

**Human Research Program
Human Health Countermeasures Element**

Evidence Book

***Risk of Orthostatic Intolerance During Re-
exposure to Gravity***

March 2008

National Aeronautics and Space Administration
Lyndon B. Johnson Space Center
Houston, Texas

TABLE OF CONTENTS: CHAPTER 9

I. PRD RISK TITLE: RISK OF ORTHOSTATIC INTOLERANCE DURING RE-EXPOSURE TO GRAVITY	9-4
II. EXECUTIVE SUMMARY	9-4
III. INTRODUCTION.....	9-4
IV. EVIDENCE	9-6
A. Spaceflight	9-6
1. Fluid shifts and Plasma Volume	9-13
2. Adrenergic function	9-15
3. Gender.....	9-16
B. Ground-based.....	9-17
1. Clinical.....	9-17
2. Hypovolemia.....	9-18
3. Bed rest	9-19
4. Gender.....	9-21
5. Animal models.....	9-22
V. COMPUTER-BASED SIMULATION INFORMATION.....	9-23
A. Mechanisms Inferred from Digital Astronaut	9-23
B. Digital Astronaut Derivation of the Mechanism of Gender Differentiation	9-25
VI. ORTHOSTATIC TOLERANCE IN A PARTIAL GRAVITY ENVIRONMENT ..	9-26
A. Lunar.....	9-26
B. Mars exploration.....	9-27
VII. COUNTERMEASURES	9-28
A. Fluid Load.....	9-28
B. Artificial Gravity.....	9-29
C. Lower Body Negative Pressure.....	9-29
D. Fludrocortisone	9-30
E. Midodrine	9-30
F. Octreotide	9-31
G. Compression garments	9-32
VIII. RISK IN CONTEXT OF EXPLORATION MISSION OPERATIONAL SCENARIOS	9-34

IX. GAPS.....	9-34
X. CONCLUSIONS	9-35
XI. REFERENCES.....	9-36
XII. TEAM.....	9-45
XIII. LIST OF ACRONYMS	9-45
XIV. APPENDIX 9-A – DEVELOPMENT OF THE DIGITAL ASTRONAUT PROGRAM	9-47

I. PRD Risk Title: Risk of Orthostatic Intolerance During Re-Exposure to Gravity

Description: Postflight orthostatic intolerance, the inability to maintain blood pressure while in an upright position, is an established, space-flight-related medical problem. Countermeasures have been identified and implemented with some success (fluid loading, compression garments) or are being evaluated (midodrine & others). Completion of these efforts is essential for determining what preventive measures should be used to combat orthostatic intolerance during future mission profiles.

II. Executive Summary

Post-spaceflight orthostatic intolerance remains a significant concern to NASA. Even the mandatory use of fluid loading, anti-gravity suits and liquid-cooling garments have not protected ~30% of astronauts returning from short duration Shuttle missions. Published data also show that orthostatic intolerance is a more serious problem after longer duration flights (5). Landing day tilt tests were performed on every American astronaut who has returned from 4-5 month stays aboard the Mir space station (n=6). Five of these six could not complete 10 minutes of upright-posture tilt testing (5). The majority of these astronauts had experienced no problems of orthostatic intolerance following their shorter Shuttle flights. Future exploration missions, such as those to the Moon or Mars, will be long duration, and astronauts will be landing on planets with no ground-support teams. The occurrence of severe orthostatic hypotension could threaten the astronauts' health and safety and success of the mission. Even for the shorter Shuttle flights, orthostatic intolerance still presents a distinct risk to both the crew and the spacecraft.

III. Introduction

Human evolution has been driven by the environment in which we exist. One major component of the environment that has influenced the development of the cardiovascular system is gravity. For our purposes, the human body is essentially a column of water and the hydrostatic forces that act on this column, due to our upright posture and bipedal locomotion, have led to a very complex system of controls to maintain blood flow to the brain. Removing humans from the effects of gravity, as well as returning them to Earth-gravity from microgravity, presents the body with significant challenges to this control system.

It is well documented that the cardiovascular system is affected by spaceflight. However, the mechanisms behind the changes in cardiovascular function due to spaceflight are still not completely understood. One of the most important changes negatively impacting flight operations and crew safety is postflight **orthostatic intolerance**. Astronauts who have orthostatic intolerance are unable to maintain arterial pressure and cerebral perfusion during upright posture, and they experience presyncope or, ultimately, syncope. This may impair their ability to egress the vehicle after landing. This problem affects about 20-30% of crewmembers that fly short duration missions (4-18 days) (8, 9, 14) and 83% of astronauts that fly long duration missions (5).

Risk of Orthostatic Intolerance During Re-exposure to Gravity

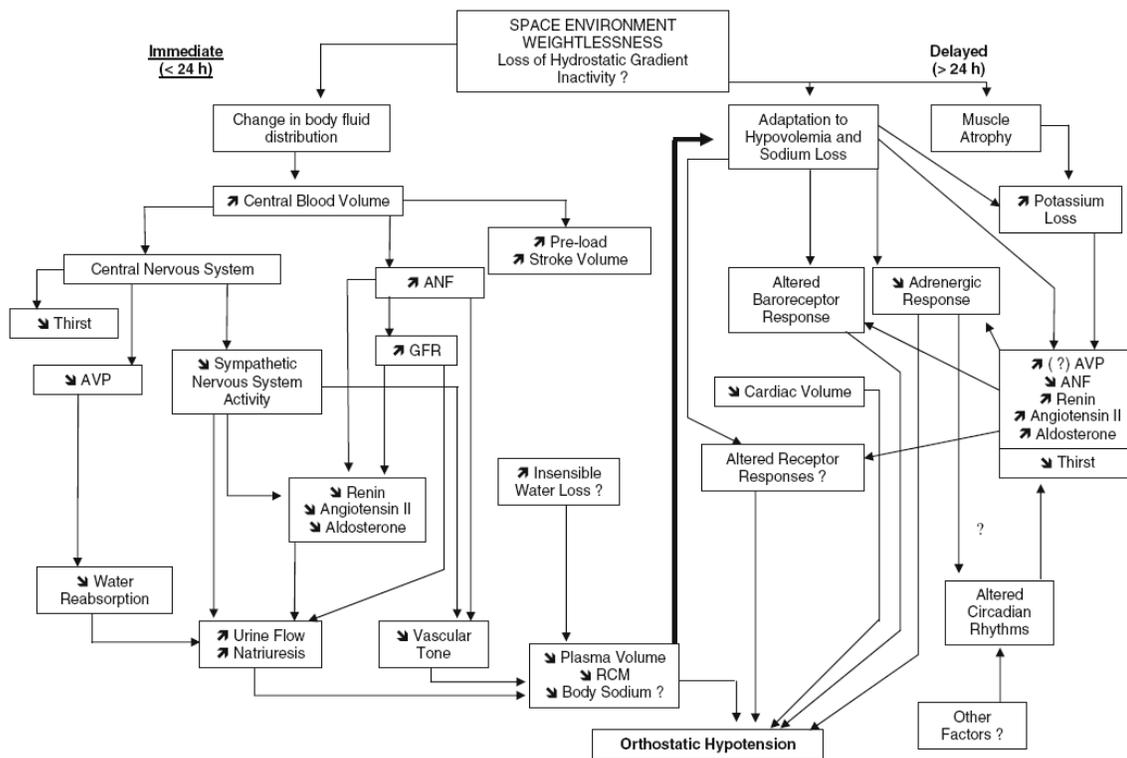


Figure 9-1. Diagram of the effects of exposure to microgravity on orthostatic intolerance. Taken from Pavy-Le Traon et al. (12).

The etiology of orthostatic intolerance is complicated and multifactorial, as shown in Figure 9-1. While the decrease in plasma volume, secondary to the headward fluid shift that occurs in space, is an important initiating event in the etiology of orthostatic intolerance, it is the downstream effects and the physiological responses (or lack thereof) that may lead to orthostatic intolerance. This is highlighted by the fact that while all crewmembers that have been tested are hypovolemic on landing day, only a fraction of them develop orthostatic intolerance during stand/tilt testing.

One physiological mechanism that has been shown to contribute to post-spaceflight orthostatic intolerance is dysfunction of the sympathetic nervous system (15), with or without failure of the renin-angiotensin-aldosterone system (16). These two control systems are activated with postural changes to the upright position. As central blood volume pools in the lower extremities, aortic-carotid baroreceptors are stimulated by low blood pressure (BP), and cardiopulmonary baroreceptors are stimulated by low blood volume. The baroreflex response via the aortic-carotid pathway is to stimulate the sympathetic nervous system to release norepinephrine, which causes systemic vasoconstriction and increases cardiac contractility, thereby maintaining blood pressure. The baroreflex response via the cardiopulmonary pathway is to stimulate the renin-angiotensin-aldosterone system which causes sodium and water reabsorption to maintain central blood volume and blood pressure. If the sympathetic nervous system and/or renin-angiotensin-aldosterone system are inhibited, orthostatic intolerance may occur.

Another possible mechanism for post-spaceflight orthostatic hypotension is cardiac atrophy and the resulting decrease in stroke volume (SV), as has been shown in multiple bed rest studies and a flight study (17, 18). Stroke volume is easily altered by mechanical and hydrostatic effects and serves as the primary stimulus to baroreflex regulation of arterial pressure during an orthostatic stress as part of the “triple product” of blood pressure control: $BP = HR \text{ (heart rate)} \times SV \times TPR \text{ (total peripheral resistance)}$ (19). Orthostatic hypotension will ensue if the fall in stroke volume is of sufficient magnitude to overwhelm normal compensatory mechanisms or if the reflex increase in HR and/or TPR is impaired by disease states or by a specific adaptation of the autonomic nervous system (20).

After adaptation to real or simulated microgravity, virtually all individuals studied have an excessive fall in stroke volume in the upright position (8, 21). Although there are conflicting data regarding changes in baroreflex regulation of heart rate and vascular resistance that may limit the compensatory response to orthostasis (22-30), it may be this excessive fall in stroke volume that is the critical factor of microgravity induced orthostatic hypotension.

While orthostatic intolerance is perhaps the most comprehensively studied cardiovascular effect of spaceflight, the mechanisms are not well understood. Enough is known to allow for the implementation of some countermeasures, yet none of these countermeasures has been completely successful at eliminating spaceflight-induced orthostatic intolerance following spaceflight. However, promising preliminary data exist for midodrine, octreotide and compression garments. Thus, further countermeasure development is required.

IV. Evidence

A. Spaceflight

The Mercury (1961-1963) and Gemini (1965-1966) missions opened the door for exploration of the physiological effects of spaceflight in humans. Post-spaceflight orthostatic intolerance became evident when the pilot of Mercury-Atlas 9 became hypotensive during an upright 70° tilt test after only 34 hours of flight. Thereafter, tilt testing was performed before and after spaceflight throughout the end of the Gemini Program. The results of the postflight tests consistently yielded increased heart rate, decreased pulse pressure and increased fluid pooling in the lower extremities for up to 50 hours after splashdown, confirming a decrease in orthostatic tolerance after spaceflight in missions of 3-14 days (3).

Based on the cardiovascular changes observed during the Mercury and Gemini missions, testing was extended during the Apollo Program (1968-1972) to achieve a more comprehensive understanding of the physiological effects of spaceflight. However, spacecraft constraints, astronaut schedules and primary mission objectives did not allow for extensive testing, and only those tests considered most important were performed. Because of the easier instrumentation, control of different levels of stresses and potential for future in-flight use, lower body negative pressure (LBNP) was implemented (protocol in Figure 9-2) as a test for orthostatic intolerance (3). However, postflight quarantine protocols exercised on Apollo 10-14 prevented the use of LBNP; and thus stand tests, which had been validated in Apollo 9, were performed after Apollo 10 and 11, whereas no tests of orthostatic intolerance were performed on Apollo 12-14 (3).

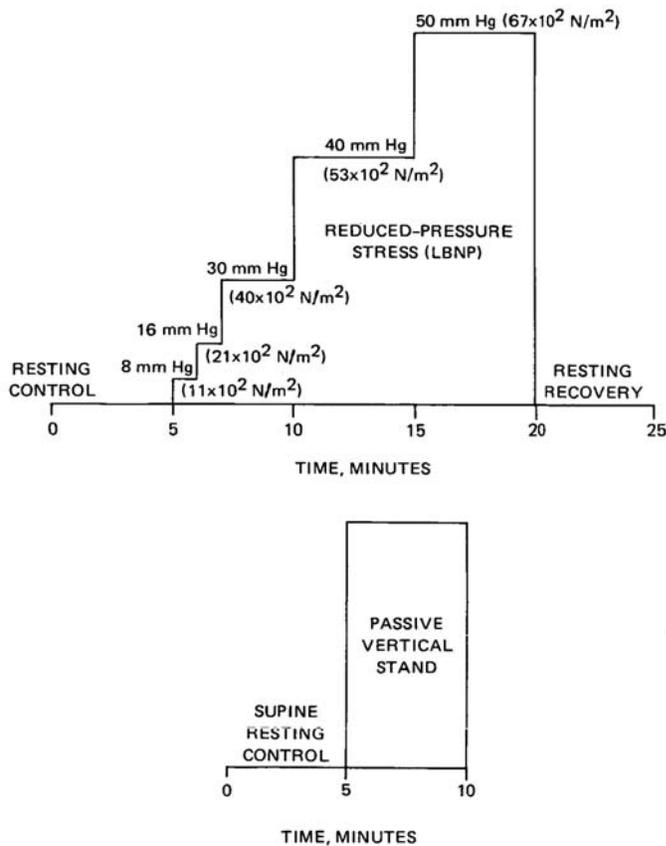


Figure 9-2. LBNP protocol as used during the Apollo program for testing orthostatic tolerance. (3)

The change in atmosphere composition and increased mobility in the spacecraft in the Apollo missions were predicted to reduce post-spaceflight orthostatic intolerance compared to the Mercury program; however, orthostatic intolerance remained prevalent. The Apollo 16 and 17 missions introduced countermeasures for orthostatic intolerance in the form of anti-hypotensive garments (3). Though the countermeasure appeared to provide moderate protection against orthostatic hypotension, testing in Apollo 16 was plagued with problems. The countermeasure for this flight was Jobst compression stockings with a pressure of 40-45 mmHg at the ankle and linearly decreasing pressure to the waist at 10 mmHg. The tight space inside the spacecraft prevented the crewmembers from donning the stockings in-flight, such that the stockings were only worn for a stand test after the LBNP orthostatic

tolerance test. Additionally, the stockings could not be fitted accurately for postflight testing due to the unquantifiable decrease in leg circumference. Finally, postflight testing was performed with ambient temperatures 10°C higher than preflight testing, augmenting the orthostatic stresses. Conversely, the countermeasure and testing conditions in Apollo 17 successfully prevented heart rate changes during LBNP. In this mission, the orthostatic test was performed in the air-conditioned Skylab Mobile Laboratory, and the anti-hypotension suit was an inflatable suit which applied lower body positive pressure from the ankles to the waist. The crewmember donned the garment before reentry, inflated it after splashdown while still in the spacecraft and did not deflate the suit until ten minutes had elapsed in the passive stand test (Figure 9-3). Though the crewmember did not exhibit the typical change in heart rate during LBNP, it should be noted that he also did not follow the trend in cardiothoracic ratio change and postflight limb volume changes (3).

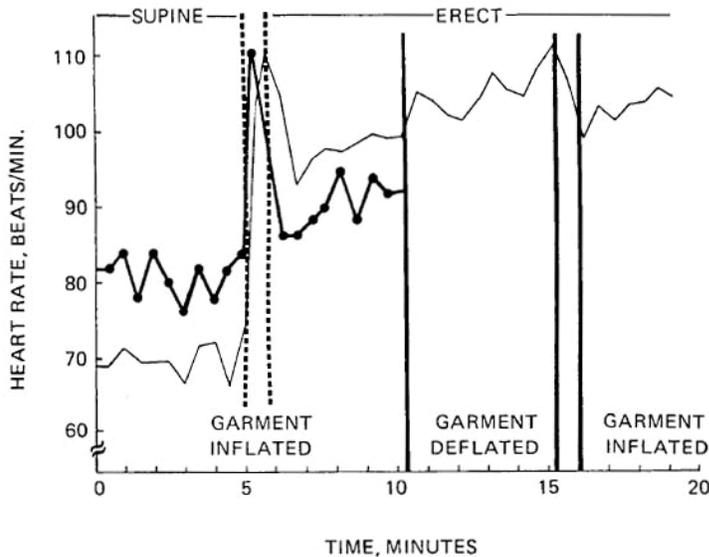


Figure 9-3. Anti-hypotensive suit protocol followed by 1 crewmember on Apollo 17 (3).

before flight. These increases in heart rate were not correlated with mission durations of 8-14 days. Additionally, body weight, calf circumference and cardiothoracic ratio were all decreased immediately postflight. These measurements had not returned to their preflight values by the third postflight examination, suggesting the changes were not entirely due to fluid loss (3). The findings of the Apollo Program aided the understanding of cardiovascular changes in spaceflight in preparation for longer duration spaceflight in the Skylab missions.

Skylab missions (1973-1974) began the era of long duration spaceflight, where each mission set the record for amount of time spent in space (28, 59 and 84 days) by astronauts. The larger spacecraft and longer duration of the missions allowed the Skylab program to assess the effects of spaceflight on more physiological parameters. However, the high cost of extensive hardware prohibited implementation of many in-flight measurements that we need today (31). The use of lower body negative pressure was extended from the Apollo Program, where LBNP was used as an orthostatic tolerance test pre- and post-spaceflight, to include in-flight testing as well. In-flight LBNP revealed the existence of orthostatic intolerance after 4 to 6 days of flight (32). Crewmen experienced a greater stress during in-flight LBNP than preflight LBNP (31), which is illustrated by their greater increases in heart rate and leg volume and greater decreases in systolic blood pressure (32). In-flight LBNP also served as an indicator of the degree of postflight orthostatic intolerance, information that aided crew health care after long duration missions.

Research from Gemini and Apollo suggested a decrease in cardiac function accompanying spaceflight, raising concerns about potential detrimental effects of long duration spaceflight on the cardiovascular system. Postflight clinical data suggested there might be an impediment to venous return as well as a myocardial effect causing decreased cardiovascular function (31). Two of the three astronauts in Skylab 4 had decreased stroke volume and cardiac output upon their return to Earth, yet the rapid recovery of cardiac volume and mass to preflight values led to the conclusion that 84 days in space is not a long-enough time to produce irreversible cardiac dysfunction (33). The cardiovascular studies that were performed on Skylab provided

Of the twenty-one Apollo astronauts (twenty-four total flights) that performed pre- and post-spaceflight orthostatic tolerance tests, thirteen exhibited an increased heart rate when at rest postflight. This heart rate returned to preflight values by the third examination, two to three days after splashdown. During immediate postflight orthostatic evaluations, astronauts exhibited an increase in heart rate and a decrease in stroke volume and systolic and pulse pressures that were greater than those responses

information about hemodynamic changes that will be valuable for future short and long duration spaceflights, including space station habitation.

The Extended Duration Orbiter Medical Project (EDOMP; 1989-1995) aimed to define the effects of short duration spaceflight in a more-controlled environment aboard the Space Shuttle Orbiter with a larger subject pool, understand the changes in cardiovascular physiology, and develop appropriate countermeasures to prevent detrimental effects of spaceflight (7). Descriptive changes on the cardiovascular system were determined in several studies, in which 24-hour Holter monitoring, blood pressure recordings and two-dimensional echocardiography were determined in flight, and heart rate and blood pressures were determined during launch and reentry. In-flight heart rate and systolic and diastolic blood pressure were decreased when compared to the preflight values, as can be seen in Figure 9-4. Upon reentry, these values increased past their preflight baseline, reaching maximal values at peak gravity (7). Such reentry measurements are no longer performed. During crewmember standing after touchdown, both systolic and diastolic pressures significantly decreased from the seated value, and the decrease in diastolic pressure was greater in the crewmembers who did not inflate their g-suits. Systolic pressure and heart rate returned to preflight values within an hour of landing, whereas all other spaceflight-induced cardiovascular changes were reversed within a week after landing.

