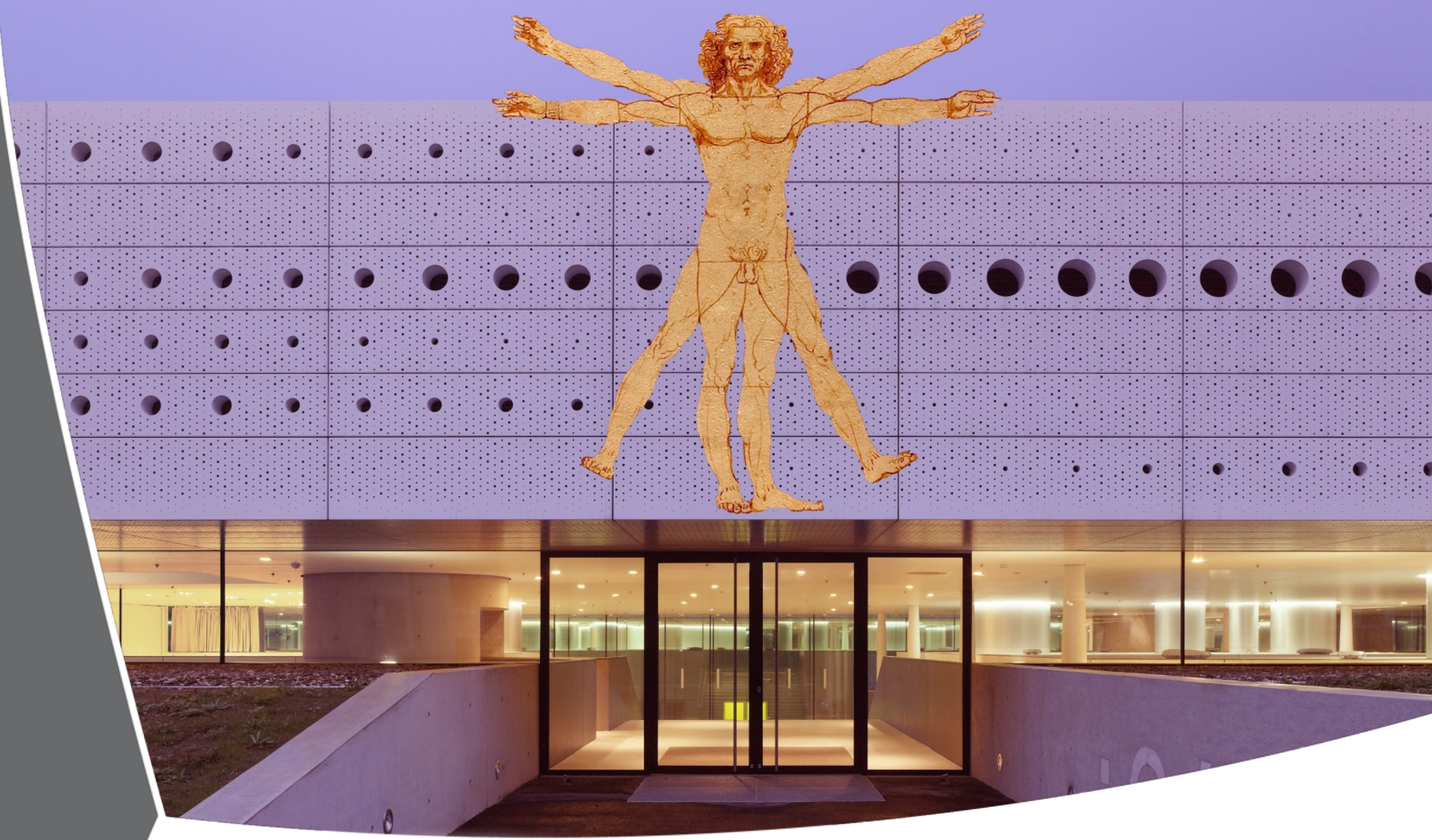

Human Physiology Workshop

9th of December 2017

Venue: DLR
:envihab
Forum
51147 Cologne
Germany
Planitzweg

DLR

Human Physiology Workshop

We are pleased to welcome you to the 2nd German Human Physiology Workshop 2017. The workshop shall provide a forum for researchers at all stages (student to professor) to meet and discuss their latest findings in human physiological research and space research and give room for mutual exchange and benefit between space and non-space scientists.

Organizers

Jörn Rittweger, Tine Becker, Friederike Wütscher (German Aerospace Center (DLR), Institute of Aerospace Medicine, Cologne)
Katrin Stang, Michaela Girgenrath, Christian Rogon (German Aerospace Center (DLR), Space Administration, Microgravity Research and Life Sciences, Bonn)

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Nandu Goswami	Medical University of Graz, Institute of Physiology, Gravitational Physiology and Medicine, Graz, Austria
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Benjamin Levine	Texas Health Resources and the University of Texas Southwestern, Institute for Exercise and Environmental Medicine, Dallas, TX, USA
Stefan Schneider	German Sport University, Institute of Movement and Neurosciences, Cologne, Germany
Alexander Stahn	Perelman School of Medicine, Department of Psychiatry, University of Pennsylvania, USA

Print

Deutsches Zentrum für Luft- und Raumfahrt e.V. (DLR)

Program

Saturday, December 9, 2017

07:45 **Registration**

08:15 **Welcome (DLR)**

Session 1:

Chair: Jens Jordan & David Green

08:30 **Klein, T.:** Isolation, Sleep and Brain Cortical Activity – an investigation in the Human Exploration Research Analog (HERA)

08:45 **Reichmuth, J.:** Vasopressin, Copeptin and Aquaporin Changes in Young healthy volunteers undergoing orthostatic challenge

09:00 **Javelle, F.:** Neurophysiologic, psychological and cognitive effects of 30 days of isolation including daily physical exercise

09:15 **Attias, J.:** Investigation of additional low-level axial load on neuromuscular responses during running in simulated lunar gravity

09:30 **Brix, B.:** Assessing Lymphatic Flow Changes in Patients with Lymphatic Disease: Effects of Physical Therapy

09:45 **Koschate, J.:** Hemodynamic regulation during (simulated) gravity changes – Consideration of transient differences between left and right ventricular cardiac output

10:00 **Hew, Y.:** Development of a Reliable Device for Peripheral Edema Quantification via Ultrasound Imaging in High Altitude Field Studies

10:15–10:45 Coffee break

Session 2:

Chair: Anja Niehoff & Alexander Choukèr

10:45 **Bury, N.:** Spatial orientation of motor performance on Earth and in weightlessness

11:00 **Flück, M.:** Integrated evaluation of clinical muscle plasticity after reconstruction and rehabilitation of the anterior cruciate ligament

11:15 **Thöne, A.:** Efficacy of electrical baroreflex stimulation is not impaired by moderate peripheral chemoreflex activation in patients with resistant hypertension

11:30 **Bolte, V.:** Effect of resistive vibration exercise and nutritional supplementation on morphological changes of thigh muscles during 21 days of head-down tilt bed rest

11:45 **Mendt, S.:** Circadian Core Body Temperature Rhythm in a Mars 520-day mission simulation (Mars500)

12:00 **Grassi, M.:** Age-related walking speed changes after 60 days of bed rest

12:15 **Ganse, B.:** Javelin throw in master athletes 70 years and older – a biomechanical video analysis of throwing techniques

12:30 **Zemann, M.:** Effects of short-term sleep restriction or fragmentation on the autonomic nervous system - Autonomous nervous system in sleep (ANSIS)

12:45–13:30 Lunch break

Session 3:

Chair: Jens Tank & Joachim Fandrey

13:30 **Manuel, J.:** In-vivo measurement of brainstem and hypothalamic centers involved in blood pressure regulation in humans: A high-resolution fMRI study with LBNP

13:45 **Trozic, I.:** Time course of Hemodynamic Parameters During Postural Changes in Stroke

14:00 **Boschert, A.:** Head down tilt and cognition – Effects of simulated microgravity on sleep quality and cognitive performance

14:15 **Diegeler, S.:** Finding NEMO – radiation induced bystander effects elicit NF-κB-dependent survival

14:30 **Trautmann, G.:** Enhanced Homer cell signal in skeletal muscle soleus (SOL) of mice with a vestibular disorder, the head tilt (het-/-) mouse model

14:45 **Faihs, V.:** Influence of acute normobaric and hypobaric hypoxia on hemodynamics, cognitive function, cerebral near-infrared spectroscopy and gene expression

15:00–15:30 Coffee break

Session 4:

Chair: Ruth Hemmersbach & Stefan Schneider

15:30 **Habigt, M.:** Unnoticed Intrinsic Autoregulation Mechanisms of the Heart

15:45 **Carvil, P.:** The effect of 4-hour partial axial reloading via the Mk VI SkinSuit upon recumbent lumbar geometry and kinematics after 8-hour hyper-buoyancy flotation

16:00 **Aebi, M.:** Cerebral oxygen delivery and autoregulation with different hypobaric and normobaric hypoxic conditions in military pilot trainees

16:15–17:00 :envihab tour & awards

17:00 Adjourn

Human Physiology Workshop

Abstracts

1

Isolation, Sleep and Brain Cortical Activity – an investigation in the Human Exploration Research Analog (HERA)

Klein, T.[1,2]*, Rossiter, A.*[3]*, Weber, J.*[1]*, Foitschik, T.*[1]*, Crucian, B.*[4]*, Schneider, S.*[1,2]*, Abeln, V.*[1]

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[2]School of Health and Sport Science, University of the Sunshine Coast, Maroochydore, Australia
[3]Centre of Human & Aerospace Physiological Sciences, King´s College London, United Kingdom
[4]NASA Johnson Space Center, Houston, TX, United States of America

