3. Results

Table 1 shows average values of AP and HR obtained at 30 s before the onset of HUT with and without GVS. No significant difference in AP and HR was observed between GVS amplitudes for both DOWN and UP groups. Thus, GVS itself did not change AP and HR of both DOWN and UP groups in the supine position.

Fig. 2 shows the relationship between CW and changes in AP (upper panel), and between the difference in SVV and changes in AP (lower panel). Changes in AP at the onset of HUT were significantly correlated with the difference in tilt angles of SVV between clockwise and counterclockwise rotations ($p<0.0001$), but not with CW analyzed by the caloric test ($p=0.064$).

Fig. 3 shows the representative responses of AP during HUT without and with GVS in one subject of DOWN group, in whom AP decreased without GVS. The somatosensory threshold was 0.6 mA in this subject. At an amplitude of 0.4 mA, the mean AP decreased by 12 mm Hg after the onset of HUT. The decrease was abolished with GVS of 0.5 mA, which was not yet sensed by the subject. AP with GVS of 0.6 mA or the amplitude of the somatosensory threshold decreased again at the onset of HUT. The averaged values of the shaded zone, time 10 to 15 s, were used to analyze changes in AP compared with those in the supine position.

Fig. 4 shows the representative responses of AP during HUT with GVS in subject of UP group, in whom AP was maintained or increased without GVS. The somatosensory threshold was 0.5 mA in this subject. At an amplitude of 0.3 mA, the mean AP was not altered during HUT. However, AP increased by 7 mm Hg with GVS of 0.4 mA, which was not sensed by the subject. An AP increase with GVS of 0.5 mA or the amplitude of the somatosensory threshold was not observed. The averaged values of the shaded zone, time 10 to 15 s, were also used to analyze changes in AP compared with those in the supine position.

Fig. 5 shows a data summary of changes in AP (left panels) and HR (right panels) at the onset of HUT from the DOWN group (upper panels) and the UP group (lower panels).

For the DOWN group, the amplitudes of the somatosensory threshold of the 15 subjects were 0.3 to 0.8 mA (0.3 mA for 7 subjects, 0.4 mA for 3 subjects, 0.5 mA for 3 subjects, 0.6 mA for 1 subject, and 0.8 mA for 1 subject). AP decreased 12 mm Hg from that in the supine position without GVS at the onset of HUT. The change was similar among the other conditions with the exception of GVS at an amplitude of 0.1 mA below the somatosensory threshold. The decrease in AP was abolished under this condition, and the value was significantly different from those of the other 4 conditions. Thus, subsensory GVS at an amplitude of 0.1 mA below the somatosensory threshold improved AP control at the onset of HUT.

Table 1
Control values of arterial pressure and heart rate.

		GVS				
		Off	−0.2	−0.1	Somatosensory threshold	+0.1
AP (mm Hg)	DOWN	91±4	86±2	87±4	88±3	88±2
	UP	94±4	89±1	94±3	89±1	89±2
HR (bpm)	DOWN	62±3	56±1	61±3	58±2	54±2
	UP	68±4	60±5	66±4	61±5	59±5

Average values of arterial pressure (AP) and heart rate (HR) obtained at 30 s before the onset of the head-up tilt (HUT) with and without galvanic vestibular stimulation (GVS) for the subjects whose AP decreased by more than 5 mm Hg at the onset of head up tilt (DOWN, n=15), and the other comprised the subjects whose AP increased or decreased by less than 5 mm Hg at the onset of HUT (UP, n=10) (mean±SE). Amplitudes are 0 mA or off, 0.2 and 0.1 mA below somatosensory threshold, somatosensory threshold, 0.1 mA over somatosensory threshold.

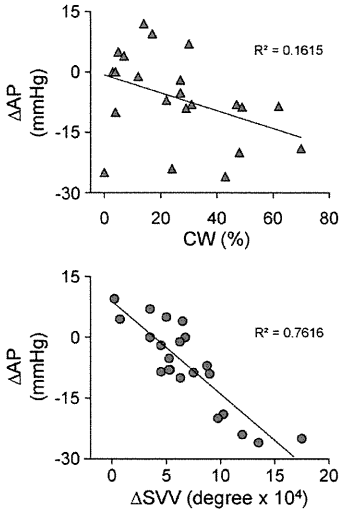

Fig. 2. Upper panel: relationship between caloric weakness (CW) and change in arterial pressure (ΔAP) upon head-up tilt (HUT). Lower panel: relationship between the differences in degrees of the subjective visual vertical (ΔSVV) test measured from clockwise and counterclockwise directions and ΔAP upon HUT.

In the UP group, the amplitudes of the somatosensory threshold of the 10 subjects were 0.3 to 0.7 mA (0.3 mA for 3 subjects, 0.5 mA for 3 subjects, 0.4 mA for 2 subjects, 0.6 mA for 1 subject, and 0.7 mA for 1 subject). AP increased by 4 mm Hg from that in the supine position without GVS at the onset of HUT. The change was similar among the other conditions with the exception of GVS at an amplitude of

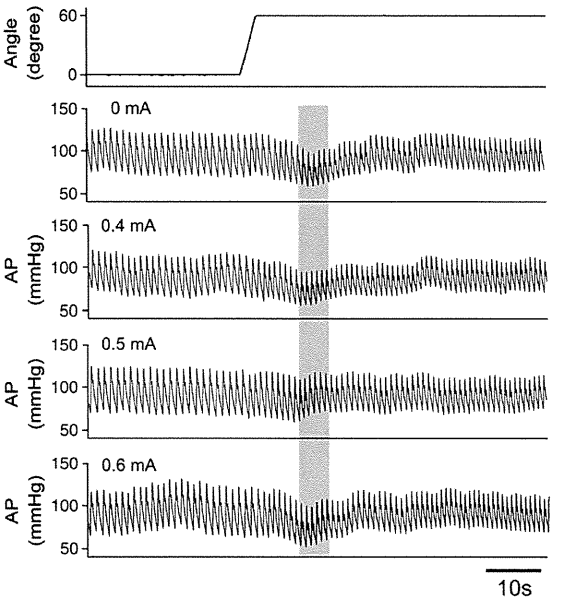

Fig. 3. Typical arterial pressure (AP) responses in the DOWN group, whose AP decreased by more than 5 mm Hg at the onset of head-up tilt (HUT) without galvanic vestibular stimulation (GVS). The figures show AP responses upon HUT without GVS (0 mA), with GVS at amplitudes of 0.4 mA (0.2 mA below the somatosensory threshold), 0.5 mA (0.1 mA below the somatosensory threshold), and 0.6 mA (the somatosensory threshold). Averaged values of the shaded zone were used for the subsequent analysis of changes in AP.

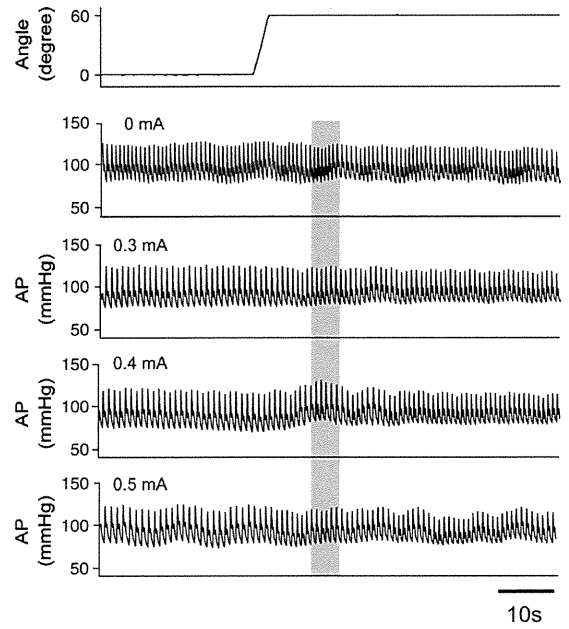

Fig. 4. Typical arterial pressure (AP) responses in the UP group, whose AP increased or decreased by less than 5 mm Hg at the onset of head-up tilt (HUT) without galvanic vestibular stimulation (GVS). The figures show AP responses without GVS (0 mA), with GVS at amplitudes of 0.3 mA (0.2 mA below the somatosensory threshold), 0.4 mA (0.1 mA below the somatosensory threshold), and 0.5 mA (the somatosensory threshold). Averaged values of the shaded zone were used for the subsequent analysis of changes in AP.

0.1 mA below the somatosensory threshold. The increase in AP was augmented under this condition, and the value was significantly different from those of the other 4 conditions. Thus, subsensory GVS with amplitude of 0.1 mA below the somatosensory threshold enhanced AP control at the onset of HUT. Contrarily, no significant difference in HR was observed among GVS amplitudes for both UP and DOWN groups. It suggests subthreshold GVS has a significant effect on peripheral vascular resistance rather than HR to change AP.

Fig. 6 shows the time course of changes in AP (left panels) and HR (right panels) with and without GVS at an amplitude of 0.1 mA below the somatosensory threshold in the DOWN group (upper panels) and the UP group (lower panels). In the DOWN group, AP decreased by 12 mm Hg at the onset of HUT without GVS, and gradually recovered to the value of the supine position. This decrease was abolished when GVS was applied. AP further increased by 40 s after the onset of HUT and recovered to that of the supine position. In contrast, AP increased by 4 mmHg without GVS in the UP group. With the application of GVS at an amplitude of 0.1 mA below the somatosensory threshold, AP further increased by 12 mm Hg, and gradually recovered to the value of the supine position. HR gradually increased during HUT in DOWN group. By contrast in UP group, HR increased quicker than AP, and recovered to the level which is not significantly different from the control. In UP group, change in HR during 5 to 10 s after the onset of HUT with GVS was tended to be higher than that without GVS, but did not reach significant level. Again, it suggests that GVS has a significant effect on peripheral vascular resistance rather than HR to change AP.

4. Discussion

In the present study, we clarify that the difference in SVV between the clockwise and counterclockwise directions is proportional to the change in AP during posture transition from the supine position to HUT. The AP control is enhanced by GVS at an amplitude of 0.1 mA below the somatosensory threshold. Thus, subsensory GVS improves AP control for subjects whose AP drops, and further augmented for subjects whose AP is maintained upon HUT.

HUT results in alteration of vestibular input (Yates and Miller, 1994) and fluid redistribution (Watenpaugh and Hargens, 1996). Fluid redistribution or footward blood shift might decrease the AP due to decreases in venous return and cardiac output (Larsen et al., 1996), but the AP is maintained in healthy subjects (Watenpaugh et al., 2002; Kamiya et al., 2003). We have clarified that the vestibular system plays an important role in this maintenance of AP at the onset of HUT in human subjects (Tanaka et al., 2009). During HUT,

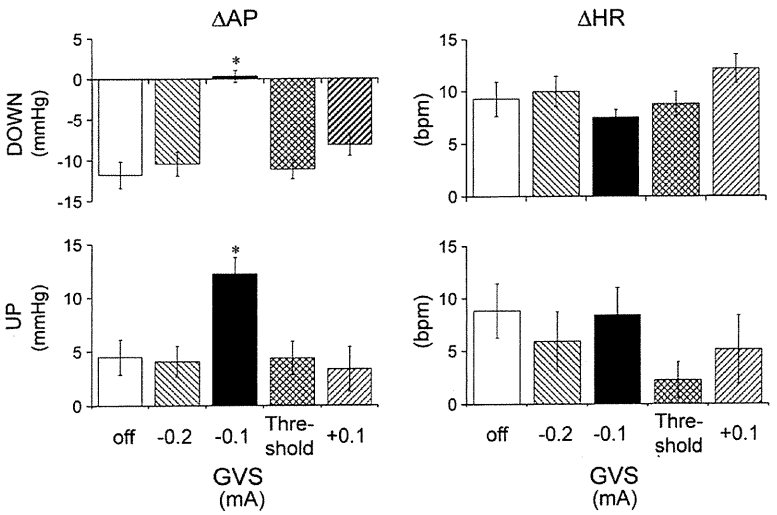

Fig. 5. Changes in arterial pressure (AP; left panels) and heart rate (HR; right panels) at the onset of head-up tilt (HUT) without (off) and with galvanic vestibular stimulation (GVS) at amplitudes of 0.2 and 0.1 mA below the somatosensory threshold (−0.1 and −0.2, respectively), the somatosensory threshold (threshold), and 0.1 mA above the somatosensory threshold (+0.1). The upper panels show summarized values from the subjects whose AP decreased by more than 5 mm Hg at the onset of HUT without GVS (DOWN). The lower panels show summarized values from the subjects whose AP increased or decreased by less than 5 mm Hg at the onset of HUT without GVS (UP). *p<0.05 vs. GVS (off), −0.2, threshold, +0.1.

