

## A LARGE HUMAN CENTRIFUGE FOR EXPLORATION AND EXPLOITATION RESEARCH

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**ABSTRACT**

*This paper addresses concepts regarding the development of an Altered Gravity Platform (AGP) that will serve as a research platform for human space exploration. Space flight causes a multitude of physiological problems, many of which are due to gravity level transitions. Going from Earth's gravity to microgravity generates fluid shifts, space motion sickness, cardiovascular deconditioning among other changes, and returning to a gravity environment again puts the astronauts under similar stressors. A prolonged stay in microgravity provokes additional deleterious changes such as bone loss, muscle atrophy and loss of coordination or specific psychological stresses. To prepare for future manned space exploration missions, a ground-based research test bed for validating countermeasures against the deleterious effects of g-level transitions is needed. The proposed AGP is a large rotating facility (diameter > 150 m), where gravity levels ranging from 1.1 to 1.5g are generated, covering short episodes or during prolonged stays of weeks or even months. On this platform, facilities are built where a crew of 6 to 8 humans can live autonomously. Adaptation from 1g to higher g levels can be studied extensively and monitored continuously. Similarly, re-adaptation back to 1g, after a prolonged period of altered g can also be investigated. Study of the physiological and psychological adaptation to changing g-levels will provide instrumental and predictive knowledge to better define the ultimate countermeasures that are needed for future successful manned space exploration missions to the Moon, Mars and elsewhere. The AGP initiative will allow scientific experts in Europe and worldwide to investigate the necessary scientific, operational, and engineering inputs required for such space missions. Because so many different physiological systems are involved in adaptation to gravity levels, a multidisciplinary approach is crucial. One of the final and crucial steps is to verify the AGP concept through a large scientific community through feedback from various scientific societies. This facility will also serve clinical research on Earth, because a multitude of health problems such as osteoporosis, frailty of the elderly, inactivity, sarcopenia, obesity, insulin resistance and diabetes, cardiovascular problems, connective tissue ageing and immune deficiency, among others stand to benefit from the fundamental insights into the effects of our ever-present terrestrial gravity gained with such a novel research platform.*

**Keywords:** hypergravity, artificial gravity, microgravity, weightlessness, human exploration, human hypergravity habitat

## VELIKA ČLOVEŠKA CENTRIFUGA ZA RAZISKOVANJE IN IZKORIŠČANJE

### IZVLEČEK

*Ta prispevek opisuje koncepte na področju razvoja platforme za spreminjanje gravitacije (Altered Gravity Platform ali AGP), ki bo služila kot raziskovalna platforma za človeško raziskovanje vesolja. Polet v vesolje povzroči številne fiziološke težave, izmed katerih se mnoge pojavijo zaradi sprememb gravitacije. Prehod iz Zemljine gravitacije v mikrogravitacijo ustvarja redistribucijo tekočin, slabost, slabšanje srčno-žilnega sistema, vrnitev v okolje gravitacije pa astronave postavi pod podobne stresne pogoje. Daljše zadrževanje v mikrogravitaciji sproži dodatne škodljive spremembe kot so zmanjšanje kostne mase, mišična atrofija, izguba koordinacije ali specifične psihološke strese. Z namenom, da bi se lahko pripravili na prihodnje človeške misije v vesolje, je potrebna raziskava za odkrivanje ustreznih protiukrepov na področju škodljivih učinkov, ki jih sprožijo spremembe gravitacije, raziskava pa bi se izvajala na Zemlji. Predlagana AGP je dejansko velik rotirajoči objekt (v premeru > 150 m), kjer ravni gravitacije segajo od 1,1 do 1,5 g, in kjer se lahko izvajajo krajši preskusi ali celo preskusi v daljših obdobjih, na primer tednih ali mesecih. Na tej platformi bodo zgrajeni objekti, kjer bo lahko samostojno živela ekipa s 6 do 8 osebami. Tako se lahko neprekinjeno preučuje in spremlja prilagajanje človeka gravitaciji 1 g ali višji gravitaciji. Podobno se lahko preiskuje tudi ponovna prilagoditev na gravitacijo 1 g po daljšem obdobju bivanja v spremenjenih težnostnih pogojih. Preučevanje fizičnega in psihološkega prilagajanja spreminjajočim ravnem gravitacije bo tako omogočilo instrumentalno in napovedno znanje, ki bo lažje določilo najboljše protiukrepe, ki so potrebni za prihodnje človeške misije na Luno, Mars in drugam. Pobuda za AGP bo vrhunskim znanstvenikom v Evropi in po svetu omogočila, da raziskujejo vse potrebne znanstvene, operativne in tehnične vložke, ki so potrebni za takšne misije v vesolje. Ker so v prilagajanje na različne ravni gravitacije vključeni različni fiziološki sistemi, je poglobljen več-disciplinaren pristop. Eden izmed zadnjih in pogloblitnih korakov je, da koncept AGP preveri širša znanstvena javnost s pomočjo povratnih informacij s strani različnih znanstvenih skupnosti. Ta platforma bo prav tako služila kliničnim raziskavam na Zemlji, saj bi lahko preučevali tudi učinke zemeljske gravitacije v primerih različnih zdravstvenih težav kot so osteoporoza, slabotnost starejših, nedejavnost, sarkopenija, debelost, odpornost za inzulin in sladkorna bolezen, srčno-žilne težave, staranje veznega tkiva in slabljenje imunskega sistema.*

