



Original Article

# Vestibular Response to Electrical Stimulation of the Otolith Organs. Implications in the Development of a Vestibular Implant for the Improvement of the Sensation of Gravito-inertial Accelerations

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**OBJECTIVE:** Electrical stimulation of the utricular and saccular portions of the vestibular nerve improves stability in patients suffering from vestibular dysfunction. The main objective of this study was to evaluate a new technique, vestibular response telemetry (VRT), for measuring the electrically evoked vestibular compound action potential (saccular and utricular) after stimulating the otolith organ (saccular and utricular) in adults. This study used evidence that the otolith organ can be electrically stimulated in order to develop a new vestibular implant design to improve the sensation of gravito-inertial acceleration.

**MATERIALS and METHODS:** Four adult patients were evaluated by using a variety of measurement procedures with novel VRT software. VRT values were obtained by stimulating with three full-band Nucleus CI24RE (ST) electrodes. Specific stimuli were used. Simultaneously, electrical ocular vestibular evoked myogenic potentials (eoVEMPs) were recorded in the contralateral side.

**RESULTS:** Electrically evoked compound action potentials were obtained in 10 of the 12 electrodes tested, and eoVEMPs were recorded when VRT was present. In addition to the validation of this technique, a set of default clinical test parameters was established. The VRT response morphology consisted of a biphasic waveform with an initial negative peak (N1) followed by a positive peak (P1), and latencies were typically 400  $\mu$ s for N1 and 800  $\mu$ s for P1. The consequences for the development of a vestibular implant for the improvement of gravito-inertial acceleration sensation are also presented.

**CONCLUSION:** The VRT measurement technique has been shown to be a useful tool to record neural response on the otolith organ, and thus it is a convenient tool to evaluate whether the implanted electrodes provide a neural response or not. This can be used for the early development of vestibular implants to improve gravito-inertial acceleration sensation.

**KEYWORDS:** Vestibular response telemetry, electrical vestibular myogenic response, vestibular implant

## INTRODUCTION

The loss of vestibular function cannot be restored in all cases, but a vestibular prosthesis can improve balance in many of these patients. Vestibular implant (VI) research has mostly focused on the detection of angular velocity of the cephalic movements through gyroscopes and stimulation of the three-ampulla crests of the semicircular canals in order to improve the vestibular ocular reflex<sup>[1,2]</sup>. However, there are movements corresponding to vertical and horizontal acceleration that still need to be implemented in a VI and that are related to the sensation of gravito-inertial accelerations. These movements are detected by the macules of the saccule and the utricle.

Cervical and ocular vestibular evoked myogenic potentials (cVEMPs and oVEMPs, respectively) are reflexes mediated by the saccule and utricle, respectively. These measurements can be elicited by air-conducted sound, bone-conducted vibration, galvanic stimulation, and vestibular cross-stimulation from the intracochlear electrodes. Though the functional significance of these reflexes is not well understood, VEMPs can be used to assess otolith integrity as well as vestibulo-collic and vestibulo-ocular pathways<sup>[3]</sup>. Vestibular cross-stimulation can be imperceptible and, as such, it likely occurs in a much higher proportion of cochlear implanted patients than previously thought. Although the exact site of vestibular activation with cochlear implants use remains unknown,

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there is evidence to suggest that electric current can bypass the vestibular end organs to more directly stimulate vestibular afferents [4].

In younger populations, the function of the otolith organ is well preserved, but this function decreases with age [5]. It has been observed that there is a reduction of hair cells in the maculae and, additionally, the size and number of neurons and fibers are reduced [6]. It has also been found that there is an age-related decrease in VEMP amplitude and an age-related increase in VEMP latency [7]. Therefore, it is expected that a VI acting on the otolith organs would be helpful, mainly by reducing the risk of secondary-to-imbalance falls in the elderly [8].

There are only a few articles in the literature related to direct stimulation of the otolith organ, and most of them are related to galvanic stimulations and not to electrical stimulations [9]. Other researchers have focused on the concept that if electric current can spread to the facial nerve and stimulate it, the possibility of a vestibular cross-stimulation might be also considered [10–12]. According to this, Gnanasegaram et al. [13] found that electrical pulses from the cochlear implant help to correct asymmetric perceptual tilt in children, especially when the stimulus is provided ipsilateral to the tilt. This effect suggests the existence of a therapeutic benefit of the implant in addition to its main auditory target and related to a possible vestibular cross-stimulation [13]. In this line, Parker et al. described VEMPs responses after cochlear implant stimulation [4].

Most of these studies focused on the oculomotor responses as objective measurement to assess the success of vestibular stimulation. Electrically evoked eye movements have been successfully reported in guinea pigs [14, 15], monkeys [16], and humans [17, 18]. These findings suggest that the electrical stimulation of the vestibule nerve can provide functional inputs.

