Bed-Rest Studies for the International Space Station

D. Schmitt & B. Elmann-Larsen
Life Sciences Unit, ESA Directorate of Manned Spaceflight and Microgravity, ESTEC, Noordwijk, The Netherlands

The microgravity experienced during space flight induces physiological changes that affect astronauts' health and performance. Simulations such as prolonged bed rest can mimic some of these changes and provide study conditions that are more accessible than during space flight itself. Previous studies, including several long and short-term bed-rest campaigns supported by ESA, have yielded significant medical data on the physiological changes induced by space flight. These data are being used extensively to study the effects of various countermeasures on those physiological changes.

Figure 1. Tilt Table – testing responses to horizontal and upright exercise

Introduction

Bed rest is a recognised tool for validating countermeasures on healthy subjects on the ground before applying them to the astronauts who will live and work on the International Space Station (ISS). It also serves to identify where there are differences between the true effects of space and those of simulation situations, as a means of achieving a better understanding of the profound mechanisms at work within the body's control functions.

For the first time ESA, together with DLR, CNES and NASDA, is performing extensive studies using short- and long-duration bed rest. The short-duration study, which involves a period of two weeks with 10 subjects, is examining the importance of reduced caloric intake on physiological de-conditioning (multiple changes resulting in reduced physical fitness). The long-duration bed-rest study, lasting three months, undertakes a variety of investigations involving 28 subjects. It focuses on countermeasures, studying the effect of an anti-osteoporosis drug as a medical counter-measure and resistive exercise as a physical countermeasure, to determine their suitability for use during long space journies.

The scale and duration of these studies is attracting interest from other international partners such as the USA and China. The physiological changes recorded during space flight and bed rest also mimic those observed as a result of certain diseases and as part of the ageing process. Significant clinical application is therefore expected as a direct result of these and similar future studies.

Background

Space life-sciences research (both at ESA and elsewhere) is predominantly focused on the effects of the space environment on physiological and biological mechanisms. The main aim of such research is to develop areas of basic or fundamental scientific investigation in order to improve the understanding of life, and to apply this knowledge to solve medical problems and support the development of biotechnology. The European Research Plan for Life and Physical Sciences and Applications in Space supports this aim by including initiatives for both preparatory and supporting research, such as access to European facilities for ground-based research and bed-rest studies.

A top-level objective identified in this research plan is 'Improving Health', through basic and applied research related to problems incurred as a result of ageing, disease or disability. Within this objective, the first priority is to understand the body's response to changes in load and mobility both in space and in the clinic. This requires a wide range of studies during space flight and through clinical investigations, e.g. bed-rest studies. The physiological changes occurring in microgravity, although differing in origin, are often similar to those due to certain diseases and to the ageing process, thereby providing new insight into the body's regulating mechanisms. These changes include:

- major changes in the circulatory system, such as altered blood-pressure and heart-rate control
- decreases in muscle mass and in the neuronal control of muscle activity
- differences in posture and locomotion control
- altered perception and cognition strategies in the brain
- bone loss, exceeding 1% per month in weight-bearing bones, in addition to potentially unrecoverable changes in structure
- changes in metabolism such as nutrition absorption and control of excretion of water and salt.

The second priority is to develop counter-measures, often tested using bed rest as the space-flight analogue, and to adapt their use for clinical rehabilitation on Earth. Nearly all space-flight-induced physiological changes observed to date have been well documented. This knowledge base is supporting specific studies on the effectiveness of counter-measures in reducing or eradicating the detrimental effects of microgravity and the absence of loading and mobility. Some current experiments in this area are focussing on resistive exercise, anti-osteoporosis drug testing, forcing appropriate blood and fluid distribution, and the use of vibration devices to trigger bone metabolism. These research areas have a large application potential in rehabilitation medicine.

A third priority is the testing of advanced instrumentation for monitoring and diagnostics. In this area, applied research is being performed in close collaboration with industry, mainly Small and Medium-sized Enterprises (SMEs) working in the biomedical field. Examples include:

- portable devices for non-invasive cardio-pulmonary monitoring
- tele-diagnostics using echocardiography and other relevant methods
- advanced gas sensors for fitness checks
- microcomputer tomography for fine bone-structure determination
- advanced techniques for measuring the electrical activity of muscles (electro-myography).

Why bed rest?

The American and Russian space programmes in the 1960's gave significant impetus to bed-rest research. Before that, a few studies had been conducted on bed-rested patients and on normal, healthy subjects starting as early as 1855. Physicians had used prolonged stays in bed to immobilise and confine patients for rehabilitation and restoration of health even before that time. The horizontal position relieves the strain of the upright posture, often used in situations of acute circulatory situations (syncope), bone fractures, muscle injuries or fatigue. However, adaptive responses occurring during bed rest proceed concomitantly with the healing process.

