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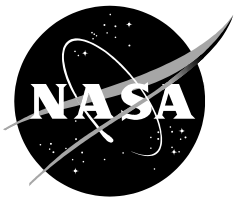

Orthostatic Intolerance Among Female Astronauts: Future Research Priorities

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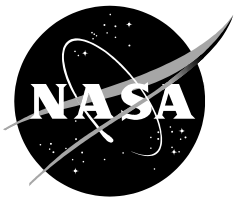

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ACRONYMS

AG	artificial gravity
AGS	anti-gravity suit
BP	blood pressure
EVA	extravehicular activity
HDBR	head-down bed rest
HUT	head-up tilt
ISS	International Space Station
LBNP	Lower Body Negative Pressure
LEO	low Earth orbit
OI	orthostatic intolerance
OTT	orthostatic tilt test
RAAS	renin-angiotensin-aldosterone system

1.0 INTRODUCTION

Spaceflight is associated with an array of adverse health outcomes including changes to the cardiovascular system.[1 2 3 4 5 6 7 8] The duration of a spaceflight is positively correlated with the time required to recover cardiovascular function and successfully complete orthostatic tilt tests (OTTs)—a standard method for assessing orthostatic intolerance (OI)—after spaceflight.[9] Although both male and female astronauts are affected by disruptions in their vascular systems during and after spaceflight, OI—leading to presyncope or near fainting during a stand or tilt test—is more prevalent among the female astronaut population.[3 5 10 11 12] Reasons for these sex differences are not completely understood, although evidence exists that a variety of mechanisms may increase risk of OI among female astronauts. Crewmembers will spend months to years in space during upcoming lunar, Mars, and asteroid missions, and addressing OI concerns is critical to overall success of these missions. This document provides a general overview of the currently proposed hypotheses for the biological mechanisms underlying OI with respect to sex differences, a brief overview of current countermeasures to mitigate the effects of OI, and proposed priorities for future work in this area that will address some of the current research gaps.

2.0 LITERATURE OVERVIEW: FACTORS INCREASING RISK OF OI FOR FEMALE ASTRONAUTS

In the context of spaceflight, addressing OI in the near future will be particularly relevant from 3 different perspectives: (1) OI experienced on return to Earth after varying periods of time spent on the International Space Station (ISS) and other low Earth orbit (LEO) missions; (2) OI experienced after lunar surface landings, extravehicular activities (EVAs), and return to Earth; and (3) OI experienced after Martian and asteroid landings, EVAs, and return to Earth after these more extended missions. Each of these undertakings will require a more in-depth understanding of how OI may impact overall mission success, which will ultimately guide the development of appropriate OI countermeasures.

OI is a cardiac event that can occur terrestrially, and during and after spaceflight.[6 7 13] Clinically, it is defined as a sudden decrease in systolic blood pressure (BP) of >25 mmHg or a decrease in diastolic BP of >15 mmHg that occurs within 3 minutes of moving from a seated or supine position to a standing posture.[5] For the body to maintain a standing posture, a carefully orchestrated sequence of vascular, neurologic, and muscular responses maintain BP—such as vasoconstriction that presses blood into the upper part of the body.[6 7 13] If this cascade of events is disrupted, an individual may experience OI.[6 7 13 14] For instance, baroreceptors, located primarily in the carotid arteries and aorta, are highly sensitive to changes in BP,[13] and if these receptors sense even a slight drop in pressure, they initiate a complex

