARE THREE TIMES LESS LIKELY TO SUFFER FROM ACUTE MOUNTAIN SICKNESS AT 3600M.

Peter Figueiredo1, Steven Landspurg1, Jon Femling2, Jason Williams2, Mark Buller1, J Philip Karl1, Janet Staab1, Reed Hoyt1, Aaron Reilly2, Trevor Mayschak2, Emma Atkinson1, Tim Mesite1, Beth Beidleman1. 1US Army Research Institute of Environmental Medicine, 2University of New Mexico

Objective: Residing at moderate altitude (1500-2400m) reduces acute mountain sickness (AMS) following rapid ascent to a higher altitude but whether residing at a lower altitude threshold confers similar protection from AMS is unknown. Methods: To determine whether moderate-altitude residents (MAR) living at 1190m experience less AMS than low-altitude residents (LAR) following active or passive ascent to HA, 78 healthy Soldiers (mean±SD; age=26±5yr) were

tested at their baseline residence at 331m (LAR; n=41) or 1190m (MAR; n=37), transported to Taos, NM (2845m), then hiked (n=39) or were driven (n=39) to HA (3600m), and stayed for 4 days. AMS-Cerebral factor score (AMS-C) was assessed at HA using the Environmental Symptoms Questionnaire twice on day 1 (HA1), five times on days 2 and 3 (HA2 and HA3) and once on day 4 (HA4). If AMS-C was ≥0.7 at any assessment, individuals were considered sick. The peak AMS incidence and severity were recorded daily and used for analyses. Results: Ascent conditions did not differentially impact AMS incidence between MAR and LAR groups. The MAR compared to LAR experienced a lower AMS incidence on HA1 (16 vs. 44%, p=0.008) and HA2 (19 vs. 39%, p=0.05), similar incidence on HA3 (14 vs. 29%, p=0.08) and lower incidence on HA4 (0 vs 17%, p=0.007). AMS-C severity was also lower in MAR compared to LAR on HA1 (0.40±0.49 vs. 0.74±0.86, p=0.04), HA2 (0.30±0.34 vs. 0.86±0.88, p=0.001), HA3 (0.30±0.36 vs. 0.56±0.69, p=0.03) and HA4 (0.09±0.14 vs. 0.35±0.58, p=0.01). MAR were approximately three times less likely than LAR to experience AMS at HA1 (OR=4.04, p=0.01), HA2 (OR=2.74, p=0.05) and HA3 (OR=2.64, p=0.09). Conclusions: Moderate-altitude residence as low as 1190m resulted in significantly less AMS following ascent to 3600m, challenging the existing altitude threshold for inducing acclimatization. Authors' views not official U.S. Army or DoD policy. Funding: USAMRDC

**Time: 1745**

**RESPIRATORY VIRAL INFECTION IS A RISK FACTOR FOR SEVERE ACUTE MOUNTAIN SICKNESS, HIGH-ALTITUDE PULMONARY EDEMA, AND COMCOMITANT CEREBRAL EDEMA: A CASE STUDY.** Jon Femling1, Aaron Reilly1, Jason Williams1, Trevor Mayschak1, Peter Figueiredo2, Steven Landspurg2, Beth Beidleman2. 1University of New Mexico, 2US Army Research Institute of Environmental Medicine.

Objective: We present the case of a 19-year-old man who developed severe acute mountain sickness (AMS), high-altitude pulmonary edema (HAPE) and high-altitude cerebral edema (HACE) after rapid active ascent to 3600m. Methods: The patient was tested at his residence (1190m), transported to Taos, NM (2845m), and hiked (5km; 15%grade, 139 min) to a high altitude (HA) of 3600m and stayed for 3 days. AMS-C was assessed using the Environmental Symptoms Questionnaire at HA twice on day 1(HA1), and five times on days 2 and 3(HA2 and HA3). The peak AMS-C score was recorded daily with an AMS-C ≥1.53 indicative of severe AMS. An actigraph estimated total sleep time and continuous pulse oximetry measured mean nocturnal oxygen saturation (SpO2) and heart rate (HR). Results: The patient awoke at 0600 after 38h of altitude exposure with a severe headache, blurred vision, dyspnea at rest, ataxia, confusion, a fever of 101°F, a HR of 115bpm, and SpO2 of 65%. He was treated with supplemental O2 (4 l/min;nasal canula) which improved SpO2 to 90% after 30min. Clinical condition prompted evacuation to nearest emergency room (2124m). Chest X-ray revealed patchy opacities consistent with pulmonary edema and molecular testing identified human parainfluenza virus. Patient was diagnosed with acute hypoxic respiratory failure, HAPE, HACE, and parainfluenza virus infection. The patient experienced severe AMS every day at HA with peak AMS-C scores of 3.17 (HA1), 2.73 (HA2), and 4.20 (HA3). Physiologic deterioration occurred at HA2 compared to HA1 with a lower SpO2 (66 vs. 76%), higher HR (107 vs. 86 bpm), and a greater percentage of sleep time spent below 65% SpO2 (49.7 vs. 1.1%). Conclusion: This case highlights respiratory infection as a serious risk factor for severe AMS,

HAPE and HACE and serves as a warning for sojourners even at a moderate altitude. Authors' views not official U.S. Army or DoD policy. Funding: USAMRDC

**Time: 1800**

## CHANGING INTRAOPERATIVE OXYGEN ADMINISTRATION COULD ALTER POSTOPERATIVE COMPLICATIONS, MORBIDITY AND COGNITIVE RECOVERY – EXPLORATORY CLINICAL RESULTS OF A RANDOMISED CONTROLLED TRIAL (PULSE Ox).

