13th INTERNATIONAL HYPOXIA SYMPOSIUM

February 19–22, 2003
Banff, Alberta, Canada
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 vasconstrictor (HPV) has been proposed to expose parts of the pulmonary capillary bed to high pressure/flow, and stress the 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 (FiO2 = 0.125, -450mmHg equivalent altitude). Relative dispersion (RD), an index of heterogeneity of blood flow (RD = standard deviation/mean) was determined. Average SaO2 during hypoxia was 89 ± 3% between HAPE (86 ± 2%, means ± SE), but was higher in CON (89 ± 3%). Normoxic RD was similar between the 3 groups. RD was increased ~15% 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, M01RR08272, RNSA Scholar’s Grant, Society of Thoracic Radiology Seed Grant (DRL).

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

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Pulmonary 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 involved 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.

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 that HPV is spatially heterogeneous in the mammalian lung is based on the observation (Hultgren et al. Science 282:951, 1998) that HPV is unevenly distributed 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 an inducible transcription factor that serves as a redox sensor of cellular hypoxia and in an oxygen-dependent manner regulates adaptive responses to hypoxia. We 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 (wv/dw) and blood free wv/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 nuclear nuclear not 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 NO-s 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-III, 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 tricuspid valve pressure gradient during 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 smooth muscle cell 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) isoforms 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 sc) 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.

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 effects in brain. These 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 Cat-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% O2 for 20 min, before and after hypoxic acclimatization during consecutive three days at 10%O2 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 OVEREX- PRESSING 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 clefs 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 muscular loading, hind limb tremor and toddler 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.

10. GENETIC MARKER FOR THE ERYTHROPOIETIC RESPONSE TO ALTITUDE.

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Abstract: 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 (Du 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), YP-2 (enolase), hydroxylase (direct cellular O2 sensor regulating binding of VHL to HIF-1α), 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 -141% 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±18% 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.

Monday February 21st, 2003

11. HYPOXIA: NEW HYPOTHESES

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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 VO₂ max, 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 exercise. 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.

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 that produces a change at sea level. In this presentation, I highlight the mathematical link between cerebral oxygen exchange at sea level—and this is reflected in the magnitude of the oxygen extraction coefficient—and a change in 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-specie
tic mitogen with potent permeability enhancing properties that has been implicated as a potential mediator of capillary leak in states of low

titude pulmonary (HAPE) and cerebral (HACE) edema. We postu-
lated 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

alvage 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

amples. Samples were immediately frozen, stored at

ers where they stayed for 4 days and collected morning NL sam-

m MUSCLE CONTRACTILE PROPERTIES.
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chronic hypobaric hypoxia occurs in humans in a variety of circum-
stances including respiratory disease and exposure to altitude and it is
known to affect skeletal muscle structure. However, surpris-
ingly little is known about its effects on skeletal muscle func-
tion. 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 proper-
ties of isolated strips of diaphragm, sternohyoid, extensor digi-
genated 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. 3.5 ± 1.9 N/cm2, mean ± SD, normoxia vs. hypoxia),
sterohyoid (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 (7.2 ±
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 sternohy-
old, 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 respira-
tory 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.

14. EFFECTS OF CHRONIC HYPOBARIC HYPOXIA ON
ISOLATED RAT RESPIRATORY AND LIMB SKELETAL
MUSCLE CONTRACTILE PROPERTIES.
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stances including respiratory disease and exposure to altitude and it is
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0.8 vs. 3.5 ± 1.9 N/cm2, mean ± SD, normoxia vs. hypoxia),
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2.9 vs. 12.9 ± 3.9) and soleus (9.0 ± 4.2 vs. 12.1 ± 3.4) muscles.
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tory and limb skeletal muscles. These findings may be relevant
to the chronic hypoxia of respiratory disease and exposure to altitude.
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College Dublin, Ireland and The Physiological Society.

15. EFFECT OF EXTRACELLULAR PO2 ON THE FALL IN
INTRACELLULAR PO2 IN CONTRACTING SINGLE MY-
OCYTES.
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This investigation tested the effect of altered extracellular PO2
(PeO2) on the intracellular PO2 (PiO2) response to contractions in
single isolated skeletal muscle cells. We hypothesized that as
PiO2 increased, thereby increasing the driving force for O2 flux,
the rate of PI O2 would be proportional to the net decrease in
PiO2. The rate of the initial metabolic response (calculated as fall in
PiO2/t) would be increased. Single myocytes (n = 12) were
dissected from lumbar muscles of adult female Xenopus laevis
and injected with a porphyrin compound for assessment of PiO2
via phosphorescence quenching. For each cell, at PeO2's of ~20
low (4–40 moderate) and ~60 (high) Torr, tetanic contractions
were induced at a frequency of 0.67 Hz for ~2 min with a 3 min
recovery between bouts. The PiO2 response to contractions was
characterized by a time delay (TD) followed by a mono-expon-
ential decline to steady-state (SS) values. The fall in PiO2 to SS
values was significantly greater at each progressively greater
PeO2 (all p < 0.05). The mean response time (TD) followed by a time
constant (t) 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 PeO2 (61.8 ± 9.4 s) and was correlated positively (r =
0.965) with the net fall in PiO2. However, the initial rate of change
of PiO2 (calculated as net fall in PiO2/t) was not different (p >
0.05) among PeO2 trials. These latter data suggest that, over
the range of 20–60 mmHg, PeO2 does not play a deterministic role
in setting the initial metabolic response across the rest-to-con-
tractions transition in isolated frog myocytes. Additionally, these
results suggest that oxidative phosphorylation in these myoglo-
bin-free myocytes may be compromised by PeO2 at values near-
by 60 mmHg. Supported by NIH AR-40155 and AR-48461 and a Parker B. Francis Fellowship.

16. EUROPEAN GENETIC ADIMEXURE PREDICTS DECREASE IN AEROBIC PERFORMANCE AT 4338 METERS IN PE-
RUVIAN QUECHUA.
Tom Brutsaert1, Esteban Parra2, Mark Shriver3, Alfredo Gamboa4, Jose-Antonio Palacios 4, Maria Rivera4, Ivette Rodriguez5, Fabiola Leon-Velarde4. The Univ at Albany, SUNY 1, Univ Toronto at Mis-
sissauga2, The Pennsylvania State Univ3, Universidad Peruana Cayetano Heredia4, Instituto Boliviano de Biología de Altura5.

Quechua natives of the highland Andes may be genetically
adapted to high altitude and thus able to resist decrements in maxi-
mal O2 consumption in hypoxia (ΔVO2max). This evolutionary hy-
thesis was tested via the measured measures of VO2max (sea level
versus 4338m) in 30 young male Peruvians of mixed Spanish and
Quechua origins. Genetic admixture level (% European genetic in-
fluence) was estimated on each individual using a panel of 22 an-
cestry-informative DNA markers. Genetic admixture explained a
significant proportion of the variability in ΔVO2max after control for
major covariate effects including sea level VO2max and the decre-
ment in arterial O2 saturation (ΔSPO2). The genetic effect reflected a
main effect of admixture on ΔVO2max (P = 0.041), as well as the in-
teraction between admixture and ΔSPO2 (P = 0.018). The latter means
that admixture was predictive of (VO2max only in subjects with a
large decrease in SPO2 at 4,338 m. In such subjects, ΔVO2max 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 (ΔVEFthresh). Similar to the previous interaction, admix-
ture was predictive of ΔVO2max only in subjects with a large
ΔVEFthresh. Together, these interactions suggest that the putative
genetic effect on ΔVO2max is mediated by a subject’s aerobic fitness
level. In particular, genetic effects may be more important (or easier
to detect) in veryathletic 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 (O2 = 10%–9%). The control animals underwent the same training while constantly breathing ambient air (O2 = 20.6%). At day 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, and 105, 20 continuous intracutaneous measurements were performed during an IHT-session. Another set of 16 Wistar rats was trained as described above. After 4 weeks of IHT, caudally based 9 × 3 cm 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 normalized after 12 h (IHT: control day: 12.0±1.3 mmHg vs. 7.8±1.1 mmHg; IHT: day 3: 14.6±1.8 mmHg vs. 6.6±1.4 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 factor (HIF), HIF promotes transcriptional responses 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 placentental 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 placentental 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-placentental delivery. Therefore, we hypothesized that HIF activity would be increased as time from placentental 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 placentetal 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 PO2 DURING ACUTE AND CHRONIC HYPOXIA.

