ABSTRACTS

14th International Hypoxia Symposium

February 22–27, 2005
Chateau Lake Louise
Alberta, Canada

Organized by Drs. Robert Roach and Peter Hackett and the International Hypoxia Symposia Advisory Committee
For more information see www.hypoxia.net

HIGH ALTITUDE MEDICINE & BIOLOGY
Volume 5, Number 4, 2004

Abstracts

1.
AN EXPERIMENT OF NATURE RELEVANT TO AUTONOMIC NERVOUS SYSTEM FUNCTION AND DISEASE?

Otto Appenzeller[1], Tamara Minko[2], Clifford Qualls[3], Vitaly Pozharov[4], Jorge Gamboa[5], Alfredo Gamboa[5], Yang Wang[4]. NMHEMC Research Foundation[1], Rutgers, The State Univ New Jersey, Piscataway, NJ,[2], Univ New Mexico, Dept Mathematics and Statistics[3], Rutgers, The State Univ New Jersey, Piscataway, NJ.[4], Departamento de Ciencias Biológicas y Fisiologicas, Universidad Peruana Cayetano Heredia, Lima, Peru[5]. *Email:* ottoarun12@aol.com

We tested the hypothesis that normal adaptation to ambient hypoxia of the high mountains, mediated by the autonomic nervous system (ANS), is accompanied by changes in gene expression. Such natural adaptation to the environment could have lessons for ANS function and neurology at sea level. Natives to high altitude are born, live and die hypoxic; they usually adapt to their environment. Chronic mountain sickness (CMS), an unexpected maladaptation to their Andean environment, is characterized by severe, especially nocturnal, hypoxia, marked erythrocytosis, ANS symptoms, but uncommon resistance to orthostatic stress. Normal cells deprived of oxygen turn on some 30 different genes to counter the deleterious effects of hypoxia. Little is known about changes in gene expression in chronically hypoxic humans. We studied 30 men. Twenty natives were examined in Cerro de Pasco (CP), 4338m., Peru, then transported to Lima, sea level, and examined 1 hour after arrival. They were rated using a hematocrit (HTC) of >65% and a clinical CMS-score (CMS-sc) of ≥12 as denoting CMS, to assess the severity of the disease, and determine normal adaptation. Using this scoring in CP we found that 15 had CMS and 5 were normal. We extracted RNA from white cells in CP and Lima. Ten US men, residing at 1500m., gave white cells for comparison. Gene expression was assessed by RT-PCR and related to CMS-scores. We focused on hypoxia inducible factor 1-α (HIF 1-α), two splicing variants of vascular endothelial growth factor, (VEGF-121 and VEGF-165), ataxia telangiectasia mutated (ATM), heme-oxygenase-1 (HMOX 1) and phosphoglycerate kinase 1 (PGK 1). Data were analyzed using ANOVA, t-tests, and correlation and regression methods. Difference were significant if $p < 0.05$. All Andeans had high gene product expression in CP and significant reduction of all gene products while normoxic in Lima ($p < 0.001$). In CMS patients, normal ambient oxygen and arterial saturation at sea level failed to restore gene product levels to values of US controls. Expression of these gene products was not responsive to normoxia alone. All gene product expressions were highly correlated. The presence of CMS was predicted by significantly higher expression levels of all gene products in both locations. Adaptation to chronic hypoxia includes slower paced physiologic adjustments and, as we show here for the first time, changes in gene product expression occurring within hours. All gene products examined here are related to ANS function, or concerned with neural protection. The increased expression of these gene products is involved in survival and adaptation of the nervous system to chronic hypoxia in the Andes. Lessons from these cellular adaptations in Andeans could lead to novel therapeutic strategies for autonomic and neurodegenerative diseases at sea level where hypoxia may play an important role. They may also impact aging of the ANS.

Acknowledgments: Funded by: NMHEMC Research Foundation.

2.
CYTOPROTECTION IN CHRONIC HYPOXIA IN THE ANDES; LESSONS FOR NEUROLOGY AT SEA LEVEL?

Otto Appenzeller[1], Tamara Minko[2], Clifford Qualls[3], Vitaly Pozharov[2], Jorge Gamboa[4], Alfredo Gamboa[4], Refica I. Pakunlu[2]. NMHEMC Research Foundation[1], Rutgers the State Univ New Jersey, Piscataway NJ.[2], Univ New Mexico, Dept Mathematics and Statistics[3], Departamento de Ciencias Biológicas y Fisiologicas, Universidad Peruana Cayetano Heredia, Lima, Peru[4]. *Email:* ottoarun12@aol.com

Sojourners to altitude are neurologically disabled. We hypothesized that altitude natives who live in ambient hypoxia require protection of the nervous system. This protection might be afforded through changes in gene expression. Such natural adaptation to the environment might have lessons for neurology at sea level. Natives to high altitude are born, live and die hypoxic; they usually adapt to their environment. Chronic mountain sickness (CMS), an unexpected maladaptation to their native Andean environment, is characterized by severe, especially nocturnal, hypoxia, marked erythrocytosis, neurologic symptoms and accelerated aging. Normal cells deprived of oxygen turn on some 30 different genes to counter the deleterious effects of hypoxia. Little is known about changes in gene expression in chronically hypoxic humans. We studied 30 men. Twenty natives were examined in Cerro de Pasco (CP), 4338m., Peru, then transported to Lima, sea level, and examined 1 hour after arrival. They were rated using a hematocrit (HTC) of >65% and a clinical CMS-score (CMS-sc) of ≥12 as denoting CMS, to assess the severity of the disease, and determine normal adaptation. Using this scoring in CP we found that 15 had CMS and 5 were normal. We extracted RNA from white cells in CP and Lima. Ten US men, residing at 1500m., gave white cells for comparison. Gene expression was assessed by RT-PCR and related to HTC and CMS-sc. We focused on Heat shock protein-70 (Hsp-70) and-90 (Hsp-90) and nicotinamide mononucleotide adenylyl transferase 1 (Nmnat-1). Data were analyzed using ANOVA, t-tests, and correlation and regression methods. Differences were significant if $p < 0.05$. All Andeans had high gene product expression in CP and significant reduction of all gene products while normoxic in Lima ($p < 0.001$). In CMS patients, normal ambient oxy-

gen and arterial saturation at sea level, failed to restore gene product levels to values of US controls. Expression of Hsp-70, Hsp-90 and Nmnat-1 was not responsive to normoxia alone. Expression of these gene products was highly correlated. The presence of CMS was predicted by significantly higher expression levels of Hsp-70, HSP-90 and Nmnat-1. Low expression predicted normal saturation and normal sleep at altitude ($p = 0.005$). Adaptation to chronic hypoxia includes slower paced physiologic adjustments and, as we show here for the first time, changes in gene product expression which can occur within hours. The increased expression of the chaperone proteins Hsp-70 and-90 and the newly discovered neuroprotective function of Nmnat-1 are involved in survival and adaptation of the nervous system to chronic hypoxia in the Andes. Lessons from these cellular adaptations in Andeans could lead to novel therapeutic strategies for neurodegenerative diseases at sea level where hypoxia may play an important role and impact aging.

Acknowledgments: Funded by: NMHEMC Research Foundation

3.

NEUROBIOLOGY OF MIGRAINE IN THE ANDES: LESSONS FOR HEADACHE AT SEA LEVEL?

Otto Appenzeller[1], Tamara Minko[2], Vitaly Pozharov[2], Clifford Qualls[3], Jorge Gamboa[4], Alfredo Gamboa[4], Yang Wang[2]. NMHEMC Research Foundation[1], Rutgers, The State Univ New Jersey, Piscataway, NJ, USA[2], Univ New Mexico, Dept Mathematics and Statistics[3], Departamento de Ciencias Biológicas y Fisiologicas, Universidad Peruana Cayetano Heredia, Lima, Peru[4]. *Email:* ottoarun12@aol.com

We hypothesized that migraine in Andean natives is related to altered gene expression. Natives to high altitude are born, live and die hypoxic; they usually adapt to their environment. Chronic mountain sickness (CMS), an unexpected maladaptation to their Andean environment, is characterized by incessant migraine, severe nocturnal hypoxia, marked erythrocytosis, acral paresthesias and uncommon resistance to orthostatic stress. Normal cells deprived of oxygen turn on some 30 different genes to counter the deleterious effects of hypoxia. Little is known about changes in gene expression in chronically hypoxic humans. We studied 30 men. Twenty natives were examined in Cerro de Pasco (CP), 4338m., Peru, then transported to Lima, sea level, and examined 1 hour after arrival. They were rated using a hematocrit (HTC) of >65% and a clinical CMS-score (CMS-sc) $\alpha$of $\geq$12 as denoting CMS, to assess the severity of the disease, and determine normal adaptation. Using this scoring in CP we found that 15 had CMS and 5 were normal. We extracted RNA from white cells in CP and Lima. Ten US men, residing at 1500m., gave white cells for comparison. Gene expression was assessed by RT-PCR and related to CMS-scores. We focused on the Na+/K+ adenosine triphosphatase α1-subunit (ATP1A1sub). Differences were significant if $p < 0.05$. All Andeans had low gene product expression in CP and significant increase in gene product while normoxic in Lima ($p < 0.001$). CMS patients had significantly lower ATP1A1sub expression than Andean controls in CP ($p = 0.008$). Low ATP1A1sub expression in CP correlated with headache ($p = 0.002$), acral paresthesias ($p = 0.004$) and CMS-score ($p < 0.001$). Low ATP1A1sub expression in CP (<135% of internal standard) predicted low saturation and disturbed sleep ($p = 0.003$) and a high CMS-score (mean of 21.3). Higher expression of ATP1A1sub predicted a normal CMS-score (mean of 11.4), higher saturation and no sleep disturbances in CP. Andean sojourners at sea level do not have migraine and expression of ATPase increases, paralleling the disappearance of all CMS symptoms. Familial hemiplegic migraine type 2 is linked to missense mutations in the ATP1A2 gene encoding the Na+/K+ pump α2-subunit. This increases susceptibility to cortical spreading depression and migraine. The paresthesias in CP are related to low total ATPase content in sural nerves. Low ATPase, by lowering the axolemmal resting potential, leads to ectopic impulse generation. By analogy the migraine in CP is initiated by ectopic impulse generation in perivascular nerves of the trigemino-vascular system. Therapeutic manipulations of ATPase might offer another therapy for migraine at sea level.

Acknowledgments: Funded by: NMHEMC Research Foundation.

4.

INSPIRATORY HYPOXIA INCREASES METAL-CATALYZED FREE RADICAL GENERATION IN HUMAN CSF.

Damian M. Bailey[1], Robin Roukens[2], Just Genius[3], Fabien Meisel[3], Jane McEneny[4], Ian S. Young[4], Thorsten Steiner[3] and Peter Bärtsch[2]. University of Glamorgan, UK and Depts of Surgery and Anesthesiology, Colorado Center for Altitude Medicine and Physiology, Univ Colorado Denver Health Sciences Center, Denver, CO, USA[1], University of Heidelberg, Germany[2], University Hospital of Heidelberg, Germany[3] and Queen's University, N.Ireland[4]. *Email:* damian.bailey@btinternet.com

The cerebrovascular endothelium is highly susceptible to damaging redox reactions that may be implicated in the morphological changes observed in the human brain during hypoxia. Thus, the aim of the present study was to examine the effects of hypoxia on the local concentration of free radicals in human cerebrospinal fluid (CSF) and determine the initiating mechanism. Twenty two subjects were randomly exposed for 18h to normobaric hypoxia ($FIO_2 = 12.0\%$) and normoxia for the collection of CSF during lumbar puncture. Samples were mixed with alpha-phenyl-tert-butylnitrone (PBN) and adducts prepared for X-band electron paramagnetic resonance (EPR) spectroscopy at 295K. In-vitro changes in the EPR signal intensity of the ascorbate radical (A-) following chemical addition was incorporated for detection of transition metals. Samples were also assayed for lipid hydroperoxides (LH), neuron specific enolase (NSE) and S100β. Hypoxia increased the concentration of PBN-adducts [hypoxia: 1811 ± 419 vs. normoxia: 1344 ± 348 arbitrary units/square root mean line width in Gauss ($AU/^{-}G$), $P < 0.05$]. Nuclear hyperfine splittings indicated trapping of "bulky" lipid-derived alkoxyl (LO·-) and alkyl (L·-) radicals (aN = 13.6G, aH β = 1.9G and aN = 14.0G, aH β = 4.1G respectively). Virtually identical splittings were also obtained following in-vitro Fenton-generation of an authentic hydroxyl radical (OH·-) and auto-oxidation of cumene hydroperoxide. Hypoxia also increased A·-(2555 ± 472 vs. 1746 ± 412 $AU/^{-}G$, $P < 0.05$) whereas no changes were observed in LH, NSE or S100 β. In-vitro addition of diethylenetriaminepentacetic acid (500μM) and desferrioxamine mesylate (500μM) to separate aliquots of

hypoxic CSF decreased A·- to 56 ± 11 and 58 ± 10% of their original values respectively ($P < 0.05$ vs. untreated control), whereas no changes were observed following addition to normoxic CSF. Treatment with iron-loaded desferrioxamine mesylate prevented the decrease in A·-. These findings are the first to suggest that hypoxia increased the availability of "free" iron and to a lesser extent copper, independently of cerebrovascular tissue or neuronal damage. In conjunction with high ambient ascorbate, this may initiate the Fenton-driven reductive decomposition of LH and thus prove the source of "downstream" species trapped in the present study.

Acknowledgments: Professors Joan Abbott, David Begley and Joe McCord. In memory of Prof. "Jack" Reeves.

5.

ACETAZOLAMIDE 125MG BID IS AS EFFECTIVE AS 325MG BID IN THE PREVENTION OF ACUTE MOUNTAIN SICKNESS (THE PROPHYLACTIC ACETAZOLAMIDE DOSAGE COMPARISON FOR EFFICACY (PACE) TRIAL).

Buddha Basnyat , Jeffrey H Gertsch, E. William Jo[1]. Himalayan Rescue Association[1]. *Email:* rishibas@wlink.com.np

Context: The dosage of acetazolamide in the prevention of acute mountain sickness (AMS) is undetermined. A well publicized report suggested that 750mg daily was essential, but in many high altitude regions including the Himalayas only 250mg per day is used for prevention. Objective: To carry out a head to head comparison to test the hypothesis that 250mg daily of acetazolamide is as effective as 750mg daily of acetazolamide in the prevention of AMS. Design: Prospective, double-blind, randomized, placebo-controlled trial in Fall 2003. Setting: Participants were drawn from a diverse population of western trekkers at Namche Bazaar (3440 m) in Nepal on the Everest trekking route as they made their way to the study midpoint (4300m) and endpoint (4928m) where data was collected. Participants: 222 healthy trekkers were enrolled and 204 completed the trial (evaluated at midpoint, endpoint, or both), making this the largest acetazolamide dosage comparison trial in the prevention of AMS. Interventions: Participants were randomly assigned to receive 325mg BID of acetazolamide (82 participants), 125mg BID of acetazolamide (74 participants), or a visually matched placebo (66 participants) beginning at 3440 m (Namche Bazaar) for up to 8 days as they ascended. Main Outcome Measures: The Lake Louise AMS Score was used to evaluate AMS incidence, defined as a score of three or greater with the presence of headache and one other symptom. Secondary outcome measures included AMS severity (Lake Louise raw score of 5 or greater), headache incidence and severity, and blood oxygen content. All groups were equal at baseline, and the 29 noncompliant participants who broke protocol (took acetazolamide or missed 3 or more study doses) were not over-represented in any one group. Composite AMS incidence for 250mg daily was 24% and for 750mg daily was 21% ($p = 0.67$), with increased AMS in the placebo group (51%). Similarly, composite headache incidence was 23 % for the 250 mg group and 15 % for the 750 mg group ($p = 0.28$) with increased incidence in the placebo group (53%). Composite AMS severity and composite headache severity showed no difference for all the three groups. In addition there was no difference between the acetazolamide groups at endpoint in oxygen saturation (82.9% for 250mg daily and 82.8 % for 750mg daily) in contrast to the placebo group endpoint oxygen saturation which was significantly less at 80.7 %. Paresthesias were more common in the 750 mg group (91%) vs the 250 mg group (76%; $p = 0.002$). Finally there was no difference in the rate of ascent in the three groups. 250mg of acetazolamide daily was not significantly different in any outcome measure when compared with 750 mg of acetazolamide daily for the prevention of AMS.

6.

EFFECTS OF SHORT-TERM NORMOBARIC HYPOXIA ON ANAEROBIC AND AEROBIC PERFORMANCE IN HIGHLY TRAINED ATHLETES.

Fabien Basset[1]. School of Human Kinetics and Recreation, Memorial Univ Newfoundland, St. John[1]. *Email:* fbasset@mun.ca

More and more athletes are opting to purchase the altitude-mimicking devices instead of making costly, frequent trips to high elevations in search of high altitude effects. However, it remains controversial with respect to the hypoxia efficiency in improving aerobic and anaerobic performances. The present study aimed, therefore, to determine if short-term normobaric hypoxia could improve anaerobic or aerobic performance. Twelve (7 male and 5 female) highly trained athletes were randomly split into 2 groups and spent 8 h per night for 2 consecutive nights a week over a 3 week period under either short-term normobaric hypoxia (SNH; simulating 3636 m altitude, $O_2 = 13.35\%$) or in normobaric normoxia (NNC) in a single-blind study. Following a 3 week washout period, athletes were then exposed to the other condition. Athletes were tested for maximal oxygen consumption and time-to-exhaustion on an electro-magnetically braked cycle ergometre before and after each period. They were also tested for anaerobic performance (Wingate test) on a modified Monark cycle ergometre. Nine blood samples were taken throughout the experiment and vastus lateralis muscle biopsies were taken before and after each experimental and control period. Significant ($p < 0.05$) increases in red blood cell count, haematocrit, haemoglobin, platelet number and erythropoietin concentration were observed. Except for a modest decrease in phosphofructokinase activity following SNH, no changes were observed in muscle enzyme activities, buffer capacity, capillary density or morphology. No performance measures were changed following SNH or NNC. The main findings of this study are that, even though significant increases in blood parameters related to oxygen-transport were observed following SNH, no measurable increases in physical performance were observed. Little or no impact of SNH was also noted on various muscle phenotypes. Our investigation brings new information about the efficiency of SNH protocol in highly trained athletes since no benefit to actual performance seems to emerge from this type of protocol.

Acknowledgments: We gratefully acknowledge Gilles Bouchard, Philippe Corbeil, Guy Fournier, Marcel Kaszap, France Lafrenière, Nancy Parent and Veronic Tremblay for their technical support, and coaches and athletes of the CNEPH and the CNGB for their participation and devotion to this work. This project was funded by the Centre National MultiSports de Montreal.

7.

HYPOXIA IMPAIRS ENDOTHELIAL FUNCTION IN INDIVIDUALS SUSCEPTIBLE TO HIGH-ALTITUDE PULMONARY OEDEMA (HAPE): THE MISSING LINK IN THE PATHOGENESIS OF HAPE?

Marc Berger[1], Christiane Hesse[2], Christoph Dehnert[3], Heike Siedler[3], Petra Kleinbongard[4], Putrika Gharini[4], Hubert Bardenheuer[1], Malte Kelm[4], Peter Bärtsch[3], Walter Haefeli[2]. Dept Anesthesiology, Univ Heidelberg, Germany[1], Dept Internal Medicine VI, Pharmacology, Univ Heidelberg, Germany[2], Dept Internal Medicine VII, Sports Medicine, Univ Heidelberg, Germany[3], Dept Medicine, Univ Düsseldorf, Germany[4]. *Email:* marc_berger@med.uni-heidelberg.de

Pulmonary vasoconstriction with an excessive rise in pulmonary artery pressure (PAP) is a key factor in the development of high-altitude pulmonary oedema (HAPE). We hypothesized that susceptibility to HAPE is related to hypoxia-induced endothelial dysfunction with an impairment of the nitric oxide (NO) vasodilator pathway. We investigated 9 HAPE-susceptible (HAPE-S) and 9 HAPE-resistant (control) individuals during normoxia ($FiO_2 = 0.21$) and 4 hours of normobaric hypoxia ($FiO_2 = 0.12$, corresponding to a PO_2 at an altitude of 4500m above see level). Endothelium-dependent and -independent vasodilation to intra-arterial infusion of acetylcholine (ACh) and sodium nitroprusside (SNP) were measured by forearm venous occlusion plethysmography and compared with concurrent changes in pulmonary artery pressure (PAP, measured by Doppler-echocardiography), plasma nitrite (measured by flow injection analysis technique), and endothelin-1 (ET-1, measured by radioimmunoassay). PAP increased from 22 ± 1 to 33 ± 2 mmHg ($p < 0.001$) during hypoxia in controls and from 25 ± 1 to 50 ± 3 mmHg in HAPE-S ($p < 0.01$ vs. controls). Starting from similar responses during normoxia in both groups ACh-induced changes in forearm blood flow markedly decreased during hypoxia in HAPE-S ($p = 0.01$) but not in controls. Endothelial dysfunction during hypoxia inversely correlated with increases in PAP ($p < 0.05$). Plasma nitrite decreased during hypoxia in HAPE-S and correlated positively with ACh-induced vasodilation ($p = 0.02$), while plasma ET-1 increased about 2-fold in both groups. In HAPE-S individuals hypoxia acutely impairs the endothelium-dependent part of the NO-cGMP-pathway whereas NO effects at the vascular smooth muscle level are preserved. This suggests that impairment of the NO pathway could contribute to the enhanced hypoxic pulmonary vasoconstriction preceding pulmonary oedema and might explain why drugs increasing vascular cGMP may efficiently prevent the occurrence of HAPE in high altitude.

8.

AUTOREGULATORY AND SYMPATHETIC INFLUENCES ON CEREBRAL CIRCULATION. EFFECT OF FAST TILTING IN HYPOXIA.

Luciano Bernardi[1], Gaia Casucci[1], Ian JC MacCormick[2], Mattew Kinsey[3], Robert C Roach[3]. IRCCS S.Matteo and Univ Pavia[1], Univ Edinburgh, UK[2], Depts. Surgery and Anesthesiology, Colorado Center for Altitude Medicine and Physiology, Univ Colorado Denver Health Sciences Center, Denver, CO[3]. *Email:* lbern1ps@unipv.it

The importance of autoregulation (AR) in the control of cerebral blood flow (CBF) is unclear because of simultaneous sympathetic influences induced by most test maneuvers. A mechanically induced fast BP drop could unmask a pure AR response, if there is a measurable delay before the onset of sympathetic compensation. We tested the applicability of fast (1s) supine-to-upright tilting (TUP), by monitoring mean BP (Colin®) and mid-cerebral flow velocity (transcranial Doppler, TCD), in 23 healthy subjects (21.2 ± 0.4yr) acutely exposed (within 12h) to hypobaric hypoxia (5200m, barometric pressure 405mmHg, APEX-2) and after O_2 administration, conditions known to impair and partially restore AR, respectively. In each condition, 20s TUP was repeated 6 times, TCD and BP were averaged and normalized (−100% = maximal drop from TUP onset). Assuming that absence of any regulatory control on CBF would determine equal BP and TCD patterns from onset of TUP, we calculated the excess TCD with respect to BP: before BP nadir (taken as marker of onset of sympathetic compensation) as evidence of AR, and after BP nadir as evidence of AR+sympathetic response. 1s after TUP, BP dropped by 38.6 ± 5.0% (hypoxia) and by 37.0 ± 5.6% (O_2) (p:ns) of maximal drop during TUP. BP nadir (= −100% BP drop) was reached after 8.2 ± 0.8s (hypoxia) and 8.2 ± 0.8s (O_2) (p:ns). Before BP nadir, TCD exceeded BP by 29.3 ± 6.2% of maximal drop (hypoxia), and by 59.2 ± 13.5% (O_2) ($p < 0.01$ vs. ($p < 0.01$ vs hypoxia). After BP nadir, TCD exceeded BP by 53.3 ± 8.5% ((hypoxia), and by 81.0 ± 13.1% (O_2) ($p < 0.05$). Thus, AR is impaired in hypoxia; O_2 reduces both early (before BP nadir) and late TCD drop, suggesting improvement in both AR and sympathetic influences on CBF. TUP is a simple noninvasive and physiological challenge providing relative contribution of AR and sympathetic activity on CFB control.

Acknowledgments: APEX-2 organizers and volunteers.

9.

DOES EXCESSIVE INCREASE IN VENTILATION DURING ACCLIMATIZATION HELP IN REACHING THE SUMMIT OF MT. EVEREST AND K2 WITHOUT OXYGEN?

Luciano Bernardi[1], Annette Schneider[2], Luca Pomidori[3], Elisa Paolucci[3], Annalisa Cogo[3]. IRCCS S.Matteo, Univ Pavia, Italy[1], Univ Regensburg, Germany[2], Univ Ferrara, Italy[3]. *Email:* lbern1ps@unipv.it

We tested whether a higher ventilation and a higher ventilatory sensitivity to hypoxia were necessary prerequisites to climb Everest or K2 without oxygen. We studied 11 elite climbers (2004 Italian Expedition to Everest and K2) - at sea level (SL), after arriving at the Everest base camp (5200m, HA-1, after 6 days above 3500m), and after 9-day acclimatization at 5200m (HA-2). We measured resting oxygen saturation (SaO_2) minute ventilation (Vm), breathing rate (BR), hypoxic ventilatory response (HVR), vital capacity, maximal voluntary ventilation (MVV), ventilatory reserve (RESERVE) at $SaO_2 = 70\%$ (defined as $100 \times (MVV-Vm)/MVV$), and 2 indices of ventilatory efficiency (Vd/Vt and SaO_2/Vm). The summits of Everest or K2 were reached 29 and 61 days after HA-2, respectively. Five climbers (Group1) summited without oxygen support, the other 6 (Group2) did not summit (4 subjects) or used oxygen. At SL and HA-1, all variables were similar in the 2 groups. At HA-2, although Vm, BR and HVR increased in both groups vs SL, Group1 showed smaller increases in Vm (to 13.3 ± 0.8 vs 19.2 ± 0.6 L/min, $p < 0.001$), BR (to 10.7 ± 1.9 vs 20.2 ± 0.8 br/min, $p < 0.001$), HVR (to -2.14 ±

0.51 vs -5.09 ± 1.03 L/min/% SaO_2, $p < 0.05$), and so had greater RESERVE (66.6 ± 6.3 vs 26.7 ± 8.8%, $p < 0.01$) as compared to Group2. Ventilatory efficiency was higher in Group1 (Vd/Vt : 0.09 ± 0.01 vs 0.16 ± 0.02, $p < 0.05$, SaO_2/Vm: 6.66 ± 0.39 vs 4.64 ± 0.13 %/L/min, $p < 0.001$). Thus, despite the undoubted role of environmental, technical and psychologic factors, successful climbers had smaller increases in their responses to hypoxia during acclimatization, but consequently had greater available reserve for the summit. Ventilatory efficiency may be important in preventing excessive increases in ventilation, thus allowing a sustainable ventilation even in the extreme hypoxia at the summit.

Acknowledgments: Funded By: IMONT, Ev-K2-CNR

10.

MYOCARDIAL CAPILLARY LEAKAGE AS POTENTIAL MECHANISMS OF LEFT VENTRICULAR DIASTOLIC DYSFUNCTION AT HIGH ALTITUDE.

Alain Bernheim[1], Stephanie Kiencke[1], Marco Maggiorini[2], Manuel Fischler[2], Heimo Mairbäurl[3], Hans-Peter Brunner-La Rocca[1]. Cardiology, Univ Hospital Basel, Switzerland[1], Intensive Care Unit, Univ Hospital Zurich, Switzerland[2], Medical Clinic VII, Sports Medicine, Univ Heidelberg, Germany[3]. *Email:* klinmax@usz.unizh.ch

Left ventricular (LV) diastolic dysfunction was described at high altitude. Interventricular interaction due to pulmonary hypertension was made responsible for this, but recent data provided evidence for an additional mechanism. Myocardial capillary leakage due to hypoxia may be one potential mechanism. We, therefore, studied the effect of two drugs acting by different mechanisms on LV diastolic function at high altitude. Of 36 healthy subjects, 27 had a history of high altitude pulmonary edema (HAPE), the latter being randomly assigned to placebo (n = 9) and to 2 active therapies (tadalafil 10mg bid n = 8, dexamethasone 8mg bid n = 10) starting on the day before ascent. Subjects ascended in <24 hours to 4559m. Echocardiography was performed after an overnight stay and at low altitude (490m) <1 month prior to ascent. LV diastolic function was assessed by transmitral inflow pattern and pulmonary venous flow, pulmonary pressure by transmitral pressure gradient (dPTR). LV Diastolic function was normal at low altitude in all subjects (E/A 1.6 ± 0.4, atrial reversal 23 ± 5 cm/s). At high altitude, dPTR increased from 19 ± 5 to 38 ± 12mmHg ($p < 0.001$). In control subjects, E/A-ratio decreased by 13 ± 20%. The decrease tended to be larger in placebo treated HAPE susceptible subjects (23 ± 15%) and in those treated with tadalafil (23 ± 14%). In contrast, E/A-ratio did hardly change in dexamethasone treated HAPE susceptibles (decrease 4 ± 15%, $p = 0.01$ versus other subjects). The increase in atrial reversal tended to be smaller in dexamethasone treated subjects (12 ± 14 vs 24 ± 27%), but this difference was not statistically significant ($p = 0.13$). Changes in dPTR from low to high altitude did not correlate with changes in parameters of diastolic function of the LV. Thus, LV diastolic dysfunction does not seem to be the primary cause by interaction of both ventricles. In addition, may be significantly improved by treatment with dexamethasone, suggesting that myocardial capillary leakage may contribute to LV diastolic dysfunction.

Acknowledgments: Hartmann-Müller Foundation, Zurich; Crivelli Foundation Lugano.

