50. THE EFFECTS OF ACE GENE POLYMORPHISM ON CARDIORESPIRATORY RESPONSES TO HYPOXIA.

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INTRODUCTION: The insertion homozygote (II) of the ACE gene appears to confer an advantage at high altitude. We have demonstrated an excess of the Insertion (I) allele in elite mountaineers. Nature 1998; 393:221-2). This raises the question: Does the presence of the Insertion homozygote improve performance because of either enhanced ventilatory adaptation or by optimising cardiovascular responses to hypoxia? METHODS: We studied 33 healthy subjects (M:F, 25:8; Age, 18-33). Genotyping was performed on mouthwash samples using specific DNA probes (II: n=9;ID; n=15;DD: n=9, i.e. subject group demonstrated Hardy-Weinberg equilibrium). Each subject underwent maximal cardiopulmonary exercise testing (Sensormedics Vmax29, CA., USA) using breath-by-breath analysis. Anaerobic threshold (AT) was determined. Subjects then underwent steady-state exercise at 50% of the workload at AT under conditions of normoxia and normobaric hypoxia (FiO_2 12.5%). Heart rate, VO_2, VCO_2, tidal volume, respiratory rate and SpO_2 were measured and minute volumes; ventilatory equivalents and oxygen pulse were calculated. To maximise any differences between either genotype, analyses was performed on the two homozygote groups. Statistical analyses were by ANOVA. RESULTS: Heart rate responses to hypoxia in the II group were significantly higher at rest ($p=0.004$), however whilst trends occurred to suggest an increased ventilatory response to hypoxia in the II group during hypoxic exercise ($p=0.116$), these were not significant. CONCLUSION: Our current study suggests enhanced performance in II homozygotes may be attributable to enhanced heart rate response to acute hypoxia. No significant difference in ventilatory response was demonstrated between groups. Further studies to examine cardiac output responses in relation to ACE genetics are underway.

51. POLYMORPHISMS IN THE RENIN-ANGIOTENSIN SYSTEM IN THE QUECHUA, A HIGH-ALTITUDE NATIVE POPULATION.

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There are some data suggesting that cardiovascular disease may be less common in high-altitude native populations than it is in sea level populations and that this may be due to increased cardiovascular efficiency associated with adaptive responses to high-altitude hypoxia. If there is a predilection to cardiovascular fitness in these populations, it may be reflected by an under-representation of alleles associated with cardiovascular disease. There are several such alleles at polymorphic loci in the genes encoding components of the renin-angiotensin system (RAS). We determined frequencies of four of these in Quechua, a high altitude Andean population, and compared them to those determined in two lowland populations: Caucasians of Western European descent and AmerIndians (Mayan) from the Campeche State of the Yucatan. The polymorphisms examined were the insertion/deletion polymorphism in intron 16 of the angiotensin converting enzyme (ACE) gene, the C/A1166 mutation in the untranslated 3' region of the angiotensin 2 receptor (type 1) gene, an intronic substitution in the renin gene (G/AI9-83) and the Met235Thr mutation (T/C704) mutation in angiotensinogen (AGT). There were no significant differences in allele frequencies between the two Native American populations for any of the polymorphisms. Frequency of the ACE allele associated with heart disease was higher in the Caucasians than in the Amerindians (56 % vs. ~27%) whereas the converse was seen for AGT allele associated with hypertension and cardiovascular disease (42% vs. ~78%). This study found no evidence for an over-representation of the RAS alleles associated with cardiac fitness in the Quechua when compared to a lowland Native American population.

52. CARDIOPULMONARY FUNCTION IN LADAKHI AND TIBETAN HIGHLANDERS.

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Genetic differences in high altitude adaptation are well documented. We studied Ladakhi and Tibetan residents of high altitude in Ladakh, India to determine potential effects of age, gender, and ethnicity on gas exchange and pulmonary function. Physical examinations, including pulse oximetry, end-tidal PCO_2, and spirometry, were conducted on resting subjects at altitudes ranging from 3300 m (Leh) to 4647 m (Lake Tsomoriri). Approximately 600 subjects ranging in age from 20 to 82 were studied. At 3300 m, Ladakhis had higher heart rates than Tibetans in both genders and higher $PETCO_2$ in females. As predicted, Hb was higher in males for both groups. In contrast to prior work with smaller samples, there was no gender difference in SaO_2 at any altitude. At 4600 m, Tibetans showed higher peak flows and lower PETCO2 than Ladakhis. Males had higher Hb and lower heart rates. Ladakhi males had higher diastolic BP than females (91 vs. 81) with no difference in systolic BP. There was no gender difference in BP for Tibetans. An important spirometry finding for both groups was high airway conductance (mid maximal expiratory flow) at 130 – 150% of predicted values compared with control sojourners (102% of predicted). Tibetan males had a higher peak flow (as % predicted) than females (105 vs. 93%) but no difference in MMEF. Tibetans and Ladakhis also had increased airway conductance expressed as FEV1/FVC compared with sojourner controls (115 vs. 98 %). Higher airway conductance may be an important adaptation in reducing the respiratory work of increased ventilation at high altitude.

53. ACCLIMATISATION TO HIGH ALTITUDE BY HIGH-ALTITUDE NATIVES RESIDENT AT SEA LEVEL.

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High-altitude (HA) natives have a blunted ventilatory response to acute hypoxia (AHVR). By way of contrast, sea-level (SL) natives increase AHVR on acclimatisation to hypoxia. Recently, it has been suggested that HA natives recover much, if not all, of their AHVR if resident at SL. The question thus arises, do HA natives, who are resident at SL and who have recovered their AHVR, demonstrate a SL native response and increase AHVR when exposed to HA, or do they demonstrate a HA native response and reduce AHVR? To address this issue, we measured AHVR (under isocapnic conditions) in 15 HA natives resident at SL and 14 SL natives. These measurements were made first at SL, and then repeated daily after they had been transported to 4,300 m (453 Torr) for 5 days. In the HA native group that were resident at SL, AHVR increased by 0.94 l/min/% from the 1st day of arrival to the 5th day at HA, and, in the SL native group, AHVR increased by 0.76 l/min/% over the corresponding time period. These increments were significant, but did not differ between the groups. We conclude that acclimatisation to HA does not differ between HA natives resident at SL who have recovered their AHVR and SL natives.

This study was supported by the Wellcome Trust.

54. INCREASED INCIDENCE OF PREECLAMPSIA LOWERS BIRTH WEIGHT AND INCREASES INTRAUTERINE MORTALITY AT HIGH ALTITUDE.

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Objective: Residence at high altitude decreases birth weight due to intrauterine growth restriction (IUGR) and increases the incidence of preeclampsia in Colorado. We asked whether preeclampsia is more common at high altitude in Bolivia and if so, decreases birth weight and raises intrauterine mortality. Methods: We reviewed medical records for consecutive, singleton deliveries with >2 prenatal visits from 1/96-3/98 at Sta Cruz (SC, 300 m, n=813) and La Paz (LP, 3600 m, n=1610). We combined preeclampsia (PE, hypertension + proteinuria) and gestational hypertension (GH, hypt w/o proteinuria) due to insufficient proteinuria determinations. Gestational age was considered as wks from last menstrual period or by clinical exam when values differed by >2 wk, and IUGR as <10th percentile for the age and sex-specific sea level values. Results: The two groups were similar in parity, weight gain but the LP women were older (30±0 vs 28±0 yrs) and had more prenatal visits (7±0 vs 6±0). PE/GH was ~3-fold more common at high altitude. Birth weight was lower at high vs. low altitude, due to IUGR, and reduced further in PE/GH compared with normotensive women. Babies of normotensive women also weighed less at high vs. low altitude (table). Intrauterine mortality was ~10-fold greater in PE/GH vs. normal women. Conclusions: An increased incidence of preeclampsia/gestational hypertension contributes to altitude-associated IUGR and raises intrauterine mortality in Bolivia. (Supported by NIH-TW01188, HL 60131 and the assistance of Bolivian hospital and clinic personnel).

Table (X±sem)	Sta Cruz	La Paz
PE/GH, %	6.8	17.7*
birth wt,all gm	3366±18	3084±12*
normal	3385±18	3120±13*
PE/GH	3049±114+	2953±37+
gest. age, wks	38.9±.06	38.7±.05
normal	39.0±.06	38.9±.05
PE/GH	37.7±.4+	38.2±.2+
preterm, %	8.4	10.5
IUGR, %	5.9	16.7*
intraut mort^all	7.6	12.0
normal	2.8	5.6
PE/GH	57.7+	44.9+

*=p<.05 lo vs hi alt, +=p<.05 nl vs PE/GH, ^=deaths/1000 livebirths

55. ISCHEMIA/HYPOXIA-INDUCED EFFECTS ON SMOOTH MUSCLE CYTOSKELETON AND VASCULAR TONE.

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Objective: To investigate the effect of increasing periods of ischemia/hypoxia on the actin cytoskeleton of vascular smooth muscle and how this correlates with vascular tone in middle cerebral arteries (MCAs). Methods: MCAs from male Wistar rats were made ischemic/hypoxic by surgically placing a 5-O nylon monofilament into the internal carotid artery and advancing it until it occluded the MCA. Successful occlusion was determined using laser Doppler flowmetry. Four groups of animals were compared, all with different periods of ischemia/hypoxia: sham-operated Control (n=6), 15 min. (n=6), 30 min. (n=7) and 120 min. (n=8) of ischemia/hypoxia. MCAs were then carefully dissected and mounted in a specialized chamber that allowed control of intravascular pressure and measurement of lumen diameter. The amount of vascular tone at 75mmHg was determined, after which arteries were fixed with formalin (pressurized) and stained for filamentous actin (F-actin) with fluorescently-labeled phalloidin, a specific probe for F-actin. F-actin content was determined using confocal microscopy. Results: The amount of tone was similar between Control and 15 min. of ischemia/hypoxia (27±2% and 25±2%, p>0.05), but was significantly diminished after 30 and 120 min. (12±2 and 8±2%, p<0.01 vs. control). F-actin content also decreased at the longer ischemic/hypoxic periods and correlated significantly with vascular tone (p=0.04) such that the lesser the tone, the lesser the F-actin content. Fluorescence intensity for Control, 15, 30, and 120 min. of ischemia/hypoxia was (x107): 3.21±0.25, 2.54±0.32 (p>0.05), 2.32±0.15 (p<0.01) and 2.22±0.16 (p<0.01). Conclusions: These results demonstrate that ischemia/hypoxia disrupts the actin cytoskeleton in smooth muscle and diminishes vascular tone of MCAs in a threshold-dependent manner. This effect likely exacerbates brain tissue damage during stroke, including infarction and edema formation.

56. A SINGLE SUBCUTANOUS BOLUS OF RECOMBINANT ERYTHROPOIETIN NORMALIZES CEREBRAL BLOOD FLOW AUTOREGULATION AFTER SUBARACHNOID HEMORRHAGE IN RATS.

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Erythropoietin (EPO) has been demonstrated to mediate neuroprotection when the recombinant form is directly injected into ischemic rodent brain. However, recent studies revealed that expression of EPO receptors in brain capillaries provides a specific route for circulating EPO to enter the brain. We investigated the in vivo effects of subcutaneously administrated recombinant EPO on impaired cerebral blood flow (CBF) autoregulation after experimental subarachnoid hemorrhage (SAH) in Sprague-Dawley rats. Four groups of rats were investigated: Group A: sham operation plus vehicle (isotonic saline); Group B: sham operation plus EPO; Group C: SAH plus vehicle; Group D: SAH plus EPO. SAH was induced by injection of 0.07 ml of autologous blood into the cisterna magna. EPO (400 IU/kg s.c.) was given immediately after the subarachnoid injection of blood or saline. 48 h after the induction of SAH, CBF autoregulatory function was measured using the intracarotid 133Xe method. Cerebral autoregulation was intact in both sham-operated groups (lower limits of mean arterial blood presssure: 101±7 mmHg and 101±5 mmHg in groups A and B, respectively). In the vehicle treated SAH-group, the relationship between CBF and blood pressure was best described by a single linear regression line, indicating a disturbed CBF autoregulation. A subcutaneous injection of EPO immediately after the induction of SAH normalized autoregulation of CBF (lower limit in group D: 114±8 mmHg, NS compared with groups A and B). The results suggest that activation of endothelial EPO receptors may represent a potential therapeutic strategy in the treatment of cerebrovascular pertubations after SAH.

57. PLASMA ERYTHROPOIETIN AND SOLUBLE TRANSFERRIN RECEPTOR DURING AND AFTER ALTITUDE EXPOSURE.

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The present study was designed to evaluate the time course of markers of erythropoiesis during and after high altitude exposure. Plasma erythropoietin (EPO), soluble transferrin receptors (sTfR), hematocrit and hemoglobin concentrations were measured in two different conditions at high altitude : A) during Operation Everest III (COMEX '97), at 0, 5000, 6000, 7000 and 8000m simulated altitude; B) at Vallot observatory (4350m) after 3, 5 and 7 days at altitude and 6 and 18 hours after returning to sea-level (SL). Epo and sTfR were measured using chemoluminescence (Nichols Advantage). In experiment A, exposure to progressive altitude induced a significant parallel increase in EPO (from 19± 5 to 654 ± 514 mU/ml at 8000m, p<0.01) and sTfR (from 17.5±4.2 to 121.4±54.8 mmol/l at 8000m, p<0.001). In experiment B, increase in EPO was transient, with a maximum at 3 days (+452%, p<0.001) and EPO was back to basal values after 6h return to SL, whereas sTfR peaked after 7 days at altitude (+86%, p<0.001) and were still elevated after 18 hours at SL (+64%, p<0.001). In conclusion, the time course of plasma EPO and sTfR differ with altitude exposure and return to SL. Combined measurement of both parameters may allow to distinguish between altitude-induced and exogenous EPO-induced increase in erythropoiesis.

58. EXCESSIVE ERTHROCYTOSIS (EE), CHRONIC MOUNTAIN SICKNESS (CMS) AND PULMONARY GAS EXCHANGE IN THE ANDES.

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Patients with CMS and EE have high blood viscosity and suffer a gradual but inexorably fatal disease, which is marked by poor tissue perfusion. High altitude mammals have high levels of nitric oxide (NO) by-products in blood and urine suggesting an attempt to vasodilate and improve perfusion to tissues in hyperviscous states. Methods: We studied the relationship between hematocrit (Hct) and arterial blood gases (ABG) in men living at 4280 meters in Cerro de Pasco, Peru. We also measured urinary nitrates as a marker of NO activity. Results: 28 subjects (EE) had Hct > 65%, range 66-91%. 27 (HA) had Hcts = 65%. There was an inverse correlation of PaO_2 and Hct and positive correlation between Hct and CMS score, diastolic BP, uric acid. Urinary nitrates were not elevated in either group. Conclusion: CMS is associated with astounding EE, impaired oxygenation, relative hypoventilation but does result in increase in NO synthesis. (Supported by a grant from Baxter)

59. ACE AND ENOS GENE POLYMORPHISM AND MONGE'S DISEASE.

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Objective: Analysis of the association between alleles of the eNOS and ACE genes and Monge´s disease. High altitude long time residents are at risk of developing chronic mountain sickness (CMS), a clinical condition characterised by the loss of adaptation to environmental hypoxia. Racial differences, familial clustering, and animal studies are suggestive of a genetic involvement in Monge's disease. CMS manifests by an excessive erythrocytosis, hypoventilation and in most cases pulmonary hypertension. The physiological response mounted to compensate the requirement of O2 in hypoxia appears insufficient in CMS patients and leads to chronic hypoxemia and to a progressive deterioration of neurological, circulatory and respiratory systems. Endothelial nitric oxide synthase (eNOS) is a gene that encodes a nitric oxide producing enzyme, which is involved in maintaining the basal vascular tone, blood flow and pressure. ACE gene product is involved in the regulation of blood pressure. eNOS Glu298Asp polymorphism shows OR = 0.84 (0.28 <OR< 2.54; p =0.9) and VNTR polymorphism OR = 1.48 (0.39 <OR< 5.80; p= 0.7). Insertion/ deletion ACE gene polymorphism shows OR = 1.04 (0.41 <OR< 2.60; p= 0.89). These results shows no evidence of association between eNOS and ACE gene loci and Monge's disease. Interestingly, control group haemoglobin (Hb) values (g/dl) show a correlation with ACE genotypes II (18.40 ± 0.97), ID (18.66 ± 1.11) and DD (19.75 ± 0.93), with p= 0.48 (II and ID) and p= 0.018 (II and DD), not observed in the CMS group. These results suggest that ACE is related to the polycythemic response to environmental hypoxia in the control group.

60. SLOW BREATHING RESTORES OXYGEN SATURATION IN ANDEAN ALTITUDE NATIVES.

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Slow respiration improves oxygen saturation (SaO^2) and ventilatory efficiency in chronic or acute hypoxia (Bernardi, Lancet, 1998). We analyzed the relationships between respiratory parameters and polycythemia in Andean altitude natives to test whether 1) polycythemia could be associated to ventilatory inefficiency 2) changes in breathing pattern could benefit subjects with different levels of polycythemia. In 31 natives of Cerro de Pasco, (4338m, Peru), with variable degrees of polycythemia (hematocrit, Ht, from 44 to 76%), during spontaneous breathing (SBr), controlled breathing at slow (6/min) and normal (15/min) rates, we measured ventilation (VE), end-tidal carbon dioxide (CO_2), SaO_2, hypoxic and hypercapnic ventilatory responses (HVR, HCVR, at SBr only), before and after 45 min. of normoxia (CP+ox). During SBr, SaO_2 correlated inversely, and CO_2 correlated directly with Ht ($p<0.0001$), whereas VE and HCVR did not; HVR showed lower (inverse) correlation with Ht ($p<0.01$). During controlled breathing SaO_2 increased ($p<0.0001$) in all subjects, but, at 15/min this was associated to increased VE ($p<0.0001$) and reduced CO_2; at 6/min an even greater SaO_2 increase occurred without changes in VE and CO_2. The extent of increase in SaO_2 during 6/min (reaching even 17%) depended on baseline SaO_2 ($r= .63$, $p<0.0005$) and correlated inversely with resting HVR ($p<0.05$) and Ht ($p=0.05$): i.e. more compromised subjects improved more. During CP+ox the same pattern was observed, despite an increase in VE and SaO_2 ($p<0.0001$) during SBr in all subjects. These results suggest that 1) a functional (rather than lung organic) alteration, likely due to abnormal breathing pattern, may cause the association between low SaO_2 and high Ht 2) slow breathing improves ventilatory efficiency and may potentially reverse the abnormalities seen in Andean altitude natives

61. FUNCTIONAL BAROREFLEX DYSFUNCTION IN ANDEAN ALTITUDE NATIVES IS PARTIALLY RESTORED BY IMPROVED OXYGENATION.

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Andean altitude natives with chronic mountain sickness (CMS) have neurologic/autonomic symptoms at altitude, which disappear at sea-level. Whether autonomic/baroreflex abnormalities contribute to CMS and reverse with normoxia is unknown. We measured RR interval (RR), systolic blood pressure (SBP), and respiratory variabilities, by spectral analysis, in 31 natives of Cerro de Pasco (CP), (4338m, Peru), with variable degrees of CMS (CMS score 4-26, average 12.9±1.3) at baseline and during carotid baroreflex modulation by sinusoidal neck suction (NS) at 0.1Hz (LF, sympathetic modulation on SBP, vagal and sympathetic on RR), and at 0.2Hz (HF, vagal modulation on RR), in CP before and during normoxia (CP+ox), and in Lima, after one night sleeping at sea-level (SL). Subjects were divided according to CMS score (CMS+: =/> 12, N=15, CMS-: <12, N=16). In CP, compared to CMS-, CMS+ showed reduced resting HF ($p<0.05$), reduced HF-NS modulation on RR ($p<0.02$), and reduced LF-NS on RR ($p>0.02$) but not on SBP, indicating preserved sympathetic modulation but reduced cardiac and baroreflex vagal modulation. CP+OX slightly increased RR modulation, particularly in CMS-, so all differences became more significant. At SL, CMS score dropped in all subjects to 2.9-±0.5 ($p<0.0001$); spontaneous and NS-induced modulations remained unchanged in SBP, whereas RR resting and NS-induced HF increased ($p<0.01$) in CMS+, attenuating the differences with respect to CMS- ($p<0.05$ during both LF-NS and HF-NS). Resting HF ($p<0.01$) and HF-NS in RR correlated inversely with CMS score ($p<0.0002$) in CP. Vagal and baroreflex dysfunction may be implicated in the origin of CMS symptoms; this is at least partially reversible with improved oxygenation.

62. CENTRAL DEPRESSION AFFECTS VENTILATORY PARAMETERS IN HIGH ALTITUDE ANDEAN NATIVES WITH OR WITHOUT POLYCYTEMIA.

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We evaluated the hypothesis that hypoxia depresses, instead of stimulates, ventilation in Andean altitude natives with polycythemia. We then studied 31 natives of Cerro de Pasco (CP), (4338m, Peru) with variable degrees of polycythemia (Hemoglobin from 14.9 to 25.3 g/dL, hematocrit, Ht, from 44 to 76%). We measured hypoxic (HVR) and hypercapnic (HCVR) ventilatory responses, minute ventilation (VE), end-tidal carbon dioxide (CO_2) and oxygen saturation (SaO_2) in CP before and after 45 min. of normoxia (CP+ox), and in Lima, sea-level, after one night of sleeping in normoxia (SL), and after 45 min (SL+hyp) of breathing 12% O_2. Subjects were divided according to their hematocrit (Ht+: =/> 55%, N=19, Ht-: < 55%, N=12). In CP, HVR was normal in Ht- and reduced in Ht+ ($p>0.01$), and the values correlated with Ht ($p<0.01$). VE was similar, but SaO_2 was lower and CO_2 higher in Ht+ vs Ht-. CP+ox increased VE in all subjects ($p<0.0001$) and in both groups, and normalized SaO_2; immediately after CP+ox, HVR results no longer different in Ht+ vs Ht-. At SL, VE, SaO_2 and CO_2 increased ($p<0.01$), though HVR slightly decreased ($p<0.05$) in all subjects. SL+hyp further increased VE in all subjects, though the increase was less pronounced ($p<0.05$) in HT+, and during SL+hyp SaO_2 dropped more in Ht+ than in Ht- ($p<0.05$). HCVR was similar in all groups and conditions. The increase in VE with acute oxygen administration or with transfer to sea level, suggests that at altitude Andean natives may undergo central depression, regardless of their hematocrit levels. Although HT+ subjects show a lower response, improving blood oxygenation may partially reverse the depressant effects of acute hypoxia in Andean altitude natives.

63. USEFULNESS OF REGULATED BREATHING UNDER HYPOXIC CONDITIONS.

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Lowlanders during mountain climbing and high altitude trekking invariably experience acute mountain sickness (AMS) due to hypoxia. It has been found that highlanders have lower incidence of AMS as compared to lowlanders due to differences in Hyper Ventilatory Response (HVR). Lowlanders who migrate to higher altitude for the purposes of meditation are well protected from the ill effects of hypoxia. It is also well known that animals have lower incidence of AMS. One of the physiological factors involved in the process of acclimatization is the communication from the Hypothalamus to the Pituitary-Adrenal system. In animals hypothalamic function is more efficient than in man. The hypothalamus gets inputs from olfactory system to the supra-optic and para-ventricular areas of hypothalamus through well-established pathways. The inputs of signals such as oxygen content and the temperature of the air inhaled are prime factors in the hypothalamic regulation of AMS. Large number of clinical and biochemical observations (by the authors) on various groups of people during eight major Himalayan expeditions up to an altitude of 7300 meters have indicated the direct role of olfactory system in the process of acclimatization. Authors have experimental evidence on the role of olfactory system in hypoxic and hypothalamic adaptations. Rats whose olfactory nerves were destroyed, when exposed to hypoxic and hypothermic conditions failed to adapt as compared to the control group. Biochemical and physiological parameters studied in both human volunteers and laboratory animals strongly support the hypothesis that the Olfactory-Hypothalamo-Pituitary-Adrenal Axis (OLPHIA) is the prime regulatory mechanism in acclimatization to high altitude conditions.

64. THE EFFECT OF 12% OXYGEN GAS MIX ON PERIPHERAL AND CEREBRAL OXYGENATION AND THE RESPONSE TO SUPPLEMENTARY CARBON DIOXIDE.

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Background. Acute mountain sickness (AMS) occurs amongst some individuals who ascend rapidly to high altitude. Symptoms include headache, dizziness, ataxia and nausea. New non-invasive techniques to assess cerebral perfusion including near infra-red cerebral spectroscopy (NIRS) have recently become available and may offer an insight into the mechanisms involved in the development of AMS. Methods The acute effect of 12% oxygen on peripheral oxygenation and cerebral perfusion was investigated in 17 subjects (3 female; age 22-56) at 150m. Once a steady state had been achieved, supplementary CO2 was then added to the 12% oxygen. A Harvard dry gas meter was used to measure minute ventilation (VE). Arterial oxygen saturation (SaO2) and end tidal CO2 (PETCO2) were measured using a Propac Encore Monitor; NIRS regional cerebral oxygenation (rSO2) was measured using a Critikon 2020 monitor (Johnson and Johnson, UK). Transcranial Doppler (TCD) middle cerebral artery velocity (MCAV) was assessed using a Logidop 3 TCD machine (Scimed, UK) by a single trained observer.

	$PETCO_2$	SpO_2%	rSO_2%	MCAV cms-1	Minute ventilation l min-1
Baseline	39(3.1)	97.6(1.2)	69.7(2.8)	53.1(8.1)	6.5(2.3)
12% oxygen	36.0(3.5)*	39(3.1)*	63.7(3.1)*	58.9(10.3)8	7.8(1.9)*
12% O_2+CO_2	46.2(6.3)**	93.6(5.6)**	69.0(3.0)**	62.4(8.5)**	11.0(5.1)**

Statistics: Mean (SD), Paired t test * $p<0.05$ vs Baseline, ** $p<0.05$ vs 12% oxygen. Conclusion. 12% oxygen resulted in a fall in SpO_2, $PETCO_2$ and cerebral rSO_2. Although the $PETCO_2$ fell in this acute study, there was a rise in MCAV, suggesting that the hypoxic vasodilatory stimulus had over-ridden the vasoconstrictor effect of the reduced $PaCO_2$. Carbon dioxide had measurable short term effects in hypoxic individuals at sea level. The mechanisms include increase in minute ventilation, improved arterial saturations, a shift to the left in the oxygen dissociation curve and vasodilation of specific vascular beds including in particular the cerebral circulation.

