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Effects of Sex and Gender on Adaptation to Space: Cardiovascular Alterations

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Abstract

Sex and gender differences in the cardiovascular adaptation to spaceflight were examined with the goal of optimizing the health and safety of male and female astronauts at the forefront of space exploration. Female astronauts are more susceptible to orthostatic intolerance after space flight; the visual impairment intracranial pressure syndrome predominates slightly in males. Since spaceflight simulates vascular aging, sex-specific effects on vascular endothelium and thrombotic risk warrant examination as predisposing factors to atherosclerosis, important as the current cohort of astronauts ages. Currently, 20% of astronauts are women, and the recently selected astronaut recruits are 50% women. Thus there should be expectation that future research will reflect the composition of the overall population to determine potential benefits or risks. This should apply both to clinical studies and to basic science research.

Cardiovascular Adaptations

The National Aeronautics and Space Administration (NASA) decadal review of the role of sex and gender adaptations to spaceflight has as its goal to insure the health and safety of male and female astronauts during long-duration space missions. Based on literature and data from space- and ground-based research studies and observations on the impact of sex- and gender-based health during spaceflight and on terrestrial environments, this manuscript assesses the cardiovascular similarities and differences in how men and women adapt to spaceflight and the research progress made in the past decade.

With the aging of the astronaut population, issues of cardiovascular health and disease in midlife come to the forefront and will likely differ by sex and gender. Risk factors for cardiovascular disease emerge at different prevalence in both genders, and preventive therapies may differ. Unique to women is their progression from the initial hormonal concern with oral contraceptive therapy to the use of menopausal hormone therapy.

This document explores the sex- and gender-based differences in cardiovascular risk and cardiovascular disease to buttress research needs and opportunities. It reviews the accomplishments of both ground-based and spaceflight research studies and identifies critical gaps in information for future research. The visual impairment intracranial pressure (VIIP) syndrome, which has components of cardiovascular physiology as contributory factors, is discussed as well.

Cardiovascular Disease: Background Information

Cardiovascular (CV) disease is the leading cause of death in women, with women developing CV disease about a decade later than their male peers. There are major differences in risk factors (e.g., smoking and diabetes have a more adverse impact on women). Clinically, women have greater CV morbidity and mortality, in part because they do not consistently receive optimal preventive strategies, diagnostic procedures, and treatments, although gender gaps continue to narrow. The sex and gender differences of effects of radiation exposure during spaceflight on cardiovascular risk factors

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and cardiovascular disease require ascertainment; the physiologic ''aging'' characteristics of spaceflight should be examined for their effect on both cardiovascular risk factors and cardiovascular disease.

Unique to women and their cardiovascular disease are hormonal concerns. Oral contraceptives designed to suppress menstruation and prevent pregnancy may increase blood pressure. There is no evidence that they increase risk of myocardial infarction, but they do increase the risk of venous thromboembolism. Differences with newer oral contraceptive formulations are unexplored (these newer agents likely will be used in future spaceflights). Menopausal hormone therapy, a new consideration as female astronauts age, has potential effects on autonomic blood pressure, volume status, and orthostatic tolerance, all of which must be investigated at baseline, during and after spaceflight. Little ground-based data are available regarding the effects of hormonal levels/oral contraception as it relates to space flight. Some studies state that no oral contraceptives were used, while other studies do not identify use or lack of use of oral contraceptives. Therefore, the lack of coherent study design among experiments to look at sex differences as they may relate to space flight presents a challenge. Not all studies of hormonal levels as they relate to space flight synchronized menstrual cycles.

Exercise effects in women in simulated space studies show that exercise can improve orthostatic tolerance, preserve cardiac volume, and increase cardiac mass. Gender comparisons will be important as well as the gender effects of preconditioning prior to spaceflight.

During the past decade, little new research has been conducted in space to address cardiovascular differences related to sex and gender. Orthostatic tolerance is an important variable, with an increased prevalence of orthostatic intolerance in female compared with male astronauts, although few studies have targeted women (and even fewer studies involve minority women). Women have a greater loss of plasma volume than men following spaceflight, which mandates gender-based evaluation of countermeasures.

