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Human: Bed Rest/Head-Down-Tilt/ Hypokinesia

Marie-Pierre Bareille and Alain Maillet

MEDES, Toulouse, France

13.1 Introduction

Many space agencies and in some cases even individual investigator teams around the world are involved in organizing bed-rest studies. However, the conditions in which these studies are performed are quite diverse. Differences lie, for example, not only in the organization and the environmental conditions of studies (duration of studies, angle of the bed, sunlight exposure, sleep/wake cycles, nutritional standards and control, etc.) but also in the scientific measurements taken. Indeed, like in a spaceflight, several scientific experiments are always carried out in the framework of ground-based studies. Thus, the scientific results of such studies may be affected by all these factors, and this complicates drawing overall conclusions and comparing results between the different studies. Furthermore, the experimental conditions are not always fully detailed in the scientific publications, and sometimes the authors report their results as if their experiment was the only one conducted in the study.

Therefore, in the past ten years, efforts were gradually made by the space agencies, the teams conducting bed-rest studies and the scientists to standardize as far as possible the design, the format, support and conduct of the studies. Recently, in order to achieve better standardization of bed-rest studies in the spaceflight context, an International Academy of Astronauts (IAA) study group was initiated, including members from most of the entities who are actively pursuing this type of activity.

This chapter focuses on the study design and logistics of bed-rest studies as used in the main facilities conducting studies around the world trying to emphasize the factors affecting the results and why.

13.2 Experimental Models to Mimic Weightlessness

The most used methods to simulate microgravity on Earth include immersion, bed rest, chair rest, isolation, hyperbaric environments and immobilization of animals. None of these techniques precisely duplicate near weightlessness because gravity cannot be entirely eliminated on Earth. However, two separate approaches, head-out water immersion and bed rest, have provided possibilities for long-term exposures and produce changes in body composition (including body fluid redistribution) and cardiovascular and skeletal muscle characteristics that resemble the effects of microgravity [1]. The common physiological denominator is the combination of a cephalad shift of body fluids and reduced physical activity.

13.2.1 Bed Rest or Head-Down Bed Rest?

Toward the end of the 1960s, Soviet investigators evolved a new method of bed rest in which the subject was positioned with the head lower than the feet, rather than horizontal, after having analyzed subjective comments of cosmonauts received after flight. Indeed, they complained to their medical staff that on their return from space they had a hard time sleeping because they had the sensation that they were slipping off the foot of the bed. They tried to correct the situation by raising the foot of the bed until it felt horizontal and they could get back to sleep. Every night they lowered the foot of the bed a little until lying horizontal felt normal again. They also suggested that the head-down-tilt position more closely reproduced the feelings of head fullness and awareness experienced during flights. Russian researchers took note of this observation and surmised that perhaps the head-down position on Earth was closer to what it felt like to be in space. The head-down bed-rest (HDBR) simulation model was born (Figure 13.1). The first study compared responses from horizontal bed rest and –4° head-down tilt. Since then, additional studies have been conducted with head-down positions ranging from –2° to –15° and lasting for 24 hours to 370 days [2]. In general, head-down bed rest induces findings more rapidly and profoundly than its horizontal counterpart [1]. The Soviets tested –15°, –10° and –5° for comfort, acceptability and magnitude of response and decided –6° was the best compromise. In many ways, HDBR made it in fact more comfortable for the subjects. They could lean over the side of the bed to eat. They could raise their knees as well since that only increased the head-ward fluid shift. In 1977/1978 joint USA/USSR 7-day studies done both at the IMBP (Institute

