Chapter 13

RECOMMENDED RESEARCH ON ARTIFICIAL GRAVITY

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Based on the summaries presented in the above sections of what is still to be learned on the effects of artificial gravity on human functions, this chapter will discuss the short- and long-term steps of research required to understand fundamentals and to validate operational aspects of using artificial gravity as an effective countermeasure for long-duration space travel.

Figure 13-01. Artist view of the ISS after completion. Photo courtesy of NASA.

1 INTRODUCTION

Maintaining an Earth-normal physiological baseline requires gravity. The previous chapters have amply emphasized the importance of gravity to almost every body system. However, we do not yet fully understand how these different systems rely on gravity as a controlling or enabling stimulus. Going into space, coupled with essential ground research, has made it possible to begin to answer these questions.

Gravity pulls in one direction only, i.e., downward, towards the center of the Earth. As mobile bipeds, humans have the choice of orienting themselves towards the force of gravity in every conceivable direction, mostly in intermittent patterns. They also reduce its effectiveness on the body during night sleep or in continuous bed rest, and enhance it as with various activities.

Several aspects of how we sense and use the force of Earth's gravity appear to be involved in maintaining normal health and fitness: the pull of gravity in the +Gz (head-to-foot) direction, exertion against gravity forces during normal activity, the element of "change" provided by postural and other movement and orientation, and directional cues about our spatial orientation relative to the gravitational vertical. Without regular exposure to these +Gz forces, as during spaceflight (Clément 2005) or bed rest (Sandler and Vernikos 1986), important cardiovascular, musculoskeletal and neural, primarily vestibular-mediated functions, are compromised.

Past studies and research approaches have focused on varying the characteristics of the gravitational stimulus, i.e., its direction or intensity. Resulting changes in physiological functions were logically attributed to the role of the stimulus. An overlooked aspect is that, like other sensory stimuli, the sensitivity to gravity, and consequently the response to changes in gravity, can also change with the physiological status of the organism, its age, gender, time of day, fitness, health, and genetics. Until we know more about gravity dose-response relationships in healthy ambulatory persons, we will continue to make assumptions that space deconditioned individuals respond in exactly the same way.

The study of the effects of accelerations smaller and greater than 1 g might prove to be of great interest in medical research, both at the molecular, cellular, and clinical levels. Ground-based experiments have demonstrated that paraplegics with some residual muscular function in their legs were able to ambulate when the acceleration along the body longitudinal axis was equivalent to lunar gravity. Artificial gravity generated by short-radius centrifuges may have clinical applications toward the treatment of problems such as osteoporosis in the sedentary elderly, heterotopic ossification (i.e., the formation of lamellar bone where bone does not usually form in soft tissues) in young paralyzed individuals, bone fractures in sports requiring prolonged bed rest, articular deterioration aggravated by weight bearing, and perhaps also in certain forms of pulmonary edema (Cardus 1994).

Figure 13-02. "TransHab" was an inflatable 8-m diameter ISS module that could be converted into crew quarters for future manned missions to the Moon and Mars. Photo courtesy of NASA.

2 POTENTIALS TOOLS FOR INVESTIGATION

As discussed in the previous chapters, key research questions need to be addressed before artificial gravity can be prescribed to humans en route to Mars. These questions include: How much artificial gravity, i.e., at what duration and level, is needed to prevent this deconditioning? Is 1 g a necessity or is a fraction of gravity sufficient? If intermittent artificial gravity is enough, how many centrifugation exposures per day are required? More importantly, from a medical point of view, what is the tolerance of human body to repeated centrifugation?

Although a definite answer to these questions will only come from validation studies performed in space, some important preliminary screening and evaluation studies can be carried out during ground-based studies on Earth. In fact, the difficulty and expense of spaceflight experiments or feasibility demonstrations mandate the appropriate use of ground facilities to design and test artificial gravity concepts.

Analog environments to simulate the effects of weightlessness on long-duration physiological deconditioning have been studied for many years. The most widely used human model is continuous bed rest, with head tilted down by 6 degrees. Bed rest is known to result in muscle atrophy, bone loss, redistribution of body fluids and body mass, and decreases in plasma volume and red blood cells (Sandler and Vernikos 1986). After bed rest, subjects show orthostatic intolerance similar to that typically demonstrated by returning astronauts. Although the physiological consequences of bed rest are in most respects quite similar to those of weightlessness, there are a few notable differences. For example, while diuresis is common during the early days of bed rest, it has not been clearly demonstrated in space (Norsk 2001). In addition, bed rest does not produce the full range of vestibular disorders characteristic of space travel. It is likely that postural disturbances seen after bed rest are more attributable to muscle disuse than vestibular deconditioning.

