2013 DECADAL STUDY

The Impact of Sex & Gender on Adaptation to Space

A Joint Study by the National Aeronautics and Space Administration and the National Space Biomedical Research Institute

Cardiovascular Alterations

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Terrestrial Medicine-Based Consensus of the Impact of Sex and Gender on Cardiovascular Alterations

- **Cardiovascular (CV) disease leading cause of death in women**
  - Young women have less CV disease compared to men and may be best suited for long space missions
  - Gender differences in risk factors - ↑ risk smoking, diabetes in women
  - Greater CV morbidity, mortality in women once disease is present
  - Women do not consistently receive optimal preventive strategies, diagnostic procedures, treatments because of perception of low risk
  - Need to explore sex/gender effects of radiation exposure of spaceflights on CV risk factors, CV disease

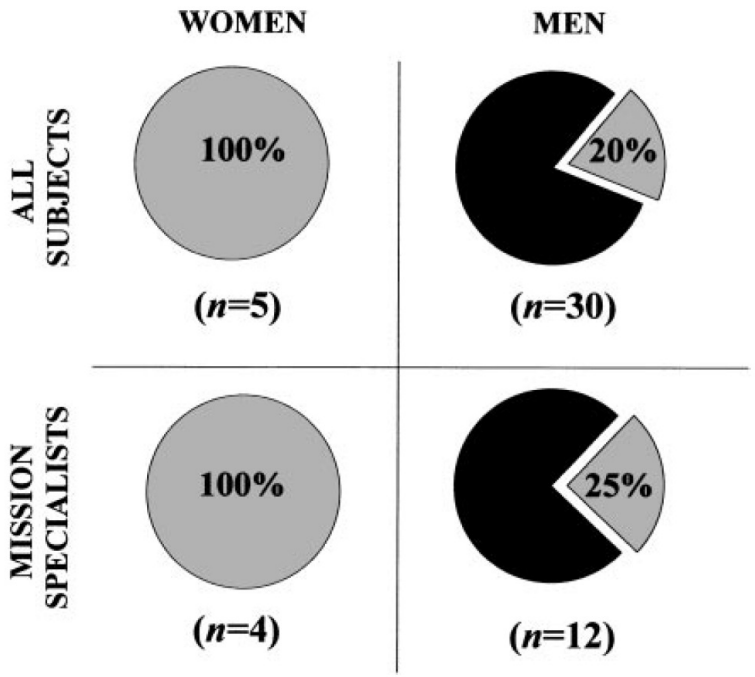
- **Hormone concerns unique to women**
  - Oral contraceptives (OCs) may ↑ blood pressure
    - No evidence ↑ risk MI but ↑ risk VTE
    - differences with newer OC formulations
  - Menopausal hormone therapy (MHT)
    - Effects on autonomic BP control, volume status, orthostatic tolerance

- **Exercise effects in women – simulated space studies**
  - ↑ Orthostatic tolerance, preserved cardiac volume, ↑cardiac mass
  - ? Gender effect of preconditioning prior to spaceflight

Current Understanding of the Impact of Sex and Gender on Cardiovascular Alterations in Space

- In the past decade, little space flight research has been conducted that addresses cardiovascular (CV) differences due to sex or gender (low n, few female astronauts).

- Orthostatic tolerance: significant progress made regarding mechanisms and countermeasure development
    - Women have smaller hearts and blood volumes than men, which make them more susceptible to orthostatic intolerance after microgravity exposure
  – Women have a greater loss of plasma volume than men following spaceflight
    - Evaluation of countermeasures
  – Sex differences in response to CV stress – women ↑ HR, men ↑ vascular resistance



Waters, JAP, 2002

Current Understanding of the Impact of Sex and Gender on Cardiovascular Alterations in Space II

- Arrhythmia: none identified during short duration flight, some arrhythmias found during long duration flight. Exciting study just completed, waiting for results (Bungo, Levine).
  - Unknown if spaceflight increases risk of arrhythmias, sex/gender differences have not been studied
    - Baseline sex differences in supraventricular, ventricular arrhythmias
    - Baseline sex ECG differences
  - New work largely centers on acquired CV disease due to spaceflight

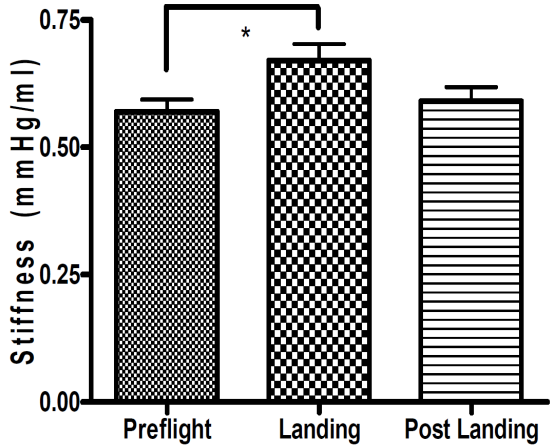


Figure 1. Estimated arterial stiffness of male astronauts ten days before, immediately after, and three days following a mission. *p= 0.0145. Data are reported as means +/- SE.

