Article

A Single Fast Test for Semicircular Canal Dehiscence – oVEMP n10 to 4000Hz – Depends on Stimulus Rise-time

Ian S. Curthoys [1*], Ann M. Burgess [1], Leonardo Manzari [2] and Christopher J. Pastras [3]

[1] Vestibular Research Laboratory, School of Psychology, the University of Sydney, NSW, Australia; ian.curthoys@sydney.edu.au
[2] MSA ENT Academy Center, Cassino, 03043, Italy: lmanzari62@gmail.com
[3] Faculty of Engineering and Science, Macquarie University, christoper.pastras@mq.edu.au
* Correspondence: ian.curthoys@sydney.edu.au

Abstract: We have previously reported that a single test measuring oVEMP n10 to 4000Hz stimuli (either bone-conducted vibration (BCV) or air-conducted sound (ACS)) provides a definitive diagnosis of semicircular canal dehiscence (SCD) in 22 CT-verified patients with a sensitivity of 1.0 and specificity of 1.0. Such a single short screening test has great advantages of speed, minimizing testing time and the exposure of patients to stimulation. However some studies of the 4000Hz test for SCD have reported sensitivity and sensitivity values somewhat less that what we reported.
We hypothesised that rise-time of the stimulus is important for detecting the oVEMP n10 to 4000Hz, just as we had shown for 500Hz and 750 Hz BCV. We measured oVEMP n10 in 15 patients with CT-verified SCD in response to 4000Hz ACS or BCV stimuli with rise-times of 0, 1 and 2 ms. Increasing rise-time reduced OVEMP n10 amplitude. This result is expected from the physiological evidence from guinea pig primary vestibular afferents which are activated by sound or vibration are jerk detectors. Therefore for clinical VEMP testing short rise-times are optimal (preferably 0ms).

Keywords: otolith; vestibular; oVEMP; utricular; clinical audiovestibular testing; vestibular screening test

1. Introduction

A defect such as thinning or absence of the bony casing of the semicircular canal, is referred to as a semicircular canal dehiscence (SCD) ([1,2] see Wackym [3]for a recent extensive review). SCD results in changes in the mechanical operation of the labyrinth [4,5] which causes characteristic symptoms (such as dizziness, autophony etc) but the symptoms are idiosyncratic so an objective indicator of the SCD is required for diagnosis. Clinically this has meant the use of vestibular evoked myogenic potentials (VEMPs) to sound or vibration. VEMPs are small myogenic potentials recorded in response to ACS or BCV (see [6] for a review). The ocular VEMP (oVEMP) is predominantly due to activation of utricular type I receptors and irregular primary afferents from the striola of the utricular macula [7-9].

Experiments on guinea pigs recording single primary vestibular afferent neurons which are activated by sound or vibration stimulation has shown these are calyx-bearing irregular primary afferents from the striola of the otolithic maculae [8,9]. These receptors and afferents have very precise and short latencies to transient BCV and ACS, such as brief tone bursts or clicks. As such they are very sensitive to the very onset of the stimulus envelope [10]. Increasing the rise time of the stimulus reduces that onset transient and so reduces the effectiveness of the stimulus for activating the receptors and irregular afferents which are responsible for VEMPs [8]. So in light of those neural results a short rise-time should be ideal for activating the type I receptors and irregular primary afferents and so causing an oVEMP n10.

The oVEMP is especially valuable in identifying patients with a dehiscence of a semicircular canal – compared to VEMPs in healthy subjects, the amplitude of the oVEMP

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increases and the threshold for establishing the oVEMP decreases in SCD patients [11] compared to healthy subjects [12]. By comparing the oVEMP n10 amplitudes in patients with CT-verified SCD to n10 amplitudes in healthy subjects Manzari et al showed that a useful cut-off criterion for diagnosing SCD was an oVEMP n10 to 500Hz BCV greater than 10 μV (baseline to peak)[12]. So, at the Cassino clinic 95% of healthy subjects have oVEMP n10 amplitudes less than 10 μV when stimulated by 500 Hz BCV stimulus with the clinic standard 1 ms rise-time. That criterion of 10 μV oVEMP n10 had a sensitivity of 1.0 and the specificity of 0.97 for detecting SCD in that particular group of CT-verified patients. So it was recommended that patients having an oVEMP n10 amplitude greater than 10 μV should be suspected of possibly having an SCD.