Andrew Cumpstey1, Anna Clark1, Magdalena Minnion1, Helen Moyses1, Daniel Martin2, Mark Edwards1, Martin Feelisch1, Michael Grocott1. 1University of Southampton, 2University of Plymouth

Background: The World Health Organization (WHO) recommends that all anaesthetised patients receive 80% oxygen during surgery to reduce the risk of surgical site infections (SSI) but did not consider the effect this might have on other clinical outcomes. The Cochrane collaboration concluded insufficient evidence exists for routinely administering high oxygen concentrations intraoperatively to reduce SSIs, and that doing so might increase mortality.Objective: This exploratory study aimed to investigate whether changing intraoperative oxygen concentrations might alter other postoperative complications, postoperative morbidity and cognitive recovery.Methods: Twenty-eight adult patients undergoing major (defined as needing a central venous catheter as part of planned anaesthetic technique) abdominal surgery for cancer resection received either 30%, 55% or 80% oxygen (randomised allocation) throughout anaesthesia. Rates of (radiologically reported) atelectasis, cognitive recovery, and infective post-operative morbidity (Post Operative Morbidity Survey, POMS) were all collected up to seven days after surgery. Total critical care length of stay was also recorded.Results: Higher oxygen concentrations were associated with lower rates of atelectasis (n[%]: 6[75%] / 8[80%] / 3[30%] for 30% / 55% / 80% oxygen respectively, p = 0.045). Postoperative cognitive recovery scores (Mean[SD]: 0.7[3.1] / -0.1[2.5] / -1.8[3.3], p = 0.277), POMS infection scores (n[%]: 5[71%] / 5[56%] / 3[33%], p = 0.307) and critical care length of stay (Median[IQR]: 3[2-4] / 2.5[2-3.75] / 3[2-5.25] days, p = 0.870) were not different between groups.Conclusion: Changing the administered intraoperative oxygenation concentration may alter postoperative clinical outcomes and adequately powered clinical studies are urgently needed to investigate the impact of this.Funding: Doctoral Fellowship (Southampton NIHR Biomedical Research Centre)

## 0800-0930 Oxygen sensing in the lungs

### 0800-0815 Ventilatory And Heart Rate Responses to Hypoxia Associate with Pre- and Post-Menopausal Status and Genetic Signatures in Tibetan Women in Mustang, Nepal—James Yu

James Yu[1], Esteban Moya[1], Wanjun Gu[1], David Witonsky[2], Anna Di Rienzo[2], Sienna Craig[3], Christina Buchanan[4], Frank Powell[1], Cynthia Beall[5], Tatum Simonson[1]. [1]Section of Physiology, Division of Pulmonary, Critical Care, and Sleep Medicine, Dept. of Medicine, University of California San Diego, La Jolla, CA, USA, [2]Department of Human Genetics, University of Chicago, Chicago, IL, 60637, USA, [3]Department of Anthropology, Dartmouth College, Hanover, NH, USA, [4]Recreation, Exercise & Sport Science Department, Western Colorado University, Gunnison, CO, USA, [5]Department of Anthropology, Case Western Reserve University, Cleveland, OH, USA

Objective: To determine associations with ventilatory and heart rate responses to hypoxia and genetic signatures in pre- and post-menopausal Tibetan women residing at high altitude. Methods: We measured minute ventilation (VI) and heart rate (HR) during room air and acute hypoxic conditions in 376 Tibetan women (aged 46-86) residing in Mustang, Nepal (>3500m). We determined the hypoxic ventilatory response (HVR, -ΔVI/DSpO2) and hypoxic heart rate response (HHRR, -ΔHR/DSpO2), with a minimum reduction of 10% oxygen saturation (SpO2), while maintaining a constant end-tidal CO2 (ETCO2). We tested for associations of HVR and HHRR with age and [Hb] with individuals grouped by pre- vs post-menopausal status. We conducted a genome-wide association study (GWAS) and positive selection scans in a larger group of 421 Tibetan women. Results: Post-menopausal women had significantly lower HVR and HHRR (0.21 ± 0.01 L/%O2 and 0.65 ± 0.02 BPM/%O2, respectively) compared to pre-menopausal women (0.34 ± 0.03 L/%O2 and 0.92 ± 0.05 BPM/%O2), even when controlling for age. HVR and HHRR associated positively with resting SpO2 ($p < 0.05$). [Hb] associated negatively with age in the post-menopausal group but had no association with age in the pre-menopausal group. The GWAS identified a genomic region associated with ETCO2 in room air ($p<5e-8$). An overlap between positive selection scan results and an a priori list of gene candidates related to control of breathing revealed gene regions undergoing selection that are associated with ventilatory parameters. Conclusion: Post-menopausal Tibetan women residing at high altitude exhibit lower ventilatory and heart rate responses to hypoxia compared to pre-menopausal and gene regions are associated with ventilatory traits. Funding: Supported by NSF 1831530 to CMB and NIH 1R01HL145470 to TSS.