Four mechanistic studies were performed to explore the etiology of post-spaceflight orthostatic hypotension, concentrating on changes in autonomic control (7). The first three studies concluded post-spaceflight cardiovascular responses were characterized by decreased orthostatic tolerance, increased low-frequency R-R spectral power, decreased carotid

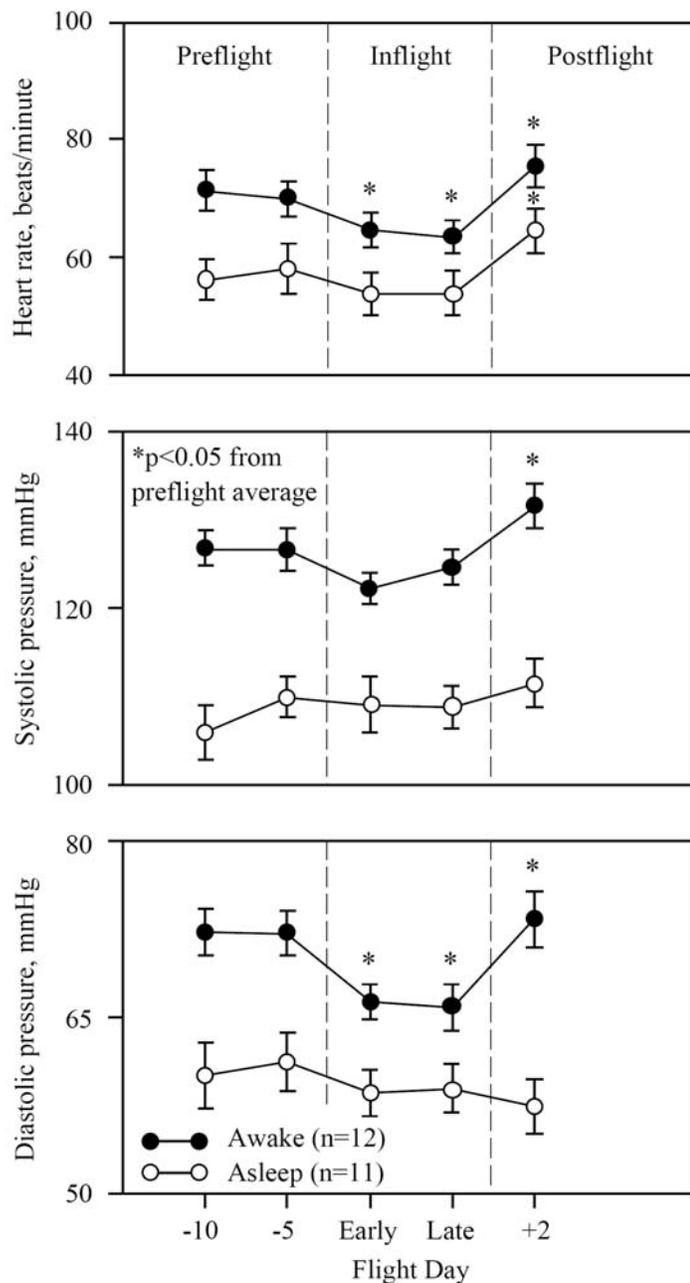


Figure 9-4. Changes in heart rate and blood pressure during spaceflight (7).

baroreceptor response, and altered blood pressure and heart rate responses to Valsalva maneuvers. Catecholamine analyses revealed norepinephrine and epinephrine levels were increased when the astronauts were both resting and standing postflight (Figure 9-5). Three days after landing, the astronauts' norepinephrine levels when they were standing remained increased, while their epinephrine levels had returned to preflight values. The fourth mechanistic study delved into the differences between postflight presyncopal and non-presyncopal crewmembers, and found those in the non-presyncopal group had significantly greater norepinephrine response upon standing, leading to greater peripheral vascular resistance. Analysis of preflight data yielded normal cardiovascular measures in both groups, yet the presyncopal group was characterized by significantly lower diastolic blood pressure and lower systolic blood pressure and peripheral vascular resistance when they were supine. However, it should be noted that plasma volume losses were not significantly different between the presyncopal and non-presyncopal groups (7).

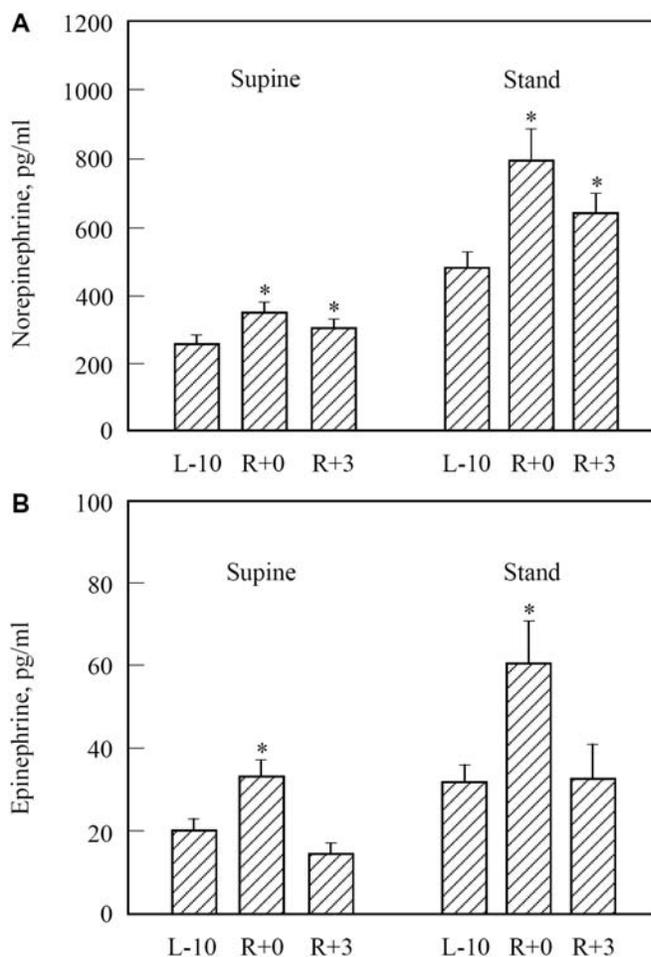


Figure 9-5. Supine (n=23-24) and standing (n=15-16) catecholamine analysis pre- and post-spaceflight (7).

The last goal of the EDOMP, evaluating countermeasures to increase postflight plasma volume, consisted of four studies implementing different LBNP protocols, salt and fluid loading, and fludrocortisone (7). The first protocol applied lower body negative pressure in a step-wise fashion ranging from 0 to -60 mmHg in 5-minute intervals (ramp). The treatment (soak) consisted of a ramp to -50 mmHg, followed by a decompression at -30 mmHg for approximately 3.5 hours with a fluid and salt load during the first hour. The pre- and post-soak ramps were compared, and results showed the heart rate response post-soak was significantly less than that pre-soak, suggesting the soak treatment was effective for the first 24 hours. The second LBNP protocol required crewmembers to perform a soak within the 24 hours before landing. Upon landing, diastolic pressures and heart rate when the astronauts were seated and standing were lower in the LBNP group than in crewmembers who did not perform the soak. However, testing conducted one to three hours after landing showed no significant differences in heart rate or blood pressures during a stand test

as well as no significant differences in plasma volume losses. The third countermeasure study (which was instituted well before EDOMP), a mandatory fluid and salt load before reentry (6), did not allow for any conclusions due to a lack of control of fluid ingestion in-flight and

postflight before testing. The last countermeasure, fludrocortisone, proved unsuccessful since it was not well-tolerated by the crewmembers and did not result in any differences in plasma volume or orthostatic tolerance (7). The implemented countermeasures in the EDOMP were not successful in preventing post-spaceflight orthostatic intolerance. However, the knowledge gained about spaceflight-induced cardiovascular changes and differences between orthostatic tolerance groups has provided a base for development of future pharmacological and mechanical countermeasures. Since EDOMP, investigators continue to report orthostatic intolerance following spaceflight.

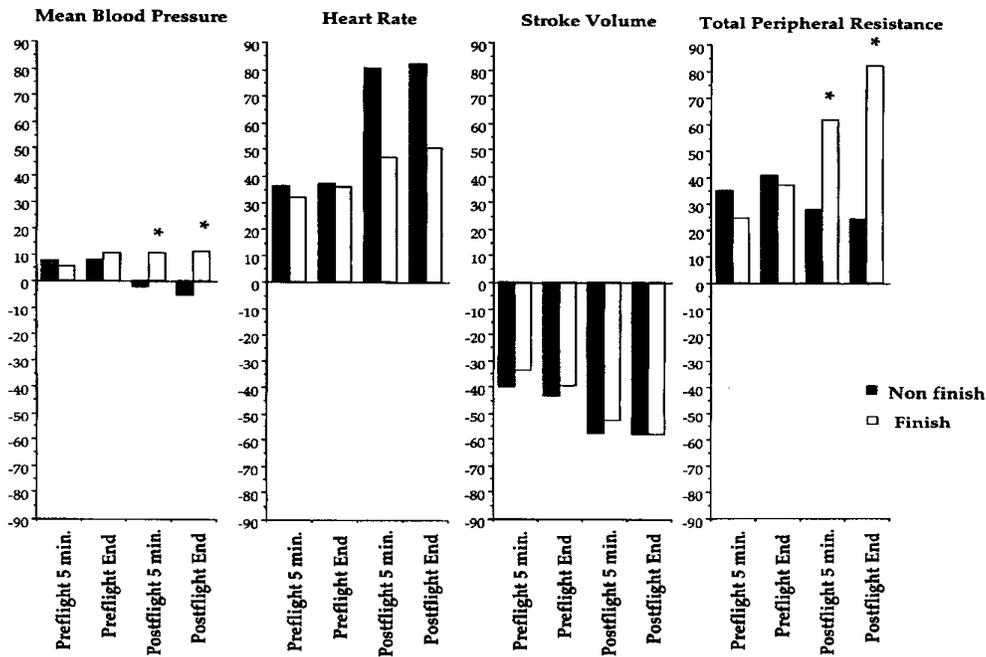
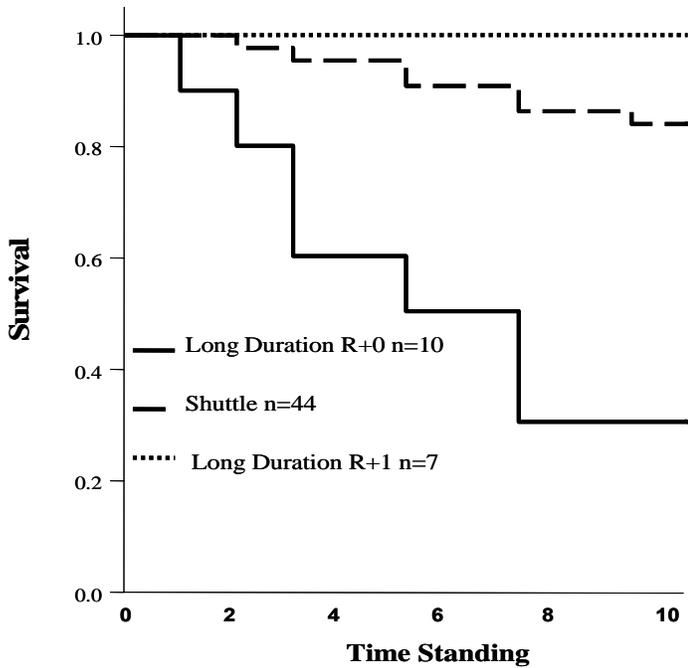


Figure 9-6. Hemodynamic responses to standing (5 finishers, 7-9 non finishers) before and after spaceflight (21).

Buckey et al (34) showed these effects following three Spacelab missions (Figure 9-6). They found an increase in heart rate, decrease in systolic pressure and a decrease in stroke volume during a post-spaceflight five-minute stand test; all of these are hallmarks of orthostatic intolerance. Other studies, utilizing a ten-minute stand/tilt test have shown similar results (Figure 9-7) as well as a decrease in standing time following short duration spaceflight (5, 8, 9, 14, 35). These studies report orthostatic hypotension that results in presyncope (light headedness, nausea, tunnel vision, or a systolic pressure below 70 mmHg) in 20-30% of returning crewmembers.



The data for long duration crewmembers is more limited, but suggests a more severe spaceflight effect. The incidence of post-spaceflight orthostatic hypotension increases to greater than 80% on landing day following long duration (~ 6 months) spaceflight (5). The survival analysis in Figure 9-7 shows this difference where the 50% survival is much lower as is the total failure rate at 10 minutes (compared to short duration spaceflight). It is interesting to note that this figure also shows that even long duration crew have recovered sufficiently to pass a 10 minute tilt test following only one day of recovery.

Figure 9-7. Summary survival analysis of Shuttle, Mir and ISS crewmembers.

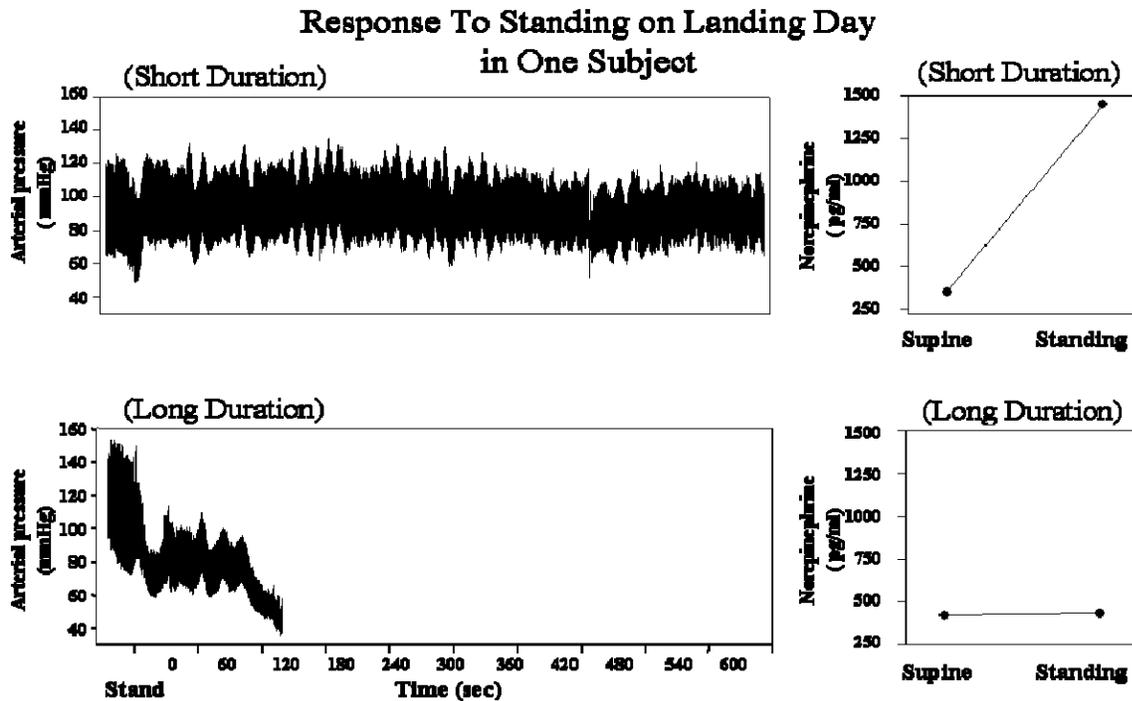


Figure 9-8. Effects of spaceflight on a single crewmember. Left panels show the blood pressure responses to an 80-degree head-up tilt. Right panels show the norepinephrine released during the tilt. This crewmember completed the tilt after short duration spaceflight with normal norepinephrine response, while he failed the tilt test after ~2 minutes following long duration spaceflight and did not increase norepinephrine release upon exposure to tilt.

Figure 9-8 shows the tilt responses of a single astronaut to both a short duration flight (top) and a long duration Mir flight (bottom). These data show a normal tilt response following a shuttle flight with no indications of orthostatic intolerance and a normal norepinephrine increase to tilt. The bottom panel, however, shows that following long duration spaceflight the crewmember could not complete more than two minutes of tilt before hypotension caused the test to be terminated. This crewmember also failed to mount any adrenergic response to tilt following this long duration spaceflight.

An important point that must be made is that these survival analyses under report the true rate of orthostatic intolerance on landing day, because crewmembers who are very ill on landing day are either not tested (and are thus not included in these calculation) or testing is delayed until the crewmember is sufficiently well to participate in testing. Thus the true figures for presyncope following short duration spaceflight and long duration spaceflight are, in reality, higher than the reported figures of 20-30% and 83%.

1. Fluid shifts and Plasma Volume

When astronauts enter microgravity, a cephalad fluid shift occurs which invokes a reflex-mediated hypovolemia. One of the first physiological changes noted during the Apollo program was the decrease in plasma volume, exhibited by the decrease in weight of the crewmen (36). One third of the average five percent weight loss was regained within 24 hours postflight, suggesting this fractional change was due to a loss of fluid. The remainder of the body weight loss was attributed to tissue loss, which is characterized by a longer recovery time (36). Serum and urine samples were analyzed for endocrine and electrolyte changes from pre- to post-spaceflight in order to better understand the etiology of the plasma volume losses of 4.4% upon return to Earth. The cephalad fluid shift and consequent fluid loss were thought to occur during

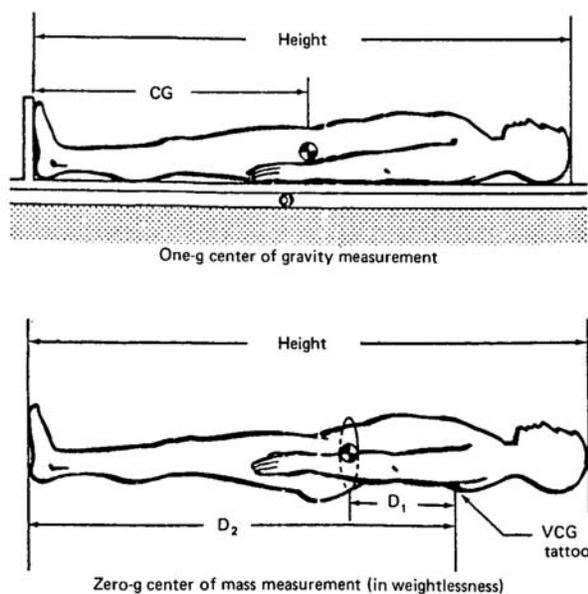


Figure 9-9. Illustration of the changes in center of mass during spaceflight, from (4).

the first two days of spaceflight, as seen in bed rest subjects. The smaller plasma volume loss in spaceflight was attributed to an elevated urinary aldosterone level upon landing. Although the time course of the plasma volume losses was unknown due to the lack of in-flight measurements, the degree of plasma volume loss was independent of the duration of the Apollo mission (36). In-flight anthropometric measurements during Skylab allowed for the determination of time course and magnitude of fluid shifts. Photographs of the crewmen illustrated the commonly noted puffy faces and “chicken legs” exhibited during spaceflight as well as postural changes (4). Fluid shifts were further measured by anthropometric techniques and the determination of the center of mass.

The effect of the cephalad fluid shift characteristic of spaceflight on the center of gravity is illustrated in Figure 9-9. As in

Risk of Orthostatic Intolerance During Re-exposure to Gravity

earlier missions, plasma volume losses were reported, but to a higher degree than in the Apollo program, with average losses of 8.4%, 13.1% and 15.9% for Skylab 2, 3 and 4 (37). The time course of recovery from fluid losses can be seen in Figure 9-10. Blood volume analysis also showed a postflight decrease in red cell mass, which did not begin to reconstitute until at least 30 days postflight; this delay is suggestive of an inhibition of bone marrow (37).

<i>First Skylab mission</i>	<i>Commander</i>	<i>Scientist Pilot</i>	<i>Pilot</i>	<i>Mean</i>	
Premission volume (ml)	3042	3506	3472		
	<i>Percent</i>	<i>Percent</i>	<i>Percent</i>	<i>Percent</i>	<i>Percent</i>
R+0 ¹	-2.5	-10.3	+ 2.6	(* -12.3)	-8.4
R+13	-1.2	- 5.6	+14.1	(* - 2.5)	-8.1
R+42	+8.5		+18.6	(*+ 1.4)	+4.9
R+67	-5.7	- 1.1	+17.0	(* 0.0)	-2.3
<i>Second Skylab mission</i>					
Premission volume (ml)	3157	2798	3885		
	<i>Percent</i>	<i>Percent</i>	<i>Percent</i>		<i>Percent</i>
R+0 ¹	-18.4	- 9.1	-11.8		-13.1
R+14	+ 0.1	+14.7	+ 2.0		+ 5.6
R+45	+ 2.8	+11.7	+ 6.8		+ 7.1
<i>Third Skylab mission</i>					
Premission volume (ml)	3067	3620	3195		
	<i>Percent</i>	<i>Percent</i>	<i>Percent</i>		<i>Percent</i>
R+0 ¹	-15.7	-19.2	-12.9		-15.9
R+14	+ 8.6	+ 7.4	+13.0		+ 9.7
R+31	+ 6.4	+17.7	+ 5.9		+10.0

¹ R+, Recovery + day(s).
* Percent change calculated using R + 67 day value.

Figure 9-10. Plasma volume losses following three Skylab missions (37).

