Vestibulosympathetic reflex during orthostatic challenge in aging humans

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Monahan, Kevin D., and Chester A. Ray. Vestibulosympathetic reflex during orthostatic challenge in aging humans. Am J Physiol Regul Integr Comp Physiol 283: R1027–R1032, 2002. First published August 1, 2002; 10.1152/ajpregu.00298.2002.—Aging attenuates the increase in muscle sympathetic nerve activity (MSNA) and elicits hypotension during otolith organ engagement in humans. The purpose of the present study was to determine the neural and cardiovascular responses to otolithic engagement during orthostatic stress in older adults. We hypothesized that age-related impairments in the vestibulosympathetic reflex would persist during orthostatic challenge in older subjects and might compromise arterial blood pressure regulation. MSNA, arterial blood pressure, and heart rate responses to head-down rotation (HDR) performed with and without lower body negative pressure (LBNP) in prone subjects were measured. Ten young (27 ± 1 yr) and 11 older subjects (64 ± 1 yr) were studied prospectively. HDR performed alone elicited an attenuated increase in MSNA in older subjects (Δ106 ± 28 vs. Δ20 ± 7% for young and older subjects). HDR performed during simultaneous orthostatic stress increased total MSNA further in young (Δ55 ± 15%; P < 0.05) but not older subjects (Δ−5 ± 4%). Older subjects demonstrated consistent significant hypotension during HDR performed both alone (Δ−6 ± 2 mmHg) and during LBNP (Δ−7 ± 2 mmHg). These data provide experimental support for the concept that age-related impairments in the vestibulosympathetic reflex persist during orthostatic challenge in older adults. Furthermore, these findings are consistent with the concept that age-related alterations in vestibular function might contribute to altered orthostatic blood pressure regulation with age in humans.

vestibular; blood pressure regulation; orthostasis; baroreflex; autonomic nervous system

ASSUMPTION OF THE UPRIGHT posture initiates reflex-mediated increases in vasoconstrictor muscle sympathetic nerve activity (MSNA) (3). Failure to increase MSNA and vascular resistance in the face of gravitationally induced peripheral venous pooling and translocation of central blood volume produces hypotension and compromises vital organ perfusion (2, 24). Accordingly, reflexive modulators of MSNA activated during orthostatic stress are of physiological and clinical significance.

An extensive body of experimental literature has accumulated examining baroreflex-mediated increases in MSNA during orthostatic stress in humans under varying and diverse physiological conditions (3, 4, 22, 25, 27, 32). In patients with autonomic failure, who demonstrate a diminished ability to increase peripheral vascular resistance during baroreceptor unloading, orthostatic stress can produce persistent hypotension (30). These data indicate the critical role of the baroreflex in the adaptation to the upright posture in humans. Additionally, the vestibular system is activated during changes in posture. Vestibular activation reflexively alters sympathetic nerve activity and subsequently vascular resistance (8, 17, 20, 28, 36). These increases also appear critical in the adaptation to the upright posture (5, 9). Collectively, these experimental findings indicate that both baroreflex- and vestibular-mediated increases in MSNA and vascular resistance contribute critically to orthostatic blood pressure control.

In humans, the incidence of orthostatic hypotension increases with advancing age (26). Furthermore, orthostatic hypotension is associated with an increased rate of mortality (13). Thus, mechanisms underlying orthostatic blood pressure regulation are clinically important, particularly in older individuals. One mechanism that may contribute to the age-associated increase in the incidence of orthostatic hypotension is the vestibulosympathetic reflex. Consistent with these suggestions, the vestibulosympathetic reflex is impaired with age (21). Age-associated impairment in the vestibulosympathetic reflex likely results from functional and anatomic changes that occur within both central and peripheral aspects of the vestibular system with age (6, 12, 23, 31). However, it is not currently known whether the age-related impairments in the vestibulosympathetic reflex are detrimental to orthostatic blood pressure control in older adults. Thus, we tested the hypothesis that the ability of the vestibulosympathetic reflex to increase MSNA is impaired resulting in im-

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paired blood pressure regulation during orthostatic stress with age in humans. The results of this study are consistent with the concept that the age-related impairment of the vestibulosympathetic reflex persists during orthostatic challenge in humans.

METHODS

Subjects

We prospectively studied 21 (10 young and 11 older) healthy volunteers who were normotensive, nonobese, non-smokers, and not taking any medications known to affect autonomic/cardiovascular function. All subjects were sedentary to recreationally active. On the basis of their age, subjects were classified as either “young” (18–35 yr) or “older” (55–70 yr). Both men and women were studied because sex does not influence the vestibulosympathetic reflex in either young or older subjects (17, 21). Written informed consent was obtained from all subjects after verbal explanation of the experimental protocols. The experiments were approved by the Institutional Review Board at the Pennsylvania State University College of Medicine and meet the American Physiological Society’s “Guiding Principals For Ethical Principles For Research Involving Human Subjects” (1).

