Research Article

Enhanced Vestibulo-ocular Reflex to Electrical Vestibular Stimulation in Meniere's Disease

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ABSTRACT

Meniere's disease is characterized by sporadic episodes of vertigo, nystagmus, fluctuating sensorineural hearing loss, tinnitus and aural pressure. Since Meniere's disease can affect different regions of the vestibular labyrinth, we investigated if electrical vestibular stimulation (EVS) which excites the entire vestibular labyrinth may be useful to reveal patchy endorgan pathology. We recorded three-dimensional electrically evoked vestibulo-ocular reflex (eVOR) to transient EVS using bilateral, bipolar 100-ms current steps at intensities of 0.9, 2.5, 5.0, 7.5 and 10.0 mA with dual-search coils in 12 unilateral Meniere's patients. Their results were compared to 17 normal subjects. Normal eVOR had tonic and phasic spatiotemporal properties best described by the torsional component, which was four times larger than horizontal and vertical components. At EVS onset and offset of 8.9 ms latency, there were phasic eVOR initiation ($M=1,267^\circ/\text{s}^2$) and cessation ($M=-1,675^\circ/\text{s}^2$) acceleration pulses, whereas during the constant portion of the EVS, there was a maintained tonic eVOR ($M=9.1^\circ/\text{s}$) at 10 mA. However in Meniere's disease, whilst latency of EVS onset and offset was normal at 9.0 ms, phasic eVOR initiation ($M=1,720^\circ/\text{s}^2$) and cessation ($M=-2,523^\circ/\text{s}^2$) were enlarged at 10 mA. The initiation profile was a bimodal response, whilst the cessation profile frequently did not return to baseline. The tonic eVOR ($M=20.5^\circ/\text{s}$) exhibited a ramped enhancement of about twice normal at 10 mA. Tonic

eVOR enhancement was present for EVS >0.9 mA and disproportionately enhanced the torsional, vertical and horizontal components. These eVOR abnormalities may be a diagnostic indicator of Meniere's disease and may explain the vertigo attacks in the presence of declining mechanically evoked vestibular responses.

Keywords: Meniere's disease, electrical vestibular stimulation, vestibulo-ocular reflex, enhancement

INTRODUCTION

Meniere's disease is an inner ear disorder characterised by sporadic episodes of spontaneous vertigo, nystagmus, fluctuating sensorineural hearing loss, tinnitus and aural pressure. The aetiology although unknown is believed to be due to endolymphatic hydrops (Schuknecht 1968; Rauch et al. 1989; Naganawa et al. 2012; Gibson 2010) causing distortion or rupture of the membranous labyrinth (Minor et al. 2004; Sajjadi and Paparella 2008). Meniere's disease has many stages, and in the early stages, not all the clinical features present concomitantly or different features present sequentially as a different part of the vestibular and cochlear labyrinth is affected. In Meniere's burn-out stage, hair cell death is believed to be caused by mechanical damage from hydrops resulting in caloric response decline and hearing loss.

Electrical (galvanic) vestibular stimulation has been used in research and clinical assessment of the vestibular system for a century. The traditional technique of prolonged and sustained electrical vestibular stimulation (EVS) over seconds to minutes generates nystagmus

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where the slow-phase of the vestibulo-ocular reflex rotates away from the cathodal side towards the anodal side of stimulation (Fitzpatrick and Day 2004). Sustained electrical stimulation generates variable results due to influence by other ocular motor systems such as saccade and smooth pursuit or by adaptive changes which has latencies longer than 150 ms. Recently we developed a novel, repeatable, transient 100-ms galvanic vestibular stimulation with a sharp, definite onset and offset and measurement of the vestibulo-ocular reflex in the first 150 ms after stimulus onset, which overcomes these problems. We term this galvanic stimulation subset as EVS and its vestibular response as electrically evoked vestibulo-ocular reflex (eVOR) (Aw et al. 2008). This transient type of galvanic stimulation with definite onset had also been used in galvanic vestibular evoked myogenic potentials (De Waele et al. 2002). The advantage of transient EVS is that it evokes a reproducible three-dimensional eVOR pattern in normal subjects with precise onset and offset latencies of Aw et al. (2006, 2008). Any departure from this normal eVOR pattern may be a unique signature of the disease such as the eVOR impairment after gentamicin vestibulotoxicity (Aw et al. 2008).