**Ključne besede:** hipergravitacija, umetna gravitacija, mikrogravitacija, breztežnost, človeško raziskovanje, človeški življenjski prostor v hipergravitaciji

## INTRODUCTION

Space flight research makes use of the unique microgravity environment, where the gravitation is compensated by the fact that spacecrafts are in free fall, to learn about the effects of weight on the human physiology and psychology. When we consider a physical entity like weight (accelerated mass) acting upon a system, researching weight is basically not any different from exploring *e.g.* temperature (Aschoff & Wever, 1958; Brink & Werber 1994) or pressure (Foster & Butler, 2009). In order to understand how a physiological and psychological system responds to an environmental variable we need to modulate it. For many systems it is therefore as relevant to look at responses to hypergravity (larger than Earth 1g) as it is to consider hypogravity or even near weightlessness. Since humankind developed the capability of going into space, numerous space flight experiments, some of significant duration, have been performed, initially on board the Soviet Salyut (Grigoriev et al., 1994), later on the American Skylab (Johnston et al., 1977) in the early nineteen seventies, on Mir mainly during the 1990s and currently on the International Space Station, ISS. Some cosmonauts/astronauts were under near weightless conditions for several months and longer. In sharp contrast, most hypergravity studies have been performed using short exposure times. If one is interested in the long-term effects of gravity on human physiology we also need to expose humans to hyper-gravity for periods of days, weeks or even months. In his flying career the Russian cosmonaut Sergei Krikalev has been exposed to hypo-gravity conditions on board orbital space stations for more than 800 days in total. There has never been a single person exposed to more than 1.0 g for a period of time anywhere near to these 800 days, despite the fact that a hyper-gravity facility is far less complex than a micro-gravity platform. In fact, the longest period to which humans have been exposed to hypergravity was for a few weeks during pilot studies performed in Downey (California, USA) and Pensacola (Florida, USA in the 1960s) but only few publicly accessible reports have been released from these studies.

### Concept and Objectives

Humans in space experience problems at many different levels. Microgravity and gravity transitions both have enormous impacts on the human physiology, behavior, psychology as well as operations and well-being (Schmidt et al., 2009). g-Level transitions are acutely problematic for various physiological systems such as the neuro-vestibular, cardiovascular and fluid regulation system, whereas prolonged microgravity causes undesirable adaptations in *e.g.* muscle, bone and the immune system. Such drastic changes in the physiological system, and especially those in the nervous system, in turn affect both individual psychology (cognition, emotion, motivation, activity levels and cycles, etc.) and psychosocial factors such as social perception and interaction. Going from an Earth gravity level into microgravity puts significant stress on all these systems, but the reverse is also true, *i.e.* moving from a microgravity ( $\mu$ -g) into a gravity environment. Going from  $\mu$ -g (hypo-gravity) to 1g is equivalent to going from

1g to hyper-gravity, although the effects might be different in magnitude.

Human spaceflight is one of the few areas of research where all these physiological and psychological changes take place in the same subject (Kanas & Manzey, 2008; NASA, 2005 Williams et al., 2009). In essence, during spaceflight we see many physiological changes similar to those typical of ageing (Asher, 1947; Biolo et al., 2003; Blottner et al., 2006; Corcoran, 1991; Gannon et al., 2009; Narici et al., 2002; Vernikos et al., 2010). One can regard spaceflight as an extremely accelerated 'ageing' process. Therefore, the need for countermeasures that tackle these deleterious effects drives many research efforts in different institutes throughout the world.

In contrast to typical clinical studies, the number of astronauts is usually extremely limited, *i.e.*, at most a dozen of astronauts can take part in one experiment. However, results from space experiments drive other ground-based research projects where larger groups of subjects can be included (Clemets, 2011). To date only two ground-based simulations of the effects of long duration spaceflight are used; 'bed-rest' (Armbrecht et al., 2011; Arbeille et al., 2008, Pavy-Le Traon et al., 2007) and 'dry immersion' (Iwase et al., 2000; Moukhina et al., 2004; Navasiolava et al., 2011). During bed-rest studies healthy subjects continuously stay for a period of weeks to months, in a bed that is tilted 6 degrees head down. Dry immersion is a model where healthy subjects are immersed for typically one week in a bath, without making contact with the water by means of a sealing cloth. Both experimental models generate comparable physiological effects as microgravity, mainly for the muscular (Moriggi et al., 2010), bone (Belavý et al. 2011) and cardiovascular systems (Perhonen et al., 2001; van Duijnhoven et al., 2010). However, for the neuro-vestibular system, neither of these ground-based models seems appropriate because the subjects are still exposed to 1g. In this regard it is important to note that in recent years more compelling evidence is emerging on the role of the neuro-vestibular system on other physiological systems such as muscle, bone or circadian rhythms (Levasseur et al., 2004), suggesting that simulations that fail to include neuro-vestibular changes may be lacking important components.