sympathetic outflow response.[13] Because microgravity exposure induces headward fluid shifts that affect the cardiovascular system, both male and female astronauts can experience OI after they return to Earth or immediately after they land on an extraterrestrial surface.[14 15 16] After acute adaptation to spaceflight (~first 10 days), central venous pressure decreases [17] and this is accompanied by left ventricular mass decreases of 12% [18] and increased sympathetic activity.[19] Chronic spaceflight adaptation (as measured 1 month into a spaceflight of 5 months or more) has been associated with decreases in BP and respiratory frequency along with stable heart rate and heart rate volume.[20] After this period of 'functional adaptation' to the space environment, the most pronounced cardiovascular changes have been noted after landing—when significant changes in heart rate, heart rate volume, and BP have been observed.[20] According to recent evidence, 60% to 80% of astronauts returning from long-duration spaceflight (~6 months) experienced OI during 10 minutes of 80° head-up tilt tests conducted 4 to 6 hours after landing.[21 22] Although the mechanisms underlying the association between spaceflight and OI are not completely understood, some researchers have hypothesized that the microgravity-induced reduction in stroke volume during spaceflight may alter neurohumoral regulation by blunting the carotid-cardiac baroreflex[23 24] and increasing heart rate after landing—ultimately decreasing standing vasoconstrictor response and increasing risk for OI.[14 25] Women may be at a slightly increased risk of OI than men after spaceflight due to the following proposed mechanisms: (1) more difficulty in maintaining venous return and cardiac output, as observed in upright posture and during gravitational stress tests;[2 3 26] (2) lower BP and lower levels of peripheral resistance;[27] (3) greater increases in heart rate in the presence of cardiovascular stressors;[28 29 30 31 32 33 34 35] (4) greater losses of plasma volume during spaceflight compared to men;[3 26 34] and (5) the effects of estrogen—which promotes vasodilation,[36 37 38 39 40] particularly in premenopausal women.[41]

3.0 COUNTERMEASURES TO MITIGATE OI

3.1 Overview

Managing OI terrestrially involves raising a person's standing BP without also raising their supine BP to (1) reduce the individual's orthostatic symptoms; (2) increase their standing time; and (3) improve their ability to perform daily tasks.[42] Currently, no single treatment protocol adequately achieves all of the above goals, thus current measures for managing OI involve a combination of volume expansion, compression garments, postural adjustment, and vasoconstrictor drugs.[42] Current countermeasures to mitigate OI in astronauts after flight includes a similar array of methods: exercise combined with volume

expansion;[7 43 44 45 46 47 48 48 49 50 51] fluid loading (using broth/salt tablets and water);[7 51] compression garments (e.g. Kentavr[52] lower-body gradient compression garments);[53 54] nutritional considerations (e.g. protein/amino acid supplementation);[55 56] and pharmacological countermeasures (e.g. Midodrine, Octreotide).[7 57 58 59 60] Artificial gravity (AG) using short radius centrifugation has also been explored as a method to counteract cardiovascular deconditioning and improve orthostatic tolerance in crewmembers.[61] Although the countermeasures above are prescribed for both male and female crewmembers, a few considerations for their use and development with respect to sex differences are briefly discussed below.

3.2 Exercise Regimes

Bed rest studies are often used to assess whether prescribed exercise routines can improve orthostatic tolerance.[43 44 52 62 63] Although studies have confirmed that a combination of resistive and aerobic exercise training programs during bed rest or during spaceflight can protect both sexes against losses in muscle strength and endurance, and lean leg mass,[62 64] women often have lower muscle strength and cardiovascular endurance than men,[65 66] which may place them at an elevated risk for OI after spaceflight, despite intensive exercise countermeasures. For instance, in a recent bed rest study led by Lee et al. (2014), the indicators of muscle strength and endurance measured in female subjects were at the lower end of the spectrum of those observed among ISS astronauts.[62] To address this deficiency, individualized exercise routines targeting improvements in cardiac volume and mass (both shown to improve orthostatic tolerance)[44 62] have been recommended. Effective exercise countermeasures for less-fit individuals (as determined before bed rest or spaceflight) would include the use of high-intensity exertion exercises to maintain intramuscular pressure; whereas, for more-fit individuals, tailored frequency and periodization regimes (increasing and decreasing volume and intensity) are thought to be more beneficial.[62] Substantial sex differences have also been noted in muscular strength across different body regions, which should also be accounted for when creating these tailored exercise programs.[66] Although countermeasures are evaluated by their ability to maintain preflight performance levels, crewmembers of exploration missions may be required to perform certain tasks (under normal or emergency situations) that are not 'scaled' to preflight fitness levels; for instance, maintaining trunk and lower-body musculature will be especially important when landing on an extraterrestrial surface because no support personnel will be available to help the crew egress the vehicle.[62 67 68] A previous study assessed 13 Space Shuttle astronauts before their mission, and 2 had insufficient fitness levels to complete a simulated emergency egress.[69] Thus, focusing on the effectiveness of exercise