Definitive diagnosis of Meniere's disease is difficult due to variability of vestibular and cochlear loss. The American Academy of Otolaryngology—Head and Neck Surgery (AAO-HNS) criteria set out some guidelines for diagnosis of “definite” Meniere's disease to include vertigo and hearing loss (Monsell et al. 1995). However, in the early stage, a quarter of patients can present with either hearing loss or vertigo only (Kitahara et al. 1984; Wladislavosky-Waserman et al. 1984). Due to this propensity of Meniere's disease to affect different parts of the vestibular labyrinth, transient EVS may be a useful stimulus to assess the vestibular function because it stimulates the entire vestibular labyrinth and may evoke a unique abnormality pattern that can characterize Meniere's disease. Our study aimed to investigate if the eVOR to transient EVS was altered in Meniere's disease.

METHODS

The protocols for this study were approved by local Ethics Committees in accordance with Helsinki II Declaration. The use of the brief 0.1 ms 10 mA EVS falls within the guidelines of our approved human subject protocol, and the same protocol had been used to study normal subjects (Aw et al. 2006) and patients with gentamicin vestibulotoxicity (Aw et al. 2008).

Subjects

Twelve unilateral Meniere's patients that satisfied the AAO-HNS criteria for “definite” Meniere's disease,

grouped as left Meniere's disease (nine right and three left, seven females and five males, age range = 28–79 years, $M=56.5$ years, $SD=4.5$), were tested with binocular dual-search coils in Royal Prince Alfred Hospital, Australia. The Meniere's patients were diagnosed based on clinical assessment of episodic attacks of spontaneous vertigo, nystagmus, hearing impairment, tinnitus and aural pressure together with the tests shown in Table 1: (a) bi-thermal caloric tests using water irrigation at 44 and 30 °C were conducted with canal paresis determined with Jongkee's formula as $\geq 25\%$ (Proctor et al. 1986); (b) air-conducted click cervical vestibular evoked myogenic potentials (VEMP) with cervical VEMP asymmetry ratio (AR) where: $AR = 100 \times (Al - Ar) / (Al + Ar)$ (Al and Ar represent the amplitude of the left and right side, respectively) with ipsilesional cervical VEMP considered reduced and abnormal if $AR \geq 33\%$ (Taylor et al. 2011) and (c) pure-tone audiogram. All patients had caloric canal paresis ($M=76.9\%$) and 95 % confidence interval (CI) [68.5, 85.3]. The mean ipsilesional cervical VEMP was reduced in eight “definite” Meniere's patients with AR of ($M=60.0\%$, 95 % CI [80.0, 33]), but four patients had normal bilateral cervical VEMPs. All 12 “definite” Meniere's patients had ipsilesional hearing loss of ($M=70$ dB, 95 % CI [57, 83] at 0.5 kHz) and ($M=60$ dB, 95 % CI [44, 76] at 2.0 kHz). Prior to EVS testing, all patients were managed with a low salt diet and drug therapy with no prior exposure to ear surgery and intratympanic gentamicin. All EVS and clinical tests were conducted during the interictal period of Meniere's disease. Results from the Meniere's patients were compared to 17 normal subjects (three females and 14 males, age range = 25–70 years, $M=39.6$ years, $SD=16.9$). We tested one early “possible” Meniere's disease patient (P8) (male, age = 31 years) with caloric canal paresis of 80 %, normal hearing and normal bilateral cervical VEMPs to determine if early Meniere's disease showed similar abnormal enhanced eVOR observed in the “definite” Meniere's group.

Recording system

Three-dimensional (torsional (x), vertical (y) and horizontal (z)) eye positions evoked by EVS were recorded using the scleral search coil technique with pre-calibrated dual-search coils (Skalar, the Netherlands) in supine head-fixed subjects viewing a fixed target consisting of a lighted 2-mm green LED located straight ahead at 600 mm. During testing, the ambient lighting in the laboratory was switched off. The subject's head was centred in the transmitter field coils (660 mm³, 66 and 100 kHz, CNC Engineering, USA) during the recording (Aw et al. 2006, 2008). Search-coil and current-switch signals were sampled at

TABLE 1

Individual and mean magnitudes of tonic and phasic eVOR correlated with the duration of disease, clinical vestibular and cochlear assessments in 12 “definite” Meniere’s patients