The problem with this single criterion of n10 greater than 10 μV to 500 Hz Fz BCV is that some perfectly healthy subjects show oVEMP n10s which are this large but the subjects are completely asymptomatic [12]. The ideal diagnostic indicator would be a stimulus where healthy subjects have a very poor or absent response to the stimulus. In the interim it has been reported that many phenomena apart from semicircular canal dehiscence can cause enhanced oVEMP n10s to 500Hz stimulation (e.g. even intracochlear schwannoma [13]) so the amplitude of the response to 500Hz is not specific for SCD. That is why the use of 4000Hz to identify SCD was developed. (Variants of that 4000Hz test are now referred to as "high frequency VEMPs "[14]). A method with few stimulus presentations is to be preferred, and in 2013 we reported that a single test consisting of just 50 presentations of a 4000Hz stimulus, either BCV or ACS had excellent diagnostic accuracy. In 2013 Manzari et al showed that 22 patients with a CT verified SCD had clear oVEMPs to 4000Hz, whereas 27 healthy subjects did not show a detectable oVEMP n10 to this very high frequency [15]. Thus a single test, averaging the response to just 50 stimuli at 4000Hz, is a very valuable initial screening test for patients with a suspected SCD [15,16]. Recent developments have been refined to optimize both sensitivity and specificity of high frequency cVEMP and oVEMP for detecting SCD and it has been argued that "VEMP tests using high frequency stimuli are the most accurate single diagnostic test for SCD "[17,18].

Others have confirmed the high specificity and sensitivity of high frequency stimuli to be a very effective way of identifying SCD [14,17,19]. However there have been some reports where the measured specificity and sensitivity of the 4000Hz test for SCD has been lower than what Manzari et al found [19,20].

There are many possible reasons for that reduced result, but one reason is that some studies with lower sensitivity and specificity have used long rise-times. As we explain below the new neural evidence shows that vestibular primary afferent neurons responding to sound and vibration which are responsible for VEMPs , are activated by the rate of change of the BCV or ACS envelope. Increasing rise-time reduces that rate of change and so would be expected to reduce the amplitude of the oVEMP n10 response to 4000Hz and so reduce the sensitivity and specificity of the 4000Hz test. The Lin et al study used a very long rise-time of 4ms [20]. To test that hypothesis we tested 15 patients with CT verified SCD and measured their oVEMPs to both 4000 Hz ACS and BCV with rise-times of either 0, 1, or 2ms, with the prediction being that increasing the rise-time should cause smaller oVEMP n10 potentials. In some patients we also tested with 8000 Hz which had been shown to be almost as effective for SCD detection as 4000Hz in the earlier study [15].

2. Materials and Methods

All subjects gave informed consent for inclusion before they participated in the study which was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the MSA ENT Academy Center Institutional Review Ethics Committee 03-2014.

There were 15 patients : 7 males, 8 females ranging in age from 27 to 81 with average age 55 years. They were tested with informed consent. See Table 1 for patient demographics. The inclusion criterion was that these patients had been tested previously and demonstrated enhanced oVEMP n10s and so had received CT scans which confirmed their SCD. Only patients with CT-verified unilateral SCD were included.

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Table 1. Patient demographics.

PATIENT	GENDER	AGE	AFFECTED SIDE
1	F	75	left
2	M	75	right
3	M	62	left
4	M	81	left
5	M	51	right
6	M	39	left
7	F	46	right
8	M	32	right
9	F	27	left
10	F	51	right
11	F	39	left
12	F	57	right
13	M	75	left
14	F	59	left
15	F	61	left

We measured the averaged oVEMP n10 component in response to 50 presentations of short tone bursts (at 4/s) of either binaural ACS delivered by Telephonics TDH49 headphones at 120 dB SPL or BCV delivered by a hand-held Bruel and Kjaer minishaker 4810 to the midline of the forehead at the hairline (a location called Fz) at a force level of around 130 dB FL re 1μN (see Figure 1)[21]. Surface EMG electrodes beneath both eyes recorded oVEMP n10 for both eyes simultaneously. The stimulus frequency was 4000Hz and the rise-times, plateau times and fall times were 0-2-0, 1-2-1, 2-2-2 milliseconds with a zero-crossing start. We also tested some patients at 8000Hz with the same rise, plateau, and fall times. Patients did not find these frequencies and intensities uncomfortable.

