Analogs of microgravity: head-down tilt and water immersion

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Watenpaugh DE. Analogs of microgravity: head-down tilt and water immersion. J Appl Physiol 120: 904–914, 2016. First published February 11, 2016; doi:10.1152/japplphysiol.00986.2015.—This article briefly reviews the fidelity of ground-based methods used to simulate human existence in weightlessness (space-flight). These methods include horizontal bed rest (BR), head-down tilt bed rest (HDT), head-out water immersion (WI), and head-out dry immersion (DI; immersion with an impermeable elastic cloth barrier between subject and water). Among these, HDT has become by far the most commonly used method, especially for longer studies. DI is less common but well accepted for long-duration studies. Very few studies exist that attempt to validate a specific simulation mode against actual microgravity. Many fundamental physical, and thus physiological, differences exist between microgravity and our methods to simulate it, and between the different methods. Also, although weightlessness is the salient feature of spaceflight, several ancillary factors of space travel complicate Earth-based simulation. In spite of these discrepancies and complications, the analogs duplicate many responses to 0 G reasonably well. As we learn more about responses to microgravity and spaceflight, investigators will continue to fine-tune simulation methods to optimize accuracy and applicability.

astronaut; space flight; weightlessness; bed rest; dry immersion; simulation

As soon as we considered exploring space, concern arose about associated biomedical challenges and problems and how to allay them. This, in turn, led to the need to simulate spaceflight on Earth, and multiple methods have been developed to do so. This review focuses on these analogs of microgravity: the theoretical underpinnings and features of the various analogs, findings from research applying them, and how well those findings match observations from actual spaceflight. Other mini-reviews in this issue address acute microgravity produced by parabolic flight, ground-based simulation of musculoskeletal deficits from long-duration space flight, use of simulated microgravity to test countermeasures against deconditioning, simulation of the isolation and confinement of spaceflight, and microgravity simulation in animals.

Water immersion, bed rest, and head-down tilt each fill many biomedical and/or recreational purposes besides microgravity simulation. While those applications are beyond the scope of this article, that does not exclude them from informing simulation of microgravity. Because of its brevity, this mini-review only supplements and does not supplant other recent and comprehensive surveys of the present and related topics (cited below). Also, because of the length limitations or simply the lack of data to review, several critical systems and functions (e.g., gastrointestinal, immunologic, reproductive, and thermoregulatory) are not discussed.

Fundamental Concepts and Other Background

The terms 0 G, microgravity, and weightlessness are used synonymously. Whether in orbit or deep space, the net effect on an organism is the same: zero external loading imposed by gravity, zero internal forces or pressures created by gravity (down to the molecular level), and zero perception of gravity. Long-standing precedent in aerospace medicine uses G with a subscript (x, y, or z) to represent gravity or gravity-like acceleration in a given direction relative to the body [x: dorso-ventral, y: lateral, and z: rostro-caudal axes (23a)]. This article follows that precedent. Also, the term “astronaut” applies to humans in space regardless of nationality.

Our wake-sleep state and posture (axial orientation to gravity) each impact all aspects of human function. On Earth, we regularly cycle between upright (1 Gv) and recumbent (0 Gv) positions with our 24-h wake-sleep rhythm. This biduality is deeply ingrained by evolution, and we are learning its importance. Spaceflight deletes the gravitational component of this cycle and challenges the circadian component as well.

Most investigators agree that our baseline state in 1 G is upright posture (seated or standing), so one expects this as the baseline control posture for studies of human responses to microgravity and its surrogates. Sitting is more stable and
quiescent than standing, and may, therefore, be preferred in many cases. However, baseline posture is sometimes necessarily recurrent for technical reasons. Even when this is not the case, researchers often collect baseline data in both upright and supine positions, because for many questions, there is interpretative value in comparing the acute effect of posture change (gravity) on Earth to the longer-term effect of microgravity in space (69, 77, 119).

We know gravity, and thus its absence, importantly influences many processes inside individual cells (68, 112). Cytoskeletal mechanotransduction of gravity appears to mediate these effects, and the intracellular responses, in turn, impact how cells in tissues contribute to macrophysiology of the organism. Current Earth-based organismal analogs of microgravity cannot expect to eliminate or screen molecular-level effects of gravity.

Prelaunch conditions and orbital insertion complicate comparisons of actual microgravity to simulation methods, particularly when those methods purport to simulate the first few hours/days of acclimation to spaceflight (115). Two-plus hours in the supine, legs-up prelaunch position causes a rostral fluid shift that activates many of the hypothesized responses to microgravity, such that those responses may be attenuated or absent in subsequent 0 G (72). Then, the several-minute process of launch to orbit applies up to 3-4 Gz. Stowe et al. (102) used centrifugation to provide Space Shuttle launch and landing G profiles before and after 16 days of head-down tilt bed rest (HDT), respectively. They found that cortisol, epinephrine, and immunologic responses to the above protocol were “strikingly similar to those from actual Shuttle missions”. They did not directly compare to HDT without before/after launch/landing simulations. Even their efforts cannot attain the psychological stress of spaceflight, which carries the risk of death of at least 1%. (A study design imposing such risk to healthy research subjects would not pass institutional review.) The necessary events preceding existence in microgravity importantly complicate comparison of simulation methods with reality.

