CONTROLLED SUPERFICIAL PRESSURE TO ASSIST THE CIRCULATORY SYSTEM OF ASTRONAUTS

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ABSTRACT

One of the most critical issues for space exploration is the fluid shifty suffered by astronauts. This condition is caused because there is no gravity acting to pull blood into the inferior part of the body. Cardiovascular regulation is one of the main source of danger for orbital and long term human missions. With carefully designed set of exercises is possible to avoid significantly consequences for the space traveler. However, as the space programs develop and the number of hours in space has augmented, providing extra support for assisting the circulatory system is essential for manned mission success.

The circulatory system consists of a vast network of vessels and arteries capable of irrigating through the blood different organs and tissues. This process is responsible to bring oxygen and nutrients in order to supply energy to cells and systems as well as subtract products of excretion such as sweat, urine, and feces. The circulatory system also works on hormones transportation and, most important, guaranteeing the homeostasis.

This system is closely linked to the blood pressure and blood flow regulation, which can lead to an increase in heart rate and, consequently, to a systemic imbalance of blood pressure. Such process can affect different organs in various ways. Some of them will cause astronaut dizziness, increase of intracranial pressure, optical nerve pressure, and vision impairment. All of them combined or individually could interfere directly into inflight and EVA tasks. Furthermore, on the return to Earth most astronauts experience orthostatic intolerance, which shows symptoms such as lightheadedness, nausea, fatigue, and fainting upon standing or sitting upright when they return from a spaceflight.

This work intends to demonstrate how a preventive technique creating a superficial pressure, built in a suit, which gives astronaut freedom of movement, should be seriously considered. This technique consists of a pneumatic pressure of a corporal segment divided in several zones independent of each other, sequentially inflated. The wearable devise proposed would involve an annular division. Thus, intermittent pressure can be achieved by inflating the segments from distal to proximal suit compartments and, gradually, in each compartment, in order to stimulate the superficial blood flow.

SIMULATION OF CARDIOVASCULAR RESPONSES TO GRAVITY TRANSITIONS IN SUBORBITAL SPACEFLIGHT BY SUCCESSIVE HEAD DOWN AND UP TILTING

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Keywords: *blood pressure, tilting, suborbital spaceflight, orthostatic tolerance, push-pull*

ABSTRACT

As commercial suborbital spaceflight becomes feasible, the extent of physiological loading as well as the inherent medical risks during the launch, stay in microgravity and re-entry constitute critical issues. Of particular importance will be not only the thorough medical screening of potential space voyagers, but also the implementation of analog testing procedures to mimic the transitions of the involved physiological systems. In this context, jet pilots experience a lowering of their tolerance to positive G-loading when the maneuver is preceded by a negative G-load. During jet flight this so called “push-pull” effect occurs at G-load changes within a time span of seconds, whereas during suborbital spaceflight a similar transition will cover several minutes. Therefore, the aim of this investigation was to test an analog model which should partly mimic the physiological changes during suborbital spaceflight.

24 male jet pilots of the Air Force (age range 23-29 years) participated in the tilt testing. The test protocol consisted of the following three successive stages: lying supine (5 minutes), head down tilting (HDT) at 15 degrees for 5 minutes, and head up tilting (HUT) at 70 degrees for 10 minutes. During the tilt testing continuous and noninvasive beat by beat recordings of arterial blood pressure (CNAP®500) and heart rate variability (Polar®S810i at 1000 Hz) were performed. The evolution of the rhythmic components in the recorded time series were analyzed by wavelet based multiscale time-frequency distributions. Repeated measures ANOVA was performed for the means of the cardiovascular variables during the three successive stages.

The main finding was the highly significant (p=0,000) decrease of mean blood pressure by the transition from the supine posture (mean 88,1±11,2 mmHg) to HDT (mean 81,9±12,8 mmHg), and the highly significant (p=0,000) increase of mean blood pressure by the transition from HDT to HUT (mean 96,3±14,9 mmHg). A high inter-individual variability was noticed as strong and weak responders to the posture transitions with loss of consciousness in one subject. Blood pressure fluctuations assessed by the individual standard deviation of the mean blood pressure did not change by the transition from the supine posture (3,0 mmHg) to HDT (p>0,05), but increased highly significantly (p=0,000) by the transition from HDT to HUT (from 2,9 to 4,6 mmHg). The time-frequency analysis of the HRV revealed strong sympathetic activation by the transition to HUT revealed by the emerging dominance of low frequency oscillations around 0.1 Hz.

Our HDT-HUT maneuver is only partly able to simulate the transition from weightlessness to re-entry in the atmosphere, because less G-load impact and transition can be produced than commercial suborbital flight would be able to. Nevertheless, successive HDT and HUT resulted in (patho-) physiologically relevant blood pressure changes even in trained jet pilots supporting the notion of a push-pull effect in the time range of minutes. Our findings indicate that further research is needed to assess the “physiological fitness” for commercial suborbital spaceflight, especially in relation to accompanying medical conditions, age, gender and presumably physiological threshold phenomena.

EXPLORING THE IMPACT(S) OF SPACEFLIGHT ENVIRONMENT ON THE ASTRONAUT'S VASCULAR FUNCTION: A JOINT MOHAMMED BIN RASHID SPACE CENTER AND EUROPEAN RESEARCH INSTITUTES PROJECT

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The impacts of weightlessness and an oxygen deprived environment on the vascular system of astronauts in space travelling are not clearly understood. It has been shown that the spaceflight's environment resulted in vascular damage, especially endothelial dysfunction, as well as the triggering angiogenesis as reported in the recent SpaceX CRS-8 ISS space mission (The Spheroids project). However, the molecular mechanism(s) of those vascular changes are not completely explored. Understanding those mechanisms is critical not only for the development of effective countermeasure tools for the vascular disorders of the space traveler in the future, but also for combating the number one killer diseases here on Earth. In this project, sponsored by the Mohammed Bin Rashid Space Center, UAE partners along with European partners from Austria and Belgium, *the aim is to comprehensively determine the changes that occur in the vascular system of astronauts during and after the spaceflight in the International Space Station (ISS) mission*. Our overall hypothesis is that microgravity, together with hypoxia, result in vascular damage, including endothelial dysfunction. Oxidative stress and inflammation are the main molecular contributors underlying this dysfunction. We also postulate that there is higher expression of several oxidative stress and inflammatory mediators and genes, including inducible nitric oxide synthase (iNOS), hypoxia inducible factor (HIF-1α), E-selectin, Interleukin (IL) IL-8 IL-1β, IL-6, IL-12, Vascular Cell Adhesion Molecule-1 (VCAM-1), and vascular NADPH oxidase (NOX) genes. Furthermore, microgravity and the hypoxic space environment triggers angiogenesis via increasing levels of vascular endothelial growth factor (VEGF), fibroblast growth factors (FGFs), and other pro-angiogenic factors. In addition, we expect that there will be an activation of various cellular metabolic pathways such as glycolysis, fatty acid metabolism among others, which have been recently shown to be key players in the angiogenic process. The vascular endothelial function will be assessed for the astronauts and compare to control individuals (i.e. age and gender matching) on the ground, before, during and after ISS spaceflight using non-invasive clinical diagnostic methods such as flow mediated dilation (FMD), changes in retinal microvasculature, vascular stiffness using Pulse Wave Velocity (PWV), and intimal medial thickness. Furthermore, various oxidative stress and inflammatory biomarkers will be measured from blood samples from both astronaut and control groups. In addition the transcriptomic, targeted genomics and circulatory miRNAs basis of endothelial dysfunction and angiogenesis in astronauts and control individuals before, during and after the spaceflight will be investigated and analyzed. These analyses may result in the identification of novel diagnostic and prognostic biomarkers for cardiovascular diseases. Thus, it will provide more accurate and early diagnostic biomarkers for space travelers leading to more effective countermeasures and better screening tools and therefore serving as an application of personalized medicine.

ELUCIDATING THE IMPACT(S) OF HINDLIMB UNLOADING AND HYPOXIA ON VASCULAR FUNCTION:
A JOINT MOHAMMED BIN RASHID SPACE CENTER AND EUROPEAN RESEARCH INSTITUTES PROJECT

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Spaceflight's environment is known to result in vascular damage, especially endothelial dysfunction, as well as the triggering of angiogenesis (new blood vessel development). In this unique project, sponsored by the Mohammed Bin Rashid Space Center, UAE partners along with European partners from Austria and Belgium, will investigate the impact of hindlimb unloading (HLU) and hypoxia on vascular health in mice. HLU has been used extensively to demonstrate the effects of unloading, as well as to simulate the effects of cephalad fluid shifts as seen during spaceflight. The overarching hypothesis that will be tested is that the *cephalad fluid shifts, together with other factors in the spaceflight's environment, especially hypoxia, result in vascular damage, including endothelial dysfunction.* Specifically, assessed will be the time course of endothelial dysfunction and angiogenic parameters during HLU. The endothelial cells (ECs) of those animals will be harvested and their genomic, transcriptomic and proteomic signatures will be examined and compared between animals subjected to low or normal gravity as well as to hypoxic or normoxic conditions.

The hindlimbs of rodents, will be elevated so that approximately 30° head-down tilt occurs, thus causing headward shifts in fluids and unloading of the weight from the hind limbs. A 30° angle of unloading is used as it is sufficiently provides normal weightbearing on the forelimbs and unloads the lumbar vertebrae. 4 groups of mice with different conditions to simulate the spaceship environment will be used: 1) No hindlimb unloaded condition (+ Gravity) plus normoxia; 2) No hindlimb unloaded condition (+ Gravity) plus hypoxia; 3) Hindlimb unloaded (HLU) condition (- Gravity) plus normoxia; 4) Hindlimb unloaded (HLU) condition (- Gravity) plus hypoxia. The time course of sampling will be as follows: Baseline, following 1, 3, 7, 14, 21 day(s) of HLU and during recovery +1 day and recovery 3 days. The basic measurements of the blood pressure and vascular changes in these mice will be conducted using non-invasive measurements. Furthermore, the mice will be euthanized and tissue samples collected. The endothelial cells (ECs) will be isolated and then further transcriptome analysis carried out. Special attention will be given to genes and biomarkers involved in EC activation and inflammatory status (interleukins, VCAM-1, ICAM-1), senescence, barrier function (junctional molecules), vasoregulation, etc. In particular, alterations in the expression of metabolic pathway genes will be investigated (glycolysis, fatty acid oxidation, glutamine metabolism, mitochondrial function, redox homeostasis, etc). BIOMEXTM allows pathway mapping thus facilitating the identification of metabolic pathway adaptations in the various conditions.

The results of this interdisciplinary proposal are particularly important for understanding the timing and the molecular mechanisms of vascular dysfunction in HLU model that simulate astronaut environment in spaceflight.

POTENTIAL LONG-TERM CARDIOVASCULAR HEALTH RISKS OF SPACEFLIGHT: RESULTS FROM THE VASCULAR SERIES AND FUTURE DIRECTIONS

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Explorations and habitation of the Moon and Mars will expose humans to prolonged periods of altered gravitational loading, social isolation, and elevated levels of radiation. Cardiovascular deconditioning has long been recognized as a consequence of physical unloading during spaceflight resulting in loss of physical fitness and an increased propensity for impaired blood pressure regulation on return to Earth. Largely unknown are other potential cardiovascular health consequences of spaceflight. NASA recognized this knowledge gap for future long-duration, exploration missions, asking the question: can manifestations of sub-clinical or environmentally induced cardiovascular diseases during spaceflight be predicted? The experiments of the Vascular Series (Vascular, Vascular Echo, and Vascular Aging) were designed to obtain evidence regarding structural and functional changes characteristic of increased risk for arteriosclerotic and atherosclerotic cardiovascular disease. Eight astronauts (4 women) in the Vascular study (Am J Physiol 310: H628-H638, 2016) returned from spaceflight with 17-30% increases in carotid artery stiffness ($P=0.005$) and increased insulin resistance based on fasting blood glucose and insulin measurements ($P<0.001$). Routine exercise sessions for the astronauts typically amounted, in this study, to ~30 min/day aerobic cycling or treadmill running. Even with longer sessions of resistive exercise most days, the astronauts had prolonged periods of physical unloading that probably contributed to decrements in cardio-metabolic health. The follow-up study, Vascular Echo, is collecting on-orbit ultrasound data with the French Space Agency (CNES) robotically controlled ECHO device to track changes in arterial properties across 6-months in space. Among other indicators of arterial stiffness, this study conducted the first measurement of carotid-femoral pulse wave velocity in space, with preliminary data showing >10% increase in the first four astronauts. Arterial stiffness properties will also be determined from pulse wave analysis by the Mobil-O-Graph, an ambulatory blood pressure device recently launched to ISS by the Canadian Space Agency. Preliminary data with this device during pre- and post-flight testing observed a 6% increase in pulse wave velocity in five astronauts. Two new measurements will be added in the Vascular Aging study that recently launched its first astronaut. Continuous physical activity and an index of fitness will be derived from the new Canadian Space Agency device Bio-Monitor, a smart shirt to be worn for 72h at various times in the mission. The activity data will be related to quantitative assessment of insulin resistance during oral glucose tolerance testing inflight and on return to Earth. Blood biomarkers will explore dynamic hormonal regulations of cardio-metabolic and bone health. Overall, the Vascular Series experiments are revealing potential long-term cardiovascular health risks associated with placing highly fit and healthy men and women into a microgravity environment for prolonged periods of time. These risks are expected to be further elevated for humans, with increased vascular oxidative stress related to exposure to elevated galactic cosmic radiation, on leaving low-Earth orbit.

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MARSOBSERVER FOR INTELLIGENT MEDICAL CARDIOVASCULAR RISK ASSESSMENT IN SPACE AND EXTREME ENVIRONMENTS ON EARTH

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Long-term spaceflights for scientific and commercial space exploration or even upcoming space tourism cause extreme stress to the human body, especially to the cardiovascular system. Personalized assessment of the cardiovascular system and autonomous nervous system of the astronauts and space tourists might help to indicate the early beginning of functional abnormalities and may avoid critical states of the human physiological system during space flight. The technological development in human physiology equipment is crucial to maintain crew and passenger health during space missions and ensuring that crew members are in the required physical condition to perform their tasks. A digital, intelligent, mobile, and wearable diagnostic assistant system of high usability is developed for multimodal analysis of cardiovascular and autonomous nervous functionality during a space mission.

The electro-optical MARSobserver system (**M**edical **A**rtificial Intelligence Based Cardiovascular **R**i**s**k Observer) detects the electrical heart activities (ECG) via few electrodes at the chest or in Einthoven configuration at the extremities and the arterial pulse wave optically using a finger clip or ear clip at the ear lobe. Both technical measurement modalities, ECG and pulse wave detection, are electronically synchronized and controlled by a microcontroller. After analog-digital conversion the detected signals are stored on a memory card within the detection system. In parallel the data can be transmitted to an external mobile monitor for visual online control and to a data evaluation unit (tablet, laptop, …) for extended data evaluation via USB or wireless Bluetooth transmission protocols.

The sensor unit of the electro-optical diagnostic assistant system in pocket-sized format can be mounted on the user's belt or put into a pocket and it is well prepared for portable applications. The electrical and optical sensors are easy to applicate. The data acquisition system is characterised by a high degree of usability for users without intensive medical training.

On basis of physiological constraints, hemodynamic properties, and the combination of both synchronized electrical and optical measurement modalities the system provides comprehensive and preventive information about the cardiovascular physiological state. In addition the use of artificial intelligence (AI) algorithms support and enable the interpretation of personalized health problems: Based on the ECG recordings AI-algorithms allow the recognition of heart beat irregularities and heart diseases. Sophisticated AI algorithms in temporal and frequency domain can be used as an assistant system for cardiac infarction detection and risk evaluation for sudden cardiac death. Temporal and spectral analysis of the heart rate variability allow a detailed view into the autonomous nervous system with information on the sympathetic-parasympathetic balance, autonomous nervous regulation ability, and stress resistance. The integrated AI-algorithms act as an early warning system and stress indicator. Intelligent data evaluation allows the calculation of cardiac output. Multispectral optical pulse wave detection enables the calculation of oxygen saturation. Continuous photoplethysmographic pulse wave monitoring provides the pulse wave transit time and pulse wave velocity. The analytical combination of optical pulse wave detection and electrical heart signal recording allows the calculation of blood pressure variability. No cuff is needed for determining the blood pressure properties. The intelligent combination of pulse wave transit time, pulse wave velocity and in addition the detailed evaluation of the pulse wave contour allow the calculation of arterial stiffness.
On earth the mobile electro-optical intelligent assistant system in pocket-sized format can also be used for research purposes in extreme environments.

CARCINOGENESIS INDUCED BY SIMULATED EXPOSURE TO SPACE PARTICLES

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Keywords: *Carcinogenesis, particles, space radiation, health risk, EMT*

ABSTRACT

Carcinogenesis of space high *z* and high energy (HZE) particles is one of the top concerns for healthy risks of manned space exploration. Among the HZE particles, -rays are more abundant than any other kind of heavy ions and more intensively ionizing than protons; therefore, their biomedical risks have attracted much attentions even though their contribution to space radiation-induced carcinogenesis remains vague. In order to mimic the outer-space radiation environment, we exposed immortalized human embryonic lung epithelial Beas-2B cells to paticles emitted by ^{241}Am isotopes at a total dose of 0.2, 0.4 or 0.5 Gy with a dose rate of 0.02 Gy every three days. After exposure, we subcultured cells for various passages before examining their tumor-forming ability. We found that, (1) All samples exposed and subcultured for 50 passages formed tumors in NOD/SCID mice but the volume and weight of the tumors formed by fractionated exposure were larger than those of single exposure at the same total dose. Meanwhile, control samples formed only one nodule among 13 injections, which was not a tumor as examined pathologically. (2) Fractionated exposure more prominently induced epithelial-mesenchymal transition (EMT) than single exposure; moreover, EMT was a gradually developing process and became more and more remarkable during subculture. (3) The cancer stem-like subpopulation of CD133+/CD44- cells increased during subculture in a dose-dependent manner and that in fractionatedly exposed samples was relatively higher than the single exposure with the same total dose. All these findings underscore the cancer risk of space -particles.

GAMMA RADIATION INDUCED DNA LESIONS IN IMMUNOGLOBULIN GENES: A PILOT STUDY

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ABSTRACT

Propose: Space radiation has been shown to suppress the adaptive immune response and is one of the main health risks during long-term exploration spaceflights. As a core component of the humoral immune response in the immune system, the immunoglobulin molecules have two kinds of domains: (i) the constant region with relatively constant amino acid sequences and (ii) the variable region with a rich diversity of amino acid sequences. Earlier studies have demonstrated that spaceflights lead to changes in the transcription and expression level of immunoglobulins and somatic hypermutation frequency in the model animals. Researches evaluating the damaging impact inflicted by space radiation on the DNA sequence of immunoglobulin constant and variable regions coding genes can unveil important molecular aspects which are useful to elaborate the mechanism of immune system dysfunctions induced by space radiation.

Methods: In this study, two DNA sequences were used as representative of the immunoglobulin constant region and the variable region coding genes, respectively: the full sequence of Homosapien immunoglobulin alpha-1 heavy chain constant region gene (CA1) and partial sequence of Homosapien immunoglobulin heavy-chain variable region gene (HVA) to evaluate the impact of γ-irradiation. The DNA damage induced by γ-irradiation was detected via electrophoresis and through combination of glycosylase and Sanger sequencing. After DNA samples were irradiated with different doses e.g. 25Gy, 100Gy, and 500Gy, the integrity of DNA strands was evaluated using gel electrophoresis. The base excision repair glycosylases and Sanger sequencing were utilized to detect the base damage sites. This method is very sensitive detect the specific locations of DNA lesions.

Results: Results demonstrated that different doses of gamma-ray radiation induce no significant variation on the integrity of the DNA strand, even at a high dose of 500Gy. One base damage at the site of 125bp of HVA (the germline gene encoding the variable region) was detected at 500Gy gamma-irradiation. However, no DNA damage was detected in CA1 (the germline gene encoding the constant region) under three doses of γ-irradiation.

Conclusions: In summary, this study suggests that germline genes encoding variable regions may be more susceptible to DNA damage than the constant region encoding genes under the same radiation dose and experimental conditions. Compared to the previous studies which only quantitatively reported the extent of radiation damage, herein, this study for the first time identified the random DNA damage sites caused by gamma radiation.

Keywords: Space biology, Gamma radiation, Immunoglobulin, Base lesions, Base excision repair.

BYSTANDER EFFECTS INDUCED BY DIFFERENT LET RADIATION IN HUMAN ASTROCYTE

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***Keywords**: Astrocyte, Radiation, Bystander effects, Exosomes, LET*

ABSTRACT

Purpose : Radiation-induced bystander effects (RIBE) refer to the biological effects caused by irradiated cells that are not directly affected by radiation and can accept the signals generated by irradiated cells, thus showing similar biological effects to those of irradiated cells. The irradiation of human beings in space is nearly 400 times that of ordinary people on the ground. Many astronauts will suffer from radiation damage to varying degrees after the completion of space flight missions, especially brain cells damage, resulting in functional changes of the nervous system. As supporting cells, glial cells are widely distributed in the central and peripheral nervous system, and their radiation damage affects the whole brain and even the function of the body. While studying the long-term effect of radiation, bystander effect has become an important radiation effect which cannot be ignored. In addition, bystander effects of glial cells induced by radiation were different under different types of radiation exposure. Therefore, in this paper, different linear energy transfer (LET) rays were used to simulate the radiation threat in space, and an in vitro radiation model of astrocytes was established, aiming at focusing on indirect long-term non-target effects on brain glial cells of astronauts exposed to space radiation.

Methods : In this paper, human astrocyte U87 MG was taken as the research object to establish an in vitro culture model, and the effect of bystander cells on cell proliferation, cell cycle and apoptosis was studied by using medium transfer experiment under different irradiation parameters. And analyze the molecules that can transmit biological signals contained in the conditioned medium, including proteins, RNA and other functional molecules.

Conclusions : The experimental results showed that human astrocytes U87 MG presented different bystander effects under different LET rays, the bystander effects of promoting proliferation and migration under low LET ray gamma induction, and the bystander effects of inhibiting cell proliferation under high LET ray heavy ion induction. It was also confirmed that exosomes, as an important transfer medium, could deliver proteins, MicroRNA and other biomolecules to bystander cells. Subsequently, we conducted a preliminary analysis on the differential expression profiles of proteins in the exosomes of irradiated cells and verified some related MicroRNAs through qRT-PCR. The results showed that the bystander effects induced by different LET radiation on U87 MG cells to promote or inhibit proliferation were achieved by regulating the pi3k-akt-mtor pathway. This provides a potential molecular target for us to further investigate the mechanism and molecular mechanism of the important bystander effects induced by different types of radiation in the brain. To supplement the theoretical basis for the radiation protection of the astronauts and the medical care guarantee.

VARIATION OF SPACE RADIATION EFFECTS ON HUMANS WITH GENDER AND AGE

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ABSTRACT

Humans traveling to space is due to increase exponentially in the near future, with both fast development of space tourism (Blue Origin, SpaceX, Virgin Galactic, and other companies) and impending manned trips/missions to the Moon and Mars. And while the duration of such trips varies from hours (in space tourism), to days (trips to the International Space Station and to the Moon) and months (Mars), in all cases some exposure to harmful radiation will occur, from both gamma ionizing radiation and solar proton events. One recent interest has been the variation of space radiation effects on humans with gender and age, with studies focusing on the gamma radiation as well as charged particles (Kato et al. 2011, Billings et al. 2014, Babyan et al. 2018). Most interestingly, these investigations have attempted to bring out the different effects of the radiation with ranges of doses and under space conditions depending on both gender and age.

We review the literature on this crucial topic; indeed, it will be of high interest to national space agencies and private space tourism companies to know whether younger or older, male or female, astronauts will be more or less greatly affected by space radiation during short or long trips. We also propose experiments and new lines of investigations to help make further progress in this vital field.

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THE BIOLOGICAL EFFECTS IN DIFFERENT BRAIN REGIONS TO HEAVY ION IRRADIATION

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Keywords: Heavy ion*, Biological effects, Radiosensitivity, Brain regions*

ABSTRACT

In the long-term manned space flight, astronauts face problems such as radiation, microgravity, and narrow space. Heavy ion radiation with cumulative biological effects can cause irreversible damage to the astronaut's body. After long-term flight and exposure in space radiation, astronauts have functional changes in the central nervous system such as fatigue, memory loss, mood changes, etc. However, due to the different cell composition and function between different regions of the brain, the sensitivity of heavy ion radiation may be different in different regions. In this study, rats in the experimental group were irradiated with single high dose of 15 Gy vertically on the back of the head with a $^{12}C^{6+}$ ion beam (primary energy, 165 MeV/u; LET, 30 KeV/μm; intensity, 0.3~0.5 Gy/min). The data showed that atrophy in the parietal cortex and occipital cortex were induced, the number of neurons that have atrophy is significantly different in various regions, the parietal cortex was the most obvious, followed by occipital cortex, while no pathological change was found in the cortical temporal lobe, hippocampus, striatum and cerebellum after 1~3 months of radiation. Rats in the experimental group were irradiated with single high dose of 3.4 Gy vertically on the back of the head with a $^{56}Fe^{26+}$ ion beam (primary energy, 163 MeV/u; LET, 500~1000 KeV/μm; intensity, 0.5~0.7 Gy/min). After one month of irradiation, glucose metabolism in the striatum and pons was significantly decreased, and the degree of striatum was the most significant, glucose metabolism in the superior colliculus, auditory cortex, etc. increased, the superior colliculus is the most obvious. After two months of irradiation, glucose metabolism in the striatum and pons were continued to drop, glucose metabolism in the piriform cortex, hippocampus, etc. appeared to decrease obviously, the degree of piriform cortex was the most significant. After three months of irradiation, glucose metabolism in the striatum was significantly increased while no significant changes in other regions. In conclusion, the sensitivity of different brain regions to heavy ion irradiation is different. The region of glucose metabolism changes after 1~3 months of irradiation shows dynamic changes with time in different regions, the striatum undergoes constant changes in glucose metabolism after 1~3 months of irradiation.

EVIDENT BIOLOGICAL EFFECTS OF SPACE RADIATION IN ASTRONAUTS

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Keywords: *Space radiation, biological effects, astronauts*

ABSTRACT

Astronauts in space are exposed to cosmic radiation that consists primarily of protons and other heavy charged particles. Potential health risks associated with space radiation exposure include cancer, damage in the central nerve system, degenerative tissue effects and acute radiation syndrome. Spaceflight environmental factors other than radiation may also contribute to some of these identified radiation risks. Consequently, it is difficult to determine whether some of the diseases in astronauts, such as cancer, are caused by space radiation or, say, immune dysfunction, or both. Nevertheless, space radiation exposure is considered to be the primary cause for three reported physiological and biological effects in astronauts. 1) Light flash. Light flash was first experienced by Apollo astronauts on their trip to the Moon when the eyes were closed. Scientists later reproduced this phenomenon on the ground by exposing the eyes of test subjects to high-energy charged particles. Whether light flash is associated with permanent eye damage is unknown, but it could be a psychological stress factor since the astronauts are constantly reminded of the radiation environment during space travel. 2) Development of cataract. Like the general population, astronauts will develop cataract as they age, but exposure of the eye to space radiation would cause an early onset of age related cataracts. 3) Chromosome damage in astronauts' lymphocytes detected after long-duration space missions. Since the beginning of International Space Station (ISS) missions, chromosome aberrations in the lymphocytes of ~40 crewmembers pre- and post-ISS missions have been analyzed to estimate the biological dose received during flight. Chromosome aberrations were also analyzed in the pre-flight blood samples after ex vivo exposure to gamma rays to determine individual sensitivities. Statistical analysis of the pre- and post-flight chromosome aberration data indicate that the damage during spaceflight depends on the blood-forming organ (BFO) dose. The difference in the post-flight damage between individuals is also partially explained by the difference in the pre-flight dose-response. In addition, the relative biological effectiveness (RBE) in comparison to the *ex vivo* dose response to gamma irradiation is about 3. These three effects can be related, directly or indirectly, to the various health risks associated with space travel.

COMPARATIVE ANALYSIS OF G-TOLERANCE BY COSMONAUTS ON THE STAGE OF RETURN TO EARTH FROM MISSIONS OF VARYING DURATION

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Introduction. The practice of space missions advocates for the possibility of extended exposure in microgravity. However, even constant use of the set of countermeasures against the negative effects of microgravity cannot abolish all signs of body deconditioning that reveals itself by degraded g-tolerance during reentry and poor orthostatic stability after landing.

Purpose. Evaluation of g-tolerance and detection of cardiovascular deconditioning symptoms developed by cosmonauts descending in Soyuz vehicles after 121- to 200-day missions.

Methods. Analyzed were the data about +Gx (chest-to-back) tolerance of cosmonauts descended in Soyuz vehicles after 52 missions to the Russian segment of the International space station. The missions were accomplished in the period between 2003 and 2016. The cosmonauts were distributed into groups depending on mission duration: group 1 - n=7, 121-150 days; group 2 - n=29, 151-180 days; and group 3 - n=16, 181-200 days. G-tolerance was assessed by analysis of reported subjective sensations and objective indicators, i.e. ECG_{DS} and pneumogram. On the day of landing the cosmonauts were interviewed and subjected to skin examination. Data statistical processing was performed using the Kruskal-Wallis non-parametric test for comparison of independent groups and quality criterion χ^2.

Results. Analysis evidenced for predominately satisfactory +Gx tolerance. Sensations and objective reactions to re-entry varied between the groups. The number of disorders pointing to development of the CVS deconditioning grew with extension of the period in microgravity: visual disorders ($p<0.05$), a slight increase of HR, disturbances of the cardiac rhythm ($p<0.05$) and conduction, change of the end part of the ventricular complex. Frequency of autonomic vestibular disorders also grew with the period in microgravity ($p<0.05$). After landing, all the cosmonauts exhibited signs of orthostatic instability. Syncope, the most obvious manifestation of CVS deconditioning, was observed in cosmonauts on return from 179- and 198-day missions.

Conclusions. Analysis of g-tolerance as a function of mission duration demonstrated significant differences in manifestation of the CVS deconditioning between the groups of cosmonauts. These findings will make the groundwork for preparations for manned exploration missions, and implementation of the idea to create an artificial gravity-based system to counteract with the adverse effects of microgravity. Indeed, adaptation to space microgravity can be prevented by designing space exploration vehicles equipped with AG generators and developing physiologically effective regimens.

CHARACTERISTICS OF THE ACCURACY OF CONTROL OF MOVEMENTS UNDER MICROGRAVITY CONDITIONS

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The number of studies performed recently has shown that hypogravitational motor syndrome is characterized by the changes in all the structures of motor system (Kozlovskaya et al., 1987; Reschke et al., 1997). Motor control disturbances, such as kinematics changes of locomotion and decrease of postural stability etc. are constantly registered after exposure to weightlessness or simulated microgravity (Gurfinkel V.S., 1969; Kozlovskaya I.B., 1981). These changes are caused by development of a number of negative motor disturbances like decrease of muscle tone and maximal voluntary contraction force (Kakurin L.I., 1971; Ch. A. Berry, 1973; Grigoriev A.I. et al, 2004), decrease of accuracy of muscle contraction forces reproduction, increase of motor task execution time, number of errors which form a hypogravitational ataxia syndrome (Chkhaidze L.V., 1968; Chekirda I.F., 1974; Kozlovskaya I.B., 2003).

The goal of this work was to study the effects of long term space flights (SF) and simulated microgravity on the characteristics of precise voluntary movements.

The study was carried out with participation of 30 Russian cosmonauts – members of 146-182 days ISS missions and 12 healthy volunteers who were exposed to 5-days of the microgravity simulation in the Dry Immersion model (DI) (Shulzhenko E.B., Vil-Villiams I.F., 1975). To study the precise voluntary movements control of the force gradation task executed with single-joint isometric plantar flexions has been used during which the subject should differentiate the number of movements (from minimal to the maximal one) with the minimal difference between neighboring efforts. The initial minimal effort that serves as an absolute threshold of the control system and the mean between neighboring efforts – considered as a differential threshold were analyzed. The cases when the subsequent effort didn't exceed the previous one were defined as errors. The number of executed efforts and errors were also analyzed. Experiments were carried out of cosmonauts before flight and on the 3rd, 7th and 10th days after landing. The studies in DI experiment were performed of before, twice in the course of DI and on the next day after its completion. Data were analyzed with method of Wilcoxon nonparametric criteria.

The results of the study revealed significant decrease of precise abilities of motor task execution after SF accomplishment. The number of efforts decreased by 16±7,8% together with 2 times increase of errors' number ($p<0,05$). Variability of parameters under study was also increased after SF revealing the decline of the motor control system abilities.

Under conditions of simulated microgravity the subjects executed the motor task as a rule correctly. However data analysis has shown a decrease of leg movement control system accuracy.

The number of properly selected efforts in the sequence of movements declined by 15–32% and an increase of the differential thresholds ($p<0,05$). At the same time the number of errors also decreased. We consider that to be a result of training.

Thus, exposure to support withdrawal conditions is followed by a decrease of precision in muscle force control.

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HUMAN METABOLIC DOWNREGULATION FOR ENHANCED ±1-G⊕ TOLERANCE: STEPPING-STONE HUMAN EXPERIMENTAL PROOF-OF-CONCEPT

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Keywords:

Metabolic Rate, Torpor, G-Force, Weightlessness, Tolerance

Because gravitational force acts directly on *"mass-ive"* objects, it is of no great surprise that both gravitational (accelerative or decelerative) & reduced gravitational (±1-G⊕) time-dose tolerance decrease with increased body-mass, more specifically, the metabolically active enzyme body-mass.[1-3] Indeed, body-mass, along with body-temperature are the two main variables of the basic & fundamental rate-of-living metabolic life-equation, the equation that determines the metabolic rate of (enzyme-driven) life &, hence, affect the ±1-G⊕ time-dose tolerance.[4-6] In an adult human at basal metabolic rate (BMR), the counter-gravity metabolic *"stress"* contributes ~30% to the metabolic cost.[3-6] Moreover, the lower the MR the greater the time-dose tolerance, so that mammals in metabolic torpor, i.e., in a sub-BMR state, show greater tolerance to gravitational loading & unloading despite the counter-gravitational metabolic costs contributing proportionately more to the metabolic "stress" than at BMR, because there is now more allocated scope for it since the thermoregulatory burden is reduced in dormancy & likewise the active enzyme mass. For example, an adult 75 kg human-sized Siberian black bear in hibernation tolerates as much as 8 months of sedentary behavior.

Furthermore, because metabolic time is the direct inverse of metabolic rate, a profound reduction in metabolic rate will result in a commensurate degree of "biodilation" &, hence, an enhanced ±1-G⊕ time-dose tolerance.[4,7-19] Indeed, human G_Z-tolerance, the second least tolerable of the G-forces increases by 30-40% per °C of core cooling,[20] & the attainment of sub-BMR in dormant mammals does not merely offer enhanced tolerance of both gravitational loading & unloading but a whole host of other, major, stressors, including, e.g., radiation, starvation, isolation, inactivity, infection, hypoxia, hypercapnia, hypo/hyperthermia, decompression illness, etc., etc., & even the stress of time per se since dormancy results in biodilation; 0-G would allow realizing it greatest degree of biodilation.

Hence, one may suspect that if a human could realize animalesque sub-BMR one might similarly offset many, most, of the adverse effects of the space environment on humans in one simple brushstroke, at least for interplanetary transfers, emergencies or nocturnally. Of course, such a feat, let alone the ability to sustain it, remains a three centuries elusive & enigmatic grand-challenge; it's an approach first suggested, of sorts, by Kepler in the early 1600s as a means to tolerate the extreme G-forces of launch.[21-2] Since realizing such a phenomenal capability would be an outright complete "human in space" game-changer, an attempt to realize such a capability should not be merely relegated to the pages of Hollywood sci-fi. Time ago, it was decided to take that critical & cut-chase step towards this lofty goal, & presented here, a stepping-stone glimpse of core-cooling & metabolic downregulation capabilities in a human.

Specifically showcased, albeit attenuated, a constellation of classic, animalesque physiological hallmarks involving on-demand, ultra-rapid & spontaneous (unassisted) temperature- dependent/independent metabolic downregulation, of the brain & viscera to below the circadian nadir, measured with MRI & "pill" thermometry, & (whole-body) sub-basal oxygen downregulation, measured via indirect respirometry.[23] Though this "flash" manifest-variant occurs transiently, it has direct & immediate application for mitigating the risk of both G_Z-induced loss-of-consciousness as may occur in near-term-pending sub-orbital spaceflight, i.e., an expensive downside. Moreover, when combined with rapid & large hydrostatic pressure exposure training, it offers an on-the-cheap & highly effective analog means of unlimited G_X acclimatization. An on-site demo of all these capabilities could be easily & readily staged.

MATHEMATICAL MODELING OF PHYSICAL PERFORMANCE OF COSMONAUTS ON ISS – A STEP TOWARDS THE SYSTEM OF COUNTERMEASURES TO NEGATIVE EFFECTS OF MICROGRAVITY IN MISSIONS TO MOON AND MARS

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A success of an interplanetary mission will largely be determined by the level of the cosmonaut's physical performance. It is advisable to use orbital flights to the International Space Station to clarify the physiological mechanisms of human body functioning in zero gravity. The results of research on the ISS serve as the basis for creating the concept of a system for the prevention of hypogravitational disorders in interplanetary missions. Development of mathematical models of physical performance will allow to use these results when creating a decision support system for training process control in autonomous space missions. Such a decision support system should ensure that the maximum of astronaut's physical fitness is attained by the time of landing on the surface of a celestial body.

Methods

Assessment of the level of performance of 5 cosmonauts was made on the basis of determining the response of the cardiovascular system to the physical activity during an ordinary locomotor exercise. Physical training of astronauts on the ISS was carried out on a four-day micro-cycle. Training on a treadmill consisted of three days performed according to the prescribed protocols, and one day of training according to a personal protocol. In addition to the locomotor training, a second training session was performed on a bicycle ergometer or power trainer, alternating every other day.

Results

The mathematical model is based on the analysis of the response of the cardiovascular system to the performance of four types of locomotion during the three preceding days. The fast running in the active mode of the treadmill, the fast running in the passive mode of the treadmill, the slow running in the active mode and the slow running in the passive mode are analyzed. The physical performance is predicted for the next day on the basis of this information. A mathematical model has been proposed to predict the level of a cosmonaut's physical performance. The physiological cost, calculated using a model based on physical training, was close to the results of the standard test MO-3. At present, human performance models for the entire space mission have been built, and what is especially important, these models are applicable for each day of the first 30 days of the space mission. Usually, in such an early period of adaptation to the conditions of weightlessness, an assessment of the level of a human physical performance, using standard tests under the ISS conditions, is not performed. The first month of the flight can be considered as an example for short flights to the Moon and to lunar orbit.

Conclusion

The physical training parameters affecting the physical performance of a human in space flight are determined and a sufficiently accurate mathematical model of physical performance change for various phases of the space mission is constructed, and that is especially important for the initial phase, which is analogous to the lunar expedition.