Patient	Age (years)	Meniere's disease	Meniere's disease duration	Magnitude of			Clinical vestibular and cochlear assessment			
				Tonic eVOR	Phasic eVOR	Phasic eVOR	Caloric test (%)	Cervical VEMP (%)	Audiogram (dB)	
Side	°/s	Initiation (°/s ²)	Cessation (°/s ²)	Canal paresis	Asymmetry ratio	0.5 kHz	2.0 kHz			
Patient means	56.5		5.7	22.1	2,039.6	2,636.3	76.7	60.0	74.6	67.5
P1	45	L-MD	2	35.2	2,507	3,616	100	65	100	100
		R-normal							15	5
P2	76	L-MD	6	31.3	922	1,546	100	100	110	110
		R-normal							20	40
P3	47	L-normal	10						15	15
		R-MD		29.7	2,459	3,910	65	55	65	65
P4	28	L-normal	8	26.5	3,809	4,697	60	100	30	10
		R-MD							75	45
P5	50	L-normal	1	22.5	1,888	2,770	70	0	5	5
		R-MD							70	60
P6	54	L-normal	14	22.3	2,426	2,831	90	70	10	25
		R-MD							75	70
P7	40	L-normal	5	19.5	2,616	2,278	100	100	10	10
		R-MD							65	45
P9	62	L-normal	8	18.5	1,417	2,280	65	100	20	10
		R-MD	4	18.2	1,956	2,807	60	0	80	85
P10	63	L-MD							60	30
		R-normal							10	20
P11	59	L-normal	3	16.8	1,780	2,322	75	0	15	10
		R-MD							70	40
P12	79	L-normal	2	13.9	1,365	1,437	65	100	25	35
		R-MD							60	65
P13	75	L-normal	5	14.7	1,142	1,426	70	30	25	15
		R-MD							65	65

Vestibular assessments showed caloric canal paresis and cervical VEMP asymmetry. Audiological assessment of individual hearing loss and mean hearing loss of all patients on affected side at 0.5 and 2.0 kHz, whilst hearing on normal side was displayed only for comparison

L-MD left Meniere’s disease, R-MD right Meniere’s disease

5 kHz with 24-bit resolution (NI PCI-4472, National Instruments, USA) with Labview (Version 7.1, National Instruments, USA). Resolution of the recording system was 0.1 arcmin for horizontal and vertical components and 0.3 arcmin for torsional component. Maximum errors and cross-coupling were $<2\%$ (Aw et al. 2006, 2008).

Electrical vestibular stimulation

Bilateral, bipolar EVS comprised transmastoid, 100 ms constant current steps at intensities of 0.9, 2.5, 5.0, 7.5 and 10.0 mA in left-cathode/right-anode (lc/ra) or right-cathode/left-anode (rc/la) EVS configuration delivered via 9 cm² surface electrodes (Aw et al. 2006, 2008). At each current intensity and configuration, the subjects were tested with 60 repetitions of EVS delivered at 1/s. We defined the eVOR from cathodal EVS of the affected ear as ipsilesional eVOR and cathodal EVS of the unaffected ear as contralesional eVOR.

Topical anaesthesia (Emla 5 % cream, AstraZeneca, Sweden) was applied to the mastoid area beneath the surface electrode about 15 min before the EVS in order to reduce any pain and discomfort associated with the 7.5 and 10.0 mA EVS, and hence, the EVS was well-tolerated by all patients, with the discomfort level described to be equivalent to the caloric test.

Data analysis

The subjects were tested with 60 trials for each EVS current intensity and configuration. Using an automated Labview (National Instruments, USA) software program, any data trial with blinks or saccades were removed, then the remaining data trials of between 30 and 40 repetitions were filtered, averaged and computed in three dimensions in rotation vectors and Euler angles as eye position, velocity and acceleration in space-fixed coordinates (Aw et al. 2006, 2008). The automated Labview software conducted a trend analysis on the eVOR response curve whereby if the response exceeded two standard deviation of the mean for $>5\%$ of the response duration, it is considered as having a saccade or blink and trial was discarded. Leftward, downward and clockwise directions from subject's view were positive for horizontal (z), vertical (y) and torsional (x) eye rotations. EVOR latency was defined as the interval between EVS onset and when torsional velocity first exceeded 1 standard deviation of its baseline noise before stimulation. Tonic eVOR was the mean torsional velocity during a 30-ms period, 70 ms after EVS onset. Phasic eVOR was the mean peak torsional acceleration at initiation and cessation. Magnitudes ($\sqrt{x^2 + y^2 + z^2}$) of the

tonic eVOR velocity and phasic eVOR accelerations were determined to show the total output of the three (torsional, vertical and horizontal) components of the eVOR.