65. A REDUCTION IN THE INCIDENCE OF ACUTE MOUNTAIN SICKNESS AND HIGH ALTITUDE PULMONARY EDEMA AT 4250M IN NEPAL.

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In 1976, acute mountain sickness (AMS) was reported as 53% at 4250m (observed at Himalayan Rescue Association (HRA) in Nepal) and High Altitude Pulmonary Edema (HAPE) was 2.5%. To establish whether the incidence of AMS and HAPE had changed over 24 years, we observed the incidence of AMS over 8 weeks, in the trekking population, at the same site at 4250m. Subjects volunteered from trekkers visiting the HRA for education, not necessarily medical treatment. (No specific inclusion/exclusion criteria). A questionnaire was used to determine AMS symptoms as well as intercurrent illnesses, medications, and other demographic data. We observed 909 subjects (M=603 and F=306): AMS was reported in 257/909 subjects (M=158 F=99) as determined using Lake Louise Score (headache plus one other symptom). The incidence of AMS was 28%, a 47% reduction since 1976. There was no significant difference in the number of males and females reporting AMS, nor a significant difference between the severity of AMS in males (mean=3.6 (SD=1.6)) and females (mean=4.8 (SD=2.2)). HAPE was only diagnosed twice in this population making the incidence less than 1% in this setting. We suggest that reduction in AMS (and HAPE) is due to a combination of factors, including improved awareness of the signs and symptoms of mountain sickness. This may be from information individuals found from sources such as guidebooks, encouraging slower ascent or descent if symptoms persist, as well as the availability of medications for prophylaxis and treatment. We conclude that the incidence of AMS is 28% at 4250m and has shown a 47% reduction over a 24 year period, associated with a reduction in the cases of HAPE. We would like to acknowledge the assistance of the HRA and support of Medex.

66. NEAR INFRA-RED CEREBRAL SPECTROSCOPY AND THE CARBON DIOXIDE CEREBROVASCULAR RESERVE.

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Cerebrovascular reserve capacity (CVRC) is defined as the ability of cerebral resistance vessels to dilate in response to cerebrovascular vasodilatory stimulus. Trans-cranial Doppler assessment of the time averaged mean middle cerebral artery velocity (TAMV) is conventionally used to assess the CVRC. Recently near infra-red cerebral spectroscopy (NIRS) CVRC has been assessed in normal subjects at sea level and has been shown to correlate closely with the TCD TAMV CVRC. We describe the use of NIRS CVRC at altitude for the first time. Twelve healthy non-smoking subjects (ten men) aged 24-53 years were studied at 150m and a month later at 3459m. Pulse oximetry (SpO_2) and end tidal CO_2 ($PETCO_2$) were measured using a Propac Encore Monitor; the oxygenated haemoglobin (HbO_2), and deoxygenated haemoglobin (HDO_2) were measured using a Critikon 2020 monitor; middle cerebral artery velocity (MCAV) was assessed using a Logidop 3 machine (Scimed, UK). Power was obtained from a Honda 1.5kw generator. 3% supplementary carbon dioxide was used as the cerebral vasodilatory stimulus at both altitudes.

TAMVmax-TAMVmin /Δ $PETCO_2$= TCD CVRC

$HbO2CO2$-$HbO2BL$/Δ $PETCO_2$= NIRS HbO_2 CVRC

$HbDO2CO2$-$HbDO2BL$/Δ $PETCO_2$= NIRS $HDO2$ CVRC

Results. The TCD CVRC was greater at sea level than at 3459m; 149.7(50.9) vs 32.9(4.2) ($P<0.036$). The NIRS HbO_2 CVRC was greater at sea level than at 3459m; 0.97(0.37) vs 0.14(0.11) ($P<0.03$). The NIRS $HbDO_2$ CVRC was greater at sea level than at 3459m; 0.39(0.23) vs 0.11(0.12) ($P<0.0004$).

There is a reduction in the ability of the cerebral resistance vessels to vasodilate on acute exposure to 3459m when assessed by either by TCD or NIRS. At altitude the cerebrovasculature appears to be approaching maximal vasodilation. Theoretically an altitude might be reached where further vasodilatation may not be possible, and a further increase in cerebral oxygen requirements would result in focal or global neurological deficits.

67. NEAR INFRA-RED CEREBRAL SPECTROSCOPY AND THE ASSESSMENT OF CEREBRAL BLOOD VOLUME AT SEA LEVEL AND CORRELATION WITH SUSCEPTIBILITY TO THE DEVELOPMENT OF ALTITUDE ILLNESS.

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Background. Acute mountain sickness (AMS) is common amongst individuals who ascend rapidly to high altitude. The cranial cavity has a fixed volume, and it has been suggested that in subjects with a large brain to cranial cavity ratio are at greater risk of developing symptoms when they develop cerebral oedema. Near infra-red cerebral spectroscopy (NIRS) is a non invasive investigation that can be used to measure cerebral blood volume (CBV). With a hypoxic stimulus it is possible to plot the decline in arterial oxygen saturation (SpO_2) against the decline in cerebral NIRS oxygenated haemoglobin (HbO_2). The gradient is directly proportional to the CBV (BJA 1999; 83:418-26). In this experiment we measure sea level (SL) NIRS CBV in an attempt to predict subsequent susceptibility to AMS. Methods. 16 subjects (3 women) had NIRS CBV assessed at SL. Pulse oximetry (SpO_2) and end tidal CO_2 ($PetCO_2$) were measured using a Propac Encore Monitor; HbO2 was measured using a Critikon 2020 monitor. Baseline measurements were made, and then subjects were rendered hypoxic using 12% oxygen. Twice daily Lake Louise self-assessment questionnaires and a once daily independent clinical assessment of AMS were made during a 13 day ascent from 1340m to 5005m on foot.

	Baseline	12% O_2 minute 1	12% O_2 minute 2
SpO_2 %	97.1(1.2)	94.7(1.8)*	90.0(2.1)*
HbO_2 (mmol/l)	77.5(21.3)	76.6(20.7)*	74.8(21.5)*

Statistics: Paired t test * $p<0.001$ vs Baseline

There appeared to be a weak correlation between the SL NIRS CBV vs AMS scores ($p<0.089$). Conclusion. In this preliminary study we have been able to measure SL NIRS CBV, and have attempted to correlate this with the subsequent development of AMS within the group during an expedition to 5005m. The technique appears practical and further assessment of changes in NIRS CBV with ascent to altitude and its relationship to the development of AMS is indicated.

68. NEAR INFRA-RED CEREBRAL SPECTROSCOPY AND THE ASSESSMENT OF CEREBRAL BLOOD FLOW AT ALTITUDE.

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Background. Near infra-red cerebral spectroscopy (NIRS) is a non invasive investigation that can measure cerebral oxygenation. More recently NIRS techniques have been used to measure cerebral blood flow (NIRS CBF). The principle involves getting the subject to breath a bolus of oxygen enriched air, and by determining the rate of arrival of this O_2 bolus in the brain it is possible to calculate the cerebral blood flow (Fick Principle). In this experiment we describe its use at altitude to determine cerebral blood flow for the first time. Methods. Twelve healthy non-smoking subjects (ten men) aged 24-53 years were studied at 150m and a month later at 3459m. Pulse oximetry (SpO_2) and end tidal CO2 ($PeCO_2$) were measured using a Propac Encore Monitor. The oxygenated haemoglobin (HbO_2), and deoxygenated haemoglobin (HDO_2) and regional cerebral saturations (rSO_2) were measured using a Critikon 2020 monitor; middle cerebral artery velocity (MCAV) was assessed using a Logidop 3 trans cranial Doppler machine.

	TCD MCAV	Cerebral rSO2 Baseline	Cerebral rSO2 on 35% oxygen
Sea level	58.8(14.2)	69.7(2.6)	70.3(2.6)*
3475m	63.1(18.6)#	65.7(3.2)#	68.8(2.9)*#

Statistics: Paired t test * $p<0.005$ vs Baseline # $p<0.0001$ vs Sea level. The rate of arrival of the oxygen bolus at 3475m was considerably faster than at sea level, reflecting the higher CBF at altitude. Conclusion. In this preliminary study we have been able to measure changes in NIRS CBF at sea level and at 3475m. The technique appears practical and further assessment of changes in NIRS CBF with ascent to altitude and its relationship to the development of AMS is indicated.

69. TRANSCRANIAL DOPPLER AND NEAR INFRA-RED CEREBRAL SPECTROSCOPY: ACETAZOLAMIDE CEREBROVASCULAR RESERVE CAPACITY AT 150M AND 4600M.

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The cerebrovascular reserve capacity (CVRC) is defined as the ability of the cerebral resistance vessels to dilate in response to a cerebrovascular vasodilatory stimulus. The usual vasodilatory stimuli being either supplemental CO2 or the carbonic anhydrase inhibitor acetazolamide (Az). This study aimed to compare the Az CVRC at 150m and 4600m.

Calculations of the Az CVRC are based upon the standard equations:

TAMVmax / TAMVbaseline = CVRCTAMV

HbO2 max / HbO2baseline =CVRCHbO2

HDO2 max / HDO2baseline =CVRCHDO2

Methods. 12 subjects (1 woman) were studied at 150m and after ascent from 1340m to 5005m on foot over 13 day period and a further 5 days spent at 4600m. At the time of the 4600m study no individual had AMS. Pulse oximetry (SpO_2) and end tidal CO2 ($PETCO_2$) were measured using a Propac Encore Monitor. The near infra-red regional cerebral oxygenation (rSO_2), the cerebral oxygenated haemoglobin (HbO2) and the cerebral deoxygenated haemoglobin (HDO_2) were all measured using a Critikon 2020 monitor (Johnson & Johnson, UK). The trans-cranial Doppler middle cerebral artery velocity (MCAV) was assessed using a Logidop 3 machine (SciMed,UK). Power at 4600m was obtained from a Honda 1.5kw generator.

	150m	4600m
Az CVRC TAMV	1.15(0.2)	1.21(0.23)
Az CVRC HbO2	1.05(0.23)	1.03(0.18)
Az CVRC HDO2	1.02(0.2)	1.02(0.16)

Statistics: Paired t tests: No difference was found between the two altitude groups. Conclusion. There was no difference in the Az CVRC at 150m and in partially acclimatised subjects at 4600m using either NIRS or TCD based measurements. Az would appear to have the same vasodilatory capacity at sea level and 4600m in partially acclimatized individuals. Further studies on acute exposure are indicated.

70. CEREBRAL PERFUSION AT 0M, 2400M AND 5050M AND THE RESPONSE TO VOLUNTARY FORCED HYPERVENTILATION.

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Background. Both PiO_2 and $PeCO_2$ alter on acute exposure to high altitude. Hyperventilation has profound effects on the $PeCO_2$ and results in changes in near infra-red cerebral spectroscopy (NIRS) cerebral oxygenation (Clinical Science 2000: 98;159-164) and this study aimed to further investigate effects on cerebral perfusion. Methods. 8 subjects (5 male) aged 31-56 were studied at 0m, 2400m and 5050m, travelling by road from 0m. Nights were spent at 2,200m and 2,400m.

Pulse oximetry (SpO_2) and end tidal CO2 ($PETCO_2$) were measured using a Propac Encore Monitor; regional cerebral oxygenation (rSO_2) was measured using a Critikon 2020 monitor; middle cerebral artery velocity (MCAV) was assessed using a Logidop 3 machine; power at 5050m was obtained from a Honda 4kw generator. After baseline studies were complete, 1 minute of voluntary forced hyperventilation (FHV)was undertaken.

	0m	0m FHV	2400m	2400m FHV	5050m	5050m FHV
SpO_2 %	98.7(1.5)	99.5(1.7)*	94.6(1.5)	99.7(0.5)*	73.6(4.9)	95.5(0.9)*
$PETCO_2$	37.4(1.9)	21.9(2.8)*	36.4(2.8)	19.4(1.8)*	29.4(1.8)	7.0(2.6)*
MCAV cms-1	54.5(10.2)	37.2(16.1)*	55.9(14.8)	25.1(9.6)*	61.8(12.4)	19.6(11.3)*
rSO_2 %	69.2(2.7)	67.2(3.1)*	68.5(2.1)	68.3(2.1)	62.1(1.6)	66.9(1.34)*

Statistics: Paired t test/ANOVA * p<0.005 FHV vs Baseline at 0m, 2400m, 5050m. Conclusion. At 5050m there was a fall in SpO_2, $PETCO_2$ and rSO_2, but a rise was observed in MCAV compared to values at 0m. Hyperventilation reduced $EtCO_2$ and increased SpO_2 at all altitudes. With FHV at 0m, the reduction in MCAV overrode the small increase in SpO_2, resulting in a drop in cerebral oxygenation; however at 5050m the increase in SpO_2 was so great that despite the reduction in MCAV there is an increase in rSO_2. At the intermediate altitude of 2400m the two effects appear to approximately cancel each other out.

71. CEREBRAL, HEPATIC, RENAL, SKELETAL MUSCLE AND PERIPHERAL OXYGENATION AT 0M, 2400M AND 5050M.

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Background. Acute ascent to altitude can result in acute mountain sickness (AMS) in susceptible individuals. AMS is characterised by capillary leakage from cerebral, pulmonary, renal and peripheral vascular beds. Near infra-red cerebral spectroscopy (NIRS) allows tissue oxygenation at a depth of 4-5cms to be interrogated in a non-invasive fashion. The response of various tissue beds was investigated non-invasively using NIRS techniques on ascent to 5050m. Methods. Acute exposure to 5050m was investigated in 8 subjects (5 male) aged 31-56. Travel was by road from 0m. Nights were spent at 2,200m and 2,400m. Pulse oximetry (SpO_2) and end tidal CO_2 ($PETCO_2$) were measured using a Propac Encore Monitor. Regional cerebral (Cer rSO_2), hepatic (Hep rSO_2), left renal (Ren rSO_2), and right soleus (Sk M rSO_2) oxygenation was measured using a Critikon 2020 monitor; power at 5050m was obtained from a Honda 4kw generator.

	SpO_2	$PETCO_2$	Cer rSO_2	Hep rSO_2	Ren rSO_2	Sk M rSO_2
Sea level	98.8(1.2)	37.4(1.9)	69.0(2.5)	74.3(0.8)	75.6(2.1)	73.1(3.1)
2,400m	94.6(1.2)*	36.4(2.8)	68.2(2.1)	72.7(3.6)	69.7(3.6)*	70.3(3.3)
5,050m	72.6(5.6)#	29.4(1.8)#	62.1(1.6)#	65.8(2.3)#	68.4(4.1)#	63.1(4.9)#

Statistics: Paired t test * p<0.05 vs Sea level, # p<0.05 vs 2400m. Conclusion. Assessed by NIRs, acute exposure to 5050m resulted in profound cerebral hypoxia and, for the first time, deoxygenation of peripheral tissue. It may be possible to use similar techniques to assess various therapeutic interventions such as supplementary oxygen, carbon dioxide, portable hyperbaric chambers or drug interventions.

72. CEREBRAL PERFUSION IN SEA LEVEL COMMUTERS AT 5050M ELEVATION.

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Background. Telescopes are sited at high altitudes in order to benefit from enhanced astronomical 'seeing', the consequence of the reduced thickness of the earth's atmosphere and the reduced atmospheric pollution at high altitude. Astronomers must contend with the physical effects of hypoxia and are also required to perform complex intellectual tasks. A radiotelescope (ALMA) is planned at Chajnantor (5050m) in northern Chile: staff will reside at 2400m and commute daily to the telescope. Methods. 8 subjects (5 male) aged 31-56 ascended to the Chajnantor site travelling by road from Arica (0m). Nights were spent at Calama (2,200m) and San Pedro de Atacama (2,400m). Pulse oximetry (SpO_2) and end tidal CO2 ($PETCO_2$) were measured using a Propac Encore Monitor; regional cerebral oxygenation (rSO_2) was measured using a Critikon 2020 monitor; middle cerebral artery velocity (MCAV) was assessed using a Logidop 3 machine; power at 5005m was obtained from a Honda 4kw generator.

	SpO_2 %	$PETCO_2$	rSO_2 %	TAMV cms-1
Sea level	98.8(1.2)	37.8(1.9)	69.0(2.5)	54.5(10.2)
2,400m	94.6(1.2)*	36.4(2.8)*	68.2(2.1)	55.9(14.8)
5,050m	72.6(5.6)**	29.4(1.8)**	62.1(1.6)**	61.8(12.4)*

Statistics: Paired t/ANOVA * p<0.005 vs Sea level, ** p<0.005 vs 2,400m. Conclusion. Unacclimatised sea level residents commuting to 5050m suffer profound peripheral and cerebral hypoxia even after two nights sleeping at the intermediate altitudes of 2200m and 2400m. Oxygen enrichment (6%) of living and working areas of the telescope rather than acclimatization has been proposed. The problems associated with safe and efficient operation of telescopes at such high altitudes demands novel solutions, but also requires close supervision of the workforce at risk.

73. THE EFFECT OF ACETAZOLAMIDE ON PERIPHERAL PULSE OXIMETRY AND CEREBRAL PERFUSION IN PARTIALLY ACCLIMATISED INDIVIDUALS.

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Background. Acute mountain sickness (AMS) is common amongst individuals who ascend rapidly to high altitude. A number of strategies to prevent AMS have been adopted including slower rates of ascent and the use of the carbonic anhydrase inhibitor acetazolamide (Az). Climbers who have partially acclimatised to an intermediate altitude may be tempted to use Az prior to further ascent in the belief that additional benefits may be conferred.

Methods. 12 subjects (1 woman) who had ascended from 1340m to 5005m on foot over 13 days and had spent a further 5 days at 4600m were studied. At the time of the study no individual had AMS. Baseline pulse rate, pulse oximetry (SpO_2), cerebral regional oxygenation (rSO_2) and trans-cranial Doppler middle cerebral artery velocity (MCAV) were measured at 4600m. Following the ingestion of 500mg of oral Az the pulse rate and SpO_2 were measured at 2, 4, 8 and 24 hrs; the rSO2 and MCAV were measured at 2 and 4 hrs.

	Baseline	2 hrs post Az	4 hrs post Az	8 hrs post Az	24 hrs post Az
Pulse	61.0(9.4)	64.7(7.7)*	66.0(7.0)*	73.3(12.4)*	76.8(16.4)*
SpO_2 %	85.6(2.8)	81.95(3.9)*	81.9(4.1)*	85.7(7.3)	85.3(5.7)
MCAV cms-1	51.7(10.3)	60.5(7.0)*	52.2(9.6)*		
rSO_2 %	64.4(3.9)	64.8(2.6)	63.6(1.9)*		
HbO_2 umol-1	97.3(34)	97.3(29.1)	95.9(28.6)		
HDO_2 umol-1	51.4(11.2)	51.9(11.3)	53.5(10.9)		

Statistics: Paired t test * p<0.01 vs 0 hrs

Conclusion. A single dose of oral 500mg Az conferred no benefit to partially acclimatised individuals, and would appear to have a temporary adverse effect on peripheral saturation and cerebral oxygenation. MCAV rose at 2 hrs. There is no data to support the use of Az in partially acclimatised subjects.

74. HUMAN REGIONAL CEREBRAL HEMODYNAMICS DURING LIGHT EXERCISE AT MODERATE ALTITUDE.

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Dynamic, regional hemodynamics to the human brain are influenced significantly by exercise, hypobaric hypoxia and ventilation. In normal daily activity, most exercise is nonstrenuous and does not extend beyond 20seconds. The transient effects of short-term moderate exercise on human regional cerebral blood flows and pressures have not been reported at moderate altitude. These data may have clinical implications in populations that live or visit moderate altitudes. Using noninvasive transcranial Doppler, spectral blood velocity waveforms (6msec) from the middle cerebral artery (MCA), the basilar artery (BA), andphasic blood pressures (Collins method) were recorded in 14 healthy adults (18-45 yr) during rest and during the first 20 sec of 75 Watt upright ergometer exercise at 640 Torr ambient pressure. Blood velocity and pressure waveforms during exercise were stable and exhibited minimal motion artifacts (S/Nratio > 20 db). Even with the onset of the muscle pump, MCA and BA blood velocities showed no significant change ($p>0.10$) when averaged over the first 20 sec of exercise: mean and SD; MCA 52(16) vs 48(14) cm/s; BA 36(9)vs 34(11) cm/s. Heart rate and ventilation increased significantly ($p<0.05$)with no change in mean blood pressure. Results suggest that with the combined effects of moderate hypoxia, increased ventilation, and transition into large muscle mass exercise, regional hemodynamics (as indexed by blood velocities and radial artery pressures) in the human middle cerebral and basilar arteries (anterior and posterior regions) do not significantly change within 20 seconds from the onset of exercise at moderate altitude. Thus, routine physical activity at moderate altitude (2200M) has minimal hemodynamic and convective mass transport effects in the human brain.

75. NA^+/K^+ ADENOSINE TRIPHOSPHATASE (NA^+/K^+ ATPASE) ACTIVITY IN MICE SCIATIC NERVES DURING CHRONIC HYPOBARIC HYPOXIA.

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Burning hands and burning feet (BH/BF) is the most prominent symptom in Chronic Mountain Sickness neuropathy. We have previously described a relation between BH/BF and decreased Na^+/K^+ ATPase activity in sural nerves in high altitude natives. However, it is unknown whether Na^+/K^+ ATPase activity of peripheral nerves in chronic hypoxia differs from its sea level counterparts. To assess this problem, we used mice as an animal model. Fifteen one month old Swiss mice were divided into hypoxic (H; n=8) and control (C; n=7) groups. H group was exposed to hypoxia in a hypobaric chamber for 23 hours a day over a 21 day period at a simulated altitude of 15000 feet (4572m). After the 21 day period was completed, mice were sacrificed by cervical dislocation, sciatic nerves were extracted and homogenated. Na^+/K^+ ATPase activity in homogenates was then assayed spectrophotometrically. When comparing group C with group H, we found an increase in hematocrit (45.9 vs. 68.9%, $p<0.001$), a decrease in body weight (30.26 vs. 27.33 g, $p<0.03$), and a decrease in Na^+/K^+ ATPase activity (42.43 vs. 19.12 umoles/mg prot/h, $p<0.03$). Thus, decrease of Na^+/K^+ ATPase activity in hypoxia is probably due to downregulation of Na^+/K^+ ATPase pump density or to the effect of an endogenous inhibitor in order to reduce ATP demand. The importance of this finding in small fiber neurophaties at sea level (Chronic Pulmonary Obstructive Disease) and at high altitude (Chronic Mountain Sickness) has to be elucidated.

76. SPATIAL LEARNING IN RATS EXPOSED TO CHRONIC HYPOXIA.

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Acute hypoxia exposure produces impairment in mental functions such as learning and memory. Hyppocampus plays an important role in these functions and is also one of the most vulnerable areas to hypoxia/ischemia. However, the effect of chronic hypoxia in the learning and memory has not been evaluated. Twenty-one one month old rats were divided in two groups, hypoxic (n=10), exposed to hypobaric hypoxia for three weeks, and normoxic group (n=11). Rats were tested in the Morris Water Maze during seven days with four trials each day. Transfer test was performed in the eight day of the experiment. Latency (time) to reach the hidden platform was increased in the first days ($p<0.003$). Although in the seventh day there was no difference between both groups. Transfer test showed no differences between both groups. These results indicate that the hypoxic animals have a transient delay in spatial learning acquisition that at the end does not produce significative impairment in the strength of their memories.

77. CHRONIC HYPOBARIC HYPOXIA AND ENERGETIC METABOLISM IN MICE CEREBRAL CORTEX.

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The brain has a very high metabolic rate, however little is known about its metabolic adaptation to chronic hypoxia. Twelve 21 day old, male Swiss mice were divided in two groups, hypoxic and control. Hypoxic group was placed in a hypobaric chamber (438 mmHg) for three weeks. After that we assayed activities of enzymes of the glycolytic pathway, Krebs cycle, the respiratory chain and Na+K+ ATPase. There were no differences in Na+K+ ATPase activity or in the activity of glycolytic enzymes. In the Krebs cycle, a 66% increase of succinate dehydrogenase activity was found due to a lower Km. In contrast, respiratory chain cytochrome oxidase activity was reduced by 12% in mice exposed to hypoxia. This would suggest that the metabolic demand would be satisfied despite the respiratory chain depression (cytochrome oxidase), probably due to anaerobic energy production within the mitochondria (succinate dehydrogenase).

78. NA^+, K^+, ADENOSINE TRIPHOSPHATASE (ATPASE) ACTIVITY IN SURAL NERVES AND PERIPHERAL NEUROPATHY OF CHRONIC MOUNTAIN SICKNESS.

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Burning feet/Burning hands (BF/BH) are symptoms in small fiber neuropathies. BF/BH is a complaint (39%) in Andean natives. We biopsied sural nerves from 4 chronic mountain sickness (CMS) patients (CMS-score >12) and 6 altitude natives without CMS in Cerro de Pasco (CP, 4340 m), Peru. Three CMS patients were biopsied in Lima (150 m.), within hours after all symptoms (but not all signs) disappeared. Three additional CMS patients were biopsied in CP for morphometric analysis of the nerves. A symptom score was assigned for BF/BH. Nerves were assayed for cytochrome oxidase (CO), ATPase, substance-P (SP) and endothelin (ET) activity/content by standard methods. CO activity in nerves decreased with increasing age ($p<0.03$). Low ATPase activity was related to BF/BH symptom score ($p<0.008$) and to CMS-score ($p<0.05$). SP and ET were inversely related to hematocrit (HTC) ($p<0.001$). Inappropriately thin myelin sheaths for axon diameter, increased proportion of fibers showing remyelination and ultrastructurally occasional fibers undergoing axonal degeneration were found. Glycogenosomes, polyglucosan bodies and pleomorphic inclusions were seen in axons. Flattened Schwann cell processes associated with loss of unmyelinated fibers were present. A reduction of the basal laminal zone of microvessels when compared to sea level controls was observed. The reduction of CO with increasing age parallels the increase in CMS with advancing years. Low ATPase in nerves of subjects with BF/BH at altitude is restored at sea level concurrently with the disappearance of BF/BH and is not related to CMS. Reduction of SP and ET with increasing severity of CMS, shown by an increasing HTC, points to maladaptive responses to hypoxia in which these peptides participate. Altitude natives show structural adaptations in nerve microvessels that allow shorter diffusion distance for O_2.

79. TERBUTALINE DOES NOT PREVENT FORMATION OF HYPOXIC PULMONARY EDEMA.

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It is well established that terbutaline stimulates amiloride-sensitive Na-reabsorption across cultured alveolar epithelial cells and the reabsorption of Na and fluid instilled into the lung (JAP 74:1; 1993). This knowledge served as the basis for studying the prevention of high altitude pulmonary edema (HAPE) with beta-adrenergic agonists (A.J.Resp.Crit.Care Med. 161:A415, 2000). Here we studied, whether terbutaline treatment also prevented the formation of hypoxic edema in the isolated ventilated and perfused rat lung. Exposure of isolated lungs of normoxic rats to graded hypoxia (35%, 14.5%, 6%, 3%, 1.5% O_2) indicates that the time of survival of the isolated lungs was shortened significantly as the degree of hypoxia increased. Inhaled terbutaline did not prevent or delay hypoxic edema formation. Terbutaline arrived in the alveolar space as indicated by an increase in cAMP levels in lung tissue and perfusate. However, cAMP levels were lower in hypoxic lungs. When lungs were studied at the onset of edema formation, it was found that bronchoalveolar lavage fluid of hypoxia-exposed lungs contained great amounts of albumin which originated from the perfusate, whereas no albumin was found in lavage fluid of normoxic rat lungs. This indicates the formation of a leak for macromolecules whose formation is accelerated by hypoxia, and which appears to be similar to the leak for albumin and even red blood cells as found in broncho-alveolar lavage fluid of subjects suffering from HAPE (A.J.Resp.Crit.Care Med. 161:A418, 2000). Since leaky epithelia lack transepithelial potential, vectorial ion currents and, subsequently, stimulation of transport by terbutaline, it appears reasonable to assume that beta-agonists should not exert their action in preventing HAPE by stimulation of alveolar Na- and fluid reabsorption.

