13th INTERNATIONAL HYPOXIA SYMPOSIUM

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•• Hot Topics: Pulmonary Circulation and HAPE ••

1. PULMONARY BLOOD FLOW HETEROGENEITY DURING HYPOXIA IN SUBJECTS WITH A HISTORY OF HIGH ALTITUDE PULMONARY EDEMA (HAPE).

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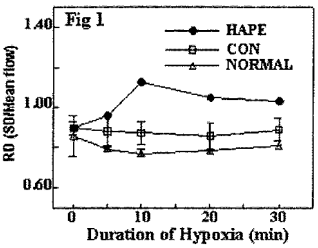
High pulmonary vascular pressures are important in the development of HAPE; uneven hypoxic pulmonary vasoconstriction (HPV) has been proposed to expose parts of the pulmonary capillary bed to high pressure/flow, and stress-related vascular injury. We therefore hypothesized that subjects with a history of HAPE would demonstrate increased heterogeneity of pulmonary blood flow during hypoxia. Six healthy subjects in 3 groups-1) HAPE, (history of HAPE, n = 1); 2) CON (control, repeated high altitude exposure to 6400 ± 610m without illness n = 3; 3) Normal (no history of altitude exposure, n = 2), underwent magnetic resonance imaging (MRI) with arterial spin labeling (ASL) using a Vision 1.5 T whole-body magnet (Siemens Medical Systems, Erlangen, Germany). MRI-ASL characterizes pulmonary blood flow distribution (resolution ~2 × 3 × 15 mm) by creating a magnetically tagged bolus using specialized radiofrequency pulses to flip proton magnetization. Pairs of images, with/without spin tagging were obtained and subtracted to yield perfusion-weighted image maps where signal intensity directly relates to blood flow. Data were collected in triplicate at each time point, in normoxia and after 5, 10, 20 and 30 minutes of normobaric hypoxia (FIO_2 = 0.125, ~4500m equivalent altitude). Relative dispersion (RD), an index of heterogeneity of blood flow (RD = standard deviation/mean) was determined. Average SaO_2 during hypoxia was not different between HAPE (86%) and Normal (84 ± 2%, means ± SE), but was higher in CON (89 ± 3%). Normoxic RD was similar between the 3 groups. RD was increased ~16% during hypoxia in HAPE, but not in CON or Normal (Fig.). Although preliminary, these results indicate that HAPE may have increased heterogeneity of pulmonary blood flow compared to CON and Normal, possibly resulting from uneven HPV. Support: NIH HL17731, M01RR00827, RNSA Scholar's Grant, Society of Thoracic Radiology Seed Grant (DLL).



2. VASCULAR ENDOTHELIAL GROWTH FACTOR IN PATIENTS WITH HIGH-ALTITUDE PULMONARY EDEMA.

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Vascular endothelial growth factor (VEGF) is a potent endothelial-cell-specific mitogen and permeability factor, known to be involved in vascular basement membrane destruction and angiogenesis. We hypothesized that VEGF might also play some pathophysiological parts in the development of high-altitude pulmonary edema (HAPE) in which the hyper-permeability edema has been evidenced to be one of its pathological features. We measured the concentrations of VEGF in venous serum and bronchoalveolar lavage fluid (BALF) in 9 patients with HAPE and 5 healthy volunteers using enzyme-linked immuno-sorbent assay. We also performed immunohistochemical staining with VEGF antibody in lung tissues of HAPE and controls. The results are shown as in the following table: Values are expressed as the mean ± SE. * The Student's t test was used for the comparisons between the HAPE patients at admission and at recovery; ** and between the HAPE patients at admission and normal controls. # lung materials of HAPE and normal controls came from a autopsied case of HAPE and surgical cases of primary lung cancer, taken from areas distant from the cancerous lesion, respectively. These findings suggest that VEGF may be insulted in the lung of HAPE and it appears less likely to have a critical part in the pathogenesis of HAPE, but rather an important role in the repair process for the impaired lung basement membrane in HAPE.

	HAPE patients (admission)	(recovery)	Controls	P value
VEGF venous serum (pg/ml)	260.7±8.7	423.7±44.7	228.8±0.5	< 0.05*
VEGF BALF (pg/ml)	42.8±9.9	79.8±5.6	265.2±34.9	<0.001**
Immunohistochemical staining#	negative		positive	

3. HYPOXIC PULMONARY VASOCONSTRICTION (HPV) IS DISTRIBUTED HETEROGENEOUSLY IN THE MAMMALIAN LUNG.

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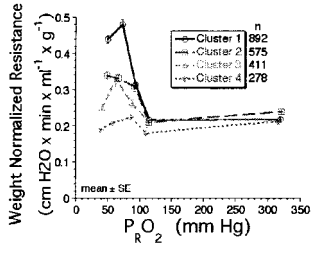
While HPV is thought to play an important role in normalizing gas exchange in the presence of lung disease, it may pose a threat to efficient gas exchange in the normal lung exposed to global hypoxia. The disproportional increase in vascular resistance has serious consequences during moderate to severe hypoxia. Hultgren's (Ann Rev Med 47:267, 1996) hypothesis for the etiology of HAPE is that hypoxic pulmonary vasoconstriction is extensive but uneven. This non-uniform response would expose the micro-vasculature to higher pressures in the less constricted areas resulting in patchy edema. The relative non-uniformity and spatial distribution of HPV have not yet been described in the intact mammalian lung. This study was undertaken to evaluate HPV for its relative uniformity in the intact animal. Regional blood flow, ventilation and PO_2 (PRO_2) within small lung regions (volume = 1.7 cm^3), of anesthetized supine pigs (heterogeneous V_A/Q distribution) and prone dogs (more homogeneous V_A/Q distribution) were studied. The animals were ventilated with an F_IO_2 of 0.50, 0.21 and various levels of hypoxia in random order. Blood flow and ventilation were measured using iv infusion of 15μm (Q) and inhalation of 1μm (VA) fluorescent microspheres, respectively. P_RO_2 was calculated for each piece at each F_IO_2 (Altemeier et al: JAP 85:2344, 1998). Lung pieces from all animals were grouped into clusters by their relative flow response to each FIO_2 without regard to spatial location (Figure). The lung pieces grouped into clusters, that varied in amplitude of HPV response rather than sensitivity to P_RO_2. Each cluster was shown to be spatially grouped. We conclude that the magnitude of regional HPV is spatially heterogeneous and is dependent on the regional variation of V_A/Q.



4. HIF HAPE AND HILLTOP RATS: A PARADOX UNFOLDING.

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Hilltop rats develop a pathological syndrome resembling Chronic Mountain Sickness (CMS) in humans. Manifestations of CMS include polycythemia, pulmonary vascular remodeling, hypertension and right ventricular hypertrophy. Paradoxically, Hilltop rats are more resistant to acute hypoxic pulmonary hypertension and high altitude pulmonary edema (HAPE) than control Madison rats. Hypoxia Inducible Factor-1α (HIF-1α) is exquisitely coupled to cellular hypoxia, enhancing expression of erythropoietin (EPO), vascular endothelial growth factor (VEGF) and inducible nitric oxide synthase (NOS-II), a potent generator of nitric oxide. Therefore, it was hypothesized that differences in HIF-1α activity or HIF-1α induced proteins may explain, in part, the apparent paradox. **Methods:** Hilltop and Madison rats were subjected to zero, 6 or 18 hours of acute hypobaria (18,000'). Pulmonary edema was documented by lung wet weight to dry weight (ww/dw) and blood free ww/dw (BFww/dw) ratios. Immunoblot assays for total lung HIF-1α, NOS-II and endothelial NOS (NOS-III) proteins were performed. Electrophoretic mobility shift assay (EMSA) of lung nuclear preps determined HIF-DNA binding activity. **Results:** Baseline gravimetric values did not differ between rats, except that Hilltop rats have significantly lower hemoglobin to hematocrit ratios. Hilltop rats had significantly lower edema measures at 18 but not 6 hours of hypoxic exposure ($p < 0.001$). Madison rats have more HIF-1α and NOS-II at baseline (5000') but respond minimally to 6 or 18 hours of acute hypoxia. Hilltop rats have lower initial levels but exhibit greater hypoxic increases of HIF-1α protein, HIF activity and NOS II, up to 18 hours of hypoxia. Surprisingly, Hilltop rats do not express NOS-III until 18 hours of hypoxia. **Conclusion:** Hilltop rats are more resistant to HAPE than Madison rats, which may be explained, in part, by a more vigorous hypoxic response of HIF-1α and NOS-II, potentially generating greater nitric oxide production.

5. PROTECTIVE EFFECT OF FEMALE SEX HORMONES AGAINST PULMONARY HYPERTENSION IN BOLIVIAN HIGH ALTITUDE NATIVES.

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There is abundant evidence that female sex hormones have protective effects in the systemic circulation in both animals and humans, but little is known regarding their role in the regulation of the pulmonary circulation. Observations in rats suggest that estrogens may have protective effects against hypoxia-induced pulmonary hypertension. We hypothesized that female sex may confer resistance against pulmonary hypertension in high altitude natives. To test our hypothesis, we performed echocardiographic measurements of the transtricuspid pressure gradient as an index of systolic pulmonary-artery pressure in young healthy Bolivians of Aymara ancestry. We studied 82 females and 99 males between 0 and 35 years of age, who were born and living at high altitude (4000 m). To provide additional information, we also measured arterial oxygen saturation and hemoglobin. The main new findings were two-fold. We found a strong direct relationship between age and systolic pulmonary artery pressure in male ($r = 0.48$, $P < 0.001$), but not in female ($r = 0.16$, $P > 0.1$) high altitude natives. Moreover, starting at the age of 12 years hemoglobin levels were significantly higher in males than in females, and there was a direct relationship between hemoglobin and pulmonary artery pressure in male ($r = 0.51$, $P < 0.001$), but not female ($r = 0.14$, $P > 0.1$) subjects. The gender-related differences in pulmonary-artery pressure were not related to differences in arterial oxygen saturation which were comparable in the two groups. These findings provide the first evidence for an age-related increase in pulmonary-artery pressure in young healthy male, but not female high-altitude natives. We speculate that female sex may protect against hypoxia-induced pulmonary hypertension in humans, either via decreased hemoglobin concentration and blood viscosity or by favorable effects of female sex hormones on pulmonary endothelial responsiveness to hypoxia.

7. ERYTHROPOIETIN PREVENTS DYSFUNCTION OF NITRIC OXIDE SYNTHASE ISOZYME EXPRESSION AFTER SUBARACHNOID HEMORRHAGE IN RATS.

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Erythropoietin (EPO) has been shown to protect against neuronal damage in models of stroke or subarachnoid hemorrhage (SAH). This effect of EPO may in part rely on beneficial effects on initial cerebrovascular inflammatory processes leading to vascular dysfunction and ischemic neuronal damage. We tested the effect of EPO on endothelium dependent vasoreactivity in isolated cerebral basilar arteries and on the expression of nitric oxide synthase (NOS) isozymes in brain and a. basilaris after experimental SAH in rats. Four groups of male Sprague-Dawley rats were studied: 1) sham operation plus vehicle; 2) sham operation plus EPO; 3) SAH plus vehicle; 4) SAH plus EPO. SAH was induced by injection of 0.3 ml of blood into the cisterna magna. EPO (400 IU/kg s.c.) or vehicle was given immediately after the subarachnoid injection of blood or saline. 48 h after the induction of SAH, vasoreactivity of isolated basilar arteries was tested by the use of an isometric Mulvany myograph. In separate series, protein levels of eNOS, nNOS and iNOS in total brain homogenates and in isolated basilar arteries were evaluated by Western blotting. EPO completely normalized the endothelium dependent acetylcholine-induced vasodilating and serotonin-induced vasoconstricting responses which were impaired by SAH. Neither SAH or EPO changed the endothelium independent vasodilating response to the NO donor nitroglycerin. Semi-quantitative immunoblotting showed that SAH upregulates the expression of nNOS in total brain homogenates and of nNOS and iNOS in basilar arteries whereas that of eNOS is downregulated. A subcutaneous bolus of EPO given immediately after the induction of SAH prevented this dysfunction of NOS isozyme expression. In conclusion, early administration of EPO after SAH may mitigate vascular inflammatory effects of SAH, thereby reducing the ischemic insult.

•• Hot Topics: Erythropoietin ••

6. LIVING HIGH—TRAINING LOW: EFFECT ON ERYTHROPOIESIS AND AEROBIC PERFORMANCE IN HIGHLY TRAINED CROSS-COUNTRY SKIERS.

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OBJECTIVES: 1) to verify whether the "living high—training low" method improves red cell mass and maximal aerobic performance, 2) to assess whether markers may predict the individual tolerance for this training method. **METHODS:** eleven athletes (6 men, 5 women) performed a 18-day training period at 1100m, by sleeping either at 1100m (Control, $n = 5$, $VO_2max = 59 \pm 9$ml/min/kg) or in hypoxic rooms (Hypoxia (10h/24h), $n = 6$, $VO_2max = 62 \pm 4$ml/min/kg), the O_2 fraction corresponding to 2500m, 3000m and 3500m (3×6days). Evaluation was conducted at 1100m, before and 15 days after the end of the training period. Measurements were VO_2max (treadmill), time to exhaustion at the velocity at VO_2max (Texh), hemoglobin (Hb), hematocrit (Hct), reticulocyte count (RETIC), erythropoietin (EPO), ferritin (Ferrit), serum transferring receptor (sTfR), red cell volume (RCV, CO-rebreathing method). All blood markers (except RCV) were also measured at the end of each altitude stage. Further, before training, all subjects performed a VO_2max test at 2500m and spent 3h at rest at 3000m (Hacute). Training load was recorded during the whole study. **RESULTS:** Training load during the study was similar between the two groups. Neither VO_2max, nor Texh were significantly modified by training, both in control (-2.5% and -14.8%, respectively, $n = 5$) and in hypoxia groups (-3.9% and -15%, respectively, $n = 5$). In Hypoxia group, VO_2max was found higher ($n = 1$), unchanged ($n = 1$) and lower ($n = 3$), assuming a variation >5%. Training coupled with hypoxic nights increased Hb, Hct, EPO, sTfR, whereas no change occurred in Control group. RETIC, VGR and Ferrit were not modified in Hypoxia group. Hacute increased EPO in both groups. However, in Hypoxia group, the changes in aerobic performance (after—before) were related neither to the decrement in VO_2max at 2500m, nor to the EPO increase in Hacute. **CONCLUSION:** The present results indicate that 18 days of "living high—training low" stimulated erythropoiesis. However, two weeks after the end of this protocol, hematological parameters had returned to normal values, and aerobic performance was not found increased. This study was supported by grants from the International Olympic Committee and the French Ministry of Sports.

8. NEURAL EPO INCREASES HYPOXIC RESPONSE AND HYPOXIC VENTILATORY ACCLIMATIZATION IN TRANSGENIC MICE.

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Neurally expressed erythropoietin (Epo) has mitogenic and neurotrophic roles protecting against apoptotic and cytotoxic events in brain. The mechanisms involve upregulation of enzymes that scavenge oxygen radicals, activation of neuroprotective factors and activation of voltage-gated calcium channels. W added to PC12 cells, Epo is able to increase intracellular Ca+2, stimulate dopamine release and increase cell viability. Because all these mechanisms are implicated in brainstem ventilatory control and respiratory acclimatization to long-term hypoxia, we hypothesize that Epo affects ventilatory response to hypoxia (HVR) and ventilatory acclimatization to hypoxia. We evaluated ventilation in neuronal Epo overexpressing transgenic (tg) and wildtype (wt) mice by whole body plethysmography. All animals were exposed to 6% O_2 for 20 min, before and after hypoxic acclimatization during consecutive three days at 10%O_2 in a hypoxic chamber. Before being exposed to chronic hypoxia, tg animals had higher HVR than the wt controls (tg vs. wt before acclimatization: 235 ± 76 vs. 202 ± 55 ml/min/100g, $p < 0.0001$) and HVR was dramatically increased in tg mice after chronic hypoxia (after acclimatization: 282 ± 48 vs. 198 ± 54 ml/min/100g, $p < 0.0001$). We conclude that neuronal Epo function in brain is not restricted to neuroprotection, but is also able to improve respiratory acclimatization to hypoxia.

9. CHRONIC EXCESSIVE ERYTHROCYTOSIS RESULTS IN SKELETAL MUSCLE DEGENERATION IN MICE OVEREXPRESSING ERYTHROPOIETIN.

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Elevated erythropoietin (Epo) plasma level is a common cause of increased hematocrit. The resulting erythrocytosis is assumed to cause higher blood viscosity that puts the cardiovascular system at hemodynamical risk. To follow the physiological consequences of chronic erythrocytosis we generated a transgenic mouse line that due to constitutive overexpression of hEpo (plasma Epo level increases 12-fold) reaches hematocrit levels of up to 90% and doubles the blood volume. Despite this excessive erythrocytosis, however, adult transgenic mice do not develop hypertension or thromboembolism. Adaptational mechanisms involve enhanced expression of endothelial nitric oxide synthase (eNOS) that results in systemic vasodilatation. Importantly, life expectancy of transgenic mice is reduced to about 7–8 months compared to a life span of 18–24 months found in wild-type siblings. Of note, exercise performance of transgenic mice was dramatically reduced. Preliminary analysis of 5–6 months old Epo-mice reveals severe degenerative processes in the skeletal muscle presented as fiber hypertrophy and altered vascular density. At this age first signs of muscular decompensation by overloading are detectable and morphologically represented by i) vacuolization of the muscle, ii) irregular endomysial clefts with tendency to fiber solidification, iii) focal, scattered fiber atrophy, and finally iv) in some areas a dramatically decreased capillary density. At 7 months, the hind limb muscle deficiency becomes obvious in most animals without additional loading. Hind limb tremor and toddle increase progressively and the animals suffer from signs of complete paraplegia. The development of muscle degeneration in an age- and gender-specific manner as well as the cause of the early death are under current investigation. Taken together, our preliminary data provide good evidence that long-term, Epo-induced erythrocytosis results in skeletal muscle degeneration.

Friday February 21st, 2003

••Hypoxia: New Hypotheses••

11. EXERCISE BEGINS AND ENDS IN THE BRAIN.

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Classically the limit to endurance of exercise is explained in terms of metabolic scope. Cardio-respiratory capacity and muscle fatigue are thought to set the limit. Indeed, the majority of studies on factors limiting endurance exercise discuss issues like VO_2max, aerobic enzyme capacity, cardiac output, glycogen stores, etc. In order words, in the classic paradigm the limits to endurance are explained with arguments of metabolic nature. However, this paradigm cannot explain the limitation to endurance exercise with large muscle groups at altitude when exercise is ended without muscle fatigue and with sub-maximal cardiac output. An at first glance astonishingly simple fact provides a basis for an explanation. Any voluntary exercise starts and ends in the brain. Indeed, a conscious decision is necessary to start a voluntary effort, and again, a conscious decision precedes the end of the effort. Based on an original idea by Hill and colleagues (1924) and data from Kayser et al (1994), Noakes et al (2001) recently developed the model of a central governor that integrates input from various sources all related to the exercise. This governor would limit the recruitment of skeletal muscle before the advent of damage to vital organs like the brain and the heart. The proposed governor would also limit exercise at sea level exercise, and may explain early exhaustion in untrained people, early exhaustion during exercise with an expiratory resistance, poor correlations between metabolic markers and marathon running time in elite endurance athletes and many other experimental data.

10. GENETIC MARKER FOR THE ERYTHROPOIETIC RESPONSE TO ALTITUDE.

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Introduction: Altitude training ("Living high-Training low") improves sea level performance in most endurance athletes. However, there is substantial individual variability in performance enhancement, due at least in part, to different erythropoietic (EPO) responses to altitude. Animal studies suggest that the EPO response to hypoxia may be transcriptionally regulated (Ou, et al, 1998), and thereby influenced by genetic mechanisms. Moreover, many highly polymorphic repeat sequences (dinucleotide, trinucleotide, or tetranucleotide) have been identified in the human genome within, or closely linked to genes specifically involved in hypoxia sensing and erythropoiesis. We hypothesized that the association of these polymorphisms with divergent phenotypic (increases in EPO) responses to high altitude would identify those genes that are responsible for individual variability in the erythropoietic response to hypoxia in humans. **Methods:** EPO concentration was measured in forty-eight competitive runners (32 men, 16 women) before and after 24-hours at a simulated altitude of 2800m. DNA obtained from leukocytes was amplified (PCR) and genotyped for polymorphic markers closely linked to candidate genes including, HIF-1α (transcriptional factor regulating EPO levels), pTEN (a down-regulator of the HIF-1α response), VHL (a posttranslational modulator of HIF-1α levels), RENOX (possible oxygen sensor in the kidney), Prolyl Hydroxylase (direct cellular O2 sensor regulating binding of VHL to HIF-1a), EPO gene, and the EPO receptor. High EPO responders (top 17%) and low responders (bottom 23%) were examined for an association between any of these polymorphisms and the specific phenotype. Results: EPO responses ranged from −41% to 400% of baseline values after 24 hours of simulated altitude. Two different polymorphic markers closely linked to the EPO gene were significantly associated with the phenotype on initial screening. When all athletes were considered, if one of the alleles of the marker was present (D7S477, homo or heterozygous) the increase in EPO was 135±α18% versus 78±14% when it was absent ($p = 0.02$). **Conclusion:** These data support transcriptional regulation of EPO synthesis in humans. There may exist a specific haplotype of the EPO gene that can be used to predict the erythropoietic response to altitude and thereby response to altitude training. Molecular determinants of the EPO gene regulating these responses remain to be identified.

12. OXYGEN-HEMOGLOBIN AFFINITY AT SEA LEVEL MAY PREDICT ACUTE ILLNESS AT ALTITUDE: THEORY AND SIMULATION.

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Acute mountain sickness carries with it serious health and economic costs. In their pursuit of the mechanisms that produce acute mountain sickness, researchers have overlooked the existence of a possible screening test, a test based on individual variation in cerebral oxygen exchange at sea level. In this presentation, I highlight the mathematical link between cerebral oxygen exchange at sea level—this is reflected in the magnitude of the oxygen extraction coefficient—and a change in brain blood flow at altitude; this link has been overlooked. A lower oxygen extraction coefficient at sea level can act—at altitude—to reduce the capacity of the intracranial compartment to accommodate brain swelling, exacerbate increases in cell volume, promote the stimulation of angiogenesis, and further cerebral edema, each of which may contribute to acute mountain sickness. In retrospect, it seems obvious that the initial state of cerebral oxygen exchange will impact the cerebral circulatory response to subsequent hypoxia. This deceptively simple notion offers us an opportunity to identify beforehand those people likely to develop acute mountain sickness when they travel to altitude.

13. NASAL LAVAGE VEGF LEVELS DURING ALTITUDE ACCLIMATIZATION.

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Vascular endothelial growth factor (VEGF) is an endothelial-specific mitogen with potent permeability enhancing properties that has been implicated as a potential mediator of capillary leak in high altitude pulmonary (HAPE) and cerebral (HACE) edema. We postulated that nasal lavage VEGF levels would increase with ascent and be highest in subjects that acclimatized poorly or developed severe altitude illness. To test our hypotheses we measured VEGF in the nasal lavage fluid of 15 people (10 male/5 female; 34.7 ± 8.7 years) collected each morning during the acute acclimatization period of a trek in Ladakh, India. Sea level (SL) nasal lavage (NL) samples were collected, the subjects and investigators then flew to Leh, Ladakh (3188 meters). The following two mornings the subjects provided NL samples. On day three the team traveled to an elevation of 5166 meters where they stayed for 4 days and collected morning NL samples. Samples were immediately frozen, stored at −70°C. A ELISA was used to determine NL VEGF levels. Data were analyzed using repeated-measures AVOVA. Multiple pair-wise comparisons were made with the Tukey-Kramer HSD procedure, with significance set at $p < 0.05$. Sea level NL VEGF (pg/mL) values were 100 ± 52 (mean ± SD) increasing significantly ($p < 0.01$) to 182 ± 59 on day 1 at 3188 meters then falling to 122 ± 54 on day 2. Again, NL VEGF increased to 165 ± 93 with ascent to 5166 meters and then fell to 74 ± 38 by day 4. One subject developed HAPE, and another failed to acclimatize, both were transported to Leh for treatment. This study demonstrates the ability to measure VEGF in the nasal lavage fluid. As postulated NL VEGF levels increased with altitude exposure and then fell with acclimatization. The lowest NL VEGF levels were found in the two trekkers who developed severe altitude illness. These findings suggest that an appropriate induction of the hypoxia response proteins and mediators (VEGF included) may be necessary for appropriate altitude acclimatization.

14. EFFECTS OF CHRONIC HYPOBARIC HYPOXIA ON ISOLATED RAT RESPIRATORY AND LIMB SKELETAL MUSCLE CONTRACTILE PROPERTIES.

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Chronic hypoxia occurs in humans in a variety of circumstances including respiratory disease and exposure to altitude and it is known to affect skeletal muscle structure. However, surprisingly little is known about its effects on skeletal muscle function. Thus, the aim of this study was to examine the effects of chronic hypobaric hypoxia on isolated contractile properties of rat respiratory and limb skeletal muscles. Adult male rats were exposed to normoxia (n = 16) or hypobaric hypoxia (n = 16, barometric pressure 450mmHg) for 6 weeks. Contractile properties of isolated strips of diaphragm, sternohyoid, extensor digitorum longus (EDL) and soleus muscle were measured in oxygenated Krebs solution in vitro. Isometric twitch and tetanic tension were determined using field stimulation with platinum electrodes. Fatigue was induced by stimulation at 40Hz with 300msec trains of 0.5Hz for 5 minutes. Chronic hypobaric hypoxia increased specific force development in diaphragm (2.3 ± 0.8 vs. 3.8 ± 1.8 N/cm2, mean ± (SD, normoxia vs. hypoxia), sternohyoid (1.7 ± 0.8 vs. 3.1 ± 0.7), EDL (2.5 ± 0.8 vs. 3.8 ± 1.5) and soleus (2.0 ± 0.7 vs. 2.8 ± 0.9) muscles. Furthermore chronic hypoxia increased peak tetanic tension in the sternohyoid (7.9 ± 2.9 vs. 12.9 ± 3.9) and soleus (9.0 ± 4.2 vs. 12.1 ± 3.4) muscles. In addition, chronic hypoxia increased fatigue of the sternohyoid, EDL and soleus muscles but had no significant effect on the diaphragm. In summary, chronic hypobaric hypoxia alters the contractile properties and fatigue characteristics of rat respiratory and limb skeletal muscles. These findings may be relevant to the chronic hypoxia of respiratory disease and exposure to altitude. Supported by Royal College of Surgeons in Ireland, Univ College Dublin, Ireland and The Physiological Society.

15. EFFECT OF EXTRACELLULAR PO_2 ON THE FALL IN INTRACELLULAR PO_2 IN CONTRACTING SINGLE MYOCYTES.

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This investigation tested the effect of altered extracellular PO_2 (PeO_2) on the intracellular PO_2 (PiO_2) response to contractions in single isolated skeletal muscle cells. We hypothesized that as PeO_2 increased, thereby increasing the driving force for O_2 flux, the fall in PiO_2 (proportional to the net increase in VO_2) and the speed of the initial metabolic response (calculated as fall in PiO_2/τ) would be increased. Single myocytes (n = 12) were dissected from lumbrical muscles of adult female Xenopus laevis and injected with a porphyrin compound for assessment of PiO_2 via phosphorescence quenching. For each cell, at PeO_2's of ~20 (low), ~40 (moderate) and ~60 (high) Torr, tetanic contractions were induced at a frequency of 0.67 Hz for ~2 min with a 5 min recovery between bouts. The PiO_2 response to contractions was characterized by a time delay (TD) followed by a mono-exponential decline to steady-state (SS) values. The fall in PiO_2 to SS values was significantly greater at each progressively greater PeO_2 (all $p < 0.05$). The mean response time (TD + time constant) was significantly faster in the low (35.2 + 5.1 s, $p < 0.05$ vs. high) and moderate (43.3 + 6.4 s, $p < 0.05$ vs. high) compared with high PeO_2 (61.8 + 9.4 s) and was correlated positively ($r = 0.965$) with the net fall in PiO_2. However, the initial rate of change of PiO_2 (calculated as net fall in PiO_2/τ) was not different ($p > 0.05$) among PeO_2 trials. These latter data suggest that, over the range of 20–60 mmHg, PeO_2 does not play a deterministic role in setting the initial metabolic response across the rest-to-contractions transition in isolated frog myocytes. Additionally, these results suggest that oxidative phosphorylation in these myoglobin-free myocytes may be compromised by PeO_2 at values nearing 60 mmHg. Supported by NIH AR-40155 and AR-48461 and a Parker B. Francis Fellowship.

