Artificial Gravity Bed rest study

Published: 13-03-2019
Last updated: 12-04-2024

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bone disorders (excl congenital and fractures)
Study type	Interventional

Summary

ID

NL-OMON48277

Source
ToetsingOnline

Brief title
AGBRESA

Condition

- Bone disorders (excl congenital and fractures)

Synonym
bone metabolism and quality

Research involving
Human

Sponsors and support

Primary sponsor: Department of muscle and bone metabolism
Source(s) of monetary or material Support: European Space Agency (ESA);National Aeronautics and Space Administration;DLR German Aerospace Center;Institute for Aerospace Medicine en derde geldstromen voor de individuele wetenschappers

Intervention

Keyword: artificial gravity, bed rest, countermeasure, spaceflight

Outcome measures

Primary outcome

One Primary objective is to assess changes in volumetric bone mineral density of the trabecular and cortical compartment as well as bone strength by means of finite element modelling (failure load, stiffness, cortical stress, trabecular stress) of the proximal femur as a weight bearing skeletal region by means of QCT measurements of the hip.

Endpoint 1: changes in total bone mineral density [g/cm3] in the proximal femur (QCT)

Endpoint 2: changes in total bone mineral density [g/cm3] in the femoral neck (QCT)

Endpoint 3: changes in trabecular bone mineral density [g/cm3] in the proximal femur (QCT)

Endpoint 4: changes in trabecular bone mineral density [g/cm3] in the femoral neck (QCT)

Endpoint 5: changes in cortical bone mineral density [g/cm3] in the proximal femur (QCT)

Endpoint 6: changes in cortical bone mineral density [g/cm3] in the femoral neck (QCT)

Endpoint 7: changes in bone strengths by means of Finite Element Analysis in the total proximal femur and femoral neck (QCT)

Another primary objective is to assess the changes of trabecular and cortical microstructure as well as bone strength by means of finite element modelling by means HR-pQCT measurements of the tibia and radius.

Endpoint 8: changes in total, trabecular and cortical bone density [mg/cm^3] at the tibia and radius (HR-pQCT).

Endpoint 9: changes in cortical thickness [µm], area [mm] and porosity at the tibia and radius (HR-pQCT).

Endpoint 10: changes in bone microstructural parameter like trabecular number [mm-1], trabecular thickness [µm], trabecular bone separation [µm] at the tibia and radius

Secondary outcome

We would like to refer to the complete research protocol for all other research variables / outcome measures of the planned study.

Study description

Background summary

Human spaceflight is currently entering the next phase of space exploration, namely towards the Moon and Mars. Linked to such ambitious goals are - by nature * physical, psychological and technological challenges which become increasingly difficult to understand and overcome with longer-duration missions: future exploration class missions may last up to several years, exposing astronauts to extreme environmental conditions and physical stressors that could cause major issues to both health and performance. Currently, some of these issues are considered as showstoppers for long-duration exploration missions with human crews. To safeguard astronauts* health, well-being and working efficiency, a comprehensive strategy to mitigate various risks is therefore required, including development of so-called countermeasures to reduce adverse responses to stressors stemming from exposure to the space

environment. Over the past 50 years of human spaceflight experience, a palette of countermeasures has been developed and tested, but they have had only limited success. This may be explained by the fact that currently applied countermeasures mitigate harmful responses of specific systems of the human body. Future countermeasures, therefore, have to be approached in an interdisciplinary manner. Because all physiological systems are challenged through the application of artificial gravity (AG) by centrifugation, it has been considered that AG has the unique feature of being a multi-system countermeasure for mitigating the effects of weightlessness. The primary objective of the AGBRESA bed rest study is to compare the protective effects of one single daily bout (30 min) versus multiple daily bouts of AG (6 x 5 min) on physiological functions that are affected by simulated weightlessness. A secondary objective is to document the user*s point of view, such as subjective rating of comfort/discomfort, perceived exhaustion, perceived benefits, and any other psychological issues associated with the AG protocols. The research in this bed rest study is proposed and will be performed by international established research teams and characterizes changes in physiological and psychological systems; systems of interest include, but are not limited to musculoskeletal, sensorimotor, cardiovascular, cerebrovascular, ocular, functional performance, cognition and behavioral health.

Study objective

The primary objective for the measurements in the VieCuri in Venlo is to measure the structure and bone density of the hip and lower leg and forearm; for technical reasons, these measurements can not take place in Cologne:
3 (three) CT measurements (QCT) of the hip: 1 x before bed rest, 1 x after bed rest and 1x 1 year after end of the bed rest
4 (four) HR-pQCT measurements of the Tibia and Radius: 1 x befor bed rest, 1x after bed rest and 1, and 2 years after the end of the bed rest

Quantitative computed tomography (QCT) is a medical technique that measures bone mineral density (BMD) using a standard X-ray Computed Tomography (CT) scanner with a calibration standard to convert Hounsfield Units (HU) of the CT image to bone mineral density values. QCT differs from DEXA in that QCT is a truly 3D bone density exam; meaning QCT can measure the metabolically-active trabecular interior bone separately from the dense cortical bone. Since trabecular bone is affected earlier and to a greater degree than cortical bone, QCT is able to detect changes in bone mass earlier in the proximal hip than other bone mineral density exams. In the AGBRESA study, QCT scans are used to evaluate bone mineral density of the proximal Femur.

