Structure and hearing preservation in cochlear implant surgery

Saad Jwair

Colofon

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Structure and hearing preservation in cochlear implant surgery

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(met een samenvatting in het Nederlands)

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Saad Jwair

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Promotiecommissie

Promotor: Prof. dr. R.J. Stokroos

Copromotoren: Dr. H.G.X.M. Thomeer
Dr. H. Versnel

Voor mijn ouders

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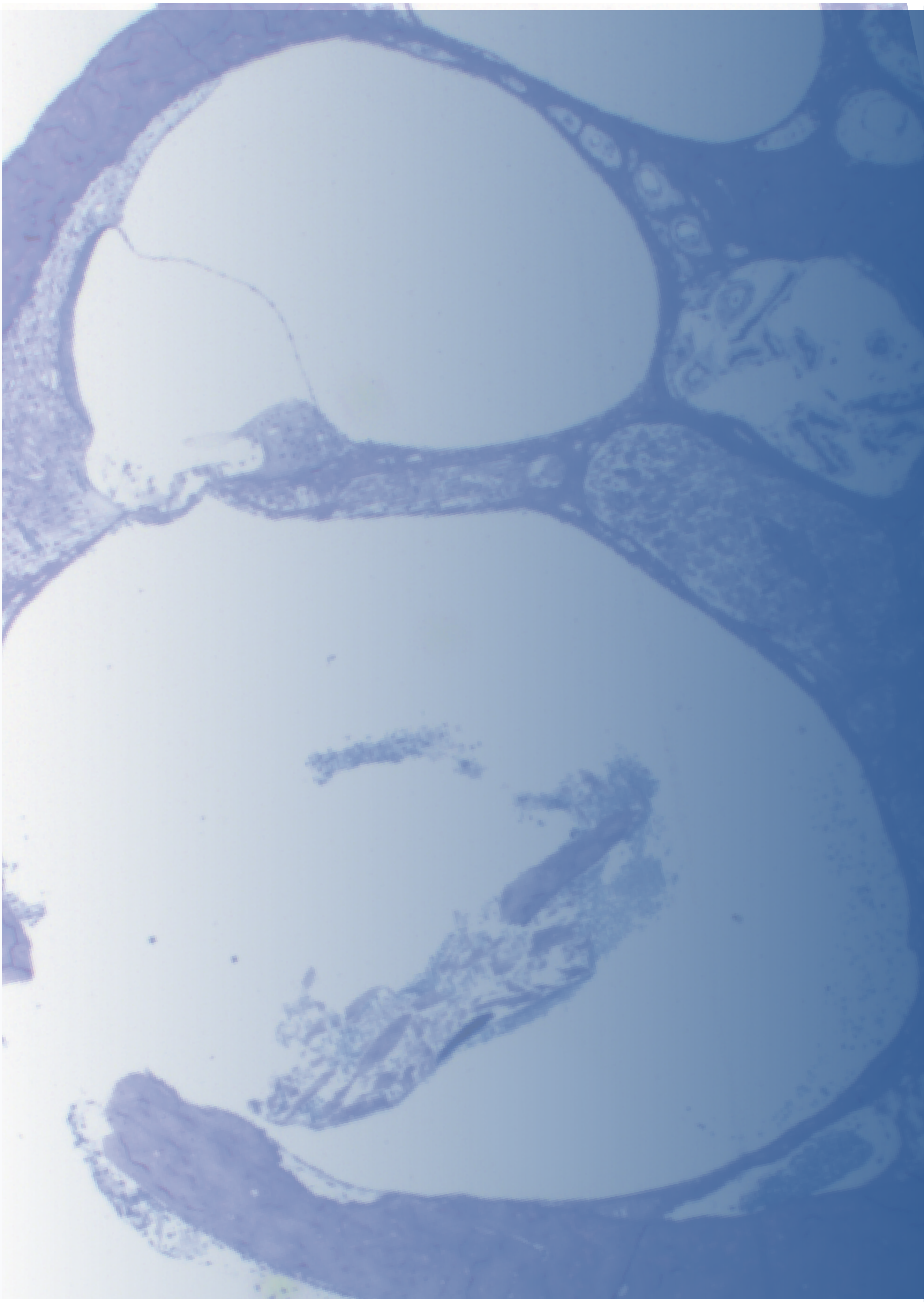

Chapter 1

General introduction

General introduction

The prevalence of hearing loss is increasing. Currently, more than half a billion people suffer disabling hearing loss worldwide. Disabling hearing loss is recognized as an important health issue that can lead to depression, insecurity and social isolation (Carlson 2020). Sensorineural hearing loss (SNHL) is primarily caused by loss of hair cells, and is the predominant cause of hearing loss in general. Hair cell loss can be caused by many factors, which are among others aging, noise exposure, ototoxic medications and hereditary conditions. However, in most patients with profound SNHL no cause can be identified.

Most adults with hearing loss can be treated with hearing aids. In cases with profound hearing loss (i.e. ≥ 90 dB hearing level at high frequencies; and score ≤ 60% on word-recognition testing) hearing aids might not be sufficient to comprehend speech in daily life (Carlson 2020). In those cases a cochlear implant (CI) can be considered. In contrast to hearing aids which amplify sounds, a CI bypasses the affected hair cells and directly stimulates the auditory nerve via electrical current pulses. Auditory perception underwent a tremendous development with CI, from sound detection in the 1980s to speech understanding in the last decades. Today, however, speech understanding with CI is still suboptimal, especially in difficult listening situations where background noise is present (Miranda et al. 2014; Gifford et al. 2017; Badajoz-Davila & Buchholz 2021). In addition, music perception is generally poor (Wilson et al. 2017; Brockmeier et al. 2010). Literature shows that preserving residual hearing in CI recipients leads to better hearing outcomes (Turner et al. 2004; Gifford et al. 2013). Hearing preservation is achievable if surgical trauma, inherent to cochlear implant surgery, is minimized.

This thesis focuses on improving cochlear implantation surgery by minimizing structural trauma to the cochlea. In this introductory chapter, we first explain normal hearing, followed by the cochlear anatomy and cochlear function. Subsequently, important aspects of the cochlear implant and cochlear implantation surgery are introduced. Finally, hearing and structure preservation, which are key concepts in this thesis, are explained.

Normal hearing

Sound is transmitted from the source through the air by pressure waves. In order to hear, these waves need to be received by the ear and processed by the brain in order to identify and comprehend sounds. In mammals, the ear is categorized into three parts, i.e. the external, middle and inner ear. The external ear consists of the auricle and ear canal, and the middle ear consists of the tympanic membrane and the bony ossicles called the malleus, incus and stapes. The external and middle ear play an important role in mechanically amplifying sound waves, before reaching the inner ear. Sound amplification is especially important due to reflection of sound waves, leading to loss of energy, that occurs during the transition between two mediums, i.e. from air in the external and middle ear to liquid in the inner ear. The inner ear has two main sensory functions: balance and hearing. On the one hand, the vestibular organ, consisting of the otolith organs in the vestibule and its three semi-circular canals, is dedicated to balance. On the other hand, the cochlea (meaning snail in ancient Greek) is dedicated to hearing. The cochlea is essential in transforming the acoustical sound pressure waves received by the external ear, and mechanically amplified by the middle ear, to action potentials needed by the brain to actually perceive sound.

Cochlear anatomy

The inner ear, which is embedded inside the petrous part of both temporal bones on the lateral side of the skull, consists of a bony and membranous part that houses both the vestibular organ and the cochlea. The bony labyrinth forms the outer shell that protects the inner membranous part of the labyrinth. These two parts have different embryonal origins, the bony labyrinth is derived from the mesoderm, while the membranous part is derived from the ectoderm.

The membranous part of the labyrinth houses the membranous vestibular structures (i.e. cupulae, the utricle and saccule) and cochlear structures (i.e. cochlear duct), and is filled with endolymph. Endolymph is a fluid that has high concentrations of potassium, and low concentrations of sodium. The endolymph is secreted among others at the stria vascularis of the cochlear duct, and travels very slowly between the cochlear duct and the vestibular structures, and is eventually resorbed by the endolymphatic sac. The endolymph-filled space of the cochlear duct is called scala media (SM). The cochlear duct contains the actual auditory receptor organ, the organ of Corti, which is supported by the basilar membrane. Looking at a cross section of the organ of Corti, perpendicular to the basilar membrane, there is one inner hair cell (IHC) row, located medially, and three outer hair cell (OHC) rows, located laterally. Humans have around 3500 IHCs and 12000 OHCs. These hair cells are named after their hair-like bundles (i.e. cilia) on their apical surface. The cilia are arranged from short to tall, and only deflect together and in one plane, either towards the longest cilia or towards the smallest cilia upon basilar membrane movement. The cilia can deflect from their resting state due to their close proximity to the relatively rigid tectorial membrane, which covers the organ of Corti.

The bony labyrinth consists of both a vestibular component (semi-circular canals and vestibulum) and an auditory component (cochlea). The space between the bony and membranous labyrinth is filled with perilymph (i.e. outer fluid), which resembles cerebrospinal fluid (i.e. high sodium concentrations, and low potassium concentrations). The perilymph-filled space is connected to the subarachnoid space (i.e. site of cerebrospinal fluid secretion and resorption) via the cochlear aqueduct. The cochlea is the bony shell that surrounds the membranous cochlear duct. The cochlea consists of two perilymph-filled spaces, the scala vestibuli (SV) and scala tympani (ST), which are connected at the cochlear apex via the helicotrema. At the cochlear base, the SV is closed by the oval window membrane, and the ST by the round window membrane. As the name would suggest, however, the SV transitions seamlessly into the vestibule, and therefore the perilymph can travel freely between the perilymph-filled spaces of the vestibular and cochlear system.

The three scalae (ST, SV and SM) spiral together in ~2.75 turns in humans (~4 turns in guinea pigs) in a tube shape around the cochlear core. The cochlear core or central axis is conically shaped, and called the modiolus, which is broader at the base and tapers gradually towards the cochlear apex. The modiolus consists of spongy bone where the auditory nerve is formed from peripheral fibers. The auditory nerve consists of mainly axonal fibres coming from the spiral ganglion cells (SGCs), i.e. group of neuronal cell bodies located in separate compartments of the modiolus (in Rosenthal's canal). On their turn, these ganglion cells receive sensory input from predominantly the inner hair cells of the organ of Corti via the peripheral processes.

Looking at a midmodiolar plane shows that the SV and ST are located respectively above and below the SM, but are medially directly bordering on each other (see Figure 1). The cochlear tube gradually becomes smaller towards the cochlear apex, with differences in size between the scalae. This aspect is different between species, e.g. in guinea pigs, the scala tympani becomes much faster smaller when moving from base to apex compared to humans. In general, both SV and ST are much larger than the SM, with ST being largest at the cochlear base, while the SV gradually occupies more space towards the cochlear apex. The barrier between SM and SV is formed by Reissner's membrane. The medial barrier between ST and SV is formed by the osseous (i.e. bony) spiral lamina, which branches of the cochlear modiolus, and spirals, like the cochlear duct, around the modiolus. Laterally, at the organ of Corti, the barrier between ST and SM is formed by the basilar membrane. Even more lateral, the spiral ligament, a thickened periosteum, forms the lateral wall of predominantly the cochlear duct, which is connected to the basilar membrane and Reissner's membrane.

Cochlear function

Sound waves are passed through and amplified by the external and middle ear, causing the footplate of the stapes, and therefore also the oval window, to move inward and outward. Important herein is to consider that the perilymph-filled space of the cochlea is one continuous tube with on both ends two flexible membranes, the oval window and round window membrane. Inward movement of the oval window causes increased pressures inside this space, however, the perilymph is largely incompressible. This is solved by the round window membrane, which is pushed outwards or pulled inwards with respectively inward or outward movement of the oval window.

The sound waves passed through to the perilymph lead to an upward and downward movement of the basilar membrane. This movement appears like a travelling wave that moves transversely along the length of the basilar membrane. The traveling wave reaches gradually maximal amplitude, and flattens out quickly after reaching its maximal amplitude. The basilar membrane place of maximum amplitude is dependent on the frequency of the sound wave, with higher frequencies displacing the BM at basal end of the cochlea, and lower frequencies more towards the apex. Based on this position along the basilar membrane, frequencies are filtered by the cochlea, which is called tonotopy. Especially at low sound intensities the non-linear highly tuned traveling wave is apparent, at higher sound intensities wider regions along the BM are activated, causing low frequencies to excite neural responses in basal regions as well as apical regions, i.e. less able to achieve frequency filtering.

The cochlear tonotopy is achieved by a passive and active component. The passive component is related to the mechanical properties of the basilar membrane. At the base the basilar membrane is narrow and rigid, which gradually becomes more wide and flexible towards the apex.

The OHCs actively contribute to this frequency coding. Namely, the traveling wave is strengthened by OHCs predominantly in a region basal from the place of maximal amplitude. The upward movement of the BM deflects cilia towards the longest cilia, creating shearing forces between the rigid tectorial membrane and deflecting cilia. These shearing forces open cation channels that are sensitive to mechanical movement. Upon depolarization due to influx of potassium, the OHC contracts (i.e. electromotility), thereby shortening the cell, which enhances the initial basilar membrane movement. This enhancement increases the frequency selectivity and hearing sensitivity in general. The cation channels can also be closed if the cilia deflect towards the shortest cilia, thereby hyperpolarizing the hair cells. In essence therefore, the OHC detects the up and downward movement of the basilar membrane by current flow that is mediated through mechanically gated cation channels. The current flow is largely possible due to the potassium-rich endolymph, in which the cilia of hair cells reside.

Besides the OHCs, the IHCs are also auditory sensory receptor cells that detect basilar membrane movement. Upon mechanical movement of the basilar membrane, and enhancement of this mechanical movement by the OHC, the IHCs transduce this mechanical movement into electrical activity (i.e. mechanoelectrical transduction). Similar to OHC, the IHC cilia deflect due to movement of the BM, which opens cation channels. The resulting influx of potassium ions depolarizes the IHCs. This depolarization increases the chance of neurotransmitter (glutamate) release into the synapse between the IHC and peripheral processes of the SGCs (i.e. the auditory nerve cell bodies). Every IHC sends input to 10-20 SGCs, and each SGC receives input from only one IHC. Upon release of glutamate action potentials can be generated in the SGCs. The action potentials travel along the SGCs axon (i.e. auditory nerve fibers) to synapses in the brainstem. The majority of the auditory nerve fibers (~95%) originate from the IHCs. The remaining auditory nerve fibers are efferents to IHCs or OHCs. This means that the majority of the auditory information to the brain is derived from the IHCs. The tonotopy that arises in the cochlea is maintained all the way to the auditory cerebral cortex.