Acknowledgments

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NON-24 H ENVIRONMENTAL PERIODS LEAD TO EXTENSIVE ALTERATIONS IN PHYSIOLOGY AND DECREASE IN ADAPTATION

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Circadian clocks control the physiological and behavioral rhythms to adapt to the environment with a period of ~24 h. During space exploration or under other certain special circumstances, humans or other organisms have to encounter cycling environments with non-24 h periods. However, the influences and mechanisms of the extreme light/dark cycles on the circadian clock remain unclear. Firstly, we show that in the filamentous fungus *Neurspora crassa*, some non-24 h conditions even elicit faster growth. However, the ratio of microconidia production decreased in the non-24 h conditions, suggesting that multiple factors are involved in determining the fitness of circadian rhythms to the environment. In human society, a substantial quantity of jobs require non-24 h working/rest or shift schedules, which cause more or less misalignment in the circadian rhythms and disorders as a consequence. In this work, we conducted a sleep deprivation (SD) and non-24 h working/rest schedule (8 h-on/4 h-off) experiment over 10 days in total, and measured the changes in a series of physiological and cognitive parameters. The results show that although the subjects could sleep during the schedule, their sleepiness increased significantly. Actigraphy data suggest that a 12-h schedule might result in chronic sleep deprivation. Along with the increased sleepiness revealed by the Karolinska Sleepiness Scale (KSS) questionnaire, the neurobehavioral Psychomotor Vigilance Test (PVT) data reveal that compared to the control period, the reaction time of the subjects was significantly delayed. The saliva insulin levels were significantly changed in the morning in SD and non-24 h cycles. Salivary biochemical parameters were also altered, including aspartate aminotransferase (AST) and K^+. 16S rRNA-based analysis of the salivary microbiota showed differentially changed patterns in bacteria composition and concentration. Together, these data demonstrate that in different organisms, no-24 h environmental periods might bring about extensive changes in physiology, metabolism and behavior, as well as decrease in the adaptability to the environment.

COSMONAUTS' LOWER LIMBS VENAE CONDITION IN LONG-TERM SPACEFLIGHTS AND DEFINITION OF POSSIBILITY OF ORTHOSTATIC TOLERANCE FORECAST

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Deterioration of orthostatic tolerance of cosmonauts during spaceflights has been remaining one of the most important and still unsolved problems of space medicine. Therefore necessity of reliable and well-timely forecast of orthostatic tolerance is obvious. According to many scientists opinion, the lower limbs veins play an important role in the genesis of orthostatic disorders. That is why forecast of orthostatic tolerance of cosmonauts using lower limbs veins investigations data in spaceflights is relevant.

Purpose of the research: to study cosmonauts' lower limb's veins condition in long-term (6 month long) spaceflights and definition of possibility of the in-flight orthostatic tolerance forecast.

Methodology of calf's occlusal plethysmography provided registration of calf's volume changes under occlusal test. Capacity, distensibility and filling rate of veins were evaluated. Researches were made 1-3 days before the tests during the spaceflight with LBNP (lower body negative pressure) exposure, which provided impartial evaluation of veins condition and allowed to check possibility of cosmonauts' orthostatic tolerance forecast using lower limbs veins investigation data. Plethysmographic researches were made on 33 cosmonauts 60 and 30 days before spaceflights, on the second and on the fifth month of flights, and on the 0 and +8 days after the flight.

Research results. All surveyed cosmonauts had increased capacity and distensibility of veins different degree of manifestation throughout spaceflights. Filling rate of veins was decreased in most of cosmonauts (27 from 33), however its' values was above pre-flight level in 6 cosmonauts.

Forecast of LBNP-tolerance during spaceflights was made on basis of changes in capacity, distensibility and filling rate of veins and combination of all these parameters changes. Individual forecast of LBNP-tolerance confirmed in 27 of 33 subjects (81,8%).

Combination of moderate increase of capacity and distensibility of veins with pronounced decrease of filling rate during spaceflights was accompanied with slight decrease of LBNP-tolerance.
When two signs were observed (significant increase of capacity and distensibility of veins without increase of filling rate), moderate decrease of LBNP-tolerance was observed.
Combination of all three signs (expressed increase of capacity and distensibility of veins as well as increase of veins filling rate) was the indicator of pronounced decrease of LBNP-tolerance.
6 cosmonauts weren't proved to have direct correlation between LBNP-tolerance and intensity of lower limbs veins changes.

For the first time changes of lower limbs veins condition were determined, they allowed to forecast three degrees of decrease of cosmonaut's orthostatic tolerance in weightlessness, which is confirmed in real spaceflight studies by LBNP tests in 81,8% researches. Above mentioned physiological changes should be considered as one of the most significant reasons of orthostatic tolerance decrease in spaceflights.

SIMULATED MICROGRAVITY INDUCES MITOCHONDRIAL DYSFUNCTION AND ENDOPLASMIC RETICULUM STRESS IN RAT CEREBRAL ARTERIES

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Keywords: *Hindlimb unweighting, Mitochondrial dysfunction, Endoplasmic reticulum stress; Cerebral artery*

ABSTRACT

Microgravity-induced cerebrovascular remodeling is reported to play an important role in post-spaceflight cardiovascular deconditioning, and oxidative stress injury has been suggested to occur. To elucidate the underlying mechanism for this condition, we investigated whether simulated microgravity induces mitochondrial dysfunction and endoplasmic reticulum stress in rat cerebral arteries.

Four-week hindlimb unweighting (HU) was used to simulate microgravity in rats. Mitochondrial reactive oxygen species (ROS), mitochondrial membrane potential ($\Delta\psi_m$), mitochondrial permeability transition pore (mPTP) opening, mitochondrial respiratory control ratio (RCR), MnSOD/GPx activity and expression, and mitochondrial malondialdehyde (MDA) were examined in rat cerebral VSMCs. Then the ER stress markers GRP78 and CHOP, as well as the coupling proteins of mitochondria-ER structure were examined. Compared with the control rats, mitochondrial ROS levels, mPTP opening, and MDA content increased significantly, $\Delta\psi_m$, RCR, MnSOD/ GPx activity and protein abundance of mitochondrial MnSOD/GPx-1 decreased in HU rat cerebral arteries, which were reversed by NADPH oxidase inhibitor apocynin and mitochondria-targeted antioxidant mitoTempol. Besides, the mitochondrial fusion protein Mfn1/2 were decreased while the mitochondrial cleavage protein Drp1 and Fission 1 as well as the IP3R were significantly increased by 4-week HU. The Ca^{2+} concentration in cytoplasm were significantly increased while were significantly decreased in mitochondria and endoplasmic reticulum. These alterations were all restored by mitoTempol. Furthermore, CHOP and GRP-7 were increased by 4-week of HU in a time-dependent manner, suggesting the activation of ER stress.

The above results suggest that simulated microgravity resulted in cerebrovascular mitochondrial dysfunction and ER stress, with the former may playing a role in the activation of the later. The cerebrovascular mitochondrial dysfunction and ER stress may be the underlying mechanism for the cerebrovascular remodeling.

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THE PHENOTYPE OF CEREBRAL VASCULAR SMOOTH MUSCULE CELL OF SIMULATED MICROGRAVITY RAT ARE REGULATED BY MITOCHONDIAL OXIDATIVE INJURY AND ENDOPLASMIC RETICULUM STRESS

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Keywords: *Hindlimb unweighting, Mitochondria oxidative stress, Endoplasmic reticulum stress, Phenotype switching, Vascular smooth muscle cells*

ABSTRACT

Recent works suggested that microgravity-induced cerebrovascular remodeling can contribute to cardiovascular deconditioning. Phenotypic switching is a major initiating factor for VSMC proliferation and vascular remodeling under physiological and pathophysiological conditions. This study aimed to investigated whether mitochondrial oxidative stress and endoplasmic reticulum (ER) stress are involved in phenotype transition of vascular smooth muscle cells (VSMCs) of rat cerebral arteries.

Male Sprague-Dawley rats were subjected to 4-week hindlimb unweighting (HU) and the VSMCs were subjected to clinorotation to simulate the effects of microgravity. ER-resident transmembrane sensor proteins (IRE1, PERK, and ATF6), mitochondrial oxidative stress, phenotypic (contractile and synthetic) markers and PI3K/Akt signaling pathway of rat cerebral VSMCs were examined. We found that the levels of p-PERK, ATF4, ATF6, GRP78 and CHOP were increased in a time-dependent manner, while p-IRE1 was attenuated after 12 h of simulated microgravity. The PERK/p-PERK signaling and CHOP were continuously maintained, and were further augmented by PERK overexpression and attenuated by mitochondria-targeted antioxidant MitoTempo. And the mitochondrial oxidative stress and the PI3K/Akt signaling were also activated in HU rat cerebral VSMCs, which were enhanced by PERK overexpression and attenuated by MitoTempo. Compared with controls, the α-SMA, calponin, SM-SHC and caldesmon levels of cerebral VSMCs in the HU group were decreased, while the OPN and elastin levels were increased, and this synthetic phenotype switching of VSMCs was augmented by PERK overexpression and the PI3K activator 740Y-P but reversed by MitoTempo and ER stress inhibitors (PBA and TUDCA).

These results suggest that ER stress in cerebral VSMCs may be caused by mitochondrial oxidative injury during simulated microgravity, and the cross talk between mitochondrial oxidative stress and ER stress as well as the downstream PI3K/AKT/mTOR pathway played an important role in synthetic phenotype switching of VSMCs. This work proposed a novel mechanism for simulated microgravity-induced cerebrovascular remodeling, which may prompt new countermeasures for orthostatic intolerance and even oxidative stress-related disorders.

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EXPOSURE OF INSPIRATORY NEGATIVE PRESSURE BREATHING ON COSMONAUTS DURING SPACEFLIGHT

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Keywords: *lung volumes, inspiratory negative pressure breathing, bioimpedance, fluid shifts, spaceflight*

ABSTRACT

The negative pressure breathing (NPB) has been considered as a preventive means for blood redistribution in sustained microgravity (Tikhonov et al., 1992, 2003; Donina, Baranov et al., 2013). The aim of our study was to investigate the effects of inspiratory NPB (NPBin) on breathing pattern and body fluid distribution in cosmonauts during spaceflight. The lung function (volumes and flows, breath-hold time) was estimated in details before NPBin exposure as well. The 16 cosmonauts participated in the experiment UDOD (in Russian) on ISS: they were examined before, during spaceflight and after landing. All cosmonauts included in the study were well trained for providing the experimental procedure by themselves. The special mask for inspiration through -20 cm H2O resistance was used. Breathing rate, intramask pressure and impedance of head, body and limbs have been monitoring before (5 min) and during NPBin (20 min). The obtained data has shown no significant differences in lung volumes and flows when we compared the preflight and flight sessions (although some cosmonauts demonstrated slightly shifts in volumes in spaceflight but the values were in normal range). The breath-hold time was expectedly increased in microgravity as we have revealed before (Baranov et al., 2009). Generally, NPBin led to significant decrease of breathing rate. No statistically significant changes in body and head impedance at NPBin compared with tidal breathing were found. However, the response to NPBin in cosmonauts characterized by pronounced individual differences as in breathing pattern as in impedance variations. The effectiveness of NPBin as a preventing means for fluid shifts in cosmonauts (astronauts) during spaceflight is discussed and needs the further studies.

MEASUREMENTS OF NEUTRON RADIATION ON THE INTERNATIONAL SPACE STATION USING BUBBLE DETECTORS: MATROSHKA-R AND RADI-N2

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Protection of crewmembers from radiation is a high priority for long-duration human spaceflight, including proposed exploration missions to the Moon and Mars. Radiation in deep space is a mixed field due to galactic cosmic rays (GCRs) and solar particle events. In low-Earth orbit (LEO), protons and electrons trapped in the Van Allen radiation belts also make a major contribution to the radiation field. Neutrons encountered in LEO, for example on the International Space Station (ISS), are produced predominantly by nuclear interactions of GCRs and trapped protons with various elements in the walls and interior components of the spacecraft, and by neutron albedo from GCRs incident on the Earth's atmosphere. Previous investigations in LEO, including experiments using bubble detectors, have shown that neutrons contribute significantly to the total radiation dose received by crewmembers. A significant contribution from secondary neutrons is also expected for exploration missions in deep space.

For over a decade, bubble detectors have been used to characterize neutron radiation for the Matroshka-R experiment, conducted in the Russian segment of the ISS, and for the Radi-N and Radi-N2 activities in the US segment. The goal of the ongoing Radi-N2 activity is to characterize the neutron dose equivalent and energy distribution in multiple locations (Columbus, the Japanese Experiment Module, the US Laboratory, Node 2, and Node 3) over a prolonged period of time, enabling an assessment of potential influence quantities such as location within the ISS, solar activity, and spacecraft altitude. The Radi-N and Radi-N2 results, collected over a ten-year period, suggest that these potential influences do not strongly affect the neutron field. In the same time period, Matroshka-R measurements have been conducted in the Pirs docking module, the Mini Research Modules, MRM1 and MRM2, the Zvezda Service Module, and the Functional Cargo Block (FGB). The modules in the Russian segment vary greatly in size and mass, and exhibit different neutron fields depending on their secondary neutron production.

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OUTLINE OF THE CONCEPT OF RADIATION PROTECTION IN INTERPLANETARY SPACE FLIGHT

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The eve of the 60th anniversary of orbital flights it is time to think seriously about further human entry into space. Certainly, the conquest of the Moon took place half a century ago. But its colonization is still very far away. The main obstacle is radiation from various sources: galactic and solar cosmic rays (GCR and SCR). Radiation «cocktail» in space are dangerous, given the threat of secondary neutrons and gamma-radiation.

An overall conception of human radiation safety in orbital flights is acutely needed. It should take into account all possible short- and long-term consequences of human exposure in space. Possible brain disorders should be verified separately considering the combined effects of other flight factors, which include the hypomagnetic environment in interplanetary flight. It is also necessary to take into account the risk of non-avoiding radiations threats, in particular, during missions on Mars and Moon. In the second case, it is essential to know the minimum and maximum doses in all areas of the spacecraft flight: near-earth flight, interplanetary travel, Mars orbit and stay on Mars with dangerous secondary radiation of neutrons from the ground. Contemporary science is not yet able to predict well the solar proton events and our knowledge of the spectra of cosmic radiation and methods of calculating doses during the passage of various radiation types through the substance are very limited. Therefore, the new concept can be called «the concept of choosing a lesser evil». The ALARA principle, of course, is not canceled, but put on the brink of possible. The structure of the radiation monitoring system on the Martian ship includes a central device for processing and analyzing radiation information from: on-board systems (ground services considering communication delays and ballistic data) and on-board and individual dosimeters, magnetometer, x-ray spectrometers of the Sun and charged particles. It is necessary to provide a channel of information exchange with the crew of the spacecraft.

The concept should provide solutions for the most required tasks: minimizing the risk of overexposure by selecting the most convenient flight period and efficient use of the spacecraft mass with creating shelters from all types of radiation for crew members, including the specifics of neutrons, individual monitoring of crew members, diagnosis of solar flare and the beginning moment of proton flux increase, identification of radiation exposure levels and dose rates in various spacecraft modules and application of the whole stockpile of protection means (radioprotectors, radiomodulators, radiomitigators, hibernation, hypostasis, artificial magnetic field, etc.). In the long-distance flight crew should be a physician specializing in radiation medicine and medical radiobiology. In the first-aid kit one should have medicines that will be a kind of contemporary «summa of radiobiology». The crew should be selected from the most radioresistant cosmonauts (according to geno-and phenotypic criteria).

STUDY ON BIOSENSORS OF SPACE RADIATION

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Key words: Radiation, toxicity, biosensors, promoter, reporter

ABSTRACT

With the development of the space industry, the extension of space time in orbit, and the gradual realization of man's desire to live in space, the radiation will fill the living space. Hundreds of millions of people will are exposed to radiation directly or closely. The results of animal experiments in recent years have demonstrated the hazards of electromagnetic radiation primarily concentrated on nervous system toxicity, induced tumors(especially brain tumors, leukemia) and reproductive system damage. Space electromagnetic radiation exposure has the characteristics of wide area, hidden effect and cumulative effect. In order to quickly and easily detect the magnitude of radiation toxicity, four emerging radiation biosensors have been established. Engineered bacteria sensors carrying four promoters of SoxR, RecA, Cda and SulA and enhanced green fluorescent protein (EGFP) fusion gene related to SOS reaction and oxidative stress reaction, that is the promoter-reporter system. First, the four biosensors were treated with chemical damage agents, they all expressed more green fluorescent protein after stimulation, and then γ-ray irradiation was performed. According to the treatment, the sensor with the highest sensitivity was selected as the SulA promoter engineering bacteria sensor under radiation. The promoter-reporter fusion gene was obtained by PCR and Overlap PCR, and inserted into the vector PUC19, then transformed into *E. coli* DH5α. After double-enzyme digestion and sequencing verification, the successful engineered bacteria sensor were disposed of by chemical oxidant. And physical radiation stimulation be carried out once the result was positive. The results showed that the four engineered bacteria sensors successfully responded to the oxidant hydrogen peroxide and physical radiation, and the green fluorescence intensity gradually increased with the increase of physical radiation dose (0 - 15Gy). Among them, the green fluorescence of SulA engineered bacteria sensor was the most obvious after stimulation compared with the control group. The use of synthetic biology methods to successfully establish a physical radiation sensor based on biological effects, with simple preparation, visibility of results, meeting fast, wide range, online monitoring needs, solving the problem of excessive background value in chemical sensors. The calculation was based on the value of SFU, SFU increased obviously with the increase of radiation dose. All biosensors positively correlated with radiation dose. The next plan is choosing the most sensitive sensor for optimization to improve sensitivity, as a ruler to measure the space radiation dose's damage ability, which has a good reference value for space life safety.

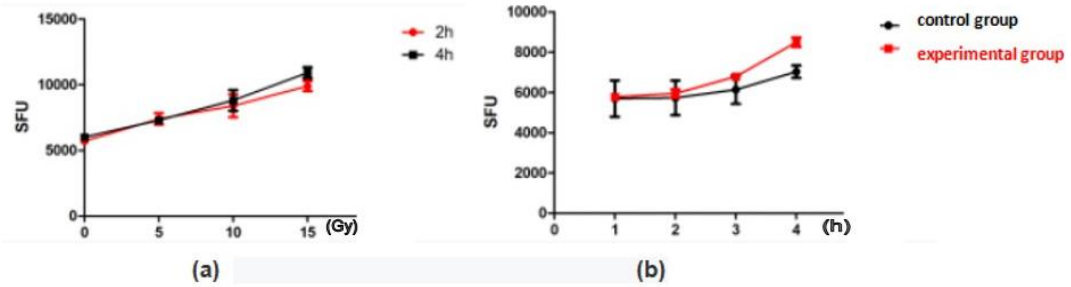

Fig. 1 The change of SFU value of the biosensors after radiation stimulation, PUC19 plasmid loaded with SulA promoter was inserted into host *Escherichia coli* DH5α biosensor strain and the fluorescence changed with time and radiation dose. Experimental group( ) compared with control group( ), while the control group received no radiation stimulation. (a) After stimulation, they were cultured for 2 hours and 4 hours, the SFU value(SFU=(fluorescence intensity value)/OD) varied with radiation dose(0Gy, 5Gy, 10Gy, 15Gy), each group had three repetitions(n=3). (b) The change of SFU with culture time was measured every hour(n=3).

GROUND ANALOG STUDIES – FIRST STEP OF THE SPACE FLIGHTS. OPPORTUNITIES FOR COOPERATION

Tatiana Agaptseva, Elena Tomilovskaya, Mark Belakovskiy, Oleg Orlov

The problem of maintenance the health, performance and optimal psychological state of astronauts becomes even more actual now, at the phase of preparation to interplanetary manned space flights and setting of planetary bases.

However, it is not always possible to study the specific features of the response of the human body to the long-term effect of negative cosmic factors in real space flight conditions. This is due to the lack of time for conduction scientific research, restrictions on the mass and dimensions of cargo to be uploaded and downloaded, safety requirements to equipment used onboard the ISS. Therefore, researchers from all over the world organize special analog experiments with the simulation of negative conditions specific for space flights.

Conditionally, the experiments can be divided into 2 types: those that simulate microgravity (like immersion), and those where main factors are isolation, artificial boring environment and crowding.

The “Dry Immersion” facility designed by the IBMP’s staff in the 1970s, is used to simulate the weightlessness. Numerous experimental studies conducted over many years have shown the high reliability of this method in simulating the effects of weightlessness and its safety for human life and health. The “dry” immersion method has indisputable advantages in simulating the effects of space flight compared to other weightlessness models, for example, antiorthostatic hypokinesia.

Currently, IBMP is conducting a series of experiments with “dry” immersion of 21-day duration. The second stage of this project, with the use of the SRC as a countermeasure against the negative effects of microgravity, is carried out with involvement of 10 male subjects, and will be completed in April 2020. After this, similar “dry” immersion experiments of various duration and with the participation of volunteers of both genders can be organized, taking into account the interests of the international scientific team.

A lot of model experimental studies in isolation have been carried out at the Institute since the 60s of the last century. Among them the following international projects can be mentioned:

- HUBES-94 to simulate some factors and the medical/psychological research program designed for the 135-day MIR mission of the European cosmonaut (EUROMIR-95);
- ECOPSY-95 – conduction of 90-day isolation of the crew consisted of 3 male subjects aged from 21 to 47 years. The main purpose of ECOPSY-95 was to study the role of biological objects, plants specifically, in formation of closed environment.
- SFINCSS-99. Purpose of this project was to obtain experimental data concerning the effects of long-duration isolation and confinement simulating a mission to the International Space Station (ISS) on the interaction within crews with heterogeneous cultural and gender composition.
- «MARS-500», purpose of which was to look closely at the interaction within the human-environment loop and to collect experimental data about health and performance of humans in isolation and confinement simulating the principle differences and limitations of an autonomous mission to Mars.

The Institute is currently conducting the SIRIUS project, which presents a series of isolation experiments of various duration with the participation of international mixed crews. The purpose of this project is to study the psychology and human performance in prolonged isolation in order to support future space research missions.

The results obtained in analog experiments conducted in IBMP are widely used to analyze the consequences of the negative effects of space flight conditions, and to develop new countermeasures, including for future interplanetary missions.

MOON LANDING SIMULATION METHODOLOGY
CONSTRUCTION OF THE WHEELED ROBOT AND ARM MANIPULATOR REMOTE CONTROL MODEL

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The Mathematical simulation dynamic systems support laboratory (MOIDS) team has developed a virtual reality (VR) stand imitating lunar rover remote control. The stand is designed for the application in isolation experiments and programs for the preparation of cosmonauts to prospective lunar missions. Currently, the stand is used in the international isolation mission SIRIUS is being held at the Institute of Medical and Biological Problems.

Modelling real time movement of a wheeled robot requires application of a simplified wheeled transport model. Full range of available approach to wheeled vehicle movement simulation can be classified according to the models into three categories:

1) kinematic models,
2) full dynamic models,
3) simplified dynamic models.

Within the project for the modelling of a lunar rover movement on the surface, the model of third category was used. This is due to the fact that the models of this type, on the one hand, can be realized relatively easily and effectively. The errors that are inherent in such models because of their incompleteness are small enough to allow qualitative (and sometimes also quantitative) modelling of all-important vehicle behavior properties.

The visual imitation assumes the use of a VR-headset consisting of the screen, lenses, case and the system for fixing the headset on the head. VR-headset parameters necessary for the tasks cosmonauts-operators preparation were determined. Besides, image rendering method with a minimal delay, alias effects compensation method and image breaks when the virtual camera is moving have been found and also an algorithm for the image distortion coefficients (image distortion) determination to compensate the headset lenses distortion has been developed.

We also developed the dynamic simulation method of the influences affecting the cosmonaut's body during the movement on the lunar surface has been developed for a three-degree-of-freedom platform (changes of the list and pitch angles and the height are taken into account).

To improve the quality of coordination between dynamic and visual simulation we considered the modified dynamic simulation algorithm considering the predicted movement of the vehicle driven by the astronaut. Experimental verification of the theoretical researches was conducted using a supporting type platform. Also, it is planned to create the training system on the basis of the CF-18 centrifuge used in the Cosmonaut Preparation Center.

The final stand includes the following components:

1) Detailed lunar rover simulation model capable of real time operation;
2) Algorithm of dynamic simulation of accelerations and its realization on a three-degree-of-freedom platform;
3) Full-function software including a lunar surface part and operated lunar rover;
4) Model of controlling the arm manipulator installed on the lunar rover.

RESULTS OF THE INTERNATIONAL STANDARD MEASURES DURING THE VAPER BED REST STUDY

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Keywords: *Bed rest, Human physiology, Analogue environments, SANS/VIIP*

The *VIIP and Psychological Envihab Research* (VaPER) study was conducted in the :envihab facility in Köln, Germany, to assess the effects of 30 days of strict 6º head-down tilt bed rest combined with ambient 0.5% CO_2 on human health and performance. A set of *International Standard Measures* were acquired to evaluate the physiological changes according to the schedule outlined in the table below.

International Standard Measures	**Before BR**	**During BR**	**After BR**
Bone Mineral Density	BR-14		BR+11
Hematology/Nutrition/Bone Markers	BR-3		BR+0
Orthostatic Tolerance Tilt Test	BR-5		BR+0
Vertical Jump	BR-5		BR+0
Maximal Aerobic Capacity	BR-3		BR+0
Muscle Strength	BR-5		BR+2
Immunology	BR-3		BR+0
Postural Equilibrium Control	BR-1		BR+0
Treadmill Locomotion Test	BR-2		BR+0
Intraocular Pressure/Ocular Ultrasound	BR-3		BR+0
Optical Coherence Tomography	BR-3		BR+0
Positive and Negative Affect Scale	BR-13, BR-1	HDT14, HDT28	BR+1, BR+12
General Health Questionnaire	BR-13, BR-1	HDT14, HDT28	BR+1, BR+12

Abbreviations: BR-: bed rest minus X days; BR+: bed rest plus X days; HDT: days in head-down tilt.

The preliminary results indicate that strict head-down tilt bed rest with elevated CO_2 induced mild immunological dysregulation (lymphocyte percentage, T/B cell counts, red blood cell count, and hematocrit). After bed rest, selenium, urinary iodine, and folate status were lower in the subjects of the VaPER study compared to those of a previous 30-day bed rest study at UTMB, which likely reflects the regional differences in diet and nutritional status of the subjects participating in these studies. Five of eleven subjects in the VaPER study were diagnosed with optic disc edema on fundoscopy imaging, and OCT measures of total retinal thickness were 4-5 times greater here compared to those of previous 14-day and 70-day bed rest studies at UTMB. The VaPER subjects who were more susceptible to these ocular changes also tended to exhibit higher negative affect and anxiety during bed rest.

MOON LANDING SIMULATION METHODOLOGY

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SIRIUS is the series of simulations of the interplanetary manned mission to the Moon with duration from 4 months to 1 year, executed in the hermetic chambers of the Institute for Biomedical Problems (IBMP) in order to analyze its medical and psychological aspects. Mission scenario, jointly elaborated by IBMP and HRP NASA, includes transit from Earth to the Lunar orbit, 2 months flying around the Moon to find a place for landing at the analog of Deep Space Gateway station, as well as landing of 4 crew members for on-surface operations. While on orbit that occurs before and after Moon landing, the international crew of 6 (3 men and 3 women from Russia and US) also performs several docks with transport vehicles and remote operation of rovers on the Lunar surface.

According to this Scenario landing on the Moon of 4 crew members (2 men and 2 women) will be simulated for the period of seven days and several egresses are fulfilled by 2 crewmembers in spacesuits. Meanwhile, the orbiting vehicle and the rest 2 crewmembers continue orbiting and provide technical assistance and advice to their mates on the surface. Landing crew utilizes hermetic chamber of 50 m^3 with thick walls for radiation protection as landing module. Crowding in such a small volume could be the source of significant discomfort for the mixed gender landing crew. This module is connected to another hermetic chamber of 350 m^3 for simulation of work in space suits.

The landing scenario dictates reproduction of the basic analog features owing to which the crew will feel very much like they are on a real mission and dismiss from their minds the life outside the modules. It must also have a reason for every event and inspire the crew to teamwork. Therefore virtual reality technology is utilized to create the visual image of the Lunar surface and of the logistics utilized by the crew during landing operations (module, rovers, instruments, etc.). Visualization and interaction with objects are formed by hybrid inertial-optical motion tracking solution developed by Lomonosov Moscow State University's MOIDS laboratory. Also all the operations and tasks that are needed to be executed during landing were based on the Protocol elaborated together with Russian Rocket and Space Corporation Energia.

These tasks include analysis of ergonomic opportunities of the space suit and biomechanics of movements in the simulated Lunar environment. For this purpose the crewmembers in space suits should move straightforward to the target, stop and turn 90° and 180°, execute squats on the knee, lie down and stand up (imitation of recovery from fall), climb the small hill and jump from it, etc. Merely the same set of movements is utilized in the Russian-American space experiment "Field test", in order to analyze functional capacity and the state of main physiological systems of astronauts and cosmonauts immediately after landing on Earth. For the same purpose we are planning to simulate loading and unloading operations, carrying of certain weights (8 kilos on Earth is equal to 50 kilos cargo on the Moon). Also the EVA Protocol includes operations with the certain set of instruments. To achieve realistic operations, real instrument's movements are translated to the virtual space. This approach is called "hybrid" or "mixed reality". The subjects are doing drilling of Lunar regolith, collecting samples, repair mechanical rover, etc.

We expect that these simulations will allow us to elaborate standard testing procedures for the ergonomic assessment of the new space instruments and technologies, work out the peculiarities of interaction of Mission control, landing and orbital crew, develop remote medical support of these operations as well as define their duration and possible workload for the astronauts.

This work was supported by the Russian Academy of Sciences (research projects 63.1, 63.2).

THE UNOOSA HUMAN SPACE TECHNOLOGY INITIATIVE ACTIVITY STATUS IN 2019

Aimin Niu, Simonetta Di Pippo, Luc St-Pierre

The United Nations Office for Outer Space Affairs (UNOOSA) launched the Human Space Technology Initiative (HSTI) in 2010 to promote international cooperation on human space flight and space exploration-related activities, create awareness among countries on the benefits of utilizing human space technology and its applications, and build capacity in microgravity education and research. Building on HSTI, in 2018 the United Nations established 'Access to Space for All', expanding our activities on human space technology, increasing opportunities for non and emerging space faring nations to use UNOOSA as the UN hub for connecting with the public and private space sector.

Since October 2018, UNOOSA organized the United Nations Expert Meeting on Human Space Technology with the theme of providing access to space. The Expert Meeting concluded with recommendations, paving the way for creating new opportunities in access to space. Meanwhile, new achievements have been made, for example: (1) A number of experiment proposals from multiple countries have been selected for flying on board the China Space Station (CSS) under the United Nations/China Cooperation on the CSS Utilization; (2) The Call for Interest (CFI) in utilizing the Airbus Bartolomeo platform has been publicized and interests in utilizing it have been expressed from multiple countries; (3) The project on utilizing the Large Diameter Centrifuge facility at ESA/ESTEC was launched, through UNOOSA and ESA partnership, and the first opportunity to utilize this facility has been announced; (4) The 4th round applications for deploying small satellites under the KiboCUBE have been solicitated and selection has been made, and the 5th round call for applications has been announced; (5) Substantial achievements on utilizing the Dream Chaser of the Sierra Nevada Corporation (SNC) has been made.

With UNOOSA adopting the strategy of Access to Space for All, our focus aims to provide Member States with an increasingly comprehensive portfolio of opportunities to access space. This strategy is being implemented by, among others, carrying out substantial projects under HSTI, which provides physical access to space, and initiating the Open Universe Initiative, which provides access to scientific space data. The on-going projects under HSTI has been providing real access to space through a wide range of modalities including space experiments, space flights, and small satellites, thus continuing to bring benefits of space technology to humanity and achieve the Sustainable Development Goals.

CELLULAR STUDIES UNDER ALTERED GRAVITY CONDITIONS – FROM GROUND TO SPACE AND VICE VERSA

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Life evolved with terrestrial gravity and throughout evolution biological systems have never experienced microgravity conditions that are encountered in space. Hence, applying microgravity and, thus, mechanical unloading in real microgravity or in suitable simulation models on Earth provides unique insights in cell biology. Using this combined approach, we observed gravity-dependent changes in membrane fluidity, arrangement of cytoskeletal elements, gene expression and cell behaviour. We will present data from our life science experiments on the DLR sounding rocket Mapheus (6 min of real microgravity) in combination with ground-based studies (simulated microgravity provided by fast rotating clinostats, hypergravity achieved in centrifuges) that extend previous studies.

The mechanisms mediating gravity influences at the cellular level may have implications above and beyond fundamental biology. Indeed, cellular mechanotransduction is crucial for many physiological processes including musculoskeletal adaptation to mechanical loading and cardiovascular regulation.
To give one example, our preliminary proteomic data already revealed a gravity-induced modulation of senescence-associated proteins by a 2-days exposure of human cardiomyocytes (hCMs) derived from human induced pluripotent stem cells (hiPSCs) on a fast rotating 2D clinostat (simulated microgravity). The mechanism is currently further elucidated by applying transcriptome, proteome and several senescence- associated cell viability assays. Live cell imaging of cardiomyocytes on a clinostat microscope demonstrated a significant decrease in beating activity from 40 to 25 per minute during 1 h in simulated microgravity compared to the static 1g control. Understanding the role of gravity on senescence is of fundamental importance to develop a strategy for prevention of heart senescence of humans exposed to long-term microgravity.

As spaceflight is accompanied by structural and functional deterioration of skeletal muscle, bone, and cardiovascular system that does not fully respond to current countermeasures, cellular studies may reveal underlying mechanisms and novel targets for interventions in space and on Earth.

THE EFFECT AND MOLECULAR MECHANISM OF SPACE MICROGRAVITY ON OSTEOGENIC DIFFERENTIATION OF HUMAN BONE MESENCHYMAL STEM CELLS

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Keywords: *hMSCs, microgravity, osteogenesis, adipogenesis, signaling pathway*

ABSTRACT

Bone formation is linked with osteogenic differentiation of mesenchymal stem cells (MSCs) in the bone marrow. Microgravity in space flight is known to reduce bone formation. In this study, we utilized a real microgravity environment of the SJ-10 Recoverable Scientific Satellite to examine the effects of space microgravity on the differentiation potential of human bone marrow-derived mesenchymal stem cells (hMSCs). hMSCs were induced toward osteogenic differentiation for 2 and 7 days in a cell culture device mounted on the SJ-10 Satellite. Firstly, we collected the samples of osteogenic induction for 2 days in space flight and ground experiments for RNA-seq analysis. The results showed that microgravity mainly affects the expression of cell cycle-related genes in the early stage of osteogenic differentiation of hMSCs, which was accordance with the ground simulation microgravity results. The genes related to stress response (including oxidative stress response, DNA damage stress response and endoplasmic reticulumstress response), inflammatory response and some signaling pathways also changed significantly. In addition, microgravity drives trans-differentiation of human bone marrow-derived mesenchymal stem cells from osteogenesis to adipogenesis. RNA-seq results showed that the expression of 10 genes specific for osteogenesis decreased under space microgravity, including collagen family members, alkaline phosphatase (ALP), and runt-related transcription factor 2 (Runx2), whereas the expression of 4 genes specific for adipogenesis increased, including adipsin (CFD), leptin (LEP), CCAAT/enhancer binding protein beta (CEBPB), and peroxisome proliferator-activated receptor γ (PPARG). In the analysis of signaling pathways specific for osteogenesis, we found that space microgravity plays a dual role by decreasing Runx2 expression and activity through the BMP2/Smad and integrin/FAK/ERK pathways. In addition, we found that space microgravity increased p38 mitogen-activated protein kinase (MAPK) and protein kinase B (AKT) activities, which are important for the promotion of adipogenic differentiation of hMSCs. Space microgravity significantly decreased the expression of Tribbles homolog 3 (TRIB3), a repressor of adipogenic differentiation. Y15, a specific inhibitor of FAK activity, was used to inhibit the activity of FAK under normal gravity; Y15 decreased protein expression of TRIB3. Therefore, it appears that space microgravity decreased FAK activity and thereby reduced TRIB3 expression and derepressed AKT activity. Under space microgravity, the increase in p38 MAPK activity and the derepression of AKT activity seem to synchronously lead to the activation of the signaling pathway specifically promoting adipogenesis.

TRANSCRIPTOMIC PROFILES OF MESENCHYMAL CELLS OF DIFFERENT COMMITMENT UNDER SIMULATED MICROGRAVITY

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Keywords: *sim-microgravity, MSCs, transcriptomic profile, inflammation*

ABSTRACT

It is established that microgravity leads to modification of the cytoskeleton and adhesive properties of mechanosensitive cells.From this point of view, MSCs being involved in the maintenance of tissue homeostasis are of particular interest. After short-term simulated microgravity (sμg) no signs of MSC stress had been identified. Estimation of proliferative activity, ROS level, mitochondrial transmembrane potential, IL-6 production and lysosome activity did not revealed any significant changes. The expression of cell adhesion molecules, cadherin, integrins was elevated during initial first 16 hrs of sμg, being normalized upon further 48-96 hrs, supposing the adaptation to modified conditions. Sμg was accompanied with up-regulation of cell interaction-associated ICAM1, and cell-matrix adhesion genes COL11A1, ITGA1, ITGA8,ITGB2, THBS3, while ITGA6, ITGA2 were down-regulated.

There were no significant alterations of cytoskeleton-encoding genes after 96 hrs of sμg. Rho signaling was characterized by down-regulation of ARHGAP (negative Rho-GTPase regulator) and Rho-kinase genes (ROCK1, ROCK2). In this pathway only Rho-dependent protein (DIAPH1), which is involved in F-actin fibers formation, was 2-folds up-regulated.

The analysis of 84 genes of signal transduction pathways, which govern cell adaption to simulated microgravity, revealed 1,5-4 folds alteration of 36 genes (11 genes were down-regulated, while 25 were up-regulated). According biological function of several gene groups were determined: transcription factors (JUN, MYC, USF1); receptor-associated activators of stress-induced signaling (A2M, CXCL9, F2R, GRB2); regulators of cell cycle and apoptosis (BCL-XL, CCND1, MCL1); inducible regulators of cellular stress (PTPN1, SOCS3, STAT4, STAT5A, STUB1).

The differential expression of 84 growth factor genes in MSCs after sμg and priming was analyzed using Growth Factors RT2 Profiler PCR Array. The examination of time-dependent shifts of MSC transcription revealed the multidirectional changes of paracrine mediator gene expression under inflammatory activation. It's interesting that sμg and priming can induce similar cell reactions of different extention when applied separately, the combined effects of these two factors did not necessarily lead to a cumulative impact as was noted in case of a number of genes (CXCL1,FGF5, GDF10, NGF, VEGFC). Those transcriptional changes may be one of the reasons for the decline of osteogenic potential of MMSCs and attenuation of their migration and adhesion under microgravity.

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TRANSCRIPTOMICS, NF-KB PATHWAY, AND THEIR POTENTIAL SPACEFLIGHT-RELATED HEALTH CONSEQUENCES

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Keywords: *Spaceflight, NF-□B, transcriptomics*

ABSTRACT

In space, living organisms are exposed to multiple stress factors including microgravity and space radiation. For humans, these harmful environmental factors have been known to cause negative health impacts such as bone loss and immune dysfunction. Understanding the mechanisms by which spaceflight impacts human health at the molecular level is critical not only for accurately assessing the risks associated with spaceflight, but also for developing effective countermeasures. Over the years, a number of studies have been conducted under real or simulated space conditions. RNA and protein levels in cellular and animal models have been targeted in order to identify pathways affected by spaceflight. Of the many pathways responsive to the space environment, the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) network appears to commonly be affected across many different cell types under the true or simulated spaceflight conditions. NF-κB is of particular interest, as it is associated with many of the spaceflight-related health consequences. This presentation intends to summarize the transcriptomics studies that identified NF-κB as a responsive pathway to ground-based simulated microgravity or the true spaceflight condition. These studies were carried out using either human cell or animal models. In addition, the review summarizes the studies that focused specifically on NF-κB pathway in specific cell types or organ tissues as related to the known spaceflight-related health risks including immune dysfunction, bone loss, muscle atrophy, central nerve system (CNS) dysfunction, and risks associated with space radiation. Whether the NF-κB pathway is activated or inhibited in space is dependent on the cell type, but the potential health impact appeared to be always negative. It is argued that more studies on NF-κB should be conducted to fully understand this particular pathway for the benefit of crew health in space.

