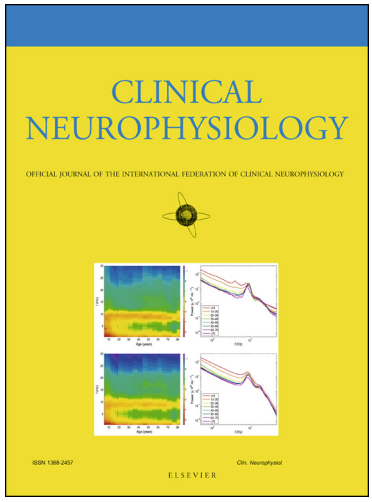


Vibration-induced nystagmus in patients with vestibular schwannoma: characteristics and clinical implications

Jeon Mi Lee, Mi Joo Kim, Jin Won Kim, Dae Bo Shim, Jinna Kim, Sung Huhn Kim

PII: S1388-2457(17)30086-X
DOI: http://dx.doi.org/10.1016/j.clinph.2017.02.023
Reference: CLINPH 2008081

To appear in: *Clinical Neurophysiology*

Received Date: 12 May 2016
Revised Date: 23 January 2017
Accepted Date: 16 February 2017

Please cite this article as: Lee, J.M., Kim, M.J., Kim, J.W., Shim, D.B., Kim, J., Kim, S.H., Vibration-induced nystagmus in patients with vestibular schwannoma: characteristics and clinical implications, *Clinical Neurophysiology* (2017), doi: http://dx.doi.org/10.1016/j.clinph.2017.02.023

Vibration-induced nystagmus in patients with vestibular schwannoma: characteristics and clinical implications

Jeon Mi Lee[a], Mi Joo Kim[b], Jin Won Kim[a], Dae Bo Shim[c], Jinna Kim[d], Sung Huhn Kim[a]

[a]Department of Otorhinolaryngology, Yonsei University College of Medicine, Seoul, South Korea

[b]Department of Otorhinolaryngology, Catholic Kwandong University College of Medicine, Incheon, Gyeonggi-Do, South Korea

[c]Department of Otorhinolaryngology, Myongji Hospital, Goyang, Gyeonggi-do, South Korea

[d]Department of Neuroradiology, Yonsei University College of Medicine, Seoul, South Korea

Corresponding author:

Sung Huhn Kim MD, PhD

Department of Otorhinolaryngology

Yonsei University College of Medicine

50 Yonsei-Ro, Seodaemun-Gu, 120-752 Seoul, Korea

Tel.: 82-2-2228-3604

Fax: 82-2-393-0580

E-mail: fledermaus@yuhs.ac

Abbreviations

CP: canal paresis; MRI: magnetic resonance imaging; MSPV: maximum slow-phase velocity; SCM: sternocleidomastoid muscle; VIN: vibration-induced nystagmus.

Abstract

Objective: To investigate the clinical significance of vibration-induced nystagmus (VIN) in unilateral vestibular asymmetry and vestibular schwannoma.

Methods: Thirteen patients with vestibular schwannoma underwent the VIN test, in which stimulation was applied to the mastoid processes and sternocleidomastoid (SCM) muscles on the ipsilateral and contralateral sides of lesions. Preoperative VIN was measured, and changes in VIN were followed up for 6 months after tumor removal. Significance of VIN was determined by evaluation of its sensitivity, correlation with vestibular function tests and tumor volume, and postoperative changes.

Results: The overall pre and postoperative sensitivities of VIN were 92.3% and 100%, respectively, considering stimulation at all four sites. Maximum slow-phase velocity (MSPV) of VIN was linearly correlated with caloric weakness and tumor volume, especially when stimulation was applied to the SCM muscle. Postoperative MSPV of VIN exhibited stronger linear correlation with postoperative changes in canal paresis value and inverse correlation with tumor size upon stimulation of the ipsilateral SCM muscle than upon stimulation of other sites. During the 6-month follow-up period, persistence of VIN without changes in MSPV was observed even after vestibular compensation.

Conclusions: Evoking VIN by stimulation of the mastoid processes and SCM muscles is effective for detecting vestibular asymmetry. It could also help determine the degree of vestibular asymmetry and volume of vestibular schwannoma if stimulation is applied to the SCM muscle.

Significance: The results of this study could provide clues for the basic application of VIN in patients with vestibular loss and vestibular schwannoma.

Keywords: vibration; nystagmus; vestibular schwannoma; vestibular loss.

Highlights

1. Evoking vibration-induced nystagmus (VIN) is useful for detecting vestibular asymmetry in vestibular schwannoma patients.
2. VIN of the sternocleidomastoid muscle provides the most accurate information on vestibular asymmetry and tumor volume.
3. VIN after total vestibular loss persists for at least 6 months even after vestibular compensation.

1. Introduction

Vibration-induced nystagmus (VIN) is nystagmus evoked by application of vibration to the mastoid process, forehead, or sternocleidomastoid (SCM) muscle. This condition is observed in patients with peripheral or central vestibulopathies (Park et al., 2010). It is thought to originate in peripheral vestibular receptors and/or proprioceptive receptors in the neck muscles (Taoka et al., 1990). However, the exact role and degree of contribution of each receptor in the manifestation of VIN is still unclear. Although vibration is thought to stimulate all vestibular organs, including the semicircular canals and otolithic afferents, it predominantly evokes horizontal nystagmus; moreover, the direction of nystagmus evoked by vibration is usually towards the healthy side in patients with unilateral peripheral vestibular loss (Dumas et al., 2008). The VIN test is a simple and reliable method for distinguishing vestibular asymmetry. In addition, the slow-phase velocity (SPV) of nystagmus has been shown to be correlated with the degree of vestibular loss (Park et al., 2008).

Vestibular schwannomas represent various degrees of vestibular loss and allow for the monitoring of acute and chronic changes in vestibular function according to vestibular compensation after tumor removal. They are, therefore, ideal models for investigating the efficacies of various vestibular function tests, including the VIN test. Although several studies have investigated VIN in patients with vestibular schwannomas (Hamann and Schuster, 1999; Dumas et al., 2008; Dumas et al., 2011), no study till date has investigated the relationship of VIN with tumor characteristics and degree of vestibular loss. Furthermore, few reports have documented the changes in VIN during the compensatory period in patients with partial vestibular loss (vestibular neuritis). Moreover, no study till date has investigated the changes in VIN after total tumor removal, which allows for evaluation of changes in VIN according to the changes in vestibular function as well as vestibular compensation after total

vestibular loss.

In this study, we aimed to investigate the acute and chronic changes in VIN after tumor removal in patients with vestibular schwannomas as well as the relationship between tumor characteristics and VIN. The results of this study could provide clues for the basic application of VIN in patients with vestibular loss and vestibular schwannomas.

2. Methods

2.1. Patient selection

Thirteen consecutive patients diagnosed with vestibular schwannoma by magnetic resonance imaging (MRI) were enrolled in this study. The mean age of the patients was 48.0 ± 7.7 years, and the male:female ratio was 4:9. All patients except one exhibited unilateral sensorineural hearing loss. Tumor resection was performed through the translabyrinthine approach in 12 patients and the middle cranial fossa approach in 1 patient. The entire vestibular nerve (superior and inferior vestibular nerves) was surgically resected along with the tumor. Patients received postoperative follow-up for 6 months. Patient characteristics and preoperative findings are presented in **Table 1.**

This study was approved by the International Review Board of the Severance Hospital in Seoul, Korea (approval number: 1-2012-0037), and written informed consent was obtained from all patients.