In 1985, consuming fluid and salt prior to landing (fluid loading) became a medical requirement, thus any data on plasma volume acquired after this date do not capture the true landing day plasma volume deficit. In spite of the fluid loading, astronauts return from space with plasma volume deficits ranging from 5 to 19% (8, 9, 14, 34, 38). Additional confounding factors to accurate measurement of spaceflight-induced plasma volume loss include ad lib water ingestion following landing and IV fluid therapy that is given to the more severely affected crewmembers.

The mechanism of the plasma volume loss has been a matter of some debate (39). There have been limited in-flight studies of plasma volume. One study shows a decrease in total body water during flight, suggesting but not proving a diuresis (40). A second study shows a decrease in plasma volume, but an increase in intracellular fluid, suggesting “3rd spacing” and not a diuresis (38); however, postflight studies from the Apollo (36) and EDOMP (41) programs do not show an increase in the intracellular fluid compartment. This disparate flight data reinforce the need for further study into this medium priority research gap.

Similar plasma volume losses (4 – 17%) have been replicated using 6° head-down tilt bed rest as an analog to spaceflight (32, 39). Most of the loss occurs within the first week, and plasma volume remains stable for the duration of bed rest. Recent bed rest studies have shown a markedly increased urine excretion upon bed rest (42, 43). Further study into this effect during spaceflight is needed and is considered a research gap.

2. Adrenergic function

It has been shown, however, that postflight orthostatic hypotension and presyncope are not dependent on the degree of postflight hypovolemia alone (9, 14). Figure 9-11 shows that plasma volume losses are similar between long duration and short duration crewmembers.

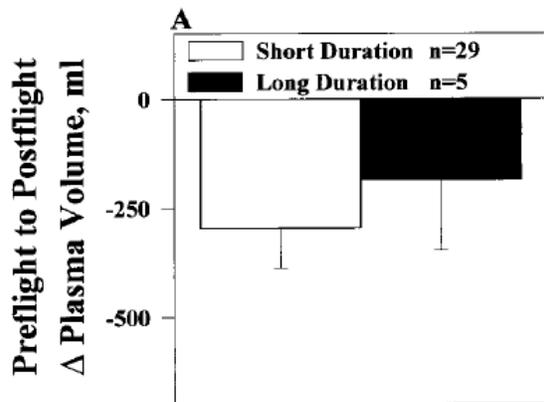


Figure 9-11. Comparison of plasma volume losses between short duration spaceflight and long duration spaceflight (5).

However, long duration crewmembers experience a higher rate of presyncope than short duration crewmembers (Figure 9-7). Also, in a recent study, Waters et al (9) reported on two groups of male short duration astronauts. One group had a 7.1% plasma volume loss on landing day and **did not** become presyncopal during tilt testing; whereas, the other group also had a 7.1% plasma volume loss, but **did** become presyncopal. The difference between groups was that the non-presyncopal group had hyper-adrenergic responses to tilt and the presyncopal group did not (Figure 9-12). Postflight data

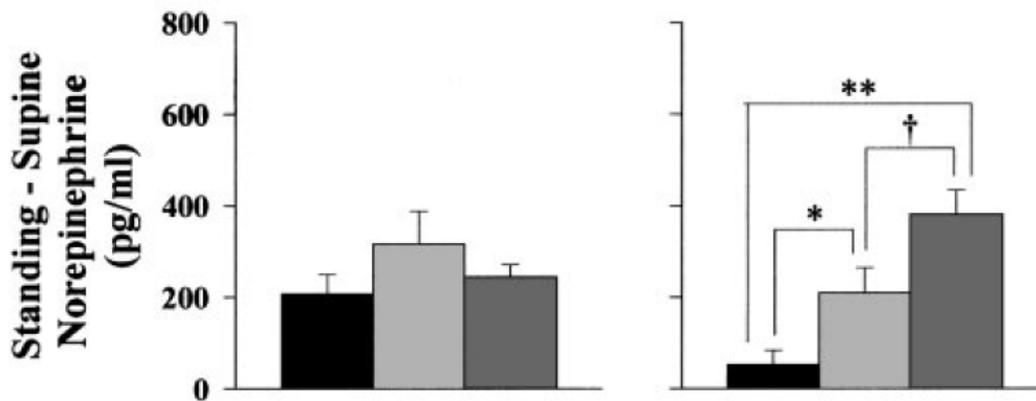


Figure 9-12. Plasma norepinephrine responses in women ($n= 4$; black bars), presyncopal men ($n= 6$; light gray bars), and nonpresyncopal men ($n =22$; dark gray bars) when tested preflight (left), on landing day (right) (9).

measuring muscle sympathetic nerve activity in six non-presyncopal male astronauts (44) also shows that sympathetic responses in these crew members are appropriate. These data are supportive of the norepinephrine spillover studies mentioned above. Unfortunately, there were no presyncopal subjects in this study and the postflight sympathetic dysfunction in that group of astronauts could not be duplicated.

Furthermore, astronauts who experienced both short and then long duration spaceflight were more likely to have a hypo-adrenergic response and become presyncopal during tilt testing after the long duration flight despite similar plasma volume losses in both flights (5). Thus, it is not the **plasma volume loss** alone that causes presyncope, but the lack of compensatory sympathetic activation.

3. Gender

The vast majority of astronauts have been male, and, consequently, any conclusions drawn regarding the physiological responses to spaceflight are male-biased. NASA has recognized that there are some significant differences in how men and women respond to spaceflight (45), including gender differences in the effects of spaceflight on cardiovascular responses to orthostatic stress (9). As can be seen in Figure 9-13, greater than 80% of female crewmembers become presyncopal during a postflight tilt test (9) compared to about 20% for men. This is an important consideration for countermeasure development, as a single countermeasure is not likely to be equally effective for both genders. This hypothesis has been confirmed by Grenon et al. (46) when they showed that midodrine was less effective in preventing orthostatic intolerance in women than men following simulated microgravity.

The incidence of orthostatic intolerance has been shown by many investigators to be higher in women than in men (9, 47-51). Waters et al. (9) nicely summarizes some of the possible reasons gender differences may cause the disparity in orthostatic tolerance. Women have greater heart rate responses than men during mental stress (52), standing (48, 53), infusions of pressor agents (54) and cold pressor tests (55). It

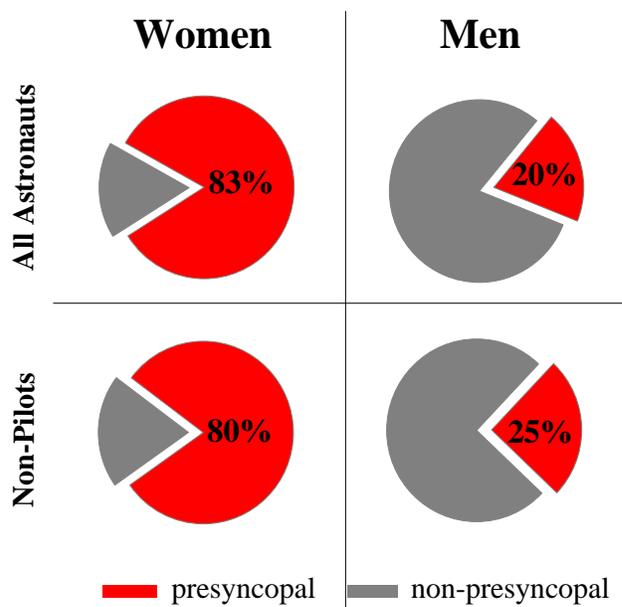


Figure 9-13. Gender-specific orthostatic response to spaceflight. Women (6 astronauts, 5 non-pilots) are much more likely to become presyncopal than their male cohorts (30 astronauts, 12 non-pilots), even when pilots, a self-selecting, highly trained subset, are removed from the analysis.

also has been shown that estrogen replacement therapy in postmenopausal women reduces muscle sympathetic nerve activity (56, 57). In addition, women have smaller increases in vascular resistance than men in response to lower body negative pressure (51, 58), standing (59), cold pressor and facial cooling tests (60) and mental stress (61). There could be several factors that contribute to the women's low vascular resistance, the most important of which is probably estrogen. Several studies in humans demonstrate an augmentation of endothelium-dependent vasodilation with estrogen (62-66). Low peripheral vascular resistance is considered one of the main drivers for post-spaceflight orthostatic intolerance (9). Another reason that women may have lower orthostatic tolerance is because of increased splanchnic blood flow compared to men (49, 67). Fu et al. (68) showed that women had lower tolerance to lower body negative pressure, most likely due to a steeper Frank-Starling relationship. They found that women had larger decreases in stroke volume in response to decrements in cardiac filling pressure compared to men and suggested that this smaller and stiffer left ventricle is the primary reason for the propensity of women to have decreased orthostatic tolerance.

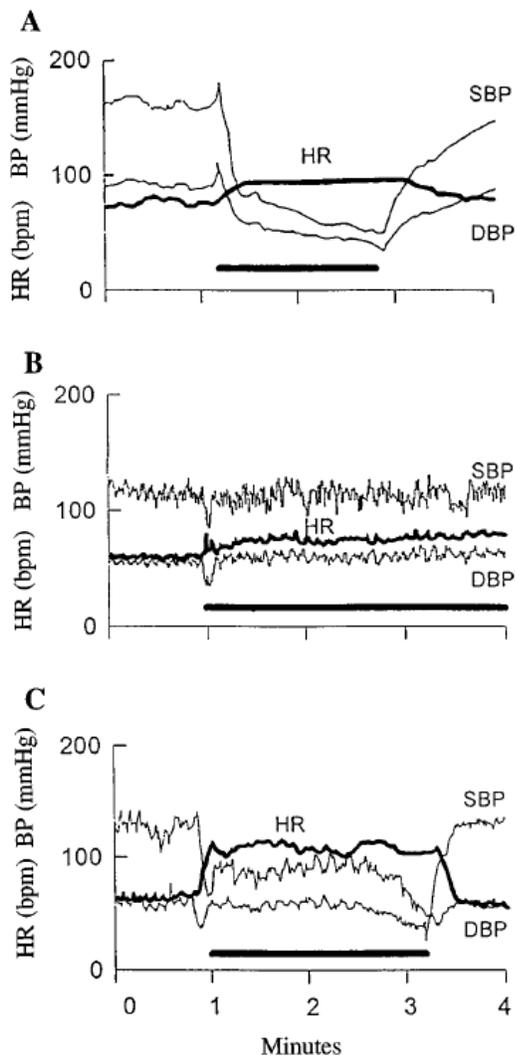


Figure 9-14. Tracings during a tilt test from a patient with autonomic failure (A), and an astronaut preflight (B) and on landing day (C). Horizontal bars are the time in upright posture (8).

below the termination threshold and the test was stopped. This pattern of orthostatic intolerance is amazingly similar to that of the adrenergic failure patient shown in Figure 9-14A. These similarities suggest that clinical research into adrenergic failure would be extremely useful in developing countermeasures to spaceflight-induced orthostatic intolerance.

Similarly, current pharmacological treatments for adrenergic failure may have application to spaceflight-induced orthostatic intolerance. Indeed, midodrine is FDA approved for orthostatic hypotension due to adrenergic failure and is currently undergoing in-flight testing on the crewmembers returning on the Space Shuttle. Such research done at NASA may also benefit the larger clinical community. Again using midodrine as an example, we uncovered a drug interaction between midodrine and promethazine that was previously unpublished (70). Healthy test subjects who received midodrine and promethazine together experienced a higher incidence of akathisia than controls or subjects with either drug alone. Anecdotal reports from emergency

B. Ground-based

1. Clinical

In 2004, slightly over 164,000 patients were hospitalized in the United States with a diagnosis of orthostatic hypotension (69). Causes of these hospitalizations ranged from simple volume depletion to autonomic failure. Previous work has shown that the pattern of post-spaceflight orthostatic intolerance is similar to that seen in patients with autonomic failure (Figure 9-14) (8). In fact the countermeasure midodrine was proposed due to its use for this purpose. Studies that involve ill subjects tend to make extrapolation to the astronaut corps difficult, thus a model that includes otherwise healthy individuals is preferable. Figure 9-14 shows the similarities between clinical orthostatic hypotension in a patient with adrenergic failure and post-spaceflight orthostatic hypotension. Before spaceflight, the astronaut exhibits normal responses to standing: blood pressure is stable and heart rate increases slightly. This crewmember had no symptoms of orthostatic hypotension, had increased norepinephrine release by 236 pg.ml and completed the full stand test. Following spaceflight, however, the same crewmember

exhibited classic signs of orthostatic intolerance during the stand test (Figure 9-14C). Systolic blood pressure decreased when the astronaut stood and heart rate increased markedly, without any increase in norepinephrine release. After ~ 2 minutes of standing, systolic pressure decreased

room physicians report similar symptoms in patients with diabetic neuropathy who present with nausea and are given promethazine while being treated for hypotension with midodrine. In the future, the knowledge of this interaction can help avoid unnecessary patient distress and hospital admissions in clinical practice.

2. Hypovolemia

Laboratory models of hypotension may illuminate the phenomenon in astronauts. Several investigators have used pharmaceuticals to induce a plasma volume loss similar to that of spaceflight. Kimmerly and Shoemaker used three days of spironolactone administration to induce a $15.5 \pm 1.7\%$ decrease in plasma volume (71, 72). While this model was useful for their purposes, spironolactone is known to have vasomotor effects, which complicate interpretation of studies involving integrated cardiovascular responses. Fu et al. used a single dose of Lasix[®],

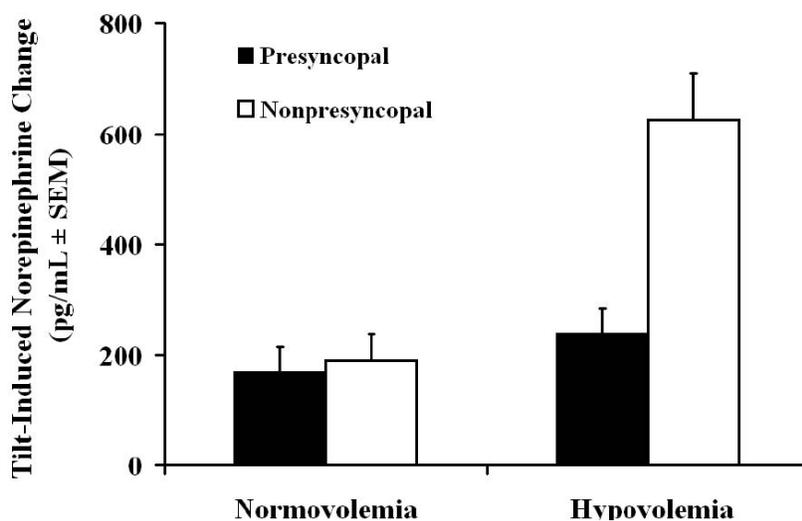


Figure 9-15. Norepinephrine responses of presyncopal (n=8) and nonpresyncopal (n=9) test subjects during normovolemia and hypovolemia tilt tests.

which decreased plasma volume by ~13% to study the effects of acute hypovolemia on orthostatic tolerance (68). Their results showed that orthostatic tolerance, as induced by LBNP, was markedly decreased in women, but not men, during hypovolemia; but they did not find any differences in norepinephrine responses between genders or between normovolemia and hypovolemia. Iwasaki et al. also used a single dose of Lasix[®] and found that the effects on cardiac filling pressures, stroke volume and high-frequency baroreflex

sensitivity were similar between hypovolemia and two weeks of head-down tilt bed rest; however, they also found that vasomotor function differed between the two protocols. Finally, Meck et al. have used a single Lasix[®] (furosemide) infusion (0.5 mg/kg) followed by 36 hours of a very low sodium diet (10 mEq/day). This protocol induces a plasma volume loss similar to that after spaceflight (8, 14, 34, 73). In six astronauts, this protocol **reproduced, with 100% fidelity, their presyncopal response seen on landing day.** Each astronaut who became presyncopal during tilting on landing day became presyncopal during tilting after hypovolemia. Conversely, each astronaut who did not become presyncopal on landing day did not become presyncopal during hypovolemia. Furthermore, those who became presyncopal after spaceflight and during hypovolemia exhibited the same etiology, a failure to release the extra amount of norepinephrine necessary to maintain standing arterial pressure when hypovolemic (Figure 9-15). The differences in these studies may be due to the hypovolemia protocol (acute vs. chronic) or in the orthostatic stimulus (tilt vs. LBNP). Regardless of these differences,

pharmacologically-induced hypovolemia has been shown to reproduce the plasma volume losses seen following spaceflight. While obviously useful for some mechanistic studies and countermeasure development, this model is limited in that the disuse (deconditioning) component of spaceflight (and bed rest) is not replicated.

3. Bed rest

Bed rest studies, particularly those at 6° head-down tilt, are traditionally used as the best ground-based analog to spaceflight. An excellent review by Pavy-Le Traon et al. describes these similarities (12), including changes in plasma volume and orthostatic tolerance that occur after only a few days of head-down tilt bed rest (Table 9-1).

Table 9-1. Comparison of spaceflight and head down tilt bed rest (12).

	Space	Bed rest (HDBR)
Height	↑ ± 1.3 cm	↑ ± 1.0 cm
Body mass/weight	↓ 3-4%	↓ 2-4%
Maximal aerobic capacity	Not measured	↓ 25%
Plasma volume	↓ 10-15%	↓ 10-15%
Urinary calcium	↑	↑
Bone density	↓ 1.6%/month	↓ 0.5-1%/month
Absorption of Ca from Gut	↓	↓
Renal stone risk	↑	↑
Muscle mass	↓	↓
Muscle strength	↓	↓
Insulin resistance	↑	↑
Nausea/sickness/vertigo	None 35% Severe 7% Moderate 23% Mild 35%	Vertigo 10% Nausea rarely present

A summary of bed rest studies showing changes in physiological measurements that contribute to orthostatic intolerance can be found in Table 9-2. All bed rest studies listed here, except one, report plasma volume losses in excess of 8%. With the exception of the Shoemaker study (74), stroke volume was shown to decrease and total peripheral resistance to increase. Heart rate was less consistent, although the majority of studies report increases in heart rate at rest and following an orthostatic challenge. These findings are very similar to those seen following spaceflight

Most of the recent bed rest studies have focused on elucidating the mechanisms of orthostatic hypotension. These mechanisms include cardiac atrophy, sympathetic dysfunction, arterial and venous alteration, etc. Numerous publications have shown a cardiac atrophy following bed rest (17, 8, 30). Levine and co-workers found that 14 days of head-down tilt bed rest results in a smaller, stiffer left ventricle, leading to a decrease in stroke volume (17). This decrease in ventricular volume and stroke volume is similar to that found by Arbeille, et al. (75) and others and is thought to be due to the decrease in myocardial workload that is experienced in bed rest as well as spaceflight. These investigators conclude that the decrease in stroke volume is a primary contributor to orthostatic intolerance.

Table 9-2. Summary of bed rest studies showing orthostatic tolerance. From Waters et al. (76).

Study	Days of Strict -6° HDBR	n		Rate of Presyncope After Bed Rest	Volume Loss, %	HR	Stroke Volume	Peripheral Vascular Resistance	Venous Pressure	Muscle SNA	Plasma Norepinephrine	PRA or Active Renin
		Total	Men/women									
Beck et al.	10	6	6/0	33%	16	↔↔↔↔	↓↓	↑↑				
Convertino et al.	30	11	11/0	40% ^a	15	↑↑ ^d	↓↓	↑↑	↓↓		↔↔↔↔	
Convertino et al.	7	11	11/0		13	↑↑	↓↓	↑↑	↓↓		↓↓	
Convertino et al.	14	8	8/0		16	↑↑		↑↑			↓↓	
Convertino et al.	30	8	8/0		16	↑↑					↓↓	↑
Crandall et al.	15	7	7/0		16	↑↑	↓	↑↑	↓			
Goldstein et al.	14	8	Not reported		16				↓		↔	
Kamiya et al.	14	20	20/0		12	↑↑		↑↑		↑		
Kamiya et al.	14	22	22/0	45%	13, 12 ^c	↔↔↔↔			↓	↔↔↔↔ ^f		
Levine et al.	14	12	11/1	↑ ^b	17	↔↔	↓↓	↑↑	↔↔			
Millet et al.	7	8	0/8	71% ^a	9	↔↔↔↔					↔↔↔↔	↑↑
Millet et al.	7	8	8/0	75%	9	↔↔↔↔					↔↔↔↔	↑↑
Shoemaker et al.	14	15	15/0	40%		↑↑↔↔↔↔	↔↔↔↔	↔↔↔↔		↔↔↑ ^e ↔↔↔↔ ^f	↔↔↑ ^e	↑
Siguado et al.	42	8	8/0	57% ^a	12	↑↑					↔↔↑ ^e	↑
Vernikos et al.	7	8	0/8		8	↑↑						↑↑
Vernikos et al.	7	8	8/0		4	↑↑						↔↔↑↑

Small arrows, effects of bed rest on variables collected at rest; large arrows, effects of bed rest on responses to orthostatic stress; horizontal double-ended arrows, no change in variable. HDBR, head-down bed rest; OT, orthostatically tolerant; OI, orthostatically intolerant. SNA, sympathetic nerve activity. ^aRate calculated from subset of subjects. ^bMost subjects experienced presyncope after a ramped lower body negative pressure protocol before and after bed rest; however, tolerance was reduced after bed rest. ^cPlasma volume losses from OI and OT groups, respectively. ^dReported as R-R interval. ^eOT group increased; OI group did not change. ^fOT group did not change; OI group decreased. ^gOT group did not change; OI group increased. Additional studies that reported data from subsets of the same subjects are not listed.