Results of computational models and electrophysiological experiments have also shown that the distance of the electrode to the neural fibers has an impact on the threshold and the amount of cross talk due to current spread [19, 20]. An intraoperative tool to measure vestibular response telemetry (VRT) is necessary to assure the efficacy of electrode stimulation in order to verify the placement of VIs [21].

In 1992, a bidirectional telemetry feature was implemented in the design of the Nucleus CI24M cochlear implant system that can be used to record auditory electrically evoked compound action potentials (ECAPs) [22]. The action potentials that result from a stimulus are recorded from a neighboring electrode, amplified, and then encoded to be transmitted via the radio frequency link back to the speech processor. Based on this research, we created a custom VRT software in our psychoacoustics and balance laboratory in the hearing loss unit of our department. This software will be presented in advance [23].

The aim of this study was to evaluate the possibility of developing a system capable of recording the ECAPs of the vestibular nerve and of electrically producing an acute stimulation of the otolith organ by using a method in patients with absence of VEMPs and profound deafness before receiving a cochlear implant. This will provide us with information for future development of VIs in order to improve the gravito-inertial accelerations in patients suffering from vestibular dysfunction and not responding to conventional treatment.

## MATERIALS and METHODS

### Subjects

Four patients (3 women and 1 man; ranging from 26 to 54 years old; mean age, 43 years) were considered in this study. The ethics committee for human research of our institution approved the procedure, and the patients gave their informed consent.

Definite unilateral Meniere's disease according to the guidelines of the Barany Society was previously diagnosed in all cases. The duration of the disease ranged from 3 to 7 years [24].

Preoperative videonystagmography showed vestibular hypofunction in the affected ear and normal function on the unaffected side. Magnetic resonance imaging (MRI) presented normal results in all cases. All patients were previously treated with intratympanic gentamicin with no positive response to treatment. Audiologically, all patients had a sensory neural hearing loss of 90 dB HL or greater, with a speech discrimination score of 10% or less and hearing deprivation for 1–6 years. The preoperative vestibular testing results were the following: VEMPs had no response in the ear to be implanted, video head impulse test showed hyporeflexia on the affected side, and the caloric test showed an asymmetry greater than 50% in all cases. All of the preoperative tests results are presented in Table 1.

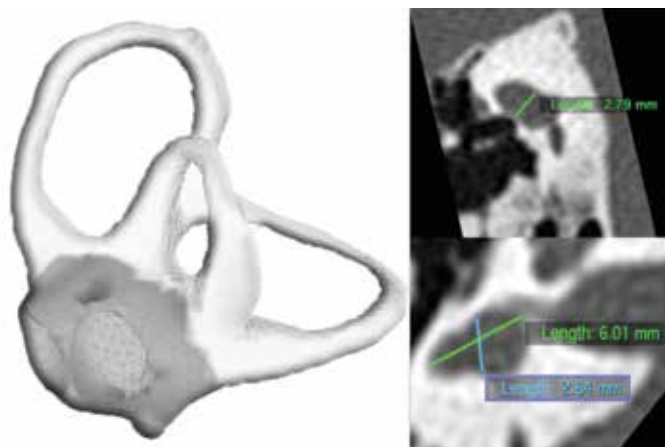
### Stimulation Technique and Surgical Approach

We used a full-band straight electrode, CI24RE (ST), from Cochlear Ltd (Lane Cove, Australia). This electrode array has a diameter of 0.4 mm on the apical part. Each electrode, on the tip, has a cylindrical band of 0.3 mm width and 0.4 mm diameter. The inter-electrode spacing is 0.2 mm on each lead. Full-band electrodes were selected to assure that the electrodes were facing the neural tissue.

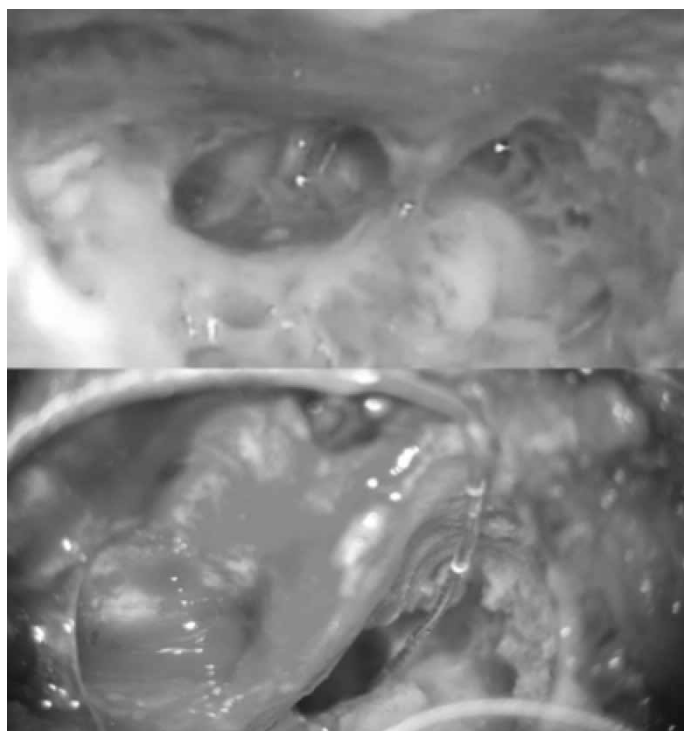
A high-resolution computed tomography (HRCT) scan of all patients was performed to measure the vestibule size. OsiriX software was used to collect all the images, in DICOM file format, of the vestibule. A MatLab script was developed to extract and reconstruct the volume of the vestibule (Figure 1). The vestibule depths varied from 2.79 to 2.53 mm: 2.79 mm, 2.71 mm, 2.53 mm, 2.61 mm.

