Time: 1600

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

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

Time: 1615

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

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

Time: 1630

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

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

Time: 1645

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

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

Time: 1700

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

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

Time: 1715

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

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

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

Time: 1730

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

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

Time: 1745

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

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

Time: 1800

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

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