11.

SILDENAFIL, L-ARGININE, NIFEDIPINE AND ACETAZOLIMIDE: COMPARATIVE EFFECTS ON PULMONARY ARTERY PRESSURE AT HIGH ALTITUDE.

Bryce Brown[1], Doug Maguire[1], Renelle Myers[1], Joyce Edmonds[1]. Univ Manitoba, Winnipeg, Manitoba, Canada[1]. *Email:* brycebrown@shaw.ca

High altitude pulmonary edema (HAPE) is characterized by hypoxic vasoconstriction and subsequent increase in pulmonary artery pressure (PAP). Nifedipine has been the vasodilator most accepted for use in HAPE. Nitric oxide (NO) is known to relax vascular smooth muscle and dilate pulmonary arteries; endogenous NO pathways can be manipulated with sildenafil and L-arginine. Acetazolamide has been used for treatment and prevention of acute mountain sickness (AMS) symptoms but has also been shown to be a pulmonary vasodilator in animal studies. This is a prospective, blinded, head to head trial of the acute effects of sildenafil, L-arginine, nifedipine and acetazolamide on PAP in acclimatized human volunteers. 18 healthy volunteers were studied at Mt. Everest basecamp (Nepal). None had a history of HAPE. All were acclimatized to 5245m for a minimum of 5 days. Echocardiographic Doppler measurements of pulmonary artery acceleration time were obtained under control and study conditions. Sildenafil 50mg, L-arginine 10g, nifedipine 20mg, and acetazolamide 125mg q12hx2 were given 60-90 minutes prior to echo measurement in 16, 15, 8 and 9 subjects respectively. 5 subjects were studied under all four drug conditions with an appropriate washout period; 5 subjects completed 3 drugs. Average systolic PAP in control, sildenafil, L-arginine, nifedipine and acetazolamide groups was 43, 34, 39, 43, 37.6 mmHg respectively. PVR decreased from baseline 25%, 13.5%, 20%, and 15.8% for sildenafil, L-arginine, nifedipine, and acetazolamide respectively. 1. Control PAP measurements correlated with previous altitude studies. 2. Sildenafil was the most effective at lowering PAP. 3. Nifedipine deceased PVR and increased cardiac output without lowering PAP. 4. Acetazolamide has modest pulmonary vasodilator properties in humans. 5. L-arginine was an inconsistent pulmonary vasodilator.

Acknowledgments: Kind cooperation of the Himalayan Rescue Association and Dr. Luanne Freer.

12.

LIVING HIGH – TRAINING LOW: EFFECTS ON ACCLIMATIZATION, ERYTHROPOIESIS AND AEROBIC PERFORMANCE IN ELITE MIDDLE DISTANCE RUNNERS.

Julien Vincent Brugniaux[1], Laurent Schmitt[2], Paul Robach[3], Jean-Pierre Fouillot[1], Gérard Nicolet[2], Françoise Lasne[4], Stéphane Moutereau[5], Niels V Olsen[6], Jean Paul Richalet[1]. EA2363, ARPE, Université Paris 13, Bobigny, France[1], CNSN, ID Jacobeys, Prémanon, France[2], ENSA, Chamonix, France[3], Laboratoire National de Dépistage du Dopage, Chatenay-Malabry, France[4], Laboratoire de biochimie, Hìpital Henri-Mondor, Créteil, France[5], Dept Pharmacology, The Panum Institute, Univ Copenhagen, Copenhagen, Denmark[6]. *Email:* j.brugniaux@smbh.univ-paris13.fr

This study was designed to verify 1) whether Living High – Training Low (LHTL) is well tolerated and induce ventilatory acclimatization, 2) whether LHTL stimulates erythropoiesis and/or improve aerobic performance, 3) if

these effects persist 15 days after the end of the training session. Eleven runners were divided into two groups, control group (CON, n = 6, VO_2max = 63.3 ml/min/kg) and hypoxic group (HYP, n = 5, VO_2max = 62.9 ml/min/kg). Athletes performed a 18-day training session by sleeping either at 1,200m or in hypoxic rooms (6 nights at 2,500m and 12 nights at 3,000m). The measurements were performed at 1,200m before (PRE), after 2 nights at 3,000m (H3000), 1 day (POST1) and 15 days (POST2) after the end of the training. Training load was recorded during the whole study. HYP developed ventilatory acclimatization at POST1. Hemoglobin, hematocrit and serum erythopoïtein were not modified along with the session. Soluble transferring receptors were increased at H3000, POST1 in both groups but remained higher at POST2 only for HYP. Ferritin was decreased at H3000 for HYP and at POST1 for CON. Reticulocyte were maintained during the session but decreased at POST2 in both groups. Red cell volume seemed to increase at POST1 (+9.2%) for HYP. VO_2max for HYP was significantly increased at POST1 (+9.6%) and tended to remain higher at POST2 (+5.2%, P = 0.08). Heart rate during submaximal test (10-min run at 19.5 km/h) progressively decreased with training to reach significance at POST2 (-4.4%) for HYP. Eighteen days of LHTL at a maximal altitude of 3,000m are well tolerated by elite endurance athletes. LHTL can improve aerobic performance over the first 15 days after return to normoxia, but this increase seems to be partly related to the changes in blood volume, suggesting that other process may be enhance during hypoxia.

Acknowledgments: This study was supported by grants from the International Olympic Committee and the French Ministry of Sports.

13.

THE EFFECT OF EXERCISE INDUCED HYPOXEMIA ON THE MAINTENANCE OF HEMOGLOBIN SATURATION DURING EXERCISE AT 3000M OF SIMULATED ALTITUDE.

Angie Bryans[1], David J. Smith[1], Jon C. Kolb[1]. Univ Calgary, Human Performance Laboratory, Canada[1]. *Email:* kolb@ucalgary.ca

The phenomenon of exercise induced hypoxemia (EIH) may affect up to 50% of moderately to highly trained individuals and potentially contribute to limitations in maximal performance. The purpose of this study was to explore whether EIH attenuates arterial oxygen saturation (SpO_2) and maximal aerobic capacity (VO_2max) differently from individuals not exhibiting EIH under the conditions of normoxia and hypoxia. Subjects (nine males, two females) were divided into an EIH group (n = 6, SpO_2 <= 90%, mean VO_2max = 54.2 ml.kg-1.min^{-1}) or non-EIH group (n = 5, SpO_2 > 90%, mean VO_2max = 53.6 ml.kg-1.min^{-1}) based on preliminary VO_2max in normoxia (1024m, FIO_2 = 20.9%). Subsequently, all subjects completed a 20 minute normoxic constant load test at the second ventilatory threshold (VT2) determined from VO_2max. These two tests were then repeated at a simulated altitude of 3000 m (FIO_2 = 16%) where VT2 was determined from the simulated altitude VO_2max test. No differences were revealed between the two groups in normoxic VO_2max, VEmax or SpO_2. However, normoxic VO_2max elicited an SpO_2 which significantly correlated (p < 0.05) with the decrease in VO_2max (r = .61) and VEmax (r = .62) during hypoxia. For EIH subjects, constant load exercise at VT2, mean VO_2 and HR decreased 21% and 3.5% respectively, while VO_2 decreased only 8.9% and HR increased 3.1% in non-EIH. Furthermore, although the EIH mean VE decreased 8.3% from normoxic to hypoxic exercise conditions, mean VE increased 28.1% in non-EIH. Correlation analysis revealed that the mean VE accounted for 46.6% of the variation in the mean hypoxic SpO_2 (p = 0.021). In conclusion, the significant difference in the ventilatory response to constant load hypoxic exercise in the EIH group, may have contributed to an inability to maintain adequate exercising SpO_2 and VO_2.

Acknowledgments: This research was supported by the Canadian Sport Centre-Calgary and Calgary Olympic Development Association.

14.

PULMONARY FUNCTION AND NOCTURNAL VENTILATION IN MOUNTAINEERS DEVELOPING HAPE.

Andreas L Christ[1], Christian F Clarenbach[1], Oliver Senn[1], Manuel Fischler[2], Heimo Mairbauerl[3], Marco Maggiorini[2], Konrad E Bloch[1]. Pulmonary Divison, Univ Hospital Zurich, Switzerland[1], Medical Intensive Care Unit, Univ Hospital Zurich, Switzerland[2], Sports Medicine, Univ Heidelberg, Germany[3]. *Email:* christian.clarenbach@usz.ch

To investigate changes in lung function, breathing patterns, and oxygenation in montaineers developing HAPE. We studied 18 mountaineers in Zurich (490m) and after ascent to Capanna Margherita (4559m), within <24 hours. Eight mountaineers developed HAPE, 10 remained well (controls). Lung function, nocturnal breathing pattern by calibrated inductive plethysmography, and oxygen saturation were measured in Zurich (490m) and at 4559m over 3 consecutive days or until HAPE was clinically and radiographically diagnosed. HAPE developed in 8 subjects within the 3 days at 4559m. Their FVC progressively decreased from a mean ± SD of 108 ± 17 %pred at 490m to 87 ± 15 %pred at 4559m (P < 0.05, last measurement before overt HAPE). FEV1 fell in proportion to FVC. Closing volume increased from 0.33 ± 0.06 to 0.51 ± 0.05 L (PAcknowledgments: Polygraphic equipment was provided by VivoMetrics, Ventura, CA, USA. Lung function equipment was provided by Pilger AG, Zofingen, Switzerland.

15.

DEXAMETHASONE AND TADALAFIL PREVENT HAPE AND SUBCLINICAL ALTERATIONS IN LUNG FUNCTION AND NOCTURNAL OXYGENATION ASSOCIATED WITH PULMONARY INTERSTITIAL FLUID ACCUMULATION.

Christian F Clarenbach[1], Andreas L Christ[1], Oliver Senn[1], Manuel Fischler[2], Heimo Mairbaeurl[3], Marco Maggiorini[2], Konrad E Bloch[1]. Pulmonary Division, Univ Hospital Zurich, Swizterland[1], Medical Intensive Care Unit, Univ Hospital Zurich, Switzerland[2], Sports Medicine, Univ Heidelberg, Germany[3]. *Email:* christian.clarenbach@usz.ch

To evaluate effects of dexamathasone and tadalafil on pulmonary function and nocturnal breathing in HAPE

susceptible subjects after rapid ascent to high altitude. HAPE susceptible subjects were studied in Zurich (490m), and over up to 3 days after ascent to Capanna Margherita (4559m) within <24 hours. They were radomized to receive either daily dexamethasone 2 × 8 mg (n = 10), tadalafil 2 × 10mg (n = 10), or placebo (n = 9), starting in Zurich. Lung function, nocturnal breathing pattern by calibrated inductive plethysmography, and oxygen saturation were measured in Zurich (490m), and at 4559m over 3 consecutive days or until HAPE was diagnosed clinically and radiographically. Prevalence of HAPE was 7/9 (placebo), 1/10 (tadalafil), and 0/10 (dexamethasone). Dexamethasone and tadalafil partially prevented the progessive decreases in FVC, FEV1, and diffusing capacity observed at 4559m in subjects receiving placebo. Closing volume increased in subjects receiving placebo and tadalafil but not in those on dexamethasone. Prevalence of nocturnal periodic breathing in the night at 4559m before HAPE occurred, or in the second night in subjects without HAPE, respectively, was lowest with dexamethasone (21 ± 17 cycles/h), intermediate with tadalafil (86 ± 47 cycles/h) and highest with placebo (96 ± 39 cycles/h; $P < 0.05$ placebo vs. both active drugs). Mean nocturnal oxygen saturation was higher with dexamethasone and tadalafil than with placebo (75 ± 5 and 70 ± 5 vs. 63 ± 10%, $P < 0.05$, all comparisons). Mean nocturnal heart rate was 66 ± 11, 89 ± 14, and 88 ± 13 beats/min with dexamethasone, tadalafil, and placebo, respectively ($P < 0.05$ placebo vs. both active drugs). Dexamethasone and tadalafil both reduced the occurrence of HAPE, and the changes in lung function associated with subclinical interstitial fluid accumulation observed before development of overt HAPE. Dexamethasone was more effective in preventing nocturnal periodic breathing than tadalafil and placebo. The relatively low heart rate in subjects on dexamethasone may reflect a less pronounced sympathetic stimulaton at high altitude.

Acknowledgments: Polygraphic equipment was provided by VivoMetrics, Ventura, Ca, USA. Lung function equipment was provided by Pilger AG, Zofingen, Switzerland.

16.

EXTRAVASCULAR LUNG FLUID ACCUMULATION AT HIGH ALTITUDE IS A TRANSIENT EVENT IN ÉLITE CLIMBERS AND DOES NOT PRECLUDE A SUCCESSFUL CLIMB.

Annalisa Cogo[1], Elisa Paolucci[1], Luca Pomidori[1], Annette Schneider[2], Luciano Bernardi[3]. Dept of Clinical&Experimental Medicine, Univ Ferrara, Italy[1], Dept. of Anesthesiology Univ Regensburg, Germany[2], Dept Internal Medicine and IRCCS Ospedale S.Matteo, Pavia, Italy[3]. *Email:* annalisa.cogo@unife.it

Extravascular lung fluid accumulation (demonstrated by increased closing volume) has been reported in recreational climbers after few hours at 4559m.Some questions remained unanswered: is this a transient event? is this event present also in elite climbers? To solve these questions we studied 9 élite climbers (M,age 32–52) during the acclimatization period of the italian expedition to Mt Everest North. Studies were performed at sea level (SL), at Base Camp(5200m, reached after 6 days >3500m)1°day (BC1) and 9°day (BC9).Between BC1 and BC2 all subjects climbed up to 7000m; after the study period all subjects climbed >7000m and 3 reached the summit without oxygen. We studied maximal(M) and partial(P) flow volume curves to detect the effect of deep inspiration, assuming that a reduction of flow rates at the last part of the volume can be interpreted as small airways narrowing if no difference is found between M and P, and urinary microalbumin(overnight collection after a rest day) as an indirect index of endothelial permeability. Expressed as mean(SE) at SL, BC1, BC2: FVC as % predicted: 111.7(1.8), 72.5(3.3)**, 107.1(1.2); MEF25% as %pred: 96(11), 66.4(5.1)**, 83(4.8); M/P40 (difference between M and P curve at partial flow 40% of FVC): 1.02(.06), 1.09 (.08), 0.79(.06); urin. microalb mcg/min: 3.7(.7), 8.8(1)**, 5(1.4). FEV1/FVC ratio was always > 70. At BC1 compared to SL urinary microalbumin is significantly increased, FVC significantly decreased and the partial flows significantly decreased with no difference between M and P curves. After 9 days all values returned similar to SL. We conclude that the results obtained at BC1 suggest small airways compression due to extravascular lung fluid accumulation but this is a transient event not precluding a successful climb.

Acknowledgments: IMONT; EV-K2-CNR

17.

NEUROCOGNITIVE FUNCTION IN MODERATE-ALTITUDE RESIDENTS (2,200 M) EXPOSED FOR 3 DAYS TO 4,300.

M. Allen Cymerman[1], Charles Fulco[1], Stephen Muza[1], Michael Zupan[2], Kenneth Kambis[1], Leonard Elliott[1], Jesse Udy[1], Paul Rock[1]. U.S. Army Research Inst Environmental Medicine[1], U.S. Air Force Academy[2]. *Email:* allen.cymerman@us.army.mil

Several studies have shown 10–20% decrements in specific neurocognitive performance during acute exposures of lowlanders to high altitude. However, no studies have investigated whether these effects were demonstrable in moderate-altitude acclimatized residents exposed for several days to high altitude. Sixteen subjects (30.4 ± 0.7 yr, Mean ± SE, 9 men and 7 women), who resided at ~2,200 m (U.S. Air Force Academy, AFA, PB = 594 torr) for at least 3 months, were given a battery of 8 validated neurocognitive tests (Automated Neuropsychological Assessment Metrics, ANAM) on 3–4 occasions designed to measure concentration, working memory, spatial processing, cognitive processing efficiency, and memory recall. The last test at AFA (baseline) was given on the morning just prior to their vehicular ascent to 4,300 m (Pikes Peak summit, PB = 458 torr) where they resided for the next 3 days. Baseline ANAM values were comparable to literature values for normal, healthy lowlanders. Subjects were then tested thrice a day for a total 10 sessions with throughput (correct responses/min) being the analyzed test variable. No training effects were evident at AFA on the following battery components: 4-choice reaction time, code substitution (learning, immediate, delayed), running memory, logical symbolic reasoning, match-to-sample, and simple alertness. No decrements in performance on any of the tests were observed during high-altitude exposure. In fact, compared to the baseline, improvements in throughput were obtained over the 3-day exposure in the alertness (7%), running memory (22%), and logical reasoning tests (17%) with no changes in code substitution (learning, immediate, and delayed) and match-to-sample. The latter tests which measure the ability for sustained concentration, visual search, learning, and recall may not have shown improvement because subjects were

either already at optimal performance levels or because hypoxia may have impaired learning on these specific tests. Moderate-altitude acclimatized residents do not demonstrate neurocognitive function decrements normally seen in lowlanders exposed rapidly to 4,300 m altitude.

18.
UPPER BODY AND RESPIRATORY MUSCLE TRAINING EFFECTS ON ALTITUDE EXERCISE ENDURANCE.
Michael Dausse[1], Thomas Fahey[1], George Swanson[1]. California State Univ[1]. *Email:* dswanson@csuchico.edu

Holm, Sattler and Fregosi, (BMC Physiol. 4(1):9, 2004) demonstrated that endurance training of respiratory muscles improves sea level cycling endurance performance. The present study extended the concept of respiratory muscle training to the improvement of altitude exercise endurance. We investigated the effects of upper body and respiratory muscle training on endurance at 80% of maximum capacity—at a simulated altitude of 7000 ft (2143 m). Eight physically fit subjects (19–34 yr; male 7, female 1) completed the study in which they acted as their own controls. Subjects, performed a progressive maximum power output test on a cycle ergometer to determine the 80% of maximum work rate exercise intensity. Applying this work rate as a step function, subjects reached exhaustion in about 20 minutes in the altitude chamber. These step tests were performed at baseline, post three weeks control period and post three weeks of upper body and respiratory muscle training treatment period. During this treatment period, subjects used a pulmonary trainer (Swanson. In Advances in Modeling and Control of Ventilation, pp. 231-136, 1998) for 30 minutes per day, 5 d per wk, for 3 wk. to achieve respiratory muscle endurance training. The subjects also performed a 3 wk weight training program to strength train assessory breathing muscles. The results in the 8 subjects indicate similar heart rate (186 ± 5, 181 ± 6, 184 ± 4 bpm;mean $\pm$ SD) and similar O_2 saturation (91.5 ± 1.9, 91.6 ± 2.4, 91.0 ± 1.7 %) for the three step tests (baseline, control, treatment). In contrast, endurance time increased from 18.3 ± 7.2 min (baseline) and 17.1 ± 8.4 (control) to 25.1 ± 12.4 (treatment) ($p < 0.05$). Five of the eight subjects had increased cycling endurance time by more than 5 minutes. These results suggest that upper body and respiratory muscle training improves endurance performance at altitude.

19.
EFFECT OF ALTITUDE ON LACTATE REMOVAL RATES FOLLOWING HIGH-INTENSITY EXERCISE.
John Davis[1], Katie Hawkins[1], Maurie Luetkemeier[1]. Alma College[1]. *Email:* davisj@alma.edu

The purpose of this study was to determine the effect of moderate altitude exposure on the washout of blood lactate following high-intensity exercise. Six healthy, active subjects (mean age = 20.1 ± 3.4 yrs) were asked to complete a graded-exercise test to exhaustion on a cycle ergometer at sea level (SL1), upon acute exposure to 3400 m (ALT1), two weeks following acclimatization at 3400 m (ALT2), and upon return to sea level (SL2). Workloads were increased every two minutes following a two-minute warmup. Venous blood lactate measurements were taken via an indwelling catheter without stasis every two minutes during, and every two minutes after the exercise was completed until lactate levels were decreased to half of their maximum values (T 1/2). T1/2 significantly increased during ALT1 (18.2 ± 6.0 min) relative to SL1 (9.0 ± 2.2 min). T1/2 decreased during ALT2 (12.4 ± 6.1 min) and SL2 (13.6 ± 3.8 min) but did not return to SL1 levels. These data suggest that altitude exposure has a direct effect on lactate washout following high-intensity exercise. The observed increase in lactate removal times upon acute exposure to altitude might be due to the hypoxic vasoconstriction that occurs at altitude. The increased lactate removal times after acute altitude exposure are significant and thus might have an impact on exercise performance at altitude. Washout times were lower after acclimatization to altitude. However, they were still elevated relative to the initial sea level values.

20.
RESPIRATORY MUSCLE STRENGTH MAY EXPLAIN HYPOXIA-INDUCED DECREASE IN VITAL CAPACITY.
Gael Deboeck[1], Jean-Jacques Moraine[1], Robert Naeije[1]. Free Univ Brussels, Belgium[1]. *Email:* rnaeije@ulb.ac.be

High altitude exposure has consistently been reported to decrease forced vital capacity (FVC), but the mechanisms accounting for this observation remain incompletely understood. We investigated the possible contribution of a hypoxia-related decrease in respiratory muscle strength Maximal inspiratory and expiratory pressures (MIP and MEP), sniff nasal inspiratory pressure (SNIP), FVC, peak expiratory flow rate (PEF) and forced expiratory volume in 1 second (FEV1) were measured in 15 healthy subjects before and after 1, 6 and 12 hours of exposure to an equivalent altitude of 4267 m in a hypobaric chamber. Hypoxia was associated with a progressive decrease in FVC (L) (5.59 ± 0.24 to 5.24 ± 0.26, mean $\pm$ SEM, $P < 0.001$), MIP (cm H2O) (130 ± 10 to 114 ± 8, $P < 0.01$), MEP (cm H2O) (201 ± 12 to 171 ± 11, $P < 0.001$) and SNIP (cm H2O) (125 ± 7 to 98 ± 7, $P < 0.001$). MIP, MEP and SNIP were strongly correlated to FVC (r ranging from 0.77 to 0.92). FEV1 didn't change and PEF increased less than predicted by the reduction in air density (11 to 20 % of sea level value compared to 32% predicted). Decreased FVC at high altitude has been previously explained by an increase in extravascular lung water. A decrease in respiratory muscle strength seemed less plausible because the sigmoid shape of the respiratory system pressure-volume curve implicating major decrease in pressure for small decreases in volume in normal subjects. However, tight correlations between indices of respiratory muscle strength and FVC in the present study may nevertheless suggest causality. We conclude that a decrease in respiratory muscle strength may contribute to the decrease in FVC observed at high altitude.

21.
INHOMOGENEOUS PULMONARY PERFUSION IN SUBJECTS SUSCEPTIBLE TO HIGH ALTITUDE PULMONARY EDEMA.
Christoph Dehnert[1], Christian Fink[2], Sebastian Ley[2], Frank Risse[2], Hans-Ulrich Kauczor[2], Peter Bärtsch[1]. Internal Medicine VII, Sports Medicine, Univ Hospital Heidelberg, Ger-

many[1], Dept Radiology (E010), German Cancer Research Center, Heidelberg, Germany[2]. *Email:* christoph.dehnert@med.uni-heidelberg.de

Inhomogeneous hypoxic pulmonary vasoconstriction (HPV) causing regional overperfusion and high capillary pressure is postulated for explaining how high pulmonary artery pressure (PAP) can lead to high altitude pulmonary edema (HAPE). Recently MRI has been proposed for the assessment of regional pulmonary perfusion. Therefore, we investigated pulmonary perfusion by contrast-enhanced pulmonary perfusion MRI during normoxia and after 2 hours of hypoxic exposure ($FIO_2 = 0.12$) in 9 in subjects susceptible to HAPE (HAPE-S) and 9 controls resistant to HAPE. As a measure for the perfusion heterogeneity the relative dispersion from the signal intensities of pulmonary perfusion MRI was determined. Relative dispersion of pulmonary blood flow showed significantly higher variation coefficients in HAPE-S already in normoxia (0.64 ± 0.10 vs. 0.58 ± 0.05; $p = 0.03$) which increased in both groups after 2 hours of hypoxia (0.78 ± 0.10 vs. 0.68 ± 0.07; $p = 0.002$). The increase was slightly but not statistically significant higher in HAPE-S (0.14 ± 0.09 vs. 0.11 ± 0.09; $p = 0.27$). Additionally PAP was determined by Doppler echocardiography. During hypoxia PAP increased from 22 ± 3 to 53 ± 9 mmHg in HAPE-S, respectively from 24 ± 4 to 34 ± 6 mmHg in controls ($p < 0.001$). This study shows a greater heterogeneity of pulmonary perfusion in HAPE-S which is already present in normoxia. This may not be of clinical relevance as long as PAP is normal but can account for regional overperfusion if PAP is increased. Thus our findings are compatible with more inhomogeneous pulmonary perfusion in HAPE-S versus controls resulting in regional overperfusion in hypoxia.

Acknowledgments: The study was supported by a research grant of Amersham Buchler.

22.

THE EFFECT OF ACUTE HYPOXIA ON COAGULATION IN HEALTHY SUBJECTS.

John Dick[1], Gillian Ross[2], Stuart McCorkell[1], Monty Mythen[1]. Centre for Aviation Space and Extreme Environment Medicine, Univ College London[1], Royal Free and Univ College Medical School[2]. *Email:* johndick95@doctors.org.uk

The rate of venous thrombosis associated with commercial air travel is between 1% and 10% in recent studies (1, 3). The relatively hypoxic and hypobaric conditions that exist at cruising altitude may have a causal role. One study (1) involving 20 healthy volunteers was able to demonstrate activation of coagulation in simulated cabin conditions (a hypoxic and hypobaric pressure chamber). The purpose of our study was to investigate whether hypoxia alone (in normobaric conditions) would produce changes in coagulation in healthy volunteers. Following ethical approval and informed consent 6 volunteers agreed to partake in a crossover trial in which coagulation markers were assessed in either normoxic (normobaric) conditions or in hypoxic (normobaric) conditions that were designed to simulate cruising altitude. The subjects acted as their own controls. Hypoxic conditions were created by use of medical grade 16% oxygen (84% nitrogen) that was delivered via a reservoir system and one-way tubing to a tight-fitting facemask with separate expiratory valves. The trial lasted 4 hours and blood was sampled for assays of prothrombin 1 and 2 fragments, thrombin-antithrombin complex and d-dimers at 0 and 180 minutes. Results were compared via paired t-test of means of differences at 0 and 180 minutes and these demonstrated no significant change in the level of anticoagulation between groups. We conclude that either hypoxia alone is not a significant risk factor for air travel related thrombosis or that a larger study may be required to demonstrate a difference.

Acknowledgments: References; 1. Hughes et al. Frequency of venous thromboembolism in low to moderate risk long distance air travellers; the New Zealand Air Traveller's Thrombosis study. The Lancet 2003: 362; 2039-2044. 2. Bendz et al. Association between acute hypobaric hypoxia and activation of coagulation in human beings. The Lancet 2000: 356; 1657–1658. 3. Scurr et al. Frequency and prevention of symptomless deep-vein thrombosis in long-haul flights: a randomised trial. The Lancet 2000: 357; 1485–1489.

23.

THE FORGOTTEN CIRCUIT-THE USE OF CLOSED OXYGEN CIRCUITS ON MOUNT EVEREST.

John Dick[1], Jeremy Windsor[1]. Centre for Aviation Space and Extreme Environment Medicine, Univ College London[1]. *Email:* johndick95@doctors.org.uk

Three days before the first ascent of Mount Everest two British climbers got to within 300 vertical feet of the summit using closed oxygen circuits, but had to turn round due to technical problems with their oxygen circuits. The successful party used open oxygen circuits, and this remains the circuit type used during extreme altitude climbing to the present day. The objective of this report is to outline the development of this closed oxygen circuit and to analyse the reasons for circuit failure. As early as 1916 Dr Alexander Kellas accurately calculated the barometric pressure upon the summit of Everest, and explained "proper oxygenation of the blood is the main difficulty at altitude". Oxygen was taken on Everest expeditions from 1921 onwards, but by 1952 there was still debate as to whether it really helped climbers as 28,000 feet had been reached on three occasions without oxygen. A series of experiments by the Physiologist Griffith Pugh in 1952 demonstrated the significant benefit of oxygen use during exercise and rest at altitude. Roxburgh had outlined the benefits of using a closed oxygen circuit to the Royal Geographical Society in 1947; less wastage and lower flows of oxygen (significant weight advantage) and prevention of heat loss by the climber (reduced energy expenditure). The development of closed circuits dates back to Ingen-Housz in 1782 and includes the work of Theodore Schwann, Henry Fleuss, Dennis Jackson and Ralph Waters. Drawing on this and previous climbing circuit designs Dr Robert Bourdillon and his son Tom designed, produced and tested the closed circuit in less than 6 months. On summit day, with temperatures of –20°C one of the circuits started to fail shortly after a change of soda lime canister; the possible causes are analysed and we postulate that hypercapnia was the principal mechanism.