**Table 1.** Summary of subjects and preoperative testing

Subject	Sex	Age	Audiological		Vestibular		
			PTA	Speech Discrimination	VEMPs	vHIT (gain)	Caloric Test (asymmetry %)
S1	F	56	101	8%	NR	0.45	60
S2	F	26	117	0%	NR	0.56	58
S3	M	50	98	10%	NR	0.54	68
S4	F	40	112	5%	NR	0.62	54



**Figure 1.** Example of HRCT vestibular reconstruction and analysis of its size.

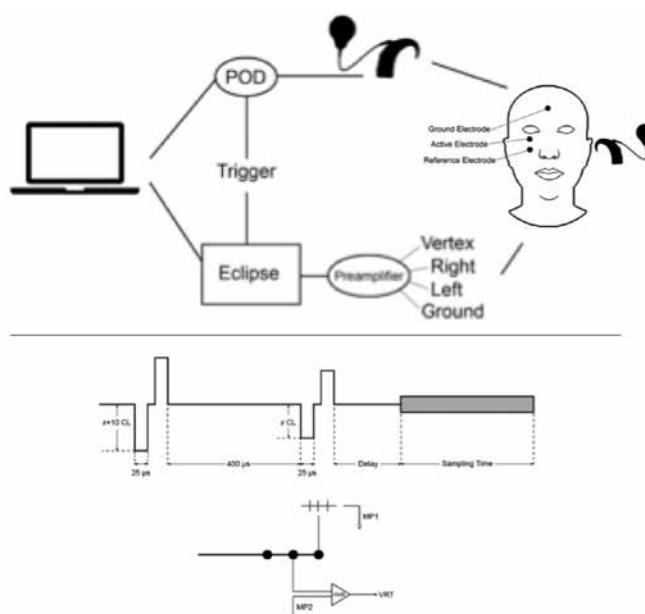


**Figure 2.** Electrode insertion.

The same surgeon performed all procedures (A.R.). Before a complete transmastoid labyrinthectomy was performed, a transmastoid approach through a posterior tympanotomy was performed. This was enlarged in order to visualize the perfect situation of the oval window superstructures. A 0.6 mm hole in the posterior area of the stapes footplate was made with a CO<sub>2</sub> laser prior to insertion. A maximum of three electrodes that correspond with 2.5 mm, were inserted in the vestibule, and the VRT measurements were performed (Figure 2). Once the measurements were completed, a regular cochlear implantation was done after labyrinthectomy. During the surgical intervention, the facial nerve was monitored by a NIM 2 system.

### Vestibular Response Telemetry Test

The Vestibular Response Telemetry software was designed by using the Nucleus Implant Communicator (NIC) library (Cochlear LTD) for Python (Python Software Foundation, v2.4) in order to obtain



**Figure 3.** Vestibular response telemetry test (VRT) and eoVEMPs surgical diagram and electrode montage. VRT parameters with the artifact-reduction paradigm shows the masker advance, masker amplitude, masker pulse width, probe amplitude, probe pulse width, measurement delay, and sampling period. During VRT recordings, one electrode served as the stimulation electrode, while the neighboring electrode was set as the recording electrode.

ECAPs from the vestibular nerve. The software automatically evaluates all of the configurations available on the cochlear implant to find the best VRT response for each patient. On average, total acquisition takes 10 minutes. The software communicates with the speech processor to capture, process, and store the measurement data on a computer (Figure 3). The VRT software controls the parameters of the stimulus used to evoke and record the response to be measured.

