

RESEARCH ARTICLE

Comparison of vestibulo-ocular reflex instantaneous gain and velocity regression in differentiating the peripheral vestibular disorders

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Abstract

Background and Aim: Vestibulo-ocular reflex (VOR) gain is the central variable for estimating VOR function, and there are several algorithms to calculate gain. The current study aimed to investigate the ability of VOR instantaneous gain and velocity regression as a possible physiological biomarker for differentiating peripheral vestibular disorders of various etiologies.

Methods: Video head impulse test (vHIT) was performed on 27 healthy volunteers (normal group) and 29 patients (pathologic group) including three types of peripheral vestibulopathies including unilateral Meniere's disease, unilateral superior vestibular neuritis, and bilateral vestibulopathy.

Results: Analyses indicated that the mean VOR instantaneous gain at 40 ms, 60 ms, 80 ms, and velocity regression at 100 ms differed significantly within the normal and pathologic groups. Also, complete normative data for VOR at 40 ms, 60 ms, and 80 ms instantaneous gain has been provided for the vHIT.

Conclusion: The findings of this study

suggest that different vestibular pathologies have a distinct effect on cupular-endolymph function, which could be tracked by VOR dynamic changes.

Keywords: Vestibulo-ocular reflex; vestibular neuritis; Meniere's disease; bilateral vestibulopathy; head impulse testing

Introduction

Neurophysiological investigation of oculomotor responses to quick head movements is now widely used as an easy and noninvasive method for correct diagnosis of peripheral and central vestibular disorders. The head impulse test (HIT), first reported by Halmagyi and Curthoys, can be used to identify the vestibulo-ocular reflex (VOR) dysfunction by observing the overt catch-up saccades that occur in the opposite direction of the head movement [1]. In addition, covert catch-up saccades can also occur during head movement to compensate the VOR deficit on the affected side. Observation of the covert catch-up saccades requires search coil or video head impulse testing (vHIT) [2]. Search coil is the gold standard for quantification of VOR dynamics. However, it has several limitations compared to vHIT when used in clinical settings. Recent studies have shown a

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significant correlation between the coil technique and vHIT in the quantification of VOR dynamics [2-4], and hence, vHIT has practical use in clinics.

The main characteristics of vHIT in identifying the vestibular deficits are VOR gain reduction and overt catch-up saccades. Different methods of VOR gain calculation have been reported in the literature; most of these methods are mainly derived from magnetic-field coil systems. Instantaneous gain is referred to as the calculation of gain at any given time after head impulse [5,6], e.g. at 60 ms. In addition to the instantaneous gain, the regression slope between the eye and head velocity can be calculated for a length of time after initiation of head impulse [6,7]. Also, a more recent technique called area or position gain has been introduced by MacDougall et al., in which the VOR gain is calculated as a function of the area under the desaccaded eye velocity and the head velocity curve [8]. Determining the VOR gain cut-offs in normal subjects by using vHIT instruments suggest similar results among different gain calculation methods. In the study by Mossman et al., instantaneous gain cut-off (two standard deviations below mean) was 0.79 at 80 ms [9]. Blöndow et al. also reported the instantaneous gain cut-off of 0.79 for 40-80 ms [10]. Luis et al. reported a 0.78 low gain cut-off for regression gain [11], and Pérez-Garrigues et al. suggested 0.80 cut-offs for position gain [12]. So far, however, there has been little discussion on the comparison of the abilities of these calculation methods to detect defective VOR responses in peripheral vestibular dysfunctions. By measuring the gain dynamics in various pathologies, it could be possible to clarify the physiological mechanism responsible for generating the oculomotor responses to head impulses. Therefore, the purpose of the current study was to quantify the VOR response dynamics in different peripheral vestibular disorders by using the instantaneous gain and velocity regression algorithms. The author's premise was that the relationship between

eye velocity and head velocity would be different in distinct peripheral vestibular etiologies.