INTESTINAL MICROBIOTA CONTRIBUTES TO ALTERED GLUCOSE METABOLISM IN SIMULATED MICROGRAVITY MOUSE MODEL

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Keywords: *hindlimb unloading, glucose metabolism, intestinal microbiota, inflammation, liver*

ABSTRACT

Exposure to space environment induces alterations in glucose and lipid metabolisms that contribute to muscular atrophy, bone loss, and cardiovascular disorders. Intestinal microbiota is also changed but its impact on spaceflight-related metabolic disorder is not clear. We investigated the relationship between glucose metabolic changes and gut dysbiosis in hindlimb unloading (HU) mouse model, a well-accepted ground-based spaceflight analog. Impaired body weight gain, glucose intolerance, and peripheral insulin resistance were found in 2-4-week HU mice. The blood glucose level could return to normal after the 4-week-HU mice underwent 2-week of ground rest. Reduced abundance of intestinal *Bifidobacterium* spp. and *Akkermansia muciniphila* was observed in HU mice and was found as early as 3 days after the initiation of HU. The ground mice that were cohoused with HU mice showed similar patterns of dysbiosis and metabolic changes as single-housed or cohoused HU mice. Compared to the ground controls, higher levels of plasma LPS-binding protein, altered transcription of pro-inflammatory cytokine *Tnfa* and glucose metabolism-related genes in the liver were observed in HU mice. The supplementation of *Bifidobacterium* spp. suppressed endotoxemia and liver inflammation, improved glucose tolerance in HU mice. The results indicate a causal relationship between dysbiosis and altered glucose metabolism in HU model. The results from cohoused ground mice further indicate that dysbiosis likely plays a major role in HU-induced persistence of glucose intolerance while the contribution of physical inactivity and impaired skeletal muscle glucose uptake/metabolism may be more limited to the induction phase at the 2nd week of HU. In addition, our data also suggest that low-grade endotoxemia and altered liver transcription of pro-inflammatory and metabolism-related genes likely connects gut dysbiosis with glucose metabolism disorder in HU model. Taken together, our results emphasize the importance of evaluating intestinal microbiota in astronauts and its effect on glucose metabolism. It also demonstrates the necessity of taking probiotics to maintain a balanced micro-ecosystem during distant space travel.

TARGETING MITOCHONDRIA FOR PREVENTING UNLOADING-INDUCED SKELETAL MUSCLE ATROPHY AND BONE LOSS

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Key words: muscle atrophy, bone loss, mitochondrial nutrients

ABSTRACT

The bone loss and skeletal muscle atrophy are severe pathogenic disorder in long-time space flight. Mitochondria, the organelles where many vital metabolic reactions proceed, are closely involved in the metabolic disruption under microgravity condition.

We and others previously reported mitochondria act as a central role in skeletal muscle atrophy. We found sedentary mitochondrial dynamics of mitochondrial fusion and fission, and activation of mitochondria-associated apoptotic signaling, was induced by unloading in muscles of unload rodent model, while mitochondrial respiration was compromised earlier than the emerging of atrophy markers, like MuRF1 and Fbx32.

Recently, we reported the involvement of SIRT3-regulated mitochondrial stress in bone formation. During osteoblast differentiation, SOD2 was specifically induced to eliminate excess mitochondrial superoxide and protein oxidation, whereas SIRT3 expression was increased to enhance SOD2 activity through deacetylation of K68, indicating that SIRT3/SOD2 is required for regulating mitochondrial stress and plays a vital role in osteoblast.

We found that reloading protected mitochondria against mitochondrial loss, abnormal mitochondrial morphology, inhibited biogenesis, and activation of mitochondria-associated apoptotic signaling induced in unload rodents. Importantly, our study demonstrates that some agents targeting mitochondria show benefits in preventing or curing muscle atrophy and bone loss, which we defined as "mitochondrial nutrient". Such as a combination of mitochondrial nutrients, including α-lipoic acid, acetyl-L-carnitine, hydroxytyrosol, and CoQ10, which we designed to target mitochondria, was able to efficiently rescue muscle atrophy via a reloading-like action. Resveratrol, another mitochondrial nutrient, efficiently reversed dexamethasone-induced mitochondrial dysfunction and muscle atrophy in both C2C12 myotubes and mice by improving mitochondrial function.

In summary, our study suggests that mitochondrial metabolic remodeling respond earlier than the atrophy & bone loss markers under microgravity, mitochondrial nutrients improving metabolic function is a novel promising approach ameliorating muscle and bone loss.

THE EFFECTS OF SIMULATED WEIGHTLESSNESS ON CALCIUM SIGNALING IN CARDIOMYOCYTE

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Keywords: *simulated weightlessness, cardiomyocyte, calcium signaling, atrophy*

ABSTRACT

Aims: The cardiovascular system is particularly affected by weightlessness, one of the important reasons is cardiac atrophy and reduced cardiac distensibility. However, the direct effect of weightlessness on cardiomyocytes remains unknown. Calcium ions serve as the secondary messenger in many crucial cardiac physiological processes including cellular proliferation, apoptosis, excitation contraction coupling and remodeling of cardiomyocytes. Negative calcium balance was observed in many space missions. However, it has not been reported that how the calcium signal changes in the cardiomyocytes under weightlessness, and what the effect of calcium signal changes on downstream signaling pathways.

Methods: In this research, clinostation was used to simulate microgravity effect, the cell culture flasks were fixed carefully to the rotating panel of the clinostat system, the clinostat was continuously rotated at 30 rpm / min, at 37 ℃ for 48 h. The control group was cultured under the same conditions as the experimental group, but without clinorotation. For Ca^{2+} measurement, the cover slip was transferred to chamber and cells were loaded with 5 uM fluo-4 AM (Molecular Probe) for 20 min at 37 ℃ in Tyrode solution. Cells were then rinsed twice with Tyrode solution and mounted on the inverted stage of a confocal scope (Zeiss LSM 710). Fluorescence excitation was performed using 488 nm laser and detection filters were set at 530 nm. Images were acquired every 3 seconds and analyzed using Interactive Data Language (IDL, Research Systems) software. WB (Western Blotting) was used for detecting the key molecules of signaling pathway, and RT-qPCR (real-time fluorescence quantitative PCR was performed to detect the expression of fetal genes.

Results: Compared with the control group, the calcium released from ER did not change significantly, however, the intercellular calcium concentration and calcium oscillation frequency were increased in the simulated microgravity group. WB demonstrated that the levels of p-CaMKII and p-HDAC4(S246) were increased obviously, which indicated the activation of the CaMKII/HDAC4 signaling pathway. RT-qPCR revealed the increased expression of fetal genes (ANP and BNP), which are the markers of cardiac remodeling. And the cell size detection showed that simulated microgravity led to the atrophy of HL-1.

Conclusions: These results indicate that simulated weightlessness leads to the increasing of calcium signaling, which activates the CaMKII/HDAC4 signaling pathway and promotes the expression of fetal genes ANP and BNP, and results in the cardiac atrophy.

PROTEIN SIGNALING MOLECULES AND AUTONOMIC REGULATION OF HEART RATE IN COSMONAUTS

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The strategy of adaptation of the human body in microgravity is largely associated with the plasticity of cardiovascular system regulatory mechanisms. The purpose of this work was to clarify urine proteome changes associated with the initial condition of the heart rate autonomic regulation mechanisms in cosmonauts who have participated in long space missions. The object of the study was urine samples and 5-minute samples of electrocardiogram (ECG) at rest in twelve male Russian cosmonauts (age 46.5±3.4 years). Collection of urine samples and ECG studies was carried out on 30-45 days before start and on 1st and 7th day after landing.

Depending on the heart rate (HR) and the autonomic regulation parameters in background studies, the subjects were classified into two groups (each consists of 6 subjects): HR in the first group was 60,12±2.21 bpm, in the second group – 75,02±3.31 bpm. About 200 different proteins were determined in urine samples, 34 of which were statistically significantly changed in the entire sample of 12 cosmonauts ($p<0,01$) at the first day after space flight when compared with background data. In addition, 28 proteins changed when comparing +1 and +7 days of the recovery period and 14 – when comparing the background and + 7 day, respectively. From the general proteins list, in accordance with the classification into two groups by the pre-flight peculiarities of autonomic regulation of heart rate, 8 proteins were revealed which are significantly different in groups ($p<0,05$) at different points of the study 02±3.31 bpm. The proteins cadherin-13, mucin-1, alpha-1 of collagen subunit type VI (COL6A1), hemisentin-1, semenogelin-2, SH3 domain-binding protein, transthyretin and serine proteases inhibitors realize a homeostatic role in individuals with different initial type of the cardiovascular system regulation.

The space flight induced urine proteome changes are significantly different in the groups identified by heart rate autonomic regulation peculiarities before space flight. All these proteins regulate the associated biological processes which affect the stiffness of the vascular wall, blood pressure level, the severity of atherosclerotic changes, the rate and degree of age-related involution of elastin and fibulin, age-related increase in collagen stiffness, genetically determined features of elastin fibers.

The increased vascular rigidity (including the aorta) and of myocardium may be regarded as a universal response to various extreme factors. Significant differences in the semi-quantitative analysis of signal proteins between groups with different types of autonomic regulation are explained by a common goal: to ensure optimal adaptation regardless of age and of the genetically determined type of responses to the extreme environmental factors effects.

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EFFECTS OF DWARF FRUIT AND VEGETABLE CROPS ON MOOD AND SLEEP IN CLOSED ENVIRONMENT

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Abstract: In manned deep-space exploration, extreme closed environments can adversely affect the mood and cognition of astronauts easily. Horticultural therapy has been proven to be effective in improving the physical, psychological and cognitive aspects of ordinary people. And variable detections report that sleep and emotion are closely linked as a result of the fact that plants can significantly regulate human's psychology, emotion and sleep through their own color, smell and their release of negative oxygen ions. To assess the effects of using horticultural therapy in closed environment, this study investigated the influence of three kinds of dwarf fruit and vegetable crops (strawberry, purple rape and coriander) on the emotion, cortisol and sleep conditions of volunteers were measured under different light environments. The synergy of plants and light environment on the sleep and emotion of volunteers working in closed cabins of “Lunar Palace I” was analyzed. The results showed that in the long-time closed environment, strawberry was better than purple rape and coriander for the mitigation of crew member’s negative emotions, while the emotion changing of different light environment do not have significant difference. The sleep quality of people is highest when they exposed to the coriander and the warm light environment of 3000K color temperature before bedtime, and the vegetables and light environment have synergistic effect on sleep. On the basis, this study further tested strawberry horticultural operation with different durations on the mood of people in closed environment through indicators including heart rate, salivary cortisol and psychological scales. The results showed that heart rate and salivary cortisol were significantly lower after horticultural operation with strawberry, and the Profile of Mood States negative mood subscale scores of “tension” and “confusion” were also significantly reduced. Furthermore, subjects exhibited significantly lower anxiety levels according to the State-Trait Anxiety Inventory and the most effective duration of horticultural operation for improving mood in this experiment was 15 minutes. These results provided a scientific basis for improving the physiological and psychological conditions of people in the long-time closed environment.

Keywords: closed environment; emotion; sleep; plant; light environment

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INTERPERSONAL INTERACTION AND PSYCHOLOGICAL STABILITY OF CREWMEMBERS UNDER CONDITIONS OF SIMULATED INTERPLANETARY SPACE FLIGHT (EXPERIMENT "SIRIUS-17")

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Crew cohesion is crucial to ensure the success of interplanetary flight. It can be assumed that the greater the gender, racial, national, and cultural differences between people or teams, the greater the difficulty in establishing harmonious and productive relationships [Kanas N. et al., 2009]. The success of an individual's adaptation in an extreme environment, especially in conditions of high autonomy, is closely related to his psychological stability [Vinokhodova A.G. et al., 2005; Solcova I. et al., 2013].

The “SIRIUS-17” experiment was organized in 2017 at the SSC RF - IBMP and simulated a 17-day flight to the Moon. The international crew of 6 people, aged 27-43 years - 3 men and 3 women - participated. The crew performed various operator activities - docking, the Moon observation, etc., and conducted numerous scientific experiments. During the 17-day isolation, a period of 36-hour sleep deprivation was simulated. A 5-minute communication delay was imitated at 5-10th days of isolation.

The objective of our research was to study the influence of factors resulting from the mixed character of the crew (gender, age, nationality, profession, etc.) on various group processes - interpersonal interactions, compatibility, communication and group effectiveness. We assessed also the psychological stability of crewmembers, by measuring of ability to self- regulation, locus of control, resilience and proactive coping (before isolation and after its completion), as well as evaluating the emotional state: mood, anxiety, emotional energy, social effectiveness in the course of isolation itself.

Methods. We used: 1) PSPA, PVQ, Sociometry and “Homeostat” to study interpersonal perception, group dynamics and effectiveness; 2) Locus of control, Resilience, Proactive coping, and Personal growth related to stress scales, as well as STAI, POMS, M.Luscher 8-colors test, weekly assessment of emotional energy, work and social efficiency – to study psychological stability.

Results. Analyzing the data, we focused on studying gender factor. Some gender differences in the structure of individual values were revealed: Self-Direction, Achievement and Power were the most significant for men, Benevolence and Universalism were the most important for women. The crew was highly cohesive by the sociometric criterion of leisure activities, and demonstrated the average cohesion with the formation of subgroups according to gender - by the criterion of teamwork. According to the “Homeostat” results, the subgroups formed by men and in accordance with functional roles in the crew, showed higher effectiveness and compatibility, than other subgroups.

On average, women, compared to men, showed better stress-resistance, more internal locus of control, higher level of emotional energy and low anxiety. At the same time, men showed better resilience and proactive coping. Statistically significant correlations between anxiety level and self-perception structure were revealed, which in turn was significantly associated with the successful adaptation in the group (i.e. sociometric status). In “SIRIUS-17” crew, the participants, critical to themselves and other people (regardless of gender), turned out to be more anxious and less popular members of the group. The data obtained are of great importance for the development of psychological selection criteria for work under long-term autonomous conditions.

The study was performed with the financial support of the Russian Academy of Sciences, project N 63.2.

DYNAMICS OF CHANGES OF ORTHOSTATIC STABILITY UNDER THE INFLUENCE OF DRY IMMERSION

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Assessment of orthostatic stability of astronauts and test subjects gives opportunity to evaluate the influence of space flight factors in real and simulated conditions on the adaptation of human organism to blood distribution. Six healthy men participated in the 3 weeks simulation of microgravity effects in an immersion bathtub. Classical passive tilt-test was carried out on an orthostatic table on the 7th and 14th day of immersion. After 15 minutes of registration of physiological parameters in horizontal position, subject's position was turned to vertical at an angle of 60 °. At the same time he was sitting on a saddle with feet handing unsupported. It is necessary to mention that for the period of conducting tilt-test for 40-45 min, subject was taken from the bathroom and placed on the tilt table. The heart rate (HR), systolic and diastolic arterial blood pressure (SBP, DBP) were registered and the systolic volume (SV).

Results: Comparison of the data obtained during the baseline period with results gained during the 7th and 14th day of stay in an immersion bathtub demonstrate significant changes in a cardiovascular system under of influence of simulated microgravity, increasing with its duration. During baseline the maximum increase of average HR reached 19 beats per min (with 67±11 to 86±9) at the 5th min of transition to vertical position, so it can be assessed as "satisfactory". During the 7th day of stay under conditions of immersion, HR increased much more, to 42 beats per min. (with 74±8 to 116±15). During the 14th day of immersion the increase was even higher, 50 beats per min (with 79±16 to 129±22). The increase of HR was permanently increasing reaching 49 and 61 beats per min at the 15^{th} min of testing (to 123±11 and 140±18 beats pre min). This result was interpreted as "unsatisfactory" and it was only getting worse throughout immersion. During baseline SBP during the tilt-test remained stable and practically did not change. During the 7th day of immersion the biggest increase in SBP was observes at the 5th min of tilt-test, so SBP increased from 129±17 up to 132±18 mm Hg. During the 14th day of immersion increase of SBP was even bigger, from 122±12 to 133±24 mm Hg. DBP also increased significantly from baseline level during immersion period. During baseline we detected the raise of DBP from 74±7 to 86±7 mm Hg. Then for the 7th day of immersion the increase of DBP was higher, from 81±6 up to 91±9 mm Hg. At the same time, during the 14th day of immersion we did not notice a further increase of DBP, on the contrary, pressure was closer to baseline values. During the tilt test, executed prior to immersion, SV decreased from 76±24 to 58±12 and 62±20 ml. For the 7th day of immersion decrease in SV reached 47±13 - 51±14 ml. Even bigger decrease was found for the 14th day of immersion, when SV decreased from 65±18 to 37±10 ml. The data obtained during a 2-week exposure to conditions of the simulated microgravity confirms the significant changes of haemodynamics and decreasing orthostatic stability.

21-DAY DRY IMMERSION: THE SPECIFICITY OF THE EXPERIMENT AND THE FIRST RESULTS

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Keywords: *Dry Immersion, simulated microgravity, space flight analog, support unloading*

ABSTRACT

The Dry Immersion model (DI) developed at the SSC RF – IBMP RAS in the 1970s has been actively used in the field of gravitational physiology and space medicine in Russia for more than 40 years. In recent years, interest in this model has increased due to publication of quantitative evidence of the benefits of Dry Immersion over other models. Studies conducted at the Institute of Biomedical Problems have shown exposure to Dry Immersion is accompanied by the development of changes in the physiological systems of the body, similar in depth and dynamics to the changes observed after short term space flights: postural muscles atony, changes in the order of involvement of motor units, hyperreflexia of spinal reflexes, motor coordination disorders, orthostatic instability, etc. Dry Immersion reproduces such factors of space flight as a supportlessness, axial weight unloading, body fluids redistribution, hypodynamia. The use of DI model is not limited to fundamental studies of the role of gravity in the activity of physiological systems. The model allows to study the efficacy of countermeasure means and methods. So, in recent years, in the immersion experiments the effects of electrical myostimulation of the leg muscles, axial weight loading, as well as support stimulation have been studied. It should be noted that the accumulated experience of DI studies covers the effects of exposures with the duration from several hours to 7 days and describes, respectively, the range of changes characterizing the stage of acute adaptation to weightlessness. Unfortunately, there is almost no information about the peculiarities of the dynamics and nature of the development of chronic adaptation processes. At present, the SSC RF – IBMP RAS has launched a new line of research on the chronic effects of DI in sensory-motor, cardiovascular, bone, immune, digestive and other systems of the body, as well as related medical risks. The subject of the report will be the first results and features of the experiment completed in the spring of 2019 under the conditions of 21-day Dry Immersion exposure.

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METAPROTEOMICS REVEALS FUNCTIONAL ALTERNATION OF GUT MICROBIOME OF CREWMEMBERS IN A SPACE ANALOGUE

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The gut microbiota has been associated with numerous disease, and individual microbiome plays an important role in an individual's response to environment, food, and drugs. Humans' exploration to the deeper space includes a closed life support environment distinct from the living condition on the earth. Multiple factors in a closed life support system, such as food, environmental conditions, and change of mood, could affect the human gut microbiota, which as a consequence may affect the mental and physical health of the host. To explore functional alternations of the gut microbiota, we carried out a study in an analogue space habitat. Stool samples were obtained before, during and after the crewmembers' habitation in the closed space analogue, bacterial cells were washed immediately and stored in -80^{o}C for metaproteomic analysis. After protein extraction and digestion, samples were analyzed though LC-MS/MS. Peptide and protein compositions were obtained through a database search and a label-free quantification process. Using multivariate statistical analysis processes, we revealed shifts of taxon-specific biomass, functional proteins and pathways in response to the habitation. Both commonality and individually different response were observed, suggesting that personalized gut microbiome modulation could be a way for maintaining astronaut's health in space.

OCT-IMAGE ANALYSIS IN MONITORING OF THE OPTIC NERVE HEAD IN COSMONAUTS ON THE INTERNATIONAL SPACE STATION

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Introduction

Ophthalmological examination of some astronauts inflight and after space flight revealed changes in the choroid, retina, and optic nerve. The changes were called Space-flight associated neuro-ocular syndrome (SANS).

Today the eye changes in astronauts are a priority in researches on the ISS. In the American segment of the ISS, modern ophthalmological equipment has been assembled: an ophthalmotonometer, a digital fundus camera, a portable ultrasound machine, and an optical coherent tomograph, which allow to investigate visual functions in the required volume. Pre-trained astronauts and cosmonauts perform these studies under telemedicine control.

The most informative research in assessing the state of the choroid, retina and optic nerve in astronauts is spectral optical coherence tomography (OCT).

Purpose. To estimate the space flight on the optic nerve by OCT-images analysis.

Material and methods. Four clinical observations of Russian cosmonauts are presented in this paper. The Spectralis I Heidelberg Engineers device was used for optical coherence tomography onboard the ISS. The analysis was performed on OCT images obtained in the 12-hour B-scan mode. The thickness of the retina in the region of the optic nerve head was determined in two places. This was the attachment of the posterior hyaloid membrane to the retina. The second place was at the end of the Bruch's membrane. Measuring were made from the Bruch's membrane to the retina in units (μm).

Results. Observation 1. The papilledema in both eyes was well visualized in fundus images and OCT images in all areas of the optic nerve head. Also, the retinal thickness was increased over 360º. The largest value of retinal thickness was in the upper region (477 units) in the right eye. The conclusion was made about the presence of papilledema II degree by Frisen scale.

Observation 2. The right eye (OD). The retinal thickness was increased from 10.00 (347 units) to 8.00 (319 units), which was only 300º in degrees. The variation in retinal thickness ranged from 319 to 479 units. The highest value (479 units) was in the upper region of the optic nerve head. In intact areas, the values ranged from 241 to 250 units. The conclusion was made about the presence of papilledema stage 1 by Frisen scale with prevalence in 300º.

Left eye (OS). The retinal thickness was increased from 3.30 (304 units) to 2.30 (286 units), which was only 345º. The retinal thickness ranged from 286 to 333 units. The largest value (408 units) was in the upper-nasal region of the optic nerve head. In the intact area in the 3.00-hour meridian, retinal thickness was 275 units. The conclusion was made about the presence of papilledema stage 1 by Frisen scale with prevalence in 345º.

Observation 3. The optic nerve head edema was not diagnosed in fundus images and OCT images. The retina thickness was increased in areas where enlarged veins exiting the optic nerve were present. The retina thickness was also increased near the macular region. Druses were there. The retina thickness was increased from the nasal region of the optic nerve in one meridian, and at the upper region in one meridian too. The conclusion was made about the presence of subclinical papilledema.

Observation 4. The optic nerve head edema was not diagnosed in fundus images and OCT images during the over space flight. The OCT-images analysis showed that prominence was +27 and +21 units was in the lower region of optic nerve head on the 36^{th} and 49^{th} days. The conclusion was made about the presence of subclinical papilledema.

Conclusion. Optical coherence tomography of the retina allows to objectivity detect papilledema than by means of fundus-ophthalmoscopy and classify by Frisen scale. Changes in the retina thickness can diagnose as subclinical stage. The OCT-images analysis has great importance in estimate the influence of various factors of space flight on eye.

CHANGES IN VENTRICULAR VOLUMES INDUCED BY SPACEFLIGHT AND CORRELATIONS WITH VISUAL ACUITY CHANGES

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Recent reports on the effect of spaceflight on the brain have shown an enlargement of the brain ventricular volume early after return from space. However, a detailed quantification and a description of its time course and possible reversibility has not yet been investigated. In our prospective study, we scanned 11 cosmonauts, with magnetic resonance imaging (MRI) methods before launch to the ISS and shortly after return to Earth. Of all subjects visual acuity measurements were obtained on the 3rd day of return from space and compared with pre flight measurements. In 7 of all cosmonauts, an additional MRI measurement was acquired 7 months after return to Earth. In addition, 11 control subjects were scanned twice with a similar time interval as between the preflight and early postflight scans of the cosmonauts. T1 weighted anatomical MRI scans were acquired for each subject and timepoint and were processed to obtain CSF volumes of different regions-of-interest (ROI's). These included the lateral ventricles (left and right combined), the third ventricle and the fourth ventricle. The sum of these three compartments was also calculated and used for further analyses. A linear mixed model was used to investigate the changes in ventricular volume across time. The interaction effect was also investigated using a 2x2 ANOVA of group (cosmonauts and controls) and timepoint (preflight and postflight).
Results show that after spaceflight the lateral ventricles increased in volume by 13.3% ± 1.9% (se) and the third ventricle by 10.1% ± 1.1%, which was highly significant. The fourth ventricle, however, did not significantly change in volume over time in cosmonauts, though there was a significant interaction effect of group and time, driven by opposing changes in ventricular volume between cosmonauts and controls. At follow-up compared to the preflight measurement, a sustained increase in volume was noted for the lateral ventricles (7.7%±1.6%) and for the third ventricle (4.7%±1.3%), though compared to the early postflight measurement, a reduction in ventricular volume is clearly noted.

Measurements of visual acuity changes in the first week after flight where compared to pre flight and the differences (usually a subclinical deterioration) showed a significant correlation with the ventricular increases, most clearly observed in the lateral ventricles (p=0.014). Although the visual acuity changes within the cosmonaut crew stayed subclinical, the correlation indicates that ventricular volume increase and visual acuity changes may share a common underlying mechanism.
These results highlight the extent of ventricular enlargement, which was previously noted without exact

quantification. Additionally, our results highlight the reversibility of the postflight changes, but the process of normalisation seems to last a long time, as it is not yet complete at 7 months after return from space. The temporal course of normalisation and the relation of the current findings with clinical parameters such as visual acuity remain to be confirmed in future studies.

DIFFUSION-WEIGHTED MRI REVEALS REVERSIBLE FLUID REDISTRIBUTION IN THE BRAIN AFTER SPACEFLIGHT

Steven Jillings[1,7], Angelique Van Ombergen[2], Elena Tomilovskaya[3], Ekaterina Pechenkova[4], Inna Nosikova[3], Liudmila Litvinova[5], Alena Rumshiskaya[5], Inessa Kozlovskaya[3], Ilya Rukavishnikov[3], Valentin Sinitsyn[6], Jitka Annen[7], Paul M. Parizel[8], Stefan Sunaert[9], Steven Laureys[7], Athena Demertzi[7] Jan Sijbers[10], Peter zu Eulenburg[11], Floris Wuyts[1], Ben Jeurissen[10]

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ABSTRACT

Though long-duration spaceflight is known to negatively impact many systems of the human body, knowledge about its effect on the brain is limited. We therefore performed automated, observer-independent analyses of the brain using diffusion-weighted magnetic resonance imaging (dMRI). dMRI has the ability to probe tissue densities and microstructural changes, something that cannot be obtained from conventional MRI scans.

We prospectively acquired multi-shell high angular resolution dMRI data of 11 cosmonauts before and after spaceflight, as well as 7 months after return (7 cosmonauts). Apparent gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) densities were estimated in each voxel directly from the dMRI scans. Non-parametric statistical analyses were performed using permutation testing and threshold-free cluster enhancement. Results were corrected for multiple comparisons with a family-wise error (FWE) rate of $p<0.05$. Results reveal that the dorsal (top) side of the cerebrum shows decreased CSF densities in voxels located near the longitudinal fissure and the (para)central sulci, while the GM density was increased in these areas. The ventral (bottom) side of the cerebrum shows increased CSF density and decreased GM density near inferior frontal, temporal, insular and inferior occipital regions. A similar effect can be observed in the dorsal and ventral parts of the cerebellum. At long-term follow- up, spaceflight-induced changes seem to reverse and in particular, the changes at the dorsal side seem to recover more completely than the changes at the ventral side.

Our results point towards a fluid redistribution within the cranium, concurrent with an upward shift of the brain. Recovery from these changes is occurring during the months after spaceflight, though normalisation is not yet complete at 7 months after return from space. The differential extent in recovery between the dorsal and ventral sides of the brain, as well as the exact temporal course of recovery require further investigation.

EYE OPTICS STUDY IN EXPERIMENTS WITH DRY IMMERSION

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ABSTRACT

There is evidence that weightlessness could lead to hypermetropic changes in the optical apparatus of the human eye. Taking advantage of the unique experimental setup at the Institute of Biomedical Problems – dry immersion baths providing imitation of weightlessness – we carried out a pilot assessment of accommodation and refraction of the subjects' eye before and after immersion. The first experimental session lasted 5 days (10 volunteers, 25-35 yrs); the second session lasted 21 days (6 volunteers, 25-35 yrs). Auto-refracto-keratometer Righton Speedy-i was used to assess accommodative response, microfluctuations of accommodation, spherical and cylindrical components of refraction in each subject before and after immersion.

The results obtained confirmed the existence of an acute initial phase of adaptation in accommodation regulatory system since, after 5 days of immersion, accommodation response changes were more prominent than after 21 days. Also, there were obtained some hypermetropic changes in refraction, but they appeared to be not statistically significant, indicating the necessity of further investigations on larger number of subjects.

Though, at first impression, the accommodation regulatory system seems to be rather robust, the data collected testify about prospects of studying optical apparatus of the eye in terrestrial modeling of microgravity conditions in addition to cosmic flight investigations.

The study is supported by the Russian Academy of Sciences.

HEMO- AND HYDRODYNAMICS OF THE EYE UNDER CONDITIONS OF EXPERIMENTAL G-FORCE

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ABSTRACT

It is well known that microgravity causes redistribution of peripheral and central blood circulation, leading to blood discirculation of the brain, decrease of venous and lymphatic outflows and, consequently, an increase in intracranial pressure. In certain cases, such processes cause changes in the visual system.
During and after a long space flight, morphological changes of the eyeball of varying severity are observed (impaired microcirculation in retinal vessels, deformation of the choroid, optic nerve edema), resulting in temporary or permanent visual impairment (Stenger M., 2014).
At present, optic nerve edema and associated visual function disorders are recognized as a risk of a long space flight (VIIP syndrome).

For the first time, in the framework of gravitational g-force modeling, as a method for prevention of vascular discirculation in long space flight conditions, comparative assessment of hemo- and hydrodynamics of the eye was carried out.
The study was conducted at the State Research Center of the Russian Federation on the unique scientific installation «Short- radius centrifuge», using overloads in the head-pelvis (+Gz) directions at the foot level up to 2.0; 2.4 and 2.9 units.

9 healthy volunteers aged 25–40 years without ophthalmopathology took part in the experiment. Evaluation of the hemo- and hydrodynamics of the eye was carried out an hour after the experimental sessions.
The blood circulation in the orbit and the choroid was assessed by means of ultrasound Dopplerography with color mapping - Color Doppler Imaging-(CDI) (LOGIQ P7).
The study of eye hydrodynamics was carried out by the method of prolonged intraocular tonography using an electronic tonograph TNC-100 (Russia). The parameters evaluated: true intraocular pressure (Po), intraocular fluid production rate (F), coefficient of chamber fluid outflow (C), Becker coefficient (KB = Po/C).
Statistically significant changes were obtained after the gravitational load of 2.9G.

An hour after the action of artificial gravity (2.9G), the systolic blood flow rate (Vc) in orbital artery was significantly changed. In 90% of cases, blood flow accelerated on average by 53% compared with background data. In the central retinal artery and the posterior short ciliary arteries, the blood flow velocity was comparable to the background value.

The results obtained can be considered as a compensatory regulation of hemodynamics of central genesis in response to the artificial gravity. High adaptive stability of the autoregulatory mechanism of retinal blood flow was revealed.

A comparative study of the results of electron tonography showed that after the action of the gravitational load of 2.9G, in 8 subjects the intraocular fluid production rate decreased by on average 35%.
The results obtained could provide the basis for further study of artificial gravity in interests of terrestrial medicine. For example, neurophysiological mechanism of regulation of ocular hemodynamics and hydrodynamics is the field of research on the pathogenesis of degenerative diseases of the visual system, including glaucoma.

The study is supported by the Russian Academy of Sciences.

INFLUENCE OF THE FIVE-DAY "DRY" IMMERSION ON THE EYE HYDRODYNAMICS

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ABSTRACT

At present, the condition of visual system in microgravity, in particular intraocular fluid dynamics, is the subject of close study. Hydrodynamics of the eye determines the quality of the intraocular fluid (chemical composition, electrolyte balance, pH), which determines the morphofunctional state of the main optical structures of the eye - the lens, cornea, vitreous body, retina.

It is known that microgravity in space flight, and microgravity modeling on the Earth cause a change in the central hemodynamics, which in turn leads to the development of compensatory changes in the water balance due to the depressor reflexes, including the Henry-Gower reflex. The basis of the Henry-Gower reflex is an efferent hypothalamus response, which manifests itself as inhibition of vasopressin and arginine release, increase in the glomerular filtration rate, increase in diuresis, suppression of spontaneous and angiotensin-II induced thirst, and decrease in sympathetic innervation.

Changes in central regulation of antidiuretic hormone and sympathetic innervation are likely to affect local regulation of intraocular hydrodynamics.

To study hydrodynamics of a healthy eye under conditions of immersive microgravity causing compensatory activation of the "hypothalamus-pituitary-adrenal" system and to assess the adaptive stability of intraocular hydrodynamic balance.

The subjects were 10 male volunteers aged 24-40 yrs, without ophthalmopathology. The results of electronic tonography of the eye and the dynamics of hypohydration were evaluated using water balance values.
Results In all subjects, the analysis of water balance in the course of acute adaptation to microgravity revealed the dynamics caused by the action of the depressor Henry-Gower reflex.
On the first day of the "dry" immersion, in 7 subjects, a pronounced negative change of water balance (180% on average). In 6 subjects, fluid intake decreased by 50% of the age norm and averaged 1050 ml.
At the first day after the immersion, in 12 eyes a decrease in the rate of intraocular fluid production (F) was found. The reduction of F varied from 40% of the background value (5 eyes) to a pathologically low value (7 eyes) causing trophic changes. The value of the trophic coefficient (TC) worsened in 12 eyes, in 6 eyes the decrease being clinically significant. By 7th day after the immersion, the values of intraocular fluid dynamics were comparable with the background ones.

The study of eye hydrodynamics in 5-day "dry" immersion experiment made it possible to evaluate the effect of compensatory hypohydration of the organism on the state of intraocular hydrodynamic balance. For the first time, a comparative analysis of electron tonography of the eye before and after the action of artificial microgravity was carried out.

It is assumed that, under conditions of "dry" immersion, the hypohydration reflex (Henry-Gower reflex) causes changes in intraocular hydrodynamics, the severity of which is in direct correlation with the strength of the compensatory hypothalamic effect on the system "Antidiuretic hormone - Angtotensin-II".

The study is supported by the Russian Academy of Sciences.

BIOMARKER OF ADAPTATION RESERVE OF VISUAL SENSORY SYSTEM

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ABSTRACT

The practical tasks of medicine in ensuring the military-professional activities of specialists working in special and extreme conditions require the search for new constructive and expertly significant methods in assessing the functional state of a person in order to optimize preventive measures aimed at maintaining professional longevity.

According to modern concepts, a key element in the structure of the general mechanism of an organism adaptation to environmental influences is the dynamic neuro-functional equilibrium of the central nervous system, as a result of the integral interaction of sensory systems with the central nervous system.

In conditions of long-term action of stress factors of the environment, e.g. in a long-term space flight, there are various pathogenetic mechanisms for the development of maladaptation of the organism. The problem of studying the adaptation under stress could be solved by a comprehensive assessment of the central nervous system condition, including the study of the in vivo morphofunctional characteristics of sensory systems.

Among them there are a method of optical bioimaging – the optical coherent tomography (OCT) of the retina, which allows a non-invasive investigation of the morphology of all layers of the retina and the choroidal shell of the eye and use the retina as a “window” into the central nervous system.

A number of studies have shown a direct correlation between changes in the thickness of the opposing zones of retinal neuroglia and the degree of development of neurodegenerative diseases of the central nervous system, such as Alzheimer's disease, Parkinson's disease and others.

OCT was used to establish a direct correlation between age and morphometric parameters of retinal neuroepithelium.

Histological studies revealed an average rate of nerve fiber loss in the optic nerve of 0.5% per year. Retinal neurons are also susceptible to age-related loss, in terms of average values the rate does not change over time. The reason for the vulnerability of neuroepithelium of the retina, as suggested, is the high metabolic demand of the tissue in combination with reduced resources.

It is known that, in conditions of chronic stress, the functional state of the body is characterized by specific metabolic and neurochemical adaptation changes, such as a decrease in the level of activity of neurotransmitters that regulate, in particular, neurogenesis in the visual sensory system.

In this regard, it can be assumed that morphometric changes in certain structures of retinal neuroglia in correlation with age can be considered as a marker of maladaptation of the functional state of the organism in a comprehensive assessment of the dynamic state of the central nervous system under the conditions of long-term stressful environmental factors.

BRAIN NETWORKS AND DEEP LEARNING APPROACHES FOR ASSESSING THE IMPACT OF MICROGRAVITY AND THE EFFICACY OF REACTIVE SLEDGE JUMPS COUNTERMEASURE TO SLEEP QUALITY

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Keywords: *Brain networks, Deep learning, Graph theory, Neuroplasticity, Sleep quality*

ABSTRACT

Maintenance of optimal cognitive and physical well-being is of crucial importance for long-term space missions and isolated environments such as the International Space Station. Sleep quality is often degraded in such extreme environments due to circadian rhythm changes, weightlessness and increased stress. However, there is not a unique pattern of these changes which may vary in relation with individual characteristics.

Aiming to identify how microgravity affects sleep physiology and whether these changes are ameliorated thanks to the reactive sledge jumps countermeasure, we employed polysomnographic (PSG) data recorded during a 60 days, head-down tilt (6°), bed-rest study. The study employed 23 male individuals aged 18 from 45 years old, assigned either to the control or to the sledge group. The data analysis compared several experimental instances (14 days before bed-rest, 21 and 50 days during bed-rest and 7 days after the study finalization).

The analysis involved manual sleep staging according to the guidelines of the American Association of Sleep Medicine (AASM). Then, we estimated cortical functional connectivity from regions of interest (ROI) belonging to resting-state networks (default-mode, sensorimotor, visual, auditory, executive control) and the thalamus. Then, quantification of the integration and segregation properties of these resting-state networks and the functional significance of each ROI was performed through graph theory concepts. Finally, we performed time-frequency heart-rate variability analysis and extraction of autonomic arousal markers from chin electromyography and blink activity. The aforementioned data were used to quantify the sleep quality of each participant. Then, predictive models based on both traditional data mining (Support Vector Machines) and deep learning (Convolutional Neural Networks) were performed. The output vector used for validating the method's efficacy was a composite set of sleep-related (adenosine, prolactin) and metabolic (insulin) biomarkers as well as macro-architecture (arousal, awakening, k-complex, spindles) features.
The microgravity effect seems to be evident on both groups. It is mainly conceptualized as a sustained activation of specific cortical regions, which are also correlated with arousal markers. These results are most evident in the control group which did not trained with the proposed countermeasure. Despite being an ongoing study, early results from the artificial intelligence component, demonstrate the efficacy of this methodology for predicting changes in sleep quality which may also be used on earth applications.

