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Human Systems Physiology

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25.1 Introduction

The main objective of this chapter is to examine bed rest as a ground-based analog for the effects of microgravity on integrative physiological systems as encountered in space flight. Many effects of microgravity are well-known and are reviewed elsewhere in this volume. However, as longer space flights are contemplated, it becomes ever more important to be able to carry out well-controlled repeatable studies that probe these effects and allow for countermeasure strategies to be developed to limit the negative effects of microgravity. The bed rest study protocol, involving subjects lying in supine position over a time interval, represents such a highly controllable experimental environment that can provide important opportunities to examine physiological function in response to reduced gravitational stress. Bed rest studies also allow for relatively easy implementation and testing of countermeasures to reduce the detrimental effects of microgravity.

25.2 Complications of Space-Based Physiological Research

While it is in some sense obvious, it is important to emphasize that in-flight experiments often suffer from a number of procedural complications that can impair the utilization and application of data collected during space flight and

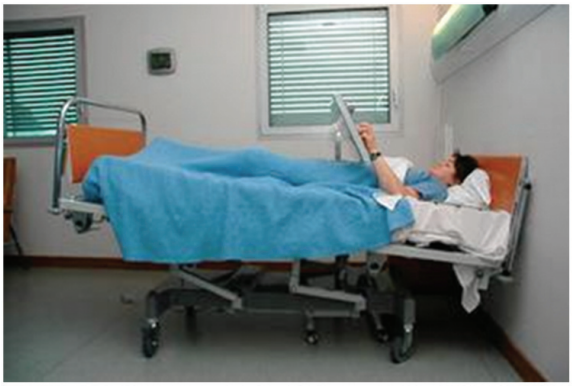

Figure 25.1 Typical configuration of the 6° head down tilt bed rest paradigm. (Image: ESA).

which can also complicate the comparison of data collected across missions [8]. These include the following:

- problems in experimental reproducibility such as limited size and uncoordinated astronaut sample populations;
- variations in quality and protocol of data measurements;
- lack of coordination in measurements across missions;
- lack of opportunity to carry out variations in experimental protocols based on new information due to restricted flight availability;
- possible usage of in-flight medication; and
- possible interference in spaceflight data from other protocols.

Therefore, there is clearly a need to have ground-based analogs of spaceflight which can be used to study spaceflight induced deconditioning and test new and novel countermeasures.

25.3 Ground-Based Analogs of Spaceflight-Induced Deconditioning: Bed Rest and Immersion

Commonly used ground-based analogs include bed rest studies and water immersion. Clearly, both bed rest studies and immersion can avoid all the above-outlined technical problems while altering various features of gravitational loading. Water immersion involves either direct contact of the body with water ("wet"), or with the body insulated from the water ("dry"). An interesting review of long-term water (dry) immersion as a model for

microgravity is given in Navasiolava *et al*. (2011), which also provides some parallel comparisons to bed rest [15]. Water immersion typically allows for one hygiene period out of immersion per day and long periods of immersion must be carried out as dry immersion, which is somewhat complicated to implement regarding experimental measurements and testing of countermeasures. As a consequence, the technical problems of water immersion are more involved than for bed rest studies. In this chapter, emphasis will be placed on bed rest studies. Some description of the bed rest study protocol will be provided along with discussion of the key question as to whether the results obtained from such studies reflect those that are obtained from spaceflight. Similarities and differences between bed rest and water immersion will also be considered where relevant.

25.4 Types of Bed Rest, Durations, and Protocols

The first studies of bed rest related to space flight began soon after human space travel began. A book published in 1986 entitled "Inactivity: physiological effects" edited by Sandler and Vernikos [20] pointed to early research as taking inactivity as a model of deconditioning and as a primary paradigm for space flight effects [16]. Over time, a broader recognition of the many interacting effects of microgravity on the body viewed as a whole organism was established as was the model of simulating microgravity via head down bed rest [12, 16, 19].