The Vestibular Response Telemetry measurements were done after insertion of the three electrodes into the vestibule, and the two reference electrodes were correctly placed and covered by tissue. An extracochlear ball electrode on a flying lead was placed under the temporalis muscle (MP1), and a plate electrode was placed on the receiver-stimulator (MP2). Monopolar stimulation (MP) was used in all trials to activate the maculae. We used the three most apical electrodes to perform the VRT measurements. The active recording electrode was selected iteratively to evaluate all of the combinations. We then studied the effect of different test parameters, including stimulation rate, number of repetitions, measurement delay, masker level, and masker advance (Figure 3).

The specific test (stimulation and recording) parameters studied included 1) measurement delay (80 to 120  $\mu$ s); 2) stimulation rate (90 or 70 Hz); 3) number of samples; and 4) number of averages (50, 100, or 150).

The setup consists of a personal computer, cochlear POD interface, Nucleus Freedom processor (Cochlear Corp., Sydney, Australia), and CI24RE (ST). Additionally, a VEMPs recording system (Eclipse Interacoustic, EP25) was included in order to confirm the stimulation of the vestibular pathway by recording eoVEMPs.

To minimize the stimulation artifacts, the developed VRT software implements the forward-masking paradigm described by Brown et al. [25] and involves a sequence of conditions: probe-only (A), masker-followed-by-probe (B), masker-only stimuli (C), and no stimulation (D). The probe-only condition yields the desired neural response plus an artifact from the probe. The masker-and-probe condition with an appropriate masker advance yields stimulus artifacts for both masker and probe, and the neural responses to the probe are absent or decreased because of the forward masking. The masker-only condition yields only the masker artifact. After the recordings of each of these four stimulation conditions were performed, extraction of the ECAP from the stimulus artifact was accomplished by using the subtraction method ( $A - (B - (C - D))$ ) to cancel the large masker stimulus artifacts found in each condition, and this allows one to extract the relatively small neural response (Figure 4). The amplitude of the probe pulse was progressively increased by a step size of 10 clinical levels (CL) from a masker level up to the maximal safe current level.

### Electrically Stimulated eoVEMPs

In order to record eoVEMPs (responses attributed to the utricular-ocular reflex pathway) simultaneously with the vestibular ECAP, they were obtained while the VRT measurement was performed intraoperatively. A trigger synchronized both systems. Responses were collected and analyzed using a two-channel surface electrode montage and Eclipse Interacoustic EP25 4.4 VEMP 4.3 recording platform.

In order to determine the accuracy of the calibration method, the active electromyogram (EMG) electrode was placed over the medial inferior oblique muscle edge contralateral to the stimulated ear, and the reference electrode was placed on the cheek 1 cm below. The montage ground electrode was placed on the mid-forehead. Impedance was kept below 5 kOhms (Figure 3).

Electromyogram signals were band pass filtered (1 to 3,000 Hz) and recorded in a 25 ms to 50 ms window relative to stimulus onset. No online artifact rejection was used. For all eoVEMP tests, two or more trials (100 sweeps each) were obtained. If such responses were not identified after two trials, testing was ended. The maximum intensity levels were set from 120 to 220 current level (CL), with a 20 CL step size, for both single 57  $\mu$ s biphasic electric pulses (25  $\mu$ s/phase with a 10  $\mu$ s interphase gap). The eoVEMPs tests were first conducted by using electrode 22 and then were repeated by using the other inserted electrodes 21 and 20.

The facial nerve was monitored in all the subjects, and no cross stimulation of the facial nerve was observed in any of these cases.

### Statistical Analysis

A descriptive statistical analysis of the data was carried out. The different neural responses of electrodes 22, 21, and 20 were observed in all subjects. A comparison between 70 Hz and 90 Hz stimulus rates remained constant. Measurements of the numerical variables of VRT and eoVEMPs were classified in absolute values with the different latency values N1 and P1 and the N1-P1 amplitudes of the different subjects as well as with the means of these measures. Student's t-test was used to determine the statistical significance (Level of significance  $p < 0.05$ ).

## RESULTS

Reliable responses with VRT across the patients under different measurement conditions were obtained. The vestibular ECAP response morphology was similar to that obtained in the auditory nerve—a biphasic waveform with an initial negative peak (N1) followed by a positive peak (P1). The impedance values of the three electrodes were within normal limits, indicating good tissue contact throughout.

Vestibular responses could be obtained from four patients (100%), and on 10 of the 12 electrodes tested (83.3%) (Table 2). The insertion into the vestibule of all the electrodes was evaluated by visual observation. No statistical variability was found in ECAP responses (Table 3). A short vestibule was found in subject 4 and only two electrodes were inserted. In the other cases, all the electrodes were placed inside the vestibule. In subject 2, no response was obtained in electrode 20.

The electrically evoked compound action potentials obtained were reliable measurements to qualify the neural survival and the localized spatial resolution. By varying the stimulus amplitude, the amplitude growth function (AGF) in all cases followed the same behavior as in the auditory nerve. This effect is considered as an indication of neural viability. In each case, the masker was kept at a constant +10 CL compared to the probe. The probe varied across 120–220CL (Figure 5).