16. EUROPEAN GENETIC ADMIXTURE PREDICTS DECREMENT IN AEROBIC PERFORMANCE AT 4338 METERS IN PERUVIAN QUECHUA.

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Quechua natives of the highland Andes may be genetically adapted to high altitude and thus able to resist decrements in maximal O_2 consumption in hypoxia (ΔVO_2max). This evolutionary hypothesis was tested via the repeated measures of VO_2max (sea level versus 4,338m) in 30 young male Peruvians of mixed Spanish and Quechua origins. Genetic admixture level (% European genetic influence) was estimated on each individual using a panel of 22 ancestry-informative DNA markers. Genetic admixture explained a significant proportion of the variability in ΔVO_2max after control for major covariate effects including sea level VO_2max and the decrement in arterial O_2 saturation (ΔSPO_2). The genetic effect reflected a main effect of admixture on ΔVO_2max ($P = 0.041$), as well as the interaction between admixture and ΔSPO_2 ($P = 0.018$). The latter means that admixture was predictive of (VO_2max only in subjects with a large decrease in SPO_2 at 4,338 m. In such subjects, ΔVO_2max was nearly 22% larger in the highest versus lowest subgroup of European genetic influence (~940 versus ~740 ml/min, respectively; $P = 0.031$). A non-significant trend for interaction ($P = 0.095$) was also noted between admixture and the decrease in ventilatory threshold at 4,338 m ($\Delta VEthresh$). Similar to the previous interaction, admixture was predictive of ΔVO_2max only in subjects with a large $\Delta VEthresh$. Together, these interactions suggest that the putative genetic effect on ΔVO_2max is mediated by a subject's aerobic fitness level. In particular, genetic effects may be more important (or easier to detect) in very athletic subjects who are more likely to show gas exchange impairment during exercise. In summary, the results of this study are consistent with the evolutionary hypothesis, and point to a better gas exchange system in Quechua as a possible explanation for the admixture effect detected.

17. INTRACUTANEOUS OXYGEN CONCENTRATION IN NORMAL AND ISCHEMIC SKIN IS INCREASED AFTER INTERMITTENT HYPOXIA TRAINING.

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In earlier studies normobaric intermittent hypoxia training (IHT) was shown to increase survival and cutaneous perfusion of ischemic skin flaps in rats. With this study we investigated the changes of intracutaneous oxygen concentration in normal skin during IHT (course study). Furthermore, we researched the changes of intracutaneous oxygen after rising ischemic skin flaps in IHT-trained and control rats (flap study). **Methods:** Course study: 16 Wistar rats were randomized into 2 groups of 8 animals each. In the study group the rats were exposed to 20 daily sessions of IHT over 4 weeks with increasing duration and decreasing oxygen content in the breathing air (O_2 = 10%–9%). The control animals underwent the same training while constantly breathing ambient air (O_2 = 20,6%). At day 5, 10, 15, 20 continuous intracutaneous measurements were performed during an IHT-session. Flap study: Another set of 16 Wistar rats was trained as described above. After 4 weeks of IHT, caudally based 9 × 3cm random dorsal skin flaps were elevated. Daily intracutaneous measurements were carried out in the proximal, intermediate and distal part of the flap in IHT and control animals until postoperative day 10. **Results:** Course study: IHT showed to significantly decrease the intracutaneous oxygen concentration during the hypoxic phases. During the IHT course this decrease proved to become less pronounced and recovery under normoxia was significantly faster. Flap study: Our measurements showed a significant increase of intracutaneous oxygen in IHT animals in all parts of the ischemic skin flap. In the intermediate part of the flap the oxygen concentration was more than doubled: IHT vs. control: day 1: 20.1 mmHg vs. 7.8 mmHg; day 3: 14.6 mmHg vs. 6.6 mmHg. **Conclusion:** IHT leads to an effective systemic adaptation to hypoxia and can be used as a preconditioning technique for skin flaps.

18. INCREASED HYPOXIA-INDUCIBLE TRANSCRIPTION FACTOR ACTIVITY CORRELATES WITH INCREASED ANAEROBIC METABOLISM IN PLACENTAS.

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We have previously presented data indicating that placentas from high altitude pregnancies have reduced activity of hypoxia-inducible transcription factor (HIF). HIF promotes transcription of proteins necessary to 'rescue' tissue from hypoxia, such as vascular endothelial growth factor (VEGF), erythropoietin, and glycolytic enzymes. The surprising finding of reduced HIF activity in high vs. low altitude placental tissue led us to speculate that we may have induced hypoxic/ischemic artifact during collection of the placenta. If the time from placental delivery to placement of tissue in liquid nitrogen was greater at low vs. high altitude, we may have introduced the appearance of reduced HIF activity at high vs. low altitude. Subsequently, we collected placental tissue within 2 minutes of placental delivery and at 5-minute intervals to 25 minutes. Magnetic resonance spectroscopy (MRS) of placental lactate and glucose indicated an increase in anaerobic metabolism up to 11 minutes post-placental delivery. Therefore, we hypothesized that HIF activity would be increased as time from placental delivery is increased, in accordance with an increase in anaerobic metabolism. **Methods:** Placental samples from the same placentas (n = 4) and time points used in the MRS study were analyzed by electrophoretic mobility shift assay (EMSA). A 22 bp oligonucleotide corresponding to the HIF binding site on VEGF was used to determine HIF binding activity. **Results:** HIF activity was reduced with increasing time from placental delivery. **Conclusion:** In placentas, HIF activity decreases with increased anaerobic metabolism. Furthermore, results from placental tissue collected within 9 minutes at high and low altitude support our previous findings; high altitude placentas, from successful pregnancies, do have reduced HIF activity as compared to placentas from lower altitude. Could high altitude placentas from successful pregnancies provide insight into the mechanisms of adaptation to hypoxia?

19. THE REGULATION OF BRAIN TISSUE PO_2 DURING ACUTE AND CHRONIC HYPOXIA.

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The regulation of brain tissue pO_2 during acute and chronic hypoxia Objectives: To determine the capacity of the brain to maintain tissue pO_2 (PtO_2) during exposure to acute and chronic hypoxia. **Methods:** We used electron paramagnetic resonance oximetry to determine the changes in PtO_2 in the brain of unanesthetized rats during acute hypoxia, as well as during acclimation to, and recovery from exposure to $^1/_2$ an atmosphere of hypobaric pressure. In one study, animals were acclimated to $^1/_2$ an atmosphere for 28 days, and a control group was maintained under similar conditions while at normobaric pressures. Brain PtO_2 was measured in both groups under normobaric, normoxic conditions. **Results:** In acute hypoxia, brain PtO_2 varies with the inspired oxygen tension. In chronic hypoxia, PtO_2 was elevated after 3 days in the experimental group, reached a maximum at 7 days and remained constant for the remainder of the 28 days (at more than double the PtO_2 of the control group (JCBFM, 2000, v20, p1632). In a second study, brain PtO_2 was measured in rats breathing both 21% and 10% O_2, before and after acclimation to 10% O_2. The PtO_2 in the brain of acclimated animals breathing 10% O_2 was not significantly different from the PtO_2 of pre-acclimated animals breathing 21% O_2. **Conclusions:** Although the brain does not maintain PtO_2 under acute hypoxia, there are adaptive mechanism initiated by hypoxia which result in acclimation to chronic low oxygen. The brain adapts to chronic hypoxia by returning the tissue to a pre-hypoxic PtO_2, indicating that there are O_2 sensitive mechanisms (such as HIF-1α) that are capable of sensing PtO_2 and initiating a cascade of events which result in the PtO_2 returning to normal.

20. PROLONGED EXPOSURE TO HYPOXIA INCREASES EXPRESSION OF Na TRANSPORTERS OF CULTURED ALVEOLAR EPITHELIAL CELLS.

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Although short term exposure to hypoxia inhibits alveolar Na-transport in A549 cells, there is an increase in mRNA expression of β1-Na/K-pump and β-ENaC as well as in whole cell (1-Na/K-pump protein after 24h of hypoxia. We wanted to know, whether prolonged exposure to hypoxia stimulates ion transport and whether treatment with dexamethasone (DEX) modulates hypoxia effects. Control and DEX-treated A549-cells (DEX, 1μM) were exposed to hypoxia (1.5% O_2) for 24h, 48h and 72h. mRNA expression was measured by real time PCR. Whole cell protein was used for Western blot analysis. Since in short term hypoxia β1-Na/K-pump and β-ENaC mRNA were affected only those were measured. Effectiveness of hypoxia exposure was seen by an increase in GAPD mRNA. DEX increased α1-Na/K-pump mRNA by 5 to 8-fold and protein by 4 to 6-fold. No change in α1-Na/K-pump mRNA occurred after 24h of hypoxia, but prolonged hypoxia increased mRNA (48h, 72h: +80%) and protein (48h, 72h: +200%). In DEX treated cells no further increase by hypoxia was seen. Dex did not increase β1-Na/K-pump mRNA. Hypoxic exposure increased β1-Na/K-pump mRNA (24h, 48h: +200%; 72h: +500%). This increase was abolished by DEX. β-ENaC expression was stimulated by hypoxia, the degree of stimulation increased with prolonged exposure (24h: 2.3-fold; 48h: 23-fold; 72h: 26-fold). DEX increased β-ENaC mRNA levels in normoxic and hypoxic cells considerably. These results indicate that despite a decrease in activity of Na-transporters in hypoxia, there is build up a new pool of Na-transporters over time, which might be recruited fast upon reoxygenation. In vivo such mechanisms improve edema clearance.

21. DOES MUSCLE VASCULAR MORPHOLOGY ADAPT TO HIGH ALTITUDE?

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High altitude induces adaptive responses to ensure oxygen supply to tissues. Hypoxia-inducible factor 1 (HIF-1) is the transcription factor for many genes that are augmented by hypoxia, including the angiogenic factor VEGF, which modify vascular morphology. In normoxia, HIF-1α subunit activity is inhibited by ubiquitin. In hypoxia, increased HIF-1α mRNA expression and activity by dissociation from ubiquitin has been demonstrated. **Aim:** We hypothesized that adaptation to altitude would increase mRNA and protein levels of HIF-1α and VEGF and result in increased muscle capillarization. **Methods & Results:** To test this, muscle biopsies were obtained from 8 Danes at sea level, and after 2 and 8 weeks of exposure to 4.100 m altitude, and from 7 Bolivians of Aymaran ancestry residing at this altitude. Surprisingly, we found no significant differences in HIF-1α or VEGF mRNA levels over time or between subject groups. Correspondingly we found no dynamic change in muscle morphology in the Danes. The main differences were a smaller average fibre area and slightly smaller capillary density in the Bolivians compared to the Danes (Table). **Conclusion:** 8 weeks or lifelong exposure to 4.100 m cause no increase in capillary density in muscle. Table 1. Muscle morphology in Danes at sea level (SL), and after 8 weeks exposure to 4.100 m altitude (CH8), and in Bolivian Aymaras. Values are mean ± SEM. *P < 0.05 compared to SL, #P < 0.05 compared to CH8.

	Cap./fiber	Cap./mm2	Mean area
SL	4.0 ± 0.2	556.2 ± 55.6	6492.2 ± 512.3
CH8	3.6 ± 0.2	578.7 ± 28.0	6059.5 ± 623.6
Aymaras	2.4 ± 0.1*#	491.0 ± 19.6#	4474.2 ± 188.4*

Saturday February 22nd, 2003

•• Hot Topics in Mountain Medicine ••

23. LUNG FUNCTION AFTER RAPID ASCENT TO HIGH ALTITUDE.

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Rapid ascent to high altitude may alter lung function, presumably due to pulmonary extravascular fluid accumulation and other mechanisms. To investigate this further, we measured lung function, closing volume by single breath nitrogen washout and pulmonary artery systolic pressure (PaP) by echocardiography in Zurich (490m) in 21 volunteers. They subsequently traveled to Mt.Rosa and ascended to 4559m within 12 hours. Two hours after arrival and after one night at 4559m, lung function, PaP and Lake Louise mountain sickness scores (LLS) were reassessed. Closing volume had increased after arrival at 4559m. In the following morning closing volumes had decreased in 11 and increased in 8 subjects compared to the previous evening. Overnight changes of closing volumes at 4559m were correlated with LLS changes ($r = 0.6$, $P < 0.01$). No subject had signs of pulmonary edema. High closing volume after arrival at 4559m are consistent with previous observations. **Conclusion:** Underlying mechanisms appear to differ among subjects: Progressive closing volume increases over 12 hours may indicate subclinical high altitude pulmonary edema, transient closing volume increases are consistent with effects of strenuous exercise or bronchoconstriction induced by high ventilation.

	490m Zurich	4559m evening	4559m morning
Vital Capacity % predicted	104±2	98±2*	97±2*
FEV1/FVC %	82±2	84±2*	84±2*
DLCO% predicted	106±5	122±4*	127±4*
Closing Volume ml	366±36	452±29*	435±38
SpO_2%	96±1	77±1*	81±1*#
Pulmonary artery systolic pressure mmHg	27±1	41±2*	40±2*

*means (±SE), P<0.05 vs. 490m, #p<0.05 vs. 4559 evening

22. METHODS FOR MONITORING HORSES IN A SIMULATED ALTITUDE STALL.

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Unlike humans, horses have been bred for athletic performance and seem to have adaptive advantages for extreme performance. Horses have a spleen that stores and releases red blood cells when the horse exercises. This release enhances blood oxygen carrying capacity and athletic performance. Can this performance be further enhanced, as it is in humans, if horses experience hypoxic exposure? As a first step to answering this question, we have initiated a pilot study by developing a stall instrumented (Colorado Altitude Training) to simulate an altitude of 12,000 feet and by initiating simple monitoring methods. Our first task was to develop a means for monitoring the equine response to an acute hypoxic exposure. There is no assay available for measuring equine EPO and surface pulse oximeters are not functional for horses. Therefore, we pursued crude methodologies. An equine AeroMask was modified by connecting the two exhalation ports together and to a 49 l plastic bag. An oxygen analyzer could be inserted to measure end-tidal as well as mixed expired oxygen tension. The end-tidal oxygen tension, as an estimate of arterial oxygen tension, together with the equine dissociation curve, yielded an estimate of oxygen saturation. Furthermore, minute ventilation was estimated from bag filling time permitting an estimate of oxygen consumption. To explore the utility of the system, as part of the larger study of performance, a horse was exposed to a simulated altitude of 12,000 feet for 8 hours a day for one month. The average data for normoxia and simulated altitude are shown below. The coefficient of variation over multiple measurements was in the range of 15%.

RR (b/min)	VT (l)	VE (l/min)	VO_2 (l/min)	S (%)
12.1	2.7	32.6	1.3	99
18.6	3.8	71.6	1.6	90

Although crude, these data suggest relative changes may be useful for monitoring horses in simulated altitude.

24. FIELD TESTING OF A NEW HIGH-ALTITUDE O_2 DELIVERY SYSTEM IN THE BOLIVIAN ANDES.

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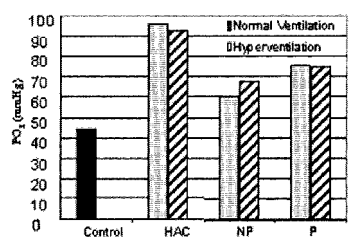
Background: At extreme altitude, bottled O_2 is expensive and cumbersome, but necessary. The PaO_2 achievable with simple mask/nasal prongs (NP) or a non-rebreathing mask (e.g. Poisk (P)) is limited by available O_2 flow and high minute ventilations (VE), which dilute inspired O_2. Furthermore, performance is limited by hypocapnia, which reduces cerebral blood flow and increases the affinity of Hb for O_2. We designed a high altitude circuit (HAC) that uses low O_2 flows to provide a constant high FiO_2 and constant $PaCO_2$ regardless of VE. We compared the PaO_2 attained at 5300 m at resting VE and during hyperventilation using the HAC with that using NP and P. **Methods:** Five healthy acclimated subjects weighing 73 ± 5 kg breathed room air at rest via the HAC. The O_2 flow required to raise PaO_2 to 100 mmHg (F100) was determined. With O_2 flow set at F100, each subject breathed at rest (5 min) and 3 × resting VE (5 min) on each of the three circuits. Tidal PCO_2 and PO_2, VE and Hb saturation were monitored. **Results:** F100 was 0.8 ± 0.2 L/min (corrected to 1.0 A). At the same O_2 flow (F100), PaO_2 was significantly greater with the HAC than with NP or P (Figure). Hyperventilation did not change PaO_2 with the HAC or P, but improved PaO_2 with NP. **Conclusion:** In field tests, the HAC demonstrated the highest efficiency of the three O_2 delivery devices. This may allow climbers to carry less O_2 or go farther with a given O_2 supply, and reduce littering. In addition, its ability to control end-tidal PCO_2 may be therapeutically useful for increasing cerebral blood flow and suppressing periodic breathing.



25. THE EFFECT OF SIMULATED ALTITUDE DURING SLEEP ON MODERATE SEVERITY OBSTRUCTIVE SLEEP APNEA.

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Field studies in Nepal have shown the replacement of obstructive events (OSA) with central events (CSA) during sleep at high altitudes in normal volunteers (Burgess K et al, Hypoxia 2001). This study was conducted to investigate whether the same effect would be evident in subjects with moderate severity OSA at a simulated altitude of 2750m. **Methods:** 5 male subjects aged 54+/−6 years (mean +/−SD), BMI 36.3+/−8.4 and previous mean apnea hypopnea index (AHI) of 32.7+/−10.7/hour were studied on two consecutive nights in the Altitude House at the AIS in Canberra and a third night at "sea level" (100m) in Manly. Two nights breathing ambient air (100m & 600m), the other breathing nitrogen enriched air simulating 2750m. Sleep was monitored by portable PSG equipment with remote monitoring (PS2, Compumedics, Melbourne). Sleep was staged using Rechtschaffen & Kales rules. Respiratory events were scored by the modified Stanford criteria. **Results:** Obstructive AHI decreased from 25.5 +/−14.4/hr at 100m to 17.3+/−9.2 at 600m to 0.5+/−5.8 at 2750m ($p = 0.004$, ANOVA). While central events increased from 0.4+/−0.5/hr at 100m to 8.1+/−5.8 at 600m to 78.8+/−29.7 at 2750m ($p < 0.001$). Mean SaO_2 decreased from 94.0+/−1.2% at 100m to 85.0+/−4.0% at 2750m. **Conclusion:** Overnight exposure to a simulated altitude of 2750m can cause the replacement of documented sea level moderate severity OSA with severe CSA. The pattern was also evident moving between 100m and 600m altitude.

27. HOW ELITE MOUNTAIN CLIMBERS TRAIN TO COPE WITH HYPOXIA.

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A group of elite climbers (n = 39) were interviewed in order to assess their physical and mental training techniques prior to attempting to summit Mount Everest. Among the climbers were one of the first climbers to summit Everest without oxygen, the oldest climber to summit (64 years), the oldest climber to attempt to summit (71 years), the climber with the most summits and three female climbers. A qualitative method of inquiry (interview) was used to assess the mental techniques used by the climbers. A quantitative method (Questionnaire/interview) was used to collect data on the physical training. The main emphasis of the training was aerobic fitness and ability to regulate one's breathing, ability to focus, ability to pray and finding inner peace. The physical modalities of training focused mostly on climbing (stairs, hills & mountains); running; cycling; hiking & cross country skiing. The mental training modalities were: meditation; yoga; breathing techniques; music and prayer. The study concluded that the three main factors that trigger mountain sickness in acclimatizing climbers are: The fear factor, inability to relax and inability to breathe correctly. All three are closely linked to one's physical and mental fitness.

26. CHANGES IN EMG DURING EXERCISE WITH A SMALL MUSCLE GROUP DURING DECREASING ARTERIAL PO_2.

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On the last meeting we have shown that during decreasing arterial PO_2 oxygen uptake during sub maximal exercise of the working forearm muscles decreased after reaching a PO_2 of 63 Torr while power was unaffected. Lactate release could not compensate for the difference in energy turnover. The aim of the present was to look for differences in recruitment pattern of the exercising muscles. **Methods:** 8 male subjects performed continuous handgrip exercise with 70% of the maximal workload reached in an incremental test. Contraction frequency was 24 per minutes. Subjects were connected to a closed spirometric system. During exercise oxygen concentration was reduced in the inspired gas by about 3% every 10 minutes down to about 9% (HYP). Contraction velocity and distance were measured continuously. For acid-base state, saturation, lactate and electrolyte determination blood was drawn from a cubital vein of the working forearm. Arterialized blood was drawn from a hyperaemized earlobe and from a superficial vein of the resting hand. Forearm blood flow was measured plethysmographically. Control experiments were performed under normoxia (NOR). EMG was determined with surface electrodes from the working muscles. **Results:** M-wave decreased under both conditions after 25 min by about 8% (HYP) and 11% (NOR). Mean frequency remained constant under both conditions. EMGrms remained constant after 25 min under NOR but decreased under HYP by about 25% ($p < 0.05$) after 25 min corresponding to a PO_2 of 63 Torr in the arterial blood. The decrease of EMGrms coincides with the beginning of the reduction in VO_2 and the slight increase in lactate release from the forearm. **Discussion:** As the pattern of the M-Wave is similar under both conditions the reduction in electrical activity seems to be caused by central influences. Whether these changes are the cause for the variation in muscle metabolism remains to be clarified.

28. DISSOCIATION BETWEEN SKELETAL MUSCLE MICROVASCULAR PO_2 AND HYPOXIA-INDUCED MICROVASCULAR INFLAMMATION.

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Systemic hypoxia produces an inflammatory response characterized by oxidative stress, and increased leukocyte-endothelial adherence and vascular permeability in mesenteric, brain, and muscle microcirculations. Hypoxia induces hypotension in anesthetized rats, which may result in blood flow-mediated reductions in venular wall shear rate and/or microvascular PO_2 (PmO_2). These experiments were performed to determine the roles of blood flow and PmO_2 on leukocyte adherence to cremaster muscle venules during hypoxia. Cremasteric venules of anesthetized rats were visualized with intravital microscopy. PmO_2 was determined with a phosphorescence decay method. The following experiments were performed: I. Untreated controls; II. Systemic hypoxia: inspired gas: 10% O_2; III. Ischemia: cremaster blood flow restriction; inspired gas: room air; IV. Cremaster hypoxia/systemic normoxia: cremaster equilibrated with 95% N2, 5% CO_2; inspired gas: room air, V. Cremaster normoxia/systemic hypoxia: cremaster equilibrated with 10% O_2, 5% CO_2, balance N2, inspired gas: 10% O_2. The following data were obtained after 10 min of each treatment: Leukocyte adherence increased significantly only when PaO_2 was low (groups II and V) even if PmO_2 was elevated (Group V). Muscle hypoxia with normal PaO_2 (groups III and IV) did not elicit leukocyte adherence. Low shear rate did not contribute to leukocyte adherence (Group II vs III). The results suggest that systemic hypoxia elicits the release/generation of a mediator which promotes microvascular inflammation.

	I Untreated	II Systemic hypoxia	III Ischemia	IV Cremaster hypoxia	V Cremaster normoxia
PaO_2, Torr	85.0±1.0	33.0±0.4	86.0±1.7	88.8±1.2	34.9±1.2
PmO_2, Torr	34.8±2.0	6.0±1.7	6.4±1.9	4.2±1.2	63.5±5.5
Venular shear rate, secs	208±18	126±25	85±22	198±22	82±18
Adherent leukocytes/100 um)	2.8±0.5	10.0±1.1	4.3±1.1	3.0±0.4	11.5±1.5

29. SLEEP CHARACTERISTICS IN ACUTE NORMOBARIC HYPOXIA IN RECREATIONAL ATHLETES.

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BACKGROUND: Many athletes routinely use sojourns to altitude to gain the reported benefits such as an improved aerobic capacity (Levine and Stray-Gundersen, 1992). Although sleep at true altitude is well understood, few studies have reported the effects of normobaric hypoxia upon parameters of sleep (Kinsman et al. 2002). **AIM:** To evaluate the acute effects of normobaric hypoxia (NH) upon sleep characteristics compared to normobaric normoxia (NN). **METHODS:** 8 healthy male recreational athletes (mean ± sd; age = 34.5 ± 6.87yr; ht = 169.1 ± 8.7cm; wt = 69.3 ± 8.2kg; VO_2 max = 56.4 ± 8.3 ml.kg/min) participated in this study. Subjects were investigated over 3 nights. Night 1 was an adaptation night and nights 2 and 3 were either NH (pO_2 = 110 mmHg) or NN (pO_2 = 159 mmHg) in a double blind, randomized design. Sleep characteristics were measured using actigraphs (Cambridge neurotechnologies, UK—a wristwatch like device which measures global activity levels), worn continuously for a 2-week period. **RESULTS:** No significant differences ($P > 0.05$) were found between NN and NH (Table 1), however, large inter-individual variation was observed. **DISCUSSION:** The findings of this study revealed a limited effect of NH upon sleep characteristics; however, large individual differences warrant further investigation. The physiological mechanisms causing these inter-individual differences are unclear.

Sleep parameter	Normobaric Normoxia (NN)	Normobaric Hypoxia (NH)
Actual wake time (mins)	43±19	55±41
Actual sleep time (mins)	393±65	387±78
% Sleep efficiency	83.70±10.97	82.73±15.03
Fragmentation index	31.01±12.63	36.93±17.98
% Moving time	13.14±3.42	16.84±8.35
Wake bouts	20.1±8.5	27.3±9.4
Mean wake bout time (secs)	148±106	111±38
Mean sleep bout time (secs)	1394±617	987±420
Total activity counts	5887±5432.5	6171±6354.4
Sleep Latency (mins)	30±44	25±39

CONCLUSION: This study presents evidence that sleep in NH may be disrupted in some individuals. Further investigation is required.

30. REDOX REGULATION OF ENERGY HOMEOSTASIS AT ALTITUDE?

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Introduction: Despite the prevalence and morbidity associated with high-altitude anorexia-cachexia, the underlying pathophysiology remains elusive. The present study examined whether the peripheral release of catabolic signaling molecules known to influence feeding behavior is subject to redox regulation. **Methods:** Following ethical approval, sixteen healthy males participated in a randomized double-blind placebo-controlled trial. Eight subjects were instructed to ingest a combination of water and fat soluble antioxidant vitamins (daily bolus dose of 1000mg L-ascorbic acid, 400 iu of dl-α-tocopherol acetate and 600mg of α-lipoic acid) and the remaining eight subjects ingested a placebo. Supplementation was initiated at sea-level (SL) 7 days prior to departure to India, for 4 days in Delhi and during a 7 day ascent to 4,780m (HA). Resting venous samples obtained at SL and at HA were assayed for metabolic regulators of energy homeostasis and ex-vivo spin trapping with α-phenyl-tert-butylnitrone (PBN) was combined with electron paramagnetic resonance (EPR) spectroscopy for the direct molecular detection of free radicals. **Results:** Antioxidants decreased the EPR signal intensity of the PBN adduct at HA [SL: 7,369 ± 2,437 vs. HA: 1,548 ± 236 arbitrary units (AU)/Gauss (G), $P < 0.05$] whereas an increase was observed in the placebo group (6,602 ± 1,813 vs. 10,599 ± 2,729 AU/G, $P < 0.05$). Antioxidants also prevented the rise in glucagon-like peptide-1 (SL: 25.2 ± 6.4 vs. HA: 29.6 ± 8.2 pmol/L, NS) observed in the placebo group (20.7 ± 9.0 vs. 27.1 ± 13.6, $P < 0.05$) whereas no selective differences were observed for insulin, glucose, leptin or non-esterified fatty acids. Furthermore, antioxidants did not influence appetite ratings or alter subsequent nutrient intake. **Conclusion:** The present findings suggest that the neuroendocrine modulation of appetite control at high-altitude is not subject to redox regulation.

31. EFFECT OF HARD EXERCISE ON PROTEINURIA AT HIGH ALTITUDE.

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Albuminuria from hypoxic glomerular leakage occurs at high altitude and is associated with acute mountain sickness (AMS). An unrelated cause of albuminuria is short duration, strenuous, aerobic exercise. This is thought to cause renal hypoxia by diverting blood to exercising muscles. The combination of hard exercise and altitude exposure might produce an additive hypoxic effect on the kidney. If hard exercise also enhances capillary leakage in the brain or lungs it may be a precipitating factor in the development of AMS. This study has assessed the effect of exercise on the production of albuminuria at high altitude. 10 subjects were studied at 140m, 3,455m, 4750m and 5,260m. All performed bicycle exercise tests at each altitude, comprising 15 minutes at VO_2max and five minutes successively at, 30, 50, and 70% of VO_2max. The graded exercise test was carried out on the same day and approximately 3 hours after the VO_2max. Albuminuria was assessed as micrograms/minute from timed urine collections taken before and during the exercise tests. Albuminuria (mean and standard error) and exercise levels at different altitudes. The results showed that exercise increased albuminuria above resting levels at each altitude. Altitude exposure also increased albuminuria above that seen at 140m, but not in all individuals. Those subjects with the highest VO_2max tended to show the highest increases in albuminuria but this was not significant in the numbers studied. Albuminuria may also have been influenced by the rate of ascent that was greatest up to 3455m. Climbing rates are normally at 40–50% VO_2max which is likely to produce less albuminuria than maximum exercise. Furthermore, climbing is undertaken for many hours compared with the short duration study described here. Future studies could be on subjects that were exercising during actual climbing, combined with continuous recording of the work and associated albuminuria.

32. EFFECT OF CAFFEINE INGESTION AT ALTITUDE ON CARDIOVASCULAR AND METABOLIC RESPONSES TO AEROBIC EXERCISE.

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While numerous studies have looked at the effects of caffeine on exercise performance at sea level, this study was designed to examine how caffeine ingestion influences exercise responses at altitude. The purpose of this study was to examine the effect of caffeine and moderate altitude exposure on the cardiovascular and metabolic responses to graded exercise. Six healthy, active subjects (mean age = 23.2 + 1.5 yr, mean weight = 77.3 + 13.1 kg, mean height = 162.2 + 22.2 cm) were tested 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). Heart rate (HR), oxygen consumption (VO_2), ventilation (VE), carbon dioxide production (VCO_2), and the respiratory exchange ratio (RER) were measured during a graded exercise cycle ergometry test to 80% of predicted heart rate maximum. Two exercise tests were administered in a randomized order, one after the ingestion of a placebo (PLAC) and one after ingesting 300 mg of caffeine (CAFF). Oxygen consumption, VCO_2, and VE at any given workload were not significantly different between the PLAC and CAFF trials at any of the testing times. However, VE at ALT1 in both the CAFF and PLAC conditions were significantly greater than at the other testing times ($P < 0.05$). RER was significantly greater at ALT 1 than the other three testing times for both CAFF and PLAC conditions ($P < 0.05$). Heart rate was higher at ALT1 than the other three testing times during exercise, but there were no differences between the CAFF and PLAC groups. These data suggest that the cardiovascular and metabolic responses to graded exercise are influenced by acute exposure to moderate altitude. However, caffeine ingestion prior to exercise does not play a role in altering those responses.

