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PhD Thesis

ELECTROCOCHLEOGRAPHY: DEVELOPMENT OF METRICS AND OPTIMIZED RECORDING TECHNIQUES

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Ai miei genitori,

la mia forza.

ABSTRACT

Introduction: Traditionally, ear surgeries where the integrity of the inner ear is compromised are considered destructive procedures. While these operations can be very successful for threatening certain inner ear diseases, they always determine a complete loss of hearing. Electrocochleography (ECochG) is a technique that allows for the measurement of the auditory evoked potentials that arise from the inner ear and spiral ganglion. As opposed to far-field recording techniques, ECochG is considered a near-field recording montage, mainly due to the proximity of the recording electrode to the source generators in the inner ear. The aims of these thesis were to investigate the potential mechanisms of hearing loss/preservation via electrophysiological measures during several types of otologic and skull base procedures (i.e., cochlear implantation, CI, Ménière's disease, MD, resection of vestibular schwannoma, VS, etc.). Additionally, an animal model was used to isolate the complex sources of the summating potential (SP) for better interpretation for clinical purposes.

Materials and methods: Patient interventions consisted of intraoperative round window ECochG during surgery: tone burst stimuli were presented from 95 to 110 dB SPL. Round window ECochG to tones and clicks was also performed in the animal model. Lastly, a group of patients scheduled to receive a lateral wall electrode underwent ECochG recorded directly from a CI electrode array during its insertion, with the Active Intraoperative Monitoring (AIM, Advanced Bionics, Valencia, CA).

Results: ECochG findings in VS and MD patients evidenced a reduced trend in amplitude of the ongoing response with increased stimulus frequency. In a case of jugular foramen tumor removal, the compound action potential magnitudes increased at all test frequencies ($p<0.01$) and serviceable hearing was confirmed by audiometric testing after tumor resection. Despite the small number of patients, heterogeneous ECochG response patterns were observed within the CI fold-over group, while regarding the ECochG-total response, all controls showed a decrease in the magnitude. The animal model evidenced that the sources of the SP include at least four components presenting a mixture of polarities and magnitudes.

Conclusions: Intraoperative ECochG may allow for real-time monitoring of auditory function during complex skull base surgery, minimizing trauma for electrode insertion and reducing complications such as tip fold-over during CI surgery. Findings of cochlear pathology were likely present in patients with VS and MD. Finally, the complex mixture of cochlear and neural sources should be acknowledged when interpreting the SP for clinical purposes.

Key words

Electrocochleography, auditory evoked response, cochlear implants, cochlear synaptopathy.

Riassunto in italiano

Introduzione: Tradizionalmente, gli interventi chirurgici otologici, in cui l'integrità dell'orecchio interno è compromessa, sono considerati demolitivi per l'udito, sebbene siano efficaci nel trattare alcune disabilitanti malattie. L'elettrocoleografia (ECochG) è una tecnica che consente la misurazione dei potenziali evocati uditivi che derivano dall'orecchio interno e dal ganglio spirale grazie alla prossimità dell'elettrodo di registrazione. Questa tesi ha l'obiettivo di indagare i potenziali meccanismi di perdita/preservazione dell'udito mediante ECochG eseguita durante diversi tipi di procedure chirurgiche otologiche e della base cranica laterale (es. impianto cocleare, IC, malattia di Ménière, MD, resezione di schwannoma vestibolare, VS, ecc.). Inoltre, è stato utilizzato un modello animale per isolare le componenti del potenziale di sommazione (SP) al fine di consentirne una migliore interpretazione clinica.

Materiali e metodi: I pazienti inclusi sono stati sottoposti a ECochG dalla finestra rotonda durante l'intervento chirurgico: gli stimoli presentati sono stati tone burst da 95 a 110 dB SPL. Anche nel modello animale è stata eseguita l'ECochG della finestra rotonda. Infine, un gruppo di pazienti programmati per ricevere un IC "lateral wall" sono stati sottoposti a ECochG direttamente attraverso il multielettrodo durante il suo inserimento, con il monitoraggio intraoperatorio attivo (AIM, Advanced Bionics, Advanced Bionics LLC, Valencia, CA).

Risultati: I risultati ECochG nei pazienti con VS e MD hanno evidenziato una riduzione nell'ampiezza della risposta all'aumentare della frequenza dello stimolo. In un caso di rimozione di un tumore del forame giugulare, il potenziale d'azione composto è aumentato a tutte le frequenze ($p<0.01$) e la preservazione dell'udito è stata confermata dall'esame audiometrico post-operatorio. Nonostante l'esiguo numero di pazienti, sono stati osservati pattern di risposta ECochG eterogenei all'interno del gruppo con tip-fold-over, mentre tutti i controlli hanno mostrato una diminuzione della risposta ECochG-totale. Il modello animale ha evidenziato che il SP presenta almeno quattro componenti, di cui due neurali, con una miscela di polarità e ampiezze.

Conclusioni: L'ECochG intraoperatoria può consentire il monitoraggio uditivo in tempo reale durante chirurgie complesse della base cranica laterale, di minimizzare il trauma durante l'inserimento del multielettrodo e di ridurre alcune complicanze come il tip-fold-over durante la chirurgia dell'IC. Segni di patologia cocleare sono risultati presenti nei pazienti con VS e MD. Infine, dovrebbe essere annoverata l'intricata origine cocleare e neurale nell'interpretazione clinica del SP.

Parole chiave

Elettrocoleografia, potenziali evocati uditivi, impianti cocleari, sinaptopatia cocleare.

CONTENTS

PREFACE

Over the past century, the field of otology, neurotology, and lateral skull base surgery has developed rapidly and constantly. Initially, the practice of otology was primarily focused on the drainage of infection of the ear and temporal bone. In the last half of the 20th century, William House and others established the transtemporal approaches to the internal auditory canal and cerebellopontine angle as well as the cochlear implant (CI) and facial nerve monitor, thereby providing the basis for the field of neurotology and lateral skull base surgery. With the advent of refined techniques and hearing devices, surgical restoration of hearing loss became reality even in individuals undergoing complex surgeries such as removal of vestibular schwannomas (VS). In the last decades, new diseases and therapeutic concepts continue to be defined thanks to the genetics of hearing loss. Today, advances in biomedical engineering and molecular biology lead the way to the next generation of developments that are already visible on the horizon. Also, there is major awareness about the diagnosis of hidden hearing loss (HHL) and a wider range of solutions to clinicians and their patients[1].

Interventions such as CI that were once considered somewhat surreal currently allow deaf people to return to the world of sound and, therefore, to life. Because of this progress, there is now the need to expand indications to these solutions and new concepts such as hearing and structure preservation have arisen[2].

Electrocochleography (ECochG) is a technique for recording evoked potentials from the inner ear and spiral ganglion. It is useful for assessing inner ear function in both laboratory and clinical settings. It was discovered somewhat serendipitously by Wever and Bray in 1930[3], who were attempting to record from cat auditory nerve fibers, and after almost 100 years of history can be considered part of the neurotology mainstream with a wide range of applications[4].

This PhD thesis represents the sum of these features of evolution that now characterize the field of otology, neurotology, and lateral skull base surgery. It requested an international collaboration with the Ohio State University Wexner Medical Center, the University of North Carolina at Chapel Hill and the IRCCS Research Hospital Casa Sollievo della Sofferenza. This PhD thesis is meant to create a “jumping-off” point for a continuous translational project starting from an animal model developed at the University of North Carolina at Chapel Hill[5] to clinical applications of ECochG in otology and neurotology practice, embracing several types of surgeries ranging from CI to Meniere’s disease (MD) and lateral skull base surgery.

INTRODUCTION

Traditionally, ear surgeries where the integrity of the inner ear is compromised are considered destructive procedures. While these surgeries can be very effective for threatening certain inner ear disorders, they always determine a complete loss of hearing. However, recent advances in CI with hearing preservation have demonstrated that hearing may be preserved despite opening of the inner ear.

Labyrinthectomies, frequently performed for MD, are very successful for treating the debilitating vestibular symptoms related to this disease[6]. However, as these surgeries involve opening of the inner ear, they always result in an ipsilateral profound hearing loss. Similarly, surgical approaches through the labyrinth, known as translabyrinthine approach, as frequently performed to remove VS, do not allow for hearing preservation[7].

Also, endolymphatic sac decompression is a surgery that is commonly performed for MD. The surgery is executed by thinning the bone over the endolymphatic sac to reduce pressure. Unlike labyrinthectomy, it is not considered "destructive" to hearing; most patients do not experience hearing loss because of the surgery, although it is always discussed as a complication. The reasons that some patients have a drop in hearing following an endolymphatic sac decompression, and others do not, is not clear. Performing intraoperative electrophysiological measures, such as ECochG, at the time of an endolymphatic sac decompression may shed light on the mechanisms at work[6].

It remains unclear, however, why exactly hearing is lost during these procedures; especially since only the vestibular portion of the inner ear is removed but the cochlear portion is left intact. The loss of perilymph fluid with subsequent loss of the endocochlear potential has been considered responsible for this. However, sporadic reports on successful preservation of some hearing remnants have been published. Further, some authors have debated that portions of the labyrinth that connect the cochlear and the vestibular portions could be blocked to avoid hearing loss[8,9].

Despite these reports, the details remain enigmatic. The studies included in this PhD thesis aims at investigating these potential mechanisms via electrophysiological measures during several types of otologic and skull base procedures (i.e., CI, MD, VS removal etc.) that will possibly allow correlation of real-time information on hearing physiology with what surgical steps are being

performed. Likely, this information could reveal not only the timing of hearing loss during these procedures but also could shed light on the underlying mechanisms.

This study will also adopt electrophysiological measurements during otologic procedures requiring a transmastoid approach. A transmastoid approach is any ear surgery that necessitates the drilling of the mastoid bone to enter the middle and inner ear such as during CI. Performing ECochG during these approaches will allow the surgeons to learn about hearing physiology in a cochlea that is not compromised by the surgical approach[10].

Potential benefits to individual participants in this study include possible preservation of hearing during these surgeries via direct physiological feedback. Society may benefit from a better understanding of these mechanisms of hearing loss and/or preservation during destructive inner ear procedures so that improved techniques can be developed that may allow for more consistent hearing preservation.

ELECTROCOCHLEOGRAPHY: HISTORY AND NEW ADVANCES

Definition

Electrocochleography (ECochG) is a technique that allows for the measurement of the auditory evoked potentials that arise from the inner ear and spiral ganglion[1]. As opposed to far-field recording techniques, such as auditory brainstem responses (ABR), ECochG is considered a near-field recording montage, mainly due to the proximity of the recording electrode to the source generators in the inner ear[11].

Technique

The measurements can be accomplished by placing the recording electrode in the ear canal or on the tympanic membrane (extratympanic), by directly positioning an electrode on the cochlear promontory near the round window (RW) niche (transtympanic), or through the facial recess onto the RW (Figure 1). Non-invasive extratympanic electrodes can be easily placed without anesthesia or patient discomfort, while the latter type of measurements requires more invasive access. Intraoperative RW measurements improve the signal to noise ratio and thus reduce the number of averaging cycles needed to attain an acceptable response in a faster acquisition time. Additionally, in the last few years, intracochlear (IC) ECochG measurements, either directly through the CI or when a monopolar probe is placed inside the RW within the cochlea have been accomplished. Also, recordings acquired noninvasively via the wireless neural response telemetry (NRT) system of a CI are cataloged as IC recordings[12].

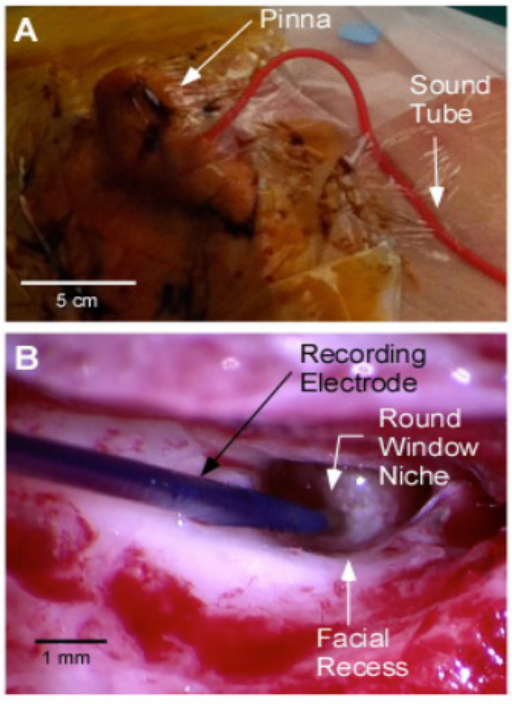


Fig. 1. A) ECochG recording montage. B) RW ECochG. Courtesy of Prof. Oliver Adunka.

ECochG potentials

ECochG responses of interest (Figure 1) comprise direct cochlear potentials, such as the cochlear microphonic (CM) from the outer hair cell stereocilia, and neural potentials, which include the compound action potential (CAP) and the auditory nerve neurophonic (ANN). Additionally, the summating potential (SP) is also of interest and is thought to have contributions from both hair cell and neural sources[5,13].

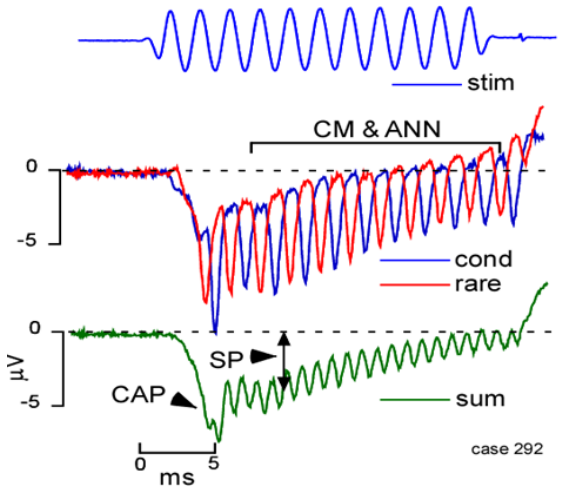


Figure 1. ECochG potentials (courtesy of Prof. Oliver Adunka).

History and traditional applications

From its discovery in 1930 by Wever and Bray[3], who were attempting to record from cat auditory nerve fibers, the major clinical use of ECochG over the years has concerned estimation of hearing thresholds. ECochG has also been traditionally used clinically as an objective measure to identify and monitor ELH[14] and MD[6]. Coats[15] first described the association between MD and the abnormally enlarged SP. Additionally, the SP/AP ratio can be increased, which is thought to be indicative of ELH[15].

Other authors have also asserted that the absolute SP response amplitudes to frequency-specific tone bursts may be more sensitive in detecting hydrops than responses to short stimuli (‘‘clicks’’) or the SP/AP ratio itself[16]. In addition, ECochG has been used for enhancing the identification of the wave I in ABR[17], and for the intraoperative monitoring of the auditory function during CI and lateral skull base surgery[18–21].

APPLICATIONS OF ELECTROCOCHLEOGRAPHY IN COCHLEAR IMPLANTATION: A SYSTEMATIC REVIEW OF THE LITERATURE

INTRODUCTION

Electrocochleography (ECochG) is a technique that consents the registration of the auditory evoked potentials that arise from the inner ear and spiral ganglion. As opposed to far-field recording techniques, such as auditory brainstem responses (ABR), ECochG is considered a near-field recording montage, mainly due to the proximity of the recording electrode to the source generators in the inner ear. The measurements can be accomplished by placing the recording electrode in the ear canal or on the tympanic membrane (extratympanic), by directly positioning an electrode on the cochlear promontory near the round window (RW) niche (transtympanic), or through the facial recess onto the RW[22]. Non-invasive extratympanic electrodes can be easily placed without anesthesia or patient discomfort, while the latter type of measurements requires more invasive access. Intraoperative RW measurements improve the signal to noise ratio and thus reduce the number of averaging cycles needed to attain an acceptable response in a faster acquisition time[23].

ECochG responses of interest comprise direct cochlear potentials, such as the cochlear microphonic (CM) from the outer hair cell stereocilia, and neural potentials, which include the compound action potential (CAP) and the auditory nerve neurophonic (ANN). Additionally, the summating potential (SP) is also of interest and is thought to have contributions from both hair cell and neural sources[5,13].

From its discovery in 1930 by Wever and Bray, the major clinical use of ECochG over the years has concerned estimation of hearing thresholds[24,25]. ECochG has also been traditionally used clinically as an objective measure to identify and monitor endolymphatic hydrops and Meniere's disease. Coats[15] first described the association between Meniere's disease and the abnormally enlarged SP. Additionally, the SP/AP ratio can be increased, which is thought to be indicative of endolymphatic hydrops. Other authors have also asserted that the absolute SP response amplitudes to frequency-specific tone bursts may be more sensitive in detecting hydrops than responses to short stimuli ("clicks") or the SP/AP ratio itself. In addition, ECochG has been used for enhancing the identification of the wave I in ABR, and for the intraoperative monitoring of the auditory function.

More recently, ECochG has demonstrated potential utility in CI. Specifically, it can be used intraoperatively during electrode insertion to mitigate possible intracochlear damage and to optimize electrode placement[26]. Further, since modern CI devices feature recording capabilities typically used as part of neural response imaging (NRI®), neural response telemetry (NRT®), or auditory response telemetry (ART®), the electrode array and its intracochlear site can be used as the recording ECochG electrode to further improve the signal to noise ratio of the measurements[27]. This

can reduce the acquisition time and improve the sensitivity so that meaningful, real-time recordings can be obtained in cochlear implant candidates[28].

Besides this application as an insertion monitor, ECochG has shown further promise in investigating hearing loss genetics[29], predicting cochlear implant performance[30], to identify the scalar location of CI electrodes, detailing diagnosis of site-of-lesion in auditory neuropathy spectrum disorder (ANSD), and improving selection of cochlear implant candidates[17].

Given the high heterogeneity of the published literature and the recent surge in interest in the use of ECochG during and following CI, the aim of the present paper was to systematically analyze the literature on this topic.

MATERIALS AND METHODS

This systematic review was written according to the Primary Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Guidelines[31,32].

Search strategy and article selection process

The National Library of Medicine through PubMed was searched for the following keywords: "Cochlear Implant" OR "Cochlear Implantation" AND "Electrocochleography" OR "ECochG". The first author collected articles published on PubMed at any time before or on February 8, 2020. Also, references of the retrieved articles and personal communications were considered potentially eligible for this systematic review.

The main eligibility criteria were English-language articles, randomized and controlled trials in humans as well as animal studies investigating the use of ECochG related to CI. There were no exclusion criteria concerning date of publication, study duration, or design. Literature reviews, technical notes, letters to the editor, case reports, case series or trials including less than 4 participants, instructional courses, and conference papers were not included in our systematic review. Papers not focused on CI and ECochG, and in which ECochG use was inconsistent were also excluded.

Data extraction and quality assessment

Three authors (Eleonora M.C. Trecca, William J. Riggs, and Oliver F. Adunka) independently screened the full-text version of each publication, conducted data extraction, and excluded those papers whose content was judged not to be relevant to the purpose of this review. When agreement

could not be reached, two others from our group (Jameson K. Mattingly, Meghan M. Hiss) were consulted, and another (Michele Cassano) was asked for data extraction and quality assessment. ECochG applications were grouped into three main domains according to the CI patient care timeline: preoperative diagnostics, intraoperative use, and post-operative follow-up. Among these three groups, topics of interest, such as hearing preservation, speech perception outcomes, electrode positioning, and study of hearing loss genetics, were identified. Additionally, papers were classified according to the ECochG technique executed in extratympanic (ET), transtympanic (TT), RW via the facial recess, and intracochlear (IC), either directly through the CI or when a monopolar probe was placed inside the RW within the cochlea. Also, recordings acquired noninvasively via the wireless NRT system of a CI were included in the IC category**.** The general features of each article (journal, first author, country, year of publication, population, human or animal setting, CI timeline, technique, topic of the paper, and study quality) were recorded in a spreadsheet. The quality of the included studies was assessed using "The Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) Statement with a score interval from 0 to 22, with a higher score indicating a better study quality. To mitigate the risk of bias, papers of all quality were included in this systematic review.

RESULTS

After excluding duplicate findings, 95 articles were retrieved. Thirty-five articles were eliminated for the following reasons (Figure 1): written in languages other than English (10 – eight in German, one in Russian, and one in Chinese); reviews, editorials, and case reports (15); written with the focus/topic on non-CI hearing devices (2 - round window vibroplasty and auditory brainstem implants). Additionally, eight papers were excluded due to not being directly relevant to the topic. Three papers were excluded because they were not focused on ECochG and three because CI had only a marginal role. Finally, one paper was eliminated because ECochG was not performed for all subjects and another article because a CI was inserted in just one patient. After the exclusions, 60 (63.8%) papers were included for final analysis. Out of these papers, 51 were collected by searching on PubMed and an additional 9 were found via personal communications and/or cross-references.