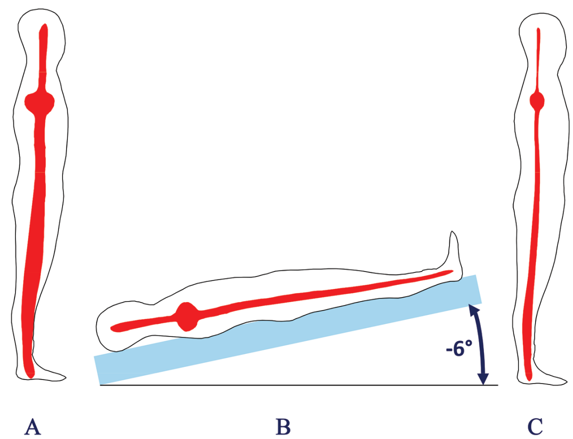

Figure 13.1 This shows the fluid shift from the lower to the upper part of the body induced by bed rest. (A) On Earth (1 g), the main part of the blood is located in the legs. (B) In Head-down bed rest (–6°), the thoraco-cephalic fluid shift stimulates central volume carotid, aortic and cardiac receptors inducing an increase in diuresis and natriuresis and a decrease in plasma volume. (C) While standing, this venous part of the blood falls to the lower part of the body (abdomen and legs). To come back to the heart, the blood has to go against the gravity. In that case, less blood comes back to the heart, the blood pressure tends to decrease. As in spaceflight, cardiovascular deconditioning characterized by orthostatic intolerance is observed at the end of bed rest.

for BioMedical Problems) in Moscow and at ARC (Ames Research Centre) in Moffett Field, CA, compared HDBR with horizontal bed rest and confirmed the added value of HDBR [3].

13.2.2 Immersion and Dry Immersion

With the advent of human spaceflight in 1961, immersion in water was used as a logical model for reducing the pull of gravity on the mass of the body. But it soon proved impractical because remaining in water for more than a day brought on unpleasant consequences. Therefore, this experimental model was used mainly for short-term studies and especially for fluid regulation [4–6].

Because the Soviets wanted to investigate on the long term in preparation of their spaceflights, they developed the dry immersion model. This model gave the possibility to the IBMP to conduct studies up to 57 days [2, 7]. Only a few number of these dry immersion systems were existing in Russia; today IBMP and a private company propose these systems for some rehabilitation centers [8]. A recent collaboration between the French Space Agency (CNES) and IBMP was initiated, and two of these systems have been installed at MEDES (Toulouse, France) to develop this experimental model in Europe and allow comparison with head-down bed rest. A first experiment is planned for 2015.

13.3 Overall Design of the Studies

13.3.1 Duration of the Studies

Since the end of the 1960s, many bed rest studies have been conducted lasting from several hours to a maximum of 370 days. The shortest studies are appropriate to investigate cardiovascular changes (4 hours to 1 week) while longer-term studies are needed to study other physiological changes, in particular bone loss and muscle atrophy (minimum of three weeks).

In the United States, the long-term studies were of 60, 70 or 90 d. In Russia, 120-day bed-rest studies have also been conducted and of course the 370 days of the Moscow study went way beyond anything that had been done before and since then.

After the first long-term bed-rest experiment performed in Europe in 2001–2002 (i.e. 90 days of head-down bed rest with human subjects), the duration of the bed-rest studies has been standardized to 5 d for short-term, 21 d for medium-term and 60 d for long-term studies.

The IAA Study Group has started writing guidelines for the standardization of bed-rest studies. The length of bed rest will be categorized into 3 different durations with associated pre- and post-bed-rest phases. The table below describes these categories.

The bed-rest studies are divided into three phases: (1) a pre-bed-rest phase for acclimation and baseline data collection, (2) a bed rest phase, and (3) a

Table 13.1 Categories for bed-rest study duration

Category	Pre-Bed-Rest Baseline Data Collection (BDC)	Head-Down-Tilt (HDT)	Post-Bed-Rest Recovery (R)
Short-Duration Bed Rest	5–7 days	5–14 days	3–6 days
Medium-Duration Bed Rest	7–14 days	15–59 days	7–14 days
Long-Duration Bed Rest	14 days (or more)	60 days (or more)	14 days (or more)

post-bed-rest recovery phase for post-bed-rest testing and reconditioning. For scheduling consistency, each study day is referred to with a conventional naming system. Pre-bed-rest days began at BR-X and ended on BR-1. Days in bed rest began at BR1. Post-bed-rest days began at BR +0 and subjects were released on BR +X.

Obviously, the standardization of the bed-rest experiment is of major importance both for the bed-rest phase and for the control phase (i.e. pre- and post-bed-rest phases).