33. EFFECTS OF RESPIRATORY ALKALOSIS ON HUMAN SKELETAL MUSCLE METABOLISM AT THE ONSET OF SUBMAXIMAL EXERCISE.

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The delayed activation of pyruvate dehydrogenase (PDH), resulting in increased production of lactate, at the onset of exercise in hypoxia may be due to respiratory alkalosis. To test this hypothesis, eight healthy male subjects exercised on two occasions for 15 min at 55% VO_2max while hyperventilating (R-Alk) ($PETCO_2$ = 19.2 ± 0.5) or breathing normally (Con) ($PETCO_2$ = 41.1 ± 1.7). Muscle biopsies were taken at rest and after 1 and 15 min of exercise. At rest, no effects on muscle metabolism were seen in response to R-Alk. In the first min of exercise, no effect was seen in phosphocreatine levels. Muscle lactate was higher (R-Alk; 20.5 ± 4.4 vs Con; 11.4 ± 2.0 mmol/kg dw) and PDH was lower (R-Alk; 1.42 ± 0.19 vs Con; 1.88 ± 0.25 mmol/min/kg ww) after 1 min of exercise. The delayed activation of PDH at the onset of exercise resulted in an increase in lactate production due to lower pyruvate oxidation. Also, glycogenolysis was higher in R-Alk compared with Con, which was attributed to a higher availability of the monoprotonated form of inorganic phosphate (Pi), resulting in an elevated rate of pyruvate production. The mismatch between pyruvate production and its oxidation resulted in net lactate accumulation. These effects were not seen after 15 min of exercise, with no further differences in muscle metabolism between conditions. The results from the present study suggest that respiratory alkalosis may play an important role in lactate accumulation during the transition from rest to exercise in acute hypoxic conditions, but that other factors mediate lactate accumulation during steady-state exercise. Research supported by CIHR (GJFH) and OGSST (PJL).

35. EFFECTS OF ACUTE EXPOSURE TO 1000 TO 4500 M ON VO_2MAX IN ENDURANCE-TRAINED SUBJECTS.

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Maximal aerobic capacity (VO_2max) has been shown to decrease at moderate altitude. However, the importance of this decrease, the altitude where it appears, the influence of training status and the mechanisms involved are not clearly identified. We aimed to evaluate the importance of factors responsible for VO_2max reduction in trained subjects exposed to acute hypoxia. **METHODS:** Nine healthy male volunteers were divided into 2 groups according to their aerobic performance : group T, trained endurance athletes (n = 5, VO_2max = 61.1 +/−6.5 ml/kg/min); group C, untrained individuals (n = 4, VO_2max = 47.2+/−1.8 ml/kg/min). Subjects performed incremental cycle ergometric tests under normoxic and normobaric hypoxic conditions (1000, 1500, 2500, 3500, 4500 meters). Heart rate (HR), arterial oxygen saturation (SaO_2), oxygen uptake (VO_2), pH and p50 (arterialized capillary blood at rest and after 2 minutes of recovery) were measured. **RESULTS:** Both groups showed a progressive reduction in VO_2max in hypoxia (significant at 1500 m for group T and 2500 m for group C). The percent change in VO_2max at 4500 m was greater for group C (−22%) than for group T (−13.5%) in spite of a greater reduction in SaO_2 at each altitude for group T (at 4500 m, the reduction was 32.8% for group T and 24.3% for group C). HRmax decreased at and above 1000 m for group T and at 4500 m for group C. There was no difference in exercise pH and p50 between the 2 groups. **CONCLUSION:** Trained subjects showed a smaller reduction in VO_2max in spite of a greater reduction in maximal O_2 transport (greater desaturation and reduction in HRmax). We hypothesize that in trained subjects a greater peripheral O_2 extraction limits the decrease in VO_2max in hypoxia but induced a greater arterial desaturation through diffusion limitation.

34. OXYGEN CONSUMPTION WHILST CLIMBING MOUNTAINS—IS A SLOW PLOD STRATEGY BETTER THAN RUSH AND REST?

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INTRODUCTION Anecdotal evidence suggests that when climbing at altitude it is preferable to climb slowly and continuously rather than by using intermittent hard exercise with rests to 'pause for breath'. **METHODS:** 6 subjects, 5 male, ages 33–65 K4b2 portable metabolic monitor used to measure heart rate, inspired and expired carbon dioxide (CO_2), oxygen (O_2), respiratory rate and volumes. The course was a 75 metre vertical ascent from 5260 metres, climbing up a rough mountain path above the Chacaltaya ski station, Bolivia. It took between 6 to 10 minutes to complete. Firstly a slow plod strategy was employed. This involved continuous climbing at a rate at which conversation could be maintained. Ascent was timed. After a two hour rest the experiment was repeated using a 'rush and rest' strategy. Subjects were asked to climb quickly, resting as needed, aiming to complete the course in the same time. On each occasion the subjects were allowed to descend the course at their own rate. **RESULTS:** Subjects felt it took considerably longer to recover following the rush and rest course. Unfortunately there were technical difficulties with the monitor: two data sets were lost no reliable CO_2 readings were obtained. (Internal temperature of monitor below working range) No significant difference in oxygen consumption between the two groups, but there was a trend towards a lower oxygen consumption in the rush and rest group. **CONCLUSIONS** Lower oxygen consumption in "rush and rest" may reflect anaerobic exercise, with oxygen debt being repaid following the period of monitoring. It is planned to repeat this study with a more subjects over a longer course. The monitor needs to be insulated from the cold.

36. PEAK AEROBIC POWER AND MUSCLE SARCOPLASMIC RETICULUM FUNCTION DURING PROGRESSIVE EXERCISE IN NORMOXIA AND HYPOXIA.

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This study investigated the hypothesis that the reduction in mechanical power output (PO) and peak aerobic power (VO_2peak) observed during exercise in hypoxia (H) compared to normoxia (N) would be associated with disturbances in sarcoplasmic reticulum (SR) function. Ten healthy males (20.7 ± 0.42 year, ± SE) performed progressive cycle exercise to fatigue, on two occasions, namely during N (21% O_2) and H (14% O_2). Tissue from the vastus lateralis muscle was extracted prior to exercise (PRE), at PO's corresponding to 40% and 70% VO_2peak (N) and at fatigue. Homogenates were analyzed for Ca2+- dependent Ca2+-ATPase activity and maximal activity (Vmax) the Hill coefficient (nH) and the Ca2+- concentration needed to elicit $^1/_2$ Vmax (Ca50) calculated. No changes ($P > 0.05$) in Vmax, nH and Ca50 were found either during exercise or between N and H. VO_2peak was depressed 21% ($P < 0.05$; 4.2 ± 0.1 vs 3.3 ± 0.1 L/min). It is concluded that reductions in VO_2peak with H are not related to alterations in SR function as measured by Ca2+- ATPase "in vitro". Supported by NSERC (Canada)

		PRE	40% V02peak (N)	70% V02peak (N)	Fatigue
Vmax (nmol/mg prot/min)					
	N	161 ± 11	147 ± 8.5	158 ± 9.4	157 ± 11
	H	167 ± 11	164 ± 13	152 ± 11	
nH	N	1.7 ± 0.1	2.0 ± 0.2	2.0 ± 0.2	2.0 ± 0.2
	H	2.0 ± 0.2	1.8 ± 0.2	2.0 ±0.1	
Ca50 (nM)	N	744 ± 133	889 ± 209	832 ± 185	791 ± 108
	H	869 ± 133	886 ± 95	838 ± 84	

37. ALTITUDE STRATEGIES FOR MAXIMIZING CYCLE SPEED.

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Endurance cycling speed can be enhanced by road racing at higher altitudes. However, a trade-off exists between the reduced drag of altitude and the reduced aerobic power associated with the lower oxygen availability of altitude. These concepts suggest there may be an optimal altitude for maximizing cycling speed. This altitude would balance diminished oxygen availability with diminished drag characteristics to produce a maximum speed. Capelli & di Prampero (Eur. J. Appl. Physiol. 71:469-471, 1995) have determined from basic principles that the optimal one hour endurance altitude is about 16,000 feet for a rode bike. Our approach extends their work by utilizing known physics of air density, a mathematical model of cycling and literature data about the altitude effect on reduced aerobic capacity. This approach results in a mathematical model from which the optimal altitude is determined. For a rode bike, neglecting rolling resistance, our results suggest an optimal altitude of 15,400 feet (similar to Capelli and di Prampero). However, for a recumbent bike, a faring can be used to further reduce drag so that rolling resistance becomes a factor and cannot be neglected. Under these conditions, the model predicts an optimal endurance altitude of about 5,700 feet. Furthermore, when a 30 s anaerobic trust to exhaustion is added to a base line endurance speed so as to maximize the peak velocity, the optimal altitude shifts to about 10,000 feet. Model sensitivity analysis indicates that these altitude estimates have a rather broad confidence interval. Therefore, our results suggest that "mile-high" altitudes maximize endurance speed but "two-mile high" altitudes maximize peak speed. Interesting, the Colorado Speed Challenge held in Alamosa (1993) at an altitude of about 8000 feet may have been held at an altitude close to optimal and resulted in average 200 meter speeds of near 70 mph.

39. EFFECTS OF SHORT-TERM MODERATE HYPOXIC EXPOSURE DURING SLEEP ON MAXIMAL AEROBIC CAPACITY AT HIGH ALTITUDE.

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Seven male college students were subjected to short-term, intermittent (only during sleep) hypoxic exposure (IHE) in a normobaric hypoxic room set at a moderate altitude (equivalent to an altitude of 2,000 m; O_2 = 16.4%), and the effects of the IHE on maximal aerobic capacity at high altitude (equivalent to an altitude of 4,000 m; O_2 = 12.7%) were examined. Hypoxic exposure was for 4 days. Each day the subjects slept for 7 hours in the hypoxic room, and the rest of the time they spent at sea level. No exercise at all was performed in the hypoxic environment. Before and after the IHE, the subjects performed a multigraded exercise tolerance test by pedaling at the simulated 4,000 m altitude. Results showed that after this IHE, maximal oxygen uptake (VO_2max) and maximal workload at an altitude of 4,000 m significantly increased. Expired volume per minute at the point of VO_2max significantly increased after the IHE. However, the red blood cell count and hematocrit level significantly decreased after the IHE, and it was surmised that temporary hemodilution had occurred. It can be said from these results that maximal aerobic capacity at high altitude improves even with short-term hypoxic exposure during sleep at a moderate altitude. It is important that hypoxic exposure to moderate (physiologically safe) altitude can improve work capacity at much higher (risky) altitude. And also, it is thought that this improvement was affected by ventilatory adaptation, and that the effects of negative changes in blood properties were small.

38. PREDICTION OF PERFORMANCE ON THE ASCENT OF MONT BLANC.

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The aim of the study was to predict performance on the ascent of Mont Blanc (4,807m) using a number of variables collected at the Gouter Hut (3817m) before and after an attempted ascent on the Mont Blanc summit. Subjects (n = 285) were tested at 3,817m prior to their ascent of Mont Blanc. Subject information included age, dwelling place, altitude experience and an altitude profile (including details of time at altitude in the last 14 days). End tidal CO_2, arterial oxygen saturation, heart rate (HR) and respiratory rate (RR) were measured using a Capnograph (Nellcor Patrick NPB74). Acute mountain sickness scores were assessed using the Lake Louise scoring system. Logistic regression was used to determine which factors, if any, are predictive of a successful ascent of Mont Blanc. Of the 285 subjects tested, summit information is available for 199 subjects. Of these 199, 184 are known to have reached summit while 15 are known to have failed. The mean ($\pm$sd) time to reach the summit from the Gouter Hut was 4.3 hrs$\pm$0.8. Pre-ascent heart rate and respiratory rate significantly affect the probability of reaching the summit. All subjects with a HR and RR under 84 beats/min and 8 breaths/min respectively, reached the summit. Faster times to the summit are associated with increasing height climbed in the past 14 days. However, the R-Squared (adjusted) is only just over 5.6% and this increases only to 6.6% if one includes the significant additional variable of age. Accordingly, neither of these is even a moderately reasonable predictor of time to the summit regardless of the fact that they are statistically significantly related to it. It was not possible to predict performance on the ascent of Mont Blanc with great precision. A biased sample may have contributed to this limited predicative capability.

40. MAGNITUDE OF DECREASES IN MAXIMAL HEART RATE IN ACUTE AND CHRONIC HYPOXEMIA.

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It is widely accepted that adaptation to hypoxemia is accompanied by decreases in maximal heart rate (mHR). In contrast, it has been debated whether this is the case during acute exposure to hypoxemia. Recently, we reported a linear decrease in mHR during acute exposure to barometric pressures of 518-355 mmHg: $mHR(AH) = mHR(SL) - 0.135 \cdot (530 - P(AH))$, where AH is acute hypoxia, SL is sea level and PAH is barometric pressure of the acute hypoxic exposure. **Aim:** We tested 1) whether this equation would accurately predict decreases in mHR to acute hypoxic exposure at two different levels; and 2) whether mHR decreases progressively during chronic hypoxia of high altitude. **Methods and Results:** 12 subjects were studied with continuous ECG during biking with incremental work loads to exhaustion. Protocol 1: mHR was determined during bike-exercise in normoxia (sea level) and during breathing of 12.6% (469 mmHg, n = 8) and 10% oxygen mixtures (394 mmHg, n = 4). The equation predicted decreases in mHR of 8 and 18 beats/min respectively. Experimentally, mHR decreased by 11 $\pm$ 3.2 and 18 $\pm$ 5.7 beats/min. In protocol 2, bike-testing were performed during normoxia and acute hypoxia (Copenhagen) and after 2, 4, and 8 weeks of adaptation to 4.100 m above sea level (Bolivian Andes). During acute hypoxia and after 2, 4, and 8 weeks of high altitude exposure mHR was decreased to a similar extent (mHR: 176 $\pm$ 8; 171 $\pm$ 4; 177 $\pm$ 7; 175 $\pm$ 4 beats/minute). **Conclusions:** The main findings were two fold. First, the equation reliably predicts decreases in mHR during acute hypoxia exposure to simulated altitudes above 3.100 m. Second, there is no clear time-dependent further decrease in mHR during prolonged stay at an altitude of 4.100 m. However, in previous studies further decreases in mHR were identified during adaptation to altitudes above 5.000 m.

41. MAXIMAL OXYGEN UPTAKE AT ALTITUDE USING A BREATH-BY-BREATH METABOLIC ANALYSER AND SUPINE CYCLE ERGOMETER.

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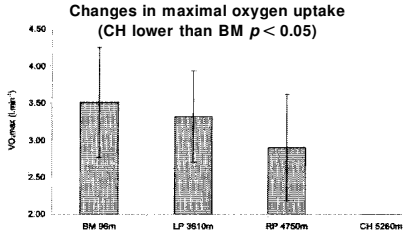
INTRODUCTION The aim of this study was to take direct measurement of maximal oxygen uptake at altitudes to 5260m using a commercially-available breath-by-breath metabolic analyser and a purpose-built, compact, lightweight ergometer that allows exercise in the supine position. **METHODS** Eight men and one woman (mean (1 SD): age 47.3 (11.8) years; height 181.1 (5.1) cm; body mass 82.7 (10.4) kg), VO_2max was measured at 4 locations: Birmingham (BM), UK (96m) and La Paz (LP) (3610m), Refugio Huayna Potosi (RP) (4750m) and Chacaltya (CH) (5260m), Bolivia. Subjects exercised on a purpose-built, supine, cycle ergometer (Figure 1) that allowed the head to remain still to permit simultaneous measurements of expired gas and cerebral oxygenation and blood flow. Oxygen uptake was measured using a portable, breath-by-breath O_2/CO_2 analyser (Cosmed K4b2). Following a 5-minute cycle warm-up, subjects completed an incremental (20 watt per minute) VO_2max test to volitional exhaustion. Data were analysed using a repeated measure ANOVA, and differences were located using Fisher's Protected Least Significance Difference post hoc test. The alpha level was set at 0.05. **RESULTS** The cycle ergometer proved to be robust, reliable and easy to use. During the expedition we experienced no failures of the ergometer during 72 maximal and sub-maximal exercise tests. Maximal oxygen uptake (Figure) decreased with altitude. **CONCLUSION** The use of reliable and portable equipment to measure the rate of oxygen uptake during standardised maximal and sub-maximal exercise tests will extend the capability for making field measurements of cardio-respiratory function. The VO_2max values are comparables with those found in other studies confirming the K42b as a reliable for use in high altitude research.



42. ANDEAN WOMEN HAVE GREATER UTERINE ARTERY (UTA) ENLARGEMENT DURING PREGNANCY THAN EUROPEAN RESIDENTS OF 3600 M.

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Babies weigh less at high altitude but multi-generational high-altitude residents are protected from this birth weight decline (Moore HAMB 2001). **Objective:** We asked if higher arterial oxygenation and/or UtA blood flow raised uteroplacental O2 delivery in multigenerational Andean vs. shorter duration European high-altitude residents. **Methods:** Subjects were 45 women of Andean (n = 50, And) or European (n = 11, Eur) ancestry who had resided in La Paz, Bolivia since birth (And) or the past 4 years (Eur). Ancestry was confirmed by genetic markers. Studies were performed at weeks 20, 30, 36 of pregnancy and again 4 mo postpartum as an index of the non-pregnant state. Arterial O2 saturation (SaO2) was measured by oximetry, hemoglobin concentration by spectrophotometry, and UtA blood flow calculated from vessel diameter and flow velocity obtained by Doppler ultrasound (ATL 3000 and an investigational Doppler). **Results:** SaO2 rose during pregnancy similarly in And and Eur subjects (table). Hemoglobin concentration was modestly higher in Eur than And women near term such that calculated arterial O2 content was slightly higher in the Eur group. Uterine artery (UtA) diameter increased with pregnancy but the increase was substantially greater ($p < .01$) in the And than Eur women. Flow velocities did not differ between groups although Eur had greater velocities at a given vessel diameter than And women. Consequently, And women tended to have greater UtA blood flow (348 ± 35 vs. 265 ± 53 ml/min, p = .09) and uterine O2 delivery (51 ± 6 vs. 40 ± 9 ml O2/min, p = .06) than Eur women. **Conclusion:** Greater UtA enlargement but not SaO2 raise uterine O2 delivery and likely protect against altitude-associated reductions in fetal growth in Andean high-altitude residents, perhaps as the result of natural selection acting on genes influencing these responses. (NIH TW01188, HL60131).

variable	Group	Non-pregnant	Week 20	Week 30	Week 36
SaO2	And	92± 0.3	94± 0.2	94± 0.2	94± 0.2
%	Eur	91± 1.8	94± 0.6	94± 0.3	94± 0.2
UtA dia	And	.26± .01	.47± .01	.48± .02	.49± .02
cm	Eur	.25± .02	.34± .02	.43± .04	.36± .04

43. SLEEP STRUCTURE AND PERIODIC BREATHING IN TIBETANS AND HAN AT 5000 M.

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Tibetans are the oldest population living permanently at high altitude. They possess several adaptations to low oxygen pressure that improve oxygen transport. We hypothesized that native Tibetans have mechanisms allowing them to maintain a better sleep structure and oxygenation during sleep at high altitude than newcomers from lower altitudes acclimatized to living at high altitude. We studied 8 healthy young Tibetans, aged 26 ± 7 years, and 6 healthy young Han aged 30.5 ± 4 years. All subjects were living on the Tibetan plateau at an altitude of around 4000 meters. Investigations were performed in Xining at an altitude of 2261 m, PB = 581 mmHg. Two full polysomnographies (PSG) were performed in a hypobaric chamber, one at the ambient altitude, the second during acute exposure to the simulated altitude of 5000 m (PB = 405 mmHg). Both PSG were done on the same night using split night design. At 2261 m no differences in sleep structure, breathing pattern during sleep or oxygenation were found, except a higher number of arousals and awakenings in Han ($P < 0.002$). At 5000 m Tibetans had a longer sleep time ($P = 0.002$), shorter stage 1 non-REM sleep ($P < 0.001$) and longer stage 2 non-REM sleep than Han ($P < 0.001$). Tibetans showed a trend to have more periodic breathing and higher mean arterial blood saturation than Han (NS). Our data suggest that Tibetans preserved better sleep structure and arterial blood oxygenation than Han during acute exposure to the simulated altitude of 5000 m.

44. PROLONGED POSTNATAL CARDIOPULMONARY TRANSITION AT 3700–4000M.

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Objective: High-altitude hypoxia influences postnatal changes in the pulmonary circulation. We documented persistence of fetal circulatory patterns and measures of pulmonary artery pressure (PPA) among healthy and sick, native and non-native infants born at 3700–4000m in La Paz, Bolivia. **Methods:** Echocardiography on 22 infants at 2 weeks, 1, 3, and 6 months estimated P_{PA} using right ventricular systolic intervals and the regression equation of Wanzhen when tricuspid regurgitation was absent. Persistence of the foramen ovale (PFO) and ductus arteriosus (PDA) was noted. **Results:** Twelve of 16 healthy infants had a PFO in the first 3 months, and approximately half of these persisted at 6 months. One healthy and one sick infant had a PDA on the first study only. P_{PA} of healthy infants was elevated in the first months, but by 6 months reached norms for childhood at 3700m. Six ill infants experienced acute pulmonary hypertension, surfactant deficiency, and/or retained fetal lung fluid at birth. One premature infant developed symptomatic pulmonary hypertension at 3 months. **Conclusion:** Postnatal changes in the pulmonary circulation occur slowly at high altitude, with greater vulnerability to incomplete or disrupted transition.

Healthy infants	**2 weeks (n=16)**	**1 month (n=16)**	**3 months (n=16)**	**6 months (n=16)**
PFO, n (%)	12 (75%)	12 (75%)	12 (75%)	7 (44%)
PEP/ET	0.24 ± .04	0.21 ± .07	0.18 ± .04	0.16 ± .03
AT/ET	0.27 ± .06	0.28 ± .06	0.28 ± .05	0.29 ± .04
P_{PA} sys (mmHg)	48 ± 9	40 ± 5	35 ± 7	29 ± 3
Sick infants	**2 weeks (n=4)**	**1 month (n=3)**	**3 months (n=5)**	**6 months (n=4)**
PFO, n	4	2	2	0
PEP/ET	NA	0.19 ± .01	0.21 ± .05	0.16 ± .02
AT/ET	NA	0.29 ± .04	0.25 ± .05	0.27 ± .02
P_{PA} sys (mmHg)	54 ± 7	39 ± 7	46 ± 15	32 ± 6

PEP=pre-ejection period, ET=ejection time, AT=acceleration time

45. UTERINE ARTERY BLOOD FLOW DURING PREGNANCY IN HIGH-ALTITUDE AYMARA WOMEN.

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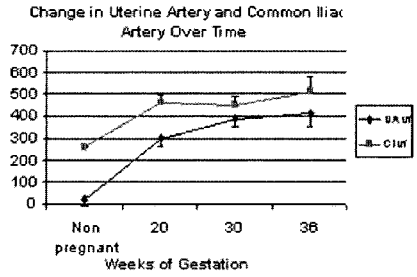
Background: Birth weight falls with increasing altitude as the result of intrauterine growth restriction (IUGR) likely due, in turn, to lower uterine artery (UtA) blood flow. The altitude-associated birth weight decline is least in the longest resident (in generations) groups, suggesting that adaptations may have occurred that raise uteroplacental blood flow to near sea-level values (Moore et al. HAMB 2001). **Study Objective:** Determine the factors responsible for raising UtA blood flow in Andean pregnant women, and whether the values near term resemble those of low-altitude residents. **Methods:** Measurements of the vessel diameters and blood flow velocities (averaged throughout the cardiac cycle) were made for the UtA, common iliac (CI), and external iliac (EI) arteries at 20, 30, and 36 weeks of pregnancy and 3 months postpartum to measure the non-pregnant state, using Doppler ultrasound (ATL 3000 and an investigational Doppler Velocimeter). **Results:** UtA volumetric flow increased as a result of an early enlargement of UtA diameter with a continued, progressive rise in flow velocity. There was a corresponding rise in CI flow, which was increasingly directed to the UtA (see figure). The increase in CI flow was due primarily to an increase in vessel diameter. The near term UtA volumetric flow appears similar to that of low-altitude residents (wk 36 value = 353 mL/min, Palmer Ob Gyn 1992), consistent with our hypothesis. This suggests that selection may have acted on the factors responsible for raising UtA diameter and flow velocity. (HL60131, TW01188)



46. HEMATOLOGICAL STUDY IN AYMARAS WITH CHRONIC EXPOSURE TO HIGH ALTITUDE (PUTRE 3500 M).

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Background: Haematological studies makes in Aymaras in La Paz (Bolivia) shown values of hemoglobin concentration of 18,8 g/dl. In contrast, with the previously describe, Sharps have low level of hemoglobin concentration near 16.6 g/dl. Objective: Determine in Aymaras population at 3500 m (Putre, Chile) hematological parameters. Subjects and **Methods:** Haematological parameters were measured in 45 voluntaries Aymaras, that live chronically in Putre. Blood sample were take from vein to determined hemoglobin concentration (g/dl); haematocrit (%); Red cell count (mill/mm2); formula was calculated: HCM, CHCM, and VCM (Cell-Dyne 1400). All values are express in mean ± SD. Results: Haemoglobin concentration of 14.9 ± 2.4 g/dl; Haematocrite of 43.9 ± 6.3%; red cell count: 4.85 ± 0.55 mill/mm2; and values of formula of HCM: 30.3 ± 2.4; MCHM: 33.9 ± 1.2 and VCM: 89.4 ± 5.7. **Conclusion:** Lower values in all haematological parameters were observed in subjects that live in Putre at 3500 m. These evidences could be suggesting a problem in a deficiency of ferrous in the population or that Aymaras population have express a difference with the Aymaras population of Bolivia.

47. CARDIORESPIRATORY RESPONSES OF CHILDREN IN PUTRE AT 3500 M. A COMPARISON BETWEEN AYMARAS AND NO-AYMARAS.

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Objectives: The study describes cardiorespiratory responses and acute mountain sickness (AMS) in a population of children that upon to high altitude in comparison with Aymaras and no-Aymaras children that live in Putre (3500m). Subjects: The population of study was: 10 children (5.8 ± 1.3 years) that upon to Arica to Putre and 10 Children no Aymaras (4.3 ± 1.6 years) that born in Arica and live in Putre and 20 Aymaras (4.2 ± 1.6 years) children that born in Arica and live in Putre. **Methods:** We evaluated Cardiorespiratory measurements included heart rate and oxygen saturation and AMS symptoms only in children that arrived to Arica with the Lake-Louise questionnaire and in children with the modified Children's Lake-Louise Score for preverbal subjects on arrival at Putre and in next morning. **Results:** An important desaturation among the children in Putre (84 ± 3, $p < 0.0001$) in comparison with a children that live in Putre (90 ± 3 no-Aymaras) and (91 ± 2, Aymaras). A major heart rate was observed is children in Putre (124 ± 11) in comparison with children no Aymaras that live in Putre (113 ± 6, $p < 0.02$) and children Aymaras that live in Putre (101 ± 12, $p < 0.0001$). A higher incidence of AMS was observed in children (87%) in Putre. **Conclusion:** Our results corroborate that children are extremely sensitive to hypoxia, as expressed by symptoms of AMS, significant desaturation and major values of heart rate, in no-Aymaras children exposes acutely to high altitude. Our findings add to the available information regarding the problems encountered when ascending to high altitude with children and support the importance of close monitoring of young children during ascent to high altitude. VRA-UDP

48. CIRCADIAN RHYTHM OF ERYTHROPOIETIN IN ANDEAN ALTITUDE NATIVES WITH AND WITHOUT EXCESSIVE ERYTHROCYTOSIS.

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Excessive erythrocytosis (EE) is frequent in the Andean region, by effect of chronic maladaptation to high altitude. Despite its poor prognosis, the main determinants are still poorly understood. Erythropoietin (Epo) levels are increased in subjects with EE, but with large individual variation. At sea level and in healthy subjects, a circadian variation of Epo (circ-Epo) has been described, with a nadir in the morning (8:00 AM) and a zenith during late evening (10:00–12:00 PM). The circ-Epo has never been determined in high altitude residents, with or without EE. In 20 Andean male natives of Cerro de Pasco, 4338m, Peru (10 with EE: hematocrit 76.6 ± 1.3%, hemoglobin 23.5 ± 0.3 g/dl, age 38.9 ± 2.5yr, and 10 controls: hematocrit 54.4 ± 0.8%, hemoglobin 16.9 ± 1.0 g/dl, $p < 0.0001$, age 38.5 ± 1.4yr) we tested whether: 1) a circ-Epo were present in controls 2) a specific alteration in circadian rhythmicity were present in subjects with EE that could be related to a possible day or night stimulus. Epo was measured (by Elisa, R&D) from sera obtained every 4 hours, starting 8:00 AM. During night a sample was taken at 5:00 AM instead of 4:00, to leave 5 hours of undisturbed sleep. Control subjects showed normal morning Epo, with a marked circ-Epo, with nadir at 8:00 AM, and zenith at midnight, with a 8:00AM–12PM variation of 65 ± 33%. EE showed consistently higher Epo values during day and night ($p < 0.001$, ANOVA), with completely disrupted circ-Epo due to a loss of the morning nadir, with no clear zenith. The 8:00AM–12PM variation was 4 ± 12 ($p < 0.05$ vs controls subjects). **Conclusions:** 1) Andean subjects without EE have a normal circadian rhythm of Epo; 2) the circadian rhythm is disrupted in EE due to the contribution of factors acting during both night and day.

