REVIEW ARTICLE

Simulating human space physiology with bed rest

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Abstract

In a recent review on bed rest studies of the past 20 years, it was concluded that head-down bed rest has proved its usefulness as a reliable simulation model for most physiological effects of spaceflight. Much of this research has been conducted to find countermeasures against the negative effects, which are associated with gravitational unloading. There have been partial successes in the prevention of, for example muscle wasting, cardio-vascular deconditioning, adverse metabolic changes, and bone demineralization. Reviews refer to bone-related measurements of the U.S. and Russian space programmes, as well as data from bed rest analogues, and conclude that in spite of the wealth of knowledge obtained thus far, many questions remain regarding bone loss, bone recovery, and the factors affecting these skeletal processes.

Bed rest research has also direct relevance for medical science on Earth. Valuable data on physiology and early reversible pathological changes that are associated with a sedentary lifestyle on Earth can be obtained. A good example is the conclusion from a metabolic protocol implemented during the 2001/2002 90-day ESA/CNES/NASDA male bed rest study. The results of that experiment on fatty acid oxidation suggest that Mediterranean diets should be recommended in recumbent patients. Some other unexpected results obtained during the ESA/NASA/CNES/CSA 60-day female bed rest study WISE-2005 may well prompt the development of a treatment for certain cardiac diseases. A nutritional supplement that was designed to alleviate skeletal muscle atrophy turned out to preserve cardiac muscle mass.

In order to optimise bed rest research, a systematic and standardised approach will be beneficial. During the last years, serious efforts have been made towards such standardisation on an international level. It is expected that results from future studies, combined with in-flight validation, will provide the answers to many biomedical problems that currently limit safe long-duration human space exploration beyond lower earth orbit. Hippokratia 2008; 12 (Suppl 1): 37-40

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In the early 90s, the European Space Agency (ESA) started performing isolation and confinement studies. As a consequence it became clear that especially bed rest studies with strict control of the gravitational unloading would be needed for comparison. In recent years ESA has led such bed rest studies resulting in a top level and valued programme. Developed through the user-driven approach of ESA's Life and Physical Sciences programme (ELIPS-1, 2000-2005), these bed rest studies were diverse in duration, interventions, operation and site. The following table provides a summary:

A critical revisit of bed rest studies

The 90-day long term bed rest study with 25 male

Table 1: ESA bed rest studies (Source: ESA announcement of opportunity AO-06-BR, published online in April 2006)

Name	Performed in year	Performed in	Pre- bed rest period	Bed rest duration	Post-bed rest period	Intervention	HDT angle
LTBR 01-02	2001/2	Toulouse, F	15 d	90 d	15 d	1) Flywheel exercise 2) Bisphosphonate	-6°
STBR 01-02	2001/2	Cologne, D	9 d	14 d	3 d	Caloric variations in nutrition, Amino acid infusion	-6°
BBR	2003/4	Berlin, D	3 d	56 d	6 d	Vibration exercise	0°
WISE	2005	Toulouse, F	20 d	60 d	20 d	1) Combined resistive exercise, aerobic exercise, Lower Body Negative Pressure 2) Nutritional supplement	-6°

volunteers (LTBR 01-02) is a good example of efficient international organisation of a multidisciplinary study. To date it has produced at least 20 peer-reviewed scientific publications. One of the study's key findings is that thigh muscle volume and training-specific performance for both knee extensors and plantar flexors were preserved by the exercise regime[1]. A highly efficient gravity-independent resistive exercise device was used for the muscular training every third day. The training with the flywheel exercise device (FWED) was highly efficient, considered its infrequent application and short exercise sessions. Unfortunately it failed to completely prevent the plantar flexor muscle loss, which amounted to 50% of that experienced by the control group. On a single fibre level, the training regime showed an incomplete preservation of slow-twitch (myosin heavy chain type I) muscle fibre size and function in vastus lateralis muscle[2]. Fibres showing a slow to fast shift in myosin heavy chain (MHC) composition were also observed. In both vastus lateralis and soleus muscles, an increase of hybrid fibres, expressing multiple MHC isoforms[3], was found. High proportions of hybrid fibres are seen in the skeletal muscles of elderly individuals of age 70-80 years[4,5].

A second countermeasure group in LTBR 01-02 received a pharmacological intervention commonly used in medical practice to treat osteoporosis. An intravenous infusion of 60mg Pamidronate disodium was given to the subjects 14 days before the beginning of bed rest. Bone mineral content (BMC) was measured at various levels of the tibia using peripheral quantitative computed tomography (pQCT). Rittweger et al. (2005)[6] demonstrated that both the Pamidronate and the FWED mitigated the BMC loss, although this was only significant at the diaphysis. A huge variability in BMC changes was noted, implying other factors affecting changes in whole-bone strength following acute mechanical disuse. When interpreting dual energy x-ray absorptiometry measurements of bone mineral density (BMD) of the proximal femur, Watanabe et al. (2004)[7] concluded that Pamidronate preserved BMD in that region.

Resistive vibration exercise applied in the Berlin Bed Rest Study (BBR) in 2003/04 was highly efficient in preserving microscopic muscle structure and function[8]. Looking at whole muscle level, loss of strengths, size, and activation was either mitigated or maintained for single parameters[9].