Cochlear implant and cochlear implantation

A CI can circumvent the loss of hair cells by directly electrically stimulating the auditory nerve with the electrode array (in short: array), which is implanted into the ST. Besides the array, a CI consists of several other parts that are located on and below the scalp. A microphone, usually placed behind the ear, receives acoustical stimuli from the environment. Those acoustical stimuli are then processed and converted to digital codes by the speech processor (also behind the ear), and sent to the transmitter coil on the scalp. The transmitter coil has a magnet that attaches to the receiver/stimulator below the scalp. The transmitter transmits the signal information using radio waves to the receiver/stimulator that is located under the scalp. The receiver/stimulator converts the digital code to electrical pulses that are sent to the array inside the cochlea. The array then stimulates the auditory nerve via the electrode contacts.

Globally, two types of arrays exist: the lateral wall (LW) and perimodiolar (PM) arrays (see Figure 1). The PM arrays are pre-curved arrays, designed to intracochlearly lower the distance to the centrally located modiolus with the auditory nerve. The PM arrays are precurved, thus they need to be straightened before implantation. The other type of array, the LW, is a 'straight' array. The LW array follows the spiral shape of the lateral wall. Thus far, both arrays are commonly used in today's clinical practice.

For approaching the cochlea during cochlear implantation the preferred route is via a retro-auricular incision, mastoidectomy, and posterior-tympanotomy. With a posterior tympanotomy, the middle ear space is approached from the mastoid through a small opening in the facial recess between the facial nerve and the chorda tympani nerve. When the cochlea is in sight through the posterior tympanotomy opening, two surgical approaches are commonly used to enter the ST of the cochlea: via cochleostomy (CO) or via the round window (RW). In the RW approach a slit like opening in the RW membrane is used to enter the cochlea. In contrast, a CO approach uses a burr-hole opening in the cochlea for entry.

Hearing and structure preservation

Initially, only patients with near-total hearing loss were eligible for a CI. Since then, eligibility criteria for a CI have broadened globally (Carlson 2020). Nowadays many CI candidates have considerable residual hearing prior to cochlear implantation. This residual hearing does not suffice to achieve adequate speech perception with amplification, hence the medical indication for a CI. The audiogram of these patients looks like a ski-slope, with low auditory thresholds at lower frequencies (0.125 – 0.5 kHz), which increase steeply for higher frequencies (1 – 8 kHz).

The preservation of this residual hearing (i.e. hearing preservation) might enable CI recipients with residual hearing to use electrical acoustical stimulation (EAS). In EAS, the acoustical hearing of a CI recipient is used for better speech perception with CI (Gifford et al. 2017). Prior research has shown that musical melody perception might be better due to hearing preservation (Brockmeier et al. 2010). Hearing preservation might lead to implementation of even broader eligibility criteria of a CI, bridging the gap for patients who achieve unsatisfactory results with hearing aids, but fall below threshold for a CI.

A major hurdle for hearing preservation can be overcome through means of limiting structural trauma to the cochlea during cochlear implantation. In addition, limiting trauma opens the way for future developments relying on cochlear structure preservation, e.g. use of corticosteroids or neurotrophin eluting CIs, or hair cell regeneration. Minimizing cochlear trauma during implantation can also reduce fibrosis and ossification on the long term making potential reimplantations easier to conduct. This latter aspect is especially relevant in pediatric patients, as they might need future reimplantation during their lifetime due to hardware malfunction or necessary upgrades. Additionally, less tissue growth (i.e. fibrosis) leads to lower impedances, thus more efficient stimulation of the auditory nerve (Seyyedi and Nadol 2014).

During cochlear implantation both the opening to the cochlea and array insertion into the cochlea can affect cochlear structures. Normally, the array is inserted into the ST, which is ideal for electrical stimulation of the auditory nerve (see Figure 1). It is a compartment that is largely void of cochlear structures, and one that follows the spiral curvature of the cochlea with a close distance to the cochlear modiolus. This aspect also allows the array to stimulate with electrodes according to the physiological tonotopy of the cochlea, i.e. with basal electrodes for the higher frequencies, and more apical electrodes for the lower frequencies. The array, however, can translocate (i.e. scalar translocation; STL) during insertion to the SV or SM, damaging important cochlear structures such as basilar membrane, organ of Corti and stria vascularis. Similar trauma can occur if a tip fold-over (TF) of the array occurs during insertion. Additionally, to insert the array into the ST, an opening must be made in either the cochlear wall of the ST (i.e. cochleostomy) or through the RW membrane. Both approaches might also affect cochlear structures, and possible interact with array insertion. Another approach, the extended RW approach is a combination of the direct RW and cochleostomy approach, and is generally considered to be a variant of the cochleostomy approach.

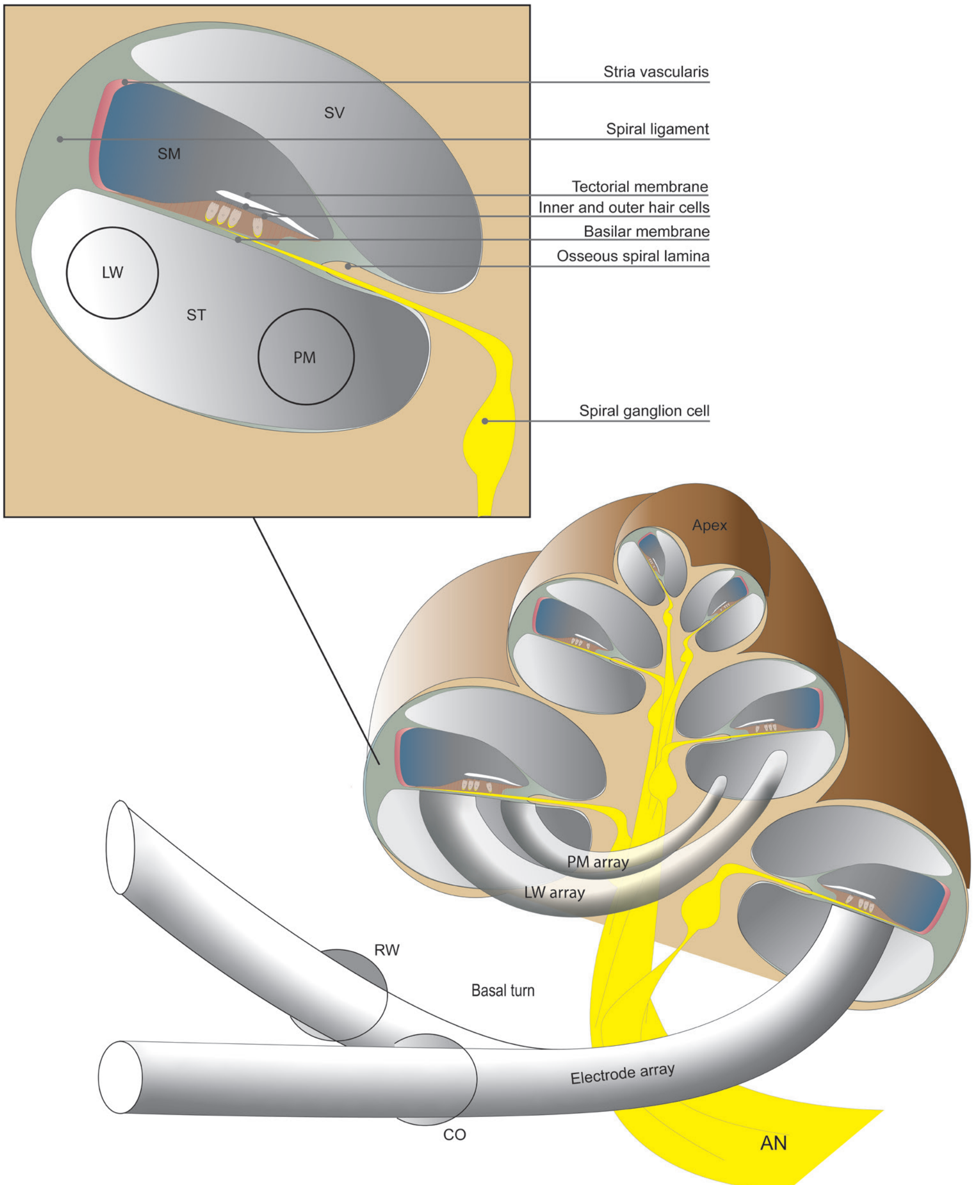

Figure 1. A cross section of the cochlea is depicted with an implanted electrode array. The electrode array is implanted in the scala tympani, using either the round window or a small hole in the cochlea (cochleostomy) for entry. The array follows the spiral curvature of the cochlea from the base of the cochlea towards the apex. Arrays usually reach at least around one turn and half, depending on the exact length of the array. Perimodiolar arrays are positioned more towards the spiral ganglion cells of the auditory nerve and beneath the osseous spiral lamina, and in contrast, lateral wall arrays are positioned laterally towards the spiral ligament and beneath the basilar membrane. RW: round window; CO: cochleostomy; AN: auditory nerve; ST: scala tympani; SV: scala vestibuli; SM: scala media; LW: lateral wall; PM: perimodiolar.

Aim of this thesis

In this thesis the effect of two types of arrays on the structural integrity of the cochlea were investigated using different research models and various methods. In CI recipients, post mortem human temporal bones and guinea pigs, a variety of methods were used: on histological, radiological and electrophysiological level. This way this thesis aims to provide a guideline in how to minimize insertion trauma during cochlear implantation surgery.

Thesis outline and chapter overview

This thesis starts with describing the incidence of hearing preservation in CI recipients in our tertiary University medical center (UMC Utrecht). Additionally, surgical factors that might influence hearing preservation rates were identified. Subsequent chapters investigate the insertion trauma during cochlear implantat surgery, with a focus on array type. First, STL and TF rates, which are two important traumatic events during array insertion, were compared between LW and PM arrays in a meta-analysis. Subsequently, in a temporal bone experiment, the structural trauma differences between the array types were investigated. Additionally, possible interaction of array type with surgical approach was investigated. Related to insertion trauma is RW membrane visibility, which was investigated retrospectively using the preoperative CTs of CI recipients. In normal-hearing guinea pigs, the functional outcomes, mainly auditory nerve function, was compared between animals with minimal, moderate and severe cochlear trauma using electrocochleography (ECochG). Finally, we discuss the protocol of a randomized controlled trial in CI patients, that was set up to investigate the combination of array type and surgical approach on hearing and structure preservation.

In *Chapter 2* the residual hearing of CI recipients was retrospectively analyzed. Postoperative tone audiograms were compared with preoperative tone audiograms approximately 3 months after surgery. Surgical factors that might affect these hearing preservation rates were investigated, such as the experience of the surgeon with cochlear implantations, use of corticosteroids, and type of array.

Chapter 3 describes a systematic review that compares STL rates between LW and PM arrays. A meta-analysis was performed with studies that evaluated both arrays in vivo using CT scans. Additionally, TF rates were also compared between the two type of arrays.

Chapter 4 describes a temporal bone experiment with fresh frozen human cadaveric heads. Insertion trauma differences between the four possible combinations of surgical approach (RW or CO) and array type (LW or PM) were investigated using histology. In addition, the diagnostic value of CT imaging using the most common radiological assessment option for STL was compared to an adapted CT scanning protocol with curved multiplanar reconstructions.

Chapter 5 describes a retrospective analysis of CI recipients regarding RW visibility. Preoperative CT scans were analyzed regarding factors that might impact visibility of the RW membrane through the posterior tympanotomy. The factors were compared with results of the RW visibility as described in the surgical reports.

In *Chapter 6* we tested the degree to which electrocochleography was affected by acute trauma during separate stages of the cochlear implantation procedure, i.e. cochleostomy and array insertion. Electrocochleography responses for each stage were evaluated in relation to cochlear structural trauma, using an electrode on the RW. Cochlear implantation was performed with flexible arrays (similar to those in humans).

In *Chapter 7* the protocol of a randomized controlled clinical study is shown. This study was set up to compare hearing preservation rate between the four possible combinations of surgical approach (RW or CO) and array type (LW or PM). Structural trauma is assessed with cone beam CT scan postoperatively. Additionally, electrocochleography similar to chapter 6, will be used to assess cochlear function during array insertion, and postoperatively up to one year after surgery.

