Hypoxia 2023: Hot Topics in Mountain Medicine, Friday afternoon, 1600-1815, Mount Temple A-B

Time: 1600

CEREBROVASCULAR FUNCTION UNDER CONDITIONS OF SIMULATED AVALANCHE BURIAL IN HUMANS. Connor A Howe1, Ryan L Hoiland1, 2, 3, 4, Travis D Gibbons1, Andrew R Steele1, JMJR Carr1, Gustavo A Vizcardo-Galindo1, Michael M Tymko1, Tison Schoenthal5, Valerie C Cates6, Anthony L Marullo6, Trevor A Day6, Mypinder S Sekhon7, Philip N Ainslie1. 1Centre for Heart, Lung, and Vascular Health, School of Health and Exercise Science, University of British Columbia, Kelowna, Canada, 2Department of Anesthesiology, Pharmacology and Therapeutics, 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, Vancouver, BC, Canada., 5Experimental Medicine, Department of Medicine, University of British Columbia, Vancouver, BC, Canada., 6Department of Biology, Faculty of Science and Technology, Mount Royal University, Calgary, Alberta, Canada., 7Division of Critical Care Medicine, Department of Medicine, University of British Columbia, Vancouver, BC, Canada.

Objective: To investigate the potential cerebrovascular and neuroprotective effects of hypothermia during conditions of simulated avalanche burial. Methods: In 14 participants (6 female), the radial artery and internal jugular bulb were catheterized to measure blood gases and intravascular pressure, collect blood specimens, and quantify cerebral oxygen delivery (CDO_2) and metabolic rate of oxygen ($CMRO_2$). Measurements were assessed before and during mild hypothermia (-1.8±0.6°C; esophageal temperature) induced via cold water (7^{0}C) immersion. Progressive hypercapnic-hypoxia was imposed during normothermia and hypothermia using dynamic end-tidal forcing in 2-minute stages (-5mmHg PaO_2; +2mmHg $PaCO_2$) to a maximal stimulus of 40mmHg PaO_2 and +20mmHg $PaCO_2$, or until volitional tolerance. Duplex ultrasound measurements of the internal carotid and vertebral arteries were used to calculate global cerebral blood flow (gCBF), CDO_2 and $CMRO_2$. Serum biomarkers of brain injury and blood brain barrier permeability, Tau, neurofilament light (Nf-L), and glial fibrillary acidic protein (GFAP) were quantified. Results: Hypothermia was associated with increased arterial oxygen content (CaO_2; 19±1 vs. 22±2mL/dL; $P<0.01$), mean arterial pressure (90±6 vs 111±10mmHg; $P<0.01$), and ventilation (14±4 vs. 43±10L/min; $P<0.01$); $PaCO_2$ was reduced as a result (43±2 vs 38±3mmHg; $P<0.01$). Conversely, gCBF was lower (840±142 vs. 696±174mL/min; $P<0.01$) and CDO_2 unaltered (160±30 vs. 150±39mL/min; $P=0.20$). With hypercapnic-hypoxia, CaO_2 was lower during normothermic-hypercapnic-hypoxia versus hypothermic-hypercapnic-hypoxia (CaO_2: 16±3 vs. 18±3mL/dL; $P<0.01$), while gCBF and CDO_2 were both increased during normothermic-hypercapnic-hypoxia (+78% and +56%, respectively) and hypothermic-hypercapnic-hypoxia (+47% and +28%, respectively). In contrast, $CMRO_2$ was selectively attenuated during hypothermic-hypercapnic-hypoxia compared to normothermic-normocapnic-normoxia (26±8 vs. 43±10mL/min; $P=0.035$). Increases in arterial Tau and GFAP were observed with normothermic-hypercapnic-hypoxia, but not with hypothermic-hypercapnic-hypoxia. Conclusion: Hypothermia decreased gCBF without altering CDO_2 or $CMRO_2$. Combined hypothermic-hypercapnic-hypoxia reduced $CMRO_2$, indicating that the combination of these stimuli may provide some form of cerebrovascular protection in the early stages of avalanche burial. Funding: NSERC, CIHR, WMS.