2.2. Measurement of tumor volume

Tumor volume was measured by a three-dimensional (3D) volume calculation program (Aquaria INtuition^{TM}, TeraRecon, Foster City, CA) using gadolinium-enhanced temporal MR images with 3-mm slice thickness. The program automatically calculated the tumor volume

by performing 3D reconstruction of the tumor using serial axial, coronal, and sagittal images. Tumor volume was measured by a blinded neuroradiologist.

2.3. VIN and other vestibular function tests

All patients were evaluated by the bithermal caloric, cervical vestibular evoked myogenic potential (cVEMP), ocular vestibular evoked myogenic potential (oVEMP), and VIN tests a day prior to surgery. The bithermal caloric test was performed at water irrigation temperatures of 30 ℃ and 44 ℃, and the canal paresis (CP) value was calculated using Jongkees' formula (Jongkees et al., 1962). The test was repeated at 1 month after tumor resection.

For the cVEMP test, active electrodes were placed on the upper half of the bilateral SCM muscles, while reference and ground electrodes were placed on the suprasternal notch and forehead, respectively. Electromyographic (EMG) signals were amplified, bandpass-filtered between 30 and 3000 Hz, and monitored to maintain background muscle activity at over 50 μV. Acoustic stimuli were 1000Hz 95 dB nHL short-tone bursts with rarefaction polarity and were delivered through an insert earphone. An average of 100 responses were recorded for each run, with the subject sitting with the head rotated sideways towards one shoulder to activate the SCM muscle (Chou et al., 2009). The cVEMP was measured by monaural acoustic stimulation with ipsilateral recording. The first positive and second negative polarities of biphasic waveform were termed waves p13 and n23, respectively. Consecutive trials were performed to confirm the reproducibility of peaks p13 and n23, following which cVEMP responses were considered present. Conversely, cVEMP responses were considered absent when the biphasic p13–n23 waveform was not reproducible. The results were defined as abnormal in the absence of cVEMP response.

For the oVEMP test, an active electrode was attached to the infraorbital ridge 1 cm below

the center of each lower eyelid and a reference electrode was placed about 2 cm below the active electrode. The ground electrode was attached to the forehead. During testing, patients were instructed to stare at a small fixed point approximately 25° above horizontal at a distance approximately 60 cm from the eyes. The recorded activity was amplified and bandpass filtered between 1 and 1000 Hz. Acoustic stimuli identical to those used in cVEMP testing were delivered to each ear. The stimulation rate was 5 Hz, the analysis time for each response was 50 ms, and 100 responses were averaged for each run. The initial negative–positive biphasic waveform comprised peaks nI and pI. Consecutive trials were performed to confirm the reproducibility of peak nI and pI, after which oVEMP responses were considered present.

Vibration-induced nystagmus was evoked by stimulating the normal (contralateral) and lesion (ipsilateral) sides of the mastoid process and the belly of the SCM muscle 25 mm below the mastoid process for 10 s, using a 100-Hz hand-held vibrator (VVIB 100; Synapsys, France), as described by Karlberg et al. (Karlberg et al., 2003). Nystagmus evoked upon stimulation was recorded by videonystagmography (SLVNG; SLMED, Korea) in the dark. Baseline eye movement was recorded prior to stimulation of the bilateral mastoid processes and SCM muscles. Subjects were instructed to continue looking straight ahead while stimulation was applied for approximately 10 s. The SPVs of the horizontal and vertical components of VIN were obtained by calculating the slope of the slow-phase eye movement in the 10-s window using the SLVNG software; the highest SPV during stimulation was considered as the maximum slow-phase velocity (MSPV; **Fig. 1**). In case of patients exhibiting spontaneous nystagmus, the MSPV of VIN was calculated by subtracting the MSPV of spontaneous nystagmus at baseline from that of VIN.

All patients received postsurgical vestibular rehabilitation for 3 months according to the

protocol followed at the institute of the senior author. Postoperative VIN and spontaneous nystagmus were evaluated at 1, 3, and 6 months post-surgery using the above-mentioned method. Vestibular compensation and postoperative balance function were evaluated through a conventional sensory organization test by computerized dynamic posturography (Equitest®, Neurocom International Inc, OR, USA) at 1 and 6 months post-surgery.

2.4. Statistical analysis

Statistical analysis was performed with the SPSS software for PC, version 21 (SPSS Inc., Chicago, IL, USA). Values are presented as the mean ± standard deviation. Differences in the MSPV of VIN during follow-up were analyzed by Student's t-test or one-way analysis of variance. Differences in sensitivity according to the stimulation site were analyzed by the chi-square test. The relationships between CP value, tumor volume, and MSPV of VIN were analyzed by linear regression analysis. The relationship between cVEMP and the vertical component of VIN was analyzed by Pearson's correlation. The threshold for significance for all tests was set at $p = 0.05$.

3. Results

3.1. Correlation between preoperative caloric weakness and tumor volume

The mean preoperative tumor volume and CP values were 4.99 ± 7.92 cm^3 (range, 0.13–24.02 cm^3) and 52.2 ± 32.9% (range, 5–100%), respectively. Upon linear regression analysis, CP values were found to be weakly correlated with tumor volume ($R^2 = 0.3120$), although the correlation between the two parameters was statistically significant ($p = 0.04$; **Fig. 2**).

3.2. Characteristics of preoperative VIN

In the present study, the lesion and normal sides were defined as the ipsilateral and contralateral sides, respectively. Among the 13 included patients, VIN was observed in 11 (84.6%) and 10 (76.9%) patients upon stimulation of the ipsilateral and contralateral mastoid processes and in 10 (76.9%) and 8 (61.5%) patients upon stimulation of the ipsilateral and contralateral SCM muscles, respectively. Although the sensitivity of horizontal VIN appeared to vary according to the stimulation site, there were no significant differences in sensitivity among the different sites and sides of stimulation ($p > 0.05$). Nevertheless, the sensitivity of VIN was the highest when calculated as the overall sensitivity including stimulation at all four sites (12/13; 92.3%).

The sensitivity of horizontal VIN was not dependent on CP value or tumor volume ($p > 0.05$). In the 12 patients who exhibited VIN, nystagmus was consistent with the fast-phase beating towards the contralateral side. The mean MSPVs of VIN during stimulation of the ipsilateral and contralateral mastoid processes and SCM muscles were 10.50 ± 12.8, 6.71 ± 8.06, 10.46 ± 11.94, and 8.31 ± 10.11°/s, respectively. It was not surprising that the MSPV in each condition exhibited wide variation given that the CP values of the included patients were also widely distributed. There were no significant differences in the SPV of VIN between the ipsilateral and contralateral sides or the mastoid process and SCM muscle ($p > 0.05$).

Vertical VIN was detected in 8 of 13 (61.5%) patients, of whom, 6 (46.2%) and 3 (23.1%) patients each exhibited vertical VIN upon stimulation of the ipsilateral and contralateral mastoid processes and SCM muscles, respectively. Patients with horizontal VIN also exhibited vertical VIN, and none of the patients solely exhibited vertical VIN. The sensitivity of vertical VIN was less than 50% regardless of the stimulation site, and it was not dependent on CP value or tumor volume ($p > 0.05$). The sensitivity of vertical VIN was significantly lower compared to that of horizontal VIN observed upon stimulation of the ipsilateral and

contralateral mastoid processes (p = 0.03 and < 0.01, respectively).