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The regulation of brain tissue PO2 during acute and chronic hypoxia Objectives: To determine the capacity of the brain to maintain tissue PO2 (PbO2) during exposure to acute and chronic hypoxia. Methods: We used electron paramagnetic resonance spectrometry to determine the changes in PbO2 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 hyperbaric pressure. In one study, animals were acclimated to PbO2 levels of 120% of ambient air for 28 days, and a control group was maintained under similar conditions while at normobaric pressures. Brain PbO2 was measured in both groups under normobaric, normoxic conditions. **Results:** In acute hypoxia, brain PbO2 varies with the inspired oxygen tension. In chronic hypoxia, PbO2 was measured by 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 PbO2 of the control group [JCBFM, 2000, v20, p1632]). In a second study, brain PbO2 was measured in rats breathing both 21% and 10% O2 before and after acclimation to 10% O2. The PbO2 in the brain of acclimated animals breathing 10% O2 was not significantly different from the PbO2 of pre-acclimated animals breathing 21% O2. **Conclusions:** Although the brain does not maintain PbO2 under acute hypoxia, there are adaptive mechanisms 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 PbO2, indicating that there are O2 sensitive mechanisms (such as HIF-1α) that are capable of sensing PbO2 and initiating a cascade of events which result in the PbO2 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 as well as β-ENaC) activity. 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 as well as β-ENaC) activity. Furthermore, we have recently shown that β1-Na/K-pump and β-ENaC mRNA levels are 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. Dext 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: 2.5-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 (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. Importantly, in Tables **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.

<table>
<thead>
<tr>
<th>Cap/fiber</th>
<th>Cap/mm2</th>
<th>Mean area</th>
</tr>
</thead>
<tbody>
<tr>
<td>SL</td>
<td>4.0 ± 0.2</td>
<td>556.2 ± 55.6</td>
</tr>
<tr>
<td>CH8</td>
<td>3.6 ± 0.2</td>
<td>578.7 ± 28.0</td>
</tr>
<tr>
<td>Aymaras</td>
<td>2.4 ± 0.1/*</td>
<td>491.0 ± 19.6#</td>
</tr>
</tbody>
</table>

22. METHODS FOR MONITORING HORSES IN A SIMULATED ALTITUDE STALL.
Dawn Howe1, George Swanson1. California State Univ1. dawnhowe@hotmail.com.

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 49l 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%.

<table>
<thead>
<tr>
<th>RR (b/min)</th>
<th>VT (l/min)</th>
<th>VE (l/min)</th>
<th>VO2 (l/min)</th>
<th>S (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.1</td>
<td>2.7</td>
<td>32.6</td>
<td>1.3</td>
<td>99</td>
</tr>
<tr>
<td>18.6</td>
<td>3.8</td>
<td>71.6</td>
<td>1.6</td>
<td>90</td>
</tr>
</tbody>
</table>

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

23. LUNG FUNCTION AFTER RAPID ASCENT TO HIGH ALTITUDE.
Oliver Senn1, Christian Clarenbach1, Manuel Fischler2, Rahel Thalman2, Marco Maggiorini2, Konrad Bloch1. Pulmonary Division, Univ Hospital, Zurich, Switzerland 1, Medical Intensive Care, Univ Hospital, Zurich, Switzerland2. oliver.senn@dim.usz.ch.

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 Mt.Rosa mountain sickness scores (LLS) were reassessed. 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 volumes increases are consistent with effects of strenuous exercise or bronchocstriction induced by high ventilation.

24. FIELD TESTING OF A NEW HIGH-ALTITUDE O2 DELIVERY SYSTEM IN THE BOLIVIAN ANDES.
Alex Vesely1, Ron Somogyi1, T Azami1, David Preiss1, Eitan Pismansky1, Ben Goodman2, Steve Iscoe3, Kyle Patterson3, Jo Bradwell3, Chris Inray4, Joseph Fisher1. Dept Anesthesiology, Toronto General Hospital1, Aircrew Performance Protection Group, DRDC Toronto, Dept Physiology, Queens Univ1, Birmingham Medical Research Expeditions Society4. alex.vesely@utoronto.ca.

**Background:** At extreme altitude, bottled O2 is expensive and cumbersome, but necessary. The PaO2 achievable with simple mask/nasal prongs (NP) or a non-rebreathing mask (e.g. Paro, 1°) is limited by available O2 flow and high minute ventilations (VE), which dilute inspired O2. Furthermore, performance is limited by hypocapnia, which reduces cerebral blood flow and increases the affinity of Hb for O2. We designed a high altitude circuit (HAC) that uses low O2 flows to provide a constant high FiO2 and constant PaCO2 regardless of VE. We compared the PaO2 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 75 ± 5 kg breathed room air at rest via the HAC. The O2 flow required to raise PaO2 to 100 mmHg (F100) was determined. With O2 flow set at F100, each subject breathed at rest (5 min) and 3 × resting VE (5 min) on each of the three circuits. Tidal PCO2 and PaO2, VE and HB saturation were monitored. **Results:** F100 was 0.5 ± 0.2 L/min (corrected to 1.0 A). At the same O2 flow (F100), PaO2 was significantly greater with the HAC than with NP or P (Figure). Hyperventilation did not change PaO2 with the HAC or P, but improved PaO2 with NP. **Conclusion:** In field tests, the HAC demonstrated the highest efficiency of the three O2 delivery devices. This may allow climbers to carry less O2 or go farther with a given O2 supply, and reduce littering. In addition, its ability to control end-tidal PCO2 may be therapeutically useful for increasing cerebral blood flow and suppressing periodic breathing.
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 SaO2 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.

Changes in EMG During Exercise with a Small Muscle Group During Decreasing Arterial PO2.

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On the last meeting we have shown that during decreasing arterial PO2 oxygen uptake during sub maximal exercise of the working forearm muscles decreased after reaching a PO2 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 10% corresponding to a PO2 of 63 Torr in the arterial blood. The decrease of EMGms coincides with the beginning of the reduction in VO2 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.

Changes in EMG During Exercise with a Small Muscle Group During Decreasing Arterial PO2 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 PO2 (PmO2). These experiments were performed to determine the roles of blood flow and PmO2 on leukocyte adherence to cremaster muscle venules during hypoxia. Cremasteric venules of anesthetized rats were visualized with intravital microscopy. PmO2 was determined with a phosphorescence decay method. The following experiments were performed: I. Untreated controls; II. Systemic hypoxia: inspired gas: 10% O2, III. Ischemia: cremaster blood flow restriction; inspired gas: room air, IV. Cremaster hypoxia/systemic normoxia; cremaster equilibrated with 95% N2, 5% CO2 inspired gas: room air, V. Cremaster normoxia/systemic hypoxia: cremaster equilibrated with 10% O2, 5% CO2 balance N2, inspired gas: 10% O2. The following data were obtained after 10 min of each treatment: Leukocyte adherence increased significantly only when PO2 was low (groups II and V) even if PmO2 was elevated (Group V). Muscle hypoxia with normal PO2 (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.
EFFECT OF CAFFEINE INGESTION AT ALTITUDE

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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 moderate and moderate altitude exposure on the cardio-respiratory 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 (SL), 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 (VO2), ventilation (VE), carbon dioxide production (VCO2), 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, VO2, and VE at any given workload were 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.

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 a-lipoic acid) and the remaining eight subjects ingested 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-butylnitron (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: 7369 ± 2437 vs. HA: 1548 ± 236 arbitrary units (AU)/Gauss (G), P < 0.05] whereas an increase was observed in the placebo group [6602 ± 1813 vs. 10599 ± 2729 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 (27.1 ± 3.6, 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.
33. EFFECTS OF RESPIRATORY ALKALOSIS ON HUMAN SKELETAL MUSCLE METABOLISM AT THE ONSET OF SUBMAXIMAL EXERCISE.

George Heigenhauser1, Paul LeBlanc1, Michelle Parolin1, Norman Jones1, McMaster Univ1. heigen@mcmaster.ca.

The delayed activation of pyruvate dehydrogenase (PDH), resulted 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% VO2max while hyperventilating (R-Alk) (PETCO2 = 19.2 ± 0.5) or breathing normally (Con) (PETCO2 = 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 monoprotinated form of inorganic phosphate (P1), resulting in an elevated rate of pyruvate production. The mismatch between pyruvate production and its oxidation resulted in 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 OGSSST (PJJ).

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

Kyle Pattinson1, Steve Myers2, John Mikes3, Chris Imray4. Birmingham Childrens Hospital, Birmingham, UK1, Centre for Human Sciences, Qinetiq, Farnborough, UK2, Good Hope Hospital, Sutton Coldfield, West Midlands, UK3, Univ Hospitals Coventry and Warwickshire NHS trust, Coventry, UK4. kyle999@pobox.com.

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 (CO2), oxygen (O2) 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 CO2 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.

35. EFFECTS OF ACUTE EXPOSURE TO 1000 TO 4500 M ON VO2MAX IN ENDURANCE-TRAINED SUBJECTS.


Maximal aerobic capacity (VO2max) 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 VO2max 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, VO2max = 61.1 ± 6.5 ml/kg/min); group C, untrained individuals (n = 4, VO2max = 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 (SaO2), oxygen uptake (VO2), pH and p50 (arterialized capillary blood at rest and after 2 minutes of recovery) were measured.