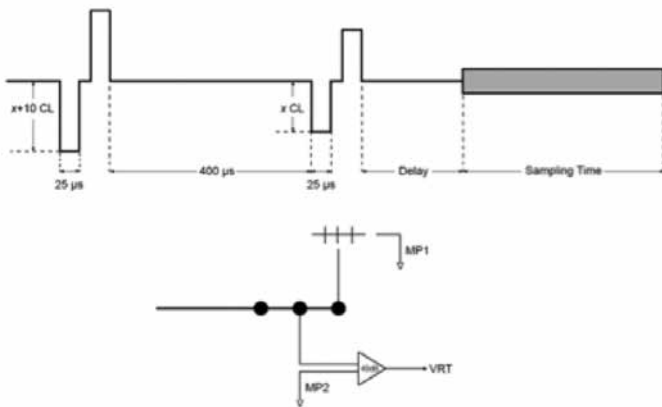
**Table 2.** Summary of measurement results

Subject	Neural Response		
	Electrode 22	Electrode 21	Electrode 20
S1	Yes	Yes	Yes
S2	Yes	Yes	DNR
S3	Yes	Yes	Yes
S4	Yes	Yes	DNI

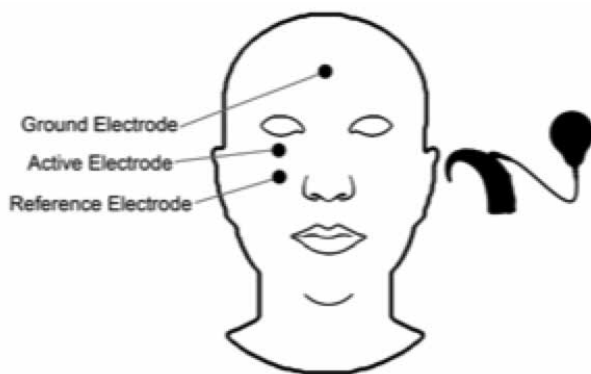
DNR – Did Not Response  
DNI – Did Not Inserted

**Table 3.** Record VRT measurements

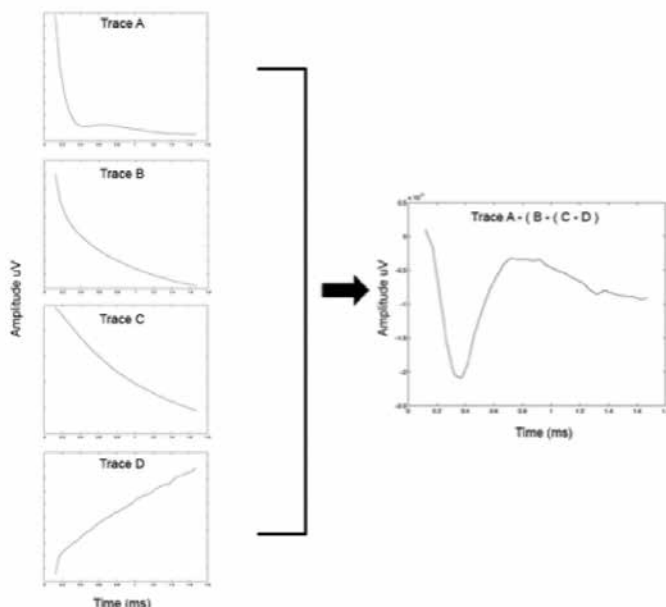
Subject	Electrode	Latencias		Amplitud
		N1	P1	P1-N1
S1	22	334 $\mu$ s	813 $\mu$ s	70.3 $\mu$ V
S1	21	420 $\mu$ s	808 $\mu$ s	56.6 $\mu$ V
S1	20	358 $\mu$ s	812 $\mu$ s	81.2 $\mu$ V
S2	22	340 $\mu$ s	821 $\mu$ s	73.5 $\mu$ V
S2	21	355 $\mu$ s	820 $\mu$ s	67.0 $\mu$ V
S2	20	-	-	-
S3	22	359 $\mu$ s	821 $\mu$ s	78.3 $\mu$ V
S3	21	348 $\mu$ s	819 $\mu$ s	66.6 $\mu$ V
S3	20	410 $\mu$ s	822 $\mu$ s	80.4 $\mu$ V
S4	22	327 $\mu$ s	822 $\mu$ s	70.2 $\mu$ V
S4	21	313 $\mu$ s	819 $\mu$ s	67.4 $\mu$ V
S4	20	-	-	-
Average		356.4 $\mu$ s	817.7 $\mu$ s	71.15 $\mu$ V