Methods

Participants

Twenty seven healthy volunteers (13 women and 14 men), aged 18-75 years (mean=41.07±13.73), and 29 patients (13 women and 16 men), aged 25-86 years (mean=47.20±14.28), with three types of peripheral vestibulopathy were registered to participate in the experiment. Patients group included unilateral Meniere's disease (MD) (n=16), unilateral superior vestibular neuritis (VN) (n=11), and bilateral vestibulopathy (BV) due to systemic gentamicin therapy (n=2).

None of the participants in the healthy control group had a history of auditory, vestibular, visual, or neurological problems. All had normal middle ear function (supported by immittance findings), normal vestibular evoked myogenic potentials normal caloric response, and normal vHIT at the plane of horizontal semicircular canals.

Diagnostic criteria for unilateral superior VN were based on a single (or a few) rotatory vertigo attack(s) lasting for several hours to several days, damaged peripheral vestibular function proven by pathological side difference (>25%) at caloric testing, normal vHIT at the plane of posterior canals, and no cochlear signs or other neurological signs [13]. Diagnosis of unilateral MD was based on the guidelines published by the American Academy of Otolaryngology, Head, and Neck Surgery [14]. In cases of BV, the diagnosis was based on the positive history of ototoxic medication, findings on physical examination, and the bilateral weakness at bithermal caloric testing. None of the patients had central vestibular disorders or visual impairment.

All procedures performed in this study were in accordance with the ethical standards of the Iran University of Medical Sciences Research Committee and with the Declaration of

Helsinki 1964 and its later amendments. Informed consent was obtained from all individual participants included in the study.

Video head impulse test procedure

The oculomotor responses were measured by EyeSeeCam™ System (EyeSeeTec GmbH, Germany). EyeSeeCam vHIT has a monocular camera, interchangeable between left and right eye, and an Inertial Measurement Unit gyroscope, which tracks the head movements in all planes. After firmly fitting the goggle on the participant's head, the eye image was adjusted. The subjects were seated 1.5 meters from the wall, and the system was calibrated by having them to fixate at luminous dots projected by a head-fixed laser at predefined horizontal and vertical 8.5 degree angles. For obtaining the VOR responses, the subjects were instructed to focus on the target on the midline and at eye level and to relax their neck muscles throughout the impulses. At least ten valid high velocities (150-300 degree/s) and low amplitude (10-20 degree) head impulses in yaw and to each side were applied manually by the main examiner. Head impulses were unpredictable in direction and time. In order to avoid interference between successive head impulses, breaks of random durations on the order of at least 2 seconds in between individual head movements were introduced.

Data analysis

Data analysis was performed offline using EyeSeeCam software. Head impulses were automatically detected according to the velocity criterion [15]. The VOR instantaneous gain (defined as the ratio of the eye and head velocity) was calculated as median values in windows of ± 10 ms at 40 ms, 60 ms, and 80 ms after head movement initiation. In addition to the instantaneous gains, the velocity regression (the absolute values of eye velocity over the head velocity between 0 and 100 ms post-impulse onset) was also computed to represent average VOR gains. After record-

ing all traces, the artifact filter was applied in order to remove the artifact traces, and the remaining artifacts and outliers were deleted manually.

Paired t-test was used to compare the VOR gains between right and left impulses in both the healthy and patient groups. Instantaneous gain and velocity regression between the groups were analyzed using multivariate analyses of variance (MANOVA). Effect sizes were estimated using the partial eta squared (η^2) statistic. For significant F values, Tukey post-hoc test was applied. All statistical tests were considered significant at $p \leq 0.05$. Data processing was performed using IBM SPSS 22.0 (SPSS Inc., Chicago, USA).