### 0815-0830 Effects of Hypoxia, Hypercapnia and Hypobaria on Pulmonary Ventilation in Pre-Term Born Adults—Benjamin Narang

Benjamin Narang[1, 2, 3], Giorgio Manferdelli[4], Grégoire Millet[4], Tadej Debevec[1, 2]
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We aimed to quantify the ventilatory responses to changes in barometric pressure (BP), and the partial pressures of inspired oxygen (PiO2) and carbon dioxide (PiCO2), in pre-term adults and their term-born counterparts. Methods: 17 full-term (Mean±SD; gestational age; 40±0 weeks) and 17 pre-term (29±1 weeks) adults completed nine 6-min exposures to combinations of normobaria (NB; BP = 739±3 mmHg) and hypobaria (HB; BP=503±3 mmHg), normoxia (NX; PiO2=153±4 mmHg) and hypoxia (HX; PiO2=107±9 mmHg), and normocapnia (NC; ~0.03%

CO2; PiCO2=0.58±0.37 mmHg) and hypercapnia (HC; ~3.00% CO2; PiCO2 = 17±4 mmHg). NB conditions were completed at 295 m, and HB conditions were completed after 21.3±0.2 hours at 3375 m. A 60-s average of minute ventilation (VE) was taken at the end of each stage from the breath-by-breath data sampled by metabolic cart (Ergocard Professional, Medisoft). Arterial blood gasses were quantified in the final 30 s of each stage after collecting arterialised capillary blood samples (ABL-90 FLEX, Radiometer). Results: Pre-term birth elicited no significant effect on any outcome reported in this study, so groups were combined for analysis of environmental condition. Relative to NB_NX_NC (11.49±2.00 L/min), HC (15.14±2.84 L/min; p<0.001) and HX_HC (15.01±2.83 L/min; p<0.001) increased VE to a similar extent, whereas HX independently had no effect (11.01±1.39 L/min; p=0.298). Under HB conditions (NX_NC; 12.16±1.64 L/min), both HX (13.15±1.53 L/min; p<0.001) and HC (15.88±2.22 L/min; p<0.001) independently increased VE. Changes in VE (or lack thereof) were reflected primarily by arterial CO2 in NB, whereas arterial O2 also reflected ΔVE in HB. Conclusions: The ventilatory responses to hypoxia, hypercapnia and hypercapnia appear unaffected by the known long-term cardiorespiratory sequelae of pre-term birth. Hypobaria may modulate the ventilatory response to moderate hypoxia. Funding: This project was funded by the Swiss National Science Foundation (320030L_192073) and the Slovenian Research Agency (N5-0152).

### 0830-0900 Sensing oxygen in the pulmonary circulation—Mary Slingo

The unique property of the pulmonary circulation to constrict in response to hypoxia, rather than dilate, brings advantages in both health and disease. Hypoxic pulmonary vasoconstriction acts to optimise ventilation-perfusion matching - this is important clinically both in focal disease (such as pneumonia) and in one-lung ventilation during anaesthesia for thoracic surgery. However, during global hypoxia such as that encountered at high altitude, generalised pulmonary vasoconstriction can lead to pulmonary hypertension. There is now a growing body of evidence that links the hypoxia-inducible factor (HIF) pathway and pulmonary vascular tone – in both acute and chronic settings. Furthermore, genetic disorders of oxygen-sensing and pharmacological manipulation of the HIF pathway have been shown to impact pulmonary vascular responses to acute and sustained hypoxia. This talk will explore these relationships in more detail, and discuss future avenues of research.

### 0900-0930 $O_2$, $CO_2$ and Breathing: What's the Controversy?!—Jerry Dempsey

We consider three fundamental concepts concerning the chemical control of breathing in health. Carotid chemoreceptors (CB) provide the sole mediation of the ventilatory response to changes in arterial oxygenation! When controlling the isolated, perfused CB at normal PO2/PCO2 in awake and sleeping animals (using the Bisgard preparation), systemic hypoxia elicits a dose:response increase in fb, VE, Vt/Ti, inspiratory and abdominal expiratory muscle EMG. Extra-CB hyperoxia also elicits a dose:response hyperventilation, with both VT and fb increased. Hyperoxic CO2 rebreathing specifically tests central CO2 chemosensitivity! When carotid chemoreceptors are denervated (awake canine or human) or isolated and inhibited with a hyperoxic/hypocapnic perfusate (canine), the responsivity of VE, Vt, fb and EMGdi to inhaled or rebreathe-induced hyperoxic hypercapnia is reduced. Central medullary chemoreceptors that are highly sensitive to CO2/H+ changes in their environment provide key, obligatory control of eupneic breathing! Numerous examples are available both between and within species (including humans) where; a) eupneic, air-breathing PaCO2 is precisely, homeostatically controlled in the absence of significant central CO2 chemosensitivity; or b) ventilatory response matches VCO2 change without alterations in PaCO2. To summarize, in contrast to accepted concepts, we propose: a) extra-CB hypoxia (via renal and/or CNS sensors?) contributes significantly to the hypoxic-induced ventilatory response; b) carotid chemoreceptors contribute to the ventilatory

response to hyperoxic CO2; and c) mechanisms linked to VCO2--not PaCO2 dominate the homeostatic regulation of air-breathing eupnea.