Time: 1615

Mechanisms of adaptation in high-altitude pregnancy: association of genotype with oxygen delivery and placental metabolism. Katie O'Brien1, Wanjun Gu2, Julie Houck3, Lorenz Holzner1, Jenna Armstrong1, Alice Sowton1, Paula Darwin1, Lilian Toledo-Jaldin 4, Lorna Moore3, Andrew Murray1, Tatum Simonson2. 1University of Cambridge, 2University of California, San Diego, 3University of Colorado, 4Hospital Materno-Infantil, Bolivia

Study objectiveTo determine whether genetic regions exhibiting strong signals of natural selection in the maternal genome of highland Andeans associate with putatively adaptive placental metabolic phenotypes. Further, we aimed to investigate metabolic phenotype in the context of preeclampsia.MethodsA cohort of 79 pregnant Andeans (18-45y, 39 with preeclampsia) living in La Paz, Bolivia (3600 - 4100m) and delivering by unlabored Cesarean section. Maternal genotyping was performed using the 1.8 million SNP Multiethnic Genotyping Array (Illumina). Placental mitochondrial function was assessed in cryopreserved villous biopsies using high-resolution respirometry (Oxygraph-2k, Oroboros). Maternal and umbilical venous plasma was obtained to measure circulating protein levels by ELISA. Using within-population selection tests (iHS) to detect signatures of natural selection, putatively adaptive haplotypes (iHS≥3) were identified; those overlapping with an a priori cellular hypoxic signaling and metabolism gene list were prioritized for association analysis. Linear regression modeling revealed associations between prioritized haplotypes and key outcome measures at an FDR corrected level of p≤0.05.ResultsA haplotype within PTPRD (iHS 3.31) associated with lower placental respiratory capacity (p=0.002). Haplotypes within 200kb of CPT2 (iHS 5.38) and both POMC and DNMT3 (iHS 3.28) associated with lower maternal plasma erythropoietin (p=0.02 and p=0.01, respectively). A haplotype within 200kb of TBX5 associated with lower protein levels of the angiogenic factor VEGF (iHS 3.65, p=0.04) in umbilical venous blood. While greater placental maximal respiratory capacity was associated with lower umbilical venous PO2 in controls (p=0.03), this relationship was absent in preeclampsiaConclusionOur results reveal novel associations between putatively adaptive gene regions and phenotypes linked to oxygen carriage and delivery, as well as placental mitochondrial respiratory capacity. These may act to preserve fetal oxygenation. Examination of these phenotypes in preeclampsia revealed disruption in the relationship between O2 delivery to the fetus and placental O2 consumption.

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Time: 1630

EXPEDITION 5300 - EARLY EFFECTS OF ACETAZOLAMIDE ON TOTAL HEMOGLOBIN MASS AND PLASMA VOLUME IN CHRONIC MOUNTAIN SICKNESS PATIENTS FROM THE HIGHEST CITY IN THE WORLD.

Aurélien Pichon1, Benoit Champigneulle2, Emeric Stauffer3, Paul Robach4, Stéphane Doutreleau2, Connor A. Howe5, Alessandra Pina6, Alberto A. Salazar-Granara7, Ivan Hancco2, Dorra Guergour8, Julien V. Brugniaux2, Philippe Connes9, Samuel Verges2. 1Université de Poitiers, MOVE UR 20296, STAPS, Poitiers, France, 2HP2 Laboratory, INSERM U1300, Grenoble Alpes University, CHU Grenoble Alpes, Grenoble, France, 3LIBM EA7424, Team "Vascular Biology and Red Blood Cell", Labex GR-EX, Université Claude Bernard Lyon 1, Université de Lyon, Hospices Civils de Lyon, France, 4National School for Mountain Sports, Site of the National School for Skiing and Mountaineering (ENSA), Chamonix, France, 5Centre for Heart, Lung and Vascular Health, School of Health and Exercise Sciences, University of British Columbia - Okanagan, Kelowna, Canada, 6Department of Cardiovascular, Neural and Metabolic Sciences, Istituto Auxologico Italiano, IRCCS, S. Luca Hospital, Milan, Italy, 7University of San Martín de Porres, Peru, 8Biochemistry Laboratory, Grenoble University Hospital, Grenoble, France, 9LIBM, EA7424, Team "Vascular Biology and Red Blood Cell", Labex GR-Ex, Université Claude Bernard Lyon 1, Université de Lyon, France