IDENTIFYING RESTING STATE NETWORKS ALTERATIONS IN LIGHT SLEEP DUE TO MICROGRAVITY CONDITIONS.

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Among several alterations of human physiology in weightlessness changes in sleep architecture is also important, especially for long duration missions in deeper Space. In the present study, the alterations in resting state networks (RSNs) during N1 sleep stage due to the microgravity are investigated. The beneficial role of the reactive sledge jumping is also examined as well as the reversibility of the detrimental effects of microgravity during the recovery period. Resting state networks are brain networks that increase their functional connectivity due to lack of external stimuli. In the present study, the RSNs under consideration are the Default Mode Network (DMN), Executive Control network (EC), Auditory Network (AN), Visual Network (VN), Sensorimotor Network (SM) and Salience Network (SN). In order to identify alterations in the functional connectivity of the networks, electroencephalographic (EEG) sleep recordings from 18 adults (aged 18-45) were analyzed. They participated in a bed-rest study which took place in the premises of 'envihab' of the German Aerospace Center in Cologne, Germany. All participants remained in a 6^0 head down tilt (HDT) supine position on bed for 60 days. The EEG recordings were acquired 14 days before the initiation of the bed-rest (BDC-14), 21, 35 and 50 (HDT21, 35 and 50) days during the experiment and 7 days after the completion (R7). Data were preprocessed with the use of 3^{rd} order Butterworth digital filters and through Independent Component Analysis (ICA) for the elimination of noise sources. The artifact-free data were divided in 30-seconds long successive, non-overlapping epochs, which were then manually scored and the corresponding sleep stage was identified by an experienced sleep expert. Following these steps, the cortical activations were reconstructed through the sLORETA inverse solution as implemented through Brainstorm software. For the estimation of the cortical functional connectivity, HERMES MATLAB toolbox was used for the calculation of the appropriate connectivity metric. Finally, Network Based Statistics (NBS) was used for the identification of the statistically significant edges. The results were visualized using BrainNet viewer.

SLEEP GENE EXPRESSION IN SIMULATED MICROGRAVITY ENVIRONMENT

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Adenosine (ADO) is involved in homeostatic sleep regulation in a site-dependent way. The adenosine receptors A1R and A2AR are the main mechanism for adenosine somnogens effect. Specifically, when A1R is inhibited in wake-promoting neurons, then sleep is induced, while activation of this type of receptors in the lateral preoptic area concludes to wakefulness promotion. The environment of space is known to cause variations in many processes that are at a homeostatic equilibrium under Earth's normal gravity. One of the conditions primarily responsible for these variations is, apart from cosmic radiation, the absence of gravity. However, the absence of gravity in space, also named zero gravity, can be simulated on Earth as microgravity, or weightlessness. Simulated microgravity is used in the study of the effects of microgravity on cellular systems on Earth. In this direction, bedrest studies have been developed and are widely used in order to assess the effects of microgravity on the ground. They allow researchers to test techniques to counteract the negative effects of living in space.

Herein, investigation of microgravity effects will be carried out on human sleep gene expression.

Therefore, 23 healthy volunteers were remained in a mandatory downhill with the head 6° downward for 60 days in the European Space Agency in Cologne. Blood samples were collected and multi-channel sleep records were performed at specific interval time during experiment. ADO measurement was implemented using immunochemical techniques. Sleep recordings were processed into stages according to the International Sleep Academy rules. Further sleep data analysis was performed. The analysis included calculating the degree of synchronization between the electrodes and analyzing their functional organization based on graph theory. To evaluate the correlation between the global graph properties and adenosine biomarkers, Pearson correlation coefficient was used, since there was adherence of these variables to the normal distribution curve (Kolmogorov-Smirnov). For all statistical tests an error alpha = 5% was set, that is, the test results were considered statistically significant at $p < 0.05$. In order to analyze data Rstudio statistical package was utilized.

Overall, the results showed a statistically significant over or underexpression of ADO gene over the time. Furthermore, they indicated a statistically significant positive correlation between the adenosine values and the length of the characteristic pathway by examining the values before the start of the experiment in combination with the values obtained on the 14th day of the experiment ($r = 0.37$; $p = 0.0253$), the 30th day ($r = 0.35$; $p = 0.0344$) as well as the mean values in these two different experimental phases ($r = 0.36$; $p = 0.0267$).

The results demonstrate that the lack of gravity affects the physiology of the human body by altering the biomarkers associated with metabolism (adenosine) and the functional association of distant brain regions. These two indicators are associated with positive correlation with each other and are affected by immobility and microbial conditions. In the future, the proposed offsets should have some effectiveness, so emphasis should be placed on designing new, more efficient vehicles to allow for a smoother adaptation of the organization to long-haul aircraft.

A MIXED REALITY PLATFORM FOR PERFORMING A COMBINATION OF COGNITIVE AND PHYSICAL TRAINING IN SPACE

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Keywords: *Mixed Reality, Cognitive training, Physical Training, Countermeasure*

ABSTRACT

Cognitive and physical wellbeing is a key aspect for astronauts and cosmonauts. Extreme conditions in outer-space require small reaction time, optimal perception and excellent physical health. All aspired space-travelers receive a vast preparation before the initiation of every mission. Also, a variety of countermeasures have been proposed to minimize the microgravity effects in the human body and mind. The present article presents an innovative approach to cognitive and physical training through a mixed reality platform combined with continuous monitoring of the user. The tool is implemented through the Microsoft HoloLens device for providing a multisensory (video, audio, tactile) stimulation for performing cognitive tasks (memory, attention, fluid intelligence, reaction time and sensorimotor tasks) while the participant is simultaneously engaged in aerobic, flexibility and muscle strength activities. All the exercises offer variations by simultaneously requiring from the participants to perform aerobic, weight-lifting and flexibility tasks. The training difficulty is almost infinitely adapted in order to continually provide brain and body with a challenging task that requires engagement in novel learning procedures and avoiding expectation or habituation effects. The participant's activity and vital bio signals are continuously monitored with smart IoT devices. Mixed reality improves the user's interaction with the platform, which combined with real-time alerts offers an innovative and pioneering approach introduces a powerful training tool ideal for mission preparation and on-board the space station use.

PERCEPTION OF TIME AND DISTANCE IN MICROGRAVITY

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Keywords: Cognition, Human performance, Distance perception, Time perception

The otolith organs of the vestibular system sense linear acceleration, and their signals are used by the central nervous system to compute velocity, i.e. the product of distance and time. Because gravity is a linear acceleration, changes in gravitational level affect the measurement of linear acceleration by the vestibular system. Therefore, our hypothesis was that the perception of distance and time might be altered in the microgravity.

Perceptions of distance and duration were investigated in 9 subjects during five ESA and CNES campaigns of parabolic flight. Distance estimates were reported verbally or demonstrated actively by subjects pulling on a rope with the eyes closed toward a memorized target [1]. Subjects were estimating distances ranging from 1 to 6 m along their x-axis (forward), y-axis (right, left), and z-axis (up-down). Duration estimates were computed from reproduction and production of durations ranging from 3.5 to 14 s using the Perspective equipment developed for the International Space Station (ISS) [2].

Distance estimates using both verbal reports and blind pulling were significantly different between normal gravity (1 g) and microgravity (0 g). Compared to the 1 g measurements, the horizontal distance estimates in 0 g were longer for distances < 4 m and shorter for distances > 4 m [1]. Vertical distance estimates were asymmetrical 1 g and symmetrical in 0 g. Durations were significantly underestimated in 0 g compared to 1 g.

These results suggest that changes in the gravitational level alter the computation of distance and time by the central nervous system based on the linear acceleration signals provided by the vestibular system. They also support the existence of an overlapping perception of time and space in a specific brain system, as evidenced by recent neuroimaging studies [3]. Experiments on perception of time and distance are currently ongoing on ISS crewmembers to verify if the same effects are observed after long-duration exposure to microgravity.

A BIOINSPIRED ANTIMICROBIAL SURFACE AS PREVENTIVE ACTING TECHNOLOGY FOR SPACE AND EARTH APPLICATION

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Keywords: *antimicrobial surfaces, bio-inspired, microbial contamination, planetary protection.*

ABSTRACT

A highly promising approach for preventing/ reducing microbial loads in sensitive areas are antimicrobial surfaces. In these areas, high humidity and temperature levels are causing microbial contamination - endangering human health, health of organisms e.g. in bioregenerative life-support systems as well as technical equipment. Antimicrobial surfaces are beneficial

- in spaceflight - w.r.t. activities in confined environments in LEO and during exploration activities - to support breeding activities of e.g. algae in bioreactors, biological experiments and to meet the COSPAR planetary protection policy
- as well as on Earth - in hygiene areas during medical activities and food handling, in swimming baths, bathrooms etc.

For confined environments in space as well as on Earth, antimicrobial surfaces must be free of any toxic substance, otherwise higher non-target organisms would be affected. This means, synthetic chemicals, silver, copper etc., as used until now, are not a suited solution, which in addition might lead to resistances of the bacteria to these toxic substances and are acting rather unspecific.

A suited alternative in this context are bioinspired technologies as using antimicrobial peptides from nature (e.g. from frog skin etc.), immobilized on surfaces. High flexibility concerning the microbial target, low toxicity and an absence of resistances are the main advantages.

Thus, goal of the ESA-funded project BALS (Bio-inspired antimicrobial lacquer for space) was the development of a new innovative antimicrobial acting lacquer based on peptides. Project partners were OHB System, Fraunhofer Institute for Manufacturing Technology and Advanced Materials (IFAM) (both Bremen, Germany) as well as the German Aerospace Center, Institute of Aerospace Medicine (Cologne, Germany).

At the symposium, an overview about goals, technology and test results (w.r.t. antimicrobial activity, adhesion on substrates as well as absence of effects on higher organisms) of the BALS activity will be given.

SPACE DEBRIS MITIGATION AND REMEDIATION AS A KEY FOR SUSTAINABILITY IN OUTER SPACE

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Keywords:
space debris; mitigation and remediation; sustainability in outer space; space law; active debris removal mechanism

Abstract

The worldwide communications have significant impacts on modern life today. These communications have become an inherent characteristic of developed society and rely on sustainable use of outer space. An important point is the space environment is extremely vulnerable and must to be protected. This became unmistakably clear through serious confrontation with the problem of space debris.

Space debris matters because modern life depends on the uninterrupted availability of space infrastructures. The risks posed by space debris propagation create challenges for sustainability in outer space.

The main purpose of this article is helping to increase the awareness of the challenges to space sustainability and therefore, to examine the legal basis for the protection of sustainability in outer space and elaborating the vital need on international cooperation for active space debris removal system.

Methodology is based on the national practice of States in connection with the international regulations in a comprehensive and holistic approach thorough examination of various literature, international legal documents, and online sources, such as international space agencies (ESA, NASA, ROSCOSMOC, etc.)

My research is based on two hypotheses. Firstly, it elaborates the current legal regime that regulates the field of outer space affairs. The question is the lacunae in existing space law regime on the implementation of space debris removal mechanisms. Secondly, the possibilities of space-faring countries to reach intergovernmental consent on cooperative space debris solutions.

By January 2017, the Space Surveillance Network (SSN) is tracking around 23000 space objects larger than 5–10 cm and by 2019 the number has increased - more than 24500 space objects orbiting the Earth. As results obtained space debris became a very critical problem. Unfortunately, most of the proposed methods for space debris removal are not successfully functional or not effective enough.

Mitigation actions have been identified and propagated into international and national standards by various spacefaring nations, such as China “China Requirements for Spacecraft Space Debris Mitigation (ISO 23312),” Australia “Australia’s Satellite Utilization Policy – 2013,” U.S. “National Space Policy, and others.” However, effects on space debris mitigation to date are insufficient.

Mitigation actions have been identified and propagated into international and national standards by various spacefaring nations. As a result the usability of outer space in the long-term requires action of both mitigation and remediation measures for existing and future space missions. As the enforcement of such technical measures depends on adequate regulation, they need to be approached from a legal perspective.

Remediation mechanism has been developed but there's still do not exist mechanisms that impose legally-binding obligations upon States. International space law neither contains the specific prohibition of creating space debris by space activities of States and international organizations nor imposes an obligation on both to remove space debris once it has been created. Nowadays the implementation of space debris removal measures on a voluntary basis only.

Thus, the removal mechanism is needed, but this sets a global challenge that can only be resolved by the joint efforts and consent of all spacefaring nations.

STYLE FEATURES IN CREWS' COMMUNICATION WITH MCC

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A standard daily summary, that is issued by Russian space psychoneurologists and contains cosmonauts' behavior analysis based on their communication with MCC, often mentions an accordance or discordance of cosmonaut's verbal behavior with his individual communication style. However, this concept has not been clarified and remains an empirical idea dependent on the analysts' personal opinions.

Searching for objective points of support that would enable to classify the individual communication styles of cosmonauts' speech, we tested V.Satir's communication styles classification. The choice was made due to the connections of styles distinguished by Satir, with stress: upon her concept, these styles would manifest themselves under stressful conditions. This principle aligns with IBMP's methodical position used since 1970s: communication analysis should be used for personal psychological state diagnostic.

Satir's approach is focused on effectiveness of information exchange, problem-solving ability versus substitution of an information flow by discussing relationships (social regulation) or emotions (affects). Every style description includes communicant's initial setting description as well as specific psychological defenses and coping strategies.

Therefore, on the first step of our study (on-board Content experiment being part of the Russian scientific program since 2015), we were detecting initial settings and linked coping strategies correlates for each style. One of the main goals was to find a relatively stable communicative style for each subject, to be able to compare its manifestations during space flights made by each subject during participation in space program. The used method was manual quantitative content analysis. Types of statements to be included in coding instruction were determined by a group of experts as a result of a preliminary search for coping strategies and manifestations of styles from Satir's approach in communication between crew and MCC. Main group of subjects included cosmonauts from ISS 43/44 - 54/55 missions, N=15.

While V.Satir described five communication styles (blaming, placating, computing, distracting, leveling), we detected domination of three of them in cosmonauts' speech. Crewmembers expressing computing communicative style, are informing MCC in a minimally necessary way, demonstrating understanding and rational consent with MCC's decisions, expressing confrontation, initiative and demands relatively rarely. Meanwhile, affective component of communication was quasi absent and social regulation component was weakly pronounced. Cosmonauts expressing computing style expressed stable and self-controlling verbal behavior.

Second frequently met style was blaming, based on an initial intention to put problems under control while finding the responsible and influencing their activity. Emotional reactivity typical for blaming in cosmonauts was described by a number of authors (e.g. N.Kanas) as emotional transfer. Blaming style manifested in confrontation and humor (as a way to get distanced from the problem situation). Blamers' confrontation included initiatives and problem-solving solutions, expressed in demands.

Placating was noticed in three subjects; this style involved higher dependence on MCC. While cosmonauts expressing this style were mostly performing their first flight, they relied on Earth's help, and in statements analyzed, there were more demands then in other styles, and mentions of lack of time were more common as well. The overall information exchange was higher in this style, as these crewmembers waited for the MCC's approval of their activity. These cosmonauts asked for MCC's additional advice and guidance (searched for support) more often than others.

Increase of blaming and placating styles in crewmembers' communication may possibly be a negative indicator that might lead to corrections in MCC's communication with the crew and additional psychological support activity for crewmembers.

SUBORBITAL SPACEFLIGHT PRE-LAUNCH PHYSIOLOGICAL PRIMING FOR ENHANCED +G to 0-G SWITCHING TOLERANCE

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Keywords: Suborbital Spaceflight, G-Force, Weightlessness, Tolerance

ABSTRACT

Suborbital spaceflight passengers will experience a cycle of extreme gravitational loading-unloading-reloading for which no simulation can completely prepare them for. Put simply, down-gearing from 4-G to 0-G & then 0-G to 6-G is not merely a delta-G of 4-G & 6-G, respectively, because passing in & out of 0-G results in unique sensations that few ever experience let alone get to practice for. As pointed-out by Anne Fisher, professional astronaut-physician, *"Your first moments in space are not always your best. The switch from 3-Gs of acceleration to sudden weightlessness can be abrupt enough to induce vomiting. I could feel the blood rushing & in 30 seconds I was going 'uh oh', I am going to be one of the ones who is not going to feel good."* The real world possibility that such *"sudden"* switching &, moreover, from significantly more hostile +G-position, i.e., +4-G_x & +4-G_z may result in a higher-than-expected incidence of passengers actually vomiting probably shouldn't be underestimated, especially because most passenger will be passed their physical prime & under the stress of being strapped to a real-world rocket may mess up their anti-G straining manoeuvers; Fisher experienced less than 2-G_z & was exceptionally well trained. In addition, a *bystander vomiting ripple effect* could ensue in such a close confines, completely ruining the experience & resulting in some major public relations disaster.

In response, outlined here, two new & novel anti-G countermeasures that might substantially mitigate such untoward ill-effects & possibly even allow expanding the passenger pool since it would also reduce the risk of G-LOC. Specifically, the technical approach involves off-setting otherwise unprepared & disadvantaged physiological systems by manipulating peripheral blood flow-volume & core-temperature to effect a more favorable, say, primed position & retard-offset G-related adverse effects. The strategy simply involves triggering & accentuating the diver's response, by means of modified pre-launch breath-holding manoeuvers to ensure a lingering diver's response on launch. The on-demand priming effects include prompt, substantial & largely lingering: cephalo-thoracic *blood-shift*; extensive body-cooling, including brain & visceral cooling of several degrees; cold-induced peripheral vasoconstriction; increased time-dose hypoxia tolerance; &, increased tolerance of G_x *chest-crushing*.[1] Indeed, one notes, that human +G_z tolerance, a poorly tolerated force, is decreased by as much as 30-40% per degree increase in core-body temperature.[2] Though the technique requires a minimum of 5 minutes to effect, pre-launch, maximum advantage requires a *warm-up* time of some 20-30 minutes. Once learned the technique permits i-limited self-practice & a considerable conditioning improvement potential; biofeedback is possible via novel non-invasive physiological gadgetry. Although the two priming techniques require some specialized training beyond what is taught in technical freediving courses they can be learned in a gradual, stepwise-personalized manner & do not involve extremely prolonged breath-holding nor deep-diving. Considering the stakes & the amount of money invested by both service-providers & customer alike, reducing the risk of untoward events seems warranted. The technique has yet to be tested under actual suborbital spaceflight conditions.

HUMAN METABOLIC DOWNREGULATION FOR ENHANCED ±1-G⊕ TOLERANCE: STEPPING-STONE HUMAN EXPERIMENTAL PROOF-OF-CONCEPT

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Because gravitational force acts directly on *"mass-ive"* objects, it is of no great surprise that both gravitational (accelerative or decelerative) & reduced gravitational (±1-G⊕) time-dose tolerance decrease with increased body-mass, more specifically, the metabolically active enzyme body-mass.[1-3] Indeed, body-mass, along with body-temperature are the two main variables of the basic & fundamental rate-of-living metabolic life-equation, the equation that determines the metabolic rate of (enzyme-driven) life &, hence, affect the ±1-G⊕ time-dose tolerance.[4-6] In an adult human at basal metabolic rate (BMR), the counter-gravity metabolic *"stress"* contributes ~30% to the metabolic cost.[3-6] Moreover, the lower the MR the greater the time-dose tolerance, so that mammals in metabolic torpor, i.e., in a sub-BMR state, show greater tolerance to gravitational loading & unloading despite the counter-gravitational metabolic costs contributing proportionately more to the metabolic "stress" than at BMR, because there is now more allocated scope for it since the thermoregulatory burden is reduced in dormancy & likewise the active enzyme mass. For example, an adult 75 kg human-sized Siberian black bear in hibernation tolerates as much as 8 months of sedentary behavior.

Furthermore, because metabolic time is the direct inverse of metabolic rate, a profound reduction in metabolic rate will result in a commensurate degree of "biodilation" &, hence, an enhanced ±1-G⊕ time-dose tolerance.[4,7-19] Indeed, human Gz-tolerance, the second least tolerable of the G-forces increases by 30-40% per °C of core cooling,[20] & the attainment of sub-BMR in dormant mammals does not merely offer enhanced tolerance of both gravitational loading & unloading but a whole host of other, major, stressors, including, e.g., radiation, starvation, isolation, inactivity, infection, hypoxia, hypercapnia, hypo/hyperthermia, decompression illness, etc., etc., & even the stress of time per se since dormancy results in biodilation; 0-G would allow realizing it greatest degree of biodilation.

Hence, one may suspect that if a human could realize animalesque sub-BMR one might similarly offset many, most, of the adverse effects of the space environment on humans in one simple brushstroke, at least for interplanetary transfers, emergencies or nocturnally. Of course, such a feat, let alone the ability to sustain it, remains a three centuries elusive & enigmatic grand-challenge; it's an approach first suggested, of sorts, by Kepler in the early 1600s as a means to tolerate the extreme G-forces of launch.[21-2] Since realizing such a phenomenal capability would be an outright complete "human in space" game-changer, an attempt to realize such a capability should not be merely relegated to the pages of Hollywood sci-fi. Time ago, it was decided to take that critical & cut-chase step towards this lofty goal, & presented here, a stepping-stone glimpse of core-cooling & metabolic downregulation capabilities in a human.

Specifically showcased, albeit attenuated, a constellation of classic, animalesque physiological hallmarks involving on-demand, ultra-rapid & spontaneous (unassisted) temperature- dependent/independent metabolic downregulation, of the brain & viscera to below the circadian nadir, measured with MRI & "pill" thermometry, & (whole-body) sub-basal oxygen downregulation, measured via indirect respirometry.[23] Though this "flash" manifest-variant occurs transiently, it has direct & immediate application for mitigating the risk of both Gz-induced loss-of-consciousness as may occur in near-term-pending sub-orbital spaceflight, i.e., an expensive downside. Moreover, when combined with rapid & large hydrostatic pressure exposure training, it offers an on-the-cheap & highly effective analog means of unlimited Gx acclimatization. An on-site demo of all these capabilities could be easily & readily staged.

METABOLICALLY-ENHANCED OFF-NOMINAL G-TOLERANCE: PRELIMINARY EXPERIMENTAL PROOF-OF-CONCEPT

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Keywords: G-Force, Weightlessness, Tolerance, Metabolic Rate, Body Temperature

ABSTRACT

Chronic gravitational unloading (e.g., weightlessness) & loading (e.g., acceleration & deceleration) tolerance, depends on metabolic rate. Tolerance is reduced in large compared to small animals due to an allometric (mass-size-related) counter-gravity metabolic cost (CGMC), specifically, enzyme-driven *mass* action.[1-6] According to the fundamental metabolic rate equation, $CGMC_{1\text{-}G\oplus}$ contributes, e.g., ~35% & ~10% to the minimum existential or basal metabolic rate (BMR) of a 100-kg human & 10-g mouse, respectively. The discrepancy is due to the absolutely greater enzyme *mass* of larger animals, even despite a lower mass-specific metabolic rate (MR_S). Furthermore, because MR is the (direct) inverse of elapsed (metabolic) time per unit mass, a time-dose tolerance effect manifests: the more prolonged the off-nominal exposure the greater the desynchrony between the many & varied metabolic *clocks*, leading to progressively greater pathological dysfunction.[7-8] However, it is known that animals in torpor, i.e., sub-BMR, can be rendered effectively *immune* to far-off $\pm$1-$G_\oplus$, even large ones, e.g., hibernating bears tolerate months of near-complete inactivity, considered a natural biomedical model of chronically protected gravitational unloading. Torpid states can so profoundly slow metabolic activity &, thus, metabolic time that animals seem metabolically *down-sized & suspended in time*. Indeed, many key pathways are temporarily uncoupled, *broken,* or remodeled for greater protection.[9] This is not altogether unsurprising since the best way to protect a complicated *metabolic machine* is to temporarily disassemble it. Metabolic depression also results in some (variable) core-body cooling even in large hibernators, which in itself boosts tolerance since MR largely depends on temperature. For example, human $+G_z$-tolerance, which is poorly tolerated, decreases by as much as 30-40% for a mere degree increase in core-body temperature, equivalent to a ~5-7% increase in MR.[10] Yet, a 100-kg hibernating bear downregulates MR to ~30% BMR with no more than 3-4°C of core-cooling, i.e., temperature-independent effects are at play, suggesting a large, untapped, off-nominal tolerance potential.[11-13] And, since torpor is expressed in an extremely varied range of mammals & known to confer unmatched-enhanced tolerance of a myriad of other major metabolic stressors, if humans could express this state they might similarly manifest broad-spectrum biomedical protection, i.e., *game-changer*.[14] Interestingly, because the CGMC contribution to the metabolic bottom-line in torpor expands vis-à-vis the thermoregulatory burden, 0-G should result in the most profound torpor. This might yet mean that it may be possible to completely offset that weightlessness & transform it into a novel space-life-support resource to maximize (time-dependent) biological shielding & conservation of resource, vital given the nature of the environment. Interestingly, the lowly MR, including cooling, of hibernating bears stands on par with that of similar sized breath-hold diving seals, an environment in which the CGMC is near-collapsed, leading some to suggest that *"the bear may 'dive' into hibernation"*, so that this strategy might be the long suspected pathway that might open the possibility to sustain this state.[12,15-19] Presented here, seal-like down-powered metabolic capabilities of some human divers.[20] Described, a telltale constellation of classic physiological hallmarks that typify this state: spontaneous, ultra-fast & profound reversible temperature-dependent/independent sub-BMR with core-body cooling.

CHARACTERISTICS OF NATURAL COLONIZATION BARRIERS OF PERIODONTIUM IN DRY IMMERSION STUDY.

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Adverse factors of the environment cause the tension of adaptation systems, leading to a change in the homeostatic parameters of the human body, changes in metabolic and physiological processes. Studies on the effect of chronic psychoemotional stress on periodontal tissue showed that stress can provoke microcirculatory disorders and disrupt metabolic processes in periodontal tissues.

As a model of microgravity, 5-day dry immersion was used in the work. The studies were conducted with the participation of 20 healthy male volunteers, who were familiar with the experimental program, who underwent a medical expert commission of the SSC RF-IBMP RAS and signed the Informed consent to participate in the research. The test subjects had an age from 19 to 26 years, their average height was 175.6±6.4 cm, body weight 70.2±4.6 kg. According to the research program, they were in an immersion bath in size of 256 x 148 x 110 cm filled with water for 5 days, the temperature of which was constantly maintained at 32-34^{0}C. Studies of periodontal tissues were carried out on the 1st day (background), on the 5th day of immersion (ending) and on the 7th day after the end of dry immersion. All studies were performed on an empty stomach, before brushing of teeth, in the supine position in the immersion bath, on the 7th day after immersion – in sitting positions. Hygiene of the oral cavity was carried out in the morning and in the evening, the teeth cleaning was carried out for three minutes with a toothbrush and toothpaste, individually used by each tester under normal living conditions. After eating, the interdental spaces were cleaned with silk flosses.

A comprehensive study showed the predisposition of periodontal tissues examined in the DI to the development of inflammatory diseases. Under the influence of microgravity, a violation was observed in at least two barriers to the colonization of periodontium. This is the barrier formed by the commensal microflora (increasing of periodontial pathogenic microflora), and the initial manifestations in the barrier formed by the humoral immunity (IgA, SIgA, IgM). Reduction of intensity of capillary blood flow in the tissues of periodontal disease, which can lead to tissue hypoxia, aggravates neurodystrophic disorders and further reduces the barrier functions of periodontal disease. The data support previous results and allow to draw a conclusion that adverse environmental factors cause tension of adaptation systems, leading to a change in homeostatic parameters of human body, changes in metabolic and physiological processes. Studies of chronic psychoemotional stress effect on periodontal tissues have shown that stress can provoke microcirculatory disorders and disrupt metabolic processes in periodontal tissues.

RUSSIAN BIOMEDICAL TECHNOLOGIES FOR LUNAR MANNED MISSIONS: CURRENT STATUS

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The Moon exploration requires the improvement of existing and the development of new biomedical technologies aimed at ensuring the safety, health and work capacity of crewmembers working on lunar orbital stations and lunar bases. Approbation and testing of these technologies are carried in the frame of «Long-term Program of Scientific and Applied Research and Experiments Planned for the Russian Segment of the International Space Station». Their results are used to develop advanced means and methods for control and prediction of the functional state of crewmembers, providing medical care, preventing adverse effects of flight factors on the human body, habitat monitoring, etc.

For example, during several flights onboard telemedicine complex for remote dental examination of cosmonauts has been successfully tested. Further development of telemedicine technologies for space medicine is planning in the studies of states of ENT-organs, periodontal and dental hard tissues. For the study of the human immune status during space flight the onboard automated complex “Immunolab” is currently being developed.

One of the main problems of crews’ biomedical support is improvement of the system for preventing adverse impacts of microgravity on human physical performance. In order to substantiate the protocols of locomotor trainings the experiment using treadmill and special restrainer for simulating lunar gravity is preparing to implementation on the International Space Station. At present, work is carrying out to substantiate the requirements to onboard automated system of physical trainings management which will provide formation of individual training regimes for each crewmember basing on data on his/her actual physical condition and on expedition forthcoming tasks.

The study of characteristics of crewmembers joint activity is actual problem of psychology of small groups. For this purpose it is planned to develop the complex “Homeostat” to obtain data on the effectiveness of cosmonauts interaction during joint operator performance.

An important aspect is ensuring the environmental safety of manned space flight. In this context, the urgent task is development methods and means for habitat microbiological monitoring. In particular, for express-diagnostics of microbial contamination of interior surfaces and equipment of the ISS the onboard complex “Electronic Nose” has been developed and successfully tested in flights. At present, it is being upgraded for expanding its diagnostic capabilities.

It should also be noted that the analysis of ways for implementation of perspective biomedical technologies testifies the increasing tendency to using onboard automated decision support systems during space flights.

More detailed description of the technologies will be presented in the paper.

TO SPACE AND BACK: CHANGES IN SURFACES PARAMETERS AND INTRACRANIAL POSITION OF THE BRAIN AFTER LONG-DURATION SPACEFLIGHT

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Keywords: microgravity; human spaceflight; surface-based morphometry; cortex

ABSTRACT

The impact of spaceflight and microgravity on the human central nervous system and its function has been investigated in only a handful of studies. Our group recently demonstrated prolonged changes in all three brain tissue types directly after long- duration space travel and even seven months after return to Earth [2]. Now we aimed to investigate the structural impact of long-duration spaceflight by means of surface- based morphometry parameters (VBM/SBM) and also look at brain position within the skull after preliminary findings indicated a potential shift.

We prospectively studied ISS cosmonauts from 2014 to 2018. Cosmonauts were scanned three times: once prior to launch ('preflight', n=12), once shortly after re- entry ('postflight', n=12; mean (SD): 9.9 (2.9) days after return, mission duration average 191 days in space) and once at follow-up on the longer term ('follow-up', n=7; mean (SD): 210 (47.3) days after return). All participants were assessed on a 3T MRI (Discovery 750; GE Healthcare, USA) For each time point, a high-resolution sagittal T1-weighted 3D fast spoiled gradient echo (FSPGR) image was acquired. Data quality assurance, preprocessing and analysis was performed with the CAT12 Toolbox within the SPM12 framework (Wellcome Department of Cognitive Neurology, London, UK). A separate quality analysis of the structural data to detect acquisition artifacts and excessive head motion during the structural scanning was performed using MRIQC [3]. Surface parameters like cortical thickness, sulcus depth, gyrification index and cortical complexity were resampled to a 32k mesh template space after smoothing with a gaussian filter. Analysis of intracranial cortical grey matter position for each time point was performed after skull-based coregistration for all participants in native space. A repeated measures ANOVA after longitudinal preprocessing with the three time points (baseline, return, follow-up) was used to test all parameters. Resulting T-contrasts were considered significant using threshold-free cluster enhancement (TFCE) at $p<0.05$ False Discovery Rate (FDR). We were able to verify an upward shift of the human brain inside the skull after long- duration spaceflight

which returned to baseline at follow-up. Cortical thickness postflight increased over the entire convexity of the cerebrum and at the same time was reduced along the base of the cortex mainly along the temporal gyri. This pattern was then reversed for the comparison of postflight with follow-up data and returned to baseline levels. For sulcus depth we found a reduction postflight compared to preflight over the convexity of the brain and around the temporal poles. This pattern also normalised at follow-up. In addition, we were able to see a significantly increased cortical complexity at follow-up compared to postflight around the temporal poles and larger degrees of gyrification around the base of the cerebral cortex predominantly in the inferior temporal and occipital gyri.

In our interpretation the results reflect the mechanical stress and wide-ranging shape changes of the brain and the cerebral cortex in particular during and after long- duration spaceflight. We attribute all of the findings to a hindered resorption of cerebrospinal fluid in microgravity resulting in an expansion of csf spaces inside the cortex and around the base of the skull thereby lifting and expanding the cerebrum and at the same time compressing the caudal grey matter compartment.

MOTION SICKNESS SYMPTOMS CORRELATED WITH BODY TEMPERATURE REGULATIN IN VESTIBULAR STIMULI

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Keywords: *Linear acceleration, Coriolis acceleration, Motion sickness susceptibility, body temperature regulation,Submaximal uptatke of oxygen*

ABSTRACT

Background Core body temperature was found to be elevated about 1° in astronauts during long-term space flight and suggested microgravity changes the set point of body temperature. And some case studies hinted the potential link between vestibular system, body temperature and sense of body ownership. We hypothesis the decrease of vestibular afferent in space may be one of the reasons for this phenomena. The relationships between temperature regulation and other vestibular stimuli physiological responses were explored in this study.

Methods Twenty-two male subjects (age: 30±4yr; height: 172±2cm; weight: 68.5±5.3kg) participated in this study. They were exposed to maximal 15min parallel swing stimuli with max linear acceleration at 4.95m/s2 and maximal 4min Coriolis stimuli (the roll speed of the rotary chair was 180°/s, the yaw or pitch speed of the head was 30°/s and at 0.125Hz frequency). The interval between these two kinds of stimuli was at least one week. Their aerobic fitness was measured at different day. Continuous ECG was recorded during the vestibular stimuli. Blood pressure and body temperature was measured before and after the stimuli. The motion sickness symptoms were scored. Heart rate variability (HRV), and relationship between exposure time, motion sickness symptom scores, HRV parameters, and changes of body temperature, heart rate, blood pressure, VO2peak or myocardial consumption of oxygen (MCO2) were analyzed.

Results Near significant negative correlation between body temperature changes and motion sickness symptom scores was found in both linear acceleration and Coriolis stimuli (Linear acceleration: r=-0.51, p =0.06; Coriolis acceleration: r=-0.56, p<0.045). During Subject who had large variations of MCO2（>5000mmHg/min）in the linear acceleration and Coriolis acceleration was inclined to have shorter exposure time and higher motion sickness symptom scores (Linear acceleration: r=-0.42, p =0.049; Coriolis acceleration: r=-0.42, p=0.051). The changes of MCO2 before and after Coriolis stimuli were correlated with VO2peak (r=0.38, p<0.042).

Conclusion Temperature regulation had its role in the symptom development during vestibular stimuli and aerobic fitness may somehow related to the motion sickness susceptibility in Coriolis acceleration. The mechanisms under the relationship between vestibular physiological responses and body temperature regulation still need further study.

SYNAPTIC PLASTICITY IN RATS HIPPOCAMPUS EXPOSED IN CLOSED COMPLEX ENVIRONMENT

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Closed complex environment is a special environment where man and machine coexist, including noise, abnormal gas, narrow space and vibration. These environmental factors will have a certain impact on the physiology and psychology of cabin crew, thus affecting the crew's performance. In this paper, a medium- and long-term (21-day) rat model was constructed by the closed complex compartment. The significant changes in average food intake, body weight, blood pressure and oxygen saturation of the rats in closed complex environment were observed compared with control group. Using the method of differential proteomics, we found 89 proteins in rat hippocampus were up-regulated and 94 proteins were down-regulated under simulated complex environment. The differentially expressed proteins were highly enriched in synapse-related proteins and exocytosis-related proteins, and were also enriched in the synthesis and metabolism of neurotransmitters. Besides, we found oxidative damage and energy metabolism disorders may occur in the hippocampus of rats modeled in a complex environment, which affect the release and clearance of rat hippocampal neurotransmitters. The toxic damage of neurons were induced by the elevation of glutamate concentration and the inhibition of gamma-aminobutyric acid synthesis. It was found that the synaptic vesicle transport in rat hippocampus was impaired and the expression of synaptic related proteins was down-regulated. Dendritic spine staining also revealed the density of dendritic spines decreased in hippocampal CA1 and CA3 regions of rats with complex environmental models. Above all, they had an effect on the synaptic plasticity of rats, which finally affected the rats learning and memory. The results can provide a more comprehensive understanding of the new molecular mechanisms of neurobehavioral development, which improve the environmental design of closed compartments and ensure the physiological and mental health of crews.

ALTERED TRANSGENE EXPRESSION IS MEDIATED BY RECOMBINANT ADENO-ASSOCIATED VIRUS IN HUMAN NEUROGLIA AND NEURONS UNDER MICROGRAVITY CONDITIONS

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Key words: *microgravity; adeno-associated virus; autophagy*

Space environment will have adverse effects on human bones, nervous system and immune system, among which microgravity condition is an important factor. Adeno-associated virus (AAV) is a replication-defective DNA virus with relatively low host immune response, weak toxicity, and long-term gene expression, which is widely used in gene therapy. In this paper, our Studies have shown that the infection activity of AAV increases under microgravity, and some studies have also shown that the activity of the virus is related to autophagy. First, the recombinant AAV virus was constructed and packaged with the enhanced green fluorescent protein (eGFP) gene, and infected with U87/U251 glioma cells and SH-SY5Y neurons under microgravity. Fluorescence microscopy and flow cytometry were used to detect fluorescence intensity and morphological changes. The results showed that microgravity promoted the transfer of AAV into cells and gene expression, affected cell adhesion, and changed the virus infection receptors. In order to detect the changes in autophagy level, the SH-SY5Y cell line expressing LC3B with red and green fluorescence was constructed using mCherry-GFP-LC3B lentivirus. Fluorescence detection showed that the autophagy level would increase under microgravity. QPCR analysis showed that microgravity increased the number of endosomes associated with autophagy in cells, which promoted the viral transport and suggested that endosomes may be a key factor in altering viral infectivity. These findings are helpful for understanding the effect of microgravity on rAAV infected nerve cells, and are of great significance for gene therapy and the study of the mechanism of viral neuro pathogenicity in space environment.

EFFECTS OF SIMULATED MICROGRAVITY ON P-GP EXPRESSION AND FUNCTION IN RAT BRAIN

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Key words: *simulated microgravity effect; rat brain; P-gp ; function ;*

ABSTRACT

Aim to study the effects of simulated microgravity on the expression and function of P-gp in rat brain. **Mothed** SD male rats were tail-suspended for 7 d and 21 d to simulate short-term and long-term microgravity effect. The protein expression, function, and ATPase activity of P-gp in rat brain were determined by the methods of western-blot, P-gp substrate (rhodamine 123) accumulation test and minimum ATP enzyme test kit. **Results/Conclusion** Compared with the normal gravity group, there was no significant difference in P-gp expression, transport function and ATPase activity in rat brain under simulated 7d microgravity effect. In addition, the expression of P-gp significantly increased by 24.0 % ($p < 0.05$), the content of Rho123 decreased by 16.3 % ($p < 0.05$) in 21 d SMG rat brain, while the P-gp ATPase activity was not obviously changed compared to NG rat. The simulated long-term microgravity effects have great influence on P-gp, and the enhancement of P-gp transport function may be caused by P-gp overexpression. This study provides basic data for changes of P-gp in the brain and might provide some useful information for rationality of drug use under the microgravity condition.