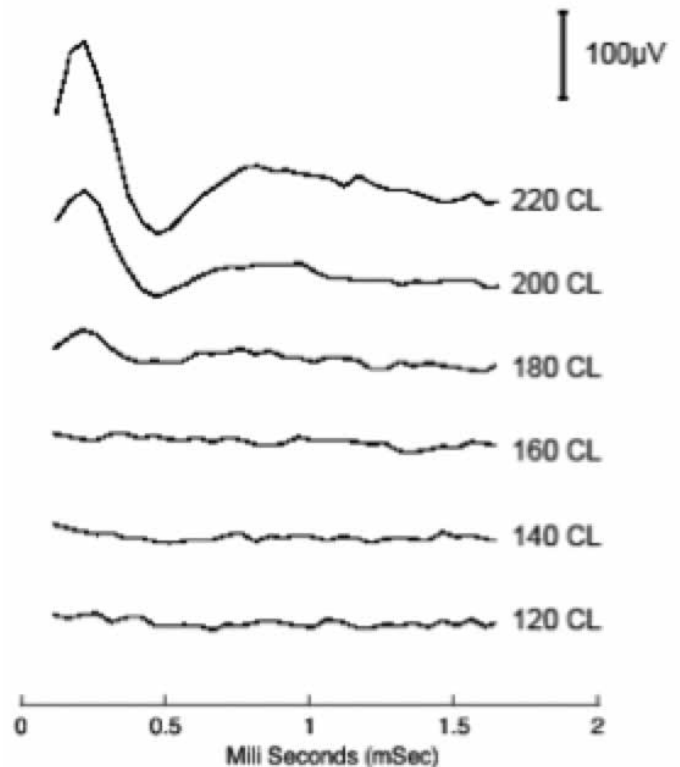
**Figure 4.** Subtraction method for reducing masker stimulus artifact. Stimulation signals from buffers A, B, C, and D are shown on the left. The subtraction paradigm was  $(A - (B - (C - D)))$ .



**Figure 5.** Examples of the ECAP waveforms that were recorded. A typical amplitude growth series indicating how the neural response changes with the stimulation level. The first negative peak (N1) of the vestibular response occurs between 370  $\mu$ s and 420  $\mu$ s after the stimulus onset, and this is followed by the first positive peak (P1) occurring at approximately 820  $\mu$ s after the stimulus onset. The response amplitude is defined as the peak-to-peak amplitude from N1 to P1. Plotting the change in response amplitude as a function of the stimulation level yields the amplitude growth function (AGF).



**Figure 6.** Amplifier saturation due to high amplification.



**Figure 7.** Comparison of stimulation rates, 70 Hz and 90 Hz, with all others parameters kept constant.

The measurement delay was evaluated in all subjects. The results showed that shorter delays were more likely to result in overloading of the measurement amplifier, producing a distorted waveform (60.0 dB gain and 80  $\mu$ s delay) (Figure 6). The increase in the delay reduces the possibility of saturating the measurement amplifier, but excessive delays could result in missing features of the waveform.

The best gain values in all cases were 40 dB. The records from all subjects show saturation at 60 dB and, in most of them, at 50 dB. Therefore, 40 dB gains recorded clear neural responses also with a short delay. The optimal gain depends on the subject and the delay selected, but in our case the best combination was 40 dB measurement gain and 120  $\mu$ s delay.

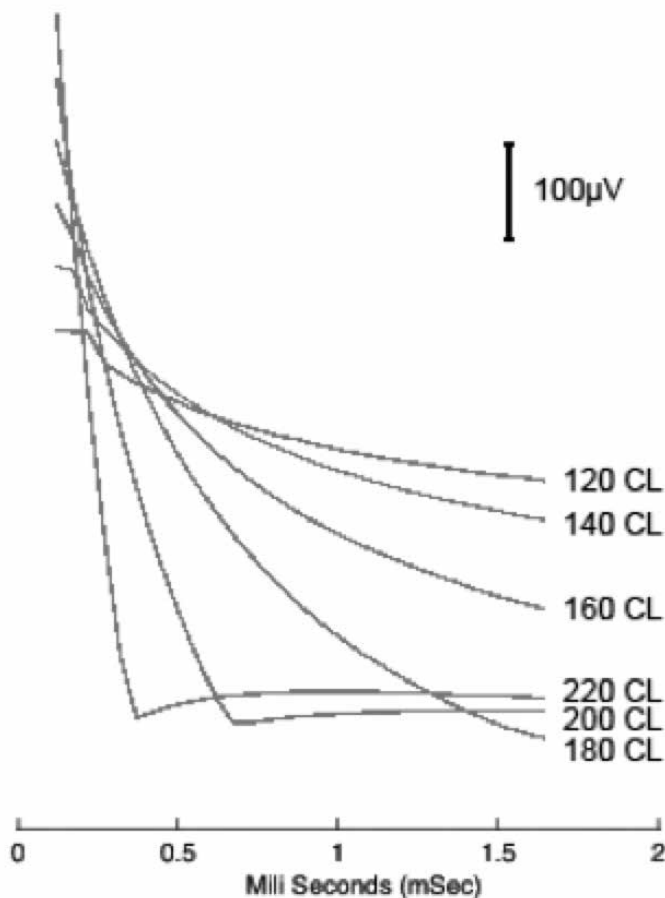
A comparison of stimulation rates (70 Hz and 90 Hz) was carried out in all subjects, and no difference in the resulting vestibular response was seen in any of the cases (Figure 7). The vestibular ECAP response duration in all the records was below 1 ms. So, considering that the sampling period of the cochlear implant device is fixed at 50  $\mu$ s, the minimum number of samples that should be taken to be sure to obtain the full VRT response is 32 samples. In all of our cases, 32-sample recordings were made, thus taking 1.6 ms.