The objective of the HR-pQCT measuzrements is to assess the efficacy of the AG training to counteract the deterioration of trabecular and cortical microstructure. DXA namely does not provide information about the bone microstructure, which is an important determining factor for bone strength. Recent developments in the field of imaging enable the evaluation of the bone

microstructure in vivo using high resolution peripheral quantitative computed tomography (HR-pQCT). From this data, new image processing techniques can be used to better characterize bone quality and strength.Measurement of dominant forearm and lower left leg will be performed using the standard positioning casts.

Study design

General research design
The bed rest study will be conducted in the: envihab facility of the Institute of Aerospace Medicine at the German Aerospace Center, Cologne, Germany. Nominally, each test person will stay in the Institute of Aerospace Medicine for a total of 88 days, of which 60 days are continuously spend in bed. Prior to and following bed rest, the subjects undergo a 14-day baseline data collection phase and a 14-day in-house recovery phase in (14 + 60 + 14 = 88 days) respectively. In addition, 4 follow-up examinations are planned (28, 90, 360 and 720 days after the end of the bed rest).

During the study, the test subjects will bring a total of four visits to the Vieçurie for the following bone Mineral density measurements:

during visits 1, 2 and 3 QCT measurements of the hip and HR-pQCT measurements of the Tibia and Radius are performed

visit 1 --> 11 days before the start of bed rest
visit 2 --> 8 days after the end of the bed rest
visit 3 --> 360 days after the end of the bed rest

During visit 4, only HR-pQCT measurements of the Tibia and Radius are performed

visit 4 --> 720 days after the end of the bed rest

Intervention

Prior to the bed rest phase, subjects will be randomly assigned to one of three experimental groups (n=8 in each group).

* Group 1: 6° HDBR with no centrifugation (passive control).
* Group 2: 6° HDBR with supine centrifugation at +1Gz at the center of mass for 30 minutes continuous per day.
* Group 3: 6° HDBR with supine centrifugation at +1Gz at the center of mass for 6 bouts of 5 minutes per day (sessions 2-6 are separated by 5 minutes of rest).

All subjects will be exposed to centrifugation at a reduced Gz level and duration during the baseline phase to re-familiarize the subjects with the

centrifugation profile(s) in the study setting. Subjects already underwent the centrifugation tolerance testing during the recruitment process.

Study burden and risks

With respect to the risks associated with the QCT and HR-pQCT measurement at the VieCuri; irradiation involves all dangers known from the interaction of ionizing radiation with tissue. When the radiation penetrates the human body during an X-ray examination, some of the radiation is absorbed in the tissue and can lead to biological changes in the cells due to chance. Depending on intensity and duration of exposure to this radiation, metabolic disturbances can be caused by changes in biologically important molecules (enzymes, proteins, genetic material). Radiation exposure, thus, can in principle lead to damage to the genome, as well as to the development of tumors. The probability of occurrence of damage is proportional to the dose level. However, there is no threshold of the dose for the occurrence of damage, i.e. the severity of possible damage is independent of the dose. The body is, however, capable on its own of rectifying this kind of damage to a certain degree with suitable repair mechanisms. The danger of resulting damage depends not only on the length and intensity of irradiation but also on the sensitivity to radiation of the exposed material. Bone exhibits a lower sensitivity to radiation compared with the stomach, lungs, colon or thyroid gland.

The cumulative radiation load for the measurements at the VieCuri is 4.32 mSv. The total natural exposure to radiation in Germany, or the annual effective dose to the public, is on average 2.1 millisievert. However, depending on the place of residence, diet and lifestyle habits, it can range from 1 millisievert to 10 millisieverts. The risk for the subject is therefore limited to stochastic radiation effects, in which the causation of a radiation-induced cancer plays the predominant role. Deterministic radiation effects can be excluded with a radiation load <100 mSv. The "official" life-long risk of radiation induction of fatal cancer was set at 5% / Sv by the International Commission for Radiological Protection (ICRP) (1991).

We would like to refer to the complete research protocol for an overview of all risks associated with the planned study, however, at this point it is worth mentioning, that there is no increased fracture risk due to changes in bone strength (not in the Radius and not in the Tibia) as a consequence of the 60 days of bed rest, since only bone-healthy subjects are included. A loss of up to 20% of the bone in a healthy person has no consequences in practice. In the study, maximum losses of up to 8% are expected in the Tibia.