Statistical analysis

Mean $\pm$ 95 % confidence intervals of the tonic eVOR velocity and phasic eVOR acceleration for each current intensity of 0.9, 2.5, 5.0, 7.5 and 10.0 mA and tonic and phasic eVOR magnitudes were determined for normal and Meniere's disease. Statistical analysis of the data was performed with S-PLUS (SolutionMetrics, Australia) and reported as standard deviation. Student's *t* test for differences between two means of independent observations was used to test for differences between tonic and phasic eVORs in normal and Meniere's disease. Ipsilesional eVOR was defined as eVOR from cathodal EVS of the affected ear and contralesional eVOR as eVOR from cathodal EVS of the unaffected ear. Student's *t* test for differences between two means of dependent observations was used to test for differences between the ipsilesional and contralesional eVOR in Meniere's disease. A significance (alpha) level of $p=0.05$ was used in the statistical analysis.

RESULTS

Normal eVOR

Normal eVOR displayed reproducible spatiotemporal characteristics such as onset latency, tonic eVOR velocity and phasic eVOR acceleration in response to EVS at intensities of 0.9, 2.5, 5.0, 7.5 and 10.0 mA. Normal binocular eVOR comprised conjugate torsional and horizontal eye rotations, approximately equal in amplitude, and rotated away from the cathode towards the anode and vertical divergence (Aw et al. 2008) (Figs. 1B and 2B). Torsional eVOR was about four times larger than vertical or horizontal component (Aw et al. 2008). Figure 1B shows a typical normal subject, whose normal tonic eVOR was $M=12.2^\circ/\text{s}$ and phasic eVOR initiation was $M=1,465^\circ/\text{s}^2$ and cessation was $M=-2,095^\circ/\text{s}^2$ at 10.0 mA EVS. After onset latency of ($M=8.9$ ms), there was a phasic eVOR initiation which has a single peak. At ~ 9 ms after the EVS offset, there was phasic eVOR cessation peak opposite in direction to phasic eVOR initiation. Tonic eVOR was approximately constant during the constant 100-ms step of EVS, and consequently, the eVOR velocity profile approximates the EVS step. At EVS offset, tonic eVOR velocity usually returned slightly past baseline.

The group means of normal subjects ($N=17$) shows comparable eVOR patterns (Fig 2B). At 10.0 mA EVS,

FIG. 1. The eVOR to EVS of intensities 0.9, 2.5, 5.0, 7.5 and 10.0 mA using a left cathode/right-anode configuration (lc/ra) from **A** a typical left Meniere's disease patient (P1, see Table 1) compared to **B** an age-matched normal subject. In Meniere's disease, ipsilesional torsional, vertical and horizontal eVOR were enhanced. Tonic eVOR

in Meniere's disease displayed a ramped enhancement which increased after phasic eVOR initiation till phasic eVOR cessation. Phasic eVOR initiation showed a bimodal response pattern, and phasic cessation did not return the tonic eVOR velocity past the baseline like normal eVOR (see arrows).

the normal tonic eVOR was $M=9.1^\circ/s$, 95 % CI [7.2, 11.0], whilst the normal phasic eVOR initiation was

$M=1,267^\circ/s^2$, 95 % CI [935, 1,599] and cessation was $M=-1,675^\circ/s^2$, 95 % CI [-1,225, -2,125].

eVOR enhancement in Meniere's disease

Meniere's patients showed characteristic abnormal eVOR enhancement to EVS. We defined the eVOR from cathodal EVS of the affected ear as ipsilesional eVOR and cathodal EVS of the unaffected ear as contralesional eVOR.