Results

Based on the evaluation of 56 participants, VOR instantaneous gain (at 40 ms, 60 ms, and 80 ms) and velocity regression gain were established as shown in Table 1. The lower limit of VOR gain was set at 2SD below the mean. No significant differences were found between VOR gain with right and left impulses in healthy subjects and BV group (paired t-test; $p > 0.05$), and the cumulative results are reported. However, in both MD and VN groups, VOR gain was lower with ipsilesional impulses as compared to contralesional impulses. Therefore, VOR gain from the affected side has only been reported. Fig. 1 shows an example of vHIT findings in a unilateral MD case. As can be seen from the upper panel (A), there is a gain reduction in the affected left side, and multiple covert and overt catch-up saccades are generated before and after stopping the head movement. However, for every head rotation activating horizontal canal on the healthy right side, the eye velocity response is nearly normal. An interesting finding was that in most of the cases of unilateral peripheral vestibulopathies, anti-compensatory quick eye movements (AQEM) were observed during contralesional impulses (Fig. 1). These quick eye movements were noticed in the direction of the head movements and could be considered

Table 1. Vestibulo-ocular reflex gain and cutoff values in healthy and pathologic groups

Population	Mean of standard deviation of horizontal vestibulo-ocular reflex (cutoff)			
	VOR40	VOR60	VOR80	VORr
Healthy group (n=27)	1.02±0.13 (0.76)	0.95±0.08 (0.79)	0.89±0.07 (0.75)	0.99±0.06 (0.87)
MD group (n=16)	0.83±0.21 (0.41)	0.73±0.19 (0.35)	0.74±0.17 (0.40)	0.80±0.20 (0.40)
VN group (n=11)	0.48±0.19 (0.10)	0.36±0.23 (0.00)	0.33±0.26 (0.00)	0.39±0.27 (0.00)
BV group (n=2)	0.58±0.12 (0.34)	0.58±0.06 (0.46)	0.60±0.02 (0.56)	0.68±0.00 (0.68)

VOR; vestibulo-ocular reflex, VORr; vestibulo-ocular reflex regression, MD; Menier disease, VN; vestibular neuritis, BV; bilateral vestibulopathy

as a peripheral vestibular sign in spontaneous nystagmus [16]. Three-dimensional (3D) reconstruction of the vHIT parameters for this MD case is also presented in Fig. 1, panel B. Multivariate ANOVA indicated that mean VOR instantaneous gain and velocity regression differed significantly within the normal and pathologic groups ($F_{(12,129)}=7.89$; $p<0.0001$; Wilk's $\Lambda=0.234$; $\eta^2=0.383$). Tests of between-subjects effects showed that different types of peripheral vestibulopathies had a statistically significant effect on median VOR gain 40 ms ($F_{(3,52)}=26.16$; $p<0.0001$; partial $\eta^2=0.60$), 60 ms ($F_{(3,52)}=38.27$; $p<0.0001$; partial $\eta^2=0.68$), 80 ms ($F_{(3,52)}=32.99$; $p<0.0001$; partial $\eta^2=0.65$), and regression gain 100 ms [$F_{(3,52)}=33.61$; $p<0.0001$; partial $\eta^2=0.65$]. Post hoc tests using Tukey's correction revealed that median gains at 40 ms were significantly different between normal group and all other vestibulopathies ($p<0.005$), and between MD and VN groups ($p<0.005$). However, no significant differences were found between BV group and MD group ($p=0.25$) or VN group ($p<0.88$). Moreover, median gain at 60 ms was significantly different between the normal group and MD ($p<0.005$) and VN groups ($p<0.005$), but not for BV group ($p=0.01$). The median gain at 60 ms was also significantly different between MD and VN groups ($p<0.005$), but not for BV group, compared to all other groups

($p\geq 0.01$). Analysis of median gain at 80 ms also revealed a significant difference between VN group with both normal and MD groups ($p<0.005$). However, there were no significant differences between other conditions ($p\geq 0.02$).

Finally, multiple comparisons of velocity regression gain at 100 ms showed a statistically significant difference between normal group versus MD and VN groups ($p<0.005$) but not for BV group ($p=0.06$). Regression gain at 100 ms also differed significantly between VN and MD groups ($p<0.005$), although this parameter was not significantly different between BV group versus all other test groups ($p\geq 0.06$).