countermeasures to maintain preflight performance levels may not be the most appropriate benchmark in certain circumstances. Tailoring exercise regimes to reduce the risk for OI while astronauts perform their many exploration mission-related responsibilities[67]—including physically demanding tasks that must be performed under time constraints—should be a future research priority.

Nutritional factors (e.g. high protein diets) should also be considered when constructing individualized exercise routines to mitigate OI.[62 70] For instance, women's protein needs differ from men's because woman are thought to oxidize less protein during exercise;[71] therefore, future exercise-focused studies should also account for the intake of selected dietary components across varying time intervals.[70]

3.3 Fluid Loading

Fluid loading to increase plasma volume and maintain mean arterial pressure during orthostatic stress[72] can also mitigate postflight OI. Although bed rest studies and spaceflight studies measuring heart rate and BP during passive stand tests have provided mixed results, it appears that fluid loading provides some protection against spaceflight-induced cardiovascular deconditioning.[72 73] Edgell et al. (2018) found that fluid loading after 28-hours of head down bed rest (HDBR) protected subjects against loss of stroke volume index and central venous pressure—although significant loss of plasma volume was still observed.[72] However, this study included male subjects only, so potential sex differences were not investigated.

Currently, crewmembers are encouraged to increase their salt intake over the last few days of their mission (~18 to 20 ml/kg body weight of sodium chloride-water solution consumed 3 to 4 times during the 12- to 20-hour period prior to landing).[74] As an additional measure to increase fluid intake, Russian cosmonauts also take a water-salt additive (0.9 g of sodium chloride and 300 ml of water) before their lower body negative pressure (LBNP-Chibis) sessions, which occur near the end of their spaceflight.[74] Increasing fluid loading in this context increases tolerance to final mission phase workloads and improves postflight reconditioning.[74] It is unclear, however, if the effectiveness of these countermeasures are different for women than men. Furthermore, measures of plasma volume after flight are confounded by the timing of the test (measured 1 day after landing) and by the intravenous administration of fluids after landing.[7] Investigating these factors in greater detail will provide important information for guiding future mission protocols.

3.4 Compression Garments

To prevent excess blood pooling, particularly within the abdominal compartment and leg vasculature, compression garments have been used to prevent OI, both terrestrially[42 75] and after spaceflight.[53 76] Currently, both the American anti-gravity suits (AGS) and the Russian Kentavr suits are effective at preventing presyncope after spaceflight.[53] However, these garments are not comfortable with noted restrictions in body movements.[53] Although the AGS provides pressure that can be tailored to each crewmember in increments of 0.5 psid (25.9 mmHg),[7] some concerns regarding the suit include (1) the need for connection to a pressure source to maintain compression; (2) the metabolic cost of ambulation due to suit inflation; and (3) comfort issues (some crewmembers report that the high pressure over the abdomen is uncomfortable).[7] Additionally, although both suits successfully countered hypovolemia-induced OI during a recent tilt test by maintaining systolic BP, the Kentavr suit required a lower level of compression to increase orthostatic tolerance.[53 68] Furthermore, little research has been performed to assess the effectiveness of these suits on women versus men. For instance, evidence indicates that greater counterpressure applied specifically to the pelvic region and less counterpressure around the legs may confer women additional benefits to mitigate potentially adverse physiologic outcomes related to OI.[34] Aside from optimizing comfort and maneuverability in the design of these garments, future studies should also consider suit fit with respect to sex differences—providing additional insight into ways to minimize the impacts of OI after spaceflight.