The included articles covered a timeframe from 2003 to 2019 (Figure 2). Of the 60 papers, 46 (76.7%) were human (Table 1) and 12 (20.0%) were animal studies (Table 2). Additionally, two studies (3.3%) involved more data sets (Table 3). Within the human studies, 21 were focused on adults, 9 were focused on pediatric patients, and 16 included both adults and children. Regarding the animal studies, 4 were conducted on guinea pigs and 8 on gerbils. In the two studies involving

more datasets, one included gerbils and human CI recipients, and another included a third data set of simulated signals. Regarding the time of CI, 11 pertained to the diagnostic phase, 43 described various aspects of intraoperative monitoring, and 10 focused on follow-up testing. Four studies discussed more than one clinical phase of care in relation to placing the implant. Regarding ECochG technique, IC ECochG was used in 30 studies, RW ECochG in 25, TT ECochG in 10, and ET ECochG from the eardrum in just one. In six studies more than one ECochG technique was used. Hearing preservation was the most common topic, followed by diagnosis of ANSD, the evaluation of speech perception outcomes, hearing assessment in CI users, electrode placement, and CI diagnostics (Figure 3). Within the 60 included articles, 32 were from the USA, 20 from other various countries (seven from Australia, eleven from Europe, and two from Asia), and 8 where the investigators were from more than one country.

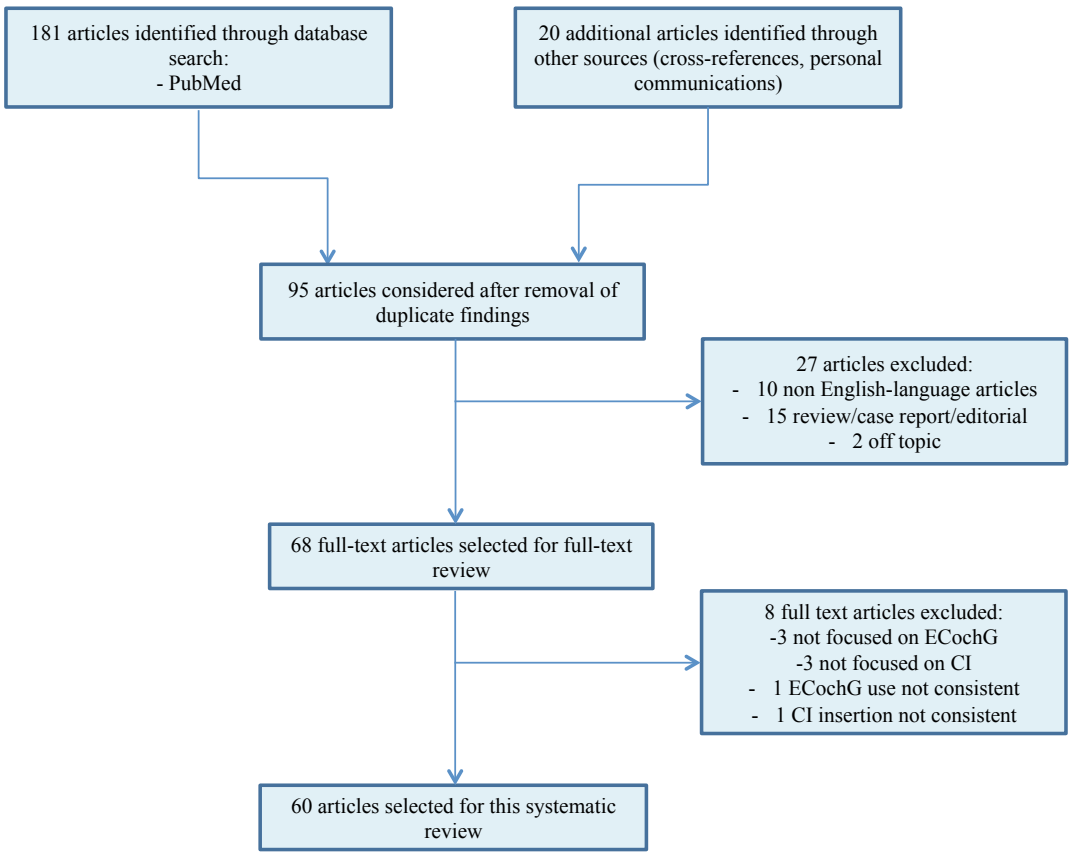


Fig. 1. PRISMA flow diagram. PRISMA indicates Primary Reporting Items for Systematic Reviews and Meta-analyses.

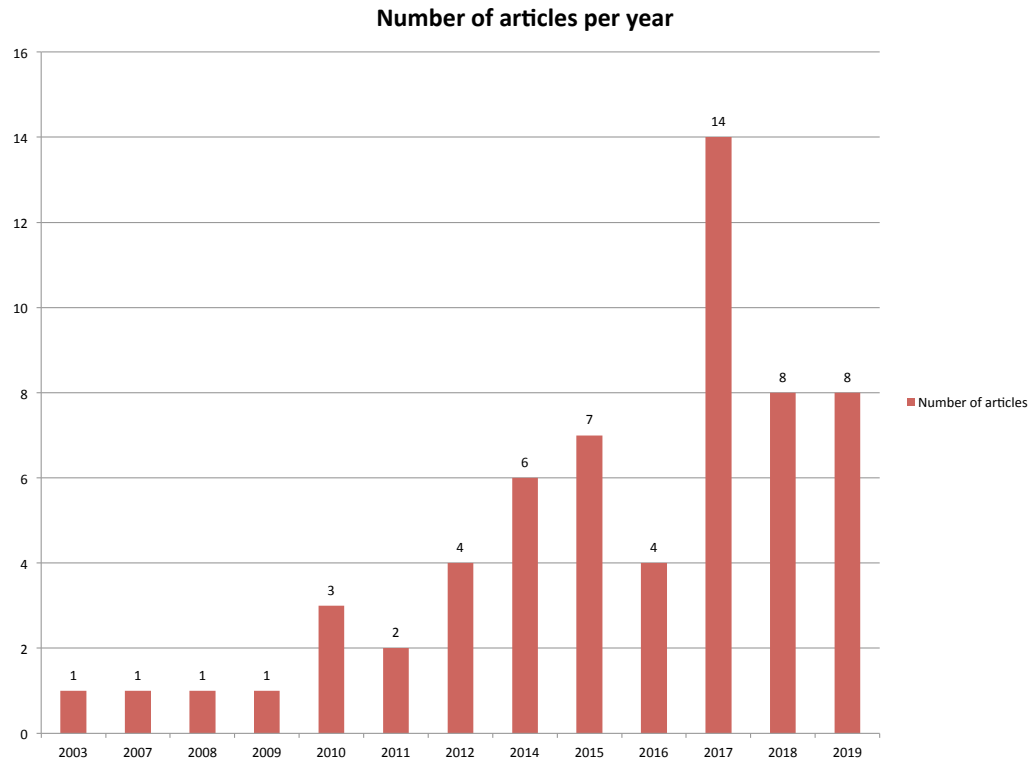


Fig. 2. Number of articles per year. The included 60 articles covered a timeframe from 2003 to 2019.

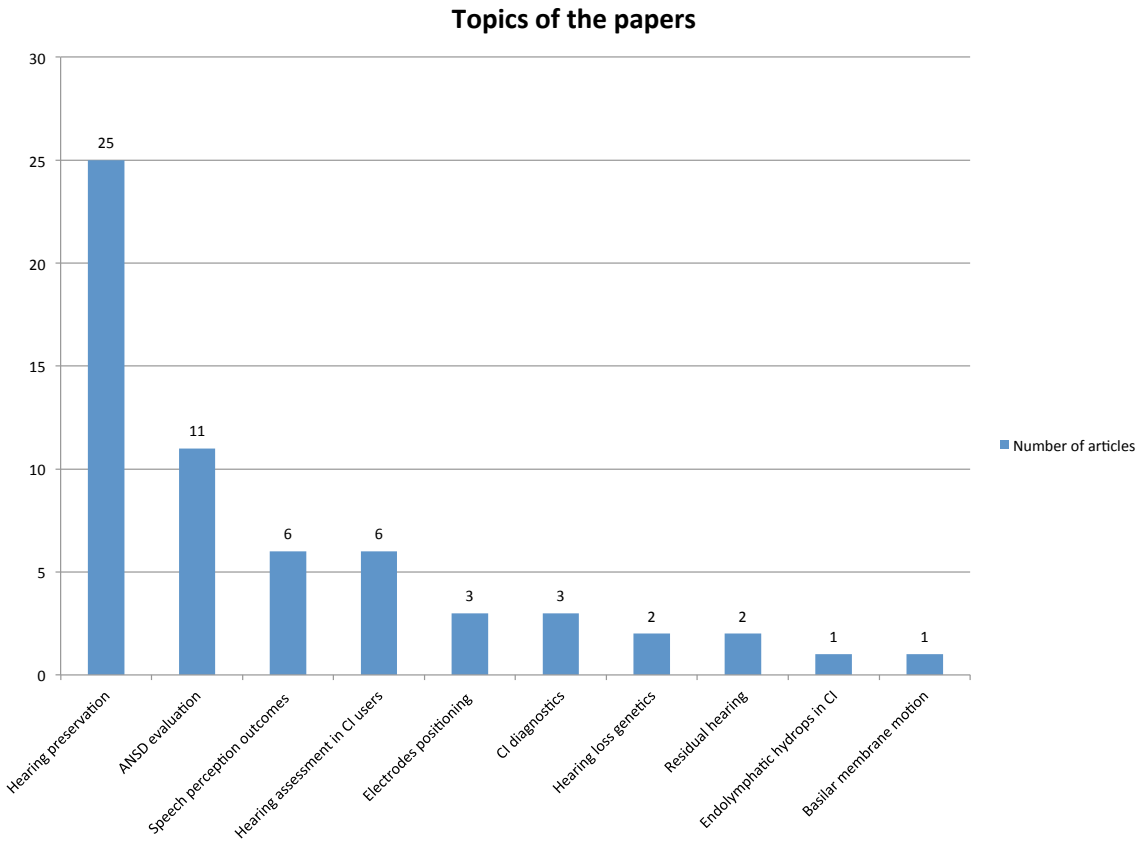


Fig. 3. Topics of the included articles. Hearing preservation was the most discussed topic.

DISCUSSION

From its discovery by Wever and Bray in 1930[3], ECochG has played a significant role in the field of otology and neurotology. Although its most well-known uses are in estimating hearing thresholds and evaluating for endolymphatic hydrops, ECochG has recently shown encouraging results in the diagnosis of ANSD, identifying noise- and age-related cochlear synaptopathy, real-time monitoring of auditory function during lateral skull base surgery, and, of most importance for this article, many aspects of CI. This last aspect has gained considerable attention in the literature over the past several years, specifically with its promise in predicting trauma within the cochlea that could compromise hearing preservation and served as the purpose/focus of this review.

ECochG in Cochlear Implantation

CIs are life-changing hearing devices which have become routinely performed and enable profound hearing-impaired patients to improve their hearing abilities and speech perception. However, the procedure is not without risk of trauma to the IC structures and thus can compromise preservation of residual hearing, and as a result, there has been significant interest in techniques to prevent or monitor this trauma, the latter of which ECochG seems to be useful[33].

Because ECochG has the potential to reliably detect trauma with CI, there is an increasing interest in the literature from the first applications of ECochG and CI in 2003 to present time, including a peak in 2017 with 14 published articles (Figure 2). Initially, ECochG was executed TT and used primarily for ANSD evaluation[34]. We also see an evolution of the technique from the first attempt to execute the intraoperative extracochlear monitoring in an ANSD patient in 2006[35], to the establishment of an animal model[36] and refinement of signal processing[37] between 2006 and 2010 in the USA. From 2010 to 2015 more investigators from all over the world explored this technology and its feasibility in CI further[38]. The human studies helped solidify the usefulness of ECochG by showing the relationship of CI users' performance and the speech perception outcomes[39]. Shortly after this time, there was an optimization of the recording speed and a device implementation with IC ECochG obtained directly through a CI from the most apical electrode. From 2015 to present time, researchers were more knowledgeable on CI diagnostics. In their animal study Forgues et al.[37] distinguished hair cell from neural potentials recorded at the RW, while Pappa et al.[5] recently studied the hair cell and neural contribution to the cochlear SP in a complex study involving more data sets. Also, in 2017 Campbell et al. studied the electrophysiological evidence of the basilar membrane motion by using intraoperative IC ECochG in humans. The aims of other quite recent animal studies were the investigation of endolymphatic hydrops in the first weeks following CI

surgery and the use of preoperative steroids to minimize insertion trauma, both by using RW ECochG[40].

While ECochG investigations have risen considerably over recent years, the applications of the technique have been heterogeneous. Interestingly, this systematic review shows that ECochG has been used the most to realize the goal of hearing preservation in 25 published papers. Conventional CI surgery is usually traumatic for residual hearing due to potential damage in various sites such as the spiral ligament, basilar membrane, osseous spiral lamina, and other structures[41]. During hearing preservation attempts, it is obviously important to minimize every kind of insertion trauma[42]. As a result, it seems that ECochG monitoring during CI can enhance the possibility of residual hearing maintenance, and potentially determine better speech perception outcomes for the patient[43]. Similarly, effective intraoperative monitoring could expand the indication for CI surgery to patients with residual low-frequency hearing and increase the number of candidates who can potentially benefit from CI[44]. According to other authors, future directions are also represented by a robotic controlled electrode insertion[45]. The possible combination of a robotic guidance with a real-time intraoperative ECochG monitoring could theoretically maximize the prevention of the implantation trauma.

The second most investigated clinical application of ECochG has been the ANSD evaluation with eleven human studies (table 1), which in turn has led to a better comprehension of hearing loss genetics in another two of the included papers in this review. Auditory neuropathies are typically detected by ECochG with an absent or abnormal CAP, even at high stimulations, in the presence of a robust CM. A detailed diagnosis of the site-of-lesion is also fundamental for the prediction of CI outcomes, which are generally worse in neuropathic patients.

ECochG has proven to be useful intraoperatively and in the post-operative phase, as well. The relationship between ECochG recordings and speech perception outcomes, which has already been mentioned regarding hearing preservation, was evidenced in six of the included studies in this review. Out of this group, Kim et al.[46] used IC ECochG measurements from cochlear implant (Nucleus Hybrid L24) users. Also, ECochG was used in another six papers to investigate the CI recipients' performance and assess their hearing level during follow-up. All papers included in this group related to the follow-up phase and used IC ECochG, thus taking advantage of the capability of modern CI features that include NRT capabilities[47–49].

One of the most innovative achievements obtained through the intraoperative monitoring has been the study of electrode positioning, though only three articles focused on this aspect have been published so far, two on humans and one using an animal model[50]. In all these articles, the most

advanced intraoperative IC ECochG technique was used. About the stimulus parameters, the two human studies used a 50-ms tone burst stimulus (500 Hz) delivered at 110 dB SPL, while in the animal research clicks and tone bursts of increasing intensity (0 to 80 dB SPL; 5 dB steps) were presented. Of the human studies, Koka et al.[26] developed an algorithm with the purpose to predict the electrode final scalar location, which was verified by postoperative computed tomography (CT) and presented with a sensitivity of 100% and a specificity of 77%. The most recent paper by Riggs et al.[50] used intracochlear ECochG to identify electrode array-induced trauma/scalar translocation. Their most interesting finding was that translocation from scala tympani to scala vestibuli may not change the biomechanics of the cochlear region which lies basal to the area of translocation. In their animal study, Helmstaedter et al.[51] proved by intraoperative IC ECochG that, among the different electric potentials, SP could be a marker for the cochleotopic position of a CI, thus, turning the CI into a "theragnostic probe".

It has long been known that ECochG provides a highly informative window into cochlear physiology; the technique was used with the purpose of further understanding the CI diagnostics in three of the included papers of this review. Gerbils are animals widely used for auditory studies because they hear into the low frequency range similarly to humans. Also, they present a simply accessible cranial anatomy[52]. The neurotoxin kainic acid (KA) is a glutamate analog, which destroys nerve terminals through excitotoxicity, the same mechanism described for cochlear synaptopathy[53]. In this series of studies about CI diagnostics, the authors used a gerbil model and pharmacological manipulations with KA with the goal of fully separating and measuring the neural and hair cell sources of ECochG recorded from the RW, under anatomical control. These results provide standard data to interpret analogous recordings from human CI subjects and in other clinical settings.

Study quality was assessed using the STROBE score[54], as it is presently being used by an increasing number of top scientific journals to improve the quality of reporting and it was recommended for authors of Otolaryngology articles and editors of Ear, Nose, Throat (ENT) journals, as well[55]. The assessment process revealed that the included studies were mostly of very high quality. Lower scores were mainly due to the number of participants, the descriptive data provided, the analysis of variables, the generalizability, and the presence of bias. Additionally, to avoid partiality, researchers not working in the same center and with whom the authors have never published were consulted for the evaluation of the papers from the authors group.

To the best of our knowledge, this study is the first systematic review discussing the applications of ECochG in the field of CI. Our study design followed the PRISMA guidelines[31], and only the original articles focused on an extensive use of ECochG before, during, and after CI were included. Unfortunately, the high heterogeneity of papers and the study populations did not allow a meta-analysis. However, cataloging and discussing all the uses of ECochG in CI was carried out to guide further research and advances in this field and, thus, improve the standard practice.

Besides the positive possibilities, the aim of this systematic review was to point out that there is still more to do. Firstly, the main efforts of researchers should be put in simplifying ECochG so that it can become accessible even to personnel with limited training and routinely performed in CI surgery. Quasi near-field measurements, such as RW ECochG, offer good signal-to-noise ratio (SNR), but require a surgical environment and must be executed under general anesthesia. Also, intraoperative ECochG is not correlated with additional risks, but makes the intervention a little bit longer. Conversely, ET ECochG can be performed in an outpatient setting, but is not able to record the CM, CAP, ANN and SP. ET ECochG had a limited impact in just one of the included articles of this systematic review, but with its minimum patient discomfort might be a promising implement in the pre-operative phase[56].

CONCLUSIONS

ECochG measurements appear to be useful in many aspects of CI. It has been shown to be feasible in animal and human models, particularly with hearing preservation, the study of ANSD patients, and the relationship of post-operative CI performance. Our review is the first that discusses the evolution of ECochG and how much progress has been achieved in a relatively short time. Further research is needed to make the technique more accessible and to understand how ECochG, together with other innovative systems, can improve the prediction of post-operative outcomes.

Table 1. Features of the human studies.