49. SLEEP-DISORDERED BREATHING AND ERYTHROPOIETIN LEVELS IN ANDEAN HIGH-ALTITUDE NATIVES WITH EXCESSIVE ERYTHROCYTOSIS.

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We tested the hypothesis that nocturnal hypoxemia due to sleep-disordered breathing (SDB) may determine excessive erythrocytosis (EE) in Andean high-altitude natives, and compared nocturnal respiratory and sleep parameters in 10 patients with EE (Ht) <70) and in 10 healthy controls (Ht > 60) living in Cerro de Pasco (4380 m), determined the effect of oxygen administration (to maintain oxygen saturation (SaO_2) >95%) for 1 hour prior to sleep, and investigated a possible correlation between SDB, and Erythropoietin (Epo) production. **Methods:** two nights standard polysomnography (baseline and after oxygen administration), Serum Epo levels measured in the evening (8:00, 12:00 PM), and next morning (5:00, 8:00, 12:AM). The sleep efficiency and structure, and the number of arousals were similar in the two groups. All subjects showed nocturnal periodic hypopneas. The apnea-hypopnea index (AHI), the duration of the hypopneas and the mean oxyhemoglobin desaturation were similar in both groups (EE: 10 ± 4, 24 ± 1 sec, 5 ± 0.6%, respectively; controls: 8.7 ± 2, 20 ± 1 sec, 4.6 ± 0.2%, respectively, all NS vs EE). Mean SaO_2 decreased from wakefulness to sleep in EE (from 83.7 ± 0.3 to 80 ± 0.8, $P < 0.01$) and in controls (from 85.6 ± 0.4 to 82.8 ± 0.5%, $P < 0.01$) and remained significantly ($P < 0.05$ or better) lower in EE. Epo levels in the morning correlated with night SaO_2 levels, but not with sleep abnormalities. Respiratory and sleep variables were not affected by oxygen administration, but Epo levels at 5:00 and 8:00 AM were significantly ($p < 0.05$) lower as compared to the same hour of the control day. Andean natives with EE show only minor respiratory disorders during sleep, but the lower SaO_2 found in EE may be relevant in initiating the abnormal Epo response leading to EE. Short-term oxygen administration induces sustained Epo suppression despite no change in respiratory and sleep data.

50. A PROTOCOL FOR DETERMINING THE CEREBROVASCULAR AND VENTILATORY RESPONSES TO INCREMENTAL STEP CHANGES OF ISOCAPNIC HYPOXIA.

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Introduction. The process of acclimatization to the hypoxia of altitude is associated with changes in ventilation1 and cerebral blood flow (CBF)[2]. However, the role of changes in CBF in ventilatory acclimatization to hypoxia (VAH) and in the etiology of acute mountain sickness (AMS) and high altitude cerebral edema (HACE) remains unclear. The aim of this study was to develop a suitable protocol for determining both the cerebrovascular and ventilatory responses to incremental isocapnic hypoxia. **Methods:** Eight healthy young males aged 25.7 ± 2.3 yrs (mean ± SD) volunteered for the study. A dynamic end-tidal forcing system was used to control end-tidal P_{CO_2} (P_{ETCO_2}) at eucapnia (1.5 Torr above normal value) and to alter end-tidal PO_2 (P_{ETO_2} in small incremental steps of hypoxia. The protocol consisted of an initial 8 min period of eucapnic euoxia (P_{ETO_2} = 88 Torr, elevation 1103m) followed by 6 descending steps (P_{ETO_2} = 75.2, 64.0, 57.0, 52.0, 48.2, and 45.0 Torr), each step lasting 90 sec. Immediately after the last step, P_{ETO_2} was elevated to 300 Torr for 5 min while P_{ETCO_2} remained at eucapnia. Then, P_{ETCO_2} was raised by 7.5 Torr for 5 min whilst P_{ETO_2} remained constant at 300 Torr. Transcranial Doppler ultrasound was used to measure peak blood flow velocity (CBFV) in the middle cerebral artery and near-infrared spectroscopy cerebral oximetry was used to determine regional oxygen saturation (SrO2) of the brain on a beat-by-beat basis. The acute hypoxic ventilatory (AHVR), cerebral blood flow (AHR) and regional cerebral oxygen saturation (AHSrO2) responses were determined by linear regression between ventilation, CBFV, SrO2 and arterial oxygen saturation (calculated from P_{ETO_2}), respectively.

Results	AHVR	AHCVR	AHR	AHS_rO_2
Mean±SD	2.01±1.77	3.33±0.75	0.49±0.17	0.89±0.42
units	l/min/%	l/min/Torr	cm/scc/%	%/%

Conclusions: This short protocol appears well suited to quantify the cerebrovascular and ventilatory responses to acute isocapnic hypoxia. Moreover, it may help further study the role of changes in CBF in VAH with chronic or intermittent hypoxia, and in the aetiology of diseases such as AMS and HACE. This study approved by Conjoint Ethics Board and supported by AHFMR, HSFA, and CIHR. 1. Tansley et al., *J. Appl. Physiol.*, 85: 2125–2134, 1998; 2. Poulin et al., *Experimental Physiol.*, 87.5: 663–642, 2002.

51. CEREBRAL BLOOD FLOW RESPONSE TO HYPOXIA DURING THE MENSTRUAL CYCLE IN YOUNG WOMEN.

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Objective: This study examined the extent to which the sensitivity of cerebral blood flow (CBF) to hypoxia is altered during the menstrual cycle in young women. *Methods*: Eight volunteers aged 28.5 ± 7.5 years (mean ± SD) took part. The women charted their menstrual cycle for four months, and were tested three times in the fourth month: follicular phase (FP), ovulation (OV), luteal phase (LP). Transcranial Doppler ultrasound was used to measure beat-by-beat peak blood flow velocity (V^- P) in the middle cerebral artery in response to 20 min of isocapnic hypoxia (PETO2 = 50.0 Torr). A dynamic end-tidal forcing system was used to control PETO2 and to hold PETCO2 constant (1.5 Torr above resting end-tidal PCO2). The V^- P responses to hypoxia were fitted to a simple mathematical model that included a gain term, two time constants, a baseline and a single pure delay (Td). *Results*: There was no significant difference between the eucapnic PETCO2 (35.7 ± 1.6, 34.6 ± 1.7, 35.2 ± 1.7 Torr between FP, OV, and LP, respectively). The baseline V^- P (67.8 ± 18.7, 61.6 ± 12.5, 64.0 ± 15.6 cm s-1) and Td were unchanged. Furthermore, the on-transients (ôon = 90.2 ± 135.8, 53.1 ± 88.6, 80.4 ± 191.6 s; ANOVA p = 0.832) and off-transients (ôoff = 51.8 ± 64.5, 19.1 ± 24.1, 68.9 ± 84.3 s p = 0.145), and the gain terms (0.67 ± 0.27, 0.48 ± 0.25, 0.56 ± 0.26 cm sec-1 (% desaturation-1); p = 0.133) were not significantly different between FP, OV and LP. *Conclusion*: We conclude that the sensitivity of CBF to hypoxia is unchanged during the follicular, ovulation and luteal phases of the menstrual cycle. This study was approved by the Conjoint Health Research Ethics Board and supported by AHFMR, CIHR, HSFA and NSERC.

52. A NEW TECHNIQUE UTILIZING NEAR INFRARED SPECTROSCOPY (NIRS) TO MEASURE CEREBRAL BLOOD VOLUME (CBV) AT HIGH ALTITUDE IN HUMANS.

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Introduction: Recent studies have implicated brain swelling in the pathophysiology of acute mountain sickness. One possible cause of this swelling is elevated CBV. This hypothesis remains untested, in part, because CBV measurement has traditionally required the use of radioisotope or imaging techniques. We report here the development of a noninvasive NIRS technique that is easily deployable in the field and yields reasonable estimates of CBV. NIRS measurement of CBV relies on inducing changes in the concentrations of oxygenated and deoxygenated hemoglobin and comparing these with changes in peripheral pulse oximetry (SaO_2%). **Methods:** Five subjects were rapidly decompressed to a simulated altitude of 16,200 ft (P_B = 426 mmHg). Following arrival, fast resaturations were performed in resting, supine subjects by having them breathe 1 breath of 40% O_2. **Results:** SaO_2% rose 9 ± 3% during resaturation from baseline of 82 ± 3%. CBV measurement by NIRS assumes that both cerebral blood flow and CBV are not affected by the measurement itself. We used end tidal CO2 ($ETCO_2$) as a proxy for CBF since changes in $ETCO_2$ correlate well with changes in cerebral blood flow (CBF). $ETCO_2$ did not change following resaturation ($p > 0.4$). The NIRS fast resaturation technique produced CBV values of 1.34 ± 0.24 (SD) ml/100g. This value is low compared to previous reports using slow desaturation at sea level, but in the same range as values obtained using indocyanine green as a NIRS tracer (*J. Appl. Physiol.* 87(5):1981–7, 1999). **Conclusion:** We conclude that the NIRS fast resaturation technique a) does not alter cerebral blood flow; b) produces values similar to the literature; and c) has a high temporal resolution and thus can be used to measure the time course of CBV changes during field and simulated high altitude experiments.

53. CEREBRAL DESATURATION AT VO_2 MAX AT HIGH ALTITUDE (5250M).

CHE Imray[1], CW Chan[1], P Collins[1], S Myers[1], S Harris[1], AW Wright[1], AR Bradwell[1]. Birmingham Medical Research Expeditionary Society[1]. *Chrisimray@aol.com.*

Ascent to altitude results in peripheral desaturation. Exercise at high altitude compounds this desaturation. This study aimed to assess cerebral desaturation at rest and on exercising to VO_2 max at 5250m. **Methods.** 9 subjects (1 female, age 32–60) were studied at 5250m. Pulse oximetry (SPO_2) was measured using a Ohmeda Biox 3740 Pulse Oximeter; Regional cerebral oxygenation (rSO_2) was measured using a Critikon 2020 monitor; middle cerebral artery velocity (MCAV) was assessed using a DWL Multi Dop T1. COLIN CBM-7000 continuous beat to beat blood pressure monitor was used to measure blood pressure. A purpose built collapsible recumbent exercise bicycle was constructed by QinetiQ, Farnborough UK. Statistics: Paired t test. **Results.** Exercise to VO_2Max at 5250m resulted in an increase in pulse rate from 72.1(11.8) to 129.9(5.3) ($p < 0.0001$). No change in mean arterial blood pressure 106.6(10.7) to 110.2(21.9)mmHg $p = 0.501$. SPO_2 fell from 81.8(4.7)% to 65.7(10.7)% ($p < 0.0001$). rSO_2 fell from 61.8(3.3)% to 58.2(2.5)% ($p = 0.0019$). MCAV fell from 75.1(19.3)cms/sec to 68(17.2) cms/sec ($p = 0.0017$). **Conclusions.** Existing assessments of cerebral perfusion at altitude have all been on resting subjects. Ascent to altitude reduces cerebral oxygenation. Exercise would appear to result in still further reductions in cerebral oxygenation. This may in part account for the anecdotal increase in AMS in those who exercise at altitude.

54. INCREASED PO_2 GRADIENT NOT CEREBRAL BLOOD FLOW IMPROVES BRAIN OXYGENATION AT ALTITUDE.

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Introduction: Above 3560 m, voluntary hyperventilation improves arterial O_2 saturation (SaO_2) and cerebral regional oxygenation (rSO_2) (1). At sea level, hypercapnia improves cerebral blood flow (CBF) and rSO_2 even if hypoxic end-tidal PO_2 is maintained (2). We tested if an increased CBF due to increased PCO_2 and reduced PO_2 associated with hypoventilation (HVE) improves rSO_2 at altitude. **Methods:** Five healthy male subjects partially acclimated to 4750 m breathed on a partial rebreathing circuit that limited alveolar ventilation (VA) to the flow of air entering the circuit. Subjects hyperventilated voluntarily while air intake to the circuit was reduced. $PETCO_2$, SaO_2, rSO_2, and middle cerebral artery blood velocity (MCABV), an index of CBF, were measured. Brain O_2 delivery (DO_2) was calculated as MCABV × SaO_2. **Results:** At rest, $PETCO_2$ was 27.3 ± 1.4 (SD) mmHg, SaO_2 90.8 ± 2.7%, rSO_2 64.0 ± 2.0%, and MCABV 66.5 ± 10.6 cm/s. Changes from resting values (*$p < 0.01$) are presented below. In three subjects, the initial phase of hyperventilation depleted blood CO_2 content such that the reduction in air intake (i.e., VA) caused a disproportionate hypoxia prior to any rise in $PetCO_2$. Results from the remaining two subjects are presented in the table. **Discussion:** Assuming constant cerebral O_2 extraction, our data imply that, at altitude, RsO_2 is more influenced by the blood-tissue O_2 gradient than by perfusion. Clin Sci 2000;98:159 J Clin Monit 2000;16:191

	ΔPetCO₂ (mmHg)	ΔSaO₂ (%)	ΔMCABV (%)	ΔDO₂ (%)	ΔrSO₂ (%)
HVE	-6.4±1.8*	7.1±1.8*	-28.7±10.2*	-23.2±10.4*	1.4±0.6*
HVE subject 1	2.7	-2.3	21.0	18.0	-0.7
HVE subject 2	2.2	-0.7	24.6	23.7	-2.0

55. THE EFFECT OF AN OXYGEN BOLUS ON CEREBRAL OXYGENATION AND BLOOD FLOW AT ALTITUDE.

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Cerebral hypoxia is central to the pathophysiology of acute mountain sickness (AMS). Whilst the beneficial effects of supplemental oxygen is well recognized, the effect of oxygen on cerebral haemodynamics at altitude is not clearly understood. **Aim:** To investigate the effects of a bolus of oxygen on cerebral oxygenation and blood flow at altitude. **Methods:** 11 healthy male subjects were studied at an altitude of 5260 metres. Subjects were well rested and studied supine using the following parameters: peripheral oxygen saturation by earlobe pulse oximetry (SaO_2), cerebral oxygen saturation by near infrared spectroscopy (rSO_2), middle cerebral artery velocities by transcranial Doppler (MCAV), continuous non-invasive blood pressure monitoring (cniBP), and pulse rate (PR). Baseline measurements were obtained and 100% oxygen was inhaled over 3 normal inspirations after which ambient air was inspired. Recording of parameters was performed at 2 second intervals for 60 seconds. **Results:** There was a significant rise in cerebral artery velocities 30 seconds after an oxygen bolus was administered. A mild rise in pulse rate was noted but no difference in the peripheral pulse oximetry nor systemic blood pressure. **Conclusion:** These results suggest that during acute exposure to oxygen at altitude, the rise in cerebral oxygenation is not due to an increase in peripheral saturation nor a change in systemic circulation. This improvement in cerebral oxygenation occurs in spite of a reduction in intracranial blood flow velocities.

	rSO_2 (%)	SaO_2 (%)	MCAV (cm/sec)	cniBP (mmHg)	PR (min)
Baseline	63.3±0.1	83.9±0.4	62.6±1.0	110.6±1.0	60.5±0.6
30 s after O_2 bolus	65.6±0.1	84.3±0.3	52.9±1.0	110.8±1.0	63.1±0.6
p value *significant	< 0.0001*	> 0.05	< 0.0001*	> 0.05	< 0.05*

56. REGION SPECIFIC CHANGES IN CEREBRAL GLUCOSE METABOLISM FOLLOWING HIGH ALTITUDE EXPEDITION.

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Functional and cognitive impairment has been reported in high altitude elite climbers. However, little is known about the relationship between neurological dysfunction and cerebral glucose metabolism short after an expedition to 8000m. In 11 male climbers we evaluated cerebral glucose metabolism before and after they climbed Mount Shisha Pangma (8048 m). During the climb AMS was assessed (Lake Louise score protocol) and a neurophysiological evaluation was performed (mini-mental test and a line-bisection test). Heart rate and oxygen saturation (SO_2) was measured daily. Normobaric hypoxic ventilatory response (HVR) and positron emission tomography using [18F]-2-deoxy-2-fluoro-D-glucose (FDG-PET) was performed before (pre) and after (post) the expedition. The difference FDGpost-FDGpre was analyzed voxel-by-voxel using statistical parametric mapping (SPM) and volumes of interest (VOI's). All 11 climbers were above 7000m and 4 of them reached the summit. The total time spent above 6000 m was 18 days. The average of lowest SO_2 was 65+4% and of highest AMS score was 9.8+2.4. One expedition member had high altitude pulmonary edema. All neurophysiological tests were normal. SPM revealed 2 areas with increased FDG-uptake after the expedition, one in the left cerebellum (+9.4%) and one in the white matter lateral to the left thalamus (+8.3%). A trend to decreased uptake was found in the right frontal cortex (−4.2%). The VOI analysis revealed increased post-expedition metabolism in an area of the right cerebellum (+11%) and the thalamus bilaterally (+3.7% left, +4.6% right). FDG-PET alterations were not correlated with SO_2, HVR and AMS score. In conclusion, we found that prolonged stay at extreme altitude led, short-term after exposure, to region specific changes in cerebral glucose metabolism without signs of neurophysiological impairment during and after the expedition. The physiological relevance of these changes needs to be established.

57. SUPINE EXERCISE CYCLE ERGOMETER FOR CEREBRAL STUDIES.

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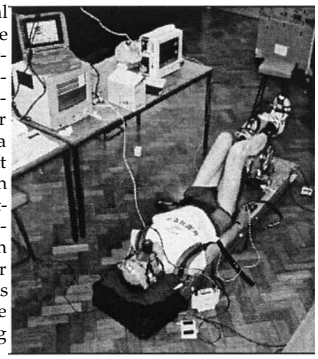
Objective An exercise ergometer was required for cerebral studies under expedition conditions. The Exercise Ergometer The ergometer was designed and developed with several novel features: The subject pedals in a supine position with the head fully supported. This allows position-critical and vibration-sensitive monitoring techniques during exercise, such as Trans-Cranial Doppler for cerebral blood flow. A strain-gauged crankset allows power measurement independent of atmospheric conditions. An adjustable brake controls resistance. A flywheel promotes smooth pedaling, comparable to cycling on the flat. To minimize weight, appropriate inertia is obtained by gearing a small flywheel to rotate at high speed. It is adjustable for people from 5′4″ to 6′2″ in height. It can be folded and carried like a rucksack. Method Nine subjects were tested at four locations in the UK and Bolivia, at altitudes between 92m and 5260m. At each altitude, the resistance was incrementally increased to volitional exhaustion to determine the power at VO_2max. Subsequently, graded exercise tests were performed, working for 5 minutes each at a steady state of 30%, 50% and 70% of VO_2max power. **Results** Concurrent measurements were made of power, cadence, expired gases, cerebral blood flow, cerebral regional oxygenation, peripheral blood oxygenation, blood pressure and pulse rate. The results were correlated and are reported in complementary papers. **Conclusion** The exercise ergometer worked reliably for the duration of the study, including a 2-week period at high altitude. It proved easy to use, compatible with other test equipment, robust yet lightweight and portable. It has the potential to be a standard tool for high altitude exercise research and other test or rehabilitation applications where the head or body needs to be supported, such as when monitoring cerebral functions.



58. IMPROVED CEREBRAL OXYGENATION DURING ACUTE HYPERVENTILATION AT ALTITUDE IS NOT DUE TO IMPROVED CEREBRAL BLOOD FLOW.

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An inadequate hyperventilatory response may contribute to the development of acute mountain sickness (AMS) in susceptible individuals. Whilst the effect of hyperventilation on cerebral blood flow and oxygenation at sea level is predictable, the physiological impact of hyperventilation on brain oxygenation at altitude remains poorly understood. **Aim:** To study the effects of acute hyperventilation on cerebral oxygenation at altitude. **Methods:** 11 healthy male subjects breathing ambient air at 5260m underwent 60 seconds of maximal hyperventilation following which each subject was allowed to breathe normally for 3 minutes. Data were recorded at baseline and 2 second intervals using the following parameters: peripheral oxygen saturation by earlobe pulse oximetry (SaO_2), cerebral oxygen saturation by near infrared spectroscopy (rSO_2), middle cerebral artery velocities by transcranial Doppler (MCAV), continuous non-invasive blood pressure monitoring (cniBP), and pulse rate (PR). **Results:** The physiological response during the brief spell of acute hyperventilation were as follows: (* significant) **Conclusion:** There is a significant rise in cerebral oxygenation with hyperventilation despite a drop in middle cerebral artery velocities and an insignificant change in peripheral oxygen saturation. This suggests that oxygen flux in the brain during high altitude acute hyperventilation might be due to a mechanism unrelated to cerebral blood flow.

	rSO_2 (%)	MCAV (cm.s-)	SaO_2 (%)	PR (min)	CniBP (mmHg)
Baseline	63.3±0.1	62.6±0.91	83.9±0.4	60.5±0.6	110.6±1.1
Hyperventilation @ 60 secs	65.6±0.4	33.9±1.2	82.1±3.4	91.6±4.2	100.5±3.8
p value	< 0.0001*	< 0.0001*	0.34	< 0.0001*	0.0006*

59. REACTIVE OXYGEN SPECIES (ROS) PRODUCTION DURING EXPOSURE TO PROGRESSIVE HYPOBARIC HYPOXIA.

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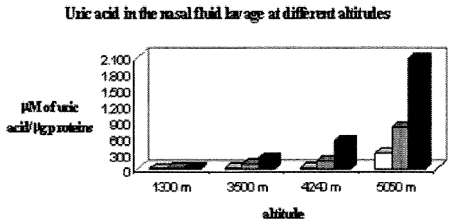
The relationship between hypoxia exposure and ROS generation is quite complex. Several lines of evidence show that ROS are generated during hypoxia but most of this evidence has been obtained in vitro and the relevance in humans is not yet well known. **AIM** to study ROS generation in healthy lowlanders during high altitude exposure. **METHOD** 5 lowlanders (3M,2F) climbed from 1300 to 5030m (Pyramid Lab, Khumbu Valley, Nepal).At altitudes of 1300m, 3500m, 4040m and 5050m samples of nasal fluid lavage were obtained (by instillation of saline solution), filtered and stored in liquid nitrogen. As index of oxidative stress we measured the activity of xantine-oxidase, an hydroxylase that produces superoxide and uric acid from purine substrates and molecular oxygen, by measuring uric acid. The presence of uric acid was evaluated trough "Uricase test", a spectrophotometric measurement made before and after addiction of Urato-oxidase enzyme. **RESULTS** due to technical problems only 3 subjects completed the protocol. Data of each subject are reported in the figure showing an increase of uric acid production with altitude. We conclude that progressive exposure to hypoxia induce an progressive oxidative stress. The results suggest that hypoxia led to an increase in the production of ROS also in humans.



60. HEMODYNAMIC EFFECTS OF SUPPLEMENTARY OXYGEN DURING EXERCISE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE.

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Exercise endurance in severe COPD is improved with supplementary oxygen (SO), which may be partly related to improvements in cardiac output (CO). 16 patients with severe COPD (FEV1 34 ± 7% of predicted) performed two bicycle exercise tests: one breathing room air (RA) and one breathing SO at a flow rate of 4 l min 1 (FIO_2 = ±35%). Testing sequence was randomized and double blinded, with 30 minutes of rest in between tests. Measurements were made of SaO_2, minute ventilation (VE), heart rate (HR) and cardiac output (CO) by means of electrical impedance cardiography. With SO, endurance time increased from 94 ± 23 to 263 ± 66 s ($P < 0.001$). In RA, SaO_2 decreased from 94 ± 2% at rest to 86 ± 5% at end-exercise. SaO_2 didn't change during exercise in SO (97 ± 1% at rest; 95 ± 3% at end-exercise). In RA, end-exercise VE was higher than after an equivalent exercise duration in SO (34.7 ± 11.0 vs 29.8 ± 9.2 l/min, $P < 0.0001$). At end-exercise in SO, VE increased to 33.7 ± 10.3 l/min, not different from end-exercise in RA. There were no differences in end-exercise HR (124 ± 13 in RA vs 126 ± 13 beats/min in SO). End-exercise CO increased from 7.7 ± 2.6 in RA to 8.6 ± 2.3 l/min/m2 in SO ($P = 0.01$) The increase in endurance time was significantly correlated to both the reduction in VE ($R = 0.62$, $P = 0.01$; comparing end-exercise RA to an equivalent duration in SO), and the increase in CO ($R = 0.69$, $P = 0.004$; comparing end-exercise RA to end-exercise SO). It is concluded that in severe COPD, the improved exercise endurance when breathing SO is not only associated with a reduction in ventilatory need, but also with improvements in hemodynamic performance.

61. THE MECHANISM OF SHORTENING OF VOLUNTARY BREATH HOLDING TIME (VBHT) AT HIGH ALTITUDE.

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This study examines the decrease of voluntary breath holding time (VBHT) with respect to increasing altitude. The aim is to correlate this phenomenon with respiratory regulation. **Materials and Methods:** The subjects in this study were 5 Expeditions from Japan to the Asian Giants. They used their own wristwatches to measure VBHT. To normalize all the data from each Expedition, instead of VBHT, VBHT% was used for the comparison between data at sea level and at altitude. Here, VBHT% = 100 × VBHT at altitude/VBHT at sea level. **Results:** The relationship between VBHT% and altitude is revealed by their graphical relationship. Each line is not a single continuous line, but it is interrupted abruptly at a certain altitude (around 2–3,000m, though it differs between expeditions), then shifted rightward. Only 2 expeditions observed VBHT on descent, in which hard recovery from once shortened VBHT was reported. **Discussion:** The reason for the shortening of breath holding time at high altitude may be that the threshold of $PaCO_2$ to breaking point of breath-hold was lowered by increase of blood pH. And also the reason of abrupt rightward shift of VBHT%-Altitude line may be that respiratory alkalosis induced by hyperventilation was corrected by stepwise discharge of bicarbonate ion through the kidney. The reason for hard recovery of VBHT even after getting down could be explained by fatigue. **Conclusion:** The rightward shift of VBHT% at high altitude may be a high altitude reaction which indicates renal regulation of respiratory alkalosis, which could be the first step to explaining high altitude acclimatization.

63. IMPACT OF BMI ON CPAP IN THE OBSTRUCTIVE SLEEP APNEA SYNDROME.

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Introduction In patients with obstructive sleep apnea syndrome (OSAS) a high body mass index (BMI) may be thought to affect inspiratory pressure in CPAP treatment by increasing respiratory load. The aim of this study was to investigate the correlation between BMI and effective CPAP, determined by auto-CPAP titration. **Materials and Methods.** One hundred and one patients with excessive daytime sleepiness had been diagnosed as having OSAS. Before initiation of nocturnal CPAP treatment, the patients were referred to an ambulatory CPAP titration (AutoSet T, ResMed, Australia). The auto-titration data were then compared to the patient's body mass index by means of correlation analysis. **Results.** The analyses of the 95 percentile and median auto-CPAP pressures and the patients BMI showed a weak, but statistically significant correlation between these parameters. **Discussion and conclusion.** A positive correlation between BMI and effective nocturnal CPAP is in line with clinical experience. However our findings show that the strength in this correlation is so weak that even large variations in BMI do not affect treatment pressure significantly.

62. EFFECT OF ALTITUDE AND DEGREE OF EUROPEAN ADMIXTURE ON THE VENTILATORY RESPONSE TO SUSTAINED HYPOXIA IN SEA LEVEL AND HIGH ALTITUDE NATIVES LIVING AT SEA LEVEL.

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High altitude Andean natives have an irreversibly blunted ventilatory response to hypoxia. This blunting represents the expression of their higher hypoxic ventilatory depression (HVD) due mostly to a decreased fast-OFF response to prolonged hypoxia, rather than to a decreased fast-ON ventilatory response to acute hypoxia. However, Andean natives differ in their level of European admixture rate (ADM, %). With this analysis we aim to estimate whether HVD is jointly affected by hypoxia, and different degrees of ADM in sea level and high altitude subjects. We analyze the ventilatory response to sustained (20 min, end-tidal PO_2 = 50 Torr) isocapnic hypoxia in 28 high altitude natives (>3,500 m) residing at sea level (HA, 7.61 ± 6.7 l/min), and on 29 sea level natives (SL, 2.68 ± 8.4 l/min). HVD values in these two groups were compared to a sea level group (SL-ADM, n = 32) in which ADM had been estimated using a panel of 20 ancestry-informative genetic markers. HVD was 1.41 ± 6.6 l/min in the SL-ADM group (p = N.S. vs SL). Dividing the SL-ADM group into low (−) versus high (+) ADM subgroups (<1% versus ~18% average European genetic influence, respectively) reveals: HVD SL-ADM(−) = 3.17 ± 7.4 l/min, versus SL-ADM(+) = −0.83 ± 5.1 l/min. Thus, lower ADM is associated with higher HVD values. In addition, HVD correlated inversely with logADM in SL-ADM group ($r = 0.36$, $p < 0.05$), yet, the highest HVD values were presented by the HA subjects ($p < 0.05$ vs SL; $p < 0.001$ vs SL-ADM (+); $p < 0.05$ vs SL-ADM (−)). We conclude that both, the place of birth (altitude) and the degree of ADM (more Quechua) might be explaining the differences observed in HVD in the Andean population.