3.5 Nutritional Factors

Terrestrial patients at risk for OI are given nutritional guidelines for increasing their orthostatic tolerance, which include taking frequent small meals, reducing alcohol and carbohydrate intake, and minimizing the number of hot drinks and foods ingested.[42] Some recent evidence suggests that additional considerations (such as sex) when formulating optimal OI preventative diet plans are also important. For instance, women have different dietary needs across their lifespans than men (e.g. increased iron needs during premenopause and perimenopause),[5 77] which may have important consequences for developing OI. Iron deficiency anemia has been associated with an array of cardiovascular complications, including volume overloads, cardiac dilation, and valvular failure[78]—all of which may increase the risk of OI.[79] The current dietary iron requirements for spaceflight are 8 to 10 mg/day for both men and women; however, little is known about how iron metabolism and iron absorption differ by sex during spaceflight.[5 80] Another important nutritional factor to consider during spaceflight missions is calcium, which is found in many foods and is important for maintaining bone

strength and integrity, homeostasis, and protecting against osteoporosis—particularly for women as they age.[81] Although calcium confers many benefits, larger doses of calcium can cause small decreases in BP.[82] Some studies of calcium kinetics have been conducted on crewmembers of Mir flights;[83] however, limited data exist regarding sex differences and calcium metabolism in relation to an array of health outcomes (including OI), in the context of spaceflight.

3.6 Artificial Gravity

AG has been explored as a single measure to mitigate multiple spaceflight-induced deconditioning effects. Studies conducted at NASA Ames Research Center found that 3 weeks of daily short radius centrifugation, improved orthostatic tolerance for both ambulatory men and women.[84 85] A similar bed rest study conducted at NASA Johnson Space Center evaluated the effectiveness of AG in preventing bed rest-induced OI, although only men were enrolled in this study because women were unable to tolerate an hour of centrifugation at the required magnitude.[86] Another group of investigators led by Evans et al. (2015) at University of Kentucky examined the orthostatic tolerance limit of 9 men and 8 women who were cardiovascular deconditioned by furosemide, and found markedly improved orthostatic tolerance after 90 minutes of AG exposure.[87] The study, which included 2 research visits (research day 1 and research day 2) separated by 21 days, included the following measures for each visit: (1) furosemide infusion; (2) the experimental condition (90 min of -6° HDBR or an individualized AG protocol—half the subjects had HDBR on research day 1, the other half had AG on research day 1); and (3) a test of the subject's OI. For the AG experiment, subjects rode supine aboard the Human Performance Centrifuge at NASA Ames Research Center after a protocol similar to that used for subjects at DLR, Cologne, Germany.[88] Interestingly, however, the exposure to AG seemed to be more effective for increasing the orthostatic tolerance limit (time required to produce a presyncopal response using a head up tilt [HUT] and LBNP device) in men (30.1% increase on AG day vs. HDBR day) vs. women (22% increase on AG day vs. HDBR day).[87] Furthermore, different mechanisms of cardiovascular regulation were noted for men and women after the AG protocol. For instance, a decrease in mean systolic BP was noted in the men after the AG exposure (11 +/- 2.9 mmHg), but not in the women, whose mean systolic BP remained the same after either the HDBR or the AG exposure.[87] The men's decrease in systolic BP derived primarily from decreases in resistance and stroke volume, whereas the women likely maintained systolic BP (following AG) primarily from an increase in stroke volume that overcame decreases in peripheral resistance[87]—possibly due to differences in the rate of cardiac output reduction,[34] beta or alpha adrenergic responsiveness,[34] and/or variations in sympathetic neural responsiveness to orthostatic stress.[89] These findings highlight the need for a better understanding of the mechanisms underlying sex

differences in BP regulation after exposure to AG to manage and develop measures for mitigating postflight OI. Additionally, the duration, magnitude, and type of AG exposure needs to be determined if AG is to be used as a countermeasure for spaceflight deconditioning.[7]