Experimental Design

Protocol 1. The purpose of this experimental protocol was to determine both the neural and cardiovascular responses to head-down rotation (HDR) (i.e., otolith organ engagement) in young and older adults. Subjects performed HDR in the prone position as previously described (28). Briefly, subjects were positioned prone on an examination table with their head extending over the end of the table, such that the head could be rotated downward without interference from the end of the table. During the baseline period, the subject’s head was passively supported in the chin-up neck-extended position. After a 3-min baseline period, the chin support was removed and the subject’s head was passively lowered to the point of maximal rotation. After a 1-min period of HDR, the subject’s head was returned to the baseline chin-up position for a period of recovery.

Protocol 2. The purpose of this experimental protocol was to determine the ability of the vestibulosympathetic reflex to increase MSNA during orthostatic stress (i.e., baroreceptor unloading). HDR was performed in young and older subjects during baroreceptor unloading elicited by lower body negative pressure (LBNP). This protocol was performed in the prone position with the subjects enclosed in a LBNP chamber up to the level of the iliac crest. The subject’s head was extended over the edge of the examination table such that the head could be rotated downward without interference from the end of the table, as in protocol 1. The protocol began with the subject’s head in the baseline chin-up-supported position. After a 3-min baseline period, LBNP at −30 mmHg was applied for a 4-min period. During minute 3 of LBNP, HDR was performed, as in protocol 1, for 1 min. After this period, the head was returned to the baseline chin-up position and LBNP continued (minute 4). After this 4-min period, LBNP was terminated. The subject’s head remained in the baseline chin-up position for a recovery period.

Measurements

Multifiber recordings of MSNA were obtained from the peroneal nerve. A tungsten microelectrode was inserted through the skin and adjusted until a site with clear spontaneous occurring sympathetic bursts was identified. A reference electrode was positioned subcutaneously 2–3 cm away from the site of the recording electrode. Previously described criteria were applied to ensure that an adequate MSNA recording site was obtained (34). Raw nerve signals were amplified (20,000–90,000 times) and filtered (700–2,000 Hz). These filtered signals were then rectified and integrated (time constant 0.1 s) to obtain mean voltage neurograms. Sympathetic recordings indicative of electrode site shifts and/or electromyogram artifact during the experimental protocols were excluded.

Continuous measurements of arterial blood pressure and heart rate were made using a Finapres photoplethysmograph (Ohmeda, Louisville, CO). Mean volume neurograms, heart rate, and arterial blood pressure tracings were collected (MacLab 8e, ADInstruments, Milford, MA) on computer for quality control purposes and later off-line analyses.

Data Analysis

Sympathetic bursts were identified from the mean voltage neurograms. MSNA is reported as both burst frequency and as total MSNA (amplitude of individual bursts) as measured by a computer program (Peaks, ADInstruments).

One between- and one within-factor repeated-measures analysis of variance were used to compare the effect of HDR on both neural and cardiovascular parameters in young and older subjects. Paired t-tests were performed to determine if responses to HDR differed between protocols 1 and 2 in each age group. Significance was set at P < 0.05 for all statistical tests. All values are presented as means ± SE.

RESULTS

Subject characteristics are presented in Table 1. Except for differences in age and resting MSNA, young and older subjects did not differ in respect to height, weight, and baseline arterial blood pressure and heart rate.

Protocol 1 (HDR Alone)

Responses to HDR in young and older subjects are presented in Fig. 1. In young subjects, HDR increased MSNA (Δ8 ± 1 bursts/min and Δ106 ± 29% for burst frequency and total MSNA; P < 0.001) but did not alter mean arterial pressure (MAP) or heart rate. Older subjects demonstrated a significant but attenuated (P < 0.05 vs. young) increase in MSNA during HDR (Δ4 ± 1 bursts/min and Δ20 ± 7% for burst frequency

Table 1. Selected subject characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Young</th>
<th>Older</th>
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<tbody>
<tr>
<td>n</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Gender</td>
<td>5m/5f</td>
<td>7m/4f</td>
</tr>
<tr>
<td>Age, yr</td>
<td>27 ± 1</td>
<td>64 ± 1*</td>
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<tr>
<td>Height, cm</td>
<td>168 ± 3</td>
<td>172 ± 4</td>
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<tr>
<td>Weight, kg</td>
<td>71 ± 4</td>
<td>75 ± 4</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>122 ± 3</td>
<td>126 ± 5</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>68 ± 2</td>
<td>71 ± 3</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>66 ± 3</td>
<td>70 ± 3</td>
</tr>
<tr>
<td>MSNA, bursts/min</td>
<td>16 ± 3</td>
<td>35 ± 4*</td>
</tr>
</tbody>
</table>