Introduction: Space and isolation missions are known to be stressful for the human organism and negatively impact the quality of sleep of crewmembers. It is well known, that sleep disturbances are associated with impairments in neuropsychological performance, however the underlying neurophysiological mechanisms are unclear and efficient countermeasures missing. This study aimed to investigate the effect isolation on sleep, blood markers and brain cortical activity during 30 days of isolation under space flight analogue conditions.
Methods: Sixteen participants (aged: 37±7 y) were isolated in four missions. During each mission 4 participants stayed inside the HERA habitat at NASA for the duration of 30 days. Seventeen participants (aged: 32±9 y) were used as a non-isolated control group and were tested simultaneously at the German Sport University Cologne. Of note, both groups were asked to exercise on a daily basis during the 30 days of the interventions. Throughout the interventions participants have worn wrist belt actigraphs to assess sleep and light exposure. From this the parameters, total light exposure during sleep, sleep efficiency and wake time after sleep onset (WASO) were calculated. Furthermore, intravenous morning cortisol and melatonin were assessed, as well as a Self-assessment questionnaire for Sleep and Awakening quality (SSA) and a five-minute resting electroencephalography (Brain Products, Munich, Germany) in a relaxed seated position with eyes closed at 4 different time points, on mission days -5, 7, 28, +5. Brain cortical activity was analyzed using low-resolution electromagnetic tomography (LORETA) to assess cortical current density. Effects of the intervention (isolation vs. non-isolation) and time were determined using repeated measures ANOVA.
Results: Cortisol was significantly increased during isolation in comparison to non-isolated participants ($p<0.01$). Melatonin was not different between the isolated and the non-isolated group ($p=0.37$). Total light exposure during sleep was not different between groups ($p=0.61$). Sleep efficiency ($p=0.54$), WASO ($p=0.73$) and subjective sleep quality (SSA, $p=0.10$) were not different between groups. Frontal cortical current density was not different between the isolated and the non-isolated groups (p=0.40) and remained unchanged throughout the intervention as there was no group*time interaction (p=0.72).
Conclusion: During 30 days of isolation sleep and cortical activity were not impaired although high levels of cortisol suggest increased level of stress. This lets us assume that the maintenance of sleep quality during isolation was associated with the maintenance of brain cortical activation during isolation. The reasons why sleep and brain cortical activation were not negatively affected by isolation, other than expected, are unclear. Further studies are needed to assess whether exercise might have positively impacted these results, as the participants exercised on a daily basis during isolation.

2

Vasopressin, Copeptin and Aquaporin Changes in Young healthy volunteers undergoing orthostatic challenge

Johannes Reichmuth [1], *Nandu Goswami* [1], *Ivana Valenti* [2] , *Grazia Tamma* [2], *Andreas Rössler* [1], *Andreas Jantscher* [1], *Rebecca Ruedl* [1]

[1] Meduni Graz, Institute of Physiolog, Austria
[2] University of Bari, Department of Biosciences, Biotechnology and Biopharmaceutics, Italy

Introduction: Orthostatic syncope, caused by an inability of the cardiovascular system to compensate a reduction in venous return to the heart. While arginine-vasopressine (AVP) has been known to increase severalfold upon presyncope, its role in orthostatic loading not leading to syncope is not known. We assessed the effect of lower body negative pressure (LBNP) which simulates orthostatic chanllenge-induced central hypovolemia on AVP, plasma copeptin (a surrogate marker of AVP) and urinary aquaporin 2 (uAQP2). We hypothesized that copeptin along with AVP and uAQP2 increase upon graded LBNP and there are gender differences in these responses.
Methods: 38 (21 female and 17 male) healthy young volunteers took part. The experimental protocol consisted of a 30-minute supine baseline period followed by 20 min of LBNP, increasing every five min by -10 mmHg up to -40 mmHg followed by 10 min of supine rest. Blood for hormonal assessments was sampled at the end of baseline, at the end of the LBNP and at the end of the recovery period. 24-hours urine samples were collected as baseline before the experiment and another urine sample was collected immediately after the end of the experimental protocol.
Results: As compared to baseline, copeptin, AVP, Copeptin and uAQP2 did not increase upon 20 minutes of graded LBNP; copeptin even showed a reduction in levels. Males had higher copeptin and AVP levels than females, a difference that became more pronounced following LBNP. There were no significant alterations of uAQP2 and no significant correlation between copeptin, AVP and uAQP2 could be found.
Our results show that graded orthostatic hypovolemia in subjects that does not lead to presyncope does not affect AVP levels. These results are in contrast to the severalfold increase in AVP seen at presyncope.

3

Neurophysiologic, psychological and cognitive effects of 30 days of isolation including daily physical exercise

F. Javelle[1], *J. Weber*[1], *T. Klein*[1], *T. Foitschik*[1], *B. Crucian*[2], *S. Schneider*[1], *V. Abeln*[1]

[1] German Sport University, Institute of Movement and Neurosciences, Germany
[2] NASA - Johnson Space Center, TX, USA

Introduction: Space missions are challenging for the human organism, where confinement might be an additional chronic stressor besides microgravity. Chronic stress is associated with an increase of cortisol and a decrease of neurotrophic factors, like BDNF and IGF-1, important for the neurogenesis and subsequently impacting cognition and mood. Exercise, on the other hand, has been shown to have the opposite effect on these physiological markers. The aim of this study was, therefore, to investigate the effect of 30 days of isolation with daily exercise on neurotrophic factors (BDNF/IGF-1), cognition and mood.
Methods: 16 participants (36,5 ±7,3 years) were isolated and 17 participants (31,9 ±8,5 years) were non-isolated for 30 days. Both groups exercised on a daily basis alternating between endurance and resistance exercises. Intravenous blood was collected in the morning on mission days -5, 7, 14, 28 and +5. Blood samples were analysed after the mission to evaluate BDNF, IGF-1, melatonin, epinephrine, norepinephrine and cortisol levels (Immunoassay and HPLC; MVZ Labor Limbach Bonn, Germany). Mood and cognition were assessed at the same time points using respectively the Positive and Negative Affects Schedule X (PANAS-X) and three popular brain games (lumosity.com). Time and groups comparisons were made using a repeated measures ANOVA with the level of significance at $p<0.05$.
Results: Stress was observed via an increase of cortisol during isolation ($p<0.0001$); other stress markers, epinephrine and norepinephrine, did not display differences. Both, BDNF and IGF-1 did not show differences between groups (BDNF, $p=0.920$; IGF-1, $p=0.094$) and remained unchanged during 30 days (BDNF, $p=0.635$; IGF-1, $p=0.074$). General positive affect of the PANAS-X showed a negative time effect ($p<0,05$) along

isolation, but the group effect slightly missed the level of significance ($p = 0.061$). Cognitive tests showed a positive time effect (p's<0.05), but no difference between groups.

Discussion: Increasing brain games performances seen in both groups might be attributed to learning processes. Isolation stress as observed via increased cortisol levels did not affect BDNF, IGF-1 and cognitive performances. However, as positive affect continuously decreased during isolation mission, it is possible that a longer isolation period would have caused further impairments. The role of exercise in this regard will be discussed.

4

Investigation of additional low-level axial load on neuromuscular responses during running in simulated lunar gravity

Attias, J[1], Süss, A[2], Mileva, K.N[3], & Green, D.A[1,2]

[1] Centre of Human and Aerospace Physiological Sciences, King's College London, London, UK
[2] KBR Wyle, Space Medicine Office, European Astronaut Centre, Cologne, Germany
[3] School of Applied Sciences, London South Bank University, London, UK

Introduction: Microgravity reduces neuromuscular activation during exercise, contributing to a loss of muscle size and function. The Mk VI 'SkinSuit' provides ~20% axial body loading (AL) via graded vertical elastic-material strain in a manner analogous to Earth's gravitational force and thus offers a potential reloading stimulus. Previous research showed no significant change in muscle activation with the addition of ~20% AL during 1Gz incremental running, possibly related to 20% AL representing a small delta from 1Gz. Thus, we sought to evaluate neuromuscular activation in response to 20% AL when running in simulated lunar gravity (0.16Gz), whereby 20% AL represents ~100% additional loading.

Methods: Eight male subjects (31.9±4.7 yrs; 178.4±5.7 cm and 73.5±7.3 kg) ran at 25% above their calculated preferred walk-to-run transition speed (PTS) for 30s on two occasions on the Vertical Treadmill Facility (VTF) and once on an AlterG treadmill as the 1Gz (CONTROL) condition, in a counterbalanced design. One VTF trial was performed whilst wearing the SkinSuit at simulated lunar gravity (016SS). The other VTF trial was performed in loose-fitting clothes at a custom-matched equivalent load, determined by adding SkinSuit-induced load for each individual to that of lunar gravity (MATCHED). Surface electromyography (EMG) activity of the right Vastus Lateralis (VL), Rectus Femoris (RF), Biceps Femoris (BF), Tibialis Anterior (TA), Lateral and Medial Gastrocnemius (GL and GM respectively) and Soleus (SOL) muscles were recorded continuously throughout the trials. Heel ground (plantar) reaction force measured by pressure-sensitive foot insoles was utilised to identify heel strike. The EMG Root Mean Square (RMS) amplitude and duration of activity as well as the Median Frequency (MDF) of the EMG power spectral density were calculated for each step. EMG parameters were normalised to the respective mean values during CONTROL and compared between the conditions (LOAD) with a one-way repeated measures ANOVA.