80. EFFECTS OF NIFEDIPINE ON ALTITUDE-INDUCED STRUCTURAL MODIFICATIONS OF PULMONARY ARTERIES.

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Chronic hypoxia induces pulmonary vasoconstriction and muscularization of pulmonary arteries, leading to pulmonary hypertension and right ventricular hypertrophy. A vasodilator treatment could inhibit this vasoconstriction by reducing the muscularization of the pulmonary arteries. The purpose of this study was to know which type of arteries are the point of impact for this treatment. Wistar rats (250 g) were submitted to chronic hypoxia (380 torr) during 15 days. Four groups of animals were studied : treated with nifedipine or saline, both in hypoxia and normoxia. The muscularization of intra-acinar arteries (< 300 mm) was evaluated in a prospective double-blind study by optical microscopy using the wall thickness index (WTI = 2 x Wall thickness x 100 / external diameter). Hypoxia increased right ventricular weight (RVW) (+ 92 %, $p < .001$), the Fulton's ratio (RV/(LV+S)) (+ 98 %, $p < .001$) and systolic right ventricular pressure (SPRV) (+ 146 %, $p < .001$). In hypoxia, nifedipine treatment decreased RVW by 17 %, Fulton's ratio by 16 % and SPRV by 26 %. RVW and SPRV were linearly correlated ($r = 0.89$, $p < .001$). Nifedipine treatment decreased WTI (- 24 %, $p < .001$), only in hypoxia, but not uniformly. The frequency distribution of pulmonary arteries WTI was shifted to the left by nifedipine treatment. Only arteries with a WTI between 30 and 40 % are modified by nifedipine. In conclusion, arteries with a WTI between 30 and 40 % appear to be specifically responsive to nifedipine and thus may be responsible, at least in part, for the development of pulmonary hypertension.

81. DECREASED NA^- BUT INCREASED CL^- TRANSPORT ACROSS THE NASAL EPITHELIUM IN HIGH ALTITUDE HYPOXIA.

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It has been shown that hypoxia inhibits ion transport in cultured epithelial cells. Here we studied, whether exposure to hypoxia at high altitude also inhibits ion transport activity of human subjects and whether there were any differences between subjects developing high altitude pulmonary edema (HAPE) and healthy controls (Co) during a study at the Capanna Margherita (4559m). In vivo transport activity was assessed by measuring the transepithelial potential difference across the nasal epithelium (NP). Our results show that NP in normoxia (Zürich, 520m) was lower by about 5mV in HAPE whereas there was no statistically significant difference between groups in amiloride-sensitive Na^- reabsorption and in low-Cl plus isoproterenol-stimulated Cl^- secretion. Ascent to 4559m caused an increase in total NP from -20mV to almost -70mV (Co) and from -15mV to -45mV in HAPE. This hyperpolarization at high altitude was due to a 2-fold increase in Cl^- conductance, whereas Na^- transport was inhibited (statistically significant only in Co). Since NP was difficult to measure at the Capanna Margherita due to dry air causing incrustation and/or inflammation of the nasal mucosa, NP was also measured in another group of randomly selected subjects during six hours exposure to normobaric hypoxia (12% O_2). Hypoxia-induced changes in NP were smaller than those observed at 4559m but also show hypoxic hyperpolarization by about 10mV and a 25% increase in low-Cl plus isoproterenol-stimulated Cl^- secretion, whereas Na^- transport was not affected. Our results indicate that hypoxic modification of transport is not an artifact induced by dry air at high altitude. They also show that activation of the Cl^- conductance precedes the hypoxic inhibition of Na^- transport and that hypoxia modulates ion transport differently in HAPE-susceptibles.

82. CHARACTERISTICS OF PULMONARY ARTERY WAVEFORM IN HIGH ALTITUDE PULMONARY EDEMA SUSCEPTIBLE SUBJECTS.

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It has been suggested that high altitude pulmonary edema (HAPE) susceptible (S) subjects present with a higher pulmonary vascular tone. Aim of the present study was to investigate pulmonary artery pressure waveform in 16 HAPE-S subjects and 14 controls (C). Pulmonary artery pressures were measured using a Swan-Ganz catheter (SGc) at 490 m and 4559 m. At high altitude, subjects inhaled 20 µg of the prostacyclin analogue Iloprost (iPG). To quantify the magnitude of pulsatility relative to mean pressure we normalized pulse pressure by mean pressure, herein referred as fractional pulse pressure (fPP). Our results are shown in the table: (Mean ± SD; SPpa = systolic pulmonary artery pressure; PP = pulse pressure; fPP = fractional pulse pressure)

		Low altitude	High altitude	iPG(20µg)
Stroke volume (ml)	C	102 ± 14	87 ± 19*	92 ± 14
	S	92 ± 19	82 ± 18*	94 ± 15*f*
SPpa (mmHg)	C	20 ± 3	37 ± 6*	24 ± 3*
	S	23 ± 4*#	59 ± 9*#	35 ± 11**f*#
PP (mmHg)	C	11 ± 2	20 ± 4*	12 ± 2
	S	14 ± 3*	34 ± 5*#	20 ± 7**f*#
fPPc (mmHg)	C	0.77 ± 0.14	0.78 ± 0.15	0.70 ± 0.09
	S	0.92 ± 0.16*	0.90 ± 0.12*	0.85 ± 0.13*

p at least < 0.05 * vs low altitude; *f* vs. high altitude; # vs C. At low altitude HAPE-s, compared to controls, present with higher SPpa, PP and fPP suggesting a decreased arterial compliance in these subjects. Ascent within 24 hours to high altitude does not change fPPc differences between the HAPE-S and controls. Inhaled iPG tend to improve pulmonary artery compliance.

83. ATRIAL NATRIURETIC PEPTIDE (ANP) AMELIORATES HIGH ALTITUDE PULMONARY EDEMA (HAPE) IN ENDOTOXIN-PRIMED RATS.

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The objectives were to: 1) validate an existing animal model of HAPE; 2) determine the vascular responses associated with this model; 3) investigate the role of ANP in ameliorating HAPE. Plasma ANP, right atrial ANP mRNA , and indices of lung injury were measured in rats primed with endotoxin (ETX) (0.1 mg/kg BW, i.p.) and exposed acutely to simulated high altitude (HA; 4,267 m; PB = 440 mm Hg). Catheters were chronically inserted into the right carotid artery, pulmonary artery, and jugular vein of rats to study vascular responses to ETX and/or HA. We investigated the role of ANP in the development of HAPE by using an antiserum against ANP (αANP). Plasma ANP levels were increased at 12 and 24 h in ETX, HA and ETX+HA groups ($P<0.05$), compared to control rats. There was an inverse relationship ($P<0.001$) between plasma ANP levels and lung wet-to-dry (W/D) weight ratios. Following treatment of rats with aANP serum, altitude-exposed rats exhibited significantly higher lung W/D ratios ($P<0.0005$). Pulmonary arterial pressure increased (50 + 20%)($P<0.035$) at 12 h in the αANP alone group and increased (51 + 15%)($P<0.02$) in the HA+αANP group at 12 h, compared to rats given normal rabbit serum. In addition, there was a significantly lower systemic arterial pressure in the ETX+HA rats compared to ETX+HA+αANP rats at 12 and 24 h ($P<0.0005$ and $P<0.02$, respectively). These results indicate that ANP, at physiological levels, prevents the development of HAPE. However, the activation of ANP secretion and the action of ANP in limiting the pulmonary edema remain to be elucidated.

84. DIFFERENCES IN PULMONARY HEMODYNAMICS BETWEEN ACUTE HYPOXIC AND CHRONIC PULMONARY HYPERTENSION.

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Right ventricular ejection characteristics reflect hydraulic load and the state of the myocardium. We compared the effect of acute hypoxic and chronic primary pulmonary hypertension on right ventricular ejection. Main pulmonary artery (PA) flow was measured by ultrasound at 520m and, after an ascent over 48 h, at 4559m (Capanna Margherita, Italy) in 11 high altitude pulmonary edema susceptible (HAPE-S) and 9 control subjects (N), and at sea-level in 8 patients with primary pulmonary hypertension (PPH). Measurements were made of PPA from the peak velocity of the tricuspid regurgitant jet, right ventricular pre-ejection time (TPE) from the R-wave of the ECG to the start of flow in the PA just above the pulmonary valve, and acceleration time (AT) from the onset of right ventricular ejection to peak flow velocity in the PA. PPA, TPE and AT were not significantly different in the N and HAPE-S at 520m. PPA in PPH was similar to HAPE-S (NS).

Subjects	Altitude	PPA (msec)	TPE (msec)	AT (msec)
Control	480 m	22 ± 2	50 ± 7	127 ± 6
Control	4559 m	37 ± 2	59 ± 4	111 ± 5
HAPE-S	480 m	25 ± 4	56 ± 5	122 ± 6
HAPE-S	4559 m	70 ± 4*	46 ± 2***	83 ± 4**
PPH	Sea level	79 ± 9	65 ± 5	119 ± 16

*P<0.001, **P<0.01, ***P<0.05 compared to controls at 4559 m; ***P<0.001 compared to PPH Thus for the same pulmonary artery pressure, right ventricular ejection is markedly shorter in acute compared to chronic pulmonary hypertension. This may reflect greater right ventricular contractility as a consequence of higher PPA and greater sympathetic activation in acute hypoxia.

85. INFLUENCE OF HIGH ALTITUDE ON LEFT VENTRICULAR DIASTOLIC FUNCTION.

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Background: Acute high altitude exposure is associated with exaggerated hypoxia-induced vasoconstriction of the pulmonary arterial bed and right heart pressure overload which, in turn, may alter left ventricular (LV) diastolic filling and contribute to the development of high altitude pulmonary edema (HAPE) in susceptible individuals. We hypothesized that impaired LV diastolic filling, as assessed by Doppler tissue imaging (DTI), is related to high altitude induced pulmonary hypertension and may play a role in the pathophysiology of HAPE. Methods: In 35 healthy individuals, systolic tricuspid regurgitant gradients (TRG) as well as conventional and DTI parameters of LV diastolic function were measured at 4559m and 550m above sea level.

Altitude	**4559m**	**550m**	**p**
TRG, mmHg	46.3±15	16.5±9.1	<0.0001
Transmitral E/A	1.1±0.3	1.4±0.3	0.0007
Septal Ea, cm/s	11.6±2.1	12.7±3.0	0.15
Lateral Ea, cm/s	15.8±2.7	17.7±5.2	0.12
Inferior Ea, cm/s	13.5±3.4	15.0±3.6	0.06
Anterior Ea, cm/s	17.3±1.5	16.6±4.2	0.37
Ea*, cm/s	14.7±1.7	15.9±3.1	0.12
Aa*, cm/s	14.5±3.9	11.7±3.1	0.02
Ea/Aa*	1.0±0.5	1.4±0.6	0.01
E/Ea*	5.1±0.9	4.8±1.1	0.53

Ea, Aa = early and late diastolic mitral annular motion velocities. *Averaged velocities obtained from the septal, lateral, inferior, and anterior mitral annulus. Conclusions: Compared to lowland, early LV filling is impaired at high altitude which itself is related to increased pulmonary artery pressure (figure). Conversely, late diastolic mitral annular motion velocity is increased at high altitude. We speculate that impaired early LV filling at high altitude is compensated by augmented atrial contraction. As long as this mechanism works, global LV diastolic filling is unaltered, and thus, may not contribute to the pathogenesis of HAPE.

86. NO ASSOCIATION BETWEEN HIGH ALTITUDE PULMONARY EDEMA (HAPE) AND ANGIOTENSIN-CONVERTING ENZYME (ACE) GENE POLYMORPHISM.

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The absence (deletion allele [D]) of a 287 base pair fragment in the ACE gene is related with higher ACE tissue activity than its presence (insertion allele [I]). Higher ACE tissue actvity leads to higher levels of Angiotensin II (AT II), which is known to elevate pulmonary artery pressure (PAP). Since abnormal rise of PAP is crucial for the development of HAPE, we hypothezised that the DD-genotype is associated with greater susceptibility to HAPE. To test this hypothesis we collected mouth wash fluid to obtain DNA from epithelial cells in 76 mountaineers whose susceptibility to HAPE was known from previous studies. 38 had a history of HAPE of whom 25 developed HAPE again during altitude exposure in our studies (Magherita Hut, 4559m). The distribution of the alleles was in Hardy Weinberg equilibrium with the following distribution of genotypes:

Genotype	DD	*ID*	II	*Total*
HAPE at 4559m	8	11	6	25
No HAPE at 4559m	17	23	11	51
Total	25	34	17	76

(Chi-square test, X2=0,0579; P=0,971 for equal distribution). Similar results were obtained, when all subjects with history of HAPE are compared with those who never had HAPE (X2=0,536; P=0,765). We conclude that the DD-genotype is not associated with greater susceptibility to HAPE.

87. POSSIBLE INCREASED RISK FOR HAPE IN CHILDREN WITH DOWN SYNDROME.

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Children with Down syndrome (DS) are living longer and are increasingly being mainstreamed into society. When a child with DS was diagnosed with HAPE, I asked the question whether and under what circumstances children with DS develop HAPE. A retrospective review of the medical records of Children's Hospital, Denver, CO was therefore performed for children with a discharge diagnosis of HAPE or other altitude related illness. A total of 52 cases of HAPE were found of which 8 also had DS. Two of the children presented with isolated severe pulmonary hypertension without clinical evidence for HAPE and were excluded. Diagnostic criteria for HAPE included the presence of crackles or frothy sputum production on exam, hypoxemia, chest x-ray findings consistent with pulmonary edema and rapid clinical improvement after descent and/or oxygen therapy. The age range of the children in the six remaining cases was 2-14 years. HAPE developed at altitudes ranging from 5,700-10,666 ft. Four children developed HAPE within 24 hours of arrival to altitude. Three children had chronic pulmonary hypertension and four had either an existing cardiac defect with left to right shunt or previously had a defect with left to right shunt which had been repaired. One child had Eisenmenger's syndrome with chronic right to left shunting of blood. Five children had pre-existing illnesses prior to travel to altitude, Children with DS frequently have medical problems such as chronic pulmonary hypertension, pulmonary vascular overperfusion or injury from existing or repaired cardiac defects and increased rates of infection. These problems all may be viewed as risk factors for HAPE and thus result in the rapid development of HAPE at relatively low altitudes. Care should be exercised when traveling to even moderate altitudes with children with DS.

88. SHORT-TERM ENDOTHELIN-A ANTAGONIST INHALATION VERSUS NITRIC OXIDE (NO) INHALATION IN EXPERIMENTAL ACUTE LUNG INJURY (ALI).

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An inhaled endothelin A (ETA) receptor antagonist was studied for 4 hrs after ALI. The results were compared with NO inhalation. In thirty pigs ALI was induced by surfactant depletion using repetitive lung lavages (until PaO_2/FiO_2 < 100 mmHg). The pigs were then assigned to three protocols: Controls: nebulization of saline (5-10 ml for 30 min); NO group (30 ppm NO inhaled continuously after ALI); LU group: nebulized ETA receptor antagonist (LU-135252, 0.3 mg/kg, inhaled for 30 min after ALI).

	Protocol	Baseline	1 h post ALI	ALI	4 h post ALI
PaO_2 [mmHg]	Controls	596 ± 14	47 ± 3	49 ± 3	54 ± 3
	NO	551 ± 14	228 ± 33*§	62 ± 4	224 ± 48*§
	LU	548 ± 13	152 ± 34*	58 ± 3	377 ± 39*§
Qs/Qt [%]	Controls	10 ± 1	57 ± 4	58 ± 4	47 ± 4
	NO	15 ± 1	30 ± 3*§	47 ± 2	27 ± 5*§
	LU	13 ± 1	36 ± 4*	53 ± 4	18 ± 2*§
Δ MPAP [%]	Controls		10 ± 5	0 ± 0	42 ± 7
	NO		0 ± 3	0 ± 0	6 ± 4*
	LU		7 ± 3	0 ± 0	14 ± 4*

* vs. Controls; § vs. ALI; D MPAP = % difference in mean pulmonary artery pressure from ALI;; Qs/Qt = intra-pulmonary shunt. In the LU and NO group all pigs survived, in the Control group 4 pigs died. In the surviving pigs, arterial pressure remained stable after ALI. Cardiac output was similar between groups. Conclusion: Inhalation of an ETA receptor antagonist improved oxygenation and blunted the increase in MPAP after ALI, without inducing systemic vasodilatation, comparable to inhaled NO.

89. DO STUDIES OF FOETAL LUNGS TELL US SOMETHING ABOUT THE AETIOLOGY OF HIGH ALTITUDE PULMONARY OEDEMA?

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The gas exchanging, alveolar surface of the lung is normally covered by a thin film of liquid that does not present a significant barrier to the diffusion of gases. However, in high altitude pulmonary oedema, alveolar gas exchange is compromised by liquid accumulating in this part of the lung. This is usually attributed to hypoxia-induced pulmonary vasoconstriction, which would increase the capillary pressure and reverse the normal, net flow of liquid from interstitium to capillary lumen. However, pulmonary hypertension does not inevitably lead to lung oedema and so other factors must be involved. Indeed, Sherrer et al. suggest that hypoxia-induced impaired of alveolar Na^+ transport may be important to the aetiology of this condition (e.g. Scherrer, et al. Adv. Exp. Med. Biol. 474: 93-107. 1999), and we have recently investigated the role of O_2 in stimulating this processes around the time of birth. Fetal growth occurs under profoundly hypoxic conditions (fetal PO_2 is ~23 mmHg) and so the alveolar epithelia experience a rapid rise in PO_2 as the new born infant takes its first breaths. This rise in alveolar PO_2 stimulates alveolar fluid clearance by evoking Na^+ transport. Our work shows that this involves a rise in the capacity of the basolateral Na^+ pump (Ramminger, et al. J. Physiol. 524: 539-547. 2000), which extrudes Na^+ from the cell, and increased expression of genes encoding epithelial Na^+ channels, which allow Na^+ influx from the alveolar lumen (Baines, et al. J. Physiol. 527: 24P). This work thus indicates that alveolar Na^+ transport is thus intrinsically sensitive to PO_2 suggesting that hypoxia may compromise alveolar fluid clearance by reducing alveolar Na^+ transport. This may well be a factor important to the development of high altitude pulmonary oedema.

90. PYSIOLOGIC RESPONSE TO MODERATE ALTITUDE EXPOSURE AMONG INFANTS AND YOUNG CHILDREN.

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Objective: Increasing numbers of children are exposed to altitude in mountain resorts. While there is extensive study of the response of adults in this altitude setting, there is little study of infants and young children. This study examines some of the physiologic responses to moderate altitude exposure among young children. Methods: A prospective trial. Children ≥3 and ≤36 months old were studied at 1610 m and after 48-hours exposure to 3109 m (10,200 ft). Measurements included end tidal CO_2, pulse, respiratory rate, pulse oximetry, near infrared spectroscopy cerebral oxygenation (StO_2), transcranial Doppler middle cerebral artery resistive index and estimates of lateral ventricle volume. Data were analyzed using the ANOVA and Pearson's correlation tests. Results: 24 children (13 girls, age 14.5 ± 10 months) participated.

	Baseline	Ascent	p	N
End Tidal CO_2 (mmHg)	31.2 ± 2.9	28.3 ± 2.4	<.0001	23
Pulse (/min)	120 ± 15	126 ± 15	.17	24
Respiratory Rate (/min)	45 ± 13	51.9 ± 15	<.0079	23
Pulse Oximetry (%)	94.6 ± 1.7	90.8 ± 2.3	<.0000	24
StO_2 (%)	78.2 ± 7.8	67.1 ± 13.2	<.0003	24
Resistive Index	.58 ± .08	.56 ± .08	.29	17

The reduction in StO_2 at altitude appeared to be related to age (r=.62, p=.002) with lower saturation found in younger children. No evidence of increased intracranial pressure was seen during ascent. Conclusion: Ascent to moderate altitude resulted in tachypnea, relative hypoxia, hypocapnia, and reduction in cerebral oxygen availability (StO_2). The reduction in StO_2 appears related to age, with infants most susceptible to desaturation at altitude.

91. SLEEP DISTURBANCE DURING ASCENT TO MODERATE ALTITUDE AMONG YOUNG CHILDREN.

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The effect of ascent to altitude on sleep has been studied extensively in adults, yet little is known about the effect on infants and young children. Children ≥3 and ≤36 months old were studied over 7 separate days. On days 1-2 children were studied at home (1610 m), day 3 at a hotel without altitude gain (travel control day), day 4 at home, days 5-6 at a hotel at 3109 m, and day 7 at home. Measurements made by ankle mounted Ambulatory Monitoring Actigraphs included: duration of total sleep period (DUR), percent time asleep during total sleep period (%TA), number of wake episodes (WE), mean duration of wake episodes (MWE), longest sleep episode (LSE), mean duration of sleep episodes (MSE), and percent light sleep (%LS). Data were analyzed using ACTION-W with the Sadeh Infant Algorithm. 30 children, 13 girls and 17 boys, ages 17.1 ± 10.1 months participated.

	Home	Travel Control	Ascent	p
DUR (min)	604.8±92.8	572.8±67.23	605.1±70.48	.36
%TA	94.6±6.4	94.9±5.3*	89.1±7.3	<.0003
WE	5.6±4.9	5.5±3.0*	8.6±5.2	<.005
MWE (min)	4.9±4.6	4.8±3.6*	8.3±5.0	<.03
LSE (min)	310.0±149.3	272.1±97.6	249.5±131.2	.42
MSE (min)	163.0±145.0	122.0±80.4	99.9±78.9	.41
%LS	45.2±11.7	43.9±11.5	39.7±9.3	.37

Sleep alterations were most prominent during the first night after ascent and trended towards baseline values on the second night. Sleep patterns among infants and young children exposed to moderate altitude are substantially disturbed demonstrated by decreased percent time asleep, increased number of wake episodes and longer duration of wake episodes during sleep. These changes are most significant during the first night at altitude and are comparable to those seen in adults.

92. PREDICTION OF ALTITUDE FROM BAROMETRIC PRESSURE.

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Accurate determination of altitude may be important in the conduct of expeditions to high altitude. The international standard atmosphere (Std Atm) model (ICAO) relating altitude to barometric pressure (PB) consistently underestimates true altitude in many mountainous regions of the world. Modern altimeters utilize the ICAO model, resulting in a progressive error as one ascends unless the instrument is repeatedly adjusted. Often when hiking or climbing one needs to know the current altitude, but with maps of variable quality in some regions of the world, reference is usually made to the altimeter. The purpose of this study was to determine whether a simple correction factor would allow accurate altitude determination from PB alone. Published and unpublished PB/altitude data were compared with West's equation, $PB = \exp(6.63268 - 0.1112h - 0.00149h^2$, (West 1996) and the ICAO Std Atm, PB = 760 * [(288 – 0.0065 h)/288]^5.256, where 288 is the assumed temperature (T) in degrees Kelvin at sea level, 0.0065 the T lapse rate in degrees per m increase in altitude, h the altitude in meters. A modified ICAO curve (ICAOmod) was constructed by allowing T in the ICAO equation to vary; this equation was regressed against the available data. Both the ICAOmod and the West equation closely fit all data points ($r2 > 0.99$) with similar residual errors. The ICAOmod is linearly shifted from the ICAO having a difference of 52 – 55 m per 1000 m in altitude. Adding 55 m to the altimeter reading for every 1000 m in altitude above sea level, the true altitude is closely approximated. Although considerable seasonal variation in PB occurs and the prediction is inaccurate at very high (or low) latitudes, the correction may prove useful to climbers in summer months in mountainous regions between ~ ± 45 degrees latitude.

93. THE EFFECT OF ALTITUDE ON COGNITIVE FUNCTION USING THE PACED AUDITORY SERIAL ADDITION TASK (PASAT).

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The Paced Auditory Serial Addition Task (PASAT) has been described as a measure of cognitive function. Subjects add together numbers that are played to them via an audio tape. The numbers are read out at three different speeds. The PASAT test was applied to 18 individuals ascending to 5005m. Altitude sickness was measured using the Lake Louise questionnaire at the heights of 1345, 1745, 2430, 3300, 5005, 4600 and 1745m. PASAT scores continued to increase for all 7 altitudes: there was no levelling of the learning effect, in contrast to previous studies. As might be expected, sickness scores were maximal at 5005 meters. Between 3300 and 5005 meters, performance decreased by 1.57 points at the lowest speed, 1.25 points at the medium speed, and 1.30 points at the fastest speed. All of these differences are statistically significant. This decrease is significantly associated with altitude sickness. Without taking account of the individual's learning effect, for every 1 point increase in the Lake Louise score at the slowest speed, there was a 1.15 decrease in PASAT score (p=0.005); for every 1 point increase in the Lake Louise score at the medium speed, there was a 0.81 decrease in the PASAT score (p=0.035). When the individual's learning effect was considered, there was a decrease in PASAT score of 1.44 for every point increase in the Lake Louise score at the slowest speed (p=0.017), and 1.03 per point increase at the medium speed (p=0.034). These associations were not significant at the highest speed. The PASAT score continues to show a learning effect beyond that previously described, and appears to reflect the cognitive decline at altitude observed in other studies.

94. EFFECTS OF ACUTE AND SUB-ACUTE EXPOSURE TO HIGH ALTITUDE ON MISMATCH NEGATIVITY IN AUDITORY EVOKED POTENTIALS.

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Mismatch Negativity (MMN) results from a pre-attentional process due to activation of short term auditory memory. MMN is a wave produced when a rare (deviant) sound is presented in a series of standard sounds. Cerebral dysfunction or acute cortisol infusion have been shown to modify MMN. The hypothesis of this study was that slight cerebral hypoxia associated with acute high altitude exposure or acute mountain sickness (AMS) may be revealed by MMN changes. Ten subjects were studied in normoxia (N), after 2 (H2) and 5 days (H5) of exposure to 4,350m (Vallot observatory), and 24 to 48 hours of re-exposure to normoxia (RN). N1 wave was recorded as part of evoked potential response. Arterialized PO_2, PCO_2, pH and plasma cortisol were also measured. Auditory evoked potentials were obtained using a system designed by INSERM, on subjects at rest, with maintained attention by reading a book. No correlation was found between variations of MMN (amplitude or latency) and plasma cortisol evolution in hypoxia. N1 latency and amplitude in the response to standard sounds were remarkably stable when N1 amplitude of responses to deviant increased at H2 and showed an even higher amplitude at RN. Amplitude of MMN decreased significantly at H2 and H5 and returned to base level at RN. Latency of MMN decreased significantly at H2 and remained shortened at RN. The MMN latency shift remaining at RN as compared with N was correlated with the residual hypocapnia assessed by PCO_2. Changes in MMN were not related to AMS score. In conclusion, changes in MMN may reflect the combined effect on the brain of changes in cerebral O_2 and CO_2 concentration.