Results of the 2001/02 fourteen day bed rest study in Cologne from Biolo et al. (2002, 2004)[10,11] contributed to the scientific basis for the design of a nutritional countermeasure, which was applied in the Women International Space Simulation for Exploration study (WISE-2005). A diet with a higher protein content (1.6 instead of 1.0 g per kg body weight per day) and enriched with free leucine, valine, and isoleucine was given to the nutrition countermeasure group in this study. The aim of mitigating muscle mass and function loss was not achieved, tough, as published in two recent papers by Trappe S. and Trappe T. (2007)[12,13]. The authors report much more successful results from the exercise countermeasure group, where an exercise regime combined the FWED with aerobic running exercise on a vertical treadmill in lower body negative pressure as described by Watenpaugh et al. (2000)[14]. This exercise protocol prevented thigh muscle volume loss, and thigh and calf muscle strength loss. Seventy-five percent of calf muscle volume loss was prevented, as compared to only 50% in LTBR 01-02. Comparing Trappe's conclusions (2007)[12] with the results of Alkner and Tesch (2004)[1] it can be inferred that the female subjects in the exercise group of WISE-2005 did better than the male subjects in the exercise group of LTBR 01-02. The female control and nutrition groups seemed to have a worse outcome after 60 days bed rest for thigh muscle mass loss than the men after 90 days (21-24% loss vs. 18%). Calf muscle mass loss was in the same range after 60 days bed rest in women compared to men after 90 days bed rest (29-28% vs. 29%). From the results of the authors, obtained in two separate controlled clinical studies on small groups of female and male healthy subjects, it seems that women may be more susceptible to skeletal muscle deconditioning caused by gravitational unloading. This adds further to the need to develop, test, and validate countermeasures for space and Earth in women and men. The present inequality in the number of female and male subjects investigated for space- and simulated space physiology is undesirable and should be compensated in the future. According to a literature review by the group of Trappe et al. (2007)[13] it seems that only 7% of the approximately 500 individuals that have been specifically studied for skeletal muscle responses to unloading, were women. Harm et al. (2001)[15] looked specifically at gender issues related to spaceflight physiology. The authors concluded at the time that the available data allowed only for conclusive differences in the orthostatic stand test after short-term shuttle missions (5-16 days), where women were more susceptible to presyncope. A recent publication of a group looking at cardiovascular physiology in WISE-2005 states that the female volunteers in the control group reacted differently to men after bed rest on the variable of leg vascular resistance. Convertino et al. (1997)[16] observed that baseline leg vascular resistance was elevated in men after 14 days of head-down bed rest. After 56 days head-down bed rest in WISE-2005, Edgell et al. (2007)[17] found a trend to decreased leg vascular resistance in the female subjects of the control group.

There is no doubt that bed rest research in the last 40 years has provided a treasure of data, which can be applied for the benefit of space travellers and citizens on Earth. Investigating healthy subjects in an environment of absent gravitational forces along the body axis allows for example research on early changes of prolonged inactivity without other vascular risk factors. With results of WISE-2005, Demiot et al. (2007)[18] showed that in women undergoing prolonged bed rest impairment of endothelium-dependent function at microcirculatory level occurs, along with an increase in circulating endothelial cells.

ESA framework for future bed rest studies

In ESA-led countermeasure research, results from previous bed rest studies have been logically incorporated in the design of follow-on studies. In order to further optimise the yield of upcoming studies, ESA has taken the lead in defining a standardised framework for future bed rest studies. Details can be found elsewhere (e.g. ESA 2006 announcement of opportunity "Life sciences research in space simulation using the model of bed rest"). In brief, the framework consists of -6° head-down tilt bed rest with 3 fixed durations:

Short-term bed rest (STBR)

• Aims at countermeasure screening addressing primarily the cardiovascular system, using functional and surrogate measures

• Surrogate markers as outcome measures for bone and muscle systems

• Crossover design with one control- and several treatment groups (up to 3), with a wash out period in between. Eight to twelve subjects

• A minimum of five days ambulatory period

• Bed rest duration of five days

• Post-bed rest period can be variable and depends on the individual study.

Medium-term bed rest (MTBR)

• Countermeasure screening & confirmation of countermeasure concept; refining of protocols

• Functional and structural outcome parameters for cardiovascular and muscle systems, surrogate markers for bone

• Possibility of crossover design with one control- and a few treatment groups (max. 2), with a wash out period in between. Eight to twelve subjects

• Ambulatory period pre bed rest 7-14 days

• Bed rest duration 21 days

• Post bed rest ambulatory and recovery period 7-14 days

Long-term bed rest (LTBR)

• LTBR is used for a final validation of a set of countermeasures prior to implementation in spaceflight

• In these settings variables that provide more functionally relevant outcome measures for efficiency can be evaluated i.e. structural and functional changes in bone and muscle.

• LTBR should be preceded by a 14 days ambulatory period, whereby five days are needed to adapt to diet and environment. During the ambulatory period, the usual individual physical activity should be maintained.

• The duration of LTBR shall be 60 days, followed by a rehabilitation period of 14 days

Conclusions

Appraising the current literature one of the biggest challenges appears to be the bone system. Given the enormous inter-individual responses to unloading and countermeasures, it becomes clear that many more studies in a systematic fashion must be conducted before final solutions can be determined. The time-course of changes in bone, which are detectable with imaging technology has so far dictated the need for long duration studies. Fortunately, imaging is getting more and more refined. Recently, Rittweger et al. (2006)[19] published pQCT data of bone loss during a 24 day unilateral leg suspension study. Heer et al. (2005)[20] demonstrated how in strictly controlled metabolic conditions the osteoclast activity can be reliably measured in short-term bed rest. It seems probable that with a series of short- and mid-term studies, using standardised metabolic and imaging measurements, countermeasure protocols and devices can be developed, refined and optimised for near-complete protection of all physiological parameters affected by gravitational unloading. One very promising approach is ESA's new short-arm centrifuge, used alone or in combination with other countermeasures. Optimised countermeasure protocols will require final validation in long-term studies.

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