3.7 Pharmaceutical Agents

Pharmaceutical agents to minimize the impact of OI will also need to be considered in the context of sex differences. Midodrine, a vasopressor that increases standing systolic BP and reduces orthostatic lightheadedness, is commonly prescribed to minimize the effects of OI.[7 42 90] During a 16-day HDBR study to test the hypothesis that alpha-adrenergic stimulation would mitigate OI, midodrine protected against excessive decreases in BP and presyncope.[90] Because the peak therapeutic effect of midodrine is ~1 to 2 hours after intake,[57] midodrine is thought to be a particularly effective agent for mitigating postflight OI.[7] One female crewmember who had previously experienced postflight presyncope, took 10 mg of midodrine after a subsequent spaceflight, and showed noted improvements in orthostatic tolerance.[91]

Despite the potential benefits and the promising findings noted above, concerns have been raised that midodrine may be less effective in preventing OI in women than in men, due to basal differences in volume-mediated parasympathetic and adrenergic systems and in venous tone.[92] Furthermore, terrestrial examinations have determined that midodrine may interact with other medications, such as promethazine, inducing effects such as increased akathisia (agitation and restlessness)[93] and prolonged QT interval[7] (time from when cardiac ventricles first contract to when they relax—longer periods are associated with adverse cardiac events such as sudden cardiac death).[94] Other side effects associated with midodrine include supine hypertension, scalp paresthesia (abnormal tingling), and pilomotor reactions such as goosebumps.[42] Although midodrine is the currently preferred pharmaceutical countermeasure for mitigating the impact of postflight OI, a better understanding of modifying factors (such as sex) and risk for adverse reactions would provide valuable information with regard to its use during exploration class missions.

Fludrocortisone—a synthetic mineralocorticoid—expands plasma volume and increases vascular alpha-adrenoceptor sensitivity.[95 96 97] When plasma volume fails to adequately increase with salt supplementation or patients do not respond to midodrine, they are often prescribed fludrocortisone.[42] Although often prescribed terrestrially for OI,[42] fludrocortisone's effectiveness as a countermeasure for spaceflight-induced OI has been limited. Investigators of one recent study of 25 male astronauts found that fludrocortisone maintained plasma volume after a short-duration mission, although the medication (taken 7 hours before landing) had no impact on postflight OI (as assessed via stand tests).[98] Additionally, fludrocortisone has been associated with a range of adverse events (e.g. severe

hypokalemia [low potassium] and excessive supine hypertension)[42] and frequent monitoring of serum potassium and supine BP is advised after intake.[95 96] As with midodrine, further examinations of this medication are needed before recommending it as a countermeasure for postflight OI.

Lastly, octreotide (commonly seen under the brand name Sandostatin) is an octapeptide that mimics naturally occurring somatostatin (a hormone produced in many locations in the body, including the gastrointestinal tract, pancreas, hypothalamus, and central nervous system)[99] that has been successfully used to treat hypotension.[100 101 102] At least one study found that octreotide was more effective than midodrine for preventing OI in patients with autonomic neuropathy; octreotide induced marked increases in cardiac output and venous tone.[101] Its use after spaceflight presents certain challenges, however, because octreotide must be slowly infused or given subcutaneously.[7] Although one recent examination found octreotide improved orthostatic tolerance in both sexes during a 45-minute tilt test,[103] as with the other 2 medications discussed above, little is understood with regard to potential sex difference when prescribed as a treatment for OI, both terrestrially and after spaceflight.

In conclusion, better understanding of the effectiveness of each of the medications above—in addition to the other countermeasures discussed—would improve both the use and the refinement of these methods to prevent OI after spaceflights of varying duration.

4.0 FUTURE RESEARCH PRIORITIES TO BETTER UNDERSTAND OI SEX DIFFERENCES

As noted in the discussion above, many previous examinations aimed at better understanding and mitigating the impacts of spaceflight-induced OI indicted a need to better understand differences with respect to sex. The following section discusses some of the top priorities for research that could lead to a better understanding of spaceflight-induced OI in the context of sex differences. An improved understanding of the mechanistic components that contribute to OI will ultimately improve our ability to effectively manage this adverse cardiovascular outcome, both terrestrially and within the space environment.

