FINAL REPORT

Title: Vestibular modulation of autonomic responses to orthostasis

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Grant#: NAG9-1262

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Introduction:
Orthostatic intolerance and related functional impairment remain a common problem for astronauts upon return from space. Despite considerable effort to develop countermeasures for this problem, a fundamental question remains unanswered: What is the cause of orthostatic intolerance? Post-flight symptoms vary widely and include both vestibular and orthostatic intolerance manifestations. The role of vestibular disturbances in orthostatic intolerance is unknown. Although it is known that vestibular signals project to the vasomotor centers of the brainstem in cats, there has been no prospective study of vestibular system effects on blood pressure control *during orthostasis* or on *orthostatic tolerance* in humans. Most fundamental, it remains unknown whether otolith inputs play an important role in the cardiovascular adjustments to the upright position in humans. The altered vestibular function after spaceflight may influence orthostatic tolerance indirectly (producing intolerable symptoms requiring recumbent posture) and/or directly (by affecting autonomic responses to orthostasis). Post-flight vestibular disturbances are complex and probably include some involvement of otolith inputs, semicircular canal inputs and related inputs. The purpose of this proposal was three-fold: 1) to determine the otolith contribution to the cardiovascular adjustments to the upright position; 2) to determine whether altering otolith or semicircular canal inputs affect blood pressure regulation during orthostasis; 3) to determine whether altering otolith or semicircular canal inputs affect orthostatic tolerance.

Critical Path: These studies primarily address Critical Path Roadmap Risk # 6, Diminished Cardiac and vascular Function, and in particular question #6f: *What are the physiological and environmental factors by which space fight decreases orthostatic tolerance?* However, they also address the primary Risk #15: *Motion Sickness.* The studies address potential mechanisms of interaction between vestibular inputs (which contribute to motion sickness) and cardiovascular control. These goals were met by addressing the following specific aims.

Aim 1: To determine the role of otolith input in mediating the cardiovascular adjustments to the upright position.

Hypothesis 1: The change in otolith orientation with assuming the upright position contributes significantly to the pressor responses to orthostasis.

Aim 2: To determine how otolith orientation affects the occurrence of pre-syncopal symptoms during an orthostatic stress.

Hypothesis 2: A positive otolith orientation (60° vs. 0°) will improve orthostatic tolerance by enhancing the normal cardiovascular compensatory responses to orthostasis.

Aim 3: To determine the effect of semicircular canal stimulation (with caloric testing) on the cardiovascular adjustments to orthostasis.

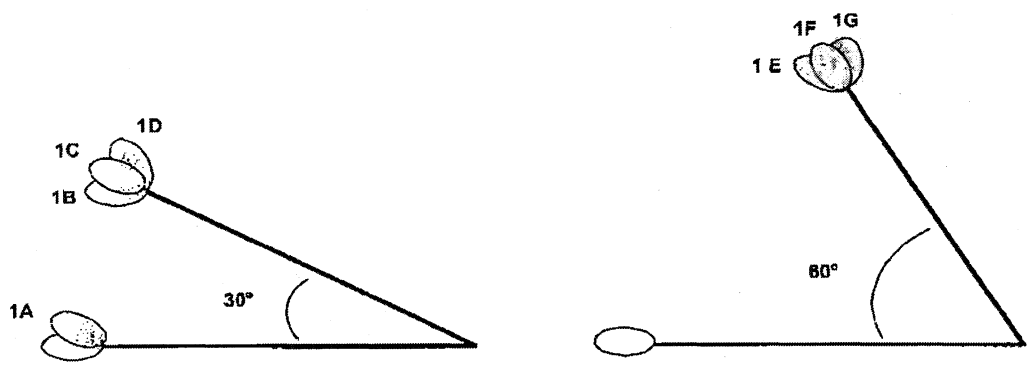
Hypothesis 3A: Semicircular canal stimulation provokes blood pressure and heart rate lability during sustained orthostasis.