Values are means ± SE. SBP, systolic blood pressure; DBP, diastolic blood pressure; MSNA, muscle sympathetic nerve activity; m, males; f, females. *P < 0.05 compared with young.
In older subjects, LBNP increased MSNA (Δ13 ± 2 bursts/min and Δ162 ± 71% for burst frequency and total MSNA; P < 0.01) to a similar degree as in young subjects. However, in contrast to a further increase in MSNA when HDR was performed during minute 3 of LBNP in young subjects, older subjects did not demonstrate a further increase in total MSNA from baseline (Δ4 ± 1 bursts/min and Δ−5 ± 4%; P < 0.05 for burst frequency). Additionally, HDR performed during LBNP decreased MAP (Δ−7 ± 2 mmHg; P < 0.001). This decrease in MAP during HDR in minute 3 of LBNP (Δ−7 ± 2 mmHg) was similar in magnitude to the decrease in MAP during HDR performed without LBNP in protocol 1 (Δ−6 ± 2 mmHg). Heart rate increased during LBNP but was not altered by HDR performed during LBNP.

**DISCUSSION**

The present finding of an attenuated increase in MSNA during otolithic engagement in older adults and total MSNA). Unlike young subjects (Δ−1 ± 1 mmHg), HDR decreased MAP in older subjects (Δ−6 ± 2 mmHg; P < 0.01). Heart rate was not altered by HDR.

**Study 2 (HDR During LBNP)**

Responses to HDR during orthostatic stress in young and older subjects are presented in Fig. 2. Young subjects demonstrated a significant increase in MSNA during LBNP (Δ12 ± 1 bursts/min and Δ162 ± 31% for burst frequency and total MSNA). HDR performed during minute 3 of LBNP increased MSNA further (Δ9 ± 2 bursts/min and Δ53 ± 15% for change from levels during LBNP; P < 0.01). When the head was returned to the baseline chin-up position during minute 4 of LBNP, MSNA returned to pre-HDR levels. MAP was well maintained throughout LBNP and during HDR. Heart rate increased during LBNP (Δ6 ± 1 beats/min; P < 0.001) and was further increased when HDR was performed during minute 3 of LBNP (Δ4 ± 1 beats/min; P < 0.05). All variables returned to baseline levels during recovery.
confirms our previous demonstration that aging attenuates the vestibulosympathetic reflex (21). The primary new finding from the present study is that age-associated impairment of the vestibulosympathetic reflex persists during orthostatic challenge in older adults and results in the inability to maintain arterial blood pressure. Collectively, these experimental findings are consistent with the concept that age-related impairment in the vestibulosympathetic reflex may compromise the ability of the vestibular system to participate in orthostatic blood pressure regulation in older humans. As such, it is possible that these age-related alterations in the vestibulosympathetic reflex contribute mechanistically to altered orthostatic blood pressure regulation with age in humans.

The mechanisms underlying this age-associated impairment in the vestibulosympathetic reflex remain unclear but likely involve age-related changes in both central (i.e., reductions in hair cell number) and peripheral aspects (i.e., reductions in afferent projections) of the vestibular system (6, 12, 23, 31). Changes in the vestibular system of these types would likely produce generalized deficits in vestibular function. Consistent with this suggestion, the vestibulosympathetic reflex and both the vestibulococular and vestibulospinal reflexes are impaired with age (7, 16, 29). Thus, it is likely that functional and morphological changes within the vestibular system contribute to the age-associated impairment in the vestibulosympathetic reflex. Additionally, increases in MSNA during HDR appear to be proportional to the level of head rotation (8). Thus, the attenuated increase in MSNA during HDR in older subjects could have resulted from a smaller degree of head rotation during HDR possibly resulting from reduced neck flexibility with age. However, it is unlikely that the stimulus to the otolith organs differed between the experimental groups because we previously reported identical levels of maximal head rotation in prone young and older subjects during HDR (21). We also did not observe any noticeable differences between the two age groups.

In addition to the attenuated increase in MSNA during HDR, we also demonstrated that HDR performed during orthostatic challenge (i.e., LBNP) does not increase MSNA further in older adults. These data indicate that the vestibular systems’ ability to participate in orthostatic blood pressure regulation may be impaired with age. Thus, it is possible that impairment of the vestibulosympathetic reflex with age contributes to the increased incidence of orthostatic hypotension with age. This appears especially true because baroreceptor unloading in the older subjects elicited marked increases in MSNA.