Over the years, researchers working in the area of gravitational and spaceflight physiology have used subjects who were bed-rested in the supine position or at various levels of head down tilt such as 5°, 10°, or 15° (referred to here as head down bed rest, HDBR). For the details of bed rest studies that have used different angles of tilt as well as varying durations of bed rest, the reader is referred to Sandler and Vernikos [20]. To mimic the effects of microgravity, 6-degree head down supine body position is the standard implementation, which acts to equilibrate the distribution of blood and tissue volume, simulating the lack of gravitational pull to the lower body [12, 16].

Bed rest studies can be adjusted to mimic various space flight durations as well. Typical duration spans are short-term (5–7 days), medium-term (21 days), and long-term studies (60–90 days). Bed rest studies can be restricted to all male or all female studies such as a 90-day male bed rest study in 2001/2002 and the 60-day female bed rest study WISE-2005 [12].

Recently, there have been initiatives to introduce some standardization in bed rest study protocols to allow for greater cross-study exploitation of data [6, 12]. Such standardization would reduce confounding influences and allow for the comparison of different systems or different measurements under a common perturbation.

25.5 Physiological Systems Affected by Spaceflight and Bed Rest

Lack of gravity poses many challenges, which can impair the function of a number of physiological systems. On the other hand, microgravity represents a unique window for observing the response of physiological systems because it represents the suspension of those evolutionary challenges that shaped such systems. Bed rest studies allow for more delicate, complex, and even invasive measurements, which may be difficult or impossible to implement or to accurately carry out in space such as bone marrow biopsies or complex sonographies.

Direct information on microgravitational effects in space flight and information from bed rest studies reenforce the understanding of effects in both areas, and together, both sources of information can provide further novel information on physiological system function in general and in specific processes. For example, bed rest and spaceflight are both accompanied by loss of plasma volume and hemoconcentration, thus leading to a higher risk of blood clotting with potential dire consequences. We are not aware, however, of any study that examined clotting changes during spaceflight. On the other hand, there are several studies, which have examined the effects of physical inactivity during bed rest on clotting [9].

Similarly, recovery from bed rest immobilization provides an important surrogate for astronaut recovery after flight as well. Deconditioning following either weightlessness or bed rest shares many effects and symptoms characterized by orthostatic intolerance (OI) [4]. Hence, studies that reflect on the origin of OI and the efficacy of countermeasures in the bed rest context can be expected to translate into countermeasures in space. The review by Convertino [4] provides useful examples of this observation. In addition, studies in both microgravity and bed rest conditions can provide information on the physiology and clinical problems related to OI and potential countermeasures for patients suffering from OI.

A great deal of research related to physiological effects of microgravity in space and simulated microgravity during bed rest has been published, and

review articles summarizing this research have appeared as well. In this section, we mention several reviews in specific areas as well as general reviews, which cumulatively set the context for taking bed rest as a valid surrogate for space microgravity. We now discuss some key physiological systems where important parallels can be made between the physiological effects of microgravity and bed rest. These areas include the autonomic nervous system, musculo-skeletal system, cardiovascular system, neuro-vestibular system, immune system, and the renal system.

Autonomic nervous system (ANS): The ANS is involved in the control of cardiovascular, thermoregulatory, respiratory, metabolic, gastrointestinal, and many other systems, and gravity influences these systems not only directly but also through feedback control mechanisms involving autonomic function which are thus impacted by a lack of gravitational stress from multiple sources. For example, sympathetic-vestibular links to blood pressure control are influenced by bedrest [7] as have effects of microgravity on baroreceptor sensitivity [1].

Musculo-skeletal system: Due to a lack of gravitational loading on the musculoskeletal system, muscle loss and bone loss occur during bed rest and spaceflight [10]. Indeed, bed rest has been recognized as a very useful and appropriate model for bone loss observed in space flight and microgravity [6, 13, 24]. The effects during bed rest on bone mineral density, bone markers, and calcium balance, and excretion are qualitatively consistent (although of lesser magnitude) to those deleterious effects seen in space flight [13]. Bed rest has also been used to test countermeasures to mitigate these effects. The review by Leblanc *et al* (2007) provides an extensive comparison and assessment of bed rest and space flight data on bone loss [13].