Spaceflight-induced effects are not entirely due to microgravity. It is known that g-level transitions also cause several physiological changes (Paloski et al., 2008). Going from one g on Earth to micro-g in space, provokes problems, but the reverse transition does as well, *i.e.* upon return of the astronauts from space to Earth, while for systems such as the skeleton, the time needed to recover is longer than the mission duration (Vico et al., 2000). Whereas on Earth, medical support is omnipresent during the days and weeks after return, this will not be the case when landing on the Moon, let alone on Mars. To increase the success of the human exploration program, understanding the changes that take place during gravity-level transitions and during prolonged altered gravity is fundamental. Such research protocols help to define countermeasures in order to mitigate the deleterious effects emerging from these challenging conditions.

Post-flight scientific evidence shows that the inner ear utricular nerve-afferent sensitivity is strongly regulated by exposure to even a short duration in microgravity experienced during orbital missions, requiring hours to days to recover after the return to Earth (Boyle *et al.*, 2001). Transition from hyper-g to normal gravity resembles the transfer from 1g to microgravity, and might be used as a valid analog ground-based

model. Human studies have also shown that when astronauts were exposed for one hour to 3 times the force of gravity, they experienced after this centrifugation session comparable symptoms of space motion sickness as they experienced on board the Space Shuttle (Ockels et al., 1990; Bles et al., 1997). Thus the transition from 3g to 1g was similar in the broad sense to the transition from 1g to microgravity. However, only the neuro-vestibular responses were investigated in these studies, leaving open the questions related to other organ systems.

During the last two decades, many studies have presented evidence of alterations in molecular mechanisms and signal transduction processes in cells of the immune system as a direct result of reduced gravity (Cogoli et al., 1984; Boonyaratankornkit et al., 2005). Together with clinical observations, these studies raise serious concerns as to whether spaceflight-associated immune system weakening ultimately precludes exposure to long-duration space flight (Crucian et al., 2009). Therefore, it is a fundamental question whether a gravity continuum exists for the signal pathways of immune system cells, which might support the use of hypergravity as a countermeasure treatment on immunity. It might be argued that hypergravity could be applied as a possible therapeutic strategy to strengthen the human immune system on Earth.

Since several crewmembers will live and work on board the AGP, this facility could also be used for psychological studies. The AGP could be complementary to other space flight related analogs such as pressurized modules, isolation chambers, underwater habitats, submarines, as well as Arctic and Antarctic stations or the Mars-500 study (Angener, 2012; Harrison et al., 1991; Inst. of Medicine, 2002; Kanas & Manzey, 2008; Olsen, 2002).

Another of the technological capabilities of such a hyper-gravity platform would be for testing new life support systems (Czupalla et al., 2005; Hendrickx et al., 2006) or as a low pressure (hypoxic) environment such as foreseen for the Moon and Mars bases (Lieberman et al., 2005). In addition, the crew could be used for testing new training methods for flight-like space operations. While human experiments are running, parallel studies using animals and plants can also be performed. Given the size of the AGP, a further application of the system is in geophysical fluid mechanical studies, where a large-scale Coriolis force is required to properly simulate planetary phenomena (Orr et al., 2008).

Rather than mimicking the effects of microgravity, hypergravity can be used to study how the different physiological systems react to changing gravity, in particular going from 1g to more than 1g, and vice versa. Such studies are complementary to the research conducted on board the ISS, and contribute to the space exploration program from a completely novel and different angle of attack. Directly related to this knowledge are medical issues in e.g. the ageing population. Diseases associated with the contemporary life style such as osteoporosis, sarcopenia, cardiovascular diseases and obesity can be addressed using the AGP (Trappe, 2009; Vernicos & Schneider, 2010). The outcome of these multidisciplinary studies will provide us with the best possible and collaboratively conceived arguments to actually develop such a facility, taking into account the input from all involved scientific, engineering, and operational disciplines.

## The Altered Gravity Platform (AGP)

To study the effect of altered gravity conditions, we propose the use of a ground based research platform, to be called the Altered Gravity Platform, AGP, that as a baseline consists of a habitat for 6 or more subjects, and where the adaptations to altered gravity can be studied during prolonged experiments. Human behavior and adaptation will be studied when subjects are subjected to different g-levels along the gravity continuum. If we consider this paradigm of a gravity continuum, *e.g.* that physiological processes scale with the magnitude of applied acceleration (Tou et al., 2002; van Loon et al., 2005; Wade, 2005) one may learn about the long-term adaptation of the body to different g loads. How fast does the human body adapt to a hyper-g load, but also how fast does the body respond when returning to 1g after long duration centrifugation?