Results: SkinSuit induced 0.17±0.01Gz AL on average (range: 0.13 to 0.23Gz), thus loading during 016SS and MATCHED ranged between 0.29-0.39Gz. The PTS in 016SS (5.4±0.05km/h) was significantly lower than MATCHED (6.3±0.1km/h) and CONTROL (9.5±0.1km/h; $p<0.001$). EMG RMS amplitude in both unloaded trials was significantly lower than during CONTROL for all muscles ($p<0.05$), although no difference was observed between MATCHED vs. 016SS for the RF (0.35±0.05 vs. 0.46±0.06), BF (0.31±0.06 vs. 0.36±0.08), SOL (0.49±0.05 vs. 0.64±0.08) and TA (0.50±0.05 vs. 0.69±0.07). In contrast, VL activity was 61.6% greater during MATCHED vs. 016SS. RF, GL and SOL MDF in both 106SS and MATCHED was lower than CONTROL ($p<0.01$), with no difference between the unloaded trials. In contrast, EMG activity duration was unaffected by LOAD for all muscles. Whilst a tendency to shift to a later onset and offset of activation in 016SS vs. MATCHED was observed for all muscles, statistical significance was not achieved.

Conclusion: The SkinSuit produced an analogous neuromuscular stimulus to the VTF in 4 of 7 muscles recorded, showing potential as a low-level reloading stimulus to the neuromuscular system during running in partial gravity. However, analysis of movement kinetics and kinematics may help to understand the mechanisms underlying the differential between-muscle EMG responses.

5

Assessing Lymphatic Flow Changes in Patients with Lymphatic Disease: Effects of Physical Therapy

Bianca Brix [1], *Gert Apich* [2], *Andreas Roessler* [1], *Sebastian Walbrodt* [1], *Nandu Goswami* [1]

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[2] Lymphedema Clinic, General Hospital Wolfsberg, Carinthia, Austria.

Lymphedema is manifested in a chronic swelling that arises due to a stasis in the lymph flow. This disease affects approximately 140 million people worldwide. The non-invasive treatment of this chronic debilitating disease is a 3-week complete decongestive physical therapy, which consists mainly of bandaging and compression of the affected body parts to control the swelling.
One of the important factors in blood pressure regulation is the maintenance of the level of blood volume, which depends on several factors including the rate of lymph flow. Since the fluid balance between interstitium and plasma is maintained by lymph flow and microvasculature filtration, it is important to understand and assess lymph flow. This can be measured directly using cannulation of lymphatic vessels, which is not clinically feasible, or indirectly by the tracer appearance rate, which is the rate at which macromolecules appear into the blood from the peritoneal cavity. However, indirect lymph flow measurements do not always provide consistent results.
Through its contribution to osmotic pressure and resistance to flow, the macromolecule hyaluronan takes part in the regulation of tissue hydration and the maintenance of water and protein homeostasis. It arrives in blood plasma through lymph flow. Lymphatic hyaluronic acid (HA, hyaluronan) concentration is several times higher than that in plasma, suggesting that the lymphatic route may account for the majority of HA found in plasma.
We present here preliminary findings from our ongoing project which assesses HA levels, as a non-invasive surrogate marker of lymph flow in lymphedema patients undergoing physical therapy, and thereby advancing knowledge in the poorly understood area of fluid dynamics in lymphedema patients. The role volume regulating hormones (renin, aldosterone, atrial natriuretic peptide, vasopressin) play during the physical therapy in lymphedema patients - during which up to 5-15 liters of fluid are mobilized from each limb - will also be discussed.

6

Hemodynamic regulation during (simulated) gravity changes – Consideration of transient differences between left and right ventricular cardiac output

Koschate, Jessica [1], *Drescher, Uwe* [1], *Thieschäfer, Lutz* [1], *Werner, Andreas* [2], *Dumitrescu, Daniel* [3], *Hoffmann, Uwe* [1]

[1] German Sport University Cologne, Institute of Physiology and Anatomy, Cologne, Germany
[2] German Air Force, Centre of Aerospace Medicine, Aviation Physiology Diagnostic and Science, Königsbrück, Germany
[3] Herzzentrum der Universität zu Köln, Klinik III für Innere Medizin, Cologne, Germany

Introduction: Changes in gravity result in altered central venous return (Gunga et al, Aviat Space Environ Med;65: 274, 1994) and left (Q'_{LV}) as well as right ventricular cardiac output (Q'_{RV}), which are assumed to be asymmetrically different (Petersen et al., Ann Biom Eng 30: 247-259, 2002; Toska & Walløe, JAP 92:1671-1676, 2002). Technically, this is difficult to assess continuously. A device to simulate simple gravity changes is a tilt table (TT). In aviation investigations, usually human centrifuges (HCF) or parabolic flights (PF) are used. There is evidence for comparable cardiovascular regulations during PF and TT (Schlegel et al., JAP 85:1957-1965, 1998), and there might be similarities with HCF experiments (van Loon, Front Astron Space Sci 3: 1-5, 2016). The different gravity changes were not tested in the same subjects, yet. To describe the differences regarding the pulmonary vascular filling in more detail, Q'_{RV} was calculated from pulmonary oxygen uptake ($V'O_2$pulm) and the measured Q'_{LV}. The aims were therefore to investigate, if the cardiovascular and pulmonary responses to (simulated) changes in gravity are comparable between TT, HCF and PF, and if there are differences between Q'_{RV} and Q'_{LV}.
Methods: Nine healthy, male subjects (31 ± 3 y, 181 ± 7 cm, 79 ± 7 kg) were tested on a TT, in a HCF and during PF. A regular PF sequence (BASE [1g] – HYPER1 [1.8g] – MICRO [µg] – HYPER2 [1.8g]– REC [1g]) was

simulated on TT using tilted postures of 65° – 90° – -6° – 90° – 65°, in HCF with 1.7 – 2.1 – 1.2 – 2.1 – 1.7posGz, and were repeated 15-16 times. All participants were tested in the seated, upright position while performing four different physical maneuvers (relax, lower body muscle contractions, forced ventilation (jet maneuver), and combination of muscle contractions and forced ventilation) during µg or its analogous (-6°, 1.2posGz). Heart rate (HR) and blood pressure (BP) were recorded beat to beat using Portapres M2 (Finapres Medical, Amsterdam, The Netherlands). Applying the Modelflow Algorithm, left ventricular stroke volume (SV) was calculated and Q'_{LV} was computed, multiplying HR and SV. Gas exchange was measured breath by breath (Zan 600, Zan Meßgeräte, Oberthulba, Germany). $V'O_2$pulm was then divided by the arterio-venous oxygen concentration difference (avDO_2) during the last 30 s of BASE to calculate Q'_{RV}. All data were interpolated to 1s-intervals. For the presented aims, the four relaxed sequences were superimposed.

Results/Discussion: There were considerable differences regarding the cardiovascular and pulmonary responses to changing (simulated) gravity between TT, HCF and PF. Regulatory responses during TT were more pronounced compared with HCF and PF. Especially SV and therefore Q'_{LV} and Q'_{RV} were different between the three conditions. During the MICRO phase SV decreased during TT, was similar in PF and increased during HCF. Q'_{LV} was decreased during TT, similar in PF and increased during HCF. Q'_{RV} was, in contrast, considerably increased throughout MICRO in the TT condition, to a less degree in PF and almost similar during HCF. During HYPER2, Q'_{LV} and SV increased clearly in the TT and PF experiments and decreased during HCF. These differences are explicable with the different hydrostatic factors in the three conditions, which obviously alter cardiac pump function. A quantification, using the calculated Q'_{RV}, shows relevant differences between Q'_{RV} and Q'_{LV}, possibly indicating an asynchronous blood flow distribution between systemic and pulmonary circulation. Although the method only allows an estimation of relative changes, the possibility to estimate Q'_{RV} non-invasively and continuously might yield a potential clinical application for e.g. patients with pulmonary hypertension to investigate vascular compliance in more detail.

7

Development of a Reliable Device for Peripheral Edema Quantification via Ultrasound Imaging in High Altitude Field Studies

Yayu Monica Hew [1], *Ulrich Limper* [2], *Jens Tank* [2]

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[2] Deutsches Zentrum für Luft- und Raumfahrt (DLR), Institute of Aerospace Medicine, Germany

Introduction: Peripheral tissue edema is characterized by tissue fluid excess and indicates the failure of microcirculation and an aggravated metabolic situation of the affected tissues. Even a healthy person can, when exposed to extreme environments such as high altitude or weightlessness, develop swelling of the peripheral tissue. Personal susceptibility of edema formation has not been predicable yet due to the lack of repeatable and reliable tissue ultrasound measurements to access these edema developments. The goals of this project are **1.)** To develop and validate a simple mechanical device to align the ultrasound probe with the tissue of interest in a precise and reliable manner at various body locations **2.)** To allow for reliable quantitative assessment of the peripheral edema in field studies and at bed side.

Methods: A versatile ultrasound probe fixture device was developed and used to perform high frequency ultrasound imaging (10 to 18 MHz) at tibia and forehead locations at 4554 m altitude. Six volunteers within the research team participated in the operational testing (3 males and 3 females, aged from 25 to 55). Their tissue thicknesses were monitored each day for 4 to 8 days at tibia and forehead locations. Highly automated image processing schemes incorporating machine learning classifiers are also implemented to minimize analysis biases during tissue thickness identification and evaluation.

Results: The mechanical fixture device demonstrated highly repeatable ultrasound edema measurements at tibia and forehead locations. The fixture device can be set up rapidly with an initial setup time of 30 minutes, and a follow-up setup time of 10 minutes or less for each measurement thereon. In the initial analysis using the automated image processing algorithm, we observed a mean tibia tissue between 3.06 to 5.09 mm among our volunteers. The mean tibia tissue thickness is 3.80±0.51 mm among females, and 4.90 ± 0.61 mm for males. During the stay at the altitude, we observed a maximum tibia tissue variation of 1.78 mm. The uncertainty of the current method (including both the mechanical and the image analysis components) gives a maximum uncertainty in mean tibia tissue thickness of 0.17mm among the automated fits. However, further work is still required in automating the ultrasound image tissue measurement as only 36 to 49% of eligible ultrasound image have their tissue boundaries properly detected.