RESULTS: Both groups showed a progressive reduction in VO2max in hypoxia (significant at 1500 m for group T and at 4500 m for group C). There was no difference in 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 VO2max in spite of a greater reduction in maximal O2 transport (greater desaturation and reduction in HRmax). We hypothesize that in trained subjects a greater peripheral O2 extraction limits the decrease in VO2max in hypoxia but induced a greater arterial desaturation through diffusion limitation.

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

Howard Green1, Todd Duhamel1, Shelley Sandiford1, Jennifer Perco1, Univ Waterloo1.

This study investigated the hypothesis that the reduction in mechanical power output (PO) and peak aerobic power (VO2peak) observed during exercise in hypoxia (H) compared to normoxia (N) could 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% O2) and H (14% O2). Tissue from the vastus lateralis muscle was extracted prior to exercise (PRE), at PO’s corresponding to 40% and 70% VO2peak (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. VO2peak was depressed 21% (P < 0.05; 42 ± 0.1 vs 33 ± 0.1 L/min). It is concluded that reductions in VO2peak with H are not related to alterations in SR function as measured by Ca2+- ATPase “in vitro”. Supported by NSERC (Canada).
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. This 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. Interestingly, 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.

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 3,817 m 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 CO₂, 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 (±sd) time to reach the summit from the Gouter Hut was 4.3 hours (±0.8). Pre-ascent heart rate and respiratory rates 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 predictive capability.

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; O₂ = 16.4%), and the effects of the IHE on maximal aerobic capacity at high altitude (equivalent to an altitude of 4,000 m; O₂ = 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 multi-graded exercise tolerance test by pedaling at the simulated 4,000 m altitude. Results showed that after this IHE, maximal oxygen uptake (VO₂max) and maximal workload at an altitude of 4,000 m significantly increased. Expected volume per minute at the point of VO₂max 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.

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(530-F(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 bike-riding 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 ± 3.2 and 18 ± 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 ± 8; 171 ± 4; 177 ± 7; 175 ± 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 (SD): age 47.3 (11.8) years; height 181.1 (5.1) cm; body mass 82.7 (10.4) kg). VO2max was measured at 4 locations: Birmingham (41m), UK (96m) and La Paz (LP) (3610m), Refugio Huayna Potosi (RP) (4750m) and Chacaltaya (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 O2/CO2 analyser (Cosmed K4b2). Following a 5-minute cycle warm-up, subjects completed an incremental (20 watt per minute) VO2max 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 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 VO2max values are comparable with those found in other studies confirming the K4b2 as a reliable tool for use in high altitude research.

**Changes in maximal oxygen uptake (CH lower than BM p < 0.05)**

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

Lorna G. Moore1, Megan Wilson2, Lorna G. Moore2, Susan Niemerz3, Patricio Andrade2, Enrique Vargas2, Lorna G. Moore1, University of Colorado Health Sciences Center1, Clinica del Sur and Caja Nacional de Salud, La Paz, Bolivia2, Instituto Boliviano de Biología de Altura, La Paz, Bolivia3, University of Colorado, Denver Health Sciences Center4, susan.niemerz@ucdenver.edu.

**Objective:** High-altitude hypoxia influences placental changes in the pulmonary circulation. We documented persistent fetal circulatory patterns and measures of pulmonary artery pressure (PAP) 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 right ventricular systolic intervals and the regression equation of Wang et al. was used to calculate pulmonary artery pressure. **Results:** Of 16 healthy infants, 1 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. **Conclusion:** Pulmonary hypertension, surfactant deficiency, and/or retained fetal lung fluid at birth. One premature infant developed symptomatic pulmonary hypertension at 3 months. **Contribution:** Postnatal changes in the pulmonary circulation occur slowly at high altitude, with greater vulnerability to incomplete or disrupted transition.

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

Jan Zielinski1, Tian-Yi Wu2, Xiano-Qin Wang2, Hau-Wei Cheng3, Robert Pflyczewski4, Pawel Sliwinski1, Institute Jan Zielinski4, Robert Plywaczewski 1, Pawel Sliwinski 1. Institute Immunology Medical School Univ Birmingham5, steve.myers@ntlworld.com.

**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 (SD): age 47.3 (11.8) years; height 181.1 (5.1) cm; body mass 82.7 (10.4) kg). VO2max was measured at 4 locations: Birmingham (41m), UK (96m) and La Paz (LP) (3610m), Refugio Huayna Potosi (RP) (4750m) and Chacaltaya (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 O2/CO2 analyser (Cosmed K4b2). Following a 5-minute cycle warm-up, subjects completed an incremental (20 watt per minute) VO2max 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 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 VO2max values are comparable with those found in other studies confirming the K4b2 as a reliable tool for use in high altitude research.

**Changes in maximal oxygen uptake (CH lower than BM p < 0.05)**

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

Susan Niemerz1, Patricio Andrade2, Enrique Vargas2, Lorna G. Moore3, University of Colorado Health Sciences Center1, Clinica del Sur and Caja Nacional de Salud, La Paz, Bolivia2, Instituto Boliviano de Biología de Altura, La Paz, Bolivia3, University of Colorado, Denver Health Sciences Center4, susan.niemerz@ucdenver.edu.

**Objective:** High-altitude hypoxia influences placental and fetal vasculature. We characterised pulmonary haemodynamics of fetal vessels to investigate potential adaptation to high altitude. **Methods:** Consecutive newborns were studied at 3700–4000m in La Paz, Bolivia. **Results:** Of 16 healthy infants, 1 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. **Conclusion:** Pulmonary hypertension, surfactant deficiency, and/or retained fetal lung fluid at birth. One premature infant developed symptomatic pulmonary hypertension at 3 months. **Contribution:** Postnatal changes in the pulmonary circulation occur slowly at high altitude, with greater vulnerability to incomplete or disrupted transition.

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<th>Healthy Infants</th>
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<td>PAP, mm Hg</td>
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UTERINE ARTERY BLOOD FLOW DURING PREGNANCY IN HIGH-ALTITUDE AYMARA WOMEN.

Megan Wilson1, Susan Nierneyer1, Fernando Armaza2, Miriam Lopez3, Enrique Vargas3, Lonna G. Moore1,2, Univ Colorado Denver, Denver, CO1, Univ Colorado Health Sciences Center, Denver, CO2, Instituto Boliviano de Biología de Altura, La Paz, BO3, Megan.Wilson@UCHSC.edu.

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 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. (HL0131, TW01188)

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 migrated to high altitude in comparison with Aymaras and no-Aymara children that live in Putre (3500m). Subjects: The population of study was: 10 children (5.8 ± 1.3 years) that upon to Arica and live in 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 questionnaire 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 ± 2, p < 0.0001). A higher incidence of AMS was observed in children (85%) 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

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

Luciano Bernardi1, Nadia Casiraghi1, Lucia Spicuzza2, Alfredo Gamboa3, Annette Schneider4, Antonio Morí1, Eloisa Arbustini1, Fabiola Leon-Velarde6, Cornelius Key1, IRCCS S.Matteo and Univ. Pavia, Italy1, Univ Catania, Italy2, Univ. Peruana C. Heredia, Lima, Peru3, Univ Regensburg, Germany4, Item1p@unipro.it. Circoadaptive 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 (6:00 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, 4388m, 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, 1.38 ± 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 stimuli. 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 ± 25%. 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 ± 2 (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.
SLEEP-DISORDERED BREATHING AND ERYTHROPOIETIN LEVELS IN ANDANE HIGH-ALTITUDE NATIVES WITH CEREBRAL BLOOD FLOW RESPONSE TO HYPOXIA

Lucia Spiczucka1, Nadia Casiraghi2, Alfredo Gamboa3, Cornelius Keyh, Annette Schneider, Antonio Murer1, Fabiola Leon-Velarde1, Giuseppe DeMaria1, Luciano Bernardi1. Univ Catania, Italy1, IRCCS S.Matteo and Univ. Pavia, Italy2, Univ. Perugia C. Heredia, Lima Peru3, Univ Regensburg, Germany3, lbernlp@unipr.it.

We tested the hypothesis that nocturnal hypoxemia due to sleep-disordered breathing (SDB) may determine excessive erythropoiesis (EPO) 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 >70) living in Cerro de Pasco (4380 m), determined the effect of sleep intervention (to maintain oxygen saturation (SaO2) >95%) for 1 hour prior to sleep, and investigated a possible correlation between SDB and Erythropoietin (EPO) production. Methods: Patients had 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 efficiency and structure, and the number of arousals were similar in the two groups. All subjects showed nocturnal period hypopneas. The apneic-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, 4.7 ± 0.5%, respectively, all NS vs EE). Mean SaO2 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 SaO2 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 or better) 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 SaO2 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.