The direction of vertical VIN varied according to the site and side of stimulation in each patient. While 5 patients exhibited up-beating nystagmus, 2 exhibited down-beating nystagmus under at least one condition of stimulation. One of the patients exhibited variations in vertical VIN according to the stimulation area — VIN upon stimulation of the ipsilateral mastoid process had a down-beating component, while that upon stimulation of the contralateral mastoid process and ipsilateral SCM muscle had an up-beating component. The mean MSPVs of vertical VIN during stimulation of the ipsilateral and contralateral mastoid processes and SCM muscles were 2.67 ± 3.43, 0.72 ± 1.45, 2.12 ± 2.53, and 0.88 ± 1.71°/s, respectively. The MSPVs of vertical VIN upon stimulation of the ipsilateral and contralateral mastoid processes and SCM muscles were significantly lower compared to the corresponding MSPVs of horizontal VIN (p = 0.04, 0.01, 0.02, and 0.02, respectively). There were no significant differences in the MSPVs of vertical VIN between the mastoid process and SCM muscle; however, the MSPV of vertical VIN upon stimulation of the ipsilateral side was significantly greater compared to that upon stimulation of the contralateral side (p = 0.02). Given that cVEMP could be indicative of the inferior vestibular nerve function, we attempted to determine the correlation of abnormal cVEMP with the sensitivity and direction of vertical VIN; however, abnormal cVEMP was not significantly correlated with either of the parameters (p > 0.05). We also attempted to analyze the relationship between the horizontal/vertical nystagmus and oVEMP, which represents the remnant function of the utricle and superior vestibular nerves. However, most patients (84.6%) showed no response to oVEMP testing, and we were unable to find any correlation between the oVEMP results and the parameters (p > 0.05).

These results indicate that the sensitivity of vertical VIN was lower compared to that of

horizontal of VIN, and vertical VIN appeared as a part of torsional eye movement.

3.3. Correlation of preoperative MSPV with CP value and tumor volume

The relationship of MSPV of horizontal VIN with tumor volume and CP value was investigated by linear regression analysis. Since the sensitivity of vertical VIN was less than 50% regardless of the stimulation site, and the direction of vertical VIN varied according to the stimulation site, the number of patients exhibiting each variation was not adequate for analysis of correlation between vertical VIN and other factors; therefore, vertical VIN was excluded from linear regression analysis. The preoperative MSPVs of VIN upon stimulation of the ipsilateral and contralateral mastoid processes and SCM muscles were positively and linearly correlated with both CP value (p = 0.021 [R^2 = 0.40]; 0.014 [R^2 = 0.43]; 0.002 [R^2 = 0.60]; and 0.011 [R^2 = 0.46]; respectively; **Fig. 3A**) and tumor volume (p = 0.04 [R^2 = 0.33]; 0.0001 [R^2 = 0.75]; 0.003 [R^2 = 0.56]; and 0.001 [R^2 = 0.66]; respectively; **Fig. 3B**). Although there were no significant differences in mean MSPV between the stimulation sides in either the mastoid process or the SCM muscle ($p > 0.05$), the correlations of the MSPV of VIN with tumor volume and CP value during stimulation of the SCM muscle were stronger compared to those during stimulation of the corresponding mastoid process; the lone exception to this trend was the correlation between the MSPV of VIN upon stimulation of the contralateral mastoid process and tumor volume **(Fig. 3)**.

3.4. Postoperative changes of VIN

All patients exhibited resolution of spontaneous nystagmus at 3 months post-surgery and showed no response at all in bithermal caloric testing, cVEMP, or oVEMP on the ipsilateral side. The sensory analysis scores of the vestibular system, evaluated by dynamic

posturography, had improved (from 37.3 ± 29.5 to 68.4 ± 10.9; $p = 0.003$) and were within the normal range in all patients at 6 months post-surgery, which indicates postoperative compensation of static and dynamic imbalances. All 13 patients exhibited horizontal VIN beating with the fast phase towards the contralateral side regardless of the site or side of stimulation during 1 to 6 months of postoperative follow-up. Vertical VIN was observed in 8 patients at 1 and 3 months post-surgery and in 11 patients at 6 months post-surgery; however, similar to the preoperative trends, the direction and MSPV of vertical VIN were irregular, and the sensitivity of vertical VIN varied according to the stimulation site. Therefore, we were unable to evaluate the statistical significance of postoperative vertical VIN data (data not shown). The MSPVs of horizontal VIN upon stimulation of the contralateral mastoid process and SCM muscle had significantly increased between baseline and 1 month post-surgery (from 6.7 ± 8.1 to 12.6 ± 7.3°/s and from 8.3 ± 10.1 to 14.3 ± 6.2°/s, respectively; $p = 0.03$ and 0.04, respectively; **Fig. 4**). Postsurgical changes in VIN upon stimulation of the ipsilateral mastoid process and SCM muscle and the contralateral SCM muscle (determined by the differences in corresponding pre and postoperative MSPVs) exhibited a significant linear correlation with the change in CP values (ipsilateral mastoid process, $p = 0.03$, $R^2 = 0.35$; ipsilateral SCM muscle, $p = 0.003$, $R^2 = 0.57$; and contralateral SCM muscle, $p = 0.04$, $R^2 = 0.33$; **Fig 5A**). The change in CP values was determined by the difference in pre- and postoperative CP values, and postoperative CP values corresponded to 100%, i.e., patients showed complete canal paresis. Changes in VIN were also significantly and inversely correlated with preoperative tumor volume ($p = 0.014$ [$R^2 = 0.43$], 0.004 [$R^2 = 0.55$], 0.012 [$R^2 = 0.45$], and 0.0004 [$R^2 = 0.70$] upon stimulation of the ipsilateral and contralateral mastoid processes and SCM muscles, respectively; **Fig. 5B**). The correlations of tumor volume and change in CP value with the MSPVs of VIN upon simulation of the ipsilateral

and contralateral SCM muscles were stronger compared to those observed upon stimulation of the corresponding sides of the mastoid process. There were no significant changes in the MSPVs of VIN upon stimulation of any of the four areas between 1 and 6 months post-surgery ($p > 0.05$; **Fig. 4**).

4. Discussion

The main findings of this study can be summarized as follows. First, the sensitivity of VIN for evaluation for vestibular weakness in patients with vestibular schwannoma varied according to the stimulation site — the horizontal component of VIN was more sensitive and revealing than the vertical component. Considering the results of VIN upon stimulation at all four sites, the sensitivity of horizontal VIN was over 90%. Second, the strength of correlation of the MSPV of VIN with CP value and tumor volume also varied according to the stimulation site. The optimal stimulation sites for stronger correlation of the MSPV of VIN with tumor volume and CP value were the bilateral SCM muscles. In addition, the correlations of postoperative changes in the MSPV of VIN with preoperative tumor volume and postoperative changes in CP values were stronger when stimulation was applied to the SCM muscle. Third, after unilateral vestibular deafferentation, the sensitivity of VIN increased to 100% regardless of the stimulation site and side and persisted without changes in MSPV for 6 months post-surgery even after vestibular compensation.

4.1. Differences in sensitivity of VIN according to the stimulation site

The sensitivity of preoperative VIN in the present study was different from those reported previously. Previous studies (Kawase et al., 2011; Piras et al., 2013) that employed different stimulation sites (e.g., the mastoid bone or dorsal neck muscle) reported sensitivities of VIN

ranging from 40% to 60% for the evaluation of vestibular schwannoma, which indicates that the sensitivity of VIN varies according to the stimulation site and method in patients with vestibular asymmetry and/or vestibular schwannoma. Furthermore, there were differences in the direction of evoked nystagmus between the two previous studies — while Piras et al. reported variable directionality of VIN (fast phase towards the ipsilateral or contralateral side), Kawase et al. reported a constant direction in all patients exhibiting VIN (fast phase towards the contralateral side). Therefore, we attempted to evaluate the differences in sensitivity and magnitude of VIN upon stimulation of four different areas. In the present study, evoked nystagmus in all cases tended to beat towards the contralateral side.