Conclusion: The tissue thickness evolution could be monitored and quantified in a systematic manner through the usage of the designed device and the image processing software developed during the high altitude field test. Thus, this project provides a promising technique proposed for simple and reliable edema quantification and edema evolution tracking.

8

Spatial orientation of motor performance on Earth and in weightlessness

Nils-Alexander Bury[1,2], *Otmar Bock*[1]

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Introduction: On Earth, spatial orientation is defined by vector model of three reference frames: the direction of gravity; the visual surround and the orientation of the own body`s longitudinal axis. The absence or the incongruence of these reference frames during spaceflight might challenge astronauts' spatial orientation and thus lead to performance errors, to the detriment of the mission's success. The purpose of the study was to investigate spatial orientation in weightlessness as it manifests not in perception but rather in motor performance. Additionally, we compared the data to prone body posture on Earth, so that gravity pulled orthogonally to the body / task. In more detail, subjects are asked to flip a series of switches into the "off" position.
Methods: Twenty-one participants (10 female; 28.5 ± 3.8 years) were tested in two conditions (in parabolic flight and on Earth). Both conditions were characterized by a lack of meaningful gravitational cue, also on Earth, since participants lay prone. The visual surroundings were occluded. Participants were asked to flip an omnidirectional switch "down" in order to turn a visual stimulus off. The experimenter avoided any definition of "down", i.e., participants were *not* told to move the switch in the direction of the own long body axis / other body parts, or of the additional visual cues. The cues about their visual vertical (labeling) were congruent / dissociated from the egocentric vertical, or totally absent.
Results: When egocentric and visual reference frames coincided, results revealed no significant difference between the conditions – responses showed only a slight clockwise shift from the vertical. If visual reference frame was absent, the subjective vertical was also egocentric-orientated – slightly more clockwise. Results of dissociated reference frames showed a significant difference to the congruent reference frames. Overall, there were no differences between the conditions.
Conclusion: We conclude that the vector model for the subjective *perceptual* vertical could also be applicable for the subjective *motor* vertical. Based on the similarity of responses, one might argue that experiments could be done in prone body posture on Earth. However, it could be proved that all participants tried first to push the switch 'down' in direction of gravity (on Earth), which indicates that their spatial orientation was not re-orientated. This still indicates a difference between spatial orientation in weightlessness and on Earth.

9

Integrated evaluation of clinical muscle plasticity after reconstruction and rehabilitation of the anterior cruciate ligament

Martin Flück[1], *Claudio Viecelli*[1], *Andreas Bapst*[1], *Daniel Suter*[1], *Jean-Marc Lüthy*[2], *Martin Bühler*[2], *Helgard Claassen*[2], *Hans Hoppeler*[2], *Christian Gerber*[1,3]

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[2] Department of Orthopedic Surgery, Inselspital Berne, Switzerland
[3] Department of Anatomy, University of Berne, Switzerland

Introduction: Recovery of knee extensor function after reconstruction of an insufficient ACL may take several months to complete even when accompanied by physical therapy. We assessed molecular and cellular alterations in the knee extensor muscle, *m. vastus lateralis*, from the insufficient and the healthy contralateral leg at reconstructive surgery (week 0), after ambulant physiotherapy (week 9), succeeding rehabilitation training (week 26) and subsequent voluntary physical activity (week 52 and 260 weeks) and tested whether associations would exist with clinical parameters of knee (in)stability up to 16 years after reconstruction.
Methods: Biopsies were collected from the insufficient and healthy leg of 9 patients (29 years, 8 males, 1 female) at time points 0, 9, 26, 52 and 260 weeks respective to surgery to characterize cellular composition

(capillaries, fiber types, myofibrils, mitochondria) and expression of molecular regulators of the myogenic (myoD, myoG) and metabolic phenotype (respiratory complex I-V, tenascin-C, VEGF). Clinical indices of knee stability were assessed at time points 0, 52, 130, 260, 832 weeks.

Results: Clinical indices of knee function for the insufficient leg (drawer test) were improved 52 weeks after reconstructive surgery and tended to worsen, alike the Ahlbaeck arthrosis index, 5 and 16 years after surgery. Structural characteristics of metabolic and mechanical functioning of *m. vastus lateralis* muscle, such as total mitochondria density, capillary to fiber ratio and slow type fiber percentage, deteriorated in both the insufficient and healthy leg at time points 0, 9 and 52 weeks after reconstructive surgery. The before mentioned phenotypic characteristics, except the volume density of subsarcolemmal mitochondria, returned to the levels seen in the healthy leg 260 weeks after surgical reconstruction. Altered expression of protein markers of mitochondrial respiration complexes I-III in m. vastus lateralis from the insufficient leg emphasized the down-regulation of mitochondrial metabolism in knee extensor muscle after reconstructive surgery, while altered expression of myoD and tenascin-C documented myogenic reactions after 9 weeks in the healthy leg. Clinical indices of knee joint arthritis/instability at reconstruction correlated with MCSA of muscle fibers at week 9 and shifted to relationships with mitochondrial volume density at week 26.

Discussion: The findings suggest reduced muscle activity as cause of the early deterioration of slow-oxidative muscle fibers in m. vastus lateralis with the rupture of a critical ligament and highlight that plasticity of metabolic and mechanical muscle properties with rehabilitation are graded in proportion to knee stability. Collaterally, the findings also comprise the first evidence for the reversibility of slow-to-fast fibers transformation in humans.

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Efficacy of electrical baroreflex stimulation is not impaired by moderate peripheral chemoreflex activation in patients with resistant hypertension

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Introduction: Electrical baroreflex activation therapy (BAT) represents an additional treatment option in drug-resistant hypertension. The carotid sinus baroreflex and the carotid body chemoreflex may inhibit each other. In hypertensive patients, the chemoreflex may be tonically active and diminish BAT efficacy. We tested the hypothesis that the response to electrical carotid sinus stimulation is larger under hyperoxic than under hypoxic conditions.

Methods: We included 11 patients (4 women, age: 67±8 years, BMI: 31.6±5.2 kg/m²) with resistant hypertension (6±2 drug classes) who had been implanted with a BAT device (CVRx, Rheos or neo). We recorded ECG, blood pressure (SBP), ventilation, SpO2, end-tidal CO2 and O2 fractions, and muscle sympathetic nerve activity (MSNA). Patients were exposed to normoxia followed by isocapnic hypoxia to activate peripheral chemoreceptors (SpO2: 79.0±1.5%), and hyperoxia to inhibit peripheral chemoreceptors (40% end-tidal O2 fraction) in randomized order. During each exposure, we turned BAT on and off thrice for 4 minutes to assess stimulation responses.

Results: During normoxia, BAT reduced SBP from 164±27 to 151±25 mmHg (means±SD, $p<0.001$), HR from 64±13 to 61±13 bpm ($p=0.002$), and MSNA from 42±12 to 36±12 bursts/min ($p=0.004$). Hypoxia increased SBP 8±12 mmHg ($p=0.057$), HR 10±6 bpm ($p<0.001$), MSNA 6±6 bursts/min ($p=0.077$), and ventilation 10±7

l/min (p=0. 002). Responses to BAT were not different under hypoxic vs hyperoxic conditions; SBP: -15±7 vs -14±8 mmHg (p=0.771), HR: -2±3 vs -2±2 bpm (p=0.701), and MSNA: -6±4 vs -4±3 bursts/min (p=0.531).
Conclusion: Our results confirm the efficacy of electrical carotid sinus stimulation in a subgroup of patients. In contrast to the hypothesis, our data suggest that moderate peripheral chemoreflex activation does not diminish acute responses to electrical carotid sinus stimulation in patients with resistant hypertension.

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Effect of resistive vibration exercise and nutritional supplementation on morphological changes of thigh muscles during 21 days of head-down tilt bed rest

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Introduction: Human skeletal muscle is known to atrophy during exposure to microgravity with especially the anti-gravity muscles of the lower back, the pelvis and the lower limbs undergoing structural and functional changes (Baldwin 1996; Fitts et al. 2001). Such muscle changes can impair the astronauts' performance throughout and after their space missions. Even though exercise countermeasures are currently used on the International Space Station (ISS), these training programs are continuously optimized to prevent and reduce microgravity induced muscle atrophy. Resistive exercise has been shown to be effective in reducing muscle loss during microgravity, however, current training programs are very time consuming and cannot completely prevent muscle atrophy. It has been speculated that the effect of resistive exercise can be enhanced using additional vibration stimuli (Salanova et al. 2015) or nutritional supplementation (Cermak et al. 2012). The aim of this study was therefore to investigate the efficiency of a resistive vibration exercise protocol combined with protein supplementation as a countermeasure over 21 days of 6° head-down tilt bed rest.
Methods: The "Medium duration nutrition and vibration exercise" (MNX) study was conducted in 2012 and 2013 at the Institute for Space Medicine and Physiology (MEDES Clinique d´Investigation, Toulouse, France) under the leadership of the French (CNES) and European Space Agency (ESA). The study was performed in a cross-over design with three different campaigns each lasting 34 days. Each campaign consisted of 7 days of basic data collection (BDC-7 – BDC-1), 21 days 6°head-down tilt bed rest + intervention (HDT 1 – HDT 21) and a 6 day recovery period (R+1 – R+6). The 'wash-out' phase between the study campaigns was 4 months. The following interventions where applied during the bed rest period: resistive vibration exercise (RVE), nutrition + resistive vibration exercise (NeX) and control (CON). The RVE intervention group performed a vibration exercise protocol, the NeX intervention group comprised of the same exercise protocol intervention plus an high-protein diet. Each subject (N = 8) participated in all three study campaigns with the order of the interventions randomized. MR imaging of both thighs in the transverse plane was performed using a 1.5 T magnetic resonance imaging (MRI)-scanner (Magnetom Avanto, Siemens Healthcare, Erlangen, Germany). A T1-weighted spin-echo sequence (slice thickness: 4 mm, interslice distance: 0.8 mm, TR: 641 ms, TE: 11 ms, flip angle: 180°, field of view: 229x420 mm, matrix: 512x140 pixels, in-plane resolution: 0.8x0.8 mm) was recorded over the full length of the thigh at BDC-7, HDT 21 and R+6. The anatomical cross-sectional areas (ACSA) of the rectus femoris, the vastus medialis, the vastus intermedius, the vastus lateralis, the sartorius, the hip adductors and the knee flexors of the left thigh were segmented and evaluated using semi-automated segmentation software (Hudelmaier et al. 2010). A two-way (time and group) analysis of variance (ANOVA) with repeated measures was used to detect significant differences (p<0.05) between groups at the different time points (Duncan's post-hoc-test).
Results/Discussion: ACSA of all examined muscle groups (except for the vastus medialis in the NeX group) decreased significantly (p<0.05) within study groups during immobilization. Comparing the absolute differences of ACSA between the groups, the lateralis displayed a decrease of -1.5 ± 1.5 cm² in the NeX group, which was significantly (p<0.05) less than in the CON and RVE groups (CON: -3.3 ± 1.3 cm² and RVE: -3.9 ± 1.5 cm²). Thus, nutritional supplementation in combination with whole body vibration training may have a positive effect and delay on the reduction in muscle ACSAs at the measured site.
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Circadian Core Body Temperature Rhythm in a Mars 520-day mission simulation (Mars500)