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

Chantel T. Debert1, Kojiro Ide2, Jimmy Vantanajal1, Marc J. Poulin1. University Calgary, ctdebert@ucalgary.ca.

Objectives: This study examined to 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) vol-unteered for the study. A dynamic end-tidal forcing system was used to measure peak blood flow velocity (CBFv) in the middle cerebral artery in response to 20 mmHg steps of hypoxia (PhO2) at an elevation of 15.7 Torr above normal value, and to alter end-tidal PO2 (PhO2) in small incremental steps of hypoxia. The protocol consisted of an initial 8 min period of eucapnic euoxia (PhO2 = 80 Torr, elevation 1100m) followed by 6 descending steps (PhO2 = 75.2, 70.9, 57.0, 52.0, 48.2, and 45.0 Torr), each step lasting 90 sec. Immediately after the last step, PhO2 was elevated to 300 Torr for 5 min while PhO2 remained at euoxia. Then, PhO2 was raised by 7.5 Torr for 5 min whilst PhO2 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 (CBF) and regional cerebral oxygen saturation (AHsRO2) responses were determined by linear regression between ventilation, CBFv, SrO2 and arterial oxygen saturation (calculated from PetO2), respectively.

A PROTOCOL FOR DETERMINING THE CEREBROVASCULAR AND VENTILATORY RESPONSES TO INCREMENTAL STEP HYPOXIA.

Jon Kolb1, Philip Ainslie2, Kojiro Ide3, Marc Poulin3. Faculty Kinesiology, Univ Calgary3, Dept Physiology and Biophysics, Faculty Med, Univ Calgary, kolb@ucalgary.ca.

Introduction. The process of acclimatization to the hypoxia of altitude is associated with changes in ventilation and cerebral blood flow (CBF). However, the role of changes in CBF in ventilatory acclimatization to hypoxia (AH) 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 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 (CBR) and regional cerebral oxygen saturation (AHsRO2) responses were determined by linear regression between ventilation, CBFv, SrO2 and arterial oxygen saturation (calculated from PetO2), respectively.
Cerebral Desaturation at VO2 Max at High Altitude (5250m).

CHE Imray1, CW Chan1, P Collins1, S Myers3, S Harris1, AW Wright2, AR Bradwell1. Birmingham Medical Research Expeditionary Society1. 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 VO2 max at 5250m. Methods. 9 subjects (1 female, age 32–60) were studied at 5250m. Pulse oximetry (SO2) was measured using a Ohmeda Biox 3740 Pulsoximeter; Regional cerebral oxygenation (rSO2) 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 VO2Max 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. SPO2 fell from 81.8(4.7)% to 65.7(10.7)% (p < 0.0001). rSO2 fell from 81.8(3.3)% to 58.2(2.5)% (p < 0.0001). MCAV fell from 78.1(15.3)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.

The Effect of an Oxygen Bolus on Cerebral Oxygenation and Blood Flow at Altitude.

Colin Chan1, Phil Collins2, Alex Wright3, Kyle Pattinson3, Peter Forster4, Chris Imray1. Birmingham Medical Research Expeditionary Society1, ScanMed2. colin@cpruden.com.oxon.co.uk.

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 5200 metres. Subjects were well rested and studied supine using the following parameters: peripheral oxygen saturation by earlobe pulse oximetry (SaO2), cerebral oxygen saturation by near infrared spectroscopy (rSO2), 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.

Increased PO2 Gradient Not Cerebral Blood Flow Improves Brain Oxygenation at Altitude.

Eitan Prisman1, Alex Vesely2, David Press2, Ron Somogyi3, Takafumi Azami4, Phil Collins3, Chris Imray1, AR Bradwell3, Joshua Faller3. P. York Univ, Toronto, Ontario Canada1, Dept Anesthesia, Toronto General Hospital, Ontario Canada2, Univ Toronto, Ontario Canada3, Nagoya City Univ, Dept Anesthesiology and Respirology, Dept Physiology, Birmingham Medical Research Expeditionary Society1, Walsgrave Hospital, Coventry, UK4, Dept Immunology, Medical School, Univ Birmingham, UK5. etianpyork.co.uk.

Introduction: Above 3560 m, voluntary hyperventilation improves arterial O2 saturation (SaO2) and cerebral regional oxygenation (rSO2) (1). At sea level, hypercapnia improves cerebral blood flow (CBF) and rSO2, even if hypoxic end-tidal PO2 is maintained (2). We tested if an increased CBF due to increased PCO2 and reduced PO2 associated with hyperventilation (HVE) improves rSO2 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. PETCO2, SaO2, rSO2, and middle cerebral artery blood velocity (MCAVB), an index of CBF, were measured. Brain O2 delivery (DO2) was calculated as MCAVB x SaO2. Results: At rest, PETCO2 was 27.3 ± 4.15 (SD) mmHg, SaO2 90.8 ± 2.7%, rSO2 640 ± 20%, and MCAVB 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 CO2 content such that the reduction in air intake (i.e., VA) caused a disproportionate hypoxia prior to any rise in PetCO2. Results from the remaining two subjects are presented in the table. Discussion: Assuming constant cerebral O2 extraction, our data imply that, at altitude, rO2C is more influenced by the blood-tissue O2 gradient than by perfusion. Clin Sci 2000;98:159 J Clin Monit 2000;16:191

<table>
<thead>
<tr>
<th>PETCO2</th>
<th>SaO2</th>
<th>MCAV</th>
<th>cniBP</th>
<th>PR</th>
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<tr>
<td>(mmHg)</td>
<td>(%)</td>
<td>(cm/sec)</td>
<td>(mmHg)</td>
<td>(min)</td>
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<td>HVE</td>
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Regional Specifie Changes in Cerebral Glucose Metabolism Following High Altitude Expedition.

Tobias Merz1, Valerie Trerey3, Urs Hafri3, Christine Spengler3, Urs Schwarz2, Alfred Buck2, Marco Maggiorini1. Medical ICU, Univ Hospital Zurich, Switzerland1, PET Center, Univ Hospital Zurich, Switzerland2, Surgery, Surgery Hospital Aarau, Switzerland3, Physiology, Univ Zurich, Switzerland4, Neurology, Univ Hospital Zurich, Switzerland5, Emeritus Univ, Zurich, Switzerland6. Unifmatur.unizh.ch.

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 (SaO2) 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 sea level, 4 of them reached the summit. The total time spent above 6000 m was 18 days. The average of lowest SaO2 was 65.5±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, +4.0% right). FDG-PET alterations were not correlated with AMS, HVR and AMS score. In conclusion, we found that prolonged stay at extreme altitude led, short-term after exposure, to regional 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.

<table>
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<tr>
<th>VOI</th>
<th>SaO2</th>
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<td>Baseline</td>
<td>63.3±10.1</td>
<td>83.9±10.4</td>
<td>62.6±1.0</td>
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SUPINE CYCLE ERGOMETER FOR CEREBRAL STUDIES.

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Objectives. 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 pedalled in a supine position with the head fully supported. This allows position-critical and visual-motion-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 allows resistance. A flywheel promotes smooth pedalling, 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 920m and 5260m. At each altitude, the resistance was incrementally increased to volitional exhaustion to determine the power at V0max. Subsequently, graded exercise tests were performed, working for 5 minutes each at a steady state of 30%, 50% and 70% of V02max 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 rehabilitation applications where the head or body needs to be supported, such as when monitoring cerebral functions.

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 the role of this evidence has been obtained in vivo 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 5030m 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 "Urinalysis test", a spectrophotometric measurement made before and after addition of Uroto-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 a progressive oxidative stress. The results suggest that hypoxia led to an increase in the production of ROS also in humans.

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 undertook 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 (SaO2), cerebral oxygen saturation by near infrared spectroscopy (rSO2), middle cerebral artery velocities by transcranial Doppler (MCAV), continuous non-invasive blood pressure monitoring (cnBP), 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.

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 3% SO at a flow rate of 4 l min⁻¹ (FiO2 = 0.35%). Testing sequence was randomised and double blinded, with 30 minutes of rest in between tests. Measurements were made of SaO2, minute ventilation (VE), heart rate (HR) and cardiac output (CO) by means of electrical impedance cardiacography. With SO, endurance time increased from 94 ± 263 ± 66 s (P < 0.001). In RA, SaO2 decreased from 94 ± 2% at rest to 86 ± 5% at end-exercise. SaO2 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 9.6 ± 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 PaCO2 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.

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.
Fabiola León-Velarde1, María Rivera-Chira1, Alfredo Gamboa1, fabiolv@upch.edu.pe.
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 PO2 = 50 Torr) isoapnic hypoxia in 28 high altitude natives (>3,500 m) residing at sea level (HA, 7.61 ± 0.71 m/min) and on 29 sea level natives (SL, 2.68 ± 0.81 m/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 ± 0.61 m/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 ± 0.74 m/min versus SL-ADM(+) = 5.15 ± 0.71 m/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.