When we sleep, we spend at least a third of the day experiencing gravity along a different axis (Gx) than the longitudinal (Gz) axis, without experiencing the physiological effects of weightlessness or continuous bed rest. Cleary, a period of continuous 6-8 hours per day of Gx stimulation is sufficient to protect from deconditioning. During continuous bed rest, Vernikos and colleagues at NASA Ames have showed the potential protection afforded by 2-4 hours of daily standing or walking (Gz) in preventing orthostatic intolerance, plasma loss or calcium loss, but not in maintaining aerobic capability (Vernikos *et al.* 1996). Bed rest therefore offers the possibility to investigate the minimum gravity load needed along Gx and Gz axis as a countermeasure for some of the effects seen in space.

Another technique used to simulate the deconditioning effects of spaceflight is dry immersion (see Figure 1-14). This treatment produces rapid fluid shifts, manifested by a pronounced involuntary diuresis, with loss of electrolytes and decrease in plasma volume. Although, a decline in orthostatic intolerance is typical after dry immersion, the magnitude of the change varies across subjects, in particular between athletes and non-athletes. There are also problems associated with hygiene and precise thermal control with this method (Nicogossian 1994).

Short- and long-radius centrifuges, as well as slow rotating rooms, all have their roles in ground-based studies. For in-flight studies, however, a centrifuge should be small enough to fit into a Shuttle middeck or in the ISS modules. Human-rated centrifuges have already flown on board the Spacelab modules during the IML-1 (see Figure 3-16) and Neurolab (see Figure 3-17) missions. Studies have shown that these centrifuges could be easily accommodated within an ISS module. However, given the small sizes of the modules, these centrifuges present the disadvantage of having the subject body placed across the axis of rotation, thus generating +Gz force at the head and –Gz forces at the feet. An additional ISS module with a larger diameter, such as the descoped TransHab (Figure 13-02) is the only possibility for having a human-rated centrifuge in the short term. Later flight accommodations could consider the Crew Exploration Vehicle, or a lunar or Mars habitat centrifuge. Eventually, the effects of continuous artificial gravity could be studied by experimenting with spinning vehicles in space (Table 13-01).

- *Ground studies in long radius centrifuges*
  - *To determine the tolerance to acceleration*
- *Ground studies in short-radius centrifuges*
  - *To determine the artificial gravity prescription to counteract the physiological effects of bed rest*
- *Ground studies in slow rotating rooms*
  - *To determine the adaptation and readaptation requirements*
  - *To determine the human factors constraints*
- *Short-radius centrifuges on board the ISS*
  - *To evaluate intermittent centrifugation*
  - *To validate ground-based findings*
- *Spinning the space vehicle*
  - *To evaluate continuous centrifugation*
  - *To determine min. radius and max. rotation rate requirements*
  - *To evaluate perceptual effects*
  - *To validate human factors constraints*
  - *To validate ground-based findings*
- *Short-radius centrifuges on Moon or Mars habitat*
  - *To test protocols and operations necessary to protect crews during long stay on the lunar or Martian surface, if needed*

Table 13-01. Practical research program for evaluating and validating the effectiveness of artificial gravity during spaceflight.

3 ANIMAL MODELS

There is no question that human subjects must be used for research on artificial gravity development and testing. Human studies are essential to consider the unique aspects of the upright biped, especially with respect to cardiovascular implications of gravity gradient. Furthermore, human factors issues, essential to the success of artificial gravity in flight, can only be worked out with human subjects.

Nevertheless, this research needs to be supplemented where appropriate, by animal experiments. As mentioned above, the limited experience on artificial gravity in space comes mostly from animal studies. Animal centrifuge facilities have flown on several space life sciences missions, and a dedicated centrifugation module is in preparation for the ISS.

Animal studies would provide a useful adjunct to the human studies for the following principal reasons. First, animal tests will reduce the total numbers of human subjects needed, and thereby make schedule and cost targets achievable. Both cost per subject and schedule-associated costs are far lower using animals compared to humans. Furthermore, the large sample size possible using animals to test artificial gravity regimens yield results with less scatter (lower error), and thus improve the basis for drawing definitive conclusions regarding success or failure of the test conditions. Modeling on the basis of a well-defined set of animal responses allows extrapolation from a limited data set derived from human subjects. Finally, tests with animals can include invasive telemetry, hazardous procedures, and post-mortem tissue analysis to define artificial gravity prescriptions.

3.1 Non-Human Primates

Primate models used in spaceflight experiments have included rhesus monkeys, squirrel monkeys, capuchins, chimpanzees, cynomologous monkeys, and pig-tailed macaques. Many of these flights were of short duration, ranging from 5 to 14 days (see Clément and Slenzka 2006 for review).