Study Nº	Source	Title	Year	Country	Study population	CI phase	Technique	Topic	STROBE score*
1	Tejani VD et al.	Impact of stimulus frequency and recording electrode on electrocochleography in Hybrid cochlear implant users.	2019	USA	6 adults	Intraoperative	IC	Hearing assessment in CI users	20
2	Ehrmann-Müller D et al.	Evaluation and therapy outcome in children with auditory neuropathy spectrum disorder (ANSD).	2019	Germany	32 children	Diagnostic/ Follow up	TT	ANSD evaluation	19
3	Riggs WJ et al.	Intracochlear Electrocochleography: Influence of Scalar Position of the Cochlear Implant Electrode on Postinsertion Results.	2019	USA	21 adults	Intraoperative	IC	Electrode positioning	22
4	Ramos-Macias A et al.	Intraoperative Intracochlear Electrocochleography and Residual Hearing Preservation Outcomes When Using Two Types of Slim Electrode Arrays in Cochlear Implantation.	2019	Spain/Australia	15 adults	Intraoperative	IC	Hearing preservation	21
5	Haumann S et al.	Monitoring of the Inner Ear Function During and After Cochlear Implant Insertion Using Electrocochleography.	2019	Germany	10 adults	Intraoperative	RW, IC	Hearing preservation	22
6	Tejani VD et al.	An improved method of obtaining electrocochleography recordings from Nucleus Hybrid cochlear implant users	2019	USA/Korea	8 adults	Follow-up	IC	Hearing assessment in CI users	22
7	Dalbert A et al.	Changes of Electrocochleographic Responses During Cochlear Implantation Presented at the Annual Meeting of ADANO 2016 in Berlin.	2019	Switzerland	8 adults	Intraoperative	RW	Hearing preservation	21
8	Kim JS et al.	Postoperative Electrocochleography from Hybrid Cochlear Implant users: An Alternative Analysis Procedure.	2018	USA	34 adults	Follow-up	IC	Hearing assessment in CI users	22
9	Giardina CK et al.	Intracochlear Electrocochleography: Response Patterns During Cochlear Implantation and Hearing Preservation	2018	USA	36 subjects (5 adults, 31 children)	Intraoperative	IC	Hearing preservation	22

10	Shearer AE et al.	In Vivo Electrocochleography in Hybrid Cochlear Implant Users Implicates TMPRSS3 in Spiral Ganglion Function	2018	USA	8 subjects (7 adults, 1 child)	Diagnostic	IC	Hearing loss genetics	19
11	Fontenot TE et al.	Residual Cochlear Function in Adults and Children Receiving Cochlear Implants: Correlations With Speech Perception Outcomes.	2018	USA	178 subjects (84 adults, 94 children)	Intraoperative	RW	Speech perception outcomes	22
12	Koka K. et al.	Intra-Cochlear Electrocochleography During Cochlear Implant Electrode Insertion Is Predictive of Final Scalar Location	2018	USA	32 adults	Intraoperative	IC	Electrode positioning	21
13	Giardina CK et al.	Response Changes During Insertion of a Cochlear Implant Using Extracochlear Electrocochleography.	2018	USA	63 subjects (45 adults, 18 children)	Intraoperative	TT, RW	Hearing preservation	22
14	Dalbert A et al.	Assessment of Cochlear Function during Cochlear Implantation by Extra- and Intracochlear Electrocochleography	2018	Switzerland/ USA	77 adults	Intraoperative	TT, IC	Hearing preservation	22
15	Campbell L et al.	Electrophysiological Evidence of the Basilar-Membrane Travelling Wave and Frequency Place Coding of Sound in Cochlear Implant Recipients.	2017	Australia/ Germany	6 subjects	Intraoperative	IC	Basilar membrane motion	17
16	Harris MS et al.	Patterns Seen During Electrode Insertion Using Intracochlear Electrocochleography Obtained Directly Through a Cochlear Implant	2017	USA	17 subjects (5 children, 12 adults)	Intraoperative	IC	Hearing preservation	22
17	Riggs WJ et al.	Intraoperative Electrocochleographic Characteristics of Auditory Neuropathy Spectrum Disorder in Cochlear Implant Subjects.	2017	USA	267 subjects (167 children, 163 adults)	Intraoperative	RW	ANSD evaluation	22
18	Koka K et al.	Feasibility of Using Electrocochleography for Objective Estimation of Electro-Acoustic Interactions in Cochlear Implant Recipients with Residual Hearing	2017	USA	12 subjects	Follow-up	IC	Hearing assessment in CI users	18
19	O'Connell BP et al.	Intra- and Postoperative Electrocochleography May Be Predictive of Final Electrode Position and Postoperative Hearing Preservation.	2017	USA	18 adults	Intraoperative	IC	Hearing preservation	22

20	Harris MS et al.	Real-Time Intracochlear Electrocochleography Obtained Directly Through a Cochlear Implant	2017	USA/ Argentina	14 subjects (both pediatric and adults)	Intraoperative	IC	Hearing preservation	22
21	Kim JR et al.	Intracochlear Recordings of Acoustically and Electrically Evoked Potentials in Nucleus Hybrid L24 Cochlear Implant Users and Their Relationship to Speech Perception	2017	USA/Korea	25 adults	Follow-up	IC	Speech perception outcomes	20
22	Koka K et al.	An Objective Estimation of Air-Bone-Gap in Cochlear Implant Recipients with Residual Hearing Using Electrocochleography.	2017	USA/Israel	4 adults	Follow-up	IC	Hearing assessment in CI users	20
23	Bester CW et al.	Characterizing Electrocochleography in Cochlear Implant Recipients with Residual Low-Frequency Hearing.	2017	Australia	45 adults	Intraoperative	IC	Residual hearing	22
24	Koka K et al.	Electrocochleography in Cochlear Implant Recipients With Residual Hearing: Comparison With Audiometric Thresholds	2017	USA	20 adults	Intraoperative	IC	Residual hearing	22
25	Fontenot TE et al.	Clinical role of electrocochleography in children with auditory neuropathy spectrum disorder.	2017	USA	104 children	Intraoperative	RW	ANSD evaluation	22
26	Scott WC et al.	The Compound Action Potential in Subjects Receiving a Cochlear Implant.	2016	USA	242 subjects (112 adults and 130 children)	Intraoperative	RW	Speech perception outcomes	22
27	Dalbert A et al.	Assessment of Cochlear Trauma During Cochlear Implantation Using Electrocochleography and Cone Beam Computed Tomography.	2016	Switzerland	14 adults	Intraoperative	RW	Hearing preservation	22
28	Adunka OF et al.	Round window electrocochleography before and after cochlear implant electrode insertion.	2016	USA	31 subjects (14 children, 17 adults)	Intraoperative	RW	Hearing preservation	22
29	Kaga K et al.	Auditory nerve disease and auditory neuropathy spectrum disorders	2016	Japan	17 adults	Diagnostic	ET	ANSD evaluation	14
30	Dalbert A et al.	Extra- and Intracochlear Electrocochleography in Cochlear Implant Recipients.	2015	Switzerland	9 adults	Intraoperative	TT, IC	Hearing preservation	20
31	Santarelli R et al.	Audibility, speech perception and processing of temporal cues in ribbon synaptic disorders due to OTOF mutations	2015	Italy/ Spain/ USA	8 children	Diagnostic	TT	Hearing loss genetics	20
32	Dalbert A et al.	Correlation of Electrophysiological Properties and Hearing Preservation in Cochlear	2015	Switzerland	19 adults	Intraoperative	RW	Hearing preservation	22

		Implant Patients.							
33	Santarelli R et al.	OPA1-related auditory neuropathy: site of lesion and outcome of cochlear implantation.	2015	Italy	10 children	Diagnostic/ Follow-up	TT	ANSD evaluation	22
34	Formeister EJ et al.	Intraoperative round window electrocochleography and speech perception outcomes in pediatric cochlear implant recipients.	2015	USA	77 children	Intraoperative	RW	Speech perception outcomes	22
35	Stuermer KJ et al.	The correlation between ECochG parameters and early auditory behavior after cochlear implantation in children.	2015	Germany	18 children	Diagnostic	TT	ANSD evaluation	19
36	Campbell L et al.	Cochlear response telemetry: intracochlear electrocochleography via cochlear implant neural response telemetry pilot study results.	2014	Australia	5 adults	Follow-up	IC	Hearing assessment in CI users	19
37	McClellan JH et al.	Round window electrocochleography and speech perception outcomes in adult cochlear implant subjects: comparison with audiometric and biographical information.	2014	USA	32 adults	Intraoperative	RW	Speech perception outcomes	21
38	Calloway NH et al.	Intracochlear electrocochleography during cochlear implantation.	2014	USA	26 subjects (17 children, 9 adults)	Intraoperative	RW, IC	Hearing preservation	22
39	Fitzpatrick DC et al.	Round window electrocochleography just before cochlear implantation: relationship to word recognition outcomes in adults.	2014	USA	84 subjects (52 children, 32 adults)	Intraoperative	RW	Speech perception outcomes	22
40	Mandalà M et al.	Electrocochleography during cochlear implantation for hearing preservation.	2012	Italy	27 adults	Intraoperative	RW	Hearing preservation	22
41	Choudhury B et al.	Intraoperative round window recordings to acoustic stimuli from cochlear implant patients.	2012	USA	25 subjects (11 children, 14 adults)	Intraoperative	RW	Hearing preservation	20

42	Aimoni C et al.	Hearing threshold assessment in young children with electrocochleography (ECochG) and auditory brainstem responses (ABR): experience at the University Hospital of Ferrara.	2010	Italy	272 children	Diagnostic	TT	ANSD evaluation	18
43	Wang LE et al.	Application of intraoperative round window electrocochleography for screening the patients with auditory neuropathy.	2009	China	32 patients (from 1 to 31 years)	Intraoperative	RW	ANSD evaluation	20
44	McMahon CM et al.	Frequency-specific electrocochleography indicates that presynaptic and postsynaptic mechanisms of auditory neuropathy exist.	2008	Australia	14 children	Diagnostic	RW	ANSD evaluation	20
45	Gibson WP et al.	Auditory Neuropathy: An Update	2007	Australia	39 children	Diagnostic	RW	ANSD evaluation	16
46	Mason JC et al.	Cochlear Implantation in Patients With Auditory Neuropathy of Varied Etiologies	2003	USA	6 subjects (4 adults, 2 children)	Diagnostic	TT	ANSD evaluation	16

Abbreviations: CI, cochlear implant; ANSD, Auditory Neuropathy Spectrum Disorder; ET, extratympanic; TT, transtympanic; RW, round window; IC, intracochlear. *Scores interval from 0 to 22, with higher scores showing better study quality.

Table 2. Features of the animal studies.

Study Nº	Source	Title	Year	Country	Animal model	CI phase	Technique	Topic	STROBE score*
1	Helmstaedter et al.	The Summating Potential Is a Reliable Marker of Electrode Position in Electrocochleography: Cochlear Implant as a Theragnostic Probe.	2018	Germany	10 guinea pigs	Intraoperative	IC	Electrode positioning	22
2	Lo J et al.	Intraoperative force and electrocochleography measurements in an animal model of cochlear implantation	2017	Australia	32 guinea pigs	Intraoperative	IC	Hearing preservation	22
3	Lo J et al.	The Role of Preoperative Steroids in Atraumatic Cochlear Implantation Surgery.	2017	Australia	48 guinea pigs	Diagnostic/ Follow-up	RW	Hearing preservation	22
4	Smeds H et al.	Endolymphatic hydrops is prevalent in the first weeks following cochlear implantation	2015	Australia	21 guinea pigs	Intraoperative/ Follow-up	RW	Endolymphatic hydrops in CI	22
5	Forgues M et al.	Distinguishing hair cell from neural potentials recorded at the round window.	2014	USA	23 gerbils	Intraoperative	RW	CI diagnostics	22

6	Choudhury B et al.	Electrophysiologic consequences of flexible electrode insertions in gerbils with noise-induced hearing loss.	2014	USA	16 gerbils	Intraoperative	RW, IC	Hearing preservation	21
7	DeMason C et al.	Electrophysiological properties of cochlear implantation in the gerbil using a flexible array.	2012	USA	21 gerbils	Intraoperative	IC	Hearing preservation	20
8	Ahmad FI et al.	Detection of intracochlear damage during cochlear implant electrode insertion using extracochlear measurements in the gerbil.	2012	USA	15 gerbils	Intraoperative	TT	Hearing preservation	22
9	Choudhury B et al.	Detection of intracochlear damage with cochlear implantation in a gerbil model of hearing loss.	2011	USA	22 gerbils	Intraoperative	IC	Hearing preservation	20
10	Suberman TA et al.	A gerbil model of sloping sensorineural hearing loss.	2011	USA	10 gerbils	Intraoperative	IC	Hearing preservation	19
11	Campbell AP et al.	Correlation of early auditory potentials and intracochlear electrode insertion properties: an animal model featuring near real-time monitoring.	2010	USA	16 gerbils	Intraoperative	IC	Hearing preservation	21
12	Adunka OF et al.	Intracochlear recordings of electrophysiological parameters indicating cochlear damage.	2010	USA	9 gerbils	Intraoperative	IC	Hearing preservation	20

Abbreviations: CI, cochlear implant; ANSD, Auditory Neuropathy Spectrum Disorder; ET, extratympanic; TT, transtympanic; RW, round window; IC, intracochlear. * Scores interval from 0 to 22, with higher scores showing better study quality.

Table 3. Features of the studies involving more data sets.

Study Nº	**Source**	**Title**	**Year**	**Country**	**Study population**	**CI phase**	**Technique**	**Topic**	**STROBE score***
1	Pappa AK et al.	Hair Cell and Neural Contributions to the Cochlear Summating Potential.	2019	USA	2 data sets: 57 gerbils, human CI recipients (n=334)	Intraoperative	RW	CI diagnostics	22
2	Fontenot TE et al.	A Model-Based Approach for Separating the Cochlear Microphonic from the Auditory Nerve Neurophonic in the Ongoing Response Using Electrocochleography.	2017	USA	3 data sets: human CI recipients (n=285), gerbils, simulated signals	Intraoperative	RW	CI diagnostics	22

Abbreviations: CI, cochlear implant; ANSD, Auditory Neuropathy Spectrum Disorder; ET, extratympanic; TT, transtympanic; RW, round window; IC, intracochlear. *Scores interval from 0 to 22, with higher scores showing better study quality.

FOUR SOURCES OF THE SUMMATING POTENTIAL: OUTER HAIR CELLS, INNER HAIR CELLS, SPIKING AND DENDRITIC COMPONENTS

INTRODUCTION

Electrocochleography (ECochG) measures the auditory-evoked potentials originating from the inner ear and distal portion of the cochlear nerve. First discovered by Wever and Bray[3] while recording from the auditory nerve fibers (ANFs) in the cat, its traditional use has been the assessment of hearing thresholds and the objective diagnosis of endolymphatic hydrops[57]. However, recent applications encompass measurements of the auditory function before, during, and after cochlear implantation or lateral skull base surgery[10,43,58,59], as well as detailed diagnosis of the site of lesion in patients affected by auditory neuropathy spectrum disorder (ANSD)[29,60–62] and the evaluation of auditory dysfunction related to synaptopathy and hidden hearing loss[63]. ECochG potentials include sensory potentials, namely, the cochlear microphonic (CM) from the outer hair cells (OHCs) and inner hair cells (IHCs), and neural potentials, such as the compound action potential (CAP) and the auditory nerve neurophonic (ANN). Lastly, the SP to tones is an offset of the baseline that persists for the duration of the tone, and clicks are seen as a rising edge prior to the onset of the CAP. An increased SP has proven to be a reliable indicator of endolymphatic hydrops[64] and an increase in the SP is also an ECochG indicator for cochlear synaptopathy[63]. A change in polarity of the SP during an insertion of a cochlear implant may be indicative of electrode position[51]. Thus, changes in the size and polarity of the SP appear to be useful indications of cochlear function. However, to fully exploit its various uses, a complete understanding of its sources is necessary. The SP is often considered to arise entirely from hair cells, with the contribution from IHCs occurring at lower thresholds than OHCs[65,66]. However, other reports show a neural component as well, because the SP changes after application of neurotoxins, such as TTX, CNQX, or kainic acid[5,67], and can be reduced at high stimulus rate, which would not be expected for a purely hair cell potential[59]. Each of the sources can vary in polarity depending on the location of the recording site and as a function of frequency and intensity.

From the round window of the gerbil, pharmacological studies show that OHCs provide a negative polarity (relative to neck muscle), while the IHC and neural components are positive. The sizes of the contribution from each source vary across frequency and intensity such that the overall polarity could be either positive or negative. Like the hair cells, the neural component is also a mixture of sources, composed of both a spiking component based on action potentials and a dendritic component derived from the summed EPSPs within the postsynaptic terminals. The purpose of this study was to further delineate the neural contributions to the SP from these two components. To do this, a pharmacological model was developed where the spiking components could first be removed

by TTX, a sodium channel blocker that prevents action potentials but not EPSPs, and then kainic acid, which removes the postsynaptic terminal entirely through excitotoxicity. By combining these methods with our previous model for selectively removing OHCs, the contributions of OHCs, IHCs, and the two neural components could be isolated and studied across
a range of frequencies and intensities.

MATERIALS AND METHODS

Animal Model

Twenty-seven male Mongolian gerbils (Meriones unguiculatus), weights between 60 and 80 g, were included in this study. The sex was restricted to males because the numbers per group were too small for stratification by sex. The gerbils were taken from Charles River laboratories (Wilmington, MA, USA). All animal protocols were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (National Research Council 2011). All experiments were reviewed and approved by the Institutional Animal Care and Use Committee at the University of North Carolina at Chapel Hill where the research was carried out.

Experimental Design

The design of the experiment is shown in Fig. 1. Gerbils with two hearing conditions were used based on ototoxin exposure: untreated, ostensibly normal hearing (NH) animals, or treated animals where OHCs were removed with a combination of furosemide and kanamycin (FK).

Normal hearing in the untreated animals was confirmed by comparing the CM magnitude across frequency with a series of 24 animals from a previous study. In addition, in all NH cases, the thresholds to the CM and CAP were within 15 dB of 0 dB SPL at 4 kHz.

All animals then went through an acute recording experiment where ECochG was performed prior to introduction of TTX, after TTX, and again after kainic acid. In this way a variety of waveform subtractions could be made to isolate contributions from the different sources. In Fig. 1, the elements contributing prior to and after the treatments are indicated. Contributions could be determined either directly as in the case of IHCs (which are the only elements remaining after treatment with FK and kainic acid) or by subtraction to obtain the OHC and neural contributions. It is important to note that the isolation of OHCs is only available across animals with the two hearing conditions. The neural components are available as within animal subtractions for each animal group.

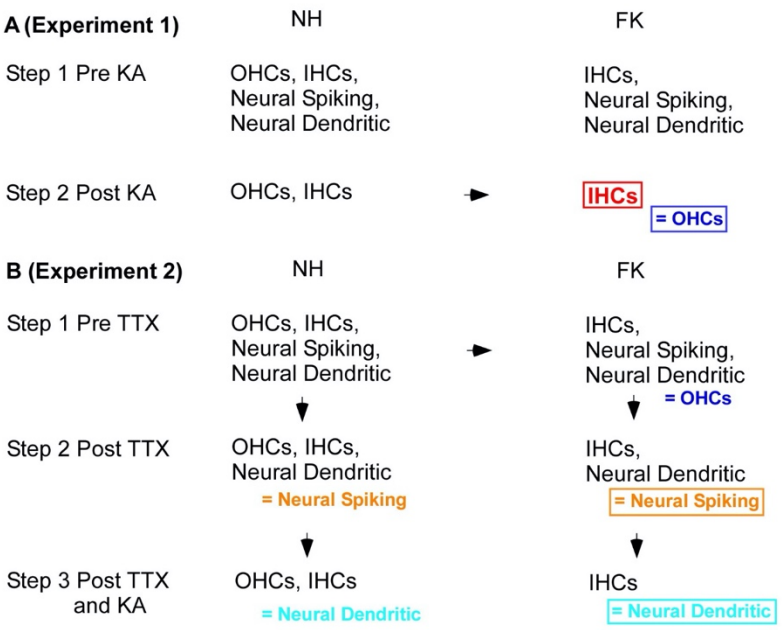


Fig. 1. Experimental design to isolate sources of the SP. The two hearing conditions (NH and FK) are shown at the top (columns), steps at left(rows) indicate when recordings were taken, and arrows (both down and across) indicate subtractions to isolate sources. Colored text indicates where a source could be isolated.

Production of FK Animals

The FK animals were injected with 200 mg/kg kanamycin (SQ) and 100 mg/kg and furosemide (IP), dosages that were shown previously to remove OHCs from all but the apical parts of the cochlea and to leave IHCs intact[5]. Survival time was 7–10 days.

The effects of the FK treatment are variable with greater or lesser amount of the apical OHCs remaining, but the treatment reliably results in OHC losses from the base to at least the 2-kHz region of the cochlea. An example of the hair cell distribution remaining after FK treatment is shown in Fig. 2. intact [5]. Survival time was 7–10 days.

The effects of the FK treatment are variable with greater or lesser amount of the apical OHCs remaining, but the treatment reliably results in OHC losses from the base to at least the 2-kHz region of the cochlea. An example of the hair cell distribution remaining after FK treatment is shown in Fig. 2.

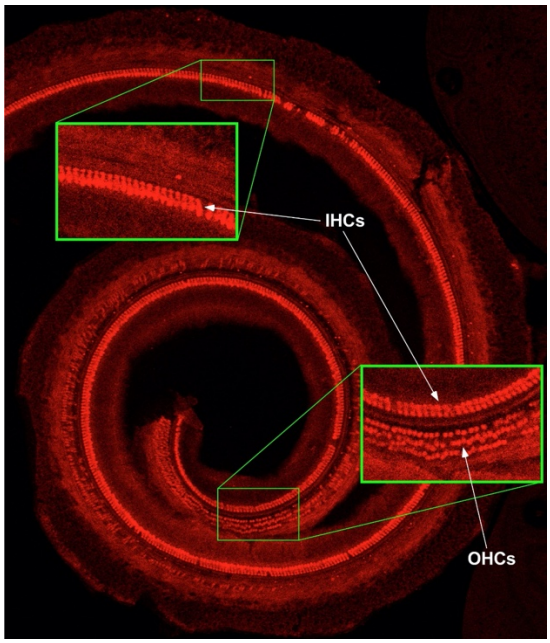


Fig. 2. Confocal image of the basilar membrane from an FK animal immunolabeled for myosin VIIA that showing OHCs and IHCs.
OHCs are present in the apex (insert, lower right) but not in the base (insert, upper right). IHCs are present throughout. The white bar marks the point where surviving outer hair cells begin to appear, which is about the 1 kHz point in the gerbil cochlea (Muller 1996; Hutson et al. 2021). Scale = 300 µm.
(Courtesy of Prof. Douglas Fitzpatrick)

Surgery and Electrocochleography (ECochG) Recording

Animals were anesthetized with an intraperitoneal injection of urethane (1.5 g/kg) in combination with Nembutal (10 mg/kg). Once the anesthetic plane was reached, the fur over the bulla was shaved and a subcutaneous injection (0.1 cc) of a local anesthetic (Lidocaine) delivered under the skin overlying the bulla. Each animal also received a subcutaneous injection of sterile saline (0.1–0.2 cc) and 0.05 mg/kg atropine to retard mucus secretions in the animal's airway. The animal's head was placed in a head-holder, and body temperature was maintained at 37°C with a custom-made hot-water circulating heating pad and a rectal thermometer. After pinna removal, and retraction of the thin muscle overlying the bulla, a small hole was made in the bulla sufficient to view and gain access to the round window for ECochG recording.

