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Orthostatic hemodynamics in the vertebral artery and blood pressure in patients with orthostatic dizziness/vertigo

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ABSTRACT

Objectives: Orthostatic dizziness/vertigo (ODV) is a common symptom and is believed to occur due to the cerebral hypoperfusion caused by orthostatic hypotension (OH). However, the detailed mechanism underlying ODV onset is poorly understood. The vertebral artery (VA) mainly supplies blood to the central vestibular system; therefore, the orthostatic decrease of VA blood flow could possibly lead to ODV. This study investigated the orthostatic blood pressure and VA hemodynamics in ODV patients to elucidate the hemodynamic mechanism underlying ODV onset. Furthermore, the influence of orthostatic hypotension (OH) on VA hemodynamics was examined because OH is probably the most common cause of ODV.

Methods: This study included 181 patients with ODV and 73 control patients without ODV. All subjects underwent an active standing test to measure the extracranial Doppler (ECD) sonography spectrum of the VA and blood pressure (BP). VA blood flow velocity and BP were simultaneously measured for each patient in the supine static position and then in the upright standing positions following 3 min of standing. We investigated the orthostatic change in the average of flow velocity in bilateral VAs (VAFV) and BP for ODV patients compared with the control patients.

Result: VAFV in ODV patients was significantly reduced when standing up compared with the control patients. In the ODV patients, there was no difference in orthostatic decrease in VAFV between patients those with OH and without OH. However, the VAFV in the standing position was significantly lower in patients with OH than without OH. In cases with OH, the ODV patients exhibited a greater decrease in VAFV compared with the control patients, but this was not statistically significant. In the absence of OH, a significantly greater orthostatic decrease in VAFV was observed in ODV patients compared with the controls.

Conclusion: Our findings suggest that the orthostatic decrease of VA blood flow is deeply involved in the hemodynamic mechanism underlying ODV onset and is possibly associated with OH and other etiologies.

1. Introduction

Some patients present with different symptoms such as faintness or floating, rotatory, or swaying sensations when rising from a sitting or lying position to a standing position

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[1–3]. These characteristic symptoms related to standing are collectively regarded as orthostatic dizziness/vertigo (ODV) [1–4]. The diagnostic criteria of ODV associated with hemodynamics were defined by the International Society for Neurootology (Bárány Society) in 2019 [4], and ODV is believed to occur due to hypoperfusion of the global brain including central vestibular region [5]. Because the vertebral artery (VA) mainly supplies blood to the brainstem and cerebellar region associated with the central vestibular system [6], the orthostatic decrease of VA blood flow may possibly produce ODV. However, it remains unclear whether orthostasis induces hemodynamic changes and the detailed mechanism underlying the onset of ODV is poorly understood. Therefore, it is crucial to determine hemodynamics in the VA related to the central vestibular system alter in patients presenting with ODV upon standing.

In this study, we investigated the orthostatic blood pressure (BP) and VA blood flow in ODV patients to elucidate the hemodynamic mechanism underlying the onset of ODV. Furthermore, influence of orthostatic hypotension (OH) on VA hemodynamics was examined because OH is thought to be the most common cause of ODV.

2. Subjects and methods

In this study, of all 1385 patients with dizziness/vertigo who visited our dizziness and balance clinic in 5 years, 181 patients with ODV (64 men and 117 women; age range, 23–87 years; mean age, 50.9±1.5 years) were included. Additionally, 73 patients without ODV (17 men and 56 women; age range, 19–83 years; mean age, 52.6±2.0 years) who visited our clinic in the 6-month period were recruited as historical control. There were no significant differences among the ages of patients with ODV and control patients. Meanwhile, the exclusion criteria in the patients with ODV and controls were as follows: (1) postural orthostatic tachycardia syndrome (POTS) and syncope; (2) history of cardiovascular disorders such as arrhythmia, valvular disease, etc.; (3) history of cerebrovascular disorder; (4) blood problems such as polycythemia, abnormal hematocrit, etc.; and (5) musculoskeletal abnormalities that lead to difficulty in maintaining the standing position. ODV was defined as complaints of dizziness, unsteadiness, light-headedness, or vertigo triggered by a change of body posture from lying to standing or sitting to standing or the presence of the aforementioned symptoms while standing in an upright position and their resolution when sitting or lying.