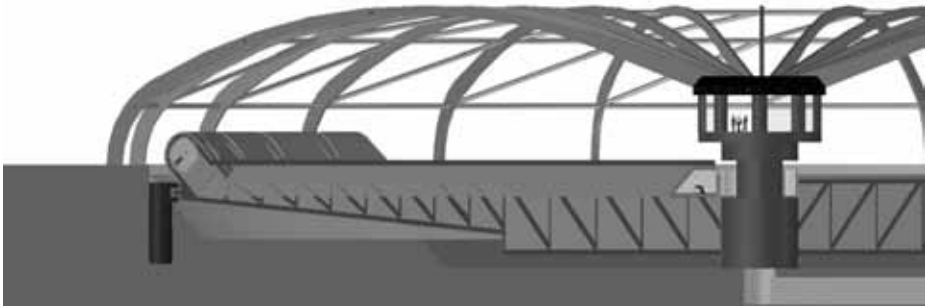
The concept of the AGP was initiated in a Topical Team of the European Space Agency (ESA) (van Loon et al., 2009a, 2009b). This concept is also supported by the United States, Japanese and Canadian space agencies; NASA, JAXA and CSA, respectively. The Topical Team members have discussed the gravity levels and angular velocities for which the human body could be safely exposed to for extended periods of time. Also, experimental protocols addressing the countermeasures as well as basic human physiological and psychological research were proposed. Issues such as ethics, safety, as well as the required technology were addressed. The outcome of these discussions will be shared with scientists, engineers and operators to provide profoundly conceived arguments for designing and building such a facility, taking into account the input from all involved scientific, engineering and operational disciplines.

The AGP consists of a rotating platform within a weather-protected shell. The Topical Team's scientific requirements regarding acceptable rotation rates suggest a reference radius in the order of 75 m. The nominal test range will be 2 g at the outer rim, which is achieved by a rotation at 4.5 rpm, hence a tangential speed of 35.7 m/s or some 128.5 km/h. These values are considered as baseline at this point, and may change according to the requirements emerging from future, more detailed, analysis from scientists and operational experts.

A modular habitat is installed along the 75 m radius, to accommodate various scientific requirements and operational functions. A 75 m radius allows for the installation of up to 47 units of 10 m each along a 471 m perimeter. In such a maximum configuration and considering a baseline habitat-width of 3.75 m, this will add up to a total of 1,762 m<sup>2</sup>, including 1400m<sup>2</sup> of usable space. The modules will include functions such as living and working accommodation, labs, life support systems, and storage. The 'gravinauts' will be subjected to altered gravity confined in the Gz direction; this is realized with a variable tilting system that positions the floor between 0° (no rotation) and 60° (2g level) to compensate for the radial acceleration imposed on the modules. The large platform surface allows testing stations at various distances from the AGP rotation axis, thus providing various gravity levels at the same revolutions. The platform is internally balanced with a system of counterweights ensuring rotational stability.

In nominal operations the start and stop of the AGP will be below vestibular threshold, *i.e.* it will take up to several hours for reaching full speed or stopping the rotation. This is to avoid acute motion sickness or cardiovascular events, and to take into account the energy efficiency and the inertia of the platform. Constant rotation can last from hours up to six months without stopping the facility.

Although the platform and habitat have ample space for the storage of spare parts, food and water, a flexible resupply system is foreseen to permit the wide range of planned studies. Here a transition unit can be loaded with supplies while in the static center of the platform and then rotated up to speed to synchronize with the main platform. At that point a “radial transition unit” transports items from the system center to the outer radius. This design allows the resupply of the modules without stopping the system, and importantly provides the possibility for bringing in or evacuating individuals during operations.



*Figure 1: Concept drawing for the AGP. The habitat (shown on the left with a standing subject) is located eccentric to the platform center to subject the subjects and module contents to centrifugal force up to 2 times the gravity normally experienced on Earth. The motor drives (in red) are placed along the platform's perimeter. In the center (right side of cartoon) the rotating and radial transition units can be seen. Note human figures standing in the center of the AGP, while a subject is located in a 45° tilted cabin while the AGP is running with a total load to the subject of  $\sqrt{2}g$ .*

In the current configuration the platform has a design mass of about 1000 metric tons. The rotating the structure is foreseen by means of electric linear motors located at the perimeter, a system based on existing MAGLEV technology (Gieras et al., 2012). The absence of mechanical wear ensures the required autonomy for long-duration studies. The location of the active components on the non-moving part (around the platform) allows for easy access for maintenance and repair during rotation.

The static center area will be safely accessible for goods and people by means of an underground tunnel. This center area could also host a visitor center with an observation



deck that will be used for public outreach and educational purposes. Around and level with the rotating platform an area will give direct access to the platform when it is stationary. This area will be used for technical work on the system and for emergency exits. Evacuation from the platform could also be done towards the center by using the resupply unit during rotation or by stepped corridors in the platform structure during non-rotation.