For recording oVEMPs, patients laid supine on a bed with their head supported on a pillow but positioned with the chin pitched slightly nose down. During each test they were required to look straight up (toward the top of their head) to a fixation point at approximately 25 deg above their visual straight ahead and during stimulation to maintain fixation on that fixation dot, located approximately 60 to 70 cm from their eyes. The standard oVEMP montage was used: for each eye the active (+) electrode was positioned on the infraorbital ridge 1 cm below the lower eyelid, and the reference (−) electrode about 2 cm below the active electrode [21]. The electrodes were aligned with the pupil as the subject looked directly upward. Unrectified EMG was amplified and sampled at 20 kHz and band-pass filtered between 3 and 500 Hz, and 50 trials were averaged with an ICS Chartr EP 200 averager (Otometrics, Denmark). Means and two-tailed 95% confidence intervals were calculated, and the level of statistical significance was set at $p < 0.05$[22].

3. Results

Increasing rise-time decreases the amplitude of oVEMP n10 to both ACS and Fz BCV stimulation in SCD patients. An example of the raw data for two CT-verified SCD patients in response to 4000 Hz tone bursts with varying rise-times is shown in Figure 1. It is clear that the amplitude of the n10 component of the oVEMP decreases, for both ACS and BCV 4000Hz stimuli, as rise-time increased (Figures 1 and 2). These decreases are statistically significant. The additional data using 8000Hz shows how the n10 is dependent on rise-time.

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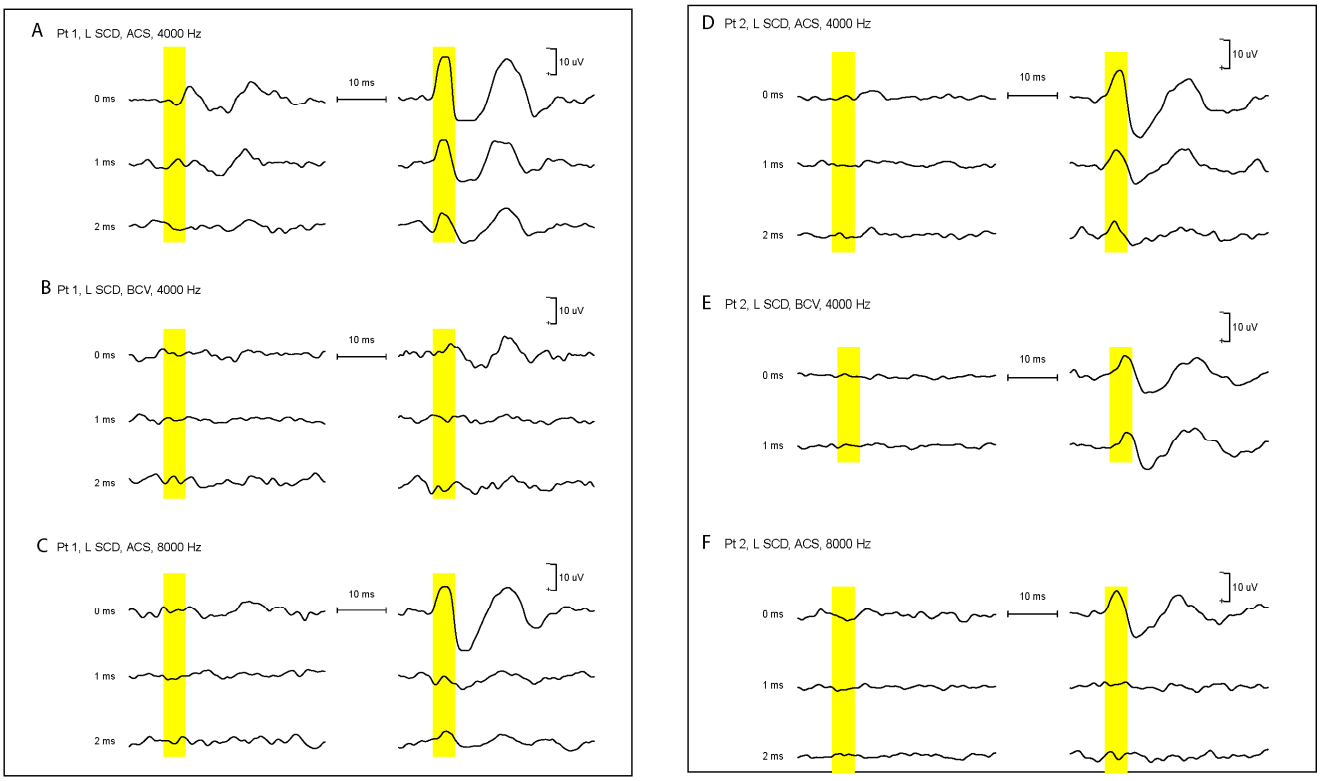

