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

Although orthostatic intolerance is a recognized consequence of spaceflight, symptoms studies have been performed on only a few subjects. One possible mechanism to account for this is a decrease in vascular function during bed rest. This study evaluated the effects of 90 days of head-down tilt bed rest on vascular function using reactive hyperemia and sublingual nitroglycerin (NTG) in a cohort of healthy volunteers. Of interest, there was no difference in flow-mediated hyperemia when comparing the leg or arm. NTG did not change in either the leg or arm. In females, there was an increase in intimal-medial thickness in the anterior tibial artery; however, there was no significant difference in anterior tibial artery in males. In conclusion, 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.

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.

METHODS

• Volunteers are included in this study of men and 5 women from the Flight Analog Project being conducted at NASA in cooperation with NASA.
• To determine arterial function (flow-mediated dilation and direct dilation), data were collected on arterial diameters and areas baseline, during reactive hyperemia (5 minutes in the arm, 7 minutes in the leg) and following administration of sublingual nitroglycerin (0.4 mg). Monitoring of the brachial artery was performed above the antecubital fossa while the anterior tibial artery was measured proximal to the ankle. Baseline images were obtained with special attention paid to acquiring images that had well visualized intimal-medial structure.
• For measurements during reactive hyperemia, diameters were obtained by ultrasonography. Measurements during administration of sublingual nitroglycerin, diameters were obtained with a caliper following drug administration and continuing up to 3 minutes after maximum dilation of vessel.
• To determine venous function, pharmacological agents were slowly infused in the femoral and foot veins. Using ultrasonography, ven diameters and areas were measured. Phentolamine sulfat (100 mg i.v.) was used to block parasympathetic tone to improve venous return. 0.05 mg/kg of Atropine (0.5 ml i.v.) was used to block parasympathetic tone through the autonomic nervous system. Following the autonomic nervous system block, there was no statistical difference between the two groups. Thus, they were then infused with further agents. To determine maximum dilation of the veins, 1 ml of 0.8% saline was infused into the foot vein (n=5) and the foot vein (n=5) and 2 ml of 0.8% saline was infused into the femoral vein (n=3) and the femoral vein (n=3). Using the autonomic drugs, we were unable to detect any differences in the dorsal hand or foot vein responses to pharmacological agents during bed rest.

RESULTS I: Reactive Hyperemia

• Baseline
• Anterior Tibial Artery

RESULTS II: Sublingual Nitroglycerin

• Baseline
• Anterior Tibial Artery

RESULTS III: Intimal Medial Thickness

• Baseline
• Anterior Tibial Artery

RESULTS IV: Venous Function

• Female
• Male

CONCLUSIONS:

These data show that some arterial and venous function 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.

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.

Limitations

A major limitation for this study is the subject number at the varying time points. This is largely due to the forest evacuation of subjects for Hurricane Rita. Those subjects, therefore, only completed 44-53 days of the designed 90 day bed rest protocol. Thus, 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.