How Do We Simulate Human Existence in Microgravity?

The most common ground-based methods used to simulate human spaceflight are horizontal bed rest (HBR), HDT, head-out water immersion (WI), and dry immersion (DI; Fig. 1). Near the genesis of space flight simulation in the late 1970s, HDT supplanted horizontal BR as the bed rest model of choice. Subjective/empirical inflight observations of headward fluid redistribution exceeded those seen with horizontal bed rest. Because of this, investigators experimented with head-down positioning to accentuate the fluid redistribution and thus better approximate that seen in spaceflight (53, 59, 61). HDT angles used range from ~4° to 15+°, but 6° became the most common angle used (54). Bed rest studies reviewed below are almost exclusively 6° HDT. This tilt angle produces approximately –0.1 Gz [= sin(–6°)]. Bed rest studies allow arm support of the head for eating, and HDT studies may permit brief periods of horizontal posture for activities such as showers.

Instead of minimizing or “tuning” Gz forces with HBR or HDT to mimic microgravity, water immersion seeks to neutralize those forces with buoyancy. During head-out WI, water level is most often set at the suprasternal notch, but this may vary (29). Subjects usually sit, but some studies employ standing or rarely other positions. Water temperature is thermoneutral (34–35°C). Because of deleterious cutaneous effects of prolonged WI (108), immersion in silicone liquid was briefly explored (121). Soviet scientists developed DI in the 1970s (reviewed thoroughly in Ref. 76). DI consists of head-out WI with subjects “kept dry by use of a waterproof, highly elastic cloth” (96). The buoyant force from air between the cloth and skin lifts subjects into a semirecumbent posture under water (Fig. 1). Developers and proponents of DI call it “supportlessness” because the uniform buoyant force imposes no localized surface pressures. The seat and/or feet experience some localized pressure in conventional “wet” WI.

Many fundamental physical, and thus physiological, differences exist between microgravity and our methods to simulate

Fig. 1. This figure depicts upright standing posture in 1 G (A), weightlessness in microgravity (B), and the most commonly used ground-based methods for simulating human existence in microgravity: water immersion (C), dry immersion (D), horizontal bed rest (E), and head-down tilt (F). Upright posture (A) and horizontal bed rest (E) are the two basic postures we assume relative to gravity during normal Earth-bound wakeful activity and sleep, respectively. Sitting (not shown) is a more stable and quiescent upright posture than standing, and may, therefore, be preferred in some cases. Upright and horizontal supine posture is the reference postures most commonly used to investigate acute effects of gravity on humans and to serve as a baseline control and recovery conditions for comparison to simulated and actual microgravity.
it, and between the different methods. Table 1 is self-explanatory concerning these differences.

Sensorimotor and Neurovestibular Function

It may be unrealistic to expect ground-based models to simulate sensorimotor conditions of spaceflight. There is no perceptual or biomechanical “down” in space, the head and appendages have weight on Earth but only mass in space, and the viscosity of water in immersion resists motion much more than air (23). As implied above, none of the common ground-based models of weightlessness reproduce the otolith unloading and associated neurovestibular consequences experienced in space. This unloading is thought to be a key mechanism of space motion sickness (SMS) (46, 60). Bed rest and head-out water immersion do not elicit motion sickness. However, Coats and Norfleet (20) demonstrated that horizontal (face-down) or inverted whole body immersion (−1 Gz or −1 Gx otolith stimulation, respectively) in a false-vertical visual environment can cause motion sickness. How closely this duplicates SMS remains to be determined, but it does present a visual-vestibular “sensory conflict” thought to underlie SMS (46, 60). Although anecdotal, the first report of SMS supports the model: Gherman Titov felt like he was flying upside down upon achieving orbit in 1961, and he became ill a few hours later (40). The occurrence of motion sickness during parabolic flight does not predict who will get SMS during spaceflight (40), yet elevated disconjugate eye torsion during parabolic flight may be predictive (25). SMS constitutes one of the earliest, most common, and potentially most dangerous threats to astronaut well-being and performance, so validated methods to study it on Earth would be valuable.