Discussion

Several reports have shown that the traditional calculation of VOR gain is not an adequate measure of vestibulo-ocular reflex, even in healthy subjects [17]. VOR gain is traditionally calculated using eye velocity at peak head acceleration. However, peak head acceleration is exactly where the greatest goggle slippage can occur. Considering these limitations, there is a trend to use most of the data for an impulse to calculate VOR gain. Instantaneous and regression gains are among the best-proven methods for calculating gain, and many clinicians base their diagnosis by simply looking at these numbers. The main question in this study sought

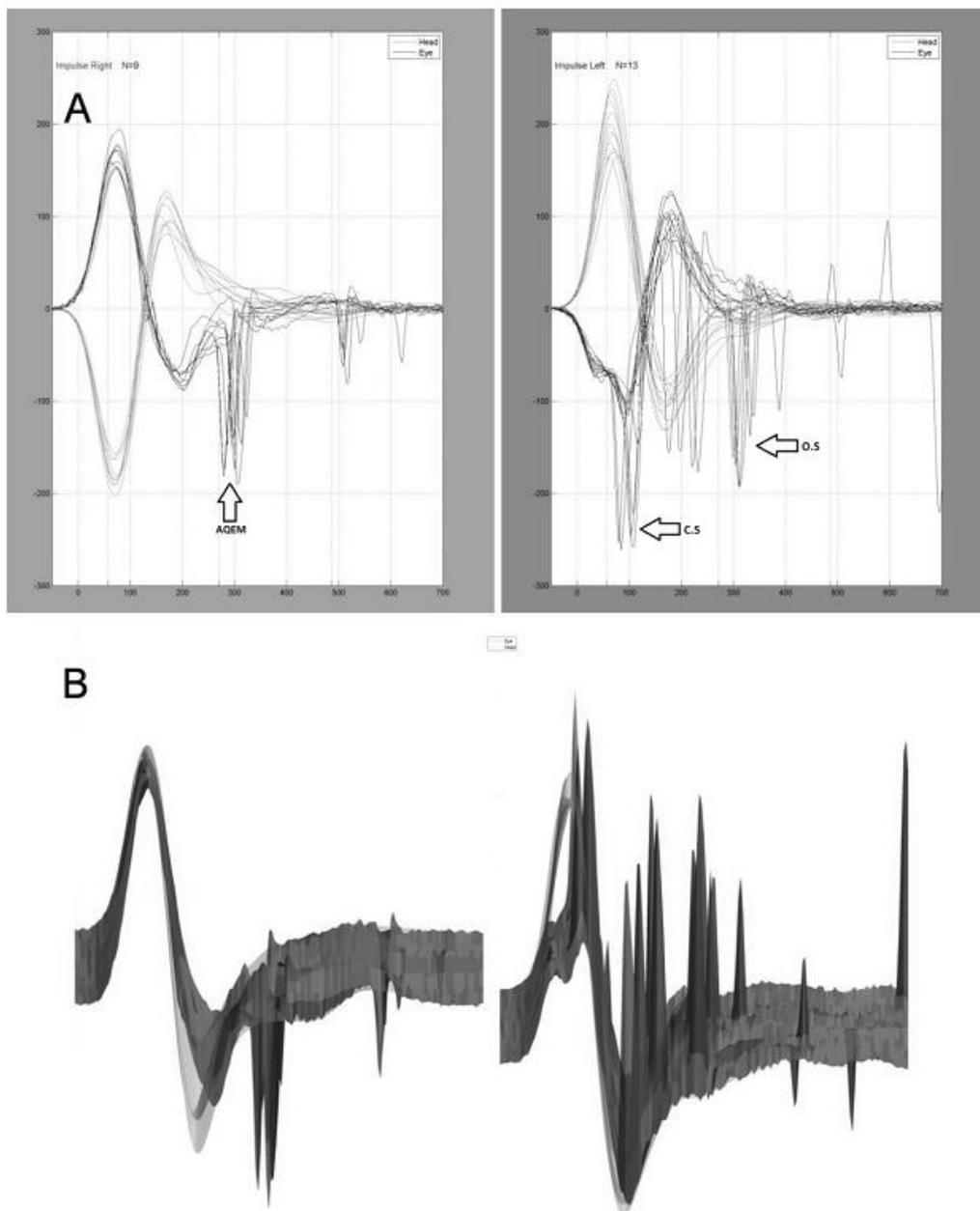


Fig. 1. An example of vHIT findings in a unilateral MD case. Two-dimensional views of eye and head movements to the affected left side and healthy right side (A). Refer to the text for further explanation. At the bottom, 3D vHIT reconstruction of the same case is shown in 700 ms time domain (B). AQEM; anti-compensatory quick eye movements, CS; covert saccades, OS; overt saccades.

to determine the possible ability of these calculation methods to differentiate pathologic VOR responses in distinct peripheral vestibular etiologies. The results confirmed that VOR gain dynamics are susceptible to different patient conditions. Gain reduction is considered as the main

variable for estimating VOR function that could separate the normal group from pathologic groups. Insignificant difference between the normal and BV group at VOR80 and VORr may partly be explained by the lack of adequate sample size. Instantaneous gains at 40 ms, 60 ms, 80 ms, and velocity regression

at 100 ms were also significantly different between MD and VN groups. These results seem to be consistent with other research works, which reported different vHIT findings in MD and VN patients [18,19]. Manzari et al. suggested that VN causes reduced horizontal VOR gain for head turns to the affected side, whereas in MD attack, horizontal VOR gain for head turns to the affected side is normal or even enhanced [19]. However, the current study could not demonstrate ipsilesionally normal or enhanced vHIT gain values in MD patients. This rather contradictory result may be due to a different stage of the disease in our patients. One of the major limitations in the neurophysiological assessment of vestibular patients is that the actual level of vestibular function is unknown. During the stages of the vestibular disorder, cupular-endolymph biomechanical changes can occur, leading