There are known gender differences in response to cardiovascular stress, with women characteristically responding with an increase in heart rate and men with an increase in vascular resistance. It is uncertain whether this explains the male advantage for reentry orthostasis, but delineation of mechanisms should provide the rationale for countermeasures.

It is not known whether spaceflight increases the risk of arrhythmias, nor have sex or gender differences been studied. Baseline gender differences in supraventricular and ventricular arrhythmias and baseline gender differences in the electrocardiogram are likely relevant.

Visual Impairment Intracranial Pressure Syndrome

The VIIP syndrome, first identified in 2005, is currently NASA's leading spaceflight-related health risk.[1] The syndrome manifests with changes to ocular structures such as optic disc edema, choroidal folds, cotton wool spots, globe flattening, and distended optic nerve sheaths (ONSD), and with changes to visual function such as hyperopic shifts, scotomas, and enlarged blind spots.[2,3] In a few of the cases, post-flight lumbar puncture demonstrated elevated cerebrospinal fluid pressure reflecting increased intracranial pressure (ICP). Some of the observed signs and symptoms persist for months to years after flight, although the implications for long-term health are yet unknown. The leading pathophysiologic hypotheses for the VIIP development include microgravity-induced cephalad fluid shifts along with loss of gravity-assisted drainage of venous blood from the brain, leading to cephalic congestion and increased ICP. Although not all crewmembers have manifested overt signs or symptoms of the VIIP syndrome, it is assumed that all astronauts exposed to microgravity have some degree of ICP elevation in-flight. The concern surrounding VIIP stems from the fact that prolonged elevations of ICP can cause long-term loss of visual acuity and peripheral visual fields,[4] and could be related to mild cognitive impairment seen in the analog terrestrial population of idiopathic intracranial hypertension (IIH).[5,6] Similar changes to eye structure and function were also observed in short-duration flyers, with lesser severity and a shorter timeframe to resolution.

The closest terrestrial analog to VIIP is the syndrome of IIH, which is more prevalent in young, overweight women, although the reason for this sex difference is still unclear.[4,7] In contrast, VIIP is slightly more predominant in males. Out of 41 International Space Station crew members to date, 25 underwent VIIP-specific medical evaluations, including extensive vision testing, refraction, tonometry, pupillary reflexes, extraocular muscle balance, biomicroscopy, fundoscopy, ocular coherence tomography, ocular ultrasound, and magnetic resonance imaging (MRI) of the eyes, orbits, and brain. The 25 evaluated crewmembers include 17 males (68%) and 8 females (32%). Five of the 8 evaluated females (62.5%) manifested evidence of the VIIP syndrome, compared with 14 of the evaluated 17 males (82.3%). This difference was not statistically significant ($p = 0.09$).[8] However, female crew members presented with milder signs and symptoms (mild globe flattening, mild optic disc protrusion on MRI or ultrasound, minor changes in refraction), compared with male crew members (who in general had more marked globe flattening, overt optic disc edema, marked ONSD, larger changes in refraction, etc.). There are insufficient data to evaluate for sex differences among short-duration crew members.

The sex differences observed in VIIP severity may be related to higher vascular compliance in women,[9] which may be protective. A younger age is also associated with higher vascular compliance and the female crew members who manifested VIIP are younger (mean age 44.25 years) than their male counterparts (48.57 years, $p = 0.039$). High-acceleration jet pilot training (65% of men vs. 25% of women, $p = 0.024$)[8] may lead to lower vascular compliance and higher VIIP susceptibility. As further research elucidates VIIP syndrome etiology, underlying sex-related differences will also be elucidated.

Research Review

Animal models

Hindlimb unloading (HLU) of rodents was introduced as an analog of spaceflight[10] to incorporate the relative physical inactivity of the lower limbs and altered arterial blood pressure distributions that mimic those experienced by humans going from normal upright body posture on Earth to spaceflight. Spaceflight involving animal models have recently highlighted cardiovascular adaptations. Few studies though have compared female to male rodents to gain insight into

potential sex differences. Baroreflex activation of heart rate was not different between male and female rats after 14 days of HLU.[11] Female rats started from a lower baseline renal sympathetic nerve activity, but both sexes had similar reductions in baroreflex sensitivity after 14 days of HLU.[11]