Long-term space flight may cause ophthalmic pathology and reduced visual acuity that persists postflight (67, 105). Mader et al. (67) found that 11% of Shuttle astronauts and 33% of International Space Station (ISS) astronauts exhibited postflight ocular refraction decrements that may “remain unresolved years after flight”. In-flight radiation exposure appears to increase risk of cataract formation (105). Glasses can normalize acuity, but preventing the problems is clearly preferable. Only posture change/bed rest have been used to simulate ophthalmic effects of spaceflight. One study including both acute HDT (20 min) and chronic ISS data showed approximately three-fold greater increases in optic nerve sheath diameter and central retinal artery peak systolic velocity in space relative to those seen with acute supine to HDT transition (98).

Baseline posture of the astronauts was not reported, but it was assumed to be supine on the basis of other information in the article. Intraocular pressure increases of 20–92% observed in the first hour of spaceflight by Draeger et al. (28) exceed pressure increases with acute (15°; Ref. 66) and chronic HDT (6°; Ref. 106). Neither bed rest nor WI are known to alter the lung itself and on thoracoabdominal mechanics during bed rest. For both bed rest and spaceflight, they also observed no significant reduction of FRC and saw increased pulmonary diffusing capacity may permit the reduced ventilation needed to support gas exchange requirements.

Ground-based simulation methods duplicate some, but not all, of the above findings. Montmerle et al. (74) saw no change in peak expiratory flow or vital capacity at 113 days of HDT, both of which match findings in chronic 0 G (85). However, they also observed no significant reduction of FRC and saw reduced, instead of increased, lung diffusing capacity during chronic bed rest, both of which differ from 0 G findings. Guo et al. (44) saw no change in any measure of pulmonary function during 4 days of HDT. In the only work comparing pulmonary function in bed rest and microgravity using identical methodology, Prisk et al. (86) found significant discrepancies and concluded that “HDT was a poor model of the effects of microgravity on pulmonary” function. They attributed the discrepancies to transverse (Gx) gravitational effects on the lungs itself and on thoracoabdominal mechanics during bed rest that disappear in space. For both bed rest and spaceflight, they collected baseline data in both supine and standing posture, and they used standing 1 G data as the primary baseline state.

Pulmonary Function

Gravity and, thus, microgravity affect pulmonary function, yet unlike many other organ systems, these effects do not lead to deconditioning or compromise postflight function. Prisk (85) recently and thoroughly reviewed effects of microgravity on the lung. After transients associated with initial acclimation to microgravity, respiratory functional parameters change and stabilize as follows relative to standing 1 G conditions: 20% decreases in residual volume and functional residual capacity (FRC), 15% decrease in resting tidal volume, doubling of the abdominal contribution to tidal breathing, 9% increase in resting respiratory rate (opposite seen by Ref. 110), 7% decrease in resting ventilation, a 25% reduction in lung tissue volume, a 28% increase in lung diffusing capacity, and significant decreases in (but not complete nulling of) indices of regional variability in ventilation. The latter finding was surprising because predictions held that regional differences in ventilation would largely disappear in microgravity. Given that resting metabolic rate changes little in microgravity (14) and barring other changes in the oxygen delivery chain, the increased pulmonary diffusing capacity may permit the reduced ventilation needed to support gas exchange requirements.

HDT duplicates these observations to some extent. After 42–90 days in HDT, it took subjects an average of 42% longer to complete the aforementioned obstacle course (90). Koppelmans et al. (57) saw less of an increase (23%) after 70 days of HDT. Posture and gait have not been studied after immersion. Subjects are rarely, if ever, motion sick during or following bed rest or immersion. Lack of motion sickness constitutes a major discrepancy between space flight and its models.
Table 1. Physical, physiological, and other features of existence in normal upright postures in 1G, microgravity, and the primary methods used to simulate microgravity, including crude assessment of relative variability of those features across conditions