Many studies have shown that there is a disruption in the way the autonomic nervous system regulates the cardiovascular system following bed rest. Eckberg and Fritsch (25) and Convertino (22) showed decreases in baroreflex gain following short duration bed rest, which indicates a dysfunction in the carotid baroreflex. Muscle sympathetic nerve activity (MSNA) has been studied as an indicator of the signal sent from the nervous system to the blood vessels (sympathetic tone); however, there have been conflicting results from this research. Kamiya et al. (77) studied male subjects after 120 days of head-down tilt bed rest. During a graded tilt test (30 and 60 degrees), MSNA was measured in the tibial nerve. Resting MSNA and heart rate were higher following bed rest and baroreflex slopes for MSNA were steeper during tilt following bed rest, but there were no presyncopal subjects following this prolonged bed rest. The authors concluded that the augmented MSNA response increased vasomotor tone and prevented presyncope. In a follow-up study, these same authors studied 22 male volunteers before and after 14 days of bed rest (78). In this study, 10 subjects became presyncopal during post-bed rest tilt testing. In the hypotensive subjects, MSNA was lower throughout the tilt and was suppressed during the last minute of tilt. This pattern was not seen in the subjects who were able to complete the tilt test. These subjects responded similarly to their previous study. These data directly support the data that show a decreased norepinephrine response during postflight tilt testing. Pawelczyk et al. (79) also measured MSNA following bed rest. In this study LBNP was used as an orthostatic stress. They found that MSNA was increased during LBNP following bed rest; however, this response was appropriate given the changes in stroke volume and cardiac filling pressure and thus reflex control of MSNA was not altered. These data highlight the difficulty in comparing bed rest studies.

Finally, vascular function, whether arterial or venous, has been shown to be modified after bed rest. In the review paper by Pavy-Le Traon (12), the authors stress that the inability to sufficiently increase peripheral resistance is an important factor in the etiology of post-spaceflight and post-bed rest orthostatic intolerance. This points not only to the importance of the sympathetic nervous system, but also the vasculature. Lower limb arterial resistance has been

shown to decrease during head-down tilt bed rest as well as spaceflight, but carotid artery resistance did not change.

Nitric oxide (NO) has been hypothesized to contribute to orthostatic intolerance through its effects on the vascular smooth muscle. Bonnin et al. (80) showed that flow-dependent dilation of the brachial artery was increased following seven days of bed rest and that this increase was negatively correlated to post-bed rest orthostatic tolerance. There was no change in the response to nitroglycerin, implying an endothelium-dependent (for example, NO) effect. Bleeker et al. (81) did a similar study in the femoral artery following horizontal bed rest. They found augmented arterial dilation in response to flow and nitroglycerin, implying an endothelium independent mechanism, likely an increased sensitivity to NO in the vascular smooth muscle. It is known that different vascular beds respond differently to the same stimuli, which may explain these differences.

Taken as a whole, these studies may seem disparate, but upon careful examination they all point to a decreased venous return as critical to the development of orthostatic intolerance. Similar mechanisms are likely at play during spaceflight and help inform future countermeasure development.

Limitations in the current literature are highlighted in Table 9-2, the most obvious of which is the lack of standardization in the bed rest protocols. The number of days in bed rest varies from 7 to 42 days, and a standardized protocol in use in the current NASA bed rest project includes 90 days of bed rest.

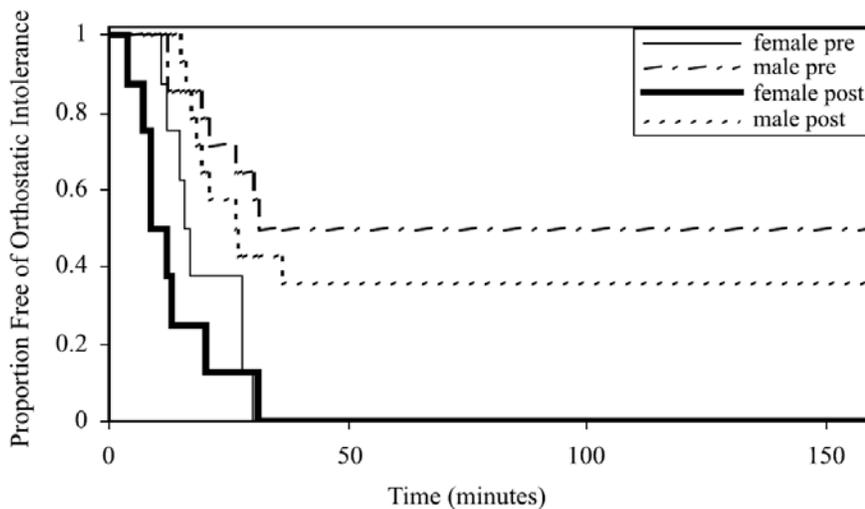


Figure 9-16. Presyncopal survival (15 females, 14 males) following head-down tilt bed rest. From Grenon et al (13).

4. Gender

A common limitation in bed rest studies is the very low number of female subjects studied. This is traditionally done to reduce the variability in the data and to eliminate the scheduling issues related to the menstrual cycle. However, female astronauts have been and will continue to be an integral part of the space program, so it is important to study the effects of spaceflight on both genders.

As with spaceflight, women have been found to be more susceptible to orthostatic intolerance than men after head-down tilt bed rest (13). This gender difference, which is often seen even before bed rest, is illustrated in the survival analysis recently published by Grenon et al. (Figure 9-16). The literature and mechanisms are addressed in the gender section under Spaceflight above.

5. Animal models

There are a number of animal models that have been used to study the mechanisms of spaceflight-induced orthostatic intolerance. The most commonly used model is the hindlimb unloaded rat, which has been extensively reviewed (82, 83); however, there are several important limitations to this model. The first is the difference between quadrupeds and bipeds: mechanisms of reflex control of blood pressure must be carefully considered in this context. The second is that the hindlimb unloading method does not eliminate weight bearing in all four limbs (Figure 9-17), in fact the 30° angle recommended for hindlimb unloading maintains relatively normal foreleg loading (82)

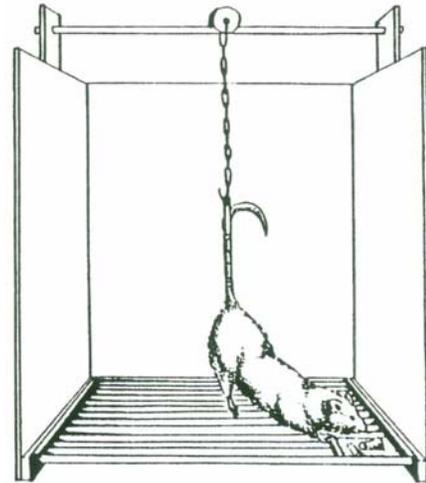


Figure 9-17. Hindlimb unloaded rat model. The rat is tethered to the top of the cage and must locomote with the forelimbs only (1).

However, even with these limitations, this model reproduces the cephalad fluid shift that occurs in spaceflight (83) and has proven to be a useful tool in investigating the mechanisms of post-spaceflight orthostatic intolerance (84, 85). Hasser and Moffitt showed a diminution in baroreflex function, a decrease in sympathetic nerve activity, an increase in vasopressin release and an augmented hypotensive response in hindlimb unloaded rats (85). These data support those seen in humans following spaceflight (14). Additionally, female hindlimb suspended rats have been shown to have a decreased ability to respond to a hypotensive stimulus (86), also similar to gender differences in humans following spaceflight (9).

A significant strength of the hindlimb unloaded rat model is the ability to perform in-depth mechanistic studies. This ability is illustrated beautifully by work that has shown changes in vascular structure and function in the rat model (see (10) for review). Arteries (10) and arterioles (87) of rat hindlimb become thinner and less able to contract in response to KCl, while arteries and arterioles of the upper body either increase in thickness or are unchanged (Figure 9-18). While these detailed vascular measurements have not been done on astronauts, similar results have been observed in long duration head-down tilt bed rest (88). Other vascular

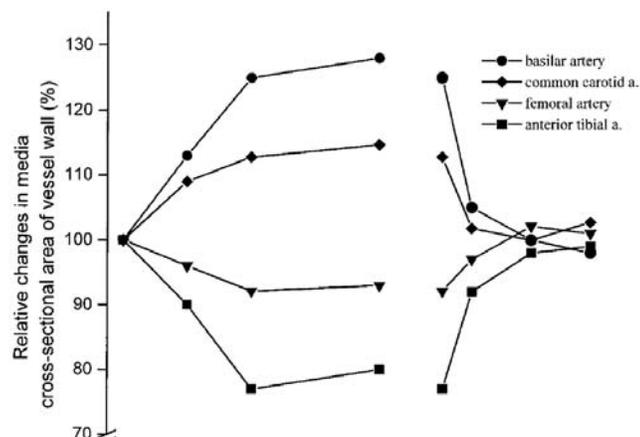


Figure 9-18. Summary figure of the changes in arterial wall cross sectional area during and after 4 weeks of hindlimb suspension (10).

mechanisms that have been investigated include capacitance function, nitric oxide production and prostaglandin release. Ma et al. (89) showed localized changes in NO metabolites and NO synthase protein content, showing that NO mediated dilation is not globally affected by simulated microgravity but, rather, is increased in some arterial beds and decreased in others. Woodman et al. (90) add to this knowledge base by showing that NO-dependent dilation and eNOS expression in arterioles are also differentially affected based on the type of muscle they feed: vessels that have reduced flow due to HLU have reduced dilation and eNOS expression, and vessels in adjacent muscle groups that do not show decreased blood flow to HLU have no changes. All of these studies point to a significant vascular component to orthostatic intolerance. It is difficult to acquire these types of measurements following spaceflight, thus vasomotor function has been indirectly measured and reported as resistance (9, 91, 92). Technology has progressed to the point that more direct measures of vascular dynamics can be measured, primarily with noninvasive ultrasound, and it will be interesting to see how well these studies match the animal data.

V. Computer-Based Simulation Information

A. Mechanisms Inferred from Digital Astronaut

The mechanisms of orthostatic intolerance upon reentry were investigated using the Digital Astronaut. This model has been cited in numerous publications, and a thorough validation is included in Appendix A (93). After simulating exposure to extended microgravity, the model predicted changes in vital signs and hemodynamics similar to those observed in astronauts during spaceflight (94). Also noted were the adaptive compensatory changes produced as fluid shifts from dependent areas, which result in a diuresis with loss of plasma volume and resetting of the baroreceptors while effective central volumes and cardiac output are maintained (Figure 9-19).

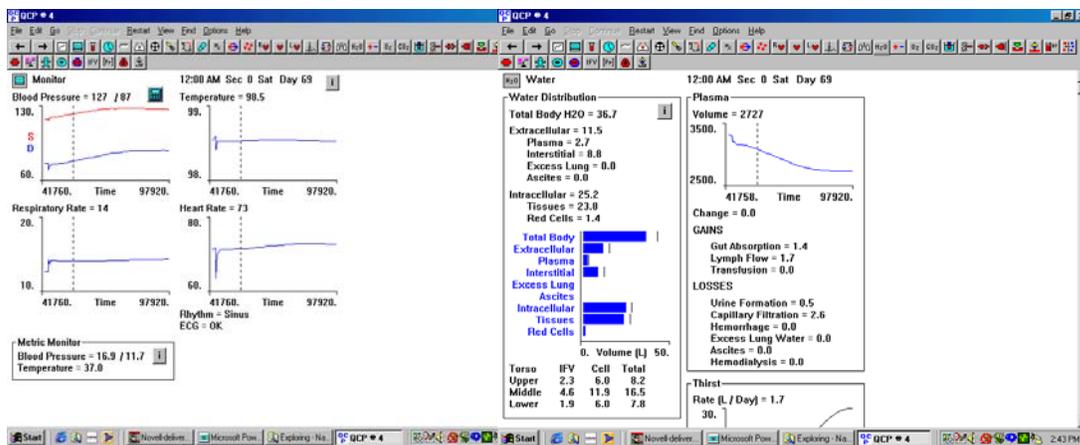


Figure 9-19. Model-predicted hemodynamic changes in microgravity (left panel). The right panel depicts the longitudinal changes over several days in fluid distribution and vital signs in a human who has been exposed to microgravity. The first panel shows both general and specific fluid compartments. In the bar graphs section, the single line represents the point where the individual was before the exposure while the solid bar shows their current status after being in microgravity for that amount of time. Also represented are the rates of fluid fluxes at that point in time.

Of particular interest is the relative contracture of the extracellular fluid compartments and change in capacitance of the veins in the lower extremities secondary to this volume loss. The compliance (pressure-volume relationship) of these veins is determined by:

1. adrenergic tone
2. surrounding muscle tone
3. external compressive forces of the interstitial fluids.

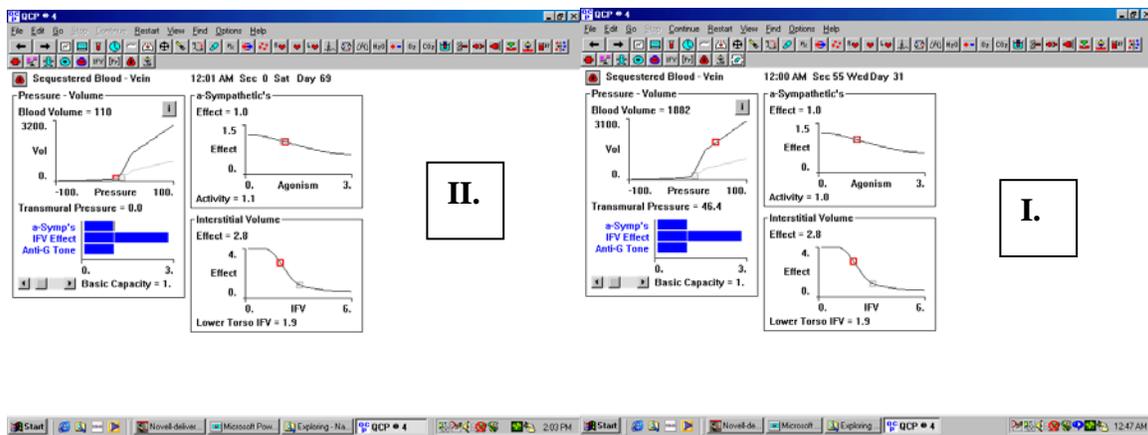


Figure 9-20. Shown are the changes in venous compliance of the lower extremity veins during exposure to microgravity over several days (A) and then upon return to the earth environment (B). The curves show the relationship between fluid volume and pressure within the veins (compliance). The dark lines or curves in A are the current state after exposure to microgravity and the lighter line represents the initial condition before exposure. With graph B, the dark lines shows the curve change several minutes after reentry while the lighter curve shows the state of the compliance before reentry.

Simulated exposure to microgravity shifts this pressure-volume curve secondary to the loss of fluid from the interstitium. During spaceflight this compliance change has little impact on hemodynamics due to the low pressure requirements necessary to drive venous return. Upon return into Earth's gravity, the model predicted a sequestering of blood in these now lower-compliance vessels with a resulting orthostatic intolerance occurring when the astronaut stands (Figure 9-20).

Compensatory mechanisms counteract the fall in blood pressure in most individuals, and the effects are noted to be transient (Figure 9-21). While varying the cardiac function and baroreceptor sensitivity can potentiate this intolerance, the change in capacitance of the lower extremity veins resulting from a loss of external fluid forces in the dehydrated extracellular compartment was the initiating mechanism associated with postflight orthostasis.

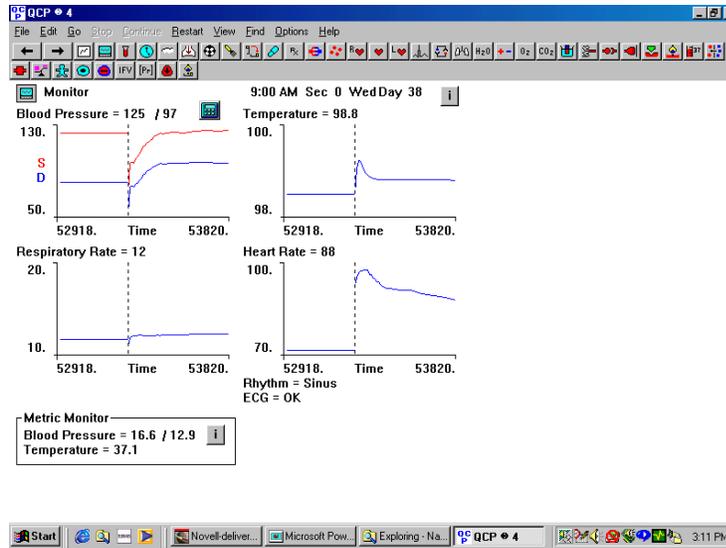


Figure 9-21. Hemodynamic transients and compensations upon reentry into gravity. The first panel demonstrates the vital signs of a returning astronaut during a tilt test after reentry. This individual (male anatomy) is one who is able to compensate for the orthostatic stress and recover his blood pressure after standing.

B. Digital Astronaut Derivation of the Mechanism of Gender Differentiation

The model suggests that postflight orthostasis is accentuated in women due to their inherent lower center of gravity (15%) and proportionately larger mass in the lower extremities (94). When this simple anatomic assumption is incorporated into the simulation without any other complex physiologic or hormonal changes, the orthostasis was more pronounced and overwhelmed all the counter-regulatory interactions as demonstrated by recurring falls in blood pressure upon repeated attempts to stand erect (Figure 9-22).

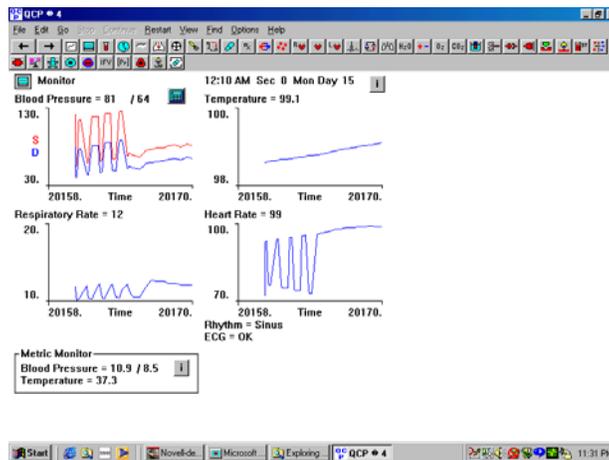


Figure 9-22. This figure demonstrates the simulated vital signs of an astronaut with female anatomy (lower center of gravity) who undergoes the same tilt test after reentry. The individual is unable to compensate for the orthostatic stress and has syncope and collapses. Since the model demonstrates real behavior, the supine position allows her to recover and she tries to stand again and undergoes repeated syncopal spells every time she tries to maintain an upright posture until she eventually gives up and stays supine.

VI. Orthostatic tolerance in a partial gravity environment

A. Lunar

It is not known if lunar gravity will be sufficient to protect crewmembers from the detrimental effects seen during exposure to microgravity. This is a significant research gap. No studies of orthostatic tolerance have been made in a partial gravity environment, thus the only available data are from bed rest studies. While 6° head-down tilt has been used as an analog for the deconditioning associated with microgravity, 10° head-up tilt has been proposed as an analog of lunar gravity. By using a 10° head-up tilt, the resultant force along the spinal axis of the body is 1/6 that normally seen on Earth (Figure 9-23).

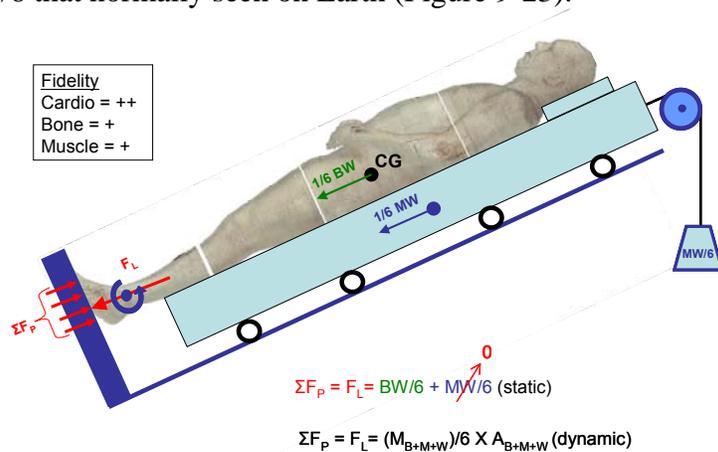


Figure 9-23. Representation of the bed that is proposed for lunar gravity simulation testing. This bed allows for weight bearing on the feet and some exercise while minimizing friction.