In *Chapter 8* the outcomes of this thesis in relation to the literature are discussed. This chapter also provides concluding remarks, and future perspectives

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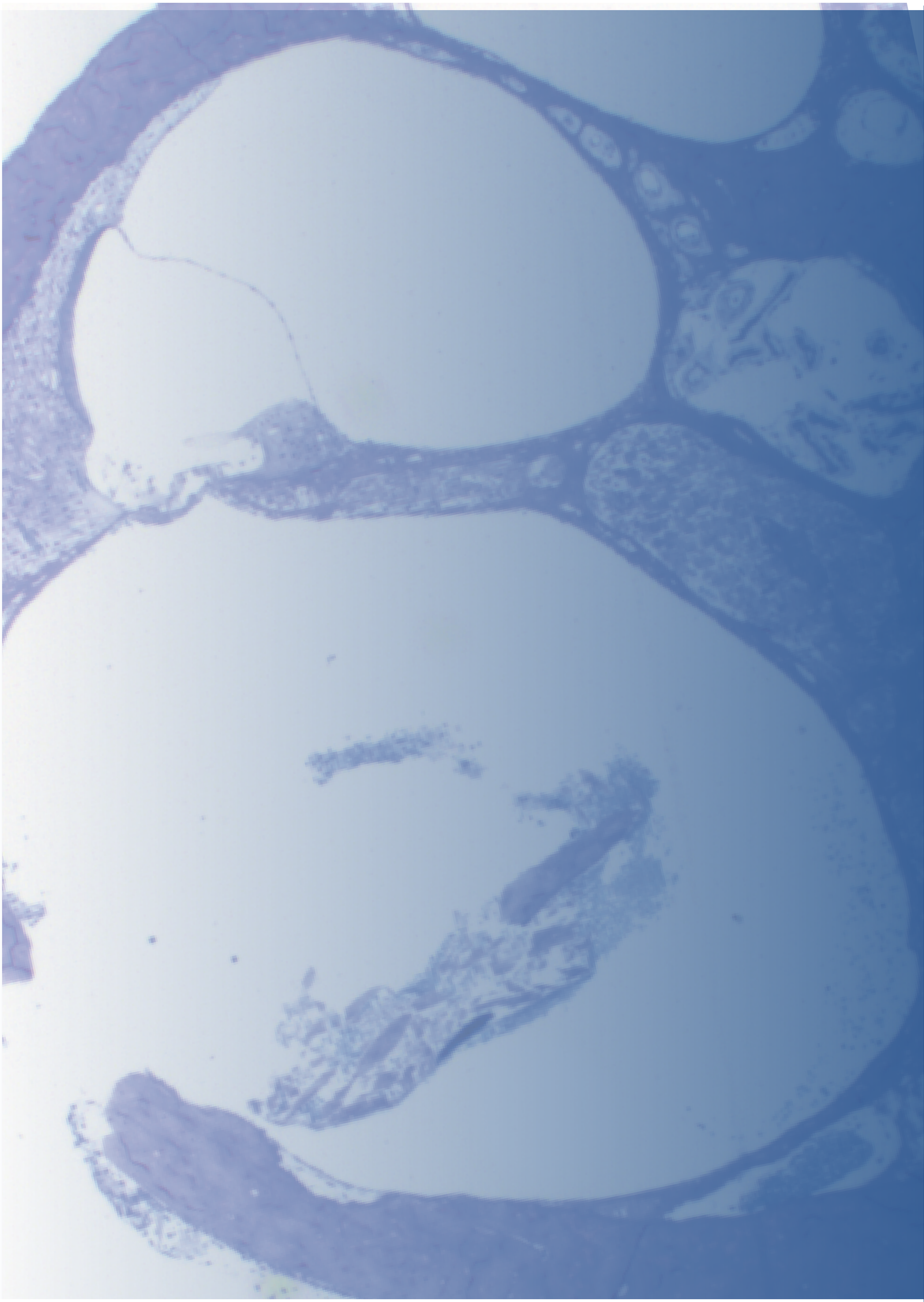

Chapter 2

Hearing preservation in cochlear implant recipients: a cross-sectional cohort study

Ellen Kant; Saad Jwair; Hans G.X.M. Thomeer

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Abstract

Objectives

A surge of new developments resulted in several treatment options for cochlear implants (CI) candidates in the last 5 years. By reviewing our CI population of this period, we aimed to investigate hearing preservation rates and the effect of the different treatment options on hearing preservation.

Methods

Retrospectively, all adult CI recipients with preoperative residual hearing at lower frequencies (mean threshold < 80 dB hearing level) in a single tertiary referral center between 2015 and 2020 were analysed. Patients were classified in four groups based on their hearing preservation outcome. Subsequently, differences between the four groups regarding several patient dependent and independent factors were investigated.

Results

In this study 140 patients were included, which is 46% of the total population that received a CI in our cohort. Complete hearing preservation was achieved in 14 patients (10%), and complete loss of residual hearing in 48 patients (34%). The lateral wall array, and local application of corticosteroids were associated with improved hearing preservation. Intravenous corticosteroids, local hyaluronic acid, and surgical experience had no effect on hearing preservation rates. Speech perception was not improved in patients with residual hearing, compared to patients without residual hearing.

Conclusion

Approximately half of all adult CI recipients had residual hearing at lower frequencies before surgery, unfortunately the majority lost their residual hearing after cochlear implantation. In current medical practice electrode choice has a clear effect on hearing preservation rates, with LW array recipients having better hearing preservation rates than PM array recipients. The medical treatment of severely hearing-impaired patients with CIs is currently lacking in preserving the residual hearing.

Introduction

The success of cochlear implants (CI) has led to a more diverse population of CI recipients. Originally, only patients with near-total hearing loss were eligible for a CI. Nowadays, however, more and more CI recipients have considerable residual hearing at lower frequencies prior to implantation. This development has led to a renewed focus on achieving hearing preservation (HP) in the CI-field (Carlson, 2020).

HP might be important for three main reasons. 1) CI-recipients might benefit from their residual hearing as it can be used for electric-acoustic stimulation (EAS) (Abbas et al., 2017). The use of EAS can improve speech perception in difficult listening situations with background noise or even improve musical melody recognition (Gifford et al., 2013). 2) By achieving HP a new category of patients can benefit from a CI, e.g. patients suffering from tinnitus (Van de Heyning et al., 2008). 3) Preventing hair cell loss might potentially halt auditory nerve degeneration to a degree, resulting possibly in better electric hearing outcomes in CI recipients (Liberman, 2017).

Although there is no lack of studies investigating HP, no consensus exists on how to achieve HP (Snels et al., 2019). This study aims to provide a comprehensive retrospective overview of HP outcomes of a general CI population of a large tertiary referral center. In addition, the effect of HP on speech perception outcomes, and other factors on HP, including surgical experience, were investigated.

Methods

Patients

A retrospective cohort study was performed of adult patients who underwent cochlear implantation in a single tertiary referral center (UMC Utrecht) from January 1st 2015 to 23th October 2020. The patients were identified using a CI registration list. Patients with a preoperative pure tone average threshold (PTAlow) < 80 dB HL (decibels hearing level) for the 125, 250 and 500 Hz frequencies were eligible for inclusion. The following exclusion criteria were used:

1. revision surgery
2. implantation at age < 18 years
3. history of otologic surgery in the implanted ear
4. signs of acute or chronic middle ear infections and/or mastoiditis during surgery
5. incomplete electrode insertion
6. inner ear malformations or otosclerosis

All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and declaration of Helsinki. Ethical approval for this study was obtained from the local medical ethical review board of UMC Utrecht (METC file: 21/018). Strobe reporting guideline was used for this manuscript.

All CI recipients receive at least one year after surgery rehabilitation services. In the first three months at least 4 sessions are planned with audiologists and speech therapists. Evaluation sessions are held at 3 and 12 months postoperatively.

Data extraction

The following data were collected from the electronic medical records: age at implantation, cause of deafness, side of implantation, date of implantation, name of surgeon, electrode-array type, use of perioperative corticosteroids (local or systemic), use of hyaluronic acid, pre- and postoperative PTAlow outcomes of the implanted and contralateral ear, and consonant/vowel/consonant (CVC) word test outcomes.

Data analysis

The pure tone audiogram outcomes were subtracted from medical records with SAS enterprise Guide. The HP scores of 125 Hz, 250 Hz and 500 Hz were separately calculated by adapting the equation of Skarzynski et al. 2013:

$$HP\ (\%) = \left[1 - \frac{(\text{thresholdPost} - \text{thresholdPre})}{(\text{outputmax} - \text{thresholdPre})} \right] \times 100$$

HP = Hearing preservation in %; thresholds in decibels hearing level (dB HL); outputmax = maximal detectable hearing level of the audiological setup at the tested frequency (i.e. 125 Hz = 70 dB HL, 250 Hz = 85 dB HL and 500 Hz = 115 dB HL).

The HP scores were categorized, also according to consensus paper of Skarzynski et al. 2013, as follows: complete HP (>75%), partial HP (>25% - 75%), minimal HP (0 - 25%) and complete loss of hearing (no measurable hearing). These HP scores were also checked manually. In cases with a difference between the pre- and postoperative hearing level at the same frequency of 5dB, which is equal to the margin of error of the audiometry, HP on this frequency was considered as complete HP.

The CVC-word test outcomes were extracted preoperatively (approximately 6 months prior to surgery), and postoperatively at 3 and 12 months. The preoperative CVC scores were obtained with hearing aids in both ears. Postoperative CVC scores were obtained with activated CI and hearing aid contralaterally to adequately determine the speech perception shifts. These CVC scores were obtained in a situation without background noise. Patients with one-sided hearing impairment were included in the analyses for HP, but excluded for speech perception tests.

The pure-tone-audiometry outcomes were extracted of the contralateral non-implanted ear in 45 patients to evaluate deterioration of hearing levels irrespective of surgery. The electrode array type was categorized as perimodiolar or lateral wall. The Midscala electrode array of Advanced Bionics was classified as perimodiolar electrode array, because it is precurved.

Results

A total of 470 patients underwent cochlear implant surgery. Of this group, 307 patients were adult and underwent primary cochlear implantation. In total, 140 patients were eligible for inclusion (46% of all adults with primary cochlear implantation). See Figure 1 for the in/exclusion flowchart. At time of implantation mean age of the included patients was 61 years (SD: 17), with 64% male. Most patients suffered from bilateral idiopathic progressive sensorineural hearing loss (n=101, 72%). See Table 1 for the demographics.

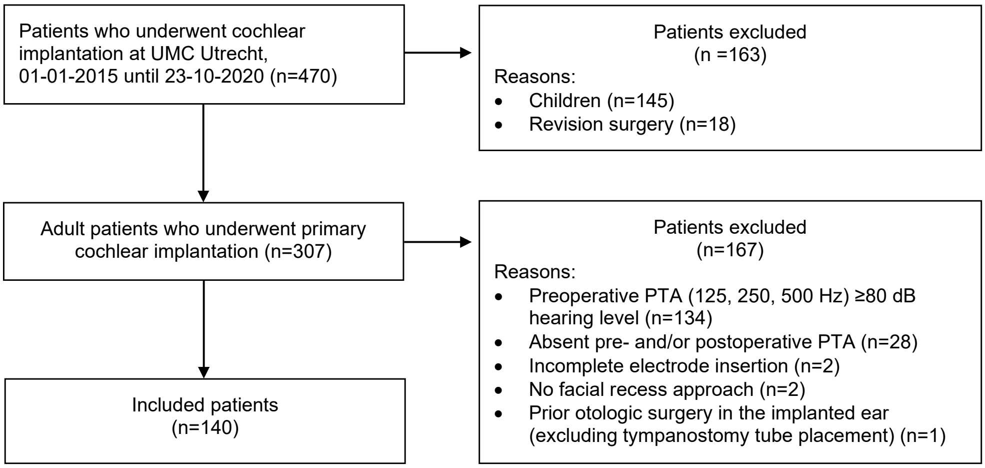

Figure 1. Flow chart of patient selection
(PTA = pure tone average)

Hearing preservation

Descriptive data is shown in Table 2. Complete HP was achieved in 14 patients (10%), partial HP in 36 patients (26%), minimal HP in 42 patients (30%) and complete loss of residual hearing in 48 patients (34%). At random, PTAlow outcomes were extracted of the contralateral non-implanted ear for 45 patients, showing no difference between pre- and postoperative outcomes ($p>0.05$). Average time between cochlear implantation and postoperative tone audiogram was 88 days for all patients ($p>0.05$, between groups).

Table 1. Demographics of included patients

Patient demographics	N=140 (%)
Age at implantation, *mean (SD)*	61 (17)
Gender	
Female	51 (36)
Male	89 (64)
Medical indication for cochlear implantation	
Bilateral IPSNHL	101 (72)
Sudden deafness unilateral	7 (5)
Usher syndrome	5 (4)
DFNA9 mutation	5 (4)
Other	22 (15)

Abbreviations: N = number, SD = standard deviation, IPSNHL = Idiopathic progressive sensorineural hearing loss

Patient dependent factors

The mean age of all patients was 61 years. This was only significantly lower when comparing complete HP group with minimal HP group (H-test (3) = 8.01, p=0.046). However, there was a very weak correlation between age and HP as continuous measure (r = -0.21). Gender (χ2 (3) = 4.41, p>0.05) and side of implantation (χ2 (3) = 3.49, p>0.05) were not different between HP groups. Weak correlation was observed between preoperative PTAlow and HP as a continuous measure (r = -0.19). Taken together, no baseline differences between HP groups were identified.

Patient independent factors

Looking at electrode array, PM arrays were used in 66 patients (47%), of which 4 had complete HP (6%) and 31 complete hearing loss (47%). A LW array was used in 74 patients. Ten patients had complete HP (14%) and 17 patients had no preservation of their hearing (23%). Patients with LW arrays had better HP than patients with PM arrays (χ2 (3) = 9.87, p=0.019). 48 patients (34%) received intravenous corticosteroids during surgery. Total dose ranged between 4 mg to 24 mg, varying in 1-3 administrations. Use of intravenous corticosteroids was not associated with HP (χ2 (3) = 7.48, p>0.05). Local corticosteroids were administered in eight patients, of which three had complete HP and five had partial HP. Use of local corticosteroids seems to be associated with better HP (Fisher's= 8.75, p=0.012), although all 8 patients also received a LW array. Hyaluronic acid was received by 105 patients (75%), with no differences between HP groups (χ2 (3) = 1.72, p>0.05).