In all subjects, BP and the extracranial Doppler (ECD) sonographic spectrum of the VA were recorded in the supine and standing positions. BP was measured at the brachium using an automated BP monitor (BP-102i II, Japan Colin, Aichi, Japan). ECD sonography (DFM-4500, Hayashi Electronic, Kanagawa, Japan) [7] was performed to measure the blood flow velocity of the right and left VAs individually at the cervical intervertebralis (segments C5 and C6). During ECD sonographic examinations, the time-averaged maximum flow velocity equivalent to a mean velocity was calculated from the doppler waveform obtained automatically from five cardiac cycles. Each patient remained in the supine position for 10 min before the measurements. After the blood flow velocities of the VAs and the BP were measured in the supine position, these variables were simultaneously measured after the patients stood for 3 min. OH was defined as a ≥20mmHg decrease in systolic BP or ≥10 mmHg decrease in diastolic BP according to the consensus statement on the definition of OH by the American Autonomic Society and the American Academy of Neurology [8]. In this study, we used the average value of the flow velocities in the bilateral VAs to assess VA hemodynamics and hereinafter abbreviated it to VAFV. The orthostatic change in VAFV (ΔVAFV) was calculated using the following formula: ΔVAFV (cm/s) = VAFV in the supine position − VAFV in the standing position. The decrease rate (DR) in VAFV was calculated using the following formula: DR (%) = ΔVAFV / VAFV in the supine position × 100. These variables were used to evaluate orthostatic effects on VAFV.

All statistical analyses were conducted using EZR version 1.53 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R version 4.0.2 (The R Foundation for Statistical Computing, Vienna, Austria). Unpaired *t*-tests were performed in all statistical analyses. All data for the VAFV were expressed as the mean ± SE, and $p < 0.05$ indicated statistical significance.

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the clinical research ethics board of Nara Medical University Hospital (Approval No. 620). The participants provided their informed consent to participate in this study.

3. Results

In the 181 with ODV, VAFV, as an indicator of VA hemodynamics, decreased from 15.5 ± 0.4 cm/s in the supine position down to 13.5 ± 0.5 cm/s in the standing position, whereas VAFV in 73 control was 13.3 ± 0.6 cm/s in the supine position and 13.2 ± 0.7 cm/s in the standing position. The orthostatic decrease in VAFV as expressed by ΔVAFV was 2.0 ± 0.4 cm/s in the ODV group, versus 0.04 ± 0.5 cm/s in control group. There was a significantly greater decrease in the ODV group than in the control group (p=0.005) (Fig. 1).

The decrease rate (DR) of VAFV exceeding 10% of the baseline value (VAFV in the supine position) was observed in 92 of 181 (50.8%) ODV patients and 26 of 73 (35.6%) control patients, respectively. Moreover, 48 (26.5%) of the ODV patients and 10 (13.7%) controls displayed a DR exceeding 30%. Patients with ODV displayed a much higher frequency of decreased VAFV than controls (Table 1). The mean DR of VAFV were 9.7 ± 2.4%, and -8.0 ± 5.8% in the ODV and control groups, respectively, with a significant difference (p = 0.001).

Among the 181 ODV patients, 30 (16.6%) accompanied OH and 151 (83.4%) did not, while 11 (15.1%) had OH and 62 (84.9%) did not among the 73 control patients. The VAFV in ODV patients with OH and without OH was reduced from 13.8 ± 1.2 cm/s to 11.5 ± 0.9 cm/s and from 15.9 ± 0.5 cm/s

Table 1. Orthostatic decrease rate of VAFV in patients with ODV and control patients without ODV.

Decrease rate (DR) of VAFV (%)	Number of patients	
	ODV patients (n = 181)	Control patients (n = 73)
30≦ DR	48 (26.5%)	10 (13.7%)
10≦ DR <30	44 (24.3%)	16 (21.9%)
-10≦ DR <10	41 (22.7%)	19 (26.0%)
-30≦ DR <-10	33 (18.2%)	11 (15.1%)
DR <-30	15 (8.3%)	17 (23.3%)
DR of VAFV (mean ± SE)	9.9±2.4	- 4.8±2.7
	**	

ODV, orthostatic dizziness/vertigo; VA, vertebral artery; VAFV, blood flow velocity of VA.
ΔVAFV = VAFV supine position – VAFV upright position.
Decrease rate (DR) of VAFV (%) = ΔVAFV / VAFV supine position × 100.
**, $p < 0.01$.