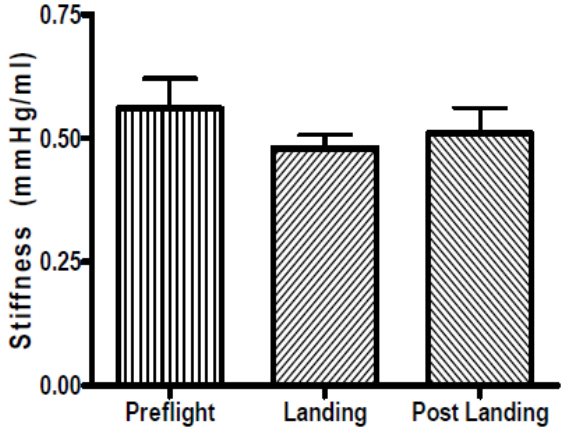


Figure 2. Estimated arterial stiffness of female astronauts ten days before, immediately after, and three days after a mission. Data are reported as means +/- SE.

Tuday, et al, 2011

Current Understanding of the Impact of Sex and Gender on Cardiovascular Alterations in Space

- Substantial ground based research designed to evaluate sex differences
- Studies involving animal models in the last 10 years reveal important effects on vascular structure and function but are largely equivocal regarding sex/gender differences
- Comprehensive study in women of effects of bed rest, completed in 2005 -WISE-2005 (3 groups of 8 women, 24 total) at least 10 published papers
  - Women experienced similar reduction in cardiac mass during bed rest as observed in studies of men (Dorfman)
  - Reduced leg vascular resistance in women at rest and following infusion of Isoproterenol; men in other studies had higher vascular resistance to same infusion. These contrasting findings might partially explain sex/gender differences in orthostatic tolerance
- Other NASA funded bed rest studies showed sex differences in baroreflex sensitivity (Arzeno) and stroke volume (Fu).

Current Understanding of the Impact of Sex and Gender on Cardiovascular Alterations (VIIP) in Space

VISUAL IMPAIRMENT INTRACRANIAL PRESSURE (VIIP) SYNDROME

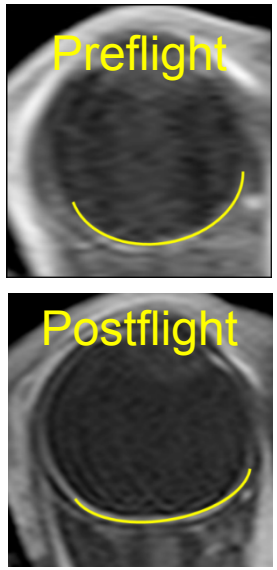
- Background
  - Newly identified risk, multiple studies underway
  - NASA's leading spaceflight-related health risk

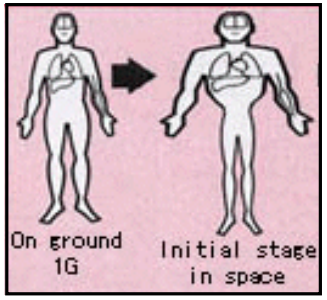
- Main signs and symptoms are ocular
  - Changes to ocular structures: Optic disc edema, choroidal folds, cotton wool spots, globe flattening, distended optic nerve sheath
  - Changes to ocular function: Decreased near visual acuity, enlarged blind spot
  - Unknown implications for long-term health

- Pathophysiologic hypothesis involves interplay between cardiovascular, ocular and central nervous system:
  - Microgravity-induced cephalad fluid shifts
  - Loss of gravity-assisted venous drainage from brain