95. PATHOGENESIS OF PULMONARY AND CEREBRAL OEDEMA AT HIGH ALTITUDE.

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Alveolar capillary blood hypertension versus low alveolar air tension is the cause of acute pulmonary oedema. Natural adaptation and distribution of species on the surface of the Earth is relative to Altitude. The mass per volume unit of the atmospheric air is the determinant physical factor and, the Lung in its thoracic ensemble achieves this task, integrating and balancing blood and air circulations. Consequently, Man has a limit for his safe displacement in altitude, the boundaries of which are roughly limited between sea level and about three thousand meters. Cyclic contraction of the muscles of the lobular bronchioles produces two simultaneous main mechanical effects: Decreases the lobular length, thus increasing the pleural lumen, to open way for alveolar-capillary blood circulation. Floodgate action. Decreases the bronchiolar capacity, increasing the mass per volume unit of the contained air, thus increasing its molecular expansive forces. Pump action. The following muscle relaxation also enables two simultaneous main mechanical effects: Allows the molecular expansion of the previously pressurized air, for its displacement towards the alveoli, expanding them, in balance with the circulating capillary blood, for gas exchange, while also displacing the oxygenated blood towards the pulmonary veins. Complementary pump and Press actions. Elastic retraction of the lobular structure follows, impelling the used air towards the extra-pulmonary airways. Pneumatic Pump action Muscles contraction of the lobar bronchi accomplish a similar mechanical role to that of the lobular bronchioles, for air intake and distribution among the lobules, and pulmonary blood balanced circulation, as well as for abdominal press action, also evoking, reflex via, costal expansion for floodgate action to balance abdominal-thoracic and cranial blood circulation towards the right ventricle. Failure of these extra-pulmonary mechanical effects causes visceral oedema.

96. ADAPTATION TO HYPOXIA IN SURGICAL PATIENTS.

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Patients undergoing abdominal surgery have arterial hypoxemia for several days after operation, even in those without pulmonary complications. The extent and duration of tissue hypoxia depends on the magnitude of the operation. In our series of gastrectomized rats exposed to 10% oxygen postoperatively for 6 days, body weight loss, a poor negative nitrogen balance, and an accelerated protein breakdown were observed compared with the normoxic rats. Oxygen availability is a putative factor modulating wound healing, since protein synthesis is particularly involved oxygen supply. In contrast, hypoxia causes a series of physiological adaptations so that energy can be supplied to the tissues to maintain cellular activities. We demonstrated in rats that have undergone catheterization operation that (1) hypoxia depresses energy expenditure, which leads to a normoxic level of hepatic ATP; (2) fat is a main metabolic fuel during hypoxia; and (3) hypoxia leads to the development of a pathway which shunts pyruvate and glutamate to alanine and alpha-ketoglutarate, allowing efficient energy production. Our other data suggest that renal handling of phosphate participates in energy metabolism during postoperative hypoxia by retaining phosphate in the body. We have pursued other active ways to adapt to postoperative hypoxia. (1) In renal ischemia/reperfusion injury model, we observed that if a single 5-min renal ischemia was induced prior to the clamping, better GFR values were obtained as compared with those in the control group. (2) Four h-hypoxia caused a marked reduction in the arterial oxygen pressure and blood pressure as compared with normoxia in rats. In contrast, when the rats were pretreated with the sublethal endotoxin prior to the hypoxic exposure, the animals showed a resistance to these hypoxia-induced events. In conclusion, the negative influence of hypoxia would be reduced if we introduced some stress before the hypoxic event.

97. BACK TO THE MOUNTAIN AFTER MYOCARDIAL INFARCTION.

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The aim of our study was to assess patients with previous myocardial infarction, during an excursion at moderate altitude. Seventeen patients (mean age 57.1 years, range 44-68), with a documented clinical history of myocardial infarction, were evaluated at sea level by a maximal exercise test and 24-hour Holter monitoring. They were studied in three separate groups during a five-hour excursion at moderate altitude (1700-2500 m), reached in two hours by car. In addition to ECG-Holter recording throughout the excursion day, arterial oxygen saturation and blood pressure were measured at rest, at sea level, at the foot of the ascent and on arrival at maximum altitude. During the excursion, the patients neither complained of any symptom nor showed ECG changes suggesting myocardial ischemia. Peak heart rates were similar to those reached during the maximal exercise test. Arrhythmias were comparable to those recorded at sea level. Only at maximum altitude did resting heart rate and blood pressure respectively increase and decrease, slightly but significantly. Arterial saturation progressively decreased from sea level to the start of the excursion and to maximum altitude. After the experience, the patients were enthusiastic and extremely gratified. In conclusion, physical activity at moderate altitude could be safely and advantageously included in rehabilitation programs.

98. VARIATION OF TRANSCUTANEOUS O_2 SATURATION DURING SLEEP IN A RAID FROM SEA-LEVEL TO DOME C (3600M), ANTARCTICA.

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Transcutaneous O_2 saturation (SpO_2) and heart rate (HR) were monitored during sleep in 8 subjects during a 22 days raid in Antarctica from sea-level (Dumont d'Urville base, 0m) to Dome C (altitude 3600m, Pb = 641 mmHg), and back to sea-level. Actual barometric pressure was measured daily and was lower than predicted by Civil Aviation standards. Monitoring (Nonin apparatus 8500 M) was performed during 8 to 10 hours, using a finger probe at various altitudes during the raid. Mean sleep SpO_2 decreased and HR increased with altitude exposure. Cyclic variations of SpO_2 and HR, evaluated by Moving Fast Fourrier Transform, were observed in all subjects above 2000 m, as a possible consequence of periodic breathing. SpO_2 cyclic episodes were sometimes associated with brief bursts of tachycardia. Total time spent with cyclic SpO_2 increased with altitude. The period of cyclic events was between 20 and 35 seconds and tended to decrease during sleep. For the same barometric pressure, mean SpO_2 and the incidence of cyclic episodes were higher on the way back to sea-level than during the ascent. In conclusion, exposure to lower altitudes in Antarctica than expected in other regions, induces periodic breathing resulting in oscillations in SpO_2 and HR, and sometimes brief episodes of tachycardia, inducing transient cardiovascular overload.

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99. PORTABLE NEPHELOMETER FOR SPECIFIC PROTEIN TESTING IN REMOTE LOCATIONS.

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Measurement of serum or urine proteins at remote clinics or in mobile, field laboratories is difficult because existing instruments are large and require a stable electricity supply. Our requirement was to measure urinary microalbumin excretion in trekkers during a Himalayan expedition to 5,000 meters. Urine albumin excretion correlates with symptoms of acute mountain sickness so stat results might help clinical decision making when symptoms and signs are confusing. In order to measure urine albumin during the trek we modified a small nephelometer (Minineph™; size 23 x 23 x 8.5 cm; weight 2.4kg) so that it could function on disposable batteries and evaluated it for measuring urinary microalbumin in a mountain environment. The microalbumin test comprised a six minute, end-point assay with a sensitivity of 6mg/L and an upper limit of 60mg/L using 40mL of neat urine and performed with manual pipettes. At sea-level, using the battery-powered nephelometer, the microalbumin assay correlated well with a radial immunodiffusion assay (R = 0.98; slope 1.099; intercept 0.044 mg/L) and gave similar results using either battery or mains power (R = 0.99). At an altitude of 4,900 meters and at -10ºC the instrument functioned normally with control mean albumin levels of 22.5mg/L (+/-7%) compared with 23.6mg/L (+/-5%) at sea-level. Twenty subjects were tested for microalbumin in a timed collection at sea level and altitude. At sea-level, one subject excreted more than 6 mg/L whilst at altitude seven subjects excrete more than 6 mg/L and values ranged from 6 to 30 mg/L (0.15-2mg/hour). In conclusion, the battery-powered portable nephelometer was used to confirm a previous observation that urine albumin excretion increases during exposure to the hypoxia of altitude. Disposable or rechargeable batteries would allow the use of the Minineph™ in a variety of remote or extreme environments that occur in many parts of the world.

100. URBAN ACCIDENTAL HYPOTHERMIA: 18 CASES ADMITTED TO OUR CRITICAL CARE CENTER.

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Introduction: Our center is located in the residential suburbs of Tokyo, which belongs to the temperate latitudes and has a population of 12 million. In urban settings various factors can trigger hypothermia and we investigated their features. Methods: We reviewed 18 patients with accidental hypothermia admitted to our center between April 1999 and November 2000. They were classified into 3 groups (each group included 6 patients) and evaluated. Group A: exposure to cold outdoors; Group B: exposure to cold indoors; Group C: slight exposure to cold while sleeping in bed. Results: Group A: The mean age was 57.8(31-88). The initial mean core temperature (MCT) was 29.0±0.3 patients were coma and 2 were cardiopulmonary arrest(CPA) on admission. The causes were head trauma(2), subarachnoid hemorrhage(1), intoxication(1) and unknown(2 CPA). Except for the intoxicated patient, the others died. Group B: The mean age was 63.5(31-83). MCT on admission was 30.3? and 3 patients were coma. 3 patients lived alone and it cost some days before rescue. The causes were stroke(2), intoxication(1), suicide(1) and unknown(2 advanced age over 80). Past histories were chronic renal failure(2), diabetes mellitus(2), hypertension(2) and etc. Only one patient who developed DIC and pneumonia died. Group C: The mean age was 71.7(59-88). MCT on admission was 31.8±0.3 patients were coma and 2 were CPA. 4 patients showed remarkable hypoglycemia accompanied with malnutrition, liver dysfunction, dipsomania, and diabetes mellitus. 1 patient suffered from diabetic ketoacidosis. 3 patients including 2 CPA with long lasting malnutrition died. Conclusions: In Group A initial MCT was the lowest although being the youngest, and primary diseases were so serious that outcomes were poor. In Group B old persons who live alone with chronic diseases and suicide attempts by middle-aged persons were characteristic. The outcomes were generally good. In Group C the mean age was the oldest and general conditions were extremely poor accompanied with hypoglycemia. It is certainly true that seriousness of the primary illness affects outcome in this review.

101. CALORIC DEFICIT AFFECTS MOOD STATE ALTERATIONS AT HIGH ALTITUDE.

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Weight loss negatively alters mood state at sea level (SL) as does acute exposure to high altitude (HA). Transient sojourn to HA causes anorexia of unknown etiology resulting in significant weight loss. It is not known if an additive effect of altitude and weight loss on mood alterations occurs with induction to HA. We hypothesized that mood state would be more impaired by caloric deficit at HA than by caloric deficit at SL. Nineteen male subjects (22 ±0.9 yr, M ±SE) were randomly assigned to two groups. Both groups completed a 7 d sea level diet stabilization period to determine energy requirements. The Profile of Mood States Bipolar Form (POMS-BI) was administered mornings of the SL stabilization period to establish baseline values. Subjects were then provided nutritious diets with a 40% deficit in daily energy intake; 1) HYPO (n=10) remained at SL for 21 d where they were administered the POMS-BI each morning, 2) DEF (n=9) subjects were transported to 4,300 m where they remained for 21 d and were administered the POMS-BI each morning. After 21 d, body mass decreased 5.20 ±0.54 kg and 3.39 ±0.47 kg for the DEF and HYPO groups at HA and SL respectively. All HA subjects experienced negative ($p \leq 0.05$) alterations in mood during the first 2-5 d. Mood returned to baseline within 7 d of HA exposure as is consistent with the literature. A significant ($p \leq 0.05$) decrease in mood of the DEF subjects at HA compared to the SL HYPO group occurred on days 13-17. These data suggest that there is an additive effect of altitude on mood during chronic exposure to HA accompanied by caloric deficit when compared to SL controls.

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102. A NEW METHOD FOR MEASURING UNSTEADINESS AT ALTITUDE.

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Unsteadiness is a feature of acute mountain sickness (AMS). We have developed a qualitative test to assess changes with increasing altitude and with the development of AMS. Recordings were made of the number and duration of contacts per minute of a wobble board to a horizontal metal base plate using a simple electrical circuit between the base plate and the edge of the board. Three one-minute tests were performed on five occasions during a trek to high altitude by 20 subjects(16 male, 4 female). After the initial measurements at 1345m there were no significant changes in unsteadiness over time up to an altitude of 5005m. The ten older subjects (over 31 years) were more unsteady than the ten younger subjects ($p<0.001$). Lake Louise self-assessment scores at high altitude correlated with unsteadiness scores in both older ($r=0.71$) and younger ($r=0.70$) but the slope was much steeper in older subjects. Conclusion: A simple reproducible quantitative test of unsteadiness has been developed which was easy to perform in the field. Initial results showed a significant relationship with AMS in older subjects but the test may not be sufficiently sensitive in younger subjects.

103. CLINICAL OBSERVATIONS ON ACETAZOLAMIDE (AZ) PROPHYLAXIS IN NEPALESE PORTERS.

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Introduction: In October 1999 BMRES trekked to Kanchenjunga North Base Camp (altitude 5005 metres) in Nepal to study the effects of mild to moderate Acute Mountain Sickness (AMS) in our group. Porters ascending to this altitude at the beginning of the season might have developed AMS as they were unacclimatised, so we offered them prophylaxis with Az. Objective: To determine whether Az was beneficial to Porters and well tolerated. Methods: On Day 9 of the trek, at 3300 metres, 28 Porters going to Top Camp (5005 metres) started taking Az 250mg daily, after its benefits and side effects were explained. 20 Porters planning to descend after 3960 metres were not offered Az prophylaxis, nor were the 20 BMRES members. The Lake Louise questionnaire was used to score AMS symptoms on the morning of Day 11 at 3960 metres. AMS was defined by a total score of 3. Porters were asked about ability to carry their load and about Az side effects. Results: No Porters taking Az had AMS and their load felt lighter. Most (75%) untreated Porters and 20% of BMRES members had AMS. Untreated Porters were more severely affected (mean AMS score 4, range 1-7) than BMRES members (mean AMS score 1.5, range 0-4). Adverse reactions to Az were mild and infrequent. Conclusions: Az seems effective and tolerable at a modest dose in Porters, but controlled trials are needed to establish its benefit.

104. EFFECT OF PRE-ACCLIMATIZATION TRAINING BY EXPOSURE TO NORMOBARIC HYPOXIA IN MIDDLE-AGED CLIMBERS AIMING HIMALAYAN 8000M PEAK; PART 1.

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Normobaric hypoxic room is recently developed. It is suitable for long-term training (including sleep), because going in and out is quite easy compared with traditional hypobaric hypoxic chamber. We used the room for pre-acclimatization training of middle-aged climbers who challenged Mt. Cho Oyu (8201m) in Himalaya. Nine men aged 45-64 participated in this study. Five of them trained for 7 days in the room (T7), two trained 4 days (T4), and the remaining two did not trained in the room (T0). T7 and T4 performed 60-90 minute exercise at 3000-6000m (equivalent hypoxia) and slept for 7 hours at 2000-3500m daily. Total staying duration in the room was 9-10 hours per day. Arterial oxygen saturation (SpO_2) was about 80-90% at rest and about 80% during sleep in the room. Eleven days after the training, the subjects started for Himalaya. At an equivalent altitude (ranged in 2000-4000m), SpO_2 values measured in Himalaya were higher than that of pre-acclimatization training period. For the summit assault, all of them used bottled oxygen above 7600m. Three of T7 and two of T4 succeeded to reach the summit (success rate: 71%) including a 64 years old men who attained the oldest record of reaching the summit. On the other hand, all of T0 did not succeed. The age of succeeded subjects were 45-64 (56.4±8.4) years, and their VO_2max were 34.3-50.9 (39.6±6.8) ml/kg/min. The genotype of angiotensin converting enzyme of them were II or ID (all of 50s' and 60s' subjects were II). These results suggest that it is possible to reach 8000m summit even if the 60s' years old climbers whose physical fitness (i.g; VO_2max) is not so high. It is also indicated that pre-acclimatization training by using normobaric hypoxic room is effective.

105. EFFECT OF PRE-ACCLIMATIZATION TRAINING BY EXPOSURE TO NORMOBARIC HYPOXIA IN MIDDLE-AGED CLIMBERS AIMING HIMALAYAN 8000M PEAK; PART 2.

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The effect of 7 days pre-acclimatization training for Himalayan expedition (Cho Oyu, 8201m) of middle-aged climbers was examined. The subjects were five climbers who were 60.6 ± 5.9 (mean ± SD) years old. Everyday they performed 60 - 90 minute treadmill walking and pedaling exercise, and slept for 7 hours in a normobaric hypoxic room at a simulated altitude equivalent to 2000 - 6000m. In order to monitor the acclimatization, they performed an incremental pedaling exercise everyday under hypoxia equivalent to 4000m high. Arterial oxygen saturation (SpO_2) and heart rate (HR) were monitored throughout the test. Blood samples were collected from fingertip every morning. After hypoxic training, HR at the same work load decreased and SpO_2 increased significantly ($P<0.05$). Mean corpuscular volume and mean corpuscular hemoglobin did not change throughout the training period, whereas red blood cell count, hemoglobin concentration and hematocrit level decreased. In the expedition, three of the subjects including 64 years old climber succeeded to reach the summit using supplementary oxygen above 7600m. These results suggest that short-term intermittent hypoxic training improves physical work capacity under hypoxic environment, in spite of the decrease of hemoglobin concentration and hematocrit level , and may be useful for improvement of high-altitude climbing ability. High correlation was observed between %HRmax and SpO_2 during the incremental pedaling test. Individual difference in the slope of regression line between %HRmax and SpO_2 was also noted. The slope of the two climbers who could not reach the summit were steeper than that of the climbers who were successful. It suggest that the slope of these relationship will be an useful index for estimation of physical aptitude at altitude.

106. FROSTBITES IN JANUARY, AMPUTATION IN JUNE? OR HOW CAN THE WAITING PERIOD BE SHORTENED - A CASE REPORT FROM SIMOBIL SKIEVEREST 2000.

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A 24-year climber suffered from frostbites on his toes during Mt. Everest ascent. Manifesting all three degrees of frostbites, the management started only some hours after reaching the top. The treatment in hyperbaric chamber started on 3rd day after injury, during next months he has undergone at least 30 therapy cycles. Diagnostically, the DSA and the Th99 scintigraphy has been made in order to show the level of needed amputation prior to skin and tissue demarcation. The last amputation surgery was done in the 3rd month after the frost injury.

107. . RAPID ADAPTATION AND HEALTH RISKS USING CABLE CARS IN HIGH ALTITUDES.

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In the Alps, billions of tourists are using cable cars up to high altitudes. Just after arrival at these altitudes some typical physiological reactions suddenly happen regarding ventilation, gas exchange and heart/circulation. Many tourists visiting these altitudes only as sojourners are pregnant, children or individuals suffering from pre-existing health disorders. When going down by a cable car the sudden rise of the air pressure frequently leads to serious problems. Acute mountain sickness doesn't seem to play any role. Long-time observations at the Kitzsteinhorn (Kaprun/Austria) show that there is no risk of altitude-related death using cable cars up to altitudes of more than 3000 metres. As a conclusion, the few possible risks of a cable car trip to alpine altitudes for a limited number of individuals will be generally overshadowed by far by a fantastic and unique adventure for the public.

108. THE EFFECTS OF THE INTERVAL HYPOXIC TRAINING (IHT) IN NON-INSULIN-DEPENDENT DIABETES MELLITUS (NIDDM) PATIENTS.

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Adaptation to hypoxia is characterized by time-dependent increase in hypoxic ventilatory response (HVR) and by slow increase in sympathetic activity (SA) at sympathoadrenal system (SAS), which testify to the relationship of these processes with the existence of common regulatory mechanism for them. The aim of this study was to detail a possible relationship between HVR and SAS activity during adaptation to intermittent hypoxic training (IHT). We examined the HVR indexes, venous blood (VB) and daily urine (DL) catecholamines (CA: dopamine - DA, norepinephrine - NE, epinephrine - E) and DOPA levels in young and elderly people during 14 days of IHT. The decreased HVR in elderly age was accompanied by increased DA, DOPA levels in VB and DL which obviously were formed by the age-related disturbances in storage/uptake mechanism for this agents. The possible causes for age-related decrease in HVR could be the diminished DA synthesis in carotid bodies (CB) and/or the inhibitory influence of blood DA as regard the peripheral mechanisms of breathing regulation. We supposed that peculiarities of CA metabolism in SAS and CB (as a part of SAS) would be an essential factor in breathing regulation. Adaptation to IHT was accompanied by the increase in HVR, which was more expressed in young people. The reciprocal changes in blood DOPA (increase - in young, decrease - in elderly), increased blood NE concentration in both groups and increased E in young were testifying the SAS activation during IHT. After IHT the negative correlation between DA, DOPA excretion and HVR was observed as well as between DA excretion and lung ventilation indexes. If DA, DOPA levels in VB and DL are the markers of SA, these correlations imply a relationship between SA and effective ventilation during IHT adaptation.

109. INTERMITTENT NORMOBARIC HYPOXIA ENHANCES ACCLIMATION.

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Physiologic and symptomatic adaptation to hypobaric hypoxia has been extensively investigated during the past one and one-half centuries. Recently endurance athletes and high altitude climbers have had access to portable normobaric hypoxic chambers which may stimulate changes similar to those observed during acclimatization to altitude or acclimation via decompression chambers. To date few controlled studies using normobaric hypoxia have assessed the effective exposure time and exposure repetitions, nor have attempted to quantify the outcome variables. Thus, the objective of the present study was to administer a hypoxic ventilatory response (HVR) test prior to implementing a novel acclimatization protocol to intermittent normobaric hypoxia while continually monitoring physiologic and symptomatic acclimation. Six healthy active males (age 18-27yr) volunteered for this investigation. The hypoxic ventilatory drive was assessed according to the methodology of Weil et.al. (1970). The intermittent normobaric hypoxic treatment consisted of 5 successive 12 hour overnight exposures to a simulated altitude of 4300m. Near infrared pulse oximetry was used to continually monitor $\%SaO_2$ and heart rate throughout each exposure. The Lake Louise Acute Mountain Sickness Scoring System (LLSS; Roach, 1993) was administered to evaluate the severity of symptoms associated with AMS. Responses to the LLSS were collected immediately before and then twice during each normobaric hypoxic exposure at approximately 4 and 13 hours respectively hours. Results indicated that the highest AMS scores occurred during the initial hours of exposure, and that the symptomatology was reduced over the course of the five nights in all subjects. The HVR was inconclusive as an indicator of AMS in this subject pool. It would appear that other variables such as $\%SaO_2$, respiratory rate, tidal volume, and hematological status may operate synergistically as predictors of AMS during acclimation to intermittent normobaric hypoxia.

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110. MODERATE HYPOXIA SUPPRESSES EXERCISE INDUCED PROCOAGULANT CHANGES AND INDUCES FIBRINOLYSIS.

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Altitude and hypoxia have been implicated as stimulating coagulation and the risk for thrombosis. However, previous studies were either uncontrolled field studies or used extreme environmental conditions. Since exertion is known to affect hemostasis, we sought to control for this factor by using a standardized exercise hypoxia protocol. We exercised 8 subjects using a treadmill, and obtained samples at baseline, after hypoxic exposure, and at maximal oxygen consumption (V02Max) both at room air and with 12% oxygen (equivalent to 14,000ft [4600m] altitude). At room air (21% FIO_2) at 100% VO2Max we found no significant change in platelet count when compared to baseline (212,000±12,00 to 211,000±4,00/uL), but a rise in mean platelet volume (mpv) (8.8±.2 to 9.5±.2 fl), reticulated platelets (1%0±.1 to 2.4%±.48) von Willebrand's antigen 109±9 to 201±21 IU/ml), Factor VIII activity (132±15 to 388±8 IU/ml), F1.2 (0.9±.3 to 2.2±.5 nmol/L), and D-dimers (147±29 to 5999±3600 nmol/L) plus shortening of the euglobulin clot lysis time (EGCLT) by 72%. Levels of plasminogen activator inhibitor 1 (PAI-1) rose from 20.6 ng/ml to 37.8 ng/ml (87%) and tissue plasminogen activator rose from 4.7±.9 to 26.5±6 (460%). Exposure to 12% FiO_2 for 30 minutes resulted in a modest rise in platelet count (209,000±10,000 to 223,000±7,000/uL), and reticulated platelets (1.0±.3 to 1.7±0.8%) but no changes in factor VIII or von Willebrand antigen. F1.2 did increase from 0.5±11 to 1.4±.66 nmol/L but there was wide individual variation. D-dimers did not change but the EGCLT shortened by 32% and levels of PAI-1 and tPA remained unchanged. With hypoxic exercise to VO_2max there were further increases from baseline in platelet count (266,000±14,000/uL), and reticulated platelets (2.8±1.1%). Factor VIII (272±46 IU/ml)and von Willebrand's antigen (170±18 IU/ml) rose with hypoxic exercise but the effect was less dramatic than with exercise alone. There was no increase in F1.2. D-dimers increased only slightly (200±38 nmol/l) but the EGCLT shortened by 80%. Levels of PAI-1 only increased by 10% but tPA levels rose by 500%. Thus, it appears that moderate hypoxia may exert an antithrombotic effect by both damping exercise induced procoagulant changes and stimulating fibrinolysis.

111. NORMOBARIC INTERVAL HYPOXIA INCREASES EXERCISE TOLERANCE IN PATIENTS WITH CAD.

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Recently we demonstrated diminished cardiorespiratory responses to similar submaximal work loads in healthy students after the application of normobaric interval hypoxia. However, the efficacy of interval hypoxia in the elderly has not been studied in placebo-controlled experiments. Therefore, we compared the effects of interval hypoxic training and ambient air breathing on exercise tolerance and aerobic capacity in elderly men with and without coronary artery disease (CAD).16 elderly men (8 healthy and 8 patients with prior myocardial infarction; age: 50 – 70 years) were randomly assigned in a double blind fashion to the placebo and the hypoxia group. After an incremental spiroergometric pre-test participants underwent a 3-week breathing program (5 sessions per week). For the hypoxia group each session consisted of 3 - 5 hypoxic (14 – 10 % oxygen) periods (3 – 5 min) with 3 min normoxic intervals. The placebo group inhaled normoxic air in the same way. After the 3-week breathing program oxygen consumption (+2.0 ±1.3 vs. –1.1 ±1.2 ml/min/kg; P<0.01), oxygen saturation (+1.75 ±0.88 vs. +0.38 ±0.91 %; P<0.01) and minute ventilation (+14.3 ±12.5 vs. +2.1 ±6.6 l/min; P=0.03) at maximal work loads had increased from baseline in the hypoxia vs. placebo group. At the same submaximal work loads (1.5 watts/kg) heart rates and rate-pressure products were lower after interval hypoxia (P<0.05). Haemoglobin concentration was higher after interval hypoxia vs. normoxic air (P<0.05). Subgroup analyses revealed all changes to be more pre-dominant in patients with CAD. No side effects occurred. Interval hypoxic training was well tolerated from elderly men with and without CAD. After 3 weeks interval hypoxia exercise tolerance and aerobic capacity were increased especially in persons with CAD. These effects seem due to increased arterial oxygen saturation during exercise and/or enhanced oxygen transport capacity. Concomitantly, sympathetic stimulation by similar work loads are reduced.