64. CAPNOGRAPHY AT HIGH ALTITUDE.

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OBJECTIVES The purpose of the experiment was to elucidate factors associated with capnograph malfunction, a common problem on altitude research expeditions. **METHODS** Four capnographs were tested in an altitude chamber at altitudes corresponding with those during our recent experiments in Bolivia (see table below). The following parameters were measured Flow rates through each capnographs tubing using a rotameter A gas containing 5% CO_2 was used to measure calibration. Machines were not recalibrated between altitudes. **RESULTS** (X = No reading) **CONCLUSIONS** Altitude affects capnograph function independently of other environmental variables. These results correspond with field observations. Flow rates in all monitors other than K4b2 decrease with decreasing barometric pressure until the machine no longer reads. Following this, flow rate is unpredictable. Collective fan laws predict reduced flow with decreased barometric pressure.1 Changes in CO_2 readings emphasize the importance of recalibration on change of altitude. An altered refractive index of air is the likely explanation2 .K2b4 appears to compensate. Electronics in some monitors may sense reduced barometric pressure as air leak within the monitor2. K4b2 is the only monitor that we tested which is functional at 18000 feet. REFERENCES CHEST 1995;108:1577–80 Personal communication, Datex-Ohmeda, Finland

altitude/pressure mmHg	260ft/756	12kft/483	15kft/429	18kft/379
Datex-Ohmeda S/5				
Flow (ml/min)	180	125	100	100
Corrected flow	180	157	133	142
CO_2%	5.1	4.0	3.2	X
Datex Cardiocap				
Flow (mls/min)	150	170	100	100
Corrected flow	150	214	133	142
CO_2%	5.1	X	X	X
Ohmeda 4700				
Flow(mls/min)	320	200	200	190
Corrected flow	320	251	267	270
CO_2%	4.6	3.0	2.9	X
Cosmed K4b2				
Flow(ml/min)	200	180	180	180
Corrected Flow	200	226	240	255
CO_2%	4.66	4.9	5.0	5.08

65. HYPOBARIC HYPOXIA IS NOT A DYSPNOGENIC FACTOR IN HEALTHY SUBJECTS AT REST.

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Dyspnea is a complex symptom. Sensations of difficult breathing in cardiorespiratory diseases may vary in quality and may have different pathophysiologic bases. Lack of oxygen may exert its effects on dyspnea via both an increase in ventilation and as a direct dyspnogenic stimulus. However, relatively few studies have formally examined the effects of hypoxia on dyspnea, and the relationship between hypoxia and dyspnea is unclear. In the present study, we evaluated changes in arterial blood gases, the magnitude of dyspnea (Borg scale) and the level of consciousness (mini-mental state examination, MMSE) in 27 healthy male subjects, using a hypobaric hypoxic chamber in which the barometric pressure was gradually lowered to a simulated altitude of 6000m, at a rate of 30 m/min (2 Torr/min). The subjects included both mountain climbers and non-climbers. Arterial blood samples were obtained at an interval of 1000m via a catheter inserted into the radial artery. All measurements were carried out during the resting state at a sitting position. Two medical doctors breathing oxygen entered the chamber for the measurements and for safety of the subjects. The mean PaO_2 at a simulated altitude of 0, 2000, 3000, 4000 and 6000m were 95.4 ± 4.1(SD), 68.1 ± 6.5, 55.3 ± 5.3, 46.8 ± 4.8, 41.8 ± 4.9 Torr, and the $PaCO_2$ were 40.0 ± 1.9, 38.9 ± 2.9, 38.4 ± 2.1, 36.8 ± 3.0 and 31.9 ± 2.3 Torr. While there was a significant decrease in PaO_2 and $PaCO_2$, the Borg scale and the score of MMSE did not change even at the simulated altitude of 6000m. No subjects complained of dyspnea during the study. These results indicate that hypobaric hypoxia is not a dyspnogenic factor in healthy subjects at rest and that an increase in ventilation derived from heightened ventilatory demand does not produce dyspnea at rest (Grant-in-Aid for Scientific Research Japan #12670578).

66. EFFECTS OF CHRONIC HYPOBARIC HYPOXIA ON UPPER AIRWAY EMG RESPONSES TO ACUTE HYPOXIA AND ASPHYXIA IN THE RAT.

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The upper airway (UA) dilator muscles play a crucial role in maintaining airway patency. We recently demonstrated that chronic intermittent hypercapnic hypoxia impairs rat UA EMG responses to acute hypoxia and asphyxia. This finding may be particularly relevant to clinical disorders that are characterized by recurrent episodic hypoxia such as the sleep apnoea syndrome. Chronic exposure to prolonged continuous hypoxia occurs in humans in a variety of circumstances, however very little is known about the effects of chronic hypoxia on UA muscle function. The present study was designed to examine the effects of long-term exposure to continuous hypoxia on UA EMG activity and responses to acute physiological stimuli. Adult male rats were exposed to normoxia (n = 5) or hypobaric hypoxia (n = 5, barometric pressure 450mmHg) for 6 weeks. At the end of this period, sternohyoid (a representative UA dilator muscle) EMG activity was recorded during normoxia, hypoxia (10% O_2 in N2) and asphyxia (10% O_2 and 3% CO_2) under pentobarbitone anaesthesia. Chronic hypobaric hypoxia significantly reduced sternohyoid EMG responses to acute hypoxia (+23.1% vs +3.1%, % change from baseline, normoxia vs. hypoxia) and asphyxia (+32.0% vs +6.7%). In summary, chronic continuous hypobaric hypoxia significantly impairs (blunts) rat UA EMG responses to acute hypoxia and asphyxia. Impaired reflex activation of the UA dilator muscles predisposes to UA collapse, which could lead to further hypoxemia thereby exacerbating the condition. The results may also partly explain the association of obstructive sleep apnoea and chronic obstructive pulmonary disease, the so-called "overlap syndrome." Supported by Univ College Dublin, Ireland and the Royal College of Surgeons in Ireland.

67. EFFECT OF L-ARGININE SUPPLEMENTATION ON EXPIRED NO AND RESPIRATORY SYMPTOMOLOGY WITH ACUTE EXPOSURE TO AN ALTITUDE OF 4383 METERS.

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Nitric oxide (NO) production is known to be affected by acute exposure to altitude. In the lung, the decrease in NO is thought to contribute to an increase in pulmonary arterial pressure and, in turn, ventilation/perfusion mismatching. These changes in the lung environment with ascent to altitude may be related to changes in respiratory sensations, sensations of acute mountain sickness and potentially high altitude pulmonary edema (HAPE). In order to examine these relationships subjects drank a mixture containing 12 gm of L-arginine in 250 ml of fruit punch 8 times evenly spaced in a 48 h period. This mixture was consumed 24 h prior to and during a 24 h acute ascent to 4356 m. L-arginine is a substrate for the synthesis of NO and when consumed in the diet or injected IV, plasma L-citruline concentration increases. Four adult subjects (3 males; 1 female) were transported in sport utility vehicles from White Mountain Research Center (Owens Valley Research Laboratory) in Bishop, CA (1235 m) to the White Mountain Summit Hut (4356 m). We measured exhaled NO, exhaled breath condensates, blood O_2 saturations, respiratory related sensations at rest and during exercise, and sensations of acute mountain sickness. In 2 of the 4 subjects, exhaled NO was greater at timepoints 0 , 4, 8, 12, and 24 h after reaching the Summit Hut during the L-arginine condition. Three of the 4 subjects had higher overall Lake Louise Scores at 24 hours during the L-arginine condition. Two of the 4 subjects had higher respiratory related sensation scores at 24 h during the L-arginine condition. These results suggest that L-arginine supplementation with ascent to altitude has variable effects on pulmonary NO production that are not associated with symptoms of acute mountain sickness and/or respiratory discomfort. Although there appeared to be no relationship between exhaled NO and other measures, L-arginine supplementation did result in consistently lower O_2 saturations 4 to 8 h and higher Lake Louise Scores 12 to 24 h following ascent.

68. HYPOCAPNIA CONTRIBUTES LITTLE TO INCREASING SaO_2 AT ALTITUDE.

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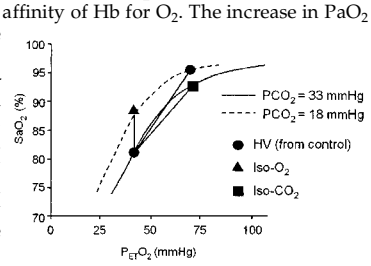
Introduction: Hyperventilation at altitude increases SaO_2 and PAO_2, but decreases $PACO_2$. The combination of reduced cerebral blood flow and increased affinity of Hb for O_2 due to the respiratory alkalosis would reduce cerebral O_2 delivery. We devised breathing circuits to maintain $PACO_2$ constant during hyperpnea (iso-CO_2) and PAO_2 constant during hyperventilation (iso-O_2). Our aim was to identify the contribution of hypocapnia to the hyperventilation-associated increase in SaO_2 at altitude. **Methods:** Five healthy males were studied at 4750 m. Each was studied while breathing through a sham circuit, the iso-O_2 and iso-CO_2 circuits at resting ventilation, and after 5 min of breathing at 4× resting ventilation. We monitored SaO_2 and tidal PO_2 and PCO_2. **Results:** With the iso-CO_2 circuit, hyperpnea increased PAO_2 by 20.3 ± 5.0 mmHg ($p < 0.05$). With the iso-O_2 circuit, hyperventilation decreased $PACO_2$ by 11.4 ± 4.3 mmHg but PAO_2 did not change (+2.4 ± 2.7 mmHg, NS). In all three conditions, the increase in SaO_2 was a function of the slope of the Hb-O_2 dissociation curve at the initial SaO_2. Figure 1 illustrates the independent effects of changes in PAO_2 and $PACO_2$ on SaO_2 during hyperventilation in the subject with the lowest initial SaO_2. **Discussion:** This is the first demonstration of the specific contribution of hypocapnia to increases in SaO_2 during hyperventilation at altitude. Decreases in PCO_2 contributed little to raising PAO_2 but increased the affinity of Hb for O_2. The increase in PaO_2 accounted for most of the increase in SaO_2. The SaO_2 data fit, within experimental error, the theoretical predictions of Kellman's "virtual PO_2" equation. Breathing circuits that allow hyperpnea but maintain isocapnia at altitude may optimize O_2 delivery to the brain and other tissues.



69. WHAT HAPPENS TO RESPIRATORY CHEMOREFLEXES AT ALTITUDE?

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Introduction: Ventilatory acclimatization to 3 weeks of altitude hypoxia may result from changes in respiratory chemoreflexes. We measured the thresholds and sensitivities of the central and peripheral respiratory chemoreflexes during chronic exposure to hypoxia at altitude (>3600 m) and after return to sea level, hypothesizing that they would adapt. **Methods:** We used modified rebreathing tests at end-tidal isoxic levels of 50 and 150 mmHg to measure the chemoreflexes; the former enhances the peripheral chemoreflex response, and the latter attenuates it so as to measure the central chemoreflex response. Five healthy male volunteers performed the two rebreathing tests at sea level, 2 days (acute) and 17 days (chronic) after arrival at 3600 m, and 2 and 5 days after returning to sea level. [HCO3−] and [H+] of venous blood samples were measured at sea level, after 17 days at altitude, and during de-acclimatization. **Results:** The chemoreflex sensitivity to CO_2 at both levels of isoxia was unchanged throughout the test period. However, the chemoreflex CO_2 thresholds measured at both isoxic levels decreased significantly ($p < 0.05$) at altitude and remained decreased until 5 days after returning to sea level, when it increased significantly but remained lower than the pre-exposure control. Nevertheless, when [HCO3−] was used to convert the CO_2 thresholds to [H+] thresholds, the threshold changes were no longer evident. By contrast, estimates of strong ion difference decreased significantly at altitude. Implications: Acclimatization to altitude resulted in increased ventilation as indicated by the decrease in [HCO3−]. Although we hypothesized that changes in the respiratory chemoreflexes would be responsible, none were evident. Consequently, we suggest that changes in strong ion difference may account for the increased ventilation.

71. PHYSIOLOGICAL EFFECT OF COORDINATED BREATHING UNDER HYPOXIC ENVIRONMENT; A QUANTITATIVE STUDY OF DEEP AND ABDOMINAL BREATHING.

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Voluntary coordinated breathing such as hyperventilation is effective method to avoid decreasing SpO_2 under a hypoxic environment. However, we also suffer negative effects such as extra loss of CO_2, body fluid and temperature because of the remarkable increase of ventilation volume. To find reasonable breathing method at high altitude, we compared physiological responses of "deep breathing (DB)", "abdominal breathing (AB)" and "normal breathing (NB)" under hypoxic environment and sea level. Eight male subjects kept sitting in rest, and tried three kinds of breathings (DB, AB and NB) in normobaric hypoxic room set at sea level and hypoxia (equivalent height of 2000m and 4000m). When the subjects use DB or AB, they controlled inhaling duration for four seconds and exhaling duration for six seconds (six times a minute) by themselves. And we measured VE, VO_2, VCO_2, SpO_2 and HR of every condition. When the subjects used DB or AB, SpO_2 raised clearly from the NB level at any altitude, and the degree was more remarkable at the higher altitude. The VE increased significantly when the subjects took DB, while it was almost the same with that of NB when they used AB. The amount of VO_2 and VCO_2 significantly increased when they used DB or AB, but the increase was larger in DB than AB. The change of HR was not significant among the three breathings. The DB can make much improvement of SpO_2 than that of AB. But DB also increase much amount of VE. On the other hand AB can increase fairly amount of SpO_2 without significant increase of VE. Therefore, the AB is more reasonable breathing method under a hypoxic environment.

70. CHANGES IN HYPOXIC VENTILATORY RESPONSE (HVR) DURING 8 WEEKS AT 3800M ALTITUDE.

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Ventilatory acclimatization to hypoxia increases ventilation (VI) and the isocapnic HVR over 2 to 14 days of hypoxia but previous results suggest that HVR may decrease again after 4 weeks at altitude (Wild. Env. Med 11: 172–179, 2000). We measured the time course of acclimatization in humans (4 M, 1 F: 23–41 yrs) at sea level and during 8 weeks at 3,800m ($PIO_2 \sim 90$ Torr). HVR ($\Delta VI/\Delta SaO_2$) was measured after pre-oxygenation ($PIO_2 > 200$ Torr 20 min) by stepping to $SaO_2 = 90\%$ maintaining $PETCO_2 = 2.5$ Torr above the hyperoxic value. Isocapnic HVR was measured again by stepping to $SaO_2 = 80\%$ after 5 and 11 min at $SaO_2 = 90\%$ to quantify hypoxic ventilatory decline (HVD). Subjects increased PaO_2 and SaO_2 breathing ambient air during 8 wks at altitude. HVR increased after 1 day and remained elevated after 8 wks ($p < 0.05$). HVR decreased after 8 min of acute hypoxia and VI decreased further after 14 min of acute hypoxia without further change in HVR ($p < 0.05$). Hence, HVD manifest as an initial decrease in O_2-sensitivity but later as a general decrease in ventilatory drive. This pattern of HVD was similar at all time points. Hence, hypoxic desensitization and blunting of the HVR did not occur after 8 wks of hypoxia in these subjects and changes in the HVR during 8 wks of hypoxia do not involve changes in HVD. Support: NIHMOI RR00827, NIHL17731, and WMRS.

72. INDIVIDUAL MINUTE VENTILATION IN HIGH ALTITUDE RATS IS SUBJECTED TO A DETERMINANT DOPAMINERGIC PERIPHERAL DRIVE.

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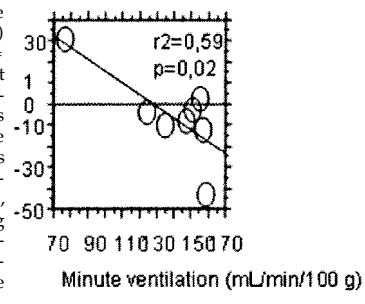
Individual minute ventilation in high altitude rats is subjected to a determinant dopaminergic peripheral drive. The role carotid body dopamine during hypoxic ventilatory acclimatization (HVA) remains unclear. Most of the reports show decreased dopaminergic inhibitory drive on breathing during long-term hypoxia, while transgenic mice lacking the dopaminergic D2 receptors (D2R) showed blunted HVA. In male rats permanently living at high altitude (HA, 3,600 m, La Paz, Bolivia), we previously reported that carotid body dopamine content is 40 times higher than in sea level controls. The present study questions the D2R-dependent dopaminergic influence on resting minute ventilation (Ve) and Hypoxic Ventilatory Response (HVR) at HA. Minute ventilation in normoxia and following a brief hypoxic exposure (10% O_2, 10 min) were first recorded after saline injection (ip) by whole body plethysmography in 8 adult male rats born and bred in La Paz. Forty-height hours later, the same animals were studied after injection of domperidone (1 mg/kg, ip), a peripheral D2R antagonist acting on carotid bodies. While domperidone had no effect on Ve in normoxia (138 ± 10 after saline vs. 132 ± 6 mL/min/100g after dopmeridone) and hypoxia (253 ± 16 after saline vs. 222 ± 15 mL/min/100g after domperidone, p = NS), there was a clear correlation between Ve after saline injection (x axis) and the net effect of domperidone to increase (+) or decrease (−) Ve (y axis; r2 = 0,59; p = 0,02). These data indicate that i) carotid body D2R-dependent dopa-minergic drive is not a major component of the enhanced Ve in HA male rats and ii) as we previously reported in sea level female rats, individual levels of resting minute ventilation are subjected to a determinant peripheral dopa-minergic drive from the carotid bodies.



73. ADAPTATION OF VENTILATION IN MOUNTAINEERS CLIMBING TO 4559M.

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We investigated ventilatory adaptation in unrestrained mountaineers climbing in the high Alps. 26 volunteers were studied in Zurich (490m) before ascending to Mt.Rosa and while climbing from 3650m to 4559m within 4–6 hours with a break at 4200m. Breathing patterns were continuously monitored without airway instrumentation using novel, light-weight equipment incorporating calibrated respiratory inductance plethysmography, pulse oximetry and ECG. In each subject breathing pattern variables, oxygen saturation (SpO_2) and heart rate were averaged over 10 minutes at various altitudes at rest, and during hiking. Rebreathing into a bag of known volume at various altitudes confirmed accuracy of tidal volumes by respiratory inductance plethysmography within 15%. The table shows group means (±SE). After 1 night at 4559m ventilation at rest remained unchanged at 8.8 ± 0.6 L/min, SpO_2 increased to 81 ± 0.8%

Activity	Rest	Hiking					
Altitude m	490m	3650m	4200m	4559m	490m	3650m	4200m
Ventilation L/min	4.6±0.3	6.6±0.5*	8.2±0.5*#	8.8±0.6*#	44.8±2.6	52±3.4	57.9±4*
Tidal Volume ml	247±17	337±30*	384±26*	436±30*#	1371±73	1356±87	1478±106
Breath Rate 1/min	20±1	21±1	23±1	21±1	33±1	39±1*	40±1*
Heart Rate 1/min	61±2	80±2*	92±2*#	91±2*#	143±1	145±3	152±3*
SpO_2%	95±0.5	90±0.7*	80±1*#	76±0.8*#§	93±0.4	74±1.1*	70±1.8*#

* p<0.05 vs 490m, # vs 3650m, § vs 4200m within same activity

($P < 0.05$ vs. previous evening). **Conclusion:** Non-obtrusive monitoring of breathing patterns in mountaineers during natural activities is feasible and accurate. Ventilatory adaptation to high altitude is predominantly achieved at rest by increased tidal volume and during hiking by increased breath rate.

Saturday February 22nd, 2003

••Poster Session II••

75. DNA MICROARRAY ANALYSIS OF HYPOXIA-INDUCED FATIGUE IN SKELETAL MUSCLE.

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We are presenting results of extension to cDNA microarray analysis of tests of a genetic model of hypoxia-induced fatigue in skeletal muscle. Mathematical modeling and subsequent confirmatory breeding tests showed that, in mice, heritable differences in tolerance of treadmill exercise (time elapsed to a behavioral endpoint, tet ,) in 10.49% O_2 after 8 weeks' exposure to 380 Torr is associated predominantly with the expression of 2 unlinked autosomal loci. A striking feature of the inheritance pattern is the presence in the hypoxia-exposed F1, but not in the normoxic control F1 sample, of a very large epistatic interaction between the two loci. However, the magnitude of the genetic effect and its variability decreased somewhat in successive generations formed from backcrosses to the low-performing parental strain, which is indicative of lesser contributions from modifying genes. In order more completely to characterize genetic contribution to the test variable tet, DNA microarray (Invitrogen Corp.) experiments were performed to measure levels of expression in 5184 genes in the non-segregating generations (parental inbred strains C57BL/6 and BALB/c and their F1 hybrid) in normoxia/hypoxia comparisons for each genotype (N = 5 for each of 6 experimental cells). Data were transformed and standardized to a uniform scale across all 30 arrays. Analysis was done using Significance Analysis of Microarrays (SAM) software (Tusher, et al., 2001, PNAS 98(9): 5116–5121) with minimal false discovery rate. Significant differences in gene expression were uncovered in each comparison. Included as candidate genes are Hypoxia-inducible factor 1 alpha, Cofilin 2 (muscle isoform), Heat shock protein (71kDa), Beta-actin, and two protein kinases. Although the analysis is in an early stage, the number of genes involved is small. This raises the possibility of critically defining both the inheritance of differences in fatigue in skeletal muscle induced by a particular type of exercise and the associated physiology.

74. EFFECT OF PROGRESSIVE HYPOXIA WITH MODERATE HYPERCAPNIA ON VENTILATORY VS. VAS RESPONSES IN HUMANS.

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Objective: Ventilatory response to CO_2 combined with hypoxic stimulation has been well documented as exhibiting a positive interaction between the two stimuli. Using modified Read's method, we previously confirmed this in an open loop CO_2-ventilation condition (Respir. Physiol. 126, 17-181, 2001). The purpose of this study is to compare the effect of progressive hypoxia with moderate hypercapnia on ventilatory and respiratory sensation responses in humans. **Methods:** This study was carried out on 15 young healthy adults (4 males and 11 females). The subjects were exposed to progressive hypoxia under three different end-tidal PcO_2 ($PETcO_2$) levels: normocapnia, 2, and 4 mmHg higher than normocapnia. Defined as NC0, HC2 and HC4 runs, respectively. We measured ventilatory parameters and respiratory sensation by visual analog scale (VAS). **Results:** The slope of the SpO_2-ventilation response curve became steeper as the $PETcO_2$ elevated, as expected. There was significant slope augmentation in the HC4 run compared with the NC0 run (−0.52 vs. −0.40 l/min/%SpO_2, $p < 0.05$). On the other hand, the slope of the SpO_2-VAS response curve exhibited no significant change. **Conclusion:** Our study showed that moderate steady hypercapnia synergistically augmented the ventilatory response to progressive hypoxia whereas such positive interaction was not detected in the VAS response. We speculate that the metabolic ventilatory and behavioral respiratory control systems may have played more of a role in the former and latter findings, respectively.

76. HYPOTHERMIA ADAPTATION IMPROVES HEART-TOLERANCE TO HYPOXIA: STUDY ON FUNCTION AND MITOCHONDRIAL GENE EXPRESSION.

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Previously we have used cross adaptation to test adaptive capacity in mountaineering performance. We also observed that hypothermia treatment prior to ischemia could induce cross adaptation to resist subsequent ischemia with accumulation of metabolites in isolated hearts (Ning et al. AJP 274:H786, 1998; JAP 92:2000, 2002). In this study we proved further evidence for hypothermia protection during myocardial hypoxia without metabolite accumulation. Two Langendorff rabbit heart groups were subjected to hypoxia (Infusate PO_2 = 38 mmHg). A hypothermia group (H) was progressively reduced temperature to 29°C within 20 min and maintained for 10 min prior to hypoxia, and for 45 min during hypoxia. The re-oxygenation was completed at 37°C for 45 min. A normothermia control group (C) was held constantly at 37°C. Pilot study showed that this protocol was the best one to improve tolerance, although treatment with 29°C either prior to or during hypoxia also showed protection. Lactate and CO_2 levels were measured in the coronary effluent to monitor metabolite status. Hypothermia prior to hypoxia decreased myocardial oxygen consumption (MVO_2) 79 ± 3% of the baseline value and significantly increased oxygen efficiency estimated by dP/dtmax/MVO_2 and PRP/MVO_2, where PRP is developed pressure (DP) × heart rate. Hypothermia improved functional recovery about 3-fold ($P < 0.05$ vs. C) during re-oxygenation, including DP, dP/dtmax, PRP, and MVO2. Hypothermia hearts maintained mRNA level for mitochondrial membrane specific protein βF1-ATPase, while it decreased in C. However, hypothermia did not further enhance HSP70-1 induction compared to C. Lactate and CO_2 accumulation levels were the same between the groups during hypoxia. The CO_2 production (aerobic metabolism) was much higher in H than C during re-oxygenation. In conclusion, hypothermia adaptation improves myocardial hypoxia tolerance associated with preservation of βF1-ATPase signaling, indicating cross adaptation directly in the organ.

77. NON-INVASIVE BEAT-TO-BEAT BLOOD PRESSURE MEASUREMENT AT HIGH ALTITUDE.

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Introduction Non-invasive beat-to-beat blood pressure measurements were undertaken during various physiological tests performed by the Birmingham Medical Research Expedition Society (BMRES) at high altitude. The blood pressure measurements were taken to complement cerebral blood flow velocity, cerebral and peripheral perfusion and respiratory gas measurements during exercise, hyperventilation, oxygen bolus and Viagra studies. **Method** Beat-to-beat blood pressure was measured by the validated radial artery tonometry technique utilizing a Colin Medical CBM-7000 continuous blood pressure monitor (Aichi, 485-8502, Japan). The principle of applanation tonometry involves the artery being partially compressed, against a hard surface, in this case the radial bone. The Colin arterial tonometry method uses a linear array of piezoelectric transducers located in a wrist sensor housing. The sensor exerts sufficient pressure on the skin to partially flatten the underlying artery; the intra-arterial pressure is then transmitted to the sensor, as the tension forces in the artery wall are perpendicular to the forces exerted by the sensor and by the blood pressure acting on the inner surface of the arterial wall. The resultant arterial waveform is then automatically calibrated with a conventional brachial oscillometric cuff measurement. The Colin CBM-7000 monitor displays numerical beat-to-beat blood pressure values, pulse rate and the arterial blood pressure waveform, which was exported in an analogue format for external recording. **Results** In excess of seventy thousand beat-to-beat blood pressure measurements were successfully recorded throughout the expedition, during all experiments, up to an altitude of 5250m. **Conclusions** Arterial tonometry as a method of determining non-invasive beat-to-beat blood pressure, during physiological testing at altitude, is a particularly suitable technique, owing to the robust nature of the measurement devices and the fact that the measurement site is not affected by temperature variations which affect systems utilizing peripheral sites for measurements.

78. CARBOHYDRATE SUPPLEMENTATION AFTER EXERCISE AFFECTS MOOD STATE AT HIGH ALTITUDE.

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At sea level, carbohydrate ingestion **during** prolonged strenuous exercise maintains blood glucose levels, improves performance and, enhances mood. The effect of carbohydrate supplementation on mood **after** prolonged exercise at high altitude has not been investigated. **PURPOSE:** To determine if carbohydrate supplementation during passive recovery from prolonged exhaustive exercise at 4300 m will alter mood state. **METHODS:** 16 healthy informed male subjects were divided into 2 groups matched for age (25.2 ± 1.8 yr), weight (77.5 ± 2.9 kg), and VO_{2max} (51.0 ± 2.36 mL/kg/min^{-1}). In double-blind fashion, fasted subjects performed a maximum effort 720 KJ time trial on days 3 and 10 of residence at 4300 m. At the beginning of the time-trial and every 15 minutes thereafter, one group (FED) consumed a 10% carbohydrate solution (0.7 g/kg bw) while the other group (TREATMENT) consumed an indistinguishable placebo drink. Water was given ad lib during exercise. Work rate was self-adjusted. Prior to exercise and during recovery at 5 and 20 min post exercise, subjects completed the Feelings Profile (FP), a 19 item short form (Jackson, et al. 1991) of the Profile of Mood States. Within 20 min post exercise, TREATMENT subjects consumed a 10% carbohydrate (0.7 g/kg bw) drink while the FED group consumed the placebo. Fluid volumes were adjusted for exercise duration. **RESULTS:** For the TREATMENT group at 20 min of recovery, post-exercise carbohydrate supplementation decreased *confusion* on days 3 and 10, and increased *fatigue* on day 10. **CONCLUSION:** During recovery from exhaustive exercise at high altitude, post-exercise carbohydrate supplementation effectively reduces confusion but unexpectedly increases feelings of fatigue. These data may reflect a competition for blood flow between the brain and the carbohydrate-suffused gut. Supported by: The Borgenicht Program, The Jeffress Memorial Trust, The Veterans Administration, and The U.S. Department of Defense.

79. A MUCH SIMPLIFIED METHOD FOR PRECISE AND ACCURATE MEASUREMENT OF VCO_2.

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Commercial metabolic carts typically measure VCO_2 by synchronizing and integrating flow and PCO_2 signals—a method prone to error, especially in the presence of some rebreathing. We describe a simplified method of calculating VCO_2 using a rebreathing circuit and compare VCO_2 so measured with that measured by a metabolic cart and bag collection in 14 volunteers. **Methods:** We used a partial rebreathing circuit that presents the fresh gas and then the rebreathed gas in sequence. Turning down the fresh gas flow (FGF) below minute ventilation (VE) results in rebreathed gas entering the anatomic dead space and thus does not affect the $PetCO_2$. VA is identified as the FGF where $PetCO_2$ begins to rise. In that case, $VCO_2 = FGF \times FETCO_2$. **Results:** Each bag collection was treated as an independent measurement. The difference (M +/− SD) in VCO_2 measured by the bag collection and our method was 8 ± 38 mL/min and the metabolic cart was 8 ± 52 mL/min. On a breath-by-breath basis, the coefficient of variation with our technique and the metabolic cart were 3.4% vs. 33.1%, respectively. **Conclusions:** VCO_2 can be precisely and accurately measured using a partial rebreathing circuit from the fresh gas flow and $PetCO_2$.