DIFFERENT AFFERENT SYSTEMS AS A TRIGGER IN MODULATION OF THE OTOLITH-OCULAR REFLEX AFTER LONG-TERM SPACE FLIGHTS

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Keywords: *otolith-ocular reflex; ocular counter rolling; afferent systems; space flight; centrifugation.*

The vestibular (otolith) function is highly suppressed during space flights (SF) and the study of these changes is very important for safety of SF. Centrifugation as a countermeasure after long duration SF can lead to changes in vestibular function – one of the main functions of operator activity, as a complex of changes involved by different afferent systems.

The study of the vestibular function (particularly, otolith-ocular reflex - OOcR) in clinical and space medicine uses different methodologies. However, different methods and methodologies can influence outcome results of the studies.

The current study addresses the question whether the OOcR results obtained by different methods are different, and what is the role of the different afferent systems in the modulating of the OOcR.

25 Russian cosmonauts were enrolled in our study, crewmembers of long duration missions on the ISS. Cosmonauts were examined in pre- and postflight space experiments "Sensory Adaptation" (static reflex) and “GazeSpin” (static reflex during centrifugation) twice before SF and three times after. We used 2 different video oculography (VOG) systems for assessment of the OOcR obtained in each experiment.

Comparison of these systems didn’t result into significant and systematic differences in measurements of the OOcR. Analysis of the static torsion otolith–ocular reflex (OOR), static torsion otolith–cervical–ocular reflex (OCOR) and static torsion otolith–ocular reflex during eccentric centrifugation (OOREC) shows that OOREC was less OOR and OCOR (before flight and late postflight days). But all OOcRs were significantly decreased in all cosmonauts taking part in the study.

Analysis of the results of ocular counter rolling (OCR) obtained by different methods (OOR, OCOR and OOREC) showed that different afferent systems were involved in our tests.

LONGITUDINAL MODIFICATIONS IN FUNCTIONAL BRAIN CONNECTIVITY AFTER SPACEFLIGHT

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ABSTRACT

How the brain adapts to the weightless environment of space remains an open question. We sought to investigate longitudinal brain plasticity changes with altered demands in sensorimotor neural processing in microgravity conditions. We hypothesised that vestibular and multisensory cortical brain areas will show altered connectivity characteristics after long- duration spaceflight, adaptable across time.

We acquired resting-state functional magnetic resonance imaging (rsfMRI) data from 12 cosmonauts (12 males, mean age of 45y, mean of 6 previous months in space) before launch to the ISS and after return to Earth. Eight cosmonauts received further follow-up scanning 7 months after return to Earth. Data were preprocessed by correcting for slice timing and head motion during data acquisition, coregistering the functional with the structural data, normalising to MNI space and smoothing using a Gaussian kernel with a full-width at half- maximum of 6mm. Furthermore, outlier scans were detected and removed using the artifact detection tool (ART), bandpass filtering of 0.008 – 0.09Hz and linear detrending were applied. Finally, signal from white matter and cerebrospinal fluid were entered as nuisance variables using anatomical component correction (aCompCor). Hypothesis-free analysis of rsfMRI data was carried out to investigate changes in overall connectivity for each voxel in the brain. Hypothesis-driven analysis using a region-of-interest (ROI) in the right parietal operculum 2 (rOP2), a key area involved in vestibular processing, was performed as well. Voxel-wise statistical parametric testing was performed at whole-brain uncorrected threshold of $p<0.005$ and at cluster-level False-Discovery Rate threshold of $p<0.05$.

The exploratory analysis revealed increased participation of the right angular gyrus (rAG) to whole-brain connectivity and decreased participation of the right frontal pole (rFP). At follow- up, the increases of the rAG normalised back to baseline and the decreases of the rFP were sustained.

Consecutive classic seed-based analysis using the rAG and rFP as ROI's showed that the rAG had higher connectivity with bilateral supramarginal gyri and left frontal pole after spaceflight compared to baseline measurement. The rFP had lower connectivity with bilateral sensorimotor cortex and middle frontal gyri. The hypothesis-driven analysis revealed decreased connectivity between the rOP2 and the right-sided angular gyrus, inferior temporal gyrus, anterior cingulate gyrus and several frontal areas at postflight compared to baseline scan. At follow-up, all the observed changes normalised to baseline.

Altered connectivity with the angular gyrus is meaningful within the context of the perception of upright, which is severely probed during spaceflight. The right-sided connectivity decreases of the rOP2 are consistent with the dominant hemisphere hypothesis for vestibular processing and spatial perception and reflect the reduction in vestibular signal processing in space. Our findings point to a dynamic underlying neuroplasticity mechanism for adjusting to new environments with altered demands in sensorimotor, visuospatial and cognitive processing.

DYNAMICS OF RECOVERY OF FUNCTIONAL CAPABILITY AFTER LONG-TERM SPACE FLIGHTS. RESULTS OF ONGOING EXPERIMENT "FIELD TEST"

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Keywords: *Field Test, space flight, interplanetary mission, functional capacity, recover after space flight*

ABSTRACT

The program of extra long duration space flights including exploration missions is widely discussed at present time. However, there is an increasing amount of evidence showing that physical capacity of cosmonauts is significantly reduced after long-duration space flights. It is evident that the most impaired systems and functions are those that rely on gravity, particularly vertical posture and gait. Because of the disturbances in activity of these systems, motion sickness induced by spaceflight can be observed. While the severity of particular symptoms varies, disturbances in spatial orientation and alterations in accuracy of voluntary movements are persistently observed after long-term space flights. All currently available data are purely descriptive and are not suitable for predicting operational impacts of such decrements upon landing on planetary surfaces or asteroids. There are no data on the recovery dynamics of functionality of various body systems; hence it is difficult to model and simulate the cosmonauts' activity after landing and to develop countermeasure methods and prescriptions. However, the videos of cosmonauts and astronauts walking and performing other tasks shortly after return from space flight speak volumes about their level of deconditioning. A joint Russian-American team is carrying out a study which is addressed specifically to the aforementioned data gaps. The study consisted of 11 tests directed to evaluation of sensory-motor and cardiovascular systems' state at different stages of recovery period after long term space flight. Most of them are based on rather simple natural movements which will be necessary to perform after landing on the surfaces of space objects – transition from seated and prone positions to standing, walking, stepping over obstacles, tandem walking, etc. Most of the tests are performed in the medical tent at the landing site, some other which require a big amount of special equipment are performed later in Star City and Johnson Space Center. The results of the studies with participation of 42 crew members of ISS long term missions revealed significant decline of functional capacity, orthostatic tolerance, accuracy of voluntary movements and high level of motion sickness on the landing day. The recovery process continued during the next 2 weeks, however, the accuracy of complicated locomotor test (tandem walking test) was altered even on the 12th day after landing.
The study is supported by the Russian Academy of Sciences and NASA.

THE EFFECT OF LONG DURATION SPACEFLIGHT ON THE BRAIN AND IT'S RECOVERY AS MEASURED BY VOXEL BASED MORPHOMETRY

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Long-duration spaceflight is known to negatively impact many systems of the human body, though knowledge of its effect on the brain remains limited. We therefore performed automated, observer-independent analyses of the brain using magnetic resonance imaging (MRI). We prospectively acquired T1 weighted scans of 11 cosmonauts before and shortly after 6 months long-duration spaceflight. Seven cosmonauts received an additional follow-up scan on average 7 months after return from the ISS. We performed whole-brain volumetric analyses of gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) tissue compartments through a voxel-based approach.

Result: At the postflight time point, which is within the first 2 weeks after landing, we observed decreases in GM volume in caudal and ventral areas of the cerebral cortex, while there and in the ventricles CSF volume increased. At the vertex, we found a reduced CSF compartment in combination with increased cortical thickness (CT) postflight. WM volume postflight was reduced in two regions. At follow-up, i.e. 7 months after return, regained GM volume was found in orbitofrontal and temporal regions. CSF volume was increased throughout the subdural space, while cerebral WM volume was generally reduced. CT returned to baseline levels at follow-up. No tissue volume differences were found in a matched control group.

Discussion: Our findings can be explained by both a redistribution of bodily fluids within the skull, as well as by changes in mechanical pressure causing subtle deformations of brain morphology. The observed changes are seen in regions, which might be most susceptible to cortical deformations and water accumulation or drainage, such as the temporal poles, orbitofrontal gyri, insula and dorsal fronto-parietal areas. Between the postflight and follow-up scans, normalisation processes seem to be ongoing, again inducing morphological changes and fluid redistribution. Seven months after return to Earth, normalisation does not seem completed so these results suggest a longer time course for full recovery than for some other physiological systems. Overall, our results reveal for the first time changes in different brain tissue volume compartments and morphological characteristics shortly after spaceflight, as well as at long-term follow-up. The course of normalisation and the relation of our findings to other clinical parameters require further investigation.

MEDICAL SELECTION OF THE FIRST GERMAN COMMERCIAL FEMALE ASTRONAUT

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INTRODUCTION: 60 women had been to space-none of them was German. That was the reason for a CEO of a German space personnel provider to advertise a vacancy for a first German female astronaut. The required professional background was at least a Bachelor‘s degree in a „STEM“ field or equivalent military education and several years of related professional experience. The applicant should have some media competency, should be able to communicate and work in teams as well as being fluent in English. Experience in aviation or diving, as well as knowledge of Russian language was advantageous. A medical certificate for private pilots and a video of the applicant needed to be also submitted with the application. 408 well educated women applied.

MATERIAL AND METHODS: The medical and psychological selection was performed by the German Aerospace Center and followed in the structure the last European astronaut selection. 120 women were selected by the private company due to their application and a skype interview. They all had to fill out a pseudonymized questionnaire, that was created by the Flight Medicine Clinic of the German Aerospace Center as an initial medical screening. 85 persons were recommended for further evaluation. They completed the first step of the psychological selection from which 30 women entered the second stage of the psychological selection. 8 applicants were finally psychologically selected and underwent medical examinations including haematology, internal medicine, stress electrocardiogram, ophthalmology, neurology, ENT, gynaecology, dentist, psychiatry, bone density and anthropometry.

RESULTS: During the initial medical screening phase applicants were denied because of metric, trauma or pregnancy reasons. In the end 6 applicants were considered medically fit by an experienced space medicine board for becoming a commercial astronaut. Reasons for rejection were the exclusion criteria mentioned in „ Medical Standards and Certification Procedures for Space Flight Participants”. No medical data were given to the private company.

Finally two women were chosen by a panel under the leadership of a German astronaut, to undergo commercial astronaut training. Because of radiation protection we decided to perform the necessary radiation examinations only in the finally selected applicants. That was very difficult to implement concerning desired examination and secure large data transfer as the candidates were far away at that time. After six months one of the selected astronaut candidate quit and a new one was selected from the pool of the final six psychological and medical fit candidates.

CONCLUSION: The international space agencies standards for commercial astronauts differ a lot from the requirements for professional astronauts. Therefore the rate of denials for medical reasons was much smaller compared to the last ESA astronaut selection. As many applicants came out of the space area it made sense to pseudonymize the medical information for decision making to exclude possible bias.

BIOPRINTING RATIONAL FOR EXPLORATION MISSIONS

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Today, human exploratory missions to the Moon or Mars, are widely considered as the next logical steps in human space exploration and, lately, settlements. Such space exploration activities are involved with long exposure of humans in space and, in case of increasing distances to Earth, no abort possibilities. Crews on such missions have to be self-sustaining, not only concerning food and drink, wastes, but also with respect to medical treatment. Health issues are raised by the environmental conditions in space, such as the influence of altered gravity, radiation, isolation. In addition the health risks of illness or injury human beings are faced on Earth, are also present in space. However, in case of long distance travels the medical infrastructure on Earth is not reachable in a reasonable amount of time for medical care. In order to protect human lives and health, such space exploration missions have to consider a medical infrastructure onboard, so that medical treatment of a wide range of health issues can be provided.

Within the scope of the PLT-Space project (**P**rinting of **L**iving **T**issues for **Space** Exploration), initiated and funded by the European Space Agency, ESA, the potential implementation of 3D- bioprinting as a promising technology to enable long duration missions, far away from our home planet has been evaluated. Bioprinting can provide support in medical treatment and improves the autonomous functionality of the medical structure. By printing skin, bones, cartilage and in the future organ-parts the medical treatment of skin issues, injuries or organ disorder can be supported offering an important contribution to a medical infrastructure during space exploration missions. The different printing technologies have been evaluated as to space-adaptability and also infrastructure-requirements for transplantation of bioprinted tissue have been discussed.

TOWARDS THE CREATION OF A NEW MEDICAL CONTROL STRUCTURE FOR FUTURE LUNAR EXPEDITIONS

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ABSTRACT

Currently, a number of medical control systems have been developed for manned space missions. For the implementation of future manned programs for the exploration of the moon, especially for the creation and establishment of a base on the lunar surface, it is necessary to create a new system of medical control that focuses on the registration and determination of the level of blood glucose for the psychophysiological control of the cosmonauts that will inhabit it. The designed system must take into account the peculiarities of lunar expeditions and have a clear, powerful and fairly simple for the user, a non-expert physiologist, a decision support system (DSS).

Medical control (MC) is performed according to the pathogenetic principle, which is focused on the identification and diagnosis of the most probable predicted conditions and diseases, where scheduled screening examinations, individualization of diagnostic examinations and correction of the examination program depending on the condition of the crew members are carried out.

For the medical control of lunar manned expeditions, the decision must be made at the lunar orbit and at surface of the moon. The MC includes operational control during active areas of flight and extravehicular activity (EVA), daily monitoring and in-depth medical examinations performed according to the program or as directed. The daily medical monitoring will includes a constant subjective assessment of their condition by the crew members themselves, environmental monitoring and observation. Medical specialists will support the crew from the Ground Control Center.

In the case of the psychophysiological control, the crew will take themselves the blood glucose sample as part of the daily medical exams by developing and implementing a new method for measurement of this parameter. As part of this new method, it is necessary to create and develop a new device that is able to obtain blood glucose samples in a non-invasive way, with the aim of not interrupting the program of activities assigned to cosmonauts. Therefore, the new glucometer will be designed to obtain the sample in the lobe of the ear by using infrared sensors, previously making a functional analysis of the electronic and optical elements that make up this new device, which should work properly under environmental conditions characteristics of the moon.

It is necessary to make a record of glucose, since the increase of this parameter can affect the emotional and psychological skills of cosmonauts, so we can determine if they are fit to continue with the mission or if it is necessary to return to the planet ground, as they can put other crew members at risk. This is supported by a psychological and physiological evaluation.

These types of medical examinations conducted in the interests of diagnostics are also used to obtain scientific medical information and are an integral part of the program of medical research in long-term space missions (LTSM).

ETHOLOGICAL AND PHILOSOPHICAL VIEWPOINT OF HUMANS IN SPACE: PAST AND FUTURE

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Topics: multidisciplinary Studies related with Humans in Space; Cognitive and Behavioral Effects of Deep Space Missions; Mars exploration

First man on the Moon was the success of a planet discovery in the past Apollo missions. Humans on Mars and beyond are the challenge of future planetary explorations. One step performed by the astronaut Neil Armstrong opened the way for understanding the adaptation steps of humankind from the mother Earth to autonomous deep-space missions.

Monitoring an interplanetary crew was one of the objectives of multidisciplinary investigations in the knowledge of long duration adaptive processes. What could be the crewmembers' behavioral profiles in isolation, in confinement and in extended periods of time? A wide panel of approaches with suitable tools was implemented in real situation (space shuttle, orbital stations) and during experimental simulations (polar expeditions and confinement campaigns). Current investigations concern ecological life support systems to be integrated in the requirements of a first crew living in controlled, confined and isolated habitat. The ethological discipline was involved in all of these investigations. It is in the interface of physiology, psychology, sociology and anthropology with a systemic and integrative viewpoint. Previous observation, description and quantification of the individual and social behaviors helped to answer the preliminary question. The future crewmembers going into space will be definitively interactive men and women with personal experiences, own social rules and new cultural habits. They will have their individual identity and they will be as a group entity at the evolution scale.

Reflecting upon what could be a successful crew in deep space and remote time becomes a philosophical issue. Are humans only Earthmen? The tool is in the imagination, representation and integration of a new framework. The first step will be to release from terrestrial cues (perceptive, cognitive, communicative) to move toward other dimensions of space in an optimal way. Thus the world to which humans belong is the one they discover. The discussion is opened.

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EXPERIMENTAL MOTION SICKNESS SUSCEPTIBILITY IN WOMEN AT DIFFERENT PHASES OF THE MENSTRUAL CYCLE APPLIED TO FUTURE SPACE FLIGHTS.

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Today the total number of female astronauts from different countries reached 62 women (Wikipedia, Jan. 24, 2019). It is well known, that the adaptation period to weightlessness, as well as post flight re-adaptation to Earth gravitation in male and female astronauts are associated with the possibility of development the space motion sickness (SMS) symptoms.

According to Mark S. et al., 2014, in the period of adaptation to weightlessness women - astronauts showed greater susceptibility to SMS than men - astronauts (50% in women, versus 38% in men). However, other studies (Harm,1990; Reschke et al., 2014) didn't find the significant differences in experimental MS susceptibility among male and female volunteers.

Present report demonstrates the results of investigation of experimental motion sickness (MS) susceptibility at 15 healthy woman volunteers (aged from 25 up to 37 years) during various phases of the menstrual cycle on 4-year observation period. Experimental MS was simulated by cumulative Coriolis stimulation (CCS) - prolonged 10-min stimulation by cumulative Coriolis (precessional) accelerations, according to Markaryan et al., 1966. Investigation protocol included: background testing, CCS test at 1st-2nd days of menstrual cycle ("menses phase"), CCS test on 7-10 days after the end of the menstrual cycle. MS severity was estimated according to the MS severity diagnostic scale developed by Graybiel A., Lackner, J.R.,1980.

It was found that in 14 of 15 women the average CCS test tolerance time during background and period without "menses" was 10.0 ± 0 minutes, with vestibular-vegetative symptoms (VVS) of 0.2 ± 0.19 points, without significant sensory reactions (SR). Only one woman had MS symptoms: VVS (2 points) and SR (1 point – "pitching illusion").

During 1st-2nd days of "menses phase" only 9 out of 15 women demonstrated tolerance to MS without VVS and SR. 6 volunteers demonstrated a tendency to reduce tolerance to MS ($P > 0.05$). The average CCS test tolerance time in these woman was: 9.7 ± 0.29 min, with VVS -1.2 ± 0.8 points and SR - 1±0 points. One woman from the last group showed the VVS of 12 points, that's why the CCS test was stopped.

The received results of decreased MS susceptibility in some women during "menses" phase are well combined with the results of experimental animal studies. Grassi et al., 2012 showed that synaptic response and plasticity in the medial vestibular nucleus depend on sex and cyclic fluctuation of 17β-estradiol (E2) during "estrous" cycle (the menstrual cycle in animals) in female rats. Their results demonstrate an influence of circulating E2 on vestibular synaptic transmission and plasticity that in some cases may contribute to the sex and menstrual cycle dependence of symptoms in human vestibular pathology. Following up on these studies, Dieni et al., 2018 hypothesized that E2 impacts VOR adaptation by affecting cerebellar synaptic plasticity at the parallel fiber-Purkinje cell (PF) synapse. Their findings suggest that E2 might regulate changes in VOR adaptation by acting locally on cerebellar and extra-cerebellar synaptic plasticity sites.

Our investigation demonstrates the evident relationship between experimental MS susceptibility and menstrual cycle in some women. These data don't exclude the possibility of increased space MS susceptibility in women-astronauts during "menses" phase on adaptation period to weightlessness, as well as post flight re-adaptation to Earth or another Planets gravitation. This fact should be considered during astronauts selection procedure when planning space missions to the Moon and Mars with the participation of female astronauts in the crew.

HUMAN METABOLIC DOWNREGULATION FOR GENERAL STRESS & 0-G TOLERANCE: (PRELIMINARY) PROOF-OF-CONCEPT EXPERIMENTS

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Keywords: Stress Tolerance, Weightlessness, Metabolic Rate, Body Temperature, Torpor

ABSTRACT

Metabolism powers & sustains life, & chronic gravitational unloading tolerance, e.g., weightlessness, is reduced, in part, because terrestrial life typically only experiences 1-$G_{\oplus}$ loading or more; considerable 1-$G_{\oplus}$ unloading can occur via aquatic venturing. Larger animals, however, are subjected to a much greater, mass-related counter-gravity metabolic cost (CGMC), more specifically, enzyme-driven *mass* action, so that removing this component to the metabolic burden bottom-line leads to substantial desynchrony between the various metabolic reactions, as indicated by the rate-of-living life-equation.[1-6] According to the basic, *fundamental*, earthly life metabolic rate-of-living life-equation, on Earth, $CGMC_{1\text{-}G\oplus}$ contributes ~35% & ~10% to the minimum existential or basal metabolic rate (BMR) of a 100-kg human & 10-g mouse, respectively. This is due to the absolutely greater enzyme *mass-load* that comes with increased size; the non-linear discrepancy is due to the lower pound-for-pound or mass-specific metabolic rate (MR_S) of larger animals, here reduced to $1/12^{th}$, even though gravitational forces acts on each unit of flesh-mass & scales directly with gravitational force, which should otherwise result in a 10,000-fold difference. Furthermore, because elapsed (metabolic) time is the just the inverse of MR per unit mass, a time-dose tolerance effect manifests, so that prolonged off-nominal exposure results in progressively greater desynchrony between the various, many metabolic *clocks &*, thus, unsurprisingly resulting in dysfunction & pathological manifestations.[7-8] However, it is known that animals in torpor, i.e., sub-BMR states, can be rendered effectively *immune* to even far-off 1-$G_{\oplus}$, very large ones too, e.g., hibernating bears tolerate months of near-complete inactivity, considered a natural biomedical model of chronically protected gravitational unloading. Torpid states can so profoundly slow metabolic activity &, thus, biological times that animals suddenly appear as if metabolically *down-sized & suspended in time*, & thus more immune. Indeed, many key pathways are temporarily uncoupled, *broken,* or remodeled for greater protection, others are upregulated by the off-nominal expsoure.[9] This is not altogether unsurprising since the best way to protect a complicated *metabolic machine* is to temporarily disassemble it. Metabolic depression also results in some (variable) core-body cooling even in large hibernators, which in itself boosts tolerance since MR largely depends on temperature. For example, human +G_z-tolerance, which is poorly tolerated, decreases by as much as 30-40% for a mere degree increase in core-body temperature. equivalent to a ~5-7% increase in MR; cooling reverse it.[10] Yet, a 100-kg hibernating bear downregulates MR to ~25-30% BMR with no more than 3-4°C of core-cooling, i.e., temperature-independent effects are at play, suggesting a large, untapped, off-nominal tolerance potential.[11-13] And, since torpor is expressed in an extremely varied range of mammals & known to confer unmatched-enhanced tolerance of a myriad of other major metabolic stressors, e.g., extreme acceleration/deceleration, thirst, starvation, isolation, confinement, inactivity, infection, intoxication (e.g., hypercapnia/oxia), hypoxia, hypo/hyperthermia, ionizing-radiation, darkness, decompression-illness, even time itself, if humans could express this state they might similarly manifest broad-spectrum biomedical protection, i.e., *game-changer*.[14] Interestingly, because the CGMC contribution to the metabolic bottom-line in torpor expands vis-à-vis the thermoregulatory burden, 0-G should result in the most profound torpor. This means it may be possible to *completely* offset any lingering adverse effect of weightlessness in large animals, like humans, & transform it into a novel space-life-support resource, to maximize (time-dependent) biological shielding & conservation of resource, i.e., vital given the extreme & austere. Interestingly, the lowly MR & other vitals of hibernating bears stands on par with that of similar sized breath-hold diving seals, an environment in which the CGMC is near-collapsed, leading some to suggest that *"the bear may 'dive' into hibernation"*, so that this strategy might be the long-suspected pathway that opens-up the possibility of bear-like sustaining this state.[12,15-19] Revealed here, seal-like, down-powered metabolic capabilities of human breath-hold divers, specifically, a telltale constellation of classic physiological hallmarks that typify this state: spontaneous, ultra-fast & profound reversible temperature-dependent/independent sub-BMR with core-body cooling.[20]

MICROBIOLOGICAL SAFETY OF INTERPLANETARY FLIGHTS: TRADITIONAL AND EXPECTED CHALLENGES, AND PREVENTIVE MEASURES

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The microbiological risk factors for crews of interplanetary expeditions and lunar bases include both already known and possible new factors. Among the first are the factors of confined habitats, where interchange of microorganisms and genetic determinants occur, an increase in the potential of pathogenicity in the “human-microorganism-artificial habitat” system, causing the risk of auto- and cross-infections, the subsequent weakening of colonization barrier, the presence of anthropo-technological niches of pathogenic microbes in space station habitats, as well as weightlessness factor, that ensure stability of bacterial aerosols, and radiation factor. Among “new” factors of microbiological risk, possibility of exogenous contamination of crew members by “cryptic” microorganisms during EVA and work on the surface of the planets are also considered. Chemo-lithotrophic microorganisms, possibly inhabiting other planets, represent a separate danger. The presence of methane on Mars can be evidence of the presence of both methanogens and methanotrophs, and they can be fairly easily integrated into the human body using and/or generating methane. Another factor that seems to be more natural for lunar bases with high crew turnover is the ability to change the properties of natural human microbial consortia, left by crew, leaving the moon and undergoing changes under the influence of complex of factors of lunar surface - hypomagnetic environment, proton, neutron and gamma irradiation. When new crew will arrive, it will be easily colonized with this microbial consortium, which, having been phylogenetically relevant to human organism, could be modified unpredictable way.

Cosmonauts have increased recipient capacity due to weakened colonization resistance. Therefore, the development of tools and methods for the prevention microbial diseases is extremely important for implementation of interplanetary missions. New autoprobiotics can be used as possible preventive agents, since they do not have problems with colonization and do not have allergic complications. There is a great positive experience of using auto-probiotics based on enterococci, bifidobacteria and lactobacilli to optimize human intestinal microflora in various experiments - normobaric and hyperbaric isolation, dry immersion and others in various forms - tablets, lyophilized products, sour milk products, “periodontal dressings”, etc.

A large and promising group consisted of studies of new effective collection probiotic strains of microorganisms - representatives of species that are not related to those traditionally selected for probiotics. Thus, there are positive results of using corynebacteria for sanation of the upper respiratory tract and salivary streptococcus for periodontal sanitation.

The preliminary results of the use of autoprobiotics and new probiotic cultures in experiments simulating altered habitat conditions, as well as in clinical studies, indicate their undoubted effectiveness. The absence of allergic complications, biological incompatibility and high engraftment suggests the effectiveness of autoprobiotics in the implementation of interplanetary missions.

CIRCADIAN RHYTHM AND SLEEP DURING PROLONGED ANTARCTIC RESIDENCE AT CHINESE ZHONGSHAN STATION

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Keywords: *Antarctica, winter-over, light–dark cycle, circadian rhythm, sleep*

ABSTRACT

Objective.—Residence at Zhongshan Station (69°20’24’’S, 76°20’40’’E) for over 1 year exposes winter-over members to marked changes of light-dark cycle, ranging from the constant daylight of polar days to the constant darkness of polar nights, in addition to geographic and social isolation. This extreme photoperiodic environment may increase the risk of sleep disturbances and circadian desynchrony. The aim of this study was to investigate the circadian rhythm and sleep phase of Chinese winter-over expeditioners at Zhongshan Station.

Methods.—This study was conducted on 17 healthy male participants before departure from Shanghai and during residence at Zhongshan Station for 1 year (before winter, mid-winter, and end of winter). Sequential urine samples over 48 hours were obtained, 6-sulphatoxymelatonin in urine was assessed, and the circadian rhythm was analyzed by a cosine curve-fitting method. Participants’ sleep parameters were obtained from wrist actigraphy and sleep logs. Morningness-Eveningness Questionnaire and Seasonal Pattern Assessment Questionnaire were completed.

Results.—The acrophase of 6-sulphatoxymelatonin rhythm, sleep onset, sleep offset, and mid-sleep time were delayed significantly ($P < .05$) in Antarctica relative to departure values. The subjects had greater eveningness preference ($P < .05$) in mid-winter in Antarctica. The Global Seasonality Score and the prevalence of subsyndromal seasonal affective disorder increased ($P < .05$) during winter.

Conclusions.—Our results indicate that during polar nights Chinese expeditioners experienced the following problems: delayed circadian rhythm and sleep phase, later chronotype, and incidence of subsyndromal seasonal affective disorder. An appropriate combination of artificial bright light during dark winter months and a strict social schedule are recommended in a winter-over station in Antarctica.

APPLICATION AND TEST OF IMPACT-ADHESION MECHANICS IN SPACE MICROGRAVITY

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Keywords: *Space microgravity, bio-inspired gripper, impact-adhesion mechanics*

ABSTRACT

Grasping and manipulating non-cooperative target in space is the key technology of human spaceflight, while many docking mechanisms which are successful on the ground would be undermined and limited in space. Aiming at this problem, the gecko in nature provides an excellent prototype and solution, that is, capture with impact-adhesion mechanism. In order to apply impact-adhesion mechanics into space environment, a bio-inspired gripper was developed with an overall consideration of attachment and detachment mechanism in gecko; then a dynamic analysis on gripper grasping was presented through Lagrange method; finally, a verification test experiment was designed, in which we simulated the space environment by means of air bearing, meanwhile the impact-adhesion process and the contact forces were recorded by a high speed camera and a six-component force sensor, respectively (Fig. 1A). The experimental results showed that with the impact velocity ranging from 3 to 11cm/s and the impact angle ranging from 0 to 15 degrees, the gripper (2.45kg weight) can grasp and manipulate the floating target (200kg weight) lightly and easily (Fig. 1B); oblique impact at a small angle (around 5°) would be benefit for grasping at a low speed (around 2cm/s), while a large impact angle (>10°) can generate serious transverse vibration, which may directly lead to the failure of grasping; the high power-absorbing gripper system can largely reduce the rebound force, and the gripper terminal can generate up to 50N and 15N adhesive forces in normal and tangential direction, respectively (Fig. 1C). Our work would broaden the application field of impact-adhesion mechanics and provide a variety of solutions to docking or grasping method in space, moreover, it can lay the theoretical and experimental foundation for the adhesive capture technique.

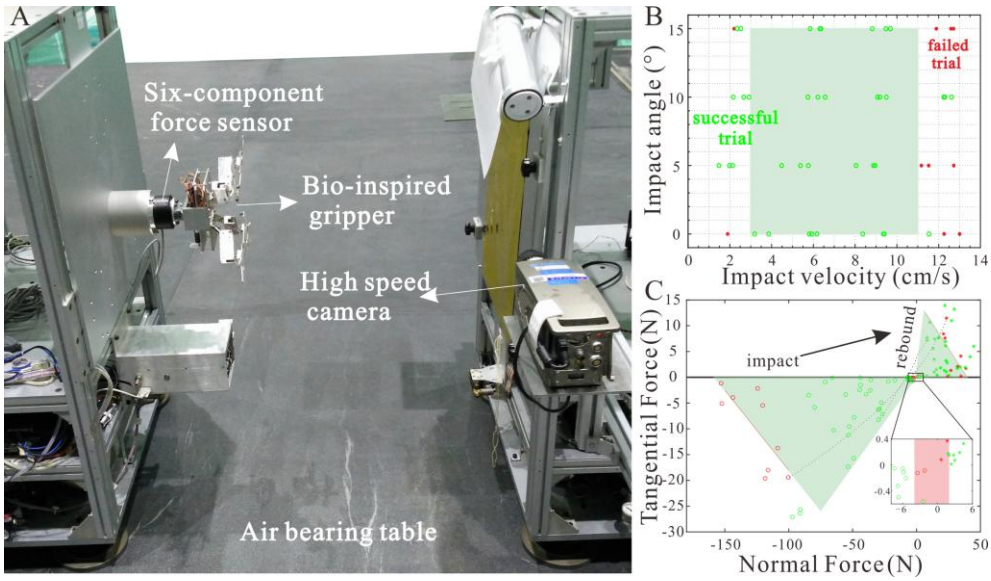

Fig. 1 (A) The verification testing system that simulates impact-adhesion in space microgravity; (B) the velocity and angular space of successful trial as well as failed one; (C) normal and tangential contact forces during impact and rebound process.

A METHOD OF REMOTE MONITORING OF THE OPERATOR FUNCTIONAL STATE IN SPACE FLIGHT CONDITIONS USING ACOUSTIC SPEECH ANALYSIS

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Studying the communication of astronauts with the Mission Control Center (MCC) is a routine procedure for remote medical and psychological monitoring of space crews. The main advantage of this method is the ability to monitor the psychophysiological status of astronauts directly in the course of carrying out their real professional activities without using additional equipment and without spending time of the crew. Presently, only the content side of speech is analyzed mainly, while the analysis of the speech acoustic characteristics is less common due to technical limitations in sound recording. Nevertheless, the acoustic characteristics in speech better reflect the deep features of the astronaut's psychophysiological state due to their lesser susceptibility to conscious control. The analysis of the acoustic characteristics allows to evaluate the dynamics of the subject's emotional and functional states, it is also less energy-consuming and allows the analysis of speech in real time.

In contrast to the study of emotions in colloquial speech, the study of the human operator functional state is possible only with prolonged research. Changes in the fundamental frequency should be compared with its norm in the context of speech behavior during the day, several days or weeks - then it will be possible to observe changes in the functional state, mental resources or increasing mental asthenia. Most modern methods of speech analysis are carried out with the help of technical means and specialized computer software, which allows researchers not only to collect objective and extensive databases, but also to study oral speech in its dynamics.

The method proposed by us is based both on methodological approaches implemented in previously conducted space and model experiments, and on modern methods and technologies for analyzing the acoustic characteristics of speech. It was tested in a number of model experiments in the Institute for Biomedical Problems RAS, including short-radius centrifuge (SRC) studies and during the 21-day dry immersion.

By analyzing the acoustic characteristics, some aspects of the psychophysiological state, stress reaction and ways of coping with stress in a human operator were studied. Records of communication between the subjects and the Control Center during the implementation of various angular acceleration modes on the SRC were used for speech analysis. The results of the experiment on the SRC mainly reflect the changes in the operator's functional state under a short-term exposure to extreme environmental factors. In experiments using dry immersion, a less intense but more prolonged effect on the human body is modeled. During the 21-day dry immersion, changes in the frequency characteristics of human speech under conditions of long-term simulated microgravity were studied. Audio recording of voluntary speech was carried out twice a day (morning and evening). This format of audio reports partially reproduces daily planning conferences (DPC) performed by cosmonauts at the beginning and end of their working day, and also simulates time-delayed audio messages during a communication delay.

We propose the following interpretation of acoustic characteristics in the context of assessing the human operator psychophysiological state:

- The presence or absence of pauses between the utterances of the communication participants (MCC and the subject) indicates the degree of arousal;
- The speech volume indicates the degree of activation and arousal;
- The change in the ratio of high and low pitch reflects changes in the psychophysiological state of the operator in preparation for and during the stress exposure;
- Degree of speech smoothness can be an indicator of the psychophysiological "price" of the activity.

The results of the method testing prove its efficiency and validity, allowing us to plan further studies in a series of model experiments (e.g., SIRIUS in IBMP), thus preparing the scientific, methodological and technical basis for on-board research.

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COMMUNICATIVE COPING STRATEGIES AND ANXIETY LEVEL IN SIRIUS-17 ISOLATION EXPERIMENT

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With the increase in space mission duration, autonomy becomes one of the significant stress factors that need special attention. During the planned flight to Mars, communication delays might make it impossible to ensure the permanent mission control (MC) psychological support for the crew. While the autonomy factor gets combined with a diversity of other stress factors (such as microgravity, sensory deprivation, etc.), a person should effectively cope with stress either by himself or with support from a limited circle (crew members). For the moment, tactics of cosmonauts selection for long-distance crews remain uncertain, and a search for measurable psychological prognostic indicators of effective coping with stress under isolation stays relevant.

A study by A. Vinokhodova and P. Kuznetsova made in MARS-500 isolation experiment, showed correlation between state anxiety and capacity for emotional self-regulation (as an aspect of psychological stress resistance). Crewmembers with low state anxiety showed higher results in positive emotional self-regulation that was developing throughout the experiment, while crewmembers with higher anxiety results showed an opposite trend.

Communicative coping strategies are one of stress manifestations, representing psycho-emotional tension degree (lower when effective coping strategies are used and higher with ineffective coping strategies). In space psychology, P. Suedfeld became pioneer in studies of coping strategies, using this approach in analysis of astronauts' diaries and interviews (2009). Approach toward coping strategies as effectiveness indicators for stress adaptation was used in S.L. Bishop's (2010) studies in FMARS experiment. We use this approach in Content on-board experiment, part of ISS Russian segment scientific program from 2015 (Gushin et al., 2016). The main method used in Content experiment is content analysis of crew communication with Mission control. One of the points of interest is coping strategies (as in stress coping concept of Lazarus & Folkman, 1984) in cosmonauts' speech, their individual patterns and dynamics throughout the space flight.

SIRIUS-17 experiment took place in IBMP (Moscow, Russia) in October-November, 2017. Participants of a 17-days isolation includes three men (aged 33-44) and three women (aged 28-37). In SIRIUS-17 experiment, the effect on the psycho-emotional state of the crew was studied (with factors such as sensory deprivation, social isolation, sleep deprivation). In particular, impact of state anxiety for the choice of coping strategies with stress was examined.

The study method included content analysis of SIRIUS-17 crew-MC daily planning conferences (to find coping strategies in speech in each crewmember) and C. Spielberger's State-Trait Anxiety Inventory (STAI, to determine state anxiety in each participant).

STAI results divided crewmembers into low and average anxiety level groups. High anxiety subjects tend not to pass selection test for chamber experiment participation (as well as for for space flights). Data analysis showed that anxiety level has a negative impact on the choice of coping strategies. Crewmembers with average anxiety level tended to use coping strategies to lower emotional tension (e.g. "informing", "self-control" content analysis categories), while low anxiety level participants used more coping strategies aimed at problem resolution (e.g. "initiative", "demands", "claims" content analysis categories). We confirmed data obtained by A. Vinokhodova and P. Kuznetsova about state anxiety's influence on choice of coping strategies.

SIRIUS-17 was the first experiment in a series of studies to be held in IBMP during the next several years. More data is needed to confirm the first preliminary results obtained in the 17-days isolation experiment.

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INVESTIGATIONS OF SLEEP QUALITY IN MICROGRAVITY

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The question of how cosmonauts sleep in conditions of weightlessness, of course, has both a scientific interest and importance of solving practical problems. Nowadays, there is no generally accepted opinion on how good the quality of sleep is for the space crew to perform all complex flight operations.

Researches on sleep quality are very rare and often limited only with questionnaires. In October 2007 the scientific experiment SONOCARD was launched on board of the International Space Station (ISS) in search of methods for assessing the cosmonaut's functional state and their recovery during a night sleep. For 5 years, the experiment was conducted on Russian crew members of the ISS every month. The central place in evaluation of the results of non-contact registration of physiological signals belongs to analysis of heart rate variability (HRV). The method has been successfully adopted by various fields of medicine and physiology for evaluation of the state of autonomic regulation. In addition, the signal allowed us to identify periods of motor activity, assess to respiratory rate and other characteristics. Moreover, trends in the night-time changes in autonomic balance and activities of the regulation components will make possible to interpret better the available data of numerous scientific experiments performed on the ISS in the daytime.