Table 2. Comparison of several factors between the hearing preservation groups

		All	Complete HP	Partial HP	Minimal HP	Complete hearing loss	Statistics
Patient dependent factors; n (%)							
Mean age at implantation, (SD)		61 (17)	53 (17)	60 (16)	65 (16)	61 (17)	H (3) = 8.01 **p=0.046**[A] r=-0.21[B]
Gender	F	51	3 (6)	14 (27)	12 (24)	22 (43)	χ^2 (3) = 4.41
	M	89	11 (12)	22 (25)	30 (34)	26 (29)	p>0.05[C]
Side	L	70	6 (9)	22 (31)	22 (31)	20 (29)	χ^2 (3) = 3.49
	R	70	8 (11)	14 (20)	20 (29)	28 (40)	p>0.05[C]
Bilateral IPSNHL		101	10 (10)	33 (33)	30 (30)	28 (28)	Fisher's = 20.77 p>0.05[D*]
Mean pre-operative $PTA_{low,}$ dB HL, (SD)		57	53 (20)	49 (16)	60 (16)	62 (15)	r=-0.19[B]
Patient independent factors; n (%)							
Electrode	PM	66	4 (6)	13 (20)	18 (27)	31 (47)	χ^2 (3) = 9.87
	LW	74	10 (14)	23 (31)	24 (32)	17 (23)	**p=0.019**[C]
Intravenous corticosteroid	Yes	48	9 (19)	12 (25)	15 (31)	12 (25)	χ^2 (3) = 7.48
	No	92	5 (5)	24 (26)	27 (29)	36 (39)	p>0.05[C]
Local corticosteroid	Yes	8	3 (37.5)	3 (37.5)	2 (25)	0 (0)	Fisher's=8.75
	No	132	11 (8)	33 (25)	40 (30)	48 (26)	**p=0.012**[D]
Hyaluronic acid	Yes	105	11 (11)	29 (28)	32 (30)	33 (31)	χ^2 (3) = 1.72
	No	35	3 (9)	7 (20)	10 (29)	15 (42)	p>0.05[C]
Total		140	14	36	42	48	

Statistical tests: A. Kruskal-Wallis test; complete vs minimal HP; B. Pearson correlation coefficient; C. Chi-square test for contingencies; D. Fisher's exact test; * defined for all medical indications, only bilateral idiopathic progressive sensorineural hearing loss shown. Abbreviations: n = number, HP = hearing preservation, SD = standard deviation, F = female, M = male, L = left, R = right, IPSNHL = Idiopathic progressive sensorineural hearing loss, PTAlow= pure tone average of 125, 250 and 500 Hz, PM = perimodiolar electrode array, LW = lateral wall electrode array, dB = decibel, HL = hearing level.

Surgical experience

The majority of implantations were done by one surgeon (n=102), and these HP outcomes were analysed. Before 2015 this surgeon performed around 40 implantations. There was no correlation between experience in days and HP (all patients: r = -0.05, p>0.05; only PM arrays: r = 0.19, p>0.05; only LW arrays: r = -0.07, p>0.05). The remainder of the patients (n=38) were implanted by one of five surgeons, sample sizes were too low (range 2-19) to show a meaningful distribution of HP.

Speech perception

Total of 110 CI recipients had CVC scores available at 3 months after surgery, see Figure 2. Before surgery average CVC score was 33 points (range: 0-77). Three months after surgery 11 cases had no improvement of CVC score (i.e. CVC score shift between -25 and 0), while the remaining 99 cases had increased CVC scores compared to preoperative scores (range: 2-86). Cases with no residual hearing had largely same distribution of CVC-score shift as the whole cohort. The preoperative CVC word test scores were comparable between groups. CVC-score shifts were not different between HP groups at 3 and 12 months after implantation (p>0.05).

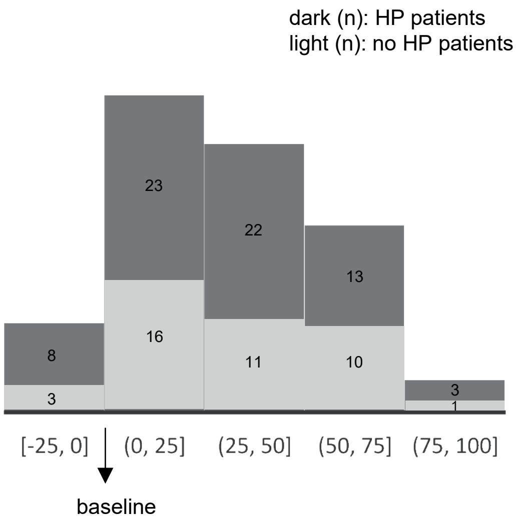

Figure 2. The CVC score shift distribution (in bins of 25 points) of patients with complete loss of residual hearing (n=41), and patients with minimal-to-complete hearing preservation (n=69) 3 months after cochlear implantation. HP = hearing preservation

Discussion

This retrospective cohort study provides a comprehensive overview of a general adult CI population of the last 5 years. Almost half of the adult patients (46%) who underwent primary cochlear implantation had residual hearing at lower frequencies. Complete HP was achieved in 10% of these patients, partial HP in 26%, minimal HP in 30% and complete loss of residual hearing was seen in 34%. LW arrays in general, and intraoperative local corticosteroids usage in small sample set of 8 patients, were associated with better HP. Speech perception of patients with residual hearing was not better than patients without residual hearing after surgery. Lastly, surgical experience had no effect on HP outcomes.

Hearing preservation

Several different classifications are used to indicate HP at lower frequencies after CI surgery (Snels et al., 2019). Studies similar to our study, described complete HP rates ranging between 0% to 68% (Causon et al., 2015; Mamelle et al., 2020; Iso-Mustajärvi et al., 2020). Based on these studies, and others, residual hearing at lower frequencies deteriorates over time. Direct comparison between our study and other studies is therefore somewhat limited, as most of the previously mentioned studies (Mamelle et al., 2020; Iso-Mustajärvi et al., 2020) measured at an earlier timepoint than our study (around 40 days vs 88 days in this study). It is likely that HP depends on direct acute trauma during cochlear implantation resulting in inflammatory ototoxic processes, which impacts inner ear homeostasis and manifests as hearing deterioration at longer term. The deterioration over time could also be independent from cochlear implantation, and might be related to progress of the disease itself. All in all, it is very difficult to establish final HP outcomes, if at all possible, considering that residual hearing is probably continuously deteriorating to some degree.

Patient independent factors

In our study, patients with LW arrays had more often complete HP than patients with PM arrays (14% vs 6%). Scalar translocation is regarded as severe insertion trauma, occurring more often with PM arrays, and negatively influences residual hearing of CI recipients (Jwair et al., 2021). Therefore, this difference is probably linked to scalar translocation. It is unknown whether these differences between LW and PM arrays remain the same on the longer term. Another factor, hyaluronic acid, had no effect on HP in our study. Another study showed a correlation between HP and use of hyaluronic acid (Garcia-Ibanez et al., 2009). However, this was a weak correlation, and is the only study, to our knowledge, showing a direct effect of hyaluronic acid on HP rates.

Speech perception

Preserved residual hearing can improve speech perception in patients with EAS. In our cohort, only one individual made use of EAS. We therefore looked at the effect of HP on speech perception with only electrical hearing. Data regarding this relationship is, to our knowledge, scarce. We did not see a correlation between HP and the speech perception test without background noise. Importantly, potential benefits of preserved residual hearing could arise if speech perception with background noise was tested. We hypothesize that it is likely that trauma and inflammation caused by cochlear implantation can affect outer and inner hair cells (i.e. loss of residual hearing), and not directly the auditory nerve at the short term. The potential benefit of preserved residual hearing at the lower frequencies on speech perception, especially in difficult listening situations such as musical melody recognition and background noise, and on speech perception related factors (e.g. intonation and listening effort), remains unclear.

Conclusion

Approximately half of all adult CI recipients had residual hearing at lower frequencies before surgery. The majority of these patients lost their residual hearing after cochlear implantation. In current medical practice, only electrode choice seems to have a clear effect on hearing preservation rates. Much improvement is needed in cochlear implant surgery in order to preserve the residual hearing of CI recipients in the future.

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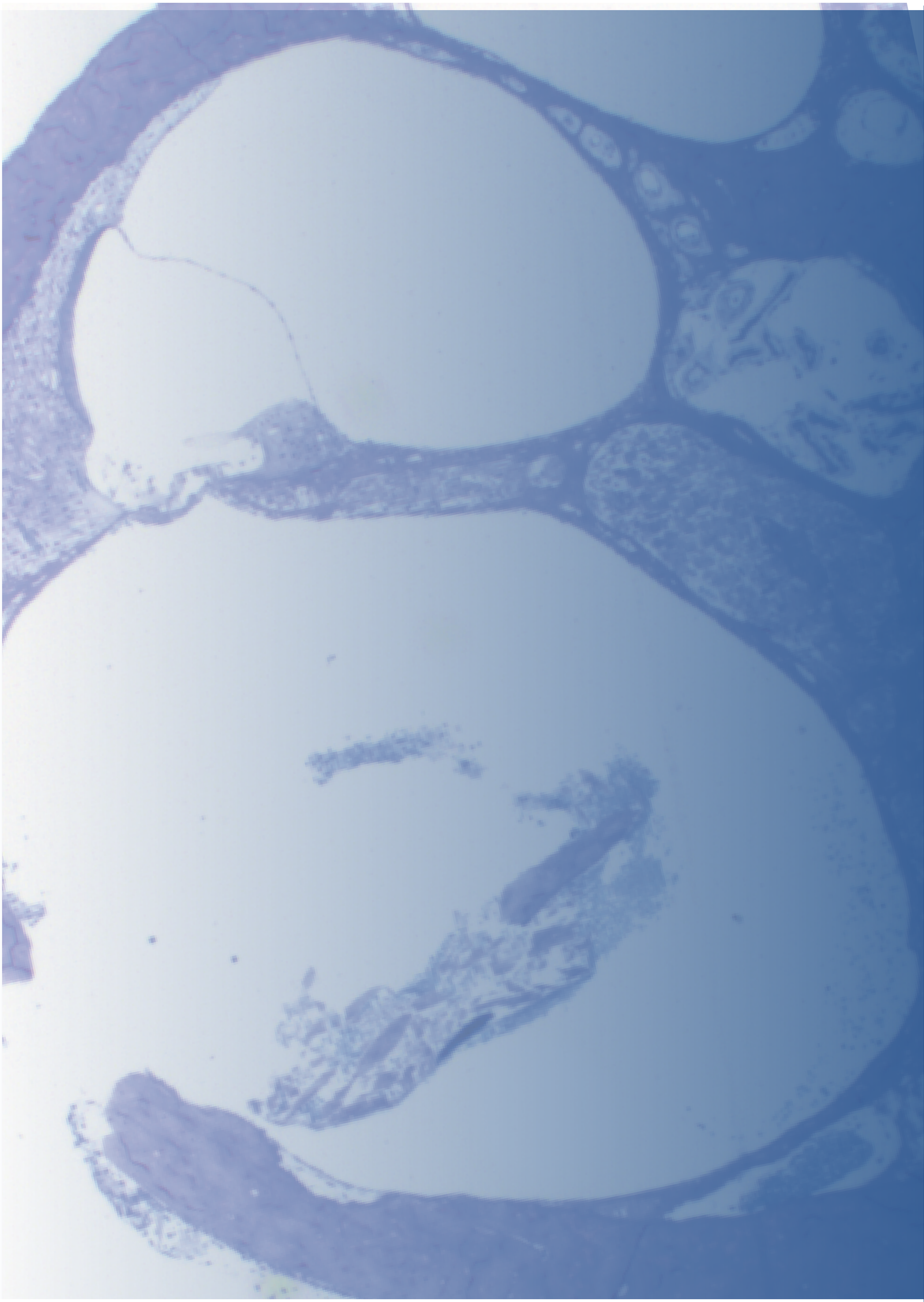

Chapter 3

Scalar translocation comparison between lateral wall and perimodiolar cochlear implant arrays - A meta-analysis

Saad Jwair, Adrianus Prins, Inge Wegner, Robert J. Stokroos, Huib Versnel and Hans G.X.M Thomeer

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Abstract

Objectives

Two types of electrode arrays for cochlear implants (CIs) are distinguished: lateral wall and perimodiolar. Scalar translocation of the array can lead to intracochlear trauma by penetrating from the scala tympani into the scala vestibuli or scala media, potentially negatively affecting hearing performance of CI users. This systematic review compares the lateral wall and perimodiolar arrays with respect to scalar translocation.

Methods

Pubmed, Embase, and Cochrane databases were reviewed for studies published within the last 11 years. No other limitations were set. All studies with original data that evaluated the occurrence of scalar translocation or tip fold-over (TF) with postoperative computed tomography (CT) following primary cochlear implantation in bilateral sensorineuronal hearing loss patients were considered to be eligible. Data were extracted independently by two reviewers.

Results

We included 33 studies, of which none were randomized controlled trials. Meta-analysis of five cohort studies comparing scalar translocation between lateral wall and perimodiolar arrays showed that lateral wall arrays have significantly lower translocation rates (7% vs. 43%; pooled odds ratio = 0.12). Translocation was negatively associated with speech perception scores (weighted mean 41% vs. 55%). Tip fold-over of the array was more frequent with perimodiolar arrays ($X^2 = 6.8$, $P < .01$).

Conclusion

Scalar translocation and tip fold-overs occurred more frequently with perimodiolar arrays than with lateral wall arrays. In addition, translocation of the array negatively affects hearing with the cochlear implant. Therefore, if one aims to minimize clinically relevant intracochlear trauma, lateral wall arrays would be the preferred option for cochlear implantation.

Introduction

The indications for cochlear implantation are continuously expanding. Originally, CI was indicated in patients with profound bilateral sensorineural hearing loss (SNHL). Nowadays, patients with significant residual hearing or with unilateral hearing loss may be considered for a CI, as well as patients with medical indications other than hearing loss such as tinnitus (Van de Heyning et al., 2008). These developments have led to renewed interest of the scientific community to investigate insertion trauma of the electrode array and methods to minimize the trauma (Carlson et al., 2011).

New electrode arrays have been developed considering both minimization of insertion trauma and optimization of the electrode-nerve interface. Globally, two types of arrays are distinguished: the lateral wall (LW) and perimodiolar (PM) arrays. The PM arrays are pre-curved arrays, developed to intracochlearly lower the distance to the centrally located modiolus with the auditory nerve, in theory achieving better frequency resolution by less spread of excitation across electrodes and lower battery consumption as lower currents are needed to activate the nerve (Balkany et al., 2002; Davis et al., 2016). These precurved arrays are straightened before implantation, usually with a stylet. The surgeon will remove the stylet during insertion in the cochlea, the so-called advance off stylet insertion method, which enables the array to curl around the modiolus. Another way of extracting the stylet during insertion is making use of the insertion device (Midscala electrode, Advanced Bionics corporation), or replacing it by a different method with a removable external sheath (Cochlear corporation). The other type of array, the LW, is a ‘straight’ electrode array. Nowadays, the LW array is introduced in the cochlea without an insertion tool, and will achieve its final curled position by following the lateral wall of the cochlear duct. Thus far, both electrode arrays are commonly used in today’s clinical practice as they each have their specific advantage. The electrode-neuron distance is smaller for the PM array than for the LW array, which is an advantage for neural stimulation as argued above, but on the other hand, the risk of damaging neural structures is larger.