The platform is weather protected by means of a dome-shaped roof structure. This guarantees stable conditions inside and gives full control of the aerodynamic aspects of the rotating structures. Technical installations will be in the non-rotating center, around, and under the rotating platform. A Mission Control Center will include facilities for preparing experiments and technical, operational, and maintenance areas. The large unobstructed roof surface could accommodate a field of solar photovoltaic panels to reduce the running cost of the facility. The objective is to construct a low energy building using passive solar gains and cogeneration principles, thus making the best use of waste energy and heat dissipation of its technical systems to further reduce the energy demand. Furthermore, the building will require a medical facility in order to guarantee the safety and medical follow-up of test subjects. A location near an existing hospital is recommended.

### **Scope of the AGP project**

After 50 years of bioastronautics research, human space flight has entered a new phase of exploration towards the Moon, Mars, and asteroids. In that context, the primary objective of the next bioastronautics research program is to extend our knowledge of the effects of long-duration space flight on crew health and performance, further develop efficient countermeasures, and facilitate post-flight re-adaptation to the terrestrial gravitational environment (NASA, 2005). Such basic research is a prerequisite activity aimed at improving the capability for interplanetary travel and life on other planet surfaces, as the current countermeasures regarding the physiological and psychological changes associated with long-duration missions in orbit are far from being fully adequate.

The classical approach used so far in space research, which consisted of investigating adaptations to microgravity as per organ functions, needs to evolve toward a strong integrated model of the physio-pathological adaptation of multiple organ systems. Understanding the mechanisms of the adaptation of the human body as a whole to altered gravity conditions, including hypergravity, requires investigations from the molecular level up to integrated systems levels. Long-duration studies in the AGP, combining results obtained in a large population of both male and female subjects, together with a suite of contemporary instrumentation for human research, would significantly contribute to this knowledge.

Human missions to the Moon and Mars include long transit time in microgravity and stay in reduced gravity, as well as transitions in gravity levels during launch and re-entry. A better understanding of these transitions is essential to develop adequate countermeasures.

For decades, clinicians, physiologists and psychologists have worked separately without taking full advantage of potential strong common interests and “cross-fertilization”. This is also true for ground-based research, for example the research on ageing and chronic diseases. In our search for the environmental factors that fuel the pandemic of chronic diseases, we face a paradox. We know that our modern western societies have adopted a sedentary lifestyle. Such a lifestyle has been associated with an increased risk of numerous burdensome chronic diseases such as musculoskeletal, cardiovascular and coronary diseases, stroke, cancer, obesity and type 2 diabetes. Physical inactivity annually results in more than two million deaths worldwide and combined with a poor diet, is classified as one of the major causes of mortality (Agostini et al., 2010, Fogelholm, 2010; Thijssen et al., 2010). However, the causal relationships between sedentary behaviors and obesity and its related metabolic disorders are essentially based on observational epidemiological studies. We know from paired controlled animal studies where rats (Moran et al. 2001), hamster, rat, guinea pig, and rabbit (Katovich, 1978; Pace et al., 1985) or chickens (Smith et al., 1963) have been exposed to long duration chronic accelerations that fat mass decreases while bone density and cardiac capacity increases. Such observations deserve appropriate hypergravity human studies to see if these effects translate to humans.



*Figure 2: Left: Human centrifuge, Karolinska Institute, Stockholm, Sweden. Right: DESDEMONA facility at TNO-Soesterberg, The Netherlands.*

In the process of establishing more detailed design requirements for the AGP, two series of pilot experiments are foreseen, one in Stockholm (Sweden) in the Karolinska Institute (Pettersson J., 2006) where a 7.25 m radius centrifuge is operating, and one pilot study at TNO Soesterberg (the Netherlands) with the DESDEMONA facility (Bles et al., 2009) (See Figure 2).

A major issue regarding the use of centrifuges concerns spatial disorientation and vertigo caused by Coriolis forces and cross-coupling angular accelerations, when a subject moves in a rotating environment (Dizio et al., 2001; Elias et al., 2008; Eyeson-Annan et al., 1996; Muth, 2000). The pilot experiments mainly aim at determining levels of threshold and susceptibility for spatial disorientation, sensorimotor coordination and motion sickness in groups of healthy volunteers and results from such studies will inform the final AGP design.

## CONCLUSIONS AND FUTURE DIRECTIONS

After many decades, in which the main task for progress in medicine was to collect the “parts catalogue” of the human body and uncover molecular regulatory mechanisms, the challenge for the first decades of the 21st century in medicine is to unify the respective knowledge and enable a more integrative and individualized medicine. Space biology and medicine integrate complex studies on humans and are therefore well suited to this challenge. The AGP offers great potential for successful steps in this endeavor.

The transition of gravity research from physiological functions to a more integrated approach requires a focused, competitive research strategy for solving targeted risks of human health and individual and group performance. Reaching these goals and measures will not only provide the basis for critical, high quality health care for crews on orbit, but also result in a wealth of novel physiological and psychological data to investigate. Studies performed in the AGP will undoubtedly yield solutions for the medical challenges for long-term space missions. The lessons learned will provide the basis for evidence-based decisions of issues such as immunology, mineral metabolism, protein synthesis, chronobiology, cardiology, and nutrition in space taken as a whole. The AGP will also provide the basis for the design and testing of new countermeasures to be used both in space and on Earth in ageing, rehabilitation, or training.