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Introduction: A growing body of research indicates that misalignment of circadian rhythms can be detrimental to mental and physical health. Long-term space missions may potentially alter circadian rhythms, causing a critical risk for crew health and safety. Continuous recordings of core body temperature (CBT) are a well-established approach in describing circadian rhythms. However, determining the circadian rhythm of CBT in subjects during normal daily activities is inaccurate, since for example physical exercise increases CBT. Several factors may mask the suprachiasmatic nucleus driven endogenous oscillator. Therefore, the purpose of this study was to assess the impact of a 520-day simulated interplanetary mission to Mars on the circadian rhythm of CBT after using a "purification" method on collected CBT.
Methods: Physical activity was continuously recorded for 24 h via a wristwatch and CBT was measured via a Double Sensor on the forehead [1]. Six measurements were conducted throughout the mission, three during "flight towards Mars" (Isolation day (ISO) 20, ISO 80, ISO 140) and three during "flight back towards Earth" (ISO 320, ISO 400, and ISO 460). To unmask the underlying endogenous (sinusoidal) rhythm, the procedure "purification by intercept" was applied. A linear regression of recorded temperatures on activity over the previous 30 min enables an intercept temperature (zero activity) [2]. Each temperature profile was then subjected to the cosinor method and quantified by the fitted curve parameters: i) mesor (midline estimating statistic of rhythm), ii) amplitude (half of the difference between highest and lowest value of the fitted curve), iii) acrophase (time point of fitted curve maximum), and iv) the percentage rhythm (how well the cosine model fits the data).
Results: Despite considerable inter-individual variation, the visual inspection of the data at "the beginning of the flight to Mars" (ISO 20) and at "the beginning of the way back to Earth" (ISO 320), showed that rhythm parameters mesor, amplitude, and acrophase hardly changed. On the other hand, at ISO 460 mesor and amplitude sharply decreased, as well as rhythm acrophase sharply increased. We speculate that the latter could be related to the exposure of blue light, which was exclusively employed during ISO 439-499 [3]. The percentage rhythm of purified CBT was significantly smaller compared to that of unpurified CBT.
Conclusion: Since our "purified" CBT corresponds less well to a sinusoidal rhythm compared with unpurified CBT, the chosen purification approach was unable to eliminate the effect of physical activity for accessing the endogenous (sinusoidal) rhythm of CBT using Double Sensor recorded CBT and wrist actimetry of human subjects in simulated space flight.
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Age-related walking speed changes after 60 days of bed rest

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Introduction: Nowadays, it is well known that walking speed is used as functional test to measure health status among individuals and decreases in walking speed are associated mainly with physical impairment, decreased functionality and aging. Bed rest is known to reduce the functionality of many body systems, including the musculoskeletal system. Thus, it would be interesting to study how the walking ability is affected by age in combination with 60 days of strict immobilization. The main hypothesis is that younger subjects will have a faster daily walking speed after bed rest and depict a faster recovery time compared with older subjects regardless by whether they are in the training group or control group.
Methods: 11 male subjects were equipped with a tri-axial accelerometer on the waist throughout the recovery period (14 days) after 60 days of bed rest and asked to wear it as much as possible (at least 10 hours of adherence every day). Before starting the immobilization period subjects were randomly separated into two groups, the training group (n: 7, age: 29.5 ± 6, height: 184 ± 4.7 cm, weight 81.5 ± 4.2 kg) which performed daily training sessions on a device to mimic natural reactive jumps during bed rest, and the control group (n: 4, age: 31 ± 7.5, height: 179 ± 2.1 cm, weight 73 ± 8.7 kg) which did not perform any physical activity. Two statistical models have been used to study the effect of age on the subjects. The first one splitting subjects into two more groups based on age, one group below 30 years old (n: 6, age: 25.3 ± 2.3, height: 183.6 ± 5.5 cm, weight: 81.8± 3.5 kg) and the second one above 30 years of age (n: 5, age: 35.8 ± 4.1, height: 180.4 ± 2.8 cm, weight: 74.4 ± 8.7 kg).
First model:

$$y = \beta_0 + \beta_1 * \log(time) + \beta_2 * group + \beta_3 * age\ group + \beta_{12} * \log(time)*group + err$$

The second model replace the variable *age group* with age for each subjects, resulting in:

Second model:

$$y = \beta_0 + \beta_1 * \log(time) + \beta_2 * group + \beta_3 * age + \beta_{12} * \log(time)*group + err$$

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Javelin throw in master athletes 70 years and older – a biomechanical video analysis of throwing techniques

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Introduction: Master athletics has gained popularity and many older athletes actively take part in competitions, even at international scale. While many studies have been conducted on the javelin throwing technique and biomechanics of young elite athletes, no data is available on athletes at high age. This study was conducted to gain a better understanding of changes in javelin throw in old athletes and to learn more about the decline in performance in a very healthy population.
Methods: During three master athletics championships, each throw of male javelin throwers 70 years and older was filmed and the best throw of each athlete selected. The following parameters were analyzed and correlated with the age-graded performance: the angle of release, angle of attitude, angle of attack, elbow angle just before the pull and the number of steps in the approach run. Values are compared to published angles of young elite athletes.
Results: 27 athletes between 70 and 89 years of age were included in the study. The average distance thrown was 25.1m (+/- 7.4m). The athletes between 70 and 79 years of age throw with a 500g javelin and averaged 30.1m (+/- 6.2m). The older group between 80 and 89 years of age throws with a 400g javelin and had an average result of 20.4m (+/- 5.3m). The main results are that the athletes' age-graded performance highly correlates with all five parameters analyzed (each $P < 0.001$). A higher elbow angle just before the pull, a

larger number of steps in the up-run, lower angles of attitude and higher angles of release and attack were connected to better results. Compared to young elite athletes, the angles of attitude and release were lower and the elbow angle higher. Typical age-related changes in the javelin throwing technique were found and recommendations are given for master athletes based on the present analysis.

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Effects of short-term sleep restriction or fragmentation on the autonomic nervous system - Autonomous nervous system in sleep (ANSIS)

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Introduction: Nighttime sleep has a physical and mental regeneration function indicated also by the parasympathetic activity. It is not yet systematically investigated what effects sleep fragmentation or sleep deprivation compared to undisturbed sleep has on the autonomic nervous system.
The aim of our study is to objectify the regenerative function of normal sleep as well as deficient sleep with non-invasive parameters of the autonomic tone.
Methods: The prospective randomized cross-over study includes 20 healthy male participants (mean age: 39,9 ± 7,4 years, mean BMI: 25,5±2,2 kg/m²). The protocol consists of one baseline night, one intervention night of either sleep deprivation (5 hours) or sleep fragmentation (light on every hour) and two recovery nights of undisturbed sleep. Each participant undergoes a total of 8 nights, experiencing both interventions (sleep deprivation and fragmentation), separated by a wash-out phase of one week. During bed time and testing EEG, ECG, EOG and EMG are registered. Each night before sleep and each morning after sleep ECG and continuous blood pressure are recorded under paced breathing at 12/min with a portable polygraphy device (SOMNOtouch™). Parameters of the autonomic tone (standard deviation of normal to normal R-R intervals (SDNN) and Kerdo-Index (1-diastolic blood pressure/heart rate)) are calculated for the baseline and intervention nights.
Results: SDNN increases after every night. Compared to baseline the restriction raises the SDNN from 2,2±17,8 ms to 22,0±26,7 ms. Fragmentation lowers the SDNN from 16,2±33,1 to 10,8±24,3. The difference between restriction and fragmentation in SDNN elevation is statistically significant: 25,3ms (p= 0,03). Heart rate decreases slightly after sleep. Neither of the interventions cause significant differences. The Kerdo-Index shows no consistent reaction to sleep. The parameters of heart rate variability enhance after sleep. The elevated SDNN indicates an improved interplay between sympathetic and parasympathetic regulation. Restriction is associated with higher SDNN values and seems to have a deeper impact of the regeneration of the autonomic tone. Despite this, further investigation is necessary, because the high standard deviation shows an impact of interindividual differences.

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In-vivo measurement of brainstem and hypothalamic centers involved in blood pressure regulation in humans: A high-resolution fMRI study with LBNP

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Introduction: The human body has several systems to regulate blood pressure, one of which is the baroreflex. It is mediated by a number of nuclei in the brainstem and hypothalamus that via autonomic efferents adjust the mean arterial pressure by altering both the force and speed of the heart's contractions, as well as systemic vascular resistance. While cortical centres influencing the baroreflex have been studied in humans using functional magnetic resonance imaging (fMRI), the brainstem region suffers from strong physiological noise that makes detection more difficult.