Objective: Chronic Mountain Sickness (CMS) syndrome, combining excessive erythrocytosis and hyperviscosity symptoms in highlanders, remains a public health issue in high-altitude areas, especially in the Andes, with limited economic and therapeutic approaches. The objectives of this study were to assess in CMS-highlanders permanently living in La Rinconada (5100-5300m, Peru, the highest city in the world), the short-term efficacy of acetazolamide (250mg q.d) and atorvastatin (20mg q.d.) to reduce hematocrit (Hct), as well as the underlying mechanisms focusing on intravascular volumes.Methods: Forty-one males (46±8 years) permanently living in La Rinconada for 15 [10-20] years and suffering from CMS (mild CMS for 90% of them) were included in this randomized, double-blinded, parallel, and placebo-controlled study. Hct (primary endpoint) as well as arterial blood gases, total hemoglobin mass (Hbmass) and intravascular volumes were assessed at baseline and after 19±2 days of treatment with the carbon monoxide rebreathing method.Results: ACZ was effective to improve PaO2 by +13.4% (95% CI: 4.3 to 22.5%, p=0.007) and to decrease Hct by -5.2% (95%CI: -8.3 to -2.2%, p=0.004), whereas no significant early changes in Hct were shown in the placebo and atorvastatin groups. CMS score only significantly decreased in the ACZ group (p=0.03) The decrease in Hct in the ACZ group was explained by an increase in plasma volume of +17.6% (95% CI: 4.9 to 30.3%, p=0.01) without any significant decrease in Hbmass (-2.6%, 95% CI: -5.7 to 0.5%, p=0.09).Conclusions: Short-time ACZ uptake was effective to reduced Hct in CMS-highlanders living at extreme altitude >5000m. The early effect on Hct seems mostly mediated by a restoration of plasma volume rather than a decrease in Hbmass. Atorvastatin uptake had no short-term effect on Hct.Funding: The study was sponsored by Grenoble Alpes University foundation and the French National Research Agency.

Time: 1645

EXPEDITION 5300: MICRO- AND MACROVASCULAR FUNCTION IN THE HIGHEST CITY IN THE WORLD. Julien V Brugniaux1, Yann Savina1, Aurélien Pichon2, Lucas Lemaire1, Connor A Howe3, Mathilde Ulliel-Roche1, Sarah Skinner4, Elie Nader4, Nicolas Guillot4, Émeric Stauffer4, Mathieu Roustit1, Ivan Hancco1, Paul Robach5, François Esteve1, Vincent Pialoux4, Elisa Perger6, Gianfranco Parati6, Philip N Ainslie3, Stéphane Doutreleau1, Philippe Connes4, Samuel Vergès1. 1Université Grenoble Alpes, France, 2Université de Poitiers, France, 3University of British Columbia, Kelowna, British Columbia, Canada, 4Université Claude Bernard Lyon 1, France, 5National School for Skiing and Mountaineering (ENSA), France, 6Istituto Auxologico Italiano, IRCCS, Sleep Disorders Center & Department of Cardiovascular, Neural and Metabolic Sciences, San Luca Hospital, Italy

Background. Since vascular responses to hypoxia in both healthy high-altitude natives and chronic mountain sickness (a maladaptive high-altitude pathology characterised by excessive erythrocytosis and the presence of a variety of symptoms – CMS) remain unclear, the role of inflammation and oxidative/nitrosative stress on the endothelium-dependent and -independent responses in both the micro- and macrocirculation, in healthy Andeans at different altitudes and in CMS patients, was examined. Methods. 94 men were included: 18 lowlanders (LL), 38 healthy highlanders permanently living at 3,800 m (n=21 – HL-3,800) or in La Rinconada, the highest city in the world (5,100-5,300 m) (n=17 – HL-5,100/No CMS). Moreover, 14 participants with mild (CMS score 6-10 – Mild CMS) and 24 with moderate to severe CMS (CMS score ≥11 – Mod/Sev CMS) were recruited. All undertook two reactivity tests: i) local thermal hyperemia (microcirculation – LTH) and ii) flow-mediated dilation (macrocirculation – FMD). Endothelium-independent function (glyceryl trinitrate – GTN) was also assessed only in La Rinconada. Results. Both conductance and skin blood flow velocity during LTH as well as FMD progressively decreased with altitude (LL>HL-3,800>HL-5,100/No CMS). CMS also induced a decrease in FMD (HL-5,100/No CMS>Mild CMS=Mod/Sev CMS), while GTN restored vascular function. Both oxidative stress and nitric oxide metabolites increased with altitude only. Principal component analysis, used to define inflammatory profiles, revealed that increasing inflammation with altitude was associated with a progressive decline in both micro- and macrovascular function in healthy highlanders. Conclusions. Both micro and macrovascular function are affected by chronic exposure to hypoxia, the latter being further compounded by CMS.