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## REFERENCES

- Agostini, F., Mazzucco S., & Biolo, G. (2010).** Metabolic adaptation to inactive lifestyle from muscle atrophy to cardiovascular risk. *Annales Kinesiologiae*, 1(1), 47–60.
- Angener, O. (2012).** Platforms for stress and immune research in preparation of long-duration space exploration missions. *Stress challenges and immunity in space*. Edt. A. Chouker. Springer-Verlag Berlin, Heidelberg, 417–424.
- Armbrecht, G., Belavý, D. L., Backström, M., Beller, G., Alexandre, C., Rizzoli, R., et al. (2011).** Trabecular and cortical bone density and architecture in women after 60 days of bed rest using high-resolution pQCT: WISE. *Journal of Bone and Mineral Research*, 26(10), 2399–2410.
- Arbeille, P., Kerbeci, P., Mattar, L., Shoemaker, J. K., & Hughson, R. (2008).** Insufficient flow reduction during lbnp in both splanchnic and lower limb areas is associated with orthostatic intolerance after bedrest, *American Journal of Physiology - Heart and Circulatory Physiology*, 295, H1846–H1854.
- Aschoff, J., & Wever, R. (1958).** Modellversuche zum Gegenstrom-Waermeaustausch in der Extremitaet. *Research in Experimental Medicine*, 130, 385–395.
- Asher, R. A. J. (1947).** The dangers of going to bed. *British Medical Journal*, 1(2), 967–968.
- Belavý, D. L., Armbrecht, G., Richardson, C. A., Felsenberg, D., & Hides, J. A. (2011).** Muscle atrophy and changes in spinal morphology: is the lumbar spine vulnerable after prolonged bed-rest? *Spine*, 36(2), 137–145.
- Biolo, G., Heer, M., Narici, M., & Strollo, F. (2003).** Microgravity as a model of ageing. *Current Opinion in Clinical Nutrition & Metabolic Care*, 6, 31–40.
- Bles, W., de Graaf, B., Bos, J. E., Groen, E., & Krol, J. R. (1997).** A sustained hyper-g load as a tool to simulate space sickness. *Journal of Gravitational Physiology*, 4(2), 1–4.
- Bles, W., & Groen, E. (2009).** The DESDEMONA Motion Facility: Applications for Space Research. *Microgravity Science and Technology*, 21(4), 281–286.
- Blottner, D., Salanova, M., Püttmann, B., Schiff, G., Felsenberg, D., Buehring, B., et al. (2006).** Human skeletal muscle structure and function preserved by vibration muscle exercise following 55 days of bed rest. *European Journal of Applied Physiology*, 97(3), 261–271.
- Boonyaratankornkit, J. B., Cogoli, A., Li, C. F., Schopper, T., Pippia, P., Galleri, G., et al. (2005).** Key gravity-sensitive signaling pathways drive T cell activation. *The Federation of American Societies for Experimental Biology Journal*, 19(14), 2020–2.
- Boyle, R., Mensinger, A. F., Yoshida, K., Usui, S., Intravaia, A., Tricas, T., et al. (2001).** Neural readaptation to 1G following return from space. *Journal of Neurophysiology*, 86, 2118–2122.
- Brinck, H., & Werner, J. (1994).** Efficiency function: improvement of classical bioheat approach. *Journal of Applied Physiology*, 77(4), 1617–1622.
- Clement, G. (2011).** *Fundamentals of Space Medicine*. 2<sup>nd</sup> Edition. Springer: New York.
- Corcoran, P. J. (1991).** Use it or lose it. The hazards of bedrest and inactivity. *The Western Journal of Medicine*, 154, 536–538.
- Cogoli, A., Tschopp, A., & Fuchs-Bislin, P. (1984).** Cell sensitivity to gravity. *Science*, 225, 4658, 228–230.
- Crucian, B., & Sams, C. (2009).** Immune system dysregulation during spaceflight: clinical risk for exploration-class missions. *Journal of Leukocyte Biology*, 86(5), 1017.
- Czapalla, M., Horneck, G., & Blome, H. J. (2005).** The conceptual design of a hybrid life support system based on the evaluation and comparison of terrestrial testbeds. *Advances in Space Research*, 35(9), 1609–1620.