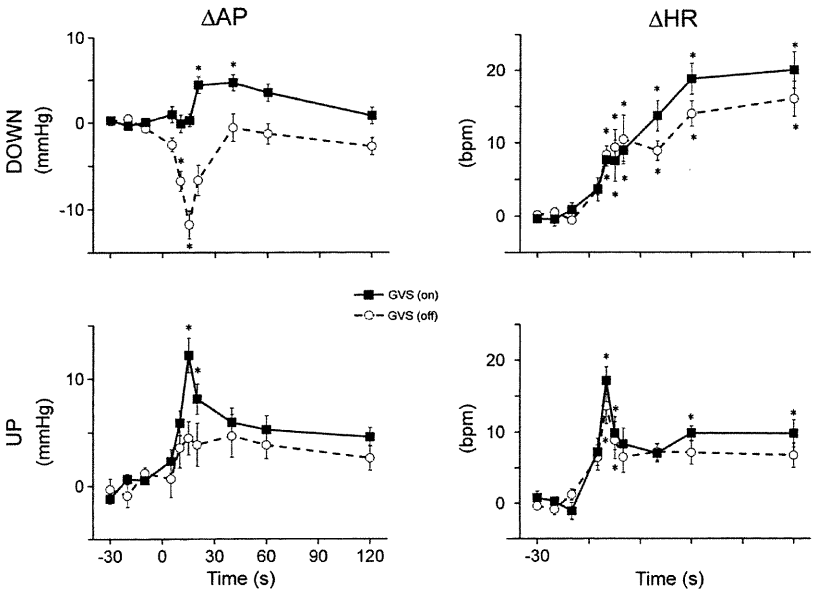

Fig. 6. Time course of changes in arterial pressure (AP: left panels) and heart rate (HR; right panels) with galvanic vestibular stimulation (GVS) of 0.1 mA below the somatosensory threshold (GVS (on)) and without GVS (GVS (off)) during head-up tilt (HUT). The upper panels show summarized values from the subjects whose AP decreased by more than 5 mm Hg at the onset of HUT without GVS (DOWN). The lower panels show summarized values from the subjects whose AP increased or decreased by less than 5 mm Hg at the onset of HUT without GVS (UP). *$p<0.05$ vs. AP or HR during supine position.

both semicircular canals and otolith organs of the vestibular system are stimulated by pitch rotation and changes in the direction of gravity for the body, respectively (Fitzpatrick and Day, 2004). However, it has been considered that the otolith organs are more important for sympathetic nerve activity and AP control during postural change, rather than semicircular canals (Kaufmann et al., 2002; Carter and Ray, 2008). In the present study, we analyzed the relationship between the symmetry of vestibular function and the change in AP. The caloric weakness or deviation of the semicircular canals and the related functions were not correlated with changes in AP upon HUT. However, deviation of the otolith and the related functions examined by SVV testing correlated well with changes in AP. The results are consistent with the findings noted above, and this is the first demonstration that deviation of the otolith and the related functions are proportional to the AP change during HUT. If the function does not deviate, AP is well maintained during HUT.

SVV is a sensitive tool for detecting imbalances in the "graviceptive pathway" from the otolith to the cortex, and is involved in the perception of verticality (Friedmann, 1970; Brandt et al., 1994; Aoki et al., 2008). Normal is considered to be a less than 1° deviation from the real vertical (Friedmann, 1970). Lesions of the otolith and the pathway below the pontine level cause ipsilateral tilts of the perceived vertical, but lesions above the level cause contralateral tilts (Brandt et al., 1994). In the present study, the difference between left and right deviations of the function was analyzed. The quite small difference, which was less than 0.002°, correlated with the change in AP at the onset of HUT. The pathway, including the otolith organs, might not correctly sense the change in the direction of gravity for the body due to the deviation, and AP might not be maintained even if each inherent function, i.e., the results from SVV, is within normal range. SVV is also affected by visual effects, and visual roll motion induces deviation of the visual vertical (Bronstein et al., 1996). The clockwise and counterclockwise roll motions of the bar before adjustment might affect the results (Lorincz and Hess, 2008). However, the otolith and related pathways, rather than the visual effect, should be more important for control of AP upon HUT. This is because unlike during SVV, the subjects closed their eyes using an eye mask upon HUT; however, the changes in AP were significantly correlated with the SVV results.

When GVS of 0.1 mA below the somatosensory threshold was applied to the subjects in the DOWN group, the decrease in AP was diminished, and the AP remained at the level of the supine position. In the UP group, AP was further increased with GVS. GVS of 2–4 mA given 500 ms after R-wave of electrocardiogram increases sympathetic nerve activity in supine position (Voustianiouk et al., 2006). We did not measure the sympathetic nerve activity in the present study, but the activity might not be modulated so much by GVS itself since AP and HR did not change with GVS of the low amplitudes used in the present study. However, this weak stimulation might have improved the sensitivity of the otolith organs. The response of the vestibulocardiovascular reflex with the weak GVS was likely the phenomenon seen in the somatosensory system. Below-threshold electrical stimulation to the skin improves tactile sensitivity (Dhruv et al., 2002), and stimulation to the muscle improves joint position sensitivity (Collins et al., 2010). The mechanism is unclear, but the phenomenon that noise increases in the quality of detection performance or signal transmission is known as stochastic resonance. As a result of this phenomenon, electrical stimulation to the muscles improves position sense and balance control (Gravelle et al., 2002; Ross et al., 2007). In the present study, we found a similar phenomenon in the vestibulocardiovascular reflex. As the phenomenon used for rehabilitation of sprains (Ross et al., 2007) and treatment of neuropathies (Dhruv et al., 2002), GVS at the amplitude of 0.1 mA below the somatosensory threshold may be used for maintaining cerebral blood flow and the prevention of orthostatic hypotension. However, GVS-induced hypertension may be required attention for patients of hypertension or subjects like UP group. GVS does not only induce electrical activation in peripheral vestibular afferents but also affects different cortical–vestibular areas and neighboring cortical regions (Utz et al., 2010). However, the trapezius muscle stimulation in a similar fashion did not change the response of AP (our unpublished data). Thus, stimulation of the area, i.e., stimulation over the mastoid processes is considered to be important for AP control via the cardiovascular organs.

Without GVS, AP recovered during the late phase of HUT probably due to the baroreflex. Because the baroreflex is a negative-feedback

system (Sagawa, 1983), its activation should be slower than that of the vestibulocardiovascular control mechanism (Nakamura et al., 2009). The vestibular system senses gravitational changes and reflexively affects AP regardless of the occurrence of gravitational change-induced fluid shift. However, the baroreflex is activated after the change in AP due to the fluid shift (Gotoh et al., 2004). From this viewpoint, baroreflex is also functioning at the onset of HUT in DOWN group without GVS. Without baroreflex, AP should be more decreased as seen in aged subjects (Tanaka et al., 2009). AP or input for the arterial baroreceptors should be lower than that at the heart level or at the finger with the blood pressure cuff during HUT. Baroreflex should work to recover this lower AP to the control level. Overcompensation or further increase in AP compared to that during supine position seen in Fig. 6, might be additional effects of the baroreflex control.

This interaction between vestibular system and baroreflex control can be further considered with change in HR. In DOWN group, HR gradually increased during HUT. By contrast in UP group, HR increased quicker than AP, and recovered to the level which is not significantly different from the control. This difference might be explained by the difference in the direction of the input to the baroreceptors at the onset of HUT, i.e., lower or higher AP compared to that during supine position. In DOWN group that otolith function is unbalanced, AP decreased due to footward blood shift. Negative feedback system via the baroreceptors works to return AP, and HR is further increased. Contrarily, a change in direction of gravity is detected accurately by the vestibular receptors in UP group that otolith function is balanced. Vestibular system reflexively changes HR and probably peripheral resistance before AP decreases due to blood redistribution. The vestibular system acts quickly as a feedforward system against gravitational change. However, the response via feedforward control can induce overcorrect error (Gotoh et al., 2004). In the present study, the overcompensated AP and HR were compensated by the baroreflex, and HR recovered to the control level in UP group. Respiration, i.e., tidal volume and respiratory rate affects AP and HR control (Hayano et al., 1994; Mesquida et al., in press), but GVS at this amplitude did not affect spontaneous breathing (our unpublished data).

As a limitation, we focused in AP and HR in the present study, and did not measure cardiac output or any blood flow. HUT causes not only fluid shift in the blood vessels, but also transcapillary fluid shift to the tissues due to increase in hydrostatic pressure in the lower body. If transcapillary fluid shift in the lower body was not recovered during resting period, venous return and cardiac output might not be similar for each measurement. However, the difference is averaged and considerably balanced by varied order of measurements.

In conclusion, the functional balance of the graviceptive pathway, including the otolith organs is important for the control of AP at the onset of HUT in human subjects. The AP control is enhanced by subsensory near-threshold GVS.

Acknowledgment

This study was supported by the Grant-in-Aid for Scientific Research promoted by the Japan Society for the Promotion of Science.

References

Abe, C., Tanaka, K., Awazu, C., Morita, H., 2008. Strong galvanic vestibular stimulation obscures arterial pressure response to gravitational change in conscious rats. J. Appl. Physiol. 104, 34–40.

Aoki, M., Sakaida, Y., Hayashi, H., Yamada, N., Mizuta, K., Ito, Y., 2008. The orthostatic dysregulation of blood pressure in dizzy patients. J. Vestib. Res. 18, 223–229.

Asai, M., Aoki, M., Hayashi, H., Yamada, N., Mizuta, K., Ito, Y., 2009. Subclinical deviation of the subjective visual vertical in patients affected by a primary headache. Acta Otolaryngol. 129, 30–35.

Brandt, T., Dieterich, M., Danek, A., 1994. Vestibular cortex lesions affect the perception of verticality. Ann. Neurol. 35, 403–412.

Bronstein, A.M., Yardley, L., Moore, A.P., Cleeves, L., 1996. Visually and posturally mediated tilt illusion in Parkinson's disease and in labyrinthine defective subjects. Neurology 47, 651–656.

Carter, J.R., Ray, C.A., 2008. Sympathetic responses to vestibular activation in humans. Am. J. Physiol. Regul. Integr. Comp. Physiol. 294, R681–688.

Collins, A.T., Blackburn, J.T., Olcott, C.W., Miles, J., Jordan, J., Dirschl, D.R., Weinhold, P.S., 2010. Stochastic resonance electrical stimulation to improve proprioception in knee osteoarthritis. Knee 18, 317–322.

Dhruv, N.T., Niemi, J.B., Harry, J.D., Lipsitz, L.A., Collins, J.J., 2002. Enhancing tactile sensation in older adults with electrical noise stimulation. Neuroreport 13, 597–600.

Doba, N., Reis, D.J., 1974. Role of the cerebellum and the vestibular apparatus in regulation of orthostatic reflexes in the cat. Circ. Res. 40, 9–18.

Enticott, J.C., Dowell, R.C., O'Leary, S.J., 2003. A comparison of the monothermal and bithermal caloric tests. J. Vestib. Res. 13, 113–119.

Fitzpatrick, R.C., Day, B.L., 2004. Probing the human vestibular system with galvanic stimulation. J. Appl. Physiol. 96, 2301–2316.

Friedmann, G., 1970. The judgement of the visual vertical and horizontal with peripheral and central vestibular lesions. Brain 93, 313–328.

Gotoh, T.M., Fujiki, N., Matsuda, T., Gao, S., Morita, H., 2004. Roles of baroreflex and vestibulosympathetic reflex in controlling arterial blood pressure during gravitational stress in conscious rats. Am. J. Physiol. Regul. Integr. Comp. Physiol. 286, R25–30.

Gravelle, D.C., Laughton, C.A., Dhruv, N.T., Katdare, K.D., Niemi, J.B., Lipsitz, L.A., Collins, J.J., 2002. Noise-enhanced balance control in older adults. Neuroreport 13, 1853–1856.

Hayano, J., Mukai, S., Sakakibara, M., Okada, A., Takata, K., Fujinami, T., 1994. Effects of respiratory interval on vagal modulation of heart rate. Am. J. Physiol. 267, H33–40.

Kamiya, A., Michikami, D., Fu, Q., Iwase, S., Hayano, J., Kawada, T., Mano, T., Sunagawa, K., 2003. Pathophysiology of orthostatic hypotension after bed rest: paradoxical sympathetic withdrawal. Am. J. Physiol. Heart Circ. Physiol. 285, H1158–1167.

Kaufmann, H., Biaggioni, I., Voustianiouk, A., Diedrich, A., Costa, F., Clarke, R., Gizzi, M., Raphan, T., Cohen, B., 2002. Vestibular control of sympathetic activity. An otolith-sympathetic reflex in humans. Exp. Brain Res. 143, 463–469.

Larsen, P.N., Moesgaard, F., Madsen, P., Pedersen, M., Secher, N.H., 1996. Subcutaneous oxygen and carbon dioxide tensions during head-up tilt-induced central hypovolaemia in humans. Scand. J. Clin. Lab. Invest. 56, 17–24.

Lorincz, E.N., Hess, B.J., 2008. Dynamic effects on the subjective visual vertical after roll rotation. J. Neurophysiol. 100, 657–669.

Melvin, T.A., Della Santina, C.C., Carey, J.P., Migliaccio, A.A., 2009. The effects of cochlear implantation on vestibular function. Otol. Neurotol. 30, 87–94.

Mesquida, J., Kim, H.K., Pinsky, M.R., in press. Effect of tidal volume, intrathoracic pressure, and cardiac contractility on variations in pulse pressure, stroke volume, and intrathoracic blood volume. Intensive Care Med.

