Aging Attenuates the Vestibulosympathetic Reflex in Humans

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Background—The vestibular system contributes to sympathetic activation by engagement of the otolith organs. However, there is a significant loss of vestibular function with aging. Therefore, the purpose of the present study was to determine if young and older individuals differ in their cardiovascular and sympathetic responses to otolitic stimulation (ie, head-down rotation, HDR). We hypothesized that responses to otolitic stimulation would be attenuated in older adults because of morphological and physiological alterations that occur in the vestibular system with aging. 

Methods and Results—Arterial blood pressure, heart rate, muscle sympathetic nerve activity (MSNA), and head rotation were measured during HDR in 11 young (26±1 years) and 11 older (64±1 years) subjects in the prone posture. Five older subjects performed head rotation (chin to chest) in the lateral decubitus position, which simulates HDR but does not alter afferent inputs from the vestibular system. MSNA responses to HDR were significantly attenuated in older as compared with young subjects (P<0.01). MSNA increased in the older subjects by only 12±5% as compared with 85±16% in the young. Furthermore, HDR elicited significant reductions in mean arterial blood pressure in older (Δ−6±1 mm Hg; P<0.01) but not young subjects (Δ1±1 mm Hg). In contrast to HDR, head rotation performed in the lateral decubitus position did not elicit hypotension. MSNA responses to baroreceptor unloading and the cold pressor test were not different between the age groups.

Conclusions—These data indicate that aging attenuates the vestibulosympathetic reflex in humans and may contribute to the increased prevalence of orthostatic hypotension with age. (Circulation. 2002;105:956-961.)

Key Words: aging ■ nervous system, sympathetic ■ blood pressure ■ physiology ■ reflex

Aging is associated with an increased prevalence of orthostatic hypotension in humans.1 Orthostatic hypotension has been shown to be associated with increased mortality rates.2 Moreover, the rate of dizziness and falls increases with age,3,4 with falls being a well-known cause of morbidity and mortality in older people.5,6 The causes of these falls are multifactorial, but orthostatic hypotension and concomitant dizziness appear to be significant factors. One mechanism that may contribute to the age-related increase in orthostatic hypotension is attenuation of the vestibulosympathetic reflex. This reflex is a neural feedback system that regulates sympathetic neural outflow through afferent input from the vestibular system.7,8 Current studies suggest that the vestibular apparatus and vestibular nuclei of the brain stem undergo significant morphological changes with aging that result in diminished physiological responses to vestibular stimuli.9–12 However, currently there are no studies that have determined the effect of age on the vestibulosympathetic reflex.

We have reported previously that head-down rotation (HDR) in the prone position elicits increases in muscle sympathetic nerve activity (MSNA) in young, healthy adults.8,13–15 Evidence indicates that the vestibulosympathetic reflex mediates the increase in MSNA during HDR. Other possible mechanisms such as activation of neck muscle afferents,13 baroreflexes,8,16 alterations in visual input,8 and nonspecific receptors in the head activated by increases in cerebral pressure15 have been shown not to mediate this response. In the present study, we examined sympathetic and cardiovascular responses to HDR in the prone position in young and older adults. We hypothesized that MSNA and cardiovascular responses to HDR would be attenuated in older subjects because of the known physical and functional changes in the vestibular system that occur with aging. The results of the present study indicate that the vestibulosympathetic reflex is attenuated with aging.

Methods

Subjects

Twenty-two healthy, normotensive, nonsmoking, unmedicated volunteers, varying widely in age, were studied prospectively. Subjects were classified as “young” (20 to 35 years) or “older” (55 to 70 years). Written informed consent was obtained from all subjects after verbal explanation of the experimental protocol. Study approval was obtained from the Institutional Review Board at The Pennsylvania State University College of Medicine.

Experimental Design

Subjects lay prone on a padded table with their neck extended and chin supported as previously described.8,15 This head position...
approximates the gravitational orientation of the head when in the upright posture. The protocol consisted of a 3-minute baseline period with chin up followed by 2 minutes of HDR. For HDR, the chin support was removed and the head was passively lowered until the neck was maximally flexed. This movement of the head (in the vertical plane) alters vestibular activation of otolith organs but not semicircular canals once the head becomes stationary. The time period between removal of chin support to the chin contacting the chest was ~5 seconds. MSNA, arterial blood pressure, heart rate, respiration, and head position were measured continuously in all subjects. Five subjects repeated the protocol but with their bodies in the lateral decubitus position. The head was supported throughout the maneuver. This maneuver simulates HDR, but unlike HDR the afferent input from the otolith organs are not altered with this head rotation. MSNA was not recorded in these subjects.