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

**1000-1130 Advances in Hypoxia Research II**

**1000-1015 Cardiopulmonary and Right Ventricular Performance in Response to Acute Hypoxia—William Cornwell.** University of Colorado Hospital. Aurora, CO, USA.

Acute hypoxia causes pulmonary hypertension, though its effect on exertional right ventricular (RV) performance is controversial. The objective of this study was to characterize exertional RV performance during acute hypoxia. Methods: Ten healthy participants (34±10 yrs, 7 males) completed three visits: Visit 1 and Visit 2 consisted of noninvasive normoxic (fraction of inspired oxygen [FiO2]=0.21) and normobaric hypoxic (FiO2=0.12) cardiopulmonary exercise testing (CPET) to determine normoxic/hypoxic maximal oxygen uptake (VO2max) in counter-balanced order. Visit 3 included an invasive hemodynamic assessment, where participants were randomized 1:1 to testing with Swan-Ganz catheter or conductance catheter to quantify RV energetics and performance via RV pressure-volume (PV) analysis. Arterial oxygen saturation was assessed by co-oximetry using arterial blood from radial arterial catheterization. During Visit 3, participants completed invasive submaximal CPET testing at 50% normoxic VO2max, followed by exposure to progressive hypoxia at an FiO2 of 0.17, 0.15 and 0.12 delivered through Douglas bag reservoirs over a ~40-minute period. Thereafter, participants completed submaximal CPET at 50% hypoxic VO2max at an FiO2=0.12. Results: VO2max values during normoxic and hypoxic testing were 3.11±0.69 L/min and 1.93±0.35L/min, respectively (P<0.01). Median (interquartile range) mean pulmonary arterial pressures (PAP) at an FiO2 of 0.21 and 0.12 were 8(8,14) and 14(13,19), respectively, P<0.01. Metrics of RV contractility, lusitropy and energetics were augmented in response to progressive hypoxia. Exertional ventriculoarterial coupling was preserved at FiO2=0.12. Conclusions: Among healthy adults, resting and exertional RV function are preserved in response to acute exposure to hypoxia at an FiO2=0.12 and the associated increase in PAP and ventricular afterload. Acknowledgements: This study was supported by National Institute of Health / National Center for Advancing Translational Sciences Colorado Clinical and Translational Science Awards Grant Number UL1 TR002535 (LF) and Colorado Pulmonary Vascular Disease Research Award (LF).

**1015-1045 Targeting Hypoxia Signaling for ARDS Treatment—Holger Eltzschig**

Acute lung injury is a severe form of lung inflammation causing acute respiratory distress syndrome (ARDS) in patients1. ARDS dramatically impacts the morbidity and mortality of surgical patients or patients with infections, including emerging viral diseases2. For example, the main cause of death in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is ARDS. Nevertheless, most patients with ARDS or acute lung infections recover seamlessly without developing ARDS. Our studies have shown that during ARDS (including SARS-CoV-2), hypoxia-inducible factor HIF1A is stabilized in alveolar epithelia and functions as an endogenous regulatory pathway to dampen alveolar inflammation3-6. Ongoing studies identified microRNA miR-147 as a direct target of HIF1A. Functionally, mice with alveolar epithelial deletion of miR-147 show increased lung injury in response to SARS-CoV-2 infection. mRNA

sequencing and subsequent in silico miR-147-target analysis revealed reduced antiviral responses and identified SARS-CoV-2 ORF8 as a direct miR-147 target. Moreover, mice infected with SARS-CoV-2 and treated with miR-147 packaged in DOPC nanoliposomes showed significant protection with enhanced antiviral responses and improved survival. Proof-of-principle studies in patients with COVID-19 highlighted this pathway in human SARS-CoV-2-associated ARDS. In addition, a recently completed phase-2 clinical trial (n=448) in hospitalized patients with SARS-CoV-2 infection and concomitant hypoxia randomized patients to the HIF activator vadadustat or placebo. The data from this trial support the safety of vadadustat in critically ill patients and indicate a high likelihood of benefit for preventing or early treatment of lung injury in patients hospitalized with COVID-19. Together, these ongoing studies highlight that hypoxia-signaling can be targeted to prevent or treat patients with lung infections or ARDS.

**1045-1130 New Horizons in Hypoxia Signalling—Peter Ratcliffe**

In human and animal cells transcriptional responses to hypoxia are transduced by the HIF (hypoxia inducible factor) hydroxylase pathway. In this system, oxygen sensitive signals are generated by the catalytic action of a set of 2-oxoglutarate dependent dioxygenases that hydroxylate specific prolyl and asparaginyl residues to promote the proteolytic destruction and inactivation of (HIF)-alpha sub-units. This system has been shown to direct multiple cellular and systemic responses to hypoxia. However, the demands of human oxygen homeostasis, requiring responses over widely different time-scales and oxygen gradients, suggest that other systems must contribute to this process. In this context, several recent developments that connect the HIF hydroxylase system to other processes of oxygen sensing will be outlined. This includes adaptive and developmental roles of the HIF-2 isoform in excitable chemo-sensing cells in the carotid body and adrenal medulla and a parallel system of N-cysteine dioxygenation linked to proteolysis, which regulates G-protein signalling. The extent to which these newly identified processes contribute to physiological oxygen homeostasis will be reviewed.