Aim 4: To determine the effect of semicircular canal stimulation (with caloric testing) on orthostatic tolerance.

Hypothesis 4: Semicircular canal stimulation accelerates the onset of pre-syncope.

Materials & Methods:

Study 1: This study was performed to address aim 1. The response to *seven perturbations (1A-G)* involving combinations of *head-up tilt* (0°, 30° and 60°) and neck position to affect *otolith orientation* (30° flexion or extension) were obtained in *random order*. Figure 1 illustrates the seven conditions with the otolith orientation labeled



(relative to a 0° horizontal position). Table 1 shows the tilt levels, neck orientation and resulting otolith orientation (relative to horizontal) for each perturbation. Each perturbation was sustained for 5 minutes and at least 5 minutes of recovery was allowed between each perturbation.

FIGURE 1. Illustration of the tilt angle and otolith orientation for each perturbation in study 1.

Table 1. Orthostatic and Otolithic Orientation of Each Perturbation

	Tilt Level (degrees)	Neck Orientation (degrees)	Otolith Orientation (degrees)
1A	0	+30 (flexion)	30
1B	30	-30 (extension)	0
1C	30	0 (body plane)	30
1D	30	+30 (flexion)	60
1E	60	-30 (extension)	30
1F	60	0 (body plane)	60
1G	60	+30 (flexion)	90

Otolith orientation is relative to the horizontal position (0°)

Dependent variables: Heart rate, arterial pressure, sympathetic nerve activity, stroke volume, left ventricular end-diastolic dimensions and volumes, left ventricular end-systolic dimensions and volumes, calculated cardiac output, calculated systemic vascular resistance, cerebral blood flow velocity and estimated flow rate, spectral power for high (0.2-0.4 Hz) and low (0.03-0.15 Hz) frequency oscillations of heart rate and arterial pressure (as indices of parasympathetic and sympathetic tone).

Independent variables: Head-up tilt levels (0, 30° and 60°), otolith orientation to horizontal position (0, 30°, 60°, and 90°).

Study 2: This study addressed *specific aim 2* by assessing the heart rate, arterial pressure, sympathetic nerve activity, heart rate and blood pressure variabilities, respiration, responses to sustained orthostasis (30° head-up tilt plus lower body negative pressure at 10, 20 and 30 mmHg) with and without otolith input (0° vs. 60° otolith orientation). The responses to graded orthostasis to tolerance or to completion of the stress will be studied with a supine otolith orientation (0°) or upright otolith orientation (60°) produced by changes in head position on the tilt table. Graded orthostasis was delivered by head-up tilt to 30° combined with graded LBNP (0, -10, -20 and -30 mmHg) for 5 minutes at 0, -10 and -20 mmHg, and up to 10 minutes at -30 mmHg. The total stress level of LBNP and duration of stress was used to quantify orthostatic tolerance as in previous studies [37, 38]. The tilt angle of 30° was added as an additional 30 mmHg of LBNP for this calculation.

Dependent variables: Heart rate, arterial pressure, sympathetic nerve activity, thoracic impedance, orthostatic tolerance (cumulative stress), spectral power for high (0.2-0.4 Hz)

and low (0.03-0.15 Hz) frequency oscillations of heart rate (as indices of parasympathetic and sympathetic tone).

Independent variables: Otolith orientation to horizontal position (0 vs. 60°).

Study 3: This study addressed *specific aims 3 and 4* by assessing the heart rate, arterial pressure, SNA, heart rate and blood pressure variabilities, responses to graded orthostasis (lower body negative pressure at -30, -40, -50 and -60 mmHg) with and without semicircular canal stimulation (caloric ear canal irrigation). Three experimental protocols were performed on 2 separate days: On day 1, the subject's orthostatic tolerance will be determined by the time to onset of pre-syncopal physiological and subjective symptoms during graded LBNP. On day 2, the LBNP protocol was repeated twice: Once with a cold caloric stimulus sufficient to sustain a vestibulo-ocular response (nystagmus measured with electrooculography); and once with a thermoneutral caloric stimulus which produces no vestibulo-ocular response. The caloric stimuli were delivered one level of negative pressure *prior* to the onset of pre-syncopal symptoms determined in the baseline studies on day 1 (e.g. caloric testing will be applied during -30 mmHg if the preliminary study terminated at -50 mmHg). The order of the two protocols was randomized among subjects.