Stimulation and recording for ECochG was controlled by a Biologic Navigator Pro (Natus Medical Inc., San Carlos, CA). Recording was through a stainless-steel facial nerve monitor probe (Neurosign, Magstim Co., Wales, UK) placed in the round window niche and used as the non-inverting input. Inverting and ground inputs were from needle electrodes over the contralateral mastoid and tail, respectively. Sound delivery was through an Etymotic ER-3b speaker (Elk Grove Village, IL, USA) with the sound tube sealed in the ear canal. Acoustic stimuli were tone bursts and clicks, alternating in condensation and rarefaction phases, with 100 repetitions to each phase, across a range of intensities from 0–90 dB SPL. Tone bursts were (2, 3, 4, 6, and 8 kHz), Calibration was done in the ear canal through a probe tube attached to a microphone and measuring amplifier (model 3982, B&K, Belgium). ECochG recordings were taken using a 0.1 Hz high pass filter and low pass filters of 5–15 kHz depending on stimulus frequency. The stimulation rate was 11.1 cycles per second.

Recordings in NH and FK animals were taken before and after application of tetrodotoxin (TTX) to remove the contribution of the spiking neural elements and kainic acid (KA) to remove both spiking and dendritic elements.

Concentration of TTX used was 0.015 mM, and KA was 100 mM in artificial perilymph consisting of (in mM): 127.5 NaCl, 3.5 KCl, 25 $NaHCO_3$, 1.3 $CaCl_2$, 1.2 $MgCl_2$, 0.75 NaH_2PO_4, and 11 glucoses, and pH adjusted to 7.3 with HCl. After each application of neurotoxin there was a 1-h wait for the drug to diffuse through the round window and cochlea before the ECochG measurement. In NH control animals, artificial perilymph was used without the addition of KA or TTX.

Data Analysis

The digitized data was analyzed through custom routines in MATLAB (R2021a, Mathworks, Natick, MA). The ECochG data was used to extract the SP from the sum of the stimuli to each phase. The SP is more visually apparent in the summed responses because it removes hair cell and neural components of the responses that change with phase. To tones, the summed waveform was then further smoothed with a triangular filter with the number of points contained in 1 cycle of the stimulus frequency. The SP was measured as the average of a 1 ms time window that was within a few ms prior to stimulus offset, i.e., at a point where the response had reached steady state and was thus beyond the time where perturbations associated with the stimulus onset such as the CAP might affect the SP measures.

The protocol was used on 27 gerbils. A factor affecting yield of successful experiments is the effect of time after anesthesia on the responses. That is, there was generally some decline during the experiment, and since later responses are subtracted from earlier ones to isolate the components (Fig. 1), the results will be affected by the degree to which the responses change as a function of time rather than the effects of the TTX or KA. The criterion used to assess the effect of time was the change in the CM, which, because it is produced by hair cells, should not be affected by the removal of the neural components. The frequencies used (2–8 kHz) are above the range of neural phase-locking that produces the auditory nerve neurophonic in the gerbil, so the CM should be the only AC component in the steady-state response. For inclusion in the analysis, the CM needed to remain within 2 dB of the range at the start of the preceding step, so the total decline for the two steps had to be less than 4 dB. In the 15 cases included, the total decline in the CM ranged from 1.1 to 3.4 dB with a mean of 2.3 ± 0.9 dB (standard deviation).

Histological Analysis

At the end of the recording session, animals were euthanized with an overdose of sodium pentobarbital, the cochleae removed "en bloc" and immersed in 4% paraformaldehyde in 0.1 M phosphate buffer for at least 24 h. The Cochlea was then decalcified for 2–3 days in 10% EDTA. At that time the otic capsule was removed, the basilar membrane was carefully dissected away from the lateral wall and modiolus (see Hutson et al. Fig. 3) and prepared for histological examination. The location of surviving hair cells in FK-treated animals was charted after staining the basilar membrane with iron hematoxylin and hair cells counted in 250 μm increments using a Zeizz Axioscope light microscope and 40 X objective (Carl Zeiss, Thornwood, NY). Alternatively, the basilar membrane was immunostained for the detection of hair cells. The membrane was rinsed in phosphate-buffered saline (PBS), blocked for 2 h in 5% normal donkey serum with 1% Triton X 100 in PBS, transferred to primary antibody solution overnight (Myosin VIIa at 1:200 in blocker solution; Proteus Biosciences; 25–6790, Ramona, CA, RRID:AB, 10,015,251), rinsed 3 X 15 min in PBS, followed by a fluorescently tagged secondary antibody for 2 h (1:500; Thermo-Fisher; A10042, Waltham,MA, RRID:AB_2534017), washed in PBS, and mounted between coverslips. Fluorescent material was imaged with a Zeiss 700 scanning laser confocal microscope (Carl Zeiss Microscopy GmbH, Jena, Germany) at X 5 magnification; the images were viewed and analyzed with Fiji for ImageJ).

Statistical Analysis

Within-animal effects were studied with linear mixed models in SPSS (v28, IBM, Armonk, NY) to isolate significant effects of the treatments where the random factor was the animal number and the fixed factors were frequency, intensity, and the three treatment conditions, i.e., pre- and post-TTX and then post-KA. Animals in the experimental groups were randomized, i.e., two animals were obtained at a time, and one was assigned to the NH arm and one to FK, until the desired sample of 5 animals/group was reached. The NH control group was run after the experimental groups were completed. Data collection at the time of ECochG was automatic so no blinding to condition was performed. Histological analysis was done without knowledge of physiological results.

RESULTS

Example of the Treatment Effects at a Single Frequency and Intensity

Examples of "grand average" responses for five animals each in the two initial hearing conditions (NH and FK; Fig. 3) show that for this frequency and intensity (8000 Hz at 80 dB SPL), the average effect of the TTX was to remove the CAP, as expected, and to remove a positive polarity

component of the SP, driving it more negative by comparison (Fig. 3A, B). The effect of the KA was to remove a negative polarity contribution to the SP, so it again became more positive, although less than the original waveform. The remaining waveform, after both treatments, represents the combination of the OHCs and IHCs for the NH animals, and IHCs only for the FK animals. These results show that, after subtraction, the spiking and dendritic components were opposite in polarity (Fig. 3C, D). For both parts of the neural component, there was adaptation in terms of at least a partial return to baseline by the measurement point (black bar in A and B). The variability across animals, shown in Fig. 3E, F, indicates that the "v-shaped" trend was observed after the treatments in 5/5 cases for the NH animals and 4/5 for the FK. Note that for the NH animals, the pre-treatment SP could be either positive or negative while for the FK animals, it was always positive, due to the lack of a negative polarity contribution from OHCs. Also, as a reference for the relative sensation levels of the stimuli, the thresholds for the FK animals to the CM at 4 kHz were approximately 30 dB higher than for the NH animals, and the maximum responses of the CM were proportionally lower as well.

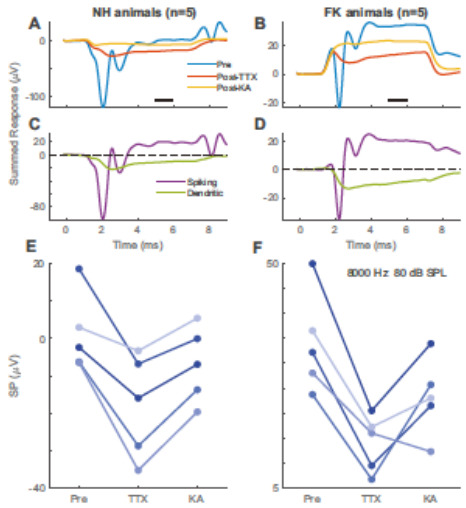


Fig. 3. Examples of responses to the different treatments for a single frequency/intensity combination (8000 Hz, 80 dB SPL) and data analysis to extract the neural spiking and dendritic contributions to the SP. A. Grand average of the alternating phases for 5 normal hearing (NH) animals. The point where the SP was measured (bar) became more negative after TTX, and then more positive after KA. B. Grand average data for 5 animals with outer hair cells removed with FK. The directional changes in the SP polarity after the TTX and KA were the same as NH animals. C and D Spiking and dendritic components derived after subtractions of the data in A and B, respectively. E and F Pattern of the SP changes for each of the 5 animals making up the grand averages in A and B. The pattern was similar in 9 of the 10 animals, and only 1 FK animal was different.

Statistical Comparisons

Overall, the effects of TTX and KA were significant compared to the within-animal, pre-treatment baseline M (Tables 1 and 2). Using the SP as the output variable and animal ID as the random variable, linear mixed models for each animal group showed significant fixed effects of frequency, level, and treatment (pre-TTX, post-TTX, and post-KA). The interaction of frequency and level was also significant for both groups.

The NH group showed significant interactions of treatment with frequency and level, but the FK animals did not. The interaction in the NH animals suggests a relationship between the treatments and the presence of OHCs. That is, the presence of the negative polarity from the OHCs causes the

pre-treatment SP to vary greatly in both magnitude and polarity as a function of frequency and intensity, in contrast to the FK animals where it is always positive. As expected in control animals (Table 3), there were significant main effects of level and frequency, and a significant interaction between level and frequency but the main effect of treatment was not significant. There were some missing conditions for 3000 Hz for one animal each in the FK and NH control animals due to a programming error.

TABLE 1

Mixed linear model results for NH animals (n = 5375 conditions)

Type III tests of fixed effects[a]

Source	Numerator of	Denominator of	F	Sig
Freq	4	252	30.029	<0.001
Level	4	252	9.583	<0.001
Treatment[b]	2	252	17.110	<0.001
Freq* level	12	252	6.245	<0.001
Freq* treatment	8	252	2.785	0.006
Level* treatment	8	252	3.736	<0.001
Freq* level* Treatment	24	252	0.889	0.618

[a] Dependent variable: SP

[b] Treatments are Pre-Drug, Post TTX e Post KA

TABLE 2

Mixed linear model results for NH animals (n = 5213 conditions)

Type III tests of fixed effects[a]

Source	Numerator of	Denominator of	F	Sig
Freq	4	168	23.350	<0.001
Level	2	168	76.435	<0.001
Treatment[b]	2	168	42.446	<0.001
Freq* level	8	168	2.242	0.027
Freq* treatment	8	168	0.673	0.715
Level* treatment	4	168	0.787	0.535
Freq* level* Treatment	16	168	0.104	1.000

[a] Dependent variable: SP

[b] Treatments are Pre-Drug, Post TTX e Post KA

TABLE 3

Mixed linear model results for NH animals (n = 5357 conditions)

Type III tests of fixed effects[a]

Source	Numerator of	Denominator of	F	Sig
Freq	4	282	34.930	<0.001
Level	4	282	29.235	<0.001
Treatment[b]	2	282	1.916	0.149
Freq* level	16	282	12.139	<0.001
Freq* treatment	8	282	0.156	0.996
Level* treatment	8	282	0.398	0.921
Freq* level* Treatment	32	282	0.069	1.000

[a] Dependent variable: SP

[b] Treatments are Pre-Drug, Post TTX e Post KA

Distributions of Spiking and Dendritic Contributions to the SP Across Frequency and Intensity

In Fig. 4A and B, we show the spiking and dendritic components across all frequencies and intensities tested for the NH and FK animals, respectively. The graph is presented as a function of level, with frequency as a parameter. In each case, the spiking part of the neural component (filled symbols, solid lines) had a positive polarity, while the polarity of the dendritic component (open symbol, dashed lines) was negative. The magnitudes of the components increased with intensity in general, and there was relatively little effect of frequency, but there were exceptions to both (e.g., NH to 2000 Hz and FK to 6000 Hz). The 2 kHz deviated substantially from the other frequencies for both hearing conditions, suggesting that the action of the neurotoxins and or ototoxic treatments may have been less effective towards the apex. From the experimental design (Fig. 1), each of four components that contribute to the SP (OHC, IHC, neural dendritic, and neural spiking) can be isolated based on subtractions, or in the case of IHCs determined directly in the FK animals. The results in terms of grand averages for each component at one frequency/intensity combination are shown in Fig. 5. The IHCs and OHCs from this independent data set have large and opposite polarities, as reported previously, while the neural spiking and dendritic components also have opposite polarities but with smaller magnitudes. The OHC curve in this case was isolated from pretreatment NH and FK animals (see Fig. 1).

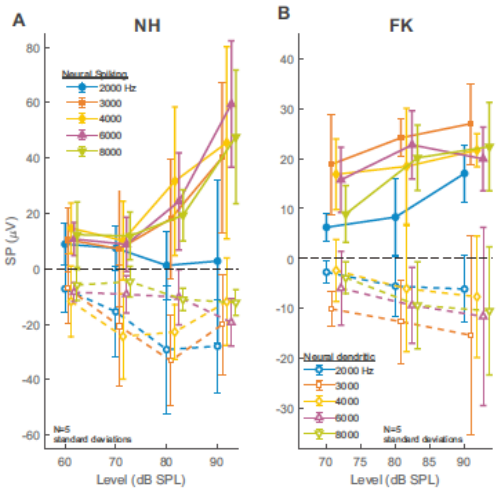


Fig. 4. Neural spiking and dendritic components for the two animal groups across frequency and intensities. A) NH animals. B) FK animals. Error bars are standard deviation. Solid symbols and lines = neural spiking, open symbols, and dashed lines = neural dendritic.

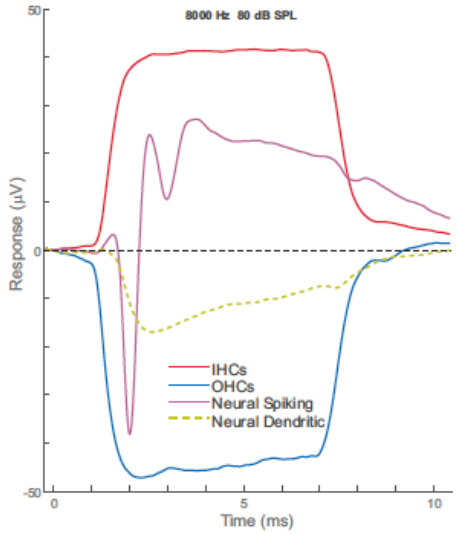


Fig. 5. Grand averages of the isolated IHC, OHC, and neural spiking and dendritic sources at one frequency/intensity combination (8000 Hz, 80 dB SPL).

Responses to Clicks and Time Course of the Different Potentials

Examples of the response to clicks for the different treatments and two hearing conditions are shown in Fig. 6. For the NH case, the click responses to condensation and rarefaction phase stimuli at 50 dB SPL (Fig. 6A) show a slight asymmetry in the first cycle of response (compare arrows at negative and positive points on the y-axis). This asymmetry is responsible for the first part of the SP in the sum (Fig. 6B) and persists through the TTX and KA treatments, indicating it is derived from hair cells. Subtracting the curves as before yields the neural spiking and dendritic components (Fig. 6C). For the FK case, at 60 dB SPL, because the responses to OHCs have been removed, the first cycle of deflections is from IHCs only (Fig. 6D). The asymmetry is much greater than when OHCs are present, and in the opposite direction. In the sum curve (Fig. 6E), the initial deflection is positive rather than negative and is also relatively, although not completely, stable after each treatment (arrowhead). After subtraction (Fig. 6F), the isolated potentials show that the peak of the dendritic response occurs slightly after the negative peak of the CAP and then returns to baseline

rather than reaching steady state. The initial peak associated with the spiking component (arrowhead) is an artifact of the subtractions due to the small changes after the treatments in Fig. 6E.

To observe the time course for all four components of the SP, the grand average results to an 8 kHz tone (Fig. 7A) and to clicks (Fig. 7B) are shown on an expanded time axis and with the OHC response flipped to a positive polarity to better appreciate the relative timing of each event. The first event to both stimuli was the response of OHCs which rose sharply, followed by the IHCs which, to both stimuli, had a shallower slope. The differences in onsets and time constants between OHCs and IHCs across frequencies and intensities were reported previously for tones and the pattern shown here is consistent with that report. The neural components followed in time, with the large spiking component (the CAP) rising quickly and the smaller dendritic component having a slower time course, as seen in the examples in Fig. 5. As noted previously, the peak of the dendritic potential occurred after the large deflection of the CAP. The contributions of the components reached a steady state to tones but clicks returned to baseline with time.

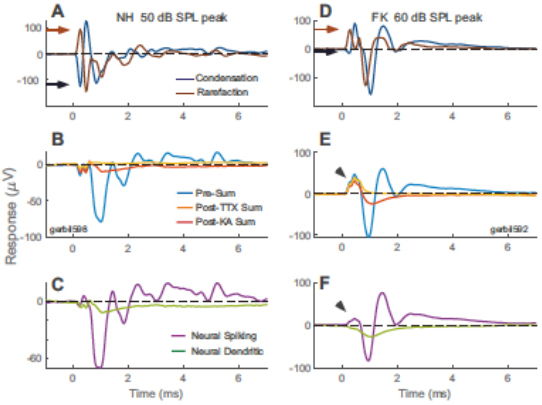


Fig. 6. Responses to clicks. A–C Example from an NH animal. D–F Example from an FK animal. In each case, the top panels (A and D) show the responses to condensation and rarefaction phase stimuli, and the arrows indicate the negative and positive peaks of the first response. The middle panes (B and E) are the sum of the two phases before and after each treatment, and the bottom panels (C and F) are the spiking and dendritic components determined by the subtractions as in Fig. 1. The arrowheads in E and F show a slight change in the early response with the different treatments and in the subtractions; this is presumably hair cell responses changing over time rather than a direct effect of the neurotoxins.

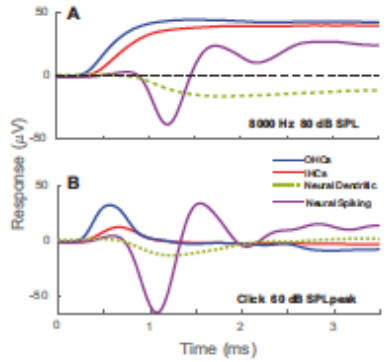


Fig. 7. Grand average response to tones and clicks on an expanded scale to see the time courses of the responses. A The onset portion of the grand average responses in Fig. 6. The sequency in time is outer hair cells, then inner, then the neural dendritic and spiking components close together. B Responses to clicks, the time sequence of the components is similar, but the components do not reach steady state.

DISCUSSION

The main result was that the neural contribution to the SP consists of spiking and dendritic components, so that together with the OHCs and IHCs, there are at least four components that combine to produce the SP. Like IHC and OHCs, the two neural components have opposite polarity when recorded at the round window, seen both in NH animals and animals where the OHCs were selectively removed with ototoxins. The study of the SP has a long history as one of the more complex potentials produced in response to sound, and a clinical history as a sensitive and specific indication for Meniere's disease. Other uses, such as an indicator for cochlear synaptopathy and monitor for tonotopic position during cochlear insertions, are also proposed. In this study we continued to dissect the complex nature of the SP and will consider this complexity in relation to its possible clinical applications.

Technical Considerations and Limitations

A key issue with subtractions as in Fig. 1 is potential declines over the time of the experiment that are unrelated to the neurotoxins. Controls for this were to monitor the CM, which should not be affected by the neurotoxins, and to do sham experiments with artificial perilymph only.

The frequency range used was limited because the equipment and recording configuration used clinical equipment identical to that used for similar recordings from the round window of cochlear implant subjects recorded intraoperatively. This limited the upper frequency to 8 kHz. The lower bound of 2 kHz was because the FK treatment reliably removed OHCs to about this range, and complete removal of OHCs is required to isolate the IHC response and determine the OHC contribution by subtraction. However, the data in Fig. 4 indicates that to the 2 kHz stimuli, the neurotoxin and/or ototoxin diffusion may be incomplete at more apical CF regions. The intensity range was limited to 60–90 dB SPL for NH animals and 70–90 dB SPL for FK animals. The high intensity limit was arbitrary, but it seems unlikely that the results would be much altered if higher intensities were used. To lower intensities, the SP was often too small for subtractions to be reliable. The neurotoxins should not affect the hair cells stereociliary responses that produce the CM. However, the removal of the synapse with KA may affect the basolateral surface that can in turn influence the production of an SP (described more fully below). Importantly, the TTX should not influence the hair cells since the synapse remains intact and only action potentials are prevented, so an effect on the SP from blocking spiking activity is evident.

Neural Components of the SP

Initial studies of the SP suggested a possible neural origin, but over time, these were discounted for a purely hair cell origin based on asymmetries in the CM primarily of OHCs). However, asymmetries are greater in IHCs than OHCs (see Fig. 6) and have opposite polarities, at least as recorded at the round window. Possible reasons for the polarity difference between OHCs and IHCs were discussed in our previous report and include an operating point on opposite sides of the 50% channel open/closed position at rest, or differences in the location of the "center of gravity" of the generators). In humans, the SP varies in polarity and magnitude across frequency and intensity or with hearing condition, suggesting similar interactions of inputs from sources with different polarities.

