Gender differences in bed rest: preliminary analysis of vascular function

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Orthostatic intolerance is a recognized consequence of spaceflight. Numerous studies have shown that women are more susceptible to orthostatic intolerance following spaceflight as well as bed rest, the most commonly used ground-based analog for spaceflight. One of the possible mechanisms proposed to account for this is a difference in vascular responsiveness between genders. We hypothesized that women and men would have differing vascular responses to 90 days of 6-degree head down tilt bed rest. Additionally, we hypothesized that vessels in the upper and lower body would respond differently, as has been shown in the animal literature. Thirteen subjects were placed in bedrest for 90 days (8 men, 5 women) at the Flight Analogs Unit, UTMB. Direct arterial and venous measurements were made with ultrasound to evaluate changes in vascular structure and function. Arterial function was assessed, in the arm and leg, during a reactive hyperemia protocol and during sublingual nitroglycerin administration to gauge the contributions of endothelial dependent and independent dilator function respectively. Venous function was assessed in dorsal hand and foot veins during the administration of pharmaceuticals to assess constrictor and dilator function. Both gender and day effects are seen in arterial dilator function to reactive hyperemia, but none are seen with nitroglycerin. There are also differences in the wall thickness in the arm vs the leg during bed rest, which return toward pre-bed rest levels by day 90. More subjects are required, especially females as there is not sufficient power to properly analyze venous function. Day 90 data are most underpowered.

Gender differences in bed rest: preliminary analysis of vascular function

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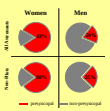
ABSTRACT

Orthostatic intolerance is a recognized consequence of spaceflight. Numerous studies have shown that women are more susceptible to orthostatic intolerance following spaceflight as well as bed rest, the most commonly used ground-based analog for spaceflight. One possible mechanism to account for this is a difference in vascular responsiveness between genders. We hypothesized that women and men would have differing vascular responses to 90 days of 6° head-down tilt bed rest. Additionally, we hypothesized that blood vessels in the upper and lower body would respond differently, as has been shown in the animal literature. We employed a 30 minute, 80° head-up tilt as an orthostatic stress to test the cardiovascular deconditioning to bed rest. Direct arterial and venous measurements were made with ultrasound to evaluate changes in vascular structure and function. Arterial function was assessed, in the arm and leg, during a reactive hyperemia protocol and during sublingual nitroglycerine administration to gauge the contributions of endothelial dependent and independent dilator function, respectively. Venous function was assessed in dorsal hand and foot veins during the administration of various combinations of ketoralac, phenylephrine, isoproterenol, acetylcholine, L-NMMA and nitroglycerin to assess constrictor and dilator function. Both gender and day effects are seen in flow-mediated dilation, but none are seen with the endothelium-independent dilator nitroglycerin. There are also differences in arterial wall thickness in the arm vs. the leg during bed rest. More subjects are required, especially females as there is not sufficient power to properly analyze venous function. Day 90 data are most underpowered.

INTRODUCTION

- Orthostatic hypotension continues to be a problem following spaceflight, especially long duration spaceflight.
- Females are more susceptible to orthostatic hypotension and presyncope.



- Numerous citations in the literature point to a venous return issue, this may include differences in arterial or venous function.
- Animal literature shows a differential remodeling of vasculature that leads to structural and functional changes. There is also bed rest evidence for increased arterial dilator function.
- We studied arterial and venous function in subjects confined to 90 days of head-down tilt bed rest, which is the most widely accepted ground-based analog of spaceflight.

HYPOTHESIS

We hypothesized that gender will influence the vascular responses to bed rest.

We also tested the hypothesis that arteries in the arm and leg would remodel during bed rest. Additionally, we tested the hypothesis that they would follow different patterns of remodeling during head down bed rest.

METHODS

•Thirteen subjects are included in this study (8 men and 5 women) from the Flight Analogs Project being conducted at UTMB in conjunction with NASA.

• To determine arterial function (flow-mediated dilation and direct dilation), data were collected on arterial diameters and flows at baseline, during reactive hyperemia (5 minutes in the arm, 7 minutes in the leg) and following administration of sublingual nitroglycerin (0.4mg). Imaging of the brachial artery was performed above the antecubital fossa while the anterior tibial artery was measured proximal to the knee. Baseline images were obtained with special attention paid to acquiring images that had well visualized intimal-medial borders. For measurements during reactive hyperemia, diameters were measured 30 seconds post-occlusion until 5 minutes post-occlusion. For measurements during administration of sublingual nitroglycerin, diameters were measured 3 minutes following drug administration and continuing until 2 minutes after maximum dilation of vessel.