In addition to the attenuated increase in MSNA during otolith organ engagement, HDR produced hypotension in older adults. The magnitude of the decline in arterial blood pressure during otolithic engagement appears similar irrespective of the preceding state of sympathoexcitation (Δ−6 ± 2 and Δ−7 ± 2 mmHg for HDR performed alone and HDR during LBNP). These data indicate that engagement of the vestibulosympathetic reflex by HDR in older adults elicits hypotension that notably persists in the face of orthostatic challenge. These data are in contrast to data in young subjects that demonstrate significant increases in MSNA and preserved arterial blood pressure in response to otolithic engagement even during experimentally induced increases in baseline levels of MSNA and arterial blood pressure (18, 19). Our demonstration that otolithic engagement elicits hypotension in older adults is not the first example of vestibular activation producing hypotension in humans (21). Additionally, in several previous animal studies, vestibular activation has been demonstrated to produce hypotension (10, 33) as well as vestibular lesion-producing hypotension during whole body tilt in cats (5). However, our data (present study and Ref. 21) are the first to show this pattern in older humans.

Currently, the mechanism(s) underlying the reductions in arterial blood pressure during otolithic engagement in older adults are not known. Because increases in MSNA during HDR increase calf and forearm vascular resistance in young subjects (15), it is possible that deficits in the transduction of increases in MSNA into increases in vascular resistance during HDR contributed to the hypotension in older adults. Consistent with this suggestion, Davy and colleagues (4) demonstrated that the transduction of increased MSNA into vascular resistance changes is impaired with age during LBNP applied to elicit similar reductions in central venous pressure to avoid group differences in baroreceptor unloading (11, 14). Thus, it is possible that the reductions in sympathetic vascular transduction noted during LBNP with age contribute to, but cannot fully explain, the reductions in arterial blood pressure. Thus, it is likely that vasodilation occurs in some other (i.e., nonmuscle) vascular bed. Presently, we are not able to determine where vasodilation occurs but rather can only speculate that it plays an obligatory role in producing hypotension during otolithic engagement in older adults.

Vestibular activation produces discretely patterned effects on vascular tone in animals (i.e., both vasoconstriction and vasodilation) (10). Lesion of the vestibular nerve produces persistent hypotension in the cat during whole body upright tilting (5). These data establish that an intact neural vestibular pathway appears critical for maintenance of arterial blood pressure during upright tilting. This association between increasing afferent vestibular outflow and maintenance of arterial blood pressure during orthostasis is likely mediated by removing the vestibular-mediated stimuli to increase vasoconstrictor nerve traffic and subsequently its influence on vascular tone. Additionally, these data provide the experimental basis to suggest that conditions associated with impaired vestibular function may produce hypotension or alter blood pressure control during orthostasis by attenuating increases in vasoconstrictor neural outflow (i.e., MSNA) or augmenting peripheral vasodilation through an unknown mechanism. In this context, attenuation of the vestibulosympathetic reflex with age likely represents
a model of impaired vestibular function and is consistent with the persistent hypotension that occurs during HDR in older humans. Additionally, during postural change when the otolith organs are engaged, alterations in vestibular function could contribute to altered orthostatic blood pressure control.

We do not believe that the higher levels of MSNA in the older subjects at baseline or during LBNP contributed to an inability to increase MSNA during HDR in the two protocols. The ability to increase MSNA in response to orthostatic stress (LBNP) appears to be well preserved with age in humans (present study and Ref. 21) as does the ability of a cold pressor test to increase MSNA (21, 35). To specifically test this issue during LBNP, two subjects performed LBNP at −40 mmHg for 4 min with the addition of apnea for 30 s at the start of the third minute of LBNP. Unlike HAP, apnea during LBNP increased MSNA from 25 to 39 bursts/30 s (ΔTotal MSNA 200%) and from 27 to 34 bursts/30 s (ΔTotal MSNA 52%) for the two subjects, respectively. This finding clearly indicates that MSNA responsiveness to HDR was not limited by high activity during LBNP in the older subjects (i.e., no ceiling effect).

It could be argued that MSNA responses to otolith engagement are delayed in older subjects and thus prevented us from observing increases in MSNA with HDR during LBNP. Zakir et al. (37) demonstrated a transient reduction in renal SNA following stimulation of otolithic afferent nerves. This finding suggests a time-dependent effect of sympathetic responses to vestibular activation. However, the study by Hume and Ray (8) showed the MSNA response to otolith engagement by HDR was maximally activated within 1 min and persisted for 30 min during the maneuver. From this study, we do not believe that using 1 min of HDR in the older subjects prevented us from observing a sympathetic response during LBNP.

In summary, the age-related impairment in the vestibulosympathetic reflex persists during orthostatic challenge in humans. Unlike responses in young adults, HDR performed during sympathoexcitation (i.e., LBNP) does not further increase MSNA in older adults but does provoke hypotension that is of similar magnitude to that demonstrated during HDR performed alone. These consistent and persistent reductions in arterial blood pressure during otolithic activation in older adults provide experimental evidence consistent with the concept that orthostatic blood pressure regulation during otolithic engagement is impaired with age and as such may contribute to altered orthostatic blood pressure regulation with age in humans.

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