More recently, adaptive physiological responses have been measured in normal healthy subjects in a horizontal or slightly head-down-tilted supine position during prolonged bed rest as analogues for the adaptive responses of astronauts exposed to the microgravity environment. The recumbent position and prolonged continuous bed rest result in loss of most hydrostatic pressures, virtual elimination of longitudinal compression of the spine and long bones of the lower body, reduced muscular force and psycho-social changes. Bed rest is therefore considered a valid analogue for a number of aspects of space-induced physiological changes leading to de-conditioning.

Figure 2. Micro-neurography registration of electrical signals in a single nerve fibre

The 2001/2002 ESA DLR Short-Term Bed-Rest Campaign

Two bed-rest studies have been initiated in 2001, one short-term described here, and one long-term described in the next section.

Stimulated by findings that with few exceptions space crews lose bodyweight during longer stays onboard an orbiting spacecraft, this phenomenon has been investigated extensively over the last decade. Initially, even up until 1993, it was assumed that the weight loss was due to loss of body water, as its magnitude could easily be explained in that way. The so-called 'fluid shift' – whereby a major part of the fluid in the lower part of the body would move to the upper body in space due to lack of the pull normally exerted by gravity – was the basis for this very plausible assumption, in that the body would attempt to get rid of the excess of fluid in the trunk region. This theory also supported the observation that the circumference of the legs became smaller when in space.

It has now been shown via accurate metabolic studies, however, that the water-loss hypothesis does not hold. It appears that water and also salt are retained in the body to a greater extent than on the Earth; this observation cannot therefore justify maintaining the loss-of-water hypothesis. Instead, the same metabolic studies show that less food is being ingested per day on average during a space flight, and it is speculated that this relative under-nutrition could be a reason for some of the other negative effects observed, and specifically those related to muscle and bone metabolism. Nutritional aspects, coupled with the general unloading in space, which is the primary parameter simulated by using bed rest, may be two main factors causing the weight-loss and tissue changes. A potential effect on the manner in which the circulatory system maintains its responsiveness when exposed to gravitational stress may also be linked with the nutritional state.

Figure 3. Measuring food intake

Figure 4. Analysis of metabolic turn-over

The 2001-02 Short-Term Bed Rest study is composed of four equally long study periods, three months or more apart, investigating the same ten subjects in each of them. It addresses the nutrition-related questions raised above.

In a so-called 'crossover randomised study design' (randomisation of the sequence in which subjects perform the four phases), each person goes through four phases identical in duration and type of examination, but varying in terms of: (a) body position and (b) nutritional state. Each bed-rest study needs a set of control values gathered during an upright-body phase, while the nutritional state includes both a normal state and a state of relative under-nutrition.

By performing the same experiment and examinations during these four, time-wise-identical phases, and observing each of the four possible combinations of body position and nutritional state, the goal is to describe the differences in the observed parameters, which investigate: (a) potential changes in the way in which circulation is controlled under these conditions, (b) changes in the metabolism of bone, muscle and fat tissue, (c) whether there are changes to the kidney's function in regulating excretion of fluid and salt, (d) stress-related factors, and (e) general markers for energy turnover and food intake.

Overall, this short-term bed-rest study is expected to provide very important data on the effects of body position and nutrition on the different body functions, based on very accurate monitoring of the effect of food intake.

The 2001/2002 ESA–NASDA–CNES Long-Term Bed-Rest Campaign

Weight loss is one of several adverse effects of longer space flights. General 'adaptation' to weightlessness, which takes the form of de-conditioning or deterioration of many of the body's systems, involves a long list of additional changes, for which a good understanding of the basic mechanisms involved could help in developing suitable and effective counter-measures.

Another aspect of pure scientific research is that the effects of microgravity on humans are unique in nature. This means that changes, as an effect of continuous unloading, only occur with that particular speed (fast!) and with that particular characteristic when the subject is 'weightless' onboard a spacecraft for a longer period, i.e. several days or more.

The development of countermeasures has been a major goal since the early days of longer-duration space flight. Large variations in the seriousness of the microgravity-induced symptoms from one crew member to another, and the fact that in certain cases very large losses of bone mass or severe deterioration in muscle performance, balance function or circulation control over a period of three to six months can be observed, have been the prime reasons for seeking to understand the underlying mechanisms. The goal is to use this knowledge to develop the most effective countermeasures, but this has proved be a very ambitious goal because there are still serious gaps in our understanding of the basic mechanisms involved. Such countermeasures are therefore what the 2001-02 Long-Term Bed-Rest Study at the Space Clinic MEDES in Toulouse is focussing on.