•To determine venous function, pharmacological agents were slowly infused in either the hand and foot veins. Using ultrasound, vein diameters and areas were measured. Phenylephrine (3,160 ng/0.1 ml) was used to pre-constrict the veins through the duration of the study. Either indomethacin (12.5 µg/0.05 ml, n=10) or ketorolac (3.0 µg/0.1 ml, n=3) was used to block prostaglandins through the duration of the study. Analysis was performed comparing the two prostaglandin blockers. There was no statistical difference between the two groups. Thus, they were pooled for further analysis. To determine maximum dilation of the vessel, an acetylcholine dose response curve was created with the following dosages: 0.1 nmol/0.05 ml; 0.316 nmol/0.05 ml; 1.0 nmol/0.05ml; 3.16 nmol/0.05 ml; 10 nmol/0.05 ml; and 20 nmol/0.05ml. Using the acetylcholine dose that caused the greatest dilation and L-NMMA (50 µg/0.05 ml), % inhibition of NO was determined. Lastly, nitroglycerin (16 pmol/ 0.1 ml) was administered as a measure of endothelium-independent dilator function.

RESULTS I : Reactive Hyperemia

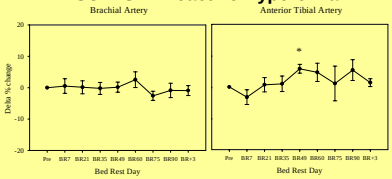


Figure 2. Reactive hyperemic responses (flow-mediated dilation) during bed rest for all subjects. These graphs show the difference between pre- and post-occlusion (delta) for each time point. There were no statistical differences in the brachial artery, left panel. There was a significant difference in the anterior tibial artery, right panel, on bedrest day 49.

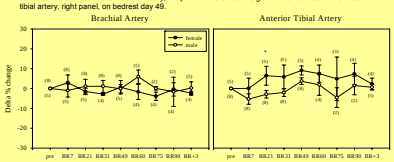


Figure 3. Reactive hyperemic responses (flow-mediated dilation) during bed rest separated by gender. These graphs show the difference between pre- and post-occlusion (delta) for each time point. There were no significant differences in the brachial artery, left panel. There was a significant difference in the anterior tibial artery, right panel, delta on bedrest day 21 between men and women.

RESULTS II : Sublingual Nitroglycerin

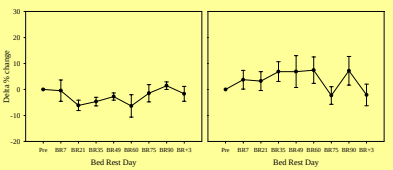


Figure 4. Direct arterial dilation with nitroglycerin. These graphs show the difference between pre- and post-drug ingestion (delta) for each timepoint for all subjects. There were no statistical differences in the brachial artery, left panel, or in the anterior tibial artery, right panel.

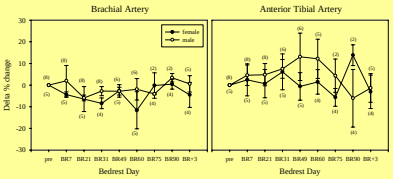


Figure 5. Direct arterial dilation with nitroglycerin. These graphs show the difference between pre- and post-drug ingestion (delta) for each timepoint for all subjects separated by gender. There were no statistical differences in the brachial artery, left panel, or in the anterior tibial artery, right panel.

RESULTS III: Intimal Medial Thickness

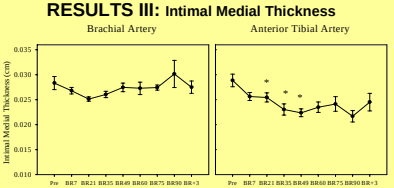


Figure 6. Intimal medial thickness. The intimal medial thickness (cm) decreased during bed rest in the anterior tibial artery only (right panel). * = p ≤ 0.05 within group for bed rest day compared to pre bed rest.