Time: 1700

THE EFFECTS OF STEPWISE REDUCTIONS IN SUPPLEMENTAL OXYGEN ON OXYGEN SATURATION AT REST AND DURING EXERCISE AT EXTREME (SIMULATED) ALTITUDE.

Denis Wakeham1, 2, Andrew Tomlinson1, 2, Peter Hackett3, Matthew Howrey1, Murugappan Ramanathan1, Marcus Payne1, Dean Palmer1, Renie Guilliod1, 2, James Berry1, 2, Tony Babb1, 2, Benjamin Levine1, 2, Christopher Hearon1, 2. 1Institute for Exercise and Environmental Medicine, Texas Health Presbyterian Hospital Dallas, Dallas, Texas, USA, 2The University of Texas Southwestern Medical Center, Dallas, Texas, USA, 3Altitude Research Center, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA

Nearly all (95%) high-altitude mountaineers use supplemental oxygen when climbing peaks at or above 8000m, typically at a flow rate > 4 l/min. Despite its high utilization, the physiological effects and optimal dosing strategies for supplemental oxygen use at extreme altitude are unknown. Therefore, we determined the effects of stepwise reductions in supplemental oxygen flow (nominal: 6, 4, 2, 1 and 0 l/min) using the SUMMIT Oxygen mask during rest and cycling at 60 and 120 Watts (W) at extreme simulated altitude in a hypobaric chamber (282mmHg; 8100m), and during rest at 253mmHg (8848m), in 3 un- and 3 partially acclimatized individuals (age, 34 ± 8 years; 2 females). We recorded oxygen saturation (SpO2) and heart rate (both via photoplethysmography) during 4-minute exposures to each flow rate. During rest at 282 mmHg, SpO2 decreased ($P<0.0001$) with stepwise reductions in supplemental oxygen (6l/min: 99±0%; 4l/min: 96±1%; 2l/min: 91±1%; 1l/min: 83±2%; 0l/min: 70±8%). The reduction in SpO2 led to increases in heart rate (6l/min: 70±1 bpm; 0l/min: 113±13; $P<0.0001$). The pattern of SpO2 and heart rate changes were similar during exercise (60W and 120W) and during rest at 253mmHg. Without supplemental oxygen, 3 participants were able to exercise at 60W; no participant could exercise at 120 Watts. Notably, 1l/min of supplemental oxygen (4-fold lower than standard practice) offset all hypoxemia-related symptoms at rest, whilst during 60W of exercise (ascent rate of ~250-350m/hr) 2l/min maintained participants' SpO2 above 60% (68±2%), below which participants developed hypoxemia-related symptoms. In conclusion, supplemental oxygen flow rates of 1l/min at rest and 2l/min during exercise at extreme simulated altitude were sufficient to maintain oxygen saturation at a level that offsets hypoxemia-related symptoms in un- or partially acclimatized persons.

Time: 1715

ALTITUDE RELATED ADVERSE EFFECT AND THERAPEUTIC BENEFIT OF SUPPLEMENTAL OXYGEN IN PATIENTS WITH PULMONARY VASCULAR DISEASE DURING AN OVERNIGHT STAY AT 2500M.

Simon R Schneider1, Julian Müller1, Meret Bauer1, Laura Mayer1, Lea Lüönd1, Tanja Ulrich1, Michael Furian1, Aglaia Forrer1, Esther I Schwarz1, Konrad Bloch1, Mona Lichtblau1, Silvia Ulrich1. 1University Hospital Zurich, Clinic of Pulmonology, Zurich, Switzerland

