



Original Article

# Increased Velocity Storage in Subjects with Meniere's Disease

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**OBJECTIVE:** Velocity storage mechanism is a multisensory rotation estimator; it compensates for errors in the information provided by the peripheral vestibular organs by means of an adjustment in the duration of the vestibular signal. The aim of this study was to determine the activity of the velocity storage mechanism in the presence of a labyrinthine disorder, using galvanic vestibular stimulation to cause direct activation of the vestibular afferent neurons.

**MATERIALS and METHODS:** Forty-one subjects with definite Meniere's disease (MD) and 36 healthy volunteers were evaluated using a 20-s galvanic vestibular stimulation.

**RESULTS:** We found a post-stimulus nystagmus overshoot exclusively in subjects with MD (47% in subjects with unilateral disease and 82% in subjects with bilateral disease), but no overshoot in healthy subjects.

**CONCLUSION:** Because post-stimulus nystagmus overshoot is caused by the velocity storage mechanism, this finding suggests an increase in the velocity storage in subjects with a labyrinthine disease.

**KEYWORDS:** Velocity storage, vestibular, eye movement, vestibulo-ocular reflex, Meniere disease

## INTRODUCTION

Vestibular research has reported the existence of a central neural process called the velocity storage mechanism (VSM) [1-3]. This mechanism compensates (by means of a central processing) for inaccuracies in the information provided by the peripheral vestibular sensors, thus achieving a more accurate estimate for rotation velocity, inertial motion, and orientation relative to the earth-vertical axis. This is accomplished through a prolongation of vestibular signals, which can be observed in the vestibular nuclei [4]. This prolongation of signals caused by VSM can manifest in multiple ways; an easily observable one is the nystagmus overshoot after the cessation of an optokinetic stimulus, known as the optokinetic after nystagmus (OKAN) [5].

A previously published study [6] entitled "Velocity storage in labyrinthine disorders" concluded that unilateral peripheral vestibular loss was associated with a complete loss of velocity storage for canal input. This conclusion was made after observing a decrease in the time constant of the vestibulo-ocular reflex (VOR) in subjects after surgical resection of an acoustic neuroma when tested using chair rotation. Our study complements the research conducted by those authors, through the evaluation of patients with Meniere's disease (MD).

To properly recognize the activity of VSM in labyrinthine disorders, we selected subjects with MD as a model of labyrinth disease, and we used galvanic vestibular stimulation (GVS) to cause a direct activation of the vestibular afferent neurons [7]. The advantage of GVS is that it stimulates both vestibular nerves symmetrically even in the presence of a labyrinth disease, avoiding the risk of asymmetrical stimulation of the vestibular nuclei [8].

The main aim of this study was to investigate the differences in the post-galvanic responses (a response caused by VSM) in darkness between subjects with definite MD and healthy volunteers and to determine the extent to which VSM can be affected by the presence of a labyrinthine disorder.

## MATERIALS and METHODS

### Subjects

Seventy-seven subjects, comprising 41 subjects with definite MD according to AAO-HNS 1995 criteria [9] and 36 healthy volunteers, gave their informed consent to participate in the study and confirmed that none of them took medication that would interfere with

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their vestibulo-ocular motor function. No subject had spontaneous nystagmus at the beginning of the session.

The experiment was performed in a tertiary referral hospital and was approved by our institutional ethics committee (approval code FPNT-CEIB-04A).

### Galvanic Stimulation

Galvanic stimulation was delivered via surface electrodes of 660 mm<sup>2</sup> (Natus JellyTab; Natus Medical Incorporated, Mundelein, IL, USA) placed over each mastoid process.

A battery-powered galvanic stimulator (IDEE; Maastricht University, Maastricht, The Netherlands) was used for all subjects. A 4 mA constant DC current was delivered to the electrodes by pressing the “stimulate” button and released from the “stimulate” button switch when the current was switched off. The rise and fall time of the current source was approximately 0.5 s. The output current was reversed in polarity by means of a selection switch.

### Procedure

Subjects were evaluated in a dark room, seated in a padded chair, using a 50 Hz sampling infrared videonystagmography (VNG Ulmer Synapsys; Marseille, France); the complete absence of possible sources of light was confirmed before the start of the recordings to ensure the absence of visual fixation. The subjects Reid’s line (imaginary line between the inferior margin of the orbit and the upper margin of external auditory meatus) was positioned in an approximately earth-horizontal plane, allowing for comparable orientation across subjects.

Testing was performed in darkness in a single session. There were two conditions, each consisting of 10 s of eye movement recording prior to the onset of GVS, followed by 20 s of recording during GVS delivery. A post-stimulus recording of 40 s was performed to permit an accurate assessment of the offset responses. The first condition was cathode left anode right (CLAR) and the second was anode left cathode right (ALCR).