A general serious constraint, which limits the speed with which progress can be made in this field, is the small number of observations possible due to the limited number of astronauts flying. In principle, each individual can only serve once for the observation of a certain variable, whereas a number of observations are necessary to draw valid conclusions. This is why a highly focused selection process is extremely important when choosing crew-based experiments. A further complication during the ISS construction phase is that crews generally have such a heavy work schedule that time for other research is very limited.

Some responses can be provoked better by using the bed-rest simulation model than others. The focus of the study started in August 2001 at MEDES has been on bone and muscle tissue. The changes seen in space crews bear similarities with the effects of being bed-ridden for long periods. Bone loss in astronauts has similarities with osteoporosis, which is an age- and to a significant extent also a sex-related disease, which particularly afflicts women over the age of fifty or so. A particularly important finding is that while osteoporosis normally occurs later in life and affects persons belonging to a certain risk-group, astronauts are usually younger, healthy individuals who suddenly begin to exhibit bone-mass loss when in the space environment.

In this co-operative study between the Japanese Space Agency NASDA, the French Space Agency CNES and ESA, one Japanese and nine European teams from five European countries have been selected. They will look, in particular, into the effect of bed rest on muscle and bone tissue, but at the same time will study whether exercise- and medication-based countermeasures are effective in counteracting the effects of immobilisation. They will simulate the situation in space by keeping fourteen volunteers in a six-degree head-down tilted position for three consecutive months. The volunteers will be divided into three groups: one will be the control group, one will undertake a certain type of exercise three times a week, and the last group will receive medication for the stabilisation of bone tissue.

Bed-rest studies of the sort described are in many respects just as complex a those during a space flight:
– planning begins 1–2 years prior to the start of the study
– experiment selection is very similar to that for a manned space flight, in terms of combination of disciplines and relative interdependence

Figure 5. The exercise countermeasure – leg force pushing a set of flywheels

Figure 6. Regular control of dynamic exercise capacity

– the same constraints as for a manned spacecraft apply in terms of general logistics, limited resources, general personal load estimation, ethical aspects, time and availability limitations, etc.

Consequently, space-agency personnel with the relevant experience and research groups who have experience of manned space flights are best-suited for managing such an undertaking.

Clinically, the study should prove extremely important. In particular, we expect to make crucial findings regarding how to maintain muscle mass while immobilised during long-term bed rest, which will benefit millions of patients. The other main focus of the study is to investigate and carefully describe the migration of calcium, bone's main building block, by exploiting a new combination of methods and tools.

Figure 7. Localised QCT: high resolution analysis and imaging of a slice of the forearm

In particular, this is the first time that a combination of nutrition monitoring, X-ray scanning (Dual X-ray Absorptiometry, DEXA, the gold standard) and Quantified Computer Tomography (QCT) have been combined in a single study, whilst at the same time testing different countermeasures on parallel groups. It is believed, for instance, that calcium is released from the bound state in the loaded part of the skeleton as a result of exposure to microgravity and then migrates dissolved in the blood, but the basic mechanisms involved are not at all well understood.

The study is to be seen firstly as a simulation of the present-day length of crew visits to the ISS, and secondly as a first step to investigating the effects and possible countermeasures when crews will be travelling in space for much longer periods, for instance to visit Mars. In addition, apart from their direct importance for manned space flight, such study activities tend to attract the involvement of more and more clinical experts who have had no prior exposure to the effects of space.

Older people who have to be bedridden for long periods have an increased risk of sustaining bone fractures thereafter. Astronauts who are otherwise completely healthy can lose bone structure very fast when exposed to microgravity. Bed rest and the development of bone-tissue changes in healthy young individuals combine these two situations, in a scientifically, trans-disciplinary and sophisticated manner. An added quality of such a study is that the overall effect on the major body systems is investigated, whereas traditional medical research is not geared to this level of ambition. This is because clinical research has the relative luxury, compared to the manned-space-flight situation, of having a large number of volunteers available and therefore tends to address narrower questions, in much smaller 'steps'.

Once this study has been completed, we hope to be able to contribute valuable new ideas on how to reduce the risks associated with clinical bed-rest situations on the ground, and also to develop more modern techniques for maintaining healthy bone and muscle tissue throughout life.

Future work

Following a recent Call for Ideas for simulation models, the need to continue using bed rest as an analogue to space flight is clear. Other analogues will also be looked at in the near future. The problems to be addressed are numerous and a long-term commitment to such studies will be put in place.

In anticipation of future manned space travel within the Solar System, preparatory activities are envisaged within the strategic framework for European space exploration, especially in the new Aurora programme. Here the use of 'space analogues' other than bed rest, such as Antarctic bases for example, is a must. Analogues for confinement and isolation are essential to address such scientific and technical issues as advanced life-support systems, habitability, communications and medical, physiological and psychological problems, which cannot all be fully tested using the ISS only. The use of Antarctic bases for 12–16 months of isolation is also the most suitable analogue for manned missions to Mars.