Acknowledgments: The Alpine Club The Royal Geographical Society

24.
DEXAMETHASONE INHIBITS SYMPATHETIC ACTIVITY IN HAPE-SUSCEPTIBLE MOUNAINEERS AT 4559M.
Lorenz Dorschner[1], Johann Debrunner[1], Manuel Fischler[1], Christian F. Clarenbach[2], Andreas Christ[2], Konrad E. Bloch[2], Heimo Mairbäurl[3], Marco Maggiorini[1]. Intensive Care Unit, Univ Hospital Zurich, Switzerland[1], Pulmonary Division, Univ Hospital Zurich, Switzerland[2], Medical Clinic VII, Sports Medicine, Univ Heidelberg, Germany[3]. *Email:* klinmax@usz.unizh.ch

High altitude pulmonary edema (HAPE) is associated with increased sympathetic activity. Therefore we investigated the effect of HAPE-prophylaxis with glucocorticoids and phosphodiesterase-5 inhibitors on sympathicovagal balance in HAPE-susceptible mountaineers. After low altitude-examination (LA, 490m), 29 HAPE-susceptible subjects were randomized to receive prophylaxis with dexamethasone ($n = 10$), tadalafil ($n = 10$) or placebo ($n = 9$) at high altitude (HA, 4559m). We measured autonomic modulation by calculating the ratio of the low and high frequency-components (LF/HF) in the R-R-interval, systolic and diastolic blood pressure (SBP, DBP) until occurrence of HAPE and/or severe acute mountain sickness (AMS) or on HA-day 3. HAPE developed in 7 subjects receiving placebo, 1 receiving tadalafil and none receiving dexamethasone. In those receiving Placebo, HAPE was diagnosed on day 2 and 3 in 4 and 3 subjects respectively, and in those receiving tadalafil on day 3. In the dexamethasone-group heart rate (HR) did not change from LA to HA (65 ± 10/min (mean $\pm$ SD) to 63 ± 14/min, $p = 0.71$), whereas in the tadalafil-group HR increased from 66 ± 10/min to 86 ± 14/min ($p = 0.001$) and in the placebo-group from 67 ± 11 to 87 ± 13/min ($p < 0.001$). At HA HR was significantly higher in those subjects receiving tadalafil and placebo compared to dexamethasone ($p = 0.001$). SBP and DBP was on average (all subjects) 122 ± 12mmHg and 80 ± 14mmHg at LA, and 127 ± 15mmHg ($p = 0.44$) and 83 ± 17mmHg ($p = 0.43$) at HA. SBP and DBP were not significantly different between groups at both altitudes. In the dexamethasone-group LF/HF tended to decrease after ascent to HA (2.2 ± 1.9 vs. 1.3 ± 1.8, $p = 0.086$). In subjects receiving tadalafil and placebo, LF/HF-ratio tended to increase from 2.6 ± 1.6 to 9.0 ± 8.4 ($p = 0.072$) and from 1.8 ± 0.9 to 9.0 ± 10 ($p = 0.056$), respectively. At HA the LF/HF-ratio in the dexamethasone-group was significantly lower than in the other two groups ($p=0.047$). Our results indicate that in HAPE-susceptible subjects dexamethasone, but not tadalafil, prevented high altitude-related increase in HR by an inhibition of the sympathetic activity.

25.
PATENT FORAMEN OVALE AT HIGH ALTITUDE.
Gerald Dubowitz[1], Philip Bickler[1], Nelson Schiller[1]. Univ California San Francisco[1]. *Email:* dubowitz@anesthesia.ucsf.edu

Patent Foramen Ovale (PFO) is present in 10–35% of normal individuals and is a known risk factor for embolic events in hyperbaric and hypobaric settings. We hypothesized that PFO was a contributing factor to the development altitude related illness after gradual ascent. We determined the incidence of PFOs at sea level and altitude (5000m) and their influence on performance and illnesses, including HAPE and AMS. A total of 41 consented healthy volunteers underwent transthoracic contrast Doppler echocardiography at sea level and after a 17 day trek to 5000m. AMS (Lake Louise score) and performance (determined by visual analogue score) were assessed. Complete data were available in 26/41 subjects. Of 41 subjects, seven PFOs (17%) were identified at sea level with agitated saline contrast and metered Valsalva. One additional subject was PFO negative at sea level but PFO positive at altitude. No statistical relation was found between PFO and non PFO groups compared with either AMS, HAPE ($n = 3$) or performance. This study failed to support our hypothesis that PFO was a contributing factor to performance, AMS and HAPE. This has important implications in offering appropriate advice to individuals traveling to altitude. Also, with the availability of simple closing methods, it may prevent unnecessary procedures (e.g. inappropriate device deployment) in subjects found to have PFOs. It is possible that identifying a PFO appearing only at altitude merely represents the sensitivity of the technique. Equally, it could imply that dynamic changes in cardio-pulmonary blood flow may be responsible for a PFO appearing during hypoxia. A hypoxic challenge at sea level may, therefore, be a more useful screening tool for determining the presence of PFOs. We conclude there is no evidence that the presence of an asymptomatic PFO should be a contraindication to travel to high altitude.

Acknowledgments: This work was conducted in association with Medical Expeditions 2

26.
PREDICTING ACUTE MOUNTAIN SICKNESS IN CLIMBERS ASCENDING TO HIGHER ALTITUDES.
Gerald Dubowitz[1], Terry O'Connor[1], Philip Bickler[1]. Univ California San Francisco[1]. *Email:* dubowitz@anesthesia.ucsf.edu

Acute mountain sickness (AMS) is a common condition in individuals traveling to high altitude. Currently no measurements reliably predict susceptibility to AMS before travel to altitude or once at altitude. Our previous study (O'Connor 2004) found no relationship between SpO_2 and AMS at 3080m, whereas a correlation was found elsewhere (Roach 1998) at higher altitudes (4200m-6194m). The purpose of this study was to determine whether SpO_2 at 3080m might instead predict future development of AMS during ascent to higher altitude (4367m). After obtaining informed consent, we observed 45 volunteers who had recently arrived at 3080m on Mt Rainier (Washington, USA). Subjects completed a survey, which included demographics and ascent profiles. Subsequently, resting arterial oxygen saturation (SpO_2) and pulse rate were measured using pulse oximetry. Within 12 hours of the initial study, subjects attempted to climb to 4367m and on their return the incidence of AMS during the ascent was determined using Lake Louise Score. Twenty subjects (44%) had AMS (defined by a headache plus a Lake Louise score of greater than 2). Low oxygen saturation did not significantly predict AMS upon further ascent (OR: 0.8; 95% CI, 0.6-1.1; $p = 0.08$, Backwards Stepwise Logistical Regression). Furthermore there was no difference in mean oxygen saturation between groups with different AMS scores ($p < 0.05$, ANOVA). While

some previous studies at higher altitudes have shown that decreased oxygen saturation predicts acute mountain sickness in individuals already at altitude who wish to ascend higher, our results (at 3080m–4367m) did not demonstrate this. It is possible that greater altitude confers an increased risk of sub-clinical high altitude pulmonary edema (HAPE), making saturation changes more diagnostic. Therefore we conclude that at this altitude, pulse oximetry is of limited use in predicting AMS in subjects who wish to ascend higher.

27.

THE INFLUENCE OF CONSECUTIVE MEASUREMENT OF ISOCAPNIC AND POIKILOCAPNIC HYPOXIC VENTILATORY RESPONSE ON RESTING END TIDAL CO_2.

Gerald Dubowitz[1], Emily Ginsburg[1], Philip Bickler[1]. Univ California San Francisco[1]. *Email:* dubowitz@anesthesia.ucsf.edu

Hypoxic ventilatory response (HVR) has previously been assessed using several methods. We used a standardized protocol in 15 healthy subjects observing 20mins of HVR during isocapnia (iHVR) followed by 20mins poikilocapnic HVR (pHVR). In the pHVR study, (n = 15), mean end-tidal carbon dioxide tension ($ETCO_2$) was 33.6mmHg (baseline), 30.3 mmHg (5mins) and 31.0mmHg (20mins). This represents pHVR of 0.13mmHg/%. We hypothesized that the starting $ETCO_2$ was decreased due to testing immediately after iHVR. We therefore set out to determine whether performing a separate pHVR test would produce more reliable result. We re-tested 5 of our original 15 subjects (M = 4; F = 1) who had prior consecutive isocapnic and poikilocapnic studies. On a separate day, under the same testing conditions, we performed one isolated 20-minute poikilocapnic test (SaO_2 = 80%) preceded by 5mins O_2 (titrated for $SaO_2 > 250$mmHg). Mean $ETCO_2$ was 36.2mmHg (baseline), 30.1mmHg (5 mins) and 31.1mmHg (20 mins). pHVR = 0.26mmHg/%. This represents a mean baseline $ETCO_2$ 8% higher than with consecutive testing. $ETCO_2$ at 5 and 20mins were not significantly different. We conclude that consecutive testing significantly decreases the resting $ETCO_2$. $ETCO_2$ was low in both studies, perhaps due to hyperventilation at rest. Reports that increased oxygen tensions can stimulate ventilation and may influence the resting $ETCO_2$, although the significance of this in humans is unclear. Additionally, residual lactate from prior hypoxic (in this case iHVR) testing may influence the subsequent test. In summary performing an isolated poikilocapnic test produces a higher $ETCO_2$ than the consecutive test, which significantly affects the resulting calculated HVR. More subjects need to be studied to validate this result and to establish how long a rest period is needed to assess HVR using consecutive testing.

28.

INTERMITTENT HYPOXIC TRAINING PROTECTS CANINE MYOCARDIUM FROM INFARCTION AND ARRHYTHMIAS.

Igor Ehrenburg[1], Elena Tkatchouk[1], Pu Zong[2], Setty Srinath[2], Roberto Martinez[2], Wei Sun[2], Johnatan D. Tune[2], Robert T. Mallet[2], H. Fred Downey[2]. Clinical Research Laboratory, Hypoxia Medical Academy, Moscow, Russia[1], Dept. of Integrative Physiology,Univ North Texas Health Science Center. Fort Worth, USA[2]. *Email:* igor_ehrenburg@hypoxia.msk.ru

To investigate cardiac protective effects of normobaric intermittent hypoxia training, six dogs underwent intermittent hypoxic training for 20 consecutive days in a normobaric chamber ventilated intermittently with N2 to reduce FIO_2 to 9.5–10%. Hypoxic periods, initially 5 min and increasing to 10 min, were followed by 4 min normoxic periods. The hypoxia-normoxia protocol was repeated, initially 5 times and increasing to 8 times. After training, the resistance of ventricular myocardium to infarction was assessed in an acute coronary artery occlusion – perfusion experiment. The heart was dyed to delineate the area at risk (AAR) and stained with triphenyl tetrazolium chloride to identify infarcted myocardium. During coronary occlusion and reperfusion, systemic hemodynamics and global left ventricular function were stable. Infarction was not detected in four hearts, and was 1.6% of AAR in the other two hearts. Collateral flow was very low in four of these hearts. In contrast, 6 sham-trained dogs and 5 untrained dogs subjected to the same occlusion/reperfusion protocol had infarcts of 36.8 ± 5.8% and 35.2 ± 9.5% of the AAR, respectively. Hypoxia-trained dogs had no ventricular tachycardia or ventricular fibrillation, whereas 3 sham trained dogs had ventricular tachycardia and 2 had ventricular fibrillation. Three untrained dogs had ventricular fibrillation. In conclusion, intermittent hypoxic training protects canine myocardium from infarction and life threatening arrhythmias during coronary artery occlusion and reperfusion. The mechanism responsible for this potent cardioprotection merits further study.

Acknowledgments: (Supported by NIH grants HL-64785 and HL.)

29.

EFFECT OF CARBOHYDRATE INGESTION ON THE VENTILATORY RESPONSE TO CARBON DIOXIDE.

Lindsay Eller[1], Philip Ainslie[2], Marc Poulin[3]. Faculty of Kinesiology, Univ Calgary, Calgary Canada.[1], Faculty of Medicine, Univ Calgary, Calgary Canada.[2], Faculties of Medicine and Kinesiology, Calgary Canada.[3]. *Email:* poulin@ucalgary.ca

During ventilatory acclimatization to hypoxia (VAH) there is a leftward shift of the relationship between ventilation (VE) and end-tidal PCO_2 ($PETCO_2$), together with an increase in the slope of this relationship, known as the acute hypercapnic ventilatory response (AHCVR). Oxidation of carbohydrate (CHO) compared with fat results in greater CO_2 production and, at the same arterial PCO_2, higher VE. We hypothesized that dietary intake of CHO could induce changes in the AHCVR, in the absence of the primary hypoxic stimulus itself. In a balanced design, following an overnight fast, the effect of a diet (720 kcal) high in CHO (80% energy intake from CHO, 10 % fat, 10% protein) or a continued fast were investigated in 10 healthy male subjects. Using the dynamic end-tidal forcing technique, the AHCVR ($PETCO_2$ = +9 above rest; $PETO_2$ = 88 Torr) was assessed prior to (baseline), and following (90 and 180 min) each trial (fast, CHO). Resting measurements of $PETCO_2$ were made between each AHCVR test. In the CHO condition, AHCVR decreased

(baseline, 5.3 ± 2.2 l min^{-1} Torr-1; 90 min, 4.3 ± 1.8 l min^{-1} $Torr^{-1}$; $P < 0.05$), the intercept of AHCVR was shifted to the left (baseline, 35.2 ± 2.4 Torr; 90 min, 33.0 ± 1.6 Torr), and resting VE increased (baseline, 13.8 ± 4.1 l min^{-1}; 90 min, 18.6 ± 4.2 l min-1; 180 min, 17.0 ± 6.5 l min^{-1}). With fasting, there were no changes in AHCVR, intercept, or resting VE. In both conditions, resting $PETCO_2$ did not change. In summary, when compared to a continued fast: (i) acute ingestion of CHO produced marked changes in VE at rest with no change in $PETCO_2$; (ii) this diet-induced hyperpnoea may explain some of the changes evident in the slope and intercept of the AHCVR; and (iii) whether dietary interventions could be used to aid VAH warrants further research.

Acknowledgments: This study was approved by the Ethics Board and supported by AHFMR and CIHR.

30.

EFFECTS OF THE PHOSPHODIESTERASE-5 INHIBITOR TADALAFIL AND DEXAMETHASONE ON PULMONARY ARTERIAL PRESSURE DURING EXERCISE AT 4559M IN HAPE-SUSCEPTIBLES.

Manuel Fischler[1], Lorenz Dorschner[1], Johann Debrunner[1], Hans-Peter Brunner-La Rocca[2], Stephanie Kiencke[2], Alain Bernheim[2], Heimo Mairbäurl[3], Marco Maggiorini[1]. Intensive Care Unit, Univ Hospital Zurich, Switzerland[1], Cardiology, Univ Hospital Basel, Switzerland[2], Medical Clinic VII, Sports Medicine, Univ Heidelberg, Germany.[3]. *Email:* klinmax@usz.unizh.ch

Excessive pulmonary hypertension is a hallmark in subjects susceptible to high altitude pulmonary edema (HAPE-s), but the contribution of exercise to the development of pulmonary edema is unknown. Eight HAPE-resistant (HAPE-r) and 25 HAPE-s subjects were exercised at low (LA) and high altitude (HA). HAPE-s received a prophylaxis with dexamethasone (2 × 8mg; n = 10), tadalafil (2 × 10mg; n = 8) or placebo (n = 7). Cardiac output (CO) (impedance cardiograph) and the pressure gradient of the tricuspid regurgitation (dpTI) (Doppler-echocardiography) were assessed at rest, and at 20% (Ex20) and 40% (Ex40) of VO_2max. At LA on average (all subjects) CO increased from 5.6 ± 1.1 l/min (rest) to 11.1 ± 1.6 l/min (Ex40) ($p < 0.001$) and at HA from 5.7 ± 1.3 l/min to 10.9 ± 2.2 l/min ($p < 0.001$). In HAPE-r at LA CO was at rest, Ex20 and Ex40 ~1 l/min higher than in HAPE-s ($p = 0.014$), but was not different between treatment-groups at HA. At LA dpTI was higher in HAPE-s, the difference being 2 mmHg at rest, 9 mmHg at Ex20 and 16 mmHg at Ex40 ($p < 0.005$). At HA dpTI was 16 mmHg at rest, 18 mmHg at Ex20 and 19 mmHg at Ex40 higher in placebo than in HAPE-r ($p < 0.01$). Compared to placebo, at rest and during exercise (Ex20; Ex40) tadalafil and dexamethasone caused a parallel shift of the dpTI/CO-relationship to lower dpTI, the difference between placebo and tadalafil being 14 mmHg ($p < 0.05$), and between placebo and dexamethasone 17 mmHg ($p < 0.005$). Our results suggest a higher pulmonary vascular tone in HAPE-s than in HAPE-r subjects at LA. At HA, compared to HAPE-r, the parallel shift of the dpTI/CO-relationship to higher dpTI in HAPE-s, suggests an increased closing pressure in the latter. Both tadalafil and dexamethasone prevented hypoxic pulmonary vasoconstriction at rest and during exercise.

Acknowledgments: Hartmann-Müller Foundation, Zurich; Crivelli Foundation Lugano, Switzerland.

31.

MAXIMAL EXERCISE CAPACITY AT HIGH ALTITUDE IS NOT INFLUENCED BY PROPHYLAXIS WITH DEXAMETHASONE OR TADALAFIL IN HAPE-SUSCEPTIBLE SUBJECTS.

Manuel Fischler[1], Lorenzo Dorschner[1], Johann Debrunner[1], Hans-Peter Brunner-La Rocca[2], Stephanie Kliencke[2], Alain Bernheim[2], Konrad Bloch[3], Heimo Mairbäurl[4], Marco Maggiorini[1]. Intensive Care Unit Univ Hospital Zurich, Switzerland[1], Cardiology, Univ Hospital Basel, Switzerland[2], Pulmonary Division, Univ Hospital Zurich, Switzerland[3], Medical Clinic VII, Sports Medicine, Univ Heidelberg, Germany[4]. *Email:* klinmax@usz.unizh.ch

The extent to which prophylactic therapy with dexamethasone or tadalafil in HAPE-s subjects influence maximal exercise capacity at high altitude is not known. We therefore tested in 25 HAPE-s subjects maximal exercise capacity (VO_2max) at low altitude (LA) and after randomisation to a prophylaxis with dexamethasone (2 × 8mg,n = 8), tadalafil (2 × 10mg,n = 8) or placebo (n = 9) at HA. Cardiopulmonary exercise was performed on a cycloergometer in supine position 4h after arrival at 4559m. During exercise we measured heart rate (HR) and cardiac index (CI) by impedance cardiography, oxygen consumption and SpO_2 by pulse oximetry. At HA 7 subjects with placebo, 1 with tadalafil and none with dexamethasone developed HAPE($p < 0.001$). CI was not different between low and high altitude nor between treatment groups at both altitudes. At HA compared to LA, VO_2 max% predicted decreased in subjects receiving dexamethasone from 130 ± 22% to 74 ± 13%($p < 0.001$), in those receiving tadalafil from 117 ± 20% to 62 ± 13%($P < 0.001$) and in those receiving placebo from 121 ± 23% to 63 ± 11%($p < 0.001$). At HA VO_2max was not different between groups. At HA maximal exercise load SpO_2 was significantly lower than at low altitude. At HA Sp02 was 66 ± 7% with dexamethasone, 69 ± 5% with tadalafil and 61 ± 6% with placebo(p = ns). At HA, maximal work load HR was significantly lower in all groups compared to LA($p < 0.001$). HR decreased on average (all subjects) from 169 ± 11/min to 154 ± 12/min($p < 0.001$), but was not different between groups Our results show that dexamethasone and tadalafil prophylaxis in HAPE-s subjects did not influence $V0_2$max. a few hours after arrival at HA. VO_2max was not altered by the later development of HAPE in the placebo treated group, suggesting an irrelevant effect of a subclinical HAPE, if any, on exercise performance at high altitude.

32.

CARDIOVASCULAR FUNCTION DIFFERS DURING TWO PATTERNS OF INTERMITTENT HYPOXIA IN HUMANS.

Glen E. Foster[1], Donald C. McKenzie[1], A. William Sheel[1]. Univ British Columbia, Vancouver, Canada[1]. *Email:* gefoster11@hotmail.com

The purpose of this study was to determine the mean arterial pressure (MAP) and heart rate (HR) responses to two patterns of intermittent isocapnic hypoxia (IH). Subjects (M, 26 ± 1 yrs) were randomly assigned to one of two IH groups, each having 10 hypoxic exposures over 12 days; long duration IH (LDIH, n = 9) inhaled 12% O_2 for 30 min, short duration IH (SDIH, n = 9) inhaled 12% O_2 for 5 min separated by 5 min normoxia for 1 hr. The

hypoxic ventilatory response (HVR) was determined on day 1 and day 12. MAP, HR, and minute ventilation (VI) were measured during eupnea and during the first and last 5 min of each hypoxic exposure to LDIH and SDIH on days 1, 3, 5, 8, 10, and 12. HVR and VI were not different between IH groups. HVR (l/min/%SaO_2) increased significantly after 12 days of IH (Day 1 = 0.84 ± 0.12; Day 12 = 1.20 ± 0.24; $p < 0.05$) but VI, MAP, and HR during LDIH and SDIH did not. VI during the first and the last 5 min of hypoxia was not different. MAP did not differ between groups during the first 5 min of hypoxia (SDIH = 92.7 ± 2.3 mmHg; LDIH = 90.4 ± 2.3 mmHg); but, during the last 5 min of SDIH, MAP was significantly greater than LDIH (SDIH = 98.5 ± 2.4 mmHg; LDIH = 92.4 ± 2.4 mmHg; $p < 0.01$). HR was not different during the first 5 min of SDIH and LDIH (71 ± 3 bpm); however, during the last 5 min HR was slightly greater in both groups (73 ± 3 bpm; $p < 0.01$). In conclusion, acute exposure to SDIH results in an increase in MAP by the end of each exposure while LDIH does not. The rise in MAP does not increase over 12 days of IH despite a significant increase in HVR.

Acknowledgments: Support: NSERC, CFI, and MSFHR.

33.

PLASMA FROM HYPOXIC RATS INDUCES MICROVASCULAR INFLAMMATION IN NORMOXIC CREMASTER.

Norberto Gonzalez[1], Teresa Orth[1], Julie Allen[1], John Wood[1]. Univ Kansas Medical Center, Kansas City KS USA[1]. *Email:* ngonzale@kumc.edu

Hypoxia induces rapid inflammatory responses in mesenteric, pial and skeletal muscle microcirculations of the rat. We observed a dissociation between microvascular PO_2 and inflammation: leukocyte-endothelial adherence (LEA) and mast cell degranulation (MCD) occurred in cremaster muscles of rats breathing 10% O_2, even if the muscle was maintained normoxic. The opposite, cremaster hypoxia/ systemic normoxia, did not produce LEA or MCD. One possible explanation of these data is that inflammation is mediated by a substance released from a distant site. If this mediator is carried by the circulation, plasma from hypoxic rats should elicit inflammation in normoxic microcirculations. This hypothesis was tested by applying plasma from conscious rats breathing 10% O_2 for 5 minutes onto cremasters of normoxic rats. The donor plasma had attained normoxic PO_2 when applied onto the cremaster. The cremaster microcirculation was studied using intravital microscopy. Plasma from hypoxic, but not from normoxic rats, increased LEA from 2.7 ± 0.8 to 12.3 ± 2.4 leukocytes / 100 ⟨μ⟩m of venule, elicited MCD, and reduced arteriolar diameter (AD) to 74 ± 4% of control within 10 minutes of application onto normoxic cremasters. No changes in LEA, MCD, or AD occurred when plasma from blood rendered hypoxic in vitro was applied to normoxic cremasters, suggesting that the substance responsible for the effects of plasma is not generated in blood cells. Plasma from donors pretreated with cromolyn, which prevents hypoxia-induced LEA and MCD, had inflammatory effects similar to those of plasma from untreated hypoxic donors. This suggests that the effects on LEA, MCD and AD are not due to inflammatory mediators released into the circulation of the donor rat by adherent leukocytes These results support the idea that a substance released from a distant site contributes to initiate the inflammatory response to hypoxia.

Acknowledgments: NIH HL39443.

34.

HISTAMINE, A NOVEL TRANSMITTER IN RODENT CAROTID BODY SENSOR CELLS.

Manfred Gratzl[1]. Univ Munich, Germany[1]. *Email:* gratzl@lmu.de

Sensor cells in the carotid body depolarize during hypoxia and the concomitant rise of intracellular calcium levels causes transmitter release. The nature of the principle transmitter released by the sensor cells is unknown. Immunocytochemistry, immunoblotting, RT-PCR studies followed by sequencing and quantification of histamine were applied. We revealed that the sensor cells in rat and mouse carotid bodies possess the components of the neuroendocrine exocytosis apparatus, the synaptosome-associated protein of 25 kDa (SNAP 25) and syntaxin1. Moreover, we found that the sensor cells of juvenile rats have not only the vesicular monoamine transporter 1 (VMAT1), transporting catecholamines, but also VMAT2, which is highly specific for histamine. In addition we discovered that the sensor cells express the histamine biosynthesis enzyme, histidine decarboxylase. Also, we detected large amounts of histamine in the juvenile rat carotid bodies (164 pmol/carotid body) and observed that hypoxia increased histamine release from isolated rat carotid bodies. Finally, RT-PCR experiments indicated the presence of H1, H2 and H3 histamine receptors in the carotid body. Our data suggest that histamine released by carotid body sensor cells may stimulate sensory nerve fibers, whose perikarya are located in the petrosal ganglion of the glossopharyngeal nerve. Since the central branches of the petrosal ganglion cells terminate in the respiratory nuclei located in the brainstem, histamine may be involved in the control of breathing.

Acknowledgments: Pia Koerner and Agnes Schaefermeyer were supported by a predoctoral fellowship from Deutsche Forschungsgemeinschaft.

35.

BARORECEPTOR CONTROL IN SEA-LEVEL AND HIGH ALTITUDE DOGS.

Roger Hainsworth[1], Jonathan Moore[1], Mark Drinkhill[1], Jose Luis Macarlup£[2], Maria Rivera-Chira[2]. Inst Cardiovascular Research, Univ Leeds, Leeds, UK[1], Dept Biological Sciences & Physiology, Universidad Cayetano Heredia, Lima, Peru.[2]. *Email:* medrh@leeds.ac.uk

Baroreceptor and chemoreceptor reflexes are known to interact so we were interested to determine whether baroreceptor responses would differ between chronically hypoxic high altitude living animals (HA) and sea level (SL) ones. Dogs were anaesthetized, the carotid sinus regions isolated and perfused at controlled pressures, and a hindlimb vascularly isolated and perfused at constant flow (perfusion pressure is related to resistance). Comparisons were made in 6 SL and 8 HA (4338m) dogs. PaO_2 in SL and HA dogs were 106.2 ± 8.5 and 47.4 ± 2.1 mmHg. Plots of vascular resistance against carotid pressure allowed calculation of maximum gain and the correspond-

ing carotid pressure ("set point"). We found that the gains of the reflex were not significantly different between the groups (SL -1.8 ± 0.5, HA -2.1 ± 0.9). The "set point" of the reflex was lower in the HA dogs (90.4 ± 7.9 versus 116.5 ± 6.5 mmHg, $p < 0.03$). Changing systemic blood gases in SL to same as HA dogs and vice versa had no significant effect. However, perfusing the carotid regions with hyperoxic blood increased "set point" in the HA but not the SL dogs, although it still remained lower in HA than in SL dogs (101.5 ± 6.7 versus 119.8 ± 6.3, $p < 0.04$). These results have shown that, although the gain of the baroreceptor reflex was similar in HA and SL dogs, the curve is displaced to lower pressures in the HA animals. This shift can be partly but not entirely attributed to stimulation of carotid chemoreceptors.

36.

CARDIOVASCULAR CONTROL AND BLOOD VOLUMES IN HIGH ALTITUDE RESIDENTS.

Roger Hainsworth[1], Victoria Claydon[1], Lucy Norcliffe[1], Jonathan Moore[1], Maria Rivera-Ch[2], Fabiola Leon-Velarde[2], Otto Appenzeller[3]. Univ Leeds, Leeds, UK[1], Universidad Cayetano Heredia, Lima, Peru[2], NMHEMC Research Foundation, Albuquerque, USA.[3]. *Email:* medrh@leeds.ac.uk

The ability to control blood pressure during gravitational stress (orthostatic tolerance) is dependent on plasma volume and on the control of peripheral vascular resistance and of cerebral blood flow. High altitude dwellers, and particularly those with chronic mountain sickness (CMS), have high haematocrits and this study determined their plasma and blood volumes and cardiovascular reactions to gravitational stress. The subjects were 11 healthy residents at 4338m (HA) and 11 CMS patients. Haematocrits were $53.6 \pm 1.2\%$ and $67.8 \pm 2.0\%$. Studies were carried out both at their normal HA residence and within 24 hours of arrival at sea level. At the HA study, plasma volumes, determined by Evans blue dilution, were not significantly different (HA 39.3 ± 1.9, CMS 34.8 ± 1.6 ml/kg) but packed cell volumes were significantly higher in CMS (71.7 ± 7.3 and 45.3 ± 2.6 ml/kg). Orthostatic tolerance (time to presyncope in a test of head-up tilting and lower body suction) was similar in both groups and much greater than in lowland dwellers (HA 46.2 ± 1.2, CMS 47.2 ± 1.2, UK controls 34.3 ± 6.3 min). Responses of forearm vascular resistance (mean blood pressure/brachial blood velocity by Doppler), measured during the orthostatic stress were greater in the HA subjects. HA subjects also showed better control of the cerebral circulation as assessed from the correlation between cerebral blood velocity (transcranial Doppler) and pressure. We found little difference between observations at altitude and at sea-level. We suggest that the exceptionally good orthostatic tolerance in all these subjects is related to the large packed cell and blood volumes. However, in CMS subjects, who have even larger blood volumes, the advantage of this is offset by less effective vascular control.

37.

COMPUTERISED COGNITIVE ASSESSMENT IS MORE SENSITIVE THAN WRITTEN TESTS AT 5100M ALTITUDE ABOVE SEA LEVEL.