- Dizio, P., & Lackner, J. R. (2001).** Coriolis-force-induced trajectory and endpoint deviations in the reaching movements of labyrinthine-defective subjects. *Journal of Neurophysiology*, 85(2), 784–789.
- Elias, P. Z., Jarchow, T., & Young, L. R. (2008).** Incremental adaptation to yaw head turns during 30 RPM centrifugation. *Experimental Brain Research*, 189(3), 269–277.
- Eyeson-Annan, M., Peterken, C., Brown, B., & Atchison, D. (1996).** Visual and vestibular components of motion sickness. *Aviation, Space, and Environmental Medicine*, 67(10), 955–962.
- Fogelholm, M. (2010).** Physical activity, fitness and fatness: relations to mortality, morbidity and disease risk factors. A systematic review. *Obesity Reviews*, 11(3), 202–221.
- Foster, P. P., & Butler, B. D. (2009).** Decompression to altitude: assumptions, experimental evidence, and future directions. *Journal of Applied Physiology*, 106, 678–690.
- Gannon, J., Doran, P., Kirwan, A., & Ohlendieck, K. (2009).** Drastic increase of myosin light chain MLC-2 in senescent skeletal muscle indicates fast-to-slow fibre transition in sarcopenia of old age. *European Journal of Cell Biology*, 88(11), 685–700.
- Gieras, J. F., Piech, Z. J., & Tomczuk, B. (2012).** Linear Synchronous Motors. Transportation And Automation Systems. CRC Press Baco Raton, FL USA, 323–362.
- Grigoriev, A. I., Morukov, B. V., & Vorobiev, D. V. (1994).** Water and electrolyte studies during long-term missions onboard the space stations SALYUT and MIR *Journal of Clinical Investigation*, 72, 169–189.
- Harrison, A. A., Clearwater, Y. A., & McKay, C. P. (1991).** From Antarctica to outer space: Life in isolation and confinement. New York: Springer-Verlag.
- Hendrickx, L., De Wever, H., Hermans, V., Mastroleo, F., Morin, N., Wilmotte, A., et al. (2006).** Microbial ecology of the closed artificial ecosystem MELiSSA (Micro-Ecological Life Support System Alternative): reinventing and compartmentalizing the Earth's food and oxygen regeneration system for long-haul space exploration missions. *Research in Microbiology*, 157(1), 77–86.
- Institute of Medicine (2002).** Safe passage: Astronaut care for exploration missions. Washington, DC: National Academies Press.
- Iwase, S., Sugiyama, Y., Miwa, C., Kamiya, A., Mano, T., Ohira, Y., et al. (2000).** Effects of three days of dry immersion on muscle sympathetic nerve activity and arterial blood pressure in humans, *Journal of The Autonomic Nervous System*, 79, 156–164.
- Johnston, R. S., & Dietlein, L. F. (1977).** Biomedical Results from Skylab Washington, DC: NASA SP-377.
- Kanas, N., & Manzey, D. (2008).** Space psychology and psychiatry. New York: Springer.
- Katovich, M. J. & Smith, A. H. (1978).** Body mass composition, and food intake in rabbits during altered acceleration fields. *Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology*, 45(1), 51–55.
- Levasseur, R., Sabatier, J. P., Etard, O., Denise, P., & Reber, A. (2004).** Labyrinthectomy decreases bone mineral density in the femoral metaphysis in rats. *Journal of Vestibular Research*, 14(5), 361–365.
- Lieberman, P., Morey, A., Hochstadt, J., Larson, M., & Mather, S. (2005).** Mount Everest: a space analogue for speech monitoring of cognitive deficits and stress. *Aviation, Space, and Environmental Medicine*, 76(6 Suppl), B198–207.
- Moran, M. M., Stein, T. P., & Wade, C. E. (2001).** Hormonal modulation of food intake in response to low leptin levels induced by hypergravity. *Experimental Biology and Medicine*, 226(8), 740–745.