The rhesus monkey provides a biomedical model with close phylogenetic ties to humans. Rhesus monkeys have been the subjects of studies on the effects of exposure to microgravity on thermoregulation, immune responses, musculoskeletal system, cardiovascular system, fluid balance, sleep, circadian timing, metabolism, neurovestibular/neurosensory, and psychomotor responses. In ground-based studies, rhesus monkeys have served as subjects in bed rest and dry immersion experiments as well as in centrifugation (both continuous and intermittent) experiments. The systems examined in many of these studies have paralleled those examined during spaceflight.

The rhesus monkey confers many advantages as a research subject in the field of artificial gravity. First and foremost, the rhesus monkey is the most widely accepted biomedical non-human primate model for the human. Secondly, the rhesus has a bipedal upright posture, and thus experiences the ambient force environment along the same body axes as the human. Third, the reproductive cycling of the female rhesus is menstrual, similar to humans. Fourth, the cognitive abilities of the rhesus monkey allow the use of psychomotor testing to discern the effects of artificial gravity on neurovestibular physiology, performance, and behavior. Finally, the larger size of the rhesus also allows for collection of larger tissue samples and provides the ability for simultaneous measurement of multiple physiological and behavioral factors.

3.2 Rats

Rats are the most commonly used biomedical research model and thus a great deal is known about their normal physiology, including characteristics of well-established strains. The relative uniformity of specific strains also present fewer of the confounding factors that are typical of human studies and thus studies are likely to be both easier to interpret and to repeat. Rats offer a number of other advantages as a model system for countermeasure development. Rats, unlike primates, do not require special isolation or quarantine procedures. With modest caging and care requirements, higher numbers of subjects can be accommodated to increase the statistical power of analyses. Rats readily adjust to centrifugation and since they can also be used in hind limb immobilization and tail-suspension studies, they can also serve as models for deconditioning. Previous centrifugation and suspension studies also provide a baseline against which artificial gravity protocols can be evaluated. Similarly, rats can be used in exercise studies of metered activity using running wheels or treadmills.

Rats also provide opportunities for more invasive or terminal procedures that would not be possible with human subjects. Rats can be used for studies involving both acute and chronic implantation, including use of catheters, electrodes, and telemetry. When fully implanted, these also provide the means for completely hands-off data collection, including monitoring of blood pressure and flow, ECG, and heart rate, as well as temperature and activity. Rats can also provide repeated samples of fluids such as blood or urine. Post-mortem tissue sampling is easily accomplished, and at considerably less expense than alternates such as non-human primates. The short generation time and rapid development of rats also lend themselves to developmental studies. Further, the time scale of some changes, for example muscle wasting in microgravity or hind limb unloading is more rapid than in humans, thus shorter and multiple studies could be accomplished in the same time frame using rats.

Figure 13-03. Drawing courtesy of Lawrence Young.

Rats are also relatively well studied in microgravity, and share the advantages of other non-human spaceflight subjects in not having conflicting schedules and operational duties to confound experimental findings. Thus rats have been important in contributing to our understanding of spaceflight changes in musculoskeletal, neurovestibular, immune, developmental, cardiovascular and metabolic physiology. Rats flown on the Russian Bion biosatellite have also provided the only in-flight evidence for the efficacy of 1-g centrifugation in preventing many of the degenerative changes seen in microgravity (Figure 13-03). Validation of artificial gravity as a countermeasure during spaceflight will almost certainly begin with rodent studies, since both habitats and a flight centrifuge are in development for use with rats and mice on board the ISS (see Figure 3-13). With no human-rated centrifuge being flown in the foreseeable future, initial in-flight studies using artificial gravity will necessarily be performed with rodents.

Rats are not without disadvantages however. Their small body size, relative to rhesus monkeys for example imposes limits on how much instrumentation, including telemetry, can be used in a given animal. Small body size also means that smaller blood and urine volumes are available, especially in the case of repeated sampling. Unlike rhesus, which sit for most of the time in an upright posture, rats are quadrupedal and thus the acceleration vector in both normal gravity and during centrifugation is from dorsal to ventral rather than from head to foot. Consequently, fluid shifts and muscle loading necessarily differ from bipeds. Weight is also distributed among four limbs rather than being principally borne on two. Rats also differ from both rhesus and humans in being nocturnal, which reverses the relationship of certain endocrine cycles, notably that of melatonin, to that seen in diurnal species, including rhesus and humans. In addition, rats have poorly consolidated circadian cycles, including sleep and wake. Rats are thus not ideal models for human sleep and circadian rhythms. Rats are also estrous in their reproductive cycle. Finally, although much is known about the physiology of rats, some responses do not match those of humans, limiting their utility for some studies.