<table>
<thead>
<tr>
<th>Feature Type</th>
<th>Upright in 1G</th>
<th>Microgravity</th>
<th>Horizontal Bed Rest</th>
<th>Head-Down Tilt</th>
<th>Head-Out Water Immersion</th>
<th>Dry Immersion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Environmental Pressure</strong></td>
<td>atmospheric + surface*</td>
<td>atmospheric</td>
<td>atmospheric + surface*</td>
<td>atmospheric + surface*</td>
<td>atmospheric + water depth below neck + surface*</td>
<td>atmospheric + water depth below neck (semi-recumbent)</td>
</tr>
<tr>
<td>Variability</td>
<td>low</td>
<td>mostly low (exception: EVA†)</td>
<td>low-moderate</td>
<td>low-moderate</td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td>Extravascular (tissue) Pressure</td>
<td>atmospheric + contractile (muscle) + surface*</td>
<td>atmospheric + contractile (muscle)</td>
<td>atmospheric + contractile (muscle) + surface*</td>
<td>atmospheric + contractile (muscle) + surface*</td>
<td>atmospheric + water depth + contractile (muscle) + surface*</td>
<td>atmospheric + water depth (semi-recumbent) + contractile (muscle)</td>
</tr>
<tr>
<td><strong>Variability</strong></td>
<td>high</td>
<td>low-moderate</td>
<td>low-moderate</td>
<td>low-moderate</td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td><strong>Gravitational Intravascular Pressure Gradient</strong></td>
<td>none</td>
<td>low-moderate</td>
<td>only in Gx or Gz (non-Gx) axes</td>
<td>low-moderate</td>
<td>low-height (seated or standing)</td>
<td>[sin(tilt angle) × height$] + non-Gz axis</td>
</tr>
<tr>
<td>Variability</td>
<td>moderate</td>
<td>moderate</td>
<td>moderate</td>
<td>moderate</td>
<td>moderate</td>
<td>low</td>
</tr>
<tr>
<td><strong>Vascular Transmural Pressure</strong></td>
<td>hemodynamic + inertial + local gravitational - local tissue</td>
<td>hemodynamic + inertial - local tissue</td>
<td>hemodynamic + local gravitational - non-Gz - local tissue</td>
<td>hemodynamic + local gravitational - non-Gz - local tissue</td>
<td>hemodynamic#</td>
<td>low hemodynamic#</td>
</tr>
<tr>
<td>Variability</td>
<td>moderate-high</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td><strong>Cerebrospinal Fluid Pressure</strong></td>
<td>hydrodynamic + inertial + local venous + CNS tissue</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td>Variability</td>
<td>moderate</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>[sin(−tilt angle) × height$]</td>
<td>low</td>
</tr>
<tr>
<td><strong>Biomechanical Conditions</strong></td>
<td>1 Gz tethered or inertial forces only</td>
<td>0–1 Gz and Gz, 0 Gz</td>
<td>−0–1 Gz and Gz, sin(tilt angle$)Gz</td>
<td>−0–1 Gz and Gz, sin(tilt angle$)Gz</td>
<td>1 Gz</td>
<td>−0.5 Gz</td>
</tr>
<tr>
<td>Variability</td>
<td>moderate</td>
<td>moderate</td>
<td>moderate</td>
<td>minimal localized (seat and/or feet) Gz; viscous conditions</td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td><strong>Visual Orientation Relative to Gravity</strong></td>
<td>none (gravity not perceived)</td>
<td>0°</td>
<td>moderate</td>
<td>moderate</td>
<td>0°</td>
<td>−30°</td>
</tr>
<tr>
<td>Variability</td>
<td>moderate</td>
<td>high (gravity not perceived)</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td>Circadian Environment</td>
<td>24 h ~ 90 min, with superimposed 24 h</td>
<td>24 h</td>
<td>24 h</td>
<td>24 h</td>
<td>24 h</td>
<td>24 h</td>
</tr>
<tr>
<td>Activity Level</td>
<td>low-moderate</td>
<td>moderate</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td><strong>Thermal Environment</strong></td>
<td>ambient terrestrial atmospheric conduction, convection, radiation</td>
<td>approximately thermoneutral; no gravity-dependent convection</td>
<td>thermoneutral; terrestrial atmospheric conduction, convection, radiation</td>
<td>thermoneutral; terrestrial atmospheric conduction, convection, radiation</td>
<td>thermoneutral; high conduction; moderate convection; low radiation</td>
<td>thermoneutral; moderate conduction; minimal convection; low radiation</td>
</tr>
<tr>
<td>Variability</td>
<td>moderate-high</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td>Immunologic stimulation</td>
<td>no/minimal limitations</td>
<td>very limited</td>
<td>somewhat limited</td>
<td>somewhat limited</td>
<td>somewhat limited</td>
<td>somewhat limited</td>
</tr>
<tr>
<td><strong>Psychosocial Interaction</strong></td>
<td>no/minimal limitations</td>
<td>limited</td>
<td>limited</td>
<td>limited</td>
<td>limited</td>
<td>limited</td>
</tr>
<tr>
<td>Variability</td>
<td>moderate-high</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
</tr>
</tbody>
</table>

P denotes pressure. Physiological Ps based on approximately 100% transmission of external Ps into soft extraskeletal tissues, and approximately 0% transmission of external Ps into CNS tissues due to enclosure in cranium and spine. *Localized P from support of body surfaces oriented ~ orthogonal to gravity vector (e.g., soles of feet on ground). †EVA, extravehicular activity; suit internal P atmospheric. §P proportional to height relative to hydrostatic indifference level (arterial, venous, or CSF); local gravitational P = pgh (114). #Vascular transmural P below water surface. Above water surface (head), vascular transmural P will be similar to upright 1G conditions.
days of DI, Popova et al. (84) noted a less obvious increase in the abdominal component of quiet breathing than seen in space (both relative to seated 1 G conditions), and a decrease in expiratory reserve volume offset by an increase in inspiratory reserve volume not seen during spaceflight. Therefore, pulmonary effects of both HDT and immersion differ from effects of microgravity, and in different ways.