Scalar translocation (STL) of the electrode array, in which the electrode array translocates from the scala tympani to the scala vestibuli or media, can cause intracochlear trauma by piercing the cochlear partition (Wanna et al., 2014). In a non-ossificated normal-shaped cochlea, the array should completely reside in the scala tympani after insertion. It is unknown, however, whether hearing with the CI is affected by STL (Holden et al., 2013). In addition to trauma, STL leads to an unfavorable position of the array for stimulation of the auditory nerve, which can also negatively affect the hearing outcomes (Holden et al., 2013). Lastly, tip fold-over (TF) of the array can lead to insertion trauma with similar detrimental effects (Trakimas et al., 2018).

The exact position of the CI in the cochlear duct can be visualized in vivo with improved imaging possibilities, with fewer artefact formation and good spatial resolution, like the cone beam computed tomography (CB-CT) (An et al., 2018; Boyer et al., 2015; Ketterer et al., 2018). In the past, it was only possible to study STL in cadaveric temporal bone studies (Lenarz et al., 2006). Recent developments have also led to improved analytic methods, using a micro-CT atlas to increase the accuracy of the CI location postoperatively (Wanna et al., 2014). Therefore, it is possible to study preservation of the delicate anatomy of the cochlea in CI recipients.

Since STL of the array can lead to intracochlear trauma and possible unfavorable positioning with respect to stimulation of the nerve, it is relevant to know the STL rate for different array types, and the impact of STL on speech perception. Several studies over the last decade have employed postoperative CT of STL. Therefore, we compared with a systematic review of those studies the STL rate of LW and PM array types, and speech perception outcomes of patients with STL.

Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). There is no review protocol registered.

Study Selection

A systematic search was conducted in Pubmed, EMBASE and the Cochrane Library. See supplemental appendix for the full search. We limited the search to a period of the last eleven years: May 1st 2009 to June 1st 2020. Since 2009, when the first CB-CT scan of a CI was described (Ruivo et al., 2009), higher spatial resolution CTs, needed for assessing the scalar location, became available. To avoid introducing a bias, we included all publications in this period, also if the publication reported results that were obtained before this period. No other limitations were set.

Study Eligibility Criteria

Studies were considered eligible if they provided original postoperative CT data on the occurrence of STL or TF of the array following cochlear implantation. Only primary insertions as treatment for severe to profound bilateral SNHL were included. Studies comparing LW to PM arrays as well as one-armed trials evaluating either type were considered to be eligible.

Assessment of Methodological Quality

Two researchers (SJ, AP) independently assessed the relevance and risk of bias for the selected studies using predefined criteria. Assessment of risk of bias was based on the Cochrane Collaboration's tool for assessing risk of bias (Higgins et al., 2011). We included all but one item: we left out blinding of participants/personnel as blinding of personnel is impossible, and as this item is unlikely to influence scalar location of the array. We added three other items, which considered the standardization of the cochlear implantation procedure and outcome measures: (1) middle ear approach, (2) insertion approach, and (3) postoperative CT. If there were disagreements between both researchers, these were resolved by discussion.

Data Extraction and Analyses

The articles selected for analysis were checked for investigation site, investigators and time period of investigation to avoid including the same patients twice. In case of overlapping study population, the largest study was selected for this systematic review. Some studies with the same patients were included if they provided unique data. Descriptive data of each study was extracted by two authors (SJ, AP) and included age, angular insertion depth from round window (RW) (Escude et al., 2006), surgical approach, array, hearing outcome, STL and TF. Hearing outcome included both postoperative acoustic hearing assessed by tone audiometry, and speech perception scores with a CI. Our primary outcome was STL of the array. We also compared STL rate for LW and PM arrays for round window insertions only, to exclude a possible confounding factor of surgical approach (i.e. leading to a different insertion axis (Torres et al., 2018). Secondary outcomes were TF of the arrays, and differences in speech perception and preservation of residual hearing between STL group and non-STL group. The Midscala array of Advanced Bionics was defined as PM, because it is a precurved electrode. If a minimum of one electrode contact was likely to be in the scala vestibuli or scala media, we categorized it as translocated. Primary insertions in the scala vestibuli were not seen as STL, unless otherwise indicated. To avoid errors, the two researchers cross-checked the extracted data. For the meta-analysis, odds ratio was used as a summary measure.

Results

Study Selection

A total of 2128 unique articles were retrieved from three databases, see the PRISMA flow-chart in Figure 1. We screened the title and abstract, and excluded articles based on the exclusion criteria. The resulting 78 articles were assessed for eligibility by a whole read, leading to 42 excluded studies. In total, 33 articles were included for analysis.

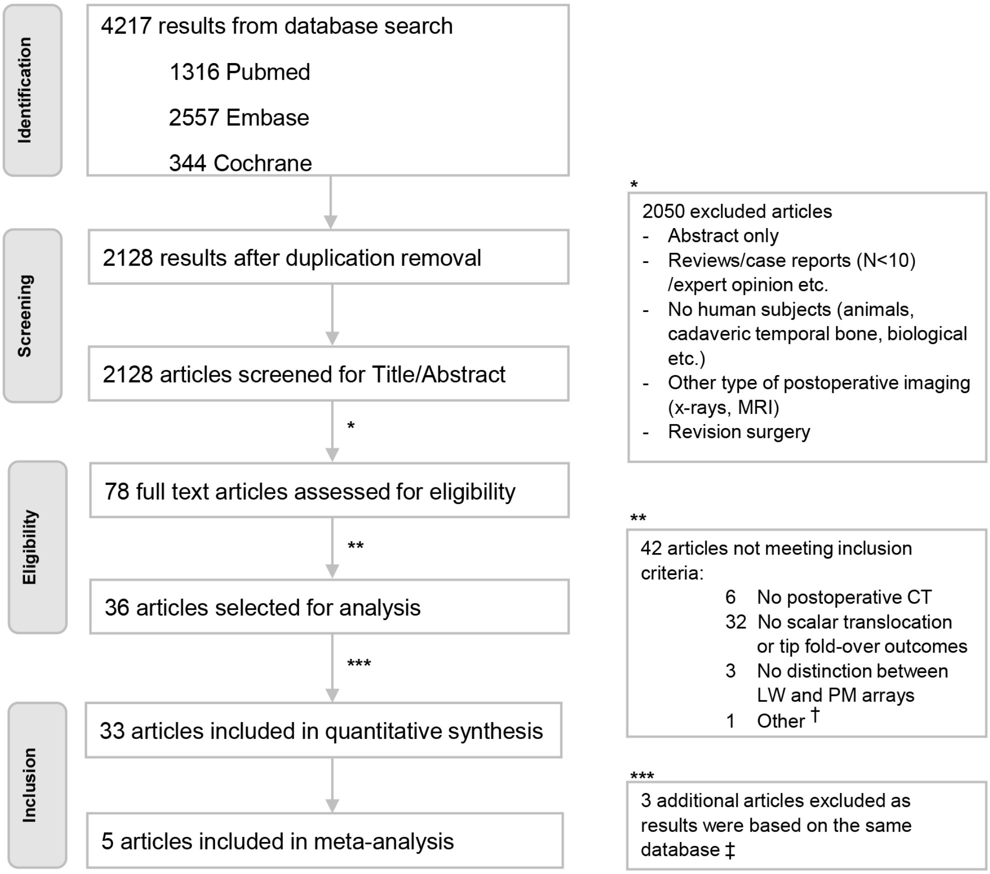

Figure 1. Flow chart of search results and study selection

† Articles excluded as array location was based partly on surgeon's report

‡ Largest study was selected for analysis if studies reported on the same database

Assessment of Methodological Quality

The relevance of 33 articles was scored for study population, treatment, outcome measures and comparison LW versus PM, see Table 1. Regarding studied population and treatment, all included studies investigated cochlear implantations as a treatment for patients with severe or profound bilateral SNHL. In these studies, primary cochlear implantations were performed in non-ossificated normal-shaped cochleas. Regarding outcome measures, two studies (O'Connell et al., 2016; Wanna et al., 2015) were less relevant as they used a subgroup of their previous studies (O'Connell et al., 2016; Wanna et al., 2014). However, we still included these studies for the analysis of speech perception as they provided unique data. Lastly, five comparative cohort studies (without studies (O'Connell et al., 2016; Wanna et al., 2015)) were identified, comparing LW arrays versus PM arrays (Boyer et al., 2015; Dalbert et al., 2016; James et al., 2019; O'Connell et al., 2016; Wanna et al., 2014).

The risk of bias was also assessed (Table 1). There was no randomized controlled trial comparing LW and PM arrays. Only two studies assessed the outcomes blindly (Boyer et al., 2015; Wanna et al., 2014). Most other studies were one-armed trials, investigating either LW or PM arrays. Concerning the middle ear approach, most studies (n=21) used the posterior tympanotomy with facial recess approach; a different middle ear approach, e.g. endaural approach, was not mentioned. All other studies (n=12) did not report the middle ear approach. The insertion approach of the included studies was mostly unstandardized (n=16). Eleven studies standardized the insertion approach (Aschendorff et al., 2017; Fan et al., 2018; Hassepass et al., 2015; Iso-Mustajarvi et al., 2020; Koka et al., 2018; Mittmann et al., 2017; Nassiri et al., 2020; Nordfalk et al., 2016; O'Connell et al., 2017; Shaul et al., 2020; Zelener et al., 2020). Selective reporting bias was low in all included studies; the proposed outcomes in the method sections were met in the result sections. However, there might still be selective reporting bias, as the prospective studies were not registered in a trial database beforehand, and the other studies were retrospective cohort studies. None of the studies were scored as overall low risk of bias.

Scalar translocation

The baseline characteristics of the analyzed studies were extracted (Table 2). There were five comparative studies (Boyer et al., 2015; Dalbert et al., 2016; James et al., 2019; O'Connell et al., 2016; Wanna et al., 2014). The five studies were comparable, as they assessed the same outcome for both LW and PM arrays across a large range of arrays. Therefore, we conducted a meta-analysis of these studies that compared STL rate of LW and PM arrays (Boyer et al., 2015; Dalbert et al., 2016; James et al., 2019; O'Connell et al., 2016; Wanna et al., 2014). The outcome is shown in Figure 2. The heterogeneity was moderate (I^2=28%, P=0.23). The use of LW arrays yielded 7% translocation and PM arrays yielded 43% translocation. The difference is significant: pooled odds ratio is 0.12, 95% confidence interval is [0.06 - 0.24]; (P<0.001). In two studies, in which the arrays were inserted through the round window and which showed virtually no heterogeneity (I^2=0%, P=0.85), the translocation rate with LW array was 2% and with PM array 22% (pooled odds ratio, 0.11; 95% confidence interval: [0.02-0.65], P=0.01; Figure 2) (Boyer et al., 2015; Wanna et al., 2014). Fourteen one-armed studies evaluating the translocation rates in PM arrays, showed a translocation rate of 0 to 71%, see Figure 3(Aschendorff et al., 2017; Aschendorff et al., 2011; Durakovic et al., 2020; Iso-Mustajarvi et al., 2020; Ketterer et al., 2018; Koka et al., 2018; Mittmann et al., 2015; Nassiri et al., 2020; O'Connell et al., 2017; Riggs et al., 2019; Shaul et al., 2018; Shaul et al., 2020; Sipari et al., 2018; Zelener et al., 2020). The CI-532 of Cochlear corporation had no STL in three (Aschendorff et al., 2017; Iso-Mustajarvi et al., 2020; Shaul et al., 2020) of the five studies solely investigating this array. Seven one-armed studies which evaluated translocation rates in LW arrays, showed a translocation rate of 0 to 20% (Figure 3) (An et al., 2018; Dalbert et al., 2016; Fan et al., 2018; Fischer et al., 2015; Hassepass et al., 2015; Nordfalk et al., 2016; O'Connell et al., 2017).

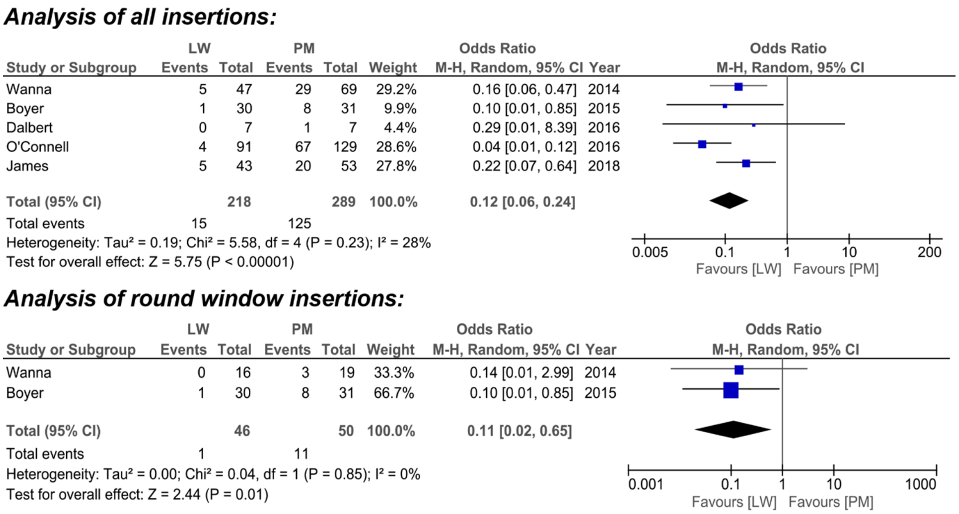

Figure 2. Forest plots presenting odds ratio for scalar translocation of lateral wall (LW) versus perimodiolar (PM) arrays. The scalar translocation rate is significantly lower when using a LW array compared to a PM array, also if only round window insertions are analyzed. Results are based on a random effects Mantel-Haenszel model. An event is scalar translocation.