Lower body negative pressure (LBNP) was used to demonstrate preserved baroreflex control of MSNA with age. Young (n=9) and older (n=9) subjects were positioned in a LBNP chamber sealed at the level of the iliac crest. After a baseline period, LBNP was applied at ~30 mm Hg for 2 minutes.

Additionally, the young and older subjects performed a cold pressor test in which the hand not used for continuous arterial blood pressure monitoring was immersed in ice water (~4°C) for 2 minutes after a baseline period. This was done to address if there was a "ceiling effect" for MSNA in the older subjects and to test if reflex sympathetic responsiveness between older and young subjects were comparable.

### Measurements

Multifiber recordings of MSNA were made with a tungsten microelectrode inserted into the peroneal nerve located in the popliteal fossa. A reference electrode was inserted subcutaneously in close proximity (2 to 3 cm) to the recording electrode site. The recording electrode was adjusted until a site with clear, spontaneously occurring sympathetic bursts was obtained. Established criteria for acceptable recordings of MSNA were applied. Raw nerve recordings were amplified (20,000 to 50,000 times), filtered at a bandwidth of 700 to 2000 Hz, then rectified and integrated with a 0.1-second time constant to obtain mean voltage displays of nerve activity. Sympathetic recordings that suggested electrode site shifts or electromyographic artifact during the data collection were excluded.

Angular rotation of the head was measured by a custom-built electrogoniometer. Continuous measurements of arterial blood pressure and heart rate were made with a Finapres blood pressure monitor (Ohmeda), and respiration was measured by a strain-gauge pneumotrace.

Mean voltage neurograms, arterial blood pressure, respiration, heart rate, and head position were collected (MacLab 8E, ADInstruments) continuously on a computer system for real-time display and later off-line analyses.

### Data Analysis

Sympathetic bursts were identified from inspection of mean voltage neurograms. MSNA was expressed as burst frequency and total MSNA (ie, sum of bursts amplitude) as measured by a computer program (Peaks; ADInstruments). Relative changes from baseline are reported for total MSNA. The data were analyzed by means of ANOVA with repeated measures. Significance was set a priori at P<0.05. Because responses between the first and second minutes of HDR were not significantly different, the mean values for the 2-minute period are reported. All data are presented as mean±SEM.

### Results

#### Subject Characteristics

Physical characteristics of subjects are presented in the Table. Besides age differences, young and older subjects differed in baseline levels of MSNA (20±3 and 36±4 bursts/min, respectively, P<0.01) but not in height, body mass, or resting arterial blood pressure and heart rate.

### Influence of Age on Responses to HDR

HDR elicited cardiovascular and sympathetic responses in both young and older subjects (Figure 1). In young subjects, HDR increased MSNA burst frequency by 7±1 bursts/min (P<0.01) and total activity by 85±16% (P<0.001). Mean arterial blood pressure (MAP) (Δ1±1 mm Hg) and heart rate (Δ1±1 beats/min) were not significantly changed by HDR (Figure 1). Responses in older subjects differed significantly from the younger subjects. Increases in MSNA to HDR were...
significantly less (P<0.01) in the older subjects when expressed as burst frequency (Δ3±1 bursts/min) and percent change in total MSNA (Δ12±5%). Associated with the attenuated MSNA response in the older subjects was a significant fall in MAP (Δ−6±1 mm Hg; P<0.01) (Figure 1). As in young subjects, heart rate was not significantly changed by HDR in older subjects (Figure 1). Original recordings of both MSNA and arterial blood pressure in a young subject and an older subject are presented in Figure 2. There was no significant difference in the degree of head rotation between the young and older subjects during HDR (113±6° versus 108±4° in the young and older subjects, respectively; P=0.45).

Responses were not affected by subject sex in this study in either group. In the older subjects, the increases in burst frequency and total activity to HDR were 4±1 and 3±1 bursts/min and 17±13% and 10±5% for women and men, respectively. MAP was reduced during HDR by −8±3 and −5±2 beats/min for the older women and men, respectively. These results support our previous findings in young subjects that sex does not affect responses to HDR.14

Effect of Head Rotation in the Lateral Decubitus Position

Five older subjects performed head rotation (chin to chest) while lying on their side in the lateral decubitus position. This maneuver simulates HDR but without altering the input from the otolith organs. In contrast to HDR, this maneuver did not elicit a fall in arterial blood pressure in the older subjects. Both MAP (94±5 versus 96±6 mm Hg for baseline versus head rotation, respectively) and heart rate (67±5 versus 68±6 beats/min) were unchanged during this head maneuver (Figure 3).