Cardiovascular Function

Disappearance of gravitational pressures in human tissues and circulation leads to immediate effects and long-term sequelae that are well documented relative to other aspects of spaceflight, yet still incompletely and controversially understood. The most striking and surprising acute response is reduction of central venous pressure in space relative to 1 G supine and upright values, yet with the expected increase in cardiac volume (15). Mechanisms continue to be discussed, but a combination of a more spacious intrathoracic volume with reduced systemic extravascular (tissue) pressures in microgravity may explain the paradoxical finding (26, 39, 88, 119). As discussed above, “preacclimation” to microgravity from prelaunch conditions and orbital insertion may also, in part, explain the conundrum (115). Earth-based microgravity analogs all produce the expected increase of CVP in association with the central fluid shift, so that they do not reproduce accurately this early component of acclimation to microgravity (13, 52).

Some findings suggested that spaceflight attenuates cardiac baroreflex gain (30, 33), but questions remain concerning the methods leading to those conclusions (49, 119, 120, 123). Those questions aside, simple logic prevails: if existence in microgravity compromised the cardiac arm of the baroreflex, one would expect attenuated inflight and postflight heart rate responses relative to those observed preflight to equivalent stimuli. No spaceflight, bed rest, nor immersion study has shown this, and in fact, the opposite invariably occurs: an exaggerated heart rate response (7, 17, 24, 30, 35, 48, 50, 65, 76, 83, 119, 124, 128). Furthermore, resting heart rate is usually elevated after spaceflight and its models. To say that vagal baroreflex sensitivity is abnormally attenuated in a range of heart rate control in which sympathoexcitation increasingly drives chronotropy is specious (33, 123). Di Rienzo et al (24) concluded that “no deconditioning seems to occur in the baroreflex control of the heart” in space.

Convertino and Cooke (21) stated “there is no compelling experimental evidence to support significant occurrence of cardiac dysrhythmias” in space. The same is true for 0 G simulation (76), although one work suggested that HDT increases risk of dysrhythmias (94). There is compelling evidence for microgravity-induced reduction of cardiac chamber volumes and myocardial mass during spaceflight. After initial transient increases in left ventricular end-diastolic volume (LVEDV) during the first hours to days of spaceflight, LVEDV then decreases by roughly 15% from baseline supine levels, which approximates the reduction seen upon assuming upright posture (82, 119). LVEDV stabilizes thereafter. Aside from the above-mentioned discrepancies in initiating mechanism, long-term HDT and DI largely duplicate these cardiac changes (17, 27, 45, 58, 76, 122).

The chronic reduction in chamber volumes in space is associated with ~9-12% reductions in left ventricular (LV) mass (82, 104). LV mass similarly decreases 8–16% during HDT (17, 27, 45, 58, 82, 83, 122). After LVEDF reduction stabilizes, 0 G-induced myocardial atrophy and functional decrements may continue to progress: Martin et al. (70) reported increased LV end-systolic volume, and reduced ejection fraction, in astronauts after long- but not short-duration spaceflight. Long-duration HDT also reduces cardiac compliance and, thus, performance (45, 83). Astronauts do not “lie down” to sleep in space, so there is no nightly rostral fluid shift and cardiac distension, as occurs on Earth, with recumbence. This nighttime distension the heart experiences during sleep on Earth may help maintain full cardiac “range of motion,” so that loss of this postural/circadian variability in space contributes to atrophy (116).

Multiple studies and methodologies document that resting sympathetic nervous system activity (SNA) in 0 G stabilizes at levels approaching or equal to 1 G upright levels (19, 33, 77). Therefore, it is surprising that systemic vascular resistance (SVR) decreases in space relative to 1 G upright conditions, thereby approaching supine 1 G levels (77, 79, 80). Increased cardiac output and reduced blood pressure both contribute (78, 109). Decreased SVR may not involve the leg circulation, because vasoconstriction there approximates that seen in upright posture on Earth (117). This implicates the splanchnic circulation. Explanations for SVR reduction in spite of sympathoexcitation in microgravity include reduced peripheral blood volume from central fluid redistribution, vasodilation from neurohumoral effects of central fluid redistribution, and chronic elimination of local veno-arteriolar and myogenic reflexes (78). Basic physics may provide still other explanations, such as increased intravascular volume due to circular vs. elliptical vascular cross sections in 0 G, elimination of gravitational friction between flowing blood and vessel walls (37), and possibly even elimination of gravitational increase in blood viscosity. The reduced blood pressure, blood pressure variability, and increased heart rate variability seen in space correspond more closely to supine than upright 1 G conditions (110).

Although there is inconsistency, immersion and bed rest initially produce the expected sympathoinhibition and vasodilation, and after days to weeks, SNA and vascular resistance usually increase relative to baseline levels (19, 34, 50, 76, 95, 107). Again, baseline posture determines nature and degree of responsiveness: antithorostatic stimuli deviate much further from upright than recumbent conditions (69, 119).