Nakamura, Y., Matsuo, S., Hosogai, M., Kawai, Y., 2009. Vestibular control of arterial blood pressure during head-down postural change in anesthetized rabbits. Exp. Brain Res. 194, 563–570.

Ross, S.E., Arnold, B.L., Blackburn, J.T., Brown, C.N., Guskiewicz, K.M., 2007. Enhanced balance associated with coordination training with stochastic resonance stimulation in subjects with functional ankle instability: an experimental trial. J. Neuroeng. Rehabil. 4, 47.

Sagawa, K., 1983. Baroreflex control of systemic arterial pressure and vascular bed. In: Shepherd, J.T., Abboud, F.M. (Eds.), Handbook of Physiology, The Cardiovascular System. American physiological society, Maryland, pp. 453–496.

Tanaka, K., Abe, C., Awazu, C., Morita, H., 2009. Vestibular system plays a significant role in arterial pressure control during head-up tilt in young subjects. Auton. Neurosci. 148, 90–96.

Utz, K.S., Dimova, V., Oppenlander, K., Kerkhoff, G., 2010. Electrified minds: transcranial direct current stimulation (tDCS) and galvanic vestibular stimulation (GVS) as methods of non-invasive brain stimulation in neuropsychology—a review of current data and future implications. Neuropsychologia 48, 2789–2810.

Voustianiouk, A., Kaufmann, H., Diedrich, A., Raphan, T., Biaggioni, I., Macdougall, H., Ogorodnikov, D., Cohen, B., 2006. Electrical activation of the human vestibulosympathetic reflex. Exp. Brain Res. 171, 251–261.

Watenpaugh, D.E., Hargens, A.R., 1996. The cardiovascular system in microgravity. In: Fregly, M.J., Blatteis, C.M. (Eds.), Handbook of Physiology, The Gravitational Environment. American physiological society, Maryland, pp. 631–674.

Watenpaugh, D.E., Cothron, A.V., Wasmund, S.L., Wasmund, W.L., Carter III, R., Muenter, N.K., Smith, M.L., 2002. Do vestibular otolith organs participate in human orthostatic blood pressure control? Auton. Neurosci. 100, 77–83.

Yates, B.J., Miller, A.D., 1994. Properties of sympathetic reflexes elicited by natural vestibular stimulation: implications for cardiovascular control. J. Neurophysiol. 71, 2087–2092.

Zeng, F.G., Fu, Q.J., Morse, R., 2000. Human hearing enhanced by noise. Brain Res. 869, 251–255.

Exp Brain Res
DOI 10.1007/s00221-011-2989-0

RESEARCH ARTICLE

Evidence for vestibular dysfunction in orthostatic hypotension

Mitsuhiro Aoki · Yuzuru Sakaida · Kunihiko Tanaka · Keisuke Mizuta · Yatsuji Ito

Received: 8 November 2011 / Accepted: 12 December 2011
© Springer-Verlag 2011

Abstract There is little definitive evidence of the clinical significance of the vestibular-cardiovascular reflex in humans, despite the fact that the vestibular system is known to contribute to cardiovascular control in animals. The present study involved 248 dizzy patients (127 male patients and 121 female patients) aged 65 years and younger. We classified all participants into three groups based on their vestibular evoked myogenic potential (VEMP) responses; absent VEMP, asymmetry VEMP and normal VEMP. To investigate the effect of the otolith disorder, which was estimated by the VEMP, on the orthostatic blood pressure responses, the subjects' systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate were monitored during the orthostatic test after they actively stood up. The male patients in the absent VEMP group had a significant drop in their DBP at 1 min after active standing up ($P < 0.05$) without any change in their SBP. Conversely, male patients in the asymmetry VEMP and normal VEMP groups showed a significant increase in the SBP at 1 min after active standing up ($P < 0.05$). Female patients in the absent VEMP group did not show any significant drop in their blood pressure after standing up ($P > 0.05$). In the entire group of participants, a total of 19.6% of the patients in the absent VEMP group fulfilled the criteria for orthostatic hypotension (OH), which was significantly > the 8.6% of patients in the normal VEMP group and the 7.2% in the asymmetry VEMP group ($P < 0.05$). Our results suggest that vestibular disorders due to the dysfunction of otolith organs provoke OH.

Keywords Graviceptor · Otolith · Orthostatic hypotension · Dizziness · Subjective visual vertical · Vestibular evoked myogenic potential

M. Aoki (✉) · Y. Sakaida · K. Mizuta · Y. Ito
Department of Otolaryngology, Gifu University Graduate School of Medicine, 1-1 Yanagido, Gifu City 501-1194, Japan
e-mail: aoki@gifu-u.ac.jp

K. Tanaka
Department of Radiotechnology, School of Health Science, Gifu University of Medical Science, 795-1 Nagamine Ichihiraga, Seki-City, Gifu 501-3892, Japan

Published online: 29 December 2011

Introduction

The otolith, one of the graviceptive organs, receives a signal of tilt with respect to the gravitational vector and informs the brain about rapid changes in posture. Long-term bed rest results in rapid physical deconditioning with the development of orthostatic hypotension (OH). This can be explained by the plasticity of the vestibular-cardiovascular pathway. However, the mechanisms underlying this phenomenon remain unclear (Yates et al. 2000). Animal studies have demonstrated considerable evidence that the bilateral removal of the labyrinthine inputs reduces orthostatic tolerance (Doba and Reis 1974; Jian et al. 1999). It appears that stimulation of otolith receptors in humans, as in animals (Yates and Miller 1994; Woodring et al. 1997), can produce cardiovascular alterations. Essandoh et al. (1988) reported that head-down neck flexion in the prone position produces a rapid decrease in blood flow of the forearm and calf in male subjects. Additional studies confirmed this finding, however, the mechanisms responsible for the results were not identified (Normand et al. 1997; Ray and Hume 1998). Nevertheless, the studies performed to date have supported the hypothesis that the vestibular system contributes to eliciting the required changes in blood pressure during movement and changes in posture (Yates 1992; Aoki et al. 2000).

We previously reported that the graviceptor of otolith organs may have a direct influence on the blood pressure in humans and that the vestibular system may contribute to the initial arterial pressure control during posture transition (Yates et al. 1999; Aoki et al. 2000; Yates et al. 2000; Tanaka et al. 2009). However, there is little definitive evidence to demonstrate the clinical significance of the vestibular-cardiovascular reflex in humans, despite the fact that the vestibular system is known to contribute to cardiovascular control in animals (Yates et al. 2000). Hypothetically, the vestibular-cardiovascular reflex is a mechanism that serves to maintain a constant blood pressure during unexpected changes in posture that place the longitudinal axis parallel to the gravitational vector. Based on this hypothesis, the hypofunction of the graviceptor may induce OH.

Ray has demonstrated that the there is no gender difference in the vestibulosympathetic reflex since sympathetic activation during head-down rotation in the prone posture was similar in males and females (Ray 2000). However, some studies have reported that gender difference in cardiovascular regulation induces lower tolerance to various orthostatic challenges in females compared with males (Gotshall et al. 1991; Convertino 1998). Female subjects have demonstrated a greater incidence of syncopal episodes during standing after spaceflight and have less responsive cardiovascular functions than male subjects (Hordinsky et al. 1981). Female subjects also have significantly less lower body negative pressure tolerance and have lower baroreflex sensitivity than male subjects (Convertino 1998; Gotshall 2000). In addition, the menstrual cycle in females alters blood pressure regulation (Dunne et al. 1991). Consequently, the gender differences in the cardiovascular regulation should also be considered to fully evaluate our hypothesis. We therefore assessed the orthostatic cardiovascular responses in male and female patients suffering from dizziness separately.

Methods

Subjects and ethical considerations

We collected data obtained from 467 patients visiting our hospital for dizziness from 2009 to 2010. In this study, 67 male patients and 58 female patients older than 65 years were excluded because clinical tests associated with otolith organs often show abnormal results even in healthy elderly patients. We additionally excluded 85 patients (33 male patients and 52 female patients) who were taking antihypertension drugs or drugs for heart disease and 9 patients (4 male patients and 5 female patients) with dizziness due to central nervous system involvement of cerebral infraction, cerebellar hemorrhage or Parkinson's disease. This study therefore consisted of 127 male patients and 121 female patients seeking treatment for dizziness.

The local Ethics Committee of Gifu University Graduate School of Medicine approved this study. After a complete description of the study, written informed consent was obtained from all patients.

Subjective visual vertical testing

A previous clinical study demonstrated that the measurement of the subjective visual vertical (SVV) was a sensitive tool for detecting an imbalance in the otolith function (Gresty et al. 1992), and abnormal deviation of the SVV is presumed to depend on the location and the extent of the lesions in the vestibular organs and/or nerves (Vibert et al. 1999). The subjects in this study were seated upright, and their head was held in place by a chin-rest. A 15-cm-long rod of charged fluorescent tape 5 mm wide was placed in front of each subject at a distance of 1 m. It was positioned at eye level and, in complete darkness (i.e. no frame, no disk), the starting position of the rod was tilted to either the left or right (approximately 40°). The subjects were required to adjust the rod without time constraints to the gravitational vertical with a potentiometer by a rotating handle. Eight trials (4 trials in each direction) were performed for each patient. The performance in the SVV adjustment was expressed as the deviation from the gravitational vertical (0°) measured in degrees of deviation. Deviations to the left (counter-clockwise) were counted as negative and deviations to the right (clockwise) as positive. We defined the mean error of <2° as normal (Friedmann 1970). The average SVV was shown as the absolute value of the deviations to both sides (Table 1).

Bithermal caloric testing

Surface electrodes were placed beside the lateral angle of both eyes and frontal region of the head to detect eye movements as electronystagmography (ENG). The signal was amplified, monitored and recorded continuously at a rate of 120 Hz using an analog-to-digital converter with programming software (CHARTR VNG/ENG, LCS Medical, Schaumburg, IL, USA). The ENG data were passed a low pass filter with a high cutoff frequency of 30 Hz. The amplitude was calibrated with angle of the eye movement in advance. Subjects were shielded light using goggle and positioned in supine with head inclined 30° up from horizontal. The external auditory canals were alternately irrigated with warm air (50° C) for 60 s, then, after a recovery period, cool air (24° C) for 60 s using air caloric stimulator (CHARTR NCA 200, LCS Medical, Schaumburg, IL, USA). The maximal slow phase eye velocity (MSPV) of nystagmus was calculated following each irrigation.

Table 1 The results of neuro-otological examination in the three groups of patients classified by their VEMP responses

	n	Age	VEMP amplitude of p13n23 (μV)		SVV (°)	CP% (%)	DHI
			Better side	Worse side			
Male patients							
Absent VEMP	50	47.9 ± 8.6	18.5 ± 16.1**	11.8 ± 12.2**	1.7 ± 1.9*	37.5 ± 31.9**	34.0 ± 23.5
Asymmetry VEMP	38	49.4 ± 11.4	63.9 ± 18.1	21.3 ± 14.4**	1.8 ± 2.1*	28.9 ± 24.5	28.9 ± 21.4
Normal VEMP	39	45.0 ± 10.5	74.0 ± 22.4	64.2 ± 19.1	1.0 ± 0.9	20.1 ± 21.8	35.6 ± 24.2
Female patients							
Absent VEMP	48	45.8 ± 9.0	22.5 ± 16.7**	17.0 ± 15.8**	1.5 ± 1.4	19.1 ± 21.5	37.2 ± 24.4
Asymmetry VEMP	33	45.2 ± 10.7	69.8 ± 24.6	26.0 ± 17.3**	1.3 ± 1.0	16.9 ± 20.0	37.5 ± 22.0
Normal VEMP	40	42.5 ± 8.5	75.3 ± 16.2	63.5 ± 12.7	1.3 ± 1.1	13.3 ± 15.7	37.3 ± 21.0

The number of patients, their average age, the VEMP amplitude of p13n23, the SVV, the CP% and the DHI score of the three groups in male and female patients

The values are the averages and SD

VEMP vestibular evoked myogenic potential, *SVV* subjective visual vertical, *CP%* canal paresis percentage, *DHI* dizziness handicap inventory

**, * Significant difference from the normal VEMP group at $P < 0.01$ and $P < 0.05$

Jongkees's formula was used to determine the semicircular canal paresis (CP) by using the MSPV (with a 25% difference in the CP being considered significant) (Lee et al. 2009). The bilateral hypofunction (MSPV of nystagmus for cold and warm caloric stimulus should not exceed 10°/s) was defined as 100% in CP.