The major part of the research involved studying the sleep quality and the functional reserves recovery during night sleep after extravehicular activity.

The analogue of the space device was used by us in isolation studies – “Mars-500” and “Sirius” also for analysis and evaluation of night sleep during various imitation of space flight to another planet.

At present, having experience in analyzing such records, we are planning to start a new space experiment on the ISS since 2020 year. A small sensor that will be located on the chest responds to micro-vibrations produced by heart contractions. Thanks to the new technology and computer analysis capabilities, it can be done much better and more successfully.

BODY TEMPERATURE REGULATION IN HUMANS ON EARTH AND IN SPACE

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Heat exchange between an organism and its environment occurs via conduction, convection, radiation, and evaporation (ref.1). Under terrestrial conditions, heat exchange for an adult occurs mainly by radiation and convection, and the body core temperature fluctuates by only +/- 0.5°C throughout the day, i.e. the "circadian rhythm". In space the heat loss pathways are challenged due to the lack of natural convection which results in the diminished occurrence and/or efficiency of evaporation. We have recently developed a non-invasive heat flux device (Double Sensor, T_{core}®) that can be used to monitor core body temperature changes in humans. Three investigations will be presented. They dealt with core body temperature changes under terrestrial and micro-g conditions: i) during rest and exercise in a climate chamber at 10°C, 25°C, 40°C ambient temperature (ref. 2), ii) during long-term bed-rest (ref. 3,4), and finally iii) during rest and exercise in space (ref. 5). In the first study (study A), the heat flux sensor methodology was tested in comparison to nasopharyngeal and rectal temperatures in 20 male subjects; in the second study (study B) 7 males were monitored during long-term bed rest, and in the last study core body temperature changes were determined in 11 astronauts during a regular $\dot{V}O_2$ ergometer testing before flight, several times in space on the ISS, and after spaceflight (study C). Study A showed that the recordings of the Double Sensor differed by -0.16 to 0.1°C from the mean rectal temperature, study B proved that the device correlated well ($r>0.704$) with the rectal temperature recordings, and study C revealed that the astronauts had marked and prolonged increases during exercise in core body temperature, sometimes >40°C, in space on the ISS ($p<0.01$). Changes in body core temperature can be markedly attenuated in space. Further studies on this topic are urgently needed because i) the frequency, length, and intensity of extravehicular activities will increase in future and ii) any alteration of the circadian rhythms might aggravate the physical, psychological, and cognitive performance of humans in space. Finally, the new technology might be used on Earth in different clinical and occupational health settings, which will be demonstrated.

Acknowledgements
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NEW APPROACHES TO THE DEVELOPMENT OF MS AND PHD EDUCATIONAL PROGRAMS IN THE FIELD OF SPACE BIOLOGY AND MEDICINE

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Keywords: *Space biomedicine education*

ABSTRACT

The interplanetary missions, as a new milestone of space exploration, requires new approaches in training in the field of space biology and medicine. Far space exploration demands the development and implementation of new biotechnologies, application of methods of system biology and development of personalized medicine approaches. A new Moscow state University facility - the faculty of Space Research was founded and the recruitment of students was opened in 2017. Bachelors and masters are trained at the new faculty. Last year, the master's program "Biomedical space research" was started up. The training program includes various courses including Physiology, Cell and Molecular Biology, Bioethics, Space Biology, Psychology, Gravitational Physiology, Space Medicine and so on.

It is important that students are involved in experimental research from first semester of their training. The Institute of Biomedical Researches (IBMP) of RAS provides an facilities for this experimental work. Together with the tutors (Heads of the labs) they are discussed the main experimental directions and got an approval to start with their own research in selected field. The special time for experimental research is scheduled in their timetable. The MS thesis will be defended at the end of second year of training. BS and MS students participate in scientific events like the Conference of Young Investigators of IBMP and Scientific Summer School with presentation and discuss new directions in field of space biology and medicine with their tutors and graduated postgraduated students from other Institutions.

IBMP has its own Postgraduated Department more than 50 years. From the 2014 postgraduated education became a third step of high education. The educational activity is licensed and has an accreditation in the Ministery of Science and Education. The PhD students are trained in two directions: biology sciences and basic medicine. We have more than 30 PhD students per year. After graduation of PhD Program the PhD students defend their thesis and are awarded PhD degree in Physiology as well as in Aviation, Space and Hyperbaric Medicine. Most of them continue their investigation at IBMP.

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HUMAN-CENTERED HUMAN–ROBOT NATURAL SPATIAL LANGUAGE INTERACTION*

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Abstract

In order to achieve the goal of human guiding robot navigation with natural language, based on the "human-centered" design principle, this paper proposes a model to design the future robot which enables an efficient human–robot natural spatial language interaction.

Firstly, based on the cognitive mechanism of human-human spatial language interaction, this paper puts forward a human-intelligent-isomorphal scheme of robot spatial environment perception and spatial language processing. For spatial environment perception, a robot should be able to (1) perform level-1 and level-2 spatial perspective-taking (SPT), which means the robot can infer what the other can see and how something looks to the other, and (2) perceive the spatial world in various forms of spatial frames of reference (s-FoRs). For spatial language processing, a robot should be able to (1) understand and speak natural language in various s-FoRs, and (2) convert from a given s-FoR to other s-FoRs.

Secondly, based on the individual differences in cognitive ability and preference among people, this paper emphasizes the cognitive human-factors related to efficient human-robot interaction. The SPT abilities varies among people, therefore, the robot should aware of this variance and adopt people's perspective when people have difficulty with SPT. Moreover, different people may have different preference on s-FoRs, and the robot should be able to quickly detect people's preference and adjust to that FoR.

Thirdly, based on people's special mind judgment and social cognition to robot, this paper emphasizes the social human-factors related to efficient human-robot interaction. As a special man-made artificial-intelligent creature, the robot is perceived as similar to but also different from our human. On the one hand, people unconsciously employed social rules (e.g., stereotype, in-group bias, and reciprocity) to robot. One the other hand, people is more likely to abuse a robot than to a person. The appearance, language, and movements of a robot (bottom-up cues), and people's knowledge about the robots (top-down cues; e.g., acquired from manuals or advertisements) both influence people's judgment about the mind of the robot, which further affect people's behavior and attitude toward the robot. It is important to design these bottom-up and up-down cues to set the robot's mind fitting for its task requirement.

Keywords: human–robot interaction; natural language; perspective taking; spatial frames of reference; individual differences; mind; social cognition

A CONVOLUTIONAL NEURAL NETWORK MODEL FOR THE IDENTIFICATION OF THE INSTANTANEOUS PHYSIOLOGICAL STATE USING CAMERA IMAGES

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Keywords: *artificial intelligence, remote biomonitoring, heart rate, spaceflight, spatial information*

ABSTRACT

Various sensor technologies have been employed to monitor the instantaneous heart rate (HR) during spaceflight including ballistocardiography. Especially during the performance of physical exercises, HR includes relevant information about the physiological state of a subject. Transducers placed on the chest or arm are the most widely used devices to monitor these HR dynamics. As a non-invasive technology, responses of the blood to visible or infrared light stimuli are used to calculate instantaneous HR (Photoplethysmography, PPG). However, all these methods require a specific contact with the body. As a contactless technique, remote measurement of the PPG is possible with the use of advanced cameras that have improved spatial and temporal resolution properties. This remote measurement approach is named as imaging PPG (iPPG).

The data collected through the iPPG systems should be further analyzed in order to deduce the instantaneous HR information. For this purpose, preferentially temporal waveforms of the iPPG data are used to track HR rather than using the spatial data. In the alternative approach of this study, a Convolutional Neural Network (CNN) algorithm was adapted to perform a classification on the measured iPPG dataset. Two dimensional images were used to train the CNN model including 2 layers of 64 filters with a dimension of 3 x 3. Rectifier linear unit (Relu) activation function was used following a dropout operation. Then a dense layer was implemented with a flattened input finalized by another dense layer of three outputs.

Visual data of the face were collected for three conditions using Bassler camera with a sampling frequency of 250 Hz having a spatial resolution of 370x265 pixels. The experiments were performed in an eye closed seated position for three minutes. A minute of resting was followed by single leg extension and double leg extension exercises each lasting one minute. The forehead area was segmented from each image instance based on the locations of the markers that were attached to the scalp. Randomly selected 80% of the images were used to train the CNN while the remaining 20% were used for evaluation. As a result of the classification, 99% accuracy was obtained for the discrimination of the three conditions in the test dataset. It was observed that high precision and accuracy values mostly depended on the HR levels which differed between the three conditions. The CNN was able to extract from the instantaneous spatial architecture of the images the temporal HR dynamics which were embedded in that special spatial distribution. Thus, this study proposes a CNN model with high accuracy for the extraction of physiological conditions using the spatial data obtained from an instant of image measured in 4 ms.

RESEARCH ON PYROLYSIS TECHNOLOGY OF SPACE TRASH ARTIFICIALLY PRODUCED IN LONG-DURATION SPACE MISSIONS

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Keywords: *space station; pyrolysis; solid waste; reutilization*

ABSTRACT

As human space exploration moves towards deep space, humans are getting farther away from Earth bases, the access to supplies and opportunities has become limited. This poses a serious challenge to how to extend the in-orbit mission time with limited supplies. One feasible way is the trash-to-gas project, reported by NASA, which is to
effectively reduce the volume for more life support equipment and convert trash into high-value products that might include propellants or life supports[1]. Of which, medium temperature pyrolysis method is more potential and promising, the solid waste can be made harmless by high temperature treatment. In this project, we choose 4 typical space station food wastes, based on records from previous ISS and Chinese space simulation experiment, including Shrimp fried rice, Beef ,Chow Mein and Millet gruel. First, we characterized the pyrolysis characteristics of different space solid wastes, typical space food analysis results are shown in table 1. Next, the key kinetics features were obtained by a standard pyrolysis experiment at 10 K/min from 20ºC to 1000ºC. The evolved gases distribution was gained by using a thermogravimetric analyzer with GC/MS. In addition, quantitative assessments of the primary resource gases – carbon dioxide, carbon monoxide, and methane was provided by the GC. Figure 1 shows the result of millet gruel. Other gas products, present in much smaller amounts, the char residue is typically less than 25-30% of the initial mass of the solid waste[2]. Otherwise, we analyzed the product distribution of different solid wastes in different pyrolysis stages, and studied the pyrolysis mechanism of single component solid wastes. Typical space food analysis results are shown in table 2. The LRR project has developed versions of a logistics and waste model for human exploration missions[3]. Further work would be carried on the pyrolysis experiments on the standard waste model, to select the optimal conditions.

Table 1 - Proximate and ultimate analysis of typical space station food waste

Sample	Proximate analysis(%)				Ultimate analysis(%)		
	M_{ad}	A_{ad}	V_{ad}	FC_{ad}	C	H	N
Shrimp fried rice	7.8%	64.7%	2.5%	25.0%	33.23%	7.349%	29.45%
Beef	2.6%	81.7%	1.4%	14.3%	31.05%	7.399%	26.90%
Chow Mein	6.3%	67.6%	4.6%	21.5%	32.50%	7.395%	23.40%
Millet gruel	9.5%	70.5%	2.4%	17.6%	30.66%	6.911%	29.47%

Table 2 - Pyrolysis parameters of four typical space station food waste

Sample	*T*/ ºC	T_{max}/ºC	A/min^{-1}	*E*/(KJ/mol)	R^2
Shrimp fried rice	244~343	305	7.05×10^{10}	134.99	0.994
Beef	195~496	343	5.36×10^{7}	134.67	0.954
Chow Mein	225~442	288	1.13×10^{9}	117.85	0.974
Millet gruel	250~353	300	7.30×10^{10}	139.96	0.985

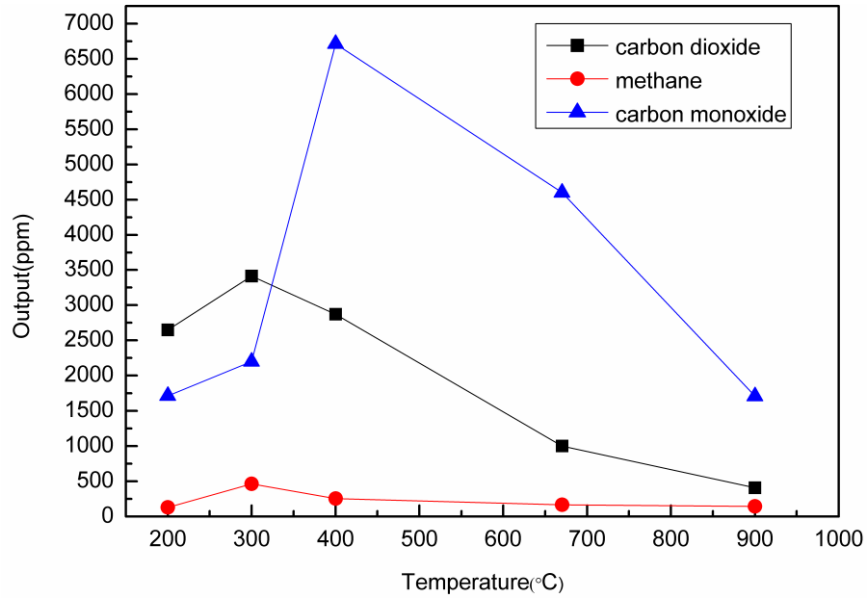

Figure 1 - Carbon dioxide, methane, carbon monoxide production of millet gruel under standard pyrolysis experiment

Comments:

This subject is of great significance for solving the problem of solid waste reduction and turning waste into treasure within the limited space.

ROLE FOR INTERNATIONAL CIVIL AVIATION ORGANISATION (ICAO) IN THE COMMERCIAL SUBORBITAL AND ORBITAL SPACE TOURISM: OPPORTUNITIES AND CHALLENGES

Vijay Kumar, Dr S R Subramanian, Dr (Prof.) K D Raju

ABSTRACT

The prospect of newer space activities such as Orbital; Sub-orbital; or Point -to- Point travel has made outer space busier like never before. However, the current international legal, and regulatory regime has not been so coherent to deal with this challenge. Since, the commercial suborbital and orbital space tourism (CSOST) and Point-to-Point Travel require launch activities involving the airspace which has been traditionally used by the aviation sector, the identifiable legal framework is essential to regulate the same.

However, the sustainable benefit of this space activities could be realized only when an international law relating to outer space pave the way for CSOST clearly and bring uniformity or singularity in/among international organizations. Currently, the United Nations through the Committee on the Peaceful Uses of Outer Space (COPUOS), and the Office for Outer Space Affairs (UNOOSA) deal the matter relating to outer space. Of late, in 2015, the ICAO and UNOOSA attempted to bring together the aviation and space communities together through “Aerospace Symposium”, “to explore [the] existing regulations and practices as well as safety management and systems engineering methods with regard to civil aviation, suborbital flights and developments in space transportation.”

In the wake of increased CSOST activities, it is being felt that there is a clear need for a specialized organization which could work as the regulatory, guiding international body. In respect of several issues concerning CSOST such as Space Traffic Management (STM), Spaceports, Space Vehicles, Space Stations, Safety and Security Standards, and Liability mechanisms, it is opined that the ICAO can adequately address the same. Since, ICAO has a prior track record and have been recognized as a specialized agency of the United Nations in/for the aviation sector, it is argued that the ICAO is capable of doing the same for CSOST. Considering the importance of the area, the ICAO has included space transportation in its list of emerging priorities.

It is, in the light of above, the Part I of the paper details about the CSOST, its rising importance, and viability in the current context. Since the CSOST is a recent technologically-enabled phenomenon, it is pertinent to examine the existing international law pertaining to outer space to assess the viability of CSOST under the current international law regime. Therefore, the Part II of the paper explores the international law relating to CSOST. In Part III, the paper examines the role of different international organizations that are dealing with the space activities and specifically the CSOST. The role of the United Nations will be critically analyzed in this part. In Part IV, the paper makes an argument in support of ICAO as an organization which could establish the coherence between airspace and outer space. To conclude, the paper advocates for the comprehensive role of ICAO for the success of CSOST and subsequently arising challenges.

Key Words: ICAO, CSOST, International, Space

HYGIENIC ASPECTS OF CHEMICAL SAFETY OF THE AIR ONBOARD MANNED SPACECRAFTS DURING LUNAR MISSIONS.

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The forthcoming lunar missions and long autonomous flights in deep space exploration (flights to Mars) will require an automatic control system for sanitary and hygienic safety of the air environment which needed to be integrated with life support systems of the spacecraft. The automatic control system will provide a quick respond in real-time mode including hygienic preventive measures aimed at reducing the toxic risks to the crew's health, which is especially important in case of abnormal and emergency situations. The basis of the system will be the chemical and analytical monitoring of harmful substances in the air of the spacecraft, as an objective criterion, to establish priorities in making optimal management decisions.

Currently, the main elements of air quality monitoring strategy are formulated, as well as, toxicological and hygienic requirements for chemical and analytical monitoring tools.

The monitoring and information system will control the components of the complex in nominal mode and emergency situations. In relation to interplanetary missions, the system includes:

- control of chemicals in the air of spacecraft (volatile organic compounds and inorganic substances) and data transmission to the Earth using telemetry in real time mode.
- individual control of CO_2 in the breathing zone for every crew member.

In this regard, today, an important area of research that requires a priority decision is the development of promising chemical analytical technologies to create an analytical complex operating in real time mode and providing continuous and dynamic monitoring of harmful substances in the air of spacecraft. The complex has to take into account the specifics of a long-term autonomous manned flights.

The automatic control system requires:

- informational and predictive system of toxicological and technical assessment in case of emergency situation to setup an effective operation mode for air cleaning and regeneration system and the algorithm of toxicological measures for the operational decision-making to ensure crew safety;
- informational and calculation system to analyze the distribution of chemicals in modules in case of emergency situation for operational toxicological risk of crew members;
- establishing of hygienic standards for the combined effects of the main adverse environmental factors (chemical, ionizing radiation, weightlessness) and permissible concentrations of CO_2 for 5-years space flight;

The first phase is the development and implementation of chemical analysis equipment for operational monitoring of CO_2 distribution on the ISS. CO and other pollutants, in case of the emergency situation (thermo-oxidative destruction of polymers (fire events), depressurization of coolant systems, to assess the toxic risk for each crew member:

- continuous, dynamic monitoring of O_2, CO_2, CO, NH_3, CH_4, HF, HCL, HCN in real-time mode onboard the ISS;
- individual monitoring of CO_2 exposure concentrations in the breathing zone of each crew member.

Supported by a contract (16-03-930) from RSC-Energia, a grant (64.1) from the Russian Academy of Sciences

EVALUATION OF AN ALTERNATIVE SOLUTION FOR WATER MICROBIAL MONITORING OF FECAL CONTAMINANTS FROM WATER IN THE INTERNATIONAL SPACE STATION

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ABSTRACT

To keep astronauts in good health and to prevent infection by the spacecraft environment, it is necessary to periodically control the level of contamination of air, surface and water. During future manned space mission, crew will have to be independent for a long period: the tests procedure must be as simple as possible, with long shelf-life reagents.

The Aquapad 1ml experiment was developed for Thomas Pesquet Proxima mission (2016-2017) in collaboration between the French Space Agency (CNES) and bioMérieux. It aimed to evaluate a new solution for microbial water monitoring (total count parameter in 1 ml of water sample).
As the Aquapad 1ml, the Aquapad 100ml is also based on PAD (Paper Analytical Device), a bioMerieux patented technology which allows bacterial growth inside a cellulosic support containing culture medium powder.

Since most waterborne diseases are related to fecal contaminations, water microbiology is largely based on the need to identify indicators of fecal pollution such as E.coli, and Enterococci in large water sample sizes . The worldwide reference methods used for monitoring of fecal contamination of All water intended for human consumption water is done on 100 ml of water. The legal standard is absence of these contaminants in the water samples to be analysed .

Compared to the Aquapad 1ml, the new Aquapad 100ml aims to detect and quantify the fecal contamination of 100 ml of water and allows the detection of both *E. coli* and *Enteroccocus* bacteria.

Compared to the reference method, the Aquapad 100ml method
- does not need any Laboratory infrastructure to be performed *i.e*. benches, filtration ramp
- does not need any skills in microbiology
- is easy to use and rapid
- allow the detection of both Gram + and Gram - bacteria from the same sample .

More precisely, the workflow of the Aquapad 100mL is as follows: the 100 ml volume drinking water to analyze is injected inside the Aquapad 100ml . The disposable embeds a filtration membrane that traps the bacteria on its surface and a PAD with specific and chromogenic dry culture medium components that solubilize in contact with water. The filtered water going out of the disposable could be reinjected in the ISS water recycling system.

If *E. coli* bacteria are present in water, red dots will appear after an incubation step (1 red dot = 1 Unit Forming Colony). The coloration of the dot will be green for *Enterococcus* bacteria. Thus, the Aquapad 100ml provides a multiplex detection and quantification of two different types of fecal contaminants from the same water sample.

Numerous experimentations done in laboratory showed good microbiological performances of the Aquapad 100mL . This was a pre requisite to perform additional experimentations in parabolic flights. These flights are considered as optimal tools for the evaluation of the operational workflow and fluidics analysis of new disposables such as the Aquapad 100ml in microgravity environment. A parabolic flights campaign is scheduled in April 2019 in Bordeaux (France). The French Space Agency and bioMérieux teams will do together the 0g experimentations and analyze the Aquapad 100ml performances for microbial monitoring of fecal contaminants from water.

Presentation of the results and their analysis will be done at the 22nd Humans in Space Symposium

INTEGRATION OF DIFFERENT METHODS OF ORGANIC WASTE RECYCLING FOR THE ORGANIZATION OF HIGHLY CLOSED MATTER TURNOVER IN BTLSS

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Keywords: biotechnical life support systems, organic waste processing, wet combustion, soil-like substrate, plant unit.

ABSTRACT

The organization of long-term mass transfer processes in biotechnical life support systems (BTLSS) with high closure requires mineralization of organic waste of plant and animal origin, as well as household waste. The products of mineralization of such waste should be integrated into the overall mass transfer of BTLSS. This integration is ensured by the efficiency of methods of processing organic and sanitary waste to products assimilated by the plant unit. The SB RAS Institute of Biophysics is developing a biological-soil-like substrate (SLS), and physical-chemical — wet combustion in a water solution of hydrogen peroxide, waste utilization methods, which are tested in long-term (up to several months) experiments with physical models of BTLSS. In the course of such studies, it is possible to identify a number of features in the interaction between the technical, biological and chemical components of the system.

This paper presents the results of a series of experiments performed during the five years of organizing the flow of the substance between the waste unit and the higher plants unit using different types of organic waste: human metabolites (gaseous, liquid and solid excreta), plant waste (wheat straw, an inedible biomass of vegetable crops), fish waste (scales, viscera and heads) and sanitary waste (cotton material and the gray water after washing dishes).

The methods allowing normalization and activate the processes of biological mineralization of organic material in SLS, increase the depth of purification of the gas environment (both in BLSS as a whole and in the unit of physical and chemical waste utilization), increase the degree of mineral elements transfer in the form available to plants during wet combustion of organic waste are shown. Principles of application of wet combustion for different types of organic waste have been developed. The results of experiments on the cultivation of a number of crops (wheat, lettuce and radish) using solutions of mineralized waste of various types are presented. A comparative assessment of yields (mass, mineral and biochemical composition) obtained under using the mineralized solutions prepared with new techniques and without them is given. The estimation of increasing of the closure degree of mass exchange for a number of elements in the BLSS at the use of developed technologies and technological methods is presented. The integrating possibilities of the mineralization products of different waste types into general matter turnover process to increase the closure degree of BTLSS have been discussed.

This study was carried out at the IBP SB RAS and supported by the grants of the Russian Science Foundation (Projects No 14-14-00599П; No17-74-10147) and the framework of subject No. 56.1.4. in accordance with State Program for IBP SB RAS for 2013-2020.

PROTEIN SIGNALING MOLECULES AND AUTONOMIC REGULATION OF HEART RATE IN COSMONAUTS

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The strategy of adaptation of the human body in microgravity is largely associated with the plasticity of cardiovascular system regulatory mechanisms. The purpose of this work was to clarify urine proteome changes associated with the initial condition of the heart rate autonomic regulation mechanisms in cosmonauts who have participated in long space missions. The object of the study was urine samples and 5-minute samples of electrocardiogram (ECG) at rest in twelve male Russian cosmonauts (age 46.5±3.4 years). Collection of urine samples and ECG studies was carried out on 30-45 days before start and on 1st and 7th day after landing.

Depending on the heart rate (HR) and the autonomic regulation parameters in background studies, the subjects were classified into two groups (each consists of 6 subjects): HR in the first group was 60,12±2.21 bpm, in the second group – 75,02±3.31 bpm. About 200 different proteins were determined in urine samples, 34 of which were statistically significantly changed in the entire sample of 12 cosmonauts ($p<0,01$) at the first day after space flight when compared with background data. In addition, 28 proteins changed when comparing +1 and +7 days of the recovery period and 14 – when comparing the background and + 7 day, respectively. From the general proteins list, in accordance with the classification into two groups by the pre-flight peculiarities of autonomic regulation of heart rate, 8 proteins were revealed which are significantly different in groups ($p<0,05$) at different points of the study 02±3.31 bpm. The proteins cadherin-13, mucin-1, alpha-1 of collagen subunit type VI (COL6A1), hemisentin-1, semenogelin-2, SH3 domain-binding protein, transthyretin and serine proteases inhibitors realize a homeostatic role in individuals with different initial type of the cardiovascular system regulation.

The space flight induced urine proteome changes are significantly different in the groups identified by heart rate autonomic regulation peculiarities before space flight. All these proteins regulate the associated biological processes which affect the stiffness of the vascular wall, blood pressure level, the severity of atherosclerotic changes, the rate and degree of age-related involution of elastin and fibulin, age-related increase in collagen stiffness, genetically determined features of elastin fibers.

The increased vascular rigidity (including the aorta) and of myocardium may be regarded as a universal response to various extreme factors. Significant differences in the semi-quantitative analysis of signal proteins between groups with different types of autonomic regulation are explained by a common goal: to ensure optimal adaptation regardless of age and of the genetically determined type of responses to the extreme environmental factors effects.

The work was supported by RFBR grant № 18-34-00524, basic Russian Academy of Sciences themes 64.1 and 65.3 for 2013–2020 years.

APPLICATION OF PROSTHESIS ACCELEROMETERS TO RESTORE CONTROLLED MOVEMENTS IN MICROGRAVITY CONDITIONS

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Introduction: The microgravity conditions in orbit and celestial atmospheres are physiologically compromising for humans, who are accustomed to the 1-G environments on Earth. Of these, motor and fine-dexterity tasks involving the extremities, particularly in locomotion, grasp and release, are influenced becoming delayed and placing greater force demands. With the accelerating pace of prosthesis developments, research has reached frontiers in the development of biomechanical systems providing both sensory and motor feedback platforms to the user. A recent study has suggested the use of accelerometers in the control of prosthetic arms. The authors hereby propose incorporating this same technological innovation into loading suits designed for use in orbit or celestial environment.

Prosthesis model: Conventionally, accelerometers have been designed to utilize input of EMG signals to quantify the neuromuscular signaling patterns of the innervating motor units. Kyberd and Poulton (2017) suggest the use of a tri-axial system whereby sensors and controllers are employed to detect and correct for 1) segment orientation, 2) motion compensation, and 3) inertial platform. Segment orientation is a compensatory mechanism for the accelerometer that takes into consideration the gravitational forces and tri-dimensional, spatial alignments in order to accommodate the motor demand accordingly. Motion compensation adapts for the positioning using the surrounding prosthetic limb segment kinematics. Inertial platform uses holistic, mathematical analysis of prosthesis in interaction with an object of interest.

Model for loading suit incorporation: Here the authors suggest the design of accelerometers within prosthetic elements embedded within loading suits, which use EMGs for input signal detection, quantification, and predictive output modeling. This will be used as a means to effectively reproduce the same three parameters of the current model. Moreover, gravitation is not expected to have an effect as this system exploits conceptions in alignment with the Equivalence Principle, which states that forces due to gravity and acceleration are indistinct. This suggests technology can conceivably be designed to accommodate both prosthetic users and non-prosthetic users in space. It is anticipated that this technology can enhance tasks such as repairs or construction or perhaps in recreational design when considering commercial and private human access to space.

DISUSE IMPAIRS THE MECHANICAL COMPETENCE OF BONE BY REGULATING THE CHARACTERIZATIONS OF MINERALIZED COLLAGEN FIBRILS IN CORTICAL BONE

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Introduction The mechanical properties of the bone play a decisive role in the resistance of the bone to fracture. Clinically, the quantity of the bone in the mineral phase has been considered as the gold-standard indicator for the risk of bone fracture. However, the bone is a complex tissue with a hierarchical-structure consisting of organic matrix, mineral hydroxyapatite, and water. Collagen comprises up to 90% of the organic matrix in the bone, and is vital for its mechanical behavior. To date, the morphological and mechanical responses of the mineralized collagen fibrils in the bone matrix to mechanical loading have been largely overlooked. Moreover, how the mineralized collagen fibrils in bone respond to musculoskeletal disuse remains unknown. The purpose of the present study was to outline the morphological and mechanical alterations of the mineralized collagen fibrils under mechanical loading and after disuse. The deformation mechanisms of the healthy and disused bone at the microscopic scale were investigated.

Methods BALB/c male mice at ten weeks of age were used in the present study. An atomic force microscopy-based imaging and indentation approach was introduced and integrated with a murine tibia axial loading model. Morphology of the mineralized collagen fibrils of the murine cortical tibia was imaged after demineralization. The in situ elastic modulus of the fibrils was quantified under the progressive loading conditions at 0 N, 3 N and 6 N. Furthermore, a hindlimb tail-suspension unloading model was adopted to induce bone loss in mice. the morphology of the MCFs in the bone matrix was scanned using atomic force microscopy. The nano-indentation approach was adopted to assess the in situ mechanical properties of the single MCF. Nano-indentation was used to assess the micro-scale mechanical properties of the demineralized bone surface. Bone deformation regimes of both the normal and the disused bone at the nanoscale level under mechanical loading were analyzed and discussed.

Results and Discussion Results suggested that the mineralized collagen fibrils were stretched in the early phase of bone deformation, characterized by the elongation of the D-periodic spacing. Reorientation of the collagen fibrils was demonstrated in the subsequent phase of bone deformation. The in situ radial elastic modulus of the collagen fibrils remained constant under different loading conditions.

The orientation and D-periodic spacing of the collagen fibril remained unchanged during bone loss. By contrast, disuse significantly reduced the elastic modulus of the fibrils. Under axial mechanical loading, the collagen fibrils in the disused tibia were significantly misaligned. Although the D-periodic spacing of the fibrils increased under loading, no group difference was observed. Elastic modulus of the fibrils returned to the same level across different groups during load-bearing condition.

Conclusions In conclusion, the present study indicates that the orientation and D-periodic spacing of the mineralized collagen fibrils in the antero-medical aspect of the cortical tibia remained unchanged after disuse. However, disuse reduced the in situ radial elastic modulus of the collagen fibrils. During load-bearing conditions, the collagen fibrils in the disused bone were misaligned. Meanwhile, the in situ radial elastic modulus of the collagen fibrils was returned to the same level as the control, which implied that there may be a compensation mechanism for the disused bone to resist mechanical loading at the nanoscale. These findings presented unique adaptation regimes of the collagen fibrils in cortical bone during disuse. The observation offers the possibilities of revealing the deformation mechanisms of bone in the relevant pathological process.

TARGETING SR STRESS TO MITIGATE DISUSE-INDUCED MUSCLE ATROPHY DURING STIMULATED MICROGRAVITY.

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Mechanical loading is necessary for the development and maintenance of musculoskeletal system. Removal of loading via microgravity, paralysis and prolong bed rest leads to rapid loss of muscle mass and strength. Typically, the muscle atrophy and weakness sets up by ≈5-6 days of unloading and progressively become worse. To date, no effective pharmacological therapy exists to boost muscle mass and force during prolong unloading, partly because the mechanisms are poorly understood. Dysfunction of protein folding by Endo/Sarco-plasmic reticulum (ER/SR), a condition called ER/SR stress is implicated in diseases of various cell types, but its contribution to muscle detriment during mechanical unloading remains elusive. Recent evidence suggest that the chronic activation of SR stress and its downstream signaling pathways, the unfolded protein response (UPR) in the skeletal muscle is associated with various catabolic & degenerative diseases and myopathies. Mitigating SR stress prevents muscle atrophy and/or weakness in congenital myopathies but such intervention has not been tested during mechanical unloading. Further, some component of UPR might be protective to muscle health which require proper dissection of relative role(s) of individual UPR arms in muscle impairment. However, establishing a direct causality between SR stress and muscle detriment during unloading requires measuring muscle mass and force in conditions with or without chronic SR stress, which has not been done to date. Due to difficulty of performing experimental interventions in humans, various animal models have been developed to recapitulate disuse muscle atrophy such as denervation, prolong sedation and cast immobilization. These experimental models induce muscle loss but fail to mimic conditions of prolong bed rest or space flight due to off-target effects of nerve injury, anesthetic drugs or mechanical strain by cast. Here, we are using a mouse model of hind-limbs suspension as an experimental model for microgravity-induced muscle loss. Hind-limbs suspension has an advantage over other models in recapitulating microgravity conditions because it induces muscle atrophy by mechanical unloading while still allowing limb movement. Currently, the mice hind-limbs are being subjected to 1 & 4 weeks of mechanical unloading and are injected with pan-SR stress inhibitors or inhibitors of individual UPR arms. We are measuring the degrees of activation of SR stress and its downstream effects on skeletal muscle biochemical and functional health at various time points of unloading. The gastrocnemius muscle from the hind-limbs is used for investigations because of large body of literature on the response of this muscle to disuse. We report no significant change in the body mass of the unloaded mice when compared to control group. However, there was significant atrophy ($p < 0.05$) of the gastrocnemius muscles when compared to loaded control, starting at ≈6 days of unloading. Reduced muscle mass was partly due to significant reduction in the cross-sectional area (CSA) of single muscle fibers ($p < 0.05$) in the gastrocnemius muscles, while the total fiber count was unchanged. The grip strength of the hind-limbs, adjusted to body mass was significantly reduced ($p < 0.05$) when compared to loaded controls. These changes were accompanied by increased protein expression of SR chaperons GRP94 and BiP which relate to increase in the SR stress. Currently we are investigating the effect(s) of inhibition of pan-SR stress and individual UPR on the biochemical and functional properties of gastrocnemius muscles.

Since currently no pharmacological drug exists to offset skeletal muscle atrophy and weakness associated with prolong disuse, our studies might offer novel therapeutic targets to skeletal muscle impairment during conditions of prolong mechanical unloading such as microgravity.

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TARGETING MITOCHONDRIA FOR PREVENTING UNLOADING-INDUCED SKELETAL MUSCLE ATROPHY AND BONE LOSS

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Key words: muscle atrophy, bone loss, mitochondrial nutrients

ABSTRACT

The bone loss and skeletal muscle atrophy are severe pathogenic disorder in long-time space flight. Mitochondria, the organelles where many vital metabolic reactions proceed, are closely involved in the metabolic disruption under microgravity condition.

We and others previously reported mitochondria act as a central role in skeletal muscle atrophy. We found sedentary mitochondrial dynamics of mitochondrial fusion and fission, and activation of mitochondria-associated apoptotic signaling, was induced by unloading in muscles of unload rodent model, while mitochondrial respiration was compromised earlier than the emerging of atrophy markers, like MuRF1 and Fbx32.

Recently, we reported the involvement of SIRT3-regulated mitochondrial stress in bone formation. During osteoblast differentiation, SOD2 was specifically induced to eliminate excess mitochondrial superoxide and protein oxidation, whereas SIRT3 expression was increased to enhance SOD2 activity through deacetylation of K68, indicating that SIRT3/SOD2 is required for regulating mitochondrial stress and plays a vital role in osteoblast.

We found that reloading protected mitochondria against mitochondrial loss, abnormal mitochondrial morphology, inhibited biogenesis, and activation of mitochondria-associated apoptotic signaling induced in unload rodents. Importantly, our study demonstrates that some agents targeting mitochondria show benefits in preventing or curing muscle atrophy and bone loss, which we defined as "mitochondrial nutrient". Such as a combination of mitochondrial nutrients, including α-lipoic acid, acetyl-L-carnitine, hydroxytyrosol, and CoQ10, which we designed to target mitochondria, was able to efficiently rescue muscle atrophy via a reloading-like action. Resveratrol, another mitochondrial nutrient, efficiently reversed dexamethasone-induced mitochondrial dysfunction and muscle atrophy in both C2C12 myotubes and mice by improving mitochondrial function.

In summary, our study suggests that mitochondrial metabolic remodeling respond earlier than the atrophy & bone loss markers under microgravity, mitochondrial nutrients improving metabolic function is a novel promising approach ameliorating muscle and bone loss.

THE PROTECTIVE EFFECT OF HEMOJUVELIN ON UNLOADING MUSCLE ATROPHY AND ITS MECHANISM

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Abstract

Transforming growth factor-β1 (TGF-β1) contributes to unloading muscle atrophy, inhibition of TGF-β1 signaling is a promising therapeutic strategy for the muscle atrophy. Hemojuvelin (HJV or Hjv as the murine homolog) is a membrane-bound protein that is highly expressed in skeletal muscle, heart and liver. In hepatic cells, Hjv acts as a co-receptor for bone morphogenetic protein (BMP), a TGF-β subfamily member. The aim of this study was to investigate whether Hjv plays an essential role in unloading muscle atrophy by acting as a co-receptor for TβRIIin TGF-β1 signaling. In the present study, we demonstrated that HJV was significantly downregulated during the hindlimb unloading-induced muscle atrophy of mice compared to their controls. Overexpression of Hjv rescued the dystrophic effects. Unlike its function in hepatic cells, the BMP downstream phosphorylated p-Smad1/5/8 signaling pathway was unchanged, but TGF-β1, TGF-β receptor II (TβRII), and p-Smad2/3 expression were increased in Hjv-deficient muscles. Mechanistically, loss of Hjv promoted activation of Smad3 signaling induced by TGF-β1, whereas Hjv overexpression inhibited TGF-β1/Smad3 signaling by directly interacting with TβRII on the muscle membrane. Our findings identify an unrecognized role of Hjv in skeletal muscle by regulating TGF-β1/Smad3 signaling as a coreceptor for TβRII. Unlike the TGF-β1/Smad3 pathway, Hjv could be a reliable drug target as its expression is not widespread. Novel therapeutic strategies could potentially be devised to interfere only with the muscle function of Hjv to treat unloading muscle atrophy in spaceflight.

Keywords Hemojuvelin; Hindlimb Unloading; Muscle Atrophy; TβRII; TGF-β1

DISORDER OF IRON METABOLISM INHIBITS THE RECOVERY OF UNLOADING-INDUCED BONE LOSS IN HYPOMAGNETIC FIELD

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Key words

hindlimb unloading, reloading, hypomagnetic field, geomagnetic field, iron storage.