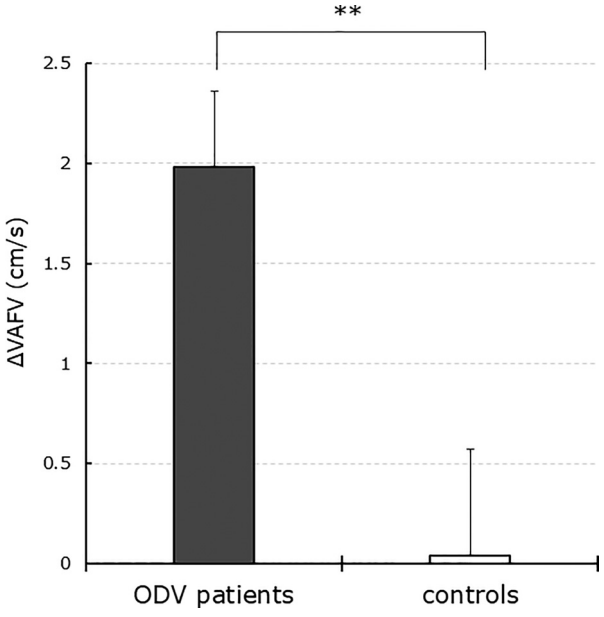

Fig. 1. Orthostatic decrease of VA blood flow in ODV patients and controls The orthostatic decrease in VAFV (ΔVAFV) in ODV patients is significantly greater than in control patients. ODV, orthostatic dizziness/vertigo; VA, vertebral artery; VAFV, blood flow velocity of VA.

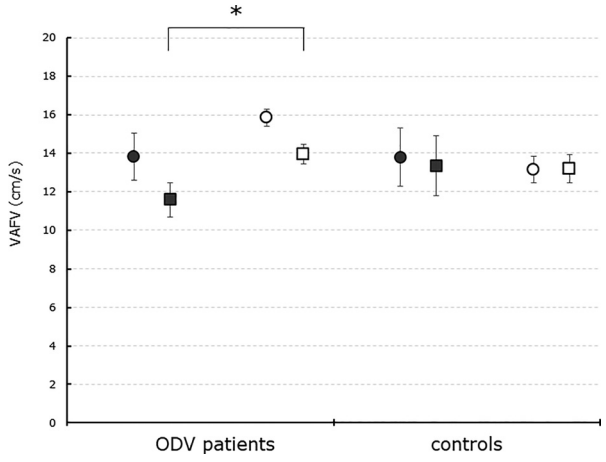

Fig. 2. Involvement of OH in orthostatic VA hemodynamics in ODV patients and controls; VAFV in supine and standing positions in ODV patients and controls The VAFV in the standing position was significantly lower in ODV patients with OH than those without OH, but not for the VAFV shown in the supine static position. ●, indicates patients with OH in supine position; ○, indicates patients without OH in supine position; ■, indicates patients with OH in standing position; □, indicates patients without OH in standing position OH, orthostatic hypotension; ODV, orthostatic dizziness/vertigo; VA, vertebral artery; VAFV, blood flow velocity of VA; *, $p < 0.05$.

to 13.9 ± 0.5 cm/s when standing up, respectively. The VAFV in the standing position was significantly lower in ODV patients with OH than those without OH (p = 0.049) but not for the VAFV in the supine static position (Fig. 2).

In contrast, in the patients with OH, the controls displayed a slight change in VAFV, which decreased from 13.8 ± 1.5 cm/s in the supine position to 13.3 ± 1.6 cm/s in the standing position. ΔVAFV was 2.3 ± 1.0 cm/s in the ODV group, versus 0.5 ± 1.1 cm/s in the control group. The ODV patients exhibited not a significant but greater decrease in VAFV as compared to control patients (Fig. 3A). Among patients without OH, ΔVAFV was 1.9 ± 0.4 cm/s in the ODV group, whereas ΔVAFV was unchanged in the control group (−0.03 ± 0.6). In the absence of OH, the orthostatic decrease was significantly greater in ODV patients than in control patients (p = 0.009) (Fig. 3B).