Vestibular evoked myogenic potential (VEMP) electromyogram activity

The VEMP evoked by clicking sounds has been clinically used as a robust, reproducible screening test of otolith function (Colebatch et al. 1994; Welgampola and Colebatch 2005). For our patients, the VEMP electromyogram activity was recorded from the upper half of the bilateral sternocleidomastoid (SCM) muscle using surface electrodes, with a reference electrode on the upper edge of the sternum and a ground electrode on the forehead. The subjects were asked to turn their head to the contralateral shoulder before starting the measurement and to hold this position exactly in order to achieve a constant tonic activation of the SCM (100–200 μV) during the whole recording period. Rarefaction clicks of 0.1 ms duration were presented at a rate of 5/s through a headphone. The click intensities were 135 dBSPL referred to the perceptual threshold for normal subjects (0 dB nHL; 40 dB peak-equivalent SPL). The EMG signal was amplified and bandpass filtered (5–2,000 Hz), and the responses to 100 stimuli were averaged (Neuropack MB-2200, Nihon Kouden, Japan). The response consists of an initial positivity or inhibition (p13) followed by a negativity or excitation (n23). We defined the VEMP threshold as the lowest level at which both the p13 and n23 were definable and replicable, and we measured the amplitude of the p13n23 response for the VEMP. The amplitude of the p13n23 response was calculated from the average of two replicable trials. We defined the patients with responses in the bilateral p13n23 amplitude of <40 μV, which was determined as the lowest value of individual data obtained from normal subjects (Su et al. 2004) or without definable p13 waves bilaterally as the absent VEMP group, those with laterality more than double the amplitude of the p13n23 as the asymmetry VEMP group and those with a normal response bilaterally as the normal VEMP group (Fig. 1; Table 1).

The orthostatic Schellong test

The Schellong test was also performed in the mid-morning, and the subject' blood pressure (BP) and heart rate (HR) were automatically assessed with Automated BP Monitor (Colin Corporation) with subjects in the supine position for 10 min. Thereafter, the patients were asked to get up from the bed and stand up naturally without support or any standing device, such as forearm crutches or leg braces. All patients stood up within 20 s, and their systolic blood pressure (SBP), diastolic blood pressure (DBP) and HR were measured at approximately 1 min after actively changing from the supine position to the upright position. Following that, they were asked to maintain an upright posture quietly for 3 min, and their SBP, DBP and HR were monitored at 1 min intervals.

The changes in the SBP, DBP and HR after active standing up in comparison to the average data for the 10 min in the supine position (rest) were evaluated. We adopted the criteria for OH based on the American Autonomic Society (AAS) and the American Academy of Neurology (AAN), which define OH as a SBP decrease of at least 20 mm Hg or a DBP decrease of at least 10 mm Hg within 3 min of standing up (Freeman et al. 2011).

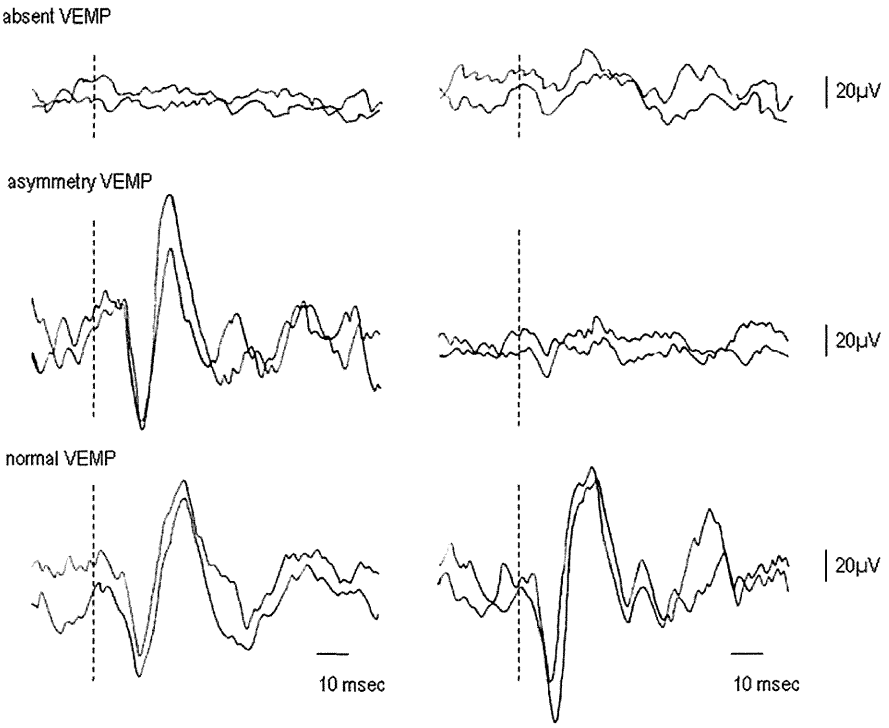

Fig. 1 Simultaneous averages of SCM electromyogram recorded from a subject in each group. The stimulus was delivered at the *vertical dotted line*, and the responses to 100 stimuli were averaged. The subjects were classified into three groups according to the amplitude of initial biphasic p13n23 *waves* (absent VEMP group, asymmetry VEMP group and normal VEMP group)

Dizziness handicap inventory questionnaire

The dizziness handicap inventory (DHI) comprises 25 questions designed to assess a patient's emotional (9 questions), functional (9 questions) and physical (7 questions) limitations. Each question provides a choice of 3 replies: "yes" (4 points), "sometimes" (2 points) and "no" (0 points). The maximum of 100 points indicates the greatest disturbance to the patient and the minimum of 0 points suggests that there is no handicap (Jacobson and Newman 1990). The DHI assesses precipitating physical factors associated with dizziness/unsteadiness and functional/emotional consequences of symptoms as a measure of disability in patients with dizziness and unsteadiness.

Statistical analyses

The statistical analyses were performed by a one-way ANOVA for the age, the DHI score, the CP%, the SVV, the VEMP amplitude, the average BP and HR during a 10-min rest period among the three groups classified by VEMP test. In addition, the statistical significant difference in the changes of the SBP, DBP and HR at 1, 2 and 3 min after standing up in comparison to average data during the 10-min rest period was determined by the use of a paired t test. The difference in the change of the SBP, DBP and HR after standing up between 2 groups classified by the degree of SVV (SVV $\leq 2°$ vs. SVV $>2°$) (Friedmann 1970) and the CP% (CP% $\leq 25\%$ vs. CP% $>25\%$) (Lee et al. 2009) were also statistically analyzed by unpaired t test. The significant difference in the percentage of patients who qualify for a diagnosis of OH was analyzed among the three groups using Fisher's LSD test. The level of significance of $P < 0.05$ was adopted throughout the study. The illustrated values in this text are the mean $\pm$ 1 SD.

Results

We classified our participants into three groups based on their VEMP responses as described above (Fig. 1). The average SVV and CP% of male patients in the absent VEMP group were significantly larger than those in the normal VEMP group ($P < 0.05$, Table 1). There were no significant differences between the groups with respect to the patient age, DHI score, or average SBP, DBP or HR during a 10-min rest period in male patients ($P > 0.05$, Table 1). There were also no significant differences in the SVV, CP%, age, DHI score, or the average SBP, DBP or HR during a 10-min rest period found between the groups in the female patients ($P > 0.05$, Table 1).

On the other hand, the male patients in the absent VEMP group presented a significant drop in their DBP at 1 min ($P = 0.03$, Fig. 2). The DBP at 2 min after standing up was

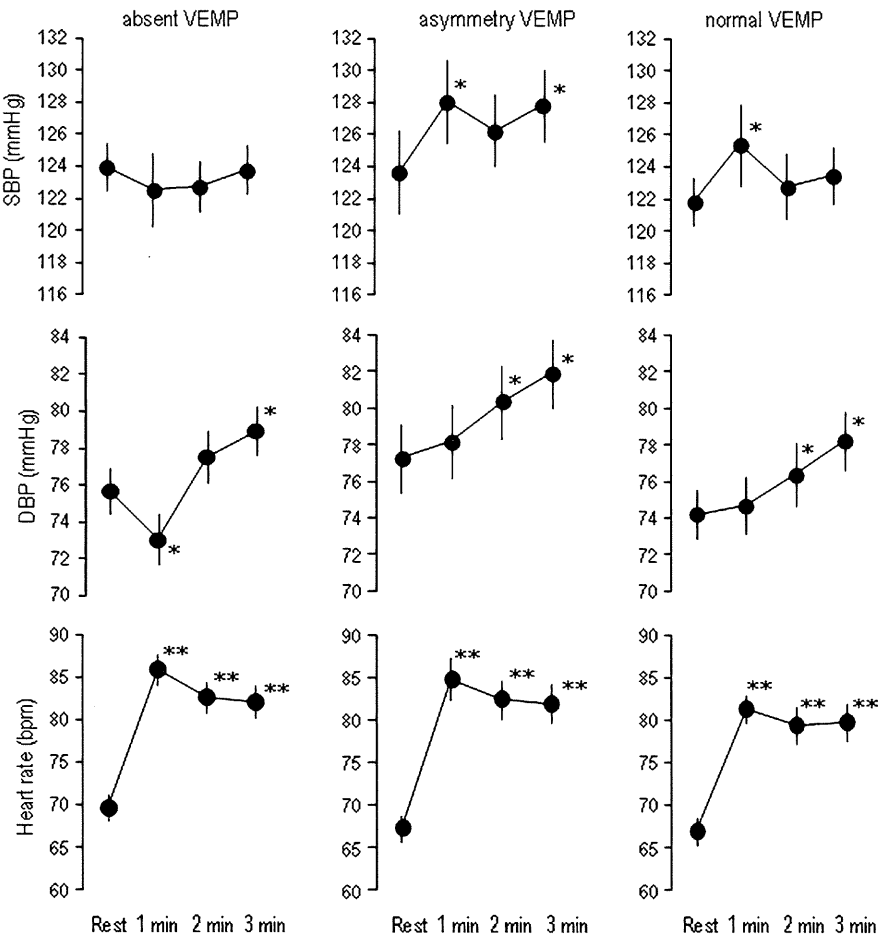

Fig. 2 The change of the SBP, DBP and HR (mean and standard error) after standing up in the absent VEMP group ($n = 50$), the asymmetry VEMP group ($n = 38$) and the normal VEMP group ($n = 39$) in male patients. **, * Significant difference in SBP, DBP and HR from average data during a 10-min rest period at $P < 0.01$ and $P < 0.05$

not significantly different from the average DBP during a 10-min rest period ($P > 0.05$, Fig. 2) despite the fact that the DBP at 2 min in the other 2 groups significantly increased in comparison with the average DBP during the 10-min rest period ($P < 0.05$, Fig. 2). Male patients in the asymmetry VEMP and normal VEMP groups showed a significant increase in their SBP at 1 min after standing up ($P = 0.04$, $P = 0.03$, Fig. 2). However, the male patients in the absent VEMP group did not show any change in their SBP after standing up ($P > 0.05$, Fig. 2). The SBP of female patients in the absent VEMP and the asymmetry VEMP groups tended to decrease at 1 min after standing up, while the SBP of female patients in the normal VEMP group significantly increased after standing up ($P = 0.049$, Fig. 3). The DBP of female patients in the normal VEMP group increased at 1 min after standing up ($P = 0.03$, Fig. 3). In contrast, the DBP in the absent VEMP and asymmetry VEMP groups did not change after standing up ($P > 0.05$, Fig. 3). There were no significant differences in the changes of the HR after standing up between any of the groups in either the male or the female patients ($P > 0.05$, Figs. 2, 3).

The SBP in male patients with a SVV $\leq 2°$ significantly increased at 1 min after standing up, whereas the SBP in male patients with a SVV $>2°$ tended to decrease at 1 min after standing up. A similar result was found in the response of the DBP after standing up (Table 2). There were no significant differences in the SBP and DBP responses after standing up between male patients with CP% $\leq 25\%$ and male patients with CP% $>25\%$ ($P > 0.05$, Table 2). In female patients, the BP responses after standing up were not affected by the degree of SVV and the CP% ($P > 0.05$, Table 3).