Relative to upright 1 G conditions, microgravity hypothetically reduces vascular transmural pressures below the hydrostatic indifference level, and increases those pressures above it, although these changes have not been directly confirmed in humans (119, 127). After 3 wk of HDT, Platts et al. (83) saw a 20% decrease in leg artery wall thickness, and Palombo et al. (81) reported “inward remodeling” of the femoral artery, both of which imply vascular smooth muscle atrophy from chronic unloading. Leg venous compliance may not change in microgravity (117), and simulation methods produce variable results (12, 31, 111, 125).

Detrimental effects of spaceflight and its analogs on cerebral circulatory function may occur only after many weeks (11). After a 16-day flight, Iwasaki et al. (47) noted maintenance, if
not improvement, in their measures of cerebral flow autoregulation. Surprisingly, they also saw somewhat improved maintenance of cerebral blood flow during orthostatic testing inflight and postflight relative to preflight responses. Using similar methods, Jeong et al. (51) observed similar evidence of improved cerebral autoregulation after 18-day HDT. They also found that post-bed rest intravascular volume replacement reset autoregulatory gain to pre-bed rest levels, which implies that the HDT-induced change in cerebrovascular function results from systemic vs. local circulatory mechanisms. After space flights of much longer duration (58–199 days), Zuj et al. (129) observed reduced instead of increased cerebral autoregulatory capability.

The splanchnic circulation is less studied due to relative inaccessibility, but no less important than more distal circulations, and perhaps more so. In agreement with prior HDT findings (10), Arbeille et al. (6) measured 36–45% increases in portal vein cross-sectional area (CSA) in space relative to supine baseline conditions, and even greater inflight jugular and femoral vein CSA increases. Zhang (127) and Zhu et al. (128) each recently reviewed microgravity-induced changes in cardiovascular structure and function.

**Fluid/Electrolyte and Erythrocyte Metabolism**

Both spaceflight and its surrogates lead to 10–15% reduction of extracellular fluid (ECF) volume, but the mechanistic pathways differ completely (26, 115). Both immersion and bed rest elicit natriuresis and diuresis within hours, and by classic textbook mechanisms, but the opposite occurs in space. Astronauts drink and urinate very little during the first day inflight, and fluid intake and output remain at low-normal levels thereafter (63). Early inflight hypodipsia and anti-diuresis occur without or with SMS, so the responses do not depend on illness. Anti-diuretic hormone, normally associated with thirst, is markedly elevated early inflight (63), probably secondary to the stresses of launch/orbital insertion and early inflight responsibilities. Central circulatory volume expansion during this time is also well documented (see Cardiovascular Function above), and is known to elicit atrial natriuretic peptide secretion and other neurohumoral mediators of ECF reduction (119). As summarized previously concerning early acclimation to microgravity, “If stress-induced ADH elevation and central blood volume expansion compete in central nervous control of thirst and in control of diuresis, then central blood volume expansion clearly wins control of thirst, whereas ADH wins control of renal water excretion” (115).

With reduction of intravascular ECF (plasma) volume in space, parallel reduction of erythrocytes becomes necessary to maintain blood viscosity. Furthermore, without gravitational requirement for blood volume below the hydrostatic indifference level, less blood is needed for gas transport, including during exercise (see next section) (3). Therefore, reduced erythropoietin and other mediators of erythrocyte homeostasis downregulate red blood cell number over the first days of spaceflight, and microgravity analogs usually reproduce this finding (3, 43, 55, 76).

**Orthostatic Tolerance and Exercise Capacity**

Upon reentry and return to upright 1 G existence, the reduced blood and ECF volume, systemic vasodilation, and small, stiff heart, all of which are appropriate for weightlessness, become maladaptive. While immersion and bed rest fail to simulate all aspects of existence in microgravity, recovery from these three conditions is more similar. Reacclimation to Earth gravity reengages familiar and predictable physiological processes.

The most established causes of postflight/bed rest/immersion orthostatic intolerance are, in rough order of validation and importance: 1) reduced ECF volume (35, 76, 119), 2) myocardial remodeling to a smaller, stiffer heart (82), and 3) insufficient baroreflexive vasoconstriction (5, 47, 129). As discussed above, the chronotropic response to simulated and actual orthostasis operates quite well during and after spaceflight and its substitutes. The relative importance of cerebrovascular, splanchnic, and/or leg circulatory deficiencies is unresolved.

If there is a difference between recovery from spaceflight and its models, it may be vestibular in origin. Do postflight motion sickness or vestibulo-sympathetic reflex problems contribute to orthostatic intolerance in ways not easily simulated? The vestibulo-sympathetic reflex is well established, particularly in the prone, head-down neck flexion model (126). Questions remain concerning participation of this reflex in orthostatic cardiovascular control (118).