112. EXERCISE-INDUCED ARTERIAL DESATURATION IS RELATED TO REDUCED MUSCLE NA^+-K^+-ATPASE CONTENT IN ICE HOCKEY PLAYERS.

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Based on previous research, in which we demonstrated that training in normabaric hypoxia results in a down-regulation of Na^+-K^+-ATPase content in skeletal muscle (Green et. al. J.Appl. Physiol. 86: 1745-1748, 1999), we hypothesized that ice-hockey players who exhibit exercise-induced hypoxemia (EIH), would show lower pump content that those who were normoxic (EN). To investigate this problem, members of a Univ ice-hockey team (n=19) performed progressive cycle exercise to fatigue for measurement of peak aerobic power (O_2 peak) and for measurement of EIH, defined as a reduction in arterial 0_2 saturation ($Sa0_2$) greater than 4%. Muscle tissue was extracted from the vastus lateralis and used to measure Na^+-K^+-ATPase content using the [3H] ouabain binding technique. In EIH (n=7) compared to EN (n=9), the lower (P<0.05) $Sa0_2$ (7.2±0.5 vs 3.0±0.3%) was not accompanied by differences in O_2 peak whether expressed in l/min. (4.44±0.13 vs 4.53±0.09) or in ml/kg/min (52.2±2.1 vs 51.4±1.4). However, Na^+-K^+-pump content (pmoles/g wet wt) was lower (P<0.05) by 7.2% (279±17 vs 259±7.3). Analyses of pre to post season changes in Na^+-K^+-ATPase indicated an increase (P<0.05) of 4.3% (255±7.7 vs 266±5.8 pmoles/gm wet wt), which occurred in the absence of changes in O_2 peak (52.1±1.2 vs 50.4±2.0). Since Na^+-K^+-ATPase content is not different than in untrained controls, it would appear that high-intensity intermittent exercise, particularly when accompanied by EIH, is not an appropriate stimulus for up-regulation of the cation pump levels.

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113. THE ROLE OF THE AUTONOMIC NERVOUS SYSTEM (ANS) IN THE REDUCED MAXIMAL CARDIAC OUTPUT (QT) AFTER ACCLIMATIZATION AT ALTITUDE.

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In altitude-acclimatised subjects, exercise Qt and VO_2 are tightly coupled and follow the sea-level (SL) relationship while maximal Qt is reduced. The mechanism of reduced maximal Qt remains debated, but one possibility is reduced sympathetic or increased parasympathetic activation of the heart. To explore this theory, five healthy subjects performed maximal bicycle exercise at SL and after two weeks of acclimatisation at 3,810 m (Post-Ac). Subjects breathed gas mixtures with varying FIO_2: at SL .209 and .125; Post-Ac .209 and .34, ensuring comparable high and low PIO_2 at both locations. Sympathetic blockade was performed with propanolol (PRO, 6 mg IV), parasympathetic blockade with glycopyrrolate (GLY, 0.8 mg IV). Qt was measured by acetylene uptake and indexed for BSA. Peak workload and VO_2 were lower in low PIO_2, but unaffected by acclimatisation or either of the two drugs. Peak-exercise data:

		Control		PRO		GLY	
	PIO_2	SL	Post-Ac	SL	Post-Ac	SL	Post-Ac
CI	High	11.0±6	10.2±7	10.0±5	9.3±5	10.8±6	10.1±5
(l/min/m2)	Low	10.1±3	9.0±4	9.3±4	8.5±4	9.8±5	9.0±3
HR	High	186±2	183±3	151±2	145±1	186±2	188±2
(bpm)	Low	180±3	170±4	152±2	139±2	185±3	184±2

Post-Ac, peak cardiac index (CI) was reduced 18% breathing ambient air (p<0.005), returning to SL values in high Po2. Despite a small reduction in peak normoxic CI at SL with PRO, post-Ac peak CI breathing ambient air was unaffected by either PRO or GLY. On the other hand, PRO reduced and GLY increased peak HR post-Ac, as expected. We conclude that while the ANS considerably affects peak HR, it plays little or no role in the reduction of peak cardiac output at the altitude of this study.

114. LACTATE PRODUCTION DURING HYPOXIC EXERCISE IS REDUCED BY THE ACTIVATION OF PYRUVATE DEHYDROGENASE WITH DICHLOROACETATE.

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We have previously shown that the activation of pyruvate dehydrogenase (PDH) is delayed at the onset of exercise in hypoxia. The objective of this study was to activate PDH with dichloroacetate (DCA) prior to exercise and thereby reduce lactate production during hypoxic exercise. Six subjects cycled for 15 min at 55% O_2 max (determined during normoxia) while breathing 11% O_2 after they received an infusion of saline (CON) or DCA. Muscle biopsies of the vastus lateralis were taken at rest, after 1 and 15 min. DCA increased PDH activity (PDHa) at rest from 0.7 ± 0.2 in CON to 3.1 ± 0.4 mmol/min/kg ww. After 1 min of exercise, PDHa was still greater with DCA compared to CON (2.9 ± 0.2 vs. 1.9 ± 0.2 mmol/min/kg ww). As a result, lactate accumulated to a lesser extent with DCA compared to CON (13 ± 4 vs. 21 ± 4 mmol/min/kg dw). Although PDHa was similar after 15 min of exercise (3.0 ± 0.4 vs. 2.7 ± 0.3, DCA vs. CON), lactate accumulation was still significantly reduced with DCA compared to CON (46 ± 12 vs. 69 ± 6 mmol/min/kg dw). Activation of PDH with DCA significantly increased the proportion of energy derived from oxidative phosphorylation, demonstrating that lactate production during hypoxia cannot solely be due to an oxygen limitation.

115. HEART RATE RESPONSE TO HYPOXIC EXERCISE: ROLE OF DOPAMINE D2 RECEPTORS AND EFFECT OF OXYGEN SUPPLEMENTATION.

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This study examined the effect of dopamine D2-receptor blockade on the early reduction of maximal heart rate at high altitude (4,559 m). We also attempted to clarify the time-dependent component of this reduction and to what extent it is reversed by oxygen breathing. Twelve normal subjects performed two consecutive maximal exercise tests without and with oxygen supplementation, respectively, at sea level and after 1, 3 and 5 days at altitude. On each study day, the D2-receptor antogonist domperidone (30 mg, N = 6) or no medication (N = 6) was given 1 h before the exercise sessions. Compared with sea level, hypoxia progressively decreased the maximal heart rate from day 1 and onwards; also, hypoxia by itself increased plasma norepinephrine concentrations after maximal exercise. Domperidone further increased maximal norepinephrine concentrations but had no effect on maximal heart rate. On each study day at altitude, oxygen breathing completely reversed the maximal heart rate to values not different from sea level. In conclusion, blockade with domperidone demonstrated that hypoxic exercise in humans activates D2-receptors that results in a decrease in circulating levels of norepinephrine. However, dopamine D2-receptors do not play a major role in hypoxia-induced reduction of the maximal heart rate. The data suggest that postganglionergic desensitization and not degradation of cardiac adrenoreceptors is responsible for the early decrease in heart rate at maximal hypoxic exercise.

116. MAXIMAL HEART RATE DECREASES WITH INCREASING ACUTE HYPOXIA.

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The decrease in maximal heart rate in chronic hypoxia is well described. However, in acute hypoxia this is not the case. Thus the purpose of the present study was to investigate maximal heart rate in various acute hypoxic conditions. Five sea level natives participated in the study and were investigated at sea level (SL), and after acute exposure to simulated altitudes of 3300, 4300, 5300, and 6300 meters. The three lowest altitudes were simulated in a hypobaric chamber at barometric pressures of 518, 459, and 404 mmHg. The 6300 meters altitude were induced by breathing 9% O_2 in N2 at sea level from a Douglas bag. At all conditions maximal cycle ergometer exercise was performed, within 15 minutes of hypoxic exposure, starting with a light 5 minute warm-up, and thereafter increasing the workload by 80 W every 2½ minute until exhaustion was reached. Maximal heart rate decreased with increasing altitude and maximal plasma norepinephrine (NE) and lactate (La) concentration did not change in any of the hypoxic conditions compared to sea level.

	HR (beats•min-1)	NE (nmol•l-1)	La (mmol•l-1)
SL	191 ± 3.3	20.0 ± 2.7	12.4 ± 1.2
3300	189 ± 3.4*	19.9 ± 2.4	12.30 ± 0.9
4300	182 ± 3.0*	20.6 ± 3.3	11.3 ± 1.2
5300	175 ± 2.9*#	18.5 ± 2.6	11.6 ± 0.8
6300	165 ± 1.3*&	21 ± 2.6	12.0 ± 0.6

Values are mean ± SEM. *P<0.05 compared to SL, #P<0.05 compared to 4300 m., &P<0.05 compared to 5300. In conclusion maximal heart rate decreases in acute hypoxia in a similar progressive manner with increasing altitude as in chronic hypoxia, and the decrease does not seem to be related to a decrease in maximal norepinephrine concentration.

117. PHYSIOLOGICAL PROPERTIES OF MUSCLE AND BLOOD IN MICE WITH AN INHERITED CAPACITY FOR HYPOXIC EXERCISE.

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It has previously been shown that two genes of major effect are principally responsible for hypoxic exercise tolerance in mice. When subjected to treadmill exercise under hypoxic conditions, mice that had been pre-exposed to 1/2 atmospheric PO_2 for 8 weeks had a genotype-specific capacity for hypoxic treadmill exercise (measured as time to exhaustion or tet). Two inbred strains of mice were used, BALB/cBy (C), which had low tet's and C57BL/6By (B6), which had intermediate tet's. These parental strains were crossed to form F1 hybrids that had exceptionally high tet's. Hematocrit and hemoglobin P50 increased in all animals that were exposed to hypoxia, but not in a manner that correlated with hypoxic performance. Activities were measured for enzymes of glycolysis, the Krebs cycle and fatty acid oxidation in left ventricle, in soleus muscle, which is predominantly slow twitch, and in extensor digitorum longus (EDL), which is predominantly fast twitch. Most striking was a reduction in the oxidative capacity of left ventricle, which is consistent with a decreased mitochondrial content in this tissue. Again, however, the changes were uniform and did not correlate with hypoxic performance. Contractile properties of isolated EDL and soleus were also measured. Tetanic stimulations revealed that the F1 mice (best performers under hypoxia) had a significant reduction in the tension-time integral following hypoxic exposure in both muscles. This was not seen in the B6 or C mice. In EDL, F1 mice also showed a reduction in peak force following hypoxic exposure, while in B6 and C mice peak force increased. These and other results suggest that adaptations in muscle fiber type are partly responsible for the inherited differences in hypoxic exercise capacity.

118. ANTIOXIDANTS AND EXERCISE PERFORMANCE AT SIMULATED ALTITUDE.

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Powers and Leeuwenburgh (Med. Sci. Sports Exerc. 31:987-997, 1999) review the literature and suggest that oxidants may be contributors to muscle fatigue during acute exercise. Pycnogenol (Proanthocyanidin, a broad-based antioxidant) seemed to extend exercise endurance on an 85% max test conducted in our laboratory at sea level. The present study was designed to extend this pilot to cyclists at a simulated altitude of 7000 feet. Using a double blind placebo-controlled cross-over design, 40 cyclists were randomized into two groups. After base-line, each group was given either placebo or Pycnogenol (200 mg/day) for 4 weeks and then crossed over for the remaining 4 weeks. A computrainer was used at 75% max while breathing 16.5% oxygen. Time to exhaustion, heart rate and oximetry were measured each week for 9 weeks as well as 8-isoprostane (urine), ORAC, and vitamin C & E plasma values measured at base-line, 5th week and 9th week. Thirty-two cyclists, sixteen in each group (25 % women), finished the study. About half were able to guess correctly when they were on pycnogenol. There were no systematic differences in endurance times, heart rate or arterial saturation between placebo and pycnogenol. ORAC values were higher than baseline for both placebo and pycnogenol. However, pycnogenol was not different from placebo. Eight-isoprostane values were reduced about 20% with pycnogenol as compared to baseline and prior placebo, suggesting less oxidative damage under pycnogenol. However, these changes did not reach statistical significance. Although there was an initial trend suggesting an increase in Vitamin C with pycnogenol, this trend was not consistent for both groups. There were no systematic changes with Vitamin E. In this study at a simulated altitude of 7000 feet, a broad-based antioxidant does not modify exercise performance although oxidative damage may be reduced.

119. FEMALE BLOOD LACTATE CONCENTRATIONS ARE UNCHANGED WITH SUBMAXIMAL EXERCISE INTENSITIES UNDER ACUTE HYPOBARIC HYPOXIA.

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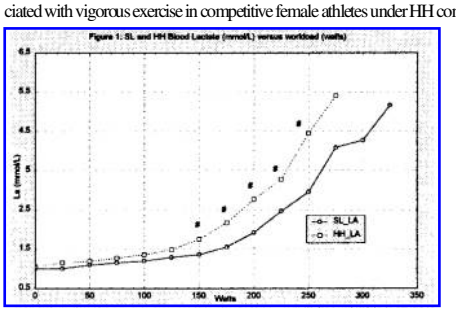
The purpose of this study was to characterize the exercise blood lactate response of females under sea level (SL) and hypobaric hypoxic (HH) conditions. Fifteen competitive female cyclists living at a residential altitude of 1,640 to 2,460 m underwent two exercise tests under varying barometric conditions (760 mmHg and 483 mmHg). The exercise tests were conducted in a hypo/hyperbaric chamber under randomized single blind conditions. A mass spectrophotometer was used to analyze inspire and expired gases. Blood samples were analyzed in duplicate using a spectrophotometer to determine blood lactate concentration (mmol/L). The results indicated that there were no significant differences in submaximal blood lactates concentration (below 150 watts) between 760 and 483 mmHg (Figure 1). At a workload of 150 watts, there was a significant difference in SaO_2 between the two conditions (SL SaO_2 = 95.9 + 2.6 vs HH SaO_2 = 79.1 + 4.8, $p < .05$). However, there was no significant difference in VO_2 at 150 watts ($p > .06$) indicating VO_2 was preserved at this exercise intensity. Analysis of the relationship between venous lactate at 150 watts with SaO_2 and VO_2 under each condition indicated a significant correlation between absolute VO_2 and blood lactate ($r = 0.546$, $p < .05$). At workloads greater than 150 watts or a VO_2 greater than or equal to 74.88% of HHVO2max there was a significant increase in blood lactate concentration with HH. In conclusion, it appears that females have similar blood lactate concentrations at submaximal workloads between SL and HH conditions. Our results indicate that the absolute VO_2 at 150 watts accounted for 29.8% of the variance in blood lactate concentration at 150 watts. Further study is needed to account for the increases in blood lactate concentrations associated with vigorous exercise in competitive female athletes under HH conditions.



120. ACUTE HYPOXIA DECREASES MUSCLE OXYGEN UPTAKE DURING EXERCISE WITH A SMALL MUSCLE GROUP WITHOUT AFFECTING POWER.

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The influence of hypoxia on muscle oxygen uptake, muscle blood flow and lactate production during exercise is still a matter of debate. Exercise with large muscle groups cause large systemic effects probably influencing those quantities. To elimi-nate these systemic effects we performed experiments with a small muscle group (forearm) working under graded hypoxia.

Methods: 19 male subjects performed continuous hand-grip exercise between 50% and 75% of the maximal workload reached in an incremental test. Contraction fre-quency was 24 per minutes. During exercise oxygen concentration was reduced in the inspired gas by about 3% every 10 minutes down to about 9%. Contraction velocity and distance were measured continuously. For acid-base state, HBO_2, HB, PO_2 and lactate determination blood was drawn from a cubital vein of the working forearm and arterialized blood from an earlobe. Forearm blood flow (Q) was meas-ured plethysmographically. 8 subjects performed control experiments under nor-moxia (CON). The determination of VO_2 by plethysmography and $AVDO_2$ was vali-dated in 4 different ways. Results: HBO_2 decreased from about 94 to 71 +/- 10.6 % in arterialized blood and from 44 to 29.3 +/- 9.7% in venous blood under hypoxia. $AVDO_2$ thus decreased from 107.9 +/- 16.1 to 80.7 +/- 13.3 ml/l with the increasing degree of hypoxia. Blood flow did not rise significantly to compensate for the de-creased $AVDO_2$. Neither contraction frequency nor contraction distance changed significantly. Thus power remained constant. The extra amount of lactate released is not sufficient to compensate for the reduced oxygen uptake. Conclusion: As a con-sequence of the reduced oxygen delivery VO_2 during exercise is reduced. A shift in substrates used for energy production or a change in recruitment of muscle fiber types might be causes for the declining VO_2.

121. FITNESS DEPENDENT EXERCISE INTENSITY DURING BACK COUNTRY SKIING.

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We studied the relationship between the degree of fitness and the individual chosen intensity during back country skiing. 22 skiers (13 males, 27 – 55 years and 9 females, 30 – 55 years) underwent ergometric testing (cycling) at an altitude of 2315 m. At the workload of 2W/kg, heart rate (HR), blood lactate concentration (Lab) and arterial oxygen saturation (SaO_2) were determined. Based on the obtained Lab values, the total group was divided into a well trained (T, Lab = 1.8 – 3.3 mmol/l) and an untrained (UT, Lab = 3.4 – 6.6 mmol/l) group. During back country skiing from 1900 m to 2800 m at the usually applied intensity, HR and Lab concentrations were measured. Whereas the T group showed a mean Lab of 2.6 mmol/l (± 0.43; SD) during cycling and 3.1 mmol/l (± 0.87) during back country skiing, the mean Lab of the UT group was 4.7 mmol/l (± 0.98) during cycling and 2.3 mmol/l (± 0,35) during back country skiing ($p < 0,05$; MANOVA). Despite the same relative skiing intensity (% HRmax) Lab was higher in the T group compared with the UT group ($p < 0,05$). These data suggest that both, well trained and untrained mountaineers chose the same relative intensity (% HRmax) during back country skiing. However, the absolute intensity and Lab were higher in the T group. This observation might be related to anecdotal reports concerning the higher incidence of acute mountain sickness in well trained mountaineers.

122. EFFECTS OF MODERATE ALTITUDE EXPOSURE ON ARTERIAL OXYGEN SATURATION, HEART RATE AND OXYGEN CONSUMPTION DURING GRADED EXERCISE.

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The purpose of this study was to examine the effect of moderate altitude exposure on the cardiovascular responses to graded exercise. While several studies have looked at the acute responses, we were specifically interested in looking at the relationship between exercise arterial oxygen saturation, heart rate and oxygen consumption before and after acclimatization. Six healthy, active subjects (mean age =25.5±.82 yr, mean weight = 81.0±4.5 kg, mean height 177.0±4.5 cm) were tested at sea level (SL1), upon acute exposure to 3400 m (ALT1), two weeks following acclimatization at 3400 m (ALT2), and upon return to sea level (SL2). Oxygen saturation (SaO_2(%), heart rate (HR), and oxygen consumption (VO_2) were measured during a graded exercise cycle ergometry test to exhaustion. Oxygen saturation was higher initially ($P<0.05$) before exercise for SL1 and SL2 (98.1±1.3, 98.5±1.4) than ALT1 and ALT2 (89.4±2.1, 93.7±2.1). The decrease in SaO_2 at maximal exercise was greater at altitude (ALT1= 77.4±3.1, ALT2 = 78.8±2.9) than sea level (SL1 = 93.2±1.4, SL2 = 94.6±2.0. However, at any submaximal level of exercise SaO_2 was lower at ALT1 than ALT2. Heart rates at rest were higher at altitude, however there were no differences in maximal heart rates. Oxygen consumptions at any given workload were not different but VO_2max was lower ($P<0.05$) at (40.6±4.5) than SL1 (45.5±3.8), ALT2 (50.2±4.3) , or SL2 (56.2±6.1). These data suggest that SaO_2 during graded exercise is lowered by acute altitude exposure but is partially restored after two weeks of acclimatization. Furthermore, VO_2max increased after acclimatization to moderate altitude and increased further upon return to sea level.

123. PHYSICAL EXERCISE AT LOW LEVEL ALTITUDE HYPOXIA INDUCE DIFFERENT METABOLIC AND HORMONAL CHANGES.

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Objective: A controlled study was designed to quantify the effect of 4 months training at medium altitude (2000 m) and the effect of low altitude (200 m) on physical exercise. Methodology: 12 cross-country skiers were studied after 4 months training at 2000 meters beforehand, after exercise and during recovery, a similar physical effort was done after returning at 200 meters. Blood samples: baseline overnight fasted venous samples were obtained before, at the end of exercise and after a recovery period for the measurement of various metabolites i.e.: lactate, free fatty acids, betahydroxybutyrrate, free carnitine, acetylcarnitines and long chain acylcarnitines; plasma concentration of several hormones: insulin, cortisol, growth hormone, renin, aldosterone, prolactin and, alkaline reserve were measured as well. Results: Free plasma carnitine and its fractions remained constant during exercise at 2000 meters, free carnitine decreased but short chain acylcarnitines and long chain acylcarnitines were increased both after exercise and recovery at 200 meters. Lactate, free fatty acids and βOH butyrrate were elevated after exercise at 200 meters. Plasma renin activity was more elevated after exercise at 200 meters, while aldosterone level was more elevated at 2000 meters. Prolactin insulin and cortisol were increased after exercise at medium altitude (2000 m.) while at low altitude (200 m) after exercise growth hormone levels were increased. Alkaline reserve was also decreased at 200 meters after physical exercise. Conclusions: Our study gives indirect evidence for a better metabolic performance at medium altitude during and after vigourous physical exercise (cross-country ski), a consequence of adaptation in well trained subjects. On returning at low altitude we observed increased lactate and acyl carnitine production after exercise implying that oxidation of fatty acids by respiratory chain offers potentially less fueling. The hormonal and metabolic changes we observed, are likely due to complex multifactorial events.

124. INTRACRANIAL HEMORRHAGES AFTER SUSTAINED HYPOXIA IN WARM RATS.

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Hypoxia elicits hypothermia in small animals and this response may be cerebro-protective. Three groups of rats instrumented with Mini-mitters to record body temperature (Tb) and level of activity (La) were exposed to 10% O_2 for 63 hours (h) at ambient temperatures (Ta) of 29° C, 25° C and 21° C. At the onset of hypoxia, Tb declined by 1.1° C at 3.5 h, 2.3° C at 4.5 h and 5.6° C at 5.5 h in the 29° C, 25° C and 21° C groups, respectively. Subsequently, Tb climbed to hyperthermic levels in the 29° C group but returned toward pre-hypoxic levels in the 25° C and 21° C groups. Thus, the hypothermic response is transient and its magnitude depends upon Ta. During hypoxia, La was depressed most at 29° C and least at 21° C. Hypoxia disrupted daily rhythms of Tb and La at all three levels of Ta. Hemorrhages were not observed in rats studied 2 h after hypoxia. By contrast, neuropathological examination revealed severe and diffuse subdural hematomas and intraventricular hemorrhage in rats studied 48 h post –hypoxia in the 29° C group. However, major pathology was not observed in rats studied 48 h after hypoxia in either the 25° C or 21° C group. We conclude that sustained hypoxia elicits spontaneous intracranial hemorrhages in rats acclimated to their thermoneutral Ta of 29° C. Appearance of hemorrhages is delayed following return to normoxia. These observations support the view that spontaneous hypothermia in small animals during hypoxia is both a function of Ta and cerebro-protective. (Supported by Am Lung Assoc grant 00—358 and UB Center for Sleep Disorders Research.)

125. DOES GINKGO BILOBA PREVENT ACUTE MOUNTAIN SICKNESS (AMS) IF BEGUN 1-DAY BEFORE RAPID ASCENT?

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Objective: Previous studies suggest that 5-days of prophylactic Ginkgo decreases the incidence of AMS during gradual ascent. We sought to evaluate its efficacy if begun 1-day before rapid ascent. Methods: In this double-blind, randomized, placebo-controlled trial, 26 participants residing at sea-level received Ginkgo (60mg TID) or placebo starting 24hrs before ascending Mauna Kea, Hawaii. Subjects were transported from sea-level to the summit (4205m) over 4hrs including 1hr of acclimatization at 2835m. The Lake Louise Questionnaire constituted the primary outcome measure at baseline, 2835m, and after 4hrs at 4205m; AMS was defined as a Lake Louise Self-Report Score (LLSR) >3. Subjects who developed "severe" AMS with either Clinical Assessment (LLCA) score >2 on items 1/2; LLSR+LLCA >6; any LLSR item >3; or SaO_2<70% were removed from the study for safety considerations and immediately transported to lower altitude. Results: The Ginkgo (n=12) and placebo (n=14) groups were well matched (58% vs. 50% female; 31±9 vs. 34±10yrs; 54% vs. 53% Caucasian). Two (16.7%) subjects on Ginkgo and 9 (64.3%) on placebo developed severe AMS and were removed from the study ($p=0.021$); all recovered without sequelae. Mean LLSR at 4205m was significantly lower for Ginkgo vs. placebo (3.3±2.0 vs. 5.1±2.2, $p=0.038$). Ginkgo was associated with a 33% lower incidence of AMS compared with placebo (58% vs. 86%, $p=0.19$). Surprisingly, 73% (n=19) of subjects developed AMS. Because of the unexpectedly high incidence of severe AMS, we halted the study after enrolling 26 of 100 subjects to re-evaluate our study protocol. Conclusions: This study further supports the use of Ginkgo in prevention of AMS. This is the first study to demonstrate that 24hr pre-treatment with Ginkgo may significantly reduce the severity of AMS prior to rapid ascent to 4205m. Supported by NIH#RR11091.

126. GINKGO BILOBA REDUCES INCIDENCE AND SEVERITY OF ACUTE MOUNTAIN SICKNESS.

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Context: Two Himalayan studies found ginkgo biloba prevented acute mountain sickness, (AMS) during gradual ascent. Objective: The purpose of this investigation was to determine the effectiveness of prophylactic ginkgo biloba on incidence and severity of AMS during rapid ascent. Design: The design was a double blind, placebo-controlled cohort study. The two groups were matched for age, gender and rate of ascent. Subjects: Forty college students residing at 1400 m (4,597 ft.) volunteered for the study. Intervention: Subjects received either ginkgo biloba 120mg orally or placebo twice a day, starting five days prior to the ascent of Pike's Peak (2 hours by vehicle to 4300 m (14,110 ft.) and continued while at elevation overnight. Primary Outcome Measures: The ESQ-III (short form) and Lake Louise Score (LLS) AMS questionnaires were completed before ascent and at altitude, either at 24 hours after ascent or when removed from the study because of symptoms. An ESQ score of > 0.7 and a LLS of > 3 were required for AMS. Results: Ginkgo versus placebo (7 of 21 with AMS vs. 13 of 19 with AMS, respectively) indicated a reduced incidence in the ginkgo group of 33% vs. 68%, $p<0.02$. Ginkgo also reduced the severity of AMS by both scores (mean ESQ = 0.77+0.20 vs. 1.59 +0.32, ginkgo vs. placebo, $p<0.03$; mean LLS = 3.9 +0.6 vs.6.2+0.9, $p<0.05$). SaO_2 was inversely correlated with severity of AMS. Age, gender, and hematocrit did not relate to AMS. Conclusion: Ginkgo biloba taken five days prior to rapid ascent to 4300m reduced the incidence and severity of AMS.