A total of 22% of the male patients in the absent VEMP group fulfilled the criteria for OH proposed by the AAS (Freeman et al. 2011), while only 7.9% of patients in the asymmetry VEMP group and 7.7% of patients in the normal VEMP group met the criteria for OH ($P = 0.058$). In the female patients, the positive ratios were 16.7% in the absent VEMP group, 3% in the asymmetry VEMP group

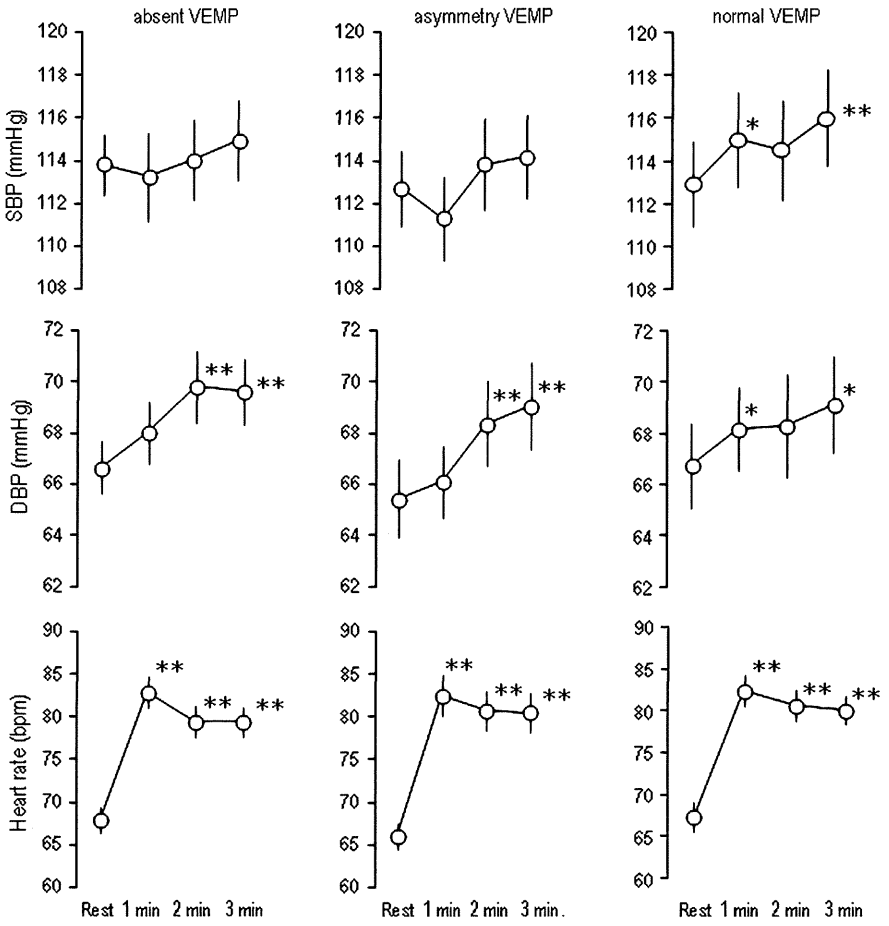

Fig. 3 The change of the SBP, DBP and HR (mean and standard error) after standing up in the absent VEMP group ($n = 48$), the asymmetry VEMP group ($n = 33$) and the normal VEMP group ($n = 40$) in female patients. **, * Significant difference in SBP, DBP and HR from average data during a 10-min rest period at $P < 0.01$ and $P < 0.05$

and 10% in the normal VEMP group. There were no significant differences in the positive ratios among the three groups ($P > 0.05$). In all participants, 19.6% of patients in the absent VEMP group fulfilled the criteria for OH, which was significantly > the 8.6% in the normal VEMP group and the 7.2% in the asymmetry VEMP group ($P = 0.03$, $P = 0.02$).

Discussion

Complaints of light-headedness and even fainting when standing up are related to a marked transient decrease in the arterial BP that also occurs in healthy subjects upon standing up. This initial BP response to the upright position is exclusively associated with active rising. In passive tilting, any decrease in the BP is much smaller and in most cases is absent. The response thus appears to be due to muscle contraction. The effort of standing compresses the venous vessels in the contracting muscle of the legs, which causes an immediate translocation of blood toward the heart and increase the cardiac output. The increase in cardiac output is not sufficient to make up for the drop in the total peripheral resistance induced by standing up, resulting in a transient decrease in the SBP (Wieling et al. 2007). The abrupt increase in HR upon standing, which peaks at ~3 s after the onset of standing up, induces an abrupt inhibition of cardiac vagal tone. These effects can be attributed to diminished activation of the arterial baroreceptors by the temporary decrease in BP and the arterial BP recovers after ~7 s. The magnitude of the decrease of the initial BP and the increase of the initial HR on standing up are increased by lengthening the period of preceding rest (Wieling and Lieshout 1997). Hypothetically, the increase in the arterial BP via the vestibular-cardiovascular pathway resulting from the changes in the graviceptive signals may support the recovery of the BP immediately after standing up.

A possible role of signaling via the vestibular-cardiovascular pathway, which acts in a feed-forward system, may be to prevent a decrease in BP by shifting the blood flow to the lower body during standing, rather than regulating the arterial BP (Kaufmann et al. 2002; Tanaka et al. 2009). However, the increase in the arterial BP via the

Table 2 The difference in the orthostatic cardiovascular responses between two groups of male patients classified by their degree of SVV or their CP%

The differences in the changes of the SBP, DBP and HR after standing up between two groups of male patients classified by their degree of SVV (SVV ≤2° vs. SVV >2°, A) and the CP% (CP% ≤25% vs. CP% >25%, B)

The values show the average and SD

SBP systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *SVV* subjective visual vertical, *CP%* canal paresis percentage

**, * Significant difference from that at rest at $P < 0.01$ and $P < 0.05$

	Rest	1 min	2 min	3 min
A				
SVV ≤2° ($n = 99$)				
SBP (mm Hg)	123.2 ± 12.6	126.1 ± 18.6*	124.5 ± 15.2	125.2 ± 13.8*
DBP (mm Hg)	75.7 ± 9.8	75.6 ± 11.3	77.9 ± 11.1**	79.6 ± 10.3**
HR (bpm)	67.8 ± 13.7	84.2 ± 17.6**	81.5 ± 17.8**	81.5 ± 17.9**
SVV >2° ($n = 28$)				
SBP (mm Hg)	123.4 ± 10.1	121.4 ± 11.1	121.6 ± 11.2	124.0 ± 10.0
DBP (mm Hg)	76.0 ± 8.5	73.9 ± 8.3	78.3 ± 11.0	79.5 ± 10.7**
HR (bpm)	69.0 ± 10.0	83.6 ± 11.8**	81.5 ± 12.7**	80.6 ± 12.5**
B				
CP% ≤25% ($n = 68$)				
SBP (mm Hg)	122.3 ± 11.4	124.7 ± 17.0	123.9 ± 13.2	124.7 ± 12.6*
DBP (mm Hg)	75.2 ± 8.8	75.4 ± 10.0	77.7 ± 10.5**	80.0 ± 10.3**
HR (bpm)	67.7 ± 10.6	84.7 ± 14.5**	82.3 ± 15.0	82.2 ± 15.0**
CP% >25% ($n = 59$)				
SBP (mm Hg)	124.3 ± 10.1	125.5 ± 11.1	123.7 ± 11.2	125.1 ± 10.0
DBP (mm Hg)	76.3 ± 10.2	74.9 ± 11.5	78.3 ± 11.7*	79.1 ± 10.5**
HR (bpm)	68.5 ± 9.8	83.4 ± 11.3**	80.7 ± 12.2**	80.4 ± 12.3**

Table 3 The differences in the orthostatic cardiovascular responses between two groups of female patients classified by the degree of SVV or CP%

The differences in the changes in the SBP, DBP and HR after standing up between two groups of female patients classified by their degree of SVV (SVV ≤2° vs. SVV >2°, A) and their CP% (CP% ≤25% vs. CP% >25%, B)

The values show the average and SD

SBP systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *SVV* subjective visual vertical, *CP%* canal paresis percentage

**, * Significant difference from that at rest at $P < 0.01$ and $P < 0.05$

	Rest	1 min	2 min	3 min
A				
SVV ≤2° ($n = 93$)				
SBP (mm Hg)	113.3 ± 10.8	113.2 ± 12.7	114.5 ± 12.3	115.2 ± 14.7*
DBP (mm Hg)	66.8 ± 9.0	67.5 ± 9.1	69.4 ± 10.7**	69.3 ± 10.1**
HR (bpm)	67.8 ± 10.9	82.5 ± 13.2**	80.4 ± 12.8**	80.5 ± 12.3**
SVV >2° ($n = 28$)				
SBP (mm Hg)	113.2 ± 11.0	113.8 ± 16.7	113.4 ± 16.7	115.0 ± 14.7
DBP (mm Hg)	65.1 ± 7.9	67.4 ± 8.4**	67.4 ± 10.4*	69.2 ± 9.8**
HR (bpm)	65.3 ± 10.6	83.1 ± 12.3**	79.3 ± 12.3**	77.9 ± 12.1**
B				
CP% ≤25% ($n = 105$)				
SBP (mm Hg)	112.8 ± 10.7	112.8 ± 12.9	113.8 ± 12.8	114.7 ± 12.3*
DBP (mm Hg)	66.6 ± 8.7	67.6 ± 8.9*	69.1 ± 10.5**	69.3 ± 10.1**
HR (bpm)	67.6 ± 10.9	82.6 ± 13.1**	80.6 ± 12.5**	80.4 ± 12.2**
CP% >25% ($n = 16$)				
SBP (mm Hg)	116.0 ± 11.4	117.0 ± 15.1	116.9 ± 16.8	118.3 ± 15.8
DBP (mm Hg)	64.9 ± 8.8	67.2 ± 8.7*	67.5 ± 11.4	69.4 ± 9.9**
HR (bpm)	64.7 ± 10.4	82.6 ± 12.0**	77.3 ± 13.2**	76.6 ± 12.8**

vestibular-cardiovascular pathway can be induced by changes of the graviceptive signal, but not by the changes in the arterial BP resulting from a shift in the blood flow. The system therefore has an error, potentially leading to an over-increase in the BP although this can be usually corrected by a negative feedback system, such as baroreflex. One study has clearly demonstrated that there are increases in muscle sympathetic nerve activity and calf vascular resistance during head-down rotation. These responses are mediated by an engagement of the otolith organs and not the semicircular canals (Ray and Carter 2003). The adjustment and increase of BP by the otolith organ are entirely appropriate during active movement; however, they may be inappropriate when provoked by passive movements.

Measuring the initial responses (the first 30 s) after standing up may be an effective way to detect the effects of vestibular disorders on BP responses after standing up.

However, we investigated the response during the early phase of stabilization (1–2 min after standing up) because the response has been commonly used in the clinical evaluation of neural circulatory control (Wieling and Lieshout 1997). We were able to find significant differences in the changes in BP responses even in the early phase of stabilization after standing up in the orthostatic Schellong test, which has been used in everyday practice. The increases in the HR after standing up were uniformly observed in all participants of this study. These results suggest that the significant drop in the BP after standing up is not the result of a decreased ability to produce compensatory HR responses. Further studies using the sequential beat-by-beat measurements of BP may detect a more severe drop in the BP after standing up in patients of the absent VEMP group. However, the clinical significance of our results for dizzy patients remains unclear, because there was no significant difference in the score on the DHI among the three groups.

The male patients in the absent VEMP group showed a significant drop in their DBP at 1 min after standing up; however, no significant change was noted in the DBP at 1 min after standing up in the asymmetry VEMP and the absent VEMP groups. A clinical study demonstrated that the symptoms associated with unilateral otolith dysfunction may be more swiftly compensated in comparison with dysfunction of the lateral semicircular canal (Hafstrom et al. 2004). The effects due to disorders of the vestibular-cardiovascular reflex in the asymmetry VEMP group might also be rapidly compensated. Patients with bilateral vestibular dysfunction often suffer from continuing symptoms because of the vestibular decompensation. Our results may therefore indicate that the bilateral disorders of otolith organs may greatly influence the initial BP control during posture transition for long time relatively (Yates et al. 1999), thus resulting in the occurrence of either lightheadedness or fainting when standing up rapidly.

Ray demonstrated that there was no gender difference in the vestibulosympathetic reflex since sympathetic activation during head-down rotation in the prone posture was similar in males and females. We herein considered the gender difference for the following reasons. First, the SBP of female patients in the absent VEMP group tended to decrease at 1 min after standing up, but the difference was not significant. We speculated that some female patients might stand up more slowly to avoid transient OH in comparison with male patients since females generally have greater orthostatic intolerance due to their decreased responsiveness in terms of the mechanisms that underlie BP regulation under orthostatic challenge. Therefore, it is possible that the compression of the venous vessels in the contracting muscle of the legs due to the effort of standing in females is weaker than that in males, resulting in a smaller transient initial decrease in the arterial BP by standing up in females. Second, there were no significant differences in the average SVV and CP% among the three female groups classified based on the amplitude of the VEMP. The gender difference in the VEMP responses has not been reported. Our results therefore suggest that the vestibular dysfunction in female patients might be well compensated for or might possibly be small regarding the extension of the lesions in the vestibular organs and/or nerves, resulting in that the BP response of female patients in the absent VEMP group was similar to that of female patients in the normal VEMP group. In addition, the BP regulation is altered by the menstrual cycle (Dunne et al. 1991). However, our study did not control for the menstrual cycle in female patients; therefore, our results may have been different if the menstrual cycle in the female patients had been strictly controlled.

The criteria for OH were fulfilled in 19.6% of patients in the absent VEMP group, which was significantly greater than the positive ratio for OH in the normal VEMP group. Our results therefore support the hypothesis that graviceptive disorders due to dysfunction of otolith organs may provoke OH. Patients with vestibular damage often complain of light-headedness and unsteadiness upon rapid motion, and these symptoms have been thought to be due to vestibular-ocular or vestibular-spinal reflex disorder. In addition, the elderly often complain of symptoms associated with OH, which have been explained by a decline of venous return associated with muscle weakness, the decrease in fluid volume, the increase of venous compliance, dysfunction of the baroreflex and the degradation of cardiac performance (Rutan et al. 1992). The otolith organs are vulnerable to degradation due to aging, and the vestibular-cardiovascular response may be diminished with age (Ray and Monahan 2002; Tanaka et al. 2009). Clinical physicians should therefore consider that lightheadedness and fainting when standing up may be associated with hypofunction of the vestibular-cardiovascular reflex due to an otolith disorder. Although further studies are needed to evaluate the precise mechanism, we believe that the presence of a graviceptive disorder due to disease and/or advanced age may induce OH.