Cardiovascular system: The bed rest model can very effectively reflect the effects of microgravity on the cardiovascular system and in particular cardiovascular deconditioning and orthostatic intolerance (see [4]). The effect of reduction in plasma volume induced by microgravity impacts cardiac function in a variety of ways and reduces baroreflex sensitivity as well [24]. Many of these effects can also be seen in HDBR (see [16]), indicating the appropriateness of this model for studying the effects of microgravity as well as potentially linking these effects with the deconditioning in aging (see below).

Neurovestibular system: This system integrates mechanisms related to posture, eye movements, spatial orientation, and higher cognitive processes such as 3-D vision. This system also plays a role in the respiratory and cardiovascular systems, as well as many other regulatory mechanisms such

as circadian regulation. Weightlessness impacts vestibular function in many ways, and HDBR may also induce related effects. The study by Dyckman *et al* (2012) indicates an impact of bed rest on the vestibulo-sympathetic response, which may influence blood pressure control and hence play a role in orthostatic intolerance [7]. This study illustrates the point that, given the complexity of interacting systems, the parallels between microgravity and head down bed rest need to be carefully considered when drawing inferences in specific scenarios.

Immune system: This complex system is certainly influenced by spaceflight and can be be affected by many factors including stress and exposure to radiation [6]. Bed rest studies related to immune system effects can differ from effects seen in space [6]. Hence, it is not clear how appropriate the bed rest model is for immune effects although it can serve as a comparison for other models [6]. The immune system response highlights again the fact that care must be taken when considering parallels between space flight microgravity and bed rest.

Renal function, volume regulation and aquaporins: Body water balance is regulated by vasopressin. Vasopressin signaling promotes water reabsorption in the renal collecting duct by triggering redistribution of the water channels Aquaporin-2 (AQP2) from intracellular vesicles into the plasma membrane [23]. AQP2 is partially excreted in the urine [22] and can represent a useful noninvasive biomarker for understanding the physiological renal response (and adaptation) to alteration in external gravity. AQP2 excretion has been evaluated as a biomarker of renal adaptation to microgravity in both water immersion and HDBR models [22, 23].

In addition to the studies and reviews on specific physiological topics referenced above, several very useful general reviews have been published. Pavy-Le Traon *et al* (2007) provide a comprehensive review of research over the last 20 years of important areas where the effects of bed rest and microgravity overlap [16]. This review provides a convincing case for viewing bed rest as a powerful research tool and useful analog for studying the effects of microgravity. The review by Vernikos and Schneider (2010) presents many parallels between physiological effects of bed rest, microgravity, and aging, providing clear insight into how these three physiological conditions can be merged and coordinated to provide a more global view of physiological function [24]. The review by Navasiolava *et al* (2011) provides a comparative look of bed rest and water immersion [15].

25.6 Is Bed Rest a Valid Analog for Microgravity-Induced Changes?

A key issue is the degree to which bed rest represents a useful surrogate for microgravity, leading to knowledge reflecting the physiological responses to microgravity in space flight and information transferable to the design of effective countermeasures against the negative effects of microgravity. HDBR (typically at 6°) is the most commonly used protocol to mimic microgravity especially for long-duration studies [5] and in relation to complex physiological effects [6]. Horizontal supine bed rest immobilization has also been used to simulate spaceflight induced deconditioning. While both horizontal supine bed rest and HDBR cause deconditioning, cephalad fluid shifts, and the onset of hemodynamic changes appear faster during HDBR (detailed in [20]).

The acceptance of HDBR as a valid surrogate for global and specific micro-gravitational influences on human physiology emerged as a consequence of carrying out many bed rest studies focusing on specific physiological areas over a wide range of systems and comparing results to direct physiological studies of astronauts and cosmonauts. For example, OI is an important problem for returning astronauts [2] and bed rest subjects face similar problems at the end of the experimental bed rest procedure. The review of the applicability of bed rest data to the problem of OI after space flight given in [4] illustrates the usefulness of the comparison between these two manifestations of OI.

While HDBR has been widely accepted as a valid surrogate protocol for microgravity in studying physiological systems, it is important to note that the information from bed rest studies needs to be carefully assessed in its application to microgravity given that bed rest is not a perfect parallel for microgravity. For example, some research suggests that certain immune system responses are affected by stresses seen in space flight rather than as a direct result of microgravity [17, 24]. Hence, specific immune system effects may not always arise in bed rest-simulated microgravity [6] (see also discussion above on immune system).