3.3 Mice

Like rats mice are small, easily managed and have short generation times. Being even smaller than rats makes it easy to increase sample sizes and reduces required maintenance, thus making mice more cost-efficient. Generation and maturation times are further reduced from rats and thus mice may be more suitable for some developmental studies. More so than rats, genetically defined strains are seeing increased use in biomedical research with the benefit of reduced variability in studies due to differences between subjects. Numerous genetically manipulated strains have been developed with specific properties making mice uniquely suited for detailed examination of mechanisms and pathways. These include a large number of transgenic, knock-in and knockout strains, including several with deficient vestibular pathways for gravity sensing. Since many mouse and human genes are homologous, mice are well-established models for many physiological mechanisms in humans. For example, the mouse has been especially useful in immunological studies. Mice are good candidates for centrifuge studies and have been used successfully in the past.

However, mice share some of the disadvantages of rats as experimental subjects, with smaller body size further aggravating many of these. Their ability to tolerate implants and telemetry is further reduced, as is the available quantity of tissues and fluid for sampling. Like rats they are nocturnal and possess somewhat poorly consolidated circadian rhythms. Since mice have a more objectionable odor than rats, their acceptance as flight animals is also impaired. Also, since not all of their physiological responses parallel those of humans, mice may not be the best animal model for some studies, and this will need to be evaluated on a case-to-case basis.

4 CRITICAL QUESTIONS

As discussed in Chapter 4, an internal short-radius centrifuge would contribute little to the maintenance of sensory-motor calibration of movement control mechanisms of the body. Consequently, it would unlikely attenuate the spatial disorientation and the disturbance of movements and postural control following landing on Mars[1]. The alternative approach to the generation of artificial gravity in flight is to rotate the entire space vehicle or a chamber in it. Again, because of the small size of the spacecraft, significant gravity gradient would exist, but the subjects would be able to move about, thus providing a more effective way to challenge the sensory-motor and musculoskeletal systems.

It is also unclear what effect artificial gravity would have on the regulation of body fluid volume and bone mineralization. With blood volume reduced in weightlessness, a centrifuge might produce orthostatic intolerance and syncope. Possibly fluid loading before riding the centrifuge, such as used prior to return from spaceflight, and an anti-g suit would help to alleviate this problem. It is also unknown how the gravity gradient and how periodic exposures to weightless and artificial gravity conditions would have on the circulatory system and hormonal regulation, and whether there are aftereffects. Remodeling of the bones of the feet, ankles, and legs would also occur with intermittent exposure to contact forces on the feet. The potential extent and functional significance of such changes has not been explored yet.

Obviously, research on the effects of centrifugation needs to determine in priority the optimal range of parameters such as radius of rotation, rotation rate, gravity level, gravity gradient, as well as frequency and duration of artificial gravity exposure on physiological responses and well-being of the crew. However, once the optimal combination of centrifugation parameters will be found, this *artificial gravity prescription* will have operational consequences on the vehicle or mission design. For example, centrifugation exposure executed in several shorter bouts instead of one longer period is likely to improve both the efficiency and the tolerance of the centrifugation by the crew. But, in turn, such prescription will add a burden on crew time and the mission operational constraints. Therefore, both fundamental (physiological, medical, well-being) as well as operational issues need to be addressed.

During the NASA/NSBRI Workshop organized in League City in 1999 by Bill Paloski and Larry Young, participants drafted a set of critical questions to be answered by a broad artificial gravity research program. This list has been updated as follows in light of recent research and further meetings, and the likely uses of artificial gravity for a human Mars mission.

4.1 Physiological Deconditioning

4.1.1 What combination of centrifugation parameters (radius, rotation rate, gravity level, gravity gradient, frequency and duration of exposure) leads to the most effective protection of crews against bone, muscle, cardiovascular, and sensory-motor deconditioning?

4.1.2 Would additional (most likely intermittent) artificial gravity exposure be required on the Lunar or Martian surface?

4.1.3 What are the severities and time courses of the physiological consequences associated with onset (spin-up) and offset (spin-down) of centrifugation, both en route to/from Mars and on the Moon/Mars surface, in particular related to sensory-motor adaptation, orthostatic hypotension, and fluid shift?

4.1.4 What additional countermeasures are required to supplement artificial gravity exposure to form an integrated countermeasure prescription during a mission to Mars?

4.2 Crew Health and Performance

4.2.1 Is the artificial gravity prescription resulting from 4.1.1 compatible with crew health and performance, in particular related to disorientation, motion sickness, and mal-coordination caused by cross-coupled angular accelerations and/or Coriolis forces?

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[1] Except if subjects are forced to maintain balance on a short-radius centrifuge, via a freely moving backplate, for example. Such balance training, combined with the stimulation of the otolith organs when the head is off-center, could aid crewmembers in retaining terrestrial internal models of sensory-motor integration (see Chapter 4, Section 5.2).

4.2.2 What operational restrictions should be placed on crewmembers during the onset (spin-up) and offset (spin-down) of centrifugation?

4.2.3 Are exercising or other countermeasures (mechanical, pharmacological, procedural) independent of or synergistic with the effects of exposure to the artificial gravity perception resulting from 4.1.1?