Abstract

Background: Exposure of humans and animals to microgravity in spaceflight results in variously deleterious effects on bone health. In addition to microgravity, the hypomagnetic field (HyMF) also is an extreme environment in space, such as on the Moon and Mars, magnetic intensity is far weaker than the geomagnetic field (GMF) on the earth. Recently, we demonstrated that HyMF promoted additional bone loss in hindlimb unloading-induced bone loss, and the underlying mechanism probably involved in the increase of body iron storage. Numerous studies have indicated that bone loss induced by mechanical unloading can be largely restored after skeletal reloading in GMF condition. However, it is unknown whether this bone deficit can return to a healthy state under HyMF condition.
Objective: The purpose of this study is to examine the effects of HyMF on the recovery of microgravity-induced bone loss, and illustrates the changes of body iron storage in this process.
Methods: Eight-weeks-old male C57BL/6 mice were housed in an ambient temperature of 24 ± 2 °C, free to provide standard laboratory rodent food and water and maintained on a 24-hour light-dark cycle condition. Mice were subjected to HLU for 4 weeks followed by 4 weeks of reambulation in GMF and HyMF. Random grouping: the baseline group (BL, exposed to GMF for 4 weeks, n=8/group); the HLU group (hindlimb suspension for 4 weeks, n=24/group), the control group (Ctrl, exposed to GMF for 8 weeks, n=8/group). Subsequently, the HLU mice were reloaded by return to normal weight bearing and randomly divided into two groups, respectively exposed to HyMF (<300nT) and GMF (~ 50μT) conditions for another 4 weeks, represent as the HLU+GMF group (n=8/group)and the HLU+HyMF group (n=8/group).
Results: There was lower bone mineral density (BMD) and bone mineral content (BMC) in the HyMF reloading group compared to the GMF reloading group. Reloaded mice in the HyMF condition had a worse microstructure of femur than in the GMF condition. Femoral mechanical properties, including the elastic modulus, stiffness and ultimate stress, were poorer and toughness was higher in the HyMF group compared with the GMF group. Simultaneously, more iron content in serum, the tibia, liver and spleen were found under HyMF reloading than GMF reloading. **Conclusions:** HyMF inhibits the recovery of microgravity-induced bone loss, probably by suppressing elevated iron levels return to physiological level.

Figure1

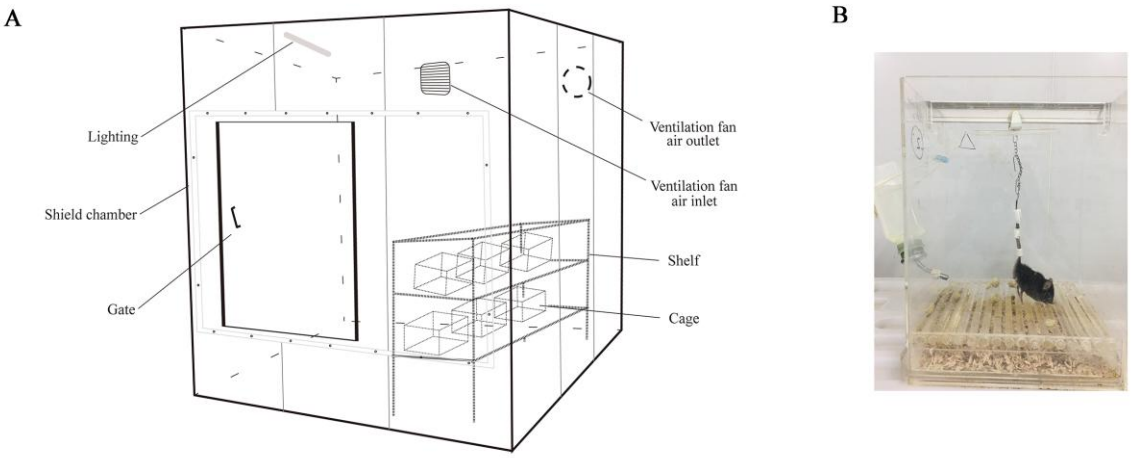

A
Lighting
Shield chamber
Gate
Ventilation fan air outlet
Ventilation fan air inlet
Shelf
Cage
B

Figure2

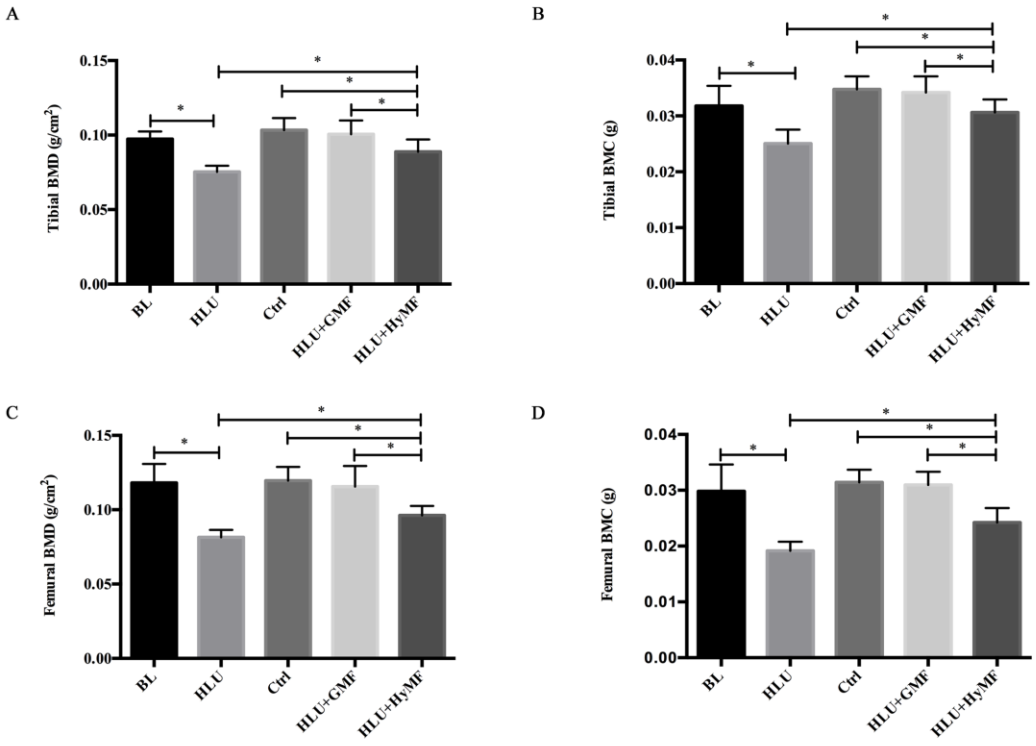

A
Tibial BMD (g/cm²)
0.15
0.10
0.05
0.00
BL
HLU
Ctrl
HLU+GMF
HLU+HyMF
B
Tibial BMC (g)
0.04
0.03
0.02
0.01
0.00
C
Femural BMD (g/cm²)
D
Femural BMC (g)

Figure3

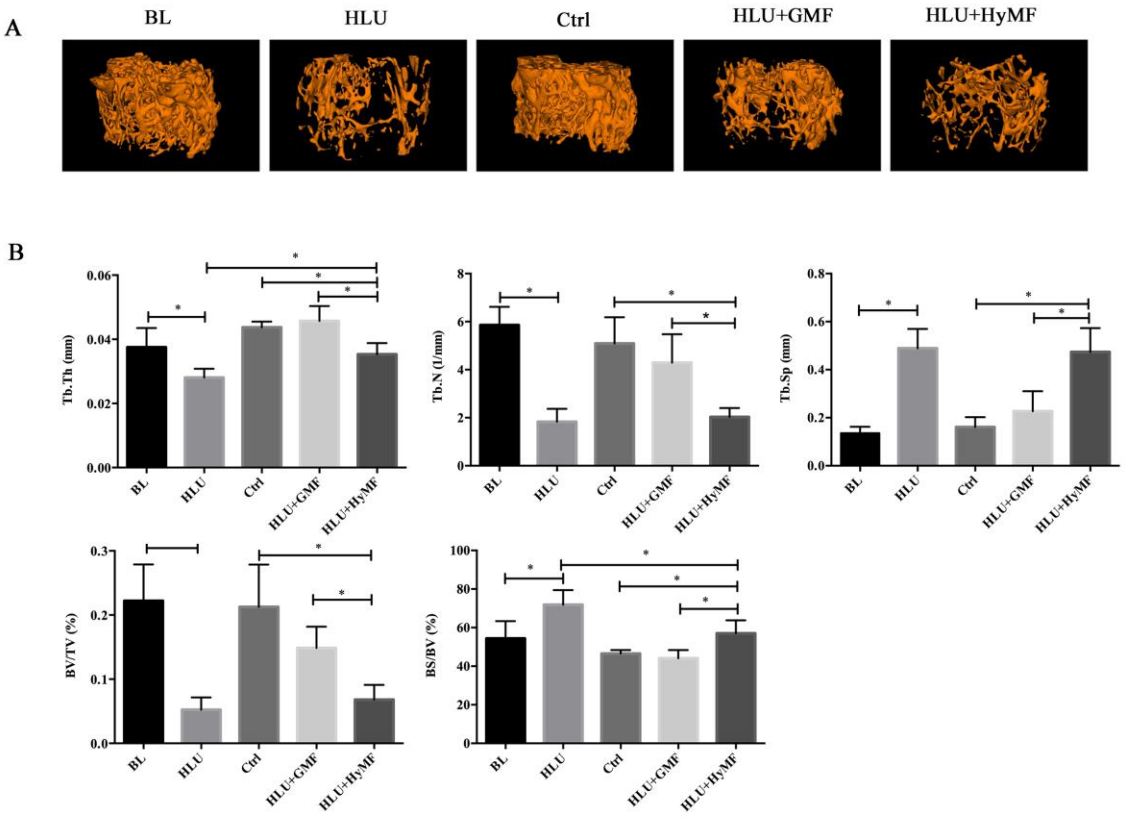

A
BL
HLU
Ctrl
HLU+GMF
HLU+HyMF
B
Tb.Th (mm)
Tb.N (1/mm)
Tb.Sp (mm)
BV/TV (%)
BS/BV (%)
BL
HLU
Ctrl
HLU+GMF
HLU+HyMF

Figure4

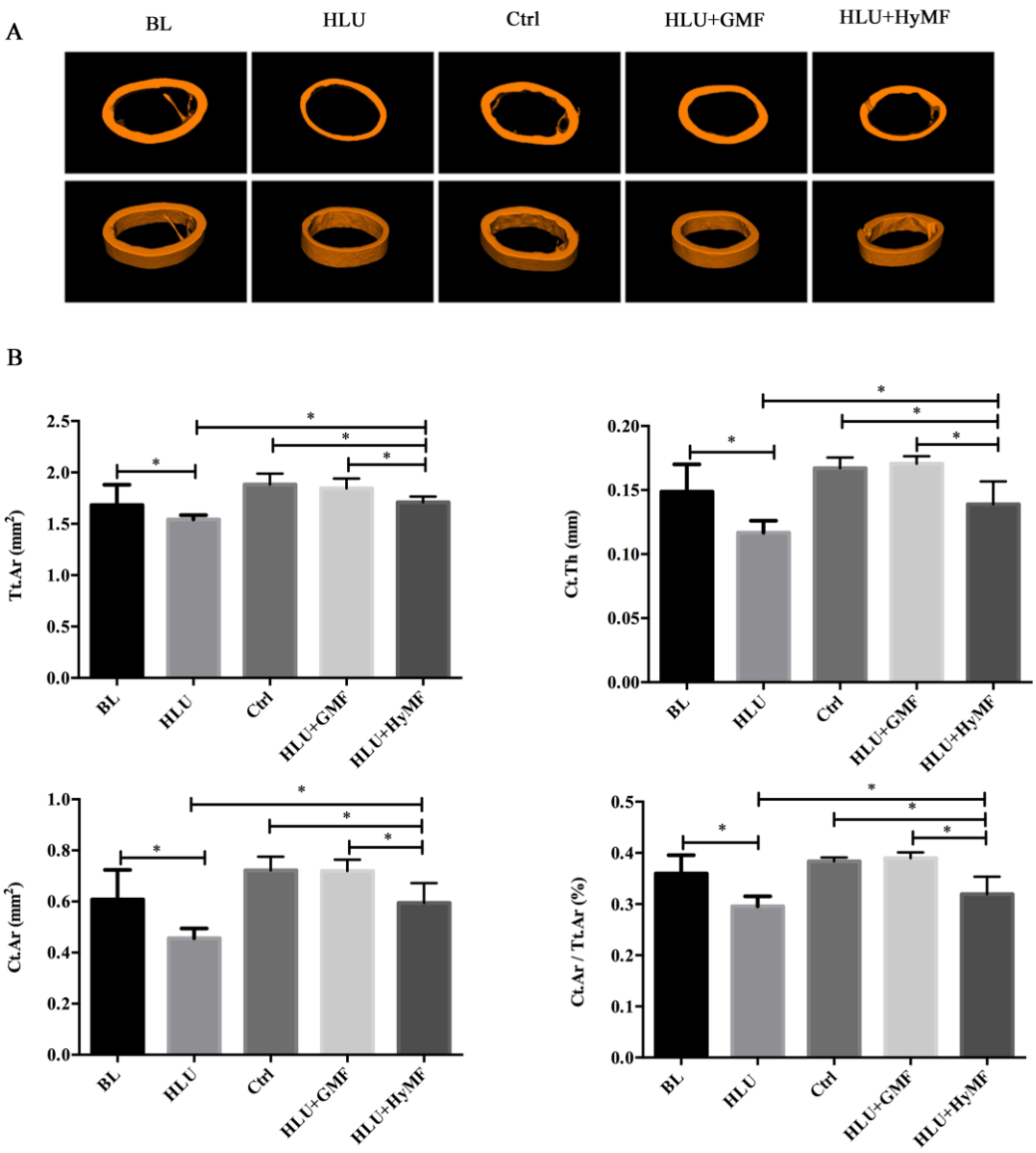

A
BL
HLU
Ctrl
HLU+GMF
HLU+HyMF
B
TtAr (mm²)
Ct.Th (mm)
Ct.Ar (mm²)
CtAr / TtAr (%)
BL
HLU
Ctrl
HLU+GMF
HLU+HyMF

Figure5

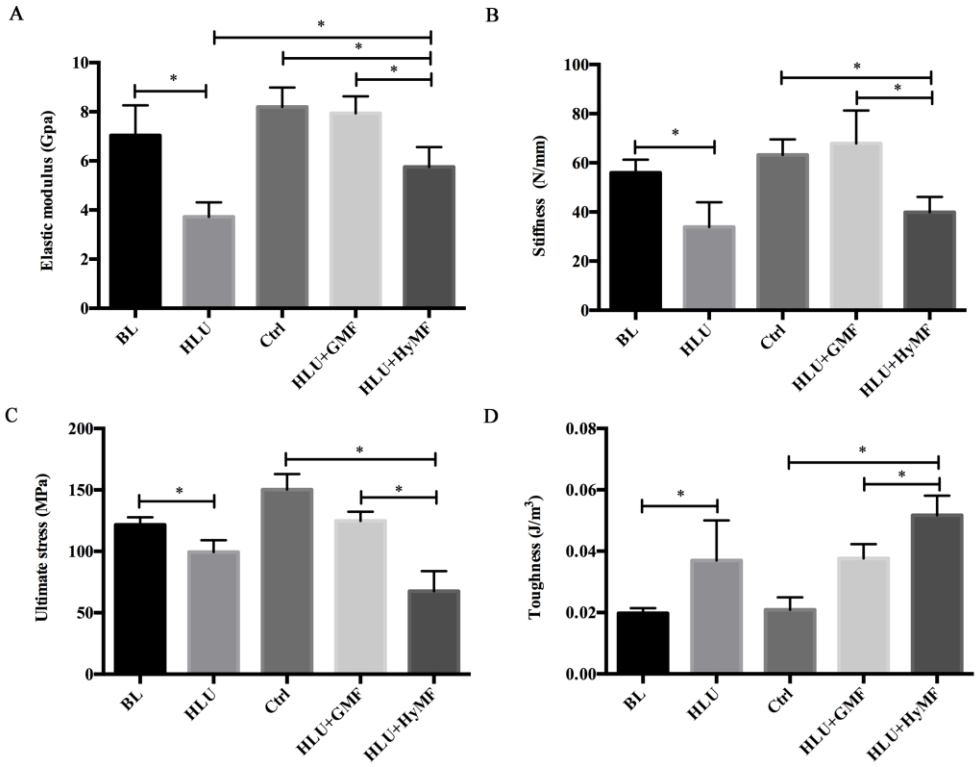


Figure6

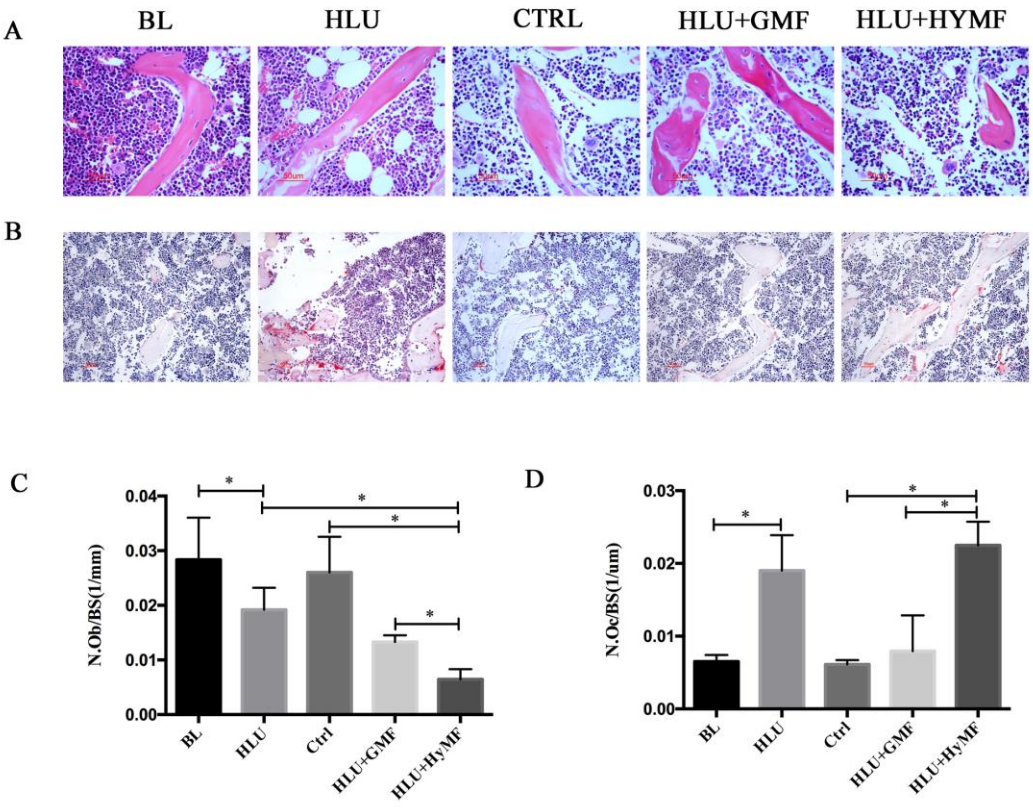
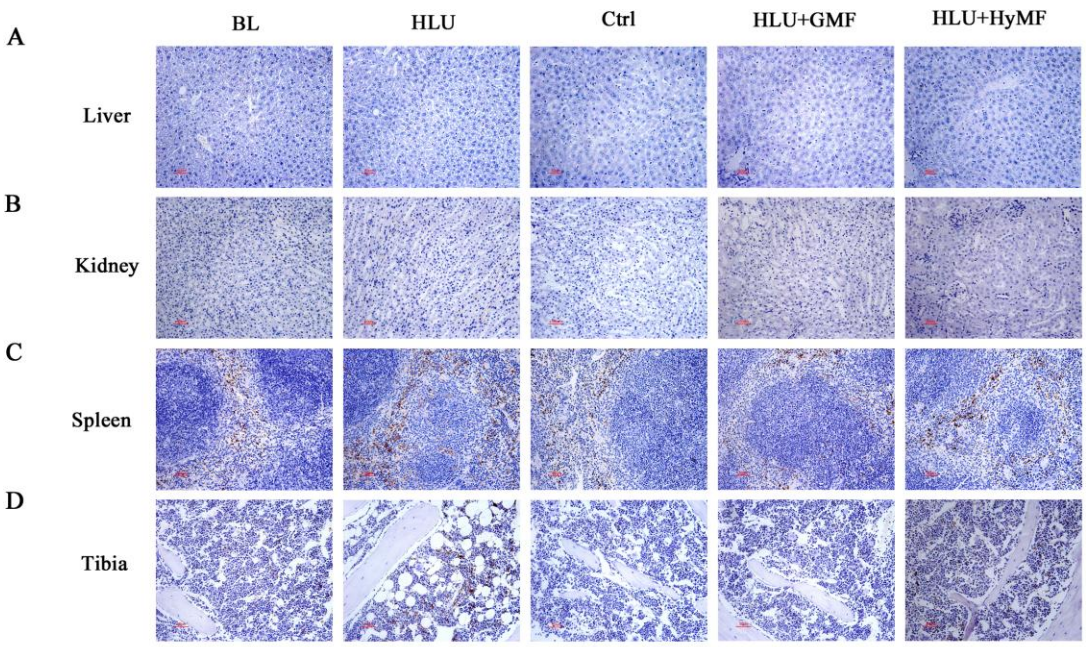
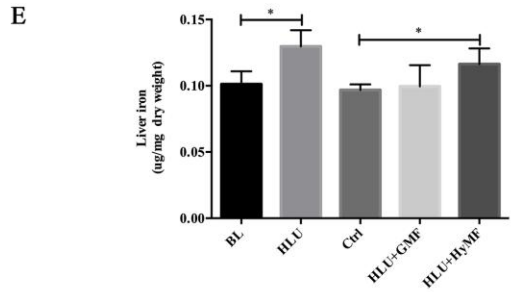
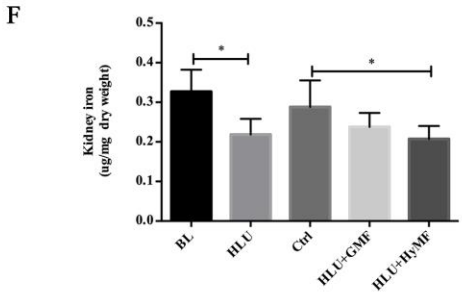
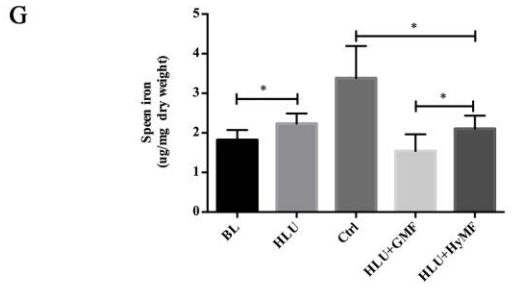

A
BL
HLU
CTRL
HLU+GMF
HLU+HYMF
B
C
N.Ob/BS(1/mm)
0.04
0.03
0.02
0.01
0.00
BL
HLU
Ctrl
HLU+GMF
HLU+HyMF
D
N.Oc/BS(1/um)
0.03
0.02
0.01
0.00
BL
HLU
Ctrl
HLU+GMF
HLU+HyMF

Figure7


A
B
C
D
BL
HLU
Ctrl
HLU+GMF
HLU+HyMF
Liver
Kidney
Spleen
Tibia


E
Liver iron (ug/mg dry weight)
0.15
0.10
0.05
0.00
BL
HLU
Ctrl
HLU+GMF
HLU+HyMF


F
Kidney iron (ug/mg dry weight)
0.5
0.4
0.3
0.2
0.1
0.0
BL
HLU
Ctrl
HLU+GMF
HLU+HyMF


G
Spleen iron (ug/mg dry weight)
5
4
3
2
1
0
BL
HLU
Ctrl
HLU+GMF
HLU+HyMF

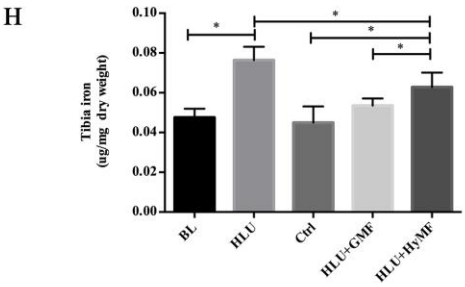

H
Tibia iron (ug/mg dry weight)
0.10
0.08
0.06
0.04
0.02
0.00
BL
HLU
Ctrl
HLU+GMF
HLU+HyMF

Figure8

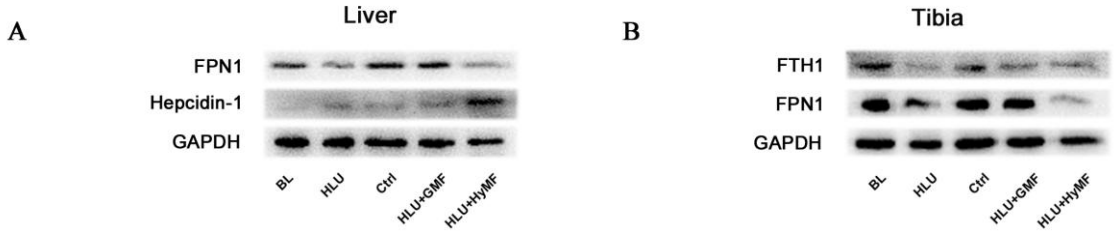


Figure9

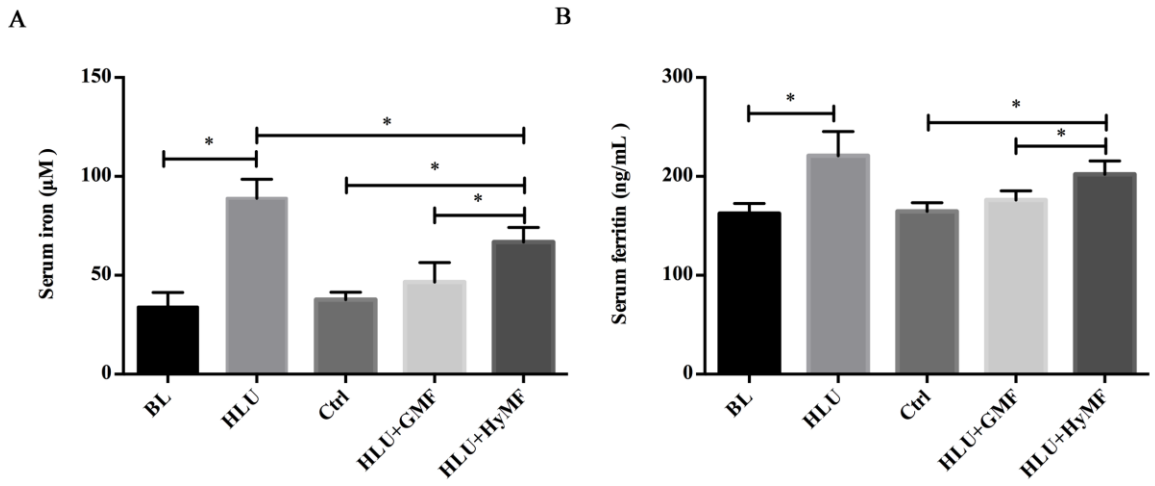


Figure10

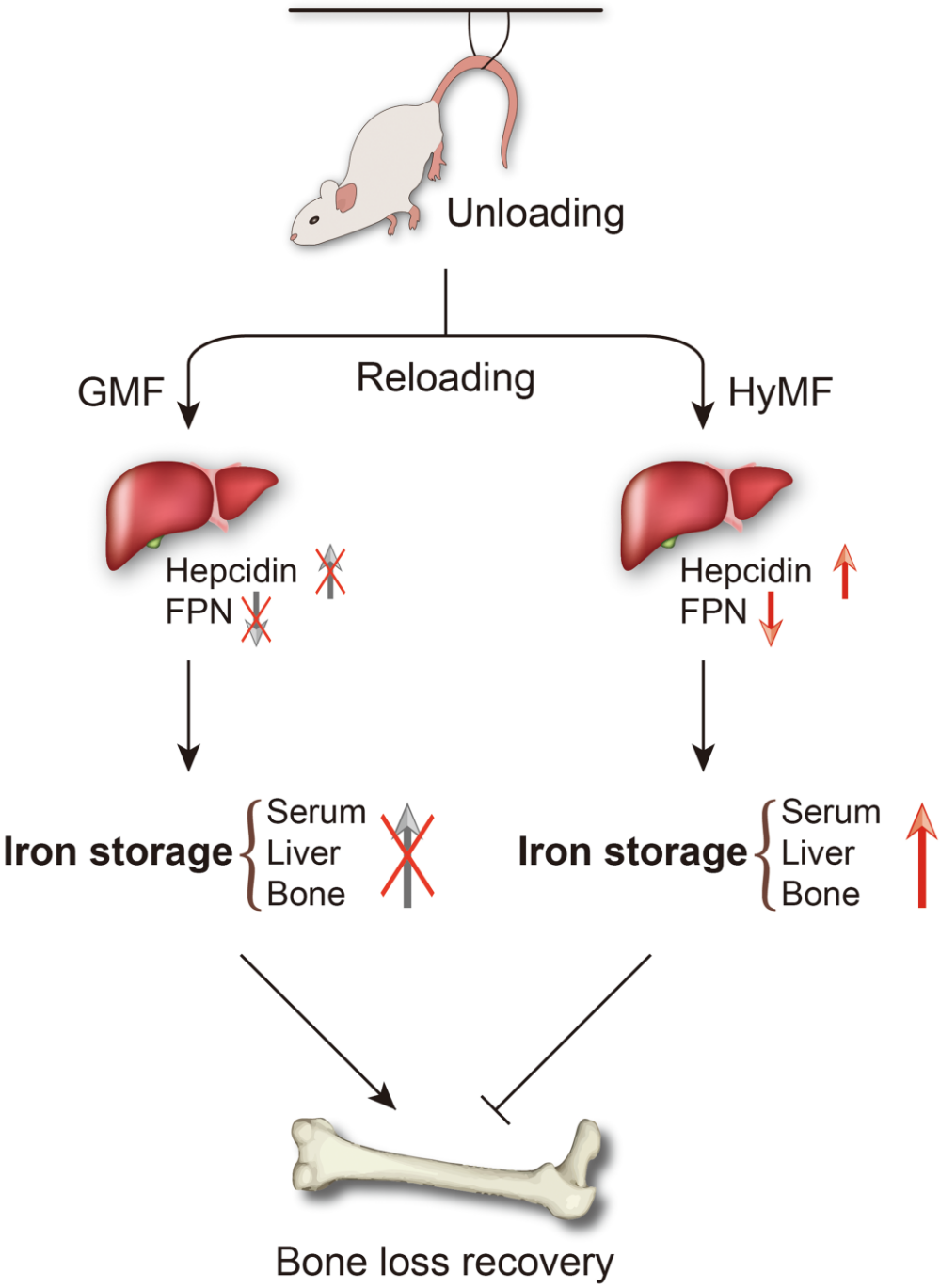


Figure Legends

Fig.1. Hypomagnetic environment experimental device. (A)The schematic drawing of geomagnetic field shielding chamber.(B) Mouse tail suspension model.

Fig.2. BMD and BMC measured by DEXA. (A) Tibial bone mineral density (BMD), (B) Tibial bone mineral content (BMC), (C) Femoral BMD, (D) Femoral BMC. BL: The baseline group, mice

were raised with under the GMF for 4 weeks. HLU: Mice hindlimb were unloaded and raised for 4 weeks. Ctrl: Mice were kept in a wooden experimental box with the normal GMF for 8 weeks. HLU+GMF: HLU mice were reloaded and raised in a wooden box for 4 weeks. HLU+HyMF: HLU mice were reloaded and raised in a GMF-shielded room for 4 weeks (n = 8/group). Data shown as Mean ± SD. *P < 0.05.

Fig.3. Cancellous microstructure of the femur in mice was analyzed via Micro-CT. (A) Three-dimensional images of trabecular architecture in distal femur. (B) Structural parameters of trabecular bone, including trabecular thickness (Tb.Th), trabecular separation (Tb.Sp), trabecular number (Tb.N) bone volume fraction (BV/TV).

Fig.4.Cortical microstructure of the femur in mice was analyzed via Micro-CT. (A) Three-dimensional images of cortical architecture in midshaft femur. (B) Structural parameters of cortical, including total area (Tt.Ar,mm^2), cortical mean thickness(Ct.Th, mm), cortical area (Ct.Ar, mm^2) and cortical area to total area (Ct.Ar/Tt.Ar, %). Data shown as Mean ± SD. *P < 0.05.

Fig.5. Mechanical properties of the femur in mice were detected through the three-point bending test. Elastic modulus (A), stiffness (B), ultimate stress (C) and toughness (D) were calculated by using displacement and force.

Fig.6.The number of osteoblast and osteoclast in the tibia of mice was evaluated by histomorphometric. (A) Hematoxylin and Eosin (H&E) staining of trabecular bone on the proximal of tibia (Bar=50μm); (B) TRAP staining of trabecular bone on the proximal of tibia (Bar=50μm); (C)The number of osteoblast was estimated by osteoblastic number/bone surface (N.Ob/BS);(D) the number of osteoclasts were evaluated by number/bone surface (N.Oc/BS).

Fig.7. Iron levels in the liver, spleen, kidney and tibia were detected. (A-D) DAB-enhanced Perls' iron staining in the liver, kidney, spleen and tibia sections (Bar=50μm). (E-H) The total iron content in the liver, kidney, spleen and tibia was detected by AAS.

Fig.8.The expression of iron metabolism related protein was assessed by western blot. (A) Protein levels of hepcidin-1 and FPN1 in the liver.(B) Protein levels of FTH1 and FPN1 in the tibia.

Fig.9.The concentration of iron and ferritin in serum was determined by mouse TIBC ELSIA kit and mouse FE ELISA kit.

Fig.10. Schematic representation of the underlying mechanisms for HyMF inhibit bone loss recovery induced by microgravity.

STRESS RELATED IMMUNE CHANGES IN LONG-DURATION MISSIONS – CAN INTELLIGENT ASSISTANCE BE A COUNTERMEASURE?

Judith-Irina Buchheim[1], Galina Vassilieva[2], Christian Karrasch[3], Till Eisenberg[4], Matthias Biniok[5], Dominique Moser[1], Matthias Feuerecker[1], Alexander Choukèr[1]

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Exposure to the space environment affects crew health and leads to significant changes of the immune system. Stress response systems can be potent modulators of immune responses and stress mitigation strategies based on a personalized approach might reduce or even prevent immune dysfunction. As part of the IMMUNO study, 12 cosmonauts participating in a long-duration (>140days) mission were monitored pre-, post-, and in-flight for stress and changes of the immune system. Blood concentrations of the endocannabinoid system were found to be highly increased in-flight indicating a strong biological stress response. Next to changes in leukocyte percentage distributions inflight, functional immune testing on ground against fungal antigen revealed an amplified TNF and IL-1 response post-flight. Concomitantly, a significant reduction in CD4+CD25+CD27low regulatory T cells occurred, likely promoting a hyper-inflammatory immune state. The Crew Interactive Mobile Companion (CIMON) is the first autonomous free flying robot designed for the International Space Station that is powered by the ground-based artificial intelligence "Watson" from IBM. CIMON shall assist crew during experimental scenarios with verbal commands or procedures and was successfully commissioned during the "horizons" mission 2018. As a major goal, CIMON will be developed driven by user acceptance and enhanced together with crew according to their demands. Further expansion of function from crew training, source of information to crew maintenance support might reduce workload and stress exposure. During future long-term missions, CIMON could also detect stress or changes in the mood of a group and provide social countermeasures to assure mission success.

Conclusion: Long-duration spaceflight triggered a sustained stress dependent release of endocannabinoids combined with an aberrant immune activation mimicking features of people at risk for inflammation related diseases. Intelligent assistance might reduce stress and support crew in their daily activities.

INFLUENCE OF ROTATION IN DIFFERENT MODES ON THE SHORT RADIUS CENTRIFUGE ON THE HUMAN IMMUNITY

Sergey Kalinin, Marina Rykova, Olga Kutko, Anastasiya Sadova, Evgeniya Antropova, Sofiya Shulgina, Kseniya Orlova, Sergey Ponomarev.

Institute of the Biomedical Problems, Russian Academy of Sciences, Moscow, Russia

Key words: immune system, microgravity, short radius centrifuge, space flight.

During the long-term space flight human organism is exposed to a lot of extreme factors such as radiation, microgravity, closed environmental conditions and others. In order to overcome the negatives effects of microgravity on different physiological systems, including the immune system, it is suggested to use a short radius centrifuge which creates an artificial gravity.

In this research the influence of 3 different regimes (2,0g; 2,4g and 2,9g) of rotation on the short radius centrifuge were tested on some parameters of human immunity. We examined 9 healthy male volunteers in the age from 25 to 40 years.

The rotation modes differed in total duration and intensity of congestion, a time of reaching a predetermined overload. The experiment evaluated changes in both innate and adaptive immunity, namely: the number of lymphocytes with phenotype: $CD3^{+}CD4^{+}$, $CD3^{+}CD8^{+}$, $CD3^{-}CD19^{+}$, monocytes and granulocytes, expressing on their surface Toll-like receptors (TLR): TLR2, TLR4, TLR6, adhesion molecules CD11/18, CD16, as well as the number of NK-cells (natural killers). During all three regimes of rotation, multidirectional changes were observed. It was shown that the number of monocytes and granulocytes expressing TLR6, CD11/18 on their surface significantly decreased, the number of $CD8^{+}$ lymphocytes moderately decreased, and the number of NK-cells increased.

Conclusion.

1) Rotation on the short radius centrifuge in the normal gravity conditions in different modes caused changes in both innate and adaptive immunity.
2) The first and the third regimes caused fewer changes then the second one therefore they are more preferable for the next testing as a potential countermeasure.

TRANSCRIPTOME ANALYSIS OF HUMAN T CELL RESPONSE TO LONG-TERM SIMULATED MICROGRAVITY

Nikolai V. Kuznetsov[1,2], **Julien Record**[1], **Anastasia A. Sadova**[3], **Sofia M. Kayunova**[3], **Sergey A. Kalinin**[3], **Olga V. Kutko**[3], **Evgenia N. Antropova**[3], **Kseniya D. Orlova**[3], **Marina P. Rykova**[3], **Sergey A. Ponomarev**[3],

Piergiorgio Percipalle[2,4], **and Lisa S. Westerberg**[1]

[1]*Department of Microbiology, Tumor and Cell biology, Karolinska Institutet, Stockholm, Sweden;*
[2]*Department of Molecular Biosciences, Stockholm University, Stockholm, Sweden;*
[3]*Russian Federation State Research Center Institute of Biomedical Problems RAS, Moscow, Russia;*
[4]*Biology Program, New York University Abu Dhabi, Abu Dhabi, United Arab Emirates*

Keywords: *Transcriptome, microgravity, T cells, cytoskeleton, actin*

ABSTRACT

In the Space humankind faces extraordinary conditions and situations that are improbable to occur naturally at the Earth surface. Therefore, it is not easy to predict the complex human body response to these conditions on multiple levels from the organ systems physiology to the cell and molecular response and to foresee possible health complications in the Space. The long-term microgravity is one of those improbable factors that humans had never met before the Space Age began. Lymphocyte mediated immune response shown to be impaired or reduced after space flight or in microgravity simulation conditions however the mechanisms of such reduction are still unknown. Preliminary observations speak for involvement of lymphocyte specific surface receptors and cytoskeleton networks proteins in microgravity mediated deleterious effects.