80. OPERATION OF A PORTABLE METABOLIC MONITOR AT LOW AMBIENT TEMPERATURE.

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INTRODUCTION The Cosmed K4b2 is a lightweight, portable metabolic monitor that measures or calculates over 100 variables. During a recent scientific expedition in Bolivia (5486m) problems were experienced when using the unit at ambient temperatures (Ta) of about 0°C. A study was therefore conducted in an environmental chamber to measure the effect on the unit of low Ta. **METHODS** At Ta of 22°C and −3°C, ambient air (20.93% O_2, 0.04% CO_2, balance N2) and a certified calibration gas (16% O_2, 5% CO_2, balance N2) were sampled continuously for 5 minutes. The O_2 and CO_2 concentrations, Ta, internal temperature of the unit (Tint), all measured by the unit, were recorded every minute. The unit was tested when powered by mains and battery. The O_2 and CO_2 sensors were calibrated at Tint of 37°C before each of the 8 tests. **RESULTS** The results obtained when the unit was battery powered (tabulated below) were similar to those obtained when it was mains powered. **CONCLUSION** When Ta was

	Value measured K4b2 (mean (1 SD))			
	O_2 %	CO_2 %	Ta °C	Tint °C
Ambient air 22 °C	21.03 (0.01)	0.01 (0.01)	22.0 (0.0)	36.8 (0.4)
Calibration gas 22 °C	15.94 (0.01)	4.98 (0.04)	22.0 (0.0)	37.0 (0.0)
Ambient air -3 °C	21.07 (0.09)	0.00 (0.01)	3.5 (3.6)	29.2 (1.5)
Calibration gas -3 °C	16.3 (0.3)	4.8 (0.1)	0.3 (0.8)	28.5 (1.5)
Heated Calibration gas -3 °C	15.99 (0.02)	5.06 (0.01)	0.83 (1.2)	36.7 (0.5)

−3°C, Tint fell below the 34–37°C range recommended by the manufacturer, which resulted in erroneous O_2 and CO_2 concentrations. When a small charcoal heater was used to maintain Tint, O_2 and CO_2 concentrations were recorded correctly. Care should therefore be taken when using the unit low ambient temperatures.

81. EFFECTS OF HYPOXIA AND DEXAMETHASONE ON Na-TRANSPORT OF ALVEOLAR EPITHELIAL CELLS.

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Hypoxic inhibition of alveolar ion transport has been associated with susceptibility to high altitude pulmonary edema. Inhibition of Na-transport activity of alveolar epithelial cells is paralleled by a decrease in the amount of transport-proteins in the plasma membrane. We wanted to know, whether decreased transport-activity is caused by a decrease in expression and weather typical oxygen sensing mechanisms are involved in O_2 signaling. Control and dexamethasone-treated (DEX, 1μM) A549 cells were exposed to hypoxia (1.5% O_2) and Cobalt-Chloride (100μM) for 24h. Levels of α1-Na/K-pump mRNA measured by PCR increased 4–7-fold by DEX, but were not affected by hypoxia. β1-Na/K-pump mRNA was not increased by DEX, but increased 4.5-fold by hypoxia. DEX abolished the effect of hypoxia on β1-Na/K-pump mRNA α1-Na/K-pump protein measured by Western blot of whole cell protein was increased by DEX (180%). Hypoxia increased α1-Na/K-pump protein up to 1.5-fold. This is in contrast to earlier findings on Na/K-pumps from isolated plasma membranes. Hypoxia had no effect on DEX treated cells. DEX stimulated the activity of the Na/K-pump measured as ouabain sensitive 86Rb-uptake (+40%). Hypoxia inhibits the Na/K-pump activity in the presence and absence of DEX (−30%). Cobalt had similar effects on expression and activity of Na/K-pumps to hypoxia. HIF-1α mRNA was decreased by hypoxia and cobalt. GAPD mRNA was increased by hypoxia and cobalt in control and DEX treated cells although levels were lower in DEX. These results indicate that the decrease in alveolar cell ion transport activity upon exposure to hypoxia is not associated with decreased mRNA and Na/K-pump protein expression. Pretreatment of cells with DEX prevents hypoxia effects on expression and increases transport activity in normoxia and hypoxia. Glucocorticoid treatment might therefore be beneficial when alveolar fluid balance is disturbed as in HAPE.

82. HYPOXIA REDUCES CELLULAR OXYGEN CONSUMPTION AND Na/K-ATPASE ACTIVITY OF ALVEOLAR EPITHELIAL CELLS.

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Hypoxia has been shown to inhibit alveolar Na-reabsorption by decreasing activity and copy number of transporters. The present study was designed to examine the significance of inhibition of ion transporters such as the Na/K-ATPase for the saving of energy during oxygen deprivation. Alveolar epithelial cells (A549 cells) were cultured in normoxia and hypoxia (24 hours, 1.5% O_2). Cellular oxygen consumption (JO_2 [pmol/s*mg protein]) was measured using high resolution respirometry in normoxia and in acute hypoxia (5, 30 min) as well as after reoxygenation (15 min) in absence and presence of ouabain and other transport inhibitors. Already after 5 min of hypoxia JO_2 was decreased by about 20%, it was decreased further (35%) after 30 min and 24 h of hypoxia. Reoxygenation of hypoxia exposed cells increased cellular JO_2. However, normoxic values of JO_2 were only reached after 5 min of hypoxia whereas JO_2 after reoxygenation remained about 25% lower in cells exposed to hypoxia for 30 min and 24 h. In normoxia, the Na/K-ATPase activity accounted for about 15% of JO_2. This value did not change during hypoxia indicating an equivalent decrease in total and Na/K-ATPase associated JO_2. Inhibitors of Na-channels had no significant effect on cellular JO_2 whereas inhibition of Na/Ca-exchange tended to decrease cellular JO_2. These results indicate that A549 cells conserve energy upon exposure to hypoxia. Decreasing the activity of the Na/K-ATPase and of Ca-transport contributes to energy saving in hypoxia. JO_2 is not fully restored by oxygenation after prolonged hypoxia, which indicates adjustments on the level of gene expression.

83. ASSOCIATION OF RENIN-ANGIOTENSIN SYSTEM GENES WITH HIGH-ALTITUDE PULMONARY EDEMA.

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The crucial pathogenesis of high-altitude pulmonary edema (HAPE) is involved with exaggerated pulmonary hypertension. The renin-angiotensin system (RAS) contributes importantly to the pulmonary hypertension through the mechanism involving the regulation of vascular tone and the maintenance of electrolytes and volume homeostasis. To elucidate the genetic pathogenesis of RAS under the pathogenesis of HAPE, we undertook the current study to identify insertion/deletion (I/D) polymorphism in the angiotensin converting enzyme (ACE) gene by polymerase chain reaction (PCR), as well as five polymorphisms in the angiotensin II type 1 receptor (AT1R) gene and Met235Thr polymorphism [a substitution of methionin (Met) by threonin (Thr) at the 235th codon] in the angiotensinogen (AGT) gene by PCR following restriction fragment length polymorphism in a Japanese population with 44 HAPE-susceptible subjects (HAPE-s group) and 51 HAPE-resistant mountaineering climbers (HAPE-r group). The results are shown as in the following table. *P value was calculated by X2 test 2 × 2 contingency table. $P < 0.05$ was considered statistical difference. It is suggested that a genetic background of the RAS might underlie the pulmonary hypertension in HAPE. The I/D polymorphism of the ACE gene and the

	HAPE-s group	HAPE-r group	*P* value*
I/D polymorphism of the ACE gene:			
D/D genotypic frequency (%)	22.2	4.2	0.011
D allelic frequency (%)	44.4	24.0	0.005
I allelic frequency (%)	55.6	76.0	
$G^{1517}T$ polymorphism of the AT_1R gene:			
G/T genotype frequency (%)	81.4	46.9	0.0006
T allelic frequency (%)	40.7	23.5	0.012
G allelic frequency (%)	59.3	76.5	
Met235Thr polymorphism of the AGT gene:			
Met/Thr genotype frequency (%)	27.9	42.6	0.286
Met allelic frequency (%)	18.6	27.7	0.151
Thr allelic frequency (%)	81.4	72.3	

G1517T polymorphism of the AT1R gene could be used as genetic markers for predicting the susceptibility to HAPE.

84. THE POLYMORPHISMS OF THE TYROSINE HYDROXYLASE GENE IN SUBJECTS SUSCEPTIBLE TO HIGH-ALTITUDE PULMONARY EDEMA.

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A blunted hypoxic ventilatory response (HVR) is proposed as a potential mechanism in the pathogenesis of high-altitude pulmonary edema (HAPE). Tyrosine hydroxylase (TH) is a rate-limiting enzyme in the carotid body responding to hypoxia to synthesize dopamine neurotransmitter to heighten ventilation. To clarify the genetic background of the TH gene underlying the blunted HVR in HAPE, we examined the informative tetranucleotide (TCAT)n microsatellite repeats of the TH gene by polymerase chain reaction (PCR) following direct sequencing and the Met81Val variant [a variant swapping valine (Val) for methionine (Met) at the codon 81st] of the gene by PCR following restriction fragment length polymorphism as well in a Japanese populations with 43 HAPE susceptible subjects (HAPE-s) and 51 HAPE resistant mountaineering climbers (HAPE-r). Additionally, the HVR in 21 HAPE-s was also measured. The results are shown as in the following table: D, and E = 5 alleles of (TCAT)n tetranucleotide repeats, respectively; ** Met, Val = methionine and valine alleles, respectively; # comparison between HAPE-s and HAPE-r by the chi-square analysis. In addition, there were no relationships observed between the HVR values of HAPE-s and the individual alleles in both polymorphisms of the TH gene. This study suggests that the blunted HVR in HAPE-s probably is not associated with the current polymorphisms of the TH gene, suggesting that these two polymorphisms may not be sufficient as genetic makers for predisposing to the susceptibility to HAPE.

(TCAT)n Tetranucleotide Repeat A-E allele* frequency (%)	HAPE-s	HAPE-r	P value#
A	25.0	21.4	0.5686
B	23.8	35.7	0.1070
C	7.1	4.1	0.3663
D	40.5	36.7	0.6050
E	3.6	2.1	0.5288
Met81Val Variant**			
Met allele (%)	64.0	67.6	0.594
Val allele (%)	36.0	32.4	

*A, B, C, D, and E = 5 alleles of (TCAT)n tetranucleotide repeats, respectively; ** Met, Val = methionine and valine alleles, respectively; # comparison between HAPE-s and HAPE-r by the chi-square analysis.

85. TREATMENT OF HAPE AND HACE WITH NOVEL BREATHING SYSTEM: CASE REPORT.

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Case report: A 65 year old doctor developed confusion, ataxia and anorexia in the evening of his 2nd day of an expedition to 4800m in Bolivia. He had marked periodic breathing, raised JVP, basal crepitations but no papilloedema. SaO_2 measured 62%. He improved during 1 hour in a portable hyperbaric chamber (Bartlett bag), which simulated a descent to 2700m. However he relapsed within one hour. **Methods:** Available O_2 supply was limited to a full E-sized cylinder containing ~500 L of O_2 at 1 A. We applied a new investigational breathing system that combines a fixed O_2 flow with entrained ambient air at a definable flow of both. When minute ventilation exceeds the sum of both fresh gas flows (FGF), the balance of the inspirate consists of rebreathed gas. Both FiO_2 and VA are determined by the FGF. The patient breathed through the circuit via a modified nasal CPAP mask. **Results:** With no added O_2, reducing FGF increased end-tidal PCO_2 by 1–2 mmHg, regulated the breathing pattern, left end tidal FO_2 unchanged at 0.12 and increased SaO_2 to 79%. Adding O_2 to the circuit at a flow of 0.5 L/min, increased end tidal FO_2 to 0.18 and SaO_2 to 87%. O_2 flow of 1.2 L/min, (i.e., depleting the tank at 0.7 L/min at 1A) was maintained overnight increasing end tidal FO_2 to 0.27 and SaO_2 to ~94%. In the morning the treatment was discontinued; the patient remained well without O_2 supplementation for about 2–3 hours while preparing for descent. Conclusions: This breathing system effectively improves SaO_2 by eliminating periodic breathing. It efficiently delivered O_2 at high altitude. This portable circuit can be configured for use in the field.

86. INHIBITION OF PHOSPHODIESTERASE-5 IN ADDITION TO INHALED NITRIC OXIDE COMPLETELY INHIBITS HIGH ALTITUDE ASSOCIATED PULMONARY VASOCONSTRICTION.

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Inhibition of phosphodiesterase-5 in addition to inhaled nitric oxide completely inhibits high altitude associated pulmonary vasoconstriction Endogenous nitric oxide (NO) synthesis and/or phosphodiesterase-5 activity is probably crucial for regulation of hypoxic pulmonary vasoconstriction at high altitude. Therefore, 22 healthy non-acclimatized mountaineers were investigated using Doppler-echocardiography at low altitude (LA) (490 m) and after rapid ascent (within 24 hours) to 4559 m. Three hours after arrival systolic pulmonary artery pressure (sPpa) was measured during NO-inhalation and 90 min after 50 mg sildenafil, first without, and then with NO (HA1). Baseline measurements were repeated the following morning before descent (HA2). Eleven of the 22 subjects developed acute mountain sickness (Lake Louise score > 5), but none high altitude pulmonary edema (HAPE). Four had a previous episode of HAPE. Mean (±SD) arterial oxygen saturation (SaO_2) was 97 ± 1% at LA, and 75 ± 4% and 78 ± 3% at HA1 and HA2, respectively ($p < 0.001$). SPpa, estimated from the tricuspid regurgitation, was on average 27 ± 3 mmHg at LA, and 44 ± 10 mmHg at HA1 and 42 ± 8 mmHg at HA2 ($p < 0.001$). Inhalation of NO, sildenafil and the combination decreased sPpa from 44 ± 10 mmHg to 32 ± 6 mmHg, 33 ± 6 mmHg and 28 ± 5 mmHg, respectively ($p < 0.001$). Sildenafil and NO combined decreased sPpa to LA level ($p = 0.16$). Mean blood pressures before and 90 minutes after sildenafil were identical (87 ± 7 vs. 87 ± 6 mmHg). We conclude that inhibition of the phosphodiesterase-5 decreases Ppa as effectively as inhaled NO without causing systemic hypotension, and that only the combination of both completely inhibited high altitude associated pulmonary vasoconstriction, which supports the role of both, endogenous NO-synthesis and phosphodiesterase-5 activity, in hypoxic pulmonary vasoconstriction at high altitude.

87. DAILY OXYGEN DESATURATION AND PULMONARY HYPERTENSION IN MODERATE-SEVERE COPD WITHOUT SEVERE HYPOXEMIA AT REST.

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Pulmonary hypertension can develop in COPD patients, usually due to chronic hypoxemia. Some patients present PH even in the absence of severe resting hypoxemia. Little is known about oxygen status during day and night in these patients. We aimed to study 24hrs monitoring SpO_2 in moderate-severe COPD with resting PaO_2 >60mmHg and correlate the presence, duration and severity of oxygen desaturations (Des) to PAP value. 20 stable moderate-severe COPD patients were enrolled. Respiratory function tests (RFT), blood gas analysis, 6′walking tests (WT), 24hrs monitoring of SpO_2, non invasive evaluation of PAP were performed. Des are defined as SpO_2 falls > 4%. **RESULTS** mean (SE): Age 69,1(1,6), FEV1%42,6(3,4), VC%87,6(3,9), PAPmmHg34,4(2,4), PaO_2mmHg71,9(1,68), $PaCO_2$mmHg 39,9(0,9), DLCO 47%(5), packs/year 54,6(7,4). A positive correlation has been found between PAP and duration of Des. When the patients were classified into 2 groups using PAP ≥ 35mmHg as cut-off (10 high PAP ≥ 35mmHg (H-PAP), 10 low PAP <35mmHg (L-PAP)) we found significant difference ($p < 0,05$) only for the duration of daily Des expressed as % of total daily time: in H-PAP 7,3(2,6) in L-PAP 1,1(0,52) and the presence of Des during WT. In H-PAP group 9/10 pts had WT Des compared to 3/10 in L PAP group ($p < 0,05$). RFT, resting BGA, severity of Des were not different. We conclude that the observation of oxygen status during daily activities should carefully be examined in COPD patients without severe resting hypoxemia together with the PAP evaluation.

88. THE EFFECT OF SILDEFANIL (VIAGRA) ON CEREBRAL HAEMODYNAMICS AT ALTITUDE.

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Sildefanil (Viagra), a vasodilating selective phosphodiesterase inhibitor, has been noted to improve pulmonary oedema at altitude. We investigated the cerebrovascular response to sildefanil with respect to blood flow and oxygenation at altitude. **Methods:** 6 male subjects (age 34–60 years) were studied 2 days after arrival at 3455m. Baseline measurements of right earlobe pulse oximetry, continuous non-invasive blood pressure monitoring, transcranial Doppler of the right middle cerebral artery and near infrared cerebral oxygen saturation were performed. 50 mg of sildefanil was then administered orally and repeat measurements made at 1 hours. Paired t test was used for statistical analysis with a p value < 0.05 considered as being statistically significant. **Results: Conclusion:** Although sildefanil appears to reduce cerebral blood velocity at 3455m, there is a small but significant increase in cerebral oxygenation on infrared spectroscopy. This is associated with a rise in pulse rate but without any appreciable change in either blood pressure or peripheral oxygen saturation. This may imply that the potential benefit of sildefanil at altitude may be due to its influence on the cerebral vascular bed in addition to its pulmonary effects.

	Pre-sildefanil	Post-sildefanil	p value
Resting pulse rate (bpm)	65.156	71.754	<0.0001*
Mean BP (mmHg)	110.93	110.076	0.6616
Earlobe oximetry (%)	92.342	92.089	0.2104
MCAV (cm/s)	59.203	54.993	0.0167*
Cerebral rSO_2 (%)	68.724	69.510	0.0013*

*significant

89. EPIDEMIOLOGICAL MODELS OF ACUTE MOUNTAIN SICKNESS (AMS).

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AMS commonly occurs at altitudes exceeding 2,500 m and usually resolves by acclimatization if further ascent is modest or avoided. We modeled AMS with data from a previous study of 302 trekkers recruited as they arrived at 3,840 m during hikes through altitudes of 1,500–6,200 m (Murdoch DR. ASEM 66:148, 1995). Based on self-reported symptoms, we estimated AMS Scores (Hackett scale) by linear regression and the probability of a positive AMS Diagnosis (Lake Louise criteria) by logistic regression. As rapid ascent is implicated with increased AMS risk, we estimated the maximum AMS probability (P[AMS]) that occurred in three recommended ascent regimens to 5,300 m: (a) 600 m/day beyond 2,500 m with a rest day every 600 m; (b) 300 m/day beyond 3,000 m until 4,200 m and 300 m every two days beyond 4,200 m; and (c) 150 m/day beyond 2,750 m with two days at 4,250 m followed by ascent at 150 m/day to 5,450 m with two rest days. Variables significantly associated with either Score or Diagnosis (but not always both) included gender, age, acetazolamide, altitude, exposure day, change in altitude on prior days, and Score on prior days. AMS probability decreased with age (Odds Ratio, OR = 1.18 per decade) and acetazolamide (OR = 3.55). Females were more susceptible than males (OR = 1.51). The maximum estimated P(AMS) associated with the recommended ascent regimens were 0.17, 0.14 and 0.06 at altitudes of 4,900, 4,200, and 4,250 m, respectively. Comparisons with data from the literature suggested that our estimates of AMS Score and probability underestimated the true values, probably because our subjects were partly acclimatized upon entering the study. Epidemiological models might be useful for testing hypotheses concerning AMS and for planning low risk ascents when calibrated with data from unacclimatized subjects.

90. HIGH ALTITUDE RESEARCH HAWAII.

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High altitude research is difficult due to isolated locations with extreme environmental conditions. We are in the early stages of developing a high altitude research laboratory at the Mauna Kea Summit (4205m). A primary concern in this initial effort was to establish broadband connectivity to the summit for the real-time transfer of physiologic and other data. The summit's location has several advantages. Hilo Airport is a major inter-island airport for commercial jet aircraft, and is a short flight away from Honolulu International Airport. Travel to the summit from the airport (and sea level) is a 90-minute drive over good roads, with snow being an infrequent factor. A hospital is 60 minutes away. Hale Pohaku (2800m) is 20 minutes from the summit, and serves as the main support area for lodging and logistics. It is ideally situated to acclimatize and support staff and subjects. The summit's main research building accommodates up to 25 people, with the lack of plumbing being the only negative. The building has been wired with 2 phone lines and broadband IP connected to the Univ Hawaii's network with a DS3 connection. We successfully accomplished transfer of multiple types of data outside of the Univ network to Honolulu and Stanford Univ. Data consisted of the following: live streaming physiologic data using NASA-Stanford developed systems (pulse oximetry, 2-lead EKG, heart rate, respiratory rate), live video teleconferencing, live audio from a digital stethoscope, and transmission of x-ray images. The Mauna Kea Summit is an ideal site for a high altitude research laboratory due to its unique location, good facilities, and broadband connectivity. With further development, we hope to open Mauna Kea as an international site for high altitude research.

91. ACUTE MOUNTAIN SICKNESS IN ADOLESCENTS.

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Aims Increasing numbers of adolescents travel to high altitude with school expeditions. This study aimed to determine the incidence of AMS in adolescents at altitude, and the practicalities of using the adult Lake Louise questionnaire in this age group. **Methods** Twelve teenagers aged 15–18 years (7 male) traveled for 21 days between 2,400m−5,200m. Daily questionnaires were completed. Group leaders (non-medical) were informed about any subject with a score > 3. Treatment/descent was then determined. **Results** All 12 subjects completed the questionnaires as requested (100%). 11 subjects suffered from AMS, 1 subject was evacuated to a lower altitude. The mean cumulative AMS score was 27.3 (range 0–53). Females appeared to have more minor symptoms over a longer time course, whereas males appeared to have more severe symptoms over a shorter time course. **Conclusions** The largest UK tour operator for this age group advocates that all travelers are given prophylactic acetazolamide above 3000m. The approach raises serious concerns: unnecessary drug use, drug side affects, subsequent restricted therapeutic options, and potential lack of awareness of AMS. This study demonstrates that a motivated group of adolescents are capable of self-monitoring for AMS. Combined with an appropriate ascent profile and support we feel this approach is safer and more appropriate.

92. DOES ACUTE MOUNTAIN SICKNESS INFLUENCE LACTATE METABOLISM AT HIGH ALTITUDE?

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The field of lactate metabolism at high altitude has perplexed physiologists, namely due to observations that post-exercise blood lactate is increased on arrival at altitude, but paradoxically decreases with acclimatization, despite maintained hypoxia and no change in oxygen delivery. Such high altitude studies have primarily involved the use of highly fit individuals as test subjects. It is possible that the results of these studies may reflect the level of training of the subjects. To investigate the role of subject selection on energy metabolism at high altitude, twelve male subjects were selected to display a broad range of fitness levels, from the power trained individual (VO_2max 39.4 ml/kg/min) to the elite endurance athlete (VO_2max 66.5 ml/kg/min). Throughout a three week acclimatization at the White Mountain Research Station (3,800m), a series of maximal and submaximal (70% relative VO_2max) exercise tests were performed and blood samples were collected to monitor plasma lactate concentration during exercise and recovery. All subjects completed the Lake Louise Acute Mountain Sickness (AMS) Questionnaire during the first five days at altitude. As a group, the subjects did not display any significant trends in lactate levels between testing periods (pre-acclimatization, acute hypoxia, acclimatized hypoxia, post-acclimatization). However, four subjects exhibiting symptoms of AMS and at the lower end of the fitness spectrum (poor responders, age 25 ± 3 years, body mass 78.4 ± 15.3 kg, VO_2max 48.2 ± 7.8 ml/min/kg) did display significantly lower lactate levels at submaximal workloads after 3 weeks of acclimatization compared to acute hypoxia. Also, peak post-exercise lactate concentrations were significantly different between the good responders (age 25 ± 3 years, body mass 75.2 ± 12.2 kg, VO_2max 58.1 ± 6.6 ml/min/kg) and poor responders during acute hypoxia testing. The results of this study suggest that AMS scoring and fitness level should be considered when analyzing metabolic data.

93. ALTITUDE RESIDENCE AND ARTERIAL OXYGEN SATURATION ARE INDEPENDENT RISK FACTORS FOR AMS AT THE KILIMANJARO.

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Little is known about the risk factors predisposing to the development of acute mountain sickness (AMS) in climbers going to the summit of the Kilimanjaro. Therefore, we investigated, using the Lake Louise score protocol, 204 climbers, 76 women and 117 men, (mean age 35 years) staying overnight at the Kibo hut (4700m). Climbers reached this altitude between day 3 and 4 of their trek. A multivariate logistic regression analysis was performed for the following possible AMS risk factors: age, sex, body mass index (BMI), AMS history, altitude of home residence, acclimatization days (sleep at an altitude $>$ 2500m) during previous 3 months, medication intake during expedition and arterial oxygen saturation (SaO_2). Our analysis revealed that an $SaO_2 < 81\%$ ($p = 0.007$) and a residence at an altitude of $<$ 700m ($p = 0.038$) were independent risk factors for the development of AMS. In females, but not in males, the use of a malaria prophylaxis was an independent predictor for less AMS ($p = 0.024$). The prevalence of AMS was 22% (15/67) vs. 45% (25/55) in climbers with a $SaO_2 < 81\%$ ($p = 0.007$), 15% (3/20) vs. 39% (66/171) in those living $\geq$ 700m and 21% (8/37) vs. 47% (19/40) ($p = 0.039$) in females taking malaria prophylaxis. Univariate analysis showed a trend for a decreased incidence of AMS in climbers taking acetazolamide ($p = 0.096$) and in females with a BMI between 22 and 26 kg/m2 ($p = 0.084$). We conclude that in mountaineers climbing the Kilimanjaro a low SaO_2 and a residence below 700m are independent risk factors for the development AMS, and that others, such as age, sex, BMI, AMS history and acclimatization are not associated with the condition.

94. PREVALENCE OF ACUTE MOUNTAIN SICKNESS AMONG TOURIST CLIMBING KILIMANJARO.

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Trekking expeditions to the Kilimanjaro are popular, however, prevalence of acute mountain sickness (AMS) is unknown. Therefore, using the Lake Louise AMS protocol at the altitude of 2700m, 3700m and 4700 m we assessed the prevalence of AMS before dinner and the following morning. A total of 269 climbers, 94 women and 174 men, (mean age 36 years, range 13–76 years) were interviewed during their ascent to the summit. According to the Lake Louise AMS definition (score $\geq$ 5 points) the prevalence of AMS before dinner was 12.3% at the altitude of 3700m and 18% at 4700m ($p < 0.01$). The mean Lake Louise score being 1.9 ± 1.9 at 3700m and 2.9 ± 2.5 at 4700m ($p < 0.05$). After overnight rest, a total score of $\geq$ 5 points in the self-assessment section (SAS) of the protocol was found in 3.6% of the climbers at 2700m, 4% at 3700m and 36.4% at 4700m ($p < 0.01$). During overnight rest the percent of climbers with a SAS score of $\geq$5 decreased by 3.1% at 3700m ($p < 0.05$) and increased by 18.8% at 4700m ($p < 0.01$). Sixty-six climbers reached the altitude of 4700 on day 3 and 135 on day 4. In these two groups, the morning SAS score was $\geq$5 in 35.4% and 37.7% of the climbers, respectively (p = ns). We conclude that, compared to similar altitudes in the Alps, the prevalence of AMS at the Kilimanjaro is slightly lower, this probably because of a slower rate of ascent. The prevalence of AMS symptoms was not different whether the summit was climbed on day 4 or 5. Overnight rest improved AMS symptoms at the altitude of 3700, but worsened it at the altitude of 4700m.

95. ACUTE ALTITUDE EXPOSURE ALTERS PUPIL BUT NOT OCULOMOTOR REFLEXES.

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Unlike visual function, the effects of hypoxia on oculomotor and pupil reflexes have not been well defined. In order to determine the effects of acute altitude exposure, initial pupil diameter (IPD), constriction amplitude (CA), constriction latency (CL), and saccadic velocity (SV) were measured in 26 (25 ± 8 yr, mean $\pm$ SD) and 9 women (29 ± 11 yr) before and after a 2.5-hr decompression to 459 mmHg (13,318 ft). After $<$1hr, IPD and CL were reduced (6.0 ± 1.0 to 5.7 ± 1.0 mm, $p = 0.003$ and 302 ± 28 to 296 ± 27 msec, $p < 0.001$, respectively). No gender differences were obtained. To determine the possible effect of hypobaria, 18 men (25 ± 5 yr) were driven to the summit of Pikes Peak (14,110 ft, 463 mmHg) over 1.5 h while breathing O_2. Measurements were made immediately, with and without O_2, after reaching the summit and 3 h later. Hypobaria had no effect on any of the measured variables, i.e., results obtained with O_2 at altitude were not different from those at sea level. Pikes Peak results were qualitatively similar to those obtained with simulated altitude, but temporally delayed: IPD (O_2, $<$1 h: 5.9 ± 0.8; no O_2, 3 h: 5.2 ± 1.0 mm, $p < 0.001$), and CL (O_2, $<$1 h: 302 ± 19; no O_2, 24 h: 286 ± 19 msec, $p < 0.001$). Reductions in CA were also obtained after 24 h (1.2 ± 0.4 vs. 1.0 ± 0.3 mm, $p = 0.02$). No SV changes were obtained in either environmental condition. Hypoxia-induced reductions in pupil reflexes are reproducible, objective, and time dependent and may be a harbinger of subsequent altitude-induced illnesses and an index of acclimatization.