Objective: Journeys to high altitude (HA) touristic areas became increasingly popular also among potentially vulnerable groups such as precapillary pulmonary hypertension (PH) due to pulmonary vascular disease (PVD). Scientific evidence to counsel PVD-patients for their upcoming HA trips is scarce. We investigated altitude-related adverse health events (ARAHE) during an overnight stay at 2500m and whether supplemental oxygen reverses the effects of altitude.Methods: In a randomized-sequence, cross-over trial, 27 (44% female) stable patients with pulmonary arterial or distal chronic thromboembolic PH were exposed to 2500m for around 30 hours. ARAHE requiring oxygen therapy was defined as severe hypoxemia (SpO_2<80% for >30min) Right heart function by echocardiography, acute mountain sickness (AMS), arterial blood gas and more were assessed the second day at altitude.Results: 10/27 patients experienced severe hypoxemia according to predefined safety criteria and received oxygen, 6 experienced AMS. Only one patient required oxygen the first day, all others during the night. All completed the study according to the protocol.Main significant differences between 470m and 2500m among patients not requiring oxygen were present in tricuspid regurgitation pressure gradient (mean±SD) 40±19 and 61±23; (mean-difference and confidence interval) 21(7 to 35) mmHg, in $PaCO_2$ 4.5±0.4 and 4.2±0.4 kPa; -0.32(-0.6 to -0.04) and in PaO_2 10.4 ± 1.5 and 7.2 ± 0.8; -3.42(-3.97 to -2.87) kPa, however not among patients receiving oxygen at 2500m.Conclusion: During an overnight stay at 2500m, 37% of PVD-patients experienced severe hypoxemia, which was reversed with supplemental oxygen. Significant physiological differences between 470 m and 2500 m in blood gases and right heart function among non-hypoxemic patients were detected but no longer among those receiving oxygen (Clinicaltrial.gov: NCT05107700).Funding: The Swiss National Science Foundation funded the study. Grant number: 32003B_197706

Time: 1730

MODERATE- COMPARED TO LOW-ALTITUDE RESIDENTS ARE THREE TIMES LESS LIKELY TO SUFFER FROM ACUTE MOUNTAIN SICKNESS AT 3600M.

Peter Figueiredo1, Steven Landspurg1, Jon Femling2, Jason Williams2, Mark Buller1, J Philip Karl1, Janet Staab1, Reed Hoyt1, Aaron Reilly2, Trevor Mayschak2, Emma Atkinson1, Tim Mesite1, Beth Beidleman1. 1US Army Research Institute of Environmental Medicine, 2University of New Mexico

Objective: Residing at moderate altitude (1500-2400m) reduces acute mountain sickness (AMS) following rapid ascent to a higher altitude but whether residing at a lower altitude threshold confers similar protection from AMS is unknown. Methods: To determine whether moderate-altitude residents (MAR) living at 1190m experience less AMS than low-altitude residents (LAR) following active or passive ascent to HA, 78 healthy Soldiers (mean±SD; age=26±5yr) were

tested at their baseline residence at 331m (LAR; n=41) or 1190m (MAR; n=37), transported to Taos, NM (2845m), then hiked (n=39) or were driven (n=39) to HA (3600m), and stayed for 4 days. AMS-Cerebral factor score (AMS-C) was assessed at HA using the Environmental Symptoms Questionnaire twice on day 1 (HA1), five times on days 2 and 3 (HA2 and HA3) and once on day 4 (HA4). If AMS-C was ≥0.7 at any assessment, individuals were considered sick. The peak AMS incidence and severity were recorded daily and used for analyses. Results: Ascent conditions did not differentially impact AMS incidence between MAR and LAR groups. The MAR compared to LAR experienced a lower AMS incidence on HA1 (16 vs. 44%, p=0.008) and HA2 (19 vs. 39%, p=0.05), similar incidence on HA3 (14 vs. 29%, p=0.08) and lower incidence on HA4 (0 vs 17%, p=0.007). AMS-C severity was also lower in MAR compared to LAR on HA1 (0.40±0.49 vs. 0.74±0.86, p=0.04), HA2 (0.30±0.34 vs. 0.86±0.88, p=0.001), HA3 (0.30±0.36 vs. 0.56±0.69, p=0.03) and HA4 (0.09±0.14 vs. 0.35±0.58, p=0.01). MAR were approximately three times less likely than LAR to experience AMS at HA1 (OR=4.04, p=0.01), HA2 (OR=2.74, p=0.05) and HA3 (OR=2.64, p=0.09). Conclusions: Moderate-altitude residence as low as 1190m resulted in significantly less AMS following ascent to 3600m, challenging the existing altitude threshold for inducing acclimatization. Authors' views not official U.S. Army or DoD policy. Funding: USAMRDC

Time: 1745

RESPIRATORY VIRAL INFECTION IS A RISK FACTOR FOR SEVERE ACUTE MOUNTAIN SICKNESS, HIGH-ALTITUDE PULMONARY EDEMA, AND COMCOMITANT CEREBRAL EDEMA: A CASE STUDY. Jon Femling1, Aaron Reilly1, Jason Williams1, Trevor Mayschak1, Peter Figueiredo2, Steven Landspurg2, Beth Beidleman2. 1University of New Mexico, 2US Army Research Institute of Environmental Medicine.