Figure 1A shows a typical left Meniere's patient (P1) who had a 7-year history of Meniere's symptoms. He suffered incapacitating attacks of spontaneous vertigo and nystagmus lasting 2-3 h approximately once a month. He had progressively lost all his left hearing a few years ago but still complained of left tinnitus. His caloric canal paresis was 100 %, and his cervical VEMP AR was 60 % in his left ear. In response to EVS at 0.9, 2.5, 5.0, 7.5 and 10.0 mA, his ipsilesional eVOR for the torsional, vertical and horizontal components were greatly enhanced (Fig. 1A) compared to an age-matched normal (Fig. 1B). Torsional and horizontal eVOR rotated away from cathode towards anode with a vertical divergence. His tonic eVOR displayed a characteristic ramped enhancement during the constant 100-ms step of EVS. At 10.0 mA EVS, his tonic eVOR ($M=28.2^\circ/\text{s}$) was more than twice the six age-matched normal value ($M=8.1^\circ/\text{s}$, $SD=2.3$). His phasic eVOR initiation ($M=2,026^\circ/\text{s}^2$) and cessation ($M=-3,644^\circ/\text{s}^2$) were greater than age-matched normal values of initiation ($M=1,227^\circ/\text{s}^2$, $SD=234$) and cessation ($M=-1,550^\circ/\text{s}^2$, $SD=435$). Unlike normal, phasic eVOR initiation showed a bimodal response pattern, and phasic eVOR cessation did not return the tonic eVOR velocity to slightly past baseline.

Our study compares the eVOR in unilateral "definite" Meniere's patients ($N=12$) to normal subjects ($N=17$). Ipsilesional eVOR, grouped as left Meniere's disease, showed enhancement in torsional, vertical and horizontal components in response to EVS intensities of 2.5, 5.0, 7.5 and 10.0 mA except to 0.9 mA (Figs. 2A and 4A, B). The onset latency in Meniere's disease ($M=9.0$ ms, $SD=0.3$) was similar to normal latency $t(11)=2.07$, $p=0.06$. Tonic eVOR showed a ramped enhancement to constant EVS intensities at 2.5, 5.0, 7.5 and 10.0 mA EVS. After EVS onset, phasic eVOR initiation showed a bimodal response profile. After EVS offset, phasic eVOR cessation did not return the eVOR velocity past baseline in ~75 % of patients in torsional and/or horizontal components. Higher EVS intensities of 7.5 and 10.0 mA tended to magnify the eVOR abnormalities. The mean contralesional eVOR also showed enhancement in torsional, vertical and horizontal components to EVS intensities of 2.5, 5.0, 7.5 and 10.0 mA except to 0.9 mA. Despite the contralesional eVOR enhancement, tonic eVOR was constant and approximates the EVS step. After contralesional

FIG. 2. Group means of the ipsilesional and contralesional eVOR from **A** Meniere's disease patients ($N=12$) compared to **B** normal subjects ($N=17$) in response to EVS at 0.9, 2.5, 5.0, 7.5 and 10.0 mA in left-cathode/right-anode (lc/ra) or right-cathode/left-anode (rc/la) configurations. Meniere's disease showed eVOR enhancements in torsional, vertical and horizontal components when compared to normal. In Meniere's disease, ipsilesional tonic eVOR displayed a ramped enhancement which increased after phasic eVOR initiation till phasic eVOR cessation. Ipsilesionally, phasic eVOR initiation showed a bimodal response pattern, and phasic cessation did not return the tonic eVOR velocity past the baseline like normal eVOR (see arrows). Contralesional tonic and phasic eVORs were enhanced without the abnormal tonic and phasic eVOR characteristics.

phasic eVOR cessation, tonic eVOR velocity returned slightly past baseline similar to normal.

eVOR variations in Meniere's disease

There are eVOR variations between Meniere's patients (Fig. 3A). All patients displayed tonic eVOR ramped enhancement most evident in the torsional component. Tonic eVOR enhancement was not only limited to the torsional component but also disproportionately increased the vertical and horizontal components to half or three quarters of the torsional component. Torsional and horizontal components rotated away from the cathodal stimulated ear except in (P9) where the horizontal component was small but inverted. The tonic eVOR velocity after phasic eVOR cessation did not return the torsional and/or horizontal component past baseline like normal (e.g. P1 Fig. 1A, P6 and P9 Fig. 3A) except in three patients (e.g. P4 Fig. 3A).