127. ARTERIAL OXYGEN SATURATION AS A PREDICTOR OF ACUTE MOUNTAIN SICKNESS DURING GRADUAL ASCENT TO 5100M.

Richards, Paul; Annabel Nickol; Andrew Pollard; David Collier; In conjunction with Medical Expeditions and supported by a grant from Liverpool Univ. Medical Expeditions and Dept. of Public Health; Respiratory Muscle Laboratory, Royal Brompton Hosp; Dept Pharmacology and Basic Medical Sciences, St B. (pritchi@aol.com).

Background. It has been suggested that at altitude arterial oxygen saturation (SaO_2) may be a predictor of subsequent acute mountain sickness (AMS) on further ascent. [Roach, et al., ASEM, 1998] Indeed, lower ventilation early in the course of altitude exposure is thought to be associated with AMS [Hackett et al., Respiration, 1982]. This relationship of SaO_2 and AMS was explored further during a slow ascent. Methods. Fifty five trekkers to Kangchenjunga North base camp (5100m) were studied. Each morning and evening SaO_2 recordings were made whilst sitting quietly at rest using an altitude validated pulse oximeter, Nellcor N20 and AMS scores evaluated using the Lake Louise Score. Height gain was gradual and sustained with an acclimatisation stop at 4700m. (Median time Kathmandu (1345m) to 4700m: 14 days; median stay: 2 nights). SaO_2 taken the morning of departure for the final incremental rise to base camp at 5100 was correlated with AMS score on arrival the same day and with AMS scores on the following 3 days at 5100m. Results. Mean SaO_2 at 4700m was 83.9 +/- 4.5%. The incidence of AMS (Headache and score of 3 or more) on arrival at 5100m was 7.4% and on the following 3 mornings was 9.3%, 11.1%, 5.6%. There was no correlation between SaO_2 at 4700m and AMS score on the same day arrival at 5100m (Pearson 0.21), nor on the following 3 mornings at 5100m. (-0.08, 0.002, -0.19) Conclusions. AMS incidence is much lower than previously reported [Hackett, et al., Lancet, 1976], probably due to the slow ascent rate. This may have contributed in part to the absence of a relationship between SaO_2 and AMS in this study.

128. AETIOLOGY AND PATHOGENESIS OF ACUTE MOUNTAIN SICKNESS.

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Low air mass per volume unit at high altitude is the cause of acute mountain sickness. The autonomic cyclic mechanics of the Lung start by contraction of the muscles of the lobar bronchi and those of the lobular bronchioles, which while decreasing their capacities, proportionally increase the molecular mass per volume unit of the inspired air, thus increasing their molecular expansive forces. These dynamics lead to displacement of the contained air in the sense towards lower resistance, to then expand the pulmonary structures in balanced forces, once muscular relaxation begins. Finally, the tiny intra-alveolar air masses distend the alveolar wall in balance with capillary blood pressure. These processes are accomplished by two kinds of dynamic cycles: 1. Lobar cycles, for air renovation, under Vagus Nerve command; 2. Lobular cycles, for gas exchange with the blood, under Sympathetic Nerve command. If the atmospheric mass of air per volume unit were lower to that demanded by the adaptation limits of the human specie, its molecular expansive force would be insufficient to achieve pulmonary dynamic expansion, with all that implies, as described above. Therefore, the expansive molecular forces of the alveolar air mass would be insufficient to expand the alveoli with the required tension to enable the right balance of blood and air pressure for balance for selective diffusion of Oxygen. The consequence would be pulmonary arterial blood hypertension, hypoxemia and pulmonary oedema, as is the case in Acute Mountain Sickness. Simultaneous data and graphs of Resultants of these dynamics, discovered by the Author in 1978, in the pleural space of experimental dogs, are analyzed. Related Author's published works are: "Fisiodinámica del Hombre en el Mundo" "The New Theory of Respiratory Dynamics" "Integración Dinámico Funcional del Organismo Viviente". The scientific web site: www.the-respiratory-pulse.org.ve.

129. EFFECTS OF ASPIRIN DURING EXERCISE ON THE INCIDENCE OF HIGH-ALTITUDE HEADACHE.

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Aspirin effectively prevents headache when mostly resting during acute high-altitude exposure. However, the majority of high-altitude visitors perform mountaineering activities, which might trigger headache. Therefore, we tested the efficacy of aspirin against headache when exercising during acute high-altitude exposure in a randomized, double blind, placebo controlled trial.31 healthy volunteers (20 males, 11 females; age: 22-59 yr) were transported to an altitude of about 3000 m and climbed up to 3800 m. They then descended to a mountain hut at 3480 m and spent 2 nights there. Tablets (placebo or 320 mg aspirin) were administered three times at 4 hr intervals, beginning 2 hr before arrival at high-altitude. Headache scoring and measurements of heart rate, blood pressure, and arterial oxygen saturation were performed repeatedly. Ninety-three percent (14/15) of the placebo group and fifty-six percent (9/16) of the aspirin group developed headache when mountaineering activities were performed during acute exposure to high-altitude ($P < 0.05$). Five hours after arrival at high-altitude, means+SD of resting oxygen saturation were 86.1 ± 2.1 % with aspirin and 85.7 ± 2.8 % with placebo ($P = 0.66$). However, subjects of the aspirin group developed headache at saturation values lower than or equal to 86 % and those of the placebo group at values lower than 90 %. Although the prophylactic intake of about 1 gram of aspirin reduced the headache incidence when exercising during acute high-altitude exposure, the incidence of headache was higher than previously shown for resting conditions. Aspirin enabled tolerance to lower arterial oxygen saturation without development of headache and exercise seems to have the opposite effect.

130. THE POSSIBILITY OF OCCURRENCE OF ACUTE MOUNTAIN SICKNESS AND/OR RESPIRATORY DISEASE AMONG JUNIOR HIGH SCHOOL STUDENTS CLIMBING AT MOUNTAIN.

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Background: The major physiologic stress encountered at high altitude is caused by the exposure to hypobaric hypoxia. In some articles, acute and chronic pulmonary and cardiac adaptation to high-altitude is reviewed. High-altitude pulmonary edema (HAPE), acute mountain sickness (AMS) and high-altitude cerebral edema (HACE) are very important high-altitude disease. Purpose: This study was organized to examine the possibility of occurrence of AMS and/or respiratory symptoms at moderate altitude for only one night exposure. Methods: In Nagano pref., junior high school students go up to the moderate altitude mountain on only overnight climbing for school event every year. In 1999, we performed the questionnaire examinations before and after climbing to the mountain of altitude from 2,670m to 3,033m. Results: In the 5149 students, 56 (0.8%) had fever rising, 120 (1.9%) had abdominal pain, 39 (0.6%) had nausea and 108 (1.7%) had headache. 13 (0.2%) and 22 (0.3%) developed asthma attack, and hyperventilation, respectively. The symptoms of AMS were very high level. These results suggest that the exposure to a moderate altitude environment for only one night may cause mild AMS in junior high school students.

131. HEART RATE VARIABILITY IN ACUTE ALTITUDE ILLNESS.

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There is little known about autonomic nervous system modulation in Acute Mountain Sickness (AMS), High Altitude Cerebral Edema (HACE), and High Altitude Pulmonary Edema (HAPE). We examined autonomic modulation in altitude illness of varying severity. Subjects included 27 trekkers at 4,200 meters in Nepal: 9 subjects with AMS, 3 with HACE, and 2 with HAPE, compared to 13 healthy age- and sex- matched controls. Oxygen Saturation ($Sa0_2$), Lake Louise Score (LLS) for altitude illness, and 10-min continuous electrocardiogram (EKG) were obtained. Subjects with AMS, HACE, and HAPE were tested twice, once when they were acutely ill (mean LLS: 9.2±0.7) and again 24 hours later with recovery (LLS: 2.3±0.8, $p<0.0001$). EKGs were later analyzed for extraction of respiration, and heart rate variability (HRV) using spectral analysis (low frequency, LF, 0.04-0.15 Hz, index of sympathetic activity, and respiration-related high frequency, HF, 0.15-0.40 Hz, index of parasympathetic activity). Higher LLS and lower $Sa0_2$ correlated linearly with increased HR ($p<.001$ for both), decreased HRV($p<.005$, $p<.009$ respectively), and decreased parasympathetic activity ($p<.001$ for both). LF modulation exhibited a biphasic behavior. In the subjects with mild illness, LF modulation was initially increased and later decreased with recovery. In subjects with more severe illness, LF modulation was initially decreased or absent and then increased with recovery. In contrast, parasympathetic activity, lnHF, was decreased in all sick subjects compared to controls ($p=.017$), and subsequently increased to control values with recovery. This pattern was essentially identical in AMS, HACE, and HAPE. This decrease in overall autonomic modulation with severe altitude illness parallels that seen in patients with severe Heart Failure and subjects performing extreme exercise, in whom extreme sympathetic activation blunts LF and HF, while amelioration/recovery produces autonomic remodulation. Parasympathetic activity is associated with health, and sympathetic activity is associated with illness at altitude.

132. LIMITED PROTECTION FROM AMS AFTER INTERMITTENT SHORT EXPOSURES TO SIMULATED ALTITUDE.

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A previous study suggested a useful symptomatic benefit during a mountain ascent after intermittent exposures to hypobaric hypoxia lasting 10 hr. This study used a similar protocol but exposures were only of 4 hr duration. On each of 5 successive days, 4 test subjects were exposed to simulated altitude in a hypobaric chamber for a 4-hr period, the first at 2700m, the second at 3300m and then 3 at 4000m. 12 hr following the last exposures the subjects together with 3 controls travelled by air to 2240m, then by road reaching 4150m 48 hr after the last chamber exposure before attempting to reach 5600m on foot 12 hr later. AMS symptoms scores were recorded using the Lake Louise questionnaire, SaO_2 was recorded using a portable pulse oximeter and haemoglobin by a colorimetric method from finger prick samples. Blood was taken before and after chamber exposures in test subjects and before and after the mountain ascent in both groups. 2,3,DPG was measured in test subjects before and after chamber exposures. Hb was higher after the climb in all subjects but this was more marked in test subjects + 20.7 ± 5.5 gm/l than controls +7.7 ± 5.1 gm/l. Test subjects had a 15% rise in 2,3,DPG during chamber exposures. All subjects retreated at 4920m on initial summit attempt for technical reasons. There was no difference in oxygen saturation between test and control subjects at any time. 2 of 4 test subjects had significant AMS symptoms (score > 4) whereas all 3 controls had scores > 4. The greater increase in Hb during the climb and rise in 2,3,DPG before the climb suggest some stimulation of acclimatisation by chamber exposures. Although limited by very small numbers, the study did not confirm a benefit during the climb. Intermittent exposures to simulated altitude (< 4 hr) may not be adequate.

133. ACUTE MOUNTAIN SICKNESS IS RELATED TO SLEEP DESATURATION AT HIGH ALTITUDE.

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The aim of this study was to investigate the relationship between AMS (assessed by the Lake Louise questionnaire) and sleep disordered breathing, measured at different altitudes. Methods: We studied 14 normal volunteers (8 males, 6 females; age: 36 ± 10 years; mean + SD) at 6 different altitudes from sea level to 5050 meters over a time period of 12 days in the Nepal Himalaya. Polysomnographic measurements (including respiratory disturbance index (RDI) and minimum sleep 0_2 saturation (Min $Sa0_2$) were recorded on the first or second night at each altitude using a 13 channel portable polysomnograph. Arterial blood gases were measured after each sleep study sitting up, awake and fasting. Oxygen desaturation with exercise and the Lake Louise AMS questionnaire were also measured at each altitude. Results: Mean Lake Louise Score was significantly correlated with increasing altitude ($r2 = 0.95$, $p < 0.0 1$) as expected. Furthermore, we found a positive significant relationship between Lake Louise Score and overall central RDI ($r2 = 0,21$ $p < 0.0001$) while a negative significant correlation was found between the Lake Louise Score and $Pa0_2$ ($r2 = 0.35$, $p < 0.0001$) as well as $PaC0_2$ ($r2 = 0.32$, $p < 0.0001$). Min $Sa0_2$ during sleep ($r2 = 0.42$) and oxygen saturation with exercise ($r2 + 0.40$) both correlated inversely with the Lake Louise Score ($p < 0.0001$ in both cases). Conclusion: Our data suggests that sleep disordered breathing at high altitude is related to acute mountain sickness. Desaturation during sleep and exercise appear to be more important determinants of AMS than sleep quality or daytime resting $Pa0_2$.

134. EFFECT OF RATE OF ASCENT AND ACUTE MOUNTAIN SICKNESS ON ARTERIAL OXYGEN SATURATION IN VISITORS TO 4250M.

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Pulse oximetry is a non-invasive readily available tool for assessing arterial oxygen saturation (SpO_2) in individuals at high altitude and elsewhere. Although pulse oximeters are available without prescription and it is suggested that SpO_2 may be a predictor of future AMS, the value of readings made without medical assessment is unclear. Little data is available for predicting normal values at specific altitudes and there is no evidence that AMS is associated with specific SpO_2 values. We set out to study the normal range of SpO_2 readings in visitors at the Himalayan Rescue Association (HRA) at 4250m in Nepal. We also hoped to determine whether saturation alone correlates with the presence of AMS (using the Lake Louise criteria). We studied 645 subjects (Female=199, Male=446) mean SpO_2=87% (SD=4.41%, range=57% -98%). Within the study group 139/645 reported AMS. A direct correlation was found between the number of nights taken to reach 4250m and saturation. There was no correlation of the presence of AMS with SpO_2 and no sex differences were observed. We conclude that SpO_2 at 4250m would normally be between 84% and 91% in the majority of subjects, this value is higher if more time is taken to reach altitude. While SpO_2 generally increases directly with the number of nights at altitude, there is considerable inter-individual variation, with a wide range of possible values in otherwise normal subjects. In this study SpO_2 alone could not predict the presence of AMS. (However, no attempt was made to use SpO_2 to predict the risk of future AMS) Therefore, we suggest SpO_2 is used in association with clinical assessment and not as an isolated tool for diagnosis of the presence of AMS. We would like to acknowledge the assistance of the HRA and support of Medex.

135. ELEVATED URINARY LEUKOTRIENE E4 LEVELS AT HIGH ALTITUDE.

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Background: Increased levels of urinary leukotriene E4 (LTE4) have been correlated with acute mountain sickness (AMS) scoring and with the development of high altitude pulmonary edema. The significance and pathophysiologic mechanisms underlying these findings are unclear. Objective: To evaluate the changes in urinary LTE4 that occur in response to high altitude and to correlate them with AMS scoring. Design: We performed a prospective study evaluating the effect of altitude on urinary LTE4. Urinary samples and Lake Louise AMS scores were obtained from fifteen long-term sea level dwellers at sea level, 11,500 ft, 15,000 ft, 15,500 ft and 16,500 ft. Pre and post exercise urine samples were collected at sea level, 11,500 ft and 16,500 ft. Setting: A high altitude research expedition in Ladakh, India. Participants: Ten volunteers and five researchers without a history of severe AMS, high altitude pulmonary edema (HAPE) or high altitude cerebral edema (HACE). Results: Compared to sea level, urinary LTE4 increased significantly ($p < .05$) with incremental increases in altitude, from 39.7 pg/mg cr at sea level to 92.3, 79.8, 63.1 and 261.6 at 11,550 ft, 15,000 ft, 15,500 ft and 16,500 ft respectively. LTE4 returned to baseline over 1-3 days with acclimatization to each incremental increase in altitude. Urinary LTE4 levels did not correlate with Lake Louise AMS scoring. Neither non-steroidal inflammatory drugs nor exercise significantly affected urinary LTE4 levels. Conclusions: We conclude that urinary LTE4 increases in response to incremental increases in altitude and returns to baseline over one to three days with acclimatization. Urinary LTE4 levels do not correlate with severity of AMS. Whether leukotriene activation plays a primary adaptive or pathophysiologic role in high altitude illness, or is merely a secondary or associated phenomenom is unclear.

136. ACUTE MOUNTAIN SICKNESS AND RISK OF ACCIDENT IN THE ALPS.

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The aims of our investigation was to assess in a population of members of the Italian Alpine Club the frequency of altitude-related symptoms and accidents occurring during mountaineering activities, with a view to establishing possible risk factors. A cross-sectional survey was conducted using a self-report questionnaire. Statistical analysis included the chi-square test and a forward stepwise multiple logistic regression model. The study cohort consisted of 1632 members (1232 males and 400 females) (mean age 40 years, range 10-92): 38.5% practised climbing (climbers), 61.5% only hiking (hikers). During the previous year's mountaineering activities, 41% of the respondents complained of altitude-related symptoms: 189 respondents (11.6%) met the case definition for acute mountain sickness according to Lake Louise diagnostic criteria. This syndrome was more frequent in the climbers (17%) than in the hikers (8.2%) ($p<0.0001$), but no associations were found with any pre-existing diseases, cigarette smoke, alcohol consumption and the practice of other sports. During their mountaineering activities, 14.5% of the respondents reported an accident, occurring more frequently among the climbers (24%) than the hikers (8.5%) ($p<0.0001$). Thirty-four percent of the climbers who had had an accident reported symptoms of mountain sickness, compared to 11% of the hikers. According to our logistic regression model, the probability of a member of the Italian Alpine Club meeting with an accident during mountaineering activities appeared to be associated not only with age and factors related to intensity and difficulty, but also with episodes of acute mountain sickness and/or symptoms of anxiety or irritability, unusual fatigue, and temporo-spatial disorientation. In conclusion, in Alpine territory too, mild maladjustment to altitude could be a risk factor in the aetiology of a mountaineering accident. Accordingly, we recommend proper acclimatisation, even at the Alps' moderate-high altitudes.

137. POSTURAL INSTABILITY AND ACUTE MOUNTAIN SICKNESS DURING EXPOSURE TO 24 HOURS SIMULATED ALTITUDE (4300 M).

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Previous studies have demonstrated that moderate to severe hypoxia lasting several minutes can have detrimental effects on postural stability. We hypothesized that postural stability would be adversely affected by continuous exposure to a simulated altitude of 4300 m for 24 h. Because dizziness and disequilibria may also be sensitive indicators of Acute Mountain Sickness (AMS), we also hypothesized that postural instability and AMS symptom severity, as measured by the Environmental Symptom Questionnaire (ESQ-C), would be correlated. As part of a double-blind, placebo-controlled crossover study of the effects of montelukast, a specific leukotriene receptor blocker, on the development of acute mountain sickness, postural instability was measured using a dynamic, computer-controlled unstable platform in 11 volunteers (9 men and 2 women). As no balance effects were obtained with 10 mg of montelukast administered 25 and 1 h prior to ascent, only data from the placebo phase of the study are reported. Compared to sea level, significant increases in postural instability were obtained after 2h (31%, $p=0.005$) and 23h (23%, $p=0.042$) altitude exposure. There were no significant altitude-stability effects when subjects closed their eyes or were asked to follow a moving target on the computer monitor. Five of 11 subjects exceeded the 0.7 ESQ illness score at both 11 h and at 20 h of exposure. However, no correlation was obtained between the ESQ-C and postural instability. These results suggest that postural stability is adversely affected during 23 h of exposure to 4300 m, but does not appear to be correlated with the severity of AMS.
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138. FEMORAL AND PULMONARY VASCULAR RESISTANCES IN THE NEWBORN LLAMA SUBMITTED TO ACUTE HYPOXEMIA.

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The fetal llama, a species adapted to the chronic hypobaric hypoxemia of pregnancy at altitude, shows a 5 fold increase in femoral vascular resistance during acute hypoxemiaa. No data is available regarding the fetal or neonatal pulmonary circulation. We tested the hypothesis that the intense femoral vasoconstriction observed in utero persists in the newborn llama submitted to hypoxemia and that this potent vasoconstriction is also observed in the pulmonary circulation. Under ketamine anesthesia, 3 neonatal llama (2-3 days old) were instrumented with vascular catheters and Transonic flow probe around a femoral artery. In addition we placed a Swan Ganz catheter into the pulmonary artery. Three days after surgery, all neonates were submitted to 3h protocol, consisting of 1h of normoxia, 1h of hypoxemia and 1h of recovery. Hypoxemia was induced by reducing the newborn FiO_2 (PO_2 = 31 ± 3 mm Hg, descending aorta; mean ± SEM). Arterial blood gases, cardiac output (thermodilution), femoral blood flow and systemic and pulmonary arterial pressures were measured throughout the experimental protocol. Vascular resistances were calculated. Heart rate increased from 99 ± 10 to 140 ± 5 min-1 and cardiac output rose from 209±6 to 274±18 ml x min-1 x kg-1 in hypoxemia. Femoral and pulmonary vascular resistances increased 160 % and 130 % respectively during hypoxemia. These data showed that the intense femoral vasoconstriction observed in utero was still present but attenuated in the neonatal period. Moreover, the pulmonary vasoconstriction with hypoxemia in the newly born llama is higher in magnitude than that measured in newborn lambsb. Further studies are needed to confirm these results.

a. Giussani et al Am J Physiol 271: R73, 1996; b. Schreiber et al Pediatr Res 19:437, 1985. Supported by FONDECYT 1970236-Chile and The Wellcome Trust.

139. MITOCHONDRIAL RESPIRATORY CHAIN IN RENAL CELL CARCINOMAS.

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The von Hippel Lindau tumor suppressor gene (VHL) product, pVHL, has been shown to down-regulate Hypoxia-Inducible Factor (HIF-1) in response to normoxia. The fact that pVHL abnormality induces familial or sporadic clear-cell renal cell carcinomas (CCRCC) gave rise to the concept that adaptation to hypoxia is a prerequisite for tumoral growth. We have studied four types of renal tumors. 1) Low grade CCRCC are associated with VHL gene alterations but rarely present with other genetic defects. 2) In high grade CCRCC, additional genetic alterations are frequently encountered. 3) The chromophilic type of RCC is not associated with VHL alterations, but familial forms are caused by modifications of the gene coding for Hepatocyte Growth Factor receptor. 4) The benign renal tumor oncocytoma is characterized by an increased number of mitochondria and various genetic modifications, but is never associated with VHL alterations. Determination of respiratory chain enzyme activities and of mitochondrial DNA ratio showed clear-cut differences between CCRCC and the other RCC. Citrate synthase, succinate dehydrogenase, succinate cytochrome c reductase, cytochrome oxidase, and the mitochondrial DNA ratio were drastically reduced in CCRCC samples when compared with normal tissue sample from the same kidney. By contrast, these mitochondrial activities and DNA ratio were increased in oncocytomas. In chromophilic tumors, only a slight decrease of mitochondrial enzyme activities could be detected. Mitochondrial ATPase activity was decreased in high grade CCRCC, but maintained in other tumoral types, reflecting probably an adaptive response to the mitochondrial defect in low grade CCRCC. We conclude that VHL gene alteration induces specific changes of mitochondrial activities, and that metabolic phenotype is probably secific for a given oncogenic transformation.

140. HYPOXIA & ADHESION MOLECULES.

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Exposure of cells in vitro to hypoxia has been shown to result in increased expression of adhesion molecules (AM). In man, circulating AM are reported to be increased in sleep apnea (J Appl Physiol 1999;87:10-14), asthma (Ann Allerg Asth Immunol 2000;84:539-41) and with acute mountain sickness (Chest 1997;112:1572-78) – all conditions associated with hypoxia. However, the effects of exposure to hypoxia on circulating AM in normal man are not known. Six healthy normal subjects were studied at baseline, at the end of 30 minutes of breathing a hypoxic gas mixture (11% O_2 in nitrogen), and at intervals thereafter for 8 hours. The arterial O_2 saturation during the hypoxic gas exposure ranged between 76% and 80%. At baseline, between-subject coefficients of variation for plasma intercellular adhesion molecule1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), E-selectin, and L-selectin, were 12.1%, 26.8%, 60.6%, and 16.0%, respectively. There were no significant ($p>0.1$) changes in circulating ICAM-1, VCAM-1, or E-selectin following hypoxic exposure. However, L-selectin decreased significantly ($p<0.05$) after 30 mins of hypoxia (1013.6±162.4 ng/ml vs 935.6±137 ng/ml), followed by a significant increase 2 hours after hypoxia (1032.0±149.3 ng/ml, $p<0.03$). These preliminary data are consistent with a downregulation of basal expression of L-selectin with hypoxia, followed by increased expression of L-selectin with reoxygenation, as shown previously in vitro for other adhesion molecules (Am J Physiol 1999;276:H2044-52). These and previous data suggest that hypoxia-induced changes in the expression of adhesion molecules may play a role in the inflammatory aspects of diverse hypoxic states.

141. DECREASED HIF-1ALPHA, INCREASED VEGF IN HIGH ALTITUDE PLACENTAS (3100 M).

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There is a 3-4 fold increase in the rate of pregnancy - induced complications in high (HA) vs. low altitude (LA) residents. Pregnancies at HA are associated with placental adaptations that include reduced uteroplacental artery remodeling and increased maternal and fetal angiogenesis. Since hypoxia-inducible factor-1a (HIF-1α) and vascular endothelial growth factor (VEGF) are key factors in hypoxia-induced angiogenesis, the objective of this study was to compare HIF-1α and VEGF in HA vs. LA placentas. Tissues from the 12 HA and 12 LA term placentas were analyzed by IHC, Western and Northern blot analyses, and gel shift analysis (HIF-1α). In HA and LA placentas, VEGF was located primarily on the fetal side of the placenta in the syncytial trophoblast of the terminal villi and the endothelial lining of fetal capillaries, while HIF-1α was primarily located on the maternal side of the placenta in the invading cytotrophoblast. There was less HIF-1α at HA (median = .559 [IQR .224-1.116]) vs. LA (median = 1.389 [IQR 1.35-1.65]), p = .017. In contrast, there was more VEGF at HA vs. LA (blot 1 - 3.22±1.1 vs. 1.2±.42, blot 2 – 5.16±1.5 vs. 3.38±1.1). (Data are standardized to ß-actin control and are reported as mean ± SD.) Preliminary data using Northern blot and gel shift analyses indicate no differences in HIF-1α mRNA and activity at HA vs. LA. These data suggest that placental adaptation to HA is associated with a reduction in HIF-1α on the maternal side with a concomitant increase in VEGF on the fetal side. Surprisingly, our results suggest no relationship between VEGF and HIF-1α under hypoxic conditions in vivo in the placenta.