The best configuration was 32 samples at 40 dB gain and a delay of 120  $\mu$ s, and 50, 100, and 150 repetitions were evaluated. The best result was for 150 repetitions, which gave a clear neural response.

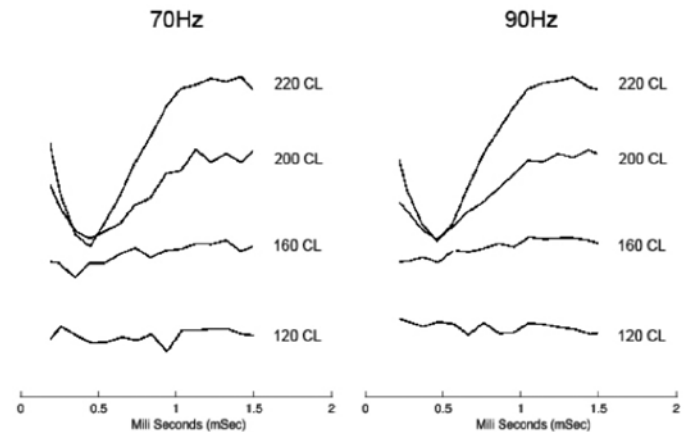
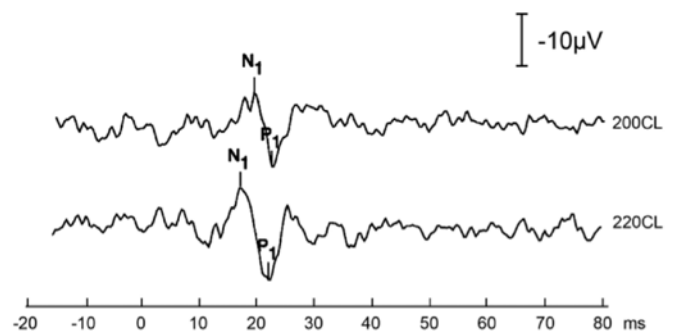
During the VRT recordings, an eVEMPs was also performed in order to determine the correlation between measurements. All of the

**Table 4.** Record eoVEMPs measurements

Subject	Electrode	Latencias		Amplitud
		N1	P1	P1-N1
S1	22	13 ms	18 ms	8.4 $\mu$ V
S1	21	15 ms	17 ms	11.42 $\mu$ V
S1	20	11 ms	20 ms	10.3 $\mu$ V
S2	22	7 ms	13 ms	10.0 $\mu$ V
S2	21	10 ms	16 ms	9.6 $\mu$ V
S2	20	-	-	-
S3	22	12 ms	21 ms	10.5 $\mu$ V
S3	21	14 ms	20 ms	9.9 $\mu$ V
S3	20	11 ms	17 ms	8.6 $\mu$ V
S4	22	14 ms	14 ms	10.9 $\mu$ V
S4	21	9 ms	22 ms	7.9 $\mu$ V
S4	20	-	-	-
Average		11.6 ms	17.8 ms	9.75 $\mu$ V

**Figure 8.** eoVEMPs responses in the contralateral eye electrically stimulated by an electrode in the macula region. Negative is up in this figure.

ears tested for eoVEMPs were nonresponsive to acoustic stimulation preoperatively. In all the ears, an electrically stimulated oVEMP was present when VRT was present (Figure 8). Electromyographic activity was monitored in real time. The recorded eoVEMP response was a

**Figure 9.** Detail of the electrode to stimulate the otolith organ in humans. Pat. 2015/00835. PCT/ES2016/000021**Figure 10.** Voltage recordings during biphasic current-driven stimulation using one electrode of the arrays with a 5 kOhm impedance at different current levels.

biphasic waveform with an initial negative peak (N1) followed by a positive peak (P1), and as previously described by Parkes et al.<sup>[4]</sup>, no statistical variability was found in eoVEMPs responses (Table 4).