  → Cephalic congestion, ↑ intracranial pressure, effecting eyes

Globe Flattening





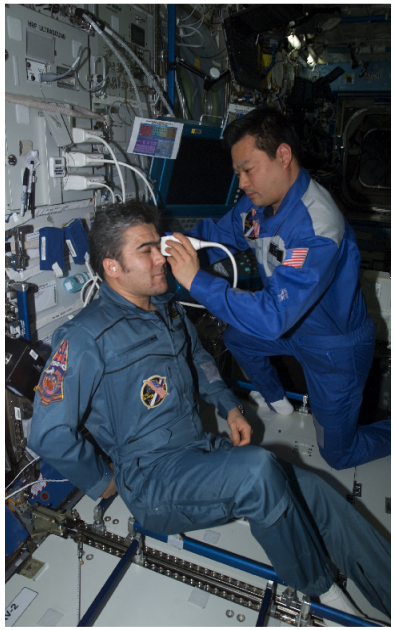
Current Understanding of the Impact of Sex and Gender on Cardiovascular Alterations (VIIP) in Space

VISUAL IMPAIRMENT INTRACRANIAL PRESSURE (VIIP) SYNDROME

- Terrestrial analog to VIIP - Idiopathic Intracranial Hypertension (IIH) - More prevalent in young overweight women, reason unclear
- VIIP is slightly more predominant in males
  - 82.3% among males, 62.5% among females (no statistical signific.)
- Severity of signs/symptoms much milder in females
  - Higher vascular compliance in females may be protective
  - Female crew also younger (younger age = higher compliance)
  - 65% of the males vs. 25% of the females (p=0.024) have high-acceleration jet pilot training, which may be associated with lower vascular compliance and higher VIIP susceptibility
- Path forward
  - NASA's Human Research Program planning several studies which may shed light on the sex difference in VIIP, using bed-rest, animal and computer models, and data mining of crew data

Fundoscopy on ISS

Eye Ultrasound on ISS



Recommended Research Priorities

- **Overarching considerations**
  - All cardiovascular areas relevant to NASA mission, worthy to investigate in women – gendered perspectives can make research better, inform methods used and questions asked
  - Over-sampling of women in research studies – gender distribution should reflect prevalence of specific disease/condition
- **Orthostatic intolerance** disproportionately impacts women, who are underrepresented in current studies
  - Sex-specific mechanisms: autonomic activity, estrogen levels, lower center of gravity, younger age
  - Relevance of sleep deprivation effect by gender
- Vascular function/stiffness with **aging**
  - Spaceflight simulates aging
    - Effects on vascular endothelium, thrombotic risk → atherosclerosis
    - Neurohomonal sex differences
  - Retinal artery narrowing, measure of microvascular disease, predicts CV risk, mortality in women not men – other vascular beds require evaluation

Recommended Research Priorities II

- **Atherosclerosis** – emphasis on novel biomarkers, noninvasive imaging
  - Evaluate in both men and women, ? gender differences
  - Evaluate re baseline risk, changes after spaceflight
  - Candidate biomarkers – hs CRP, micro RNAs
  - Candidate atherosclerotic imaging studies – ankle brachial index (ABI), carotid intima-media thickness (cIMT), coronary artery calcium (CAC)
  - role of Thrombosis, and Inflammation
    - Thrombosis
      - ↑ risk VTE, PE, thrombotic stroke in women vs men - ? estrogen effect
      - ? relevance to spaceflight re OCPs, MHT
    - Inflammation
      - Women ↑ inflammatory-mediated autoimmune disease
      - Gender differences markers of inflammation (eg hs CRP)
      - Gender differences in effect of spaceflight on markers of inflammation
      - Some evidence for oxidative stress, active research field
- Sex differences in **genomic markers** of aging with spaceflight

Research Infrastructure Required to Enable Progress

- Sex and gender differences should be incorporated into the Risk/ gap/task structure of the Human Research Program.
  - do all countermeasures work comparably in men and women?

- Must increase science participation by crew members, perhaps disproportionately by women.
  - Encouraging that new astronaut class 50% women

Summary

- Decadal review of sex/gender in adaptation to spaceflight goal → insure health/safety of male and female astronauts during long-duration space missions

- With aging of astronaut population, issues of cardiovascular health/disease in midlife come to forefront
  - Likely differ by sex/gender

- Sex differences in orthostatic hypotension, vascular stiffness with aging, thrombosis, and inflammation exist and may have an important impact on the outcomes of the female astronaut. While current studies show that differences exist, most have **small subject numbers**, with limited scientific validity.

- Sex/gender-based differences in cardiovascular risk and cardiovascular disease help identify research needs and opportunities

- Given that 20% of astronauts are women (50% of recently selected class), suggest adaptation of NHLBI approach to inclusion of women in research studies
  - Expectation that funded studies reflect composition of overall population at risk for disease