An unique 21-day microgravity simulation study using dry immersion system facility at the Institute of Biomedical Problems (IBMP) in Moscow, Russian Federation was performed in 2018-2019 on ten healthy male volunteers in the age of 25-40 years without any undertaken countermeasures to investigate the normal response of healthy human organisms to long-term simulated microgravity (SMG). Our project as a part of above study deals with detection and measurements of multiple parameters of human immune system response to MG. Using whole blood samples obtained in the dry immersion SMG experiment we investigate changes in expression of specific cytoskeleton genes and surface receptor molecules along with perturbation of cell cytoskeleton network structures. Particularly, we focus on cell and transcriptome reactions to long-term SMG treatment of T lymphocytes - one of important cell types involved in the development of human adaptive immune response. We apply global transcriptome sequencing and extensive and powerful bioinformatics analysis at New York University Abu Dhabi (NYUAD) to follow SMG induced changes in transcriptional regulation of cytoskeletal gene networks detected in T cells. Furthermore, we record and quantify an observed notable effects of microgravity simulation on the cytoskeletal arrangements, cell shape and attachment behavior of T cells using an original *in vitro* cell spreading assay. Currently, the analysis of the data is ongoing and we expect to discover new SMG induced effects on the transriptome and behavior of T cells. Also we will investigate further how to overcome or reduce the deleterious effect of microgravity on T lymphocyte activation and function that is crucial for the effective functioning of immune system of cosmonauts and astronauts during long-term space flight.

CONDITION OF THE HUMAN INNATE IMMUNITY SYSTEM IN THE 21-DAYS “DRY” IMMERSION

Sergey Ponomarev, Marina Rykova, Sergey Kalinin, Olga Kutko, Anastasiya Sadova, Evgeniya Antropova, Sofiya Shulgina, Kseniya Orlova.

Institute of the Biomedical Problems, Russian Academy of Sciences, Moscow, Russia

Key words: immune system, microgravity, “dry” immersion, toll-like receptors.

It is a well-known fact that a lot of parameters characterizing human immune system condition changes during the space flight. Alas up to the present moment there is no equipment that could evaluate in real-time regime changes in the cellular component of the human immune system on the board of the ISS, therefore ground based analogues are used to trace the changes.

In this experiment a number of key parameters characterizing the state of the cellular component of the signal pattern-recognition receptors (PRR) system of innate immunity cells of six healthy volunteers aged from 27 to 32 years, participants of the experiment with 21-day “dry” immersion without countermeasures were studied. In the peripheral blood of the participants, the content of monocytes and granulocytes expressing the signal PRR of the Toll-like (TLR) family with surface TLR1, TLR2, TLR4, TLR5, TLR6 and intracellular (TLR3, TLR8, TLR9) localization was determined. In addition, surface and intracellular TLRs were stimulated with appropriate ligands in 24-hour cultures in vitro. The results of the studies have shown that 21-day "dry" immersion has a significant impact on the cellular components of the natural resistance system of the human body. The changes observed in the experiment are a reflection of the complex adaptation process occurring in the innate immunity system during the stay in the conditions of 21-day “dry” immersion, which simulates main effects of microgravity.
Conclusion.

It was shown that the 21-days “dry” immersion without countermeasures has a significant negative impact on the cellular parameters of the innate human immunity, which is manifested in a decrease in the activation potential of natural resistance cells.
Summarizing the results obtained in the experiment, we can make the following conclusions:
1) 21-days “dry” immersion without countermeasures causes various changes in the relative and absolute content of monocytes and granulocytes of the human peripheral blood.
2) The number of stimulated $TLRs^{+}$ monocytes by the relevant ligands decreases throughout the experiment.

A PROTOTYPE DEVICE FOR CELL RESEARCH IN SPACE

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Keywords: *Space biology, Cell culture device, Microfluidic chip, Intercellular interaction, Protein extraction.*

ABSTRACT

Cell culture is one of the most commonly used technology in biological research. In space environment, cell culture were commonly carried out in Teflon culture bag, Thermanox coverslips or other traditional tool with a cell culture incubator. Those tools are low integrated and disable to precisely control the environment around the cells. However, high integrated device enable us more efficient usage in limited experimental resource in space. Meanwhile, precise control in environment around cells is crucial in some studies focused on single cells analysis or cell-cell interaction. Thus, we developed a prototype device for cell culture in space. This prototype device includes six units, injection pump, valve and pump group to liquid reagents unit, reagents and waste storage unit, cell culture unit based on microfluidic chip, microscope imaging system, electronic control unit. Nowadays, three basic functions of this device were developed. The first function, cell culture with automatic operation to cells, was achieve using valve and pump group unit to liquid reagents and cell culture unit based on microfluidic chip. Cells were cultured in a single-chamber microfluidic chip maintaining the temperature at 37 °C by thermoelectric heater. Using valve and pump group unit to liquid reagents, the cells in the microfluidic chip can be trypsinized, dyed, lysed. Then the cells or cell lysates can be further analyzed using other devices. The second function, cell co-culture, was achieve using a dual-chamber microfluidic chip divided by a semitransparent membrane. Two kinds of cell were separately cultured in two chambers but culture medium were shared. The third function, online continue microscope imaging, was achieve using a microscope with CCD camera. This function was used to record the cell morphology change during the whole experiment. In addition, more function can be developed by developing new microfluidic chips or adding some new components to the device. In summary, this prototype device integrated cell culture, microscope imaging and cell sample collecting is highly integrated and flexible. Therefore, we conclude that this prototype device can be a valuable tool for cell research in space.

EFFECT OF SHORT-ARM CENTRIFUGATION AND EXERCISE ON SKELETAL MUSCLE-PUMP BAROREFLEX – SPIN YOUR THESIS!

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2. *Department of Biomedical Physiology and Kinesiology, Simon Fraser University, Burnaby, British Columbia, Canada*

Poor orthostatic tolerance, notably a high incidence of fainting due to low systolic blood pressure, is a serious problem that affects astronauts returning from the ISS. We developed a model of interaction between systolic blood pressure (SBP) and postural muscle activation. The skeletal muscle-pump baroreflex (SMPB) affects the venous return from lower limb vasculature, thereby contributing to overall orthostatic tolerance. This use of the SMPB is an indirect mechanism that can affect orthostatic tolerance by way of mechanical compression of veins by skeletal muscle contraction. We are interested how exercise in a proposed hypergravity countermeasure affects the SMPB as part of the "Spin your thesis! Human Edition" program of the European Space Agency. In this project we used centrifugation as a model to assess a) whether artificial gravity would activate the SMPB; and b) if squat exercises would affect SMPB activation. Therefore, we compared skeletal muscle pump baroreflex responses during a 6-minute stand test before and after centrifugation and squatting exercise in hopes of determining how to protect astronauts from fainting when they return to gravity after long stays in weightlessness.

Experiments were carried out at the German Aerospace Center (DLR) in Cologne using the Short Arm Human Centrifuge at envi:hab to simulate hypergravity. Eleven healthy male participants were recruited. The centrifugation protocol consisted of two centrifugation phases, separated by a 15-minute break. The exact protocol was performed as follows: 5 minutes of baseline, 5 minutes at 1 g followed by 5 minutes of squatting at 1g, 15 minutes supine break (no rotation), 5 minutes at 1.5g followed by 5 minutes of squat exercises at 1.5g. Pre- and post-spinning, a supine-to-stand test including squats was performed. After 5 minutes of supine baseline, the participant stood for 6 minutes with closed eyes, followed by 5 minutes of squat exercise and 5 minutes of standing. Medical monitoring included continuous blood pressure and heart rate measurements. For cardio postural measurements, a scientific electrocardiogram was added. Electromyography was performed to detect muscle contraction in four of the major calf muscles and postural sway was measured using a force platform.

We evaluated the possible deleterious effects of centrifugation by comparing interactions between cardiovascular and skeletal muscular activity before and after the centrifugation protocol. Interactions in all frequency bands between SBP and surface electromyography (sEMG) did not vary between the supine-to-stand tests before and after centrifugation (all $p>0.05$), nor between SBP and RR-interval (all $p>0.05$). The causal relationships between SBP and sEMG, and SBP and RR-interval also remained unchanged (all $p>0.05$). Some differences were detected when comparing the non-exercise phases of the centrifugation protocol. Due to technical challenges, the current analysis only includes results from four participants in the 1g centrifuge phase. Three comparisons yielded a statistically significant difference between protocol phases. The time of significant interaction between SBP and sEMG was least in 1g centrifugation and greatest during the baseline preceding the 1g centrifugation in both LF ($p=0.0084$) and VLF ($p=0.024$) frequency bands. The time of significant interaction between SBP and RR-interval differed between 1g centrifugation and the supine period preceding 1.5g centrifugation ($p=0.0139$) while the causal relationships were unchanged.

AUGMENTING EXERCISE PROTOCOLS WITH INTERACTIVE IMMERSIVE VIRTUAL REALITY (VR) ENVIROMENTS

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Keywords: *Virtual reality, exercise performance, exercise motivation, behavioral health*

ABSTRACT

Long term health maintenance and operational performance is one of NASA's grand challenges for astronauts on future long-durations missions. The objective of this research effort is to investigate the use of Virtual Reality (VR) during exercise training on human performance and behavioral health. VR is usually described as "an advanced form of human-computer interface that allows the user to interact with and become immersed in a simulated, computer-generated environment in a naturalistic fashion". VR can be considered the leading edge of a general evolution of interfaces such as telephone, television, and computers with the ultimate goal of full immersion of the human sensorimotor channels into a vivid and interactive experience. The use VR technology in health is increasing with a variety of possible applications, for example, to help brain injury patients walk again, to provide therapy for psychological disorders, or to aid surgeons in performing complex robotic surgery. Previous research has also shown that VR can "acutely" motivate exercise in healthy subjects, the elderly population, and children with autism. However, the effects of VR on behavioral health, motivation, and long-term performance has not been proven. Thus, we propose to investigate how the use of VR may improve motivation, improve adherence to an exercise protocol, and enhance physical effort and performance for longer exercise durations. We propose to conduct a pilot study in collaboration with the HRCF (Human Research Clinical Facility) at Texas A&M University in which subjects will undergo an integrated resistive and aerobic exercise protocol (similar to the newly developed SPRINT protocol developed by NASA) over 2 weeks. Two groups of 10 subjects will participate in the study: the first group will be immersed in a VR simulation during the exercise sessions and the second group will not. While the study has broad applicability, subjects will be representative of the astronaut population (healthy, fit, age 20-60) and with equal gender balance. We will collect a variety of objectives and subjective measures to evaluate both physical performance as well as behavioral health including stress, motivation, and exercise adherence.

Exercise scenarios in VR will be synchronized with the intensity of the exercise protocol and the subject will experience motion over and/or through a simulated terrain. Certain actions that correspond with exercise motions may also be motivated by obstacles or other game-like features in the simulation. Physical performance will be measured during each exercise session with a heart rate monitor (V800, Polar). Cardiac output and metabolic performance (Innocor-Innovision) data will also be collected. Behavioral health dependent measures will include heart rate variability and salivary cortisol levels (which are measures of stress). Additionally, a series of questionnaires will also be implemented: Perceived Stress Scale (PSS), Profiles of Mood States (POMS), Perceived Restorative Scale (PRS), Sport Motivation Scale (SMS), and Competitive Cooperative Scale (CSS). Results from this study will be analyzed to determine the impact of augmenting exercise protocols with interactive immersive VR environments. Data will be collected during the upcoming months, and they will analyzed and presented at the HIS 2019.

STUDIES OF THE EFFECTS OF VARIOUS REGIMES OF A SHORT-RADIUS CENTRIFUGE ROTATION ON THE DYNAMICS OF WATER-ELECTROLYTE METABOLISM MARKERS AND THE FLUIDS SHIFTS IN BODY REGIONS

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Keywords: short radius centrifuge, fluids shifts, water-electrolyte metabolism

A short radius centrifuge (SRC) is a promising means for preventing the negative effects of microgravity on human body, both in interplanetary manned flights and during periods of planetary activity. Therefore, presently an important task of space medicine is the selection of optimal regimes of artificial gravity creating using the SRC.

The system of water-electrolyte metabolism regulation is one of the physiological systems quickly reacting to changes in the gravitational environment. Therefore, the analysis of changes in the concentration of electrolytes and of water-electrolyte metabolism markers gives an objective picture of the changes occurring in the body at different values and / or duration of acceleration.

The main objectives of this work were the monitoring of the fluids redistribution in body regions using the method of polysegmental bioimpedance analysis (PBA), and assessing of the electrolyte concentrations dynamics, indices of the renin-angiotensin-aldosterone system, natriuretic peptides, and markers of endothelial functional state during rotation of volunteer subjects on SRC.

Nine healthy male volunteers (25-40 years, height 165-185 cm, weight 69-96 kg) took part in the study. Three different regimes of SRC rotation with duration 45 - 60 min and acceleration of the head-pelvis (+Gz) direction were tested. The rotation consisted of three phases of constant acceleration up to 0.2 g, 1.05 g and 2 g / 2.4 g / 2.9 g with a rotation radius of 235 cm, and of mirror three phases of constant stopping. The relative change in active resistance at a probing current frequency of 5 kHz was estimated using the PBA (SPRUT-2, Russia, MEDASS). The collection of venous blood in the supine position and the collection of saliva was carried out in the background period and immediately after the rotation stopped.

As a result of the study, a profile of individual reactions of the water-electrolyte exchange system of subjects was obtained. A comparative analysis of changes in the concentrations of aldosterone and plasma renin activity in the blood was carried out, showing that the most expressed changes occurred during the second rotation regime ($p < 0.005$). A reliable increase in the concentration of cortisol in saliva was shown after each rotation regime ($p < 0.01$). It was shown that the electrical resistance of the head and chest regions during the SRC rotation increased maximally by + 16% and + 23%, that indicates a decrease in blood filling; at the same time, the electrical resistance of the leg regions decreased by –17%. Thus, the PBA works well for recording the fluid redistribution during rotation on the SRC, and can serve as an instrumental basis for diagnostics and prediction of syncopal states.

IBMP SHORT-ARM CENTRIFUGE: GOALS AND EXPECTATIONS

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Introduction. A wealth of research data on medical support of cosmonauts aboard Russian orbital complex Mir and the International space station (ISS) aggregated at IBMP bears witness that life in microgravity is conducive to deconditioning of the cardiovascular and musculoskeletal systems as prime targets, hypohydration and hypovolemia, disorders in metabolism and neuroendocrine regulation. The system of countermeasures and protection on the ISS Russian segment levels these changes partly as it cannot make up for the hydrostatic blood pressure, weight loading on bones and muscles and changes in the afferent systems functioning. The best countermeasure to the microgravity negative effects can be a periodic use of artificial gravity (AG) generated by an onboard short-arm centrifuge (SAC).

Purpose. Development of a full-scale countermeasure system against the cardiovascular diseases, and portable telemedicine tools for cardiovascular monitoring compatible with the space medicine technologies.

Methods. SAC constructed at IBMP is a new-generation Russian product designed with reliance on previous experience and current global trends. In some aspects our SAC surpasses international analogs enabling to address a broad range of space-related challenges. We conducted 27 test runs with participation of 9 essentially healthy human subjects aged 25 to 40 years. The subjects were exposed to head-to-pelvis accelerations (+Gz) at maximum 2.0. 2.4 and 2.9 units to the feet (regimens 1, 2, and 3, respectively). Mathematical modeling of an optimal regimen was based on magnitudes of hydrostatic blood pressure and accelerations to be achieved in microgravity for the hydrostatic pressure being equal to that on Earth. SAC effectiveness was evaluated with a battery of cardiovascular, muscular and sensory tests, some of which are used on the ISS RS. The test battery was composed following the Guidelines for standardization of bed rest studies in the spaceflight context developed under the auspices of the International Academy of Astronautics.

Results. Hemodynamic changes at all three rotation regimens remained within the physiological norm. Significant were changes in linear blood velocity along the arterial vessels. Changes in cerebral circulation were not noteworthy. There were differences in reactions to rotation of arterioles, venules and capillaries in the upper and lower extremities. Analysis of bio-impedometry data showed that the total volume of liquid in legs made an increase at all SAC regimens. We succeeded in assessment of the effect of different rotation regimens on support afferentation. Integral evaluation of the ocular sensory system showed high stability at all regimens. Level of stress and psychophysiological reactions were linked with physics of rotation and novelty for the test-subjects confirmed by the effect of training.

Conclusions. The selected rotation regimens have prospects as a countermeasure to the effects of microgravity on human organism. The on-going ground studies of artificial gravity will lead to developing SAC for demonstration in orbital manned missions. Also, the results of our studies may highlight areas of investigations to the benefit of practical medicine such as the neurophysiological control of intraocular hydrodynamics and its relation to pathogenesis of glaucoma.

ANAEROBIC METABOLISM THRESHOLD AS AN INDICATOR OF CHANGES IN THE LEVEL OF PHYSICAL PERFORMANCE AFTER SPACE FLIGHT

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Development of a system for the prevention of hypogravitational disorders for an interplanetary mission implies the attainment of a high level of human physical performance by the time of reaching the surface of a celestial body. One of the reliable ways to assess the level of performance is to assess the threshold of anaerobic metabolism, that is, the time of transition from aerobic mechanisms of energy supply to muscle activity to anaerobic, when performing physical activity of increasing intensity.

The study involved 5 cosmonauts (age 43 + 2 years, weight 84 + 6 kg, flight 169 + 18 days). A test assessing the level of physical performance of a cosmonaut was used in an experiment in order to determine the changes in the energy supply system of muscular activity caused by prolonged stay in weightless conditions.

The test includes an execution of locomotion with a step-wise increasing speed from 3 to 15 km/h in the mode of moving the treadmill with the help of a motor, an increment of speed by 1 km/h occurred every 30 s. This test was performed 30-60 days before a space flight and on the 8-13th day after the completion of the flight.

During the test, O2 consumption, CO2 emissions, pulmonary ventilation were recorded. The study was approved by the Commission on Biomedical Ethics. All subjects signed an informed consent to participate in the experiment.

The maximum running speed in the test before the flight was 15 km / h for all subjects. After the flight, the maximum speed of 4 cosmonauts was 15 km / h, and one cosmonaut had a speed of 13 km / h. Before the flight, oxygen consumption increases with increasing speed, but at a speed of 15 km / h the maximum oxygen consumption was not reached. After the flight, oxygen consumption reaches a plateau at speeds from 10 to 13 km per hour, which indicates a decrease in the aerobic capacity of the organism.

CO2 emissions increased in line with the increase in run speed both before and after the flight, but after the flight it was higher than in the background testing by an average of 10% at all test levels.

Before and after the flight, pulmonary ventilation increased with increasing running speed. Ventilation anaerobic threshold was observed only after the flight. It is registered at a speed of 13 km / h. The respiratory coefficient, calculated as the ratio of CO2 emission to O2 consumption, before the flight had a value of no more than 1, and after the flight it exceeded the value 1 at a speed of 12 km / h.

Thus, after a space flight, activation of anaerobic mechanisms of energy supply of muscle activity is shown at an intensity of physical activity that is significantly less than before the flight. One can talk about an earlier activation of maximum reserves of the systems for ensuring muscular activity, in particular, respiratory system, the cardiovascular system, the blood system and the oxygen utilization system in muscles.

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COUNTERMEASURES FOR VESTIBULAR AND SENSORIMOTOR DISTURBANCES AS NASA, RUSSIA AND OTHER INTERNATIONAL SPACE FLIGHT PROGRAMS PREPARE FOR LENGTHY MISSIONS

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A joint NASA and Institute of Biomedical Problems (IBMP) study, designated as the Field Test, was designed to investigate the immediate postflight effects of long duration spaceflight on the sensorimotor, vestibular and proprioceptive systems, and to track these changes using tests that emphasize functional behavior typically associated with everyday living. Results of the Field Test have shown that the existing inflight countermeasures, which stress strength and endurance, are not adequate to prepare the returning crewmembers for autonomous postflight recovery without the assistance of extensive landing support personnel. As NASA prepares for future Gateway Missions new and specific preflight, potential inflight countermeasures must be designed and tested to enable crewmembers to function without the support typically associated with today's post-mission recovery methods. This paper will explore some nontraditional and untried strategies designed to assist crewmembers to safely egress from their spacecraft following a landing, whether on a stable planetary surface or in the water.

Currently all international landings have taken place in a Russian Soyuz capsule where there is no wave motion and the crew are assisted during egress by a significantly large landing party. At this point the only extraneous motion the crew experience is being carried from the space craft into the medical tent. Movements of the crewperson on Earth preflight are highly ordered due to contemporaneous and sequential patterns of sensory messages that occur as a consequence of voluntary movement. This orderly patterning is obtained by the sensitivity and dynamics of the sensory organs themselves. Small corrections to the purposeful movements are consciously determined but typically so automatic that we are not aware of their use until a small error in movement is actually perceived and corrected. While significant training may be helpful, there is only a limited number of approaches that may work. (1) Preflight Sensorimotor and Inflight Balance Training: This countermeasure approach employs both preflight and inflight balance training because they serve complementary functions. Preflight sensorimotor training is designed to improve the general ability to adapt while experiencing challenging and conflicting novel sensory information in particular disruptive vestibular information. Inflight training serves to keep the proprioceptive system tuned to respond to upright balance challenges by assisting the proprioceptive input tuned to respond to downward axial forces while the preflight sensorimotor training serves to facilitate the ability to rapidly reweigh sensory channels and produce the appropriate motor output required for effective balance and locomotor control. (2) Stroboscopic Vision to Mitigate Motion Sickness: Stroboscopic vision provides a nonpharmacological alternative for the prevention of space motion sickness by preventing retinal slip caused by changes in the vestibulo-ocular reflex. Used in conjunction with low levels of motion sickness drugs, the stroboscopic goggles effect could be augmented. It is imperative that the goggles be worn prior to the crew's exposure to changes in the gravitational state. (3) Visual and Tactile Spatial Orientation Aides: To mitigate disruptions in spatial orientation a tactile spatial awareness system (TSAS) system and visual aids are proposed. The TSAS system provides, small tactors placed around the torso that vibrate according to the actual body tilt angle relative to gravity or a designated upright. Visual orientation aids provide an artificial horizon that projects inside the spacecraft to provide a spatial orientation cue, alternatively this information could be placed onto the helmet visor of an astronaut.

EVALUATION OF QUANTITATIVE ANALYSIS METHOD OF MICROBIAL CONTAMINATION FROM METAL SURFACE OF CHINA'S SPACE STATION

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Abstract

With an endless yearning for space, more and more spacecraft are being built, and then boosted by rockets to carry out various space tasks. According to relevant reports, microorganisms are ubiquitous in the International Space Station and MIR. It is also proved that the microbes in the orbit may corrode the material of space station. The CSS is expected to be completed in 2022 and will be in orbit for more than 10 years. If the concentration of microorganisms is not well controlled, the health of astronauts and the reliability of instruments will be threatened. In order to evaluate the number of microbes, accurately, on the low-biomass metal surface such as China's Space Station (CSS), a model bacterial strain *Bacillus* sp. TJ-1-1 that appeared in the highest abundance on the surface of CSS was used to represent 10^2-10^9 cells/100cm^2 of contamination levels. Here, we present the findings of the first comprehensive effort to compare 4 most common analytical approaches (contact plate, spread plate, qPCR and BacLight™) from the prospect of quantifying the number of viable microbial cells associated with CSS surfaces, which are correlated with differential sampling methods and areas. The results indicated that, for 10^2 cells/100cm^2, contact plate is the most convenient and reliable method. For the contamination level ≥10^3 cells/100cm^2, 121cm^2 sampling area, BacLight™ method is the most reliable way. 121 cm^2 sampling area is more suitable for the analysis of the metal surface of space station, which is usually a low-biomass surface. The results of this study empower current and future culture dependent and independent microbial sampling and processing methodologies.

SPACE EXPERIMENT «TEST»

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In the space experiment «Test», starting from 2010, regular sampling of fine sediment from the outer surface of the Russian Segment of the International Space Station (ISS) in orbit of 400 km is carried out. The samples taken are sealed in vacuum overboard in sterile containers and delivered to Earth for laboratory studies of the chemical composition of the sediment and the presence of viable spores of microorganisms in it. For the period 2010-2018 years astronauts in the process of space-walk took 23 samples from the surface of the ISS. Since the beginning of the “Test” experiment, the detection rate in samples from the external surface of the ISS of viable units of spore bacteria and fungi is about 50%. In one sample taken from the external surface of the ISS, along with spore microorganisms, a consortium of non-spore-forming bacteria was found, which included a radiation-resistant bacterium of the species *Deinococcus aerolatus.*

To solve the issue of the origin of microorganisms contaminating the station surface, in 2017 on the outer surface of the ISS were placed four «Test-Exhibit» devices with bioobjects unprotected from the influence of space factors for periods of 1 to 2 years in areas with different illumination and position relative to the velocity vector. The studies were carried out both on previously isolated from the external surfaces of the ISS in experiment «Test» of viable bacteria *Bacillus pumilus* and *Aureobasidium pullulans*, and on the collection (museum) archae *Methanosarcina mazei* S-6T VKM B-1636T. Investigations of exposed microorganisms returned to Earth in 2018 indicate that they can maintain their viability in open space for 1 year.

A post-flight comparative analysis of genome fragments based on molecular-genetic methods for studying microbial species before and after exposure for 1 year in open space was carried out using the BLAST system software and Vector NTI. As a result of the studies, no significant changes were detected in the nucleotide sequences of the analyzed houskeeping genes. The strains originally isolated from the external surface, in particular *Bacillus pumilus*, were not typical in terms of biochemical activity. High surviving rate of exposed microorganisms proves their resistance to the conditions of the open space. This means that the exposed microorganisms are able to maintain viability under impact of the hard cosmic radiation.

The results of the experiment can be a powerful argument in confirming the existence of extremophile microorganisms on Earth that have an increased resistance to space conditions. The established presence of a near-object environment on the surface of the ISS is important for studying the resistance of materials of surfaces and making technical decisions on safety

of near-planet stations.

The most interesting scientific data obtained by Russian scientists during the implementation of the experiment «Test» is a good demonstration of the possibilities of using the ISS as a unique scientific platform or testing ground for conducting research in the field of exobiology and planetary protection.

STUDY OF P-GLYCOPROTEIN IN RAT INTESTINE UNDER SIMULATED MICROGRAVITY EFFECT

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***Keywords:* Simulated microgravity effect, P-gp, rat**

ABSTRACT

Redistribution of fluids in the body caused by microgravity can lead to multiple system damage to the human body. In order to protect astronauts' safety and working performance in space, drugs are often used for protection and treatment. In addition to the conventional transporters located on the surface of intestinal epithelial cells, P-glycoprotein (P-gp) plays a very important role in a variety of drugs transmembrane transport through effluxing function. The present study is aimed to investigate the function and expression of P-gp in rat intestine under simulated microgravity effect. Rats were tail-suspended to simulate short (7-day) and long term (21-day) microgravity effect. Cyclosporin A was used as substrate to detect the efflux function of P-gp, and the expression of P-gp was determined by Western Blot. It was found that the function of P-gp was weaken in 7-day simulated microgravity (SMG) exposed rats, while the expression of P-gp was also down-regulated under 7 and 21-day SMG condition. The mechanism is not clear yet. These down-regulated expression of P-gp may lead to a significant increase in blood intake of P-gp substrate drugs under microgravity conditions, if the dosage is based on the ground level. These findings might be useful for safety of medication use in space travel. The mechanism of P-gp variation under simulated microgravity will continue to be studied in the future.

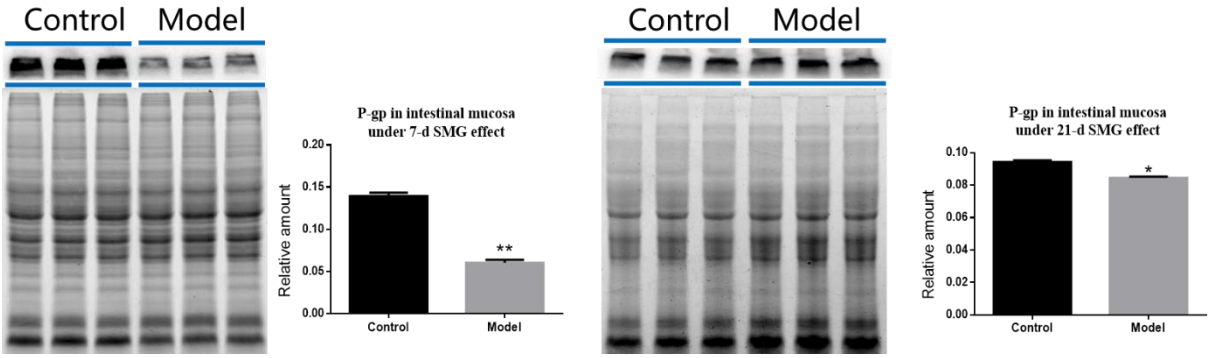

Fig. 1 The expression of P-gp under 7 and 21-d SMG effect

(* P<0.05, **P<0.01, compared with control group)

STUDY ON DRUG METABOLIC ENZYMES IN INTESTINE OF TAIL-SUSPENDED RATS BASED ON PROTEOMICS APPROACH

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Keywords: **drug metabolic enzymes, rat intestine, simulated microgravity effect, proteomics**

ABSTRACT

To explore changes of metabolic enzymes in small intestine of rats under simulated microgravity effect, the present study investigated 14 days (14d) simulated microgravity (SMG) effect on intestine drug metabolic enzymes in rats. After the rats were tail suspended for 14d, intestine samples from control and 14d SMG rats were collected for label free differential proteomic analysis. 335 differentially expressed proteins were identified, and 190 proteins were up-regulated while 145 proteins were down-regulated. 335 proteins were categorized into 37 KEGG pathways with DAVID (version 6.8), including metabolic pathways, biosynthesis of antibiotics, metabolism of xenobiotics by cytochrome P450, drug metabolism-cytochrome P450 and so on. CYP3A2, 2D1, 2E1, 1A2, ADH (alcohol dehydrogenase) and GSTM (glutathione S-transferase M) were identified as differentially expressed drug metabolic enzymes. HPLC-MS data indicated that all of them except GSTM were significantly down-regulated under SMG effect. Protein expression by western blot or activity of these proteins were further studied. The results showed that compared with the control group, the expression of CYP3A2, 2D1 and 1A2 protein significantly decreased with a fold of 55.3%, 24.5% and 31.7%, respectively. CYP2E1 did not show significant change in 14d tail-suspended rats. ADH showed a 31.5% decrease and GSTM showed 64.6% increase in 14d tail-suspended rats compared with control group. Activities of total ADH decreased significantly with a fold of 38.% and 19.2%, respectively. GSTM activity was almost not changed. This study presented basic research data for understanding changes of intestine metabolic enzymes, which might take a limited view for potential safety and efficacy of astronauts drug administration under microgravity condition.

IDENTIFICATION OF SPACE QUALIFIED ACID TOLERANT MICROBES WITH POSSIBLE CAPACITY OF ALUMINUM CORROSION AND THE EVALUATION OF THEIR ACID PRODUCTION UNDER SPACE CONDITIONS

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Corrosion of Aluminum (Al) in spacecraft is an essential problem for astrology as this metal is used for various mechanical parts of spacecraft equipment due to its strength, durability etc. However, it can yet be corroded by the various factors including microbes which play an important role in corroding Al surfaces. Scientists have already faced the corrosion problem in International Space Station (ISS) and Mir space station. Studying the microbes which can cause corrosion problems and consequently health risks is of vital importance. This research is about Microbiologically Induced Corrosion (MIC) phenomenon due to acid production. Al and acid tolerant microbial strains have been isolated from the samples of the Chinese Space Station Assembly Clean room (CSSAC) surfaces. The part of the microbial strains have been identified with 16S ribosomal RNA sequence and the most dominant bacteria was of *Bacillus* genus and fungi of *Penicillium, Fusarium* and *Aureobasidium* genus. The rest of the strains will be identified and their acid producing capacity will be studied and compared under normal and space conditions. This study might aid in carrying out further studies of the aforementioned microorganisms and therefore it will be a good asset for prevention of MIC.

Key Words: Aluminum-Corrosion, Spacecraft, Microbiologically Induced Corrosion, Acid tolerant Microbes

SIMULATED MICROGRAVITY EFFECT ON VAP-1/SSAO ACTIVITY IN STZ-INDUCED DIABETIC RATS WITH THE SIMULTANOUS ACTION OF PXS-4728A

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Vascular Adhesion Protein-1/Semicarbazide-Sensitive Amine Oxidase (VAP-1/SSAO) activity is elevated in the blood of diabetic patients. Cytotoxic metabolites by SSAO, such as Advanced Glycation End products (AGEs), may cause endothelial injury and atherosclerosis. Stress is one of the reasons for inducing diabetes. Oxidative stress plays a key role in diabetes complications. Space conditions increase oxidative stress, AGEs, and bloodstream which possibly increase the chance of diabetes. As VAP-1/SSAO is a type of marker of diabetes, it is interesting to study the effect of simulated microgravity (SM) environments on normal and diabetic rats. This research studies the role of SSAO activity in type 2 diabetes and shows the effect of PXS-4728A- a selective inhibitor of VAP-1/SSAO.

The aim of the present study is to investigate whether a selective VAP-1/SSAO inhibitor can reduce diabetes in a high-fat diet (HFD) and streptozotocin (STZ)-induced diabetic rats under the simulated space conditions. To study the effect of microgravity on VAP-1/SSAO activity in rats, the animal model of type 2 diabetes mellitus (T2DM) were applied to the SM environment by the tail suspension. For modelling T2DM, the strategy of high-fat diet (HFD) with a combination of a single low dose of STZ was developed on Sprague Dawley (SD) rats. Therefore, SD rats of the experimental group were fed with high-fat diet for 4 weeks before the injection of STZ with the dose of 35mg/kg until the end of the experiment. Blood was collected from the rat's orbital eye. After successful modelling of T2DM, tail suspension experiment was conducted for 21 days on healthy and diabetic rats. PXS-4728A was given to the experimental group with low dose (3mg/kg). The experimental group had signs of T2DM- the water consumption and the glucose level were dramatically increased while insulin level was decreased. PXS-4728A reduced the activity of VAP-1/SSAO in normal and SM exposed rats. As expecting results, SSAO activity should be increased in fasting blood plasma and brains of diabetic rats and decreased in the group treated with PXS-4728A.

Based on our results, PXS-4728A has drug-like effects with Inhibiting of VAP-1/SSAO which reduces diabetes therefore, it might have the therapeutic value for patients with diabetes and people who want to travel in space, although the further studies are required.

Keywords: Semicarbazide-Sensitive Amine Oxidase, Simulated microgravity, PXS4728A, Streptozotocin, Type 2 Diabetes, Sprague Dawley rats

EFFECT OF SPACE CONDITIONS ON CELLULOSE DEGRADAING ABILITY OF MICROORGANISMS

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Keywords: *Cellulases, space microbiota, β endoglucanase, β exoglucanase, consortium*

ABSTRACT

We are on the verge of next giant leap in space exploration and scientific research related to it. As private sector has reinvigorated the space race, several countries have affirmed their intentions of developing a robust human spaceflight program. However, microbiota of crew members, in combination with an inability to ensure complete sterility of the craft and cargo, results in the coexistence of humans and microorganisms in the spaceflight environment. It is inevitable that the ISS will also be home to an unknown number of microorganisms. Spore formers, autotrophs, multi-resistant, facultative, or even strictly anaerobic microorganisms have been detected in clean room habitats. Microbes could affect not only the foreign ecosystem but could also cause false positives during life-detection efforts. China has also developed its space research in recent years and, in the coming years, this research is expected to be carried at a more rapid rate.

Many items inside the space station including clothing of astronauts, sleeping bags etc are made of cellulose as their major component. As microorganisms have been detected in the space environment so, if any microbe, having the ability to degrade cellulose, is present inside the space station it would result in degradation of these essential items and shorten the stay of astronauts in the space and ultimately harm the space missions.

We examined cellulose degradation ability of microorganisms in the samples obtained from Chinese Space Station Assembly Clean Room before and after the space flight. All the strains were isolated in pure cultures and identified through molecular methods. Cellulose degrading ability of all the pure strains was estimated qualitatively (Congo red, FPase) and quantitatively (CMCase, Avicelase). The quantity of β endoglucanase enzyme was higher in space sample and β exoglucanase was higher in earth sample. Total protein content was also slightly higher in space sample compared to earth sample. Moreover, Scanning Electron Microscopy (SEM), performed by using the filter paper as a substrate, showed a high cellulose degrading ability of consortium of microbes present in the space sample.

Cellulase gene, from all the strains in both types of samples, was amplified and sequenced, and the mutation between the space and earth samples was noted. Clone libraries are formed in order to estimate the portion of unculturable and culturable organisms in the consortium.

It was concluded that space environment has a significant influence on the production of cellulases. This may have occurred because of the space flight and microgravity besides other factors that may have caused change in the enzyme producing ability of microorganisms. Therefore, taking control measures, against microorganisms, is necessary in order to ensure long term stay of astronauts in space.

THE EXPRESSION OF DNA DAMAGE REPAIR GENES WERE CHANGED ON ARABIDOPSIS THALIANA SEEDS SURVIVING 303H EXPOSURE TO SPACE ENVIRONMENT

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ABSTRACT

The microgravity and space radiation were the two important stressors which can induce biological damage and genetic variation in spaceflight. It is emphasized that we must pay high attention to the DNA damage repair pathway. In order to explore the effects of plant gravitational response mechanism on space environment-induced DNA damage repair, we used the SJ-10 recoverable satellite to conduct 303-hour seed loading of Arabidopsis thaliana seeds with different gravitation responses. The biological effects of spaceflight were investigated in Arabidopsis seeds from the perspective of phenotypic to the physiological and molecular levels. We investigated the effects of gravitation and gravitropism on repair gene expressions for space environment-induced DNA damage in plant Arabidopsis thaliana at seedling growth, vegetative growth transitioning to reproductive growth. In this study, the seeds of wild-type and two mutants with defects in the gravitational response mechanism (pin2 and pgm-1) were divided into the ground control groups and spaceflight groups. And then, these seeds were cultivated in the climatic chamber. The seed vigor, root length and root apical deflection angle were measured at the seedling stage (cultivation for 7 days); and the biomass and Fv/Fm were also determined at the vegetative growth stage (cultivation for 28 days before bolting). In addition, the expression of Ku70, Rad51, XPD and OGG1 genes, as the important biomarkers, were used to assess the effects of spaceflight on the pathway of DDR. Our results showed that no significant changes were found in the germination potential and root apical deflection angle after spaceflight. In addition, the root lengths were significantly inhibited in wild-type and pin2, pgm-1 mutants after the spaceflight, while the germination rate in pgm-1 mutant as well as the biomass and Fv/Fm in pin2 mutant were significantly increased after the spaceflight. Furthermore, at the seedling stage, the gene expression of the XPD was significantly up-regulated in the wild-type, and the gene expressions of the Rad51, OGG1, XPD in pin2 mutant and the Ku70, OGG1 in pgm-1 mutant were also significantly up-regulated after the spaceflight. At the vegetative growth stage, no significant differences of the four damage repair genes were observered in wild-type, while the expressions of Rad51, OGG1 and XPD in pin2 mutant were up-regulated, and the expression of Rad51 in pgm-1 mutant was significantly up-regulated.It is speculated that the mutation may increase the sensitivity to the space environment. The expressions of DNA damage repair genes were different between the two developmental stages after the spaceflight. Moreover, the mutation of gravitropic signal transmission gene pin2 affects the sustained genes expression of HR, BER and NER pathways from seedling stage to vegetative stage; the mutation of gravity perception gene pgm-1 affects the genes expression of NHEJ and BER pathways in the seedling stage, while the HR mechanism response was initiated at vegetative stage. This study laid the foundation for exploring the molecular

biological mechanism of the real actual spatial environment.