Previous studies also showed effects of neurotoxins on the SP, but this neural contribution was not systematically explored. By combining the use of neurotoxins with animal models with and without OHCs, we were able to isolate OHC, IHC, and two neural contributions over the frequency and intensity ranges used in the current study. Here, we show that the spiking part of the SP provides a larger positive polarity contribution than previously realized, because it is opposed by a negative polarity dendritic contribution. A difference between the spiking and dendritic contributions to the SP to tones that may impact their polarity is their site of origin. The dendritic potential resides in the terminals next to IHCs, and thus the distribution of active fibers is likely to follow that of the IHCs. In contrast to the local origin of the dendritic potential, the origin of the CAP may be more central. Dolan et al.[68] using the same pharmacology in NH guinea pigs reported that SP recordings from scala vestibuli had reversed polarities relative to scala tympani for the hair cell potential, but not for either of the neural components. This expected result shows that the neural potentials do not reverse in phase relative to the motion of the basilar membrane in the different compartments.

The SP and Endolymphatic Hydrops

The most significant clinical use of the SP is based on its increase in subjects with confirmed Meniere's disease. The basis for the increase is thought to be the pressure from endolymphatic hydrops, the pathophysiological correlate of Meniere's disease, compressing the space between the tectorial and basal membranes resulting in an increased asymmetry in the OHC input/output function and a larger SP. The increase is seen both with clicks and tones. However, according to our results, the increased SP to tones (i.e., becoming more negative in our recording configuration) could also occur through diminished IHC or spiking neural activity. Since hearing loss is typical with Meniere's disease, some effects on these elements are expected. For clicks, an increase could also be due to increased output from OHCs, decreased output from IHCs, or an increased dendritic

component. The spiking component is not likely to be involved because the CAP dominates the earliest part of the spiking response.

The SP and Cochlear Synaptopathy

Recent articles have suggested that an increased SP can also be a correlate of cochlear synaptopathy, or loss of neural responses without concomitant losses in hair cells. The correlation was observed by comparing SP to clicks between the best and worst performers on a battery of word tests. Yet, because of the complexity of the SP, there could be several explanations for the correlation. The initial rise in response is the same in both groups, and this rise can be attributed to the OHCs (note that the recording direction is reversed between most research and clinical studies). OHC function also appeared similar between the groups based on distortion product otoacoustic emissions. After the initial rise, there is an inflection with a slope change, which is reduced in the best performance group and increased in the worst performance group. During this brief period prior to the onset of the CAP, active sources of the SP other than

OHCs are the IHCs which include the neural dendritic component. A reduced neural dendritic response would be expected with cochlear synaptopathy, but since it has the same polarity as the OHCs, a reduction in the dendritic response cannot account for an increased slope in the worst performers. In addition, a change in the IHC transduction process does not seem likely. However, an increase in IHC resting potential would reduce the contribution to the SP, and a possible correlate of a loss of synapses due to excitotoxicity could be a less tight basolateral surface. Thus, a reasonable hypothesis for the increase in the SP in the worst performing group is a less asymmetric operating point in IHCs, due to a higher resting potential, compared to the best performers.

The SP as a Monitor During Cochlear Implantation

Recently it has been suggested that the tuning of the SP to frequencies as a function of position can indicate the tonotopic region of a particular contact. All the SPs reported in that study had positive polarities and were in response and to relatively high frequencies. The tuning shown for the SP was greater than that of the CM or CAP. The difference in asymmetry between OHCs and IHCs makes it is likely that the dipoles for IHCs are relatively more basal than for OHCs, so caution must be used in interpreting the SP data. A study of the SP in guinea pig assessed its properties at four points along the cochlea from base to apex as a function of frequency and intensity.

They noted systematic changes in the SP that were consistent with a wide spread of excitation, i.e., the peak SP and CM to 3000 Hz and 80 dB SPL was in the basal turn (turn 1), rather than near its CF region in turn 3. Thus, using the SP during a CI insertion where typically high intensities are

used and time is limited might be challenging, but as a post-insertion measure for identifying position of contacts, the SP could be useful.

A difficulty in using the SP for human CI subjects is that in most subjects, it is quite small, at least at the round window. However, in some CI subjects, the SP is substantial, and a variety of morphologies is seen from large and negative in Meniere's and ANSD subjects, to small potentials when associated with a CAP, and to positive polarities with and without a CAP where IHC and/or spiking components may dominate. Thus, the variety of SP morphologies is consistent with a plurality of a sources.

CONCLUSIONS

This study used pharmacology with round window ECochG in gerbils to isolate four sources of the SP, including OHCs, IHCs, and two from the auditory nerve, one related to synaptic potentials (neural dendritic) and one to firing of action potentials (neural spiking). The sources vary by time course and polarity, and to some degree, by frequency and intensity, so that any final SP is a complex mixture of the sources. Thus, interpreting SP changes in clinical situations requires consideration of the complex interactions involved.

COCHLEAR PATHOLOGY IN SUBJECTS AFFECTED BY VESTIBULAR SCHWANNOMA AND MÉNIÈRE'S DISEASE: RESULTS OF INTRAOPERATIVE ELECTROCOCHLEOGRAPHY

INTRODUCTION

Vestibular schwannomas (VSs) are benign tumors of the vestibular division of the eighth cranial nerve. Their clinical manifestation can vary considerably among individuals, but more than 90% of patients present with hearing loss. Another common otologic complaint is tinnitus, which is unilateral in most cases. Vestibular symptoms include sporadic vertigo and can simulate the course of Ménière's disease (MD), while chronic disequilibrium is more frequent in bigger neoplasms. However, there are also cases of large tumors with subclinical/silent presentations and the mechanism underlying the sensorineural hearing loss (SNHL) is still unclear. The most accredited hypothesis for the SNHL has been mechanical compression caused by VSs on the auditory nerve compromising neural transmission and/or the vascular supply leading to the cochlea resulting in concurrent SNHL. Some authors have also evidenced the potentiality of VS-biological secretions in causing ototoxic and neurotoxic effects on the cochlea[69].

Histologic reports of temporal bones of ears with VSs have indicated findings of endolymphatic hydrops (ELH) in some cases. These alterations together with other characteristics of cochlear degeneration, such as loss of hair cells and cochlear neurons, atrophy of the stria vascularis, and precipitate within the endolymph or perilymph, could be responsible for the SNHL determined by VSs. However, the cochlear modifications caused by these tumors are not well elucidated and it is still uncertain if VSs can cause ELH[70].

Electrocochleography (ECochG) is an electrophysiological technique, which comprises the auditory evoked potentials originating from the inner ear and the distal portion of the auditory nerve. The cochlear microphonic (CM) is a sensory potential recorded from the outer hair cells with inner hair cell components, which are physiologically overshadowed by the CM from outer hair cells in normal ears. Neural potentials from the auditory nerve fibers include the compound action potential (CAP) and the auditory nerve neurophonic (ANN). Lastly, the summation potential (SP)[5,13] originates from both the outer and inner hair cells and auditory nerve. Besides ECochG traditional application to evaluate hearing thresholds, one of the long-standing uses of ECochG has been to objectively measure the presence of ELH. Positive findings for these conditions would be considered an increased SP/CAP ratio (e.g., >0.5) to broad band clicks as well as abnormally enlarged SP magnitudes to tone bursts. However, more recently other authors evidenced that the tone burst SP amplitude measurements were useful in the diagnosis of MD, while the click SP/CAP

measurements did not present statistically significant differences between groups of ears with and without MD. Over the last few years ECochG has appeared particularly promising in the intraoperative monitoring of peripheral auditory function during lateral skull base surgery, during all phases of cochlear implantation (CI) with special regards to the achievement of hearing preservation, and in the diagnosis of auditory neuropathy spectrum disorders (ANSD) and cochlear synaptopathy[12]. The most encouraging results have been obtained with quasi near-field measurements, such as round window (RW) ECochG, when the active electrode is placed through the facial recess. More recently, intracochlear (IC) recordings, executed by positioning the monopolar probe inside the cochlea or by recording directly through the CI, appear promising.

Given the potentialities of intraoperative ECochG, the main objective of this investigation was to utilize RW ECochG in ears with known VS and compare those findings with subjects expected to exhibit ELH, such as those with MD, with the purpose to determine if ELH is one feature of cochlear degeneration associated with VS. In fact, the previous literature evidenced that VS secretions could determine cochlear effects, including EH, and *postmortem* histopathological examination confirmed those findings. Therefore, the leading hypothesis of this research to be confirmed by using intraoperative RW ECochG was that the subjects with VS would exhibit similar SP amplitudes as those with MD.

MATERIALS AND METHODS

This research was conducted in accordance with the ethical standards originating in the Declaration of Helsinki and informed consent was obtained for all subjects. Intraoperative RW ECochG was performed in individuals undergoing translabyrinthine VS removal and in subjects with MD during labyrinthectomy or endolymphatic sac decompression and shunt surgery (ELS). Recordings are routinely performed at the Ohio State University for research purposes with the aim of understanding response changes in auditory physiology as a result of intraoperative events (Institutional Review Board protocol #2015H0087).

Subjects

All subjects with surgically confirmed VS (n=60) were aged ≥18 and had normal middle ear status, established by otoscopy or tympanometry. The largest diameter measured in one of the three planes of projection was registered as the tumor size[71]. Data from seven subjects with VS were excluded due to various technical problems with intraoperative ECochG (e.g., excessive electrical noise contamination; open circuit due to high impedance; cable failure). Additionally, adult subjects (n=24) undergoing labyrinthectomy or ELS for poorly controlled vestibular symptoms associated

with MD participated in this study. MD was diagnosed by the treating physician and classified as definite and probable MD. Note, many of the subjects included in this study have been described separately in two previous publications, however, in addition to a new comparison analysis, 19 new participants have been added to this data set.

Surgery and ECochG recording set up

After induction of general anesthesia, neuromonitoring electrodes were positioned in the patient's scalp: the inverting electrode was placed on the contralateral non-operative mastoid, while the ground electrode was located at the glabella. Tone-burst stimuli were provided in alternating phase polarity (condensation and rarefaction) through Etymotic earphones (ER-3b) connected by a sound tube to a foam insert in the external auditory canal of the operative ear. A standard mastoidectomy was completed including a facial recess to have access to the round window niche and perform intraoperative ECochG by placing a monopolar probe into the round window, which acted as the active recording electrode (Neuro-Kartush probe, Integra, Plainsboro, NJ or Neurosign, Magstim Co., Wales, UK). For VS removal all recordings were made immediately before labyrinthectomy (i.e., inner ear structures were all intact). In subjects with MD ECochG recordings were acquired following mastoidectomy but before the labyrinthectomy or before decompression and opening of the endolymphatic sac in case of ELS.

A Biologic Navigator Pro (Natus Medical Inc., San Carlos, CA) was used to generate acoustic stimuli and obtain ECochG recordings. Also, a 2-cc coupler and sound level meter (System 824, Larson Davis, Depew, NY) set to fast mode was used to regulate stimulation levels in units of dB peak equivalent sound pressure level. Six frequencies (0.25, 0.5, 0.75, 1, 2, 4 kHz) were set at 90 dB nHL (0.25 kHz was presented at 80 dB nHL because of equipment limits) (96–112 peSPL). The tone bursts consisted of rise and fall times of 1 to 4 ms shaped by a Blackman window and plateaus of 5 to 20 ms. Impedances were less than 15 kOhm on all electrodes and, if higher, saline was added at the RW to decrease it. Filters had a high pass cutoff of 10 Hz while low pass filters were calibrated at 5-15 kHz for tones of 0.25 to 4 kHz (frequency dependent). It should be noted, the 10 Hz high-pass filter can cause a decline towards zero of the SP; however, all subjects in this study were measured using the same high-pass filter setting. At the end of the intraoperative measurements, a final trial with the sound tube clamped was typically executed at each frequency to assess electrical artifact, if present.

Electrophysiologic analysis

The ECochG recordings were analyzed using custom MATLAB (MathWorks, Natick, MA) scripts. The SP was calculated as the continuous deflection from baseline (either negatively or positively) from the midpoint of the alternating waveform (mean of the rarefaction and condensation waveforms) to the tone burst. The spectrum of the intraoperative ECochG recordings (i.e., CM amplitude) was obtained using fast Fourier transforms, using zero padding and a Blackman window. A CM response was considered significant if its peak was greater than the average noise level by three standard deviations. The "ongoing" response (continuous steady-state response) represents CM activity at high frequencies and CM plus auditory nerve neurophonic (ANN) activity at lower frequencies[72]. The noise level and variance were obtained from four to six frequency bins near the peak of interest. In the event the ongoing response was found not to be significant in a trial, the SP was not measured, and that trial was excluded from further analysis. All subjects were required to have a significant response at a minimum of one test frequency to be included in further analysis.

Auditory nerve function was evaluated using the "nerve score", a qualitative metric of auditory nerve function, previously described in children with auditory neuropathy. In brief, the auditory nerve response in the form of the CAP and the ANN are judged independently and scored on a scale of 0-2. A score of 2 suggests prominent nerve activity, a 1 suggests present but not distinct nerve activity, and a 0 suggests no identifiable nerve activity. The ANN is scored for test frequencies of 1000 Hz and below while the CAP is evaluated across all frequencies. The score for each component (ANN and CAP) is then added together for a total maximum nerve score if 4. The reader is referred to Riggs et al.[73] for an in-depth review of scoring criteria.

Audiometry

Audiometric testing and word recognition scores (WRS) were performed and evaluated within 6 months prior to surgery by a licensed audiologist using a standard Hughson-Westlake procedure[74] and the Northwestern University Auditory Test No. 6 (NU-6) word list[75] presented at an audiometrically indicated level. Pure tone averages (PTA) were obtained using the average air conduction thresholds at 0.5, 1, and 2 kHz. If there was no audiometric response at the limits of the audiometer, thresholds were noted as 120 dB HL.

Statistical analysis

All statistical analyses were performed using SPSS v.26.0 (IBM Corp., Armonk, NY) Independent samples t-tests were used with PTA and WRS to test for group differences. A Linear mixed model

(LMM) was used to assess differences in SP amplitudes. Here, the SP amplitude served as the dependent variable and the independent variables were group (VS, MD) and stimulus frequency. Pairwise comparisons with Bonferroni correction were used for evaluating the difference in the SP amplitude by individual stimulus frequency between groups. The nerve score was evaluated using an Independent Samples Mann-Whiney U test. All statistical tests were two-tailed, and significance was set at 95% confidence.

RESULTS

Group Demographics and Hearing Profiles

The VS group was composed of 53 subjects (23 males, 30 females; median age 56 years with range 18-77), while the MD group was composed of 24 subjects (13 males, 11 females; median age 55.3 years with range 37-82). Clinical features are shown in Tables 1 and 2. The VS tumor size was measured in its largest diameter and varied from 3.0 to 56 mm with a mean of 20.3 mm (standard deviation, SD: 10.3) (Table 1). In the MD group, 6 subjects underwent labyrinthectomy, while 18 ELS (Table 2). As described in previous literature, various types of audiometric patterns were observed in the VS group with 9 subjects affected by profound SNHL. Conversely, no subjects of the MD group were affected by profound SNHL. In the VS group the average PTA was 59.6 dB HL (SD 30.5; range: 18–120), while in the MD group it was 52.3 dB HL (SD 18.4; range 20–86.7) which was found to not be statistically different (t: -1.3; p: 0.20). The average WRS was 44.8% (SD 36.8; range 0–100) in the VS group and 73.8% (SD 25.2; range 0–100) in the MD group (Table 1), which was found to be statistically different (t: 4.04; p: <0.01). Overall, subjects affected by VS presented with similar preoperative hearing levels but poorer speech perception capabilities than the MD group.

Table 1. Clinical features of the vestibular schwannoma (VS) group.

Subject (#)	Sex	Age	Ear(s)	Tumor Size (max in mm)	PTA	WRS (%)	Absent On-going Response (kHz)	ANN Score	CAP Score	Total Nerve Score
1	M	67	Right	24	106	0	0.5, 1.0, 2.0, 4.0	2	0	2
2	M	67	Right	3	120	0	4.0	1	0	1
3	M	18	Left	33	67	8	-	1	2	3
4	M	56	Left	14	36	78	0.25, 1.0, 2.0, 4.0	2	2	4
5	F	56	Left	5	35	80	0.25, 1.0, 2.0, 4.0	2	1	3
6	M	26	Right	24	35	96	0.25, 2.0, 4.0	1	1	2
7	F	63	Left	37	18	12	0.25, 2.0, 4.0	1	1	2
8	M	39	Left	34	90	0	0.25, 2.0, 4.0	2	1	3
9	F	68	Right	14	67	8	2.0, 4.0	2	1	3

10	M	67	Left	4	52	28	2.0, 4.0	2	1	3
11	F	42	Left	22	38	64	4.0	1	1	2
12	F	57	Right	10	38	72	-	2	1	3
13	F	27	Left	19	35	88	0.25, 2.0, 4.0	1	1	2
14	M	45	Right	16	120	0	-	2	2	4
15	M	61	Right	28	72	0	4.0	0	0	0
16	F	51	Right	6	32	100	-	2	2	4
17	F	64	Right	25	27	92	-	2	2	4
18	F	58	Left	10	100	40	4.0	1	0	1
19	M	53	Right	21	50	74	2.0, 4.0	2	1	3
20	M	30	Right	30	20	92	-	2	1	3
21	F	54	Left	14	65	54	-	2	2	4
22	M	35	Left	56	45	36	-	1	1	2
23	F	68	Right	12	55	32	2.0, 4.0	1	0	1
24	M	75	Left	18	115	0	-	2	1	3
25	F	77	Right	10	53	2	2.0, 4.0	0	0	0
26	M	49	Left	12	58	44	-	2	2	4
27	F	70	Right	30	117	0	0.25	2	0	2
28	F	63	Right	30	80	60	-	2	1	3
29	F	75	Left	20	56	52	-	2	2	4
30	M	73	Right	21	66	0	4.0	1	0	1
31	M	62	Right	10	36	92	-	2	2	4
32	F	70	Right	14	45	56	-	2	2	4
33	M	60	Right	14	62	20	-	2	1	3
34	F	53	Left	15	23	100	-	2	2	4
35	F	45	Right	20	73	28	-	2	2	4
36	M	56	Left	17	37	60	-	1	2	3
37	M	62	Right	46	120	0	-	0	0	0
38	M	34	Right	35	120	0	-	2	0	2
39	F	66	Right	30	47	64	-	2	2	4
40	M	56	Right	20	50	56	-	2	1	3
41	F	39	Left	26	23	96	-	2	2	4
42	F	58	Right	35	38	68	-	2	2	4
43	F	46	Left	20	53	20	-	1	0	1
44	F	48	Left	17	61	16	-	2	1	3
45	M	51	Left	25	120	0	-	2	0	2
46	F	35	Right	17	47	28	-	2	2	4
47	F	45	Left	12	93	12	-	1	0	1
48	F	67	Left	20	61	68	-	2	1	3
49	F	72	Left	27	18	96	-	2	2	4
50	F	53	Right	17	38	100	-	2	2	4
51	F	51	Right	14	45	84	-	2	2	4
52	F	39	Right	12	32	96	0.25	2	2	4
53	M	54	Right	14	48	0	-	0	0	0

Abbreviations: PTA: pure tone average (0.5, 1, 2 kHz); WRS: word recognition score; ECochG: electrocochleography; ANN: auditory nerve neurophonic; CAP: compound action potential; M: male; F: female; Dash (-): all responses present.

Table 2. Clinical features of the Ménière's disease (MD) group.