Figure 1. (A-F). Examples of the oVEMP n10 in response to 4000Hz BCV and ACS stimuli at rise-times of 0, 1, and 2 ms for two patients. The yellow bars define the regions for the oVEMP n10. The oVEMP for the SCD ear is shown in the right columns. Increasing the rise-time from 0ms to 2ms decreases the amplitude of the oVEMP n10. In these patients we also tested the same rise-times with 8000Hz ACS stimulus (C and F). Whilst a rise-time of 0ms at 8000Hz generates a clear oVEMP in both patients, prolonging the rise-time to only 1ms abolishes the oVEMP n10. These results confirm that events at the very onset of the high frequency stimulus are of major importance in initiating the oVEMP n10.

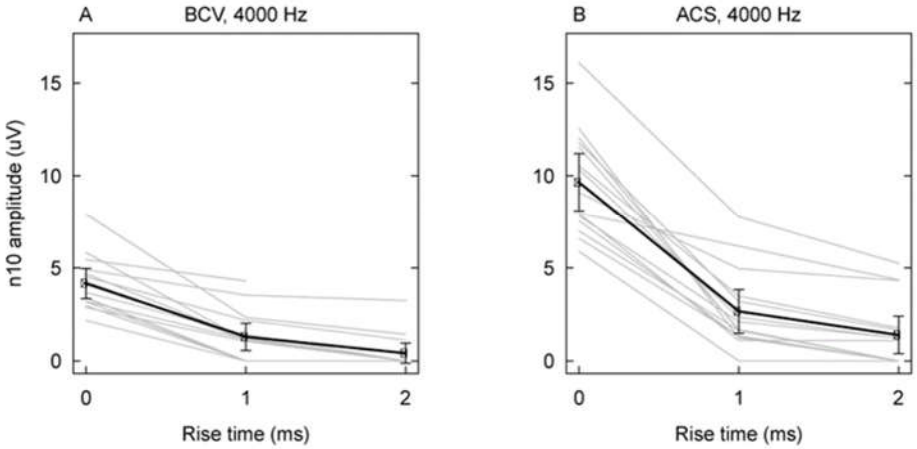

Figure 2. The averaged oVEMP n10 to 4000Hz at each rise-time for individual patients (greyed lines) and the mean across patients in black lines with error bars being 95% confidence intervals.

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4. Discussion

The results demonstrate that rise-time is a very important factor in determining the amplitude of oVEMP n10 to 4000Hz stimulation in patients with CT-verified SCD. Specifically, that stimuli with short rise-times are more effective in generating oVEMP n10 than stimuli with long rise-times. In other words the very earliest part of the stimulus is critical for generating n10. That result follows from recent clinical and neural data published since [15] that the otolithic receptors and afferents responsive to sound and vibration are sensitive to the very onset of the stimulus envelope as we explain below.

Clinical neurophysiology – healthy subjects.

Is there other evidence that it is the early part of the stimulus which is critical for generating VEMPs? Lim et al showed the major importance of the first few milliseconds of a 500Hz BCV stimulus by systematically reducing the duration of the stimulus and measuring the amplitude of oVEMP n10 response at decreasing stimulus durations (with 0ms rise-time) in healthy subjects [23]. The reduction in duration was from 10ms to 2ms and the onset acceleration was identical for all durations. The surprising result was that such a reduction in duration (which reduces the energy delivered enormously), caused no reduction in oVEMP n10 amplitude. In fact the n10 amplitude actually increased at 2ms duration: the average amplitude at 10 ms was 0.9 μV± 1.6 (SD) and the amplitude at 2 ms was 1.4 μV± 1.9 [23]. In unpublished observations we have confirmed that surprising result and extended it to show that even a stimulus of just 1 ms duration elicits an oVEMP n10 as large as one produced by a 10 ms stimulus. It is very surprising because subjectively the stimuli are completely different – a 10ms 500Hz vibration is a strong vibration, whereas a 1ms stimulus is very weak and feels like a light touch. However this very short duration stimulus with an abrupt rise-time, is as effective as a long duration stimulus in generating VEMPs. This result is very strong evidence that it is the very earliest part of the stimulus which is crucial for eliciting oVEMPs.