4.3 Other Spaceflight Environmental Factors

4.3.1 Is the physiological response to radiation exposure changed by artificial gravity exposure?

4.3.2 Is the physiological response to altered light/dark cycles changed by artificial gravity exposure?

4.3.3 Is the behavioral response to spaceflight changed by artificial gravity exposure?

4.3.4 Does artificial gravity exposure has secondary effects on wound healing, immune response or pharmacological response?

4.4 Vehicle and Mission Design

4.4.1 What is the impact of the artificial gravity system (i.e., centrifuge) in terms of weight, size, vibrations, and power requirements on the space vehicle or mission design?

4.4.1 What is the impact of the artificial gravity prescription in 4.1.1 in terms of duration and frequency on crew time and flight schedule?

5 RECOMMENDATIONS

5.1 Artificial Gravity as a Multipurpose Countermeasure

The search for effective countermeasures to spaceflight deconditioning has so far been approached on an individual systems level. Frequently a symptom was targeted without basing the choice of a countermeasure on full understanding of the mechanisms that induced it in the first place. It has been presumed that a daily bout or two of artificial gravity along the Gz axis would replace the gravitational force that constantly surrounds us and therefore affect all body systems. A few continuous hyper-gravity exposure studies in humans in rotating rooms (see Chapter 3, Section 3.1) have been of limited duration mostly addressing tolerance limits and the appearance of unpleasant side effects. With the exception of the attempts to use centrifuges in the 19th century to treat mental disorders (see Wade 2002)(Figure 13-04), most research in humans on the use of artificial gravity as a countermeasure to space deconditioning has been focused on the cardiovascular system. Animal research on the other hand has provided more information on hypergravity exposure on other physiological systems, but has predominantly focused on exposure to almost continuous (stopped daily for cleaning, frequently for an hour or two) hypergravity (Smith 1975).

Figure 13-04. Two hundred years ago, Joseph Mason Cox (1763-1818) introduced a novel technique for treating the mentally disturbed: spinning the body round a vertical axis in a centrifuge. The human centrifuge was the realization of a plan for a rotating machine proposed by Erasmus Darwin (1731-1802) that can be seen in Wade (2002).

5.2 Artificial Gravity Prescription

The prescription for artificial gravity as a countermeasure to spaceflight deconditioning must be effective, comprehensive (protect more than one system), efficient (require minimum time), rewarding (in that it is appealing and acceptable to the user or crew) and safe (no adverse side-effects). Unpleasant side effects can be expected but methods of minimizing these should be developed.

Acceptability of an artificial gravity countermeasure by the crew is a very important criterion as well. However effective, artificial gravity regimens that produce discomfort are boring or excessively time-consuming even if accepted, will probably be abandoned on a long-duration flight. This aspect is also important to know, before expensive, specialized flight-devices are designed and built.

It has long been presumed that a spinning spacecraft would provide the best artificial gravity solution to the dilemma of providing an Earth-like environment in space (see Chapter 3). However, the feasibility of building such a physiologically effective gravity-providing structure in space with a sufficient radius to minimize or eliminate gravity gradients is not likely. Nor is it unlikely, at the other end of the gravity spectrum that intermittent therapeutic doses of artificial gravity or hypergravity, provided by an on-board acceleration device would not suffice. Obviously, trade-offs between vehicle design, costs, and environmental impact must be weighted against countermeasure efficacy and reliability requirements before a decision can be made. However, such evaluation cannot be performed until after further physiologic research and vehicle design concept evaluations have been completed. [MUST CHECK THE TRANSITIONS BETWEEN THE ABOVE AND THESE LAST TWO SENTENCES. DOES THIS MAKE SENSE? -Gilles]

5.3 Developing Gravity Requirements

Whether directly or indirectly, gravity is at the root of the spaceflight deconditioning problem. Whether replacing gravity will fully restore Earth-like health in space remains in the realm of conjecture until the question is attacked in a concerted and systematic manner. For instance, we do not know what the gravity-use profile of normal healthy men and women is. Much can be learned by observing on Earth, how, when and how much humans use gravity as a physiological stimulus in the process of normal living.

The U.S. Department of Agriculture develops minimum daily requirements for nutrients by monitoring what a group of people normally eats. Continuous monitoring devices such as activity meters and accelerometers, together with daily logs, can go a long way in developing daily gravity-use profiles. Selectively depriving humans on the ground individually of each of these stimulation parameters may tell us a great deal about daily gravity requirements and patterns.

Systematic gravity-dose-response studies have not been done except for a few in animals and then only in the continuous exposure to a higher gravity mode. It's a start. Any human studies should initially address this issue even by measuring only a few parameters before settling on a particular gravity level of stimulus. Gravity in fact should become the standard against which other countermeasures are measured. For instance, current countermeasures like the exercise in LBNP or some exercise routines should be compared to artificial gravity once its dose-response is established.