Gregory Harris[1], Jennifer Cleland[2], Alex Collie[3], Kim Bennell[4], Paul McCrory[5]. Australasian College Sports Physicians, Australia[1], Univ Aberdeen, Aberdeen, Scotland[2], CogState, Melbourne, Australia[3], Univ Melbourne. Melbourne, Australia[4], Box Hill Hospital, Box Hill, Victoria, Australia[5]. *Email:* drgaharris@yahoo.com

Background: Cognitive impairment at altitudes greater than 3000m above sea-level remains poorly understood. This is partly due to the use of testing procedures that are insensitive to mild cognitive impairment. This research hypothesises that a computerised cognitive testing battery will be more sensitive to the mild impairments at high altitude than previously used 'pencil-and-paper' tests, and that cognitive impairment will be present at day 1 of exposure to high altitude, with an improvement over a week of acclimatisation back to baseline levels. 45 members of a research expedition to Nepal were tested with the Digit-symbol Substitution Test (DSST), Digit Span forwards and backwards, Trail-making test part B (TMT), Rey's Auditory-Verbal Learning task (AVLT), Word Generation Task and a computerised testing battery (CogStateTM) which has been specifically designed for serial assessment of mild cognitive impairment. Baseline testing was performed at sea-level. Repeat testing occurred within 24 hours of arrival and after 7 days at Chamlang Base Camp (5100m) after a 20-day trek from 410m. Changes in test scores from baseline to repeat were converted to z-scores for ease of comparison between tests. Both CogState and AVLT were impaired at day 1 and significantly improved at day 7 ($p < 0.05$). Both were more sensitive to impairment at day 1 than DSST, TMT, word generation or digit span backwards tests, and more sensitively detected improvement over a week of acclimatisation than digit-span forwards test. Computerised testing suggests that a failure of inhibition of inappropriate responses may be a feature of cognitive impairment at 5100m. Computerised cognitive testing may be useful in further investigating the effects of moderate to high altitude on cognitive function.

Acknowledgments: This work was carried out in association with Medical Expeditions.

38.

INTERNATIONAL HIGH ALTITUDE PULMONARY EDEMA REGISTRY: EMERGING TOOLS.

N. Stuart Harris[1], International High Altitude Research Collaborators. Massachusetts General Hospital, Harvard Medical School, Boston, USA[1]. *Email:* nsharris@partners.org

Arising from discussions held at the 5th World Congress of the ISMM (Barcelona 2003), the International High Altitude Pulmonary Edema Registry is designed to be a new and useful addition to the armamentarium of the hypoxia researcher. The Registry seeks to combine limited data from multiple, single-sites into a single, significant and readily-queriable cohort using a secured, web-based data instrument. The Registry has been designed and is governed by representatives of its international contributors, the International High Altitude Research Collaborators (IHARC). Our encrypted, password-protected, web-based system is designed to meet the requirements of instantaneous access and global reach, while insuring confidentiality of all patient data. All participants will have signed a written informed consent prior to enrollment in the Registry. The site (www.iharc.org) is accessible only to enrolled IHARC study

physicians. The IHARC researchers continue to welcome new investigators to participate in the Registry. In 2004, the Registry successfully completed beta testing of both website and data processing software. The Registry has final IRB approval for patient enrollment. In presentations at the 6th World Congress of the ISMM (Tibet 2004), the Registry was well-received and will begin formal enrollment of subjects in early 2005. We anticipate presenting our initial findings at the next Hypoxia Symposia.

Acknowledgments: We continue to tremendously appreciative of the ongoing interest and hard work of our international collaborators, of Dr. Stephen Thomas (MGH), and the MGH Faculty Research Award Grants.

39.

EXCESSIVE ERYTHROCYTOSIS LEADS TO NEURONAL, RENAL AND HEPATIC DEGENERATION, AND PREMATURE DEATH OF ADULT MICE OVER-EXPRESSING ERYTHROPOIETIN.

Katja Heinicke[1], Oliver Baum[2], Johannes Vogel[3], Peter D. Wagner[1], Max Gassmann[3], Valentin Djonov[2]. Division of Physiology, Dept Medicine, Univ California, San Diego, CA[1], Inst Anatomy, Univ Bern, Switzerland[2], Inst Veterinary Physiology, Univ Zurich, Switzerland[3]. *Email:* kheinicke@ucsd.edu

To investigate the consequences of persistent excessive erythrocytosis that may occur due to e.g. polycythemia vera, chronic mountain sickness or abuse of erythropoietin (Epo), we made use of our transgenic mouse line (tg6) that constitutively overexpresses Epo in a hypoxia-independent manner, thereby reaching hematocrit levels of up to 0.85 without developing cardiovascular complications. Decreased exercise performance was observed when exposing five months old tg6 mice to a swim test. Later in life, several tg6 animals developed paralysis of the hind limbs. Compared to wild type siblings, lifespan of tg6 mice was reduced to about 50%. Morphological analysis of all organs by light and elec-tron microscopy showed degenerative processes in the stomach and more progressive ones in liver and kidney. Four out of five tg6 animals showed severe nerve fibre degen-eration of the sciatic nerve, decreased number of neuromuscular junctions and an in-creased degeneration of skeletal muscle fibres in the quadriceps muscle. Based on our data we suggest that Epo-induced excessive erythrocytosis leads to a demyelinating neu-ropathy that is accompanied by degenerative processes in various organs, resulting in markedly reduced life expectancy.

40.

EFFECTS OF SIMULATED ALTITUDE TRAINING ON PERIPHERAL OXYGEN SATURATION LEVELS IN MULTI-SPORT ENDURANCE ATHLETES.

John Hellemans[1], Mike J Hamlin[2]. Active Health QEII, Christchurch, New Zealand[1], Social Science Tourism and Recreation Group, Lincoln Univ, Canterbury, New Zealand.[2]. *Email:* johnh@activehealth.co.nz

Simulated altitude training is becoming more popular due to its convenience and cost, however its effect on performance and its underlying physiological mechanisms are contentious. The purpose of this study was to investigate the effect of intermittent normobaric hypoxic training on the peripheral oxygen saturation levels during a standardized period of hypoxic exposure and after a 3-km time trial. Twenty-two multi-sport endurance athletes of mixed ability were randomly assigned to either a placebo (8 males, 2 females; age 32 ± 10 yrs; body weight 74 ± 11 kg; height 1.7 ± 0.1 m; training 9.5 ± 7.5 h.wk-1) or hypoxic group (5 males, 7 females; age 32 ± 10 yrs; body weight 70 ± 11 kg; height 1.7 ± 0.1 m; training 8.2 ± 3.8 h.wk-1). Subjects were given an intermittent normobaric hypoxic gas (intermittent hypoxic training, IHT) or a placebo gas containing ambient room air (placebo) in a randomised double-blind manner. Subjects breathed the gas mixtures in 5-min intervals interspersed with 5-min recovery periods of ambient room air for a total of 90 min day-1, 5 days per week for 3 weeks. The hypoxic gas was adjusted from 13% oxygen at the beginning of week 1 to 10% by the end of week 3. The IHT and placebo groups underwent a total of four 3-km time trials including a familiarisation and baseline trial before the intervention, followed by trials at 2 and 17 days after the intervention. On four separate occasions all subjects underwent a 10-min hypoxic test where they were asked to breathe normobaric hypoxic air (FIO_2 = 11%) for 5 min followed by a 5-min recovery period where they breathed normal ambient air. A familiarization hypoxic test occurred 2-weeks prior to the start of the study followed by 10-min hypoxic tests 8 days before and 1 and 22 days after the 3-week exposure period. During the hypoxic test peripheral oxygen saturation (SPO_2) was monitored and the time taken for subjects arterial oxyhaemoglobin saturation to reach 83% (Td) was recorded along with each subject's lowest oxyhaemoglobin saturation level (SpO_2minimum). SPO_2 was also recorded 20 s after the end of each time trial. After IHT, arterial oxyhaemoglobin levels did not desaturate to the same extent at the end of the time trial or during the 10-min hypoxic test. Compared to the placebo group a substantial increase in post-time trial SPO_2 resulting from IHT was likely 2 days (1.9% ± 2.8%, mean ± 90% confidence limits) but unlikely 17 days (−1.4% ± 2.6%) after the 3-week hypoxic exposure. Compared to the placebo group substantial increases in SpO_2minimum resulting from IHT were likely 1 day and possible 22 days after exposure and substantial increases in Td were possible at 1 and 22 days after exposure. Compared to baseline, IHT subjects SPO_2 increased substantially during the first half of the 10-min hypoxic test, whereas the placebo groups SPO_2 did not change. We conclude that intermittent hypoxic training can elicit changes in peripheral oxygen saturation that suggests adaptation in body's ability to cope with severe exercise and hypoxic stress.

Acknowledgments: This study was supported by the Canterbury Medical Research Foundation.

41.

EXERCISE AND HYPOXIA REDISTRIBUTE PULMONARY BLOOD FLOW TO THE DORSAL-CAUDAL LUNG REGIONS IN THE PIG.

Michael Hlastala[1], Axel Kleinsasser[2], Susan Bernard[1], Dowon An[1], Eric Falor[3], Susan Hopkins[3]. Univ Washington[1], Innsbruck Medical School[2], Univ California at San Diego[3]. *Email:* hlastala@u.washington.edu

It is known that pulmonary blood flow redistributes under conditions of hypoxia or exercise. The overall objective of this study is to examine the redistribution of pulmonary blood flow during hypoxia and exercise in the pig (brisk hypoxic pulmonary vasoconstrictive response).

Fluorescent microspheres were used to measure pulmonary blood flow distributions at rest and during incremental exercise (5 min at each of 30, 60, and 90% of VO_2 max) in normoxia (N, $FIO_2 = 0.21$) and hypoxia (H, $FIO_2 = 0.125$). SPF Yorkshire hybrid pigs (25.5 ± 0.7 Kg), trained to exercise on a treadmill and chronically catheterized (internal jugular, external jugular vein and a carotid arteries) underwent only one exercise protocol per day on consecutive days. Mean arterial pressure, pulmonary artery pressure and metabolic data were collected at rest and at 4 minutes into each exercise intensity. Fluorescent microspheres, of different colors, were injected into the jugular vein over ~30 seconds. Cardiac output was calculated using the Fick equation. After the final injection/exercise condition, the pigs were anaesthetized, intubated, given papaverine 3mg/kg and heparin, then exsanquinated. Regional perfusion was calculated from weight-normalized fluorescence in each piece. Blood flow was heterogeneous and heterogeneity did not change with H or 90% exercise. Blood flow to each piece was correlated across exercise conditions (N R2 = 0.776 ± 0.069, H 0.6471 ± 0.148). The correlation between N rest to H 90% exercise was the weakest (R2 = 0.415 ± 0.664). Pulmonary blood flow shifted to the dorsal-caudal region, most dramatically with H rest. Similar shifts in flow were seen with exercise. This dorsal caudal flow shift with H rest was diminished by H 90% exercise, likely because H at rest caused the maximum observed redistribution of flow, which could not further redistribute with exercise.

Acknowledgments: NIH HL 69868 and HL 17731.

42.

INHIBITION OF HYPOXIC PULMONARY VASOCONSTRICTION BY LOW DOSE ACETAZOLAMIDE IN CONSCIOUS, SPONTANEOUSLY BREATHING DOGS.

Claudia Hoehne[1], Philipp Pickerodt[1], Roland Francis[1], Willehad Boemke[1], Erik Swenson[2]. Univ Medicine, Berlin, Germany[1], Univ Washington, Seattle, USA[2]. *Email:* claudia.hoehne@charite.de

A previous study has shown that high dose carbonic anhydrase inhibition by acetazolamide (ACZ) (10mg/kg/h) is able to prevent hypoxic pulmonary vasoconstriction (HPV) in conscious dogs in the presence of systemic acidosis. We hypothesized that also low dose acetazolamide (2mg/kg/h) would prevent HPV while the effects of systemic acid-base changes would be minimized. Six female Beagle dogs were kept under standardized conditions. Each dog was studied twice in randomized order. Protocol 1: Controls ; Protocol 2: ACZ was given intravenously (2mg/kg bolus, followed by 2mg/kg/h continuously). During all experiments the dogs were breathing spontaneously via a ventilator circuit: first hour normoxia ($FiO_2 = 0,21$) followed by two hours of hypoxia (Controls: $FiO_2 = 0.1$; ACZ: $FiO_2 = 0.09$-0.08 to match the arterial PO_2 (PaO_2) observed during hypoxia in Controls. Mean pulmonary artery pressure (MPAP) and pulmonary vascular resistance (PVR) were continuously recorded. At the end of each experimental hour, arterial blood gases were measured. Data are given as means ± SEM; $p < 0,05$ (GLM ANOVA). During hypoxia PaO_2 was 36 ± 2mmHg ($PaCO_2$ 29 ± 1mmHg) in Controls and 39 ± 2mmHg (n.s.) in ACZ ($PaCO_2$ 29 ± 1mmHg). In Controls, MPAP increased from 13.3 ± 1 to 20.7 ± 1.3mmHg and PVR increased from 324 ± 33 to 528 ± 37dyn.s-1cm-5. In ACZ, MPAP was 13.3 ± 0.2mmHg and PVR was 320 ± 26dyn.s-1cm-5 during normoxia and did not change during hypoxia. Arterial pH increased from 7.39 ± 0.01 (normoxia) to 7.46 ± 0.01 (hypoxia) in Controls while standard bicarbonate concentration (22–23mmol/l) did not change. In dogs given ACZ, arterial pH was 7.39 ± 0.01 (normoxia) and did not change during hypoxia (7.40 ± 0.01), but standard bicarbonate concentration decreased from 21.6 ± 0.2 to 19.2 ± 0.5mmol/l ($p < 0.05$). Low dose acetazolamide (2mg/kg/h IV) prevents HPV in conscious spontaneously breathing dogs. This effect does not seem to be due to systemic acidosis previously shown to occur with high dose carbonic anhydrase inhibition.

43.

DIFFERENCES IN THE DYNAMICS OF SKELETAL MUSCLE PERFUSION AND CARDIAC PERFORMANCE IN RESPONSE TO ACUTE HYPOXIA AND EXERCISE IN VIVO.

Outi Hyyti[1], Xue-Han Ning[1], Kenneth Marro[1]. Univ Washington, Seattle, WA[1]. *Email:* outi@u.washington.edu

Exercise capacity and maximal oxygen consumption decrease in hypoxic environments and cardiac performance is viewed as the limiting factor. People commonly experience severe fatigue in the legs during climbing in high altitude and hypoxic treadmill tests. We measured cardiac performance and skeletal muscle perfusion in vivo during acute hypoxia with and without exercise to determine whether peripheral vasoconstriction could be a factor in severe fatigue during hypoxic insult, when cardiac function is still in the stage of compensation. Isoflurane (in 100% O_2) anesthetized rats were divided into 3 treatment groups: 1) inhalation of 8% O_2 for 3 minutes, 2) induction of short tetanic contractions (40% of the maximum contractile force) in the hind limb via the sciatic nerve for 4 minutes, 3) treatments 1 and 2 combined. Cardiac performance was measured with a Millar pressure-volume catheter inserted in the left ventricle via the carotid artery. Skeletal muscle capillary-level perfusion in a hind limb was measured by 1H NMR spectroscopy with 5 sec time resolution with an arterial spin labeling technique (FAWSETS) optimized especially for skeletal muscle. 1) Acute hypoxia induced an initial increase in heart rate and stroke volume, whereas skeletal muscle perfusion significantly decreased, before heart performance reached maximum. During reoxygenation heart performance gradually recovered, while in skeletal muscle a brief local hyperemic response was observed. 2) Skeletal muscle perfusion increased during tetanic stimulation. 3) Severe hypoxia induced in the middle of a 4 minute exercise bout caused a similar pattern of decreased skeletal muscle perfusion as without exercise. The results suggest that peripheral vasoconstriction could be a limiting factor in muscle performance during acute severe hypoxia.

Acknowledgments: Support NIH Grant HL64946.

44.

'VIRTUAL ALTITUDE': A HYPOTHESIS WHICH MAY EXPLAIN WHY EXCERCISE EXCACERBATES AMS.

Chris HE Imray[1], Kyle TS Pattinson[2], Steve D Myers[3], Alex D Wright[4], BMRES. Coventry & Warwickshire County Vas-

cular Unit, UK[1], Dept Anaesthetics, Oxford, UK[2], QinetiQ, Farnborough, UK[3], BMRES[4]. *Email:* chrisimray@aol.com

Arterial and cerebral desaturation was assessed at rest and on exercising to 30%, 50% and 70% and VO_2max at 150m, 3610m, 4,750m and 5250m. Nine subjects were studied, measuring digital pulse oximetry, cerebral oxygenation (NIRS) and middle cerebral artery velocities (transcranial Doppler) on a purpose built collapsible supine exercise cycle. Statistics: Paired t test. There was a reduction in both arterial and cerebral saturations with both altitude and incremental increases in exercise intensity. At high altitude, cerebral oxygenation (mean ± SD %) was reduced during submaximal exercise from 66.2 (2.5) to 62.6(2.1) at 3,610 m ($p < 0.0001$), 63.0(2.1) to 58.9(2.1) at 4,750 m ($p < 0.0001$) and 62.4(3.6) to 61.2(3.9) at 5,260 m ($p < 0.01$) and at VO_2max to 61.2(3.3) at 3,610 m ($p < 0.0001$), to 59.4(2.6) at 4,750 m ($p < 0.0001$) and to 58.0(3.0) at 5,260 m ($p < 0.0001$). Ascent to altitude reduces cerebral oxygenation, and exercise results in still further reductions. This may in part account for the anecdotal increase in acute mountain sickness (AMS) in those who exercise at altitude. Reduction of cerebral oxygen delivery during exercise may be more important than absolute altitude in determining subsequent AMS development. Oxygen delivery may be similar when comparing a resting subject at 4,500m with a subject exercising at 30% VO_2max at 4,000m, 50% VO_2max at 3,500m and VO_2max at 3,000m. In such a hypothetical situation all subjects would be at the same 'virtual altitude'. At any given altitude the 'virtual altitude' is a dynamic variable, dependent upon both absolute altitude and work undertaken. Assessing cumulative hypoxic insult (time at a 'virtual altitude') over a 24-hour period might more accurately predict the hypoxic stress an individual has experienced.

Acknowledgments: Mount Everest Foundation.

45.

HIGH ALTITUDE PULMONARY EDEMA IS REDUCED IN NEUTRAL ENDOPEPTIDASE GENE DELETED MICE.

David Irwin[1]. Colorado State Univ, Fort Collins, CO[1]. *Email:* davidcirwin@earthlink.net

Neutral endopeptidase (NEP) degrades atrial natriuretic peptide (ANP) and endothelin-1 (ET-1), two opposing peptides that affect the formation of high altitude pulmonary edema (HAPE). ANP is elevated in HAPE, and can abrogate pulmonary vascular leak in vivo and in vitro. ET-1 is a potent pulmonary vasoconstrictor, and recent evidence suggests it is increased in HAPE-prone mountaineers. We hypothesized that a decrease in NEP at high altitude would increase ANP and ET-1 concentrations, but ANP potency would mitigate the effects of ET-1 decreasing the development of HAPE. Plasma ANP and ET-1 concentrations, right ventricular pressure (PRV) and indexes of lung injury were measured in wild type (NEP +/+) mice and mice in which the NEP gene was deleted (NEP -/-). Mice were exposed to a simulated altitude (HA) of 22,000 ft (6728 m; PB = 328 mm Hg) for 24 h. At HA lung wet weight-to-body weight increased in all animals, but was greatest in the NEP +/+ mice. Vascular leak as measured by Evans blue dye was increased only in the NEP +/+ mice at HA. PRV was lowest in NEP −/− mice at LA, but increased in both genotypes at HA. Plasma ANP concentrations increased at HA, but plasma ET-1 concentrations were elevated only in the NEP −/− mice at HA. A correlation between lung wet weight-to-body weight and PRV ($r = 0.57$; $p = 0.007$) was noted We conclude that NEP −/− mice have increased ANP concentration and decreased pulmonary vascular pressure at HA, preventing high altitude-induced pulmonary vascular leak.

Acknowledgments: We thank Dr. Lu Hersch (Dept Molecular and Cellular Biochemistry, Univ Kentucky) for providing us a breeding pair of NEP gene deficient mice. This research project was supported by the American Heart Association, Desert Mountain Affiliate; Pre-doctoral grant 02152627 (David C Irwin)

46.

PRENATAL BLOCKADE OF ESTRADIOL SYNTHESIS ALTERS THE FUNCTIONAL AND MORPHOLOGICAL DEVELOPMENT OF CAROTID BODIES IN NEWBORN RATS.

Vincent Joseph[1]. Laval Univ, Canada[1]. *Email:* joseph.vincent@crsfa.ulaval.ca

The effects of ovarian steroids on carotid bodies (CB – involved in cardio-respiratory responses to hypoxia) have been described in adult mammals. Since premature newborn are chronically deprived of placental-derived hormones (including estradiol) and are at high risk for respiratory disorders, we tested the hypothesis that prenatal estradiol affects CB development. We performed i) respiratory studies using whole body plethysmography, before and 2 hours after i.p. injection of domperidone, (peripheral dopaminergic antagonist acting on CB, 10 mg/kg), and ii) morphological analysis of the CB (immunohistochemical staining with tyrosine hydroxylase, TH, a chemosensitive cells marker) on rat pups born to estradiol-deprived or control mothers. Pregnant female rats received 4androsten-4-ol-3,17dioneacetate (ATD – 5mg/day) to block estradiol synthesis, or vehicle (Veh) during the last week of gestation. Male rat pups were studied 4–5 days after birth. ATD pups (n = 15) had higher resting respiratory frequency than Veh (n = 18 - 160 ± 4 vs. 146 ± 4 breaths/min, p = 0.02). Minute ventilation was not affected by domperione injection in Veh (−4 ± 6%), but decreased in ATD pups (−23 ± 4%, p = 0.01 vs. Veh). Tidal volume increased (8 ± 7%) in Veh and decreased in ATD pups (−14 ± 4%, p = 0.01 vs. Veh). Respiratory frequency decreased in Veh (−11 ± 2%) and ATD (−10 ± 2%). CB morphological analysis show similar mean area in ATD and Veh pups, but TH positive tissue occupied 38 ± 3% of the CB in ATD (n = 9) vs. 25 ± 1% in Veh pups (n = 8 - p = 0.001 ATD vs. Veh). Our results show that prenatal blockade of estradiol synthesis enhances the dopaminergic contribution to baseline ventilation and leads to a specific hypertrophy of glomic tissue in the carotid body. As in adults, exposure to endogenous estradiol in neonates appears as a major determinant of respiratory homeostasis.

Acknowledgments: Raluca Leftre Kerth Van Diep Daon The Hospital for Sick Childrens' Foundation Fond de la Recherche en Santé du Québec Fondation de la Recherche des Maladies Infantiles Chaire de Périnatalogie Jeanne et Jean Louis-Levesque

47.

HIGH-ALTITUDE ANCESTRY PROTECTS AGAINST IUGR AND REDUCTIONS IN BIRTH WEIGHT ASSOCIATED WITH HIGH-ALTITUDE AND PREECLAMPSIA.

Colleen Glyde Julian[1], Enrique Vargas[2], Wendy MacCannell[1], J. Fernando Armaza[2], Lorna G. Moore[1]. Univ Colorado Denver and Health Sciences; CCAMP[1], Instituto Boliviano de Biologia de Altura[2]. *Email:* cgjulian@ouray.cudenver.edu

Background: Observations consistently demonstrate diminished birth weight [BW] with ascending altitude; however population comparisons reveal the extent of BW reduction depends, in part, upon high-altitude ancestry. Objective(s): To examine the influence of variable HA ancestry [Andean, European and Mestizo (admixed)] on BW, IUGR and hypertensive complications across a range of altitudes. Methods: Maternal and infant characteristics were collected from medical records of 3538 consecutive deliveries to women having 2+ prenatal visits at public or private hospitals in Santa Cruz [300m, LA], Cochabamba [2500m, MA] and La Paz or Ororro [3600-3800m, HA], Bolivia. Population ancestry was determined using parental surnames. IUGR was defined as birth weights <10th percentile for gestational age and sex using sea-level criteria. Hypertension during pregnancy was defined as two or more BP readings at least six hours apart > 140/90 mmHg, or a > 30/15 mmHg rise above values recorded at the first prenatal visit in a woman whose BP was < 140/90 mmHg before week 20 or postpartum. Severe preeclampsia [PE] was defined BP > 160/110 mmHg in late pregnancy and all other cases of PE, gestational hypertension [GH] or PE/GH were considered mild. Results: BW declined with ascending altitude [HA: 3365 + 18; MA: 3306 + 16 and LA: 3101 + 12; $p < 0.0001$], however gestational age was equivalent [p = NS]. BW diminished 70g, 56g and 39g per 1000m increase in elevation for Europeans, Mestizoes and Andeans, respectively. IUGR prevalence increased with altitude among Mestizo and European babies; Andeans were unaffected. Likewise, at HA, Andean BW was unaffected by mild or severe PE, whereas severe PE diminished Mestizo and European birth weight [−346g, −1608g, respectively]; mild PE tended to increase European BW at HA [+301.4g]. Conclusions: High-altitude ancestry protects infants from IUGR and reductions in birth weight associated with high-altitude and hypertensive complications during pregnancy.

48.

REDUCED ENDOTHELIN-1 [ET-1] AND ELEVATED NITRIC OXIDE METABOLITES [NOX] ACROSS PREGNANCY AMONG ANDEAN VS. EUROPEAN WOMEN AT HIGH [3100-3600M] ALTITUDE.

Colleen Glyde Julian[1], Megan Wilson[1], Enrique Vargas[2], Marco Vargas[2], Miriam Lopez[2], Susan Neirmeyer[1], Lorna G. Moore[1]. Univ Colorado Denver and Health Sciences; CCAMP[1], Instituo Boliviano Biologia Altura, La Paz Bolivia[2]. *Email:* cgjulian@ouray.cudenver.edu

Background: A consistent reduction in infant birth weight occurs with ascending altitude; however multigenerational high-altitude residents [Andeans] demonstrate a degree of protection from altitude-associated IUGR relative to their European HA counterparts. This difference has been attributed, in part, to greater uterine artery [UA] enlargement during pregnancy among Andeans. Objective: We asked whether maternal circulating levels of vasoactive and angiogenic proteins regulated by the hypoxia inducible factors [HIF] differed between multi-generational Andean HA residents vs. short-term HA and low-altitude [LA] Europeans. Methods: Serum or plasma was collected from women residing at LA (1610m, Denver, Colorado) and HA (3100 and 3600m, Leadville, CO and La Paz, Bolivia) altitude at 20, 30 and 36w gestation and 3 mo post-partum for a nonpregnant measure. ET-1, placental-like growth factor [PLGF], vascular endothelial growth factor [VEGF-free] and soluble Flt-1 [sFlt-1] were assessed via ELISA [R&D, UK]; NOx was measured using chemiluminescence [Sievers, CO]. Effects of pregnancy, altitude and ancestry were quantified using repeated measures and 2-way ANOVA. Results: Circulating levels of the vasoconstrictor ET-1 declined during pregnancy in both Europeans at LA and Andeans at HA; however at HA ET-1 increased during gestation among Europeans but not Andeans [pregnancy: $p < 0.05$; altitude: $p < 0.05$ and ancestry: $p < 0.05$]. NOx declined across pregnancy in all groups [pregnancy: $p < 0.05$]. Altitude decreased circulating NOx levels among Europeans [altitude: $p < 0.01$]. Andeans at HA demonstrated higher NOx levels relative to Europeans at HA [ancestry: $p < 0.001$]. With pregnancy, VEGF declined and sFlt-1and PLGF increased among all groups [$p < 0.001$], but neither altitude nor ancestry influenced their maternal circulating levels. Conclusions: Protection from IUGR and greater UA enlargement during pregnancy among multi-generational HA residents may be due, in part, to reduced production of the vasoconstrictor ET-1 and/or increased production of the vasodilator NO.

49.

CARBOHYDRATE INGESTION DURING ENDURANCE EXERCISE AFFECTS MOOD OF MODERATE-ALTITUDE RESIDENTS AT HIGH ALTITUDE.

Ken Kambis[1], Tamara Payn[2], Megan Hannon[2], Charles Fulco[2], Michael Zupan[3], Dan Cooper[1], Michael Homerick[1], Stephen Muza[2], Paul Rock[4], Allen Cymerman[2]. College William & Mary, Williamsburg, VA[1], US Army Research Inst Environmental Medicine, Natick, MA[2], US Air Force Academy, Colorado Springs, CO[3], Oklahoma State Univ, Tulsa, OK[4]. *Email:* kwkamb@wm.edu

Rapid ascent of unacclimatized sea-level residents (SL) to altitudes greater than ~2500 m coupled with prolonged and intense exercise is associated with negative alterations in mood state that are attenuated with carbohydrate supplementation (CHO). However, little information is available describing what occurs when acclimatized, moderate altitude (MA: ~2000 m) residents (>3months) rapidly ascend and stay at higher elevations. Therefore, our purpose was to determine the effect of MA residence on transient mood alterations during and after endurance exercise (with and without CHO) while residing for 3 days at 4300 m. 16 informed volunteer (9 men, 7 women; age: 30 ± 1yr) residents of MA were rapidly transported to the summit of Pikes Peak, CO (4300 m; HA). At MA and on day 1 and 3 at HA, subjects performed a maximum-effort 720 kJ cycle time-trial (TT). In a double-blind fashion, at the start of exercise and every

15 min thereafter, subjects drank either a 10% carbohydrate solution (0.7 g/kg bw [CHO, n = 9]) or an indistinguishable placebo (PLA, n = 7). Subjects freely adjusted workload and water intake. At rest, 48% and 60% VO_2max, and at 5 and 20 min post TT, subjects completed the Feelings Profile (FP), a 19-item assessment of mood state administered via touch-screen monitor. The CHO group had near-significant (P = 0.055 to 0.062) lower scores than PLA in all negative constructs. Lower (P = 0.05) Fatigue scores were found in the CHO group compared to the PLA group at 20 min. post TT. Mood returned to baseline (MA) values within 3 days at HA. Carbohydrate supplementation attenuates psychological fatigue during recovery from exhaustive exercise in MA residents exposed to HA.