63. IMPACT OF BMI ON CPAP IN THE OBSTURATIVE SLEEP APNEA SYNDROME.
Michael Laub1, Soren Berg2, Bengt Midgren1. Dept Respiratory Medicine, Univ Hospital, Lund, Sweden.1, Lund Sleep Study Group, Univ Hospital, Lund, Sweden.2. ml@laub.dk.
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. 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. Results: The analyses of the 95 percentiles 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 CPAP pressures was found in our study which might indicate a higher respiratory load in obese patients.

64. CAPNOGRAPH AT HIGH ALTITUDE.
Kyle Pattinson1, Steve Myers2, Catherine Gardner-Thorpe3. Birmingham Childrens Hospital, Birmingham, UK1, Centre for Human Sciences, Qinetiq, Farnborough, UK2, Stoke Mandeville Hospital, Aylesbury, Buckinghamshire, UK3. kyle9989@pobox.com.
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% CO2 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 Kg/I2 decreases 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. Changes in CO2 readings emphasize the importance of recalibration on change of altitude. An altered refractive index of air is the likely explanation. Kg/I2 appears to compensate. Electronic in some monitors may sense reduced barometric pressure as an air leak within the monitor2. Kg/I2 appears to compensate. Electronic in some monitors may sense reduced barometric pressure as an air leak within the monitor2. Kg/I2 appears to compensate. Electronic in some monitors may sense reduced barometric pressure as an air leak within the monitor2.

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<th>Corrected flow (litres/min)</th>
<th>CO2 (vol%)</th>
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Hypobaric hypoxia is not a dysnaptic factor in healthy subjects at rest.

Ichiro Kuwahira1, Tokuzen Iwamoto, Makoto Ishii2, Kazutaka Kamio, Mai Nishiumi2, Kenji Eguchi2. Tokai Univ Tokyo Hospital, School of Medicine, Tokai University, Japan.

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 dysnaptic 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 minutes before and after the hypoxic period, and for safety of the subjects. Mean PaO2 at a simulated altitude of 0, 2000, 3000, 4000 and 6000m were 95.4 ± 4.1 (SD), 68.1 ± 6.5, 53.3 ± 5.3, 46.8 ± 4.8, 41.8 ± 4.9 Torr, and the PaCO2 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 PaO2 and PaCO2, 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 dysnaptic 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).

Effect of L-arginine supplementation on expiered NO and respiratory symptomology with acute exposure to an altitude of 4383 Meters.

Jim Mansoor1, Ken Yoneda2, Brian Morrissey2, William Walby2, Mario Alfaro, Radhika Kajekar2, Maya Juarez2, Marlowe Eldridge3, Edward Schelegle2. Univ Pacific, Stockton, CA1, Univ California, Davis2, Univ Wisconsin, Madison3. eschelegle@ucdavis.edu.

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 gms 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 4386 m. L-arginine is a substrate for the synthesis of NO and when consumed in the diet or injected IV, plasma L-citruline 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 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 minutes before and after the hypoxic period, and for safety of the subjects. Mean PaO2 at a simulated altitude of 0, 2000, 3000, 4000 and 6000m were 95.4 ± 4.1(SD), 68.1 ± 6.5, 53.3 ± 5.3, 46.8 ± 4.8, 41.8 ± 4.9 Torr, and the PaCO2 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 PaO2 and PaCO2, 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 dysnaptic 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).

Effect of hypoxia supplementation on expired NO and respiratory symptomology with acute exposure to an altitude of 4383 Meters.

June 20th 2006.

68. HYPOCAPNIA CONTRIBUTES LITTLE TO INCREASING SaO2 AT ALTITUDE.

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Introduction: Hyperventilation at altitude increases SaO2 and PAO2, but decreases PACO2. The combination of reduced cerebral blood flow and increased affinity of Hb for O2 due to the respiratory alkalosis later reduces cerebral O2 delivery. We have measured PaCO2, PaO2, and PaCO2 constant during hyperventilation (iso-CO2) and PaO2 constant during hyperventilation (iso-O2). Our aim was to identify the contribution of hyperventilation to the hyperventilation-associated increase in SaO2 at altitude. Methods: Five healthy males were studied at 4750 m. Each was studied while breathing through a sham circuit, the iso-O2 circuit and iso-CO2 circuits at resting ventilation, and after 5 min of breathing at 4 × resting ventilation. We monitored SaO2 and tidal P02 and P02. Results: With the iso-CO2 circuit, hyperoxia increased PaO2 by 20.3 ± 5.0 mmHg (p < 0.05). With the iso-O2 circuit, hyperventilation decreased PACO2 by 11.4 ± 4.3 mmHg but PaO2 did not change (+4.2 ± 2.7 mmHg, NS). In all three conditions, the increase in SaO2 was a function of the slope of the Hb-O2 dissociation curve at the initial SaO2. Figure 1 illustrates the independent effects of changes in PAO2 and PACO2 on SaO2 during hyperventilation in the subject with the lowest initial SaO2. Discussion: This is the first demonstration of the specific contribution of hypocapnia to increases in SaO2 during hyperventilation at altitude. Decreases in P02 contributed little to raising PaO2 but increased the affinity of Hb for O2. The increase in PaO2 accounted for most of the increase in SaO2. The SaO2 data fit, within experimental error, the theoretical predictions of Kellman's “virtual PO2” equation. Breathing circuits that allow hyperoxia but maintain isocapnia at altitude may optimize O2 delivery to the brain and other tissues.
69. WHAT HAPPENS TO RESPIRATORY CHEMOREFLEXES AT ALTITUDE?
Ron Somogyi1, Joseph Fisher2, David Preiss1, Alex Vesely1, Ethan Pisman1, AR Bradwell1, Takafumi Azami2, Saafraz Mahamed3, James Duffin4. Univ Toronto, Dept Physiology1, Toronto General Hospital, Dept Anaesthesiology2, Birmingham Medical Research Expeditionary Society3, Univ Toronto, Depts Physiology and Anaesthesiology4. ron.somogyi@utoronto.ca.

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 isocapnic 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 for CO2 at both levels of isoxia was unchanged throughout the test period. However, the chemoreflex CO2 thresholds measured at both isocapnic 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 level. Nevertheless, when [HCO3−] was used to convert the CO2 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.

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

Ventilatory acclimatization to hypoxia increases ventilation (VI) and the isocapnic 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 (PIO2 = 90 Torr). HVR (ΔVI/ΔSaO2) was measured after pre-oxygenation (PIO2 > 200 Torr 20 min) by stepping to SaO2 = 90% maintaining PETCO2 = 2.5 Torr above the hyperoxic value. Isocapnic HVR was measured again by stepping to SaO2 = 80% after 5 and 11 min at SaO2 = 90% to quantify hypoxic ventilatory decline (HVD). Subjects increased PaO2 and SaO2 breathing amplitude 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 O2-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, NIHHL17731, and WMRs.

71. PHYSIOLOGICAL EFFECT OF COORDINATED BREATHING UNDER HYPOXIC ENVIRONMENT; A QUANTITATIVE STUDY OF DEEP AND ABDOMINAL BREATHING.
Shunsuke Kokubu1, Takeuteru Maekawa1, Masayoshi Yamamoto1. National Institute Fitness Sports in Kanoya1. m016011@skv.nifs.k-ac.jp.

Voluntary coordinated breathing such as hyperventilation is effective method to avoid decreasing SpO2 under a hypoxic environment. However, we also suffer negative effects such as extra loss of CO2, body fluid and temperature because of the remarkable increase of ventilation volume. To find reasonable breathing method at high altitude, we compared the 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, VO2, VCO2, SpO2 and HR of every condition. When the subjects used DB or AB, SpO2 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 VO2 and VCO2 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 SpO2 than that of AB. But DB also increase much amount of VE. On the other hand AB can increase fairly amount of SpO2 without significant increase of VE. Therefore, the AB is more reasonable breathing method under a hypoxic environment.

72. INDIVIDUAL MINUTE VENTILATION IN HIGH ALTITUDE RATS IS SUBJECTED TO A DETERMINANT DOPAMINERGIC PERIPHERAL DRIVE.
Vincent Joseph1, Magali Solares2, Jorge Solís1, Jean Marc Pequignot3, Enrique Vargas2. Centre de recherche HSFA, Université Laval, Québec, Canada1, IBBA, La Paz, Bolivia2, Írisch Univ, Zurich, Switzerland3, CNRS, Lyon, France1. joseph.vincen@crfla.ulaval.ca.