5.4 Effectiveness of a Countermeasure

5.4.1 The Measure of Effectiveness must be clearly defined

What is the measure of effectiveness of a countermeasure? What are acceptable limits of loss of tissue or function? Is it based on the average or relative loss from previous studies or missions? Is it relative to the required ability to perform? Stand? Ride a bicycle? Heal? Resist infection? The ability to recover? The recovery rate? Or just how the subjects feel?

Should the objective of a flight countermeasure be to maintain the physiological functions as before flight or to maintain physiological functions required for a minimum safety level without compromising the long-term health of the astronaut?

This is perhaps the most significant deficiency in enabling accurate assessment of a countermeasure and comparing information across simulation studies and in fact with flight data. So far, during simulation studies it has been left up to the investigator. Effectiveness has been measured most often by comparing the post-bed-rest results to similar measures taken pre-bed-rest. Alternately, the post-bed-rest results have been compared to synchronous controls housed under the same conditions or occasionally those living at home.

It is imperative that the operational experts should establish agreement on the operational requirements for a successful countermeasure. Flight surgeons, astronauts, and mission planners should be involved in setting these criteria. This is an issue that is critical to the development of effective countermeasures but even more so in the case of artificial gravity. Without this information, researchers have no accepted standard for assessing the efficacy of a countermeasure. It is therefore essential that this definition be formulated as a prerequisite to launching any extensive program in countermeasures.

5.4.2 Methods used to evaluate countermeasures must be continuously reviewed, improved and refined.

Although a great deal of progress has been achieved in establishing a battery of tests to evaluate countermeasures, the list is far too long and cumbersome. Tests may themselves have counteractive properties and lead to erroneous conclusions. They should be restricted in number to those that are most relevant to how the astronaut is expected to feel and perform. Methodologies such as the way plasma volume or aerobic capacity are measured should be standardized, so that data are directly comparable across countermeasures.

5.4.3 There is great need for quick, if not real-time, monitoring technology

This technology should be made minimally invasive, enabling more frequent or continuous monitoring, with cleaner end-points that are physiologically meaningful and performance-relevant. To allow research to build sequentially on studies, data should be made available to artificial gravity research teams as soon as possible, thus reducing repetition of negative results and delays.

5.4.4. Standardization of the support of bed-rest studies and procedures

We believe that the most efficient way of developing artificial gravity countermeasures is by using existing or adapted ground facilities, talent, and experience. Tapping into expertise across disciplines and exchanging results freely would enable earlier success.

Standardization across selected institutions enables more studies to be done in parallel and expands the information return on investment. Standardization is also very important from an ethics point of view so that all volunteers are informed and exposed to similar controlled conditions across countries and facilities. Environmental variables that will affect outcome, such as light intensity, light/dark cycles, nutrition, psychological stimulation, and intellectual stimulation, must also be standardized. During the pre-bed rest ambulatory control period or throughout in the case of synchronous controls, age diet and activity and fitness levels must be maintained. Adequate time should be allowed during this period for participants to adapt to the artificial gravity protocol so that adaptation transients do not confound the benefits of the artificial gravity treatment. This process of familiarization and adaptation could possibly (?) best be conducted before the subjects are admitted to a facility.

6 EXPERIMENTAL APPROACH

A comprehensive program is required to: (a) determine the gravity threshold required to reverse or prevent the detrimental effects of microgravity; and (b) evaluate the effects of centrifugation on various physiological functions. Part of the required research could be accomplished by using human surrogates, including nonhuman primates, on a dedicated centrifuge in low Earth orbit. Studies of human responses to centrifugation using centrifuges could to be performed during ambulatory studies, bed rest (both short- and long-duration), and in-flight studies.

Limits for artificial gravity prescription should be tested in Earth-based rotating rooms, before attempting to design a flight test. Earth-based tests are somewhat encumbered by the constant vertical surface gravity: it dominates the artificial component, prevents testing at sub-normal gravity levels, and changes the orientation of people and actions with respect to the rotation axis. Nevertheless, experiments can account for these differences. A list of potential facilities for implementing these experiments is given in Chapter 3, Table 3-01.

The following section proposes some guidelines for future experiments aiming at validating the regimes of centrifugation as a countermeasure for space missions.