Acknowledgments: Supported by: The Borgenicht Program, The Jeffress Trust, The Reves Center, and The US Dept Defense.

50.
RISE OF BODY TEMPERATURE AT HIGH ALTITUDE.

Norihiro Kamikomaki[1]. Rosai Hospital for Silicosis, Dept Cardiology[1]. *Email:* nori-k@db3.so-net.ne.jp

Low-grade fever occurs sometimes at high altitude. The objective of this research is to inspect the correlation between altitude of stay, AMS score, oxygen saturation (SpO_2) and body temperature (BT), in order to elucidate significance of rise of BT at high altitude. The subjects were members of the expedition team to Muztagh Ata (7546 m). The author recorded the modified Lake Louise AMS score, measured SpO_2 and axillary temperature during mountain climbing. We calculated Spearman's rank correlation between altitude of stay and BT, AMS score and BT, and Pearson's correlation coefficient between SpO_2 and BT of nine members. Concerning to AMS score, SpO_2, BT and altitude, Student's t-test was performed between before reaching the highest altitude and after reaching there. The correlations between altitude of stay and BT ($p < 0.0001$), AMS score and BT ($p = 0.0006$), SpO_2 and BT ($r = -0.365$, $p < 0.0001$) were significant. BT before reaching the highest altitude was higher than BT after reaching there ($p = 0.0015$), though the difference of altitudes of stay or AMS score between before and after reaching there was not significant ($p = 0.67$ and 0.115). SpO_2 before reaching the highest altitude was lower than SpO_2 after reaching there ($p = 0.0011$). BT was higher when the members went to higher place, AMS score rose and SpO_2 decreased. The O_2 dissociation curve shifts to the right when BT rises, and release of O_2 to peripheral tissue is promoted. Therefore, the rise in BT is thought to be suitable for acclimatization. After acclimatization was accomplished, BT decreased to lower level. BT rises during the process of high altitude acclimatization and facilitates release of O_2 to peripheral tissue.

51.
RELATIONSHIP BETWEEN PROTEINURIA AND BLOOD PRESSURE AT HIGH ALTITUDE.

Norihiro Kamikomaki**[1]**. Rosai Hospital for Silicosis, Dept Cardiology**[1]**. *Email:* nori-k@db3.so-net.ne.jp

Although proteinuria at high altitude is well known, its mechanisms are not fully understood. The objective of this research is to inspect the correlation between blood pressure (BP) and proteinuria, in order to elucidate the mechanisms of the occurrence of proteinuria at high altitude. The subjects were nine members of the expedition team to Muztagh Ata (7546 m). They recorded systolic BP (SBP) and urine protein (-, trace, 1+, 2+) during mountain climbing. We got delta SBP by SBP at high altitude minus SBP at sea level, then calculated Spearman's rank correlation between urine protein and delta SBP, and between delta SBP and altitude of stay. There was a significant correlation between urine protein and delta SBP ($p < 0.0001$). Delta SBP was significantly correlated with altitude ($p < 0.0001$), too. SBP rose at high altitude. The rise of SBP is regarded as the result of constriction of systemic arteries and increased cardiac output. The efferent arteries of kidneys are thought to be also constricted at high altitude, thus raise the pressure of glomeruli and those permeability causing increased leak of protein into urine. Proteinuria at high altitude is significantly correlated with rise of blood pressure.

52.
DISRUPTION OF GABA NEUROTRANSMISSION AND ENHANCEMENT OF THE HYPOXIC VENTILATORY RESPONSE IN ADULT RATS SUBJECTED TO NEONATAL MATERNAL SEPARATION (NMS).

Richard Kinkead[1], Norbert Balon[1], Sophie-Emmanuelle Genest[1], Roumiana Gulemetova[1], Sylvie Laforest[1], Guy Drolet[1]. Laval Univ, Canada[1]. *Email:* Richard.Kinkead@crsfa.ulaval.ca

Adult rats previously subjected to neonatal maternal separation (NMS) show a hypoxic ventilatory response 25% greater than controls (Genest et al. 2004). To determine whether NMS disrupts central integration of carotid body afferents, we tested the hypothesis that NMS alters GABAergic neurotransmission at the level of the nucleus of the solitary tract (NTS). Experiments were performed on two groups of rats. Pups subjected to NMS were placed in an incubator 3h/day for 10 consecutive days (P3 to P12). Controls were undisturbed. Once they reached adulthood (8 to 10 weeks), rats were anesthetized (urethane; 1.6g/kg), paralyzed, and ventilated with a hyperoxic gas mixture ($FIO_2 = 0.5$). In each group, rats either received a 50 nl microinjection of GABA (5 μM) or PBS (sham) within the NTS, or received no injection (control) prior to being exposed to moderate, followed by severe isocapnic hypoxia ($FIO_2 = 0.12$; 0.08, respectively, 5-min each). NMS enhanced both the frequency and amplitude components of the phrenic response to hypoxia vs controls. GABA injection within the NTS attenuated the phrenic response in NMS rats only. Ligand binding autoradiography experiments with [3H] muscimol showed that the number of GABAA receptors (BMAX) within the NTS was greater in NMS vs controls. These changes are consistent with a reduction in endogenous GABA release within this structure. We conclude that disruption of GABAergic neurotransmission within the NTS contributes to the enhancement of the hypoxic ventilatory response observed in NMS rats.

Acknowledgments: Supported by the Canadian Institutes of Health Reseach and the Canada Research Chair in Respiratory Neurobiology.

53.

EFFECT OF TEMAZEPAM ON SUBJECTIVE MEASURES (SLEEP QUALITY AND ACUTE MOUNTAIN SICKNESS SCORE, AMS) AT HIGH ALTITUDE.

Juliette Leverment[1], Annabel Nickol[2], Paul Richards[3], Philippa Seal[4], Gerald Dubowitz[5], Jim Milledge[6], John Stradling[2], David Collier[7], Mary Morrell[8]. Shackleton Dept of Anaesthetics, Southampton, UK[1], Chest Unit, Churchill Hospital, Oxford, UK[2], The Surgery, Essex, UK[3], Dept of Anaesthetics, The Bristol Royal Infirmary, Bristol, UK[4], Dept of Anesthesia, Univ California, San Francisco, USA[5], Dept Respiratory Medicine, Northwick Park Hospital, Harrow, UK[6], Clinical Pharmacology, Barts and the London School of Medicine and Dentistry, London, UK[7], Academic Unit of Sleep and Breathing, Royal Brompton Hospital, London, UK[8]. *Email:* annabel@medex.org.uk

The aims of this study were: (1) To verify the beneficial effect of Temazepam on subjective sleep quality and (2) Ensure that its use is not associated with increased AMS. 33 volunteers took part in a double blind crossover randomised trial of 10mg Temazepam versus Placebo on successive nights after arrival at 5000m, following a 17-day trek from 410m. Volunteers were asked whether they slept better on the first or second night. Next day AMS (Lake Louise Score) was assessed on each morning. There was no difference in subjective sleep quality: 17 volunteers slept better following Temazepam, 14 following Placebo, 1 slept equally well and 1 gave no response. Following both Temazepam and Placebo, overall mountain sickness scores were very low (Median = 1; range = 0–4), with median scores of zero for both tiredness and sleep disruption. More volunteers had scores greater than zero following Placebo than Temazepam however: 19/33 and 18/33 respectively for the overall score, 12/33 and 7/33 for tiredness and 17/33 and 12/33 for sleep disruption), with a trend towards reduction in overall score ($p = 0.07$, Wilcoxon-sign rank test) and tiredness ($p = 0.058$) though not sleep disruption ($p = 0.18$). The surprising lack of subjective improvement in sleep quality following Temazepam may reflect the slow ascent profile, and the fact that due to data loss more volunteers received Temazepam than Placebo on the first night (19 versus 14). Concern had been raised that use of Temazepam at high altitude may increase AMS, and it was reassuring there was in fact a trend towards a reduction in AMS scores, especially tiredness, following Temazepam.

Acknowledgments: This work was carried out in association with Medical Expeditions. Funding: Oxfordshire health services research committee; Royal Society of Medicine Scholarship.

54.

WEIGHT AND BODY COMPOSITION CHANGES IN MEN AND WOMEN DURING A HIGH ALTITUDE TREK.

Matthew Litchfield[1], Stephan Sanders[2], Sarah Trippick[3], Douglas Thake[4], Sandra Green[5], David Collier[6], Annabel Nickol[7], Don Patterson[3]. A1E Dept, Calderdale Royal Hospital, Halifax, UK[1], A1E Dept, Derbyshire Royal Infirmary, Derby, UK[2], Medical Expeditions, Pinfold, Hyssington, Montgomery, Powys, UK[3], Sport Science and Physiology Group, School of Science and the Environment, Coventry Univ, Coventry, UK[4], Rheumatology Dept, Nebill Hall Hospital, Abergavenny, UK[5], Clinical Pharmaology, Barts and The London, Charter House Square, London, UK[6], Chest Unit, Churchill Hospital, Oxford, UK[7]. *Email:* stephansanders@hotmail.com

Weight loss at altitude is well recognized. We assessed weight and body composition during a graduated high altitude trek. 42 volunteers (25 male) took part in a return trek from 410m to at least 5000m. Weight was measured at sea level baseline, mid-trek, on arrival at basecamp, before departure from basecamp and on return to Kathmandu; body composition (determined using skin folds and limb circumferences) was measured at baseline, basecamp arrival and return to Kathmandu. Volunteers had a progressive mean ± SD weight loss of -3.9 ± 2.5kg ($p < 0.001$, ANOVA) from a baseline of 69.4 ± 10.8kg. This was predominantly due to fat loss of $-1.9 \pm 2.1\%$ ($p < 0.001$, baseline $24.3 \pm 5.5\%$), with no significant change in muscle mass $+0.4 \pm 2.4\%$ ($p = 0.44$, baseline $43.3 \pm 4.2\%$). Weight loss was greater during the high altitude trek phase (0.25kg/day) than the preceding low altitude trek (0.09kg/day) or rest at basecamp (0.05kg/day). Baseline BMI was a determinant of weight loss ($r2 = 0.29$; $p < 0.001$). Although women lost less weight than men (2.4 ± 1.8kg versus 4.9 ± 2.3kg; $p = 0.001$), this may simply be attributable to their lower baseline BMI (22.1 ± 1.8kg versus 24.3 ± 2.1kg; $p = 0.001$). The sex difference in weight loss was attributable to differences in muscle composition (women lost $0.5 \pm 2.0\%$ muscle whereas men gained 1.1 ± 2.4; $p = 0.03$), with no sex differences in fat loss ($-1.5 \pm 2.1\%$ or women and $2.0 \pm 2.1\%$ for men; $p = 0.44$). Trekking at altitude in our group resulted in significant weight and fat loss, particularly in men. In our study combined exercise and high altitude exposure resulted in the greatest weight loss. Further studies randomising the order of altutude and exercise exposure are required to examine this relationsip further.

Acknowledgments: This work was carried out in association with Medical Expeditions.

55.

EFFECTS OF ISCHEMIC TRAINING ON LEG EXERCISE ENDURANCE.

Jack Loeppky[1], Burke Gurney[2], Yoshio Kobayashi[3], Milton Icenogle[1]. Cardiology Section, VA Medical Center, Albuquerque NM 87108[1], Physical Therapy, Dept. of Health Sciences, Univ New Mexico, Albuquerque NM 87131[2], Laboratory for Health and Human Performance, Chukyo Univ, Japan[3]. *Email:* loeppky@unm.edu

The purpose of this study was to determine whether ischemic exercise training (TrIS+EX) would increase endurance of ischemic (ExIS) and ramp (ExRA) knee extension tests, compared with exercise training (TrEX) alone. Pre and post-training tests were done on each leg of 10 healthy subjects (age: 35–68 yr) by performing 20 extensions per min. For ExRA, after 2 min of exercise with a load of 9–14% of a single maximal voluntary contraction, the load increased each min until exhaustion. ExIS was similar, but after 2 min an upper thigh cuff was inflated to 150 mm Hg instead of increasing load. One leg underwent TrIS+EX (cuff inflated to 150 mm Hg during exercise) and the other TrEX, both with a 1.1 kg weight on each leg, 4–6 times per daily session for 3–5 min each, 5 days/ week for 6 weeks. The ExIS duration increased more (120%, $p = 0.002$) in the TrIS+EX leg than in the contra-lateral TrEX leg, whereas ExRA duration increased only 16% more (NS). TrIS+EX and TrEX significantly attenuated the ventilation increase (ergoreflex) during ExIS

and the O_2 debt for ExIS was significantly lower after TrIS+EX than after TrEX, with similar trends after ExRA. TrIS+EX significantly increased the heart rate recovery rate after ExRA and ExIS and lowered systolic blood pressure after ExIS, but not after ExRA. EMG indicated that motor unit firing frequency was reduced similarly by both exercises before and after either training, indicating similar motor unit fatigue levels were reached in all exercise tests. These results indicate that low-intensity TrIS+EX increased exercise endurance and reduced the ergoreflex exercise response. Ischemic exercise training may be useful to increase regional muscle endurance in order to improve systemic exercise capacity after deconditioning.

Acknowledgments: This research project was supported by VA Merit grant A2950R.

56.

EFFECTS OF MODERATE ALTITUDE ON PERIPHERAL SWEATING.

Maurie Luetkemeier[1], John Davis[1], Heidi Ventline[1], Lauren Giordano[1]. Alma College, Alma, Michigan[1]. *Email:* luetkemeier@alma.edu

The purpose of the study was to determine the effects of acute and chronic exposure to moderate altitude (3416-m) on pilocarpine-induced peripheral sweating. Sweating was measured on the forearms of 15 healthy individuals at 4 times: (L1) Lowland (243-m) before ascent, (A1) 1-day after ascent to altitude, (A2) 16-days after ascent to altitude, and (L2) 1-day after return to lowland. Sweating was induced by pilocarpine iontophoresis for 11-min and sweat was collected for 15-min using a $7cm^2$ capsule containing a coiled capillary tube. The capsule was weighed before and after sweat collection as a means of quantifying sweat volume. Sweat gland density was determined by blotting the test site with iodine-impregnated paper for 10-sec and counting the resultant dots in each of 4 1-cm^2 blocks. The volume of sweat per gland was calculated by dividing sweat volume into the number of active sweat glands. There was no change in sweat volume, sweat gland density, and the sweat volume per gland in participants going from lowland to acute altitude exposure. There were significant reductions in all 3 variables between acute altitude exposure and 16-days of altitude exposure. There were no significant differences in these 3 variables between measurements taken following 16-days of altitude exposure and upon return to lowland. Sweat volume, sweat gland density, and the volume of sweat per gland did not declined acutely following ascent to 3416m rather the decline in these variable materialize after living at altitude for 16-days. Sweat rate, sweat gland density, and the volume of sweat per gland did not recover immediately upon descent back to lowland. These results indicate that sweating function may diminish following several weeks of exposure to 3416m and may not immediately resolve upon return to lowland.

57.

EPISODIC HYPOXIA AND RESPIRATORY PLASTICITY.

Norbert Maassen[1], Nadine Stuke[1]. Sportsphysiology Medical School Hannover[1]. *Email:* Maassen.Norbert@mh-hannover.de

Episodic hypoxia (EH) was shown to result in an increase in ventilation in goats. There are only few studies investigating the effects on ventilation in humans (McEvoy et al. 1996). Recently EH emerged in sports as intermittent hypoxia training (IHT) to improve endurance performance. In this study the time courses of ventilatory parameters during an IHT-session were examined. 9 male subjects experienced EH consisting of 5 min hypoxia (9%) alternating with 5 min normoxia for 1.5 hour (9 episodes). Heart rate and SO_2 were measured from a fingertip (infrared; Hypoxicator, Biomedtech, Australia). Ventilation was recorded breath by breath (Metalyzer IIIB, Cortex). Arterialized blood was taken from a hyperaemized earlobe to measure acid base status (ABL, Radiometer). At the end of the hypoxic episodes ventilation was about 11 l with no tendency to increase over time. Immediately after the hypoxic periods VE fell to values lower than 7 l without any tendency to change over time. Base line and the changes due to hypoxia were stable for VT, RR, flow and $PetO_2$, as well. This stability was reflected by blood gas measurements at the end of the hypoxic episodes. SO_2 did not change as well. The only variable showing a small change was $PetCO_2$ (-1 Torr over 90 min) both at the end of hypoxic and at normoxic episodes. Respiratory plasticity can not be seen in this set up. This might be caused by the non-isocapnic conditions. The decrease in PCO_2 might compensate for an increase in ventilation of about 3 l in normoxia and 6 l in hypoxia. In relation to IHT the total amount of ventilation is too low to function as respiratory training and thus to cause the improvement in performance.

58.

DIFFERENCES IN CARDIOVENTILATORY RESPONSES DURING EXERCISE BETWEEN HYPOBARIC AND NORMOBARIC HYPOXIA.

Taketeru Maekawa[1], Taisuke Enoki[1], Mitsuo Neya[2]. Dept Sports Science, Japan Inst Sports Sciences[1], Univ Tokyo[2]. *Email:* maegawa.taketeru@jiss.naash.go.jp

Physiological responses to altitude have been extensively investigated during the past one and a half centuries. Most research focused mainly on hypoxia, so it is still unclear whether "the physiological effects of hypobaric and normobaric hypoxia are similar for the same PO_2?" This study investigated the differences in cardioventilatory responses during exercise between hypobaric and normobaric hypoxia for the same ambient PO_2 equal to 147 hPa (simulating an altitude of 3000 m). Six male subjects who are not acclimated to high altitude performed an incremental pedaling exercise test under hypobaric hypoxia (PB = 701 hPa, PO_2 = 147 hPa, O_2 = 20.9%) and normobaric hypoxia (PB = 1013 hPa, PO_2 = 147 hPa, O_2 = 14.5%). To create hypoxic conditions, we used two devices: a hypobaric chamber for hypobaric hypoxia, and a normobaric hypoxic room with a membrane separation system for normobaric hypoxia. Cadioventilatory variables (oxygen uptake (VO_2), breathing frequency (fR), tidal volume (VT), minutes ventilation (VE), O_2 and CO_2 end-tidal fractions ($FETO_2$, $FETCO_2$), heart rate (HR) and arterial oxygen saturation by pulse oxymetry (SpO_2)) were measured through the test. There were no differences between hypobaric and normobaric hypoxia for VO_2, fR, VT, VE, and HR during submaximal exercise. VO_2max, VEmax, and HRmax were also not significantly different for hypobaric and normobaric hypoxia. However expressed under STPD conditions, VEmax, and VE during submaximal exercise were lower for hypobaric hy-

poxia. SpO_2 at maximal exercise was not different for the two environments. However, during submaximal exercise, SpO_2 was lower for hypobaric hypoxia. $FETO_2$ and $FETCO_2$ were higher for hypobaric hypoxia. The higher $FETCO_2$ may have affected the lower SpO_2 for hypobaric hypoxia (i.e. the oxygen dissociation curve shifts to the right). In conclusion, these results suggest that cardioventilatory responses during exercise differ between hypobaric and normobaric hypoxia for the same ambient PO_2. However, theses differences were small.

59.

PHOSPHODIESTERASE-5 INHIBITION AND GLUCOCORTICOIDS PREVENT EXCESSIVE HYPOXIC PULMONARY VASOCONSTRICTION AND HIGH ALTITUDE PULMONARY EDEMA IN SUSCEPTIBLE SUBJECTS.

Marco Maggiorini[1], Hans-Peter Brunner-La Rocca[2], Manuel Fischler[1], Thomas Bïhm[3], Thomas Lehmann[4], Konrad E. Bloch[5], Robert Naeije[6], Peter Bärtsch[7], Heimo Mairbäurl[7]. Intensive Care Unit, Univ Hospital Zurich, Switzerland[1], Cardiology, Univ Hospital Basel, Switzerland[2], Radiology, Univ Hospital Zurich, Switzerland[3], Internal Medicine, Kantonspital Chur, Switzerland[4], Pneumology, Univ Hospital Zurich; Switzerland[5], Laboratory of Physiology, Free Univ Brussels, Belgium[6], Medical Clinic VII, Sports Medicine, Univ Heidelberg, Germany[7]. *Email:* klinmax@usz.unizh.ch

High altitude pulmonary edema (HAPE) is mainly caused by excessive hypoxic pulmonary vasoconstriction (eHPV). Reduced alveolar fluid clearance might also play a role. In order to better separate these effects HAPE-susceptible subjects were randomized to receive prophylaxis with dexamethasone to enhance alveolar fluid clearance (2×8mg; $n = 10$), tadalafil to reduce eHPV (2×10mg; $n = 8$) or placebo ($n = 9$). At high altitude (HA; 4559m), HAPE was diagnosed from chest-x-rays and acute mountain sickness (AMS) using the Lake Louise score (LLs), and pulmonary artery pressure was estimated by measuring the pressure gradient of the tricuspid regurgitation (dpTI) (Doppler-echocardiography). HAPE developed in 7 of 9 subjects receiving placebo, in 1 of 8 with tadalafil and in none with dexamethasone ($p < 0.001$). Eight subjects in placebo, 6 in tadalafil, and 1 in dexamethasone had an LLs > 5 ($p < 0.001$). Subjects receiving dexamethasone or tadalafil, had at HA higher PaO_2 than P ($p < 0.001$); the highest values were obtained with dexamethasone ($p < 0.05$ vs. tadalafil); $PaCO_2$ was not different between groups. Accordingly, $AaDO_2$ was highest in placebo (18 ± 7 mmHg, vs. 7 ± 12 mmHg in tadalafil and 1 ± 4 mmHg in dexamethasone; $p < 0.001$). At HA dpTI was 49 ± 12 mmHg in placebo, 33 ± 2 in tadalafil and 33 ± 8 in dexamethasone; $p < 0.001$), and heart rate was lowest in dexamethasone (55 ± 11 b/min vs. 89 ± 15 b/min in tadalafil and 87 ± 19 b/min in placebo; $p < 0.001$), whereas blood pressure was not different between groups. IL-6 was lower in all tadalafil and dexamethasone subjects without HAPE at HA compared with placebo. Plasma glucose was not different between groups. We conclude that in HAPE-susceptible mountaineers both inhibition of the phosphodiesterase-5 and glucocorticoids prevent eHPV and HAPE. Since dpTI was lower and similar in dexamethasone and tadalafil treated subjects no definite conclusion on the involvement of alveolar fluid clearance in the pathogenesis of HAPE can be made.

Acknowledgments: Hartmann-Müller Foundation, Zurich, Crivelli Foundation, Lugano, grant n° 3.4613.04 from the Fonds de la Recherche Scientifique Medicale (FRSM), Belgium.

60.

PREVENTION OF HAPE IS NOT ASSOCIATED WITH CHANGES IN NASAL POTENTIALS.

Heimo Mairbäurl[1], Simon Peth[2], Christoph Dehnert[1], Manuel Fischler[3], Marco Maggiorini[4], Peter Bärtsch[1]. Medical Clinic VII, Sports Medicine, Univ Heidelberg[1], Medical Clinic III, Cardiology, Univ Heidelberg[2], Intensive Care Unit DIM, Univ Hospital Zürich[3], Intensive Care Unit DIM, Univ Hospital Zürich, Switzerland[4]. *Email:* heimo.mairbaeurl@med.uni-heidelberg.de

High altitude pulmonary edema (HAPE) is mainly caused by exaggerated pulmonary capillary pressure, but has also been associated with diminished alveolar reabsorption caused by hypoxia-induced inhibition of alveolar Na-transport and/or a pre-existing defective transport. In a double blind study, subjects with a history of HAPE took placebo (PLA), tadalafil (10 mg bid; TAD) to prevent pulmonary hypertension, and dexamethasone (8 mg bid; DEX) to stimulate Na-transport, two days prior to and during the 2-days stay at 4559m (HA). HAPE diagnosed by chest radiographs, occurred in PLA (70%) and TAD (12.5%) but not in DEX. Nasal potential (NP) as well as its amiloride- and chloride-sensitive components were determined as indirect measures of lung ion transport, since alveoli are not assessable to transport measurements in vivo. At HA, total NP and amiloride-sensitive NP decreased significantly in PLA and DEX. Hypoxic inhibition was prevented by TAD. Neither drug affected chloride secretion. Leukocyte Na-transporter mRNA expression was not altered by the treatment. cGMP, which affects vascular tone and Na-transport, was increased at HA in TAD and DEX. These results show that DEX, known to stimulate alveolar water reabsorption, prevented HAPE in HAPE-susceptibles without affecting nasal epithelial Na-transport, whereas TAD prevented HAPE as well as the hypoxia-induced inhibition of NP. They suggest divergent action of hypoxia and treatment on transport of nasal and alveolar epithelia. Alternatively, if NP were to reflect alveolar ion transport, HAPE-prevention ocurred independent of treatment effects on alveolar ion transport.

61.

EXERCISE MINUTE VENTILATION AS A PREDICTOR OF ERYTHROPOITIC RESPONSE.

Spencer R. McLean[1], Stephen R. Norris[1], Jon C. Kolb[1], David J. Smith[1]. Univ Calgary, Human Performance Laboratory, Canada[1]. *Email:* kolb@ucalgary.ca

Acute hypoxia augments minute ventilation (VE) mediated by peripheral chemosensory input, while circulating serum erythropoietin concentration (s-[EPO]) increases in response to reduced oxygen delivery to the kidneys. The relationship between individual variability of the hypoxic ventilatory chemosensitivity and erythropoitic precursors is uncertain. Thus, the purpose of this study was to determine if the magnitude of the VE response to acute poikilocapnic hypoxia was related to the magnitude of the increase in s-[EPO]. Six males cycled at their first ventilatory threshold for six minutes under nor-

mobaric normoxia and then for six minutes under normobaric hypoxia (FIO_2 = 15.0%). End tidal oxygen, carbon dioxide and VE were analyzed during both conditions using a Truemax 2400 metabolic cart. Four weeks later, the subjects were exposed to three consecutive 8-hour days of normobaric hypoxia (FIO_2 = 12.9+0.8%) utilizing hypoxic tent systems. Blood samples were collected for s-[EPO] analysis (Chemiluminescent Immunoassay System) before the hypoxic exposures and after each day of hypoxic exposure. Correlation analysis was used to quantify the association between the magnitude of change in VE from normoxic to hypoxic exercise and the magnitude of change in s-[EPO] from baseline to peak during the hypoxic exposures. Comparing hypoxic to normoxic exercise, VE increased by 14.6+9.3 $L \cdot min^{-1}$. The intermittent hypoxic intervention elicited an mean increase in s-[EPO] of 22.8 + 5.5 $U \cdot L^{-1}$. A negative relationship ($r = -0.808$, $p = 0.052$) was revealed between the magnitude of the increase in VE and the magnitude of the increase in s-[EPO]; subjects who demonstrated a blunted ventilatory drive to hypoxic exercise also demonstrated greater increases in s-[EPO] during resting hypoxic exposures. These preliminary results suggest that ventilatory perturbations elicited during bouts of normoxic and hypoxic exercise may have use as a predictor of the erythropoitic response to intermittent hypoxia.

Acknowledgments: This research was supported by the Natural Sciences & Engineering Research Council, Canadian Sport Centre-Calgary, Calgary Olympic Development Association, and Sport Science Association of Alberta.

62.

NEW INSIGHTS INTO SUBLINGUAL GLYCERYL TRINITRATE INDUCED HEADACHE AS A PREDICTOR FOR INCIPIENT ACUTE MOUNTAIN SICKNESS.

Roger McMorrow[1], Nigel Hart[1], Oliver Kemp[1], Neil Richardson[1]. MedEx[1]. *Email:* roger_mcmorrow@bigfoot.com

The most common symptom associated with Acute Mountain Sickness (AMS) is headache. The headache may be caused by meningeal irritation as a result of blood vessel dilatation. Glyceryl trinitrate (GTN) is known to dilate cerebral vasculature and causes headaches similar in quality to the headache associated with AMS. In previous studies to Kilimanjaro (5892m) and Pk6175 (6175m) in the Indian Himalaya, we demonstrated that GTN may be used as a predictor of incipient AMS. In this study further data were gathered from nineteen healthy adult volunteers during the MedEx 2003 expedition to Makalu base camp (5005m). Headache shift vectors (HSV) were calculated from headache scores rated pre and post sub-lingual GTN administration. Baseline HSVs were calculated for each subject at sea-level. GTN induced headache shifts were rated daily on ascent to altitude and by subtracting baseline observations normalised HSVs (nHSV) were calculated. These data were analysed using the Fisher test. No correlation ($p = 0.6$) was found between nHSV and change in the observed AMS scores (ΔAMS) over the following 24 hours where a further ascent of between 400-1000m occurred. This is contrast to the results of previous studies on Kilimanjaro and Pk6175 ($p = 0.003$ and $p = 0.005$ respectively). This may be due to the relatively slow ascent profile of the Makalu expedition (263m/day vs. 841m/day and 441m/day on the Kilimanjaro and Pk6175 expeditions respectively). These findings do not support the use of GTN as a predictor for incipient AMS where the ascent profile is less than 264m/day.

Acknowledgments: With thanks to our subjects and MedEx

63.

CHRONIC INTERMITTENT HYPOXIA IMPAIRS ENDOTHELIUM-DEPENDENT DILATION IN RESISTANCE ARTERIES.