## DISCUSSION

In this paper, we demonstrate that vestibular ECAP responses are obtained after electrical stimulation of the otolith organ by using a similar stimulation paradigm as in cochlear implants. The VRT response, which has been recorded in the human vestibular end organ, displays many of the characteristics of the compound action potential recorded in the cochlea.

The ability to record neural responses in 83.3% of the tested electrodes supports the validity of the VRT system to measure vestibular-origin ECAPs in adult subjects.

We had already demonstrated that it was possible to generate a VRT response correlated to eoVEMPs responses through an electrode placed in the otolith organs. The ideal location of the electrode was determined by monitoring the VRT performed at slightly different places during the insertion. We observed that a minimal displacement of the electrode resulted in drastic changes in the amplitude of the responses, thus stabilization of the electrode array is necessary to obtain good responses. This also indicates that the presence of ECAP obtained from VRT and the correlation with eoVEMPs responses, when the stimulus is delivered on the otolithic organ and not when the electrode is incorrectly placed, is because it is a vestibular ECAP

and not an auditory response. Also, it is important to mention that the eoVEMPs were not obtained when the auditory neural response telemetry from the cochlear implant was performed.

The best test configuration parameters are a stimulation rate of 90 Hz, amplifier gain of 40 dB, 140 sweeps, a fixed masker level equal to the probe +10 CL, a masker advance of 400  $\mu$ s, and a delay of 120  $\mu$ s, and this provides the quickest and most reliable results in the tested adults.

The Vestibular Response Telemetry records collected showed consistent patterns in waveform morphology, response latency, and amplitude growth, and they were similar to previously recorded cochlear ECAPs in human patients [26, 27]. The N1 latency of the VRT and the P1 peak are both consistent with observations in cochlear ECAPs.

Animal experiments and data in humans suggest that electrical stimulation of the vestibular end organs could be used to treat loss of vestibular function [28].

Previous research suggests that the implementation of a vestibular prosthesis provides partial restitution of the vestibulo-ocular reflex (VOR) and might also improve perception and posture in the presence of bilateral vestibular hypofunction. Additionally, Perez Fornos et al. [29, 30] suggest that VOR restoration can improve the stabilization abilities with a VI.

Vestibular implants are devices designed to rehabilitate patients suffering from a dysfunction of VOR that impairs gaze stabilization and results in an abnormal loss of visual acuity in dynamic situations. Patients suffering from bilateral vestibular dysfunction can benefit from the stimulation of the otolith organ because it might have potential effects on more complex integrative behaviors such as the perception of head orientation and posture.

The results of this study provide evidence for the benefits of chronic stimulation of the otolith organ in patients suffering from bilateral vestibular dysfunction and profound sensorineural hearing loss. Development of a device for measuring the cephalic movements in three dimensions and conveying this information in a useful way to stimulate the vestibular nerve in order to replace the function of the labyrinth through the macules of the saccule and utricle is the focus of much research (Pat. 2015/00835. PCT/ES2016/000021) (Figure 9). The compliance of the current source of the stimulation circuitry of this design and the impedance of the electrode, based on size, material, and shape, can drive the electrode with charge-balance and biphasic, triphasic, or multiphase current pulses with a maximum charge injection limit of 1000  $\mu$ A (Figure 10). In addition, the possibility to have an electrode disposition allows the design of several stimulation strategies (monopolar, bipolar, tripolar, multipolar, or command ground) in order to achieve functional stimulation of the utricle and saccule.

## CONCLUSION

Vestibular Response Telemetry provides a method to assess peripheral neural function, and the recording technique is analogous to the ECAP recordings that are widely used in cochlear implant research and clinical practice. The VRT technique is effective for recording neural responses in the maculae region and provides us with a con-

venient tool to determine if the implanted electrodes are driving a neural response and, thus, to give information to help identify the optimum electrode placement during VI surgery. The weakness of this study is the small sample size, which is due to the ethical committee conditions and to the low disease prevalence. A set of default test parameters has been established to provide a relatively quick method of measuring the vestibular ECAP in our subjects. As far as we know, this is the first study that demonstrates the electrically evoked response of the directly stimulated otolith organ in humans.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of CEIC - 764 (11/06/2015).

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

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

**Author Contributions:** Concept - A.R.d.M., A.R.M.; Design - A.R.d.M., J.C.F.G.; Supervision - A.R.M.; Resources - A.R.M.; Materials - J.C.F.G.; Data Collection and/or Processing - A.R.d.M.; Analysis and/or Interpretation - J.C.F.G., A.R.M.; Literature Search - A.R.d.M.; Writing Manuscript - A.R.d.M., A.R.M.; Critical Review - A.R.M.

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