Horizontal VINs evoked upon stimulation of the ipsilateral mastoid process and contralateral SCM muscle exhibited the highest (84.6%) and lowest (61.5%) sensitivities, respectively, although the difference between the two values was not statistically significant. Sensitivity of VIN was independent of CP values, and the MSPV of VIN was not significantly different among the four stimulation sites. If the sensitivities of VIN evoked upon stimulation at the four different sites are taken into consideration together, the overall sensitivity of VIN increased to 92.3%, although there were no statistically significant differences between the overall and individual sensitivity values. This indicates that stimulation of all four sites could increase the sensitivity of VIN for detection of chronic vestibular asymmetry. Vestibular asymmetry should be suspected when VIN is detected in at least one of the stimulation sites.

4.2. Correlation of CP value, tumor volume, and MSPV of VIN, and optimal stimulation sites for strong correlation

Previous studies have demonstrated the correlation between the MSPV of VIN and CP value

as well as the increase in sensitivity of VIN in patients with CP values > 50% (Ohki et al., 2003). In addition, several other reports have demonstrated the correlation between CP value and tumor size in patients with vestibular schwannomas (Suzuki et al., 2008; Andersen et al., 2015), although the correlations have not always been clear. These previous studies employed tumor diameter as a variable for analysis of correlation; however, we believe that tumor volume is more important for correlation analysis. Tumor diameter usually does not reflect the actual volume of the tumor because of the variations in 3D shape among tumors, which exert a critical influence on vestibular function. Therefore, we employed tumor volume as a parameter for correlation analysis. In the present study, CP value exhibited a weak correlation with tumor volume, although the correlation was statistically significant ($p = 0.04$; $R^2 = 0.3120$). This suggests that there might be microscopic features other than tumor volume that influence vestibular function — such as tumor origin, critical site for compression of vascular supply to the inner ear or nerve, and compression of adjacent nerve structures, which are difficult to identify at present. These factors might be responsible for the discrepancies in the correlations of the MSPV of VIN with tumor volume and CP value. Although the correlation between CP value and tumor volume was weak, and the MSPV of VIN did not vary significantly according to the stimulation site, as described by Karlberg et al. (Karlberg et al., 2003), the correlations of CP value and tumor volume with the MSPV of VIN upon stimulation of the bilateral SCM muscles were consistently stronger ($R^2 > 0.5$) compared to those upon stimulation of the corresponding mastoid processes (for correlation between the MSPV of VIN and CP value: $R^2 = 0.6$ and 0.46 [ipsilateral and contralateral SCM muscles] vs. $R^2 = 0.4$ and 0.43 [ipsilateral and contralateral mastoid processes]; for correlation between the MSPV of VIN and tumor volume: $R^2 = 0.33$ and 0.75 [for ipsilateral and contralateral mastoid processes] vs. $R^2 = 0.56$ and 0.66 [ipsilateral and contralateral SCM muscles]). This

trend was also evident in the correlations of postoperative changes in the MSVP of VIN with tumor volume and postoperative change in CP value. Although the MSPV of VIN upon stimulation of the contralateral mastoid process exhibited the strongest correlation with tumor volume, this was the only relationship involving the mastoid process that exhibited strong correlation; other relationships involving stimulation of the mastoid process exhibited weak correlation, which resulted in inconsistencies in correlation of different parameters upon stimulation of the mastoid process. The consistently stronger correlations of tumor volume and CP value with the MSPV of VIN upon stimulation of SCM muscle can be attributed to several factors. First, involvement of proprioception can result in a more delicate correlation of VIN with vestibular asymmetry and tumor volume. A previous report demonstrated that signals from the somatosensory neck and cervico-ocular reflex are increasingly used by the central nervous system during the compensatory period in patients with vestibular loss (Strupp et al., 1998; Schweigart et al., 2002). Thus, VIN evoked upon stimulation of the bilateral SCM muscles could have been modulated and enhanced by these somatosensory signals and cervico-ocular reflex, which could, consequently, have resulted in its better correlation with other parameters in comparison with VIN evoked upon stimulation of the mastoid processes in this study. Second, it is conceivable that direct bony stimulation could transmit to the tumor (through the vestibular nerve) more effectively during stimulation of the mastoid process than during stimulation of the SCM muscle, because vestibular schwannomas are in close contact with petrous bone, which could generate excitatory or inhibitory responses from the ipsilateral mastoid process, thus increasing or decreasing the VIN evoked upon stimulation of the contralateral vestibular apparatus. In fact, it has been reported that many sensory nerves are sensitive to direct mechanical stimuli (Julian and Goldman, 1962; Delmas et al., 2011); these reactions have mostly been studied in sensory

fibers distributed to the skin, which transmit touch, pain, temperature, and proprioception. In addition, a demyelinated nerve is reported to have a decreased threshold and be more sensitive to direct mechanical and other sensory stimuli, as seen in multiple sclerosis (Gillespie et al., 2000; Kesselring, 1997). Therefore, although there is no direct experimental evidence of sensitivity of the vestibular nerve to mechanical stimuli, it is possible that the demyelinated vestibular nerve (vestibular schwannoma) can be sensitive to direct vibratory stimuli from the petrous bone, which the tumor mass abuts. Furthermore, it has been reported that mechanosensitive channels such as TRPC3 and TRPC6 are distributed in the vestibulocochlear nerve (Quick et al., 2012). In addition to the possibility of demyelination as a cause for sensitivity of the vestibular nerve to vibration transmitted by direct contact with the petrous bone, the presence of these channels may be an additional mechanism through which the vibration stimulates the vestibular nerve. However, this hypothesis is likely to be applied to cases of vestibular schwannoma. Normally, the vestibular nerve has no direct contact with the petrous bone and floats in cerebrospinal fluid; most vibration stimulation applied to the mastoid process is dampened by the CSF, which significantly reduces the direct transmission of vibration stimuli to the nerve. As a result, the MSPVs of VIN upon stimulation of the bilateral mastoid processes differed significantly from those evoked upon stimulation of the corresponding bilateral SCM muscles (**Fig 3**). If the excitatory or inhibitory responses due to stimulation of demyelinated nerve fibers by vibratory stimulus had an additive effect on nystagmus induced upon stimulation of the contralateral vestibular apparatus, it could have led to the exaggeration or suppression of the original response, which consequently could have resulted in the large discrepancies and weak correlation observed in VIN responses evoked by stimulation of the mastoid processes. Therefore, for evaluation of vestibular asymmetry and tumor volume, it would be best to apply vibratory stimulus to the

bilateral SCM muscles, especially in patients with asymmetric sensorineural hearing loss with suspected cerebellopontine angle (CPA) tumors.

4.3. Correlation of postoperative changes in MSPV with tumor volume and changes of CP value

After tumor removal, all patients exhibited VIN with the fast phase directed towards the contralateral side. The MSPV of VIN after tumor removal in most cases was higher compared to that at baseline (**Fig 4**). Although the mean MSPVs of VIN associated with all four stimulation sites exhibited a tendency to increase 1 month post-surgery, only the changes in mean MSPVs of VIN upon stimulation of the contralateral mastoid process and SCM muscle were significant statistically. This can be explained by the relatively low MSPV and sensitivity of preoperative VIN upon stimulation at these sites. Postoperative change in the MSPV of VIN exhibited a linear correlation with postoperative change in CP values. Changes in the MSPVs of VIN upon stimulation of the bilateral SCM muscles were more strongly correlated with change in CP values than were those evoked upon stimulation of the corresponding bilateral mastoid processes. In addition, changes in the MSPVs of VIN upon stimulation of the SCM muscle exhibited stronger inverse correlations with preoperative tumor volume than did those evoked upon stimulation of the mastoid process. It is reasonable that changes in vestibular function after tumor removal in patients with low preoperative CP values should be greater compared to those in patients with high preoperative CP values. Additionally, patients with high preoperative CP values should exhibit a greater increase in the MSPV of VIN than those with low preoperative CP values. The strong correlations of changes in the MSPV of VIN with tumor volume and CP value are likely to have originated from the effects of proprioceptive signals from the neck muscle and direct stimulation of the vestibular nerve by vibration of mastoid bone, as already described above.