eVOR in "possible" Meniere's disease

We tested one early "possible" Meniere's disease patient (P8 Fig. 3B) to determine if early Meniere's disease showed similar abnormal eVOR enhancement observed in "definite" Meniere's disease. The patient had a right caloric canal paresis of 80 % but normal bilateral cervical VEMPs. He complained of fluctuating hearing loss during vertigo attacks, but normal hearing was documented during our assessment in the interictal period. This patient also displayed the tonic eVOR ramped enhancement evident in both the torsional and horizontal components. In addition, the tonic eVOR velocity after phasic eVOR cessation also did not return the torsional and horizontal component past baseline like normal. Patient (P8)'s ipsilesional tonic eVOR at 10.0 mA EVS was ($M=18.3^\circ/\text{s}$) and contralesional eVOR was ($M=12.0^\circ/\text{s}$). His ipsilesional phasic eVOR initiation ($M=1,180^\circ/\text{s}^2$) and cessation was ($M=-1,545^\circ/\text{s}^2$), and contralesional phasic eVOR initiation ($M=-967^\circ/\text{s}^2$) and cessation ($M=1306^\circ/\text{s}^2$) were similar to normal values. The mean magnitude (total output of horizontal, vertical

FIG. 3. **A** Variations of ipsilesional tonic eVOR velocity in unilateral “definite” Meniere’s disease. All patients showed enhanced step and ramped torsional and horizontal components. At EVS offset, some patients returned to the baseline normally, whilst others were slower. Horizontal component in patient (P9) was inverted. These variations in

response patterns probably reflect the patchy nature of Meniere’s pathology and the disease stage in each patient. **B** The ipsilesional tonic eVOR velocity in an early “possible” Meniere’s disease patient (P8) shows similar enhanced ramped torsional and horizontal components.

and torsional components) of his ipsilesional tonic eVOR was $M=18.6$ $^{\circ}/s$, phasic eVOR initiation was $M=1,208$ $^{\circ}/s^2$ and cessation was $M=-1,508$ $^{\circ}/s^2$.

Comparison of normal and Meniere’s eVOR

In Meniere’s disease, the ipsilesional tonic eVOR ($M=20.5$ $^{\circ}/s$, $SD=4.7$) was higher than contralesional tonic eVOR ($M=-15.2$ $^{\circ}/s$, $SD=4.9$) at 10 mA EVS, $t(11)=6.79$, $p=0.00$ (Fig. 4A). Ipsilesional tonic eVOR ($M=3.5, 8.4, 13.9, 20.5$ $^{\circ}/s$, $SD=1.2, 2.7, 4.0, 4.7$) were higher than normal for EVS intensities of 2.5, 5.0, 7.5 and 10.0 mA, $t(11)=2.52, 3.61, 6.08, 9.37$, $p=0.03, 0.00, 0.00, 0.00$, respectively, but not to 0.9 mA. Contralesional tonic eVOR ($M=-3.5, -7.8, -12.3, -15.2$ $^{\circ}/s$, $SD=1.2, 2.7, 4.0, 4.7$, respectively) was also higher than normal for EVS intensities of 2.5, 5.0, 7.5 and 10.0 mA, $t(11)=2.52, 3.61, 6.08, 9.37$, $p=0.02, 0.00, 0.00, 0.00$, but not to 0.9 mA. Ipsilesional phasic eVOR initiation ($M=1,712$ $^{\circ}/s^2$, $SD=589$) and cessation ($M=-2,523$ $^{\circ}/s^2$, $SD=870$) in Meniere’s disease were higher than normal only at

10.0 mA EVS, $t(11)=6.79$, $p=0.00$ (Fig. 4B). Since Meniere’s patients have disproportionate enhancement abnormalities in torsional, vertical and horizontal components, eVOR magnitude would serve to highlight these abnormalities as it quantified the entire eVOR output (Table 1; Fig. 4B). In Meniere’s disease at 10 mA EVS, the ipsilesional tonic eVOR magnitude ($M=22.1$ $^{\circ}/s$, 95 % CI [18.1, 26.1] was more than twice normal ($M=9.4$ $^{\circ}/s$, 95 % CI [7.1, 11.7], $t(11)=6.5$, $p=0.00$). The magnitude of ipsilesional phasic eVOR initiation ($M=2,040$ $^{\circ}/s^2$, 95 % CI [1,607, 2,472]) and cessation ($M=2,636$ $^{\circ}/s^2$, 95 % CI [2,067, 3,205]) were larger than magnitude of normal initiation ($M=1,375$ $^{\circ}/s^2$, 95 % CI [995, 1,755]), $t(11)=2.83$, $p=0.04$ and cessation ($M=1,736$ $^{\circ}/s^2$, 95 % CI [1,341, 2,131]) $t(11)=2.55$, $p=0.03$.