Methods: We used lower body negative pressure (LBNP) during high-resolution fMRI and concomitant autonomic recordings to investigate the brainstem and hypothalamic centres of the baroreflex system in humans. 15 healthy subjects were scanned using a 3T MR scanner. The protocol involved SMS-EPI functional scans (voxel size=2x2x2 mm^3) as well as T1- and T2-weighted structural scans (voxel size=1*1*1.2 mm^3). LBNP stimulation was delivered using a custom-made polycarbonate pressure chamber. Negative pressure was built up using a vacuum cleaner and controlled by a digital pressure gauge. Data was preprocessed using tools from FMRIB Software Library (FSL v5.0) including motion correction, spatial normalization and temporal high-pass filtering. The data was cropped to retain only the brainstem and hypothalamus, masked to remove adjacent areas with high physiological noise and spatially smoothed. Statistical analysis was conducted using a mixed-effects general linear model and independent component analysis (ICA).
Results: We found activations related to either the LBNP paradigm or the recorded blood pressure time-courses in multiple nuclei known to be involved in baroreflex regulation. These included the nucleus of the solitary tract, the rostroventrolateral medulla, and the paraventricular nucleus of the hypothalamus. In addition we observed strong activation of pontine nuclei. Being able to measure baroreflex nuclei in vivo is an important step to better understand this system in humans.

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Time course of Hemodynamic Parameters During Postural Changes in Stroke

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Aims and Objectives: Patients with stroke often tend to fall upon changes in posture from supine to standing. The aim of this study was to investigate the time course of hemodynamic parameters during postural changes in stroke.
Methods: Participants age 55+ years, 23 with acute ischemic stroke and 25 healthy controls were included in this study. Subjects carried out a sit-to-stand protocol. After the electrodes were placed subjects seated for 5 min, after the first 5 min subjects were assisted into the standing position (standing), and the subject was assisted to resume the initial seated position (recovery) for a further 5 min. Hemodynamic parameters were measured non-invasively: blood pressure (BP), heart rate (HR), and heart rate variability (HRV). A Linear-mixed model was conducted to compare the effect of time on hemodynamic parameters during postural changes in stroke and healthy controls.
Results: A total number of 48 subjects (Stroke: n=23; Controls: n=25) were enrolled. The mean age of stroke subjects was 66.2 ± 7.1 yrs., and controls 63.7 ±6.9-yrs. 59% of the stroke patients were males. We found a statistically significant change in the following parameters: diastolic blood pressure (DBP), mean blood pressure (MBP), cardiac output (CO), and cardiac index (CI) after the first 10 second of standing ($p<0.05$).
Conclusion: We found that there is a tendency of high blood pressure at baseline in the stroke patients compared to healthy controls. Thus, it appears that an upright posture significantly affects the cardiovascular system within the first minute of standing. As most of the falls occur in older persons during changes in posture (from supine to upright), our results suggest that problems with blood pressure regulation may be the underlying mechanism that predisposes stroke patients to falls upon standing up.

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Head down tilt and cognition – Effects of simulated microgravity on sleep quality and cognitive performance

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Introduction: Head down tilt (HDT) is a ground-based simulation of microgravity. Brain perfusion decreases during HDT with venous congestion increasing[1]. Moreover, intracranial pressure increases during HDT due to fluid shifts towards the head. Our aim was to assess indicators of intracranial pressure in combination with parameters of cognition and sleep during -12° HDT.
Methods: Eleven healthy male subjects participated in a randomized, cross-over designed study with two conditions–staying in horizontal position and being tilted to -12° HDT. Each campaign tested one condition and lasted for three days. The interventional phase started on the morning of the second day and also included one night in the respective position.Measurement blocks were carried out repeatedly during the intervention. These blocks comprised amongst others a cognitive test battery, near-infrared spectroscopy (NIRS). The tilting procedure was integrated in the first interventional measurement block in order to assess acute changes in content and oxygenation of haemoglobin by using the NIRS. During the interventional night objective sleep parameters were assessed by polysomnography. Linear mixed models were used for the statistical analysis. The level of significance was set at $P = 0.050$.
Results: In the first minutes the NIRS showed acute effects of the tilting process with a significant decrease in total haemoglobin ($P < 0.001$). The tissue saturation index dropped with tilting ($P = 0.007$) and stayed lower with HDT during the total 20 minutes of the measurement ($P = 0.050$, $g = - 0.056$). These effects diminished over time with no significant difference on the second interventional day. The Manometer test from the cognitive test battery (a means to assess information processing) yielded longer response times with -12° HDT on the second interventional day ($P = 0.016$, $g = 0.307$) as compared to horizontal position. Deep sleep ($P = 0.002$, $g = - 0.898$) and REM sleep ($P = 0.035$, $g = - 0.634$) were significantly reduced at -12° HDT, while light sleep was elevated ($P = 0.002$, $g = 1.078$). Subjective sleep quality was lower at -12° HDT ($P = 0.047$, $g = - 0.968$).
Discussion: Changes in oxygenation and content of haemoglobin as assessed by the NIRS were short-lived which hints at quick compensation. One possible adaptation mechanism is respiration as it is a major driving mechanism for cerebrospinal fluid circulation[2]. Several factors might be responsible for the significant cognitive changes at -12° HDT. Apart from the above mentioned fluid shifts and perfusion changes, impaired sleep has to be considered as well. Obstruction of the upper respiratory tract might have caused the observed sleep impairment. This obstruction might be due to fluid shifts towards the head. Yet, an important confounding variable is sliding of the subjects towards the head-end of the bed.

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Finding NEMO – radiation induced bystander effects elicit NF-κB-dependent survival

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Introduction: Radiation-induced bystander effects (RIBE) are an acknowledged issue of radiation therapy. Irradiation of tumor tissue has been shown to affect non-irradiated neighboring cells in a paracrine and endocrine manner. Transduction of bystander signaling though remains to be investigated in detail. A part of the transduction is the receptor-initiated activation of signaling pathways by secreted factors of the irradiated cell during irradiation damage response. This work focusses on the activation of the transcription factor Nuclear Factor κB (NF-κB) in bystander cells after irradiation. NF-κB is a well-known contributor to inflammatory processes by e.g. cyto- / chemokine production as well as to stress reactions such as the DNA damage response and cell cycle regulation.

Methods: Murine embryonic fibroblasts (MEF) with an intact NF-κB signaling pathway (wildtype, wt) or with a knock-out of NF-κB essential modulator (NEMO ko) were used. Clonogenic survival and cell cycle distribution were determined in directly irradiated cells and in cells incubated with conditioned medium from X-irradiated cells (bystander treatment).

Results: Directly irradiated NEMO ko cells, plated for clonogenic survival immediately after X-irradiation, display the same dose-effect curve as the wildtype (wt). But when allowed to recover for 24 h, the wt cells show a broader shoulder in the curve, indicating better repair of sublethal damage and a role of the NF-κB pathway in the repair of radiation induced DNA damages. Looking into the survival of bystander cells, the slope of the survival curves is significantly different, with NEMO ko cells surviving better than wt cells ($S_{16\ Gy}$: NEMO ko = 1.66 vs wt = 0.83). The different behavior may correlate with NF-κB dependent DNA repair in bystander cells for NEMO ko and wt cells. Cell cycle analysis revealed an arrest in G2/M phase that was delayed by 6 hours in directly irradiated NEMO ko cells compared to wt cells. This indicates that NF-κB regulated DNA repair pathways are important for recovery from radiation induced damages. Bystander NEMO ko show an even further delayed arrest at 48 h, while wt bystander cells show no G2/M arrest at all. This supports the assumption that damages have to exceed a certain threshold to be recognized as repair-worthy. As NF-κB has been reported to be involved in homologous recombination, cells with impairment in the NF-κB pathway, such as NEMO ko, register damages caused by bystander treatment differently compared to wt cells. This leads to G2/M arrest extending the time for repair in NEMO ko bystander cells.

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Enhanced Homer cell signal in skeletal muscle soleus (SOL) of mice with a vestibular disorder, the head tilt (het-/-) mouse model

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Introduction: The molecular mechanisms regulating skeletal muscle structure and function during chronic disuse in different clinical settings or exposure to microgravity are not yet fully understood. Recently the potential role of the vestibular system was proposed. Interestingly, the tonic vestibule-spinal modulation of motor activity was demonstrated in antigravity postural muscles (1-3). With the aim to further elucidate such mechanisms here we investigated Homer subcellular localization and Homer protein-protein interaction / dimerization in calf SOL and gastrocnemious (GAS) muscles of wild type (WT) and *het*$^{-/-}$ mice (An autosomal recessive mutation responsible for a vestibular disorder in affected animals characterized by an abnormal circling behavior and hyperactivity).

Hypothesis: The vestibular system play an important role on skeletal muscle structure and function regulation and the depletion of vestibular sensing result in an altered: myofiber phenotype, myofiber size, nerve-muscle cell-cell communication / neuromuscular cell signal transmission, calcium sensitive Homer cell signal.

Methods: Skeletal muscle SOL and GAS from adult WT and *het*$^{-/-}$ mice (n=6 each group) were used. Soluble (cytosol) and particulate (cytoskeleton) muscle cell fractions were prepared from the right hind limb muscles according to an established experimental protocol procedure (4). Soluble and particulate muscle cell fractions were biochemically analyzed by polyacrylamide gel electrophoresis (PAGE) in native experimental conditions and by Western blot (WB) for Homer protein content by using a panHomer antibody (5). Morphological assessment was performed on the contralateral left hind limb muscles of the same animals and groups by using a Confocal Laser Scanning Microscope Leica TCS SP8.