Barbara Morgan[1], Shane Phillips[2], Burt Olson[1], Julian Lombard[2]. Univ Wisconsin-Madison[1], Medical College of Wisconsin[2]. *Email:* morgan@surgery.wisc.edu

Episodes of sleep disordered breathing produce hypoxia, hypercapnia, and arousal from sleep. In humans, sleep disordered breathing is associated with abnormal blood flow regulation and cardiovascular diseases such as hypertension, heart failure, and stroke. Our goal was to evaluate the effect of chronic intermittent hypoxia (CIH) on endothelial function in a rat model of sleep disordered breathing. Sprague-Dawley rats (n = 6) were exposed to CIH by reducing the FIO_2 to 10% for 1 minute, 15 times per hour, 12 hrs per day. Control rats (n = 6) were housed under normoxic conditions. After 14 days, gracilis arteries (GA) and middle cerebral arteries (MCA) were isolated and cannulated with micropipettes; perfused and superfused with physiological salt solution, and equilibrated with 21% O_2 and 5% CO_2 in a heated chamber. The arteries were pressurized to 90 mm Hg and vessel diameters were measured via video micrometer before and after exposure to acetylcholine (10-7 to 10-4 M), sodium nitroprusside (10-6 M), and acute reduction of PO_2 in the perfusate/superfusate to 40 mmHg. Acetylcholine-induced dilations of GA and MCA from animals exposed to CIH were greatly attenuated, whereas responses to nitroprusside were similar to normoxic controls. Dilations in response to acute reductions in PO_2 were virtually abolished in CIH vs. control arteries. In contrast, maximal relaxation in calcium-free physiologic saline solution was unaltered by CIH. Mean arterial pressure, measured in anesthetized rats prior to vessel harvesting, was the same in CIH and control rats. These findings suggest that exposure to CIH reduces the bioavailability of nitric oxide in the cerebral and skeletal muscle circulations. CIH-induced impairments in blood flow regulation may compromise oxygen delivery during stresses such as exercise and episodes of hypoxemia caused by sleep-disordered breathing.

Acknowledgments: Supported by NIH #HL65289, #HL29587, #HL074072.

64.

CARBOHYDRATE INGESTION DURING EXERCISE AT HIGH ALTITUDE DECREASES POST-EXERCISE AMS INCIDENCE AND SEVERITY.

Stephen Muza[1], Charles Fulco[1], Michael Zupan[2], Kenneth Kambis[1], Paul Rock[1], Leonard Elliott[1], Michael Tapia[1], Megan Hannon[1], Tammara Payn[1], Ellen Glickman[1], Allen Cymerman[1]. U.S. Army Research Inst Environmental Medicine, Natick, MA, USA[1], U.S. Air Force Academy, CO, USA[2]. *Email:* stephen.muza@us.army.mil

Physical exertion early in high altitude exposure exacerbates AMS incidence and severity. High-carbohydrate

diets have been suggested as a "non-pharmacological" intervention to alleviate the symptoms of AMS. The purpose of this study was to determine if carbohydrate ingestion during prolonged cycle exercise decreased AMS symptoms post-exercise. Subjects were healthy Air Force Academy active duty members (9 men and 6 women; age: 30 ± 1 yrs; X ± SE) who had been living in the Colorado Springs, CO area (~1800 to 2200 m) for at least 3 months. Subjects performed a maximum effort 720 KJ cycle time trial (TT) starting about 2 hours after car ascent to 4300 m. Oxygen saturation (SaO_2, pulse oximeter) was recorded during exercise. At the start of exercise, and every 15 min thereafter, 9 subjects (CHO) drank a 10% CHO solution (0.7 g/kg bw) and 7 subjects (PLA) drank an indistinguishable placebo (double-blinded). All freely adjusted work rate and drank water. AMS was assessed using the validated "AMS-Cerebral (AMS-C)" factor score calculated from the Environmental Symptoms Questionnaire administered prior to and 3 and 6 h after completion of the TT. Both groups had similar TT duration (107 ± 7 min), mean work intensity (~65% VO_2peak) and SaO_2 decreases from rest to exercise (~86% to ~79%). Both groups had similar low AMS-C scores (0.204 ± 0.099) before the TT started. At 3 h post-TT, AMS severity (1.033 ± 0.185 vs. 0.341 ± 0.125, P = 0.007) and incidence (72% vs. 11%) were higher in the PLA group vs. the CHO group; but declined to similar levels (0.354 ± 0.134) 6 h post-TT. Carbohydrate ingestion during prolonged exercise early in high altitude exposure was effective in decreasing the incidence and severity of AMS symptoms post exercise.

65A.

EFFECT OF SILDENAFIL ON SIX-MINUTE WALK TEST AT HIGH ALTITUDE ON MOUNT EVEREST.

Renelle Myers[1], Doug Maguire[1], Bryce Brown[1], Zoher Bshouty[1]. Univ Manitoba[1]. *Email:* renmye@hotmail.com

Sildenafil has been shown to reverse hypoxic pulmonary vasoconstriction and may have potential benefit in reversing pulmonary hypertension secondary to ascent to altitude. This effect on exercise performance may enable climbers to achieve better exercise tolerance at altitude. We studied the effect of ascent to 5245meters on Mount Everest base camp on the six-minute walk test in 15 healthy subjects (8 females, 7 males) before and 60 minutes after the ingestion of 50mg of sildenafil. All subjects were required to walk for 6 minutes on a prepared 15 meter-long surface at base camp. Weather conditions during the test were not stormy. Heart rate and oxygen saturation were recorded at rest and at six minutes. The distance walked in six minutes was recorded. Resting values were compared to predicted values for sea level and post-drug values were compared to pre-drug levels using paired-t test. Mean age, height and weight +/-SE were 33.47+/−2.90years, 174.67+/−2.09cm and 66.85+/−3.10 kg, respectively. Mean predicted, pre and post drug six-minute walk distances +/− SE were 722+/−19m, 642+/−16m, and 661+/−13m, respectively. Exercise tolerance at base camp was significantly lower compared to predicted from sea level (mean difference 80 meters, $p < 0.004$). On average, exercise performance was 88.9% predicted. The administration of sildenafil improved exercise tolerance at high altitude by only 19 meters ($p < 0.004$). Sildenafil did not have an effect on heart rate or saturation at rest and following six minutes of exercise. Exercise tolerance is significantly reduced at altitude even when assessed by the six-minute walk test. The acute administration of sildenafil did not have a physiologically significant effect on exercise tolerance at altitude.

65B.

HYPOXIA: A COUNTERMEASURE TO MICROGRAVITY?

Vishal Nangalia[1]. North West London Hospitals Trust[1]. *Email:* vishal@spacesurgeons.com

Exposure to microgravity results in a multitude of chages to the human all of which are yet to be fully documented. Microgravity adaptation though does result in a significant decrease in ability and performance on return to a gravity environment. Various countermeasures have been proposed and are being used. However all of these are short duration or acute in application exercise, lower body negative pressure, etc. The hypothesis being discussed is whether chronic exposure to hypoxic conditions during spaceflight would result in adaptations that mitigate the detrimental effects of microgravity on the human body. Spaceflight results in deconditioning of the cardiovascular system, loss of fluid volume, bone demineralization, and atrophy of skeletal muscles particularly of the slow twitch variety. The changes in human physiology in microgravity will be paired with hypoxic adaptations in the same system and arguments will be presented for each along with mechansims of action where applicable. This is literature search and a concept paper. No data at present exists on the effect of simultaneously exposing an astronaut to microgravity and hypoxia. The Space Exploration Initiative however is an exploration driven programme and the primary driver is no longer research (as was the case for the space station and the space shuttle) and therefore previously held absolutes such as the environmental requirements for human habitation will be open for discussion. A targetted review of the adaptation to the stressors of hypoxia and microgravity will show that the chronic stress of hypoxia and the resultant adaptations to it could prove to be an important countermeasure in long duration spaceflight. Furthermore hypobaric hypoxia would in itself result in a range of benefits to the spacecraft system itself that would confer significant benefits for exploration class missions, and a brief review of these will be presented.

66.

EFFECT OF TEMAZEPAM ON OBJECTIVE MEASURES (SLEEP DISORDERED BREATHING AND NEXT DAY PERFORMANCE) AT HIGH ALTITUDE.

Annabel Nickol[1], Paul Richards[2], Philippa Seal[3], Juliette Leverment[4], Gerald Dubowitz[5], Jim Milledge[6], John Stradling[1], Mary Morrell[7]. Chest Unit, Churchill Hospital, Oxford, UK[1], The Surgery, Essex, UK[2], Dept Anaesthetics, The Bristol Royal Infirmary, Bristol, UK[3], Shackleton Dept Anaesthetics, Southampton, UK[4], Dept Anesthesia, Univ California, San Francisco, USA[5], Dept Respiratory Medicine, Northwick Park Hospital, Harrow,

UK[6], Academic Unit of Sleep and Breathing, Royal Brompton Hospital, London, UK[7]. *Email:* annabel@medex.org.uk

The aims of this study were: (1) To verify the beneficial effect of Temazepam on sleep disordered breathing of high altitude, and (2) Examine its safety for use at altitude with particular regard to nocturnal oxygenation and next day performance. 33 volunteers took part in a double blind crossover randomised trial of 10mg Temazepam versus Placebo on two successive nights soon after arrival at 5000m, following a 17-day trek from 410m. Overnight SaO_2 and actigraphy, and next day reaction time and modified maintenance of wakefulness test (MWT) were assessed. Compared to Placebo, Temazepam resulted in a reduction in periodic desaturations (PD) from a median (range) of 15 (0–81) to 9 (0–80) % of the night ($p = 0.02$, Wilcoxon sign rank test). This occurred at the expense of a small but significant decrease in mean nocturnal SaO_2 from 78 (65–84) to 77 (64–83) % ($p = 0.01$). There was no change in sleep latency or restlessness (movement and fragmentation index) as indicated by actigraphy, nor next day reaction time and MWT. We have shown that Temazepam reduces periodic breathing during sleep without an adverse effect on next day reaction time and sleepiness. The small reduction in mean SaO_2 is likely to be due to less waking with associated restoration of SaO_2, as evidenced by the reduction in periodic breathing. The fall of 1% is not likely to be clinically significant in our group, however studies at extreme altitudes, or in groups with faster ascent profiles are required to verify its safety in these situations.

Acknowledgments: This work was carried out in association with Medical Expeditions. Funding: Oxfordshire health services research committee; Royal Society of Medicine Scholarship.

67.

EFFECTS OF PHYSICAL LOADING-INDUCED INTERMITTENT HYPOXIA ON ACCLIMATIZATION.

Xue-Han Ning[1], S-H. Chen[1], C-S. Xu[2], F-R. Wang[2], H-Y. Lin[2], S-C. Zhu[2], C-H. Wei[2], P-G. Huang[2], Y-Y. Zhang[2], O.M. Hyyti[1], M. Ge[1], M.A. Portman[1]. Univ. of Washington Med Ctr, and Children[1], High Altitude Physiology Collaborative Group, Shanghai Istitute of Physiology, Academia Sinica, China[2]. *Email:* xh@u.washington.edu

Heavy physical loading and sleep periodic breathing are the major procedure to induce short-cycle intermittent hypoxia (IH) that can deteriorate hypoxemia at high altitude. Hypothesis: Physical loading induced intermittent hypoxia may deteriorate acclimatization process, if the hypoxia reaches an injury threshold. The harmful effects may relate to impairment in energy pathways of mitochondria. Human: Symptoms, ECG and cardiac reserve capacity (calculated by arterial blood pressure, heart rate, and index of cardiac ejection) were analyzed in low land comers during rest and physical loading, respectively. Animal: To avoid complex systemic effects, isolated perfused rabbit hearts were used to test the effects of IH that reached the "injury threshold". Human: Heavy work miners had severe "High Altitude Syndromes", including jaded appetite, lost body weight, headache, etc than controls ($P < 0.05$). During real labor work condition and/or work on an ergo meter at 4000 m, the miners showed a lower arterial blood saturation accompanied with abnormal ECG after heavy performance. The poor cardiac reserve capacity was accompanied with severe symptoms. Animal: IH was induced in the hearts with 2 min of hypoxic infusion and 2 min reoxygenation to mimic a kind of labor work at 4000 m. The hypoxic oxygen content was 0.22 micro mol/ml, which was an injury threshold for functional recovery. After 23 cycles, IH significantly decreased function and energy status than control ($P < 0.05$). The mitochondrial beta F1-ATPase mRNA intensity was lower than control hearts. Acclimatization was deteriorated by heavy physical loading induced IH that injures energy related pathways and results in dysfunction.

Acknowledgments: This study was supported in part by CHMC HR5836 and NSFC389.

68.

EFFECTS OF HIGH ALTITUDE EXPOSURE ON CEREBRAL HEMODYNAMICS IN NORMAL SUBJECTS.

Aurelie van Osta[1], Jean-Jacques Moraine[1], Christian Mélot[1], Heimo Mairbaurl[2], Marco Maggiorini[3], Robert Naeije[1]. Free Univ Brussels, Belgium[1], Univ Heidelberg, Germany[2], Univ Zürich, Switzerland[3]. *Email:* rnaeije@ulb.ac.be

We explored the possibility that hypoxia-induced alterations of dynamic cerebral autoregulation, critical closing pressure (CCP) or pulsatility index (PI) could be implicated in acute mountain sickness (AMS) pathophysiology. We measured cerebral blood flow velocity (Vmca) by transcranial Doppler and arterial blood pressure by finger plethysmography at 490 m, and 20 hours after arrival at 4559 m in 35 volunteers who had been randomized to tadalafil, dexamethasone or placebo as part of a study on the pharmacological prevention of high-altitude pulmonary edema. A dynamic cerebral autoregulation index (ARI) and CCP were calculated from continuous recordings of Vmca and blood pressure during transiently induced hypotension. A PI was calculated as the difference between systolic and diastolic Vmca divided by mean Vmca. Altitude was associated with an increase in a cerebral sensible AMS (AMS-C) score ($p < 0.001$), without change in average Vmca, ARI, CCP or PI. However, AMC-S score was negatively correlated to ARI ($r = -0.47$, $p < 0.01$) and to PI ($r = -0.36$, $p < 0.05$). The AMS-C score was not correlated to Vmca or CCP. ARI, CCP and PI were positively correlated to arterial oxygenation. The AMS-C score was lower in dexamethasone-treated subjects compared to high-altitude pulmonary edema-sensible controls. Neither tadalafil nor dexamethasone had any significant effect on Vmca, ARI, CCP or PI. The pathogenesis of AMS remains unknown. A leading hypothesis relates AMS to early stages of brain edema that may progress in a proportion of subjects to full blown high altitude cerebral edema (HACE). The present findings are in keeping with the notion that AMS and HACE might be caused or aggravated by an overperfusion of cerebral capillaries, leading to increased capillary filtration and a vasogenic-type cerebral edema Altitude is associated with impairment in the regulation of

the cerebral circulation that might be implicated in the pathogenesis of AMS.

69.
ADVANCES IN MOUNTAIN MEDICINE EDUCATION IN THE UNITED KINGDOM.
Kyle T S Pattinson[1], Peter Barry[1a], Peter Davis[2], Chris H E Imray[3], Nicholas P Mason[4], Paul Richards[5], Piotr Szawarski[5], David Hillebrandt[6]. Nuffield Dept Anaesthesia, Univ Oxford, Oxford, UK[1], Dept Child Health, Leicester Royal; Infirmary, Leicester UK[1a], Accident and Emergency Dept, Southern General Hospital, Glasgow, UK[2], County Vascular Unit, Coventry and Warwickshire Univ Hospitals, Coventry, UK[3], Dept Critical Care Medicine, Univ Hospital of Wales, Cardiff, UK[4], Medical Expeditions, London, UK[5], Holsworthy Health Centre, Devon, UK[6]. *Email:* kyletsp@postmaster.co.uk

In 1997 a joint commission of the International Alpine Association; the International Mountain Rescue Association and the International Society for Mountain Medicine defined a syllabus for an international diploma in mountain medicine. We have set up the first English language diploma to follow this syllabus, to teach and share the knowledge and practice of mountain medicine and to provide a benchmark for doctors wishing to practice it. The course format was developed with a pilot course by faculty members prior to the first formal intake and an analysis of educational literature to ensure appropriate teaching and assessment methods. The course consists of four one week modules: two weeks of predominantly theoretical teaching covering physiology; travel and environmental medicine, and two weeks of practical mountaineering in Scotland in winter and the Swiss Alps in summer. The faculty comprises doctors involved with mountain medicine and mountain guides from the British Association of Mountain Guides. Candidates must demonstrate previous mountaineering experience before commencing the course. Candidates and successful holders of the diploma are required to keep a log book of relevant mountaineering and medical activities Thirty candidates have now completed the course. There is sufficient demand for the course to continue annually. The course has had impact extending beyond the original aims. Increased awareness of the diploma resulted in successful treatment of a climber with frostbite in the Andes and collaboration between UK altitude research groups has also increased The effect of the diploma has exceeded expectations with regard to its impact on the British mountain medicine community.

Acknowledgments: The United Kingdom UIAA diploma in mountain medicine is supported and administered by Medical Expeditions a charitable organisation founded to promote research and education in high altitude medicine.

70.
P38 MAP KINASE: A MECHANISM FOR HYPOXIA-INDUCED VASCULAR CELL PROLIFERATION.
Andrew Peacock[1], David Welsh[1]. SPVU, Western Infirmary, Glasgow, Scotland[1]. *Email:* david.welsh@bio.gla.ac.uk

All mammals have physiological and biochemical mechanisms that are activated by hypoxia. One such mechanism is vasoconstriction of pulmonary vessels which is observed in nearly all animal species including man and is accompanied by proliferation of pulmonary vascular cells leading to remodelling. Paradoxically the systemic circulation dilates and does not remodel in the face of hypoxia. We have focused on the role of the vascular fibroblasts because they are the first to proliferate in the face of hypoxia. Cell proliferation is known to be controlled by intracellular signalling systems involving sequential phosphorylation of kinase molecules. One such signalling system is the stress activated pathway of p38 Mitogen Activated Protein Kinase. Fibroblasts were harvested from human pulmonary artery and aorta and utilised between passages 3–10. Cells were quiesced for 48 hours then stimulated with 5% serum for 24 hours with or without a specific p38 MAP kinase inhibitor (SB203580). Fibroblast replication was measured by [3H]thymidine uptake and p38 activity measured by Western Blot analysis. Serum starved pulmonary artery fibroblasts showed an increased replicative ability if kept in a hypoxic environment when compared to those in normoxia. The addition of 5% serum augmented this replicative response in the hypoxic pulmonary artery fibroblast cells. Systemic artery fibroblast cells showed no augmentation in proliferation with hypoxia whether or not they were in the presence of serum. Hypoxia gave rise to a biphasic p38 MAP kinase phosphorylation in the pulmonary artery fibroblasts optimally at 6 and 16 hours respectively, which was not seen in the normoxic pulmonary fibroblasts. The systemic artery fibroblast cells showed no increased p38 MAP kinase phosphorylation to hypoxia under any of the time points studied. Pulmonary artery fibroblasts that had been in hypoxic conditions for a period of 24 hours together with the p38 MAP kinase inhibitor no longer displayed the enhanced proliferative effects. The p38 MAP kinase inhibitor had no effect on the proliferation of normoxic pulmonary artery fibroblasts or systemic artery fibroblast proliferation. These results indicate clearly that p38 MAP kinase plays an essential role in the proliferation of human pulmonary artery fibroblasts to hypoxia, and that pulmonary and systemic cells behave quite differently in conditions of hypoxic stress.

Acknowledgments: British Heart Foundation and Chest Heart and Stroke Scotland

71.
THE K-ATP-CHANNEL OPENER MINOXIDIL PREVENTS HYPOXIC DECREASE IN NASAL POTENTIALS BUT NOT PULMONARY HYPERTENSION.
Simon Peth[1], Christoph Karle[2], Christoph Dehnert[1], Peter Bärtsch[1], Heimo Mairbäurl[1]. Medical Clinic VII, Sports Medicine, Univ Heidelberg[1], Medical Clinic III, Cardiology, Univ Heidelberg[2]. *Email:* heimo.mairbaeurl@med.uni-heidelberg.de

Hypoxia increases pulmonary capillary pressure and inhibits alveolar Na transport, two mechanisms that are discussed to contribute to hypoxic lung edem formation. Hypoxic pulmonary vasoconstriction is initiated by K-channel inhibition. Transepithelial Na-transport depends on active basolateral K-channels. It is therefore feasible to belive that activation of K-channels might prevent both pulmonary vasoconstriction and inhibition of alveolar reabsorption in hypoxia. To test this hypoxthesis, 17 healthy volunteers received a single dose minoxidil (5 mg) in a placebo-controlled crossover study and were exposed to

normobaric hypoxia (12% O_2) for 2h. Pulmonary artery pressure was measured by Doppler echocardiography; Na-transport was assesed by measuring amiloride-sensitive potentials across the nasal mucosa. All subjects tolerated minoxidil and hypoxia without problems. Arterial SO_2 was decreased to about 80% in hypoxia; the decrease was not affected by minoxidil. In hypoxia, pulmonary artery pressure increased from 25 to 40 mmHg ($p < 0.001$). Minoxidil did not prevent pulmonary hypertension, nor did it affect systemic blood pressure. Hypoxia decreased total and amiloride-sensitive nasal potentials by about 10% ($p < 0.05$). Minoxidil did not affect nasal potentials in normoxia but increased total nasal potentials (+5 mV) and amiloride-sensitive potentials (+ 3 mV) in hypoxia ($p < 0.05$). These results indicate that in normotonic subjects the antihypertensive KATP-channel opener minoxidil does not affect hypoxic pulmonary vasoconstriction but prevents hypoxic ion transport inhibition.

72.

ACETAZOLAMIDE STIMULATES ALVEOLAR FLUID CLEARANCE IN VENTILATED RATS.

Marie Runyon[1], Maneesh Bhargava[1], Douglas Wangensteen[1], David Ingbar[1], Erik Swenson[2]. Univ Minnesota[1], Univ Washington[2]. *Email:* eswenson@u.washington.edu

Acetazolamide prevents and treats acute mountain sickness (AMS) and may prevent high altitude pulmonary edema (HAPE) by reducing hypoxic pulmonary vasoconstriction (HPV). Since AMS is associated with mild abnormalities in lung gas exchange that improve with acetazolamide, and because acetazolamide alters fluid transport in a variety of other epithelia, we sought to determine whether systemic inhibition of carbonic anhydrase (CA) would alter alveolar fluid clearance (AFC) in rats. Adult male normoxic rats were anesthetized with sodium pentobarbital, treated with pancuronium bromide, intubated and ventilated. After 10 minutes of stabilization, Ringers solution with FITC-albumin tracer was instilled into one dependent lobe. Fluid removed after 60 minutes was analyzed for changes in [FITC] and the percentage of AFC was calculated. Experimental or control rats were treated 10 minutes prior to anesthesia with i.p injection of distilled water with or without 20 mg/kg of acetazolamide. AFC increased from 18.8 + 4.8 (SD) %/hour (n = 6) in controls to 33.0 + 3.8 (n = 5) with acetazolamide (2 tailed $p = 0.01$). Preliminary experiments suggested that the acetazolamide effect was not additive with terbutaline stimulation. In summary, acetazolamide increases AFC in rat lung within one hour. The mechanism of this effect is currently unknown, but since it is demonstrable under normoxic conditions it is not necessary to invoke an increase in alveolar epithelial oxygenation due to ventilatory stimulation and higher alveolar PO_2. It is more likely to involve changes in alveolar epithelial ion transport due to inhibition of CA in the alveolar pneumocytes or by numerous systemic effects of CA inhibition including diuresis and changes in systemic acid base balance.

Acknowledgments: Supported by: Will Rogers Institute; Univ Minnesota Bioterrorism Regional Center of Excellence, NIH P50 HL50152, and NIH HL 45591.

73.

ATP-RELEASE FROM RED CELLS IS INCREASED UNDER SIMULATED EXERCISE CONDITIONS.

Florian Ruppe[1], Peter Bärtsch[2], Heimo Mairbäurl[1]. Medical Clinic VII, Sports Medicine, Univ Heidelberg[1], Medical Clinic III, Cardiology, Univ Heidelberg[2]. *Email:* heimo.mairbaeurl@med.uni-heidelberg.de

ATP released from red cells has been discussed as possible mediator to control microcirculation in states of increased O_2-demand. Here we tested whether increased shear stress, deoxygenation and lactate as observed during exercise affect red cell ATP-release. HEPES-buffered suspensions of human red cells (hematocrit 10%) were exposed to shear stress in a rotating Couette viscometer. Cells not exposed to shear stress were incubated unstirred at 37°C. Desaturation ($SO_2 \sim 10\%$) was achieved by tonometry with N2 prior to shear stress exposure. Samples were centrifuged to measure supernatant ATP (luciferin-chemiluminescence) and hemolysis with a modified, high-sensitivity Drabkins assay. ATP release from red cells was calculated after correction for hemolysis. The results show that shear stress in normoxia increases supernatant ATP in a stress-rate and time-dependent manner more than can be accounted for by hemolysis. Acidification with HCl (pH 7.2) and increased lactate (15mM, pH 7.4) increased ATP release only in sheared cells whereas acidification with lactic acid had no effect on ATP release. Hypoxia under control conditions increased ATP-release in non-sheared cells by 40%. In hypoxia, shear-stress increased ATP-release further. These results indicate that increased shear stress, deoxygenation and changes in osmolarity and pH, which red cells encounter e.g. during increased muscle capillary perfusion in exercise, stimulate ATP-release from stressed cells. These mechanisms might trigger local vasodilatation and facilitate tissue blood flow in situations of increased oxygen and substrate-demand or decreased oxygen supply.

74.

EFFECT OF ANGIOTENSIN CONVERTING ENZYME (ACE) GENOTYPE ON WEIGHT DURING A HIGH ALTITUDE TREK.

Stephan Sanders[1], Matthew Litchfield[2], Sarah Trippick[3], Douglas Thake[4], David Collier[5], Hugh Montgomery[6], Annabel Nickol[7]. A1E Dept, Derbyshire Royal Infirmary, Derby, UK[1], A1E Dept, Calderdale Royal Hospital, Halifax, UK[2], Medical Expeditions, Pinfold, Hyssington, Montgomery, Powys, UK[3], Sport Science and Physiology Group, School of Science and the Environment, Coventry Univ, Coventry, UK[4], Clinical Pharmaology, Barts and The London, Charter House Square, London, UK[5], Centre for Cardiovascular Genetics, Rayne Building, 5 Univ Street, London, UK[6], Chest Unit, Churchill Hospital, Oxford, UK[7]. *Email:* stephansanders@hotmail.com

The ACE gene has two alleles, Insertion (I) or Deletion (D), distributed evenly in Caucasian populations. The I allele protects against weight loss during endurance exercise and is more common in extreme altitude mountaineers than in the general population. We hypothesized that trekkers with the II genotype would loose less weight at altitude. 42 volunteers (25 male) took part in a return 5-week trek from 410m to at least 5000m. ACE genotype was determined from a blood sample. In our group, ACE genotype was not in Hardy-Weinberg equilibrium: 18 DD (14 male), 18 ID (10 male) and 3 II (all female). There was a significant difference in baseline weight between

trekkers with II genotype (54.3 ± 10.4kg), ID (73.2 ± 10.6kg) and DD (68.2 ± 9.1kg, $p = 0.012$, one-way ANOVA), with post-hoc analysis showing this difference to be between II and ID ($p = 0.012$). Group mean BMI was 23.3 ± 2.3kg/m2, with no significant differences between genotypes. There was a significant difference in weight loss between trekkers with II genotype (0.6 ± 0.5kg), ID (−3.6 ± 2.3kg) and DD (−4.3 ± 2.0kg; $p = 0.029$), with this difference being between II and DD ($p = 0.025$). There was a significant relationship between baseline weight and weight loss ($r2 = 0.29$; $p < 0.001$). As hypothesized, trekkers with the II genotype lost less weight than those with DD. Given the surprisingly small number of trekkers with the II genotype, it is unclear whether this was due to II genotype per se, or chance lower baseline weight in this group, given dependence of weight loss on baseline weight. The gradual ascent profile of the trek may have attracted a disproportionate number of trekkers of ID or DD genotype who may appreciate more time for acclimatization.

Acknowledgments: This work was carried out in association with Medical Expeditions with Wellcome Trust funding.

75.

OFFSPRING OF PREECLAMPTIC MOTHERS ARE PREDISPOSED TO HYPOXIC PULMONARY HYPERTENSION.

Claudio Sartori[1], Pierre-Yves Jayet[1], Sébastien Thalmann[1], Thomas Stuber[2], Damian Hutter[2], Carlos Salinas[3], Céline Cucchia[1], Armando Rodriguez[3], Loyola Riveros[3], Hilde Spielvogel[3], Yves Allemann[2], Mercedes Villena[3], Urs Scherrer[1]. Internal Medicine, Univ Hospital, Lausanne, Switzerland[1], Swiss Cardiovascular Center, Univ Hospital, Bern, Switzerland[2], Instituto Boliviano de Biologia de Altura, La Paz, Bolivia[3]. *Email:* Claudio.Sartori@hospvd.ch

Adverse events in utero may predispose to cardiovascular disease in adulthood. In preeclampsia, the diseased placenta releases circulating vasculotoxic factors that cause maternal endothelial dysfunction. These factors may pass the placental barrier, and leave a persistent vascular imprint that may predispose to a pathological response in later life. Endothelial dysfunction plays a major role in the pathogenesis of hypoxic pulmonary hypertension. We hypothesized that offspring of pre-eclampsia may be predisposed to pulmonary hypertension at high altitude. To test this hypothesis, we measured systolic pulmonary-artery pressure (echocardiography) in 11 young (age, 7 ± 1 years, X ± SE) healthy Bolivian offspring of preeclampsia, and in 13 sex- and age-matched offspring of normal pregnancies in La Paz (3600 m). The major new finding was that systolic pulmonary-artery pressure was roughly 33 percent higher in offspring of preeclamptic mothers than in control subjects (36 ± 2 vs. 27 ± 1 mmHg, $P < 0.001$). This exaggerated hypoxic pulmonary vasoconstriction was not related to more severe hypoxemia or exaggerated polyglobulia. These findings provide the very first evidence that preeclampsia leaves a persistent and potentially fatal imprint in the pulmonary circulation of the offspring, which predisposes them to exaggerated hypoxic pulmonary hypertension in later life.