The pre-bed-rest phase to collect baseline data is of particular importance because the deconditioning of the subjects can start during the pre-bed-rest phase. Indeed, keeping the subjects in normal daily life condition is really challenging, and significant changes can occur among subjects if habits are changed too much (mainly in term of exercise level and diet). The goal of this pre-bed-rest period is to homogenize the subjects' pool.

13.3.2 Design of the Bed-Rest Studies

The long-term bed-rest studies use obviously a parallel design, and the medium- or short-term bed-rest studies can have a parallel or a crossover design. Of course, in that case the influence of confounding covariates is reduced because each crossover subject serves as his/her own control, and crossover designs require fewer subjects than do non-crossover designs. Nevertheless, the washout period between the two treatment periods has to be carefully evaluated, and the planning for sufficiently long washout periods does require expert knowledge of the dynamics of the recovery. Then, for a test subject, a study with a crossover design is longer and the risk of withdrawal is higher.

13.3.3 Number of Volunteers

Determining the optimal sample size for a study assures an adequate power to detect statistical significance. Hence, it is a critical step in the design of a planned research protocol. Using too many participants in a study is expensive and exposes more number of subjects to the procedure. Similarly, if the study is underpowered, it will be statistically inconclusive and may make the whole protocol a failure. In addition, even in well-designed and well-conducted studies, it is unusual to finish with a dataset, which is complete for all the subjects recruited, in a usable format. The reason could be subject factors like subjects may fail to particular questions, physical measurements may suffer from technical problems, and in high-demanding studies dropouts before the study ends are not unlikely.

Calculation of sample size requires precise specification of the primary hypothesis of the study and the method of analysis. Usually, several protocols are implemented on the same bed-rest study and this calculation cannot often be done. So the bed-rest studies include usually 8–12 subjects per group. There is always a control group used as a standard for comparison and one or two intervention groups depending on the number of countermeasures to be tested. The sample size in each group at the end of the study is of course positively correlated with the statistical power of the study. In total, the number of subjects for a study with one control and one intervention group is from 16 to 24 (i.e. 8–12 per group). Thus, a larger sample size at the beginning of the study gives a better chance to keep greater power, especially in high-demanding studies like long-term bed-rest studies or in crossover studies running on a long time with a higher risk of dropouts.

13.3.4 Number of Protocols

What is specific in bed-rest studies in comparison with classical clinical trials is the number of protocols implemented on the same study. Indeed, bed-rest studies are complex, high-demanding and expensive studies. Usually several protocols investigating different fields are selected to be implemented on the same study. The planning is then a crucial issue because it is usually very tight and the interferences between the different tests have to be anticipated and avoided as far as possible. But amazingly, publications report the results of each experiment as if the experiment was the only one implemented on the study. The hypothesis that some results may have been affected by some other tests or other activities of the subjects is almost never raised.

13.3.5 Selection Criteria

Of course the general selection criteria to be included in a bed-rest study are in principle the same for all the studies wherever they are conducted. Potential subjects have to be healthy and should not have any history of cardiovascular or other major diseases, and all undergo an extensive medical examination before being included in the study. Nevertheless, there are sometimes some discrepancies in the main criteria like the range of ages or body mass index (BMI) which have a matter of particular importance. The studies carried out in the United States screen people aged 24–55 to match the age of most astronauts, while in Europe the range was 25–45 and now 20–45. Regarding the BMI, the studies carried out in the United States screen people with a BMI between 21 and 30 and in Europe the range was 20–26.

In the international guidelines for standardization of bed-rest studies, the general age range is now 20–55 years and it is stated that smaller ranges should be defined prior to each study. The BMI has been fixed to 20–26 kg/m^2. The international recommendation for the fitness level remains vague: “in general, it should be defined which activity level/fitness level the subjects should have or should not have. There is a high variability of fitness levels between different individuals”. Indeed this decision may be more or less important depending on the main research question for each study. However, it should be taken into account that the performance level itself prior to the study as well as the ability to adapt to training/detraining may have a significant impact on the results of a study, especially in the context of bed rest. It is therefore mandatory, besides the decision whether trained or untrained subjects will be needed for the study, to select a group of test subjects that is as homogeneous as possible regarding their fitness level.