DISCUSSION

The most remarkable findings in Meniere’s disease to transient EVS were the tonic and phasic eVOR

FIG. 4. Comparison of the group means $\pm$ 95 % confidence intervals of ipsilesional and contralesional **A** tonic eVOR and **B** phasic eVOR (initiation and cessation) in Meniere's disease ($N=12$) to normal subjects ($N=17$). Comparisons of group mean magnitude of **C** tonic eVOR and **D** phasic eVOR in Meniere's disease to normal subjects. Tonic eVOR was greater than normal for EVS intensities of

2.5, 5.0, 7.5 and 10.0 mA. Phasic eVOR was greater than normal only for EVS at 10.0 mA. Mean tonic eVOR magnitude at 10.0 mA EVS showed that total response was much larger than normal. Phasic eVOR magnitude at 10.0 mA EVS showed that a bimodal response with increased pulse duration in Meniere's disease.

enhancement abnormalities. We defined the eVOR from cathodal EVS of the affected ear as ipsilesional eVOR and cathodal EVS of the unaffected ear as contralesional eVOR.

The EVS onset and offset latency was normal at 9.0 ms. Ipsilesional tonic eVOR enhancement was present for all EVS intensities except for 0.9 mA stimulation in all 12 "definite" Meniere's patients, but higher EVS intensities of 7.5 and 10.0 mA tended to magnify the eVOR abnormalities. The tonic eVOR showed a ramped enhancement during the constant 100-ms step of EVS. Furthermore, the tonic eVOR enhancement was not limited to the torsional component, but disproportionately increased the vertical and horizontal components to half or three quarters of the torsional component. Ipsilesional phasic eVOR initiation and cessation were increased at 10 mA. The phasic eVOR initiation profile was bimodal, and eVOR cessation did not return to baseline in ~75 % of Meniere's patients. The contralesional tonic and phasic eVOR patterns approximated normal, but were enhanced in amplitude.

This contrasts with the reproducible signature eVOR with normative range to EVS in normal subjects (Aw et al. 2006, 2008). After a definite onset and offset 8.9 ms latency, there were phasic eVOR initiation and cessation acceleration pulses. During the intervening 100 ms of maintained EVS current, tonic eVOR was approximately

constant (i.e. no ramp), so that the tonic eVOR velocity profile approximated the EVS current step. The predominant torsional eVOR was about four times larger than vertical or horizontal component.

Traditional mechanical vestibular function tests on Meniere's patients usually show sporadic decline in functions, but never the enhancement abnormalities to transient EVS as shown in our study. Our cohort of 12 "definite" Meniere's patients showed patchy mechanical degradation of vestibular and cochlear functions (Table 1). Three of these patients had complete caloric canal paresis, whilst nine had partial canal paresis. Two thirds of our patients had reduced ipsilesional cervical VEMP, i.e. it is considered reduced and abnormal if $AR \geq 33$ % (Taylor et al. 2011), whilst one third had normal bilateral VEMPs. All patients had cochlear involvement evidenced by the hearing loss. Semicircular canal responses to head impulse tests of individual semicircular canal function were reported to be normal, despite some caloric canal paresis (Carey et al. 2002). Similar reduction in ipsilesional cervical VEMP were reported in half the patients with Meniere's disease (Taylor et al. 2011). We also showed that the early "possible" Meniere's patient exhibited marked ipsilesional tonic eVOR enhancement abnormalities in torsional and horizontal components very similar to the "definite"

Meniere's disease (Fig. 3B). This patient complained of fluctuating hearing during vertigo attacks, but hearing impairment could not be documented during our interictal assessment, as is often the case in early Meniere's disease (McNeill et al. 2009). This suggests that the transient EVS may be used to assist diagnosis of early Meniere's disease.