Results: In both soluble and particulate skeletal muscle cell fractions two different Homer immunoreactive bands were detected. A lower Homer immunoreactive band with an apparent molecular weight of 48 kDa, the Homer monomer predicted molecular weight, and a higher Homer immunoreactive band with an apparent molecular weight of 110 kDa, corresponding to the Homer dimer. Both Homer monomer and dimer were quantitative different between soluble and particulate cell fraction and between muscle type and animal group.

Interesting, in GAS particulate cell fraction of *het*$^{-/-}$ mice no Homer dimer was present, while in SOL soluble fraction there was a twofold increase of Homer dimer when compared to WT. Finally, no Homer monomer was present in both soluble and particulate SOL muscle cell fraction WT and *het*$^{-/-}$ mice suggesting that, major differences were present for Homer monomer and dimer between postural (SOL) and non postural (GAS) muscles. Homer subcellular localization at the neuromuscular junction (NMJ) and confocal pixel intensity analysis is still on process. Morphological assessment of *het*$^{-/-}$ SOL and GAS skeletal muscles myofibers revealed 10% increased in myofiber type-I cross-sectional area compared to WT.

Discussion: Postural vs. non-postural muscles of *het*$^{-/-}$ mice are characterized by an opposite regulation of the Homer cell signal. These changes are consistent with the increased Homer signal in postural muscles. These results well overlap with the increased muscle activity (hyperactivity) of *het*$^{-/-}$ mice and their increased slow type myogenic program.

Taken together, these results suggest that the vestibular system somehow affect skeletal muscle structure and function, and this is, at least in part, translated by the Homer cell signal.

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Influence of acute normobaric and hypobaric hypoxia on hemodynamics, cognitive function, cerebral near-infrared spectroscopy and gene expression

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Introduction: Acute hypoxia in both high altitude and under normobaric conditions is associated with symptoms of acute mountain sickness (AMS) and cognitive dysfunction in humans. However, global or molecular predictors for the development of AMS are missing. Thus, the aim of this study was to investigate in non-acclimatized subjects associations between AMS and 1) hemodynamic changes, cerebral oxygen saturation and cognitive function, as well as 2) leukocyte mRNA expression of inflammatory molecules under acute hypobaric and normobaric hypoxia, respectively.

Methods: Eleven healthy subjects were examined in hypobaric hypoxia under resting and exercise conditions at 3883 m above sea level. Pulse oximetric oxygen saturation (SpO_2), cerebral near-infrared spectroscopy (NIRS) and advanced hemodynamic parameters (cardiac output (CO), cardiac index (CI), stroke volume (SV), index of contractility (ICON), thoracic fluid content (TFC), left-ventricular ejection time (LVET) and pre-ejection period (PEP)) were measured non-invasively. AMS (assessed with Lake Louise Score (LLS)) and cognitive function (Trail making test and two newly developed cognitive function tests) were assessed. Additionally, 7 out of 11 individuals were tested under normobaric conditions in a hypoxic chamber simulating a similar situation to compare these results with hypobaric environment (520m above sea level, 13.1% inspired oxygen). PAXgene blood samples of subjects were used to analyse changes in leukocyte mRNA expression of IL-1β, CXCR4 and CCR2 in normobaric and hypobaric hypoxia compared to normoxic baseline using real-time PCR (qPCR). To reappraise molecular results from normobaric and hypobaric experiments and to distinguish between hypoxic and exercise effects, we isolated peripheral blood mononuclear cells (PBMCs). PBMCs were incubated for 24 hours under normoxia, 10% and 5% hypoxia or stimulated with CD3/CD28. mRNA expression of aforementioned variables was again performed using qPCR.

Results: Under hypoxia SpO_2 (data not shown) and NIRS highly decreased (Baseline vs. normobaric hypoxia: 73.4%±8.3 vs. 62%±5.6; $p<0.05$; Baseline vs. hypobaric hypoxia: 73.4%±8.3 vs. 56.3%±11.0, $p<0.001$) and volunteers developed AMS. Heart rate, cardiac output and LLS increased, whereas LVET and SV decreased under normobaric and hypobaric conditions, especially following exercise. Hemodynamic changes did not correlate with cognitive function tests or AMS. LLS after 24h on the mountain correlated with NIRS after exercise, both in normobaric and hypobaric conditions ($p<0.01$). After 24 h on the mountain, LLS scores, indicating AMS, correlated with IL-1β ($p=0.03$; $r=0.735$) and CXCR4 ($p=0.01$; $r=0.796$) mRNA expression. In detail, CXCR4 mRNA expression highly increased immediately after exercise under hypobaric hypoxia and remained elevated after 24 h ($p<0.01$), whereas IL-1β increased after 24 h on the mountain ($p=0.04$). CCR2

increased both under normobaric and hypobaric hypoxia after exercise ($p<0.05$) and further increased until 24 h on the mountain ($p=0.01$). In contrast, in vitro CXCR4 mRNA expression remained unaltered when applying hypoxic (10% and 5%) or stimulatory conditions (CD3/CD28), suggesting that in vivo CXCR4 increase was due to a combination of both hypoxia and exercise. IL-1β strongly increased following CD3/CD28 stimulation ($p=0.006$) and 5% hypoxia ($p=0.004$) in vitro. CCR2 did not increase following CD3/CD28, but after hypoxia in vitro ($p=0.005$).
Conclusions: Acute normobaric and hypobaric hypoxia alters hemodynamic and cerebral oximetry and leads to AMS. Cognitive function tests were unaltered and did not correlate with systemic or cerebral oximetry readings and thus were insensitive to detect cerebral dysfunction under acute normobaric or hypobaric hypoxia. Additionally, non-invasive hemodynamic variables and cognitive function tests did not correlate with the development of AMS, whereas NIRS after exercise in normobaric and hypobaric hypoxia showed a correlation with LLS after 24h in hypobaric hypoxia. Also induction of molecular markers was correlated with LLS: IL-1β, CXCR4 and CCR2 gene expression revealed as regulated by hypoxia or inflammatory stimuli in vitro. Further studies are needed to analyse whether NIRS and these molecular markers may be a promising tool to identify people at risk for AMS.

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Unnoticed Intrinsic Autoregulation Mechanisms of the Heart

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Introduction: The Frank-Starling Mechanism (FSM) is the best known intrinsic autoregulation mechanism of the heart. It describes the relationship between preload and contractility of the ventricle. Besides the FSM, there are two other less known mechanisms, which play a considerable role in the intrinsic autoregulation of the heart: the Anrep effect and the shortening deactivation (SDA). The Anrep effect (also "homeometric autoregulation" or "slow force response") describes a further increase in the ventricular contractility over 1-5 minutes after an acute dilation of the ventricle. The shortening deactivation describes the inverse correlation of contractility and volume flow in the ejection phase of the ventricle.
Methods: In an acute porcine animal model (n=10) pressure and volume of the ventricles where measured by conductance catheter technique. Ultrasound flow probes and pressure sensors where used to measure aortic and pulmonary artery flow and pressure. A balloon occlusion catheter was used to reduce cardiac preload. With an inflatable occluder, which was positioned around the aorta, cardiac afterload could be increased. The end-systolic pressure volume relationship (ESPVR) was used to describe contractility and was calculated from 29 to 71 load interventions per animal. All experimental procedures and protocols used in this investigation were reviewed and approved by the local animal care committee, as well as the governmental animal care office (No. 84-02.04.2013.A476 and 8.87-50.10.45.08.257, Landesamt für Natur-, Umwelt- und Verbraucherschutz Nordrhein-Westfalen, Recklinghausen, Deutschland).
Results: During afterload increase all three intrinsic autoregulation mechanisms can be displayed. Although the end-diastolic volume (EDV) remains stable within the first beats, a sudden increase in pressure can be observed (Fig. 1: red symbols). This reflects the SDA. A second phase, with an increase in EDV and further increase in pressure, follows (FSM => Fig. 1: blue symbols). The Anrep-effect presents itself by an additional increase in pressure, stroke volume and a reduction in EDV over the following 1-5 minutes (Fig. 2). This can only be explained by a further increase in contractility.

Whereas there was no difference between the ESPVR at baseline (obtained by preload reduction) and the second phase of the afterload increase (FSM) (1.45 ± 0.63 vs. 1.26 ± 0.31, p=0.59), the ESPVR was significantly higher in the first phase (SDA) (4.58 ± 2.28, P=0.001) and after 3 minutes (Anrep) (1.78 ± 0.71, P=0.009) of afterload increase compared to baseline.

Early response to pressure increase

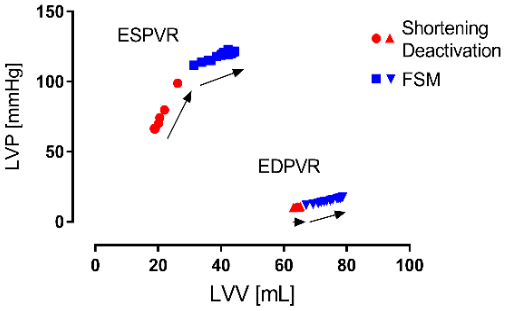

Fig. 1: Effect of an acute afterload increase on the endsystolic (ESPVR) and enddiastolic (EDPVR) pressure-volume-relationship. (LVV: Left ventricular volume; LVP: Left ventricular pressure)

Long term response to pressure increase

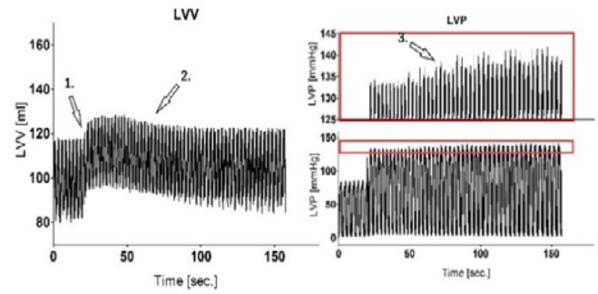

Fig. 2: Long term effect of an acute afterload increase (1.) on volume (LVV) an pressure (LVP) of the ventricle. After 20 seconds, there is an additional increase in the LVP (3.) and a decrease in the initially increased LVV (2.).