There was no effect of HLU in rats (male or sex not specified) on heart weight, body weight, or their ratio.[12,13,14] However, cardiac contractility indicators were reduced and cardiac myocytes had increased stiffness after HLU.[13]

Arterial structure and function have been extensively investigated with HLU in male rats and mice, and recently with spaceflight in female mice. Aortic rings obtained from hindlimb suspended male rats had impaired responses to drugs inducing constriction and dilation.[15,16] Female mice flown in space for 13–15 days had similar reductions in responsiveness of arteries from the gastrocnemius muscle and arteries and veins from the mesentery that was attributed to impaired calcium handling.[17,18] The arterial vasomotor responses of the mice recovered quickly after spaceflight. The internal diameters of the common carotid artery and the abdominal aorta were unchanged in male rats with HLU, but smooth muscle cell hypertrophy was found in the carotid and atrophy in the abdominal aorta.[19] Recent research has highlighted the role of the local renin-angiotensin system located within the vascular wall in development of smooth muscle cell hypertrophy and hyperplasia.[20]

Endothelial function and the production of nitric oxide are generally found to be reduced in models of HLU.[21–23] Taken together, these results suggest that hindlimb unloading effectively reduces nitric oxide, which could contribute to vascular wall dysfunction. Increased stiffness of the carotid arteries and the aorta have been observed in male rats during HLU,[24,25] possibly as a consequence of increased cross-linking in the extracellular matrix.[26]

Bed rest

Cardiovascular alterations after simulated microgravity exposure, such as 6° head-down bed rest (HDBR), appear to be similar between sexes. For example, it was found that men and women had similar cardiovascular responses to lower body negative pressure (LBNP) after short-duration HDBR compared with a control condition.[27] Cardiac atrophy occurs in women similar to men following sedentary 60 days of HDBR.[28] A similar reduction in blood volume of about 9% in men and women has been reported after 7 days of HDBR.[29,30] However, Fortney et al. found less reduction of plasma volume in women than men (-10% versus -15%) after 13 days of HDBR.[31] Conversely, Vernikos et al. observed a higher decrease in plasma volume after 3 days of HDBR in women compared with men.[32] These inconsistent findings may be attributable to differences in the duration of HDBR or the time of inclusion in relation to the menstrual cycle in women,[33] as well as the inherent noise in the measurement techniques. The lower orthostatic tolerance in women than men after HDBR cannot be modified by midodrine.[33] Different from men, cardiovascular responses to exogenous nitric oxide (sublingual nitroglycerin) are not altered by HDBR in women.[34] Prolonged bed rest may cause impairment of endothelium-dependent function at the microcirculation level in women.[35]

The largest study to examine the responses of women to HDBR was the Women's International Space Simulation for Exploration (WISE)-2005[36] project that examined the effects of 60 days of HDBR in three groups of 8 women (control, exercise and nutrition). When the data were analyzed with respect to those who could complete a 10-minute tilt after HDBR compared to those who could not, less arterial vasoconstriction and greater change in vein cross-sectional area were identified as key factors that might have contributed to poorer orthostatic tolerance. Finding some variability in orthostatic tolerance within a group is expected, as large differences between individuals have been identified in men and women, with a strong genetic component determined in studies with identical twins.[37] In this latter study, the reduction in orthostatic tolerance after 28 days of HDBR was less with an LBNP-exercise routine similar to the WISE study (13%) than in control subjects (34%), and no differences were reported between men and women.[38]

Spaceflight

Long-duration spaceflight may result in eccentric cardiac atrophy and impair cardiac compliance, leading to a prominent reduction in upright stroke volume and orthostatic tolerance in astronauts upon returning to the Earth.[39–43] Female astronauts are more susceptible to orthostatic intolerance after spaceflight than male astronauts.[9,44–46] It has been proposed that low vascular resistance responses,[9] a strong dependence on volume status,[9,11] and/or a smaller stroke volume secondary to a smaller and less compliant left ventricle[11,47,48] may be the underlying mechanisms. After spaceflight, a greater reduction in plasma volume was reported in female astronauts.[9] The change in lower extremity vein capacitance resulting from a loss of external fluid forces in the dehydrated extracellular compartment was proposed to be another potential mechanism associated with reentry orthostasis. This condition appears accentuated in women due to their inherent lower center of gravity and proportionately larger mass in the lower extremities.[49]