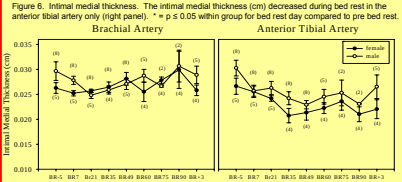
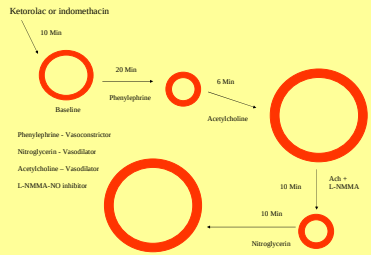


Figure 7. Intimal medial thickness separated by gender. No statistical differences were found between genders.

Dorsal Hand or Foot Vein Protocol Timeline



Ultrasound images of dorsal veins

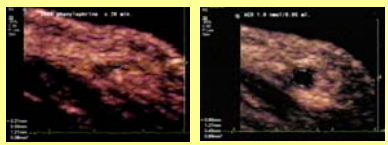


Figure 13.Ultrasound image of dorsal vein showing maximum dilation with acetylcholine, right panel, as compared to baseline pre-constriction, left panel.

RESULTS IV: Venous Function

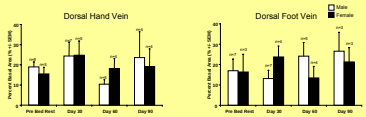


Figure 8. Phenylephrine pre-constriction (3160 ng/ 0.1 ml) by gender.

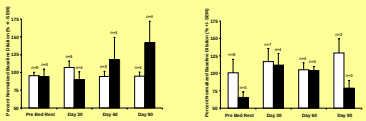


Figure 9. Effects of Prostaglandin Blockade (indomethacin (12.5 µg/0.05 ml) or ketorolac (3.0 µg/0.1 ml)) by gender.

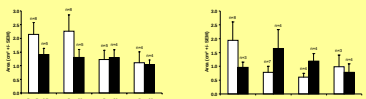


Figure 10. Maximum endothelium-dependent dilation using acetylcholine dose response curve separated by gender.

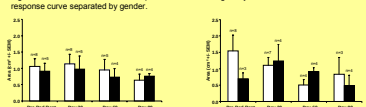


Figure 11. Acetylcholine plus L-NMMA (50 µg/0.05 ml) separated by gender showing nitric oxide inhibition by L-NMMA.

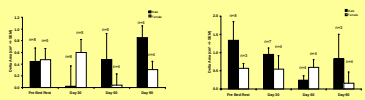


Figure 12. Endothelium-independent dilation by the NO donor nitroglycerin (16 pmol/ 0.1 ml) separated by gender.

SUMMARY

There were no differences in flow-mediated dilation response in the arm at any time point. However, the flow-mediated dilation response in the leg was significantly increased at day 49. There is a trend for a gender difference over the course of bedrest in the anterior tibial artery ($p = 0.07$). On day 21, there is a significant difference in the anterior tibial artery between men and women.

Arterial responses to nitroglycerin did not change over the duration of bed rest (day effect) in either the brachial or anterior tibial artery, however, the anterior tibial artery dilated more than the brachial artery ($p = 0.001$).

There was a marked decrease in intimal-medial thickness in the anterior tibial artery at days 21 (10.3%), 35 (20.6%) and 49 (24%).

We were unable to detect any differences in the dorsal hand or foot vein responses to pharmacological agents during bed rest.

CONCLUSIONS:

These data show that some arterial and measures change during bed rest, while others do not. The challenge is to elucidate which parameters may translate into functional decrements on long duration spaceflight. Flow-mediated dilation and intimal-medial thickness has been shown to be clinically relevant indicators of dysfunction in patients exhibiting disease.

We do not have sufficient statistical power to detect any changes in venous function. Twelve more females and 9 more males will be studied.

Further study is needed to determine if these measures can provide any insight into the effects of bed rest, or spaceflight, on cardiovascular performance in otherwise healthy subjects.

Limitations

A major limitation for this study is the subject number at the varying time points. This is largely due to the forced evacuation of subjects for Hurricane Rita. Those subjects, therefore, only completed 44-53 days of the designed **90** day bed rest protocol. Thus, only a subset of subjects completed the full 90 days of bed rest. Due to the relatively small number of women participating, the statistical power was limited.