4.1 Better Understand the Stimuli for OI After Exposure to Spaceflight

More information is required on conditions that predispose individuals to OI before, during, and after flight, with respect to sex differences.[6 7] Ground-based analogs of spaceflight and simulated EVA environments with exposure to ~1/6th G (Moon gravity level) and ~3/8th G (Mars gravity level),[7] clinical trials, and retrospective epidemiologic analyses of currently available astronaut data can all be used to better understand what stimulates OI after exposure to microgravity and other altered gravity

environments. During these assessments, it is imperative that investigators also consider how physiologic conditions involved in the development of OI interact with other systems of the body such as the immune, vestibular, and endocrine systems,[6 7] as well as other moderating factors such as race and ethnicity (e.g. risk for black people versus white people),[104] genetic predispositions (e.g. hereditary amyloidosis),[105] and other environmental influences (e.g. heat and humidity).[106]

4.2 Explore Why Plasma Volume Loss and Heart Rate Responses Differ by Sex

Presyncope occurs in individuals who have lower norepinephrine levels and lower total peripheral resistance than more orthostatic tolerant individuals.[27] During spaceflight, women appear to lose more plasma volume than men, putting them at an increased risk for OI.[3] Changes in plasma volume are based on complex physiologic mechanisms, and some researchers have speculated that because women have lower centers of gravity (~8% to 15% lower than men's)[107 108] and proportionally larger masses in their lower extremities, they experience a particularly pronounced change in their lower-extremity vein capacitance due to the loss of external fluid forces in dehydrated extracellular compartments in these areas.[109] Why spaceflight-induced fluid loss in females results in these dehydrated extracellular compartments, particularly in the lower extremities, should be more thoroughly examined.

In response to cardiovascular stressors, female astronauts respond with greater heart rate increases, whereas males respond primarily with greater increases in vascular resistance.[5 6] In a recent 6^{o} tilt HDBR study performed on 20 male and 10 female volunteers, investigators found that after 30 days of HDBR, female participants experienced a larger decrease in baroreflex sensitivity than the male subjects after continuous infusions of vasoactive drugs.[63] Some researchers have noted that male astronauts' greater vascular resistance allows them to better counter orthostatic challenges after spaceflight, although little is currently understood regarding the mechanisms responsible for this.[5 6] In general, women experience greater increases in heart rate than men during an array of situations including those that involve increased mental/psychological stress,[28 33] standing,[29 30] graded HUT tests,[35] pressor agent infusions,[31] cold pressor tests,[32] loud noises,[33] and exercise.[33] The greater increase tilt-induced heart rate in women supports the hypothesis that women experience greater vagal cardiac control during resting periods—subsequently leading to increased parasympathetic withdrawal during HUT.[110] Furthermore, the conduit and resistance vessels of men undergo stress-mediated vessel remodeling, ultimately resulting in sustained hypertension with less tissue perfusion compared to the response in women.[33] Women, conversely, exposed to similar stressors experience more burden on the heart rather than on the large arterial vessels.[111] Female pilots' cognitive performance may be more compromised than male pilots' performance in situations such as high-G maneuvers because men have

a greater capacity to use an array of physiologic measures to 'buffer' against the development of OI.[34] The downstream impacts of spaceflight-induced changes in plasma volume and heart rate that impact OI, and the associated cognitive impairments, are not well characterized. Because many factors have been independently correlated with increased heart rate (e.g. age, height, and sociodemographic factors),[112 113] these potential confounders should also be considered in future studies examining sex differences, heart rate fluctuations, and OI in the astronaut population.