Table 1. Relevance and risk of bias assessment

		Relevance[1]				Risk of Bias[1]						
Study		Study Population[2]	Treatment[3]	Outcome[4]	Comparison LW vs PM	Randomization	Blinding of outcome	Middle ear approach[5]	Insertion approach[6]	Postoperative CT[7]	Incomplete outcome data[8]	Selective reporting
Aschendorff	2011							NR				
Arweiler-Harbecker	2012							NR	NR			
Holden	2013											
Wanna	2014					NR					NR	
Boyer	2015					NR					NR	
Fischer	2015							NR				
Hassepass	2015											
Mittmann	2015											
Wanna	2015					NR	NR				NR	
Dalbert	2016					NR	NR					
Nordfalk	2016											
O'Connell	2016a					NR	NR	NR				
O'Connell	2016b					NR	NR	NR				
Aschendorff	2017											
Mittmann	2017										NR	
O'Connell	2017a											
O'Connell	2017b							NR				
Zuniga	2017							NR				
Fan	2018											

Gabrielpillai	2018							NR				
Ketterer	2018							NR	NR			
Koka	2018											
Shaul	2018											
Sipari	2018								NR			
An SY	2018							NR			NR	
James	2019					NR	NR	NR	NR			
Riggs	2019								NR			
Durakovic	2020											
Iso-Mustajarvi	2020											
Mittmann	2020							NR	NR			
Nassiri	2020											
Shaul	2020											
Zelener	2020											

Abbreviations: LW, lateral wall array; PM, perimodiolar array; NR, not reported.

1. Green = relevant or low bias, red = not relevant or high bias.
2. Green if study subjects were severe sensorineural hearing loss patients.
3. Green if study assessed cochlear implantation as treatment for severe hearing loss.
4. Green if study assessed scalar translocation and/or tip fold-over with postoperative CT.
5. Green if a mastoidectomy with posterior tympanotomy approach was used.
6. Green if study clearly standardized any of the three insertion approaches; extended round window, round window or cochleostomy. For extended round window and cochleostomy the site of drilling should be standardized (e.g. anteroinferiorly).
7. Green if the same protocol and type of CT was used for all subjects.
8. Green if <10% of outcome data was missing.

3

Table 2. Characteristics of studies reporting scalar translocation †

Studies	Year	Age (mean)	Cochlear implantations (n)	Mean angular insertion depth degrees (SD)		Surgical approach	Electrode-array
LW vs PM				LW	PM		
Wanna	2014	61	116	NR	NR	RW, ERW, CO	Cochlear, AB, MED-EL
Boyer	2015	50	61	559 (83)	370 (39)	RW	Cochlear, MED-EL
O'Connell	2016a	60	221	469 (117)	385 (56)	RW, ERW, CO	Cochlear, AB, MED-EL
Dalbert	2016	51	14	NR	NR	RW, CO	Cochlear
James	2019	58	96	median 513	median 410	RW, ERW, CO	Cochlear, AB, MED-EL
PM							
Aschendorff	2011	NR	21‡	NA	NR	CO	Contour
Mittmann	2015	NR	23	NA	NR	RW, ERW	Contour Advance
O'Connell	2017a	67	18	NA	NR	RW, ERW	Midscala
Aschendorff	2017	61	44	NA	403 (32)	RW, ERW, CO	CI-532
Shaul	2018	>60	79	NA	NR	ERW, CO	CI-512
Ketterer	2018	NR	368‡	NA	348 (36)	CO	Contour Advance
Koka	2018	NR	32	NA	378 (37)	RW, ERW	Midscala
Sipari	2018	60	28	NA	376 (39)	RW, ERW	Midscala
Riggs	2019	NR	21	NA	NR	RW, ERW	Midscala
Durakovic	2020	median 69	76	NA	NR	RW, ERW	CI-532
Iso-Mustajarvi	2020	42	18	NA	395 (26)	RW	CI-532
Shaul	2020	NR	125§	NA	NR	ERW	CI-532
Nassiri	2020	median 67	24	NA	388 (43)	RW, ERW, CO	CI-532
Zelener	2020	55	30	NA	17 (2) ¶	RW	Midscala

Zelener	2020	42	30	NA	17 (2) ¶	RW	Helix
LW							
Fischer	2015	51	63	451-495	NA	RW, CO	Flex 24,28, soft and standard
Hassepass	2015	49	39	388 (35)	NA	RW, CO	CI-422
Nordfalk	2016	58	29	576	NA	RW	Flex 24,28, soft and standard
O'Connell	2017b	median 69	48	514 (110)	NA	NR	Flex 24,28 and standard
Mittmann	2017	55	50	NR	NA	RW	CI-422/522
Fan	2018	2	26	NR	NA	RW, CO	MED-EL standard
An	2018	58	22	562 (45)	NA	RW, CO	Flex 28
An	2018	58	5	451 (78)	NA	RW, CO	CI-422

Abbreviations: AB, advanced bionics, CO, cochleostomy, ERW, extended round window; LW, lateral wall array; PM, perimodiolar array; RW, round window; SD, standard deviation; n, total number; NA, not applicable; NR, not reported

† If possible, study characteristics were separately indicated for a specific electrode-array.

‡ Including primary scala vestibuli insertions.

§ Children were left out as they did not receive postoperative CT scans.

¶ Insertion depth in millimeters.

3

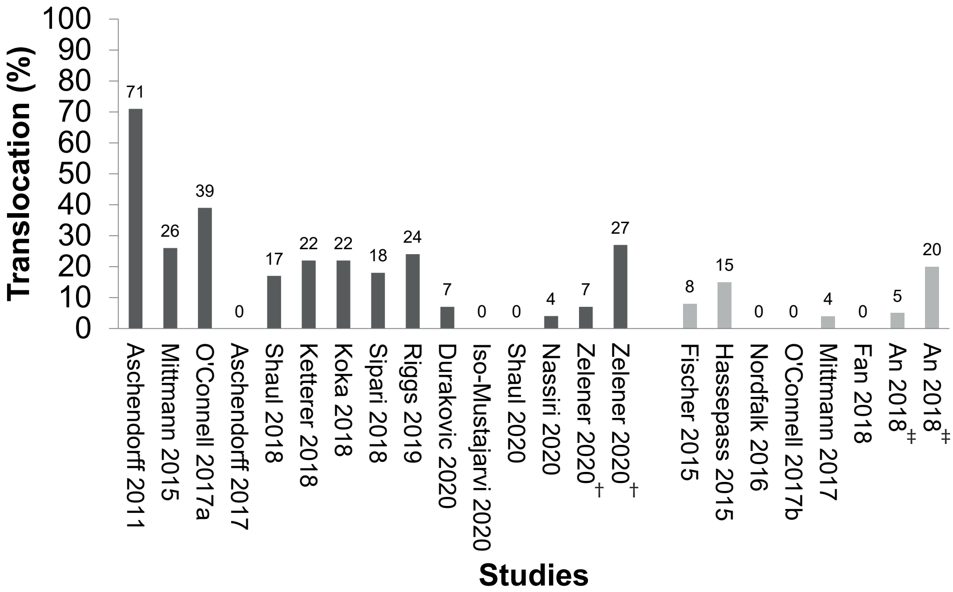

Figure 3. The scalar translocation rate presented for both the perimodiolar (PM) and lateral wall (LW) one-armed studies. Three studies of both groups had no translocation.
† same study, different array (first Midscala, second Helix), ‡ same study, different array (first Flex28, second CI422)

Scalar translocation site

Eight studies described the site of translocation in the cochlea (An et al., 2018; Boyer et al., 2015; Durakovic et al., 2020; Fischer et al., 2015; Mittmann et al., 2015; Mittmann et al., 2017; Nassiri et al., 2020; Sipari et al., 2018). For the LW group the majority of STL (n=7/9) was found below the first 90 degrees, of which three were inadvertently primarily inserted in the scala vestibuli through a cochleostomy (CO) approach (Fischer et al., 2015). Two translocations were beyond the 180 degrees. In contrast, for the PM group, most arrays translocated between 90 and 180 degrees (20/22), predominantly near 180 degrees.

Inadvertently direct scala vestibuli insertion

Very rarely, arrays are intentionally inserted in scala vestibuli, and more frequently, still rare, the scala vestibuli insertion occurs unintentionally. Two studies examined arrays that were inadvertently directly inserted in the scala vestibuli (Ketterer et al., 2018; Shaul et al., 2018). These studies investigated implantations performed by a cochleostomy approach, which included for one study also extended round window (ERW) approaches (Shaul et al., 2018). Only PM arrays were evaluated. One study solely evaluated the CI-512 array (Shaul et al., 2018) and the other study (Ketterer et al., 2018) the Contour Advance array (older version of the CI-512 array). In one study (Ketterer et al., 2018), from a total of 368 implantations, 43 arrays were directly inserted in the scala vestibuli (12%). The other study (Shaul et al., 2018) noted 7 from 79 arrays that were directly inserted in the scala vestibuli (9%). That study (Shaul et al., 2018) also looked at insertions primarily intended for the scala vestibuli (in cases with otosclerosis and post-meningitis), which resulted in 4 out of 13 arrays being translocated to the scala tympani.

Speech perception

Six studies compared postoperative speech perception scores between postlingually deafened adult CI recipients with and without translocated array (see Table 3) (Holden et al., 2013; James et al., 2019; O'Connell, Cakir, et al., 2016; Shaul et al., 2018; Wanna et al., 2014; Zelener et al., 2020). One study (Holden et al., 2013) showed that patients with STL had a worse outcome with the consonant-nucleus-consonant (CNC) words test than patients without STL ($p<0.001$). Another study (Wanna et al., 2014) showed that the STL group scored significantly less with the CNC test ($p<0.05$), but similarly as the non-STL group for the Arizona Biomedical sentences test (AzBio) and hearing in noise test (HINT). The third study (O'Connell et al., 2016) showed that the STL group scored significantly less with both the CNC test and AzBio test. The fourth study (Shaul et al., 2018) showed no difference between STL and non-STL group with the CNC word test, however, analyses of only postlingually deafened patients at 12 months postoperatively revealed worse CNC scores for the STL group (69% vs 50%; $p < 0.005$). Another study (James et al., 2019) showed that STL was associated with worse results with the French sentence test (MBAA2) both with and without background noise. Finally, the last study (Zelener et al., 2020) had small groups leading to inconclusive results. They observed non-significant worse scores for the Freiburger monosyllables test for the STL group with both PM arrays, the Midscala and Helix electrode array.

Table 3. Speech perception, normal position vs scalar translocation

Study	Year	Array type	Speech audiometry	Incl. prelingually deaf	STL (n/total)	Timing of test	Non-STL mean score	STL mean score	p value
Holden	2013	PM/LW	CNC	no	NR/114†	2 wk. – 2 y	MVA: translocation related to worse outcome		p < 0.01*
Wanna	2014	PM/LW	CNC	no	34/116‡	NR	49%	36%	p < 0.05*
			AzBio	no	NR	NR	NR	NR	p > 0.05
			HINT	no	NR	NR	NR	NR	p > 0.05
O'Connell	2016a	PM/LW	CNC	no	46/137	mo. 6 - 18	51%	39%	p < 0.05*
			AzBio	no	33/107	mo. 6 - 18	61%	50%	p < 0.05*
Shaul	2018	PM (CI-512)	CNC	yes	14/72	mo. 3	53%	45%	p > 0.05
			CNC	yes	14/72	mo. 12	58%	46%	p > 0.05
			CNC	no	10/51	mo. 3	64%	47%	p > 0.05
			CNC	no	10/51	mo. 12	69%	50%	p < 0.05*
James	2018	PM	MBAA2 list in quiet, and +10 dB SNR	no	25/96	mo. 1-12	MVA: electrode contacts in SV associated with lower speech perception scores		p < 0.01*

Zelener	2020	PM (Helix)	FMS	NR	7/19	mo. 12	50 %	22 %	not possible
			HSM quiet		7/19		65 %	35 %	
			HSM +10 dB SNR		7/19		17 %	17 %	
Zelener	2020	PM (Midscala)	FMS		2/26		56 %	30 %	
			HSM quiet		2/26		~ 50%	50 %	
			HSM +10 dB SNR		2/26		38 %	36 %	

Abbreviations: AzBio, Arizona Biomedical sentences; CNC, Consonant-Nucleus-Consonant words; dB HL, decibels hearing level; FMS, Freiburger monosyllables; HINT, Hearing in noise test; HSM, Hochmail-Schuls-Moser sentence test; LW, lateral wall array; MVA, multivariate analysis; MBAA2, French sentence test; MS, midscala electrode array; n, number; NR, not reported; PM, perimodiolar array; ScTr; scalar translocation, SV, scala vestibuli; SNR, signal noise ratio.

† 23% of all electrode contacts in scala vestibuli

‡ This represents all patients, unknown how many were included for the speech perception scores

* = statistically significant

3

We used the weighted mean to summarize the speech perception results for the postoperative word list score in quiet between the STL and non-STL group. Four out of the six studies comparing speech perception scores between STL and non-STL reported the postoperative means (see Table 3), and were therefore included (O'Connell et al., 2016; Shaul et al., 2018; Wanna et al., 2014; Zelener et al., 2020). These studies evaluated mainly PM arrays, with time of testing ranging between 3 and 18 months. In addition, three type of wordlists were used, either the CNC, AzBio or the Freiburger monosyllables (FMS). The STL group had a weighted mean of 41 % correct, and the non-STL group 55%, resulting in a difference of 14%. Apart from one study (Shaul et al., 2018), no standard deviations were reported. That study reported a standard deviation of 17% for the STL group and 21% for the non-STL group for postlingually deaf patients at 12 months postoperatively. If we assume the same standard deviations for the groups of the other studies, the difference in speech scores between STL and non-STL would be significant ($Z=5.82$, $p<0.001$), favoring non-STL.

Finally, only one study compared LW and PM speech perception scores between patients with confirmed non-translocated arrays (O'Connell et al., 2016). Specifically, they compared the CI422 array (LW) with the CI512 (PM), and reported higher AzBio scores (70% vs 46%, $P=0.02$) for the CI422 array.

Residual hearing

Four other studies compared residual hearing around four weeks postoperatively in CI recipients with and without translocated array (Table 4) (Koka et al., 2018; O'Connell et al., 2017; Riggs et al., 2019; Wanna et al., 2015). The residual hearing was assessed in two of these studies by measuring the difference between postoperative and preoperative outcomes of pure tone audiometry at the low frequencies (LF-PTA) (Koka et al., 2018; O'Connell et al., 2017). The other two studies assessed postoperative loss of functional residual hearing (<80 dB HL)(Riggs et al., 2019; Wanna et al., 2015). Three of the four studies (O'Connell et al., 2017; Riggs et al., 2019; Wanna et al., 2015) showed significantly more loss of residual hearing for patients with a STL compared to patients with normal positioned array; in contrast, one study (Koka et al., 2018) showed no effect of STL on residual hearing.