In both male and female astronauts, systemic peak oxygen uptake was well maintained during 9 to 14 days of spaceflight but was significantly reduced immediately on return to Earth, most likely because of reduced intravascular blood volume, stroke volume, and cardiac output.[50] Up to now, there is no information available regarding sex differences in the degree of aerobic deconditioning after spaceflight in humans. However, in response to simulated microgravity exposure, the relative changes in aerobic capacity are similar between sexes[51] despite the marked differences in absolute values.[45]

Recommended Research Priorities

An overarching consideration is that all cardiovascular investigations for NASA missions are relevant to women because gender perspectives can make research better and inform methods and questions. Over-sampling of women in research studies will allow a gender distribution to reflect the prevalence of the specific disease or condition in the population.

Because orthostatic intolerance disproportionately impacts women, sex-specific mechanisms should be elaborated: autonomic activity, estrogen and other hormone levels, lower center of gravity, younger age. The relevance of sleep deprivation effect by gender is important to ascertain.

Vascular function and stiffness increase with aging (see Shirway and Zou, 2010 for review [51]). Since spaceflight is

hypothesized to simulate vascular aging,[52] it is important to examine gender-specific effects on vascular endothelium and thrombotic risk as predisposing factors to atherosclerosis, as well as to examine neurohormonal sex differences. Early endothelial dysfunction is characteristic even of early atherosclerosis, and its effect on vascular compliance must be examined. Retinal artery narrowing, a measure of microvascular disease, predicts cardiovascular risk and mortality in women, but not in men; other vascular beds require gender-specific evaluation, both at baseline and with spaceflight.

In regard to atherosclerosis, there should be emphasis on novel biomarkers and noninvasive imaging in studying gender differences. The evaluation of baseline risk and changes after spaceflight is important. Candidate biomarkers include High-sensitivity cReactive Protein (hsCRP) and micro RNAs. Candidate atherosclerotic imaging studies include ankle brachial index, carotid intima-media thickness, and coronary artery calcium. Further, in regard to atherosclerosis, the roles of metabolic syndrome, thrombosis, and inflammation require ascertainment. There are gender differences in metabolic syndrome and subsequent risk for diabetes and cardiovascular disease, with population risk appearing greater in women. In regard to thrombosis, women compared with men have an increased risk of venous thromboembolism, pulmonary embolism, and thrombotic stroke, with question as to the component of estrogen effect on this increased risk. Issues of thrombosis may be relevant to spaceflight in regard to oral contraceptives and menopausal hormone therapy. Inflammation is also likely important in the development of atherosclerosis. Women have an increase in inflammatory-mediated autoimmune diseases and gender differences in the markers of inflammation (e.g., hsCRP) requiring examination. There should be exploration of gender differences on the effect of spaceflight on these inflammation markers and examination of other inflammatory markers, as well as gender differences in genomic markers of aging with spaceflight.

NASA's VIIP research arm, a part of the Human Research Program, includes in its research plan several studies which may shed light on the sex difference in VIIP, including terrestrial head-down tilt bed rest studies, hindlimb elevation rodent models, data mining, and computer modeling.

Research Infrastructure

As currently written, the Human Research Program Research Plan for the Cardiovascular Discipline makes no mention of sex or gender differences. It is imperative that these differences are recognized and that future research is directed at elucidating them, with the challenge of whether all countermeasures work comparably in women and men. It is important to increase science participation by spaceflight crew members, possibly disproportionately by women crew members. This will require a more concerted effort to educate the astronaut corps on the necessity of biomedical research, and specifically the need for research on sex and gender differences.

Summary and Recommendations

Sex- and gender-based differences in cardiovascular risk and disease can help identify research needs and opportunities. Given that 20% of current astronauts and 50% of the recently selected astronaut recruits are women, the authors suggest adaptation of the National Heart, Lung, and Blood Institute approach to including women and female animal models in ground-based analogs of spaceflight and clinical trials, namely the expectation that funded studies reflect the composition of the overall population at risk for the specific disease to be studied.

Author Disclosure Statement

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