Otolithic activation on visceral circulation in humans: effect of aging

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Sauder CL, Conboy EE, Chin-Sang SA, Ray CA. Otolithic activation on visceral circulation in humans: effect of aging. Am J Physiol Renal Physiol 295: F1166–F1169, 2008. First published August 13, 2008; doi:10.1152/ajprenal.90408.2008.—Engagement of the otolith organs elicits differential activation of sympathetic nerve activity and vascular responses to muscle and skin in humans. Additionally, aging attenuates the otolith organ-mediated increases in muscle sympathetic nerve activity and vascular responses to muscle and skin in humans. In this study, we hypothesized that 1) the vestibulosympathetic reflex (VSR) would elicit visceral vascular vasoconstriction and 2) visceral vascular response to the VSR would be attenuated in older subjects compared with young. To test these hypotheses, heart rate, mean arterial blood pressure, and renal, celiac trunk, and superior mesenteric arterial blood velocity (Doppler ultrasound) were measured in 22 young (25 ± 1 yr) and 18 older (65 ± 2 yr) healthy subjects during head-down rotation (HDR), which selectively activates the otolith organs. Mean arterial pressure and heart rate did not change from baseline during HDR in young or older subjects. Renal blood velocity (Δ −2 ± 1 cm/s) and vascular conductance (Δ −0.03 ± 0.01 cm/s·1·mmHg−1) significantly decreased from baseline during HDR (P < 0.05) in young subjects. In contrast, renal blood velocity and conductance did not change in older subjects (Δ 0.2 ± 1 cm/s and Δ0.02 ± 0.08 mmHg·cm−1·s−1, respectively) during HDR. Superior mesenteric and celiac blood velocity and conductance did not change in response to HDR in either the young or older subjects. These data suggest that renal vasoconstriction occurs during otolith organ activation in young but not older humans. Together with our previous studies, we conclude that the VSR elicits a diverse patterning of sympathetic outflow that results in heterogeneous vascular responses in humans and that these responses are significantly attenuated in older humans.

renal; splanchnic; blood flow; vestibulosympathetic reflex; vasoconstriction

UPON STANDING, an ~20% decline in cardiac output necessitates an increase in systemic vascular resistance to maintain blood pressure. Vasoconstriction of the splanchnic, renal, and skeletal muscle vascular beds is vitally important to increase systemic vascular resistance during standing (21). Kerman and Yates (10) reported electrical stimulation of the vestibular nerve in the cat significantly increased renal sympathetic nerve activity, whereas it had only a small effect on sympathetic activity to the superior mesenteric and hypogastric nerves. Additionally, renal vascular resistance was increased during stimulation of the vestibular nerve (9). These findings suggest that renal blood flow in humans should be sensitive to the activation of the vestibulosympathetic reflex (VSR) with less effect on splanchnic blood flow in humans.

We previously demonstrated differential sympathetic outflow to muscle and skin during activation of the VSR (18, 23).

The VSR elicits increases in muscle sympathetic nerve activity (MSNA) (20) but not skin sympathetic nerve activity (14, 18, 23). Moreover, the VSR elicits comparable increases in MSNA to the arms and legs but greater vasoconstriction to the calf than the forearm (1, 5, 9, 14). These data illustrate the differential activation of sympathetic outflow in response to the VSR in humans as well as the differential effects on sympathetic vascular control.

The effect of otolith activation on visceral blood flow has not been reported in humans. To determine the effect of otolithic activation on renal, superior mesenteric, and celiac trunk arterial blood flow in young and older humans, Doppler ultrasound measurements of the renal, superior mesenteric, and celiac trunk blood velocities were made at baseline and during head-down rotation (HDR). Based on the differential sympathetic outflow to the renal and superior mesenteric nerves observed in the cat by Kerman and Yates (10), we hypothesized that vascular regulation to the kidney and gastrointestinal tract would be different during activation of the otolith organs in the young. Additionally, based on our earlier work, we also hypothesized that visceral vascular responses to HDR in older subjects would be attenuated compared with young subjects (15, 19). Through a series of studies, we have demonstrated that the otolith organs mediate MSNA responses to HDR (1).