The same ECF and cardiac changes that compromise orthostatic tolerance also limit postflight, but not necessarily inflight, exercise capacity (64, 97, 119). Loss of erythrocytes, and later loss of skeletal muscle mass (and vascular smooth muscle mass?), also play a role. In microgravity, blood and ECF volume and, thus, metabolic gas transport need not pay a “gravity tax” by filling the venous and extravascular fluid reservoirs below the hydrostatic indifference level. Return to Earth reestablishes this requirement. Both immersion and bed rest do a good job of duplicating microgravity-induced deficits in aerobic exercise capacity (35, 76).

**Sleep and Circadian Rhythms**

Spaceflight impacts both sleep and circadian rhythms, but the impact of microgravity per se vs. other flight-related factors is elusive. A 24-h rhythm is maintained in spite of the ~90-min “day length” of low-Earth orbit, but that rhythm is sometimes artificially shifted before or at launch, and for specific inflight activities. Workload and unfamiliarity conspire to reduce total sleep time, especially early inflight (36, 73). Reduced delta sleep sometimes seen inflight may be secondary to reduced physical activity (42, 73). However, others have observed increased delta sleep in space (101). Both objective and subjective measures of sleep tend to normalize or even improve with extended time in space, with the greatest decrements occurring during postflight reacclimation to sleep in 1 G (36, 100, 101). Stampi (100) concluded that sleep quality and quantity can remain good and normal in space if flight planners maintain astronauts’ preflight circadian rhythm inflight, and, of course, otherwise protect their sleep. HDT and immersion, but not HBR, also reduce delta sleep (56, 93). There are no reports of sleep difficulty or pathology during recovery from any form of simulated microgravity.

Microgravity treats sleep-disordered breathing, albeit an expensive and esoteric treatment. Elliott et al. (32) saw apnea-hypopnea index decrease 59% in astronauts relative to preflight.
levels, and snoring ceased almost entirely, from 17% to 1% of sleep time. In some ways, this is surprising since rostral fluid redistribution exacerbates sleep apnea on Earth (87), so the two findings together clearly implicate gravitational pharyngeal restriction as a cause of sleep apnea. Because of this, one would not expect any microgravity simulation mode to reduce sleep-disordered breathing except perhaps upright WI, but this has not been studied. Interestingly, improved sleep quality of some Skylab astronauts inflight (36) suggests possible preflight sleep apnea, but this was before sleep apnea became recognized as a disease. Norsk et al. (80) observed overall reduction of blood pressure during spaceflight, including preservation of the normal sleep-related decrease. They posited that it may be “healthy for the human cardiovascular system to fly in space”. Relief from sleep-disordered breathing in space supports their contention.

Overall Assessment

Evidence-based medical criteria provide one frame of reference for comparing microgravity simulation methods to the actual stimulus. In this context, astronauts and subjects in ground-based microgravity simulation research comprise two cohorts. This approach acknowledges that those two cohorts represent dissimilar populations. Astronauts are almost always older, and rarely if ever serve as subjects in 0 G simulation studies. With that caveat, Table 2 grades how accurately the various analogs simulate microgravity for the systems and functions briefly reviewed here, and estimates strength of the research (level of evidence) supporting that assessment.

All things considered, HDT may simulate microgravity somewhat more accurately than other current analogs, but it is far from accurate. Also, HDT benefits from significant selection bias in these comparisons: the intuition that led 1960s–1970s era researchers to put forth and develop HDT, along with its convenience and ease of use relative to both WI and DI, led to preferential use of HDT over other models. The resulting surfeit of HDT data relative to other analogs strengthens its case, although not necessarily due to superior fidelity.

Future Opportunities

Many works are published in languages other than English. While respecting authors’ native languages, English translation of these works would benefit the authors and English-speaking readers. The ongoing recalcitrance of the U.S. National Library of Medicine to include abstracts and full-text links in Medline for older articles remains limiting and inexcusable. Fulfilling these two opportunities would enable future workers to investigate truly original questions upon the strongest possible foundation.

Given that ground-based simulation of human spaceflight offers little hope of reproducing 0 G at the molecular and intracellular levels, more vertical integration seems warranted. Can molecular-level effects of microgravity (e.g., Refs. 71 and 68) explain some of the systems-level differences between spaceflight and its models?

The field may benefit from refocusing on theoretical and empirical similarities and differences between microgravity and its simulation methods (Table 1). Wang et al. (114) postulated that either head-up tilt plus lower body positive pressure, or HDT plus upper body negative pressure, could be tuned to reproduce cardiovascular and fluid metabolism effects of microgravity more closely than current methods. Others have similarly devised imaginative modifications of existing models to improve their fidelity (9, 20, 103).