Acknowledgments This research was supported by grants-in-aid for scientific research from the Japan society for the promotion of science, a grant from the intractable diseases fund (vestibular disorders) of the Ministry of Health and Welfare, Japan and a grant-in-aid from Gifu University School of Medicine for the promotion of science.

References

Aoki M, Burchill P, Yates B, Golding JF, Gresty MA (2000) Graviceptive control of blood pressure in man. Arch Ital Biol 138:93–97

Colebatch JG, Halmagyi GM, Skuse NF (1994) Myogenic potentials generated by a click-evoked vestibulocollic reflex. J Neurol Neurosurg Psychiatry 57:190–197

Convertino VA (1998) Gender differences in autonomic functions associated with blood pressure regulation. Am J Physiol 275:R1909–R1920

Doba N, Reis DJ (1974) Role of the cerebellum and the vestibular apparatus in regulation of orthostatic reflexes in the cat. Circ Res 40:9–18

Dunne FP, Barry DG, Ferriss JB, Grealy G, Murphy D (1991) Changes in blood pressure during the normal menstrual cycle. Clin Sci (Lond) 81:515–518

Essandoh LK, Duprez DA, Shepherd JT (1988) Reflex constriction of human limb resistance vessels to head-down neck flexion. J Appl Physiol 64:767–770

Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, Cheshire WP, Chelimsky T, Cortelli P, Gibbons CH, Goldstein DS, Hainsworth R, Hilz MJ, Jacob G, Kaufmann H, Jordan J, Lipsitz LA, Levine BD, Low PA, Mathias C, Raj SR, Robertson D, Sandroni P, Schatz IJ, Schondorf R, Stewart JM, van Dijk JG (2011) Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Auton Neurosci 161:46–48

Friedmann G (1970) The judgement of the visual vertical and horizontal with peripheral and central vestibular lesions. Brain 93:313–328

Gotshall RW (2000) Gender differences in tolerance to lower body negative pressure. Aviat Space Environ Med 71:1104–1110

Gotshall RW, Tsai PF, Frey MA (1991) Gender-based differences in the cardiovascular response to standing. Aviat Space Environ Med 62:855–859

Gresty MA, Bronstein AM, Brandt T, Dieterich M (1992) Neurology of otolith function: peripheral and central disorders. Brain 115(Pt 3):647–673

Hafstrom A, Fransson PA, Karlberg M, Magnusson M (2004) Idiosyncratic compensation of the subjective visual horizontal and vertical in 60 patients after unilateral vestibular deafferentation. Acta Otolaryngol 124:165–171

Hordinsky JR, Gebhardt U, Wegmann HM, Schafer G (1981) Cardiovascular and biochemical response to simulated space flight entry. Aviat Space Environ Med 52:16–18

Jacobson GP, Newman CW (1990) The development of the dizziness handicap inventory. Arch Otolaryngol Head Neck Surg 116:424–427

Jian BJ, Cotter LA, Emanuel BA, Cass SP, Yates BJ (1999) Effects of bilateral vestibular lesions on orthostatic tolerance in awake cats. J Appl Physiol 86:1552–1560

Kaufmann H, Biaggioni I, Voustianiouk A, Diedrich A, Costa F, Clarke R, Gizzi M, Raphan T, Cohen B (2002) Vestibular control of sympathetic activity: an otolith-sympathetic reflex in humans. Exp Brain Res 143:463–469

Lee IS, Park HJ, Shin JE, Jeong YS, Kwak HB, Lee YJ (2009) Results of air caloric and other vestibular tests in patients with chronic otitis media. Clin Exp Otorhinolaryngol 2:145–150

Normand H, Etard O, Denise P (1997) Otolithic and tonic neck receptors control of limb blood flow in humans. J Appl Physiol 82:1734–1738

Ray CA (2000) Effect of gender on vestibular sympathoexcitation. Am J Physiol Regul Integr Comp Physiol 279:R1330–R1333

Ray CA, Carter JR (2003) Vestibular activation of sympathetic nerve activity. Acta Physiol Scand 177:313–319

Ray CA, Hume KM (1998) Neck afferents and muscle sympathetic activity in humans: implications for the vestibulosympathetic reflex. J Appl Physiol 84:450–453

Ray CA, Monahan KD (2002) Aging attenuates the vestibulosympathetic reflex in humans. Circulation 105:956–961

Rutan GH, Hermanson B, Bild DE, Kittner SJ, LaBaw F, Tell GS (1992) Orthostatic hypotension in older adults: the cardiovascular health study—CHS collaborative research group. Hypertension 19:508–519

Su HC, Huang TW, Young YH, Cheng PW (2004) Aging effect on vestibular evoked myogenic potential. Otol Neurotol 25:977–980

Tanaka K, Abe C, Awazu C, Morita H (2009) Vestibular system plays a significant role in arterial pressure control during head-up tilt in young subjects. Auton Neurosci 148:90–96

Vibert D, Hausler R, Safran AB (1999) Subjective visual vertical in peripheral unilateral vestibular diseases. J Vestib Res 9:145–152

Welgampola MS, Colebatch JG (2005) Characteristics and clinical applications of vestibular-evoked myogenic potentials. Neurology 64:1682–1688

Wieling W, Lieshout JJ (1997) Maintenance of postural normotension in humans. In: Low P (ed) Clinical autonomic disorders, 2nd edn. Lippincott-Raven, Philadelphia, pp 73–82

Wieling W, Krediet CT, van Dijk N, Linzer M, Tschakovsky ME (2007) Initial orthostatic hypotension: review of a forgotten condition. Clin Sci (Lond) 112:157–165

Woodring SF, Rossiter CD, Yates BJ (1997) Pressor response elicited by nose-up vestibular stimulation in cats. Exp Brain Res 113:165–168

Yates BJ (1992) Vestibular influences on the sympathetic nervous system. Brain Res Rev 17:51–59

Yates BJ, Miller AD (1994) Properties of sympathetic reflexes elicited by natural vestibular stimulation: implications for cardiovascular control. J Neurophysiol 71:2087–2092

Yates BJ, Aoki M, Burchill P, Bronstein AM, Gresty MA (1999) Cardiovascular responses elicited by linear acceleration in humans. Exp Brain Res 125:476–484

Yates BJ, Holmes MJ, Jian BJ (2000) Adaptive plasticity in vestibular influences on cardiovascular control. Brain Res Bull 53:3–9

Exp Brain Res (2012) 217:251–259
DOI 10.1007/s00221-011-2989-0

RESEARCH ARTICLE

Evidence for vestibular dysfunction in orthostatic hypotension

Mitsuhiro Aoki · Yuzuru Sakaida · Kunihiko Tanaka · Keisuke Mizuta · Yatsuji Ito

Received: 8 November 2011 / Accepted: 12 December 2011 / Published online: 29 December 2011
© Springer-Verlag 2011

Abstract There is little definitive evidence of the clinical significance of the vestibular-cardiovascular reflex in humans, despite the fact that the vestibular system is known to contribute to cardiovascular control in animals. The present study involved 248 dizzy patients (127 male patients and 121 female patients) aged 65 years and younger. We classified all participants into three groups based on their vestibular evoked myogenic potential (VEMP) responses; absent VEMP, asymmetry VEMP and normal VEMP. To investigate the effect of the otolith disorder, which was estimated by the VEMP, on the orthostatic blood pressure responses, the subjects' systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate were monitored during the orthostatic test after they actively stood up. The male patients in the absent VEMP group had a significant drop in their DBP at 1 min after active standing up ($P < 0.05$) without any change in their SBP. Conversely, male patients in the asymmetry VEMP and normal VEMP groups showed a significant increase in the SBP at 1 min after active standing up ($P < 0.05$). Female patients in the absent VEMP group did not show any significant drop in their blood pressure after standing up ($P > 0.05$). In the entire group of participants, a total of 19.6% of the patients in the absent VEMP group fulfilled the criteria for orthostatic hypotension (OH), which was significantly > the 8.6% of patients in the normal VEMP group and the 7.2% in the asymmetry VEMP group ($P < 0.05$). Our results suggest that vestibular disorders due to the dysfunction of otolith organs provoke OH.

Keywords Graviceptor · Otolith · Orthostatic hypotension · Dizziness · Subjective visual vertical · Vestibular evoked myogenic potential

M. Aoki (✉) · Y. Sakaida · K. Mizuta · Y. Ito
Department of Otolaryngology, Gifu University Graduate School of Medicine, 1-1 Yanagido, Gifu City 501-1194, Japan
e-mail: aoki@gifu-u.ac.jp

K. Tanaka
Department of Radiotechnology, School of Health Science, Gifu University of Medical Science, 795-1 Nagamine Ichihiraga, Seki-City, Gifu 501-3892, Japan

Introduction

The otolith, one of the graviceptive organs, receives a signal of tilt with respect to the gravitational vector and informs the brain about rapid changes in posture. Long-term bed rest results in rapid physical deconditioning with the development of orthostatic hypotension (OH). This can be explained by the plasticity of the vestibular-cardiovascular pathway. However, the mechanisms underlying this phenomenon remain unclear (Yates et al. 2000). Animal studies have demonstrated considerable evidence that the bilateral removal of the labyrinthine inputs reduces orthostatic tolerance (Doba and Reis 1974; Jian et al. 1999). It appears that stimulation of otolith receptors in humans, as in animals (Yates and Miller 1994; Woodring et al. 1997), can produce cardiovascular alterations. Essandoh et al. (1988) reported that head-down neck flexion in the prone position produces a rapid decrease in blood flow of the forearm and calf in male subjects. Additional studies confirmed this finding, however, the mechanisms responsible for the results were not identified (Normand et al. 1997; Ray and Hume 1998). Nevertheless, the studies performed to date have supported the hypothesis that the vestibular system contributes to eliciting the required changes in blood pressure during movement and changes in posture (Yates 1992; Aoki et al. 2000).

We previously reported that the graviceptor of otolith organs may have a direct influence on the blood pressure in humans and that the vestibular system may contribute to the initial arterial pressure control during posture transition (Yates et al. 1999; Aoki et al. 2000; Yates et al. 2000; Tanaka et al. 2009). However, there is little definitive evidence to demonstrate the clinical significance of the vestibular-cardiovascular reflex in humans, despite the fact that the vestibular system is known to contribute to cardiovascular control in animals (Yates et al. 2000). Hypothetically, the vestibular-cardiovascular reflex is a mechanism that serves to maintain a constant blood pressure during unexpected changes in posture that place the longitudinal axis parallel to the gravitational vector. Based on this hypothesis, the hypofunction of the graviceptor may induce OH.

Ray has demonstrated that the there is no gender difference in the vestibulosympathetic reflex since sympathetic activation during head-down rotation in the prone posture was similar in males and females (Ray 2000). However, some studies have reported that gender difference in cardiovascular regulation induces lower tolerance to various orthostatic challenges in females compared with males (Gotshall et al. 1991; Convertino 1998). Female subjects have demonstrated a greater incidence of syncopal episodes during standing after spaceflight and have less responsive cardiovascular functions than male subjects (Hordinsky et al. 1981). Female subjects also have significantly less lower body negative pressure tolerance and have lower baroreflex sensitivity than male subjects (Convertino 1998; Gotshall 2000). In addition, the menstrual cycle in females alters blood pressure regulation (Dunne et al. 1991). Consequently, the gender differences in the cardiovascular regulation should also be considered to fully evaluate our hypothesis. We therefore assessed the orthostatic cardiovascular responses in male and female patients suffering from dizziness separately.

Methods

Subjects and ethical considerations

We collected data obtained from 467 patients visiting our hospital for dizziness from 2009 to 2010. In this study, 67 male patients and 58 female patients older than 65 years were excluded because clinical tests associated with otolith organs often show abnormal results even in healthy elderly patients. We additionally excluded 85 patients (33 male patients and 52 female patients) who were taking antihypertension drugs or drugs for heart disease and 9 patients (4 male patients and 5 female patients) with dizziness due to central nervous system involvement of cerebral infraction, cerebellar hemorrhage or Parkinson's disease. This study therefore consisted of 127 male patients and 121 female patients seeking treatment for dizziness.

The local Ethics Committee of Gifu University Graduate School of Medicine approved this study. After a complete description of the study, written informed consent was obtained from all patients.

Subjective visual vertical testing

A previous clinical study demonstrated that the measurement of the subjective visual vertical (SVV) was a sensitive tool for detecting an imbalance in the otolith function (Gresty et al. 1992), and abnormal deviation of the SVV is presumed to depend on the location and the extent of the lesions in the vestibular organs and/or nerves (Vibert et al. 1999). The subjects in this study were seated upright, and their head was held in place by a chin-rest. A 15-cm-long rod of charged fluorescent tape 5 mm wide was placed in front of each subject at a distance of 1 m. It was positioned at eye level and, in complete darkness (i.e. no frame, no disk), the starting position of the rod was tilted to either the left or right (approximately 40°). The subjects were required to adjust the rod without time constraints to the gravitational vertical with a potentiometer by a rotating handle. Eight trials (4 trials in each direction) were performed for each patient. The performance in the SVV adjustment was expressed as the deviation from the gravitational vertical (0°) measured in degrees of deviation. Deviations to the left (counter-clockwise) were counted as negative and deviations to the right (clockwise) as positive. We defined the mean error of <2° as normal (Friedmann 1970). The average SVV was shown as the absolute value of the deviations to both sides (Table 1).