Objective: We present the case of a 19-year-old man who developed severe acute mountain sickness (AMS), high-altitude pulmonary edema (HAPE) and high-altitude cerebral edema (HACE) after rapid active ascent to 3600m. Methods: The patient was tested at his residence (1190m), transported to Taos, NM (2845m), and hiked (5km; 15%grade, 139 min) to a high altitude (HA) of 3600m and stayed for 3 days. AMS-C was assessed using the Environmental Symptoms Questionnaire at HA twice on day 1(HA1), and five times on days 2 and 3(HA2 and HA3). The peak AMS-C score was recorded daily with an AMS-C ≥1.53 indicative of severe AMS. An actigraph estimated total sleep time and continuous pulse oximetry measured mean nocturnal oxygen saturation (SpO2) and heart rate (HR). Results: The patient awoke at 0600 after 38h of altitude exposure with a severe headache, blurred vision, dyspnea at rest, ataxia, confusion, a fever of 101°F, a HR of 115bpm, and SpO2 of 65%. He was treated with supplemental O2 (4 l/min;nasal canula) which improved SpO2 to 90% after 30min. Clinical condition prompted evacuation to nearest emergency room (2124m). Chest X-ray revealed patchy opacities consistent with pulmonary edema and molecular testing identified human parainfluenza virus. Patient was diagnosed with acute hypoxic respiratory failure, HAPE, HACE, and parainfluenza virus infection. The patient experienced severe AMS every day at HA with peak AMS-C scores of 3.17 (HA1), 2.73 (HA2), and 4.20 (HA3). Physiologic deterioration occurred at HA2 compared to HA1 with a lower SpO2 (66 vs. 76%), higher HR (107 vs. 86 bpm), and a greater percentage of sleep time spent below 65% SpO2 (49.7 vs. 1.1%). Conclusion: This case highlights respiratory infection as a serious risk factor for severe AMS,

HAPE and HACE and serves as a warning for sojourners even at a moderate altitude. Authors' views not official U.S. Army or DoD policy. Funding: USAMRDC

Time: 1800

CHANGING INTRAOPERATIVE OXYGEN ADMINISTRATION COULD ALTER POSTOPERATIVE COMPLICATIONS, MORBIDITY AND COGNITIVE RECOVERY – EXPLORATORY CLINICAL RESULTS OF A RANDOMISED CONTROLLED TRIAL (PULSE Ox).

Andrew Cumpstey1, Anna Clark1, Magdalena Minnion1, Helen Moyses1, Daniel Martin2, Mark Edwards1, Martin Feelisch1, Michael Grocott1. 1University of Southampton, 2University of Plymouth

Background: The World Health Organization (WHO) recommends that all anaesthetised patients receive 80% oxygen during surgery to reduce the risk of surgical site infections (SSI) but did not consider the effect this might have on other clinical outcomes. The Cochrane collaboration concluded insufficient evidence exists for routinely administering high oxygen concentrations intraoperatively to reduce SSIs, and that doing so might increase mortality.Objective: This exploratory study aimed to investigate whether changing intraoperative oxygen concentrations might alter other postoperative complications, postoperative morbidity and cognitive recovery.Methods: Twenty-eight adult patients undergoing major (defined as needing a central venous catheter as part of planned anaesthetic technique) abdominal surgery for cancer resection received either 30%, 55% or 80% oxygen (randomised allocation) throughout anaesthesia. Rates of (radiologically reported) atelectasis, cognitive recovery, and infective post-operative morbidity (Post Operative Morbidity Survey, POMS) were all collected up to seven days after surgery. Total critical care length of stay was also recorded.Results: Higher oxygen concentrations were associated with lower rates of atelectasis (n[%]: 6[75%] / 8[80%] / 3[30%] for 30% / 55% / 80% oxygen respectively, p = 0.045). Postoperative cognitive recovery scores (Mean[SD]: 0.7[3.1] / -0.1[2.5] / -1.8[3.3], p = 0.277), POMS infection scores (n[%]: 5[71%] / 5[56%] / 3[33%], p = 0.307) and critical care length of stay (Median[IQR]: 3[2-4] / 2.5[2-3.75] / 3[2-5.25] days, p = 0.870) were not different between groups.Conclusion: Changing the administered intraoperative oxygenation concentration may alter postoperative clinical outcomes and adequately powered clinical studies are urgently needed to investigate the impact of this.Funding: Doctoral Fellowship (Southampton NIHR Biomedical Research Centre)