*1130-1600, Ski Break* and *1130-1330, Lunch, Victoria Dining Room*

**1600-1830 Hot Topics in Hypoxia II—Free Communications, Mount Temple (see next pages)**

*1900-2130 Dinner, Awards and Dance, Mt Temple Ballroom*

**Time: 1600**

## ADRENERGIC RECEPTOR MECHANISMS IN SYMPATHETIC NEUROVASCULAR TRANSDUCTION AT HIGH ALTITUDE.

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Objective: Previously, we demonstrated blunting of sympathetic neurovascular transduction (NVT) with high-altitude hypoxia. This may contribute to the maintenance of mean arterial pressure (MAP) near sea-level values despite an increase in muscle sympathetic nerve activity (MSNA). Since vascular adrenoreceptors mediate changes in vessel tone and may undergo desensitization with hypoxia, we aimed to elucidate the relationship between NVT and adrenergic receptor reactivity at high altitude. Methods: Participants (n=10; 6M, 4F) were tested following 3-11 days at altitude (Barcroft Field Station, White Mountain CA; 3800m). Changes in forearm blood flow (FBF; Doppler ultrasonography) and vascular conductance (FVC; FBF·MAP-1*100) with incremental intra-arterial infusions of phenylephrine (specific α1-adrenergic agonist) and norepinephrine (non-selective α- and β-adrenergic agonist) were determined and compared to the contralateral arm as a control. A linear slope between FBF and FVC responses and log transformed doses was used to assess adrenergic sensitivity. NVT slopes were calculated as changes in MAP (finger photoplethysmography) corresponding to normalized amplitudes of MSNA burst sequences (microneurography) using a custom software (MATLAB). Results: Resting MSNA burst frequency (27±6 bursts·min-1) and NVT slope (0.79±0.36a.u.) had a strong negative correlation (r=-0.67; p=0.0497), indicating lower vascular responsiveness in individuals with higher sympathetic activity. NVT also exhibited a strong positive relationship with both FBF (4.12±3.89mL·100mL FAV-1·min-1·log(μg·100mL FAV1·min-1)-1, r=0.73, p=0.0416) and FVC (3.94±3.52a.u.·log(μg·100mL FAV1·min-1)-1, r=0.70, p=0.0532) sensitivity to phenylephrine, but not norepinephrine (1.20±1.19mL·100mL FAV-1·min-1·log(ng·100mL FAV-1·min-1)-1 and 1.22±1.13a.u.·log(ng·100mL FAV1·min-1)-1, respectively; both p>0.05). Additionally, there was no relationship between α1-specific and non-specific α- and β-adrenergic reactivity (both p>0.05). Conclusion: Our data indicates that α1-adrenoreceptors contribute to NVT, and blunting of NVT at high altitude may be mediated

through decreased sensitivity of α1-adrenoreceptors. However, β-adrenergic vasodilation by endogenous norepinephrine may also offset NVT. Funding: NSER.

**Time: 1615**

**Putatively adaptive Andean single nucleotide variant in EPAS1 preserves mitochondrial oxygen consumption. .** Katie O'Brien 1, Juan Zuniga-Hertz2, Elijah Lawrence2, Wanjun Gu2, Ingrid Niesman3, Carlos Vasquez2, Esteban Moya2, Marco Bauk2, James Yu2, Alexis Komor2, Hemal Patel2, Andrew Murray1, Tatum Simonson2. 1University of Cambridge, 2University of California, San Diego, 3San Diego Sate University

Study objectiveTo investigate cellular metabolic phenotype downstream of a novel putatively adaptive single nucleotide variant (SNV) in EPAS1, encoding a subunit of hypoxia inducible factor HIF-2α, identified in Andean highlanders from Cerro de Pasco, Peru (4340m).MethodsThe EPAS1 SNV (rs570553380, A>G, p.[His194Arg]) was incorporated into an isogenic human cell line (HEK293T) using CRISPR base editing. Cells heterozygous for the putatively adaptive variant alongside wild type transfected and non- transfected (n =3 per cell line) were exposed to 24hrs of normoxia or hypoxia (1% O2). Mitochondrial oxygen consumption rates (OCR) and extracellular acidification rates were measured using the Cell Mito Stress Test and Glycolysis Stress Test, respectively (Agilent Seahorse XF), corrected to cell density (sulforhodamine b (SRB) colorimetric assay). Mitochondrial ultrastructure was visualized using Transmission Electron Microscopy. Cellular growth rate was measured in high glucose and galactose media using the SRB assay and cell viability using trypan blue staining and a Countess automated cell counter (Thermo Fisher Scientific). ResultsIn comparison to wild type, cells heterozygous for the putatively adaptive EPAS1 SNV revealed suppression of OCR in normoxia, including a 32% decrease in basal respiration, a 30% decrease in ATP linked respiration and a 50% decrease in maximal respiration ($p<0.05$), alongside changes in mitochondrial ultrastructure with inflated mitochondrial cristae. Following 24hrs of hypoxia, mitochondrial OCR was suppressed in wild type lines, including a 1.4 fold decrease in maximal respiration ($p<0.05$), and cells displayed the inflated mitochondrial cristae phenotype. In heterozygous cells, OCR and cristae phenotype remained unchanged from normoxic levels. No change was evident in cellular glycolytic capacity, growth rate or viability between cell lines.ConclusionTogether these results indicate cellular mechanisms downstream of a novel Andean variant in EPAS1 that may prime cells for hypoxic exposure by preserving mitochondrial O2 consumption with concomitant alterations in mitochondrial morphology.