96. INFLUENCE OF MODERATE ALTITUDE RESIDENCE ON ARTERIAL OXYGEN SATURATION AT HIGHER ALTITUDES.

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The purpose of this study was to compare the distribution of arterial oxygen saturation (SaO_2) and subjective symptoms to hypoxia in moderate altitude residents (MAR) and low altitude residents (LAR) following rapid ascent to 4,056 m (pressure altitude). Resting ventilatory parameters (open-circuit spirometry) and SaO_2 (pulse oximetry) were measured in 38 volunteers (25 men, 13 women) residing for $>$3 months near Colorado Springs, CO (MAR group). These measurements were made at 1,940 m (US Air Force Academy) and after $\sim$1hr at 4,056 m on the summit of Pikes Peak, CO following ascent by car. Resting SaO_2 was also measured at 610 m elevation intervals during the ascent. The LAR group of 39 volunteers (30 men, 9 women) were exposed to a similar ascent profile in a hypobaric chamber. Results ($\bar{X} \pm$ S.D.): At 1,940 m the MAR subjects' $PETCO_2$ and SaO_2 were 33.6 ± 2.8 mmHg and $94 \pm 1\%$, respectively, and decreased ($p < 0.001$) to 32.1 ± 4.5 mmHg and $86 \pm 2\%$ at 4,056 m. At 50 m the LAR group $PETCO_2$ and SaO_2 were 38.7 ± 2.7 mmHg and $98 \pm 1\%$, respectively, and decreased ($p < 0.001$) to 36.4 ± 3.5 mmHg and $82 \pm 5\%$ at 4,056 m. From 1,940 to 4,056 m, the MAR group SaO_2 was higher ($p < 0.001$) than the LAR group. None of the MAR subjects, but 9 of the LAR subjects reported symptoms of Acute Mountain Sickness. When referenced to published acclimatization data (Reeves et al, JAP 75:1117,1973 and Muza et al, JAP 91:1791,2001) our results suggest that prolonged residence at $\sim$2,000 m elevation induces a level of ventilatory acclimatization equivalent to residing at 4,056 m for approximately 9–12 days.

97. VALIDATION OF PULSE OXIMETRY DURING PROGRESSIVE NORMOBARIC HYPOXIA UTILIZING PORTABLE CHAMBER.

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Non-invasive estimation of arterial oxygen saturation (SpO_2) with pulse oximetry has been identified as a possible method to assess the pathology of acute mountain sickness (AMS) during sojourns to high altitude. In order to evaluate the performance of pulse oximetry and address the basic efficacy of normobaric hypoxic chambers (NHC), direct measurements of arterial oxygen saturation (SaO_2) by cooximetry (AVOXimeter 4000), were simultaneously compared with SpO_2 (Nellcor 295) using both reflectance (RS-10) and transmission (D-25) sensors (placed on the forehead and finger respectively), while the inspired oxygen fraction (FIO_2) inside a NHC (Hypoxico Inc.) was progressively reduced from .209 to .115 over a 2.5hr period. A catheter was placed in the radial artery of thirteen subjects (seven females and six males) which provided eighty-four data points over the hypoxic range. To monitor subject health status, the Lake Louise AMS self-assessment questionnaire was completed every half hour for evaluation of altitude illness like symptoms. Within subject factor MANOVA exhibited a significant time effect for SaO_2 during the progressive normobaric hypoxic exposure ($F(4,44) = 97.93$, $P < 0.0$) (Table). As well, a significant time effect was observed in AMS symptomatology ($F(3,33) = 13.51$, $P < 0.001$). No significant interaction was observed between these two factors. The major findings from this project suggests that pulse oximetry provides defendable accuracy for estimating SaO_2 during NHC exposures, although site specificity of the sensor may be a factor, especially as the severity of hypoxemia progresses. For example and in summary, this data set suggests that in response to progressive normobaric hypoxia, the performance of finger tip pulse oximetry deteriorates substantially at saturation levels below 85% when compared to the forehead position.

Method Comparison	R2	Slope	Intercept	Bias	Precision	95%CI
SaO_2 vs SpO_2(RS-10)	0.9199	1.0831x	-7.3280	0.016	2.47	-5.41 to 4.47
SaO_2 vs SpO_2(D-25)	0.8878	1.1021x	-8.5556	-0.470	3.03	-6.52 to 5.58
Sa02 vs SpO_2(RS-10) <85%	0.7281	1.0210x	-2.8018	1.378	2.72	-4.04 to 6.82
SaO_2 vs SpO_2(D-25) <85%	0.5646	1.1908x	-15.8980	1.127	4.34	-7.55 to 9.81

98. GINKGO BILOBA DECREASE ACUTE MOUNTAIN SICKNESS (AMS) AT 3700 M.

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Background: Ginkgo biloba (Gb) have two mechanisms that could be considered in the reduction of AMS: enhance cerebral circulation and have a powerful antioxidant action. Previous studies suggest that 5 days of prophylactic treatment with Gb (120 mg/12 h) decrease AMS at 4205 m, in contrast other study shown a decrease of AMS with treatment of Gb 24 h previously (60 mg/12 h). Objective: Determine effect of prophylactic treatment (Gb 80mg/12 hrs, 24 h before to ascend and treatment maintained) in subjects without experience to high altitude of 3700 m. Subjects: 32 participants residing at sea level were transported from sea level to 3700 m (Ollague). **Methods:** Three groups: a) ginkgo biloba (n = 8) received 80 mg/12 hrs; b) acetazolamide (n = 12) 250mg/12 h, and c) placebo (n = 12), 24 hrs before to ascend, start the treatment and was maintained during exposure to high altitude. The Lake Louise Questionnaire constituted the primary outcome measure at baseline, in the morning at 3700 m by 2 days; AMS was defined as a Lake Louise Self-Report Score (LLSR) >3. Oxygen saturation and arterial pressure were taken at same in each evaluation of AMS. **Results:** A significant reduction of AMS was observed in the group that received Gb (0%, $p < 0.05$) in comparison with acetazolamide (34.5%, $p < 0.05$) and placebo (54%). No differences were observed in oxygen saturation in Gb (91 ± 1) versus acetazolamide (89 ± 1) groups but a major oxygen saturations in comparison with the placebo (84 ± 1, $p < 0.05$). No differences were observed in the mean arterial pressure. **Conclusion:** This study further supports the use of Gb in prevention of AMS. This is the first study to corroborate that 24hr pre-treatment with Gb and with maintenance during exposure to high altitude is sufficient to reduce the incidence of AMS in subject without experience. Airliquide-Chile; VRA-UDP.

99. EFFECTS OF ACUTE MOUNTAIN SICKNESS SYMPTOMS ON ENERGY INTAKE: RESULTS FROM A TYPICAL HIMALAYAN TREK TO MAKALU BASE CAMP.

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High altitude induced body weight changes are in part due to a disequilibrium between energy intake and energy expenditure. Acute mountain sickness (AMS) symptoms seem to be partly responsible for the reduction of energy intake. The main goal of this research was to investigate the effects of AMS symptoms on energy intake (EI) and macronutrient distribution in healthy humans (aged 43 ± 11 yr and BMI 24.5 ± 4.1kg/m2) during a typical Himalayan trekking situation. The maximum altitude reached was 5200m. 24 h dietary recalls and AMS symptoms were recorded on all days of the trek. Subjects were eating ad libitum and took part in a 6-day climb below 2500m (low altitude 1:LA1), followed by 8 days above 2500m (high altitude:HA) and a 5-day descent below 2500m (low altitude 2: LA2). Results showed a decrease of mean caloric intake between LA1, and HA (3263 ± 821 vs 2732 ± 838 Kcal/d, respectively; $p < 0.05$) while energy intake during LA2 (3706 ± 801 Kcal/d) was significantly higher than energy intake during LA1 ($p < 0.05$) and HA ($p < 0.001$). No specific modifications in macronutrient distribution intake were observed. As expected, AMS symptoms were greater during HA than during LA1 and LA2 ($p < 0.05$). Despite a parallel increase of AMS with the decrease in energy intake observed when comparing LA1 to HA values, no significant association was observed between changes in AMS symptoms and changes in energy or macronutrient intakes. In conclusion, HA was associated with a decrease of energy intake, which did not seem to be macronutrient specific and with an increase in AMS symptoms, while the return to LA2 was accompanied by an overcompensation of energy intake and a reduction of AMS symptoms under the conditions described in this study.

100. NO EVIDENCE OF VASOGENIC BRAIN EDEMA IN SEVERE ACUTE MOUNTAIN SICKNESS.

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It was hypothesized that the symptoms of acute mountain sickness (AMS) were caused by cerebral vasogenic edema with AMS being therefore an early, benign stage of high altitude cerebral edema (HACE). Thus, we investigated the presence of vasogenic edema in severe acute mountain sickness with diffusion weighted magnetic resonance imaging and evaluated the changes of inner cerebrospinal fluid volumes (iCSF) as indicator of brain swelling. In a randomized, double-blind cross-over trial 10 subjects were exposed for 10 h to a simulated altitude of 4500 m for three occasions, either taking placebo, acetozolamide (250 mg bid) or theophylline (250 mg bid). T2 weighted images and diffusion weighted magnetic resonance imaging were obtained directly after altitude exposure under hypoxic conditions. Although nine of ten subjects had moderate to severe AMS (median Lake Louise Score 6.0), we found no indication of vasogenic edema, irrespective of the medication taken. In all subjects, we found a significant decrease in inner cerebrospinal fluid volumes (median reduction with placebo 10.3%, with acetazolamide 13.2%, with theophylline 12.2%, $p > 0.05$), indicating brain swelling. There was no correlation between AMS symptoms and fluid shift. However, we found a significant positive correlation of large iCSF and more severe AMS under placebo conditions ($r = 0.76$, $p = 0.01$). We conclude that vasogenic edema is not present in moderate to severe AMS.

101. WOBBLE BOARD (WB) ACUTE MOUNTAIN SICKNESS (AMS) AND CEREBRAL REGIONAL OXYGENATION (SPO_2).

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We have described previously (High Altitude Medicine & Biology 2; 104: 2001) a quantitative test of unsteadiness recording the number and duration of contacts per minute of a wobble board to a horizontal metal base plate. Results showed a relationship with AMS in older subjects but the test was not sufficiently sensitive in younger subjects. We have modified the board with a smaller diameter ball between the board and the recording plate and measured 23 healthy subjects ascending to 5260m. Results have been related to Lake Louise AMS scores, the Sharpened Romberg Test (SRT) of ataxia and to cerebral regional oxygenation (rSO_2) measured at the same altitude. WB improved over 17 d of the expedition from mean 14.8, 12.9secs at sea level, to 10.4, 8.7secs at 3610m, to 8.7, 7.3secs at 4750m and 6.4secs at 5260m. In the 19 subjects with full data at 5260m, WB scores did not correlate with the AMS scores ($r = 0.3$ ns) nor with the SRT (SRT normal AMS score 7.2 +/−3.7sd. SRT abnormal AMS 8.8 +/−7.6 ns) nor with rSO_2 ($r = -0.3$ ns). We conclude that this more sensitive WB is not a useful clinical measure of ataxia. In the small numbers studied WB results were not a useful measure of AMS and did not correlate with cerebral regional oxygenation. It is not a practical test for an ill subject and requires time to learn.

102. THE SHARPENED ROMBERG TEST AND ALTITUDE SICKNESS.

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Acute mountain sickness (AMS) is not usually accompanied by abnormal neurological findings and the development of truncal ataxia indicates progress of AMS to high altitude cerebral edema (HACE). Ataxia measured by the heel-toe walking test is one of the signs recommended in the Lake Louise AMS score. The Sharpened Romberg Test (SRT) of ataxia is widely used to assess divers with decompression sickness and is a quantitative measurement. In the test the subject stands on a flat surface, feet aligned in strict tandem heel-to-toe position, with arms crossed so that the hand falls on the opposite shoulder, the body is erect and the eyes shut. Subjects try to maintain this position for 60 seconds. If they fail the test is repeated for up to four attempts. Scoring is based on the cumulative time of the four trials up to a maximum 240 seconds. The relative usefulness of both tests of ataxia was evaluated in 20 healthy subjects ascending to 5260m. At 3610m SRT was normal (240secs) in 10 subjects (AMS score 1.9 +/−2.0sd) and abnormal (<240secs) in 10 subjects (AMS score 2.7 +/−2.2 NS). At 5260m SRT was normal in 12 subjects (AMS score 2.4 +/−2.0) and abnormal in 8 subjects (AMS score 4.1 +/−1.6 $p < 0.05$). Heel-toe testing at the same times showed only four abnormal results at 3610m and one at 5260m. We conclude that the SRT is simple to perform and can be quantified. The test is more sensitive than the heel-toe test and relates to AMS scores at high altitude.

103. EFFICACY OF LOW DOSE ACETAZOLAMIDE (125 MG BID) FOR THE PROPHYLAXIS OF ACUTE MOUNTAIN SICKNESS.

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Objective: To determine the efficacy of low dose acetazolamide (125 mg twice daily) for the prevention of acute mountain sickness (AMS). **Methods:** A prospective, double blind, randomized, placebo-controlled trial was carried out in the Mt. Everest region of Nepal between Pheriche (4243m), the study enrollment site and Lobuje (4937m), the study endpoint. The participants were 197 healthy male and female trekkers of diverse background and they were evaluated with the Lake Louise Acute Mountain Sickness Scoring System and pulse oximetry. The main outcome measures were incidence and severity of AMS as judged by the Lake Louise Questionnaire score at Lobuje. **Results:** There were 197 participants enrolled, and 155 returned their data sheets at Lobuje. In the treatment group there was a statistically significant reduction in incidence of AMS (placebo group, 24.7%, 20 out of 81 subjects and acetazolamide group, 12.2%, 9 out of 74 subjects). Prophylaxis with acetazolamide conferred a 50.6% relative risk reduction, and the number needed to treat in order to prevent one instance of AMS was 8. Of those with AMS 30% in the placebo group (6 of 20) vs. 0% in the acetazolamide group (0 of 9) experienced a more severe degree of AMS as defined by a Lake Louise Questionnaire score of 5 or greater ($p = 0.14$). Secondary outcome measures associated with statistically significant findings favouring the treatment group included decrease in headache and a greater increase in final oxygen saturation at Lobuje. **Conclusion:** Acetazolamide 125 mg twice daily was effective in decreasing the incidence of AMS in this Himalayan trekking population.

104. FREE RADICAL-MEDIATED VASCULAR DAMAGE IS NOT A CAUSE OR CONSEQUENCE OF ACUTE MOUNTAIN SICKNESS.

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Introduction: The present study examined whether free radical-mediated vascular damage would influence individual susceptibility to acute mountain sickness (AMS). **Methods:** Twenty four subjects were examined at sea-level (SL), within 2–3h after an active ascent from 3,200m to 4,559m (HA1) and in the mornings after the first (HA2) and second night (HA3) at 4,559m. Lake Louise (LL) AMS score was determined at all time points and venous samples were assayed to examine temporal changes in selected biomarkers of free radical-mediated lipid peroxidation (F2-isoprostanes), skeletal [total creatine phosphokinase (CPK)] and cerebral [neuron-specific enolase (NSE)] vascular damage and various proinflammatory cytokines (IL-1β, IL-6, TNF-α and TNF-α rP-60). **Results:** AMS score increased markedly at HA (0.1 ± 0.3 points at SL, $P < 0.05$ vs. 4.6 ± 3.0 at HA1, 5.6 ± 3.3 at HA2 and 3.5 ± 2.8 at HA3). Fourteen subjects were diagnosed with clinical AMS (LL score > 5 points) and of these, 4 developed HAPE. While a general increase in CPK and TNF-α rP-60 was observed at HA (vs. SL, $P < 0.05$), retrospective analyzes demonstrated no selective differences in these or any other metabolites between those with AMS compared to those who remained apparently healthy. Pooled data demonstrated an association between the magnitude of increase in NSE at HA1-3 and AMS score ($r = 0.25$, $P < 0.05$). **Conclusions:** The present findings demonstrate selective damage to skeletal muscle at HA that was independent of free radical-mediated peroxidative or inflammatory phenomena. Furthermore, increased free radical-mediated vascular damage does not appear to be a cause or consequence of AMS. While not establishing cause and effect, the association between AMS and NSE, an established marker of molecular damage to the blood-brain barrier, warrants further investigation.

105. DIRECT EVIDENCE FOR LIGHTNING-INDUCED FREE RADICAL GENERATION AND SKELETAL MUSCLE DAMAGE.

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Introduction: The present case-study examined changes in peripheral markers of free radical metabolism and skeletal/myocardial muscle damage 30h after a mountaineer had survived a direct lightning strike at 4,200m. Pre-expedition sea-level (normoxic control) data were available for comparative purposes. Control measurements were also obtained after simulated exposure to the combined stresses of inspiratory hypoxia and physical exercise in an environmental chamber. This provided an unique opportunity to examine metabolic sequelae caused directly by the lightning strike. **Methods:** Venous blood was assayed for molecular markers of skeletal [myoglobin and total creatine phosphokinase (CPK)] and myocardial [cardiac troponin I (cTnI)] muscle damage. Ex-vivo spin-trapping with (-phenyl-tert-butylnitrone (PBN) combined with electron paramagnetic resonance (EPR) spectroscopy was incorporated for the direct detection of free radicals. The simulation study involved passive and active exposure to graded normobaric hypoxia (FIO_2 of 0.21 at sea-level to 0.13 at the summit) incorporating treadmill ascent and descent rates of 2.5m/min (applying a +50° gradient) and 3.8m/min (−50°) respectively. **Results:** Compared to normoxic control data, the EPR signal intensity of the venous PBN adduct, myoglobin and CPK in the "lightning blood" was markedly greater than the increases observed following the simulation study. In contrast, no changes were observed in the peripheral concentration of cTnI. A marked decrease in the PBN adduct, myoglobin and CPK was observed within 2h following oral administration of water and lipid soluble antioxidant vitamins. **Conclusions:** These findings are the first to document lightning-induced free radical generation and selective damage to skeletal muscle in a high-altitude mountaineer. Furthermore, free radicals may contribute to the pathogenesis of lightning injury and dietary supplementation with antioxidant vitamins may attenuate associated vascular damage.

107. INTERLEUKIN-6 RESPONSE IN ACUTE AND CHRONIC HYPOXIA: ROLE OF EXERCISE INTENSITY.

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Recently is has been shown that plasma IL-6 concentration is increased during exercise in hypoxia (1), and that the increase was caused by augmented norepinephrine levels. However, since the response of IL-6 to exercise is intensity dependent, we hypothesized that if the workload is adjusted to match the same relative exercise intensity as at sea level, no changes in the IL-6 response would occur. To test this, 8 Danish sea level residents were studied during a 60 minute cycle ergometer exercise at sea level (SL), in acute (AH) and chronic hypoxia (CH), at the same absolute (abs) and same relative (rel) exercise intensity. In AHabs and CHabs the IL-6 derived response to exercise increased as found by others. However, in AHrel and CHrel no changes in IL-6 response were found compared to sea level exercise. The changes found in IL-6 during AHabs and CHabs did not match changes in circulating catecholamine levels. We conclude that the plasma IL-6 concentration is exercise intensity dependent, and that factors other than catecholamines levels are important for its regulation. Mazzeo RS, Donovan D, Fleshner M, Butterfield GE, Zamudio S, Wolfel EE, Moore LG. Interleukin-6 response to exercise and high-altitude exposure: influence of a-adrenergic blockade. J Appl Physiol 91: 2143–2149, 2001.

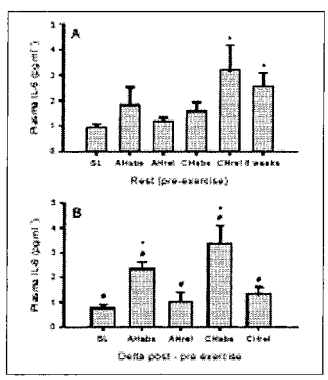

Figure 1. A: plasma IL-6 at rest at sea level, acute and chronic hypoxia. B: delta plasma IL-6 in response to 60 min of exercise at sea level, acute and chronic hypoxia. Values are mean ± SE; n = 8 in each trial. Significant differences: *P < 0.05 compared with the other trials, #P < 0.05 compared with rest.

106. COMPARISON OF GINKGO BILOBA, ACETAZOLAMIDE, AND PLACEBO FOR PREVENTION OF ACUTE MOUNTAIN SICKNESS.

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Objective: To determine the effectiveness of Ginkgo biloba and low-dose acetazolamide versus placebo as a prophylaxis for acute mountain sickness (AMS). **Methods:** Fiftynine subjects volunteered for this double-blinded, randomized placebo-controlled study. All subjects resided at an elevation of 1370m to 1645m and had not been at higher altitudes for 2 weeks before the study. Subjects received ginkgo biloba 120mg, acetazolamide 125mg or placebo twice a day for 3 days prior to ascent and during altitude exposure. Subjects all ascended to 4300m over 2 hours by car in mid afternoon and stayed overnight. The Environmental Symptoms Questionnaire (ESQ-III short form) was completed before ascent and either after 24 hours at altitude or when removed from the study as a result of AMS. An ESQ-III ≥ 0.7 and a Lake Louise Score of >2, with a headache present, was required for diagnosis of AMS. **Results:** acetazolamide reduced the incidence of AMS compared to placebo (3 of 22 vs 10 of 22 with AMS respectively). Acetazolamide also reduced the severity of AMS (mean ESQ-III = 0.79 ± 0.68 vs. 0.34 ± 0.45, $p = 0.007$, placebo vs. acetazolamide. Ginkgo tended to reduce both incidence and severity of AMS, but the difference was not statistically significant (mean ESQ-III = .79 ± .71 vs. .56 ± .59, p = 0.07, placebo vs. ginkgo. **Conclusion:** Low-dose acetazolamide and ginkgo biloba taken 3 days prior to rapid ascent to 4300m reduced both incidence and severity of AMS. Ginkgo in this study, in contrast to our previous study at this altitude, did not reduce AMS. This might be because ginkgo was started 5 days before ascent in the previous study, but this and other possibilities require further study.

108. BODY TEMPERATURE AUTONOMIC RESPONSES AND ACUTE MOUNTAIN SICKNESS.

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A few studies have reported increased body temperature (T_O) associated with acute mountain sickness (AMS), but these usually include exercise, varying environmental conditions over days and pulmonary edema. We wished to determine whether T_O would increase with AMS during early exposure to simulated altitude at rest and whether it might be related to autonomic tone. The 94 exposures of 51 men and women to reduced P_B (423 mm Hg = 16,000 ft = 4,850 m) were carried out for 8–12 hr, with duration dependent on AMS symptoms. AMS was evaluated by LL and AMS-C scores at end of exposure and T_O was measured by oral digital thermometer before altitude and after 1 (A1), 6 (A6) and 11 (A12) hr at simulated altitude. Other measurements included ventilation, O_2 consumption and autonomic indicators of plasma catecholamines, HR and HR variability. The average T_O increased by 0.5°F from A1 to A12 in all subjects ($p < 0.001$). Comparison of results between 16 subjects with lowest AMS scores (mean LL = 1.0, range = 0-2.5; mean AMS-C = 0.2, range = 0-0.9) and 16 other subjects with highest AMS scores (mean LL = 7.4, range = 5–11; mean AMS-C = 2.7, range = 1.5–3.7) demonstrated a transient decline in TO from A1 to A6 in AMS, in contrast to a rise in non-AMS (p = 0.001). Catecholamines, HR and HR variability (increased low F/high F ratio) indicated significant elevation of sympathetic activity in AMS, associated with the fall in T_O, but no change in metabolic rate. The apparently greater heat loss during early AMS suggests increased hypoxic vasodilation in spite of enhanced sympathetic drive. Greater hypoxic vasodilation and elevated HR in AMS in the absence of metabolic rate and ventilation changes suggest that augmentation of β-adrenergic tone may be involved in early AMS pathophysiology. Supported in part by U.S. Army Med Res Materiel Cmd, DAMD17-96-C-6127.

109. ANALYSIS OF HYPOXIA-INDUCIBLE FACTOR 1α (HIF1α) GENE IN ANDEAN HIGH-ALTITUDE NATIVES WITH AND WITHOUT CHRONIC MOUNTAIN SICKNESS.

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Chronic Mountain Sickness (CMS) is a maladaptation to chronic hypoxia at high altitude, common in Andean natives, and rare in Himalayan natives who live at comparable heights. The condition is characterized by hypoxemia and excessive erythrocytosis. A possible pathogenetic hypothesis is a genetic unfitness of Andean natives to their environment. A key role in cellular and systemic homeostatic responses to hypoxia is carried out by the heterodimeric protein HIF1, composed of α and β subunits. HIF1 is a transcription factor formed in hypoxia; it controls the expression of many genes in response to changes in oxygen tension. HIF1A gene (14q21-q24) consists of 15 exons, and encodes the HIF-1α subunit. Gene expression is highly regulated by cellular O_2 concentration, and determines the levels of HIF-1 activity. Our study aimed at evaluating a possible genetic correlation between allelic variants in HIF1α and CMS. The HIF1α was analyzed in 20 non-related Andean natives (10 with hematocrit (Hct) >65% and 10 with a Hct <55%), all living permanently at an altitude of 4300 m. Protein coding sequences from exon 1 to 15 were amplified from genomic DNA using primers derived from intron sequence, and designed in our laboratory. Genomic fragments amplified by PCR were automatically sequenced with ABI3100 Genetic Analyzer (Applied-Biosystems) to identify polymorphisms and/or mutations. We identified a heterozygous missense mutation (P582S, exon12) in one of the 10 subjects with Hct >65%; none carried the exon 6 G640A polymorphism (found in Caucasoid population; allele frequency estimation: in progress), and all carried the potentially unstable dinucleotide microsatellite sequence (GT)n in intron 14. These preliminary results suggest that HIF1A genes and related changes could contribute to elucidate either genetic/environment fitness or human diseases in subjects with different responses to hypoxia.

110. DOPAMINE (DA) D2- AND D1-RECEPTOR (R) MRNA LEVEL MODULATION BY HYPOXIA IN THE ARTERIAL CHEMOREFLEX PATHWAY ORGANS OF 1 DAY OLD AND ADULT RABBITS.

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Dopamine (DA) D2- and D1-receptor (R) mRNA level modulation by hypoxia in the arterial chemoreflex pathway organs of 1 day old and adult rabbits. The aim of this study was to determine the effect of age on the pattern of hypoxia-induced changes of both DA D2- and D1-R mRNA levels in the carotid body (CB), petrosal ganglion (PG) and superior cervical ganglion of 1 day old and adult rabbits exposed to either normoxia (21% O2) or hypoxia (8% O_2) for 24 h. 0.1μg of total RNA was used to amplify either D2- or D1-R mRNA (RT-PCR) with specific primers. Amplified products were prepared, hybridized with specific 32P-labelled (144 pb, D2) or (399 pb, D1) probes and signal intensities were evaluated by densitometry. The striatum, rich in DA D2- and D1-R, was used as a positive control tissue. The transcript level in hypoxia was calculated relative to normoxia, arbitrarily designated 100%. Samples without RT did not yield any amplification signals. * $p < 0.001$ vs normoxia. **Conclusion:** Hypoxia induced changes of DA D2- and D1-R mRNA levels are tissue specific and the pattern of these changes is age-dependent. Supported by APQ.

	D2-R transcript level (% of normoxia ± sem)			
	CB	PG	SCG	Striatum
1 day	- 23.1 ± 2.9*	- 21.9 ± 2.4*	- 29.1 ± 1.3*	- 0.5 ± 2.8
Adult	- 44.9 ± 8.4*	- 17.7 ± 3.8*	+ 6.1 ± 4.5	- 1.2 ± 1.8
	D1-R transcript level (% of normoxia ± sem)			
1 day	- 39.6 ± 1.8*	- 68.5 ± 2.6*	- 30.6 ± 2.8*	+ 3.7± 3.7
Adult	- 64.9 ± 4.5*	+49.7 ± 10.9*	+68.2 ± 8.7*	- 8.6 ± 3.4

111. WHITE MOUNTAIN RESEARCH STUDY -2001. LONG-TERM HYPOXIC-HYPOBARIC EXPOSURE (~3800 M) AS A TERRESTRIAL ANALOG FOR FUTURE PLANETARY MISSIONS: HAEMATOLOGICAL ADAPTATIONS AND CHANGES IN CAPILLARY DENSITY.