Individual minute ventilation in high altitude rats is subjected to a determinant dopaminergic peripheral drive. The role carotid body dopamine on the hypoxic ventilatory acclimatization (HVA) remains unclear. Measurements of the reports showed decrease 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% O2, 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-hour 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 dopemperidone) 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 set point 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.
Konrad E Bloch1, Oliver Senn3, Manuel Fischer2, Rahel Thalmann2, Marco Maggiorini2. Pulmonary Division, Univ Hospital, Zurich, Switzerland, Medical Intensive Care, Univ Hospital, Zurich, Switzerland. konrad.bloch@dim.uzh.ch

We investigated ventilatory adaptation in untrained 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 (SpO2) 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, SpO2 increased to 81 ± 0.8% (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.
Dale McCall1, Dargan Frierson1, James Blum1, Martyn Knowles1, Stephen Kinsey1. U. North Carolina-Wilmington1, mccall@uncw.edu

We are presenting results of experiments of DNA 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, tFE) in 4.9% O2 after 8 weeks' exposure to 5% O2 (tFE-5) in 4.9% O2 after 8 weeks' exposure to 5% O2 (tFE-5) at 3600 m (tFE-3600) were significantly increased over 3600 m (tFE-3600) at 4400 m (tFE-4400) at 4400 m (tFE-4400) at 5000 m (tFE-5000) at 5000 m (tFE-5000) at 5500 m (tFE-5500) at 5500 m (tFE-5500) at 5800 m (tFE-5800) at 5800 m (tFE-5800) at 6000 m (tFE-6000) at 6000 m (tFE-6000) at 6200 m (tFE-6200) at 6200 m (tFE-6200)

74. EFFECT OF PROGRESSIVE HYPOXIA WITH MODERATE HYPERCAPNIA ON VENTILATORY VS. VAS RESPONSES IN HUMANS.
Atsuko Masuda1, Yoshikazu Sakakibara2, Yoshih Ohyabu3, Chikako Yosino4, Toshio Kobayashi5, Teisuke Komatsu6, Michiko Tanaka6, Shigeru Masuyama7, Yoshiyuki Honda8. Cardiovascular, Thoracic & Medical and Dental University5, Hiroshi Yamanouchi9, Kyushu Medical and Dental University4, Konan University3, Miyazaki Prefectural University2, Chiba College of Allied Medical Sciences1, Yamaguchi Prefectural Unives1, Miyazaki Prefectural Nursing University7, Chiba University5.
gg9821530@nifty.ne.jp

**Objective:** Ventilatory response to CO2 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 CO2-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 PCO2 (PETCO2) levels: normocapnia, 2, and 3 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 SpO2-ventilation response curve became steeper as the PETCO2 elevated, as expected. There was a striking augmentation in the HC4 run compared with the NC0 run (0.52 vs. -0.40 1/min/%SpO2, p < 0.05). On the other hand, the slope of the SpO2-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.

HYPOTHERMIA ADAPTATION IMPROVES HEART-TOLERANCE TO HYPOXIA: STUDY ON FUNCTION AND MITOCHONDRIAL GENE EXPRESSION.
Xue-Han Ning1, Shi-Han Chen1, Cheng-Su Xu2, Linheng Li2, Outi Hyttynen2, Kun Qian2, Julia Krueger2, Micheal Portman1. Univ. of Washington/Childrens Hospital & Med Ctr1, Univ. of Washington2.

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 in the subsequent ischemia tolerance. The present study was conducted 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 PO2 = 38 mmHg). A hypothermia group (H) was progressively decreased 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 CO2 levels were measured in the coronary effluent to monitor metabolite status. Hypothermia prior to hypoxia decreased myocardial oxygen consumption (MVO2) 79% vs. the baseline value and significantly increased oxygen efficiency estimated by dP/dtmax/MVO2 and PRP/MVO2, where PRP is developed pressure (Dp/dt max) of heart rate. Hypothermia improved functional recovery about 3% in myocardial contraction (dp/dt max) vs. the previous evening (P < 0.05 vs. C) during re-oxygenation. The lactate accumulation was significantly higher in C. However, hypothermia did not further enhance HS70-1 induction compared to C. Lactate and CO2 accumulation levels were the same between the groups during hypoxia. The CO2 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.
78. CARBOHYDRATE SUPPLEMENTATION AFTER EXERCISE AFFECTS MOOD STATE AT HIGH ALTITUDE.


Introduction 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 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 VO2max (51.0 ± 2.36 mL/kg/min-1). In double-blind fashion, fasted subjects performed a maximum effort 20 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 In excess of seven thousand beat-to-beat blood pressure measurements were successfully recorded throughout the expedition, during all experiments, up to an altitude of 5290m. 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.

79. A MUCH SIMPLIFIED METHOD FOR PRECISE AND ACCURATE MEASUREMENT OF VCO2

David Preiss1, Takafumi Azami2, Steve Iscoe3, Ron Somogyi4, Eitan Prisman5, Alex Vesely6, Dan Nvoy7, George Voiles2, Joseph A Fisher1, Univ Toronto1, Nagoya City Univ2, Queens Univ3, York Univ4. david.preiss@utoronto.ca.

Commercial metabolic carts typically measure VCO2 by synchronizing and integrating flow and POCO2 signals—a method prone to error, especially in the presence of some rebreathing. We describe a simplified method of calculating VCO2 using a rebreathing circuit and compare VCO2 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 flow and the metabolic cart was 8 ± 2.5 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: VCO2 can be precisely and accurately measured using a partial rebreathing circuit from the fresh gas flow and PetCO2.
**V.1. EFFECTS OF HYPOXIA AND DEXAMETHASONE ON Na-TRANSPORT OF ALVEOLAR EPITHELIAL CELLS.**
Sabine Höschel1, Peter Bärtsch1, Heimo Mairbäurl1. Dept. Sports Medicine, Univ. Heidelberg1, heimo.mairbaeurl@med.uni-heidelberg.de.

Hypoxia 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-protein 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 O2 signaling. Control and hypoxia-treated (DEX, 1μM) A549 cells were exposed to hypoxia (1.5% O2) and Cobalt-Chloride (100μM) for 24h. Levels of a1-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 alveolar epithelial cells. 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 and 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.

**V.2. HYPOXIA REDUCES CELLULAR OXYGEN CONSUMPTION AND Na/K-ATPASE ACTIVITY OF ALVEOLAR EPITHELIAL CELLS.**
Kristin Heerlein1, Andre Müller Schulze2, Peter Bärtsch1, Heimo Mairbäurl1. Dept. Sports Medicine, Univ. Heidelberg1, Chil- drens Hospital, Univ. Heidelberg2. kristin_heerlein@med.uni-heidelberg.de.

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% O2). Cellular oxygen consumption (JO2 [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 JO2 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 JO2. However, normoxic values of JO2 were only reached after 5 min of hypoxia whereas JO2 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 JO2. This value did not change during hypoxia indicating an equivalent decrease in total and Na/K-ATPase associated JO2. Inhibitors of Na-channels had no significant effect on cellular JO2 whereas inhibition of Na/Ca-exchange tended to decrease cellular JO2. 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. JO2 is not fully restored by oxygenation after prolonged hypoxia, which indicates adjustments on the level of gene expression.

**V.3. ASSOCIATION OF RENIN-ANGIOTENSIN SYSTEM GENES WITH HIGH-ALTITUDE PULMONARY EDEMA.**
Hotta Junichi1, Masayuki Hanaoka1, Droma Yunden1, Yoshikiko Katayama2, Masao Ota1, Toshio Kobayashi1, Keishi Kubo1. First Dept Medicine, Shinshu Univ School of Medicine1, Dept Pharmacy, Shinshu Univ School of Medicine2, Dept Legal Medicine, Shinshu Univ School of Medicine3.

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 in 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 of the ACE gene by polymerase chain reaction (PCR), as well as five polymorphisms of the angiotensinogen (AGT) gene by PCR following restriction fragment length polymorphism (RFLP) of the 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 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 G151T polymorphism of the AT1R gene could be used as genetic markers for predicting the susceptibility to HAPE.