Few studies have been published in which head-up tilt bed rest was used as a lunar gravity analog (95-99). The duration of these studies ranged from hours (97-99) to up to six days at 10° (96) or 11° (95) head-up tilt. Two of these studies simulated the trip to the Moon by using four days of 6° head-down tilt bed rest before and after the lunar-analog portion of the studies; however, plasma volume was not measured while subjects were in the head-up tilt portion of the study. Pavy-Le Traon reports an average plasma volume loss of 11%, but the measurement was taken after four days of head-down tilt (96). This does not accurately represent the plasma volume during a lunar stay, since the initial plasma volume loss during the analog trip to the Moon and any changes during the lunar-analog portion remain unknown. In addition, the lack of diet monitoring could have affected the results of the plasma volume analysis.

Louisy found that venous capacity and emptying time increased significantly during a simulated microgravity transit to the Moon and returned to control values on the first day of simulated lunar gravity (95), indicating that lunar gravity may reverse some of the detrimental

effects of short-term microgravity. However, not only did venous capacity significantly increase on the first day of the simulated return transit, the increase in venous emptying time was larger than during the simulated transit to the Moon (95). These data suggest the two microgravity periods might be characterized by different magnitudes and time courses of change in cardiovascular parameters. Additionally, the adaptation of venous distensibility to 1/6 G could not be determined due to the short duration of the study.

Additional studies examining the effects of 10° head-up tilt (97-99) focused on the differences between various tilt angles in a supine-tilt-stand protocol where subjects were tilted for only six hours. The initial change in cardiovascular parameters characterized by the six hours of tilt did not establish any trends, indicating a transient period without predictive value for a longer-duration study. These protocols consisted of a supine rest period followed by tilt, such that the conclusions cannot be applied to tilt changes from 5° head-down to 10° head-up and vice versa. While results from previous studies suggest that exposure to lunar gravity may be protective of the microgravity transit period, it should be noted that previous studies of lunar analogs are not high fidelity models of what a lunar habitation mission will entail. Firstly, the longest lunar-analog portion of these studies lasted only six days, while the eventual lunar outpost missions will be on the order of months in duration. Secondly, subjects in previous studies did not experience ground reaction forces via a footplate at the end of a bed, but rather relied on friction to maintain position while in a head-up tilt position. The muscle contractions experienced from ground reaction forces contribute to venous return and fluid homeostasis; therefore, their absence would increase plasma volume losses. Thirdly, the subjects only exercised in one study (96), and for only 40 minutes a day, whereas astronauts will spend a majority of their day performing tasks that will exercise multiple physiological systems. Moderate exercise may, or may not, be protective of any deconditioning effects of simply lying in a 10° head-up position. Furthermore, while one echocardiographic study has been published on the effects of six hours of 10° head-up tilt (99), there are no reports in the literature regarding cardiac function during 10° head-up tilt lasting more than six hours. Finally, the existing knowledge base is composed solely of data from male subjects. There is ample evidence that women are more severely affected by the deconditioning effects of microgravity (8, 9), and therefore, must be included in any partial gravity deconditioning study.

B. Mars exploration

Mars exploration mission scenarios present a number of challenges for the cardiovascular system. Several transit/stay scenarios have been proposed. Crewmembers will face, at a minimum, a 180 day transit to Mars, a significant stay on the Martian surface of 545 days and a return transit of 180 days. A second possible scenario involves much longer transit times and a much shorter Martian stay (131 day transit/40day Martian stay/308 day return transit).

It is extremely difficult to assess the risks of either scenario given the limited data that are available. That being said, Mir and International Space Station (ISS) data suggest that the majority of crewmembers (80%) exhibit orthostatic hypotension upon landing after 180 days of flight; however, these crewmembers recover quickly. It is not known to what extent 3/8 G will induce orthostatic intolerance. It is important to note that the impact of this level of orthostatic intolerance is likely to be more serious than on Earth due to the lack of medical and support staff/infrastructure on Mars. There are no data that suggest whether a stay on the Martian surface will protect or, more accurately, contribute to recovery of crewmembers. Some believe that 3/8 G will be closer to 1 G than microgravity, but there simply is no evidence for this. The shape of the cardiovascular deconditioning curve between microgravity and 1 G is completely unknown and any discussion is, at this point, purely academic.

The return to Earth gravity will likely be the greatest challenge, from the cardiovascular standpoint, ever faced during the manned space program. Crewmembers are likely to exhibit an extremely high rate of orthostatic intolerance with adrenergic dysfunction and significant cardiac atrophy.

This gap is most in need of ground-based research to evaluate various analogs for 3/8 G and simulate various mission scenarios before any predictions can be made. The Integrated Cardiovascular Study planned for ISS will be critical for identifying the risks for cardiac structure and function. Computer modeling will play a pivotal role in guiding future research. Perhaps the most useful information will be gathered on long duration lunar missions.

VII. Countermeasures

A number of countermeasures to post-spaceflight orthostatic intolerance have been tested with varying degrees of success.

A. Fluid Load

All astronauts returning from space are required to ingest a “fluid load” of broth or salt tablets and water. The efficacy of this countermeasure was evaluated by Bungo et al. (6). These

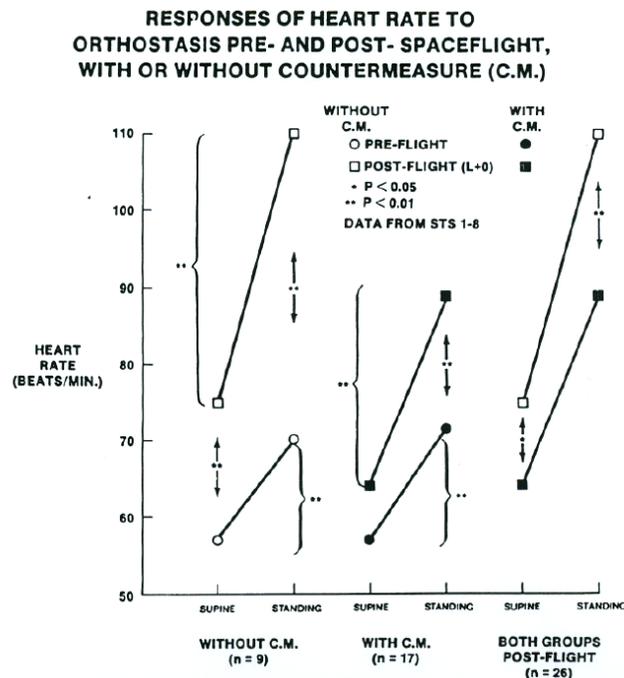


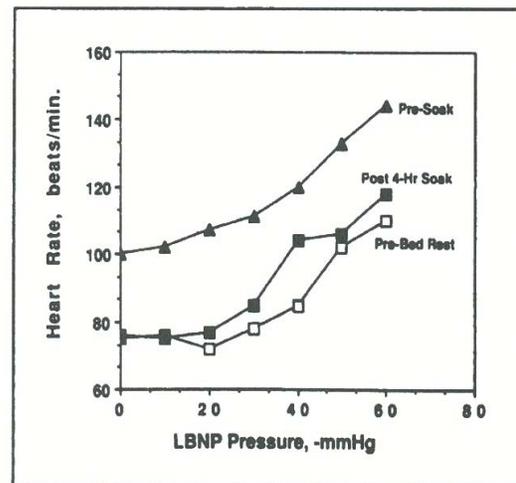
Figure 9-24. Effect of reentry Fluid loading on heart rate (6).

Figure 9-25. Heart rate response in bed rest subjects (n=10) before and after a 4 hour “soak” of LBNP. From (2).

investigators measured heart rate and blood pressure during a passive stand test before and after spaceflight (54 to 194 hours). Both variables, as well as a cardiovascular index of deconditioning, were significantly improved, but not totally restored, when astronauts used the fluid loading countermeasure compared to control flights where fluid loading was not used (Figure 9-24). Unfortunately, plasma volume was not measured during this study, so it is not known what the direct effect of the countermeasure is on plasma volume. Several studies have shown that there is still a significant plasma volume loss, even with the fluid load, which is now a medical requirement.

B. Artificial Gravity

Artificial gravity (AG) via short radius centrifugation (SRC) has been suggested as a multi-system countermeasure to spaceflight deconditioning. While the idea of artificial gravity to prevent orthostatic intolerance is not new (100), the ideal combination of AG magnitude, frequency and duration needed to prevent cardiovascular deconditioning is yet to be determined. In a head-down bed rest study, two hours a day of passive standing was sufficient to prevent post-bed rest hypotension, although four hours a day of passive standing was required to prevent plasma volume losses (101). Hastreiter and Young determined that 1.5 G_z (at the feet) on a short radius centrifuge was required to evoke calf blood flows that were similar to those when the subject was standing (102). In a non-human primate model, Korolkov et al. showed that SRC AG was successful in preventing extracellular fluid loss and orthostatic hypotension resulting from bed rest. Furthermore, they determined that 1.2 G_z , three times a week was more effective than higher G_z levels, administered four to five times a week (103). Iwasaki et al. determined that daily 1 hour exposures to 2 G_z (at the heart) was sufficient to prevent the adverse effects of 6° head-down tilt bed rest on baroreflex function and plasma volume (104, 105). Finally, combining exercise with centrifugation at 0.8, 1.2 and 1.6 G_z (at the feet) was previously shown to be effective in maintaining orthostatic tolerance after return from 3 to 28 days of simulated microgravity (106). The most efficient duration, magnitude and type of artificial gravity has yet to be elucidated.



C. Lower Body Negative Pressure

Lower body negative pressure (LBNP) is another means of producing a head-to-foot G_z force to provide an orthostatic challenge (107-109). By encasing the lower body in a rigid container, venous return can be modulated by varying the level of vacuum. This can be used to simulate standing on Earth or other gravity environments, depending on the magnitude of the LBNP. Application of LBNP as a countermeasure during spaceflight and bed rest (Figure 9-25) has been used with varying degrees of success in preventing orthostatic intolerance (107, 110-114). LBNP applied after exercise during LBNP has been shown to be effective in attenuating post-bed

rest orthostatic intolerance (115). The duration and frequency of LBNP required to make it an efficient countermeasure, however, is not operationally feasible.

D. Fludrocortisone

Fludrocortisone is a commonly prescribed medication for the treatment of dehydration and hypotension. Seven short duration crewmembers took fludrocortisone during spaceflight, seven hours before landing. Fludrocortisone successfully protected plasma volume (Figure 9-26), but had no effect on post-spaceflight orthostatic hypotension (116) thus further in-flight testing was discontinued.

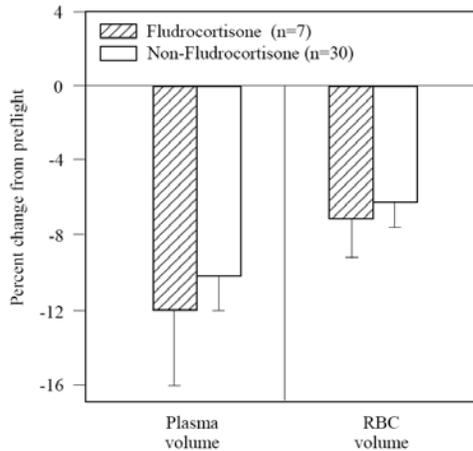


Figure 9-26. Effect of in-flight administration of fludrocortisones on plasma volume and RBC volume.

E. Midodrine

Midodrine is a relatively specific adrenergic agonist that activates alpha-1 receptors on smooth muscle in veins and arteries, decreasing venous capacity (thus preventing venous pooling) and increasing total peripheral resistance (117) in some studies, but not others (11). Midodrine does not cross the blood-brain barrier and therefore has no central stimulant effects (118). It is almost completely absorbed after oral administration and enzymatically hydrolyzed to its active metabolite, desglymidodrine, which has a bioavailability of 93% (117, 118). The peak therapeutic effect occurs between one and two hours, making it particularly attractive for landing day because it can be taken after the final decision to land and have its peak effect close to the time of the maximum G_z experienced during landing. The half-life of the active metabolite is approximately 4 hours (119).

Midodrine has proven to be a safe and effective therapy for orthostatic hypotension due to autonomic dysfunction (117-119). When given to healthy subjects, midodrine only modestly increases arterial pressure in supine and standing subjects (increases less than 10 mmHg) and decreases heart rate (less than 10 bpm) (117, 120).

Midodrine successfully protected subjects from presyncope (121) after two-week head-down tilt bed rest. Platts et al. published data from a female astronaut who had previously become presyncopal following spaceflight (11).

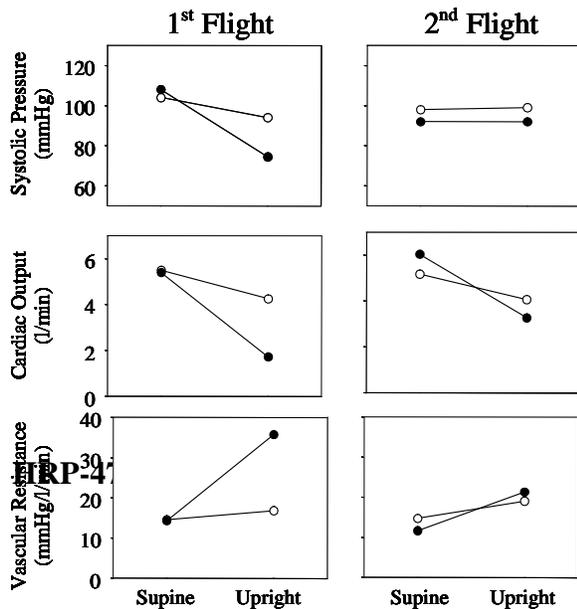


Figure 9-27. Midodrine successfully protected systolic pressure, cardiac output and vascular resistance during tilt testing (n=1). First flight was the control flight and the second flight was the midodrine trial flight. Open circles are before flight and closed circles are postflight (~ 2 hours after landing) (11).

On a subsequent flight she took midodrine one hour before her tilt test and was able to stand for the duration of the test (Figure 9-27). Her systolic blood pressure did not decrease during tilt following midodrine as it had in her prior flight without midodrine. We also found that following the flight with midodrine, her cardiac output did not decrease as was seen after her earlier flight. Interestingly, total peripheral resistance did not increase following midodrine; in fact, midodrine prevented the reflex increase in resistance that was seen in response to tilt following her first flight. This implies a venous mechanism (since a pronounced increase in arterial tone would increase resistance) for midodrine. The lack of increased resistance in this subject is different from other reports of midodrine. We have additional preliminary data for five non-presyncopal astronauts in which resistance also did not increase following midodrine. This may reflect differences between subjects that are normovolemic and those that are hypovolemic. Midodrine was the first cardiovascular countermeasure to follow the progression from clinical treatment to bed rest testing and finally to spaceflight evaluation. The final goal is to release midodrine, to medical operations, as a countermeasure with specific recommendations regarding the most effective usage. There is a significant drawback to midodrine. A double-blind, ground-based study in healthy test subjects revealed an increased akathisia response when promethazine was given with midodrine (70). This response is likely due to the fact that both drugs are metabolized by the cytochrome p450 isozyme 2D6 and in some individuals saturation of the isozyme may lead to higher plasma levels than are typically seen (122).

F. Octreotide

Octreotide is a synthetic peptide (octomer) that is an analog of the naturally occurring hormone, somatostatin. It is an FDA approved drug and is used for the treatment of acromegaly, various cancers and hypotension in patients with autonomic dysfunction (123, 124). Octreotide causes a pronounced increase in splanchnic and peripheral resistance and a decrease in splanchnic and peripheral blood flow (124). This effect is thought to be via a direct effect on the vasculature and not as a result of a gastrointestinal endocrine release, as it is present even in the absence of changes in gastrointestinal hormone levels (124) and at least 3 somatostatin receptor subtypes have been localized in human blood vessels (125). It has also been postulated that octreotide increases venous tone since it produces an increase in cardiac output, possibly through an increase in venous return (124). This makes it an especially interesting potential countermeasure for spaceflight.

Octreotide has been clinically tested for its ability to prevent post-prandial hypotension and orthostatic hypotension in subjects with autonomic failure (123, 124, 126). Octreotide was found to be superior to dihydroergotamine for constricting the splanchnic vasculature (124), and it did

not exhibit the variability (induced by differences in feeding status) that dihydroergotamine did. Similarly, octreotide was shown to be superior to midodrine in preventing both post-prandial and orthostatic hypotension in 16 patients with autonomic neuropathy (123). Since midodrine is currently the preferred pharmacological countermeasure for post-spaceflight orthostatic intolerance, it is essential to compare the two before octreotide is proposed for use in flight. Octreotide has been evaluated in the prevention of orthostatic hypotension in healthy females (67) with very promising results, and it is currently being tested in a ground based study of normal, hypovolemic subjects. Bed rest studies are in the planning stages.

G. Compression garments

Both the American and Russian space programs utilize compression garments during reentry.

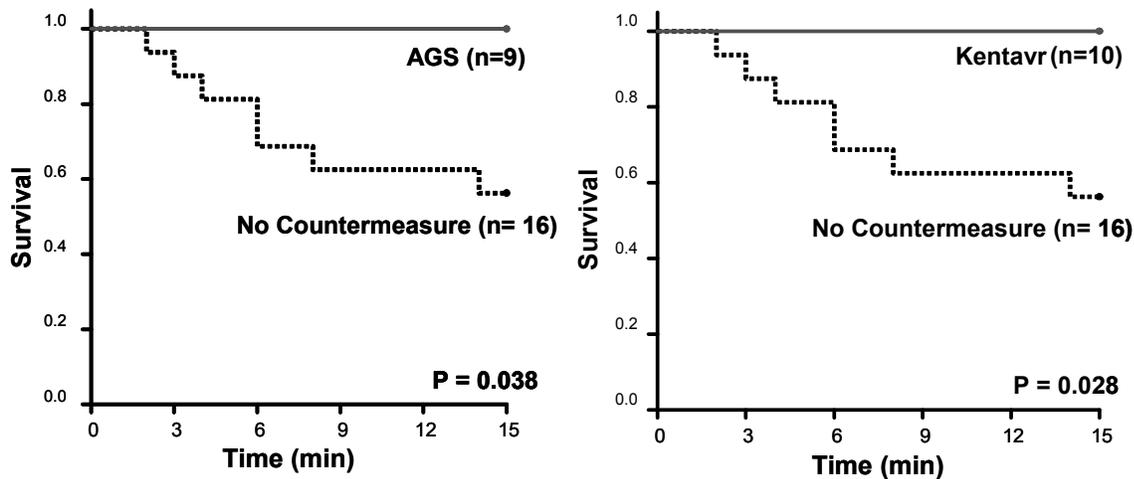


Figure 9-28. Survival analysis of tilt test standing times before and after American anti-gravity suit (left) and the Russian Kentavr suit (right).

Testing of these garments, using a hypovolemia model to mimic landing day plasma volume and orthostatic tolerance, has shown that both garments are 100% effective in preventing presyncope during a 15 minute tilt test (Figure 9-28).

Table 9-3 Comparisons between control subjects and subjects wearing compression garments (Kentavr, AGS) in the supine and standing positions (127).