METHODS

Subjects. Twenty-two young (10 men and 12 women) [age: 25 ± 1 (SE) yr; height: 172 ± 2 cm; weight: 66 ± 3 kg] and 18 older (7 men and 11 women) [age: 65 ± 2 yr; height: 168 ± 2 cm; weight: 66 ± 3 kg] subjects who were normotensive, nonsmokers, nonobese, and not taking any medications that would interfere with the measurements of the protocol were studied. In the women, we did not control for the menstrual cycle because it has been reported not to alter the VSR (11). Additionally, all subjects were fasted for at least 8 h before the experimental protocol. Eleven young and eleven older subjects participated in the renal artery measurements. Eleven young and ten older subjects participated in the superior mesenteric artery measurements. Thirteen young and eleven older subjects participated in the celiac trunk artery measurements. Some subjects participated in multiple trials (i.e., renal, superior mesenteric, and/or celiac trunk). All subjects received a physical examination before participation. Written informed consent was obtained from all subjects after verbal explanation of the experimental protocol. The Institutional Review Board of The Pennsylvania State University College of Medicine approved this study.

Experimental protocol. Renal (n = 22; 11 young and 11 older subjects), superior mesenteric (n = 21; 11 young and 10 older subjects), or celiac trunk (n = 24; 13 young and 11 older subjects) artery blood velocity was measured continuously before, during, and after HDR. In addition, mean arterial blood pressure (MAP) and heart rate (HR) were measured before, during, and after HDR.

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rate (HR) were measured throughout. All of the subjects were in the prone position while the measurements were taken. The experimental trial consisted of 3 min of baseline followed by 3 min of HDR, and 3 min of recovery.

Baseline measurements were taken with the subject’s head upright with the neck extended as close to the vertical plane as possible and the chin supported. This position approximates the gravitational orientation of the head when an individual is in the upright posture (23). For HDR, the head was maximally lowered in the vertical plane over the edge of the table. An investigator moved the head by supporting the forehead and chin, thus producing a passive head movement. Once the head became stationary, only afferent inputs from the otolith organs and not the semicircular canals were engaged.

**Measurements.** Doppler ultrasound (HDI 5000; ATL Ultrasound, Bothell, WA) was used to measure renal, superior mesenteric, and celiac trunk artery blood velocity. To scan the various arteries, the table on which the subjects lay had a section removed from just below the xiphoid process to the pelvic arch. The images could then be obtained while the subjects lay in the prone position. All arteries were scanned using the anterior abdominal approach using a curved-array transducer (2–5 MHz) with a 2.5-MHz pulsed Doppler frequency. The probe insonation angle to the artery was ≤60°. The focal zone was set at the depth of the artery. The transducer was held in the same place to record velocity tracings during each trial, and the data were obtained in the same phase of the respiratory cycle.

Continuous measurements of arterial blood pressure and HR were made by finger plethysmography using a Finapres blood pressure monitor (Ohmeda, Englewood, CO). Arterial pressure at rest was measured using an automated sphygmomanometer (Dinamap). MAP and HR measurements were collected offline. Electrocardiogram was obtained during all studies.

**Data analysis.** MAP and HR were analyzed offline using Chart software (ADInstruments, Newcastle, Australia). Doppler ultrasound tracings were analyzed using the software of the ATL to obtain blood velocity for each cardiac cycle. Because of technological limitations, it is not possible to accurately measure the diameter of the arteries in the current study using the ATL Doppler ultrasound machine; therefore, an index of vascular conductance was calculated by dividing the respective artery blood velocity by MAP of the given trial. For all trials, the 3 min of baseline were averaged together and reported as the baseline value for the respective trial. Additionally, the 3 min of HDR for each trial were averaged.

The data were analyzed using a one-between (age), one-within (HDR) repeated-measures analysis of variance for all studies. Significance was set at $P < 0.05$. All data are presented as means ± SE.

## RESULTS

HDR elicited renal artery vascular responses in the young, but not older, subjects (Fig. 1). In the young, HDR significantly decreased renal arterial blood velocity ($\Delta = -2 \pm 1$ cm/s, $4 \pm 1\%$) and vascular conductance ($\Delta = -0.03 \pm 0.01$ cm$^2$·s$^{-1}$·mmHg$^{-1}$, $5 \pm 2\%$) (Fig. 1). In contrast, renal artery velocity and vascular conductance did not change in the older subjects with HDR ($\Delta = -0.2 \pm 1$ cm/s and $\Delta = 0.02 \pm 0.08$ mmHg·cm$^{-1}$·s$^{-1}$, respectively). Figure 2 is a representative renal artery blood velocity tracing from one young and one older subject at baseline and during HDR. MAP and HR did not change in the young or the older subjects during HDR (Table 1). MAP at rest was significantly greater in the older compared with younger subjects (94 ± 4 and 83 ± 4 mmHg, respectively).