76.

EFFECT OF HYPOXIA ON RESPIRATORY SINUS ARRHYTHMIA.

Nobuko Sasano[1], Hiroshi Sasano[1], Shoji Ito[1], Takafumi Azami[1], Joseph Fisher[2], Hirotada Katsuya[1]. Dept Anesthesiology and Medical Crisis Management, Nagoya City Univ Graduate School of Medical Sciences[1], Dept Anesthesia, Toronto General Hospital[2]. *Email:* nobusasano@aol.com

Respiratory sinus arrhythmia (RSA) may exert its beneficial effect on gas exchange in the lungs by matching the pulmonary blood flow to the variations in alveolar ventilation during the respiratory cycle. We previously reported that hypercapnea increases RSA magnitude. We studied the effect of mild and moderate hypoxia on RSA magnitude when the tidal volume (VT), respiratory frequency (f), and $PaCO_2$ are maintained constant. Six healthy volunteers breathed through a mouth piece and a partial rebreathing circuit that presents the fresh gas and then the rebreathed gas in sequence. At reduced fresh gas flows, $PaCO_2$ is maintained constant independent of VT. Fresh gas flow into the circuit was set at the individual resting minute volume at O_2 concentrations (FfO_2) of 21%, 14%, and 11% while subjects kept f constant. SpO_2, $EtCO_2$, VT were monitored. Mean R-R intervals and RSA magnitude were calculated from ECG recording. SpO_2 (%) were 98.0 ± 0.6, 90.8 ± 0.7, 81.5 ± 1.2, mean R-R intervals (ms) were 858.0 ± 88.5, 809.7 ± 86.2, 766.3 ± 105.0, RSA magnitude (ms) were 19.0 ± 10.8, 17.5 ± 7.8, 14.2 ± 6.9, at FfO_2 21, 14, 11%, respectively. Heart rate increased with progressive hypoxia but there was no signifidcant change in RSA maginitude. In mild and moderate hypoxia, RSA magnitude is well-maintained and may serve its beneficial effect on pulmonary gas exchange. Our result is not consistent with the previous report; hypoxia decreased RSA magnitude.

77.

ISOCAPNIC ISOOXIC HYPERPNEA ACHIEVED BY SEQUENTIAL PARTIAL REBREATHING CIRCUIT.

Hiroshi Sasano[1], Eitan Prisman[2], Nobuko Sasano[1], Takafumi Azami[1], Shoji Ito[1], Hiroaki Ito[1], Hirotada Katsuya[1], Joseph Fisher[2]. Nagoya City Univ, Dept Anesthesiology and Rescitology[1], Toronto General Hospital, Dept Anesthesia[2]. *Email:* hirosasano@aol.com

Hyperpnea usually decreases $PaCO_2$ and increases PaO_2 according to the alveolar ventilation equation and alveolar gas equation. Therefore, it was difficult to assess independent effect of hyperpnea, CO_2 level, and O_2 level on changes in physiological phenomenon, getting rid of concomitant effect of each others. In order to assess the independent effect of these three factors, we can use a device, a sequential partial rebreathing circuit with fresh gas flow, which allows us to control volume of dead space ventilation automatically during hyperpnea and to keep both CO_2 level and O_2 level constant.To show a function of the device, we present the observed result and the principal of operation of the device induced from alveolar gas equation. Actual trace of CO_2 volume curve was obtained from a subject to show the constant alveolar ventilation volume which induce isocapnia during hyperpnea. Furthermore, in order to show a theory, isocapnic isooxic hyperpnea induced by fixed alveolar ventilation, we adopt a schema to interpret the isooxia function based on the alveolar gas

equation. Based on the established alveolar gas equation, we successfully showed that our device induced isooxia as well as isocapnia during hyperpnea. Actual trace of CO_2 volume curve indicated that our device well operates according to the theory. The device could allow us to assess the independent effect of hyperpnea, O_2 level and CO_2 level which we could not have distinguished before.

78.
STRATOSPHERIC OZONE IN THE HIMALAYA: A POSSIBLE FACTOR IN HIGH ALTITUDE PULMONARY SYNDROMES.

John Semple[1], Kent Moore[1]. Univ Toronto, Toronto, Canada[1]. *Email:* john.semple@sw.ca

Ozone is a recognized urban air pollutant and can alter pulmonary structure and function. Intrusions of stratospheric air have been shown to be associated with high impact weather events and can produce ozone concentrations estimated as high as 250 parts per billion (ppb). These concentrations, at sea level, under exercise conditions are sufficient to induce pulmonary function changes. We performed a quantitative analysis of ozone rich stratospheric intrusions on Mount Everest as well as direct surface sampling in the Himalaya to establish the presence of stratospheric ozone. A time series was observed of the total column ozone field over Mount Everest from the Total Ozone Mapping Spectrometer (TOMS) onboard the Earth Probe satellite from May to August 1998 and compared to recorded results from a portable weather station at the South Col (elevation 7,986m). An OMC-1108 ozone monitor was used to measure ozone levels in the Himalaya range in Bhutan (Oct-Nov.2004) at altitudes up to 5000 m. The TOMS instrument provided a vertically integrated measure of the ozone in an atmospheric column and high values are associated with a high impact weather event in May 1998 indicating an intrusion of stratospheric air into the upper-troposphere at the Everest summit (120–250 ppb). Surface recordings in Bhutan indicated a vertical gradient of ozone up to 30 ppb between 4000m and 5000m. Conditions ranging from bronchitis and cough to high altitude pulmonary edema are often diagnosed in climbers in the Himalaya. Etiological factors include low humidity, cold temperatures and hypoxia. These preliminary observations suggest that concentrations of ozone likely increase with altitude and levels may be sufficient to be a complicating variable in pulmonary symptoms of mountaineers under conditions of extreme exertion and hypoxia.

79.
ELEVATED INTRACRANIAL PRESSURE IN ACUTE MOUNTAIN SICKNESS MEASURED USING OPTIC NERVE SHEATH ULTRASOUND.

James Smithson[1], Dan Price[2], Phil Bickler[1], Gerald Dubowitz[1]. Univ California San Francisco[1], Alameda County Medical Center[2]. *Email:* jsmiths@itsa.ucsf.edu

Controversy exists regarding contributions of cerebral edema and elevated intracranial pressure (ICP) in the development of mild to moderate acute mountain sickness (AMS). Past attempts at estimating ICP in the field, based on tympanic membrane pulsing and intraocular pressure, have produced variable results. While not previously used at altitude, optic nerve sheath ultrasound is a reliable, non-invasive method of assessing ICP based on optic nerve sheath diameter (ONSD). We therefore adapted this technique for use at altitude to assess the relationship between AMS and ICP. Volunteers were recruited at 5160m (Everest region of Nepal). A standardized, validated technique, using commercially available ultrasound equipment, was used to measure ONSD 3mm behind the globe of the eye. AMS was assessed using the Lake Louise Score. 111 trekkers (42 female, 69 male) were examined. 36% (39/111) of subjects had symptoms of AMS (headache plus score of 2 or higher). Mean ONSD was 4.1mm (SD = 0.7mm, range = 2.83–6.36mm). ONSD was an independent risk factor for the presence of AMS (odds ratio = 4.5; 95% CI: 1.6–12.7). Enlargement of the ONSD precedes papilledema and occurs in real time with elevations in ICP. Our data suggest a significant relationship between ONSD and AMS for mild to moderate AMS. This supports the notion that cerebral edema leads to elevated ICP and severe AMS. However inter-individual variation in ONSD, including evidence of abnormally elevated ICP, was demonstrated independent of the severity of AMS. This may suggest that severely elevated ICP can occur without AMS and conversely severe AMS may occur without a significant rise in ICP. Prospective study, comparing changes in ONSD during acclimatization to baseline data, is necessary to control for significant inter-individual variation.

80.
SONOGRAPHIC EVIDENCE FOR ALTERED INTRACRANIAL PRESSURE IN EARLY ACUTE MOUNTAIN SICKNESS.

James Smithson[1], Dan Price[2], Phil Bickler[1], Gerald Dubowitz[1]. Univ California San Francisco[1], Alameda County Medical Center[2]. *Email:* jsmiths@itsa.ucsf.edu

The role of cerebral edema and elevated intracranial pressure (ICP) in the development of early acute mountain sickness (AMS) remains unknown. Ophthalmic ultrasound was recently used to measure a correlate of ICP (optic nerve sheath diameter [ONSD]) in trekkers at 5160m. Evidence of abnormally elevated ICP was found in 17% of subjects (19/111) independent of presence or severity of AMS. We therefore sought to address this issue by following ONSD changes from baseline during early acclimatization. Volunteers were examined for baseline ONSD at 1,230m and with serial exams for 24–48 hours after ascent to 3,770m. A standardized technique for documenting ONSD using B-scan ultrasound was used. AMS was assessed using the Lake Louise Score (LLS) 67 examinations were performed on 11 subjects. 82% (9/11) developed AMS (headache plus LLS = 2). Mean ONSD was 3.2mm (standard deviation [SD] = 0.46; range: 2.3–4.4). Mean change in ONSD from baseline was identical in groups with and without AMS (No AMS: −0.06mm; SD = 0.31mm, range: −0.7–0.6mm; +AMS: −0.06mm; SD = 0.26, range −0.58–0.6mm). 2 subjects developed significantly diminished ONSD (> 0.4mm change from baseline) within 4 hours at 3,770m, while 4 subjects developed significantly enlarged ONSD after 20 hours. While not all changes were significant, ONSD diminished upon exposure to altitude, then increased over time for all subjects—independent of presence or severity of AMS. This supports the notion that a certain amount of time must pass before elevated ICP develops and that

sustained, elevated ICP does not contribute to early AMS. A protracted, prospective acclimatization study may improve understanding of a time requirement for the development of elevated ICP.

81.
INFLUENCE OF HYPOXIA AND HYPOXIC EXERCISE ON PULMONARY CAPILLARY BLOOD VOLUME, ALVEOLAR-CAPILLARY CONDUCTANCE, AND LUNG WATER.

Eric Snyder[1], Ken Beck[1], Jerome Breen[2], Eric Hoffman[3], Bruce Johnson[1]. Dept Internal Medicine, Mayo Clinic, Rochester, MN[1], Dept Radiology, Mayo Clinic, Rochester, MN[2], Div of Physiologic Imaging, Univ Iowa, Iowa City, IA[3]. *Email:* johnson.bruce@mayo.edu

Hypoxia causes a rise in pulmonary vascular pressures, alters pulmonary capillary recruitment and may alter lung fluid balance. Hypoxic exercise causes further increases in pulmonary pressures and challenges the ability of the lungs to regulate water. To examine the influence of hypoxia and hypoxic exercise on pulmonary capillary recruitment and lung fluid balance, we studied 16-healthy subjects (age 29 ± 7yrs, VO_2peak 38 ± 8ml/kg/min) after 16-hr hypoxic exposure (FIO_2 12.5%, PB 732 mmHg, SaO_2 83 ± 2%), after exercise to exhaustion on a cycle ergometer (15 ± 1 min, 130 ± 43 watts, SaO_2 80 ± 4%), and again after rapid saline infusion. The fluid challenge was performed to demonstrate the sensitivity of the techniques to detect changes in lung water. Pulmonary capillary blood volume (Vc) and alveolar-capillary conductance (DM) were determined by measuring lung diffusing capacities for carbon monoxide and nitric oxide. Lung water was estimated by combining measures of lung tissue volume (CT imaging), and Vc. Saline infusion resulted in an increase in Vc (+30 ± 80%), tissue volume (+6 ± 3%), and lung water (+12 ± 11%), along with a decrease in DM (-10 ± 19%). Post hypoxia and post hypoxic exercise, subjects had an increase in Vc (hypoxia +35 ± 70%, exercise +49 ± 62%) and DM (hypoxia +10 ± 23%, exercise +20 ± 32%) and a decrease in tissue volume (hypoxia −3 ± 3%, exercise −4 ± 2%) and lung water (hypoxia −14 ± 4%, exercise −18 ± 10%) vs. baseline. These data suggest that hypoxic exposure for 16-hr (alone or with exercise) results in an increase in capillary recruitment, improved alveolar-capillary conductance and a decrease in lung water.

Acknowledgments: AHA-0410073Z, NIH-HL71478

82.
INFLUENCE OF HYPOXIA ON EXHALED NITRIC OXIDE, PULMONARY FUNCTION, AND PULMONARY VASCULAR PRESSURES IN HEALTHY HUMANS.

Eric Snyder[1], Ken Beck[2], Robert Frantz[1], Bruce Johnson[1]. Mayo Clinic[1], Guidant Corporation[2]. *Email:* johnson.bruce@mayo.edu

Nitric oxide (NO) produced within the lungs plays an important role in the regulation of a number of physiological processes, including bronchial and vascular smooth muscle relaxation. Although the source of NO in the expired air (expNO) remains unclear, it likely reflects both epithelial and endothelial sources. Hypoxia also influences bronchial and vascular smooth muscle, however, the influence of hypoxia on expNO and its relationship to changes in pulmonary function and pulmonary vascular pressures remain unclear. In the present study we sought to determine the influence of normobaric hypoxia (FIO_2 12.5%, PB 732mmHg) on expNO and the relationship to changes in pulmonary function and pulmonary arterial pressure (PAP, estimated from TR velocity). Sixteen healthy subjects participated in the study (age = 29 ± 7yrs, BMI = 25 ± 4kg/m2, VO_2peak = 38 ± 8ml/kg/min). Measures were made of pulmonary function (forced vital capacity-FVC, forced expiratory volume in 1 sec-FEV1, maximal expiratory flow at 50% of FVC-FEF50) and PAP before and after a 16-hr hypoxic exposure. With hypoxic exposure, expNO increased (from 25 ± 18ppb to 33 ± 22ppb, $p < 0.05$), pulmonary function improved (FVC +13 ± 42%, FEV1 +6 ± 13%, FEF50 +5 ± 14%, $p < 0.05$) and PAP increased (from 29 ± 7 to 37 ± 8mmHg, $p < 0.05$). Prior to hypoxic exposure there was a negative correlation between expNO and PAP ($r = -0.60$, $p = 0.02$) and a positive correlation with FEF50 ($r = 0.63$, $p = 0.01$), which remained similar post hypoxic exposure (PAP $r = -0.54$, $p = 0.03$, FEF50 $r = 0.57$, $p = 0.03$). Subjects with the largest change in expNO had the least change in PAP ($r = -0.40$, $p = 0.03$), but the largest change in FEF50 ($r = 0.45$, $p = 0.01$). These data suggest that the increase in expNO with hypoxic exposure may positively influence both pulmonary function and pulmonary vascular pressures.

Acknowledgments: Supported by AHA-0410073Z, NIH-HL71478

83.
EFFECT OF INTERMITTENT HYPOXIA AT REST ON CYCLING ENDURANCE PERFORMANCE.

Nadine Stuke[1], Michael Hilbert[1], Vladimir Shushakov[1], Norbert Maassen[1]. Sportsphysiology, Medical School Hannover, Germany[1]. *Email:* nadinestuke@yahoo.de

Russian scientists developed a model in which hypoxia and normoxia change every 5 minutes. This method is propagated to enhance endurance performance. There are still only two controlled studies investigating the effects of IHT (Julian et al. 2004; Katayama et al. 2004). Male subjects (relative performance: 3.07 Watt/kg to 6 Watt/kg) were assigned into four groups (group 1: change between hypoxia (9%) and normoxia for 1 hour (n = 5); group 2: hypoxia (9%) and normoxia for 1.5 hours (n = 9); group 3: hypoxia (9%) and hyperoxia (50–60%) for 1.5 hour (n = 9); group 4: control (normoxia) (n = 8)). For 14 days (ten workdays in a row) the athletes came once a day to breathe the mentioned gas mixtures (Hypoxicator, Biomedtech, Australia). Before and after the 14 days the athletes were investigated during a cycling endurance test until exhaustion at 80% of maximal power. The first group and the control group did not improve in cycling. Groups 2-3 increased endurance performance by more than 20 percent ($p < 0.01$). After 14 days IHT there was a significant increase in reticulocytes but no increase in totalhaemoglobin and hematocrit. Heart rate did not change. During cycling the ventilation of both hypoxia groups increases less and at the same time point ventilation is lower in the post test than in the pre test ($p < 0.001$). This is mainly due to a reduced breathing frequency. The im-

provement in cycling was not dependant on VO_2max . The improvement in endurance performance in cycling is not caused by an increased blood volume. Assuming that ventilation limits endurance performance the reduced ventilation is the reason for the improvement. The cause of the decrease in ventilation is unknown.

Acknowledgments: This study is supported by the Federal Inst Sport Science VF 0407/01/13/2002-2003

84.

EFFECT OF INTERMITTENT HYPOXIA AT REST (IHT) ON FOREARM ENDURANCE PERFORMANCE.

Nadine Stuke[1], Vladimir Shushakov[1], Norbert Maassen[1]. Sportsphysiology, Medical School Hannover, Germany[1]. *Email:* nadinestuke@yahoo.de

IHT is a model in which hypoxia and normoxia change within short periods. An alternation of hypoxia and normoxia every 5 minutes is propagated to enhance endurance performance. In this study the influence of IHT on muscular energy metabolism during exercise was investigated. Male subjects were assigned into four groups (group 1: hypoxia (9%) and normoxia for 1 hour ($n = 5$); group 2: hypoxia (9%) and normoxia for 1.5 hours ($n = 9$); group 3: hypoxia (9%) and hyperoxia (50–60%) for 1.5 hour ($n = 9$); group 4: control (normoxia) ($n = 8$)). For 14 days (ten workdays in a row) the athletes came once a day to breathe the mentioned gas mixtures (Hypoxicator, Biomedtech, Australia). Before and after the 14 days the athletes were investigated during a hand-grip endurance test until subjective exhaustion at 91% of maximal power. Arterialized blood was taken from a heated hand vein (resting arm) and a cubital vein of the working arm. Blood flow was measured plethysmographically. The increase in exercise duration of the control group was not significant (plus 20%). Groups 1-3 increased endurance performance by more than 50 percent ($p < 0.001$). Venous PO_2 was slightly lower ($p < 0.05$), PCO_2 was higher (n. s.), HbO_2 ($p < 0.05$) and pH (n. s.) were lower. Venous Lactate concentration, forearm lactate release, VO_2 and blood flow were not significantly different between pre and post test. As VO_2 and lactate-release did not change the improvement seems not to be caused by an improved energy metabolism. Improved function of Na+/K+ ATPase or Ca++-pump resulting in better maintenance of excitability or contractility might be responsible. Reduced central fatigue might be an other cause.

Acknowledgments: This study is supported from the Federal Inst Sports Science VF 0407/01/13/2002-2003

85.

AYMARA CHILDREN ARE PROTECTED FROM HIGH-ALTITUDE-INDUCED PULMONARY HYPERTENSION.

Thomas Stuber[1], Claudio Sartori[2], Damian Hutter[1], Carlos Salinas[3], Sebastien Thalmann[2], Pierre Turini[2], Pierre-Yves Jayet[2], Mercedes Villena[3], Urs Scherrer[2], Yves Allemann[1]. Swiss Cardiovascular Center Bern, Univ Hospital, 3010 Bern, Switzerland[1], Internal Medicine, Univ Hospital, 1011 Lausanne, Switzerland[2], Instituto Boliviano Biologia Altura, La Paz, Bolivia[3]. *Email:* thomas.stuber@insel.ch

Pulmonary hypertension is a hallmark of the adaptation to ambient lack of oxygen. This assumption is also thought to hold true for high-altitude native children, since invasive studies showed elevated pulmonary-artery pressure in a few children studied at high altitude. However, the data to support this assumption is extremely sparse. We, therefore measured systolic pulmonary-artery pressure (Doppler-echocardiography) and arterial oxygen saturation in 36 Bolivian high-altitude native children of Aymara ethnicity (age 6 months to 13 years, mean $\pm$ SD 7.3 ± 3.0 years) in La Paz (3600 m). We also studied 18 age- and sex-matched Caucasian children who were born or long-term residents of La Paz, and a group of healthy Caucasian children born and living in Berne, Switzerland (450 m). The major new finding was that systolic pulmonary-artery pressure in healthy Bolivian children of Aymara ethnicity was markedly lower than in children of Caucasian descent (25.1 ± 4.1 vs 34.2 ± 9.0 mmHg, $P < 0.001$), and, indeed, was similar to the one measured in children at low altitude (450 m). At high altitude, the lower pulmonary-artery pressure in the Aymara children was not related to better arterial oxygenation, because arterial oxygen saturation was lower than the one measured in the Caucasian children (88.2 ± 4.1 vs. $92.9 \pm 2.4\%$, $P < 0.0001$). These data represent the first measurements of pulmonary-artery pressure in a large group of healthy children living at high-altitude. We found that at high altitude, despite lower arterial oxygen saturation, Aymara children had roughly 30% lower pulmonary artery pressure than well adapted Caucasian children, a value that was comparable to the normal values measured at low altitude. The data challenge the long held concept that high-altitude exposure in children invariably leads to pulmonary hypertension. Protection from hypoxia-induced pulmonary hypertension may represent a specific high-altitude adaptation of the Aymaran ethnicity.

86.

PLASMA VASCULAR ENDOTHELIAL GROWTH FACTOR LEVELS DO NOT CORRELATE WITH ACUTE MOUNTAIN SICKNESS.

Andrew Sutherland[1], David Dorward[2], Kenneth Ballie[3], Roger Thompson[3], Nickhil Hirani[4]. Nuffield Depatment of Surgery, Oxford Univ, UK[1], College of Medicine and Vetinary Medicine, Edinburgh Univ, UK[2], APEX (Altitude Physiological Expeditions), c/o College of Medicine, Univ Edinburgh, UK[3], Respiratory Medicine, Univ Edinburgh, Royal Infirmary of Edinburgh, UK[4]. *Email:* aisutherland@mac.com

Vascular endothelial growth factor (VEGF) is a permeability factor and endothelial mitogen subject to hypoxic regulation. Despite hypotheses regarding VEGF-mediated alteration to blood-brain barrier permeability, the role of VEGF in the pathogenesis of acute mountain sickness (AMS) is still to be elucidated. We examined the relationship between plasma VEGF and AMS on ascent to high altitude and subsequent acclimatisation. 38 healthy lowlanders (24 male, median age 21 range 18 to 31) flew to La Paz, Bolivia (3650m) where they spent 4 or 5 days before ascending in 90 minutes by off road vehicle to the Chacaltaya laboratory (5,200m). We measured plasma VEGF in venous blood at sea level and within 6 hours, 3 days and 1 week of ascent to 5,200m. AMS was scored using the Lake Louise consensus system. Consistent with

the results of previous studies, VEGF expression at sea-level ranged from 0 to 408pmol/l. Individuals were categorised into high and low sea-level VEGF expressers using an arbitrary division at 50pmol/l. In neither group did plasma VEGF levels change significantly on ascent to 5,200m [mean (SEM)] (high expressers n = 17) 215.7 (32.1) to 216.5 (31.9) pmol/l (p = 0.99), (low expressers n = 21) 8.1 (2.4) to 11.0 (3.5) pmol/l (p = 0.50) or during subsequent acclimatisation. 26 subjects developed AMS (LLS > 3) on ascent to 5,200m and whilst sufferers had higher mean VEGF levels at each sample point, including sea-level, these differences were not significant. No relationship was found between VEGF and the severity of AMS, pulmonary artery pressure or arterial oxygen saturation. We conclude 1) there is significant inter-individual variation in basal VEGF expression 2) plasma VEGF levels are not affected by ascent to altitude 3) we found no evidence of a role for plasma VEGF in the development of AMS.

Acknowledgments: Apex2 volunteers; the ELEGI laboratory, Univ Edinburgh; Wellcome Trust Clinical Research Facility, Edinburgh; Marken; and IBBA, La Paz, Bolivia.

87.

WEIGHT LOSS WHILE SLEEPING IN A SIMULATED ALTITUDE TENT.

George Swanson[1]. California State Univ[1]. *Email:* dswanson@csuchico.edu

The purpose of the present study was to investigate the use of altitude tents as a means of weight loss in obese individuals. In this pilot study, three subjects spent up to 6 weeks sleeping in an altitude tent at a simulated altitude of 12,000 feet (Alt). The study was conducted as a cross-over design so that during the control period subjects slept in the tent at an altitude equivalent to sea level (SL). During Phase I of the study, the subjects slept at the equivalent of 5000 ft on the first night and then were "elevated" at 1000 feet per night on succeeding nights (treatment) or returned to sea level (control). In Phase II, subjects slept at 12000 ft on the first night (treatment) or at sea level (control). Subject 1 (F, 170 cm, 79.8 kg) lost 2.9 kg after 6 weeks at SL. In contrast, she lost 0 kg after 6 weeks at Alt. Subject 2 (F, 185 cm, 118.1 kg) lost 3.7 kg and 4.3 kg (Phase II) after 6 weeks at Alt. In contrast, she gained 0.2 kg and 1.5 kg (Phase II) after 6 weeks at SL. Subject 3 (M, 196 cm, 175.9 kg) lost 0.7 kg after 2 weeks at SL. In contrast, he lost 2.2 kg after two weeks at Alt. These data indicate that subject 1 lost weight during the control period and showed no further loss during the treatment period. In contrast, subject 2 and 3 lost weight during the treatment period but not during the control period. Although these data are sparse, and open to a variety of interpretations, they suggest further study is warranted for the "weight loss tent" concept.

88.

ACETAZOLAMIDE (AZ) PREVENTS HYPOXIA-INDUCED INCREASES IN INTRACELLULAR CA2+ CONCENTRATION ([CA2+]I) IN RAT PULMONARY ARTERIAL SMOOTH MUSCLE CELLS (PASMCS) INDEPENDENT OF CARBONIC ANHYDRASE INHIBITION.

Erik Swenson[1], Larissa Shimoda[2]. Univ Washington[1], Johns Hopkins Medical Institutions[2]. *Email:* eswenson@u.washington.edu

Ascent to high altitude triggers hypoxic pulmonary vasoconstriction (HPV), with severe HPV causing high altitude pulmonary edema (HAPE). We previously have demonstrated that AZ, a CA inhibitor which blunts HPV in vitro and in vivo (Deem et al., 2000; Hoehne et al., 2004) and reduces HAPE in an animal model (Berg et al., 2003), likely does so by preventing hypoxia-induced increases in PASMC [Ca2+]i. The mechanism by which this rise intracellular [Ca2+] is blocked is uncertain. In this study, we determined whether structurally different CA inhibitors, benzolamide (BZ) and ethoxzolamide (EZ), also blunt hypoxia-induced Ca2+ signaling in PASMCs. Cells were loaded with the Ca2+-sensitive dye, Fura-2, and fluorescent microscopy was used to measure the effect of hypoxia on [Ca2+]i in the absence or presence of CA inhibitors. [Ca2+]i was monitored during baseline conditions (16% O_2), exposure to hypoxia (4% O_2), and reoxygenation in the absence and presence of 10–100 mM AZ, BZ or EZ. Hypoxia caused a rapid, significant, reversible increase in [Ca2+]i. AZ dose-dependently decreased the rate and magnitude of hypoxia–induced increases in [Ca2+]i, with complete blockade at 100 mM. In contrast, even at the highest concentration, neither BZ nor EZ altered hypoxia-induced Ca2+ signaling. At 100 mM, all three CA inhibitors induced an acid shift in baseline pHi, suggesting comparable CA inhibiting capacity. These results indicate that AZ is a specific inhibitor of hypoxia-induced increases in [Ca2+]i and HPV and suggest that the mechanism by which AZ prevents hypoxia-induced Ca2+ signaling is not related to CA inhibition or intracellular acidification.

Acknowledgments: Supported by NIH grants HL671-91and HL45591.

89.

ENDOTHELIAL NITRIC OXIDE SYNTHASE POLYMORPHISMS DO NOT INFLUENCE PULMONARY ARTERY SYSTOLIC PRESSURE AT ALTITUDE.

Roger Thompson[1], Eve Smith[2], Kenneth Baillie[1], John Irving[3], David Porteous[4], David Webb[5]. Apex (altitude physiological expeditions), c/o College of Medicine, Univ Edinburgh, UK[1], College of Medicine and Veterinary Medicine, Univ Edinburgh[2], Dept Cardiology, Royal Infirmary of Edinburgh, UK[3], Medical Genetics Section, Molecular Medicine Centre, Western General Hospital, Edinburgh, UK[4], Clinical Pharmacology Unit, Univ Edinburgh, Western General Hospital, Edinburgh, UK[5]. *Email:* rogerthompson@doctors.org.uk

Previous genetic association studies have suggested that polymorphisms in the gene encoding endothelial nitric oxide synthase (eNOS) may be associated with susceptibility to high altitude pulmonary oedema (HAPE). We investigated whether eNOS polymorphisms influence systolic pulmonary artery pressure (PASP) in 40 Caucasian trekkers ascending to 5200m. We studied 2 eNOS gene polymorphisms: Glu298Asp variant and 27-base-pair variable number of tandem repeats polymorphism (eNOS4a, eNOS4b). Subjects flew to La Paz, Bolivia (3650m, 12000ft) and after 4–5 days acclimatization ascended over 90 minutes to the Chacaltaya laboratory (5200m, 17060ft) by off-road vehicle. PASP was determined by echocardiography at sea level and within 6 hours, 3 days and 1 week after arrival at 5200m. It was not possible to obtain PASP readings on seven subjects.