Tip fold-over

Eleven studies reported TF results (Arweiler-Harbeck et al., 2012; Aschendorff et al., 2017; Durakovic et al., 2020; Fischer et al., 2015; Gabrielpillai et al., 2018; Iso-Mustajarvi et al., 2020; Mittmann et al., 2020; Nassiri et al., 2020; Shaul et al., 2020; Sipari et al., 2018; Zuniga et al., 2017). Just two studies compared LW and PM arrays (Gabrielpillai et al., 2018; Zuniga et al., 2017). One study (Gabrielpillai et al., 2018) described 15 TFs from a total of 1722 implantations (0.9%). TFs occurred mostly with PM arrays (13/15), with a rate of 1.67% PM versus 0.23% for the LW insertions. The second study (Zuniga et al., 2017) described six TFs in a cohort of 303 (2%) implantations, in which a PM and LW array was used in respectively 51% and 48% of the cases with 4 tip fold-overs with PM arrays (three Contour Advance and one Midscala), and two with LW arrays (CI-422 and 1J). In total, these two studies evaluated 2025 implantations for TF, with significant more TFs with PM arrays ($X2 = 6.8$, $p<0.01$).

Six studies described the TF rate of the CI-532 electrode array (Aschendorff et al., 2017; Durakovic et al., 2020; Iso-Mustajarvi et al., 2020; Mittmann et al., 2020; Nassiri et al., 2020; Shaul et al., 2020). From a total of 622 implantations 37 TFs were identified, resulting in a TF rate of 5.9% for the CI-532. Finally, for the remaining three studies, two studies reported one TF (Fischer et al., 2015; Sipari et al., 2018), and one study (Arweiler-Harbeck et al., 2012) reported no TF.

Table 4. Residual hearing, normal position vs scalar translocation

Study	Year	Array Type	PTA (Hz)	STL (n/ total)	Timing of test	Non-STL†	STL†	p value
Wanna	2015	PM/LW	250	7/45	wk. 4	22/38 functional residual hearing (<80 dB HL)	0/7 functional residual hearing (<80 dB HL)	p < 0.01*
O'Connell	2017a	PM (Mid-scala)	125, 250, 500	6/15	wk. 2/3	threshold shift 16	threshold shift 38	p < 0.05*
Koka	2018	PM (Mid-scala)	125, 250, 500	7/32	wk. 4	threshold shift 28	threshold shift 36	p > 0.05
Riggs	2019	PM (Mid-scala)	250, 500, 1000	7/21	wk. 4	mean 53% loss 1/14: 100% loss	mean 94% loss 6/7: 100% loss 1/7: 55% loss	p < 0.01*

Abbreviations: dB HL, decibels hearing level; PTA, Pure Tone Audiometry; LW, lateral wall array; STL; scalar translocation; PM, perimodiolar array;

† threshold shifts values are in decibel

* = statistically significant

Discussion

Scalar translocation

Our study shows with a comprehensive overview of the literature that STL of the array is frequently seen after cochlear implantation and negatively affects speech perception scores. The meta-analysis, which includes five studies, shows that the STL rate is significantly lower for the LW than the PM arrays (7% vs 43%). Also the STL rate for LW arrays is still significantly lower (2% vs 22%) when only considering RW approaches. The one-armed studies show similar large differences in STL rate between LW and PM arrays. However, there was a substantial risk of bias in the included studies, mainly caused by lack of randomization, standardization of the insertion approaches (i.e. ERW, RW and CO) and inclusion of different arrays of both groups.

The possible explanation for the higher STL rate encountered with PM arrays is as follows. Nowadays, most surgeons prefer the RW approach for insertion of the array, as shown by this and previous studies (Gazibegovic & Bero, 2017; Iseli et al., 2014). The combination of RW and PM arrays introduces possible difficulties for the surgeon, because the tip or apical end of the PM array is larger than in LW arrays. This aspect might lead to increased friction forces, e.g. by obstruction at the round window entry (Jeyakumar et al., 2014; Souter et al., 2011), although the RW and scala tympani dimensions should be in theory sufficient for PM arrays (Biedron et al., 2010; Rask-Andersen et al., 2011). In addition, insertion with PM arrays requires more experience than with LW arrays. Probably, surgeons with ample experience with the PM arrays encounter fewer STLs (Aschendorff et al., 2011). This can be explained by the surgeon needing to accurately position the stylet in the basal turn of the cochlea, and subsequently perform the insertion off-stylet technique. The off-stylet technique can be done with or without an insertion tool (Gazibegovic & Bero, 2017); note, however, that Cochlear corporation has abandoned the insertion tool for their latest stylet based PM arrays for the exact reasons to avoid translocation. Lastly, the stylet itself is a semi-rigid structure that can penetrate intra-cochlear structures like the osseous spiral lamina thus causing STLs (Eshraghi et al., 2003; Wardrop et al., 2005).

The latest PM arrays of both Advanced Bionics and Cochlear, namely the Midscala and the CI-512/CI-532 arrays were included in our analysis. Notably, the CI-532 had no STL in three (Aschendorff et al., 2017; Iso-Mustajarvi et al., 2020; Shaul et al., 2020) out of five studies (Aschendorff et al., 2017; Durakovic et al., 2020; Iso-Mustajarvi et al., 2020; Nassiri et al., 2020; Shaul et al., 2020). A possible explanation for the much lower STL rate is the different method of insertion: the stylet is replaced by an external sheath tube used for guiding the array during insertion.

Location of translocation

Eight studies described the translocation site for 32 translocations (An et al., 2018; Boyer et al., 2015; Durakovic et al., 2020; Fischer et al., 2015; Mittmann et al., 2015; Mittmann et al., 2017; Nassiri et al., 2020; Sipari et al., 2018). Most translocations occurred at around 180 degrees depth, predominantly with PM arrays. Cadaveric studies have shown that translocation occurs mainly at the base of the cochlea leading to the first ascending turn of the cochlea, around 180 degrees depth, possibly caused by a steep decrease in the dimensions of the scala tympani (Avci et al., 2017; Biedron et al., 2010; De Seta et al., 2017). Increased friction intracochlearly can also be caused by the complex and heterogeneously shaped cochlear hook region at the very most basal part of the cochlea (Atturo et al., 2014; Avci et al., 2017; Biedron et al., 2010). The included studies support the notion that STL occurs mainly at the base of the cochlea, especially around 180 degrees depth.

Speech perception

Postoperative speech perception was poorer for the CI patients with STL compared to those without a STL (a weighted mean difference of 14%). Because of the low STL rate for the LW group in general (7%), these results are primarily based on the PM arrays. Previous studies have shown that speech perception improves up to one year post implantation (De Seta et al., 2016; Mosnier et al., 2015). The results show that STL negatively impacts speech perception irrespective of the timing of the test (i.e. between 1-24 months), indicating a probable irreversible effect of STL during insertion. Several factors may contribute to the detrimental effect of translocation on hearing with a CI. Translocation of the array to the scala vestibuli increases the distance to the auditory nerve compared to the normal position in the scala tympani, leading to inferior stimulation of the auditory nerve. Also, the array in the scala vestibuli might possible lead to more overlap of stimulated neural regions between electrodes (Holden et al., 2013). In addition, the STL itself can lead to damage of the structures in the cochlear partition, therefore interacting with and destruction of the fine microstructures (e.g. stria vascularis, organ of Corti and spiral ganglion cells) (De Seta et al., 2017). For instance, it may accelerate degeneration of the SGCs, by damage to these cells or indirectly by damage to residual hair cells and/or supporting cells which promote survival of the SGCs (Incesulu & Nadol, 1998; Ramekers et al., 2012; Zilberstein et al., 2012).

We identified only one study comparing LW and PM speech perception scores between patients with confirmed non-translocated arrays (O'Connell et al., 2016). They reported higher speech perception scores for the LW group. In contrast, another study reports better outcomes if the array is closer to the modiolus, even though STL was not excluded (Holden et al., 2013). The majority of the studies, however, show no difference between the two groups (Doshi et al., 2015; Fabie et al., 2018; Moran et al., 2019; van der Jagt et al., 2016; van der Marel et al., 2015). We have to note, STL was not assessed in those studies. In future studies, STL of the array should be considered in the analysis of speech perception outcomes.

Residual hearing

Preserving residual hearing is important assuming it leads to better speech understanding with CI (Incesulu & Nadol, 1998). Studies with electric and acoustic stimulation (EAS) CIs have shown that residual hearing can improve speech understanding (Gifford et al., 2017; Incerti et al., 2013; Lenarz et al., 2013). The underlying mechanisms are not clear. Two hypotheses have been put forward: the survival of the hair cells at the lower frequencies leads to better auditory nerve survival, or the acoustic stimulation of these hair cells directly contributes to the speech understanding (Bas et al., 2012; Incesulu & Nadol, 1998). There is no definitive proof for either of these hypotheses. All in all, preferably both hair cells and SGCs (i.e. the residual hearing of patients) are preserved.

Preservation of residual hearing was assessed between the STL group and non-STL group, again primarily based on the PM arrays, especially the Midscala array of Advanced Bionics Corporation (Table 3) (Koka et al., 2018; O'Connell et al., 2017; Riggs et al., 2019; Wanna et al., 2015). These studies pointed to a negative effect of STL on hearing preservation. The results of these studies were based on audiometric testing one month after cochlear implantation. However, previous studies have shown that residual hearing of CI recipients deteriorates over time (Lenarz et al., 2013; Mady et al., 2017; Quesnel et al., 2016). Therefore, it is not clear whether the difference in postoperative residual hearing between STL and non-STL persists over time.

To our knowledge, there are no studies that evaluated preservation of residual hearing for non-translocated arrays between PM and LW arrays. One study showed, without analysis of array position, that patients with LW arrays had smaller differences between post- and preoperative low frequency tone audiometry, than patients with PM arrays (Mady et al., 2017). These results are in line with our finding that STL negatively affects residual hearing of CI recipients, and occurs mainly with PM arrays. Therefore, LW arrays are probably better suited to preserve the residual hearing of CI recipients.

Tip fold-over

TF rate of the array is very low; specifically, in two large studies, investigating several arrays, it was less than 2% (Gabrielpillai et al., 2018; Zuniga et al., 2017). The TF rate was almost three times larger for the CI-532 (5.9%), which might be related to a different method of insertion, using an external sheath for insertion. The TF rate of around 2% corresponds to an older study with intra- and postoperative plain x-rays (Cosetti et al., 2012). This can be explained in two ways, either the TF rate is not different for the latest generation of arrays (except for the CI-532), or the TF rate has decreased while improved imaging techniques unmask otherwise undetected tip fold-overs.

Overall, our study shows most TFs were observed for PM arrays. This is not surprising, considering the method of implantation of PM arrays. The stylet can be too shallow or too deeply inserted before release of the array, resulting in a misalignment with the modiolar wall causing a TF (Ramos-Macias et al., 2017; Rau et al., 2010). Surprisingly, a new method of insertion for the PM arrays, the external sheath of the CI-532, has an increased chance of TF.

Conclusion

STL of the array is quite common during cochlear implantation surgery, especially when using a PM array, occurring predominantly at 180 degrees intracochlearly. In addition, STL seems to negatively affect speech perception outcomes, especially word perception scores in quiet, and residual hearing of CI recipients. Lastly, tip fold-over of the array is an infrequent and persisting phenomenon, seemingly associated with both stylet and external sheath based PM arrays. For the current medical practice we recommend choosing a LW array above a PM array for cochlear implantation to minimize intracochlear damage. However, more (unbiased) research is needed to elucidate the potential differences between the specific arrays within the PM and LW group.

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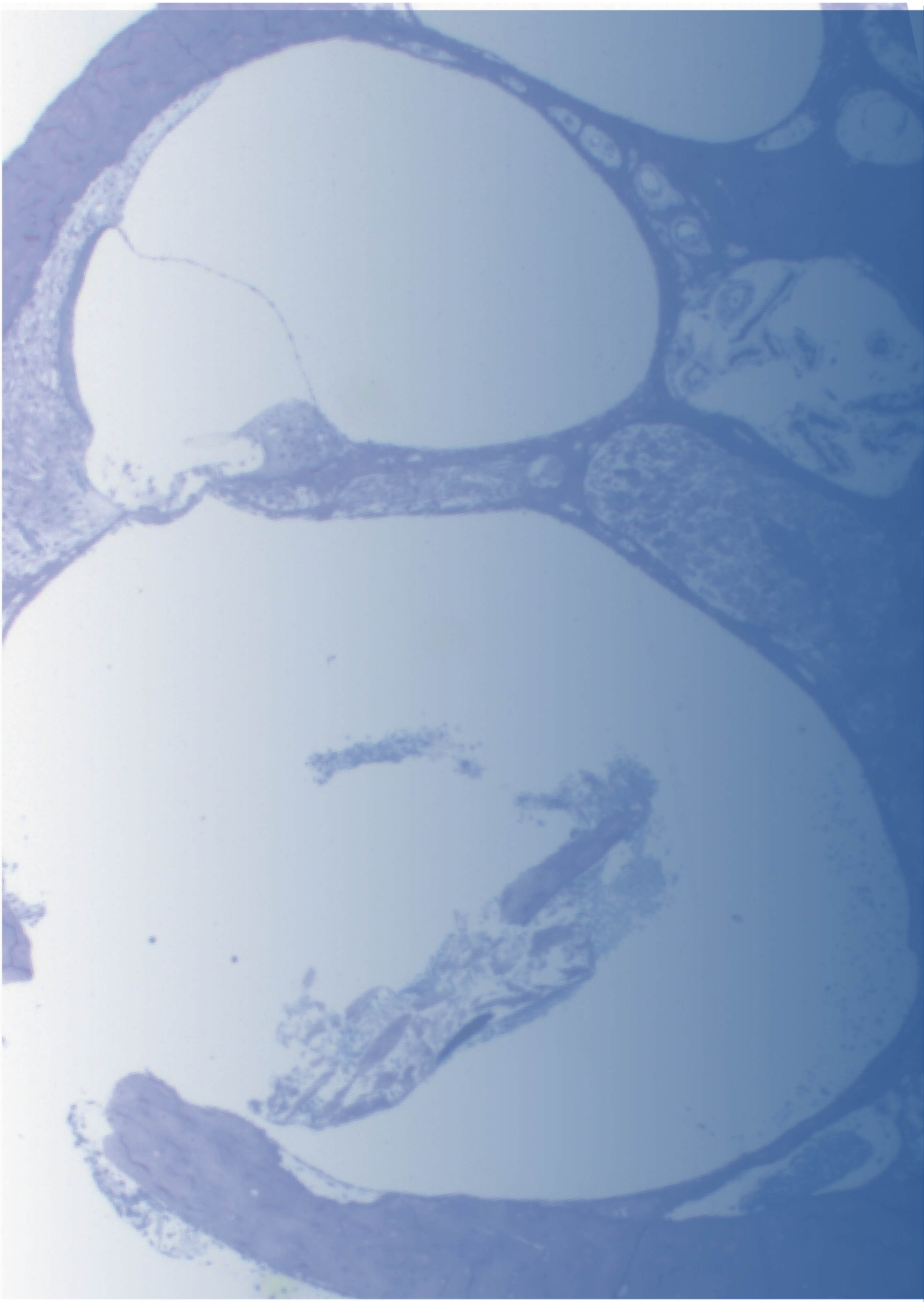