For each recording, the horizontal slow phase velocity (HSPV), vertical slow phase velocity (VSPV), and torsional slow phase velocity (TSPV) were measured automatically and registered for every eye movement. To be considered nystagmus, an eye movement should be composed of more than five fast and slow phase eye movements that occurred consecutively at a velocity faster than 1 deg/s and at a frequency higher than 1 Hz.

An overshoot or reversal of the responses at stimulus offset was defined as an eye movement of opposed direction, composed of more than five fast and slow phase eye movements that occurred consecutively at a velocity faster than 1 deg/s and a frequency higher than 1 Hz.

As all subjects had nystagmus decay, during both GVS delivery and after GVS offset, the time constant was determined by measuring the time it took the horizontal velocity to reach 37% of its maximum value (a simplified approximation to the decay constant 1/e ≈ 36.8%).

**Table 1.** Summary of the demographic features of all subjects

	Healthy volunteers (n=36)	Unilateral MD (n=30)	Bilateral MD (n=11)	p
Age (years)	47.6±12.1*	57.9±13.6	57.3±16.5	0.005
Gender				
Male	16	9	9	0.012
Female	20	21	2	0.012

\*Data are expressed as mean±standard deviation (SD)  
MD: Meniere's disease

In this study, we did not determine the ocular torsional position because the eye movements, particularly in torsion, can oscillate ±1 deg over a period of as much as 60 s<sup>[8]</sup>, resulting in a relatively large variation in the estimate of position if measured over short periods.

### Statistical Analysis

Symmetry was defined as the absence of differences in the slow phase velocity of nystagmus between the CLAR and ALCR conditions. To assess symmetry, either a t test or a Mann–Whitney Rank Sum Test were performed (the first one if the samples were accepted into the Shapiro–Wilk normality test and Equal Variance Test or the second one if the samples failed any of the mentioned tests).

Data obtained were analyzed using the statistical program SigmaPlot (Systat Software; San Jose, CA, USA).

### RESULTS

A total of 77 subjects were studied. Table 1 shows an overview of the demographic features of the subjects.

The typical response to GVS onset was a mainly torsional and horizontal nystagmus, both with slow phases directed away from the cathode. Some subjects also showed a nystagmus overshoot immediately after GVS offset, with a horizontal slow phase directed in the opposite direction of the intra-stimulus nystagmus in all cases. All the subjects reported a mild to moderate burning sensation at the stimulation site, and two subjects reported headaches that lasted several hours (both subjects belonged to the healthy volunteers group).

### Symmetry

Surface GVS onset produced nystagmus in 58 of 72 (80.6%) recordings performed in healthy volunteers (5 subjects showed no nystagmus in both conditions, 3 subjects showed no nystagmus in the ALCR condition, and 1 subject showed no nystagmus in the CLAR condition), and there were no differences in the magnitude of the eye movement responses, once the polarity was reversed, for either HSPV (p=0.568), VSPV (p=0.350), or TSPV (p=0.545). In subjects with unilateral MD, GVS onset produced nystagmus in 54 of 60 (90%) recordings (2 subjects showed no nystagmus in both conditions and 2 other subjects showed no nystagmus in the CLAR condition), and there were no differences in the magnitude of the eye movement responses, depending on the condition, for either HSPV (p=0.344), VSPV (p=0.625), or TSPV (p=0.336). Similarly, GVS onset in subjects with bilateral MD produced nystagmus in 18 of 22 (81.8%) recordings (1 subject showed no nystagmus in both conditions and 2 other subjects showed no nystagmus in the ALCR condition), and there were no differences in the magnitude of the eye movement responses, de-

**Table 2.** Summary of the post-stimulus responses

	Post-stimulus inversion	Time constant (sec)
Healthy volunteers	Absent	-
Unilateral MD	Present in 46.7% of subjects (28.3% of the recordings)	5
Bilateral MD	Present in 81.8% of subjects (54.5% of the recordings)	7

MD: Meniere's disease

**Table 3.** Summary of the characteristics of subjects with Meniere's disease

	Subjects with no nystagmus overshoot (n=18)	Subjects with nystagmus overshoot (n=23)	p
Years from disease onset	3 (2–9.75)*	8 (3–24)	0.011
Stage of MD	3 (2–3.25)	3 (3–4)	0.228
Maximum intra-stimulus SPV reached	5.7 (2.4–8.65)	5.8 (2.85–7.6)	0.775
Vertigo spells in the last 6 months	1.5 (0.0–4.5)	1.0 (0.0–7.0)	0.851

\*Data are expressed as median and 25<sup>th</sup>-75<sup>th</sup> percentiles in parentheses. MD: Meniere's disease; SPV: slow phase velocity

pending on the condition, for either HSPV ( $p=0.171$ ), VSPV ( $p=0.105$ ), or TSPV ( $p=0.156$ ). Figure 1 displays the velocity means for each group and condition.

