Effect of gender on vestibular sympathoexcitation

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Ray, Chester A. Effect of gender on vestibular sympathoexcitation. Am J Physiol Regulatory Integrative Comp Physiol 279: R1330–R1333, 2000.—Studies have suggested that premenopausal women are more prone to orthostatic intolerance than men. Additionally, it has been postulated that the vestibulosphaptic reflex is important in regulating postural-related changes in sympathetic activity. The purpose of the present study was to determine whether men and women differ in their sympathetic and cardiovascular responses to stimulation of the otolith organs elicited by head-down rotation (HDR). Heart rate (HR), arterial pressure, calf blood flow (CBF), and leg muscle sympathetic nerve activity (MSNA) were measured during 3 min of HDR in the prone posture in 33 women and 30 men. With the exception of HR (71 ± 2 and 63 ± 1 beats/min for women and men, respectively; P < 0.01), all baseline variables were not different between genders. There were no gender differences in responses to HDR. MSNA increased 72 ± 33 units (43%) in the men and 88 ± 15 units (59%) in the women during HDR (P < 0.01). CBF decreased [−0.6 ± 0.1 (15%) and −0.5 ± 0.1 (19%) ml·min⁻¹·100 ml⁻¹] and calf vascular resistance increased [8 ± 2 (21%) and 11 ± 3 (25%) units during HDR for men and women, respectively (P < 0.01)]. Both in the men and women, HR increased 2 ± 1 beats/min (P < 0.01). These results demonstrate that sympathetic activation during HDR in the prone posture is similar in men and women. Therefore, these findings suggest that the vestibulosphaptic reflex is not different between healthy men and women.

orthostatic nerve; cardiovascular control; orthostasis; gender; spaceflight

ORTHOSTATIC INTOLERANCE is the inability of the cardiovascular system to maintain adequate cerebral blood flow while in the upright posture. Symptoms associated with this syndrome include lightheadedness, nausea, and dizziness, which then may lead to syncope. Although orthostatic intolerance affects men and women both, it appears more commonly in women (19). A series of studies have shown women less tolerant to lower body negative pressure (LBNP) than men (2, 4, 8, 15, 23). In one study, it was reported that women were as much as 62% less tolerant than men during LBNP (23). Similarly, women have demonstrated greater orthostatic intolerance to standing after spaceflight (7). The exact mechanisms contributing to gender differences in orthostatic intolerance are unknown. However, because plasma norepinephrine responsiveness has been shown to be less during presyncopal LBNP and head-up tilt in women than men (1, 2, 13), this finding suggests that impaired neural mechanisms could play a role in the greater orthostatic intolerance in women.

One neural mechanism that may contribute to differences in orthostatic tolerance between men and women is the vestibulosphaptic reflex. The vestibular system has been shown to assist in the maintenance of arterial pressure during an orthostatic challenge and to activate sympathetic nerve activity in animals (3, 10, 25, 26) and humans (9, 16, 18, 21). In the cat, bilateral transection of the vestibular nerve results in an inability to compensate for postural-associated changes in arterial pressure (3, 10). However, with an intact vestibular system, arterial pressure is quickly restored with a concomitant increase in vascular resistance to compliant vascular beds. In humans, head-down rotation (HDR) in the prone posture results in a prompt increase in muscle sympathetic nerve activity (MSNA) (9, 16, 17, 21). The increase in MSNA to HDR has been attributed to the activation of the otolith organs of the vestibular apparatus (9, 16, 18, 21).

Because our previous human studies examining the vestibulosphaptic reflex have focused on physiological responses to HDR without specific consideration of potential gender differences, the purpose of this study was to compare the vestibulosphaptic reflex between healthy men and women. With increasing evidence that women are more susceptible to orthostatic intolerance, it was hypothesized that HDR would elicit smaller increases in MSNA and vascular responses in women compared with men.

METHODS

Subjects. Thirty-three women and thirty men volunteered for this study. All subjects were healthy, nonsmoking, normotensive adults and were not taking medicine at the time of the study. Data used for this study were collected both prospectively and retrospectively. Physical characteristics both for the men and women are shown in Table 1. In the 14

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women who were tested prospectively, 11 women were taking oral contraceptives. The testing procedures were explained before obtaining written consent from all of the subjects. The study was approved by the Institutional Review Board of the Pennsylvania State University College of Medicine.

**Experimental design.** All of the studies were performed with the subject positioned prone on a table to allow maximal HDR. The protocol began with a 3-min baseline period with the subject’s neck extended and the chin supported (21). After the baseline period, the subject’s head was passively lowered below the edge of the table for 3 min with the assistance of another individual. The subject’s head was then returned to the erect baseline position for an additional 3-min period of data collection.

**Measurements.** Multifiber recordings of MSNA were made by inserting a tungsten microelectrode into a peripheral nerve located behind the knee. A reference electrode was positioned subcutaneously 2–3 cm away from the recording electrode. Criteria for an acceptable recording of MSNA have been previously reported (9). The nerve signal was amplified (50,000–90,000 times) and filtered at a band width of 700–3,000 Hz. The filtered signal was rectified and integrated (time constant, 0.1 s) to obtain a mean voltage display of the nerve activity. Sympathetic recordings that indicated possible electrode site shifts or had electromyogram activity during the experiment were excluded.