4.3 Better Understand the Mechanisms Associated with Arterial Stiffness

Evidence from the literature indicates female astronauts may be less tolerant to the upright posture or gravitational stress of spaceflight than male astronauts due to their reduced ability to maintain venous return or cardiac output.[7] Upright posture on the ground creates gravity-induced hydrostatic gradients that ultimately reduce arterial pressures above the heart and increase pressures below the heart.[109 114] This gravitational vector is absent during spaceflight, significantly impacting an array of cardiometabolic biomarkers (e.g. insulin) as well as inducing measurable changes in arterial stiffness,[114] which is associated with OI. During the normal aging process on Earth, humans contend with an array of orthostatic changes that are associated with increasing levels of arterial stiffness.[115 116] During spaceflight, many of these physiologic aging processes accelerate, thus increasing levels of arterial stiffness.[2 114] A recent examination of astronauts after 6 months on the ISS found measurable changes in arterial stiffness, and female astronauts had greater spaceflight-induced increases in a carotid artery β-stiffness index than men.[114] These findings confirm earlier observations that female mice that were flown in space had increased distensibility of cerebral arteries compared to values in ground-control mice.[117] However, the 2 studies described above did not address potentially confounding factors such as arterial pressure—which should be assessed in future analyses. Future studies should use improved technology, such as the most current ultrasound devices,[118] to obtain the most accurate cardiovascular measurements. Better understanding of the etiological mechanisms underlying sex differences and arterial stiffness will lead to a better understanding of OI risk.

4.4 Estrogenic Considerations

Future studies of OI with respect to sex differences should examine the direct and indirect effects of estrogen fluctuations during different periods of a woman's menstrual cycle, and assess how this may impact OI.[6 7 11 33] The levels of female sex hormones change cyclically over the lunar month, whereas male sex hormones cycle faster: serum testosterone levels fluctuate over a 24-hour period, peaking at around 8:00 PM (20% above mean level) and falling to 35% below mean levels at around 7:00 AM.[33 119]

Currently, research is lacking into the etiologic mechanisms associated with fluctuation of menstrual cycle hormonal levels during spaceflight. Estrogen level fluctuations, which are thought to contribute to the lower vascular resistance in women than men during spaceflight, augment endothelium-dependent vasodilation.[37 38 39 40 120 121 122] Furthermore, it has been proposed that the indirect effects of estrogen in certain groups of women (e.g. premenopausal) may contribute to smaller vasoconstrictive responses to orthostatic stress compared to responses in men.[6] Additionally, the effects of the renin-angiotensin-aldosterone system, which is involved in regulating plasma volume and hemodynamic homeostasis, vary during the menstrual cycle.[123] During the midluteal phase, higher amounts of estrogen and progesterone are released into the body and are associated with more volume retention leading to an improvement in late-standing tolerance compared to tolerance during other phases of the menstrual cycle.[123]

Accounting for the effects of oral contraceptives on OI risk is also important. Data are currently lacking regarding the impact of the newest generation of prescribed oral contraceptives, which may modulate the risk for OI.[1] Furthermore, parity should also be considered because the previous number of pregnancies can affect vessel compliance and obstruction of venous return.[124] These findings highlight potential areas of future research that will improve understanding of how estrogen and other hormonal factors are associated with OI.

4.5 Use Refined Human/Animal/Computer Models that Include Both Sexes

Lastly, due to the limitations in procuring a robust and diverse astronaut dataset, many of the gaps related to OI with regard to sex differences could be remedied by including females in future etiological studies aimed at better characterizing the hydrodynamic and biochemical responses in the spaceflight environment.[6 7 109] Ground-based simulated microgravity, computer simulations, and animal studies that focus on cardiovascular deconditioning, should include both sexes. Further investigation is required to determine why female astronauts have peripheral resistance responses that often operate terrestrially on the low end of normal, and why spaceflight-induced cardiovascular and other physiologic changes lead to higher risk for OI in female astronauts.[6 27] Additionally, bed rest studies to assess how microgravity affects OI and other body systems should include women, in not only LEO simulations, but also varying gravity alterations that match lunar, asteroid, and Martian environments.

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