Superior mesenteric and celiac trunk artery blood velocity and vascular conductance did not change with HDR in the young or older subjects (Table 2). MAP and HR did not change with HDR in either age group during these trials (Table 1).
There are two major findings from this study. First, activation of the VSR causes vasoconstriction in the renal but not the superior mesenteric or celiac trunk arteries. This finding supports the concept that otolithic organs are capable of differential sympathetic outflow to anatomically distinct visceral beds. Second, otolith-mediated vasoconstriction of the renal artery is greater in young than older subjects. This finding supports the concept that the VSR is attenuated with age.

Our results are the first to report renal vasoconstriction by activation of the VSR in humans. This finding is consistent with Kerman et al. (9), who demonstrated that electrical stimulation of the vestibular nerve elicits renal vasoconstriction in the cat. Previous work from our laboratory has reported significant vasoconstriction to the arms and legs during the activation of the VSR (14). It appears that vasoconstriction to the limbs is much greater than that of the kidney. This result is consistent with those of Kerman et al. (9) who demonstrated in the cat that the magnitude of vasoconstriction in the limb vasculature was significantly larger than that of the renal vasculature. Although the reasons for this difference in vasoconstriction to the limbs and kidney are not clear, it has been proposed that, during vestibular stimulation, the vasculature of the kidney is not as responsive to sympathetic activity (4, 7, 10, 12, 16).

Head-up tilt (HUT) has been reported to increase renal vasoconstriction by 30–40% (2, 20). Additionally, we have observed a 25–30% increase in renal vasoconstriction during HUT using Doppler ultrasound (unpublished observations). This marked increase in renal vasoconstriction is much greater than that observed with HDR alone. This finding suggests that, with standing, the contribution of the VSR is less compared with other neural reflex mechanisms (i.e., baroreflexes). However, the relative contributions of the baroreflexes and VSR during postural blood pressure regulation have not been specifically tested to date. However, our previous studies clearly indicate an additive interaction between baroreceptor unloading and the VSR (3, 17).

What explains the greater vasoconstriction in the renal vasculature compared with the superior mesenteric and celiac trunk arteries? Kerman and Yates (10) demonstrated in the cat that electrical stimulation of the vestibular nerve caused a significant activation of the renal sympathetic nerve, composed primarily of vasoconstrictor efferents, but had only a small effect on the superior mesenteric nerve, composed of both vasoconstrictor and motility-regulating efferents. This differential distribution of sympathetic nerve responses observed in the cat mirrors the differential vasoconstriction observed in the renal compared with the superior mesenteric and celiac trunk arteries in humans. Thus our results support the concept that the VSR elicits a diverse patterning of sympathetic outflow in humans.

Vasoconstriction observed in the kidney along with previous findings of vasoconstriction in skeletal muscle during HDR in young subjects supports the concept that activation of the VSR can assist in regulating blood pressure during orthostasis in humans (6, 8, 14). The current findings expand on this concept by demonstrating that renal vasoconstriction, in addition to skeletal muscle vasoconstriction, may contribute to the maintenance of arterial blood pressure. Moreover, these findings support the concept that vestibular signals do not merely elicit a nonspecific response but instead act selectively to regulate blood pressure during postural changes.

The second major finding of this study is that aging attenuates renal vasoconstriction during activation of the VSR. MSNA responses to HDR are significantly attenuated in older compared with younger individuals (15, 19). These studies together support the concept that the VSR is altered with age in humans. Importantly, the current study has built upon these initial findings to demonstrate that this attenuation of the VSR has implications on the renal vasculature. Because renal vasculature is important in regulating systemic vascular resistance in response to an orthostatic challenge (16), attenuation of renal vasoconstriction may have important clinical significance. The prevalence of orthostatic hypotension in the elderly is greater than in the young (22). Furthermore, Masaki et al.
(13) found that orthostatic intolerance leads to an increase in mortality rate in the elderly population. However, additional research is necessary to precisely determine the role of the VSR during an orthostatic challenge. Our results suggest that the attenuation of renal vasoconstriction to vestibular stimulation is one potential mechanism contributing to orthostatic intolerance in the elderly population. Morbidity and mortality related to orthostatic hypotension in older individuals may improve with restoration of vestibular function.

In summary, this study generated two significant findings. First, vasoconstriction of the renal vasculature but not superior mesenteric or celiac trunk vasculature occurs in response to activation of the VSR. This finding supports the concept that differential sympathetic outflow to distinct visceral beds can be elicited by the otolith organs in humans. Second, otolithic vasoconstriction of the renal artery is attenuated in older subjects compared with young, which further supports the concept that the VSR is attenuated with age.

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GRANTS

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