**Time: 1630**

**Expedition 5300 - The increase in blood viscosity in lowlanders exposed to high altitude is not only due to the rise of haematocrit.** Emeric STAUFFER1, 2, Aurélien PICHON3, Benoit CHAMPIGNEUL4, Michaël FURIAN5, Lars KARSTNER6, 7, Ivan HANCCO4, Paul ROBACH4, 8, Julien V. BRUGNIAUX4, Philippe CONNES1, Samuel VERGES4. 1Laboratoire Interuniversitaire de Biologie de la Motricité (LIBM) EA7424, Team « Vascular Biology and Red Blood Cell », Université Claude Bernard Lyon 1, Université de Lyon, France, 2Explorations Fonctionnelles Respiratoires, Médecine du sport et de l'Activité Physique, Hospices Civils de Lyon, Hôpital Croix Rousse, Lyon, France, 3Université de Poitiers, Laboratoire MOVE, Poitiers, France , 4Univ. Grenoble Alpes, Inserm, CHU Grenoble Alpes, HP2, 38000 Grenoble, France, 5Pulmonary Division, University Hospital Zurich, 8092 Zurich, Switzerland, 6Theoretical Medicine and Biosciences, Saarland University, Homburg, Germany, 7Experimental Physics, Saarland University, Saarbrücken, Germany., 8National School for Mountain Sports, Site of the National School for Skiing and Mountaineering (ENSA), Chamonix, France

Introduction: Humans ascending to high altitude exhibit an increase in blood viscosity, which is classically attributed to the rise of hematocrit. However, blood viscosity is also dependent on the rheological properties of red blood cells (RBC). Few studies have investigated changes in RBC deformability and aggregation in lowlanders exposed to high altitude. The present study assessed the effect of acute high altitude exposure on blood viscosity and RBC rheology in lowlanders during a sojourn in the highest city in the world (La Rinconada, Peru, 5,100 m).Methods: Eleven volunteers native from lowland underwent 5 days at 3,800 m followed by 10 days at 5,100 m and another 5 days at 3,800 m. Blood was sampled 1 month before exposure to altitude (sea level pre), after 15 days at altitude and 2 weeks after return to sea level (sea level post). Blood viscosity (cone plate viscometer), RBC deformability (ektacytometry) and aggregation (syllectometry) measurements were performed on each blood fresh sample.Results: Haemoglobin concentration and haematocrit increased with altitude and returned to baseline after 2 weeks at sea level. Blood viscosity followed the same kinetic (6.9±1.5 cP at sea level pre, 16.7±3.1 cP at 5,100m and 7.3±1.3 cP at sea level post; $p<0.001$). RBC deformability decreased and RBC aggregation increased at altitude and returned to baseline after 2 weeks at sea level (elongation index at 3 Pa 0.318±0.015 UA at sea level pre, 0.322±0.048 UA at 5,100m and 0.375±0.02 UA at sea level post; $p=0.001$; aggregation index: 53.5±5.2% at sea level pre, 77.7±2% at 5,100m and 48.9±15% at sea level post; $p<0.001$).Conclusion: The increase in blood viscosity observed in lowlanders exposed to altitude is not only due to the rise in haematocrit but is also explained by a reduction of RBC deformability and an increase of RBC aggregation.

**Time: 1645**

## CEREBROVASCULAR CO2 REACTIVITY IN ADULTS BORN PRETERM AT HIGH-ALTITUDE.

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Premature birth impairs cardiac and ventilatory responses to both hypoxia and hypercapnia, but little is known about cerebrovascular responses. We, therefore, investigated cerebrovascular CO2 reactivity at both sea-level (SL) and after 2 days at high-altitude (HA, 3375m) in young healthy preterm born adult males (n=16; gestational age, 29±1 weeks), and their age-matched term born counterparts (n=15; 40±0 weeks). Participants were exposed to two consecutive 4-minute hyperoxic hypercapnic conditions (3%CO2-97%O2; 6%CO2-94%O2), followed by two periods of voluntary hyperventilation to elicit hypocapnia, at both SL and HA. We measured middle cerebral artery blood velocity (MCAv; Transcranial Doppler), end-tidal CO2 and arterialized capillary blood gases. Hypocapnic and hypercapnic CO2 reactivity, and the sigmoidal response midpoint (X0), were analyzed using a sigmoid curve fitting. Hypocapnic CO2 reactivity increased at HA compared to SL in term born (+173±326%, P=0.026), but not in preterm (-21±107%, P=0.572, respectively), adults. HA exposure increased hypercapnic CO2 reactivity only in preterm adults (+125±144%, P<0.001). In HA, both hypocapnic and hypercapnic CO2 reactivity responses were different between preterm and term born individuals (P=0.012 and P=0.020, respectively). While X0 was similarly reduced at HA in both preterm (39.4±2.4 to 29.8±2.0 mmHg, P<0.001) and term born participants (41.1±2.9 to 31.1±1.0 mmHg, P<0.001), preterm adults exhibited a lower X0 compared to their term born peers independently of HA (P=0.025). Resting MCAv increased at HA compared to SL in term born (+24±39%, P=0.036), but not in preterm (-4±27%, P=0.278), adults. The SL-to-HA increase in MCAv was correlated with the change in PaO2/PaCO2 ratio in term born individuals only (r2=0.45, P=0.035). In conclusion, exposure to HA reveals differential cerebrovascular function in preterm compared to term born adults, as assessed by CO2 reactivity.Funding: Swiss National Science Foundation (nr. 320030L_192073) and Slovenian Research Agency (nr. N5-0152).