6.1 Ambulatory Studies

6.1.1. Map daily gravity use and developing minimum daily gravity requirements

6.1.1 Determine the effectiveness of intermittent centrifugation on subjects' fitness and physiology

Research could include, but not be limited to the following topics:

a. Determine the best parameter of radius, rotation rate, and gravity level from the point of view of effectiveness, acceptability, and practicality. Include gravity levels both below and above unity.
b. Placement of the head at different distances from the centrifuge axis of rotation in order to investigate the effectiveness of intermittent otolith stimulation on long term vestibular and cardiovascular effects. (Control of head position rather than foot position will allow study of the influence of gravity gradient on the artificial gravity effectiveness.) Other postures than supine should also be investigated. The pros and cons of head restraints to reduce motion sickness need study.
c. Exercise devices and protocols for their use on the centrifuge must be developed, both to enhance the countermeasure effectiveness and to permit deconditioned subjects to tolerate the centrifugation. The importance of the venous blood pump in returning blood to the heart must be considered during high gravity-gradient centrifugation. Active vs. passive centrifugation needs further investigation. The biomechanical consequences of Coriolis effects on limb and head movements during exercise must be studied and steps must be taken to avoid repetitive stress injuries.
d. Subject position issues, including orientation relative to the radius and spin axis (e.g., supine vs. lying on the side or seated).
e. Limitations on angular accelerations of the centrifuge for normal operations to minimize vestibular disturbances while permitting adequate emergency braking.
f. Visual surround during rotation, (external, bed fixed, head fixed, or darkness) as it effects motion sickness and the compatibility with work and recreation.
h. Circadian effects as they influence the relationship between time of day and artificial gravity effectiveness, including the evaluation of artificial gravity while sleeping.
i. Gravity gradient as an advantage to the benefit of artificial gravity to cardiovascular training.

6.1.3 Compare the effectiveness of artificial gravity to LBNP and Exercise

6.2 Bed Rest Studies

6.2.1 Use Standing as 1-g Standard

a. Determine when (time of day), how often, for how long 1 g (standing) daily, passively and with activity, or combinations, (Hargens found LBNP effectiveness needed both) is needed to prevent the development of deconditioning symptoms. The advantage of this approach is that it eliminates the adverse effects of rotation.
b. Compare the obtained results between men and women.
c. Combine with other countermeasures, e.g., nutrition (does 1 g and protein enhance effectiveness on muscle?)

6.2.2 Use Centrifugation to Provide Range from 1-g to Hypergravity

a. Once the most effective 1-g modality is defined, use optimal time/duration to develop dose-response curve with the artificial gravity system (centrifuge).

b. Determine the gravity dose-response threshold or any change in sensitivity to gravity with bed rest. Include gravity levels both below and above unity.
c. Validate the best option in long-duration bed rest for comprehensive evaluation of long-term effectiveness, acceptability, and practicality.
d. Combine with other countermeasure options to reduce artificial gravity needed.

6.2.3 Use *Short-Duration* (5 days) Bed Rest for Screening

Studies have shown that in as little as 4-5 days, plasma volume and aerobic conditioning are significantly decreased, orthostatic intolerance is evident calcium excretion and bone loss markers are increased (Vernikos *et al.* 1996). Based on these parameters, 5-day bed rest studies should suffice for the rapid screening of countermeasures such as centrifugation, to narrow down intensity, duration and frequency variables. This model allows crossover design studies with repeated measures pre-bed rest, in the same subject, as well as a no treatment bed rest exposure. An interval of one month between studies was shown to be adequate for full recovery from this type of bed rest protocol.

6.2.4 Use *Intermediate-Duration* (21 days) Bed Rest for Comprehensive Effectiveness

Bed rest studies of the order of 21 days would be required for evaluating countermeasure effectiveness for those systems such as muscle and bone where techniques to detect significant changes within 5 days are not available. In addition, some studies may require a longer pre-bed-rest equilibration period on a diet or to training in the use of some device.

6.2.5 Use *Long-Duration* (60 days) Bed Rest for Validation

After independent review of the results, the most promising countermeasure candidates thus screened should then proceed to comprehensive evaluation in a long-term bed rest study protocol of 60-90 days. These studies should include balance and coordination measures. Pre-bed rest ambulatory periods of 7 to 14 days would provide more functionally relevant outcomes, such as structural and performance changes in bone and muscle. An adequate period of recovery of the order of 14 days should be included followed by long-term follow-up to assure recovery of even the slowest responding systems such as bone density.

6.2.6 Combinations of Centrifugation with Other Countermeasures

Recent approaches in testing combinations of countermeasures, such as nutrition and exercise, have yielded interesting results and show great promise. Foot vibration, nutrition, or virtual reality to reinforce directional cues when not rotating, may prevent losses in muscle mass and metabolism while, as on Earth, allow greater effectiveness of an appropriate exercise regime to maintain strength and function. This approach could also be useful in increasing compliance by introducing variety and entertainment or operational training elements.

6.3 In-Flight Studies

As discussed above, the artificial gravity design and prescriptions, once developed during ground-based studies, must be validated and tested in space. Due to the constraints of the terrestrial gravitational field, the applicability of ground-based results will be somewhat uncertain. Thus, the likelihood of successful flight operations will be significantly improved by flight validation. We recommend the following potential venues for flight validation and testing studies in both animals and humans.