<table>
<thead>
<tr>
<th>UD polymorphism of the ACE gene:</th>
<th>HAPE-s group</th>
<th>HAPE-r group</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>D/D genotype frequency (%)</td>
<td>22.2</td>
<td>4.2</td>
<td>0.011</td>
</tr>
<tr>
<td>D allele frequency (%)</td>
<td>44.4</td>
<td>24.0</td>
<td>0.005</td>
</tr>
<tr>
<td>G allele frequency (%)</td>
<td>55.6</td>
<td>76.0</td>
<td></td>
</tr>
</tbody>
</table>

**G151T polymorphism of the AT1R gene:**

<table>
<thead>
<tr>
<th>G151T polymorphism of the AT1R gene:</th>
<th>HAPE-s group</th>
<th>HAPE-r group</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>G/G genotype frequency (%)</td>
<td>81.4</td>
<td>46.9</td>
<td>0.0006</td>
</tr>
<tr>
<td>G allele frequency (%)</td>
<td>71.0</td>
<td>57.5</td>
<td>0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genotype frequency (%)</th>
<th>59.3</th>
<th>76.5</th>
<th></th>
</tr>
</thead>
</table>

**Table 1.**

<table>
<thead>
<tr>
<th>Met235Thr polymorphism of the AGT gene:</th>
<th>HAPE-s group</th>
<th>HAPE-r group</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MetMet genotype frequency (%)</td>
<td>27.9</td>
<td>42.6</td>
<td>0.286</td>
</tr>
<tr>
<td>Met allele frequency (%)</td>
<td>18.6</td>
<td>27.7</td>
<td>0.151</td>
</tr>
</tbody>
</table>

**The allicle frequency (%)**

| 81.4 | 72.3 |

**G151T polymorphism of the AT1R gene could be used as genetic markers for predicting the susceptibility to HAPE.**

**V.4. THE POLYMORPHISMS OF THE TYROSINE HYDROXYLASE GENE IN SUBJECTS SUSCEPTIBLE TO HIGH-ALTITUDE PULMONARY EDEMA.**
Masaayuki Hanaoka1, Yunden Droma1, Junichi Hotta1, Yukinori Matsuzawa1, Toshio Kobayashi1, Keishi Kubo1, Masao Ota1. First Dept Medicine, Shinshu Univ School of Medicine1, Dept Legal Medicine, Shinshu Univ School of Medicine2, Dept Legal Medicine, Shinshu Univ School of Medicine3. ydzmyp@hotmail.com.

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 (TCA)Tn microsatellite repeats of the TH gene by polymerase chain reaction (PCR) following direct sequencing and the Met8Val 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 as in a Japanese population 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 (TCA)Tn 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 polymorphisms may not be sufficient as genetic markers for predisposing to the susceptibility to HAPE.

**Table 2.**

<table>
<thead>
<tr>
<th>Tetranucleotide Repeat</th>
<th>HAPE-s</th>
<th>HAPE-r</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>25.0</td>
<td>21.4</td>
<td>0.5866</td>
</tr>
<tr>
<td>B</td>
<td>23.8</td>
<td>35.7</td>
<td>0.1070</td>
</tr>
<tr>
<td>C</td>
<td>3.8</td>
<td>2.3</td>
<td>0.8564</td>
</tr>
<tr>
<td>D</td>
<td>40.5</td>
<td>36.7</td>
<td>0.6050</td>
</tr>
<tr>
<td>E</td>
<td>3.6</td>
<td>2.1</td>
<td>0.5288</td>
</tr>
</tbody>
</table>

**Met8Val Variant**

| Met allele (%) | 64.0 | 67.6 | 0.594 |
| Val allele (%) | 36.0 | 32.4 |       |

**A, B, C, D, and E = 5 alleles of (TCA)Tn 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.**

Kyle Pattinson1, M. F. Beazley2, Peter Forster3, Peter Hillenbrand4, Ron Somogyi2, David Preiss2, Etan Prisman5, Alex Vesely6, Len Goodman6. Birmingham Childrens Hospital, Birmingham, UK1, Laurie Pike Health Centre, Birmingham, UK2, James Paget Hospital, Great Yarmouth, UK3, Good Hope Hospital, Sutton Coldfield, West Midlands, UK4, Dept Anaesthesiology, Univ Health Network, Toronto, Canada5, Aircrew Performance and Protection Group, DRDC Toronto, Toronto, Canada6. kyle@999photonix.com.

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. SaO2 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 O2 supply was limited to a full E-sized cylinder containing ~500 L of O2 at 1 A. We applied a new investigational breathing system that combines a fixed O2 bag, which simulated a descent to 2700m. However he relapsed within one hour. **Results:** With no added O2, reducing FGF increased end-tidal PCO2 by ~1.5 mmHg, regulated the breathing pattern, left end tidal FO2 unchanged at 0.12 and increased SaO2 to 79%. Adding O2 to the circuit at a flow of 0.5 L/min, increased end tidal FO2 to 0.18 and SaO2 to 87%. O2 flow of 1.2 L/min, (ie, depleting the tank at 0.7 L/min at 1A) was maintained overnight increasing end tidal FO2 to 0.27 and SaO2 to ~94%. In the morning the treatment was discontinued; the patient returned well without O2 supplementation for about 2-3 hours while preparing for descent. Conclusions: This breathing system effectively improves SaO2 by eliminating periodic breathing. It efficiently delivered O2 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 (SaO2) was 97 ± 1% at LA, and 75 ± 4% and 28 ± 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 ± 5 mmHg at HA2 (p < 0.001). Inhibition 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 combination 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 SpO2 in moderate-severe COPD patients without oxygen supplementation (WT) and during 2 weeks of nocturnal oxygen therapy (NO). We recruited 9 patients, median age 61 years (46-72). 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 (SaO2) was 97 ± 1% at LA, and 75 ± 4% and 28 ± 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 ± 5 mmHg at HA2 (p < 0.001). Inhibition 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 combination 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.

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

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Sildenafil (Viagra), a vasodilating selective phosphodiesterase inhibitor, has been noted to improve pulmonary vasodilation at altitude. We investigated the cerebrovascular response to sildenafil 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 sildenafil 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:** Although sildenafil 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 sildenafil at altitude may be due to its influence on the cerebral vascular bed in addition to its pulmonary effects.
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 at high 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 altitudes of 1,500–6,200 m (Murdock 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 (PAMS) 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 = 3.35). 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.

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 (VO2max 66.5 ml/kg/min) to the elite endurance athlete (VO2max 35 ml/kg/min). Throughout a three week acclimatization at the White Mountain Research Station (3,800m), a series of maximal and submaximal (70% relative VO2max) 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 22–3 years, body mass 78.4 ± 15.3 kg, VO2max 48.2 ± 7.8 ml/kg/min) 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, VO2max 58.1 ± 6.6 ml/kg/min) 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 Kilimanjaro hut (4,700m). 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 (SaO2). Our analysis revealed that an SaO2 <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 SaO2 <81% (p = 0.007), 15% (3/20) vs. 39% (66/171) in those living ≥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 SaO2 and a residence below 700m are independent risk factors for the development of AMS, and that others, such as age, sex, BMI, AMS history and acclimatization are not associated with the condition.

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 ± 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 O2. Measurements were made immediately, with and without O2, after reaching the summit and 3 h later. Hypobaria had no effect on any of the measured variables, i.e., results obtained with O2 at altitude were not different from those at sea level. Pikes Peak results were qualitatively similar to those obtained with simulated altitude, but temporarily delayed: IPD (O2, <1 h: 5.9 ± 0.8; no O2, 3 h: 5.2 ± 1.0 mm, p < 0.001), and CL (O2, <1 h: 302 ± 19; no O2, 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 (SaO2) and subjective symptoms to hypoxia in moderate altitude residents (MAR) and low altitude residents (LAR) following rapid ascent to 4056 m (pressure altitude). Resting ventilatory parameters (open-circuit spirometry) and SaO2 (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 ~1hr at 4,056 m on the summit of Pikes Peak, CO following ascent by car. Resting SaO2 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 (X ± S.D): At 1,940 m the MAR subjects’ PETCO2 and SaO2 were 33.6 ± 2.8 mmHg and 94 ± 1%, respectively, and decreased (p < 0.001) to 32.1 ± 4.5 mmHg and 86 ± 2% at 4,056 m. At 50 m the MAR group PETCO2 and SaO2 were 38.7 ± 2.7 mmHg and 98 ± 1%, respectively, and decreased (p < 0.001) to 36.4 ± 3.5 mmHg and 82 ± 5% at 4,056 m. From 1,940 to 4,056 m, the MAR group SaO2 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 75:117,1973; 91:1791,2001) our results suggest that prolonged residence at ~2,000 m elevation induces a level of ventilatory acclimatization equivalent to residing at 4,056 m for approximately 9–12 days.

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 ≥ 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 ≥ 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 ≥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 ≥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.
VALIDATION OF PULSE OXIMETRY DURING PROGRESSIVE NONMORBARI HYPOXIA UTILIZING PORTABLE CHAMBER.
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Non-invasive estimation of arterial oxygen saturation (SpO2) with pulse oximetry has been identified as a possible method to assess the pathologic of acute mountain sickness (AMS) during sojourns to high altitude. In order to evaluate the performance of pulse oximetry and assess the efficiency of nonmorbardic chambers, we decided to compare indirect measurements of arterial oxygen saturation (SaO2) by cooximetery (AVOXimeter 4000), which were simultaneously compared with SpO2 (Nellcor 295) using both reflectance (RS-10) and transmission (D-25) sensors (placed on the forehead and finger respectively), while the inspired oxygen fraction (FI O2) inside a NHC (Hypoxic Inc.) was progressively reduced from 20% to 11.5% over a 2.5 hr 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 hour for evaluation of altitude illness like symptoms. Within subject factor MANOVA exhibited a significant time effect for SaO2 during the progressive nonmorbardic hypoxic exposure (F (4,44) = 97.33, P < 0.001) (Table). As well, a significant time effect was observed in AMS symptoms (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 defensible accuracy for estimating SaO2 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 nonmorbardic hypoxia, the performance of finger tip pulse oximetry deteriorates substantially at saturation levels below 85% when compared to the forehead position.