We considered several hypotheses to explain and reconcile the incongruity between the enhancement of electrically evoked vestibular function with the patchy degradation of mechanically evoked vestibular function. Histopathological studies of Meniere's disease labyrinths show that parts of vestibular and cochlear sensory epithelium still have normal hair cell populations, and the vestibular nerve fibres appeared preserved despite evidence of endolymphatic hydrops such as cochlear and vestibular labyrinth distension, membranous labyrinth rupture, missing otolithic membrane (Schuknecht 1993) and membranous labyrinth herniation into the horizontal semicircular canal (Gürkov et al. 2012). Membranous labyrinth herniation found to be correlated with impaired caloric response may be insufficient to impair hair cell stereocilia deflection during high-acceleration head impulse test which was shown to be normal (Carey et al. 2002). Missing otolithic membrane will certainly impair cervical VEMP function.

One possibility is that hair cells may sustain some damage from the endolymphatic hydrops leading to denervation hypersensitivity of the primary vestibular afferent. This has been suggested as an explanation for the inverse U-shaped curve for age dependency of torsional eye movement responses to electrical stimulation in middle age (Jahn et al. 2003). We consider the mechanism of denervation hypersensitivity unlikely here because hair cell damage as a result of gentamicin vestibulotoxicity causes severe impairment of both human eVOR to transient EVS (Aw et al. 2008) and to mechanically evoked vestibular function tests such as caloric and head impulse tests (Weber et al. 2009). In addition, intra-tympanic gentamicin abolishes the galvanic cervical VEMP and stopped further Meniere's attacks of vertigo (De Waele et al. 2002). After gentamicin vestibulotoxicity, one consideration to address is whether vestibular nerve degeneration causes the human eVOR impairment to EVS. Certainly vestibular nerve impairment was not observed in the animal model because gentamicin was used to damage the hair cells but preserved the vestibular nerve so that the implanted vestibular prosthesis could be used to electrically stimulate the nerve to generate vestibular responses (Della Santina et al. 2007). Our study showed that Meniere's disease enhanced eVOR in the presence of hair cell preservation with endolymphatic hydrops changes and intact vestibular nerve (Schuknecht 1993) which contrasts with gentamicin vestibulotoxicity where hair cell death with intact vestibular nerve severely

impaired the eVOR (Aw et al. 2008) and abolished galvanic cervical VEMP (De Waele et al. 2002).

Another possibility is that during a Meniere's attack, the endolymphatic hydrops causes rupture of the Reissner membrane allowing the high potassium concentration in the endolymph to mix with perilymph which would suppress the vestibular nerve firing rate until the ionic pumps restore the electrolyte homeostasis and the rupture has healed (Schuknecht 1968). Thus, mechanically as well as electrically evoked vestibular responses would be diminished, and is not consistent with the enhanced vestibular responses we observed to electrical stimulation.

Elevated hydrostatic pressure has been shown in vitro to increase the sensitivity of the vestibular hair cells to stimulating electrical currents by acting on hair cell pressure-dependent potassium currents (Dinh et al. 2009). We conjecture that this alternate hypothesis of hydrostatic pressure buildup in endolymphatic hydrops causing vestibular hair cell hypersensitivity to electrical stimulation might be one factor contributing to the human eVOR enhancement during EVS in Meniere's disease. This eVOR enhancement also supports Meniere's susceptibility to initiate "irritative" attacks of nystagmus (Bance et al. 1991).

The problem clinicians face in diagnosing Meniere's disease is that there is no established single or subset of features in the history, physical signs or diagnostic tests that confirms the diagnosis (review: Minor et al. 2004). In Meniere's disease, mechanically evoked vestibular function tests may not always present a complete picture of the pathology because these tests target specific vestibular endorgans (Carey et al. 2002; Halmagyi 2005; Taylor et al. 2011), whilst Meniere's disease affects different vestibular and cochlear endorgans concurrently or sequentially, usually unilaterally and sometimes bilaterally. As the EVS stimulates the entire vestibular labyrinth, its non-specificity is advantageous for revealing any endorgan pathology wherever it might affect the vestibular labyrinth. Therefore, our tonic and phasic eVOR enhancement abnormalities may be useful indicators of endolymphatic hydropic changes caused by Meniere's disease, especially a ramped eVOR enhancement of $>15\%$ at 10 mA EVS. We propose that the relatively large tonic eVOR enhancement may be measured with further investigation using a modern high-speed video-oculography in the clinical setting (Jahn et al. 2003).

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Conflict of interest

The authors declare that they have no conflict of interest. Prof. GM Halmagyi is a consultant for GN Otometrics.

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