One subject withdrew with HAPE at 3650m. Six subjects descended from 5200m with symptoms of acute mountain sickness. PASP readings for these subjects are included until their evacuation. Based on the PASP data obtained, this study had power of 80% to detect a difference in PASP of <13 mmHg between the most common polymorphisms (Glu298Glu vs Glu298Asp, eNOS4b/a vs eNOS4b/b). This compares favourably with differences of >20mmHg previously described between HAPE-susceptible and normal subjects at altitude. The gene frequencies in our population with no history of HAPE (Glu298Glu 45%, Glu298Asp 37.5%, Asp298Asp 17.5 % and eNOS4b/b 72.5%, eNOS4b/a 25%, eNOS4a/a 2.5%) did not differ significantly from previously reported HAPE-susceptible groups. There was no significant difference in mean PASP according to eNOS polymorphism at any of the sample points. This study suggests that these eNOS polymorphisms do not significantly influence altitude-induced pulmonary hypertension.

Acknowledgments: We thank S. Bayliss, A. Condie and C. Graham, Wellcome Trust Clinical Research Facility (www.wtcrf.ed.ac.uk). ES won a Wellcome Trust Electives Prize.

90.

HIGH ALTITUDE CAUSES A REDUCTION IN PFA-100 CLOSURE TIME: EVIDENCE OF PLATELET ACTIVATION OR A RESULT OF INCREASED HEMATOCRIT?

Roger Thompson[1], Martin Schnopp[1], Matthew Barber[2], Elizabeth Horn[3], Carl Moores[4]. Apex (altitude physiological expeditions), c/o College of Medicine, Univ Edinburgh, UK[1], College of Medicine and Veterinary Medicine, Univ Edinburgh[2], Dept Haematology, Royal Infirmary of Edinburgh, Edinburgh, UK[3], Dept Anaesthesia, Critical Care, and Pain Medicine, Royal Infirmary of Edinburgh, UK[4]. *Email:* rogerthompson@doctors.org.uk

Numerous reports of thromboembolic events have been associated with ascent to high altitude. This was the first study to use a PFA-100™ (Dade-Behring, Sysmex UK) to assess platelet function in healthy lowlanders ascending to high altitude. 103 volunteers on the Apex 2 expedition (56 male, median age 21, range 18 to 31) flew to La Paz, Bolivia (3650m) and after 4–5 days acclimatization ascended over 90 minutes to the Chacaltaya laboratory (5200m) by off road vehicle. Blood (3mls in 0.106mol/l citrate) was sampled at sea level and within 6 hours, 3 days and 1 week of arrival at 5200m. PFA-100 closure time (CT) was recorded using collagen-epinephrine cartridges. Subjects were part of a larger study and randomised into 3 groups: antioxidant supplementation, sildenafil or placebo. We excluded one subject with HAPE, one with gastroenteritis and five with prolonged CT at sea level (>300s). No data were obtained on 10 subjects and 8.5% of readings were lost due to technical problems. 20 subjects descended from 5200m with AMS. CT is included until evacuation. Mean CT fell from 131.1s at sea level to 75.1s within 6 hours at 5200m (mean difference 54.4, CI 47.3 to 61.6, $p < 0.0001$, $n = 73$). CT varies with changes in hematocrit, however we found no correlation between the rise in hematocrit on ascent and change in CT. Change in CT over 7 days at 5200m correlated with change in hematocrit ($r2 = 0.118$, $p = 0.0159$). There was no effect of drug treatment on CT at altitude. These data suggest ascent to high altitude causes a change in platelet function, which may represent platelet activation or an effect of hematocrit on the PFA-100™ readings.

Acknowledgments: Apex2 volunteers; Sysmex UK; Wellcome Trust Clinical Research Facility, Edinburgh.

91.

PERICARDIAL EFFUSIONS OCCUR IN HEALTHY LOWLANDERS FOLLOWING ACUTE ASCENT TO HIGH ALTITUDE.

Roger Thompson[1], Kenneth Baillie[1], Mark Toshner[2], Simon Maxwell[3], David Webb[3], John Irving[4]. Apex (Altitude physiological expeditions), UK[1], Respiratory Medicine, Eastern Deanery, Cambridge, UK[2], Clinical Pharmacology Unit and Research Centre, Univ Edinburgh, Western General Hospital, E[3], , Dept Cardiology, Royal Infirmary of Edinburgh, Edinburgh, UK[4]. *Email:* rogerthompson@doctors.org.uk

Serial echocardiography was performed on the Apex 2 expedition as part of a randomised controlled trial of antioxidant supplementation. Eighty-three native lowlanders (44 male, median age 21, range 18-30) were randomised to receive antioxidant supplementation or matched placebo in a double-blind trial. Subjects flew to La Paz, Bolivia (3650m, 12000ft) and after 4-5 days acclimatization ascended over 90 minutes to the Chacaltaya laboratory (5200m, 17060ft) by off road vehicle. Echocardiography was undertaken at sea level and within 6 hours, 3 days and 1 week at 5200m, by an experienced cardiologist. Pericardial effusions were defined as a distinct circumferential separation of pericardial layers seen on two views, not including the substernal view. Two subjects withdrew with gastroenteritis and 1 did not ascend further after developing HAPE at La Paz. All data were lost from 4 subjects. Pericardial effusions were detected in 5 subjects within 6 hours of arrival at 5200m. A total of 48% (36/76) of subjects developed pericardial effusions. The percentage of subjects in the antioxidant group who had effusions on at least one study was 38% (14/37) versus 56% (22/39) in the placebo group (absolute risk reduction = 19%, 95%CI –4% to 41%, $p = 0{\cdot}12$). There was no evidence of cardiac dysfunction. Prevalence of AMS during the first 5 days at 5200m tended to be greater in the groups who developed pericardial effusions. There was no consistent difference in pulmonary artery pressure between the effusion-positive and effusion-negative subjects at each time point. This rapid onset of pericardial effusion in otherwise healthy individuals has not previously been described and is likely to affect recreational visitors to high altitudes.

Acknowledgments: We thank the volunteers and researchers who took part in the Apex 2 expedition; Instituto Investigaciones Fisicas, Universidad Mayor de San Andres; and the Instituto Boliviano Biolog°a Altura, La Paz, Bolivia. We are very grateful to Dr Catherine Labinjoh, Cardiology Dept, New Royal Infirmary of Edinburgh, for reviewing our raw echo data. We thank Cultech Ltd for supplying the antioxidant supplement; Siemens Medical Solutions for the loan of the echocardiography device; Marken, our international couriers.

92.

REGULAR SILDENAFIL DOES NOT INHIBIT ALTITUDE-INDUCED PULMONARY HYPERTENSION; A RANDOMISED DOUBLE BLIND PLACEBO-CONTROLLED TRIAL.

Email: rogerthompson@doctors.org.uk

We conducted a trial in healthy lowland participants of the Apex 2 expedition to determine the effect of regular sildenafil citrate on the elevation of pulmonary artery systolic pressure (PASP) following ascent to 5200m. 61 subjects (36 male; median age 21 years, range 18 to 31) were randomly allocated to receive 50mg oral sildenafil three times daily ($n = 20$) or matched placebo ($n = 42$). Subjects flew to La Paz, Bolivia (3650m) and after 4–5 days acclimatization ascended over 90 minutes to the Chacaltaya laboratory (5200m) by off-road vehicle. Echocardiograph recordings of PASP were made by an experienced cardiologist at sea level and within 6 hours, 3 days and 1 week at 5200m. It was not possible to obtain PASP readings on seven subjects. One subject withdrew with HAPE at 3650m. Twelve subjects descended from 5200m with symptoms of acute mountain sickness (5/20 sildenafil group, 7/41 placebo group). PASP readings for these subjects are included until evacuation. PASP for all participants rose from an average of 17.3mmHg (CI, 15.88 to 18.73mmHg) at sea level to 32.4mmHg (CI, 30.00 to 33.89mmHg) within 6 hours of ascent to 5200m ($p < 0.0001$, $n = 54$). PASP did not change significantly with time at altitude. Within 6 hours of ascent there was a non-significant reduction in PASP of 3.41mmHg in the sildenafil group (CI, -1.76 to 8.57mmHg, $p = 0.19$). There was no significant difference between groups at any other time. This study had power of 80% to detect a difference in PASP of 6.5mmHg. We found no significant reduction in PASP in those receiving sildenafil or placebo.

Acknowledgments: Apex2 volunteers; Dr John Irving; Dr Catherine Labinjoh; Pfizer UK; Siemens Medical Solutions; the Wellcome Trust Clinical Research Facility, Edinburgh; and the IIF, Universidad Mayor de San Andres, Bolivia.

93.

GREATER FREE PLASMA VASCULAR ENDOTHELIAL GROWTH FACTOR IN ACUTE MOUNTAIN SICKNESS.

Martha Tissot van Patot[1], Gig Leadbetter[2], Linda Keyes[3], Jamie Bendrick-Peart[1], Virginia Beckey[1], Uwe Christians[1], Peter Hackett[3]. [1]Dept. Anesthesiology, Univ Colorado Health Sciences Center, Dept Health Human Performance, Mesa State College, CO[2], Colorado Center for Altitude Medicine and Physiology, Dept. Surgery, Univ Colorado Health Sciences, Denver, CO[3]. *Email:* martha.tissotvanpatot@uchsc.edu

Vascular endothelial growth factor (VEGF) is a hypoxia-induced protein that produces vascular permeability, and limited evidence suggests a possible role for VEGF in the pathophysiology of acute mountain sickness (AMS), and/or high altitude cerebral edema (HACE). Previous studies demonstrated that plasma VEGF alone does not correlate with AMS; however, soluble VEGF receptor (sFlt-1), not accounted for in previous studies, can bind VEGF in the circulation, reducing VEGF activity. In the current study, we hypothesized that free VEGF (VEGF not bound to sFlt-1) is greater in subjects with AMS as compared to well individuals at high altitude. Subjects were exposed to 4300 m for 19–20 hours (baseline 1600 m). The incidence of AMS was determined using a modified Lake Louise symptom score and the Environmental Symptoms Questionnaire for cerebral effects. Plasma was collected at low altitude and after 24 hours at high altitude, or at time of illness, and then analyzed by ELISA for free VEGF, sFlt-1 and erythropoietin (EPO). AMS subjects had lower sFlt-1 at both low altitude and high altitude as compared to well subjects, and a significant rise in free plasma VEGF on ascent to altitude compared to well subjects. EPO was increased in all subjects with ascent to altitude. We conclude that increased free plasma VEGF on ascent to altitude is associated with AMS; whether it plays a role in pathophysiology of AMS warrants further study.

94.

TRAVEL TO HIGH ALTITUDE REDUCES THE EFFICACY OF WARFARIN IN 49 PATIENTS.

Martha Tissot van Patot[1,2], Colleen Dingmann[1,2], Lawrence Gaul[3], Ashley Hill[4], Kelly Fralick[3], Uwe Christians[1,2], Benjamin Honigman[2,5], MD Salman[4]. Dept. Anesthesiology[1], Colorado Center for Altitude Medicine and Physiology, Dept Surgery, Univ Colorado Health Sciences Center, Denver[2], Cardiology Group – Mountain Practice, Vail, Colorado[3], Dept. Clinical Sciences, Colorado State Univ[4]. *Email*: martha.tissotvanpatot@uchsc.edu

An ever-increasing number of people on a variety of medications travel to the mountains of the western US for vacations and business meetings. It is estimated that in Colorado, approximately 200,000 people chronically prescribed warfarin are traveling to high altitude annually. Objective: To determine whether a change in altitude can adversely affect the international normalized ratio (INR) in patients taking warfarin. A retrospective review of medical records from 8/98 to 10/03 in a cardiology clinic in Eagle County, Colorado (altitudes of residence from 2195 – 3231 m) was undertaken. INR target range, INR value and a change in altitude of >2200 m were recorded from 49 patients yielding 1009 INR measurements, 190 of which were in patients who had changed altitude within 5 days of INR measurement. INR deviation was defined as a value outside of the prescribed target range. An odds ratio (OR) of INR deviation from the target range was used to compare the change in altitude (>2200 m) to no change in altitude. The risk of a deviation in INR with a change in altitude was 5.4 times greater than without a change in altitude (95% CI 2.7,8.6). Of all travel INR values, 83% (157/190) were associated with an increase in altitude. Forty-seven % of this group (76/157) experienced a reduction of INR below the prescribed range, 17% (26/157) had an increased INR above the prescribed range, and 35% (55/190) experienced no change in INR. There is a significantly increased risk of INR deviating outside the prescribed target range in individuals who experience an altitude change of >2200 m (7,200 ft).

Acknowledgments: We would like to acknowledge the invaluable mentorship of Dr. Jack Reeves in the progression of this research.

95.

THE EFFECT OF ACE GENOTYPE AND HYPOXIC VENTILATORY RESPONSE ON ARTERIAL OXYGEN SATURATION DURING A STAGED ASCENT TO 5000M.

G Tsianos[1], J Milledge[2], E Hawe[3], M Giannitrapani[1], D Collier[4], S Grant[1], H Montgomery[3]. Univ Glasgow, Scotland[1], Northwick Park Hospital, England[2], Univ College London, England[3], Dept Clin Pharmacology, Barts, London, England[4]. *Email:* agiosgeorgios@hotmail.com

The 'Insertion' ('I', rather than Deletion, 'D') variant of the human Angiotensin I-Converting Enzyme (ACE) gene has been associated with elite high-altitude (HA) mountaineering status. In theory, an enhanced hypoxic ventilatory response (HVR) might help account for this through improved arterial oxygen saturations (SaO_2). We have performed a pilot study to investigate this hypothesis. 45 subjects underwent ACE genotyping and were studied before and during a 6 week trek to Chamlang Base Camp, Nepal, ascending from 410m to 5000m over 19–22 days. The subjects underwent pre-expedition sea-level assessment of HVR (Rebuck and Campbell, 1974) and daily oxygen saturation (SaO_2) measurements during the expedition. ACE genotype distribution was DD = 19, ID = 21, II = 5. There was an overall borderline significance ($p = 0.04$) in that those subjects with the II genotype had lower daily SaO_2 than the DD's or ID's, contrary to previous reports (Woods et al, 2002). There were no differences in HVR by ACE genotype [DD = 0.54 + 0.32 L/SaO_2, ID = 0.57 + 0.39 L/SaO_2, II = 0.56 + 0.12 L/SaO_2], $p = 0.98$, and higher daily SaO_2 values were not found in those with a brisker HVR, $p = 0.37$. ACE genotype has a greater influence on performance when acclimatisation time has been limited. The 'slow' ascent profile related to this study may thus account for the difference between these and existing data. In addition, the very small number of those with II genotype in this study weaken the strength of this observation. Further studies are required.

Acknowledgments: This work was carried out in association with Medical Expeditions MEDEX-Chamlang 2003

96.

ACE GENOTYPE AND MOUNT EVEREST.

G Tsianos[1], A Mynett, T Hubbart[2], S Grant[1], H Montgomery[2]. Univ Glasgow[1], Univ College London[2]. *Email:* agiosgeorgios@hotmail.com

The angiotensin converting enzyme gene is polymorphic, with the insertion (I) allele (rather than deletion, D) having been previously associated with elite mountaineering status in male Caucasians. We sought such an advantage in a prospective study of those attempting the ascent of the highest mountain on earth, Mount Everest (8850m). 64 high altitude mountaineers (58 males [36+ 8.8 years] 6 females [33.1+ 4.6 years]) were recruited from both Everest base camps (North side-Tibet and South side-Nepal) prior to their summit attempts in the spring of 2004. Their ACE genotype was determined, and their performance on the mountain recorded. Amongst successful summiteers (n = 42), genotype distribution was: 10 DD [24%], 22 ID [52%], 10 II [24%]; I allele frequency 0.50, and in those who failed (n = 22) 4 DD [22 %], 10 ID [53%], 8 II [25%]; I allele frequency 0.59. There were no genotype differences in those who succeeded vs. those who failed, $p = 0.56$. Although suggesting that ACE genotype may have little influence upon mountaineering success, these data take no account of racial differences, which are associated with differences in ACE genotype frequency and impact on ACE activity. In addition, data may be tainted by the use of supplementary oxygen (in all those summiting). Finally, it may be that ACE genotype influences success more when acclimatisation time has been limited. Further investigations are required.

Acknowledgments: Giorgos Tsianos was fully funded for completion of this project by the successful expedition to Mount Everest, HELLAS EVEREST 2004.

97.

CHRONIC AND INTERMITTENT MODERATE NORMOBARIC HYPOXIA INDUCES HEAT SHOCK PROTEIN 72 (HSP72) IN RAT DIAPHRAGM MUSCLE.

Jin Uchimaru[1], Yuji Ogura[1], Hisashi Naito[1], Shizuo Katamoto[1]. Univ Juntendo[1]. *Email:* jin.uchimaru@sakura.juntendo.ac.jp

The purpose of the present study was to investigate effects of chronic and intermittent normobaric hypoxia on HSP72 in rat diaphragm muscle. This experiment was approved by the Juntendo Univ Animal Care and Use Committee. Forty-eight male Wistar rats (6 weeks old: 131g) at the beginning of the study were used. Rats were assigned to one of three groups: 1) normoxia (N, n = 16), 2) chronic hypoxia (CH, n = 16), and 3) intermittent hypoxia (IH, n = 16). All groups were housed in a climate-controlled rooms (23 degrees, 60% relative humidity) with a 12:12-h dark-light cycle and fed standard rat chow and water ad libitum. CH and IH group were housed in a hypoxic room which maintained a oxygen concentration of 14.5% (3,000m) and were exposed to normobaric hypoxia for 24 and 12 hours per day, respectively. At the end of 25 and 50 days of the experimental period, the costal diaphragm (DIA) was quickly removed and frozen in liquid nitrogen. Muscle samples were stored at −85 degrees until analysis of HSP72 and muscle protein content. HSP72 was detected by the western blotting methods. HSP levels of N, CH and IH were 100%, 112%, 124% at 25days, and 100%, 163% and 185% at 50 days, respectively. Both CH and IH groups were significantly higher than N group at 50 days ($P < 0.05$). There is no difference in HSP72 between CH and IH. These data indicate that both chronic and intermittent moderate normobaric hypoxia similarly induces HSP72 in respiratory muscle of rat.

98.

CEREBRAL AND BRACHIAL BLOOD FLOW RESPONSES TO 60 MIN OF ISOCAPNIC HYPOXIA IN HUMANS.

Jimmy Vantanajal[1], Jon Ashmead[2], Kojiro Ide[1], Todd Anderson[1], Russell Hepple[3], Marc Poulin[4]. Faculty of Medicine, Univ Calgary[1], Faculty of Kinesiology, Univ Calgary[2], Faculties of Kinesiology and Medicine[3], Faculties of Medicine and Kinesiology[4]. *Email:* poulin@ucalgary.ca

Whilst it is well established that arterial hypoxia increases cerebral blood flow (CBF), relatively little is known about the vasodilator responses of other vascular beds to hypoxia, or about potential differences between the cerebral and peripheral vasculatures. We compared the sensitivities of CBF and brachial blood flow (BBF) to 60 min of isocapnic hypoxia (IH). We hypothesized that the sensitivity of CBF to IH would be greater than that of

BBF. Nine males (30.1 ± 5.2 years, mean ± SD) underwent two IH exposures separated by 60 min. A dynamic end-tidal forcing system was used to hold end-tidal PCO_2 ($PETCO_2$) constant at eucapnia (1.5 Torr above normal value) whilst controlling the end-tidal PO_2 ($PETO_2$) at the desired level. The protocol started with 10 min eucapnic euoxia ($PETO_2$ = 88 Torr). Then, $PETO_2$ was decreased rapidly to 50 Torr and held constant for 60 min. Finally, $PETO_2$ was returned to 88 Torr for 10 min. Transcranial Doppler ultrasound was used to measure beat-by-beat peak blood flow velocity (VP) in the right middle cerebral artery. BBF (right arm) was measured using echo Doppler ultrasound. The VP responses to hypoxia were fitted to a simple mathematical model (gain term (i.e., sensitivity), two time constants, baseline, time delay). The sensitivity of BBF to hypoxia was determined by the slope of the relationship between BBF and arterial O_2 saturation (calculated from $PETO_2$). IH elicited increases of 14.3 ± 4.1 and 23.5 ± 12.8 % in VP and BBF, respectively. VP and BBF remained elevated during IH with no evidence of adaptation. The sensitivity of VP to IH was smaller than BBF (1.20 ± 0.28 vs. 2.43 ± 1.51 %·% desaturation^{-1}; $P < 0.05$, ANOVA). The mechanisms by which IH elicits these differential responses remain to be elucidated.

Acknowledgments: This study was approved by the local Ethics Board and supported by AHFMR, CIHR and HSFA.

99.

HYPOXIC HYPERPNEA CAUSES MODEST MAL-DISTRIBUTION OF INTERALVEOLAR PERFUSION IN UNANESTHETIZED RATS.

Kal Watson[1], Robert Conhaim[1], E. Burt Olson[1], Edward Vidruk[1], Bruce Harms[1]. Univ Wisconsin, Madison, Wisconsin[1]. *Email:* watson@surgery.wisc.edu

RATIONALE: Although hypoxia is known to cause constriction of pulmonary resistance vessels (diams. > 50 μm), effects of hypoxia on perfusion distribution at the alveolar level are not well understood. To address this, we statistically analyzed the trapping patterns of 4 μm diam. fluorescent latex particles infused into the pulmonary circulation of unanesthetized, hypoxic rats. METHODS: Rats were placed into a plethysmograph where their minute ventilation (VE) was recorded, and where they breathed 10% oxygen (n = 4) or room air (n = 1). After 40 minutes, 4 μm diam. fluorescent latex particles (2 × 108) were infused into a chronic, indwelling femoral venous catheter. The rats were then removed from the plethysmograph, anesthetized, and their lungs were removed and air-dried. Trapping patterns of the latex particles were statistically analyzed in confocal images of the dried lungs (8 images per lung). Particle distribution is expressed as the log of the Dispersion Index (logDI), where particle clustering is proportional to how much logDI exceeds zero. LogDI = 0 is a statistically random distribution. RESULTS: VE in hypoxic rats (ml/min/100g) averaged 80.6 ± 3.1, and 32.5 ± 3.5 in the air-breathing rat ($p < 0.05$). LogDI in hypoxic rats averaged 0.68 ± 0.40 (mean ± s.d.), while log DI in the air-breathing rat averaged 0.45 ± 0.19 ($p = 0.15$). CONCLUSIONS: Hypoxic hyperpnea appears to have little effect on interalveolar perfusion distribution. Interestingly, the average number of latex particles per confocal image in the hypoxic rats was 1,953 ± 449, compared to 2,854 ± 265 in the air-breathing rat ($p < 0.05$). Our interpretation is that the more negative intrapleural pressures associated with hypoxic hyperpnea caused pulmonary microvascular vessel diameter to increase, which resulted in fewer 4 μm diameter particles remaining trapped within microvessels.

Acknowledgments: Supported by a grant from the Dept Veterans Affairs.

100.

MILD HYPOBARIC HYPOXIA DOES NOT INFLUENCE MARKERS OF COAGULATION, PLATELET, ENDOTHELIAL OR FIBRINOLYTIC ACTIVATION.

S.J. Watt[1], C.I. Jones[2], I. Ford[3], R.J. Pearse[2], V Chudasama[2], L.R. Mitchell[3], H.G. Watson[3], D.P. Gradwell[4], A.J. Batchelor[4], F.R. Rosendaal[5], J.C.M. Meijers[6], M. Greaves[3], A.H. Goodall[2], W.D. Toff[2]. Dept. Environmental and Occupational Medicine, Univ Aberdeen[1], Dept. Cardiovascular Sciences, Univ Leicester[2], Dept. Medicine and Therapeutics, Univ Aberdeen[3], RAF Centre for Aviation Medicine, Henlow[4], Dept of Clinical Epidemiology, Leiden Univ Medical Center[5], Dept. Vascular Medicine, Univ Amsterdam[6]. *Email:* s.j.watt@abdn.ac.uk

Links between air travel and venous thromboembolism (VTE) have been widely reported but it is unclear if specific factors in the aeroplane cabin increase the risk over that of seated immobility at ground level. We investigated the effects of hypobaric hypoxia, similar to that experienced during a commercial long-haul flight, on the haemostatic system in 73 healthy volunteers at low or modestly increased risk of VTE: 49 young subjects (aged 18–40 yrs) with no known risk factors, 12 users of the combined oral contraceptive pill (OC) and 12 subjects aged >50 yrs. Subjects were seated in a hypobaric chamber and exposed for 8 hours to normobaric normoxia (NN) or hypobaric hypoxia (HH), equivalent to ground level or an altitude of 8,000 feet, respectively. Each subject was exposed to both conditions, in a randomised fashion, 1–2 weeks apart. Blood was taken before, and within 20 minutes after exposure for measurement of markers of coagulation activation (TAT, F1+2, Factor VIIc/VIIa, Factor VIII, TFPI, soluble fibrin, ETP, aPC-SR), endothelial activation (sE-selectin, vWF), fibrinolysis (D-dimer, t-PA, PAI-1, PAP complex), platelet activation and responsiveness (ADP- and TRAP-induced fibrinogen binding, monocyte-platelet aggregates, sP-selectin, βTG). PT/aPTT and full blood count were also measured. The changes in each parameter (D) were compared by paired t-test. In the young, low-risk group, no significant differences were observed for any variable. In the OC and older age groups, there were also no significant differences, with the exception of the change in sE-selectin [OC: NN −0.541 ± 2.0; HH +0.901 ± 2.8ng/ml, mean ±sd, $p = 0.035$; older age group: NN −1.751 ± 2.5; HH +1.751 ± 3.2ng/ml, $p = 0.043$] and platelet responsiveness to ADP [older age group: NN +1.84 ± 4.8%; HH −5.84 ± 4.8%, $p = 0.043$]. There were no significant differences in the changes in blood cell counts with the exception of leucocytes in the older age group [NN +0.97 ± 0.59; HH +0.40 ± 0.6x109L-1, $p = 0.004$]. We conclude that, in healthy subjects, exposure to mild hypobaric hypoxia is not associated with prothrombotic alterations in haemostatic parameters and is unlikely to be a contributory factor in the aetiology of air-travel related VTE.

Acknowledgments: This study is presented on behalf of the WRIGHT Group (WHO Research Into Global Hazards of Travel) and was funded by WHO.

101.
NEW DEVICE TO MEASURE THE ALVEOLAR PO_2 AND PCO_2 AT HIGH ALTITUDE.
John West[1]. UCSD[1]. *Email:* jwest@ucsd.edu

When lowlanders go to high altitude there is an increase in ventilation that helps to limit the fall in alveolar PO_2. This is one of the most important features of the acclimatization process. However there is considerable variability between individuals and it would be valuable to be able to track the PO_2 and PCO_2. Furthermore the increasing availability of oxygen-enriched rooms at high altitude is an additional reason why it would be useful to monitor the alveolar PO_2. We have developed a self-contained battery-operated portable handheld alveolar PO_2 and PCO_2 analyzer. It works like a breathalyzer but measures O_2 and CO_2 instead of alcohol. The resting seated subject breathes normally for a minute or more and then makes a rapid expiration to residual volume into the mouthpiece. The last expired gas is trapped between two valves and a portion is drawn by a small pump through small O_2 and CO_2 analyzers. The PO_2 and PCO_2 are immediately available on a display along with the calculated respiratory exchange ratio which gives information about whether there is a steady state. A prototype using a rapid O_2 analyzer (Teledyne, UFO-130-2) has been tested at high altitude (3800 m) and tracked the decrease in alveolar PO_2 with ascent and the smaller subsequent increase during acclimatization. Calibration of the output against a mass spectrometer gave close agreement. It is expected that the device might also be valuable in a hospital emergency room, particularly in conjunction with a pulse oximeter, and also possibly at the scene of an accident where chest wall injury and hypoventilation are suspected. This new device has considerable potential.

Acknowledgments: Supported by UCSD.

102.
BLOOD PRESSURE CHANGES DURING EXERCISE AT ALTITUDE.
Alex Wright[1], Chris Imray[2], Phil Collins[3], Kyle Pattinson[4], Steve Myers[5], Steve Harris[5], Colin Chan[1], Jo Bradwell[1]. Univ Birmingham[1], Univ Hospitals,Coventry[2], ScanMed Medical Instruments[3], Univ Oxford[4], QinetiQ[5]. *Email:* a.wright@bmres.org.uk

Systemic blood pressure (BP) in humans on ascent to altitude may be unchanged or show a modest rise and tends to fall below low altitude on acclimatisation. the rise in BP during exercise (E) may be greater when hypoxic compared with sea level but data on BP changes at VO_2max are limited because of dificulties in measurments at extremes of exercise. The effect of submaximal (70%) and maximal E on mean BP was studied in 9 healthy, normotensive subjects with a non-invasive arterial tonomtry method (COlin Medical CBM-7000) comparing results at 150m with those obtained 24-36hr after arrival at 3610m, 4750m and 5260m. Results were compared using paired t tests. At 150m resting mean BP was 105 (12) mmHg, rising to 122 (7) at 70% E ($p < 0.02$) and falling to 112 (18) at VO_2max (NS compared with resting and 70% E). Resting BP did not change at higher altitudes and a similar pattern of rise at 70% E to 138 (17) ($p < 0.001$), 129 (15) ($p < 0.01$) and 122 (14) (NS) at the three altitudes respectively and a fall at VO_2max to 121 (21), 123 (18) and 107 (14)was found. The rise in BP at 70% E was greater at 3610m cf 150m($p < 0.05$) The method allowed BP to be measured automatically without disturbance from exercise on a recumbent cycle. the rise in BP during 70% E on acute exposure to high altitude was confirmed but the subsequent rises were less at higher altitudes suggesting some acclimatization was occurring. the fall in BP at VO_2max was found in almost all subjects on acute exposure but in only a third of subjects at the highest altitude. Whilst resting BP was unchanged on ascent, a greater rise in BP during 70% E was noted on acute exposure of normotensive subjects to high altitude. A fall in BP at VO_2max could play an important role in the limitation of execise at altitude in some subjects.