Because of the many substantial gravity-imposed physiological differences between upright and supine postures, investigators should as much as possible study those conditions as a “bimodal baseline” for comparison to actual and simulated microgravity. It remains imperative that authors explicitly report baseline posture in the abstract and elsewhere as needed to ensure proper interpretation of the role of gravity in the findings (69, 119).

Carbon dioxide concentrations inside the International Space Station are maintained at roughly 10 times greater than the Earth atmospheric level of 0.04%, and may increase to twice that (62). The resulting chronic hypercapnia must color in-flight physiological responses ranging from respiratory control to cerebral circulatory autoregulation to bone metabolism (4, 113). Microgravity-induced elimination of density-dependent convection could further increase FICO2, particularly during quiescent sleep, and must also affect thermoregulation and insensible fluid loss (1).

No bed rest study to date has documented the time subjects spend in various positions, much less attempted to ensure temporal equality of transverse G stimulation in all directions (±Gx and Gy). This oversight creates a bias in transverse loading dependent on subject situation and preference. A body position meter feeding data to a monitoring and prompting algorithm could minimize such bias by helping subjects spend equal time in all positions. Such a system would be akin to the clinorotation used to simulate microgravity in plants and cell culture (e.g., Refs. 1, 41, 99), except bed rest would require only one axis of rotation (a la
a rotisserie). At a minimum, the bed rest environment should facilitate subjects’ ability and desire to spend time in all positions.

The most important (and easiest!) future opportunity remains inclusion of women as subjects. Last century, and for obvious and incontrovertible reasons, the U.S. National Institutes of Health and later National Aeronautics and Space Administration sought to end historical exclusion of female subjects from research (8). Unfortunately, the initiative failed: the ratio of human gravitational physiology studies with female: male: both subjects has remained constant for decades at ~1:6:2. Of studies that included both genders, the female cadre was sometimes token (e.g., Ref. 18). At poster sessions in 2015 (meetings of the American College of Sports Medicine and the Association of Professional Sleep Societies), students presented male-only data sets with no rationale for doing so. The gender bias extends to all geographies. That large and complex projects, such as bed rest studies, generate multiple articles exaggerates the bias and makes it all the more egregious. The Journal of Women’s Health (vol. 23, number 11, 2014) recently summarized current knowledge of gender differences in space and its analogs. When women are included as subjects, interesting and important gender differences often emerge, but lack of gender differences is an equally important finding. If a hypothesis about a population is not strong enough to pervade the variability within that population, the hypothesis may not be worthy of testing.

With gender differences in mind, interindividual variability is not the bane of biological research, but instead a key to progress at the basic and applied level. Studies identifying new and important sources of variability (e.g., Ref. 65) enhance our mechanistic understanding and provide individualized tools for screening, monitoring, and training.

An oft-overlooked and experimentally difficult difference between space flight and ground-based analogs is the nature and degree of mental engagement and psychological stress. How do sociological setting, occupational circumstances, workload, and worldview (literally) of the astronaut vs. research subject impact their relative responses to experimental manipulations? One is a highly trained, quasi-famous explorer with extreme pressure to perform while at imminent risk of death, and the other is a deidentified automaton with minimal responsibilities and the ability to end involvement at any time. Are these differences important, and if so, how do we address them? As one approach, subjects in a bed rest study by Roberts et al. (92) “completed a specified objective (such as learning a foreign language)” along with other cognitive challenges and entertainment.

Literature surveys expose works that may not have deserved publication for a variety of reasons. While understanding the need to publish, as well as sample size and other limitations of flight research, we should avoid cluttering the literature with underpowered, excessively subdivided, or otherwise deficient work. A research project should never ignore prior similar work, leave its primary questions without definitive answers, or raise further questions because of poor design, methods, and/or execution. I “throw these stones” not from an ivory tower, but from my own “glass house”.

Conclusions

The laws of physics, principles of sociology, and everything in between promise that we cannot achieve fully accurate ground-based simulation of spaceflight. That said, current microgravity analogs approximate many consequences of existence in 0 G, even when mechanistic pathways differ from those in 0 G. Residual effects of gravity in the analogs explain most of the differences between modeling and reality, but other spaceflight-related nongravitational factors also contribute. Viewed through the lens of evidence-based medicine, microgravity simulation to date achieves roughly level 2–3, which is laudable considering that spaceflight would be considered a very rare “disease” in terms of prevalence. Gravitational physiology remains young and underappreciated by its sister disciplines, which creates great opportunity.

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AUTHOR CONTRIBUTIONS

Author contributions: D.E.W. conception and design of research; D.E.W. performed experiments; D.E.W. analyzed data; D.E.W. interpreted results of experiments; D.E.W. prepared figures; D.E.W. drafted manuscript; D.E.W. edited and revised manuscript; D.E.W. approved final version of manuscript.

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