Dependent variables: Heart rate, arterial pressure, cardiac impedance, orthostatic tolerance, spectral power for high (0.2-0.4 Hz) and low (0.03-0.15 Hz) frequency oscillations of heart rate and arterial pressure (as indices of parasympathetic and sympathetic tone).

Independent variables: The three caloric stimulus conditions of no caloric, thermoneutral caloric or cold-warm caloric.

Results:

Study 1: Subjects underwent three 60° upright tilts: 1) with the neck flexed passively from 0 to 30° relative to the body during a 60° tilt, such that the head moved from horizontal to 90° above horizontal (thereby producing a 0 to 1 Gz otolith stimlulation); 2) with the head and body aligned, such that they tiled together to 60° (0 to 0.87 Gz otolith stimluation); and 3) with the neck flexed 30° relative to the body during supine conditions, and the neck then extened to -30° during 60° body tilting, such that the head remained at 30° above horizontal throughout body tilting (thus producing a constant 0.5 Gz otolith condition). Within the first 20 s of tilt, arterial pressure increased most obviously in the 0 to 1 Gz otolith condition. Thoracic impedance tended to increase more in otolith-constant conditions, but no dependent variable differed significantly between tilt conditions, and no significant time x tilt interactions emerged. All three tilt conditions increased thoracic impedance (consistent with a footward shift of blood volume), sympathetic nerve activity (224-275% at 20 sec and for the subsequent 3 minutes), arterial pressure and heart rate (all variables $P < 0.01$). However, no significant differences between the three tilt conditions were observed at any of the time points recorded ($P > 0.44$). Therefore, these data suggest that the otolith organ does not contribute significantly to the normal cardiovascular adjustments to orthostasis.

Study 2: Whether an interaction does occur during prolonged orthostasis can occur and thereby affect orthostatic tolerance remains to be determined. In study 2, the effect of altered otolith input on the response to graded orthostasis and on orthostatic tolerance was investigated. Subjects were exposed to graded orthostasis with a supine (0°) orientation or an upright (+60°) orientation. The graded orthostasis was produced by a combination of 30° head-up tilt plus gradations of lower body negative pressure. The results demonstrated that there was a trend (P=0.12) for greater increases in heart rate, but not for differences in arterial pressure or vascular resistance during the graded orthostasis (P>0.3). In addition, changes in low frequency and high frequency spectral power trended toward significance (0.08<P<0.19), but did not achieve significance. In some subjects, this effect suggests that autonomic control was modestly affected by the otolith stimulus during graded orthostasis.

Study 3: In study 3, Graded LBNP was performed to orthostatic tolerance with the combined tilt and LBNP procedure described above. The graded orthostatic challenge was administered on two occasions: First, as a baseline for determination of orthostatic tolerance and then in duplicate with and without an air caloric (cold vs. thermoneutral control) to elicit semicircular canal stimulation performed at one level of LBNP below the highest tolerated level in a baseline LBNP study. The order of administration of the stimulus was randomized. Significant nystagmus was provoked by the caloric stimulus in each subject with insignificant effects on baseline heart rate (64±4 vs. 67±3, P> 0.43), mean arterial pressure (93 ± 3 vs. 90 ± 3, P > 0.37) or sympathetic nerve activity (288 ± 61 vs. 229 ± 49, P>30) consistent with previous pilot data and previous findings. The cold caloric stimulation performed during LBNP resulted in similar changes as the thermoneutral stimulus in heart rate and blood pressure suggesting that there was not a significant effect of semicircular canal stimulation. There was an increase in the high frequency spectral power of heart rate (P=0.02), but no difference in the low frequency spectral power or LF/HF ratio suggesting that there was an effect on the vagal control of heart rate, but unlikely to be a significant effect on sympathetic control of the heart. Sympathetic nerve activity changes with LBNP were similar (Δ188±43% vs. Δ231±29% with and without cold caloric stimulus, respectively. Most importantly, orthostatic tolerance was not significantly changed by the addition of the caloric stimulus (P=0.31), with 8 out of 10 subjects showing similar orthostatic tolerance.