The postoperative MSPV of VIN did not change during the 6-month follow-up period. In a previous study, 15% of patients exhibited resolution of VIN at 1 month and 55% at 1 year after onset of vestibular neuritis (Choi et al., 2007). In the present study, VIN was initially observed in 92.3% of the patients and was consistently observed in all patients during the 6-month follow-up period, without significant changes in the MSPV even after resolution of subjective dizziness and restoration of dynamic imbalance by vestibular rehabilitation. In patients with partial vestibular loss, several factors, such as spontaneous recovery of peripheral vestibular function and adaptation/compensation of vestibular function, can cause resolution of VIN. However, in patients with total vestibular loss, VIN is likely to be detected in all cases, and it likely persists for at least 6 months, with minimal changes in the MSPV in spite of compensation for dynamic imbalance during the period. To our knowledge, this is the first report about the characteristics of VIN in patients with total vestibular loss after long-term follow-up. Nevertheless, studies involving larger numbers of patients with total vestibular loss and longer durations of follow-up should be conducted to evaluate the consistency and characteristics of VIN.

4.4. Clinical implications of VIN in patients with vestibular schwannoma

For detection of vestibular asymmetry in patients with suspected vestibular loss, it would best to stimulate both the mastoid process and the SCM muscle in order to increase the sensitivity of VIN. Vestibular asymmetry should be suspected if the fast phase of VIN is unidirectional under at least one condition of stimulation. However, it should be kept in mind that even asymptomatic subjects exhibit VIN upon stimulation of the SCM muscle (Park et al., 2007). However, in such cases, the direction of VIN usually varies according to the stimulation side, and the fast phase of VIN is directed opposite to the stimulation side.

If vestibular loss is suspected after stimulation of the four sites described in this study, it would be best to estimate the degree of vestibular weakness based on the MSPV of VIN upon stimulation of the SCM muscles because of its relatively high consistency and strong correlation with CP values. Stimulation of the SCM muscle is likely to be the optimal method for evaluation of acute and chronic dizziness, because the correlation between preoperative MSPV of VIN and CP value and that between postoperative changes in the MSPV of VIN and CP values represent the status of acute to subacute and chronic vestibular disorders, respectively. In addition, patients exhibiting unilateral sensorineural hearing loss along with positive VIN should be suspected for CPA tumor, although this is not always true. Stimulation of the SCM muscle in such patients is likely to be more useful during evaluation of vestibular function in the out-patient clinic, because it would provide better data for prediction of tumor volume and vestibular asymmetry. Patients with MSPV > 10°/s and > 20°/s exhibited relatively high vestibular loss (corresponding to > 70% CP value) and tumor volume (> 20 cm^3; except one outlier in the stimulation of the ipsilateral SCM muscle). The objective MSPV of VIN evoked upon stimulation of the SCM muscle for predicting CP value and tumor volume should be established in future studies involving larger populations.

Vibration-induced nystagmus after total vestibular loss was consistent during the 6-month follow-up period in all patients. Although studies with longer follow-up duration are required to validate the usefulness of the VIN test in patients with extensive vestibular loss, the present results indicate that VIN is a useful and highly sensitive method for detecting chronic vestibular asymmetry; however, given the persistence of VIN over a long time, it is not likely to be useful in monitoring vestibular compensation, especially in patients with extensive unilateral vestibular loss.

4.5. Limitation of current study

Although our data were meaningful according to our sensitivity parameters, correlation between the amount of vestibular loss and VIN, and changes in VIN after total vestibular differentiation, a limitation of this study is that we did not evaluate individual semicircular canal function using the video head impulse test. Recent advance in the field of vestibular science enables the clinical evaluation of individual vestibular apparatus. Vertical VIN sensitivity was not as high as horizontal VIN in this study. Analysis of the correlation between vertical/torsional VIN and each remnant vertical canal function could provide more precise data for predicting the amount of remnant vestibular function, as well as the origin or involvement of the tumor in the vestibular nerve. A well-designed prospective study is necessary to provide that analysis.

5. Conclusions

Evoking VIN by stimulation of the bilateral mastoid processes and SCM muscles is a useful method for detecting vestibular asymmetry. It is also likely to be useful in estimating the degree of vestibular asymmetry and volume of vestibular schwannoma, if stimulation is applied to the SCM muscle. However, given the possibility of persistence of VIN even after compensation in patients with extensive vestibular loss, one should be careful in the application of VIN for monitoring vestibular compensation in patients with vestibular loss.

Conflict of interest

None.

Financial disclosure

This study did not receive any specific grant from funding agencies in public, commercial, or not-for-profit sectors.

References

Andersen JF, Nilsen KS, Vassbotn FS, Moller P, Myrseth E, Lund-Johansen M, et al. Predictors of vertigo in patients with untreated vestibular schwannoma. Otol Neurotol 2015;36:647-52.

Choi KD, Oh SY, Kim HJ, Koo JW, Cho BM, Kim JS Recovery of vestibular imbalances after vestibular neuritis. Laryngoscope 2007;117:1307-12.

Chou CH, Wang SJ, Young YH Feasibility of the simultaneous ocular and cervical vestibular-evoked myogenic potentials in unilateral vestibular hypofunction. Clin Neurophysiol 2009;120:1699-705.

Delmas P, Hao J, Rodat-Despoix L Molecular mechanisms of mechanotransduction in mammalian sensory neurons. Nat Rev Neurosci 2011;12:139-53.

Dumas G, Karkas A, Perrin P, Chahine K, Schmerber S High-frequency skull vibration-induced nystagmus test in partial vestibular lesions. Otol Neurotol 2011;32:1291-301.

Dumas G, Perrin P, Schmerber S Nystagmus induced by high frequency vibrations of the skull in total unilateral peripheral vestibular lesions. Acta Otolaryngol 2008;128:255-62.

Gillespie CS, Sherman DL, Fleetwood-Walker SM, Cottrell DF, Tait S, Garry EM, et al. Peripheral demyelination and neuropathic pain behavior in periaxin-deficient mice. Neuron 2000;26:523-31.

Hamann KF, Schuster EM Vibration-induced nystagmus - A sign of unilateral vestibular deficit. ORL J Otorhinolaryngol Relat Spec 1999;61:74-9.

Jongkees LB, Maas JP, Philipszoon AJ Clinical nystagmography. A detailed study of electro-nystagmography in 341 patients with vertigo. Pract Otorhinolaryngol (Basel) 1962;24:65-93.

Julian FJ, Goldman DE The effects of mechanical stimulation on some electrical properties of axons. J Gen Physiol 1962;46:297-313.

Karlberg M, Aw ST, Black RA, Todd MJ, MacDougall HG, Halmagyi GM Vibration-induced ocular torsion and nystagmus after unilateral vestibular deafferentation. Brain 2003;126:956-64.

Kawase T, Maki A, Takata Y, Miyazaki H, Kobayashi T Effects of neck muscle vibration on subjective visual vertical: comparative analysis with effects on nystagmus. Eur Arch Otorhinolaryngol 2011;268:823-7.