Risk of Orthostatic Intolerance During Re-exposure to Gravity

Control: Mean ± SEM								
	Presyncopal (n=7)				Nonpresyncopal (n=9)			
	Supine	Standing	Delta	P	Supine	Standing	Delta	P
Systolic Pressure, mmHg	112.3 ± 4.8	80.4 ± 7.0	-31.8 ± 7.3	*†‡	122.7 ± 4.9	118.6 ± 6.0	-4.1 ± 4.4	‡
Diastolic Pressure, mmHg	66.4 ± 1.5	60.6 ± 5.9	-5.8 ± 5.6		69.6 ± 3.2	72.9 ± 4.6	3.3 ± 2.9	
Heart Rate, beats/min	57.6 ± 2.9	87.9 ± 6.2	30.3 ± 4.6		72.2 ± 4.8	115.6 ± 8.0	43.3 ± 5.9	?§
Stroke Volume, mL	64.7 ± 5.7	24.3 ± 2.6	-40.5 ± 5.6	¶	58.3 ± 5.5	25.4 ± 3.5	-32.9 ± 4.1	
Cardiac Output, L/min	3.8 ± 0.4	2.1 ± 0.2	-1.7 ± 0.3		4.3 ± 0.5	3.0 ± 0.4	-1.3 ± 0.3	
Total Peripheral Resistance, mmHg/L/min	23.6 ± 3.0	32.7 ± 2.0	9.2 ± 2.6		22.5 ± 2.6	34.4 ± 4.1	11.9 ± 2.5	

Countermeasure: Mean ± SEM								
	Kentavr (n=10)				Anti-g Suit (n=9)			
	Supine	Standing	Delta	P	Supine	Standing	Delta	P
Systolic Pressure, mmHg	110.9 ± 3.8	112.7 ± 4.8	1.8 ± 3.3	†	117.8 ± 4.6	125.6 ± 5.8	7.8 ± 4.2	*
Diastolic Pressure, mmHg	69.0 ± 2.8	69.9 ± 3.3	0.9 ± 3.0		74.7 ± 3.3	75.6 ± 2.9	0.9 ± 2.1	
Heart Rate, beats/min	61.6 ± 3.0	77.7 ± 3.7	16.1 ± 1.7	§	65.0 ± 2.2	80.2 ± 3.0	15.2 ± 2.6	?
Stroke Volume, mL	60.6 ± 4.7	34.6 ± 2.0	-26.0 ± 3.8		55.8 ± 2.9	34.7 ± 2.7	-21.1 ± 2.8	¶
Cardiac Output, L/min	3.7 ± 0.2	2.7 ± 0.1	-1.0 ± 0.2		3.7 ± 0.2	2.8 ± 0.2	-0.9 ± 0.1	
Total Peripheral Resistance, mmHg/L/min	22.7 ± 1.4	32.0 ± 1.8	9.2 ± 2.1		24.7 ± 1.6	34.8 ± 2.9	10.0 ± 2.2	

One-Way ANOVA with pairwise comparisons by Holm-Sidak method. *P < 0.001, Presyncopal Delta vs. AGS Delta; †P < 0.001, Kentavr Delta vs. Presyncopal Delta; ‡P < 0.001, Nonpresyncopal Delta vs. Presyncopal Delta; ?P < 0.001, Nonpresyncopal Delta vs. AGS Delta; §P < 0.001, Nonpresyncopal Delta vs. Kentavr Delta; ¶P = 0.003, Nonpresyncopal Delta vs. AGS Delta.

At termination of the tilt test, the mean systolic blood pressure of presyncopal control subjects was 31.8 ± 7.3 mmHg lower than baseline conditions (Table 9-3). In contrast, the Kentavr subjects' mean systolic blood pressure was 1.8 ± 3.3 mmHg higher than baseline, and the AGS subjects' mean systolic blood pressure was 7.8 ± 4.2 mmHg higher than baseline. The decrease in systolic blood pressure of presyncopal control subjects was statistically significant as compared to the other groups ($P < 0.001$). However, the difference in systolic blood pressure between Kentavr, AGS and non-presyncopal control subjects was not statistically significant.

The Kentavr and AGS reduced tachycardia experienced by control subjects during the tilt test (Table 9-3). Presyncopal control subjects' heart rate increased 30.3 ± 4.6 beats/min during the tilt test, while non-presyncopal control subjects' increased 43.3 ± 5.9 beats/min. In contrast, Kentavr subjects' heart rate increased 16.1 ± 1.7 beats/min, and AGS subjects' heart rate increased 15.2 ± 2.6 beats/min. The heart rate of non-presyncopal control subjects was significantly higher than those wearing either type of anti-gravity suit ($P < 0.001$). The heart rates of Kentavr and AGS subjects were not significantly different.

The anti-gravity suits (Figure 9-29) also helped to maintain stroke volume as compared to control subjects (Table 9-3). Stroke volume decreased by 40.5 ± 5.6 ml in presyncopal control subjects and by 32.9 ± 4.1 ml in non-presyncopal control subjects. Stroke volume only decreased by 21.1 ± 2.8 ml in AGS subjects and by 26 ± 3.8 ml in Kentavr subjects. The difference in stroke volume between AGS and presyncopal subjects was statistically significant ($P = 0.003$). In addition, the stroke volume of Kentavr and AGS subjects was significantly higher than non-presyncopal control subjects over the duration of the tilt test ($P < 0.001$). There was no significant difference in stroke volume between Kentavr and AGS subjects ($P = 0.267$). Based on the testing conditions in this study, there were no significant differences between the effectiveness of the Kentavr and the AGS in preventing orthostatic intolerance.

Both suits are mechanical countermeasures that provide compression of capacitance vessels, thereby promoting venous return. However, there are some operational differences between the suits. One

Figure 9-29. Anti-gravity suits. The US antigravity suit (left) contains bladders which are pressurized to produce compression. The Russian antigravity suit (right) utilizes a compressive material and lacings to produce compression.

advantage of the AGS is that the pressure can easily be adjusted by the crewmember in increments of 0.5 psid (25.9 mmHg); the recommended pressure for re-entry is 1.5 psid (77.7 mmHg). A disadvantage of the AGS is that it must be connected to a pressure source to maintain compression. Once it is disconnected so that astronauts can egress the vehicle, the suit deflates as the subject moves. In addition, some crewmembers find the high pressure over the lower



abdomen uncomfortable. The Kentavr is a non-inflatable elastic garment (nominal compression ~30 mmHg) that maintains protection after egress. In fact, cosmonauts often continue to wear the Kentavr for several days after landing. However, one disadvantage of the Kentavr is that uncovered areas of the body (for example, knees, feet and groin) tend to swell uncomfortably if the garment is worn for an extended period of time. It also requires extensive crew time and effort to don and adjust the Kentavr. Neither garment is ideal; thus, current laboratory research at Johnson Space Center includes evaluation of Jobst compression stockings (in collaboration with the Constellation Program and Medical Operations). One crewmember wore similar, commercial compression stockings during the Apollo 16 landing and reported moderate protection from orthostatic intolerance (3). However, they were

difficult to don due to the extremely limited space in the Apollo capsule. No other flight testing has been documented. These stockings are more comfortable, much less expensive and are available in a variety of compressive profiles to allow for an individualized prescription.

VIII. Risk in Context of Exploration Mission Operational Scenarios

The principal risk of orthostatic intolerance is the inability of a crewmember to complete mission tasks that require extended periods of standing immediately upon landing. For lunar habitation missions, it has not been established what the long term effects of exposure to 1/6 G have been; thus, it is unknown whether orthostatic intolerance increases over time or if the lunar environment is protective against orthostatic intolerance. A secondary risk is the inability of crewmembers to effectively emergency egress from the vehicle in the event of an off-nominal landing. This is particularly true for long duration crewmembers. Furthermore, post-mission crew health can be impacted by orthostatic intolerance. Several instances of post-spaceflight orthostatic intolerance have been documented. For example, one crewmember twice became presyncopal at a podium during a postflight press conference and there have been several instances of crewmembers becoming presyncopal during postflight showers, meals and social events.

IX. Gaps

Orthostatic intolerance is still a potential hazard.

This remains an issue for ISS and other long duration flights. It is an egress issue and a mission performance issue. It is not known if exposure to 1/6 G and 3/8 G will cause

orthostatic intolerance or will have mitigating/protective effects on orthostatic intolerance upon return to 1 G.

Is 1/6 G exposure protective of 1 G orthostatic tolerance?

It is unknown if long term exposure to 1/6 G will protect the human body from the deconditioning seen during microgravity. This gap requires ground-based study and is being addressed by the Lunar Analog Project.

In-flight fluid distribution is not known.

Alterations in fluid distribution may affect drug distribution and this aspect of the gap should be pursued.

X. Conclusions

Postflight orthostatic intolerance is prominent in astronauts after long duration spaceflight and, though at a lesser degree, is present after short duration spaceflight. Its convoluted etiology has prevented the implementation of a fully successful countermeasure and motivates the need for new countermeasures such as midodrine. Plasma volume losses, female gender and cardiovascular deconditioning increase the risk for orthostatic intolerance, where the main risk is thought to be a hypoadrenergic response to the upright posture after spaceflight. Ground-based simulated microgravity studies and computer simulations provide additional information on the time course of cardiovascular deconditioning and causes of orthostatic intolerance. The main concern of post-spaceflight orthostatic intolerance is in the case of a non-nominal landing, where egress from the spacecraft would be impeded. In addition, it is unknown if long term exposure to partial gravity environments, such as the Moon or Mars, is protective against the cardiovascular effects of microgravity or if orthostatic intolerance will remain a risk in such missions.

XI. References

- (1) Purdy RE, Meck JV. Endothelium in Space. In: Aird WC, editor. *Endothelial Biomedicine*. New York: Cambridge University Press, 2007: 520-526.
- (2) Fortney SM. Development of lower body negative pressure as a countermeasure for orthostatic intolerance. *J Clin Pharmacol* 1991; 31:888-892.
- (3) Hoffler G.W., Johnson RL. Apollo Flight Crew Cardiovascular Evaluations. In: Johnston RS, Dietlein LF, Berry CA, editors. *Biomedical Results of Apollo*. Washington, D.C.: Scientific and Technical Office National Aeronautics and Space Administration, 1975: 227-264.
- (4) Thornton WE, Hoffler G.W., Rummel JA. Anthropometric Changes and Fluid Shifts. In: Johnston RS, Dietlein LF, editors. *Biomedical Results From Skylab*. Washington, D.C.: Scientific and Technical Office National Aeronautics and Space Administration, 1977: 330-338.
- (5) Meck JV, Reyes CJ, Perez SA, Goldberger AL, Ziegler MG. Marked exacerbation of orthostatic intolerance after long- vs. short-duration spaceflight in veteran astronauts. *Psychosom Med* 2001; 63(6):865-873.
- (6) Bungo MW, Charles JB, Johnson PC, Jr. Cardiovascular deconditioning during spaceflight and the use of saline as a countermeasure to orthostatic intolerance. *Aviat Space Environ Med* 1985; 56(10):985-990.
- (7) Charles JB, Fritsch-Yelle JM, Whitson PA, Wood ML, Brown TE, Fortner GW. Cardiovascular Deconditioning. In: Sawin CF, Taylor GR, Smith WL, editors. *Extended Duration Orbiter Medical Project: Final Report (1989 - 1995)*. National Aeronautics and Space Administration, 1999: 1-1-1-19.
- (8) Fritsch-Yelle JM, Whitson PA, Bondar RL, Brown TE. Subnormal norepinephrine release relates to presyncope in astronauts after spaceflight. *J Appl Physiol* 1996; 81(5):2134-2141.
- (9) Waters WW, Ziegler MG, Meck JV. Postspaceflight orthostatic hypotension occurs mostly in women and is predicted by low vascular resistance. *J Appl Physiol* 2002; 92:586-594.
- (10) Zhang LF. Vascular adaptation to microgravity: what have we learned? *J Appl Physiol* 2001; 91(6):2415-2430.
- (11) Platts SH, Ziegler MG, Waters WW, Mitchell BM, Meck JV. Midodrine prescribed to improve recurrent post-spaceflight orthostatic hypotension. *Aviat Space Environ Med* 2004; 75(6):554-556.
- (12) Pavy-Le Traon A, Heer M, Narici MV, Rittweger J, Vernikos J. From space to Earth: advances in human physiology from 20 years of bed rest studies (1986-2006). *Eur J Appl Physiol* 2007; 101(2):143-194.

- (13) Grenon SM, Xiao X, Hurwitz S, Sheynberg N, Kim C, Seely EW et al. Why is orthostatic tolerance lower in women than in men? Renal and cardiovascular responses to simulated microgravity and the role of midodrine. *J Investig Med* 2006; 54(4):180-190.
- (14) Meck JV, Waters WW, Ziegler MG, deBlock HF, Mills PJ, Robertson D et al. Mechanisms of postspaceflight orthostatic hypotension: low alpha1-adrenergic receptor responses before flight and central autonomic dysregulation postflight. *Am J Physiol Heart Circ Physiol* 2004; 286(4):H1486-H1495.
- (15) Goldstein DS, Pechnik S, Holmes C, Eldadah B, Sharabi Y. Association between supine hypertension and orthostatic hypotension in autonomic failure. *Hypertension* 2003; 42(2):136-142.
- (16) Jacob G, Robertson D, Mosqueda-Garcia R, Ertl AC, Roberston RM, Biaggioni I. Hypovolemia in syncope and orthostatic intolerance role of the renin-angiotensin system. *Am J Med* 1997; 103(2):128-133.
- (17) Levine BD, Zuckerman JH, Pawelczyk JA. Cardiac atrophy after bed-rest deconditioning: a non-neural mechanism for orthostatic intolerance. *Circulation* 1997; 96(2):517-525.
- (18) Perhonen MA, Franco F, Lane LD, Buckey JC, Blomqvist CG, Zerwekh JE et al. Cardiac atrophy after bed rest and spaceflight. *J Appl Physiol* 2001; 91(2):645-653.
- (19) Levine BD, Buckey JC, Fritsch JM, Yancy CW, Jr., Watenpaugh DE, Snell PG et al. Physical fitness and cardiovascular regulation: mechanisms of orthostatic intolerance. *J Appl Physiol* 1991; 70:112-122.
- (20) Robertson D, Convertino VA, Vernikos J. The sympathetic nervous system and the physiologic consequences of spaceflight: a hypothesis. *Am J Med Sci* 1994; 308(2):126-132.
- (21) Buckey JC, Jr., Lane LD, Levine BD, Watenpaugh DE, Wright SJ, Moore WE et al. Orthostatic intolerance after spaceflight. *J Appl Physiol* 1996; 81(1):7-18.
- (22) Convertino VA, Doerr DF, Eckberg DL, Fritsch JM, Vernikos-Danellis J. Head-down bed rest impairs vagal baroreflex responses and provokes orthostatic hypotension. *J Appl Physiol* 1990; 68:1458-1464.
- (23) Convertino VA, Doerr DF, Ludwig DA, Vernikos J. Effect of simulated microgravity on cardiopulmonary baroreflex control of forearm vascular resistance. *Am J Physiol* 1994; 266(6 Pt 2):R1962-R1969.
- (24) Crandall CG, Engelke KA, Convertino VA, Raven PB. Aortic baroflex control of heart rate following 15 days of simulated microgravity exposure. *J Appl Physiol* 1994; 77(5):2134-2139.
- (25) Eckberg DL, Fritsch JM. Influence of ten-day head-down bed rest on human carotid baroreceptor-cardiac reflex function. *Acta Physiol Scand* 1992; 144,S604:69-76.
- (26) Fritsch-Yelle JM, Charles JB, Jones MM, Beightol LA, Eckberg DL. Spaceflight alters autonomic regulation of arterial pressure in humans. *J Appl Physiol* 1994; 77(4):1776-1783.

- (27) Fritsch JM, Charles JB, Bennett BS, Jones MM, Eckberg DL. Short-duration spaceflight impairs human carotid baroreceptor- cardiac reflex responses. *J Appl Physiol* 1992; 73(2):664-671.
- (28) Hughson RL, Maillet A, Gharib C, Fortrat JO, Yamamoto Y, Pavy-Letraon A et al. Reduced spontaneous baroreflex response slope during lower body negative pressure after 28 days of head-down bed rest. *J Appl Physiol* 1994; 77(1):69-77.
- (29) Iwasaki K, Zhang R, Perhonen MA, Zuckerman JH, Levine BD. Reduced baroreflex control of heart period after bed rest is normalized by acute plasma volume restoration. *Am J Physiol Regul Integr Comp Physiol* 2004; 287(5):R1256-R1262.
- (30) Iwasaki KI, Zhang R, Zuckerman JH, Pawelczyk JA, Levine BD. Effect of head-down-tilt bed rest and hypovolemia on dynamic regulation of heart rate and blood pressure. *Am J Physiol Regul Integr Comp Physiol* 2000; 279(6):R2189-R2199.
- (31) Bergman SA, Jr., Johnson RL. Evaluation of the Electromechanical Properties of the Cardiovascular System After Prolonged Weightlessness. *Biomedical Results From Skylab*. Washington, D.C.: Scientific and Technical Office National Aeronautics and Space Administration, 1977: 351-365.
- (32) Johnson RL, Hoffler G.W., Nicogossian AE, Bergman SA, Jr., Jackson MM. Lower Body Negative Pressure: Third Manned Skylab Mission. In: Johnston RS, Dietlein LF, editors. *Biomedical Results From Skylab*. Washington, D.C.: Scientific and Technical Office National Aeronautics and Space Administration, 1977: 284-312.
- (33) Henry WL, Epstein SE, Griffith JM, Goldstein RE, Redwood DR. Effect of Prolonged Spaceflight on Cardiac Function and Dimensions. In: Johnston RS, Dietlein LF, editors. *Biomedical Results From Skylab*. Washington, D.C.: Scientific and Technical Office National Aeronautics and Space Administration, 1977: 366-371.
- (34) Buckey JC, Jr., Lane LD, Levine BD, Watenpaugh DE, Wright SJ, Moore WE et al. Orthostatic intolerance after spaceflight. *J Appl Physiol* 1996; 81(1):7-18.
- (35) Martin DS, Meck JV. Presyncopal/non-presyncopal outcomes of post spaceflight stand tests are consistent from flight to flight. *Aviat Space Environ Med* 2004; 75(1):65-67.
- (36) Leach CS, Alexander WC, Johnson PC. Endocrine, Electrolyte, and Fluid Volume Changes Associated with Apollo Missions. In: Johnston RS, Dietlein LF, Berry CA, editors. *Biomedical Results of Apollo*. Washington, D.C.: Scientific and Technical Office National Aeronautics and Space Administration, 1975: 163-184.
- (37) Johnson PC, Driscoll T, Leblanc AD. Blood Volume Changes. In: Johnston RS, Dietlein LF, editors. *Biomedical Results From Skylab*. Washington D.C.: Scientific and Technical Office National Aeronautics and Space Administration, 1977: 235-241.
- (38) Leach CS, Alfrey CP, Suki WN, Leonard JI, Rambaut PC, Inners LD et al. Regulation of body fluid compartments during short-term spaceflight. *J Appl Physiol* 1996; 81(1):105-116.
- (39) Norsk P. Cardiovascular and Fluid Volume Control in Humans in Space. *Current Pharmaceutical Biotechnology* 2005; 6(4):325-330.

- (40) Leach CS, Inners LD, Charles JB. Changes in total body water during spaceflight. *J Clin Pharmacol* 1991; 31(10):1001-1006.
- (41) Greenisen MC, Hayes JC, Siconolfi SF, Moore AD. Functional Performance Evaluation. In: Sawin CF, Taylor GR, Smith ML, editors. *Extended Duration Orbiter Medical Project: Final Report (1989 - 1995)*. National Aeronautics and Space Administration, 1999: 3-1-3-24.
- (42) Trappe T, Trappe S, Lee G, Widrick J, Fitts R, Costill D. Cardiorespiratory responses to physical work during and following 17 days of bed rest and spaceflight. *J Appl Physiol* 2006; 100(3):951-957.
- (43) Meck JDSWL. Multisystem Responses to Long-Duration Bed Rest: Overview. *Aviat Space Environ Med*. In press.
- (44) Levine BD, Pawelczyk JA, Ertl AC, Cox JF, Zuckerman JH, Diedrich A et al. Human muscle sympathetic neural and haemodynamic responses to tilt following spaceflight. *J Physiol* 2002; 538(Pt 1):331-340.
- (45) Harm DL, Jennings RT, Meck JV, Powell MR, Putchala L, Sams CP et al. Invited review: gender issues related to spaceflight: a NASA perspective. *J Appl Physiol* 2001; 91(5):2374-2383.
- (46) Grenon SM, Xiao X, Hurwitz S, Sheynberg N, Kim C, Seely EW et al. Why is orthostatic tolerance lower in women than in men? Renal and cardiovascular responses to simulated microgravity and the role of midodrine. *J Investig Med* 2006; 54(4):180-190.
- (47) Fu Q, Arbab-Zadeh A, Perhonen MA, Zhang R, Zuckerman JH, Levine BD. Hemodynamics of orthostatic intolerance: implications for gender differences. *Am J Physiol Heart Circ Physiol* 2004; 286(1):H449-H457.
- (48) Gotshall RW, Tsai P-F, Frey MAB. Gender-based differences in the cardiovascular response to standing. *Aviat Space Environ Med* 1991; 62:855-859.
- (49) Montgomery LD, Kirk PJ, Payne PA, Gerber RL, Newton SD, Williams BA. Cardiovascular responses of men and women to lower body negative pressure. *Aviat Space Environ Med* 1977; 48(2):138-145.
- (50) Shoemaker JK, Hogeman CS, Khan M, Kimmerly DS, Sinoway LI. Gender affects sympathetic and hemodynamic response to postural stress. *Am J Physiol Heart Circ Physiol* 2001;(281):H2028-H2035.
- (51) White DD, Gotshall RW, Tucker A. Women have lower tolerance to lower body negative pressure than men. *J Appl Physiol* 1996; 80(4):1138-1143.
- (52) Collins A, Frankenhaeuser M. Stress responses in male and female engineering students. *J Human Stress* 1978;43-48.
- (53) Schondorf R, Low PA. Gender related differences in the cardiovascular responses to upright tilt in normal subjects. *Clin Auto Res* 1992; 2:183-187.
- (54) Abdel-Rahman ARA, Merrill RH, Wooles WR. Gender-related differences in the baroreceptor reflex control of heart rate in normotensive humans. *J Appl Physiol* 1994; 77(2):606-613.