Discussion

Several studies in animals have shown that vestibular organ inputs provide input into cardiovascular regulatory centers of the brainstem. Moreover, there is evidence that vestibular activation can produce cardiovascular effects. In addition, studies from Ray *et al.* have shown that otolith stimulation by forward head rotation off of a table when in the prone position produces significant autonomic and cardiovascular responses. Last, since astronauts often experience orientation and motion sickness symptoms upon return to a 1G environment after spaceflight, it is clear that both the otolith and simcircular canal organs are affected. Therefore, it follows that these altered vestibular organ inputs may influence importantly the orthostatic-evoked cardiovascular responses, yet this had not been directly tested.

The data from the present studies suggest that otolith stimulation does not play an important role in the normal autonomic and cardiovascular adjustments to the upright position. This includes both the abrupt and sustained changes during an orthostatic challenge. The data do provide some support for subtle changes and thus, contribution to the cardiovascular response; however, in the normal healthy human, it does not appear that otolith responses are of primary importance to the cardiovascular responses as mediated by the autonomic nervous system. Previous studies have shown that semicircular canal stimuli do not profoundly affect cardiovascular responses and the current data support this outcome. Nevertheless, the caloric stimulus did provoke some change in the vagal control contributing to evidence of some cardiovascular lability. This did not however translate into impaired orthostatic intolerance.

Relevant to the critical path, it is likely that some episodes of post-flight orthostatic intolerance are a manifestation of vestibular dysfunction (hypersensitivity) and associated symptoms of motion sickness. In a normal healthy individual (not exposed to microgravity or simulated microgravity), it does not appear that the otolith system is a primary contributor to orthostatic tolerance. Although there is evidence for the potential of vestibular inputs to affect autonomic control of cardiovascular function, these data suggest that this is not of primary importance. ***But it is important to note*** that these studies were not performed in subjects exposed to microgravity with associated vestibular deficits. Thus, it is possible that the alterations of vestibular function accompanying prolonged microgravity may play a more important role in the cardiovascular adjustments to orthostasis and thus contribute to impaired orthostatic tolerance. A significant challenge to determine this role is the need for studies of astronauts rather than bedrest subjects, as the vestibular deficits are greater in the post-flight setting than in bedrest.

Otolith inputs may contribute to early transient adjustments to orthostasis. However, lack of significant main effects of tilt condition and time x tilt interactions suggests that potential otolith effects on the variables we studied are relatively subtle and ephemeral, or that other mechanisms compensate for a lack of change in otolith input with orthostasis.

Presentations:

Watenpaugh DE, *et al.* "Lack of vestibular otolith participation in human orthostatic blood pressure control", annual American Society for Gravitational and Space Biology meeting, 2001.

Smith ML. "Vestibular-Autonomic interactions in regulating orthostasis". Frontiers of Cardiology, 2002.

Smith ML. "Vestibular-Autonomic interactions in the Control of Blood Pressure". Presented at Third Biennial Space Biomedical Investigators Scientific Workshop, Jan 2003.

Publications:

Watenpaugh DE, A Cothron, SL Wasmund, WL Wasmund, R Carter III, NK Muenter, and ML Smith. Lack of vestibular otolith participation in human orthostatic blood pressure control. *Gravit Space Biol Bull* 14: 29(63),2000.

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