Kesselring J. Multiple Sclerosis. 2nd ed. Cambridge: Cambridge University Press; 1997. p. 63-68.

Ohki M, Murofushi T, Nakahara H, Sugasawa K Vibration-induced nystagmus in patients with vestibular disorders. Otolaryngol Head Neck Surg 2003;129:255-8.

Park H, Hong SC, Shin J Clinical significance of vibration-induced nystagmus and head-shaking nystagmus through follow-up examinations in patients with vestibular neuritis. Otol Neurotol 2008;29:375-9.

Park H, Lee Y, Park M, Kim J, Shin J Test-retest reliability of vibration-induced nystagmus in peripheral dizzy patients. J Vestib Res 2010;20:427-31.

Park H, Shin J, Shim D Mechanisms of vibration-induced nystagmus in normal subjects and patients with vestibular neuritis. Audiol Neurootol 2007;12:189-97.

Piras G, Brandolini C, Castellucci A, Modugno GC Ocular vestibular evoked myogenic potentials in patients with acoustic neuroma. Eur Arch Otorhinolaryngol 2013;270:497-504.

Quick K, Zhao J, Eijkelkamp N, Linley JE, Rugiero F, Cox JJ, et al. TRPC3 and TRPC6 are essential for normal mechanotransduction in subsets of sensory neurons and cochlear hair cells. Open Biol 2012;2:120068.

Schweigart G, Chien RD, Mergner T Neck proprioception compensates for age-related deterioration of vestibular self-motion perception. Exp Brain Res 2002;147:89-97.

Strupp M, Arbusow V, Dieterich M, Sautier W, Brandt T Perceptual and oculomotor effects of neck muscle vibration in vestibular neuritis. Ipsilateral somatosensory substitution of vestibular function. Brain 1998;121 (Pt 4):677-85.

Suzuki M, Yamada C, Inoue R, Kashio A, Saito Y, Nakanishi W Analysis of vestibular testing in patients with vestibular schwannoma based on the nerve of origin, the localization, and the size of the tumor. Otol Neurotol 2008;29:1029-33.

Taoka N, Mori K, Yamagata Y, Shimo-oku M Cervical afferent pathway to inferior oblique motoneuron in the cat. Brain Res 1990;510:190-4.

Figure Legends

Figure 1. (A) Measurement of slow-phase velocity (SPV). Vibration-induced nystagmus (VIN) during stimulation was recorded by videonystagmography in the dark, and SPV was calculated by dividing the degree of eye movement by the time consumed. For example, the SPV of pointed nystagmus was 23.3°/s, which was arrived at by dividing 35° by 1.5 s. (B) The bithermal caloric test was performed and the canal paresis value was calculated using Jonkee's formula. (C) Cervical vestibular evoked myogenic potential (cVEMP) responses were considered present when the peaks of p13 and n23 were reproducible.

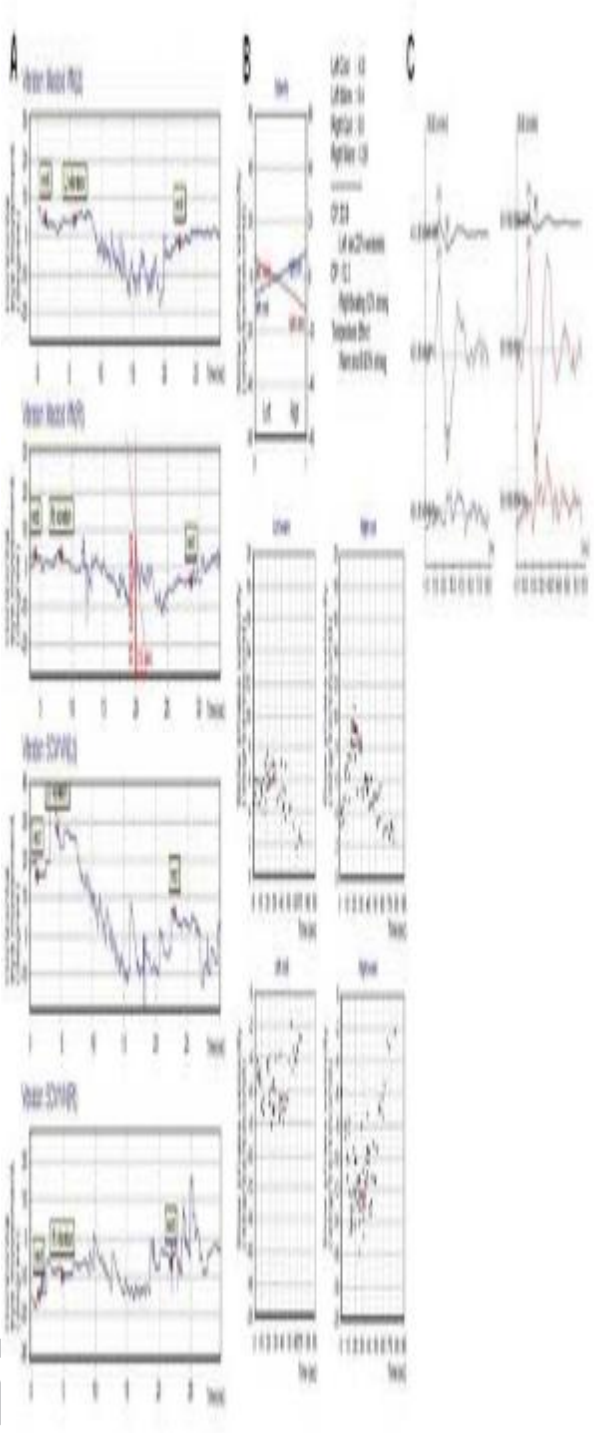
Figure 2. Correlation between tumor volume and canal paresis value. The two variables exhibited a statistically significant positive correlation with each other ($p = 0.04$, $R^2 = 0.3120$).