142. HYPOBARIC CHRONIC HYPOXIA MODIFIES OXIDATIVE PHOSPHORYLATION IN MITOCHONDRIA OF RATS ADAPTED TO HIGH ALTITUDE.

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The influence of chronic exposure to hypoxia has been studied in rats and guinea pigs living at 3,700 m of altitude. The examined parameter has been the regulation of oxidative phosphorylations in the liver mitochondria. Results have been compared to those given by animals living at sea level. Guinea pig is indigenous to the Andes and has always been adapted to altitude, whereas rats originated from the sea level have been adapted to 3,700 m since more than four years. The main steps controlling the oxidative phosphorylation flux have been identified by titrating the rate of glutamate and malate oxidation in the presence of increasing amounts of inhibitors. Specific inhibitors, acting on each studied enzyme complex or carrier involved in ATP synthesis, have been used sequentially. The guinea pig mitochondria, whether prepared from animals living at sea level or from animals living at 3,700 m exhibited similar sensitivity to the oxidative phosphorylation inhibitors. On the contrary, the control exerted by the ubiquinol - cytochrome c reductase (Complex III) and, to a lesser extent, by the adenine nucleotide translocator was decreased for rats raised at 3,700 m as compared to those maintained at sea level. In the case of the adenine nucleotide translocator, this decrease in the control coefficient was accompanied by an increase in the apparent number of carboxyatractylate binding sites. For the same rats, the control exerted by cytochrome oxidase and by the ATPase-ATP synthase was increased by hypoxia. The mechanisms by which these regulations might be induced will be discussed.

143. THE OUTPUT OF NEBULISERS AT SIMULATED ALTITUDE.

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Objective - To determine the output of different nebulisers when used at simulated altitude. Methods - Three nebulisers were assessed in a hypobaric chamber operating at simulated altitudes of sea level, 4200m and 5300m. A conventional jet nebuliser, the Cirrus + Novair II compressor (Intersurgical Ltd., Wokingham, UK), a breath enhanced jet nebuliser, the Pari LC+ with a Turboboy compressor (Pari GmbH, Starnberg, Germany), and an ultrasonic nebuliser, Sonix 2000 (Clement Clarke International, Harlow, UK), were charged with 2.5ml (5mg) of salbutamol solution, and were operated for five minutes. The salbutamol released was collected on a filter and subsequently assayed. Results - At sea level, the conventional jet nebuliser released 0.55mg of salbutamol (95% confidence intervals 0.45 - 0.64mg), the breath enhanced jet nebuliser 1.69mg (1.57 - 1.8mg), and the ultrasonic nebuliser 1.57mg (1.45 - 1.69mg). The output of both jet nebulisers fell by over 50% at simulated altitude, but the output of the ultrasonic nebuliser fell by only 23% and 13% at 4200m and 5300m respectively. Conclusions - The output of jet nebulisers is reduced at low barometric pressure, probably because of changes in the driving gas flow generated by the compressor. The output of the ultrasonic nebuliser was less affected by these conditions. Although these results are limited, they suggest that ultrasonic nebulisers may be preferable to portable compressors and jet nebulisers for drug delivery at high altitude. The difference in output must also be taken into account by high altitude researchers using nebuliser.

144. LUNG DEPOSITION OF THERAPEUTIC AEROSOLS AT SIMULATED ALTITUDE.

Barry, Peter; Nigel Hart; Catherine Wilson; Sarah Bakewell; Roger McMorrow; Steven Watt; Andrew Pollard. Medical Expeditions & Leicester Univ; Medical Expeditions Univ of Aberdeen. (pwb1@le.ac.uk).

Previous studies at sea level have suggested an increase in lung deposition of particles inhaled in low density gases (Svartengren M, et al Exp Lung Res 1989;15:575). The objective of this study was to determine whether this occurred at altitude. Six subjects inhaled salbutamol (5mg) via an ultrasonic nebuliser (Sonix 2000, Clement Clarke International, Harlow, UK) at sea level and in a hypobaric chamber at a simulated altitude of 5,000m. Blood was taken at intervals for twenty minutes and serum salbutamol measured by liquid chromatography (Dept. of Pharmacology, Univ of Dundee). Mean peak serum salbutamol levels were 2.9ng/ml at sea level (range 1.6-4.6ng/ml) and 3.3ng/ml at simulated altitude (range 1.5-5.0ng/ml). Mean difference in paired samples (Sea level minus altitude values) was -0.5ng/ml (95% confidence intervals –1.8 to 0.9ng/ml. P=0.5, paired t test). This pilot study has not demonstrated an effect of decreased ambient gas density on lung deposition of inhaled salbutamol. This is important for researchers undertaking inhalational challenges or investigating the effect of inhaled medication at altitude. Further studies are needed to determine if there are differences in regional lung deposition that were not detected in this study.

145. PCO_2 INCREASES RESPIRATORY SINUS ARRHYTHMIA IN HUMANS.

Sasano, Hiroshi; Alex Vesely; Nobuko Sasano; Ron Somogyi; David Preiss; Joseph A Fisher. Dept. of Anesthesia, Univ of Toronto. (joseph.fisher@uhn.on.ca).

Introduction: Changes in heart rate with breathing (respiratory sinus arrhythmia, RSA) result from modulation of cardiac vagal efferent activity by central respiratory drive and excitatory input to vagal motor neurons synchronous with lung inflation. The degree of RSA increases with respiratory interval and tidal volume. Vagal output of the respiratory center also increases with increases in $PaCO_2$. As $PaCO_2$ changes with respiratory pattern, the independent effect of PCO_2 on RSA is unknown. We hypothesized that increases in PCO_2 independent of changes in breathing pattern increase RSA. Methods: Six healthy seated males were studied. ECG and $PetCO_2$ were monitored. Subjects breathed air from a spirometer through a non-rebreathing valve and face mask at a frequency (f) of 15/min, and FICO2 was varied from 0 to 0.06 in order to provide three different levels of $PetCO_2$ (30, 40 and 50 mmHg). Gas flow for all three conditions was set equal to the subject's highest required minute ventilation (at $PetCO_2$ of 50 mmHg.) Subjects were instructed to maintain the average spirometer level constant throughout the experiment, thus ensuring constant tidal volume. The order of $PetCO_2$ levels was randomized and data collected for 3 min after stabilization at each $PetCO_2$. The magnitude of RSA was expressed as amplitude of high frequency component at f = 15/min (HFamp, in ms/Hz1/2). Results: The figure shows individual data, normalized to resting HFamp. At $PetCO_2$ of 30, 40, and 50 mmHg, HFamp were 72 ± 15, 106 ± 26 and 125 ± 42 ms/Hz1/2 respectively (mean ± SE); these changes were significant (one way repeated measures ANOVA). Discussion: $PetCO_2$ independently affects RSA. Increased RSA would be physiologically beneficial in CO_2 retention because it decreases physiologic dead space (Circulation 4:842-7,1996).

146. THE EFFECTS OF INCREASING ALTITUDE ON OBSTRUCTIVE AND CENTRAL APNEAS IN NORMAL SUBJECTS.

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Introduction: Poor sleep quality at high altitude has been described since the 17th century. However, there is very little data available to explain the mechanisms of poor sleep quality at altitude. The aim of this study was to assess the relationship between increasing altitude and sleep disordered breathing. Methods: We studied 14 normal volunteers (8 males, 6 females; age:36 ±10; mean±SD) at 6 altitudes from sea level to 5050m over a time period of 12 days in the Nepal Himalaya. Polysomnographic measurements (*including respiratory disturbance index (RDI), arousal index (AI) and minimum sleep 0_2 saturation (min $Sa0_2$)) were recorded on the first or second night at each altitude using a 13 channel portable polysomnograph (PS 1, Compumedics. Melb. Australia). Arterial blood gases were measured after each sleep study sitting up, awake and fasting (Stat Pal II.PPG Industries. LaJolla. Calif). Results: $Pa0_2$ and $PaC0_2$ both fell with increasing altitude as expected. Min $Sa0_2$ also fell with increasing altitude from 92±4% to 63±7%. Al rose from 20±9/h to 29±19/h ($p<0.05$, paired ttest). At low altitude the Al was due to obstructive events (obstructive RDI 4.5±7.5/h, central RDI 0/h). As altitude increased the obstructive events were replaced by central events [(obstructive RDI was 0±0.5/h ($p=0.06$), central RDI 41±36/h, ($P=0.001$) at 5050m.] No association was found between central or obstructive RDIs and $PaC0_2$ or pH. There was a strong association between min $Sa0_2$ and central RDI and a negative association between min $Sa0_2$ and obstructive RDI. Discussion: The negative association between min $Sa0_2$ and obstructive RDI was surprising. We speculate that this was due to a non-linear effect of the peripheral chemoreceptors on upper airway muscle activation. It mirrors the relationship between central and obstructive RDI in heart failure patients treated by nasal CPAP.

147. ISOCAPNIC HYPERPNEA AND METHANOL ELIMINATION: A MODEL.

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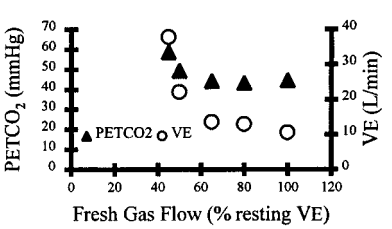
Background: Methanol can be eliminated via the lungs, but increasing ventilation to accelerate its elimination raises concerns about the adverse effects of the accompanying hypocapnia. Based on a new simple method1 of producing isocapnic hyperpnea (IH), we modeled the contribution of pulmonary elimination to total body methanol clearance. We hypothesized that at high methanol concentrations, IH would significantly accelerate its elimination. Methods: Using a commercial spreadsheet program, we simulated the elimination of methanol, assuming its distribution in all body water compartments, a blood-air partition coefficient of 2590, instantaneous equilibration with alveolar air, and a metabolic elimination rate of zero. We predicted clearance rates of methanol at ventilations of 5 and 25 L/min at an initial blood methanol concentration of 200 mg/dL (lethal limit for adults)2. Results: Increasing minute ventilation from 5 to 25 L/min increased the total body clearance rate of methanol from 1.8 to 8.8 mL/min. After 24 hours of IH at 25 L/min, blood methanol concentration fell to 145 mg/dL, compared to 188 mg/dL with a ventilation of 5 L/min. Discussion: Our model predicts that IH contributes significantly to methanol clearance. IH may provide a useful adjunct to standard dialysis treatment in highly intoxicated patients or an alternative treatment when dialysis is not available. IH should also be useful for eliminating such other common volatile toxins, such as halogenated hydrocarbons, glues, and gasoline. References: 1. Eur Resp J 12:698-701, 1998; 2. Am. J. Med. 67:804-807, 1979.

148. MAINTAINING ISOCAPNIA WHEN FRESH GAS FLOW IS LESS THAN MINUTE VENTILATION.

Fisher, Joseph A; Ron Somogyi; Alex Vesely; Hiroshi Sasano; Nobuko Sasano; David Preiss; Steve Iscoe. Dept. of Anesthesia, Univ of Toronto. (joseph.fisher@uhn.on.ca).

Introduction: Anatomic deadspace (Vd) imposes an irreducible inefficiency on mammalian breathing. We designed a circuit in which fresh gas is presented first to the lungs and the balance of the tidal volume is made up of rebreathed gas. We reasoned that the rebreathed gas would displace fresh gas from the Vd into the alveoli, optimizing the efficiency of CO_2 exchange. Methods: We constructed a manifold consisting of an inspiratory and expiratory valve in two arms of a Y-piece plus a bypass limb with a one-way valve leading from the expiratory arm to the inspiratory arm. A flexible gas reservoir was placed on each arm. Fresh gas entered the inspiratory arm between the reservoir and the valve. In four healthy males, O_2 flow was initially set equal to resting minute ventilation (Ve) and then decreased by steps of 5-10% of resting Ve. We monitored Ve, and end-tidal PCO_2 ($PetCO_2$). Results: Neither Ve nor $PetCO_2$ inreased in any subject until O_2 flow fell below 65% of resting Ve (see figure for typical results from one subject). Discussion: As neither $PetCO_2$ nor Ve changed with decreasing O_2 flow, Vd must have decreased proportionally. The O_2 flow at the inflexion point represents the alveolar ventilation (Va). Conclusion: When the last part of inspiration consists of rebreathed rather than fresh gas, the efficiency of fresh gas supply is increased as expressed by Vd/Vt = (resting Ve - Va)/Ve.



149. INCREASE IN RESPIRATORY SINUS ARRHYTHMIA DURING ISO-OXIC REBREATHING.

Sasano, Nobuko; Hiroshi Sasano; Alex Vesely; David Preiss; Ron Somogyi; James Duffin; Joseph A. Fisher. Dept. of Anesthesia, Univ of Toronto. (joseph.fisher@uhn.on.ca).

Introduction: Heart rate fluctuations linked with respiration (respiratory sinus arrhythmia, RSA) decrease the ratio of physiological dead space to tidal volume (VD/VT). We hypothesized that hypercapnia -induced increases in central respiratory drive increase the RSA magnitude during both hyperoxia and hypoxia. Methods: Five healthy adults performed a modified Read rebreathing test, during which $PETO_2$ was maintained at 150 (hyperoxia) or 50 (hypoxia) mmHg. RSA magnitude was expressed as the amplitude of the high frequency (0.15 - 0.50 Hz) band of RR interval (RRI) of the ECG (RRIHF in $ms/Hz^{1/2}$) at 1 to 5 times resting minute ventilation (VE). Results: The results obtained to date are shown in the figure. Discussion: Increases in RRIHF during hypercapnia-induced hyperpnea reduce VD/VT and improve the efficiency of CO_2 exchange (*Circulation* 4:842-7,1996). RSA magnitude increases at higher tidal volumes (VT) but decreases with increased respiratory rate. Increases in respiratory frequency during the later stages of rebreathing offset the effect of increased VT on RRIHF, accounting for the plateau in RRIHF.

150. MANIFOLD TO MAXIMIZE FiO_2 AND MAINTAIN ISOCAPNIA.

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Introduction: The standard non-rebreathing oxygen delivery mask (NRM) necessarily entrains air during inspiration1 resulting in dilution of O_2 by air during inspiration. We constructed and tested a three-valve manifold designed to maximize FiO_2 and maintain isocapnia independent of minute ventilation (VE). Methods: The manifold consisted of a Y-piece (inspiratory and expiratory arms, each containing a one-way valve) plus a bypass limb with a one-way valve leading from the expiratory to the inspiratory arm. A flexible gas reservoir was placed on each arm. Fresh gas entered the inspiratory arm between the reservoir and the valve. O_2 flow was set equal to resting VE (8 L/min) and the subject increased VE to 15, 25, 45, 70 and 105 L/min. Tidal FO2, PCO_2 and VE were monitored. Results:. As ventilation increased, FiO_2 remained above 0.9 and $PetCO_2$ was held constant (see figure for typical results). Discussion: The manifold is designed to provide fresh gas followed by rebreathed gas during inspiration. At O_2 flow equal to VE , FiO_2 = 1.0. When VE exceeds O_2 flow, the balance of the inspirate consists of rebreathed gas with a high FiO_2; however, it does not provide a gradient for CO_2 elimination as its PCO_2 is close to that in mixed venous blood. This manifold may be of value in providing high FiO_2 as well as setting $PetCO_2$ independently of VE . References: 1. Crit Care Med.1998; 26:1032.

151. EFFECT OF EXPOSURE TO MODERATE ALTITUDE ON RESPIRATORY FUNCTION IN HEALTHY LOWLANDERS.

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Respiratory function (RF) responses to altitude have been mainly studied at altitudes > 3500m showing a significant VC↓. Little information is available about RF at lower altitudes. This study is part of a project aimed to evaluate the effect of exposure to moderate altitude (2950m) on cardiovascular and respiratory function. Subjects: 27 healthy lowlanders divided in 3 groups according to age: 8 children (C), age 6-12 yrs, 9 adults (A), age 32-45, 10 elderly (E), age 60-83. They performed spirometry at sea level (sl) and at 2950m 1 hour after the arrival (by cable car)=HA1 and 24 hours later =HA2. SaO_2 was measured by pulse oxymeter. None of the subjects suffered from acute mountain sickness, 4 A, 1C reported mild headache and insomnia. RF results are expressed as % of sl value (mean±SE). SaO_2 as true value.

		FVC	FEV1	SaO2%
A	HA1	98.8(0.6)	99.1(0.64)	93.5±2.2
	HA2	97.8(0.7)	98.8(0.58)	94.1±1.7
E	HA1	99.2(0.72)	99.8(0.7)	91.4±3.6
	HA2	98.1(1.1)	99 (0.81)	92.1±1.7
C	HA1	99.3(0.68)	98.6(0.77)	88.5±1.7** vs A/E
	HA2	98.3(0.81)	99.2(0.69)	91.7±2.4

No difference in RF was found at moderate altitude vs sl. We conclude that exposure to altitudes often reached by the general population does not affect RF in healthy lowlanders. C seem to have a slower adaptation to altitude as demonstrated by lower SaO_2 values at HA1.

152. CHANGES IN RESPIRATORY MUSCLE FUNCTION DURING EXPOSURE TO HIGH ALTITUDE.

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Aims of the study were 1) to determine the time course of change in respiratory muscle strength during exposure to high altitude; 2) to compare strength changes between respiratory and forearm-flexor muscle groups; and 3) to assess the influence of acute mountain sickness and/or acute hypoxia on these processes. Ten healthy subjects (8 male) participated in the study. Measurements were performed at sea level, during a 14 day ascent to high altitude (~5050 m), and during a 14 day descent to ~2330 m. Inspiratory and expiratory muscle strengths were assessed as maximum mouth pressures (MIP and MEP, respectively) using a portable pressure transducer. Isometric grip strength was measured using a hand dynamometer. Strength measures were repeated at 5000 m during acute O_2 supplementation. Symptoms of acute mountain sickness (AMS) were assessed twice daily using a modified Lake Louise Consensus scoring system. Ascent to high altitude resulted in progressive reductions in respiratory (15 ± 3% MIP; 21 ± 4% MEP; $P < 0.01$) and forearm-flexor muscle function (7 ± 2%; $P < 0.01$) that were not due to acute hypoxia per se or the general debility of AMS. Although expiratory muscle strength returned toward sea level values during descent to a lower altitude (2 ± 2% below sea level values; $P > 0.05$), reductions in inspiratory muscle strength were only partly reversible (6 ± 2% below sea level values; $P < 0.05$). Moreover, forearm-flexor muscle strength remained below sea level values upon descent (6 ± 1%; $P < 0.05$). Estimated changes in the compressibility of gas in the lungs, based on the pressure-volume relationship of respiratory muscles, accounted for only 4% of the reduction in MIP but 19% of the reduction in MEP. A possible interaction of general muscle wasting and increased inspiratory muscle work may have accounted for the observed changes in muscle function during descent toward sea level.

153. THE EFFECTS OF SPECIFIC INSPIRATORY MUSCLE TRAINING UPON RESPIRATORY MUSCLE FUNCTION AND DYSPNOEA AT HIGH ALTITUDE.

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Respiratory muscle function is significantly reduced at high altitude. Furthermore, respiratory muscle dysfunction may be associated with dyspnoea. The aim of the present study was to explore the interactions between improvements in respiratory muscle function, specific inspiratory muscle training (IMT) and perceptual responses to dyspnoea at high altitude. Twenty-seven healthy subjects were divided randomly into 2 groups. Fourteen (9 male) formed an experimental group performing one set of 30 inspiratory efforts twice daily against a pressure threshold load equivalent to ~50% maximum inspiratory pressure (MIP) for 8 wk prior to departure. The remaining subjects (n = 13, 9 male) were a control group matched for baseline respiratory muscle function. Measurements were performed at sea level and ~5050 m following a 19 ± 3 d ascent that involved a mean daily altitude gain of 218 ± 36 m (mean ± SEM). There were reductions in inspiratory muscle strength (MIP, -16%), expiratory muscle strength (MEP, -19%) and inspiratory muscle endurance (IME, -26%) in the control group at altitude compared to sea level ($P £ 0.01$). For the experimental group, IMT counteracted the decline in MIP (+6% cf. pre-training at sea level), but not MEP (-18%; $P £ 0.01$). The decrease in IME was also attenuated by IMT (-8%; $P £ 0.01$). Exertional dyspnoea (Borg CR10) during 6 min of bench stepping was higher at altitude in both groups. Baseline and Transition Dyspnoea Indices suggested that IMT reduced the magnitude of task and effort associated with ascent to high altitude. There was no difference between the groups for mean accumulated acute mountain sickness score (AMS) ($P > 0.05$). In conclusion, specific IMT attenuates high altitude-induced reductions in inspiratory muscle function, as assessed by volitional manoeuvres. The precise functional significance of this finding remains unclear, but IMT may prove effective in developing tolerance to the respiratory discomfort associated with high altitude. Furhermore, IMT was no associated with an increased susceptibility AMS.

This work was carried out in conjunction with Medical Expeditions.

154. BREATHING REGULATION AND SYMPATHOADRENAL ACTIVITY UNDER ADAPTATION TO INTERMITTENT HYPOXIC TRAINING.

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Adaptation to hypoxia is characterized by time-dependent increase in hypoxic ventilatory response (HVR) and by slow increase in sympathetic activity (SA) at sympathoadrenal system (SAS) which testify to the relationship of these processes with the existence of common regulatory mechanism for them. The aim of this study was to detail a possible relationship between HVR and SAS activity during adaptation to intermittent hypoxic training (IHT). We examined the HVR indexes, venous blood (VB) and daily urine (DL) catecholamines (CA: dopamine - DA, norepinephrine - NE, epinephrine - E) and DOPA levels in young and elderly people during 14 days of IHT. The decreased HVR in elderly age was accompanied by increased DA, DOPA levels in VB and DL which obviously were formed by the age-related disturbances in storage/uptake mechanism for this agents. The possible causes for age-related decrease in HVR could be the diminished DA synthesis in carotid bodies (CB) and/or the inhibitory influence of blood DA as regard the peripheral mechanisms of breathing regulation. We supposed that peculiarities of CA metabolism in SAS and CB (as a part of SAS) would be an essential factor in breathing regulation. Adaptation to IHT was accompanied by the increase in HVR, which was more expressed in young people. The reciprocal changes in blood DOPA (increase - in young, decrease - in elderly), increased blood NE concentration in both groups and increased E in young were registered testifying the SAS activation during IHT. After IHT the negative correlation between DA, DOPA excretion and HVR was observed as well as between DA excretion and lung ventilation indexes. If DA, DOPA levels in VB and DL are the markers of SA, these correlations imply a relationship between SA and effective ventilation during IHT adaptation.

155. EFFECT OF DOPAMINE ON VENTILATION IN HYPEROXIA IN HIGH-ALTITUDE NATIVES.

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High-altitude natives (HA) develop a blunted ventilatory response to acute hypoxia (AHVR). This blunting of AHVR may be sufficient for HA natives to show paradoxical hyperventilation when exposed to hyperoxia. Despite this, HA natives ventilate more at HA than sea-level (SL) natives at SL. One possibility is that the carotid body chronically stimulates ventilation in a manner that cannot be suppressed by hyperoxia. To test this, we decided to investigate whether an alternative means of suppressing the carotid body (low-dose dopamine infusion) could suppress ventilation in HA natives. The effects on ventilation and end-tidal PCO_2 of a low-dose dopamine infusion were investigated under hyperoxic conditions in 19 HA natives and 24 SL natives as controls. Low-dose dopamine did not decrease ventilation or elevate end-tidal PCO_2 in either HA natives or SL controls under these conditions. In conclusion, this study provides no support for the notion that HA natives have carotid bodies that are in a state of chronic activity that cannot be suppressed by acute hypoxia.

This study was supported by the Wellcome Trust

156. HYPOXIC VENTILATORY RESPONSE AND ACUTE MOUNTAIN SICKNESS.

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Background. Acute mountain sickness (AMS) is common amongst individuals who ascend rapidly to high altitude. A number of factors have been linked to the susceptibility of an individual to developing the syndrome including the hypoxic ventilatory response (HVR). A eucapnic HVR assessment was made in 17 individuals at 150m using a 12% oxygen gas mixture. The end tidal carbon dioxide ($PETCO_2$) was allowed to drift. Methods. The acute effect of 12% oxygen on peripheral oxygenation and minute ventilation was investigated in 17 subjects (3 female)(age 22-56) at 150m. Once a steady state had been achieved, supplementary CO_2 was then added to the 12% oxygen. A Harvard dry gas meter was used to measure minute volume (MV). Arterial oxygen saturations (SaO_2) and end tidal CO_2 ($PETCO_2$) were measured using a Propac Encore Monitor. Twice daily Lake Louise self-assessment questionnaires and a once daily independent clinical assessment of AMS were made during a thirteen day ascent from 1340m to 5005m on foot.

	$PETCO_2$	SaO_2	Minute ventilation l
Baseline	39(3.1)	97.6(1.2)	6.5(2.4)
12% oxygen	36.0(3.5)*	79.7(7.1)*	7.8(1.9)*
12% O2 + CO2	46.2(6.3)**	93.6(5.6)**	11.0(5.1)**

Statistics: Mean(SD), Paired t test * $p<0.05$ vs Baseline, ** $p<0.05$ vs 12% oxygen. There was no significant correlation between the HVR and either clinical or self assessment of AMS. Conclusion. Although there was a marked increase in minute volume with the hypoxic gas mixture, there was no correlation with subsequent AMS development as assessed by Lake Louise self-assessment scores or clinical assessment. Supplementary CO_2 had a profound effect on the peripheral saturations, the mechanism likely to be an increase in the minute volume, a shift to the left of the oxygen dissociation curve and vasodilation of certain vascular beds.

157. PHYSIOLOGICAL EFFECTS OF INTERMITTENT HYPOXIA.

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The physiological processes of acclimatisation to altitude, which occur during continuous exposure, might also be stimulated by intermittent hypobaric hypoxic exposures. The study investigated a series of short intermittent exposures were associated with similar physiological effects on ventilatory control and haemoglobin (Hb) as are seen during continuous exposure. On each of 5 successive days, 4 subjects were exposed to simulated altitude (hypobaric hypoxia) in a hypobaric chamber for a 4 hour period, the first at 2700m, the second at 3300m and then 3 at 4000m. Ventilatory response to hypoxia (HVR) was measured before exposures and on days 3 and 5. Hb was measured at the same times. Oxygen saturation (SaO_2) was recorded during the last 15 min of each exposure and AMS score was recorded immediately after each exposure. During chamber exposures SaO_2 fell with increasing altitude Mean 91% at 2700m to 76% at 4000m but appeared to improve with successive exposures to 82% during the last at 4000m. Significant AMS scores (=>4) appeared at the first exposure at 4000m but fell with following exposures.