Bithermal caloric testing

Surface electrodes were placed beside the lateral angle of both eyes and frontal region of the head to detect eye movements as electronystagmography (ENG). The signal was amplified, monitored and recorded continuously at a rate of 120 Hz using an analog-to-digital converter with programming software (CHARTR VNG/ENG, LCS Medical, Schaumburg, IL, USA). The ENG data were passed a low pass filter with a high cutoff frequency of 30 Hz. The amplitude was calibrated with angle of the eye movement in advance. Subjects were shielded light using goggle and positioned in supine with head inclined 30° up from horizontal. The external auditory canals were alternately irrigated with warm air (50° C) for 60 s, then, after a recovery period, cool air (24° C) for 60 s using air caloric stimulator (CHARTR NCA 200, LCS Medical, Schaumburg, IL, USA). The maximal slow phase eye velocity (MSPV) of nystagmus was calculated following each irrigation.

Table 1 The results of neuro-otological examination in the three groups of patients classified by their VEMP responses

	n	Age	VEMP amplitude of p13n23 (μV)		SVV (°)	CP% (%)	DHI
			Better side	Worse side			
Male patients							
Absent VEMP	50	47.9 ± 8.6	18.5 ± 16.1**	11.8 ± 12.2**	1.7 ± 1.9*	37.5 ± 31.9**	34.0 ± 23.5
Asymmetry VEMP	38	49.4 ± 11.4	63.9 ± 18.1	21.3 ± 14.4**	1.8 ± 2.1*	28.9 ± 24.5	28.9 ± 21.4
Normal VEMP	39	45.0 ± 10.5	74.0 ± 22.4	64.2 ± 19.1	1.0 ± 0.9	20.1 ± 21.8	35.6 ± 24.2
Female patients							
Absent VEMP	48	45.8 ± 9.0	22.5 ± 16.7**	17.0 ± 15.8**	1.5 ± 1.4	19.1 ± 21.5	37.2 ± 24.4
Asymmetry VEMP	33	45.2 ± 10.7	69.8 ± 24.6	26.0 ± 17.3**	1.3 ± 1.0	16.9 ± 20.0	37.5 ± 22.0
Normal VEMP	40	42.5 ± 8.5	75.3 ± 16.2	63.5 ± 12.7	1.3 ± 1.1	13.3 ± 15.7	37.3 ± 21.0

The number of patients, their average age, the VEMP amplitude of p13n23, the SVV, the CP% and the DHI score of the three groups in male and female patients

The values are the averages and SD

VEMP vestibular evoked myogenic potential, *SVV* subjective visual vertical, *CP%* canal paresis percentage, *DHI* dizziness handicap inventory

**, * Significant difference from the normal VEMP group at $P < 0.01$ and $P < 0.05$

Jongkees's formula was used to determine the semicircular canal paresis (CP) by using the MSPV (with a 25% difference in the CP being considered significant) (Lee et al. 2009). The bilateral hypofunction (MSPV of nystagmus for cold and warm caloric stimulus should not exceed 10°/s) was defined as 100% in CP.

Vestibular evoked myogenic potential (VEMP) electromyogram activity

The VEMP evoked by clicking sounds has been clinically used as a robust, reproducible screening test of otolith function (Colebatch et al. 1994; Welgampola and Colebatch 2005). For our patients, the VEMP electromyogram activity was recorded from the upper half of the bilateral sternocleidomastoid (SCM) muscle using surface electrodes, with a reference electrode on the upper edge of the sternum and a ground electrode on the forehead. The subjects were asked to turn their head to the contralateral shoulder before starting the measurement and to hold this position exactly in order to achieve a constant tonic activation of the SCM (100–200 μV) during the whole recording period. Rarefaction clicks of 0.1 ms duration were presented at a rate of 5/s through a headphone. The click intensities were 135 dBSPL referred to the perceptual threshold for normal subjects (0 dB nHL; 40 dB peak-equivalent SPL). The EMG signal was amplified and bandpass filtered (5–2,000 Hz), and the responses to 100 stimuli were averaged (Neuropack MB-2200, Nihon Kouden, Japan). The response consists of an initial positivity or inhibition (p13) followed by a negativity or excitation (n23). We defined the VEMP threshold as the lowest level at which both the p13 and n23 were definable and replicable, and we measured the amplitude of the p13n23 response for the VEMP. The amplitude of the p13n23 response was calculated from the average of two replicable trials. We defined the patients with responses in the bilateral p13n23 amplitude of <40 μV, which was determined as the lowest value of individual data obtained from normal subjects (Su et al. 2004) or without definable p13 waves bilaterally as the absent VEMP group, those with laterality more than double the amplitude of the p13n23 as the asymmetry VEMP group and those with a normal response bilaterally as the normal VEMP group (Fig. 1; Table 1).

The orthostatic Schellong test

The Schellong test was also performed in the mid-morning, and the subject' blood pressure (BP) and heart rate (HR) were automatically assessed with Automated BP Monitor (Colin Corporation) with subjects in the supine position for 10 min. Thereafter, the patients were asked to get up from the bed and stand up naturally without support or any standing device, such as forearm crutches or leg braces. All patients stood up within 20 s, and their systolic blood pressure (SBP), diastolic blood pressure (DBP) and HR were measured at approximately 1 min after actively changing from the supine position to the upright position. Following that, they were asked to maintain an upright posture quietly for 3 min, and their SBP, DBP and HR were monitored at 1 min intervals.

The changes in the SBP, DBP and HR after active standing up in comparison to the average data for the 10 min in the supine position (rest) were evaluated. We adopted the criteria for OH based on the American Autonomic Society (AAS) and the American Academy of Neurology (AAN), which define OH as a SBP decrease of at least 20 mm Hg or a DBP decrease of at least 10 mm Hg within 3 min of standing up (Freeman et al. 2011).

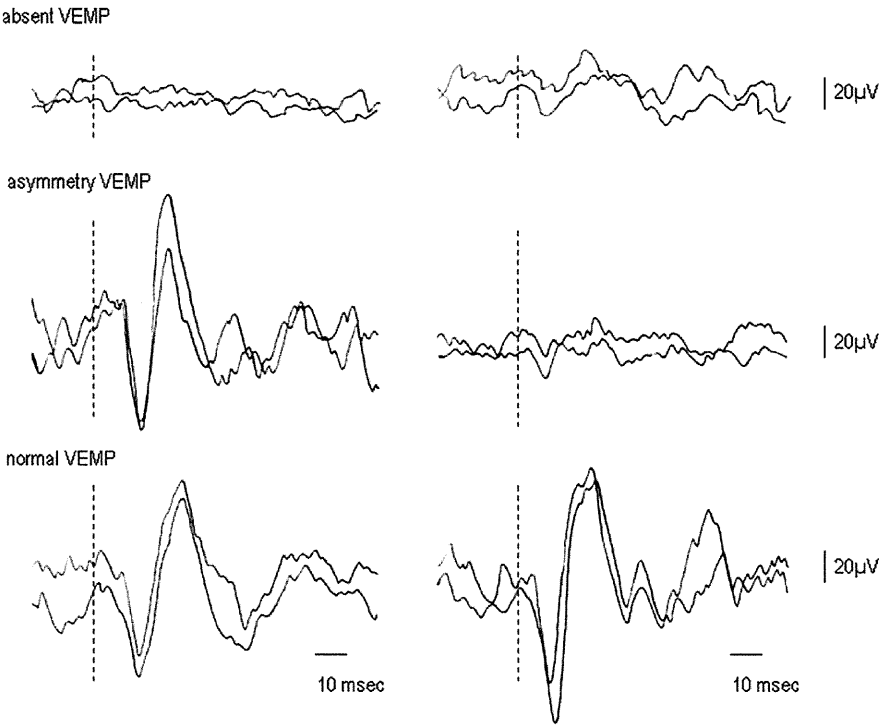

Fig. 1 Simultaneous averages of SCM electromyogram recorded from a subject in each group. The stimulus was delivered at the *vertical dotted line*, and the responses to 100 stimuli were averaged. The subjects were classified into three groups according to the amplitude of initial biphasic p13n23 *waves* (absent VEMP group, asymmetry VEMP group and normal VEMP group)

Dizziness handicap inventory questionnaire

The dizziness handicap inventory (DHI) comprises 25 questions designed to assess a patient's emotional (9 questions), functional (9 questions) and physical (7 questions) limitations. Each question provides a choice of 3 replies: "yes" (4 points), "sometimes" (2 points) and "no" (0 points). The maximum of 100 points indicates the greatest disturbance to the patient and the minimum of 0 points suggests that there is no handicap (Jacobson and Newman 1990). The DHI assesses precipitating physical factors associated with dizziness/unsteadiness and functional/emotional consequences of symptoms as a measure of disability in patients with dizziness and unsteadiness.

Statistical analyses

The statistical analyses were performed by a one-way ANOVA for the age, the DHI score, the CP%, the SVV, the VEMP amplitude, the average BP and HR during a 10-min rest period among the three groups classified by VEMP test. In addition, the statistical significant difference in the changes of the SBP, DBP and HR at 1, 2 and 3 min after standing up in comparison to average data during the 10-min rest period was determined by the use of a paired t test. The difference in the change of the SBP, DBP and HR after standing up between 2 groups classified by the degree of SVV (SVV $\leq 2°$ vs. SVV $>2°$) (Friedmann 1970) and the CP% (CP% $\leq 25\%$ vs. CP% $>25\%$) (Lee et al. 2009) were also statistically analyzed by unpaired t test. The significant difference in the percentage of patients who qualify for a diagnosis of OH was analyzed among the three groups using Fisher's LSD test. The level of significance of $P < 0.05$ was adopted throughout the study. The illustrated values in this text are the mean $\pm$ 1 SD.

Results

We classified our participants into three groups based on their VEMP responses as described above (Fig. 1). The average SVV and CP% of male patients in the absent VEMP group were significantly larger than those in the normal VEMP group ($P < 0.05$, Table 1). There were no significant differences between the groups with respect to the patient age, DHI score, or average SBP, DBP or HR during a 10-min rest period in male patients ($P > 0.05$, Table 1). There were also no significant differences in the SVV, CP%, age, DHI score, or the average SBP, DBP or HR during a 10-min rest period found between the groups in the female patients ($P > 0.05$, Table 1).

On the other hand, the male patients in the absent VEMP group presented a significant drop in their DBP at 1 min ($P = 0.03$, Fig. 2). The DBP at 2 min after standing up was

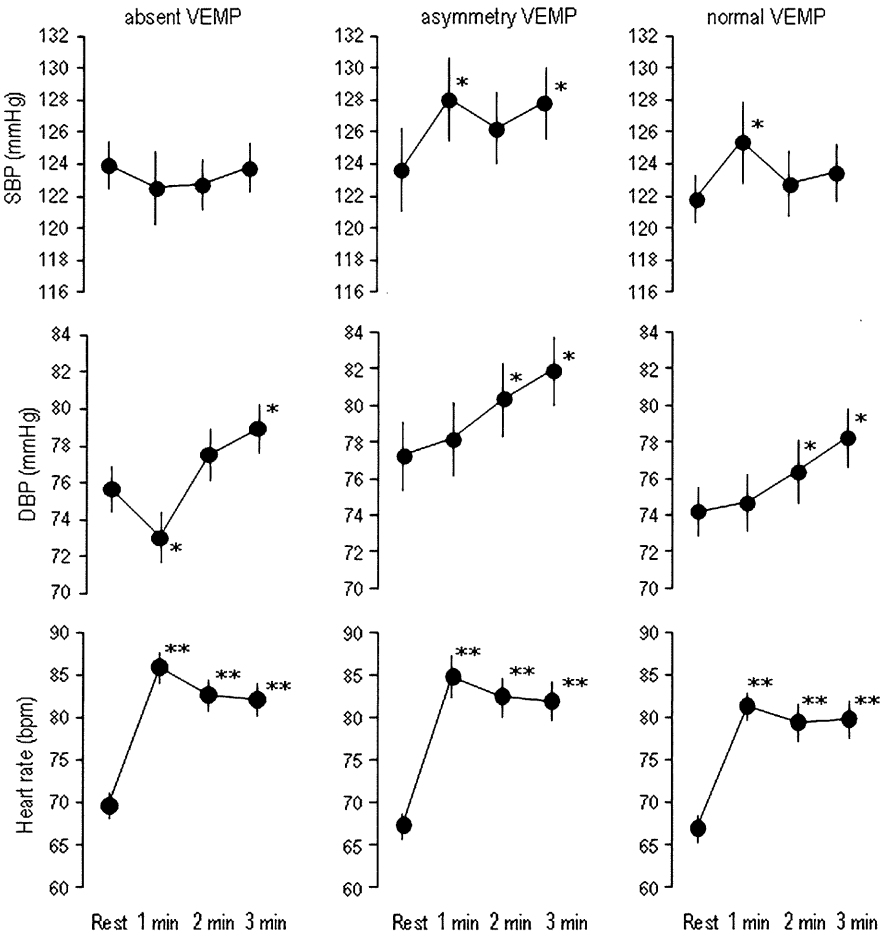

Fig. 2 The change of the SBP, DBP and HR (mean and standard error) after standing up in the absent VEMP group ($n = 50$), the asymmetry VEMP group ($n = 38$) and the normal VEMP group ($n = 39$) in male patients. **, * Significant difference in SBP, DBP and HR from average data during a 10-min rest period at $P < 0.01$ and $P < 0.05$

not significantly different from the average DBP during a 10-min rest period ($P > 0.05$, Fig. 2) despite the fact that the DBP at 2 min in the other 2 groups significantly increased in comparison with the average DBP during the 10-min rest period ($P < 0.05$, Fig. 2). Male patients in the asymmetry VEMP and normal VEMP groups showed a significant increase in their SBP at 1 min after standing up ($P = 0.04$, $P = 0.03$, Fig. 2). However, the male patients in the absent VEMP group did not show any change in their SBP after standing up ($P > 0.05$, Fig. 2). The SBP of female patients in the absent VEMP and the asymmetry VEMP groups tended to decrease at 1 min after standing up, while the SBP of female patients in the normal VEMP group significantly increased after standing up ($P = 0.049$, Fig. 3). The DBP of female patients in the normal VEMP group increased at 1 min after standing up ($P = 0.03$, Fig. 3). In contrast, the DBP in the absent VEMP and asymmetry VEMP groups did not change after standing up ($P > 0.05$, Fig. 3). There were no significant differences in the changes of the HR after standing up between any of the groups in either the male or the female patients ($P > 0.05$, Figs. 2, 3).