to different velocity profiles, which can be assessed by dynamic gain changes during head impulses [20]. In unilateral VN patients, gain decrease in the affected side was the main characteristic, and no one showed normal vHIT results. The former finding is in line with those of previous studies [1,2,10], but the latter finding differed from the findings of some of the previous researches [10]. This result may be explained by the fact that horizontal VOR deficiencies in VN patients are frequency-dependent [21,22]. Another explanation may be that central compensation during recovery stage can influence the vHIT results [10,23]. These findings cannot be extrapolated to all patients and must be interpreted with caution because, as noted before, we can never be sure about the actual level of the vestibular function unless in complete vestibular nerve section.

To the best of our knowledge, complete normative data for VOR at 40 ms, 60 ms, and 80 ms instantaneous gain is not available in the literature for the vHIT. Blödown et al. reported a 0.96 mean for VOR60 in 20 healthy controls [10]. Mossman et al. also reported a 0.94 and 0.97 mean for VOR60 and VOR80,

respectively, in 60 participants [9]. Moreover, Versino et al. reported a 0.98 mean for VOR60 in 13 subjects [24]. In addition to providing instantaneous gain and velocity regression normative data in healthy adults, the established norms were comparable to those reported in the literature [10,22,25].

One interesting finding was the observation of AQEM in most unilateral vestibulopathies. Although this finding was not analyzed further for occurrence rate, latency, amplitude, or velocity, the growing evidence supported the utility of AQEM in differentiating the peripheral and central origin of spontaneous nystagmus [16,26]. Further studies in peripheral unilateral and bilateral vestibulopathies, which take this parameter into account, will need to be undertaken.

Conclusion

In addition to providing normative data and cutoff values for VOR instantaneous gain and velocity regression and adding to a growing body of literature on vHIT testing, the findings of this study suggested the utility of VOR gain as a neurophysiological biomarker for differentiating three common peripheral vestibular disorders of different etiologies. The major limitations of this study are the small sample size, especially for BV group, and the different time course of disease among patients.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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