6.3.1 Flight Animal Centrifuge and Free Flyers Biosatellites

Flight animal centrifuges, such as the ones originally planned in the *Centrifugation Accommodation Module* (CAM) of the ISS, or those previously used in Biosatellites, are near-term venues that could provide invaluable data to calibrate and validate animal studies of intermittent or continuous artificial gravity in deconditioning animals. They could also provide the only accessible continuous partial-gravitational environment, which would allow early evaluation of the amount of deconditioning expected during long-term exposure to Mars gravity.

6.3.2 Human Short Radius Centrifuge on board the ISS

This relatively near-term venue could provide an important test-bed to calibrate/validate ground-based findings of human responses to intermittent artificial gravity. Efficacy and practicability of artificial gravity will be compared with the other countermeasures.

6.3.3 Spinning Capability of the Crew Exploration Vehicle (CEV) or within the CEV

While not likely for the lunar CEV, this capability will be essential for Mars Transit Vehicles and their precursors, if artificial gravity is included in the transit plan. If the CEV is too small to accommodate an on-board centrifuge, artificial gravity could be generated by spinning modules connected by a tether or rigid truss. Gemini-11 demonstrated the basic tether technology during a manned space mission in 1966. A recent study described in Chapter 2, Section 4.1 has investigated the requirements for spinning a manned vehicle.

6.3.4 Artificial Gravity Devices and Protocols for Lunar or Martian Surface Operations

A lunar habitat centrifuge will be essential for testing protocols and operations necessary to protect crews during long stays on the Martian surface.

7 CONCLUSION

A program for the exploration of the Moon and Mars by humans offers both challenges and opportunities for the participation of the scientific community. Foremost is the fact that particular, enabling scientific information is required if a Moon/ Mars program is ever to succeed in one of its prime goals, the expansion of human presence and human activity beyond Earth orbit into the solar system. Critical information concerns the capability of humans to adapt to long-term exposure to weightlessness or reduced gravity. The relevant life-sciences knowledge developed from studies on board the ISS will probably not be available before the Moon/Mars program is initiated. Therefore, a comprehensive solution to the problems of human adaptation to microgravity is the development and validation of effective countermeasures.

Since the reduced apparent effectiveness of the force of gravity is the major reason for the changes we see in space or during bed rest, replacing this stimulus in the variety of ways gravity acts on the body should achieve the greatest return. Theoretically, artificial gravity (or hypergravity) in space should be the most comprehensively effective countermeasure.

The best technique for implementing artificial gravity in space can only be determined after weighing a complex set of trade-offs among vehicle design/engineering costs, mission constraints, countermeasure efficacy and reliability requirements, and vehicle environmental impacts. There have been many proposals for orbital habitats that incorporate artificial gravity. Most of the analysis has focused on studies of structure, mass, deployment, axis orientation, dynamic stability, and habitability factors. In contrast, few studies have considered an internal, small-radius centrifuge. The design, construction, and operation of a continuously rotating spacecraft may pose formidable technical challenges. On the other hand, intermittent artificial gravity (likely combined with exercise) by spinning crewmembers periodically in a centrifuge within the habitable environment seems a more realistic and affordable solution.

We recommend that substantial international effort be focused on cooperative/coordinated studies designed to answer the critical questions posed above. Both human and animal models have their place in the exploration of the proper application of artificial gravity with the goal of a practical and effective flight countermeasure.

Artificial-gravity scenarios should not be a priori discarded of Moon/Mars mission designs. Indeed, the provision of artificial gravity, by ensuring crew health and performance throughout the mission, may well prove to be an architectural variable of fundamental importance. The program recommended in the NASA Task Force on Countermeasure and National Research Council reports (1997) is to carry forward, during conceptual design phases, alternatives providing for artificial gravity during the cruise flight phase, and possibly in Mars orbit as well. If satisfactory countermeasures are confidently identified during a program of orbital life-sciences research, this alternative design path can be abandoned. Conversely, if an effective artificial-gravity system is developed, research on countermeasures will become less urgent.

The most efficient means of developing an effective flight artificial gravity countermeasure is by appropriate and timely use of ground facilities. The likelihood of a successful flight validation will be significantly elevated when the ground studies are thoroughly conducted. Several current studies that contribute to the growing understanding of artificial gravity, in conjunction with exercise, are already underway in the U.S., Russia, Europe, and Japan. This research should be pursued until all critical questions are answered. One major step is to determine the relationship between the gravity dose (level, duration, frequency) and the physiological response is determined for the major body functions affected by spaceflight. Once its regime characteristics are defined and a dose-response curve is established, artificial gravity should serve as the golden standard against which all other countermeasure candidates are evaluated, first on Earth and then in space. Furthermore, it is this knowledge that will yield the greatest benefits to human health on Earth.

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