13.4 Directives for Bed Rest (Start and End of Bed Rest, Conditions During Bed Rest)

13.4.1 Respect and Control of HDT Position

The conditions of the bed-rest phase and how the –6° HDT position is maintained and controlled could also give rise to variability. Some reports state that the subjects were allowed to use the bathroom or a bedside pot—standing from squatting is an excellent orthostatic test—or sat on a bedpan on the bed, presumably as an acceptable compromise.

13.4.2 Activity Monitoring of Test Subjects

To document compliance of the subjects with the requirements, their activity shall be monitored. This should be done by redundant methods such as video control, pressure sensors, by subject monitors in person or activity measurements by an actimeter. Activity during the bed-rest period can also be recorded with telemetric electromyography on randomized study days.

For video control, the rooms of the subjects are equipped with video cameras. Video recording shall be continuous. To respect the subject privacy, the cameras should point only to their upper body. The period of non-video control should be documented in a specific form.

13.4.3 First Day of Bed Rest

It had been the custom among those running bed-rest studies in the early days to call 'bed-rest day one' (BR1) a day when subjects did not get out of bed after waking up but continued to stay in bed. This produced a very gradual response. When HDBR studies became popular, subjects were allowed to get out of bed in the morning, shower and eat breakfast while the foot of the bed was raised producing the head-down angle of –6° vs. horizontal position. Subjects would then go back to bed at 9 am to begin BR1. This routine produces a maximum possible posture change (1–0 Gz), inducing a full head-ward fluid shift that triggers a significant and consistent sequence of events lasting about 24 hours, leading subsequently to all the changes we have become so familiar with. If one stays in bed on awakening on BR1, and the foot of the bed is merely raised to the –6° angle, the initial physiological response is dampened. No significant cardiovascular and endocrine changes occur during the first 24 hours of bed rest that would normally accompany the maximal postural change [3].

How the first day of BR (BR1) begins is frequently not mentioned in published paper methodology, but can make all the difference to the time course and magnitude of changes. This is particularly true if the duration of the study is relatively short. There are very good scientific reasons (i.e. for fluid shift and initial volume regulation) for using HDBR especially if on BR1 the subject goes from standing upright to head down, in other words uses the maximum postural change to mark the beginning of bed rest [9–11].

13.4.4 Physiotherapy

Immobilization through bed rest can cause side effects, for example, neck pain, back pain or headaches. Physiotherapy can provide relief in some cases and should be considered by the medical doctors as treatment before using drugs. The aim of these massages is to prevent the muscular pain and the occurrence of thrombophlebitis. These massages will last 30 minutes and will be planned in order to avoid interference with the scientific protocols (intensity and frequency of these massages should be carefully handled in order not to be considered as countermeasures).

If allowed, stretching regimen or deep breathing exercises which are one of the most effective and easiest techniques of self-regulation have to be carefully monitored because they can respectively affect muscle and cardiovascular testing.

13.5 Operational/Environmental Conditions

13.5.1 Housing Conditions and Social Environment

Housing conditions are site- or protocol specific depending on the facility infrastructure: Participants can be accommodated one or more by room; in this latter case, subjects are matched as roommate pairs (or more) upon psychological criteria.

The social environment, visitors, communication with the outside world and access to news can all become sources of comfort or irritation. During BR studies, the participants are usually allowed to freely communicate with each other, to watch television and video, to listen to radio, to read books and magazines, to work on computer and to use the Internet. The main difference between the studies regarding the social environment is based on the possibility to receive visitors or not. In the studies conducted in Europe, at MEDES and at DLR as well, visitors (family or friends) are not allowed for the obvious reasons of the impact on the mood and psychology of the volunteers and the disparity it could create between them. Confinement and the environment could alter the physiological baseline through anxiety, loneliness, unwanted interaction with staff or strangers or lack of privacy. All or any of these could affect the results [3].

The other environmental conditions like temperature, pressure and humidity are controlled and maintained to allow physiological comfort of the test subjects.

13.5.2 Sunlight Exposure, Sleep/Wake Cycles

Subjects are expected to wake at lights on and to cease activity at lights out. Depending on the facility, the standard sleep/wake schedule lights are turned on at 06:00 or 07:00 and are turned off at 22:00 or 23:00. Nevertheless, sometimes it is necessary to interrupt the sleep period for early-morning or late-evening test procedures. Light/dark cycles can affect circadian rhythms and therefore result in lack of sleep as well.