HVR litres.min^{-1} per % SaO_2

Subject	RS	AJ	RJ	PC
Control	-1.36	-0.97	-1.81	-1.42
Day 3	-1.05	-0.78	-0.98	-0.77
Day 5	-0.97	-0.88	-1.16	-0.63

All subjects showed a fall in HVR between days 1 and 3 but little change between day 3 and 5. Hb showed little change between days 1 and 3 but a rise in all subjects (average 7.5gm/l) between day 3 and 5. HVR results are consistent with a biphasic response to altitude, previously reported during early continuous exposure. The results are consistent with intermittent exposure stimulating physiological acclimatisation.

158. EFFECT OF CO ON THE VENTILATORY RESPONSE TO CO_2 IN HUMANS.

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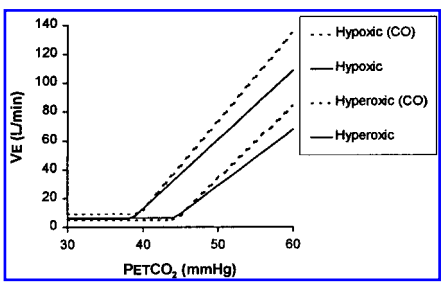
Heme-oxygenase located in the carotid body produces CO in a process that requires molecular O_2. CO has been described as acting locally as a neurotransmitter to inhibit carotid sinus nerve discharge. Thus, during hypoxia, decreased CO production has been hypothesized to stimulate ventilation by disinhibition. We hypothesized that inhalation of exogenous CO would decrease the peripheral response to hypercapnia. Methods: Five healthy young males performed hypoxic and hyperoxic rebreathing tests (to test peripheral and central hypercapnic responses respectively) before and after exposure to CO. Before each test, the subject hyperventilated for 5 min to deplete CO_2 stores. He then rebreathed from a bag while end-tidal PO_2 was held constant at either 150 or 50 mmHg. Respiratory flow, tidal CO_2 and O_2 were monitored. The subject then breathed CO at 1200 ppm until venous COHb reached 10-12%, and repeated both the hyperoxic and hypoxic rebreathing tests. Results: The figure shows the average CO_2 response curves for all subjects during hypoxia and hyperoxia, with and without CO. With CO, there was a trend to increasing slope of the CO_2 response curve during both hyperoxia and hypoxia; however, differences did not reach significance. Discussion: If CO inhibits carotid body activity, then the hypoxic ventilatory response, in which carotid bodies are stimulated, should be reduced. Preliminary data suggest that in fact both the hypoxic and hyperoxic responses are sensitized, implying that CO causes relative tissue hypoxia rather than disinhibiting the carotid responses.



159. MOUSE MODELS TO STUDY THE GENETICS OF THE HYPOXIC VENTILATORY RESPONSE.

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A substantial homology between the human and mouse genomes makes inbred mice strains a promising experimental model to distinguish effects of environment versus genetics on the hypoxic ventilatory response (HVR). However, challenges in studying the HVR in mice include (1) quantifying arterial chemoreceptor stimulus levels, i.e. measuring arterial blood gases, (2) "roll off" of the acute HVR, i.e. hypoxic ventilatory decline and (3) potential effects of changes in metabolic rate during acute hypoxia on ventilation. We studied these problems in 6 male C57BL/6 mice (29.7 +1.4 g). One day after surgery to catheterize the iliac artery, we measured arterial blood gases (150 mL), ventilation, and metabolic rate in awake mice breathing 30% and 10% O_2 for 15 min. At a given PaO_2, $PaCO_2$ was high and pHa was low compared to typical mammalian values. This is observed in other small mammals and is hypothesized to represent a physiological scaling effect. Hypoxic ventilatory decline was observed between 2 and 15 min of hypoxia but metabolic rate did not decrease. In contrast, a wild type transgenic mouse (129/J X C57BL/6) backcrossed to C57BL/6 for 5 generations (Huey et al., J. Appl. Physiol. 89:1142-1150, 2000) showed both hypoxic ventilatory and metabolic decline. Hence, factors determining the HVR are under differential genetic control and must be systematically measured to analyze the genetics of the HVR in mice. Supported by NIH-HL17731, HL-07212 and UC White Mountain Research Station.

160. HYPOXIC VENTILATORY DEPRESSION IN HIGH-ALTITUDE NATIVES LIVING AT SEA LEVEL.

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Early literature suggests that high-altitude (HA) natives have an irreversibly blunted ventilatory response to acute hypoxia (AHVR). However, recent data suggest that AHVR can be recovered in HA natives after a period of residence at sea level (SL). This study sought to determine whether these differences between studies can be explained by differences in hypoxic ventilatory depression (HVD): i.e., whether AHVR in HA natives appears to differ from that in SL natives because they exhibit different degrees of HVD when exposed to sustained isocapnic hypoxia. We measured the ventilatory to sustained (20 min) isocapnic hypoxia (end-tidal PO_2=50 Torr) in 27 HA natives resident at SL and in 29 SL natives as controls. Mean values for AHVR and HVD in HA subjects were 7.7±4.9 (mean±SD) and 3.9±5.9 l/min, respectively, in SL subjects were 9.4±5.2 and 6.1±7.1 l/min, respectively. We conclude that neither AHVR nor HVD differed markedly between HA natives resident at SL and SL controls.
This study was supported by the Wellcome Trust.

161. GENDER DIFFERENTIATION OF THE HYPOXIC VENTILATORY RESPONSE IN PREPUBERTAL RATS AT SEA LEVEL : IMPORTANCE OF PRENATAL PROGRAMMING OF THE FETUS.

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Prepubertal female rats have higher Hypoxic Ventilatory Response (HVR) than males at sea level and higher resting minute ventilation than males at high altitude (HA - La Paz, Bolivia, 3600 m). At HA, this gender-difference is dependent upon the testosterone surge of neonatal males. However, reports describing gender differentiation of the time-dependent shape of HVR in prepubertal rats are not available yet. We used 20 day-old males (n=8, 40.7 ± 1.3 grams) and females (n=8, 40.5 ± 2.6 grams) to assessed HVR by flow plethysmography at 1, 4, 8 and 15 minutes of exposure to 10 % O_2. All animals exhibited a biphasic response with a marked increase of minute ventilation (Ve), tidal volume (Vt) and frequency (Fr) followed by ventilatory roll-off. Gender differences were clearly apparent on the overall analysis (interaction hypoxia x gender, p=0.001) : Ve and Vt were higher at 1 min of hypoxia in females (300 ± 14 mL/min/100 g; 0.66 ± 0.04 mL) than males (252 ± 9 mL/min/100g; 0.51 ± 0.03 mL – $p<0.05$). Thereafter males had higher Ve at 4, 8 and 15 min ($p<0.05$) with a clear tendency to have higher Fr, while differences of Vt disappeared. Masculinization of fetal male brain is impaired by prenatal stress (PNS), a model of manipulation of the pregnant dam inducing long-term neurological alterations. We used 20 day-old PNS pups (restraint stress, 3 x 45 minutes daily, last week of gestation) to assessed HVR : all gender differences of HVR observed in control rats were absent in PNS rats (interaction hypoxia x gender, p=0.69). The effect of PNS was marked in males and absent in females. We conclude that gender differences of HVR in prepubertal rats is largely time-dependent and that the gender-related difference is sensible to prenatal programming factors such as PNS.

162. LOW SODIUM INTAKE DOES NOT IMPAIR RENAL COMPENSATION TO HYPOXIA-INDUCED RESPIRATORY ALKALOSIS IN CONSCIOUS DOGS.

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Acute hypoxia causes hyperventilation and consecutively respiratory alkalosis, often combined with increased diuresis, sodium, and bicarbonate excretion. This study investigated whether renal compensation of hypoxia-induced respiratory alkalosis is impaired by a low sodium intake. Nine conscious, tracheotomized dogs were studied twice in randomized order, either on a chronically low sodium diet (LS) (0.5 mmol sodium per kg body weight (wt) per day), or on a high sodium diet (HS) (7.5 mmol sodium). During the experiments the dogs were breathing spontaneously via a ventilator circuit: first hour, normoxia (FiO_2 = 0.21); second to fourth hour, hypoxia (FiO_2 = 0.1). At the end of each experimental hour arterial blood gases, urinary excretions, and plasma aldosterone concentration (PAC) were measured. Data are means±SEM; * $p < 0.05$ vs. normoxia, # $p < 0.05$ vs. LS. During acute hypoxia (PaO_2 34.4 ± 2.1 mmHg; $PaCO_2$ 25.6 ± 2.4 mmHg) plasma pH increased from 7.37 ± 0.2 (LS and HS) to 7.47 ± 0.03* (LS and HS). Consecutively urinary pH increased from 6.11 ± 0.16 to 6.83 ± 0.23* (LS) and from 5.77 ± 0.19 to 6.99 ± 0.25 (HS).

Protocol	UHCO3-V [µmol·kg-1·min-1]	UNaV [µmol·kg-1·min-1]	UKV [µmol·kg-1·min-1]	PAC [pg/ml]
LS Normoxia	0.018±0.006	0.11±0.01	0.34±0.12	528±103
LS Hypoxia	0.57±0.27*	0.58±0.29*	0.81±0.23*	132±39*
HS Normoxia	0.016±0.009	0.19±0.04	0.35±0.05	131±59#
HS Hypoxia	0.74±0.27*	2.36±0.57*#	0.94±0.30*	29±6*#

The plasma pH adaptation to acute hypoxia is independent of the dietary sodium intake. The fast renal bicarbonate excretion during hypoxia is not impaired by a low sodium intake. The cation combined with urinary bicarbonate in dogs on a low sodium diet is predominantly potassium. Increased sodium excretion during hypoxia seems to be mediated by the decrease in PAC during LS as well as during HS.

163. DIFFERENCES IN CARDIOVASCULAR FUNCTION ASSOCIATED WITH HIGH ALTITUDE HYPOXIA.

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It is common knowledge that humans at higher altitudes have obviously different physiologic responses to hypoxia than those residing at lower altitudes. The symptomatology is still an important method in the observation of hypoxic adaptation despite the physiologic reaction to high altitude. In order to better understand these physiologic differences, we studied the differences in circulatory function between two groups (one group adapted to a lower altitude and the other group adapted to a higher altitude) of men using 11 indices of circulatory function. 43 healthy male workers ranging from 18-24 years of age were examined under four conditions: (1) before ascending the mountain (BAM) at an altitude of 2,260m, (2) in the laboratory, where the wrists of subjects were soaked in water (T=0-2 Centigrade) for one minute after resting 5 minutes, (3) after ascending the mountain (AAM) and remaining at an altitude of 4,850m at 4, 30, 60, 90 and 180 days, and (4) after descending the mountain (ADM) to 2,260m) for 3-7 days. The symptoms were defined as normal to heavy (0-3). Results: PP, TM, and AR during the cold test increased ($P<0.01$), while MSP, MDP, MA ,TPR, VpeI, ALT, and EWK decreased ($P<0.01$). The indices of cardiovascular function on the 4th day after ascending the mountain (4,850m) changed ($P<0.05$-0.01) in spite of TPR, ALT. The parameters PP, MDP, TPR, VpeI, ALT, AR, and EWK have great utilization. Different and irregular in unadapted populations, under hypoxic conditions the subjects with changes in diastolic pressure have marked changes in cardiac function and serious hypoxic symptoms with increased time. In addition, after ascending the mountain, blood pressure rose in more of the subjects with lower blood pressure at low altitude areas, but decreased in subjects who had hypertension at low altitudes. Our study is useful for detecting an individual and/or population's degree of adaptation to high altitude hypoxia.

164. THE INDUCED EFFECTS OF ACTH AND TESTOSTERONE ON INCREASE OF ERYTHROCYTES.

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We used the pattern of mice in hypoxia (0.42a tm,22 h/d low pressure) to observe the effects of ACTH and Testosterone on blood making of marrow. We showed that erythrocyte's form of marrow has high sensitivity on erythropoietin (EPO). Under continuing influence of hypoxia, the sensitivity decreases. Giving hypoxic mice ACTH increases the hematocrit ($P<0.05$). Also the thickness of serum EPO appears to change very little. The effect of ACTH on erythrocyte production is vulnerable. However, testosterone can maintain sensitivity of blood making cells of the marrow to EPO. ACTH increases the sensitivity of the marrow to EPO and induces polycythemia.

165. TRACING INVESTIGATION OF CARDIOVASCULAR X-RAY AT HIGH ALTITUDE OF 4,000M FOR 20 YEARS.

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(quanhuili@yahoo.com).

Four indices were studied by radiograph of 61 physical workers who have migrated from highlands of 4,000 meters for 20 years. The results showed that the changes of PPA and DRIPA were indicative of changes in levels of HAPH and HAHD. As x-ray is of certain clinical value for monitoring HAPH and HAHD, it is important to examine the migrating population regularly by chest x-ray.

166. HYPOXIA AND IMMOBILIZATION INFLUENCED RELEASE OF CORTICOTROPIN-RELEASING FACTOR FROM MEDIAN EMINENCE OF HYPOTHALAMUS IN THE RAT AND REGULATED BY CENTRAL NOREPINEPHRINE.

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The change of Norepinephrine (NE) level in paraventrcular nucleus (PVN) and central amygdala nucleus (ACE) in the rats during acute hypoxia and immobilization and CRF involvement in modulation were investigated. Hypoxia was stimulated in a hypobaric chamber. NE levels in PVN and ACE were measured by HPLC, and its receptor of regulation by hypothalamic CRF were studied as well. The results are as follow. a. 5km hypoxia for 30 min and 2h produced no significant change of NE level in PVN, but at 24h NE markedly enhanced by 117.20% (vs. control, $p<0.001$), 7km for 30 min induced statistically increment ($P<0.05$). Immobilization for 30 min NE of PVN raised by 129.47% (vs. control, $p<0.001$.). b. 7km 30 min induced NE of ACE went up to 33.25% (vs. control, $p<0.05$.), 5km hypoxia 2h did to 33.90% ($p<0.01$), 5km 24h did to 112.60% ($p<0.001$.). immobilization did to 188.20% ($p<0.001$.). c. 5km hypoxia 2h and 24h caused significantly reduction of CRF in median eminence (ME)($p<0.01$.), Immobilization for 30 min elicited markedly decrease of CRF in ME($P<0.001$.). d. Hypoxia 5km 30 min caused significant CRF release from ME ($P<0.05$), that was blocked by icv antagonist of adrenergic receptor $\alpha 2$ (yohimbine), but not by $\alpha 1$ receptor antagonist (prazosine). In conclusion, acute hypoxia stimulated NE secretion of PVN and ACE, being a dependence of hypoxia intensity and time course, and the stimulating mechanisms might be different between hypoxia and immobilization. Acute hypoxia and immobilization stimulated CRF release from ME with hypoxia intensity-time course correlated manner. Adrenergic receptor $\alpha 2$ was involved in CRF release from ME during acute hypoxia.

167. THE UPREGULATION OF SOMATOSTATIN MRNA EXPRESSION IN PERIVENTRICULAR NUCLEUS OF THE RAT HYPOTHALAMUS AND ITS MODULATION BY CRF AND GLUCOCORTICOIDS DURING HYPOXIA.

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This paper is to examine the SS mRNA change in Periventricular Nucleus (PeN) of hypothalamus in rats, and the possible involvement of glucocorticoid and hypothalamic corticotropin releasing factor (CRF) during hypoxia. Hypoxia was simulated in a hypobaric chamber. SS mRNA levels in PeN were tested by in situ hybridization. Hypoxia of 5km altitude ($10.8\%O_2$) for 2h, 5h and 24h improved SS mRNA expression, raised by 34.72%, 50.31% and 95.05% ($p<0.05$) respectively. Severe hypoxia of 7km altitude ($8.2\%O_2$) for same duration increased SS mRNA expression by 97.08% ($p<0.01$), 74.90% ($p<0.01$) and 71.40% ($p<0.05$) respectively; the increased SS mRNA at 7km vs 5km for 2h hypoxia was higher by 34.34% ($p<0.05$). Prolonged hypoxia (5km 5d) exposure augmented significantly SS mRNA ($p<0.001$). One week post adrenalectomy (ADX), basal SS mRNA level was significantly increased. Hypoxia (5km 5h)-induced SS mRNA increases in the sham ADX rats were markedly abolished by a pre-treatment of high dose of dexamethasone (DEX) (500mg/rat, ip.). Meanwhile hypoxia (5km 5h)-induced SS mRNA augmentations of ADX rats were found to be further increased by central administration of CRF antagonist, α-helical CRF9-41 (2.5mg/5ml/rat, icv). It was concluded that hypoxia stimulated the expression of SS mRNA in PeN of the rat hypothalamus. Basal glucocorticoid level might depress the basal SS mRNA of PeN. However, hypoxia-activated glucocorticoids may play a role in upregulating SS mRNA in PeN, and in addition, SS mRNA level in rat hypothalamic PeN might be inhibited by hypoxia-activated hypothalamic CRF.

168. THE REGULATION OF GLUTAMATE AND GABA ON HPA AXIS DURING HYPOXIA.

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The central glutamate (Glu) and. GABA play significant role in neuroendocrine modulation. We have previously reported hypoxia activated HPA axis, stimulated CRF release which was modulated by AVP, beta-EP, NE and angiotensin II. Using simulated hypoxia of 5 and 7 km altitude in a hypobaric chamber, the effects of Glu and GABA on the secretion of CRF from paraventricular nuclei (PVN) and median eminence (ME) of colchicine-pretreated rats were examined and simultaneously the plasma corticosterone (Corts) was monitored. CRF was measured by radioimmunoassay (RIA) in ME and quantitated by immunohistochemically in PVN. The results are: 1) The level of CRF in PVN decreased by 51.4%($p<0.001$) and 32.9%($p<0.01$) after 5km hypoxia for 2 h and 6 h respectively. CRF in ME increased by 149.2%($p<0.05$) and plasma Corts had no changes during 5km 2h. 2) GABA(10ug/10ul, icv) before hypoxia (6h) enhanced CRF of PVN by 44.7%($p<0.01$), and did plasma Corts by 21.1%($p<0.05$), but CRF content in ME had no change. However, if pretreated with Bicuculline (GABA receptor antagonist,5ug/10ul), CRF in PVN decreased by 56.6%($p<0.01$), increased in ME by 182.8%($p<0.01$) and the plasma Corts had no changes.3) CRF of both PVN and ME had no significant changes in pretreated with Glu (0.2uM/10ul), but the plasma Corts increased by 11.2%($p<0.05$). In pretreated with AP-5(NMDA receptor antagonist, 20ug/10ul), CRF in PVN was increased by 57.1%($p<0.05$), but no change in ME and plasma Corts. Conclusion: In the modulation of CRF release central Glu play stimulating role but does GABA inhibiting one.

169. THE RESPONSE OF PROLACTIN AND GROWTH HORMONE OF RATS DURING HYPOXIA.

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The study was to explore the alteration of Prolactin and Growth Hormone, and regulatory mechanism of central corticotropin-releasing factor (CRF), norepinephrine (NE), glutamate, GABA, and circulating glucocorticoid during Hypoxia. Hypoxia was performed in a hypobaric chamber with 5km and 7km altitude. The level of prolactin (PRL) and growth hormone (GH) was measured by sensitive and specific radioimmunoassay (RIA) and immunocytochemistry (ICC). Body weight gain and food intake were examined, and did the regulatory mechanisms of pituitary GH and PRL during hypoxia. The results and conclusion are as follow. 1. Acute and chronic hypoxia suppresses GH secretion and synthesis, but stimulates PRL. 2. Hypoxia acutely and chronically inhibits rats body weight gain and food intake. Administration of GH reversed the changes. 3. Hypothalamic CRF suppresses pituitary GH release, hypoxia-activated high circulating glucocorticoid stimulates GH secretion.4. Hypothalamic CRF augments the activity of PRL secretion, hypoxia-induced high glucocorticoid played an inhibitory effect. 5.Central excitatory glutamate stimulates pituitary GH release and suppresses PRL secretion through NMDA receptor in rats pretreated with colchicine, and central GABA promotes GH secretion, but has the opposite action for PRL release through GABA-A receptor. 6. pituitary GH secretion was induced by central endogenous NE through alpha-2 receptor during acute hypoxia.

170. BIOCHEMICAL ADAPTATIONS IN RATS CHRONICALLY EXPOSED TO HIGH ALTITUDE.

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Biochemical adaptations to chronic high altitude remain poorly understood. We examined anaerobic glycolysis, lipid metabolism and the pentose phosphate shunt (PPS) in rats after exposure to a simulated altitude of 5500m (HA) for 3 months. Animals were sacrificed, and blood lactate levels and free fatty acid (FFA) content of plasma were measured. Anaerobic glycolysis in tissue homogenates was measured under N2 in a Warburg apparatus. The rate of CO_2 production, the total lactate produced, and tissue lactic acid dehydrogenase activity were measured. Lipid metabolism was measured in tissue slices in Krebs phosphate buffer (pH 7.4) with 4.5 µEq palmitate-1-14C under O_2. The rate of tissue uptake of palmitate, its conversion into CO_2 and its incorporation into tissue lipids were measured. The PPS pathway was evaluated by measuring the activities of glucose-6-phosphate (G-6-PD) and phosphogluconate (PGD) dehydrogenases. The rate of anaerobic glycolysis remained normal in brain, heart and skeletal muscle, whereas the rates in liver and kidney were significantly depressed after HA exposure. No differences were found in tissue lactic acid dehydrogenase or blood lactate levels between the SL and the HA animals. Chronic exposure to HA did not change in the rate of conversion of palmitate into CO_2, incorporation of palmitate into tissue lipids or tissue uptake of palmitate in heart, kidney or brain. The rate of conversion into CO_2 and tissue uptake in skeletal muscle was enhanced in HA animals, and conversion to CO_2, incorporation into lipids and tissue uptake of palmitate were enhanced in liver in HA animals. HA exposure did not alter the plasma FFA levels or the total lipid content in any tissue studied. There were no differences in the activity of either G-6-PD or PGD. Thus, chronic HA exposure did not significantly change these fundamental metabolic pathways.

171. HEPATIC REGENERATION REMAINS NORMAL IN RATS UNDER CHRONIC HYPOXIA.

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Protein synthesis is depressed or completely inhibited in cultured rat hepatocytes under anoxia and during ischemia in intact rats; hypoxic suppression of protein synthesis may represent a metabolic defense to survive hypoxia (Hochachka et al. 1996. PNAS 93: 9493). We studied hepatic regeneration, which involves protein synthesis, growth and differentiation, to test the hypothesis that suppression of protein synthesis is an adaptive mechanism during chronic, severe hypoxia. We expose rats to a simulated high altitude of 5000m (HA). Two groups of 11 rats were exposed to HA or sea level conditions (SL) for 30 days. Following this exposure, 2/3 of the liver was removed from each animal under anesthesia, and each rat was returned to its environmental condition. On each subsequent day, 2-3 rats from each group were studied. Hematocrit (Hct), plasma bilirubin, liver ornithine decarboxylase (OD), and liver uridine diphospho glucuronyl transferase (UDPGT) levels were measured. The weight of liver removed during hepatectomy, and the weight of liver remaining at 0, 24, 48, 72,and 96 hrs after surgery were recorded. The Hct rose from 43.3 to 68.6% after 30 days of HA. There were no differences between the SL and the HA animals in plasma bilirubin levels, liver OD and UDPGT activities before hepatectomy. Twenty-four hours after surgery, liver OD activity rose more than 20 fold from the pre-hepatectomy levels in both groups of animals. Thereafter, OD activity declined in both groups, and the recovery was more rapid in the SL animals. The liver regenerated steadily in both groups, and approximately 40% of the weight of liver removed by hepatectomy regenerated within 96 hrs. These results demonstrate that severe hypoxia did not inhibit protein synthesis or hepatic regeneration in intact rats.

172. ACUTE HYPOXIA AND HYPOXIC EXERCISE INDUCE DNA STRAND BREAKS AND OXIDATIVE DNA DAMAGE IN HUMANS.

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The present study investigated the effect of a single bout of exhaustive exercise on the generation of DNA strand breaks and oxidative DNA damage under normal conditions and at high altitude hypoxia (4,559 m for three days). Twelve healthy subjects performed a maximal bicycle exercise test, and lymphocytes were isolated for analysis of DNA strand breaks and oxidatively altered nucleotides, detected by endonuclease III and formamidipyridine glycosylase (FPG) enzymes. Urine was collected for 24 h periods for analysis of 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG), a marker of oxidative DNA damage. Urinary excretion of 8-oxodG increased during the first day in altitude hypoxia, and there were more endonuclease III sensitive sites on day three at high altitude. The subjects had more DNA strand breaks in altitude hypoxia than at sea level. The level of DNA strand breaks further increased immediately after exercise in altitude hypoxia. Exercise-induced generation of DNA strand breaks was not seen at sea level. In both environments, the level of FPG and endonuclease III sensitive sites remained unchanged immediately after exercise. Hypoxia seems to deplete the antioxidant system of its capacity to withstand oxidative stress produced by exhaustive exercise. DNA strand breaks and oxidative DNA damage is probably produced by reactive oxygen species, generated by leakage of the mitochondrial respiration or during a hypoxia-induced inflammation. The presence of DNA strand breaks may play an important role in maintaining inflammation processes in hypoxia.

172. 7100M OF ALTITUDE AT EARLY PREGNANCY: A CASE REPORT.

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It is not known whether acute exposure to high altitude at early pregnancy may cause harm to mother or fetus. A 38-year-old woman went during her second month of pregnancy to the Karakorum-Pakistan for a high altitude expedition. They started at 2000m of altitude and reached base camp at 5150m within 8 days where they stayed for another week. During day 15 to 22 they went to advanced base camp at 5800m twice for two days. On day 27 they went up to 6300m and stayed overnight. On day 28 they went up to 7100m and returned the same day to 6300m. The following day they returned to 5150m. The Lake-Louise Score was assessed daily and transcutaneous oxygen saturation and heart rate were measured during some nights and during the summit attempt (from 6300 to 7100m and back). Results are reported as average heart rate (avHR) and saturation (avS02) and times of more than 4% and 5% of desaturation from $avS0_2$ during the measuring time for the pregnant woman (P) and a 22-year-old female climber (NP) who both were in perfect physical condition:

time	night 14		night 19		night 20		night 27		day 28		night 30	
	P	**NP**	**P**	**NP**	**P**	**NP**	**P**	**NP**	**P**	**NP**	**P**	**NP**
altitude	5150m		5800m		5800m		6300m		7000m		5150m	
avHR	59,2	63,7	67,9	67,4	67,9	70,3	65,4	75,1	95,4	104,5	65,5	62,3
avS02	83,1	81,2	77,6	71,1	79,6	70,2	69,1	63,4	75,2	68,4	83,2	80,1
>4% $S0_2\downarrow$	5	33	52	308	22	210	16	404			63	31
>5% $S0_2\downarrow$	0	13	9	93	2	70	3	162			23	12

The Lake Louise Score was 0 for both women throughout the trip. The pregnant women showed markedly higher $avS0_2$ and lower avHR. She did not show periodic breathing or desaturation compared to the NP women. The hormonal influence and increased blood volume might lessen desaturation at altitude in pregnant women. Acute exposure to high altitude at early pregnancy might be safe but should not be recommended because of hypoxemia which might harm the fetus. (The baby was born at term and shows a normal development at 1 year of age)