EFFECTS OF ACUTE MOUNTAIN SICKNESS SYMPTOMS ON ENERGY INTAKE: RESULTS FROM A TYPICAL HIMALAYAN TREK TO MAKALU BASE CAMP.
Toms on energy intake: results from a typical (low altitude 1:LA1), followed by 8 days above 2500m (high altitude 2:HA), and a 5 day descent below 2500m (low altitude 2: LA2). Results showed a decrease of mean calcite 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 HA (p < 0.01). No significant differences 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.

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 showed 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 (BP) were evaluated at exposure to 3700 m. 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 exposure. Airliquide-Chile, VRA-UDP.
WOBBLE BOARD (WB) ACUTE MOUNTAIN SICKNESS (AMS) AND CEREBRAL REGIONAL OXYGENATION (SPO2).

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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 (rSO2) 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 rSO2 (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.

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 (4935m), 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.

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 receptor-I-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 receptor-I-60 was observed at HA (vs. SL, P < 0.05), retrospective analyses 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.

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.

FREE RADICAL-MEDIATED VASCULAR DAMAGE AND ALTITUDE SICKNESS (AMS) AND CEREBRAL REGIONAL OXYGENATION (SPO2).

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Introduction: 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 (rSO2) 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 rSO2 (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.
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-vo hypo 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 (FiO2 of 0.21 at sea-level to 0.13 at the summit) incorporating treadmill ascent and descent rates of 2.5/min (applying a +5°/gradient) and 3.8/min (−5°) 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 and increased 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 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.

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

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Recently it 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 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 (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 = 0.79 ± 0.71 vs. 0.59 ± 0.59, 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.

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: Fifteen 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 = 0.79 ± 0.71 vs. 0.59 ± 0.59, 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.

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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 difference compared to the other trials, p < 0.05 compared with the other trials, p < 0.05 compared with rest.

BODY TEMPERATURE AUTONOMIC RESPONSES AND ACUTE MOUNTAIN SICKNESS.

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A few studies have reported increased body temperature (T0) associated with acute mountain sickness (AMS), but these usually include exercise, varying environmental conditions over days and associated with a primary edema. We wished to determine whether an increase in T0 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 PaO2 (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 T0 was measured by oral digital thermometer before altitude and after (A1), 6 (A6) and 11 (A12) hr at simulated altitude. Other measurements included ventilation, O2 consumption and autonomic indicators of plasma catecholamines, HR and HR variability. The average T0 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 0-4.9) 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 TO, 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 at ventilation changes suggest that augmentation of beta-adrenergic tone may be involved in early AMS pathophysiology. Supported in part by U.S. Army Med Res Materiel Cmd, DAMD17-96-C-6127.

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ANALYSIS OF HYPOXIA-INDUCIBLE FACTOR 1α (HIF1α) GENE IN ANDANE 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. HIF1α gene (14q21-q24) consists of 15 exons, and encodes the HIF1-α subunit. Gene expression is highly regulated by cellular O2 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 CMS, 10 healthy) and 20 non-related Europeans (10 healthy, 10 CMS). We identified a heterozygous missense mutation (P582S, exon12) in one of the 10 subjects with CMS. 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 HIF1α genes and related changes could contribute to elucidate either genetic/environment fitness or human diseases in subjects with different responses to hypoxia.

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

Hannah-Christian Gunla1, Karl Kirsch, Clarence Altrey4, Gordon Bell3, Dieter Blottner4, Reinhard Gorstad1, Male Keck1, Eberhard Koralewski, Bernd Johannes, Maike Keck1, C Beatty, PW Hochachka. Center for Space Medicine Berlin1, Baylor College Houston2, Univ British Columbia2, gunkell@edat-fu-berlin.de.

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 outflow failure. Long-term hemodynamic changes in subjects 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. 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. Statistical analysis: MANOVA; SPSS 10.0 for WINDOWS. Results. Packed cell volume (PCV), hemoglobin concentrations, transferrin-receptors [TrR], 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 intracellular and extracellular VEGF concentrations, and an increase in diaphorase activity/NOS 1-3. The increase in capillary density is consistent with an increased angiogenesis as shown by the increase in capillary density combined with an upregulated diaphorase activity/NOS 1-3. It confirms that hypoxia-hypobaric environment inside the space habitats could be used to trigger angiogenesis and angiogenesis. Sponsored by DLR, Germany (DLR-Project # 50-WB 0022)

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% O2) for 24 h. 0.1 μg 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 evaluated by densitometry. The striatum, raphe, 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 APOQ.


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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 outflow failure. Long-term hemodynamic changes 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 were compared 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).
Acute hypoxia increases heart rate (HR) and cardiac output (QT) at a given oxygen consumption (VO2) 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 continuing 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 VO2max = 3.1 ± 0.7 L/min, means ± SD)—during exercise in normoxia and acute hypoxia (FIO2 = 0.125) to VO2. 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 and end-tidal CO2 extraction. Hypoxia increased venous [epinephrine] and [norepinephrine] but not [dopamine] at a given VO2 (P < 0.05, P < 0.01 and P = 0.2 respectively). HR/V02 and QT/V02 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. This 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 RR08287.

**L15. EFFECTS OF INTERMITTENT HYPOXIC TRAINING ON ACCLIMATIZATION IN ELITE CROSS-COUNTRY SKIERS.**

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In group H, interventricular septum thickness increased from 10.3 to 11.2 (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 pulmonary arterial pressure. Nocturnal desaturation was 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.

**L14. VAGAL NERVE BLOCKADE DECREASES SPO2 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 (SpO2) in hypoxic condition in humans before and after blocking vagal nerve activity with atropine. METHODS: 6 volunteers breathed hypoxic gas (11–12% O2 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. SpO2 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 SpO2 (P < 0.05, paired t-test). DISCUSSION/CONCLUSION: The decrease in SpO2 after vagal nerve 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.

**L16. THE PHYSIOLOGICAL AND PSYCHOLOGICAL IMPACT OF INTERMITTENT HYPOXIC TRAINING (IHT) IN THE PREPARATION OF THE GB BIATHLON TEAM FOR THE 2002 OLYMPIC GAMES.**

Gregory Whyte1, Andrew Lane2, Charles Pedlar1, Richard Godfrey1, British Olympic Medical Centre1, Univ Wolverhampton2. greg.whyte@bsoa.org.uk.

**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 assess 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 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 hypoxic sensitive organs, and to develop techniques preventing possible side effects. In our experimental study we studied 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% O2) 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 periodical 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: anthropometric measurements, ECG registration, analyses of blood and urine, PWC170 psychological tests, 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 PWC170 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, the other 2 sportsmen 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 periodical hypobaric hypoxia and antioxidiant 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 prazosin, 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 effect 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 dexmethasone (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; hypoxialmic Cushing suppresses GH release, which increases PRL release. Hypoxia 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%, O2). TRH levels were measured by specific radioimmunoasay. Hypoxia (5000m altitude, 10.8% O2) and severe hypoxia (7000m altitude, 8.2% O2) significantly enhanced TRH levels of ME and PVN and declined serum T3.

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% O2) and began to regain hereafter. No alteration was found with intermittent hypoxia of 2 km altitude (16.0% O2 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 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 spleen cells proliferation and DNA contents. This effect was mediated through NE. The parasympathetic system reduced hypoxia-suppressed immune responses. Intermittent hypoxia showed an elicited effect. 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 (FiO2 = 0.5). Rats were then exposed to moderate, followed by severe isocapnic hypoxia (FiO2 = 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 hypoxia, 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.
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 non-Bolivian nationals, to have immigrated there as adults. IUGR was defined as birth weight <3rd percentile for gestational age and sex using sea-level criteria.

Methods: Medical records were examined from 3565 consecutive deliveries to women with 2 babies of Andean ancestry, non-Bolivian nationals, and mestizo (“mixed”) ancestry between Bolivian vs. recent migrants from low altitude, birth weight was lower (3101 ± 3352 ± 15 gm, p < 0.01) but gestational age (38.8 ± 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 protects against altitude-associated IUGR, suggesting the involvement of unknown genetic factors.

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 inhabitable portion (A Amiloride) of the NPD at HA6. Stimulated Cl- transport with low Cl- or isoprenaline was not significantly altered.

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.

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

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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: dissociation, 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.