Ménière's disease (MD) group									
Subject (#)	**Sex**	**Age**	**Ear (s)**	**Surgery**	**PTA**	**WRS (%)**	**ANN Score**	**CAP Score**	**Total Nerve Score**
1	M	61	Right	ELS	20.0	76	1	2	3
2	F	51	Right	ELS	45.0	72	2	2	4
3	M	37	Right	ELS	55.0	52	2	2	4
4	M	42	Left	ELS	51.7	100	2	2	4
5	F	41	Left	ELS	25.0	80	1	2	3
6	M	46	Right	ELS	50.0	80	2	2	4
7	M	38	Left	ELS	28.3	80	2	2	4
8	M	61	Left	ELS	66.7	100	1	2	3
9	F	52	Right	ELS	75.0	96	2	2	4
10	F	50	Left	ELS	53.3	88	2	2	4
11	M	66	Left	ELS	45.0	88	2	2	4
12	M	59	Left	ELS	86.7	80	2	2	4
13	F	70	Right	ELS	45.0	100	1	2	3
14	F	82	Left	ELS	48.3	96	2	2	4
15	F	45	Right	ELS	25.0	68	2	1	3
16	M	66	Right	ELS	65.0	80	2	2	4
17	M	58	Right	Lab	61.7	24	2	2	4
18	F	51	Left	Lab	66.7	0	2	2	4
19	F	71	Left	Lab	65.0	76	2	2	4
20	M	62	Left	ELS	76.7	40	2	2	4
21	F	69	Left	Lab	68.3	60	1	2	3
22	F	44	Right	Lab	53.3	88	2	1	3
23	M	48	Left	ELS	20	96	2	2	4
24	M	57	Right	Lab	58.3	52	2	2	4

Abbreviations: PTA: pure tone average (0.5, 1, 2 kHz) preoperatively; WRS: word recognition score; ECochG: electrocochleography; CM: cochlear microphonic; M: male; F: female; ELS: endolymphatic sac decompression and shunt surgery; Lab: labyrinthectomy; ANN: auditory nerve neurophonic; CAP: compound action potential

ECochG Waveform Examples

Figure 1 displays example ECochG tracings from the subjects of both groups who had the most negative SP amplitudes. The left panel displays the condensation and rarefaction waveform while the right panel of each group shows the alternating waveform from which the SP was measured. For the VS group there were missing responses at different frequencies in which the patient did not have significant response in the ongoing response (Table 1), while all subjects in the MD group had measurable responses (Table 2).

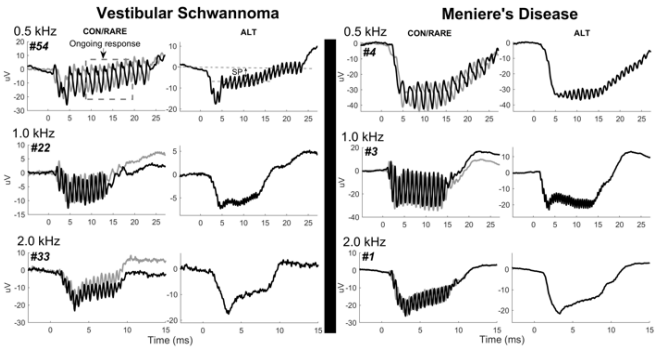


Fig. 1. Electrocochleography example waveforms from subjects who exhibited the most negative summation potential amplitude. The left panel is the response evoked by 0.5 kHz stimulus for subject #4 from the Meniere's disease group while the right panel is the response evoked by 2.0 kHz stimulus for subject #33 of the vestibular schwannoma group.

Ongoing Response

The distributions of the ongoing response amplitude for each frequency (0.25-4 kHz) for all subjects of the two groups can be seen in Figure 2. For the MD group (black circles) the median ongoing response amplitude was 21.23 dB (SD 8.7) at 0.25 kHz, 17.5 dB (SD 8.9) at 0.5 kHz, 7.2 dB (SD 7.6) at 1 kHz, 0.2 dB (SD 7.3) at 2 kHz, and -6.3 dB (SD 7.3) at 4 kHz, while for the VS group (gray circles) the median ongoing response amplitude was 10.1 dB (SD 12.1) at 0.25 kHz, 7.4 dB (SD 11.7) at 0.5 kHz, 1.4 dB (SD 13.1) at 1 kHz, -1.9 dB (SD 13.9) at 2 kHz, and -2.9 dB (SD 11.4) at 4 kHz. The maximal amplitudes of the ongoing response were similar across groups for the low to mid-frequencies (0.25, 0.5, 1.0 kHz), typically reached at approximately 30 dB, while the higher frequencies (2, 4 kHz) were reached around 10 dB in the MD group and 20 dB in the VS group. In both groups a reduced trend of the ongoing response, especially for high frequencies (1, 2, 4 kHz), was evidenced, although this was more remarkable in the VS group. These findings suggest that both groups experienced a wide variety of cochlear function reaching similar maximums but that, overall, both exhibited general cochlear pathology injury most prominent at the higher frequencies. Although MD patients are traditionally thought to suffer from low-frequency hearing loss, our results are consistent with more recent theories describing MD as a pathophysiologic process affecting the whole cochlea and consequently the whole frequency range[76].

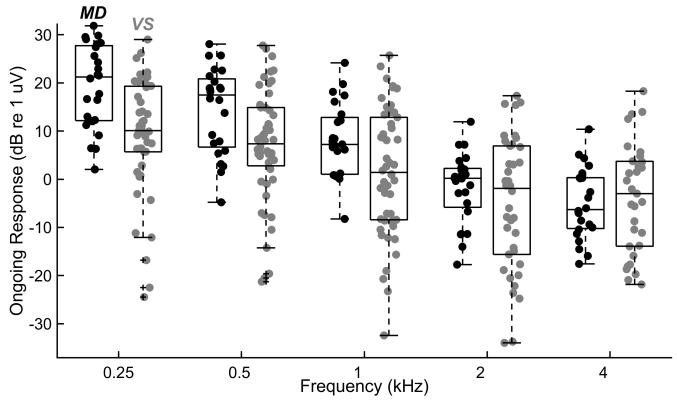


Fig. 2. Box and whisker plot of amplitudes of the ongoing response for the vestibular schwannoma (gray circles) and Ménière's disease (black circles) groups across frequencies. Note, "+" indicates an outlier.

Summation Potential (SP)

Figure 3 exhibits the distribution of SP amplitudes by frequency for each group. Here, the 50th percentile for the VS group was consistently less negative than that of the MD group across frequencies except at 4 kHz where the two groups were essentially the same. The median SP amplitude by frequency was found to be -0.2 µV (SD 1.5) at 0.25 kHz, -1.3 µV (SD 2.1) at 0.5 kHz, -1.0 µV (SD 1.4) at 1 kHz, -0.7 µV (SD 2.0) at 2 kHz, and -0.4 µV (SD 0.9) at 4 kHz for the VS group, whereas the median amplitudes for the MD group were -3.3 µV (SD 3.7) at 0.25 kHz, -7.0 µV (SD 7.0) at 0.5 kHz, -7.1 µV (SD 5.9) at 1 kHz, -4.6 µV (SD 4.6) at 2 kHz, and 0.0 µV (SD 1.2) at 4 kHz. The peak of negativity of the SP was reached by a subject of the MD group at 0.5 kHz with an SP amplitude of -28.0 µV, while in the VS group the most negative SP value was -9.6 µV found at the 2 kHz response. Interestingly, the latter was one of only six SP values (i.e., 3% of all SP data points) exhibited by the VS group who had an SP amplitude more negative than the 50th percentile of any test frequency (other than 4 kHz where the groups were the same) for the MD group.

Results of the LMM were significant for group ($F_{(1, 328)}$=131,p=<0.01), frequency ($F_{(4, 328)=}$23.4, p=<0.01), and their interaction ($F_{(4, 328)=}$12.8, p=<0.01). This suggested that the SP was different between groups, specifically that lower frequencies had larger SP amplitudes for both groups and that with decreasing stimulus frequency, the SP became increasingly more negative for the MD group as compared to the VS group. Post-hoc pairwise comparisons using Bonferroni correction found that SP values at all test frequencies (0.25-2.0 kHz) except for 4.0 kHz were statistically different between the two groups.

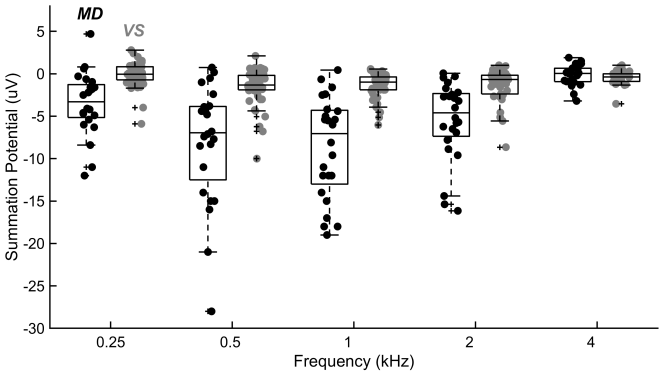


Fig. 3. Box and whisker plot of summation potential (SP) amplitudes for the vestibular schwannoma (gray circles) and Ménière's disease (black circles) groups across frequencies. Note, "+" indicates an outlier.

NERVE SCORE

As the CAP has been known to influence the SP, the function of the auditory nerve using the nerve score was evaluated. The distribution of nerve scores can be seen in Figure 4-A where it can be observed that the MD group exhibited scores of 3 or 4 whereas the VS group exhibited a wide range of nerve function (0-4). The median score was higher for the MD group (4) than the VS group (3). The results of a Mann-Whitney U test found this difference to be significant (U= 347, z = -3.4, p = 0.001). The distribution by individual subcomponent of the nerve score can be seen in Figure 4-B. When considering the ANN, the two groups exhibited similar nerve activity scored at a 2 (VS: 68%; MD: 79%) but greatly differed in the percentage of subjects that exhibited a 2 on the CAP subcomponent (VS: 40%; MD: 92%). Overall, these results suggest that the VS group exhibited a lower amount of nerve activity compared to the MD group.

A)

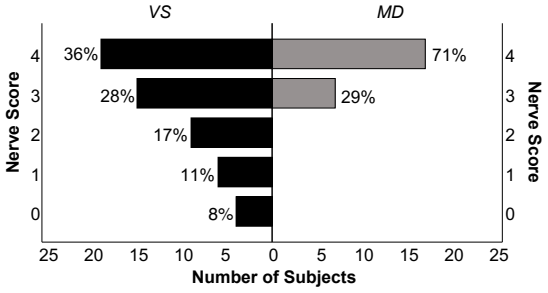


Fig. 4. A) Histogram of Nerve Scores for each group. B) Breakdown of the subcomponents (ANN and CAP) of the nerve score by group.

B)

ANN	VS	MD
0	7%	0%
1	25%	21%
2	68%	79%
CAP		
0	26%	0%
1	34%	8%
2	40%	92%

DISCUSSION

The current study investigated the behavior of the tone burst evoked SP in ears with VS and MD. Our objective was to determine if subjects with VS present with electrophysiological markers of cochlear impairment like subjects expected to be affected by ELH. To that extent, the current findings do not support our hypothesis and suggest that ELH is not a cochlear effect secondary to a VS in most subjects.

Although many hypotheses have been presented in the current literature to explain the mechanisms underlying the SNHL induced by VSs, its pathogenesis is likely multifactorial and remains debated. Among the possible explanations proposed include mechanical compression by VSs on the auditory nerve or the labyrinthine artery[77], ototoxic and neurotoxic VS-biological secretions as well as the presence of ELH[70,78,79], which has been described by radiological studies and histological reports of temporal bones, but has been rarely reported in the clinical practice, mostly in case reports.

Besides the postmortem evaluation of temporal bones, the techniques currently available to diagnose ELH are imaging techniques, namely magnetic resonance imaging (MRI), such as a delayed-FLAIR sequence acquired 4 hours 30 minutes after a gadolinium injection or a non-contrast coronal heavily T2-weighted sequence at 3 T. However, the study of temporal bones on a large scale is often limited by the finding of adequate specimens and difficulties in obtaining the complete clinical history of subjects can limit the investigation of clinical correlations of the anatomical and histological data collected. The use of MRI of ELH in MD certainly looks promising, but at the same time a recent review evidenced that quantitative MRI evaluation is often insufficient in the diagnosis of ELH and that presently the main purpose of this technique is to exclude other disorders in case of unclear disease presentations[80].

Other techniques which allow the evaluation of ELH are ECochG and vestibular evoked myogenic potential (VEMP). The latter is an emerging technique, while one of the longstanding uses of ECochG has been the diagnosis of ELH. Traditionally, extratympanic/transtympanic ECochG has been used in the diagnosis of MD, but currently more advanced quasi-near field measurements, namely RW ECochG and intracochlear ECochG have been developed[6].

To the authors' knowledge, this is the first study in the current literature to use this novel, real time approach; trying to identify and objectively quantify ELH intraoperatively by using RW ECochG in a VS group matched with a control group of MD subjects.

Key results and interpretation

The CM has been largely studied in the literature and represents a good indicator of the cochlear

function and pathology, but its efficacy in the clinical practice and in the differential diagnosis of inner ear versus auditory nerve pathology is still debated. Although a reduction of the CM has also been described in ELH, an enlarged negative SP for tone burst responses have proven to be the most reliable indicators for this purpose. As tone burst stimuli were used in this research, the SP was the main outcome measure of our analysis. Therefore, the reduction of the ongoing response amplitude at high frequencies (1, 2, 4 kHz), particularly notable in the VS group, was consistent with a decreased cochlear function, although this is not specific of ELH and might be due to other disease associated to a loss of hair cells or another cochlear dysfunction. Regarding the SP, the MD group presented with an expected large negative amplitude, consistent with ELH, while in the VS group, only a few subject's responses exhibited SP values more negative than the median of those in the MD group, possibly suggesting ELH. Thus, while overall the VS group displayed less negative SP values than the MD group, our study does not completely rule out ELH in some subjects with VS. However, based on our results, the incidence of this occurrence is low.

Another interesting finding is that the MD group had good nerve scores, indicating better neural function than the VS group. Pappa et al.[5] showed that the nerve contributes to the SP typically in a positive direction. Although the SP in the MD group is much more negative than the VS group, it is likely that the difference was not due to poorer neural function in the MD group but derives from the ELH. Conversely, the VS subjects do not have ELH, but they have poor neural function as suggested by the lower nerve score.

Limitations

A limitation of the current study is represented by the different number of participants in the two study groups, 53 VS subjects and 24 MD subjects. However, the limited number of subjects in the MD group can be justified by the fact that surgical options for MD are usually indicated in patients not responding to medical treatments and with persistent vertigo attacks. Moreover, the efficacy of ELS in controlling vertigo attacks is still controversial. Furthermore, despite a fewer number of subjects, the MD group did exhibit more extreme negative SP amplitudes, thus, the smaller number of subjects likely did not introduce any further confounds.

Finally, it should be acknowledged that at low frequencies (0.25, 0.5 kHz) the median amplitude of the ongoing response is larger for the MD group than the VS cohort. Although the other frequencies (1, 2, 4 kHz) presented a similar decreased trend, this discrepancy still might reveal a different number of hair cells between the two investigated groups, possibly also influencing the SP response which has mixed origin from the outer and inner hair cells and auditory nerve. However, we feel this effect was unlikely as there were a considerable number of subjects who had amplitudes of the

ongoing response that fell above the 50th percentile of the MD group at each test frequency.

Generalizability

Although the results of the present study did not support the hypothesis that VS causes ELH there appeared to be cochlear effects such as hearing loss caused by the VS. It should be noted that while ELH was not a common finding, there were a couple VS subjects who exhibited a large negative SP amplitude like the subjects with MD. Future research correlating the electrophysiological results with those obtained by the other radiological techniques currently indicated to study ELH, such as MRI, would likely be able to further support these findings.

CONCLUSIONS

Although radiological studies and histological reports of temporal bones published thus far have suggested the presence of cochlear alterations induced by VSs, including ELH, our electrophysiological analysis in a large group of VS subjects compared to a MD group did not support this hypothesis, evidencing a possible condition of ELH in only a couple VS subjects. Considering the longstanding use of ECochG to quantify ELH and the usefulness that intraoperative real time measurements, such as RW ECochG[7,64,81], have exhibited in the monitoring of auditory function during inner ear surgery, a possible speculation is that there might be cochlear effects determined by VSs, but not ELH, or that this condition might be sporadic and not the principal trigger of the SNHL in VS subjects.

INTRAOPERATIVE ELECTROCOCHLEOGRAPHY DURING LATERAL SKULL BASE SURGERY

INTRODUCTION

The jugular foramen is situated between the temporal and occipital bones in the posterior cranial fossa. It features a complex anatomical area that contains the inferior petrosal sinus, and cranial nerves IX-XI (pars nervosa), as well as the jugular bulb and minor meningeal branches from the occipital and ascending pharyngeal arteries (pars vascularis). Different types of lesions can arise in the jugular foramen with paragangliomas considered to be the most common tumor in this site, followed by schwannomas, meningiomas, and other rare neoplasms such as lymphomas. Depending on their specific properties, jugular foramen tumors (JFT) can cause significant morbidity due to possible injury of lower cranial nerves causing temporary or permanent laryngeal and pharyngeal dysfunction[82].

Though the surgical management of JFTs has been widely debated and reported on in the literature, the audiological testing before and after surgery has not been analyzed in detail. Here, we present a unique case of a young patient with a JFT who demonstrated an improvement of sensorineural hearing loss (SNHL) after tumor removal. In the current literature, there are very few cases of jugular foramen schwannomas that have recovered hearing after surgery and the details remain unclear[83]. This study, then, examines JFTs from a different perspective, aiming at investigating preoperative and postoperative hearing, using both standard audiometric testing (e.g., audiogram) and more novel intraoperative near-field measures of auditory function, such as electrocochleography (ECochG), to illustrate their utility during complex skull base surgeries. ECochG responses comprise the cochlear microphonic (CM), recorded from the outer hair cells, and neural potentials, such as the compound action potential (CAP). The summation potential (SP) is thought to be derived from contributions of both inner and outer hair cells as well as neural sources[5]. The advantage of ECochG is that electrophysiological recordings can allow correlation of real-time information on hearing physiology during various parts of the surgical procedure, as opposed to delayed hearing monitoring, due to the high number of averages required to obtain a reliable signal, when using intraoperative far-field auditory evoked brainstem responses (ABR). Therefore, ECochG from the round window provides better signal-to-noise ratios with fewer averages required and allows studying with more frequency specificity in the 2-4 kHz range[17].

CASE REPORT

A 22-year-old female patient presented to the clinic with right-sided otalgia. Magnetic Resonance Imaging (MRI) revealed an approximately 1.0 cm enhancing mass of the ipsilateral jugular foramen

consistent with a schwannoma (Figure 1). This was initially followed with observation through serial imaging. However, the patient began to experience progressive symptoms, primarily increasing pain in the right mastoid region, leading her to present to the emergency department on multiple occasions. Additional symptoms included mild, right-sided SNHL (Fig. 2A) and blurry vision of unclear etiology but denied any symptoms of lower cranial nerve dysfunction. Moreover, imaging revealed an interval increase in size.

Given the patient's young age and her increasing complaints, surgical resection was recommended. Intraoperative ECochG was executed during this surgery performed at the Ohio State University as it is routinely performed for research purposes with the goal of establishing a protocol that uses response changes in auditory physiology because of intraoperative events (Institutional Review Board protocol #2015H0087).

The patient subsequently underwent a combined transmastoid and cervical approach. General endotracheal anesthesia was induced. Neuromonitoring electrodes were placed and tested. A post-auricular skin incision was performed, extending down to the anterior border of the sternocleidomastoid in the neck to facilitate the planned combined transmastoid and cervical approach. Following this, the jugular vein, carotid artery, and spinal accessory nerves were identified and exposed in the neck.

A cortical mastoidectomy was performed including a facial recess to obtain ECochG recordings at the round window (RW). The bony labyrinth, the sigmoid sinus, and jugular bulb were skeletonized as well. The right jugular vein was ligated and divided to facilitate tumor resection. Further, the sigmoid sinus was compressed and the stylomastoid foramen was dissected. The mastoid segment of the facial nerve was mobilized and pushed anteriorly. This ultimately allowed the tumor to come into view. Cranial nerve XI was noted on the posterior aspect and was preserved. The remaining lower cranial nerves were seen medially within the tumor cavity and were also preserved. The tumor was addressed with an ultrasonic aspirator, coring out the lesion while leaving the shell intact. The remainder of the tumor was collapsed and removed. A gross total tumor resection was performed. Upon completion, cranial nerve VII stimulated appropriately using 0.05 mA. A drain was placed in the wound bed and hemostasis was ensured. The patient tolerated the procedure well and was without intraoperative complications.

Final pathologic diagnosis was consistent with a schwannoma (WHO grade I).

After six months, the patient demonstrated no cranial nerve deficits and recovered well post-operatively. She reported that the hearing in her right ear had improved, as confirmed by repeat audiometric testing (Fig. 2C). After three years of follow-up, the patient has not reported any change in hearing.

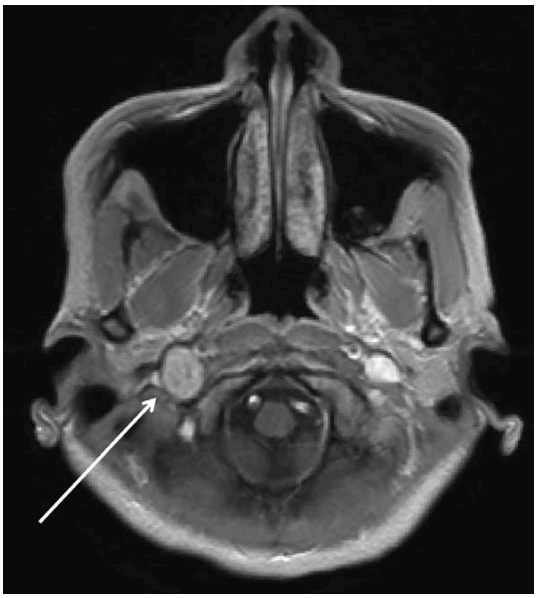


Fig. 1. Magnetic resonance imaging (MRI) with arrow showing an approximately 1.0 cm enhancing mass of the jugular foramen consistent with a jugular foramen schwannoma.