In conclusion, the AGBRESA study is an international collaboration of three main space Agencies and many institutions world-wide and, to our knowledge, the first study to investigate long-term bed rest with artificial gravity (AG) as a countermeasure. In contrast to other countermeasures tested in the past, AG generated by centrifugation has the potential to alleviate all physiological

deconditioning caused by prolonged exposure to weightlessness. Because all physiological systems are challenged through the application of AG, AG has indeed the unique feature of being a multi-system countermeasure for mitigating the effects of weightlessness. To test this hypothesis, this bed rest study is performed under the most rigorous standardized conditions known in the field. Bed rest immobilization has similar effects to a period of weightlessness, and is, in this context, used as a strictly standardized spaceflight analogue. Many of the implemented scientific methodologies are selected through peer-reviewed processes and involve a broad suite of both gold-standard and innovative monitoring technologies to provide a comprehensive understanding of the etiology of the physiological changes seen with spaceflight. In accordance with our science policy, the AGBRESA study (like the previous VaPER study) aims at including 50 percent female volunteers. Maintenance of musculoskeletal strength and function, cardiovascular integrity, but also eye sight, sleep quality and cognitive skills are all vital for astronaut safety and wellbeing and successful future long-duration spaceflight missions on board the international space station ISS, to the Moon and eventually to Mars. In our opinion, the scientific knowledge to be gained by this study justifies the extensive measures and risks as described in detail in our reseactrh protocol.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Physically and mentally healthy test subjects that are able and declare their willingness to participate in the entire study and successfully passed the psychological and medical screening
* Aged between 24 and 55 years old with a Body Mass Index (BMI) of 19 - 30 kg/m2, height between 153 -190 cm
* Non-smoker, for at least six months before the start of the study
* Capable of completing the study
* Willing to stay in bed with or without weight-bearing (artificial gravity) for 60 days
* Demonstrable medical insurance and official certificate of absence of criminal record
* Demonstrable dentist certificate

Exclusion criteria

Drug, medication or alcohol abuse (regular consumption of more than 20-30 g alcohol/day)
* A requirement for any prescription medications
* Vegetarian, vegan (during the study)
* Migraine, chronic headache
* Insomnia or other sleep disorders
* Previous psychiatric illness
* Claustrophobia
* Increased intraocular pressure
* Any eye disorder that could significantly impact or jeopardize visual function
* Hyperopia > +5.0 Diopters
* Myopia > - 6 Diopters
* Astigmatism > 3 Diopters
* History of laser surgery, glaucoma and retinal surgery
* Hiatus hernia

* Gastro-oesophageal reflux
* Gastrointestinal stenosis, dysphagia
* Current or history of chronic bowel disease
* Diabetes mellitus
* Rheumatic illness
* Current or a history of (chronic) pulmonary disease
* Current muscle or joint disease or disorder
* History of prolapsed intervertebral disc
* Chronic back complaints
* Bone fractures less than 1 year prior to study
* Kidney disorder: deviations from normal values for creatinine in plasma. Deviations from normal values (Normal values for creatinine in plasma < 1.20 mg/dl)** and eGFR***
* History of kidney stones
* History of (chronic) cystitis, hydronephrosis, pyelonephritis
* Anaemia: Hb under normal values. (Normal values of Hb for men: 13.0-17.5 g/dl; women 12.0-16.0 g/dl)**
* Elevated risk of thrombosis ****
* Pronounced orthostatic intolerance (< 10 min standing and/or not able to withstand artificial gravity)
* History of elevated intracranial pressure and associated central nervous disorders
* Current or history of hemorrhagic diathesis or coagulations disorders
* History of spinal cord disease, including radiculopathy, myelopathy, or neuropathy
* History of skull/cranial surgeries
* History of adverse events to local anesthesia
* An abnormal androgen or estrogen status (tested only upon speculation)
* Female candidate is pregnant
* Female candidate is on oral contraceptives or contraceptive patch up to 4-6 months prior to study start
* Female candidate is in menopause or post-menopause, or is on hormone replacement therapy
* Female subjects without a normal length menstrual cycle (20-36 days)
* Inability or unwillingness to perform the required tests
* A medical or orthopedic condition that would preclude bed rest or exercise, as is determined by the examining and overseeing physician of the bed rest study
* Not within two standard deviations of normal bone mineral density (measured by dual-energy x-ray absorptiometry) for hip and lumbar spine based on T-score (young adult-peak bone mass, Caucasian, sex, but not age-adjusted)
* Metal implants (or objects like metallic slivers in the eyes, or bullets or shrapnel in the body) or other kinds of bone synthesis materials that are not well-fixed; tattoos or permanent make-up incompatible with MRI
* Participation in a (clinical) study within the last 3 months before start of this study that confounds participation in the AGBRESA study
* Known history of vertigo, nystagmus, neurological conditions, vestibular or gait disorders
* Previous heart surgery
* History of cerebrovascular or brain disease, tumor, injury, surgery or malformation
* Disorders of CSF circulation (i.e. hydrocephalus, idiopathic intracranial hypertension)
* Tinnitus; sensorineural hearing loss > 30 dB, or implanted hearing device

* Known Chiari-malformation
* History of fracture(s) at proximal femur (hip area), less than 2 years, and/or with remaining deficit and/or implants
* Any other condition which makes the test subject unsuitable for study inclusion in the opinion of the project team

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-03-2019
Enrollment:	24
Type:	Actual

Ethics review

Approved WMO

Date:	13-03-2019
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL68345.068.18