**Time: 1700**

## TIME DOMAINS OF DNA METHYLATION PATTERNS DURING HIGH-ALTITUDE ACCLIMATIZATION.

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Objective: To measure changes in DNA methylation in response to acute and generational high-altitude exposure, in key hypoxia-inducible factor (HIF) pathway genes including EPAS1 (HIF-2α) and EGLN1 (PHD2). Hypothesis: Acute high-altitude exposure would produce increased methylation of the EGLN1 promoter region and decreased methylation of the EPAS1 promoter region, facilitating HIF-pathway activation. While in high-altitude natives we hypothesized that healthy individuals would have DNA methylation levels similar to acclimatized sojourners and individuals with maladaptive excessive erythrocytosis (EE) would have methylation levels comparable to sojourners on the first few days of high-altitude exposure. Methods: 31 participants of sea-level ancestry were recruited. DNA was isolated from venous

blood samples which were collected during fasting at sea level and over three days of acclimatization to 3800m elevation in Bishop, CA. In addition, 24 multigenerational Andean high-altitude residents from Cerro de Pasco Peru (4300m) were recruited and separated into control and EE groups based on hemoglobin levels. Local DNA methylation levels within EPAS1 and EGLN1 were obtained using a high-resolution melt technique. Results: Amplicons in both EPAS1 and EGLN1 showed significantly increased methylation levels in sojourners after 3 days of acclimatization as compared to their sea-level values. Additionally, EE highlanders showed higher levels of methylation in these regions than their healthy counterparts. Conclusion: These changes in DNA methylation likely play a key role in acclimatization and adaptation to chronic hypoxia and future studies will explore these mechanisms. This work has implications for understanding the role of epigenetics in diseases associated with hypoxia such as COPD, COVID-19, and sleep apnea, as well as the role epigenetics may play in long-term evolutionary adaptations. Funding: This work was funded by a UCR Regent's Faculty Fellowship and the UCR School of Medicine.

**Time: 1715**

**The ABC of hypoxia - what is the norm?.** Chris Donnelly1, 2, Sabine Schmitt1, Cristiane Cecatto1, Luiza Cardoso1, Timea Komlodi1, 3, Nicolas Place2, Bengt Kayser2, Erich Gnaiger1. 1Oroboros Instruments, Austria, 2Institute of Sports Sciences, University of Lausanne, Switzerland, 3Semmelweis University, Hungary

Hypoxia is a condition of oxygen levels below normoxia and opposite to hyperoxia. We here define the normoxic reference state by three complementary precepts: (A) ambient normoxia at sea level in the contemporary atmosphere and corresponding dissolved O2 concentrations at air saturation of aqueous environments; (B) biological compartmental O2 levels at ambient normoxia under physiological activity of healthy organisms in the absence of environmental stress; and (C) O2 levels above the respiratory oxygen control region. In the oxygen control region, the capacity for O2 consumption is compromised by hypoxic partial O2 pressure as evaluated by O2kinetics of respiration or other critical functions. The ABC of hypoxia distinguishes deviations from these reference points caused by different mechanisms: (ΔA) ambient alterations of oxygen levels; (ΔB) biological O2 demand exceeding O2 supply under pathological or experimental limitations of convective O2 transport or O2 diffusion; and (ΔC) critical oxygen pressure in oxygen kinetics shifted by pathological and toxicological effects or environmental stress. The ABC of hypoxia may be of help in the design, interpretation and communication of in vitro and in vivo experimental studies.