4. Discussion

Orthostatic dizziness/vertigo (ODV) is characterized by dizziness, unsteadiness or vertigo that is present only in the upright position or, more specifically, that develops on rising from a sitting to a standing, or from lying to a sitting or standing position. ODV ascribed to hemodynamic pathophysiology is named hemodynamic ODV, and the diagnostic criteria for hemodynamic ODV were established by the Bárány Society in 2019 [4]. Although these criteria indicate that hemodynamic ODV occurs due to hemodynamic changes upon arising from sitting or standing, the context regarding the actual hemodynamic changes of brain blood flow during orthostasis has not been addressed. Therefore, in this study, we conducted an ECD measurement of VA hemodynamics likely associated with the onset of ODV upon standing

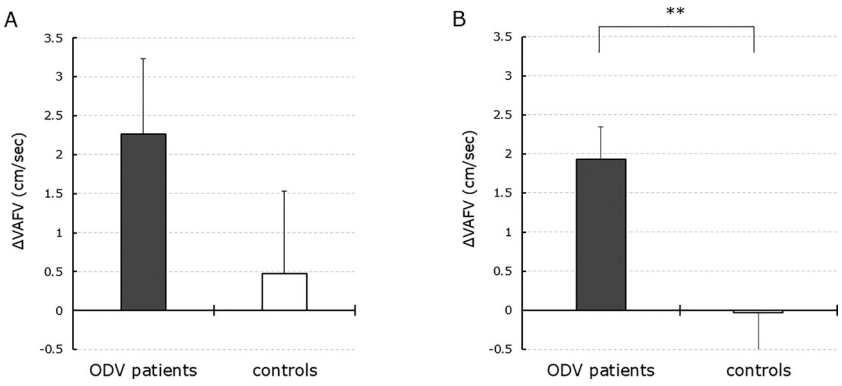

Fig. 3. Involvement of OH in orthostatic VA hemodynamics in patients with ODV and controls; Orthostatic decrease of VAFV in the presence of OH (A) and in the absence of OH (B) The ODV patients with concomitant OH exhibited not a significant but greater ΔVAFV as compared to control patients (A). In the absence of OH, ΔVAFV was significantly greater in ODV patients than in control patients (B).ODV, orthostatic dizziness/vertigo; VA, vertebral artery; VAFV, blood flow velocity of VA ΔVAFV = VAFV supine position – VAFV upright position; **, $p < 0.01$.

A few previous studies used doppler ultrasonography to investigate orthostatic induced changes of cerebral hemodynamics including VA blood flow [9,10]. A decrease of total blood flow in the bilateral internal carotid and vertebral arteries was demonstrated during orthostatic stress in patients with myalgic encephalomyelitis/chronic fatigue syndrome characterized by orthostatic intolerance symptoms such as orthostatic dizziness and light-headedness [11], whereas in healthy subjects, there was no difference in VA blood flow velocity between the supine and head up tilt positions, suggesting that VA hemodynamics is not affected by orthostatic stress [9]. In addition, another report revealed that the orthostatic stress induced decrease of VA blood flow velocities in patients with aortic stenosis is linked to orthostatic dizziness and falls [12]. In the present study with doppler ultrasonography, significantly greater orthostatic decrease of blood flow velocity in the VA was observed in patients with ODV than in those without ODV. These results indicate that VA blood flow is susceptible to orthostatic positional changes in patients with ODV. The VA mainly supplies blood to the medulla oblongata and cerebellum, which is the location of the control center in the vestibular nervous system closely related to the occurrence of dizziness/vertigo. Indeed, in the clinical entity of inadequate blood flow of VA systems such as vertebrobasilar insufficiency, dizziness/vertigo is well known to occur frequently as one of main symptoms [13]. Because dizziness/vertigo is likely to arise from hypoperfusion in this control center of vestibular nervous system due to reduction of VA blood flow, our current results suggest that the VA hemodynamics during orthostasis is strongly associated with the onset of ODV.