Conclusion: SDA is an important mechanism to increase contractility within a heartbeat and reflects a further autoregulatory mechanism of the heart for a fast adaptation to load. Besides the FSM the Anrep effect plays a considerable role as it leads to a further increase in contractility related to pre-stretch.

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The effect of 4-hour partial axial reloading via the Mk VI SkinSuit upon recumbent lumbar geometry and kinematics after 8-hour hyper-buoyancy flotation

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Introduction: Prolonged spinal unloading in microgravity has been associated with elongation, back pain and increased risk of intervertebral disc (IVD) herniation, particularly in the lumbar spine. Novel countermeasures to reintroduce axial loading in space are therefore required. This study evaluated the impact of 8h of unloading followed by 4h reloading with a novel axial loading countermeasure, the Mk VI SkinSuit, on lumbar geometry (magnetic resonance imaging; MRI) and kinematics (quantitative fluoroscopy; QF) utilising a new microgravity analogue, hyper-buoyancy flotation (HBF).

Methods: Eight male participants (28±5y; 1.77±0.05m; 73±5.3kg) gave written informed consent to participate in this study. MRI-compatible Mk VI SkinSuits were tailored for each participant, providing on average 0.19±0.03Gz axial loading at the foot (ForceShoes, Xsens). A HBF bed (part filled with saline saturated water; ~1.7gcm^3) was built within the imaging centre to allow supine transport from the HBF to the MRI scanner. Participants lay for 8h overnight on the HBF in loose attire on two separate occasions, followed by a further 4h on the HBF, once with and once without the SkinSuit. T2-weighted lumbar (L1-S1), sagittal and axial scans were analysed for lumbar length, curvature, IVD height, cross-sectional area and volume. Following MRI, participants were positioned recumbent on their side upon a motorised control table for QF. They were passively moved through two ranges of movement, 40° flexion and 40° extension, over a period of ~15 seconds at $6^{o}s^{-1}$. The c-arm fluoroscope took continuous images whilst positioned at L3/L4 with all vertebrae from L2-S1 in view. Vertebral body positions (L2-S1) were tracked throughout the motion sequences (Matlab), with each of the vertebra traced five times before a pooled average was calculated for laxity, intervertebral range of motion (IV-ROM_{MAX}), motion sharing variability (MSV) and inequality (MSI).

Results: Neither lumbar length (138.8±6.4 vs. 138.9±6.8mm) nor lordotic curvature (42±6.8 vs. 41.1±7.2°) were affected by axial reloading, post HBF. Mean IVD height tended (p<0.2) to be reduced at L3/L4 (0.4±0.7mm) and L4/5 (0.3±0.7mm). There was also a tendency for IVD cross sectional area to increase with reloading at L4/L5 and L5/S1 and for IVD volume at L2/L3 and again at L4/L5 to decrease. During flexion, whilst all median QF parameters tended to be slightly higher with reloading, only IV-ROM_{MAX} was statistically significant. During extension, there was a trend (P<0.2) for an increase in MSI with reloading. This study suggests that 4h of approximately 0.2Gz axial reloading acted to reduce disc height and decrease measures of intervertebral restraint, although this was only a minor effect with acute SkinSuit wear. Though reloading with the Mk VI SkinSuit did not significantly reduce lumbar length or lordotic curvature, at the IVD level cross-sectional area increased and volume decreased. Whether these effects are functionally significant warrants further study.

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Cerebral oxygen delivery and autoregulation with different hypobaric and normobaric hypoxic conditions in military pilot trainees.

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Introduction: Military aircrew, mountaineers and high-altitude permanent residents are exposed to severe hypoxia. In all hypoxic conditions, partial pressure of oxygen in the ambient air (P_IO_2) and arterial oxygen saturation (S_aO_2) are reduced. The cerebral autoregulation is impaired during first days or after a rapid ascent to high-altitude exposure (Ainslie PN *et al*., 2008 and 2012, Subudhi AW *et al*., 2013). Slight different physiological responses have been reported between terrestrial altitude (i.e., decreased barometric pressure, hypobaric hypoxia, HH), and simulated altitude (i.e., lowered inspired oxygen fraction %F_IO_2; normobaric hypoxia, NH) (Millet GP et al., 2012). Regarding the cerebral oxygen delivery, it was recently reported that it was similarly reduced in both HH and NH conditions compared to normoxia during time-trial cycling, but with different combination between cerebral blood flow (transcranial Doppler) and deoxygenation (NIRS) (Saugy et al., 2017). Therefore, in the present study, we investigated the effect of acute HH, NH, normobaric normoxia (NN) and hypobaric normoxia (HN; at the same barometric pressure than HH but with a hyperoxic breathing to obtain a P_IO_2 equivalent to NN) on cerebral oxygen delivery. For safety reasons, it is paramount to better understand how cerebral autoregulation and oxygenation of aircrew are affected in different hypoxic conditions or after rapid ascent in high-altitude.
Methods: Sixteen pilot trainees (25.9 ± 3.6 yr) performed a familiarization session followed by a testing session in the hypobaric chamber at the Aeromedical Center (Dübendorf, Switzerland) either in NN, 3000m HH, 5500m HH, 5500m NH and 5500m HN conditions in a randomized order. During a seated 5-min period at rest followed by a hypercapnic test (i.e., 1-min hyperventilation followed by 2.5-min 5%CO_2 breathing), cerebral oxygen delivery (cDO_2) was calculated from middle cerebral artery velocity (ΔMCAv, transcranial Doppler) and cerebral tissue oxygenation index (TOI, NIRS). cDO_2, MCAv and TOI and were also calculated during last minute of normalization in each condition. Other physiological variables (heart rate, oxygen saturation, gas exchanges) were also recorded during the entire experiment. Mean values were also calculated during last minute of normalization.
Results: Cerebral oxygen delivery at rest was maintained in all conditions compared to Normoxia during normalization and concentration test. During the hypercapnic phase, cDO_2 during first minute of
baseline and hyperventilation was not significantly different between all conditions. Cerebral oxygen delivery was significantly lower in 5500m HH (959 ± 203, P=0.042) compared to normoxia (1171 ± 182) during hypercapnia. There was no difference between other conditions. Delta middle cerebral artery velocity (ΔMCAv (cm/sec)) between baseline and hypercapnia was higher in 5500m NH (9.80 ±
14, P=0.015) compared to 5500m HH (-0.2 ± 7.2). This result shows that MCAV in 5500m HH condition was not increased when breathing 5% CO_2 gas mixture compared to baseline. There was no
significant difference between conditions regarding to ΔMCAv between hyperventilation and hypercapnia, but values were slightly lower in hypobaric conditions (5500m HH and HN). This results indicates that acute cerebral autoregulation to CO_2 could be affected in hypobaric conditions. There are interindividual differences, so results should be interpreted with caution. TOI was lower in 5500m HH (71.2 ± 5) than in NN (80.2 ± 6, P>0.001) and 5500m HN (79.6 ± 7, P<0.001). TOI in 5500m NH (75.4 ± 7, P=0.07) was lower than in NN. There was no difference between 5500m HN and NN. TOI seems to be more affected in HH than NH.

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Travel Instructions (see also: http://www.dlr.de/envihab/en/desktopdefault.aspx/tabid-9657/)

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Arriving from Cologne (A59) or Oberhausen/Duesseldorf (A3): follow the indications to Koeln/Bonn Airport (A59), then take the exit Porz-Wahn/Wahnheide. At the exit drive left (Porz-Wahnheide) and follow the DLR sign.
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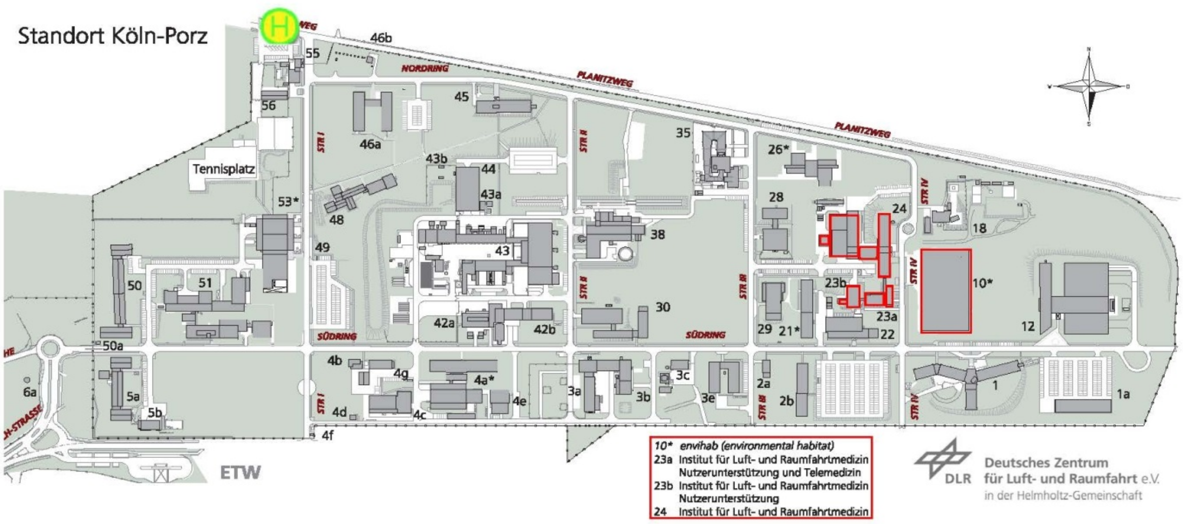

Accommodation (example):

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