**Time: 1730**

**THE IMPACT OF INFLAMMATION ON BRAIN OXYGENATION.** Jeff Dunn1, Qandeel Shafqat1, Ying Wu1. 1Department of Radiology, Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary

Low levels of oxygen (hypoxia) in the brain can have a significant impact on brain function as well as quality of life measures (sleep, concentration etc). There is increasing evidence that inflammation, both local and systemic, can cause changes in the regulation of cerebral blood flow (CBF), molecular responses to hypoxia, such as HIF-1α regulation, and vascular reactivity. Near-infrared spectroscopy can be used to assess oxygenation in human brain. We show evidence from frequency domain NIRS measures of microvessel oxyhemoglobin saturation, that there is hypoxia in many people with MS and with long covid—which may relate to inflammation. We also show data from direct measurements of brain pO2 in two animal models that are measured while awake. The Experimental Autoimmune Enchephalomyelitis (EAE) model is an inflammation induced autoimmune model that results in demyelination and immune cell activation. The lipopolysaccharide injection model is one where injection of bacterial glycolipid stimulates a systemic immune response much like septic shock. We implanted fibre optic based pO2 sensors into the brain of the mice. The sensors have fibre bundles that attach to a control system but still allow for free movement. Behaviour and either cortical or hippocampal pO2 was measured. EAE mice show fluctuations in pO2 at times of peak disease—with all animals showing hypoxia at some period. The LPS mice have similar reactions, in that significant fluctuations in pO2 occur, with many periods of severe hypoxia. We show that inflammation is associated with brain hypoxia under a range of conditions in animal models and humans. This hypoxia could impact perception of sickness as well as impair recovery processes. The hypoxia could also be a target for treatment with oxygenation strategies including vasodilators, increased hemoglobin, or oxygen therapy.

**Time: 1745**

**PUTTING HYPOXIA TO WORK: TAKING A STAB AT GENERATING INTRINSIC, RECYCLABLE MRI CONTRAST.** Joseph Fisher1. 1University of Toronto

Introduction. Gadolinium (Gd), a paramagnetic molecule used for MRI contrast is invasive, risks toxicity, allergy, and environmental pollution. Deoxyhemoglobin (dOHb) is also paramagnetic, and can be produced by making the lung hypoxic. But rapid precise targeting of lung PO2 is resisted by its large functional residual capacity. Here we report generating precise [dOHb] as MRI contrast and comparing the resulting MRI images and hemodynamic measures to those obtained with a clinical standard, Gd, in patients with brain tumors. Method. We studied 9 patients (8 M; age 23-67 y) with low to high grade glioblastoma. Lung gas control was via sequential gas delivery (SGD) and prospective gas targeting breath by breath. We applied a hypoxic gas sequences twice consecutively: from normoxia, to PO2 at 40 mmHg (SaO2 of about 75%) for 60 s, then reoxygenation to normoxia within one inspiration (total 2 min). Each patient also received an injection of 5 ml Gd. Following the hypoxia sequence and the Gd injection we ran a T2* gradient echo planar sequence with TR 1750 ms voxel size 2.5 mm isotropic. We compared resting perfusion measures generated using both dOHb and Gd, using standard tracer kinetics and a new analysis of step re-oxygenation (under review).Results. Six patients completed the study (1 had excessive motion; 2 refused Gd). All patients attained

target arterial blood gases with little discomfort. Resting perfusion measures obtained using dOHb were highly comparable to those obtained with Gd.Conclusion. Hypoxia-induced dOHb provides an attractive MR contrast agent capable of obtaining contrast imaging and resting perfusion metrics highly similar to those obtained using Gd. Precise, repeatable dOHb generation is automated, brief, non-invasive, comfortable, and suited for repeated study, such as for monitoring for tumor progression.Words: 280

**Time: 1800**

**ORGAN-SPECIFIC FUEL REWIRING IN ACUTE AND CHRONIC HYPOXIA REDISTRIBUTES GLUCOSE AND FATTY ACID METABOLISM.** Ayush Midha1, Yuyin Zhou2, Bruno Queliconi2, Alec Barrios2, Cyril Fong1, Joseph Blecha1, Henry VanBrocklin1, Youngho Seo1, Isha Jain2. 1UCSF, 2UCSF/Gladstone

Objective: Oxygen deprivation can be detrimental. However, chronic hypoxia is associated with decreased incidence of metabolic syndrome and cardiovascular disease in high-altitude populations. Previously, hypoxic fuel rewiring has primarily been studied in immortalized cells. Here, we describe how systemic hypoxia rewires fuel metabolism to optimize whole-body adaptation. Acclimatization to hypoxia coincided with dramatically lower blood glucose and adiposity. Methods and Results: Using in vivo fuel uptake and flux measurements, we found that organs partitioned fuels differently during hypoxia adaption. Acutely, most organs increased glucose uptake and suppressed aerobic glucose oxidation, consistent with previous in vitro investigations. In contrast, brown adipose tissue and skeletal muscle became "glucose savers," suppressing glucose uptake by 3-5-fold. Interestingly, chronic hypoxia produced distinct patterns: the heart relied increasingly on glucose oxidation, and unexpectedly, the brain, kidney, and liver increased fatty acid uptake and oxidation. Hypoxia-induced metabolic plasticity carries therapeutic implications for chronic metabolic diseases and acute hypoxic injuries.Of note, this story is currently In Revision at Cell Metabolism.Lab website: https://ishajainlab.com/Funding: ADM was supported by the National Institute of General Medical Sciences 409 (NIGMS) Medical Scientist Training Program, Grant T32GM141323. IHJ was supported by NIH 410 DP5OD026398. IHJ, BBQ and AMB were supported by Defense Advanced Research Projects 411 Agency, Biological Technologies Office (BTO) Program: Panacea issued by DARPA/CMO under 412 Cooperative Agreement No. HR0011-19-2-0018