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Introduction. It can be assumed that in future during long-term space flights the environmental conditions in the spacecrafts and habitats at the landing side will be hypobaric-hypoxic ones due to financial and logistic reasons. In the course of the White Mountain Research Study 2001 we investigated the human long-term adaptation to an altitude of approximately 3,800 m (Barcroft Facility, California, USA). It was the aim to study the changes regarding body composition, circulation, blood physiology, muscle metabolism, capillary density and psycho-physiology. We present here preliminary data regarding haematological adaptations and changes of capillary density in muscle fibers (m. vastus lateralis) due to long-term high altitude exposure. **Methods.** 11 male subjects (age 26.6 ± 2.1 years, body height 1.79 ± 0.05 m, body mass 74.4 ± 10.7 kg, BMI 23.5 ± 3.5) were studied. Five blood samples (before, during, and after) and 2 muscle biopsies were taken (before and after) the in total five week lasting study. Immunocytochemical/histological markers: NOS-(1,2,3), matrix metalloproteinases (MMP-7 and -9), confocal laser scanning microscopy. Statistiscal analysis: MANOVA; SPSS 10.0 for WINDOWS. **Results.** Packed cell volume [PCV], hemoglobin concentrations , transferrin-receptors [Tfr-R], and erythropoietin [EPO] concentrations increased during the exposure ($p < 0.01$). Ferritin [FER] decreased ($p < 0.01$), circulating vascular endothelial growth factor [VEGF] concentrations remained unchanged, capillary density increased by 24% ($p < 0.01$) and the diaphorase activity/NOS 1-3 increased significantly as well ($p < 0.05$). **Conclusions.** The data show that a permanent exposure to high altitude (3,800 m) causes a transient increase in [EPO] and concomitantly [FER] decrease. [PCV], [HB], and [Tfr-R] increase indicate a sustained stimulation of erythropoiesis combined with a stimulated angiogenesis as shown by the increase in capillary density combined with an upregulated diaphorase activity/NOS 1-3. It is concluded that a hypobaric-hypoxic environment inside the space craft or habitats could be used to trigger erythropoiesis and angiogenesis. Sponsored by DLR, Germany (DLR-Project # 50-WB 0022)

112. WHITE MOUNTAIN RESEARCH STUDY-2001. THE HIGH- AND LOW-PRESSURE PART OF THE CIRCULATION DURING 3 WEEKS HIGH ALTITUDE EXPOSURE (3800 M).

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At high altitude an activation of the sympathetic nervous system occurs leading to an increase of the arterial blood pressure, heart rate and venoconstriction. How the latter affects central venous pressure (CVP) and peripheral venous pressures (PVP) on the long run is hard to predict because intravascular volume is threatened by a negative water balance in general and by venous constriction which could lead to outward filtration. Long-term observations of venous pressures at high altitude were not yet done. **Methods** 11 male subjects (age 26.6 ± 2.1 years, body height 1.79 ± 0.05 m, body mass 74.4 ± 10.7 kg, BMI 23.5 ± 3.5) were studied regarding acute mountain sickness (AMS, Lake Louise Consensus), arterial blood pressure (ABP), heart rate (HR), central and peripheral venous 12–16 hours and 20 days after arrival at high altitude. ABP and HR were measured with a wrist manometer during each session 5 times within 5 minutes. CVP was measured applying the arm-down method (Cir. Res. 4: 74–78, 1956), PVP was measured in the antecubital vein the subjects resting in supine position for at least 20 minutes. Statistical analysis: MANOVA; SPSS 10.0 for WINDOWS. **Results** Self ratings of the subjects applying the AMS scores revealed that 4 out of the 11 subjects suffered from AMS. Their results must be seen separately from those of the other 7 subjects. Cluster analysis of the ABP and the venous pressure values confirmed the separation into two groups of subjects. At the average the systolic blood pressures of the AMS-subjects were higher by 6–10 mm Hg at sea-level as well as at high altitude ($p < 0.03$) as compared to the subjects showing no symptoms of AMS. The same held for the diastolic values. In the AMS subjects HR were significantly lower ($p < 0.04$). At high altitude CVP and PVP values tended to increase in the AMS ridden subjects whereas in the normal subjects CVP and PVP decreased during their stay at high altitude. These patterns differed statistically ($p < 0.04$). **Conclusions** At high altitude subjects suffering from AMS show higher ABP and increasing CVP and PVP values and lower heart rates. Their data should be treated separately from those subjects showing no symptoms of AMS. Sponsored by Deutsches Zentrum für Luft- und Raumfahrt, Germany (DLR-Project # 50-WB 0022).

113. EFFECT OF BETA ADRENERGIC AND PARASYMPATHETIC BLOCK ON HEART RATE AND CARDIAC OUTPUT DURING EXERCISE IN NORMOXIA AND ACUTE HYPOXIA.

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Acute hypoxia increases heart rate (HR) and cardiac output (QT) at a given oxygen consumption (VO_2) during submaximal exercise. The mechanism is widely believed to be increased sympathetic activation and circulating catecholamines acting on cardiac beta (β)-receptors. Recent evidence indicating a continued role for parasympathetic modulation of HR during moderate exercise, suggests a possible role for increased parasympathetic withdrawal in the increase in HR and QT during hypoxic exercise. To test this, we separately blocked the β sympathetic and parasympathetic arms of the autonomic nervous system (ANS) in 7 healthy subjects (6 M, 1 F; age = 31.7 ± 3.9 years, normoxic VO_2max = 3.1 ± 0.7 l/min, means ± SD)—during exercise in normoxia and acute hypoxia (FIO_2 = 0.125) to VO_2. Data were collected under 1) control conditions (CON), 2) after 8.0 mg propanolol IV and 3) after 0.8 mg glycopyrrolate IV, each on a different day. Cardiac output was measured using open circuit acetylene uptake. Hypoxia increased venous [epinephrine] and [norepinephrine] but not [dopamine] at a given VO_2 ($P < 0.05$, $P < 0.01$ and $P = 0.2$ respectively). HR/VO_2 and QT/VO_2 were increased by hypoxia ($P < 0.05$) in all 3 conditions. The effects of hypoxia on HR and QT were not significantly different from control with either form of ANS block. These data suggest that although acute exposure to hypoxia increases circulating catecholamine concentrations, the effects of hypoxia on HR and QT do not necessarily require intact muscarinic and β receptors in the heart. Possibly, cardiac receptors may play a primary role in elevating HR and QT during hypoxic exercise, or offer an alternate mechanism when other ANS pathways are blocked. Support NIH HL17731, MD1 RR00827.

114. VAGAL NERVE BLOCKADE DECREASES SPO_2 IN MAN.

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INTRODUCTION: Vagal nerve outflow is linked to respiration. The increase in vagal outflow in synchrony with expiration accentuates sinus arrhythmia which has been hypothesized to improve the matching of pulmonary blood flow to lung volume during each respiratory cycle. To test this hypothesis we measured oxygen saturation of arterial blood (SpO_2) in hypoxic condition in humans before and after blocking vagal nerve activity with atropine. **METHODS:** 6 volunteers breathed hypoxic gas (11–12% O_2 balanced N2) at a constant tidal volume and respiratory frequency (10/min) in synchrony with a metronome signal. The ECG was monitored for the measurement of R-R intervals. SpO_2 was measured before and after atropine administration (0.02 mg/kg). Vagal nerve blockade was verified by decrease in amplitude of R-R interval variability at respiratory frequency. **RESULTS:** Atropine increased heart rate and decreased SpO_2 ($P < 0.05$, paired t-test). **DISCUSSION/CONCLUSION:** The decrease in SpO_2 after vagal blockade is consistent with the hypothesis that sinus arrhythmia contributes to minimizing the respiratory phase-linked admixture of mixed venous blood with better oxygenated arterial blood in man under hypoxic conditions.

115. EFFECTS OF INTERMITTENT HYPOXIC TRAINING ON ACCLIMATIZATION IN ELITE CROSS-COUNTRY SKIERS.

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The purpose of this study was to evaluate the consequences of intermittent exposure to high altitude ("live high—train low") on clinical status and physiological markers of acclimatization during a training session of elite cross-country skiers. **METHODS:** eleven athletes (6 men, 5 women) performed a 18-day training period at 1100m, by sleeping either at 1100m (group C, n = 5) or in hypoxic rooms (group H, n = 6) at simulated altitudes of 2500m, 3000m and 3500m (3 × 6 days). Lake Louise AMS score and arterial oxygen saturation (SaO_2) during sleep were measured daily. Cardiac function (echocardiography) and ventilatory response to hypoxic exercise (HVRe, 30% normoxic VO_2max) were evaluated at 1100m before and 15 days after the training session. **RESULTS:** Subjects did not complain of headache, gastrointestinal or dizziness symptoms. Fatigue and sleep disturbances were frequently mentioned but there was no significant difference between the two groups. In group H, interventricular septum thickness increased from 10.3 ± 0.8 to 11.2 ± 1.3 ($P < 0.05$), 4 out of 6 subjects showed a 5 to 10 mmHg increase in pulmonary arterial pressure. One subject showed a 6 mm increase in right ventricular end diastolic diameter. Mean nocturnal SaO_2 at high altitude was 93.6, 91.7 and 89.8% at 2500, 3000 and 3500m, respectively. Three subjects showed a marked desaturation during the first two days after switching to a higher altitude (mean SaO_2 86% at 3500m). No significant change was observed in HVRe or hypoxic exercise-induced desaturation 14 days after the training session. None of these parameters were correlated with the observed changes in performance (VO_2max). **CONCLUSION:** sleeping during 18 days in hypoxic chambers (up to 3500m), while training at 1100m did not induce any significant clinical disorder; however cardiac morphological changes may occur as a result of prolonged increase in pulmonary pressure. Nocturnal saturation should be monitored to detect marked desaturation. Signs of ventilatory acclimatization had disappeared 15 days after the hypoxic exposure. This study was supported by grants from the International Olympic Committee and the French Ministry of Sports.

116. THE PHYSIOLOGICAL AND PSYCHOLOGICAL IMPACT OF INTERMITTENT HYPOXIC TRAINING (IHT) IN THE PREPARATION OF THE GB BIATHLON TEAM FOR THE 2002 OLYMPIC GAMES.

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Background: The purpose of the present study was to examine the effects of IHT on physiological and psychological measures prior to ascending to altitude. **Methods:** The biathletes (n = 8) participated in 2 altitude training camps separated by 6 weeks. Prior to each camp the biathletes completed 7 days of training in either normobaric hypoxia or normobaric normoxia (75mins at an intensity equal to lactate threshold, LT). Prior to and following the sea level training the biathletes performed a physiological profile test (bike, LT to max). At altitude athletes performed a sub-maximal exercise test (bike, first 4 stages of LT test) for the first 5 days. Daily morning monitoring included analysis of red blood cell mass (RBC), hemoglobin (Hb), hematocrit (Hct), and reticulocyte count (Rct), together with a 21-item mood questionnaire to asses anger, depression, fatigue, tension, vigor, happiness and calmness. Results were examined on a case study basis as responses to altitude varied between individuals. **Results:** Daily physiological monitoring suggested that athletes arrived at altitude partially acclimatized following IHT, evidenced by a reduction in HRrest, BPrest, sub-maximal exercise blood lactates, and increases in Hb and Rct. The lactate paradox commonly observed at altitude was absent or reduced following IHT. Psychological assessment revealed significant improvements in mood following pre-acclimation using IHT. This evidence was reinforced by anecdotal evidence from the biathletes. **Conclusions:** Normobaric hypoxic training for 75 min.day-1, for 7 days appears to be a suitable method of pre-acclimation to moderate altitude in elite biathletes. The applied nature of the present study resulted in poor control of a number of potentially confounding variables. It is suggested that there is a need for future well-controlled studies that investigate pre-acclimation using IHT.

117. INTERVAL HYPOXIC TRAINING: TISSUE SPECIFICITY AND EFFECTIVENESS.

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It is necessary to study tissue specific effects of interval hypoxic training, to determine the most hypoxia sensitive organs, and to develop techniques preventing possible side effects. In our experiments we usually study the ratio of pro- and antioxidant factors in organs and tissues which is the prognostic criterion of changing their resistance to different environmental factors. It was observed that the exposure to hypobaric hypoxia (5000 m, 6 hours daily for 30 days) results in a different reaction of the heart and liver of rats to such hypoxic training. In the heart, periodic activation of free radical oxidation is compensated by activation of antioxidant protective enzymes, the level of oxygen active forms not exceeding control, while in the liver, the sensitivity of tissue to oxidation induction increases in spite of such an activation of antioxidant system. The resistance of membrane structures after hypoxic training has changed as well. In the heart, the resistance of ion-transporting membrane systems to free-radical oxidation increases by 35–50%. At the same time, in the liver, the same exposure results in the 2-fold inhibition of plasmatic membrane Na,K-ATPase which is similar to the acute stress exposure. Thus, cardiomyocytes respond with compensatory effect to interval hypobaric training while hepatocytes are damaged. With lower intensity of hypobaric hypoxia (4000 m) the damage of membrane enzyme systems of the liver decreased and disappeared completely at normobaric hypoxic training (21 daily sessions, one session included 12 hypoxic (10% O_2) periods, 5 min each with 3 min reoxygenation). Our experiments revealed that such hypoxic training increased membrane structures resistance of the heart, liver and brain to the free-radical oxidation induction, to protease attack and other damaging factors. It means that normobaric hypoxic training is a mild adaptation exposure with "low cost" of adaptation and minimal risk of side effects.

118. HYPOBARIC HYPOXIA AS TRAINING OF SIBERIAN EXPEDITION EVEREST-2001 PARTICIPANTS.

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Research of effective methods to increase sportsmen's ability and improve their achievements is an important task in sport physiology. One of the more interesting methods is the adaptation to periodic hypobaric hypoxia. Our purpose was to devise a method of acceleration of high-altitude adaptation for participants of the Siberian expedition "Everest-2001" using hypobaric hypoxia training. Eight sportsmen (7 men and 1 woman) ages 30–52 old took part in experiment. The training process included 16 periods of hypobaric hypoxia over 50 days. The first "altitude" was 3500 m and the last was 6400 m, rate of "ascent" was 10 m/s, and exposure time was 80 min. At "altitude" the sportsmen were tested with a veloergometer for 10 min. Each sportsman chose their own exercise load with none exceeding 300 Wt. Another important part of the training process was a special bioactive anti-oxidant food complex "ABISIB" (taken 3 times per day before eating). The following data were collected before and after the training course: antropometric measurements, ECG registration, analyses of blood and urine, PWC_{170} psychological tests by Lusher, Spilberger, Mini-mult etc. At the end of the training course the sportsmen did exercises with a veloergometer at an "altitude" of 6400 m for 10 min without great effort, average PWC_{170} having increased 16% ($p < 0.05$). Two weeks later 6 sportsmen took part in "Everest-2001". They endured fast high-altitude adaptation (5200 m at once) successfully, 4 of them (3 men and 1 woman) reached the highest altitude, another sportsman became an active rescuer at 8300 m, and another was required to provide medical attention at 6400 m. Data obtained and interviews with each sportsman have demonstrated the efficiency of a training method using periodic hypobaric hypoxia and antioxidant food complex "ABISIB".

119. NOREPINEPHRINE MEDIATES RELEASE OF CORTICOTROPIN-RELEASING FACTOR IN HYPOTHALAMUS OF RATS DURING HYPOXIA.

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Norepinephrine (NE)-modulated CRF release in the hypothalamic paraventricular nucleus (PVN) of rats was studied in a simulated hypobaric chamber. NE, CRF and AVP were measured by HPLC and RIA. The results show that hypoxia equivalent to 5km for 24h and 7km for 30 min induced an increase of NE in the PVN by 117.20% and 24.33% respectively. NE in the central amygdala (ACE) was markedly increased at the same levels of hypoxia as well. A significant decrease of CRF in the median eminence (ME) of the hypothalamus was noted along with increases of NE in the PVN during hypoxia. Consequently, cAMP in the anterior pituitary and plasma corticosterone were increased significantly. Hypoxia induced not only reduction of CRF in the ME, but also in the PVN. However, CRF was not reduced in the ACE. In contrast with CRF, AVP in the ME exhibited a reverse alternation at 5km, but not at 7km hypoxia for 30 min. Hypoxia induced CRF release was reversed by treatment with prazosine, alpha-1-adreno-receptor antagonist, while further enhanced by yohimbine alpha-2-adreno-receptor antagonist. In conclusion, acute hypoxia stimulates, in an intensity and time-course dependent manner, NE release in both PVN and ACE, and consequently activates CRF release from the PVN and ME of the hypothalamus as well as corticosterone secretion. This affect is mediated by adrenergic alpha-1 and alpha-2 receptors.

120. CRF, NE, GLU, AND GC MODULATE GROWTH HORMONE AND PROLACTIN RELEASE IN RATS DURING HYPOXIA.

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Growth hormone (GH) and prolactin (PRL) release modulated by central corticotropin-releasing factor (CRF), norepinephrine (NE), glutamate (Glu) and glucocorticoids (GC) were studied in rats during simulated altitude hypoxia in a hypobaric chamber. Hypoxia (5 km for 1–7 d) suppressed body weight gains and reduced food intake (vs. control), effects which were prevented by a replacement of porcine GH (sc). After 5h simulated exposure to 5 km, the plasma GH was significantly decreased but pituitary GH increased markedly. The GH level in the pituitary was reduced during the hypoxia condition when rats were pre-treated with icv alpha-helical CRF 9-41, a CRF antagonist ($p < 0.05$, vs control). The pituitary GH levels were significantly elevated when intact and adrenoletomised (ADX) rats were exposed to this hypoxia ($p < 0.01$, vs control). Pretreating with either a high dose of dexamethasone (DEX) 500 ug ip, or low dose of DEX 199 ug ip, dropped the pituitary GH levels ($p < 0.05$, vs control). Hypoxia caused significant increases in plasma PRL and not the pituitary PRL. ADX reduced pituitary PRL under hypoxia but the effects were reversed by pretreating with icv CRF antagonist and both low and high doses of ip DEX. When rats were pretreated with icv NE, hypoxia caused significant decreases in pituitary GH and increased plasma GH These effects were reversed by pretreating with icv yohimbine, an alpha-2 adrenergic receptor antagonist. When pretreated with icv Glu, hypoxia produced significant reductions in pituitary GH and increased pituitary PRL, these effects were reversed by icv AP-5, a NMDA receptor antagonist. These results may suggest that hypoxia suppresses body weight gain, which may be relative to decreased release of GH. Hypoxia induces PRL release but inhibits GH secretion; hypothalamic CRF suppresses GH release but increases PRL release; central NE induces GH release through alpha-2 receptor affect; central Glu (by NMDA receptor) could stimulate GH secretion and suppress PRL in colchicines-treated rats under hypoxia.

121. HYPOXIA INDUCES ALTERATIONS OF THYROTROPIN-RELEASING HORMONE IN RAT HYPOTHALAMUS.

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This study examined the effects of 0.5h 2h, 24 h, 5 day, 10 day and 30 day exposure to hypoxia on TRH secretion from the median eminence (ME), response of TRH in paraventricular nucleus (PVN) of hypothalamus, and the modulation of norepinephrine (NE) on TRH in rats. The hypoxic stimulus occurred in a hypobaric chamber and a control group was at local altitude (2300m, 15.8%, O_2). TRH levels were measured by specific radioimmunoassay. Hypoxia (5000m altitude, 10.8% O_2) and severe hypoxia (7000m altitude, 8.2% O2) significantly enhanced TRH levels of ME and PVN and declined serum T3. Intraventricular injection of NE induced a decrease of TRH levels in ME and PVN (increased TRH release), and enhanced serum T3 at 7000m hypoxia for 2h. The stimulating effects of NE on TRH secretion could be abolished by icv yohimbine. We conclude that hypoxia exposure induces inhibition of hypothalamic TRH secretion from ME and PVN. Alpha-2-adrenergic receptors might play a role in the modulation of TRH release from the hypothalamus in acute hypoxia-exposed rats.

122. INTERMITTENT HYPOXIA INFLUENCES THE SECRETION OF PITUITARY GROWTH HORMONE AND THE GROWTH OF THE MALE RATS.

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We previously reported that repeated hypoxia suppressed body weight gains of rats and inhibited the growth hormone (GH) release from the pituitary. In order to understand the effects of intermittent hypoxia on changes of body weight and GH secretion, rats were exposed to hypoxia in a simulated hypobaric chamber, and the contents of GH in the pituitary were tested by immunohistochemistry. The data indicate that the rats' weight gains were markedly suppressed from the 1st to the 11th day with intermittent hypoxia of 5 km altitude (10.8% O_2) and began to regain hereafter. No alteration was found with intermittent hypoxia of 2 km altitude (16.0% O_2, vs. control). GH contents were found to be 137.04% ($P < 0.05$ vs. control), 152.03% ($P < 0.01$ vs. control) and 138.94% ($P < 0.05$ vs. control) increase with intermittent hypoxia (2 km) for 5, 10 and 15 days respectively, and 188.43% ($P < 0.01$ vs. control), 346.18% ($P < 0.001$ vs. control) and 181.93% ($P < 0.01$ vs. control) increase with intermittent hypoxia (5 km) for 2, 5 and 10 days respectively. These results indicate that intermittent hypoxia significantly increases GH contents in the pituitary in rats depending on the time course and severity of hypoxia. Moderate intermittent hypoxia (5km altitude) suppress the growth of rats, which may relate to the reduced secretion of GH. The reduced GH release is due to hypoxia-activated SS release and SS mRNA expression.(we had published in Regulatory Peptides).

123. NEUROPEPTIDES AND HYPOXIC ADAPTATION.

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The responses to hypoxia of neuropeptides in the hypothalamus that regulate neuroendocrine behavior are important for deciphering mechanisms of adaptation to hypoxia. To explore the adaptive plasticity of the responses we applied a simulated altitude hypoxia in a hypobaric chamber. Our data show that the hypothalamic neuropeptides and immune system display adaptive plasticity in gene expression and peptide modulation in rats during acute and chronic hypoxia. Hypoxia depressed cellular immune activity and attenuated spleencytes proliferation and DNA contents. This effect was mediated through NE. The parasympathetic system reduced hypoxia-suppressed immune responses. Intermittent hypoxia showed an elicited affect. Hypoxia suppressed humoral immune activity, reduced hemolysin formation and IgG production, that were modulated by Hypothalamic neuropeptides. Hypoxia-reduced humoral immune activity was modulated through hypoxia-activated HPA, stimulating hypothalamic CRF and NE that further suppressed immune function. β-EP involved in hypoxic down-regulation in humoral immune activity, T-lymphocyte DNA contents, hemolysin formation of SRBC-sensitized rat, and IgG level, acting through opiate receptor or possible sympathetic nervous system. AVP enhanced humoral immune response to hypoxia, increased hemolysin to SRBC and IgG production via V1 receptor in brain PVN. Supported by NSFC.no.30070289

124. NEONATAL MATERNAL SEPARATION ENHANCES TIME-DEPENDENT PHRENIC RESPONSES TO HYPOXIA IN RATS.

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Neonatal maternal separation (NMS) is a stress that alters programming of the hypothalamo-pituitary-adrenal axis (HPAA) orchestrating the neuroendocrine responses to stress. Anatomical and functional evidence indicate that groups of HPAA neurones activated by stress modulate respiratory activity also. We recently showed that, in awake rats, the hypoxic ventilatory response of adult males (but not females) subjected to NMS is 25% greater than controls (Genest et al, 2002). To establish the effects of NMS on respiratory control development, and begin mechanistic investigation of NMS-related enhancement of the hypoxic ventilatory response, we tested the hypothesis that NMS augments time-dependent phrenic responses to hypoxia. Experiments were performed on two groups of male rats. Pups subjected to NMS were placed in a temperature controlled incubator 3h/day for 10 consecutive days (P3 to P12). Control pups 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 ($FiO_2 = 0.5$). Rats were then exposed to moderate, followed by severe isocapnic hypoxia ($FiO_2 = 0.12$; 0.08, respectively, 5-min each). NMS significantly enhanced both the frequency and amplitude components of the phrenic nerve response to hypoxia relative to controls. Upon return to hyperoxia, post-hypoxia frequency decline was greater in NMS rats versus controls. We conclude that early life exposure to a non-respiratory stress, such as disruption of mother-pup interactions, can affect development of the inspiratory (phrenic) response to hypoxia. This research was supported by the Hospital for Sick Children Foundation and CIHR.

125. ANDEAN COMPARED WITH EUROPEAN WOMEN ARE PROTECTED FROM ALTITUDE-ASSOCIATED INTRAUTERINE GROWTH RESTRICTION (IUGR).

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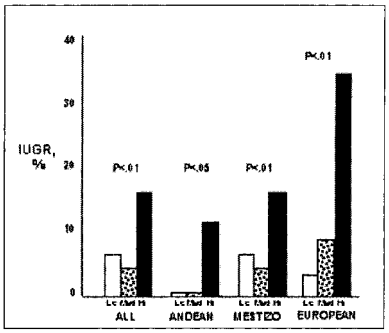
Babies born at high altitude to long-term high-altitude residents weigh more than those of recent migrants from low altitude. **Objective:** We asked whether a gradient exists such that persons of Andean ancestry are protected relative to those of mestizo ("mixed") and, in turn, European or other lowland ancestry. **Methods:** Medical records were examined from 3565 consecutive deliveries to women with 2+ prenatal visits at public or private hospitals in Santa Cruz (300 m, low), Cochabamba (2500 m, medium), and La Paz or Orurro (3600–3800 m, high). Population ancestry was judged by parental surnames. Persons of Bolivian nationality were assumed to have been born at their altitude of residence and non-Bolivians to have immigrated there as adults. IUGR was defined as birth weights <10th percentile for gestational age and sex using sea-level criteria. **Results:** Women were slightly older at high altitude but parity, number of prenatal visits, and pregnancy weight gain were similar. At high vs. low altitude, birth weight was lower (3101 ± 12 vs 3352 ± 15 gm, $p < .01$) but gestational age (38.8 ± 0.1 vs 38.9 ± 0.1 wk) and % pre-term deliveries (10.4 vs 8.8%) did not differ. IUGR babies were three times more frequent at high altitude (figure). The increase in IUGR was least in babies of Andean ancestry, intermediate in mestizos and greatest in Europeans. Within an ancestry group, there was no consistent birth weight difference between Bolivian vs. non-Bolivian nationals, suggesting that lifelong high-altitude residence had little effect. **Conclusions:** Andean ancestry protects against altitude-associated IUGR, suggesting the involvement of unknown genetic factors. (NIH TW01188, HL60131).



126. COPING WITH HYPOXIA: ELITE CLIMBERS.

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The purpose of this study was to explore the mental strategies used by successful Everest climbers, to overcome obstacles (hypoxia) while climbing Mount Everest. A group of elite climbers (n = 9) were interviewed in order to assess the mental strategies used by them to overcome obstacles while attempting a successful climb of Mount Everest. In-depth interviews were conducted with 9 elite climbers who succeeded (at least once) in reaching the summit of Mount Everest. An inductive analysis of the data revealed that the mental strategies used to overcome obstacles included: disassociation, teamwork, self-confidence, focus and short-term goal setting. Mental training is an essential part of training in preparation for coping with obstacles (hypoxia) that may prevent climbers from successfully summiting high mountains. This study shows that mental training is a useful tool in helping climbers cope with hypoxia.

127. RESPIRATORY EPITHELIAL ION TRANSPORT IS ALTERED AFTER 1 HOUR AT 4200M.

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Rationale: Respiratory epithelial ion transport plays an important role in controlling extravascular lung water and is altered on ascent to high altitude. It can be assessed *in vivo* by measuring the transepithelial nasal potential difference (NPD). **Methods:** Measurements were made in 13 healthy subjects at sea level (SL) and after 1 and 6 hours (HA1 and HA6) of hypobaric hypoxia at a simulated altitude of 4200m. NPD was measured during perfusion of the nose with 154mM NaCl at SL, HA1 and HA6, and with NaCl + 10^{-4} M amiloride; low Cl^- solution + 10^{-4} M amiloride, and low Cl^- + 10^{-4} M amiloride + 10^{-5} M isoprenaline, at SL and HA6. **Results:** Ascent to 4200m resulted in a hyperpolarization in the basal NPD at HA1 and HA6 and an increase in the amiloride inhibitable portion (Δ Amiloride) of the NPD at HA6. Stimulated Cl^- transport with low Cl^- or isoprenaline was not significantly altered.

	Basal NPD (mV)	Δ Amiloride (mV)	Δ Low Cl (mV)	Δ Low Cl + isoprenaline (mV)
SL	-20.8 ± 3.1	6.0± 1.0	-7.7 ± 1.1	-6.1 ± 1.6
HA1	-24.9 ± 2.9*	–	–	–
HA6	-31.4 ± 4.8**	11.9 ± 2.0**	-12.6 ± 2.7	-2.3 ± 2.0

Data: mean +/- SEM * p<0.05 **p<0.01 cf SL

Conclusions: The change in NPD after only 1 hour is too rapid to be due to changes in channel synthesis and suggests that hypoxia affects the conductance, open probability or trafficking of respiratory epithelial ion channels.

128. SUBLINGUAL GLYCERYL TRINITRATE INDUCED HEADACHE AS A PREDICTOR FOR INCIPIENT ACUTE MOUNTAIN SICKNESS.

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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. This study evaluated the relationship between GTN induced headache and AMS scores. Subjects were recruited from two separate expeditions to Kilimanjaro (5892m) and Pk6175 (6175m) in the Indian Himalaya comprising nine and six healthy adult volunteers respectively. 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 subtratcting baseline observations normalised HSVs (nHSV) were calculated. The data was analysed using the Fisher test. A positive correlation was found between nHSV and change in the observed AMS scores (_AMS) over the following 24 hours where a further ascent of between 400–1000m occurred (Kilimanjiro - $p = 0.003$; Pk6175 − $p = 0.005$). The relative risk of developing a large shift in AMS score (ΔAMS) given a high headache shift vector (nHSV) was found to be 5.42 and 3.71 for the Kilimanjiro and Pk6175 groups respectively. These findings support the hypothesis that sublingual GTN may be useful as a predictor for incipient AMS.