The exposure to daylight should be controlled as it elicits physiological reactions in the human body that may influence the results of bed-rest studies. Especially if study campaigns take place during different seasons, different exposure to daylight may jeopardize the results of the study. The exclusive use of artificial light would be the easiest way to control daylight. However then, supplementation of Vitamin D would be mandatory.

13.5.3 Diet

Dietary consistency and control is of paramount importance to the reliability of the results. Performance conditions of bed-rest protocols depend on the investigations performed (diet was sometimes controlled or sometimes just monitored, depending on whether nutrition protocols were included or not). Some studies strictly control diet, others feed subjects ad libitum.

Because nutrition is the source of energy and substrates used as precursors for synthesizing the functional body units (cells and their core constituents, macromolecules, proteins, DNA, etc.), and the numerous co-factors, such as micronutrients, to support enzyme activity and detoxification/repair mechanisms, nutrition is central to the functioning of the body. Conversely, poor nutrition can compromise many of the physiological systems and also mood and performance [12]. Dietary consistency and control is of paramount importance to the reliability of the results of any clinical studies. This is obvious not only for metabolic studies but also for bone, muscle and cardiovascular studies. First, the choice of the ratio of macronutrients is of crucial importance during the control pre-bed-rest period to maintain the volunteers in situations close to their usual daily life conditions. To achieve this aim, it is important that the volunteers do not have very different dietary habits. The macronutrient composition of the diet also influences the bed-rest outcomes. In a crossover design, 60-h bed rest in eight males (2 days of washout) with either a high-carbohydrate diet (70% of energy intake) or a high-saturated-fat diet (45% of energy intake as fat and 60% of saturated fatty acid) [13] showed that insulin sensitivity decreased by 24% with the high-saturated-fat diet but did not change with the high-carbohydrate diet.

Until recently in most HDBR experiments, energy intake was adjusted so that the body mass was clamped to the pre-bed-rest values [14, 15]. Of course during head-down bed rest (HDBR), body composition is altered [16], muscle mass decreases due to disuse and fat mass varies according to diet prescription. The mass clamping approach leads, however, to a positive energy balance and an increase in fat mass without changes in body mass [14, 17]. A positive energy balance due to overfeeding is a confounding factor that exaggerates the deleterious effects of physical inactivity, and the effects of overfeeding cannot be dissociated from those of simulated weightlessness. Indeed positive energy balance during inactivity is also associated with greater muscle atrophy and with activation of systemic inflammation and antioxidant defense [18, 19]. Other observations suggest that nutrition may also play a role in the cardiovascular deconditioning syndrome as observed in Muslim army pilots.

An adequate nutrient supply to accurately derive the true effects of bed rest alone is of particular importance. In order to standardize bed-rest experiments in a way that controls energy balance, one needs to adjust in real time energy intake to energy expenditure. Two long-term bed-rest studies [20, 21] during which the diet was tightly controlled confirmed that clamping fat mass may be possible [22], yet more technical precision is needed. Nevertheless, measuring daily energy expenditure remains a technical challenge, particularly when an exercise protocol is chosen to counteract any muscle and bone atrophy because it is more difficult to match total energy expenditure. The objective of a very recent study conducted by European researchers at MEDES (Toulouse, France) is to validate the minimum set of techniques mandatory to match total energy expenditure in future studies including physical exercise.

13.5.4 Testing Conditions

Considering how important the elimination of posture change by bed rest is to the fidelity of the results to microgravity, it is amazing that published papers often do not mention the position in which tests are performed. Closer scrutiny may reveal that plasma volume was measured in the seated position, or that subjects were allowed to use the bathroom [3].

13.5.5 Medications

Other factors that may interfere with the results of a bed-rest study but that are transparent to an investigator include clinical aspects of a study. For instance, a mild laxative may routinely be prescribed. Those that work by drawing fluid into the gut to soften stools may well interfere with the results. Headaches often of a sinus nature are not uncommon. Headaches may also be triggered by overhead lighting.

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