Effect of Baroreceptor Unloading

LBNP elicited similar reflex responses in MSNA in both young and older subjects. MSNA increased 135±40% in young and 139±60% in older subjects during baroreceptor unloading (Figure 4). MAP was unchanged and increases in heart rate were not different between age groups during LBNP (not shown).

Effect of Cold Pressor Test on MSNA in Older Subjects

To rule out the possibility that elevated baseline levels of MSNA in older subjects precluded us from demonstrating changes in MSNA similar to young subjects, 4 older subjects performed a cold pressor test. The cold pressor test elicited a marked increase in MSNA (Δ8±3 bursts/min and 139±69% total activity; P<0.01) (Figure 4). These responses were comparable to those observed in young subjects (n=5) when examining the change in total activity (136±41%) but less in terms of changes in burst frequency.
opioids inhibit the firing rate of vestibular neurons \( 24 \) and sensitivity of signaling pathways.\( 25 \)

The effect of endogenous opioids may result from higher impairment of the vestibulosympathetic reflex. This inhibitory effect is possible that with aging, endogenous opioids through higher suppression of the medial vestibular nucleus. \( 9,10 \)

The results of the present study support the concept that aging diminishes the vestibulosympathetic reflex in humans. Unlike young adults, MSNA responses are significantly attenuated during HDR in the aged. The mechanism(s) for the attenuation in the vestibulosympathetic reflex with age is unknown. However, experimental evidence suggests that aging is associated with significant morphological changes in both peripheral and central aspects of the vestibular system. Deficits in afferent neural feedback include a significant decline in the number of hair cells in the otolith organs with age.\( 10,18 \) These reductions in hair cells are associated with reductions in the number of kinocilia and stereocilia on the hair cells that remain. Additionally, primary afferent fibers to the cristae and maculae decline with concomitant changes in synaptic structure and dendrites of the vestibular neurons.\( 9,10 \) There is also degeneration of the otoconia of the maculae.\( 19 \) Central neural changes in the vestibular system include a 3% decline per decade in central vestibular neurons in humans,\( 12 \) which have also been reported in aging mice.\( 20 \)

These physical changes correspond with reported reductions in the vestibulo-ocular and vestibulospinal reflexes with age in humans.\( 11,21 \) On the basis of these data, we suspect that anatomic changes in the vestibular system with aging are the primary factors for the attenuation of the vestibulosympathetic reflex as observed in this study.

Several other potential mechanisms may contribute to the attenuation of the vestibulosympathetic reflex with aging. Endogenous opioids bind to sites in the medial vestibular nucleus. These same regions have been shown to be crucial in mediating the vestibulosympathetic reflex in the cat.\( 22,23 \) Electrophysiological studies have shown that opioids inhibit the firing rate of vestibular neurons\( 24 \) and that this response is more pronounced in older rats.\( 25 \) Thus it is possible that with aging, endogenous opioids through their chronic suppression of the medial vestibular nucleus impair the vestibulosympathetic reflex. This inhibitory effect of endogenous opioids may result from higher concentrations, changes in receptor density, and increase sensitivity of signaling pathways.\( 25 \)

Our data indicate that reflex control of MSNA by the baroreflexes is not different between the young and older subjects. Increases in total MSNA during LBNP were comparable between the age groups. This finding supports previous studies that report that baroreflex regulation of MSNA is either well preserved\( 26 \) or may actually be enhanced\( 27 \) with aging. Additionally, the lack of change in heart rate in response to hypotension in older adults argues against a primary role of the baroreflex in mediating differences in MSNA to HDR. Therefore, we believe that differences in baroreflex regulation of MSNA are not responsible for the attenuated MSNA response to HDR in the older subjects. Conversely, baroreflex-mediated increases in MSNA in response to the observed hypotension may actually mask the true magnitude of impairment in the vestibulosympathetic reflex with aging.