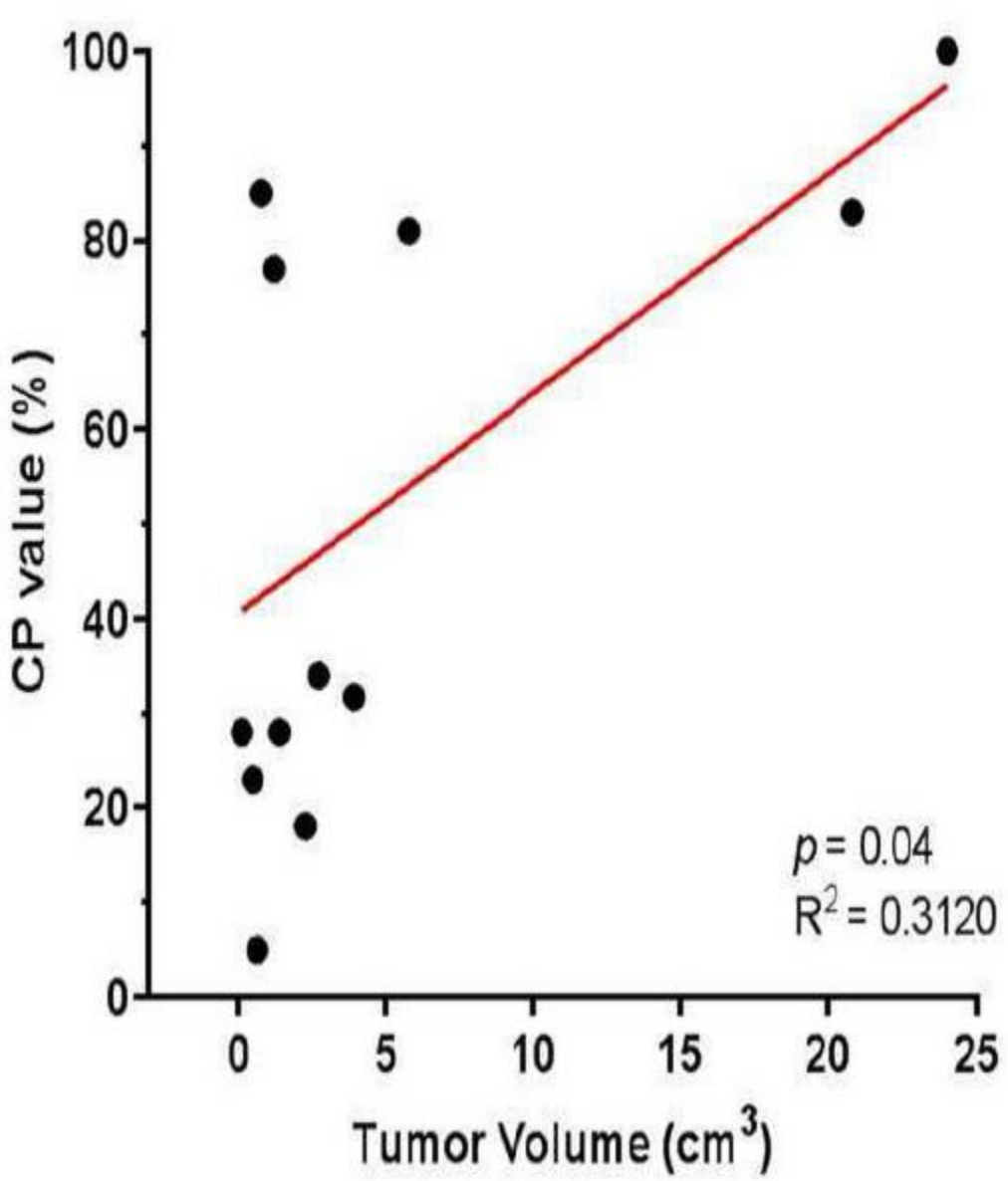
Figure 3. Correlation of preoperative maximum slow-phase velocity (MSPV) of vibration-induced nystagmus (VIN) with canal paresis (CP) value (A) and tumor volume (B). Preoperative MSPV was significantly and positively correlated with both CP value and tumor volume. Although there were no significant differences in correlation between stimulation at different sites, the MSPV of VIN exhibited stronger correlation with CP value and tumor volume upon stimulation of the sternocleidomastoid (SCM) muscle than upon stimulation of other sites.

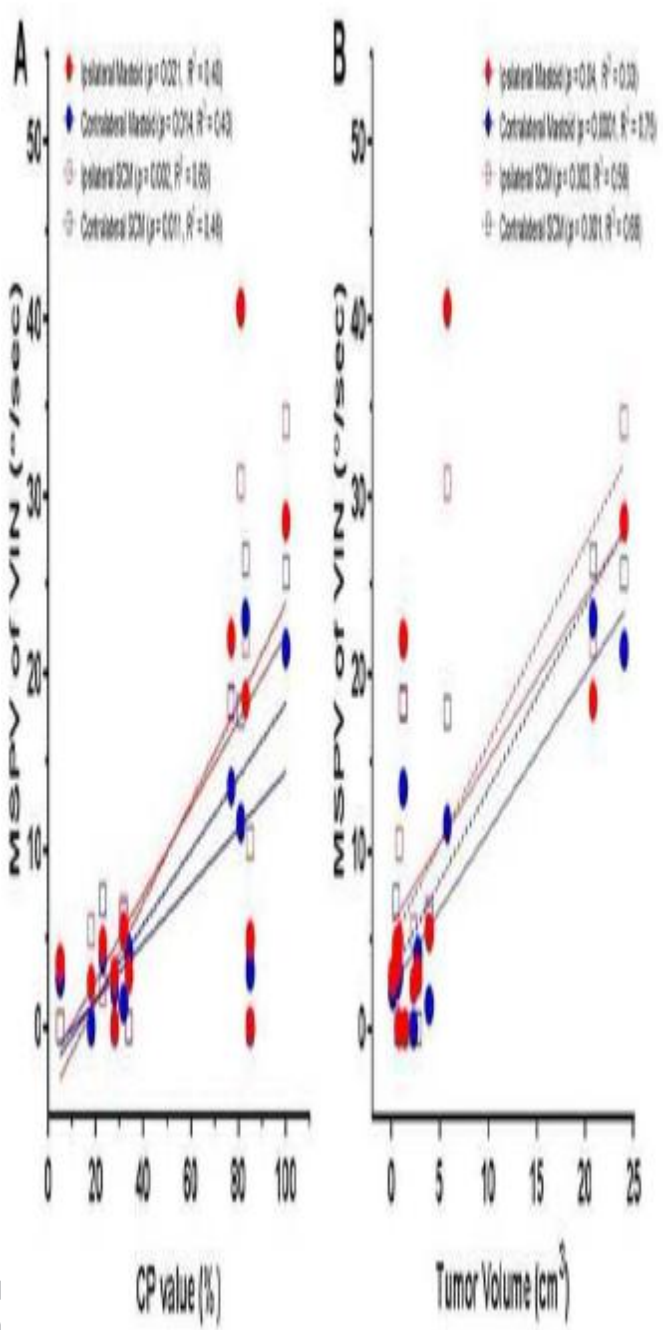
Figure 4. Serial postoperative maximum slow-phase velocities (MSPVs) of vibration-induced nystagmus (VIN) upon stimulation of the contralateral (A) and ipsilateral (B) mastoid processes and the contralateral (C) and ipsilateral (D) sternocleidomastoid (SCM)