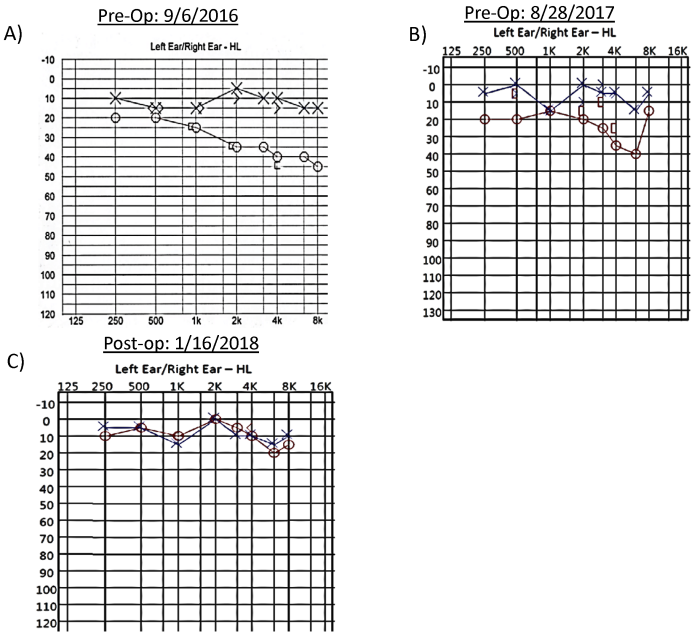


Fig. 2. Patient audiograms, (A) at presentation, (B) before operation, and (C) after tumor removal.

Intraoperative Electrophysiologic Recordings and Results

Intraoperative ECochG responses were recorded from the RW niche before sigmoid sinus dissection ("Pre"), during, and immediately following tumor resection ("Post"). Both click and tone burst (1, 2, 4 kHz) stimuli were utilized and presented at 90 dB nHL. The CAP, CM, and SP magnitudes were logged for both the pre- and post-tumor removal interval (Table 1). For statistical analysis, a paired t-test ($p<.05$) was used. Interestingly, the CAP magnitudes increased at all test frequencies ($p<.01$), indicating an enhancement in the amount of neural activity of the auditory nerve, whilst the SP and CM remained relatively stable ($p>.05$). The magnitude of the CAP to the broad band clicks

stimulus (Figure 3A) and the 4 kHz tone burst (Figure 3B) was plotted for each of the recording intervals.

Amplitude (mV)						
Stimulus (Hz)	CAP		SP		CM	
	Pre	Post	Pre	Post	Pre	Post
1000 Hz	11.5	17.4	2.2	1.5	27.0	27.0
2000 Hz	9.0	15.0	2.8	2.1	11.0	9.0
4000 Hz	7.3	13.1	2.2	3.5	13.0	11.0
Click	15.0	18.0				

Table 1. Electrocochleography results for the eighth nerve compound action potential (CAP), cochlear microphonic (CM), and summation potential (SP) before (‘‘Pre’’) and after (‘‘Post’’) tumor resection.

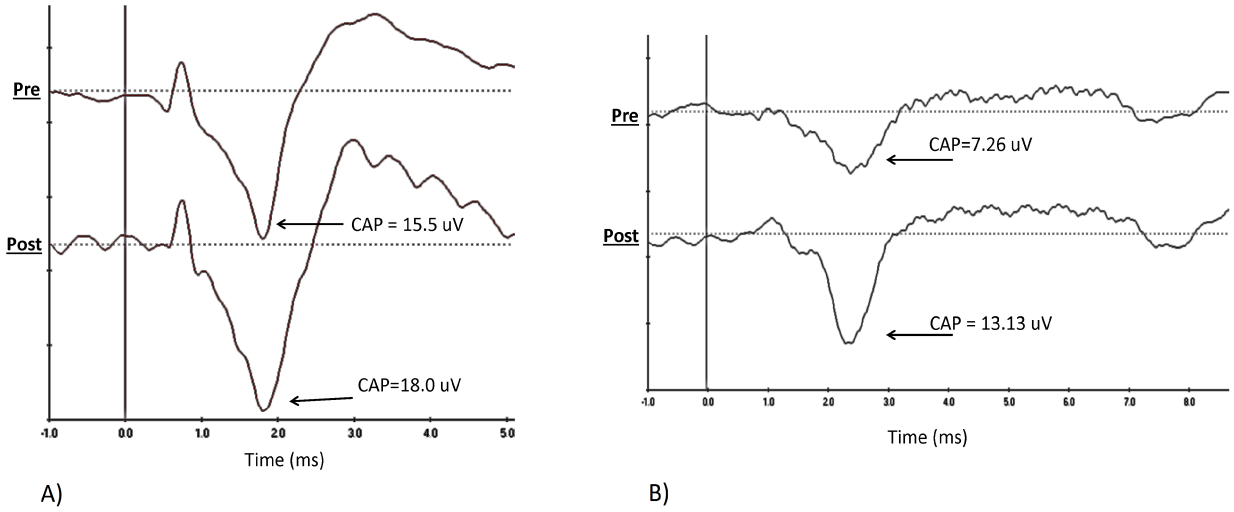


Fig. 3. Intraoperative round window electrocochleography results of the eighth nerve compound action potential (CAP) to a 90 dB nHL click stimulus (A) and the 4 kHz tone burst (B). The top tracing portrays the CAP response before tumor resection while the bottom displays the CAP magnitude after tumor removal.

DISCUSSION

JFTs comprise a wide variety of lesions, and they require a thorough clinical evaluation along with the appropriate imaging. As with many lateral skull base lesions, the management of JFTs can be challenging and necessitates the involvement of a multidisciplinary team.

Of particular interest to the present case is the hearing loss, which ultimately recovered because of tumor resection. Previous literature has discussed SNHL as a possibility of the tumor compressing cranial nerve VIII or the brainstem. Another possible explanation for this recovery could be a catecholamine-secretion-induced SNHL. Also, the involvement of the inferior cochlear vein can be related to SNHL in jugular foramen paragangliomas[84]. However, there was no direct involvement of the inferior cochlear vein in this case, though it is not possible to exclude vascular steal syndrome [85].

A plausible speculation for the change in intraoperative ECochG could be a temporary threshold shift in hearing caused by the drilling of the mastoid. The "baseline" ECochG measurement was done immediately after drilling, and then there were approximately 7 hours between drilling being completed and the second ECochG measurement. The ear had possibly recovered from the temporary threshold shift, which could potentially explain the CAP becoming larger post tumor removal. However, this would only explain the increase in ECochG CAP and not support the recovery in audiometric hearing that was seen on the post-operative audiogram. Abtahi et al.[86] showed that distortion product otoacoustic emissions (DPOAEs) and transient evoked otoacoustic emissions (TEOAEs) decreased in the initial post-operative audiogram, but then recovered a week later. Although the temporary threshold shift may be one theory, the CM and SP magnitudes did not change, suggesting neural changes only. Thus, it is different from findings of Abtahi et al.[86] because they showed that the DPOAEs and TEOAEs, which are outer hair cell measurements, decreased and then recovered. Therefore, it is likely we would have also seen a reduction in CM amplitude in conjunction with the reduced CAP amplitude.

Lourenço et al.[87] observed that changes in the CM were very sensitive to vascular interruptions. Although the mechanism underlying this patient's high frequency SNHL remains unclear, we did not see changes in the CM so this likely supports the hypothesis that the reason for the increase in CAP magnitude could be due more to neural compression of the auditory nerve without vascular compromise. We cannot rule out, however, that changes in the vasculature due to resection of the tumor resulted in improvement in the hearing as seen in the audiogram.

Cases of hearing recovery after jugular foramen schwannoma removal have rarely been documented in literature and only a few were accurately described with detailed and objective audiometric test results, such as otoacustic emissions (OAE) and ABR[88].

Hence, to the best of our knowledge, this is the first report to provide intraoperative electrophysiologic monitoring during an infratemporal fossa approach. The improvement of the CAP magnitude at all test frequencies ($p<.01$) evidenced the electrophysiological increase in the amount of neural activity of the eighth nerve. These objective results are also in accordance with the

findings of the post-operative audiogram which support the subjective hearing recovery of the patient (Fig. 2), but the mechanism underlying this remains unclear and could represent vascular changes due to the surgery, temporary threshold shifts from drilling or other currently uncharacterized reasons. Though further research is still needed, performing ECochG at the time of inner ear procedures like this may shed light on the mechanisms of hearing loss and/or preservation, and encourages future studies of ECochG during resection of tumors that have an impact on the auditory system. The timeline usually includes two measurements: the first intraoperatively immediately prior to tumor removal and the second immediately post tumor removal. In some cases, like the translabyrinthine approach, it can request one additional recording at the time of the lateral semicircular canal opening[89]. The execution of these measurements doesn't affect the surgical outcome and can allow determining which skull base techniques can help to preserve hearing. Also, implementing intraoperative ECochG during a tumor or a surgical approach that is not typically thought to significantly alter hearing can permit the investigators to learn about hearing physiology in a cochlea that is not compromised by the surgical approach.

CONCLUSIONS

Jugular foramen schwannomas are rare neoplasms and can cause various types of hearing impairment. Here, intraoperative electrophysiological responses of the inner ear support the behavioral and subjective improvement in a patient's hearing following tumor resection, thus sustaining the potential utility of continuous hearing monitoring in lateral skull base surgery.

ELECTROCOCHLEOGRAPHY AND COCHLEAR IMPLANT ELECTRODE TIP FOLD-OVER: A PILOT STUDY

INTRODUCTION

Cochlear implant (CI) surgery has become the gold standard treatment for both pediatric and adult patients affected by severe to profound hearing loss[90]. Although cochlear implantation is a relatively safe procedure, one possible complication is fold-over or rollover of the electrode tip inside any of the intracochlear structures, which is not necessarily detected by the surgeon while operating and may be the cause of revision surgery[91]. The incidence of tip fold-over rates varies among the literature but in two large cohorts has been reported to occur at a rate of 1.98%[92] and 0.87%[93] with experienced surgeons. In smaller cohorts, other authors have reported higher rates of 5.5%[94] and 4.7%[95]. In a recent systematic review[91] of 3177 implanted ears, tip fold-over occurred in 50 ears, out of which 86% (n=43) were implanted with pre-curved electrodes.

Several studies have focused on exploring various intraoperative techniques with the aim of confirming the correct position of the electrodes[96]. These studies mainly used electrophysiological measures and/or a combination of imaging modalities that may show the electrode array functioning[97].

Given the increasing interest in the use of ECochG in the real time monitoring of auditory function during lateral skull base surgery[18] and prior, during, and after CI[12], this electrophysiological technique might represent an alternative approach to detecting rollover intraoperatively. ECochG captures auditory evoked potentials of the peripheral auditory system generated from the inner ear and auditory nerve in response to acoustic stimuli (clicks, tone bursts). These potentials are the cochlear microphonic (CM), registered from the outer hair cell, the compound action potential (CAP) and the auditory nerve neurophonic (ANN), from the eighth cranial nerve, and the summating potential (SP)[5], a complex combination of both outer and inner hair cells as well as neural components. As shown by previous literature, the study of these ECochG responses may be promising in predicting the final scalar location of the CI electrodes[98] and useful to identify electrode array-induced trauma/scalar translocation.

Considering also that CM responses reflect hair cell and basilar membrane movements, the aim of this work was to present intraoperative ECochG responses observed in a series of CI electrode tip fold-overs. To the authors' knowledge, no clinical studies have thus far investigated the relationship between electrode array position (i.e., fold-over) and ECochG results.

MATERIALS AND METHODS

Pediatric subjects undergoing CI surgery (n = 5) with a perimodiolar electrode array (Cochlear 532) who were diagnosed with either auditory neuropathy spectrum disorder (ANSD) or enlarged vestibular aqueduct (EVA) were enrolled in this study. ECochG recordings were performed intraoperatively, immediately before and after electrode insertion, as they are routinely collected at the Ohio State University Wexner Medical Center for research purposes (Institutional Review Board protocol #2015H0045). Written informed consent was obtained from each subject.

Surgical Approach and ECochG Recordings

A standard transmastoid approach was performed to create a facial recess and access the round window (RW), so that the CI electrode could be inserted within the RW niche[17]. A sterile, monopolar probe (Neuro-Kartush raspatory instrument, Integra, Plainsboro, NJ) was placed on the membranous portion of the RW to serve as the recording device and a Bio-logic Navigator Pro (Natus Medical, San Carlos, CA) was used to deliver stimuli and record responses. Alternating-phase stimuli were tones bursts of various frequencies 250, 500, 750, 1000, 2000, and 4000 Hz, shaped by a Blackman window and delivered from 95 to 110 dB SPL (peak equivalent) through a foam insert via Etymotic Research (Elk Grove Village, IL) microphones (ER-3) in the ipsilateral ear.

After executing the first measurements, the recording electrode was removed, and the surgeon proceeded with a RW CI insertion. Immediately after positioning the CI, the recording electrode was placed back on the RW for post-insertion measurements of ECochG.

Following ECochG recordings, a modified Stenver's view plain radiograph was performed intraoperatively and assessed by the operating surgeon. When a tip fold-over was detected, the device was removed and reinserted during the same surgery.

Statistical Analysis

The spectrum of the ECochG responses obtained intraoperatively for each test frequency in fold-over and non-fold-over cases were extracted using fast Fourier transforms. A window was used to isolate the CM response from any contributions of an on-set potential (CAP). The metric used to calculate the magnitude of the hair cell activity was the sum of first and second harmonics across all frequencies where the response was significant, namely the ECochG-total response (ECochG-TR), first described by Fitzpatrick et al.[39]. Responses of the first and second harmonic were considered significant if they exceeded the noise floor by three standard deviations (SD). To analyze starting phase characteristics of the ECochG signal, the deflection polarity (+/-) of the first cycle of the CM

response was compared pre- to post-insertion using the condensation waveform for 500, 1000 and 2000 Hz. These areas of the cochlea are thought to lie in the region where the tip fold-over exists and were therefore chosen for analysis. If the response was inverted/out of phase 180-degree from the pre-insertion response, the subject was considered to have a phase change.

RESULTS

Of the five subjects included in this study, three presented with CI tip fold-over (fold-over group) and two with a normal placement of the electrode array (control or non-fold-over group). Mean age at implantation for the entire cohort was 5.4 years (SD= 3.8). Table 1 illustrates demographics, etiology of hearing loss (HL), surgical data, ECochG response changes and phase characteristics due to insertion for the two groups.

	Subject	Etiology of HL	Sex	Device	Ear(s)	Age (Years)	ECochG-TR Magnitude (uV) Pre-insertion	ECochG-TR Magnitude (uV) Post-insertion	Pre-Post dB Change	Phase Change: Y/N	Approach
Tip Fold-Over Group	1	EVA	Male	Cochlear 532	Left	10	6.9	7.9	1.2	N	RW
	2	ANSD	Male	Cochlear 532	Left	2	27.8	44.4	4.1	N	RW
	3	ANSD	Male	Cochlear 532	Left	10	121.9	44.3	-8.8	Y	RW
Non-Fold-Over Group	4	ANSD	Male	Cochlear 532	Right	2	92	64.4	-3.1	N	RW
	5	ANSD	Male	Cochlear 532	Right	3	50	17	-9.4	N	RW

Table 1. Demographics, etiology of hearing loss, surgical data, electrocochleography (ECochG) response changes and phase characteristics due to insertion for fold-over and non-fold-over patients.

The ECochG results in three-fold-over cases from pre- to post-insertion were different from each other. Two participants (subjects 1 and 2) did not have a change in phase, but the third case (subject 3) did exhibit a 180-degree inversion in the starting phase of the CM response (Figure 1A and 1B). Both subjects who did not exhibit a change in phase did, however, have an increase in the ECochG-TR magnitude from pre- to post-insertion, 1 uV and 16.6 uV, respectively. The single case (subject 3), which did have a phase change (Figure 2), had a 77.6 uV decrease in spectral magnitude from pre- to post-insertion (Table 1).

Non-fold-over group.

In the control group of ANSD patients, fold-over of the electrode did not occur in any case and the ECochG characteristics from pre- to post-insertion were similar across all subjects (Table 1). No case in this control group exhibited a detectable change in starting phase of the CM response from pre- to post-insertion. Regarding the ECochG-TR, all cases in this group exhibited a decrease in the magnitude from pre- to post-insertion.

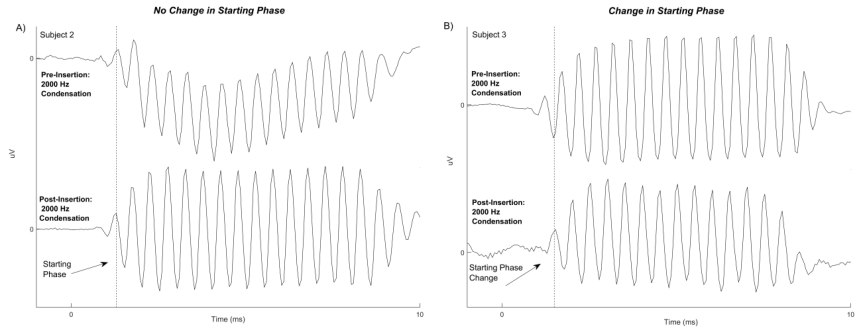


Fig. 1. Intraoperative round window electrocochleography (ECochG) results for subjects 2 and 3 of tip fold-over group. Subject 3 exhibited a 180-degree inversion in the starting phase of the cochlear microphonic response.

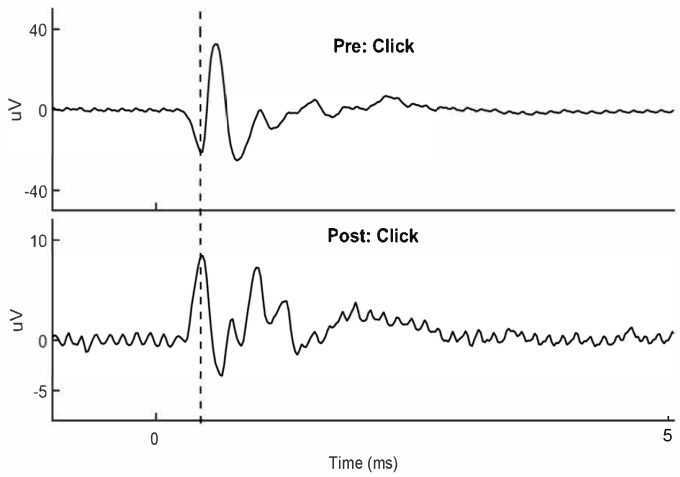


Fig. 2. Example electrocochleography (ECochG) phase inversion for subject #3 elicited by a broad band click stimulus. Condensation waveforms shown only. Dotted lines indicate phase inversion area.

DISCUSSION

This preliminary report tried to present a novel approach in identifying tip fold-over intraoperatively by using ECochG without imaging. Although the use of ECochG in CI has been thoroughly investigated, no previously published studies exist on this technique and tip fold-over.

A few researchers have carried out intraoperative and postoperative examinations, which can help identify electrode array positions. Particularly, intraoperative techniques have included fluoroscopy, CI telemetric capabilities, namely electrically evoked compound action potential (ECAP), electrode

impedance (EI) and spread of excitation (SOE), 3-dimensional (3-D) rotational X-ray, and postoperative computed tomography (CT). Although some of these methods are routinely executed, they remain mostly performed postoperatively and, in these cases, the electrode tip fold-over cannot be corrected in the same surgery.

Intraoperative Stenver's view plain film radiography may provide the surgeon information about tip fold-over, but not about scalar translocations, which is detectable by post-operative high resolution (HR)-CT scans with additional exposure to radiation for the patients. Also, intraoperative fluoroscopy is not without limitations, since it provides a 2-D planar imaging, and it is dependent on the position of the subject and the X-ray beam angle. Additionally, due to the longer time of surgery required for imaging, availability of the machine and radiation exposure to personnel and patients, especially in children, detection of fold-over is not always identifiable by fluoroscopy[99].

The initial hypothesis of this paper was that since CM reflects movement of the micro mechanical system of the inner ear[20], then there would be distinct differences between ECochG responses (reflected by changes in magnitude and starting phase) when the CI electrode array is situated in a physically different manner within the cochlea (i.e., translocation of the CI electrode from the scala tympani into the scala vestibuli; fold-over vs. non-fold-over). Moreover, according to Koka et al.[26], the phase inversion could be due to biomechanical changes of the basilar membrane, being caused by basilar membrane disruption or by-passing characteristic frequency in the cochlea. Consequently, the main supposition was that the phase change could represent some type of alteration to the basilar membrane, such as a translocation or an electrode pushing against the membrane itself.