The main cause of ODV is suggested to be OH because it might provoke the cerebral hypoperfusion [14,15]. In the diagnostic criteria of hemodynamic ODV, OH is documented as one of the criteria for a definitive diagnosis of hemodynamic ODV [4,8]. Thus, OH is commonly considered the key hemodynamic etiology of ODV. In this study, we investigated the effect of OH on VA hemodynamics in patients with ODV. Among patients with ODV, there was no difference of the decrease in VAFV between those with and without OH. However, VAFV in the standing position was significantly lower in patients with OH than in those without OH despite the lack of difference between these patients in the supine position. These results indicate that OH-induced symptoms such as ODV develop upon assuming a standing upright posture and resolve upon resuming the recumbent position [8]. Some previous studies examining the cerebral circulation during head-up tilt on a tilt table in patients with OH demonstrated that cerebral blood flow decreases in patients with ODV, whereas it does not change in patients without ODV [16,17]. Similarly, in the present study, patients with ODV and coincident OH exhibited marked, albeit not significant, orthostatic decrease of VAFV compared with the finding in controls without ODV. These results suggest that OH is responsible for VA hemodynamics during standing.

Conversely, in patients without OH, those with ODV exhibited a significantly more pronounced decrease in VA blood flow than controls while rising to the standing position in this study. These results suggest that VA hemodynamics in some ODV patients is not associated with OH. Although ODV is believed to derive from OH clinically, OH does not always correlate with ODV regarding epidemiological and clinical characteristics [3,18], and it is unlikely to be the only etiology of ODV [2,18]. From the perspective of hemodynamics, VA blood flow is considered to be determined by the VA perfusion pressure and vascular resistance [19]; thus, a possible explanation for the decrease of VA blood flow in the absence of OH could be perfusion pressure and vascular resistance in the VA. Perfusion pressure of the brain is modulated by the cerebral autoregulation, which regulates brain blood flow including that in the vertebrobasilar system in responses to change in BP [20,21]. When this autoregulation is seriously impaired, the lower BP limit shifts up because of narrowing of the autoregulated BP range. Therefore, it is suggested that even a slight decrease in BP in the absence of OH could cause a decrease in VA blood flow in ease. Another possibility is likely attributed to vascular resistance in the VA determined by structures or blood viscosity. The previous study reported that organic abnormalities in the VA including stenosis and winding [22] or high blood viscosity associated with hyper-

lipidemia or diabetes mellitus affected vascular resistance in the brain [23,24]. It is suspected that vascular resistance also might exert some influence on VA blood flow.

According to the diagnostic criteria of hemodynamic ODV, ODV would not be definitively diagnosed in patients without coincident OH since OH is a criterion for the definitive diagnosis of hemodynamic ODV [4]. Our results suggest that some patients with ODV display an orthostatic decrease in VA blood flow in the absence of OH, and they might be possibly categorized as having probable hemodynamic ODV. Thus, VA hemodynamics could be an important factor to make a diagnosis of hemodynamic ODV.

Our study is the first report to elucidate the orthostatic hemodynamics of the VA in patients with ODV and one of the underlying pathophysiological mechanisms causing ODV. However, we cannot exclude the possibilities that aging, medication use and comorbidities including diabetes mellitus and cognitive disorders as well as vestibular, vision and proprioceptive disorders may have influenced VA blood flow upon standing. Additionally, we did not examine the difference of VA blood flow velocity between right and left side in the present study since it is reported that an anatomical VA asymmetry is found in many of healthy subjects [25–28]. However, the side difference of VA hemodynamics could be associated with the onset of ODV. Further research is necessary to determine whether these factors affect orthostatic hemodynamics in the VA.

5. Conclusion

To summarize our results of this study, ODV patients demonstrated significantly more marked decrease of blood flow in VA than control patients without ODV from supine to standing. In ODV patients, a significant lower VA blood flow was shown in patients with OH on the standing upright position compared to those without OH. Furthermore, in the presence of OH, more pronounced but not significant orthostatic decrease in VA blood flow was observed in the ODV patients than in the control patients, while ODV patients without OH revealed a significant greater decrease in VA blood flow from lying to standing position.

In conclusion, our study provides the possible suggestion that the onset of ODV is closely associated with orthostatic hypoperfusion of VA possibly due to OH and other etiologies.

Declaration of Competing Interest

The authors declare no conflicts of interest associated with this manuscript.

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