Complementing that result is other evidence from studies in healthy subjects measuring the amplitude of n10 as the rise-time of 500 Hz or 750 Hz short tone bursts was varied. The data for BCV is shown in Figure 3 and they show that as rise-time was increased from 0ms to 2ms there is a very large reduction in the amplitude of n10 of about 50% for 500Hz and even more for 750Hz. Similarly Kantner et al reported that in healthy subjects that for a 500Hz ACS stimulus, a rise time of 4ms produced around 30% smaller oVEMPs on average than 0 ms rise-time [24].

In healthy subjects and also for ears with normally encased labyrinths (the healthy ear in SCD patients), 4000Hz does not elicit an oVEMP n10 [12](see Figure 1 above). This is probably because primary semicircular canal afferent neurons are not activated by ACS or BCV stimuli (as demonstrated in recordings of vestibular afferents in guinea pigs with normally encased labyrinths)[25]. However, after an SCD those previously unresponsive irregular semicircular canal neurons show strong, phase-locked activation by both ACS and BCV stimuli.[10] which extends to high frequencies. So these physiological studies show that one reason for the existence of a clear oVEMP n10 to 4000Hz is that after SCD this stimulus not only enhances the response of irregular otolithic afferents [25] but also activates irregular semicircular canal afferents which are unresponsive to high frequencies when the bony labyrinth is intact [10,25,26]. In response to Fz BCV after SCD the stimulus activates both otolithic and canal afferents, both of which phase lock to very high frequencies [10]. So the oVEMP n10 in SCD patients is a result of activation of both otolith and canal irregular afferents.

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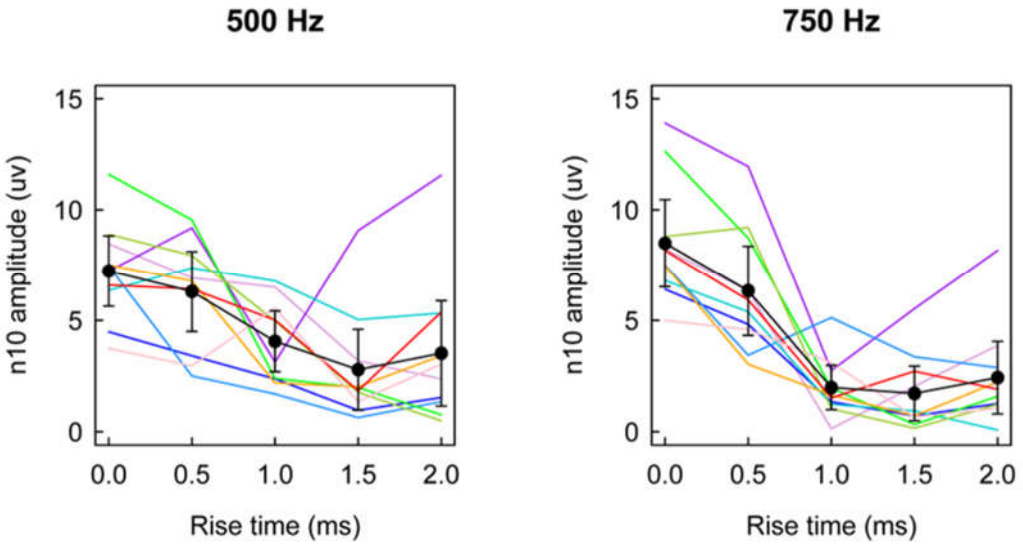

Figure 3. oVEMP n10 amplitude as a function of stimulus rise-time for 10 healthy subjects tested with tone bursts of BCV delivered to Fz with the 4810 minishaker at frequencies of 500 Hz and 750 Hz. Traces show the data for individual subjects. The black trace in each panel shows the mean over the 10 subjects. Error bars show 95% confidence intervals of the mean. Data replotted from [27].