In addition, physiological responses can vary between ground-based analogs. As mentioned above, AQP2 excretion has been evaluated as a biomarker of renal adaptation to microgravity in both water immersion and HDBR models [22, 23]. These studies revealed that while AQP2 excretion is probably not a good biomarker to monitor renal fluid regulation during acute water immersion, it could instead represent a reliable and informative parameter during prolonged bed rest and possibly under chronic adaptation

to microgravity in space. Specifically, it has been found that bed rest induces a biphasic response in AQP2 excretion which is in agreement with expected fluid redistribution in microgravity: in the early phase the decrease in AQP2 excretion is paralleled by an increase in hematocrit due to reduction in plasma volume, whereas the subsequent increase in AQP2 excretion is paralleled by a partial restoration of hematocrit likely due to an AQP2-mediated water reabsorption in an attempt to restore normal plasma volume. The increase in AQP2 excretion may be consequent to an increase in vasopressin (because of reduced plasma volume) as also observed in astronauts during microgravity. These results make urinary AQP2 excretion a reliable biomarker of renal water handling during prolonged bed rest and more appropriate in ground based models to mimic chronic adaptation to microgravity.

Confounding factors and interrelated effects that could differ between the microgravity of space and the simulated microgravity of bed rest (or water immersion) may be very difficult to analyze. For example, vestibular control depends on position, orientation, movement, vision, and gravitational signals, and interacting effects may be very complex as seen in a study of vestibular-sympathetic response and its relation to OI in short-term and long-term bed rest [7]. One needs to clearly establish whether, when and how effects differ between a fixed supine position mimicking microgravity compared to moving astronauts experiencing direct microgravity. Indeed, differences can arise in the physiological effects among the three situations of true microgravity, HDBR, and water immersion. For example, each of these three situations involves differing influences on tissue and vascular distribution of fluids [19]. Hence, for effective modeling of microgravity effects (or the effects of aging for that matter), one needs to consider whether any differences between true microgravity and microgravity surrogates can be ignored when drawing parallels for the specific phyiological mechanisms under study and when these differences may distort conclusions.

25.7 Bed Rest: A Testing Platform for Application of Countermeasures to Alleviate Effects of Microgravity—Induced Deconditioning

Countermeasures to microgravitational effects can be designed and incorporated in bed rest studies to test many potential approaches including such novel methods as short-arm centrifuge, [3] which in addition can incorporates ergometric exercise [14]. Such methods can be tested for preventing

or reducing spaceflight deconditioning impairing cardiovascular, bone metabolism, musculoskeletal, autonomic, and other system functions. Information derived from tests of possible countermeasures for spaceflight deconditioning will be critical for microgravity exposures of long duration as will be encountered, for example, during a mission to Mars. An example of analysis related to deconditioning and aerobic exercise during bed rest can be found in Lee *et al* (2010) [14], and the implementation of centrifugation as a countermeasure implemented via bed rest is illustrated in Clément and Pavy-Le Traon (2004) [3]. Combined exercise and nutrition countermeasures have been discussed in Schneider *et al* (2009) [21].

25.8 Perspectives

In addition to the direct application to space flight, bed rest and other immobilization studies have been designed and carried out to study many other physiological conditions related to a diverse set of situations such as hospital demobilization after surgery or injury, coma, paralysis, as well as to study the effects that arise due to aging. It is important to note that there is a potential for developing a powerful synergy of information relating broader bed rest problems and the problem of microgravity. In particular, there are clear potential parallels between microgravity, aging, and immobilization [24].

Bed rest (and water immersion) are global models for the effects of microgravity, influencing a number of systems simultaneously. This is an important advantage but it is also possible to consider models of microgravity that influence individual systems or specific system levels. For example, specialized devices have been used for studying the effects of reduced gravity at the cellular level [11]. Hence, one always needs to keep in mind the research goals when considering appropriate surrogates for physiological effects of microgravity and space flight.

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