In this study all cases in the control group exhibited a similar trend, decreased magnitude of the total response and no change in phase, whereas in the rollover group, one subject presented with decreased magnitude and two exhibited increased magnitude. The patient with the decrease (subject 3) had a 180-degree phase inversion, which is consistent with the initial hypothesis of a condition of an altered basilar membrane. Therefore, there were heterogeneous ECochG responses in the fold-over group. A decrease in magnitude was not a unique characteristic to fold-over. An increase in the magnitude without a phase change is interesting but not conclusive. These results may suggest that if ECochG from pre- to post- shows an increase in magnitude and a change in phase, then it raises suspicion that the electrode insertion could be possibly folded over. However, no patterns like that were observed in our case series. Further studies are necessary to confirm why the signal magnitudes increased and how changes in phase of the ECochG response, reflecting basilar membrane movement, correlate to changes in the spectral magnitude of the CM response.

The present study is not without limitations. First, the small number of participants is not representative. However, considering the low incidence of fold-over occurrence[3,4] and the need for an ideal human model (patients with significant hair cell presence) to allow for optimal analysis of the various ECochG potentials, the need for preliminary observations is justified until larger numbers can be reported. Another limitation of the current study is that only intraoperative Stenver's view plain radiography was performed. Post-operative CT scans would have provided additional information about the scalar location of the CI electrodes, but these were not obtained as CT is not routinely executed for pediatric patients at our institution.

One issue with using ECochG during CI surgery is the severity of the HL typically resulting in small ECochG responses[21]. Ideally, employing this technique in patients with residual hair cell physiology would allow for optimal analysis of various components of the ECochG response. Etiologies that would likely result in optimal ECochG recordings during CI surgery would be those with ANSD and/or EVA syndrome. Patients with severe to profound HL and ANSD typically have some degree of residual cochlear function; many undergo CI surgery, and this makes this group ideal for studying characteristics of the ECochG signal which can provide detailed information about spectral and temporal aspects of cochlear function and potentially adverse effects of electrode insertion. For comparison purposes, a group with ANSD with significant residual hair cells and without CI tip fold-over was selected. Of course, the patients' etiology of SNHL is highly heterogeneous, as the fold-over group consisted of one EVA and two ANSD patients. Although ANSD cover several entities of auditory processing disorders, the CM, which is a hair cell response, was evaluated in the current paper; therefore, regardless of what the neural deficit of patients might be, the heterogeneity of the ANSD diagnosis should not interfere with the present observations. As evidenced in the current literature, patients with EVA undergoing CI surgery presented various intraoperative ECochG patterns[24]. Additionally, inner ear malformations, such as enlarged cochlear or vestibular aqueduct, are known to produce gushers, which is an additional factor to possibly induce tip fold-overs by simply changing cochlear micromechanics via pressure gradients. Although these biomechanical effects of EVA should be acknowledged as limitations of the present study, previous literature has evidenced that the enlargement of the cochlear aqueduct commonly determines gusher while the presence of EVA has minor importance.[100]

This first paper provides preliminary data of the utility of intraoperative ECochG recorded from the RW to detect tip fold-over in humans without the aid of imaging. Further studies are needed to clarify the use of intracochlear ECochG[15] in detecting tip fold-over and if this technique can be more effective than recording from an extracochlear site.

CONCLUSIONS

Despite the small number of patients, heterogeneous ECochG response patterns were observed within the fold-over group. Even though these results are not conclusive, they can serve as a framework to begin to understand ECochG's utility in detecting intraoperative tip fold-over. In the future, this should be further explored using intracochlear methods of recording the ECochG response from the CI electrode array[10].

THE EXPERIENCE OF THE RESEARCH HOSPITAL "CASA SOLLIEVO DELLA SOFFERENZA" AND FUTURE PERSPECTIVES

INTRODUCTION

The challenge with CI surgery today is that it is not possible to monitor the function of the cochlea during electrode insertion, like with a real-time ECochG measurement. Also, patient management can be complex and time consuming, as some measurements rely on a high degree of patient cooperation and can use a variety of clinical equipment and space. Additionally, the COVID-19 pandemic has further amplified the difficulties experienced by CI recipients accessing CI services and the shortage of audiological professionals worldwide[101].

Recently, technology has emerged to record the response of the cochlea to acoustic stimulation directly from the CIs electrodes, as it is being introduced into the cochlea (real-time electrocochleography, rt-ECochG)[59,102]. Surgical intervention in response to intraoperative ECochG measurement can reduce trauma and save residual hearing during CI, as demonstrated in a random clinical trial[103]. Also, Koka et al.[104] have shown a robust correlation between ECochG measurements and behavioral audiograms, which is useful in fitting and follow-up for the patient.

The aims of this research were to investigate the impact of intraoperative hearing monitoring on residual hearing during CI and to compare results obtained by objective and behavioral audiometry.

MATERIALS AND METHODS

Patients were enrolled at the Research Hospital Casa Sollievo della Sofferenza from November 2020 to March 2023. Written informed consent and institutional review board approval were obtained.

Participants

The participants were adults of either sex, ranging in age from 18 to 80 years, undergoing CI with acoustic hearing in the ear to be implanted (80 decibels hearing level (dB HL) or better at 0.25-0.5 kHz). These individuals underwent ECochG recorded directly from a CI electrode array during its insertion, with the Active Intraoperative Monitoring (AIM, Advanced Bionics, Advanced Bionics LLC, Valencia, CA). The ECochG response was used to provide real-time feedback. The primary outcome was the preservation of residual hearing. To be eligible for participation, the patient had to be scheduled to receive the lateral wall electrode (CI HiRes Ultra3D HiFocus L23, Advanced Bionics, Advanced Bionics LLC, Valencia, CA).

The lateral wall electrode

The new lateral wall electrode (HiFocus SlimJ, Advanced Bionics, Valencia, CA) was systematically designed on the basis of mCT studies of human cochlea anatomy[105]. The main goal is reliable structure preservation surgery using RW insertion, with minimal disturbance of the cochlear fluids and a wide electrical coverage of the full frequency range. One of its main features is controlled surgical handling. The SlimJ is 23mm long with 16 active electrode contacts and allows for easy RW insertion due to the tip design. A blue marker indicates to the surgeon when the electrode array is fully inserted. The wing located at the most proximal part of the SlimJ is used to grip the electrode steadily and helps to ease the insertion process. The electrode diameters are smaller than that of the scala tympani along the cochlea to minimize risk of trauma to IC structures.

Surgical approach and ECochG recording set up

A standard transmastoid approach was performed to create a facial recess and access the round window (RW), so that the CI electrode could be inserted within the RW niche (Figure 1).

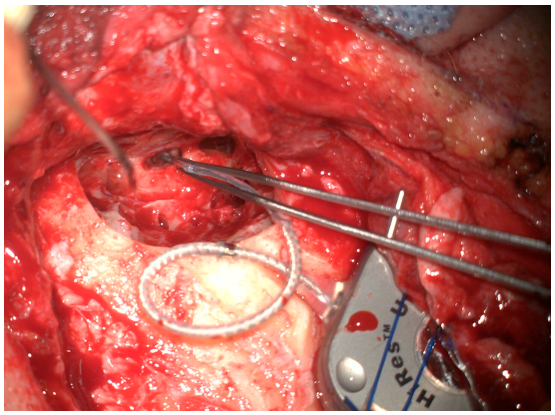
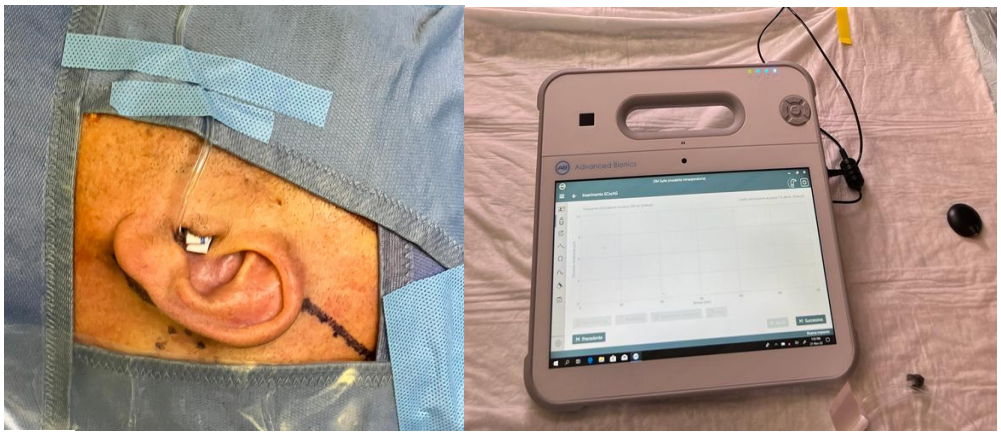


Figure 1. CI surgery with standard transmastoid approach and positioning a CI HiRes Ultra3D HiFocus L23 (Advanced Bionics, Advanced Bionics LLC, Valencia, CA).



A) B)

Figure 2. A) ECochG recording montage. B) Active intraoperative monitoring (AIM, Advanced Bionics Advanced Bionics LLC, Valencia, CA).

The in-the-ear tube phone for the delivery of the acoustic stimulus during ECochG was placed in the external ear canal after application of surgical prep, which was applied carefully to avoid flooding the external ear. The pinna was then folded anteriorly and held in place by a sterile self-adhesive plastic surgical film to isolate the external ear canal and the ear-insert from the surgical field. The implant package was placed in a subperiosteal pocket. Prior to electrode insertion, the implant system's external antenna/coil was placed inside a sterile, clear plastic telescope bag, brought into the operative field, and transcutaneously connected to the implant's receiver-stimulator. The AIM system was activated to ensure communication with the implant and that acoustic stimuli were being generated (Figure 2).

Active intraoperative monitoring (AIM)

The AIM system offers rt-ECochG measurement with monitoring of the auditory function of the patient's cochlea during electrode insertion, objective audiometry with fast and automated objective measurement of thresholds and objective measures suite designed for intra-operative and post-operative clinical use. At the click of a button, the AIM system can perform objective audiometry from 125 Hz to 4000 Hz in seconds using the patient's implant. This objective measurement requires no patient collaboration, making it especially useful when working with younger or harder-to-test patients. Designed for intra-operative and post-operative clinical use by surgeons and audiologists, the AIM system can perform quick neural response imaging (NRI)[106], electrically evoked stapedius reflex threshold (ESRT)[107], impedance measurements. Also, these measures can be conducted quickly and without requiring patient interaction. The modern and intuitive user interface makes the AIM system easy to use by any trained hearing healthcare professional. When the testing is done, the data can be exported, reviewed, or shared easily.

Behavioral audiometry

Audiometric testing was performed and evaluated within six months before surgery by a licensed audiologist. Pure tone averages (PTA) were obtained using the average air conduction thresholds at 0.5, 1, 2, 4 kHz. If there was no response at the limit of the audiometer, thresholds were noted as 120 dB HL.

Statistical analysis

Descriptive analysis giving mean values plus standard deviation was used to define the main clinical, audiological, and demographic characteristics. Qualitative data were summarized as percentages.

RESULTS

Seven patients were scheduled to receive the HiFocus SlimJ with AIM system (Advanced Bionics, Advanced Bionics LLC, Valencia, CA) from November 2020 to March 2023. Four patients did not show ECochG responses and had to be excluded, while three subjects (two females, one male; average age: 59 ±7.8) with acoustic hearing in the ear to be implanted were enrolled in this study (Table 1). Mean insertion time was 383±281 seconds (Figure 3). All surgeries were performed by the same surgical team.

Table 1. Demographic and audiological details of the study sample.

Subject	**Age at implant (years)**	**Sex**	**Side**	**CI electrode**	**Etiology**	**Pre-op mean PTA*^**	**Objective audiometry (AIM)*°**	**Insertion time (sec)**
1	70	Female	Left	HiFocus™ SlimJ	Unknown	80.0	83.25	780
2	58	Male	Left	HiFocus™ SlimJ	Otosclerosis	101.25	107.75	220
3	54	Female	Right	HiFocus™ SlimJ	Unknown	105.0	101.75	150

* PTA= pure tone average (0.5, 1, 2, 4 kHz)

^ Pre-operative evaluation; ° Intra-operative evaluation

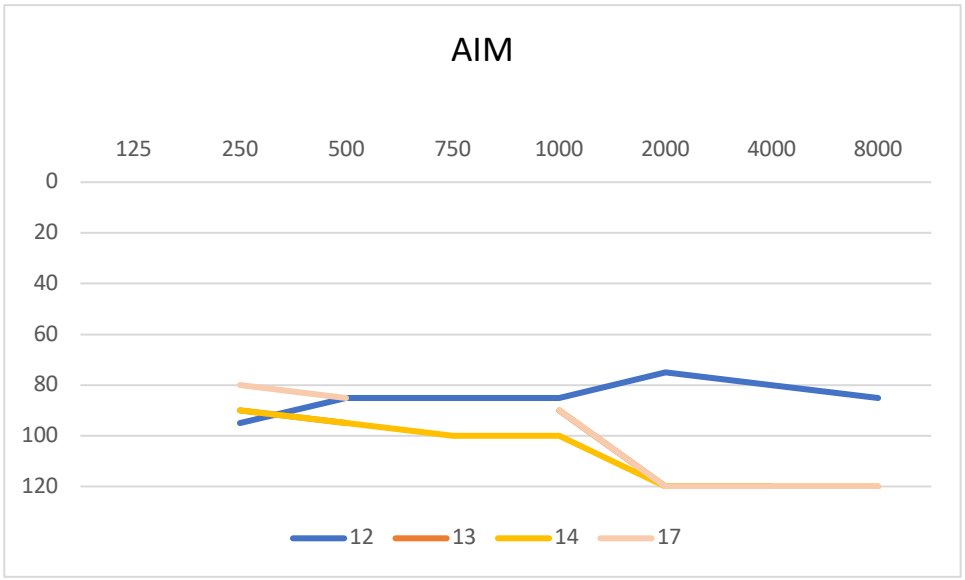


Figure 3. Mean insertion time.

DISCUSSION

Criteria for CI have expanded in the last few years to partial deafness treatment (PDT)[108] and achieving hearing preservation has become crucial in this category of patients. Other types of slim straight arrays such as the Cochlear Nucleus SRA and Med El Flex electrodes have shown good hearing preservation results with median postoperative hearing losses ranging from 15 to 20 dB HL[109,110]. This preliminary case series combining an atraumatic lateral wall electrode with rt-ECochG evidenced that objective audiometry by AIM system is in accordance with preoperative behavioral audiometry (ranging from 3 to 6 dB HL) with encouraging hearing preservation rates. As evidenced by Lenarz[111], insertion of SlimJ in combination with ECochG measurement appears promising in guarantying hearing preservation, more than an atraumatic electrode alone. Time added to surgeries by using AIM was <10 minutes.

Future perspectives

Patients are going to be followed at 1, 3, 6, 9 and 12 months. Besides objective audiometry obtained directly through the CI, contralateral residual hearing is going to be measured as a control to mitigate the risk of bias given by a worsening of hearing loss because of other causes. Other measures are going to be the frequency to place mismatch and the ESRT.

Limitations

Not all participants meeting the inclusion criteria had functional hearing either before or after implantation. Caution needs to be exercised in extrapolating the outcomes to patients in whom electroacoustic stimulation is the goal. The follow-up period was not included as it is relatively short and this limits applicability of data as hearing loss following surgery can progress over one year. Future studies will focus longer term follow-up on a larger cohort of subjects and make comparisons to other electrode array types used within our institution as well as match the ECochG results with a control group where ECochG was not performed.

CONCLUSIONS

ECochG-based intervention during CI can recover not just the ECochG signal, but also residual hearing. Using this method, electrode insertion can be optimized to maximize both depth and hearing preservation. Further work is required to distinguish between those ECochG drops that are associated with a loss of residual hearing, and therefore likely associated with intra- cochlear trauma, and artifacts that do not cause a hearing loss. While methods are evolving based upon

observational data, none have yet been implemented in an interventional setting. Real-time monitoring of cochlear function during electrode insertion is proving to be the most effective approach to the preservation of residual hearing available.

CONCLUSIONS

The past informs the present, as the saying goes, and this is certainly true of the field of ECochG. Similarly, it is usual for previous interpretations to become invalid as new advances are made and it can sometimes be difficult to realize that a protocol is no longer adequate and needs updating. Almost 100-year history of ECochG has evolved quickly, especially in the field of CI where the necessity of achieving hearing preservation remains crucial. As evidenced, ECochG proved several applications from the pre-operative to the post-operative phases, including the possibility to detect intraoperatively rare complications (i.e., tip fold-over[21]) that may be the cause of revision surgery. Promising results have also been evidenced in the field of lateral skull base surgery to achieve hearing preservation during procedures considered traditionally destructive for the inner ear[18], while further research is needed to clarify the mechanisms underlying the pathophysiology of hearing loss in patients affected by VS[19]. Finally, with this PhD thesis I hope to have clarified some of the main ideas, terminology, and origins of ECochG measurements, and to have encouraged other researchers that may help in simplifying ECochG so that it can become accessible even to non-medical personnel and routinely performed in an outpatient setting. In this context the application of the AIM system is already present in CI patients and seems promising.

LIST OF ABBREVIATIONS

- Cochlear implant (CI)
- Vestibular schwannomas (VS)
- Hidden hearing loss (HHL)
- Meniere's disease (MD)
- Electrocochleography (ECochG)
- Auditory brainstem responses (ABR)
- Round window (RW)
- Intracochlear (IC)
- Neural response telemetry (NRT)
- Cochlear microphonic (CM)
- Compound action potential (CAP)
- Auditory nerve neurophonic (ANN)
- Neural response imaging (NRI®)
- Neural response telemetry (NRT®)
- Auditory response telemetry (ART®)
- Auditory neuropathy spectrum disorder (ANSD)
- Primary Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)
- Extratympanic (ET)
- Transtympanic (TT)
- "The Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) Statement
- Kainic acid (KA)
- Ear, Nose, Throat (ENT)
- Auditory nerve fibers (ANFs)
- Outer hair cells (OHCs)
- Inner hair cells (IHCs)
- Normal hearing (NH)
- Kanamycin (FK)
- Tetrodotoxin (TTX)
- Sensorineural hearing loss (SNHL)
- Endolymphatic hydrops (ELH)
- Endolymphatic sac decompression and shunt surgery (ELS)

- Word recognition scores (WRS)
- Northwestern University Auditory Test No. 6 (NU-6)
- Pure tone averages (PTA)
- Linear mixed model (LMM)
- Vestibular evoked myogenic potential (VEMP)
- Jugular foramen tumor (JFT)
- Distortion product otoacoustic emissions (DPOAEs)
- Transient evoked otoacoustic emissions (TEOAEs)
- Real-time electrocochleography (rt-ECochG)
- Active Intraoperative Monitoring (AIM, Advanced Bionics, Advanced Bionics LLC, Valencia, CA)
- Neural response imaging (NRI)
- Electrically evoked stapedius reflex threshold (ESRT)
- Partial deafness treatment (PDT)

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It is true…It is such a big and beautiful world!

APPENDIX

This PhD thesis resulted in 5 PubMed publications so far. Here is the list for full-text reading:

- Lutz BT, Hutson KA, Trecca EMC, Hamby M, Fitzpatrick DC. Neural Contributions to the Cochlear Summating Potential: Spiking and Dendritic Components. J Assoc Res Otolaryngol. 2022 Jun;23(3):351-363. doi: 10.1007/s10162-022-00842-6. Epub 2022 Mar 7. PMID: 35254541; PMCID: PMC9085993.
- Trecca EMC, Adunka OF, Hiss MM, Mattingly JK, Moberly AC, Dodson EE, Cassano M, Prevedello DM, Riggs WJ. Intraoperative Electrocochleography in Subjects Affected by Vestibular Schwannoma and Ménière's Disease: Comparison of Results. Ear Hear. 2022 May/Jun;43(3):874-882. doi: 10.1097/AUD.0000000000001133. PMID: 34582395.
- Trecca EMC, Adunka OF, Mattingly JK, Hiss MM, Cassano M, Malhotra PS, Riggs WJ. Electrocochleography Observations in a Series of Cochlear Implant Electrode Tip Fold-Overs. Otol Neurotol. 2021 Apr 1;42(4):e433-e437. doi: 10.1097/MAO.0000000000003008. PMID: 33196531.
- Trecca EMC, Riggs WJ, Mattingly JK, Hiss MM, Cassano M, Adunka OF. Electrocochleography and Cochlear Implantation: A Systematic Review. Otol Neurotol. 2020 Aug;41(7):864-878. doi: 10.1097/MAO.0000000000002694. PMID: 32420718.
- Trecca EMC, Riggs WJ, Hiss MM, Mattingly JK, Cassano M, Prevedello DM, Adunka OF. Intraoperative Monitoring of Auditory Function During Lateral Skull Base Surgery. Otol Neurotol. 2020 Jan;41(1):100-104. doi: 10.1097/MAO.0000000000002441. PMID: 31498299.

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