4000 and 8000Hz are frequencies far above what are usually considered to be frequencies stimulating otolithic receptors and afferents, however there is excellent evidence that these high frequencies do activate otolithic receptors and afferents. In guinea pigs the measure of receptor response – the utricular microphonic (analogous to the cochlear microphonic) shows that utricular receptors do respond to such high frequencies (after cochlear ablation so there is no contribution to the utricular microphonic response from cochlear receptors). The microphonic shows clear responses up to above 3 kHz [28]. Recordings from single primary afferent neurons with irregular resting discharge show that after an SCD, primary otolithic and semicircular canal neurons can be activated by sound and vibration at stimulus levels used for clinical testing [10,25,26]. The most compelling evidence is that opening the bony casing of the canal causes previously unresponsive semicircular canal neurons to be activated by ACS and BCV. They are not activated at levels used for clinical testing when the canal is encased in bone. This is strong evidence that the oVEMP n10 is driven by afferent input from both otoliths and semicircular canals.

The importance of stimulus jerk for VEMPs

Jones et al have studied the VsEP in several species. This is the neural potential measured from the scalp triggered by abrupt pulses of linear acceleration and so largely otolithic [29]. Jones has shown this otolithic compound action potential is dependent on the rate of change of the linear acceleration stimulus rather than the magnitude of the linear acceleration itself. This is evidence that otolithic receptors and irregular afferents are responsible for generating VEMPs are activated by the change in linear acceleration at stimulus onset rather than just linear acceleration.

Finally very recent data has recorded the vestibular compound action potential (a measure of the synchronous activation of many primary afferent neurons) recorded in close proximity to the vestibular nerve in guinea pigs in response to brief BCV and ACS transients. Recording directly above the utricular macula in guinea pigs in response to a transient BCV stimulus that increasing the rise-time of that transient stimulus has very substantial effect on the synchronous activation of receptors and afferents, reducing the amplitude of the vestibular compound action potentials as rise-time is increased [30]. The long rise-time acts to "smear" the synchronous activation of otolithic afferents and so greatly reduces the amplitude of the vestibular compound action potential to BCV clicks.

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Rise-time in clinical VEMP testing

When air-conducted tone bursts were originally demonstrated to elicit VEMPs over tensed sternocleidomastoid muscles, standard audiometric parameters were used for the investigation – 1 or 2 ms rise-time for the 500Hz test stimulus [31]. Those rise-times are appropriate for audiometry, where it is essential to have a slow rise-time in order to eliminate an audible click at stimulus onset, but are precisely the opposite of what is required for eliciting responses from vestibular receptors and afferents because a slow rise-time reduces the rate of change of the stimulus which is the key parameter of the stimulus activating the receptor hair cells and afferents and so causing VEMPs.

Studies of the 4000Hz test in SCD patients have used a variety of rise-times including some very long rise-times - even 4ms as used in the Lin et al study [20]). Tran et al [19] and Batuecas-Caletrio et al [14] both used 2ms and our data indicate that with such rise-times it is likely that there would be no detectable oVEMP n10 in some patients. We consider that the lower sensitivity and specificity values for the 4000Hz test may have been due in part to the fact that they did not use an optimum rise-time for the 4000Hz stimulus.

The international recommendations for VEMP testing report a number of parameters which are optimal for eliciting VEMPs but unfortunately rise-time is not given enough attention [11,32]. As is clear from these results, the high frequency VEMP test should use the shortest rise-time possible. Unfortunately, some audiometers cannot generate stimuli with a zero rise-time. However it is important for a clinician to realise that the magnitude of the oVEMP measured with a stimulus with long rise-time underestimates the true amplitude of the oVEMP n10.

Future research should examine whether other labyrinthine conditions which generate enhanced oVEMPs (such as intracochlear schwannomas) also cause enhanced oVEMP n10 to 4000Hz stimulation.

5. Conclusions

Once again, the evidence of this study shows that 4000Hz is an excellent test for identifying SCD. We agree with the conclusion of Noij et al: "VEMP tests using high frequency stimuli are the most accurate single diagnostic test for SCD "[17,18].

Increasing the rise-time of the 4000Hz test stimulus in VEMP testing of patients with CT verified SCD decreases the size of the n10 component of the oVEMP. To optimize the 4000Hz screening test for SCD it is suggested that the rise-time be kept as short as possible and preferably zero.

Given that sound and vibration activate both canal and otolith neurons, the most likely explanation of the enhanced response in SCD patients is that it is due to activation of both utricular and semicircular canal afferents after SCD. The canal contribution is supported by evidence from human patients after SCD: in SCD patients the axis of the eye movement generated by the ACS stimulus corresponds to the anatomical axis of the dehiscent canal [33].

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All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The raw data supporting the conclusions of this paper will be made available by the authors, without undue reservation

Conflicts of Interest: The authors declare no conflict of interest.

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