The SBP in male patients with a SVV $\leq 2°$ significantly increased at 1 min after standing up, whereas the SBP in male patients with a SVV $>2°$ tended to decrease at 1 min after standing up. A similar result was found in the response of the DBP after standing up (Table 2). There were no significant differences in the SBP and DBP responses after standing up between male patients with CP% $\leq 25\%$ and male patients with CP% $>25\%$ ($P > 0.05$, Table 2). In female patients, the BP responses after standing up were not affected by the degree of SVV and the CP% ($P > 0.05$, Table 3).

A total of 22% of the male patients in the absent VEMP group fulfilled the criteria for OH proposed by the AAS (Freeman et al. 2011), while only 7.9% of patients in the asymmetry VEMP group and 7.7% of patients in the normal VEMP group met the criteria for OH ($P = 0.058$). In the female patients, the positive ratios were 16.7% in the absent VEMP group, 3% in the asymmetry VEMP group

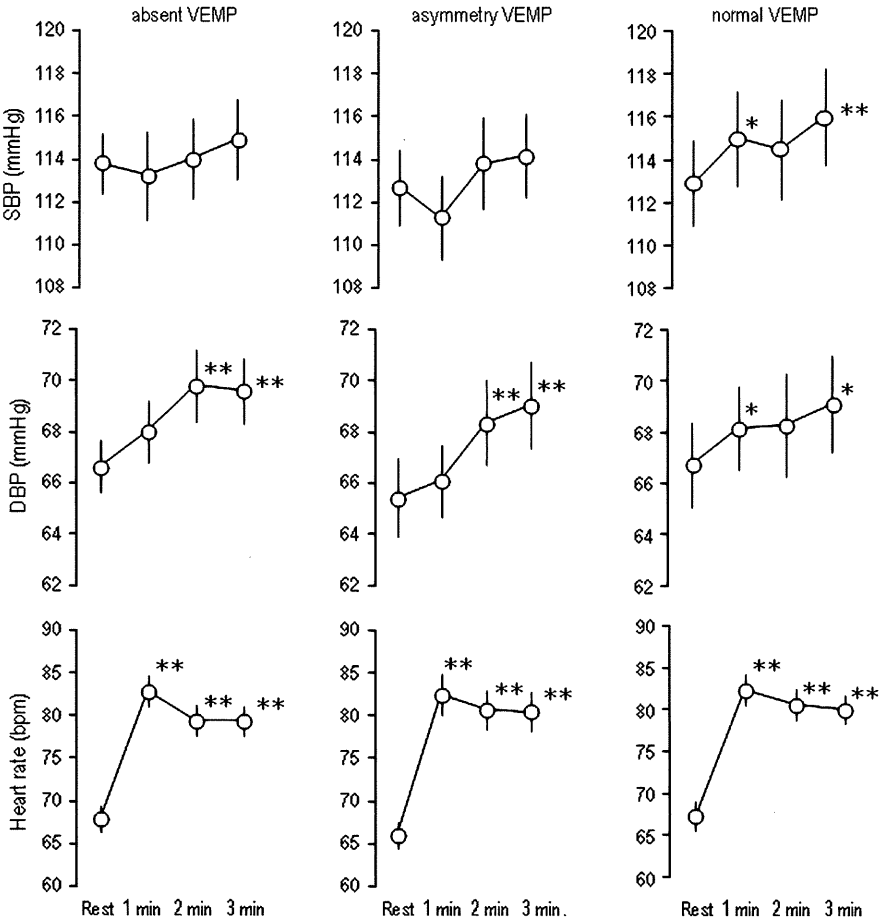

Fig. 3 The change of the SBP, DBP and HR (mean and standard error) after standing up in the absent VEMP group ($n = 48$), the asymmetry VEMP group ($n = 33$) and the normal VEMP group ($n = 40$) in female patients. **, * Significant difference in SBP, DBP and HR from average data during a 10-min rest period at $P < 0.01$ and $P < 0.05$

and 10% in the normal VEMP group. There were no significant differences in the positive ratios among the three groups ($P > 0.05$). In all participants, 19.6% of patients in the absent VEMP group fulfilled the criteria for OH, which was significantly > the 8.6% in the normal VEMP group and the 7.2% in the asymmetry VEMP group ($P = 0.03$, $P = 0.02$).

Discussion

Complaints of light-headedness and even fainting when standing up are related to a marked transient decrease in the arterial BP that also occurs in healthy subjects upon standing up. This initial BP response to the upright position is exclusively associated with active rising. In passive tilting, any decrease in the BP is much smaller and in most cases is absent. The response thus appears to be due to muscle contraction. The effort of standing compresses the venous vessels in the contracting muscle of the legs, which causes an immediate translocation of blood toward the heart and increase the cardiac output. The increase in cardiac output is not sufficient to make up for the drop in the total peripheral resistance induced by standing up, resulting in a transient decrease in the SBP (Wieling et al. 2007). The abrupt increase in HR upon standing, which peaks at ~3 s after the onset of standing up, induces an abrupt inhibition of cardiac vagal tone. These effects can be attributed to diminished activation of the arterial baroreceptors by the temporary decrease in BP and the arterial BP recovers after ~7 s. The magnitude of the decrease of the initial BP and the increase of the initial HR on standing up are increased by lengthening the period of preceding rest (Wieling and Lieshout 1997). Hypothetically, the increase in the arterial BP via the vestibular-cardiovascular pathway resulting from the changes in the graviceptive signals may support the recovery of the BP immediately after standing up.

A possible role of signaling via the vestibular-cardiovascular pathway, which acts in a feed-forward system, may be to prevent a decrease in BP by shifting the blood flow to the lower body during standing, rather than regulating the arterial BP (Kaufmann et al. 2002; Tanaka et al. 2009). However, the increase in the arterial BP via the

Table 2 The difference in the orthostatic cardiovascular responses between two groups of male patients classified by their degree of SVV or their CP%

	Rest	1 min	2 min	3 min
A				
SVV ≤2° (n = 99)				
SBP (mm Hg)	123.2 ± 12.6	126.1 ± 18.6*	124.5 ± 15.2	125.2 ± 13.8*
DBP (mm Hg)	75.7 ± 9.8	75.6 ± 11.3	77.9 ± 11.1**	79.6 ± 10.3**
HR (bpm)	67.8 ± 13.7	84.2 ± 17.6**	81.5 ± 17.8**	81.5 ± 17.9**
SVV >2° (n = 28)				
SBP (mm Hg)	123.4 ± 10.1	121.4 ± 11.1	121.6 ± 11.2	124.0 ± 10.0
DBP (mm Hg)	76.0 ± 8.5	73.9 ± 8.3	78.3 ± 11.0	79.5 ± 10.7**
HR (bpm)	69.0 ± 10.0	83.6 ± 11.8**	81.5 ± 12.7**	80.6 ± 12.5**
B				
CP% ≤25% (n = 68)				
SBP (mm Hg)	122.3 ± 11.4	124.7 ± 17.0	123.9 ± 13.2	124.7 ± 12.6*
DBP (mm Hg)	75.2 ± 8.8	75.4 ± 10.0	77.7 ± 10.5**	80.0 ± 10.3**
HR (bpm)	67.7 ± 10.6	84.7 ± 14.5**	82.3 ± 15.0	82.2 ± 15.0**
CP% >25% (n = 59)				
SBP (mm Hg)	124.3 ± 10.1	125.5 ± 11.1	123.7 ± 11.2	125.1 ± 10.0
DBP (mm Hg)	76.3 ± 10.2	74.9 ± 11.5	78.3 ± 11.7*	79.1 ± 10.5**
HR (bpm)	68.5 ± 9.8	83.4 ± 11.3**	80.7 ± 12.2**	80.4 ± 12.3**

The differences in the changes of the SBP, DBP and HR after standing up between two groups of male patients classified by their degree of SVV (SVV ≤2° vs. SVV >2°, A) and the CP% (CP% ≤25% vs. CP% >25%, B)

The values show the average and SD

SBP systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *SVV* subjective visual vertical, *CP%* canal paresis percentage

**, * Significant difference from that at rest at $P < 0.01$ and $P < 0.05$

Table 3 The differences in the orthostatic cardiovascular responses between two groups of female patients classified by the degree of SVV or CP%

	Rest	1 min	2 min	3 min
A				
SVV ≤2° (n = 93)				
SBP (mm Hg)	113.3 ± 10.8	113.2 ± 12.7	114.5 ± 12.3	115.2 ± 14.7*
DBP (mm Hg)	66.8 ± 9.0	67.5 ± 9.1	69.4 ± 10.7**	69.3 ± 10.1**
HR (bpm)	67.8 ± 10.9	82.5 ± 13.2**	80.4 ± 12.8**	80.5 ± 12.3**
SVV >2° (n = 28)				
SBP (mm Hg)	113.2 ± 11.0	113.8 ± 16.7	113.4 ± 16.7	115.0 ± 14.7
DBP (mm Hg)	65.1 ± 7.9	67.4 ± 8.4**	67.4 ± 10.4*	69.2 ± 9.8**
HR (bpm)	65.3 ± 10.6	83.1 ± 12.3**	79.3 ± 12.3**	77.9 ± 12.1**
B				
CP% ≤25% (n = 105)				
SBP (mm Hg)	112.8 ± 10.7	112.8 ± 12.9	113.8 ± 12.8	114.7 ± 12.3*
DBP (mm Hg)	66.6 ± 8.7	67.6 ± 8.9*	69.1 ± 10.5**	69.3 ± 10.1**
HR (bpm)	67.6 ± 10.9	82.6 ± 13.1**	80.6 ± 12.5**	80.4 ± 12.2**
CP% >25% (n = 16)				
SBP (mm Hg)	116.0 ± 11.4	117.0 ± 15.1	116.9 ± 16.8	118.3 ± 15.8
DBP (mm Hg)	64.9 ± 8.8	67.2 ± 8.7*	67.5 ± 11.4	69.4 ± 9.9**
HR (bpm)	64.7 ± 10.4	82.6 ± 12.0**	77.3 ± 13.2**	76.6 ± 12.8**

The differences in the changes in the SBP, DBP and HR after standing up between two groups of female patients classified by their degree of SVV (SVV ≤2° vs. SVV >2°, A) and their CP% (CP% ≤25% vs. CP% >25%, B)

The values show the average and SD

SBP systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *SVV* subjective visual vertical, *CP%* canal paresis percentage

**, * Significant difference from that at rest at $P < 0.01$ and $P < 0.05$

vestibular-cardiovascular pathway can be induced by changes of the graviceptive signal, but not by the changes in the arterial BP resulting from a shift in the blood flow. The system therefore has an error, potentially leading to an over-increase in the BP although this can be usually corrected by a negative feedback system, such as baroreflex. One study has clearly demonstrated that there are increases in muscle sympathetic nerve activity and calf vascular resistance during head-down rotation. These responses are mediated by an engagement of the otolith organs and not the semicircular canals (Ray and Carter 2003). The adjustment and increase of BP by the otolith organ are entirely appropriate during active movement; however, they may be inappropriate when provoked by passive movements.

Measuring the initial responses (the first 30 s) after standing up may be an effective way to detect the effects of vestibular disorders on BP responses after standing up.