Continuous measurements of arterial pressure and heart rate were made by a Finapres blood pressure monitoring unit (Ohmeda, Englewood, CO). CBF was measured in the contralateral leg to the nerve recording by venous occlusion plethysmography (Hokanson EC 4 plethysmograph, D. E. Hokanson, Bellevue, WA) using a mercury-in-Silastic strain gauge placed around the largest diameter of the calf muscles. Circulation to the foot was arrested by inflating a sphygmomanometer cuff around the ankle to 200 mmHg. A venous congesting cuff was placed around the upper leg and inflated to a pressure of 40 mmHg at 15-s intervals. The mean voltage neurogram, heart rate, arterial pressure tracing, and CBF were identified by inspection of the mean voltage neurogram. Total activity was calculated by summing the area of identified bursts for each minute using a computer program (Peaks, ADInstruments). Total activity was expressed in arbitrary units.

An unpaired t-test was used to compare the physical characteristics and baseline values between the men and women. HDR data were analyzed by a one-within (time), one-between (gender) repeated-measures analysis of variance. A significance level of $P < 0.05$ was used for statistical tests. Because the responses during 3-min of HDR were not significantly different, only the data for the first minute are presented. All values are presented as means ± SE.

**RESULTS**

**Subjects.** The physical and baseline characteristics for the men and women are presented in Table 1. There were no age differences between the men and women; however, body mass (77 ± 2 kg and 63 ± 2 kg) and body mass index (25 ± 2 and 23 ± 3 kg/m$^2$) were significantly greater in the men ($P < 0.01$). Resting MSNA, MAP, CBF, and CVR were not different between the men and women (Table 1). However, women had higher resting heart rates than men (71 ± 2 and 63 ± 1 beats/min, respectively; $P < 0.01$).

**Sympathetic and cardiovascular responses to HDR.** Responses to HDR were not different between genders (i.e., no significant interaction or main effect for gender). MSNA burst frequency and total activity increased significantly during HDR by 44 ± 10% and 59 ± 11% for women and 33 ± 14% and 43 ± 12% for men, respectively ($P < 0.01$; Fig. 1). The increase in MSNA corresponded with a decrease in CBF (19 ± 3% and 15 ± 4% ml·min$^{-1}$·100 ml$^{-1}$; $P < 0.01$) and an increase in arterial pressure (59 ± 11% and 43 ± 12% for women and men, respectively; $P < 0.01$).

**Data analysis.** MSNA was expressed both as burst frequency (bursts/min) and total activity. Sympathetic bursts were identified by inspection of the mean voltage neurogram. Total activity was calculated by summing the area of identified bursts for each minute using a computer program (Peaks, ADInstruments). Total activity was expressed in arbitrary units.

![Fig. 1: Responses of muscle sympathetic nerve activity (MSNA; bursts/min and total activity) in men (n = 30) and women (n = 33) to head-down rotation (HDR)](image_url)

**Table 1. Physical and baseline characteristics of the subjects**

<table>
<thead>
<tr>
<th></th>
<th>Women (n = 33)</th>
<th>Men (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>24 ± 1</td>
<td>26 ± 1</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>63 ± 2</td>
<td>77 ± 2*</td>
</tr>
<tr>
<td>Body mass index, kg/m$^2$</td>
<td>23 ± 3</td>
<td>25 ± 2*</td>
</tr>
<tr>
<td>MSNA, bursts/min</td>
<td>14 ± 1</td>
<td>15 ± 1</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>71 ± 2</td>
<td>63 ± 1*</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>98 ± 2</td>
<td>96 ± 2</td>
</tr>
<tr>
<td>CBF, ml·100 ml$^{-1}$·min$^{-1}$</td>
<td>2.7 ± 0.2</td>
<td>2.8 ± 0.3</td>
</tr>
<tr>
<td>CVR, units</td>
<td>40 ± 3</td>
<td>41 ± 4</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of subjects; MSNA, muscle sympathetic nerve activity; MAP, mean arterial pressure; CBF, calf blood flow; CVR, calf vascular resistance. *Significantly different from women ($P < 0.05$).
increase in CVR (25 ± 3% and 21 ± 6% units; P < 0.01) during HDR for women and men, respectively (P < 0.01; Fig. 2). Heart rate increased 2 ± 1 beats/min during HDR for men and women (P < 0.01). HDR did not elicit a change in MAP in both groups. All variables returned to pre-HDR values on return of the head to the upright (i.e., baseline) position.