- Moriggi, M., Vasso, M., Fania, C., Capitanio, D., Bonifacio, G., Salanova, M., et al. (2010).** Long-term bed rest with and without vibration exercise countermeasures: effects on human muscle protein dysregulation. *Proteomics*, 10(21), 3756–774.
- Moukhina, A., Shenkman, B., Blottner, D., Nemirovskaya, T., Lemesheva, Y., Püttmann, B. et al. (2004).** Effects of support stimulation on human soleus fiber characteristics during exposure to “dry” immersion. *Journal of Gravitational Physiology*, 11(2), P137–8.
- Muth, E. R., Raj, A. K., Rupert, A. H., & Lee, R. (2000).** The experience of nausea during sustained hypergravity flight with negligible angular velocity. *Aviation Space and Environmental Medicine*, 71, 522–530.
- Narici, M. V., Maganaris, C. N., & Reeves, N. (2002).** Muscle and tendon adaptations to ageing and spaceflight. *Journal of Gravitational Physiology*, 9(1), 137–138.
- NASA (2005).** The bioastronautics roadmap: A risk-reduction strategy for human exploration. NASA / SP-2004-6113, Washington, DC, USA.
- Navasiolava, N. M., Custaud, M. A., Tomilovskaya, E. S., Larina, I. M., Mano, T., Gauquelin-Koch, G., et al. (2011).** Long-term dry immersion: review and prospects. *European Journal of Applied Physiology*, 111(7), 1235–1260.
- Ockels, W. J., Furrer, R., & Messerschmid, E. (1990).** Simulation of space adaptation syndrome on earth. *Experimental Brain Research*, 79(3), 661–663.
- Olsen, J. J. (2002).** Antarctica: a review of recent medical research. *Trends in Pharmacological Sciences*, 23(10).
- Orr, A., Marshall, G. J., Hunt, J. C. R. J., Sommeria, J., Wang, C.-G., van Lipzig N. P. M., et al. (2008).** Characteristics of summer airflow over the Antarctic Peninsula in response to recent strengthening of westerly circumpolar winds. *Journal of the Atmospheric Sciences*, 65, 1396–1413.
- Pace, N., Smith, A. H., & Rahlmann, D. F. (1985).** Skeletal mass change as a function of gravitational loading. *Physiologist*, 28(6S), S17–20.
- Paloski, W. H., Oman, C. M., Bloomberg, J. J., Reschke, M. F., Wood, S. J., Harm, D. L., et al. (2008).** Risk of sensory-motor performance failures affecting vehicle control during space missions: A review of the evidence. *Journal of Gravitational Physiology*, 15(2), 1–29.
- Pavy-Le Traon, A., Heer, M., Narici, M. V., Rittweger, J., & Vernikos, J. (2007).** From space to Earth: advances in human physiology from 20 years of bed rest studies (1986–2006). *European Journal of Applied Physiology*, 101(2), 143–194
- Perhonen, M. A., Franco, F., Lane, L. D., Buckey, J. C., Blomqvist, C. G., Zerwekh, J. E., et al. (2001).** Cardiac atrophy after bed rest and spaceflight. *Journal of Applied Physiology*, 91(2), 645–653.
- Petersson, J., Rohdin, M., Sánchez-Crespo, A., Nyrén, S., Jacobsson, H., Larsson, S. A., et al. (2006).** Paradoxical redistribution of pulmonary blood flow in prone and supine humans exposed to hypergravity. *Journal of Applied Physiology*, 100(1), 240–248.
- Schmidt, L. L., Keeton, K., Slack, K. J., Leveton, L. B., & Shea, C. (2009).** Risk of performance errors due to poor team cohesion and performance, inadequate selection / team composition, inadequate training, and poor psychosocial adaptation. In J. C. McPhee and J. B. Charles (Eds.), *Human Health and Performance Risks of Space Exploration Missions: Evidence Reviewed by the NASA Human Research Program* (pp 45–84). Houston, TX: NASA Johnson Space Center.
- Smith, A. H., & Kelly, C. F. (1963).** Influence of chronic acceleration upon growth and body composition. *Annals of the New York Academy of Sciences*, 10, 410–424.

- Thijssen, D. H., Maiorana, A. J., O'Driscoll, G., Cable, N. T., Hopman, M. T., & Green D. J. (2010).** Impact of inactivity and exercise on the vasculature in humans. *European Journal of Applied Physiology*, 108(5), 845–875.
- Trappe, T. (2009).** Influence of aging and long-term unloading on the structure and function of human skeletal muscle. *Applied Physiology, Nutrition and Metabolism*, 34(3), 459–464.
- Tou, J., Ronca, A., Grindeland, R., & Wade, C. (2002).** Models to study gravitational biology of mammalian reproduction. *Biology of Reproduction*, 67(6), 1681–1687.
- van Loon, J. J. W. A., Tanck, E., van Nieuwenhoven, F., Snoeckx, L. H. E. H., de Jong, H. A. A., & Wubbels, R. J. J. (2005).** A brief overview of animal hypergravity studies. *Journal of Gravitational Physiology*, 12(1), 5–10.
- van Loon, J. J. W. A. (2009a).** The Human Centrifuge. *Microgravity Science and Technology*, 21 (1–2), 203–207.
- van Loon, J. J. W. A., Wuyts, F., Bäcker, N., Berte, J., Bok, K., Bos, J., et al. (2009b).** The large Radius Human Centrifuge 'A Human Hypergravity Habitat, H3. Paper IAC-09.A1.2.3, 60<sup>th</sup> IAC Congress. Deageon, South-Koria, 12–16 Oct.
- Vernikos, J., & Schneider, V. S. (2010).** Space, Gravity and the Physiology of Aging: Parallel or Convergent Disciplines? A Mini-Review. *Gerontology*, 56, 157–166.
- van Duijnhoven, N. T., Green, D. J., Felsenberg, D., Belavy, D. L., Hopman, M. T., & Thijssen, D. H. (2010).** Impact of bed rest on conduit artery remodeling: effect of exercise countermeasures. *Hypertension*, 56(2), 240–246.
- Vico, L., Collet, P., Guignandon, A., Lafage-Proust, M. H., Thomas, T., Rehaillia, et al. (2000).** Effects of long-term microgravity exposure on cancellous and cortical weight-bearing bones of cosmonauts. *Lancet*, 355(9215), 1607–1611.
- Wade, C. E. (2005).** Responses across the gravity continuum: hypergravity to microgravity. *Advances in Space Biology and Medicine*, 10, 225–245.
- Williams, D., Kuipers, A., Mukai, C., & Thirsk, R. (2009).** Acclimation during space flight: effects on human physiology. *Canadian Medical Association Journal*, 180(13), 1317–1323.