- (55) Girdler SS, Hinderliter AL, Light KC. Peripheral adrenergic receptor contributions to cardiovascular reactivity: Influence of race and gender. *J Psychosomatic Research* 1993; 37(2):177-193.
- (56) Hunt BE, Taylor JA, Hamner JW, Gagnon M, Lipsitz LA. Estrogen replacement therapy improves baroreflex regulation of vascular sympathetic outflow in postmenopausal women. *Circulation* 2001; 103(24):2909-2914.
- (57) Vongpatanasin W, Tuncel M, Mansour Y, Arbique D, Victor RG. Transdermal estrogen replacement therapy decreases sympathetic activity in postmenopausal women. *Circulation* 2001; 103(24):2903-2908.
- (58) Frey MAB, Hoffler GW. Association of sex and age with responses to lower-body negative pressure. *J Appl Physiol* 1988; 65(4):1752-1756.
- (59) Frey MAB, Tomaselli CM, Hoffler WG. Cardiovascular responses to postural changes: Differences with age for women and men. *J Clin Pharmacol* 1994; 34:394-402.
- (60) Kilgour RD, Carvalho J. Gender differences in cardiovascular responses to the cold hand pressor test and facial cooling. *Can J Physiol Pharmacol* 1994; 72:1193-1199.
- (61) McAdoo WG, Weinberger MH, Miller JZ, Fineberg NS, Grim CE. Race and gender influence hemodynamic responses to psychological and physical stimuli. *J Hypertens* 1990; 8(10):961-967.
- (62) Arora S, Veves A, Caballero AE, Smakowski P, LoGerfo FW. Estrogen improves endothelial function. *J Vasc Surg* 1998; 27(6):1141-1146.
- (63) Gilligan DM, Badar DM, Panza JA, Quyyumi AA, Cannon RO, III. Effects of estrogen replacement therapy on peripheral vasomotor function in postmenopausal women. *Am J Cardiol* 1995; 75:264-268.
- (64) Guetta V, Quyyumi AA, Prasad A, Panza JA, Waclawiw M, Cannon RO. The role of nitric oxide in coronary vascular effects of estrogen in postmenopausal women. *Circulation* 1997; 96:2795-2801.
- (65) Lieberman EH, Gerhard MD, Uehata A, Walsh BW, Selwyn AP, Ganz P et al. Estrogen improves endothelium-dependent, flow-mediated vasodilation in postmenopausal women. *Ann Intern Med* 1994; 121(12):936-941.
- (66) Tagawa H, Shimokawa H, Tagawa T, Kuroiwa-Matsumoto M, Hirooka Y, Takeshita A. Short-term estrogen augments both nitric oxide-mediated and non-nitric oxide-mediated endothelium-dependent forearm vasodilation in postmenopausal women. *J Cardiovasc Pharmacol* 1997; 30:481-488.
- (67) Jarvis SS, Florian JP, Curren MJ, Pawelczyk JA. Sex Differences in Splanchnic Hemodynamics during 70 degrees Head-Up Tilt. *Medicine and Science in Sports and Exercise* 2006; 38(11):S4.
- (68) Fu Q, Witkowski S, Okazaki K, Levine BD. Effects of gender and hypovolemia on sympathetic neural responses to orthostatic stress. *Am J Physiol Regul Integr Comp Physiol* 2005; 289(1):R109-R116.

- (69) Shibao C, Grijalva CG, Raj SR, Biaggioni I, Griffin MR. Orthostatic hypotension-related hospitalizations in the United States. *Am J Med* 2007; 120(11):975-980.
- (70) Platts SH, Shi SJ, Meck JV. Akathisia with combined use of midodrine and promethazine. *J Am Med Assoc* 2006; 295(17):2000-2001.
- (71) Kimmerly DS, Shoemaker JK. Hypovolemia and neurovascular control during orthostatic stress. *Am J Physiol Heart Circ Physiol* 2002; 282(2):H645-H655.
- (72) Kimmerly DS, Shoemaker JK. Hypovolemia and MSNA discharge patterns: assessing and interpreting sympathetic responses. *Am J Physiol Heart Circ Physiol* 2003; 284(4):H1198-H1204.
- (73) Waters WW, Ziegler MG, Meck JV. Post-spaceflight orthostatic hypotension occurs mostly in women and is predicted by low vascular resistance. *J Appl Physiol* 2002; 92:586-594.
- (74) Shoemaker JK, Hogeman CS, Sinoway LI. Contributions of MSNA and stroke volume to orthostatic intolerance following bed rest. *Am J Physiol* 1999; 277(4 Pt 2):R1084-R1090.
- (75) Arbeille P, Fomina G, Roumy J, Alferova I, Tobal N, Herault S. Adaptation of the left heart, cerebral and femoral arteries, and jugular and femoral veins during short- and long-term head-down tilt and spaceflights. *Eur J Appl Physiol* 2001; 86(2):157-168.
- (76) Waters WW, Platts SH, Mitchell BM, Whitson PA, Meck JV. Plasma volume restoration with salt tablets and water after bed rest prevents orthostatic hypotension and changes in supine hemodynamic and endocrine variables. *Am J Physiol Heart Circ Physiol* 2005; 288(2):H839-H847.
- (77) Kamiya A, Iwase S, Kitazawa H, Mano T, Vinogradova OL, Kharchenko IB. Baroreflex control of muscle sympathetic nerve activity after 120 days of 6 degrees head-down bed rest. *Am J Physiol Regul Integr Comp Physiol* 2000; 278(2):R445-R452.
- (78) Kamiya A, Michikami D, Fu Q, Iwase S, Hayano J, Kawada T et al. Pathophysiology of orthostatic hypotension after bed rest: paradoxical sympathetic withdrawal. *Am J Physiol Heart Circ Physiol* 2003; 285(3):H1158-H1167.
- (79) Pawelczyk JA, Zuckerman JH, Blomqvist CG, Levine BD. Regulation of muscle sympathetic nerve activity after bed rest deconditioning. *Am J Physiol Heart Circ Physiol* 2001; 280(5):H2230-H2239.
- (80) Bonnin P, Ben Driss A, Benessiano J, Maillet A, Pavy LT, Levy BI. Enhanced flow-dependent vasodilatation after bed rest, a possible mechanism for orthostatic intolerance in humans. *Eur J Appl Physiol* 2001; 85(5):420-426.
- (81) Bleeker MW, De Groot PC, Pawelczyk JA, Hopman MT, Levine BD. Effects of 18 days of bed rest on leg and arm venous properties. *J Appl Physiol* 2004; 96(3):840-847.
- (82) Morey-Holton ER, Globus RK. Hindlimb unloading rodent model: technical aspects. *J Appl Physiol* 2002; 92(4):1367-1377.
- (83) Morey-Holton ER, Globus RK, Kaplansky A, Durnova G. The hindlimb unloading rat model: literature overview, technique update and comparison with spaceflight data. In:

- Sonnenfeld G, editor. Experimentation with animal models in Space. Elsevier B.V., 2005: 7-40.
- (84) Socci RR, Wang M, Thierry-Palmer M, Emmett N, Bayorh MA. Cardiovascular responses to simulated microgravity in Sprague-Dawley rats. *Clin Exp Hypertens* 2000; 22(2):155-164.
- (85) Hasser EM, Moffitt JA. Regulation of sympathetic nervous system function after cardiovascular deconditioning. *Ann N Y Acad Sci* 2001; 940:454-468.
- (86) Foley CM, Mueller PJ, Hasser EM, Heesch CM. Hindlimb unloading and female gender attenuate baroreflex-mediated sympathoexcitation. *Am J Physiol Regul Integr Comp Physiol* 2005; 289(5):R1440-R1447.
- (87) Delp MD, Colleran PN, Wilkerson MK, McCurdy MR, Muller-Delp J. Structural and functional remodeling of skeletal muscle microvasculature is induced by simulated microgravity. *Am J Physiol Heart Circ Physiol* 2000; 278(6):H1866-H1873.
- (88) Platts SH, Martin DS, Perez SA, Ribeiro LC, Meck JV. Cardiovascular Adaptations to Long Duration Head-Down Tilt Bed Rest. In press.
- (89) Ma J, Kahwaji CI, Ni Z, Vaziri ND, Purdy RE. Effects of simulated microgravity on arterial nitric oxide synthase and nitrate and nitrite content. *J Appl Physiol* 2003; 94(1):83-92.
- (90) Woodman CR, Schrage WG, Rush JW, Ray CA, Price EM, Hasser EM et al. Hindlimb unweighting decreases endothelium-dependent dilation and eNOS expression in soleus not gastrocnemius. *J Appl Physiol* 2001; 91(3):1091-1098.
- (91) Convertino VA, Cooke WH. Vascular functions in humans following cardiovascular adaptations to spaceflight. *Acta Astronautica* 2007; 60(4-7):259-266.
- (92) Norsk P, Damgaard M, Petersen L, Gybel M, Pump B, Gabrielsen A et al. Vasorelaxation in space. *Hypertension* 2006; 47(1):69-73.
- (93) Summers RL, Coleman TG, Meck JV. Development of the Digital Astronaut Program for the analysis of the 3 mechanisms of physiologic adaptation to microgravity: Validation of the cardiovascular system module. *Acta Astronaut.* In press.
- (94) Summers RL, Coleman TG. Computer systems analysis of the cardiovascular mechanisms of reentry orthostasis in astronauts. *Comput Cardiol* 2002; 29:521-524.
- (95) Louisy F, Guezennec CY, Guell A. Leg vein hemodynamics during bed rests simulating lunar trip. *J Gravit Physiol* 1994; 1(1):100-101.
- (96) Pavy-Le Traon A, Allevard AM, Fortrat JO, Vasseur P, Gauquelin G, Guell A et al. Cardiovascular and hormonal changes induced by a simulation of a lunar mission. *Aviat Space Environ Med* 1997; 68(9 Pt 1):829-837.
- (97) Lathers CM, Diamandis PH, Riddle JM, Mukai C, Elton KF, Bungo MW et al. Acute and intermediate cardiovascular responses to zero gravity and to fractional gravity levels induced by head-down or head-up tilt. *J Clin Pharmacol* 1990; 30(6):494-523.

- (98) Lathers CM, Diamandis PH, Riddle JM, Mukai C, Elton KF, Bungo MW et al. Orthostatic function during a stand test before and after head- up or head-down bed rest. *J Clin Pharmacol* 1991; 31(10):893-903.
- (99) Lathers CM, Riddle JM, Mulvagh SL, Mukai C, Diamandis PH, Dussack L et al. Echocardiograms during six hours of bed rest at head-down and head-up tilt and during spaceflight. *J Clin Pharmacol* 1993; 33(6):535-543.
- (100) White PD, Nyberg JW, Finney L.M., White W.J. Influence of periodic centrifugation on cardiovascular functions of man during bed rest. Douglas Aircraft, co, Inc, Report *DAC-59286* . 1966. Santa Monica, CA.
- (101) Vernikos J. Artificial gravity intermittent centrifugation as a spaceflight countermeasure. *J Gravit Physiol* 1997; 4(2):13-16.
- (102) Hastreiter D, Young LR. Effects of a gravity gradient on human cardiovascular responses. *J Gravit Physiol* 1997; 4(2):23-26.
- (103) Korolkov VI, Kozlovskaya IB, Kotovskaya AR, Krotov VP, Vil-Viliams IF, Lobachik VI. Efficacy of periodic centrifugation of primates during 4-week head-down tilt. *Acta Astronaut* 2001; 49(3-10):237-242.
- (104) Iwasaki KI, Sasaki T, Hirayanagi K, Yajima K. Usefulness of daily +2Gz load as a countermeasure against physiological problems during weightlessness. *Acta Astronaut* 2001; 49(3-10):227-235.
- (105) Katayama K, Sato K, Akima H, Ishida K, Takada H, Watanabe Y et al. Acceleration with exercise during head-down bed rest preserves upright exercise responses. *Aviat Space Environ Med* 2004; 75(12):1029-1035.
- (106) Vil-Viliams IF. Principle approaches to selection of the short-arm centrifuge regimens for extended spaceflight. *Acta Astronaut* 1994; 33:221-229.
- (107) Charles JB, Lathers CM. Summary of lower body negative pressure experiments during spaceflight. *J Clin Pharmacol* 1994; 34:571-583.
- (108) Guell A, Cornac A, Faurat MM, Gauquelin G, Pavy-Le Traon A, Gharib C. Lower body negative pressure as a countermeasure against orthostatic intolerance for long term spaceflight. *Acta Astronaut* 1992; 27:103-107.
- (109) Guell A, Braak L, Pavy LT, Gharib C. Cardiovascular deconditioning during weightlessness simulation and the use of lower body negative pressure as a countermeasure to orthostatic intolerance. *Acta Astronaut* 1990; 21(9):667-672.
- (110) Arbeille P, Gauquelin G, Pottier JM, Pourcelot L, Guell A, Gharib C. Results of a 4-week head-down tilt with and without LBNP countermeasure: II. Cardiac and peripheral hemodynamics--comparison with a 25-day spaceflight. *Aviat Space Environ Med* 1992; 63(1):9-13.
- (111) Guell A, Braak L, Pavy LT, Gharib C. Cardiovascular deconditioning during weightlessness simulation and the use of lower body negative pressure as a countermeasure to orthostatic intolerance. *Acta Astronaut* 1990; 21(9):667-672.

- (112) Guell A, Cornac A, Faurat MM, Gauquelin G, Pavy-Le Traon A, Gharib C. Lower body negative pressure as a countermeasure against orthostatic intolerance for long term spaceflight. *Acta Astronaut* 1992; 27:103-107.
- (113) Hyatt KH, West DA. Reversal of bed rest-induced orthostatic intolerance by lower body negative pressure and saline. *Aviat Space Environ Med* 1977; 48(2):120-124.
- (114) Schneider SM, Watenpaugh DE, Lee SM, Ertl AC, Williams WJ, Ballard RE et al. Lower-body negative-pressure exercise and bed-rest-mediated orthostatic intolerance. *Med Sci Sports Exerc* 2002; 34(9):1446-1453.
- (115) Watenpaugh DE, O'Leary DD, Schneider SM, Lee SM, Macias BR, Tanaka K et al. Lower body negative pressure exercise plus brief postexercise lower body negative pressure improve post-bed rest orthostatic tolerance. *J Appl Physiol* 2007; 103(6):1964-1972.
- (116) Shi SJ, South DA, Meck JV. Fludrocortisone does not prevent orthostatic hypotension in astronauts after spaceflight. *Aviat Space Environ Med* 2004; 75(3):235-239.
- (117) McTavish D, Goa KL. Midodrine. A review of its pharmacological properties and therapeutic use in orthostatic hypotension and secondary hypotensive disorders. *Drugs* 1989; 38(5):757-777.
- (118) Low PA, Gilden JL, Freeman R, Sheng K-N, McElligott MA. Efficacy of midodrine vs placebo in neurogenic orthostatic hypotension. *J Am Med Assoc* 1997; 277(13):1046-1051.
- (119) Wright RA, Kaufmann HC, Perera R, Opfer-Gehrking TL, McElligott MA, Sheng KN et al. A double-blind, dose-response study of midodrine in neurogenic orthostatic hypotension. *Neurology* 1998; 51(1):120-124.
- (120) Ehringer H. [Study of human peripheral hemodynamics after i.v. infusion of a small dosage of dl-1-(2',5'-dimethoxyphenyl)-2-glycinamidoethanol-(1) hydrochloride (=st 1085)]. *Int Z Klin Pharmakol Ther Toxikol* 1971; 4(4):415-420.
- (121) Ramsdell CD, Mullen TJ, Sundby GH, Rostoft S, Sheynberg N, Aljuri N et al. Midodrine prevents orthostatic intolerance associated with simulated spaceflight. *J Appl Physiol* 2003; 90:2245-2248.
- (122) Akimoto M, Iida I, Itoga H, Miyata A, Kawahara S, Kohno Y. The in vitro metabolism of desglymidodrine, an active metabolite of prodrug midodrine by human liver microsomes. *Eur J Drug Metab Pharmacokinet* 2004; 29(3):179-186.
- (123) Hoeldtke RD, Horvath GG, Bryner KD, Hobbs GR. Treatment of orthostatic hypotension with midodrine and octreotide. *J Clin Endocrinol Metab* 1998; 83(2):339-343.
- (124) Hoeldtke RD, Davis KM, Joseph J, Gonzales R, Panidis IP, Friedman AC. Hemodynamic effects of octreotide in patients with autonomic neuropathy. *Circulation* 1991; 84(1):168-176.
- (125) Curtis SB, Hewitt J, Yakubovitz S, Anzarut A, Hsiang YN, Buchan AM. Somatostatin receptor subtype expression and function in human vascular tissue. *Am J Physiol Heart Circ Physiol* 2000; 278(6):H1815-H1822.

- (126) Hoeldtke RD, Dworkin GE, Gaspar SR, Israel BC. Sympathotonic orthostatic hypotension: a report of four cases. *Neurology* 1989; 39(1):34-40.
- (127) Tuxhorn JA, Waters WW, Ribeiro LC, Fortner GW, Platts SH, Meck JV. Evaluation and Comparison of the Kentavr and the Anti-G Suit as Countermeasures to Orthostatic Intolerance. Manuscript in preparation . 2006.

XII. Team

HOUSTON

Steven H. Platts, Ph.D., Head, Cardiovascular Laboratory and Discipline Team Lead, NASA,
Johnson Space Center

Michael Stenger, Ph.D., Cardiovascular Engineer, Wyle Labs, Johnson Space Center

Tiffany Phillips, B.S., Research Specialist, Wyle Labs, Johnson Space Center

Natalia Arzeno, M.Eng., Biomedical Engineer, Wyle Labs, Johnson Space Center

JACKSON

Richard Summers, MD, Ph.D., Professor Department of Physiology & Biophysics
and Division of Emergency Medicine University of Mississippi Medical Center, Jackson,
Mississippi

XIII. List of Acronyms

BP	Blood pressure
DBP	Diastolic blood pressure
EDOMP	Extended Duration Orbiter Medical Project
eNOS	Endothelial Nitric Oxide Synthase
FDA	Federal Drug Administration
HLU	Hind limb unloading
HR	Heart rate
KCl	Potassium chloride
LBNP	Lower Body Negative Pressure
MSNA	Muscle sympathetic nerve activity
NASA	National Aeronautics Space Administration
NO	Nitric oxide
PRD	Program Requirements Documents

Risk of Orthostatic Intolerance During Re-exposure to Gravity

SBP	Systolic blood pressure
SV	Stroke volume
TPR	Total peripheral resistance

XIV. Appendix 9-A – Development of the Digital Astronaut Program



PERGAMON



Acta Astronautica III (III) III-III



www.elsevier.com/locate/actaastro

1
2
3 Development of the Digital Astronaut Program for the analysis of the
mechanisms of physiologic adaptation to microgravity: Validation of
the cardiovascular system module

5 Richard Summers^{a,*}, Thomas Coleman^a, Janice Meck^b

^aUniversity of Mississippi Medical Center, 2500 North State Street, Jackson, MS, USA

7 ^bHuman Adaptation and Countermeasures Office, Space and Life Sciences Directorate, National Aeronautics and Space Administration
Johnson Space Center, Houston, TX, USA

9 Received 15 May 2007; received in revised form 24 November 2007; accepted 22 December 2007

Abstract

11 The physiologic adaptation of humans to the microgravity environment is complex and requires an integrative perspective
to fully understand the mechanisms involved. A large computer model of human systems physiology provides the framework
13 for the development of the Digital Astronaut to be used by NASA in the analysis of adaptive mechanisms. While project
expansion is ongoing to include all relevant systems, we describe the validation results of the cardiovascular phase of model
15 development. The cardiovascular aspects of the model were validated by benchmark comparisons to published literature findings
of changes in left ventricular mass, right atrial pressure and plasma volumes. Computer simulations using the model predicted
17 microgravity induced changes in the target endpoints within statistical validity of experimental findings. Therefore, the current
cardiovascular portion of the Digital Astronaut Program computer model appears to accurately predict observed microgravity
19 induced physiologic adaptations. The ongoing process of model development to include all spaceflight relevant systems will
require similar validations.