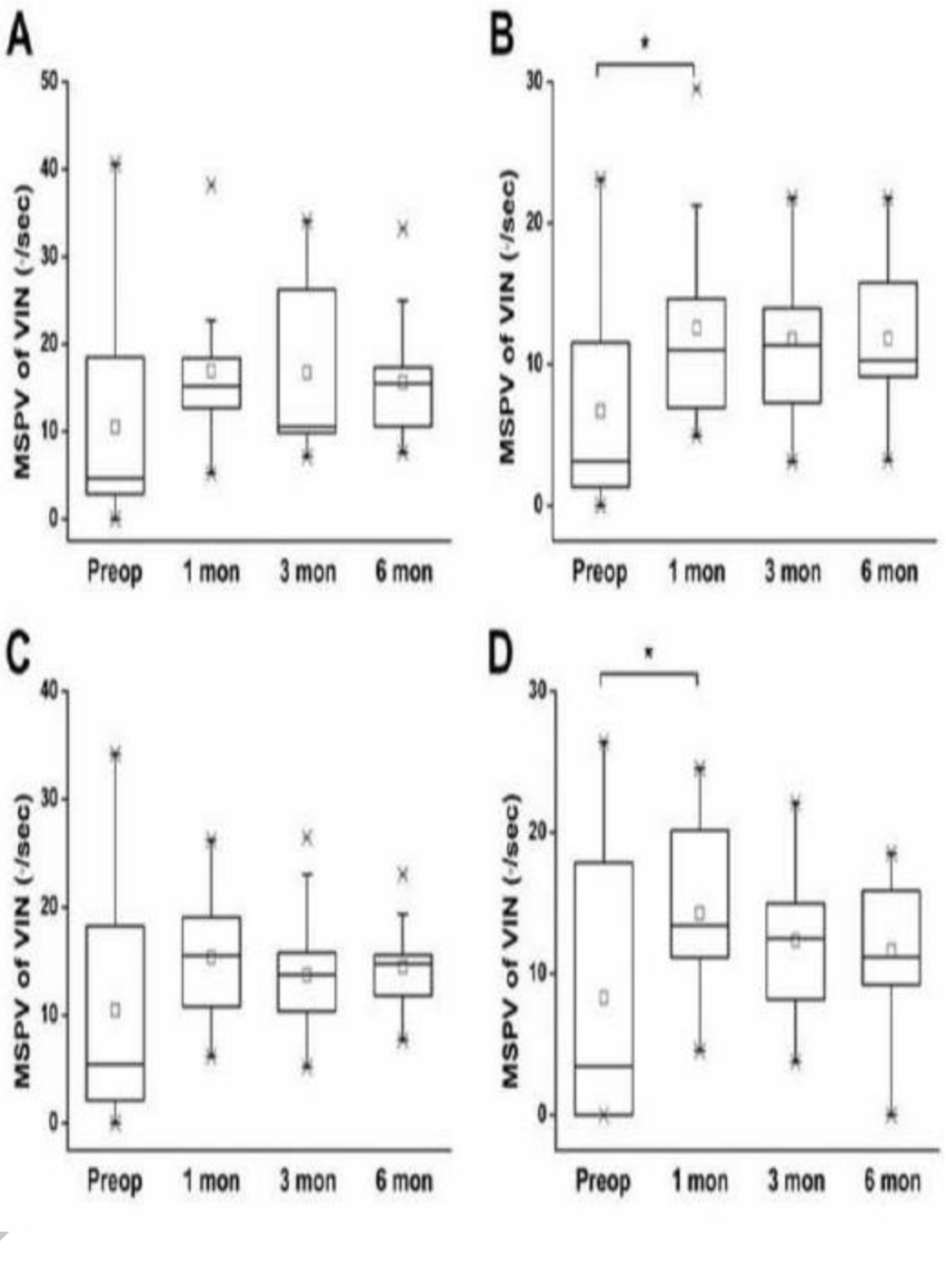
muscles. The MSPVs of VIN upon stimulation of the contralateral mastoid process and SCM muscle were significantly increased at 1 month post-surgery (p = 0.03 and 0.04, respectively). After acoustic tumor surgery, all 13 subjects exhibited VIN, which persisted without significant changes in the MSPV during the 6-month postoperative follow-up.

Figure 5. Correlation of change in vibration-induced nystagmus (VIN) with changes in canal paresis (CP) value (A) and tumor volumes (B). Changes in VIN and CP value were positively correlated, although no statistically significant correlation between the two parameters was observed upon stimulation of the contralateral mastoid process. The correlation between changes in VIN and CP value upon stimulation of the ipsilateral SCM muscle was stronger compared to that upon stimulation of the ipsilateral mastoid process. Changes in VIN and tumor volume were significantly correlated regardless of the site of stimulation; however, a stronger correlation between the two parameters was observed upon stimulation of the SCM muscle than upon stimulation of the mastoid process.




100
80
60
40
20
0
CP value (%)
0
5
10
15
20
25
Tumor Volume (cm3)
p = 0.04
R2 = 0.3120


A
B
MSPV of VNC (cm/sec)
CP value (%)
Tumor Volume (cm³)
0
20
40
60
80
100
5
10
15
20
25
30
50



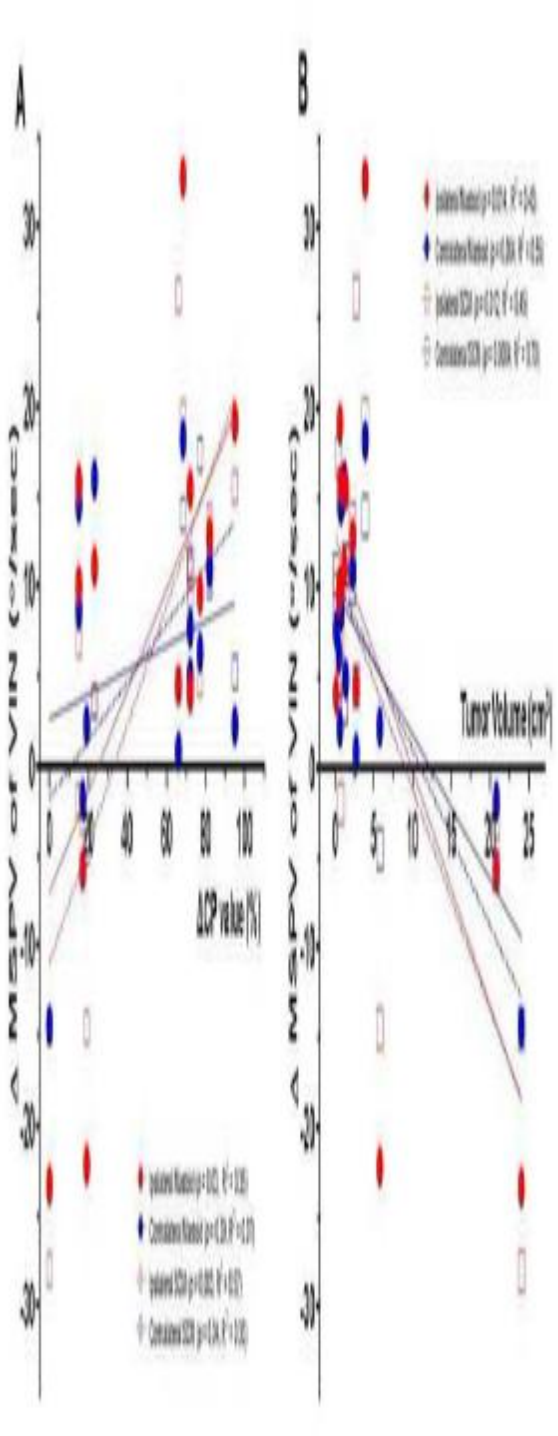


Table 1. List of patient with preoperative imaging and laboratory test findings.

Patient No.	Gender	Age	Site of Tumor	Tumor Volume (cm^3)	CP value (%)*	cVEMP‡	oVEMP¶
1	F	58	L	0.77	85.0	No Response	No Respons
2	M	51	R	3.89	31.7	No Response	No Respons
3	M	37	R	0.64	5.0	No Response	Present
4	F	52	L	2.27	18.1	Present	No Respons
5	F	36	R	1.38	28.0	Present	No Respons
6	M	49	L	0.13	28.0	Present	No Respons
7	F	54	R	5.77	81.0	No Response	No Respons
8	F	50	R	1.21	77.0	No Response	No Respons
9	F	58	R	0.77	85.0	No Response	No Respons
10	F	44	L	20.80	83.0	No Response	No Respons
11	F	50	R	2.72	34.0	No Response	No Respons
12	M	37	L	24.02	100.0	No Response	No Respons
13	F	54	L	0.49	23.0	Present	Present

*CP (canal paresis) value on bithermal caloric test was calculated using Jonkees' formula (Jongkees et al., 1962); ‡cVEMP (cervical vestibular evoked myogenic potential) response was considered present when the peaks of p13 and n23 were reproducible; ¶oVEMP(ocular vestibular evoked myogenic potential) response was considered present when the peaks of nI and pI were reproducible; †Mean hearing threshold was calculated as the average value of thresholds at four frequencies (500, 1000, 2000, 4000 Hz) in pure tone audiometric evaluation. There was no response to the stimulus in bithermal caloric testing, cVEMP, oVEMP, using pure tone audiometry on the ipsilateral side postoperatively.