MSNA is elevated with advancing age.\( 28 \) It is possible that this elevation in MSNA with age precluded us from demonstrating a comparable increase in the older subjects because of the elevated baseline levels or decreased reflex sympathetic responsiveness. However, this does not appear to be the case. In the present study, MSNA (total activity) in the older subjects was increased by 13% in response to a cold pressor test (\( \approx 10 \) times that demonstrated during HDR), suggesting that a “ceiling effect” of MSNA is not responsible for the attenuated increase in MSNA during HDR. Additionally, these increases in MSNA to the cold pressor test in the older subjects were comparable to that in the young, indicating that reflex sympathetic responsiveness in the older subjects was not attenuated. Other studies have also reported MSNA responsiveness similar to other stressors in older as compared with young subjects despite elevated resting MSNA.\( 29 \) Thus, the differential MSNA responses to HDR between the young and older subjects are unique.

An equally important effect of HDR in older individuals is the significant fall in arterial blood pressure in response to otolith organ stimulation. Because hypotension did not occur during head rotation in the lateral decubitus position, this suggests that the vestibular system and not the activation of other reflex mechanisms elicited the hypotensive response in the older subjects. Previous animal studies have reported reductions in arterial blood pressure during electrical stimulation of the vestibular nerve.\( 30,31 \) How the engagement of the vestibular system elicits hypotension during HDR is unclear, but it is probably due to changes in vascular resistance. There is no obvious indication that cardiac output would be substantially reduced during HDR in older subjects because heart rate was not significantly decreased. We have previously shown that central blood volume, estimated by thoracic impedance, is unchanged by HDR and thus changes in stroke volume are unlikely to occur.\( 8 \)

Systemic vascular resistance may be reduced in the older subjects by a number of mechanisms. It is possible that older individuals lack a sufficient increase in MSNA to maintain arterial blood pressure. In addition to their small increase in MSNA during HDR, experimental evidence suggests that there is a deficit in the transduction of increased MSNA into increases in vascular resistance in the aged.\( 32 \) However, a reduction in sympathetic-vascular transduction with age would not be likely to produce hypotension alone. The data suggest that vasodilation occurs in a yet-to-be determined vascular bed (eg, splanchn-
nic and renal). Vasodilation may have been mediated by either sympathetic withdrawal or activation of vasodilator fibers. With respect to sympathetic withdrawal, differential sympathetic outflow elicited by the vestibulosympathetic reflex has been demonstrated in both humans and animals.\textsuperscript{31,33} The presence of a vasodilator system in humans is controversial, but recent evidence suggests that it does not participate in vascular control to skeletal muscle.\textsuperscript{34} However, we cannot exclude this mechanism in other vascular beds. Finally, because the fall in arterial pressure was rapid during HDR, vasodilation mediated from humoral substances (eg, epinephrine) is unlikely.

These present findings could have clinical significance. Orthostatic hypotension increases the mortality rate in the elderly.\textsuperscript{2} As such, identification of the mechanisms that mediate orthostatic hypotension is of clinical importance. Direct evidence that the vestibular system is important in regulating arterial blood pressure during postural shifts comes from Doba and Reis.\textsuperscript{35} These investigators demonstrated that transection of vestibular nerves impaired reflexes that compensate for orthostatic blood pressure falls during head-up tilting in anesthetized cats. These findings have been reproduced recently in unanesthetized cats.\textsuperscript{36} Thus, the vestibulosympathetic reflex may be an important mechanism for the dynamic adjustment to and the maintenance of orthostasis in the upright posture. Further work is needed to determine the importance of this reflex in blood pressure regulation during movement to the upright posture in humans.

It is interesting that much of the previously noted morphological and physiological changes to the vestibular system with aging can also be observed during spaceflight.\textsuperscript{37,38} One major physiological consequence of microgravity is orthostatic intolerance. It has been estimated that nearly one half to two thirds of all astronauts have orthostatic intolerance after spaceflight.\textsuperscript{39} Despite this long-recognized problem of postspaceflight orthostatic intolerance, the physiological mechanisms responsible for this condition remain unresolved. However, impaired peripheral vasoconstriction is recognized as a possible factor in postspaceflight orthostatic intolerance.\textsuperscript{39} On the basis of the similar effects that aging and spaceflight have on the vestibular system, it seems reasonable to suspect that a diminished vestibulosympathetic reflex may also contribute to postspaceflight orthostatic intolerance. This hypothesis remains to be tested.

Summary

In summary, these data provide the first direct experimental support that the vestibulosympathetic reflex is attenuated with age in humans. These findings may have importance in understanding orthostatic blood pressure regulation with aging.

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References


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