**Nystagmus Overshoot**

Surface GVS offset produced reversed direction nystagmus of the horizontal and the torsional component (vertical component generally not affected) in some subjects.

In healthy volunteers, no nystagmus overshoot was observed in any of the 72 recordings. In subjects with unilateral MD, GVS offset produced a nystagmus overshoot in 17 of 60 (28.3%) recordings (3 subjects showed nystagmus overshoot in both conditions, 6 subjects in the CLAR condition, and 5 subjects in the ALCR condition), and there were no differences in the magnitude of the eye-movement responses, depending on the condition, for either HSPV ( $p=0.441$ ), VSPV ( $p=1.000$ ), or TSPV ( $p=0.563$ ). GVS offset in subjects with bilateral MD produced nystagmus overshoot in 12 of 22 (54.5%) recordings (3 subjects showed nystagmus overshoot in both conditions, 3 subjects in the CLAR condition, and 3 subjects in the ALCR condition), and there were no differences in the magnitude of the eye movement responses, depending on the condition, for either HSPV ( $p=0.507$ ), VSPV ( $p=0.403$ ), or TSPV ( $p=0.272$ ). Table 2 shows a summary of the frequency of occurrence of the post-stimulus responses.

In summary, 47% of subjects with unilateral MD and 82% of subjects with bilateral MD developed nystagmus overshoot at the stimulus offset. There were no significant differences between subjects who developed overshoot and those who did not with respect to the stage of MD, intra-stimulus SPV reached, or vertigo spells in the last 6 months. However, there was a significant difference regarding the years from disease onset, as shown in Table 3.

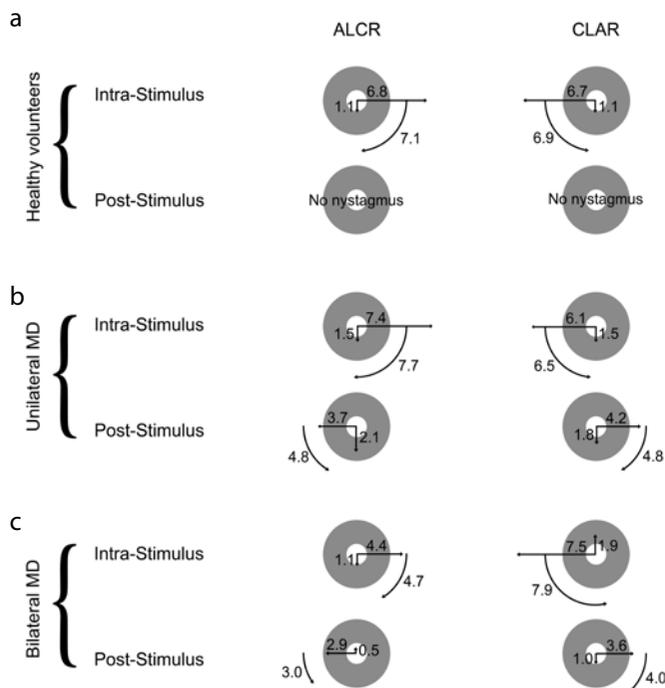
**Time Constant**

During surface GVS, all subjects who developed nystagmus reached a quite stable SPV (in every three directions measured); however, with the time constants not measurable because of the absence of a step response decay during the 20-s intra-stimulus recording (none of the subjects showed a step decrease to less than 37%).

Galvanic vestibular stimulation offset produced a nystagmus of a reverse horizontal direction, rapidly reaching a peak overshoot before decaying. Subjects with unilateral MD showed a median time constant of 5 s, whereas subjects with bilateral MD showed a median time constant of 7 s. Healthy volunteers showed no overshoot (Table 2).