DISCUSSION

The purpose of this investigation was to examine whether women and men differ in their sympathetic and cardiovascular responses to HDR in the prone posture. Because women have been reported to be less tolerant to orthostatic challenges than men (2, 4, 8, 15, 23), it was hypothesized that women’s MSNA responses to HDR would be less than men. However, contrary to the proposed hypothesis, the major finding from this study was that men and women have comparable sympathetic and cardiovascular responses to HDR. These findings indicate that the vestibulosympathetic reflex is engaged similarly in healthy men and women during HDR.

Our laboratory has been investigating the vestibulosympathetic reflex in humans. These studies have demonstrated significant increases in MSNA during HDR. Through a number of experiments, our results suggest that the increase in MSNA elicited by HDR is mediated by the vestibular system. Specifically, our previous results indicate that the otolith organs, not the semicircular canals, mediate increases in MSNA (18). Potential mechanisms such as neck afferents, central command, visual inputs, baroreflexes, and activation of nonspecific receptors from the head have been demonstrated not to contribute to increases in MSNA. Thus HDR is a simple test of altered input from the otolith organs on the sympathetic nervous system. The current study again demonstrates increases in MSNA and CVR with HDR in a large number of young subjects. However, the current study extends our previous findings by demonstrating similar MSNA and CVR responses to HDR both in men and women.

A number of studies has reported less orthostatic tolerance in women than men (2, 4, 8, 15, 23). Additionally, it has been estimated that of the 500,000 Americans suffering from orthostatic intolerance, young women comprise the largest segment of this population (19). In recent years, considerable effort has been made to determine possible mechanisms responsible for this greater incidence of orthostatic intolerance in women. Convertino (2) comprehensively examined a number of mechanisms that could contribute to lower orthostatic tolerance in women. LBNP tolerance in women was associated with attenuated heart rate responses to carotid baroreceptor stimulation, greater drop in cardiac output during LBNP, increased β1- adrenoreceptor responsiveness, lower blood volume, and lower levels of circulating norepinephrine at pre-syncpe compared with men. This latter finding of lower circulating norepinephrine in women has been also reported during head-up tilt (1, 13, 24). Decreased responsiveness of norepinephrine to LBNP and head-up tilt in women compared with men suggests that a neural mechanism could account for gender differences in orthostatic tolerance. Because the vestibulosympathetic reflex has been shown to contribute importantly to orthostasis (3, 10), it was feasible that the vestibulosympathetic reflex could be different between men and women and result in less sympathetic outflow in women when engaged. However, the results of this study suggest this is not the case.

Because input from the otolith organs was altered during HDR when other neural reflex mechanisms were not, we cannot rule out the possibility that during an orthostatic stress (i.e., LBNP or standing), central integration of the vestibulosympathetic reflex with other neural reflexes on sympathetic outflow is different in men and women. As stated previously, it has been reported that women and men respond to orthostatic stresses by activating different compensatory mechanisms (2). Additionally, these data do not rule out a role for the vestibular otolith organs in explaining gender differences in orthostasis after exposure to microgravity. Female astronauts are less tolerant to standing and exhibit more episodes of syncope than male astronauts after exposure to microgravity (7). Exposure to microgravity has been reported to change the morphological and physiological function of the otolith organs (20, 22). Consequently, the otolith organs could be unable to respond properly on reentry to the earth’s gravitational forces and could alter the vestibulosympathetic reflex.

The small increase in heart rate with the HDR was comparable between men and women. On the basis of previous work, it is believed that this small increase is related to activation of neck afferents (16). We have noted small increases in heart rate when the neck afferents, but
not the otolith organs, were engaged with different head movements. The increase in heart rate by the neck afferents may be mediated by either vagal withdrawal or sympathetic activation. Because of the rapidity of the increase in heart rate, this points to parasympathetic withdrawal. However, the current study was not designed to specifically answer this question.

Previous human studies have compared sympathetic responses to other physical stressors in men and women. Studies examining responses during cold and mental stress have found no gender differences in MSNA responses (12). Examination of the arterial chemoreflex using hypoxia has also found no differences in peak MSNA responses (11). However, earlier MSNA responses to hypoxia were noticed in women. MSNA responses to isometric handgrip have produced equivocal results. Studies have reported no difference (12) and attenuated responses (5) to isometric handgrip in women compared with men. Differences between these results may be related to what phase in the menstrual cycle the women were tested (6). The current finding that MSNA responses to the vestibulosympathetic reflex elicited by HDR is similar between men and women adds to this growing body of data regarding possible gender differences in reflex control of MSNA.

One limitation of the current study is that the menstrual cycle in the women was not controlled. Minson et al. (14) recently reported that baseline MSNA and sympathetic baroreflex sensitivity was altered by the menstrual cycle. Thus it is possible the conclusions derived from this study could be different if the menstrual cycle was controlled. However, because arterial pressure was not changed by HDR in the women, this would appear to minimize the impact of this factor.

In summary, HDR elicited similar sympathetic and cardiovascular responses in men and women. These results suggest that the vestibulosympathetic reflex is not different between healthy men and women. Thus the greater incidence of orthostatic intolerance in otherwise healthy women appears not to be related to functional differences in vestibular activation of the sympathetic nervous system.

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REFERENCES