21 Published by Elsevier Ltd.

Keywords: Digital Astronaut; Validation; Computer model

23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308
309
310
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635
636
637
638
639
640
641
642
643
644
645
646
647
648
649
650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666
667
668
669
670
671
672
673
674
675
676
677
678
679
680
681
682
683
684
685
686
687
688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731
732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747
748
749
750
751
752
753
754
755
756
757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840
841
842
843
844
845
846
847
848
849
850
851
852
853
854
855
856
857
858
859
860
861
862
863
864
865
866
867
868
869
870
871
872
873
874
875
876
877
878
879
880
881
882
883
884
885
886
887
888
889
890
891
892
893
894
895
896
897
898
899
900
901
902
903
904
905
906
907
908
909
910
911
912
913
914
915
916
917
918
919
920
921
922
923
924
925
926
927
928
929
930
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945
946
947
948
949
950
951
952
953
954
955
956
957
958
959
960
961
962
963
964
965
966
967
968
969
970
971
972
973
974
975
976
977
978
979
980
981
982
983
984
985
986
987
988
989
990
991
992
993
994
995
996
997
998
999
1000

1. Introduction

The biomedical research programs conducted through NASA and its affiliates have produced a wealth of information regarding the effects of microgravity and spaceflight on human physiology. However, synthesizing this information into a generalized understanding of the physiologic mechanisms involved

has not been forthcoming. Furthermore, the use of this information to predict outcomes, effect appropriate countermeasures and monitor acclimatization has not been completely successful. When a system under study is complex, nonlinear or involves homeostatic feedback mechanisms, as is the case for human physiology in microgravity, it is imperative that the description and analyses must also reflect a high degree of sophistication [1–3]. Simple verbal descriptions of homeostatic biological systems can be inadequate because of the difference between the sequential nature of language and the simultaneous character of

* Corresponding author. Tel.: +1 601 984 5586;

fax: +1 601 984 5583.

E-mail address: rsummers@pol.net (R. Summers).

0094-5765/\$ - see front matter Published by Elsevier Ltd.

doi:10.1016/j.actaastro.2007.12.054

Please cite this article as: R. Summers, et al., Development of the Digital Astronaut Program for the analysis of the mechanisms of physiologic adaptation to microgravity: Validation of the cardiovascular system module Acta Astronautica (2008), doi: 10.1016/j.actaastro.2007.12.054

1 parallel biologic processes. Likewise, even detailed vi- 51
 2 sual models are unable to capture the dynamic qual- 52
 3 ity of physiologic systems analysis. Computer models 53
 4 and simulations are frequently used to study and pre- 54
 5 dict physical phenomena and to assist in the understand- 55
 6 ing of technological systems. Within the last 30 years, 56
 7 biomedical scientists have also begun to use computer 57
 8 models and simulations to study biological systems [4]. 58
 9 A similar approach is being implemented to study hu- 59
 10 man physiology during spaceflight. The NASA Digital 60
 11 Astronaut Program has experienced a progressive evo- 61
 12 lution over the past decade [5–7]. The general goal of 62
 13 the program has been to create a large, integrative math- 63
 14 ematical model of human physiology having features 64
 15 that are relevant to spaceflight. This also implies incor- 65
 16 porating the transitions between terrestrial gravity and 66
 17 microgravity as well as exposures to microgravity for 67
 18 up to very long periods of time. The purpose of the 68
 19 model is to assist in the development of microgravity 69
 20 countermeasures and to serve as a reflective platform for 70
 21 the prediction of physiologic adaptive mechanisms and 71
 22 potential pathologic conditions that might arise during 72
 23 long-term spaceflight.

24 While model expansion is ongoing to include all rel- 73
 25 evant systems, in this paper we describe the validation 74
 26 results of the cardiovascular phase of the Digital As- 75
 27 tronaut model development with respect to the selected 76
 28 primary endpoints. This cardiovascular portion of the 77
 29 Digital Astronaut model is a systemic circulatory model 78
 30 and comprises a fundamental part of the benchmark 79
 31 model that is to be used as a framework for integrating 80
 the larger Digital Astronaut Project.

2. Methods

32 The current Digital Astronaut model is a special adap- 81
 33 tation of an existing benchmark computer model (Guy- 82
 34 ton/Coleman/Summers model) developed by the inves- 83
 35 tigators over the past 30 years [8–10]. The benchmark 84
 36 model contains over 4000 variables of biologic inter- 85
 37 actions and encompasses a variety of physiologic pro- 86
 38 cesses of interest to humans during spaceflight includ- 87
 39 ing cardiovascular functioning and adaptation to micro- 88
 40 gravity, bone metabolism, neurohormonal adaptations 89
 41 to weightlessness, and general nutritional and metabolic 90
 42 mass balance. The process of model building is centered 91
 43 around the concept of a hierarchy of control in which re- 92
 44 lationships are constructed primarily on a foundation of 93
 45 first principles (i.e. mass balances, physical forces). The 94
 46 current Digital Astronaut model will serve as the frame- 95
 47 work for continued future model expansion to include 96
 48 a greater detail of many of the existing systems as well 97
 49 as the addition of other systems of interest. The model 98
 can be solved using common numerical methods on a 99
 variety of computing systems. The software interface

50 supporting the model is designed to provide for sim-
 51 ple interaction of the user through a desktop platform
 52 with current personal computing technology or with a
 53 mainframe. The model and software support system al-
 54 lows scientists to perform complex systems studies and
 55 theoretical hypothesis testing on specific research ques-
 56 tions surrounding human exposure to microgravity. The
 57 model structure is presently specified in compiled C++
 58 code but is being translated into XML in a component-
 59 based format (kidney, liver, circulation, etc) with a top
 60 down profile (molecular to cellular to organ to system
 61 to whole body) and extensive documentation as a part
 62 of the model description.

2.1. Validation process

63 In order to build confidence in the integrity in the
 64 Digital Astronaut, it is necessary that the model undergo
 65 a rigorous validation process as each new system com-
 66 pletes a phase of development. The most important part
 67 of this process is the comparison of physiologic end-
 68 points that typify and define the cardiovascular adapta-
 69 tion to microgravity to those predicted by the model.
 70 While it is not expected that there will be absolute
 71 agreement between the model output and experimental
 72 findings, there should be definite qualitative/directional
 73 accuracy and good quantitative concordance [11]. Dif-
 74 ferences in model outputs and target parameters arise
 75 from the variability in biologic measurements and the
 76 lack of large amounts of consistent data. The cardio-
 77 vascular endpoints were those selected after an exten-
 78 sive meta-analytic review of the literature and consul-
 79 tation with knowledgeable scientists. The endpoints re-
 80 flect those parameters in which there is general agree-
 81 ment in the scientific community about the outcome
 82 measures and their importance as physiologic drivers of
 83 potential complications resulting from an adaptation to
 84 microgravity (such as orthostasis). The endpoints were
 85 divided into primary (hard), secondary (soft) and ter-
 86 tiary (qualitative) targets to differentiate their relative
 87 importance in the determination of model validity.

88 The model predictions are validated against experi-
 89 mental findings by demonstrating that the predicted val-
 90 ues are within the 95% confidence interval of the estab-
 91 lished target value. The confidence interval in each case
 92 is calculated using bootstrapping in the cases where the
 93 target value data is not normally distributed and using
 94 Bayesian and likelihood-based techniques when there is
 95 a meta-analysis of limited data sets [12–14]. In instances

1 where the microgravity-based data sets are extremely
 3 limited it may be that valid confidence intervals cannot
 5 be developed to statistically compare to the mean values
 7 generated by the model. In this case it will be necessary
 9 to determine that the responses are stable, directionally
 11 appropriate, and clinically insignificant and that differ-
 13 ences are no greater than 25% of the target values.

The analytic procedure involves recreating the exper-
 9 imental protocol for a virtual subject in a simulation
 11 environment. Utilizing the rich detail of the model, the
 13 particulars of the physiologic responses to the pertur-
 15 bations can be examined with an emphasis on determi-
 17 nation of the mechanisms involved in the interactions.
 Overall sequential changes in the parameters of interest
 are recorded during the entire time-course of the simu-
 lated protocol and compared to those obtained experi-
 mentally.

3. Results

19 While a variety of parameters were evaluated in the
 21 validation process, there were several select endpoints
 23 considered to be primary (hard) endpoints. The results
 25 of the comparison of these primary endpoints are re-
 27 ported in this paper. Objective changes in these param-
 29 eters upon exposure to microgravity are fairly well es-
 31 tablished in multiple studies and are characteristic of
 this adaptive state. Additionally, these endpoints are also
 thought to be the clinically most important physiologic
 drivers. The results of a comparison of the predicted
 primary endpoints with the target values from the liter-
 ature are presented below. In all instances comparisons
 of the model parameters to these target values met our
 criteria for validity.

3.1. Changes in plasma volume

35 The model predicted plasma volume changes approx-
 37 imate the target endpoints. The model was set to simu-
 39 late an ad lib fluid intake and diet for the virtual subject;
 41 however, differences in volume determinations could re-
 43 sult from individual variations in intakes in living sub-
 ject. The results of the comparison between the model
 predicted values and the target endpoints (decrease of
 plasma volume of 11%) are depicted in Fig. 1 [15–17].
 The difference between the predicted and observed re-
 ductions (12% vs 11%) is within the 95% CI of the
 target value variability ($\pm 12\%$).

3.2. Changes in central venous pressure

47 Central venous pressure (CVP) changes upon micro-
 gravity exposure have been examined in a limited num-

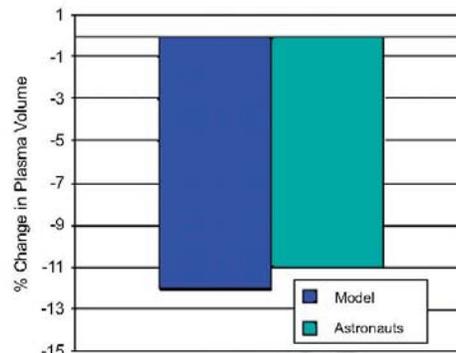


Fig. 1. Comparison of model predicted changes in plasma volume during microgravity exposure to experimental observations obtained from the literature.

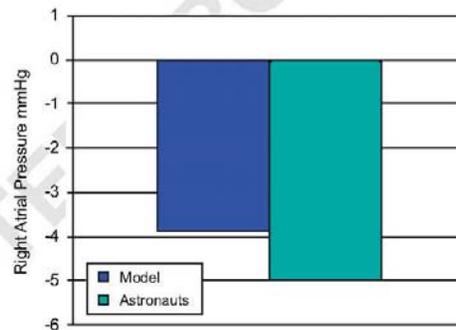


Fig. 2. Comparison of model predicted changes in right atrial pressure during microgravity exposure to experimental observations obtained from the literature.

49 ber of studies with disparate methodologies and under
 51 difficult measurement conditions. The paradoxical find-
 53 ings of these have been debated extensively in the sci-
 55 entific community. After a period of stabilization and
 57 adaptation to the fluid shifts, it appears that CVP is con-
 sistently lower during spaceflight. These changes also
 appear to persist throughout the exposure period. The
 results of the simulation studies using the Digital As-
 tronaut model predict values that are within 25% of the
 target values (Fig. 2) which is both directionally con-
 sistent and clinically insignificant [18,19].

3.3. Changes in left ventricular mass

61 For the primary endpoint of changes in left ventricu-
 lar mass (LVM) during short-term spaceflight, the model

Please cite this article as: R. Summers, et al., Development of the Digital Astronaut Program for the analysis of the mechanisms of physiologic adaptation to microgravity: Validation of the cardiovascular system module Acta Astronautica (2008), doi: 10.1016/j.actaastro.2007.12.054

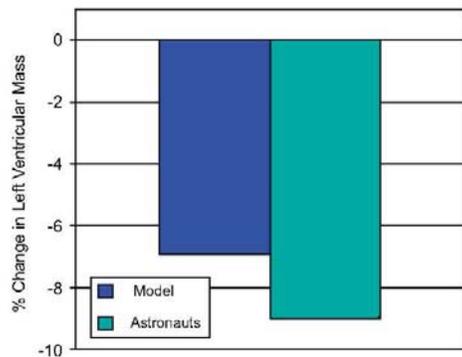


Fig. 3. Comparison of model predicted changes in left ventricular mass during microgravity exposure to experimental observations obtained from the literature.

1 predicted changes that approximate the established target endpoints. The simulation study attempted to recreate the experimental protocol of preflight and postflight measurements of LVM. The results of the comparison between the model predicted values and the target endpoints (decrease of LVM of 9%) are depicted in Fig. 3 [20–22]. The differences between model predicted LVM reductions (7%) and experimental observations (9%) appears to be within the 95% CI of the target value variability ($\pm 33\%$).

4. Conclusions

The Digital Astronaut Project is intended to develop a systems integration of current data and concepts developed from the experience of our international space research programs. A benchmark model incorporating all of this experience is being built around the foundation of a large well-established computer model of human physiology [10]. This large model serves as the integrating framework or backbone for the larger Digital Astronaut Project. The systemic circulation is perhaps the most important fundamental element of this central backbone model as it provides the major conduit for metabolic delivery and inter-organ communication. The integrity of this specific system is therefore a critical factor in the integration of all other physiologic systems. While the current paper provides no new data, it does compare cardiovascular model outcomes to published data results and thereby provides some validation to the core of the model framework.

Currently, the model is incorporating our present knowledge of human adaptations to microgravity on a

system by system basis. It is expected that the model structure will change as new research findings emerge and our general understanding of space-based physiology evolves. An assimilation of the work of the general community of space scientists into the benchmark model structure will be an important goal in the model development process. Through this process, the benchmark model becomes a dynamic compendium of our current knowledge of physiologic mechanisms and interactions and will serve as a national reference resource. The Digital Astronaut Project will provide a web-based mechanism from which space scientists can interact with the benchmark model and contribute to the expansion of the model elements. It will also be possible to compare the results of the model with new experimental data and to other dynamic models.

Ultimately, it is not enough to simply build the Digital Astronaut but it is also important that it serve a practical function. However, to be practically useful the model must accurately reflect our current state of knowledge. This paper describes the validation process and results for the latest iteration of the cardiovascular phase of the modeling efforts. In the context of this validation and systems analysis process the model can serve as a platform for the exploration and prediction of the cardiovascular effects of long-term spaceflight on humans from both the systems and whole organism perspective. The objective is to use the model as a means to better qualify and quantify ideas about interactions that take place among detailed systems under study. The model will serve as a formal statement of hypotheses concerning proposed mechanisms of physiologic functioning and when used in computer simulation studies can reveal insight into interactions among physiologic variables that may not be immediately evident (3). In its current state, the model has been used to perform a variety of practical simulations including the launch and reentry of humans into varying gravitational fields and the impact of different countermeasures in these environments. The model has also been used to predict the astronaut's ability to exercise and the special nuances of potential pathophysiologic developments during spaceflight [23].

References

- [1] J.M. Kootsey, Complexity and significance in computer simulations of physiological systems, *Federal Proceedings* 46 (1987) 2490–2493.
- [2] R.L. Summers, S.M. Hudson, J.P. Montani, Computer simulation studies and biomedical research, *AWIC, National Agricultural Library Quarterly Journal* 6 (2–4) (1996) 12–13.

Please cite this article as: R. Summers, et al., Development of the Digital Astronaut Program for the analysis of the mechanisms of physiologic adaptation to microgravity: Validation of the cardiovascular system module *Acta Astronautica* (2008), doi: 10.1016/j.actaastro.2007.12.054

- 1 [3] R.L. Summers, Computer simulation studies and the scientific
method, *Journal of Applied Animal Welfare Science* 1 (2)
3 (1998) 119–131.
- 5 [4] J.P. Montani, T.H. Adair, R.L. Summers, T.G. Coleman, A.C.
Guyton, Physiological modeling and simulation methodology:
7 from the mainframe to the microcomputer, *Journal of the*
Mississippi Academy of Science 24 (1989) 41–54.
- 9 [5] R.J. White, J.I. Leonard, J.A. Rummel, C.S. Leach, A systems
approach to the physiology of weightlessness, *Journal of*
Medical Systems 6 (1982) 343–358.
- 11 [6] R.J. White, J.I. Leonard, R.S. Srinivasan, J.B. Charles,
Mathematical modeling of acute and chronic cardiovascular
13 changes during extended duration orbiter (EDO) flights, *Acta*
Astronautica 23 (1991) 41–51.
- 15 [7] R.L. Summers, T.G. Coleman, Computer systems analysis of the
cardiovascular mechanisms of reentry orthostasis in astronauts,
17 *Computers in Cardiology* 29 (2002) 521–525.
- 19 [8] A.C. Guyton, T.G. Coleman, H.J. Granger, *Circulation: Overall*
regulation, *Annual Reviews in Physiology* 34 (1972) 13–46.
- 21 [9] T.G. Coleman, HUMAN: mathematical model of the human
body in health, disease, and during treatment, *ISA Transactions*
18 (3) (1979) 65–73.
- 23 [10] T.G. Coleman, R.L. Summers, Using mathematical models to
better understand integrative physiology, *Journal of Physiology*
25 and *Biochemistry* 53 (1) (1997) 45–46.
- 27 [11] R.L. Summers, J.P. Montani, Hypothesis testing in physiology:
a proposed methodology using computer simulation studies,
29 *Journal of the Mississippi Academy of Science* 35 (1991)
49–54.
- 31 [12] J.S. Haukoos, R.J. Lewis, Advanced statistics: bootstrapping
confidence intervals for statistics with “difficult” distributions,
Academic Emergency Medicine 12 (2005) 360–365.
- 33 [13] J. Wu, A.C. Wong, G. Jiang, Likelihood-based confidence
intervals for a log-normal mean, *Statistics in Medicine* 22
35 (2003) 1849–1860.
- 37 [14] X.Y. Su, A. Li Wan Po, Combining event rates from clinical
trials: comparison of Bayesian and classical methods, *Annals*
of *Pharmacotherapy* 30 (1996) 460–465.
- [15] W.W. Waters, M.G. Ziegler, J.V. Meck, Postspaceflight
orthostatic hypotension occurs mostly in women and is
41 predicted by low vascular resistance, *Journal of Applied*
Physiology 92 (2002) 586–594.
- [16] C.S. Leach, C.P. Alfrey, W.N. Suki, J.I. Leonard, P.C. Rambaut,
43 L.D. Inners, S.M. Smith, H.W. Lane, J.M. Kraus, Regulation of
body fluid compartments during short-term spaceflight, *Journal*
45 of *Applied Physiology* 81 (1996) 105–116.
- [17] J.V. Meck, W.W. Waters, M.G. Ziegler, H.F. deBlock,
47 P.J. Mills, D. Robertson, P.L. Huang, Mechanisms of
postspaceflight orthostatic hypotension: low alpha-adrenergic
49 receptor responses before flight and central autonomic
dysregulation postflight, *American Journal of Physiology Heart*
51 and *Circulatory Physiology* 286 (2004) H1486–95.
- [18] N. Foldager, T.A. Andersen, F.B. Jessen, P. Ellegaard, C.
53 Stadeager, R. Videbaek, P. Norsk, Central venous pressure in
humans during microgravity, *Journal of Applied Physiology* 81
55 (1996) 408–412.
- [19] R.D. Latham, J.W. Fanton, M.N. Vernalis, F.A. Gaffney, R.P.
57 Crisman, Central hemodynamics in a baboon model during
microgravity induced by parabolic flight, *Advance Space*
59 *Research* 14 (8) (1994) 349–358.
- [20] R.L. Summers, D.S. Martin, J.V. Meck, T.G. Coleman,
61 Mechanism of spaceflight induced changes in left
ventricular mass, *American Journal of Cardiology* 95 (2005)
63 1128–1130.
- [21] M.A. Perhonen, F. Franco, L.D. Lane, J.C. Buckley, C.G.
65 Blomqvist, J.E. Zerwekh, R.M. Peshock, P.T. Weatherall, B.D.
Levine, Cardiac atrophy after bed rest and spaceflight, *Journal*
67 of *Applied Physiology* 91 (2) (2001) 645–653.
- [22] R.L. Summers, D.S. Martin, J.V. Meck, T.G. Coleman,
69 Computer systems analysis of spaceflight induced changes in
left ventricular mass, *Computers in Biology and Medicine* 37
71 (2006) 358–363.
- [23] R.L. Summers, T.G. Coleman, Computer Model for
73 the Planning of Emergency Medical Management During
Spaceflight, *Annals of Emergency Medicine* 290 (2006)
75 S87.

Please cite this article as: R. Summers, et al., Development of the Digital Astronaut Program for the analysis of the mechanisms of physiologic adaptation to microgravity: Validation of the cardiovascular system module *Acta Astronautica* (2008), doi: 10.1016/j.actaastro.2007.12.054

Risk of Orthostatic Intolerance Due to Re-exposure to Gravity