**DISCUSSION**

The results of this study show symmetry in both the intra-stimulus and post-stimulus responses in healthy subjects and in subjects with MD. These results agree with the observations made by MacDougall et al. in 2003 [8] and further support the use of GVS in our study to provide a similar signal to both vestibular nuclei. GVS induces direct activation of the primary vestibular afferent neurons, as concluded by Spiegel and Scala [10] after conducting animal experiments in 1943. Subsequent studies showed that GVS acts on the distal part of the vestibular nerve, specifically in an area called the spike trigger zone, which is the site of onset of natural action potentials [11-13]. Responses to very low galvanic stimuli in healthy subjects support the hypothe-



**Figure 1. a-c.** Means of the maximum HSPV (horizontal arrows), VSPV (vertical arrows), and TSPV (semicircular arrows) responses to GVS; values in deg/s. ALCR: anode left cathode right condition. CLAR: cathode left anode right condition. (a) Results in healthy volunteers; none of them had nystagmus overshoot at stimulus offset. (b) Results in unilateral Meniere's disease subjects; 47% of subjects developed nystagmus overshoot at stimulus offset. (c) Results in bilateral Meniere's disease subjects; 82% of subjects developed nystagmus overshoot at stimulus offset

sis of the spike trigger zone as the site of action of GVS in humans<sup>[14]</sup>. The most interesting finding in our study was the occurrence of overshoot exclusively in subjects with MD. In our subjects (using a 4 mA bilateral stimulation during 20 s), overshoot appears in 0% of healthy volunteers, in 47% of subjects with unilateral MD, and in 82% of subjects with bilateral MD. These results may be explained considering the fact that VSM is a dynamic system controlled by cerebellar nodule and uvula; therefore, it is possible that when facing a peripheral vestibular hypofunction (which implies reduced vestibular afferent information), VSM may be more sensitive to stimuli coming from the vestibular nerve. In this context, a galvanic stimulation would produce a high activity of the vestibular nerve, resulting in a large velocity storage in subjects with a labyrinthine disease. This finding suggests that VSM could be hypersensitive in the presence of a labyrinthine disease.

Our results differ from the findings of Kim et al.<sup>[15]</sup> who found overshoot in 100% of healthy subjects and in 93% of subjects with a total loss of unilateral vestibular function after stimulating the affected side (using a 2 mA bilateral stimulation during 30 s). Also, our results were inconsistent with the findings of MacDougall et al.<sup>[16]</sup> who found overshoot in 100% of healthy subjects (using a 5 mA bilateral stimulation during 300 s). However, they are consistent with the findings of Dieterich et al.<sup>[17]</sup> who described overshoot in 45% of bilateral vestibular failure subjects (using a 3 mA bilateral stimulation during 6 s).

This rather contradictory result can be fully understood if we remember that VSM is an adaptive mechanism that responds progressively as it receives longer stimulus. Therefore, the longer the galvanic stimulus the higher the occurrence of overshoot, which would explain why Dieterich et al.<sup>[17]</sup> observed only 45% of overshoot after 6 s stimuli, whereas MacDougall et al.<sup>[16]</sup> observed 100% after 300 s stimuli. Thus, with a short galvanic stimulus, only subjects with labyrinthine disease will exhibit overshoot, whereas with longer stimulus, normal subjects will also exhibit overshoot.

As can be seen from the data in Table 1, subjects with MD were older than healthy subjects, but it is unlikely that a greater age is related to the occurrence of the overshoot phenomenon because the performance of VSM has been reported to decrease with age<sup>[18]</sup>.

We observed that a longer history of MD was related to a higher occurrence of the overshoot phenomenon; however, it could correspond to a confounding factor, given the fact that bilateral involvement appears in patients with a longer history of MD. Accordingly, the occurrence of nystagmus overshoot seems to be related to the single presence of a labyrinthine disorder, which is consistent with our observation that nystagmus overshoot occurs more frequently in subjects with bilateral MD than in subjects with unilateral MD.

The intra-stimulus time constant could not be determined because the decay could not be observed within 20 s (which is the duration of the stimuli used in our study), whereas the post-stimulus time constant could be easily observed and determined at 5 and 7 s in subjects with unilateral and bilateral MD, respectively. These findings are similar to the results reported by Kim et al.<sup>[15]</sup> who observed a post-stimulus time constant of 5 s using stimuli of 30-s duration; however, on the contrary, they are very different from the results re-

ported by MacDougall et al.<sup>[16]</sup>, where a post-stimulus time constant of 159 s was observed using stimuli of 300-s duration. Once again, these results can be explained by a healthy and adaptable VSM. Hence, the longer the galvanic stimulus the longer the time constant.

The findings of this study suggest an increase of velocity storage in subjects with a labyrinthine disorder. Further experimental investigations are required to determine whether this hypothesis is consistent with the results from other types of vestibular deficit.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of La Fe Hospital, reference number FPNT-CEIB-04A, approval date December 20<sup>th</sup> 2013.

**Informed Consent:** Written informed consent was obtained from subjects who participated in this study.

**Peer-review:** Externally peer-reviewed.

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