Chapter 4

The effect of the surgical approach and cochlear implant electrode on the structural integrity of the cochlea in human temporal bones

Saad Jwair, Huib Versnel, Robert J. Stokroos and Hans G.X.M Thomeer

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Abstract

Objectives

Cochlear implants (CI) restore hearing of severely hearing-impaired patients. Although this auditory prosthesis is widely considered to be very successful, structural cochlear trauma during cochlear implantation is an important problem, reductions of which could help to improve hearing outcomes and to broaden selection criteria. The surgical approach in cochlear implantation, i.e. round window (RW) or cochleostomy (CO), and type of electrode-array, perimodiolar (PM) or lateral wall (LW), are variables that might influence the probability of severe trauma. We investigated the effect of these two variables on scalar translocation (STL), a specific type of severe trauma.

Materials and Methods

Thirty-two fresh frozen human cadaveric ears were evenly distributed over four groups receiving either RW or CO approach, and either LW or PM array. Conventional radiological multiplanar reconstruction (MPR) was compared with a reconstruction method that uncoils the spiral shape of the cochlea (UCR).

Results

Histological analysis showed that RW with PM array had STL rate of 87% (7/8), CO approach with LW array 75% (6/8), RW approach with LW array 50% (4/8) and CO approach with PM array 29% (2/7). STL assessment using UCR showed a higher inter-observer and histological agreement (91% and 94% respectively), than that using MPR (69% and 74% respectively). In particular, LW array positions were difficult to assess with MPR.

Conclusion

The interaction between surgical approach and type of array should be preoperatively considered in cochlear implant surgery. UCR technique is advised for radiological assessment of CI positions, and in general it might be useful for pathologies involving the inner ear or other complex shaped bony tubular structures.

Introduction

Worldwide, the prevalence of hearing loss is increasing, with currently more than half a billion people with disabling hearing loss (Wilson et al. 2017). Severe hearing loss is recognized as an important health issue that can lead to depression, insecurity, language development delay and social isolation (Carlson 2020). Severe to profound hearing loss can be treated with a cochlear implant (CI) (Carlson 2020). A CI converts sound into electrical current pulses that stimulate the auditory nerve. The CI bypasses affected and degenerated sensory receptor cells. Outcomes of CIs have improved tremendously in the past 45 years, drastically changing the perspective for hearing-impaired patients (Carlson 2020).

However, understanding speech in background noise, and musical melody perception, are challenging or impossible for most CI recipients (Gifford and Revit 2010). In most cases, severely hearing-impaired patients have some residual hearing on the lower frequencies (Snels et al. 2019). The preservation of this residual hearing (i.e. hearing preservation) might help CI patients with speech perception (Gifford et al. 2013; Brockmeier et al. 2010; Yuksel, Meredith, and Rubinstein 2019; Turner et al. 2004). In addition, selection criteria for CI are difficult to define, and they differ among countries (van der Straaten et al. 2020). Importantly, some hearing-impaired patients fail to achieve satisfactory results with either of the treatment options for a considerable time (van der Straaten et al. 2020). On the one hand they achieve unsatisfactory results with hearing aids, but on the other hand fall below threshold for a CI because their hearing is too good. Considering that hearing deteriorates with increasing age, those patients will likely meet the selection criteria for a CI over time (Roth, Hanebuth, and Probst 2011). Broadening medical criteria for a CI, however, would permit these patients to receive a CI at an earlier time point. In addition, it would allow for CI treatment of patients with severe tinnitus but relatively good hearing (Van de Heyning et al. 2008). A major hurdle for broadening these medical criteria can be overcome by preserving the residual hearing through means of limiting structural trauma to the cochlea during cochlear implantation (Santa Maria et al. 2014). In recent years, the development of robot-assisted approaches and array insertions are being explored to this end (Caversaccio et al. 2019; Torres et al. 2018). In addition, limiting trauma opens the way for future developments relying on cochlear structure preservation, e.g. use of corticosteroids or neurotrophin eluting CIs, or hair cell regeneration (Budenz, Pfingst, and Raphael 2012; Smith-Cortinez et al. 2021). Minimizing cochlear trauma during implantation can also reduce fibrosis and ossification on the long term making potential reimplantations easier to conduct

(Ishiyama et al. 2019). This latter aspect is especially relevant in pediatric patients, as they have increased risk for reimplantation during their lifetime due to malfunctions or necessary upgrades (Lin et al. 2010).

Recent evidence shows that scalar translocation (STL) of electrode-arrays (in short: arrays), which leads to severe trauma, is frequently occurring in CI surgery (Jwair et al. 2021). Normally, the array is inserted into the scala tympani (ST), however in some cases the array translocates (i.e. STL) to scala media (SM) or scala vestibuli (SV), as illustrated in Fig. 1.

STL avoidance was on the forefront of development by manufacturers of newer versions of two type of arrays, lateral wall (LW) and perimodiolar (PM) (Dhanasingh and Jolly 2017), see Fig.1. Both array types are commonly used in medical practice. LW arrays, or straight arrays, were used initially and have been continuously developed to be less traumatic. They are smaller in diameter nowadays, more flexible, and have more rounded tips compared to previous generations. PM arrays were developed as an alternative to LW arrays to achieve a position closer to the modiolus (Gstoettner et al. 2001). They are precurved in order to follow the spiral shape of the cochlea. These arrays need to be straightened before implantation, to -which both stylet and sheath based methods exist. The stylet and sheaths are removed after achieving insertion in the basal part of the cochlea during insertion, allowing the array to curl against cochlear modiolus and reducing the electrode-neuron distance for electrical stimulation. This in theory achieves better frequency resolution by lessening the spread of excitation across electrodes. PM arrays, although smaller than previous generations, are in general larger in diameter than the latest LW arrays, probably because of aforementioned methods needed to insert these arrays into the cochlea (Dhanasingh and Jolly 2017).

The surgical approach for insertion might also be an important factor in STL. Two approaches are mostly used for array insertion (Jiam et al. 2016). The round window (RW) approach is conducted, after drilling of the bony overhang to expose the RW membrane, through a slit like opening in the RW membrane for entry in the cochlea. In contrast, a cochleostomy approach (CO) uses a burr-hole opening in the cochlea, anterior and inferior to the RW membrane, for entry (Fig. 1). Another approach, the extended round window, is a combination of RW and CO approach. The RW and CO approaches lead to different insertion angles that likely influence intra-scalar positioning of arrays (Breinbauer and Praetorius 2015). While the conventional CO approach is still widely used, CI surgeons currently gravitate towards use of RW

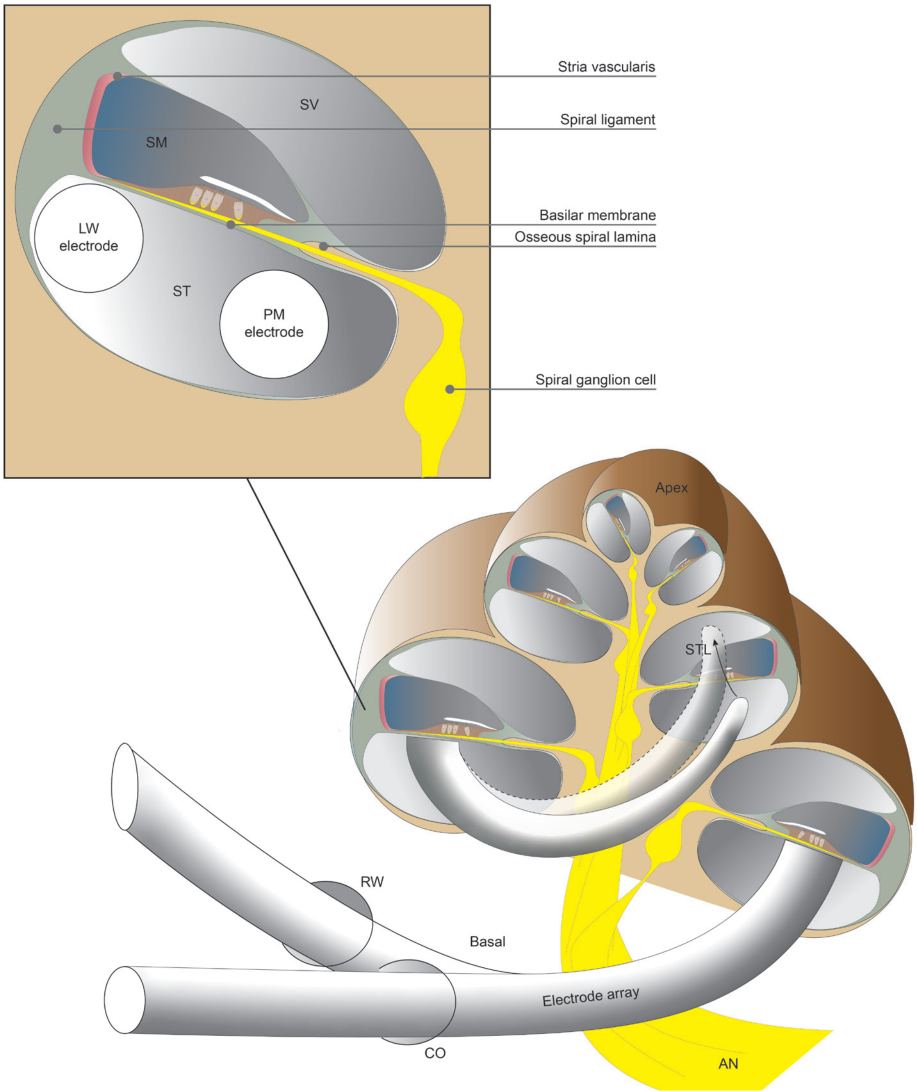

Figure 1. A cross section of the cochlea is depicted with an implanted electrode array. The electrode array is implanted in the scala tympani, using either the round window or a small hole in the cochlea (cochleostomy) for entry. The array follows the spiral curvature of the cochlea from the base of the cochlea towards the apex. Arrays usually reach at least around one turn and half, depending on the exact length of the array. Perimodiolar arrays are positioned more towards the spiral ganglion cells of the auditory nerve and beneath the osseous spiral lamina, and in contrast, lateral wall arrays are positioned laterally towards spiral ligament and beneath basilar membrane. In some cases the array can translocate during insertion (i.e. STL) from ST to SV or SM, which is detrimental for the structures that lie in between. RW: round window; CO: cochleostomy; AN: auditory nerve; STL: scalar translocation; ST: scala tympani; SV: scala vestibuli; SM: scala media; LW: lateral wall; PM: perimodiolar.

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approach, as it is perceived to be less invasive to cochlear structures (Roland, Wright, and Isaacson 2007; Gudis et al. 2012; Iseli, Adunka, and Buchman 2014).

To this date, no study has addressed the effect of both surgical approaches and the latest types of arrays on STL. Previous studies have investigated both variables separately regarding trauma severity. Studies showed that RW approach leads to less intracochlear trauma than CO approach (Richard et al. 2012; Wanna et al. 2014), although a systematic review showed inconclusive results (Havenith et al. 2013). In addition, another systematic review showed that LW arrays induce less severe cochlear trauma compared to PM arrays (Jwair et al. 2021). Possible interaction between electrode choice in relation to surgical approach have not been systematically studied thus far. An example of such an effect is the smaller size of entry to the cochlea of a RW approach, compared to CO, possibly leading to more friction and trauma during PM array insertion than insertion with a LW array. Based on above mentioned findings in literature, our hypothesis is that the combination of RW approach with LW array leads to the least severe cochlear trauma in the form of STL. To this end, we designed a temporal bone experiment with fresh frozen cadaveric heads investigating the four commonly used combinations of CO or RW with LW or PM. In addition, the diagnostic value of CT imaging using the most common radiological assessment option for STL was compared to a CT scanning protocol with curved multiplanar reconstructions.

Methods

Specimen

Fresh frozen human cadaveric heads were obtained from the department of Anatomy in the UMC Utrecht. The specimens were derived from bodies that entered the department of anatomy through a donation program. From these persons written informed consent was obtained during life that allowed the use of their entire bodies for educational and research purposes. These methods are in accordance with UMC Utrecht guidelines, and in accordance to the Dutch law. According to local medical ethical board of UMC Utrecht no additional approvements were required, and thus additional ethical approval was waivered. Ages at death ranged from 59 to 93 years; cause of death was unknown. The specimens were frozen within 48 h postmortem at -20 °C. The specimen were supplied at random by the prosector for this study. The prosector was not aware of the study purpose. The specimens were thawed 16 to 24 h before implantation at room temperature (approximately 20 °C). In total, 16 cadaveric heads were bilaterally implanted with an array. The 32 ears were distributed equally over four groups: PM-CO, PM-RW, LW-CO, LW-RW.

Cochlear implantation surgery

Array insertion was performed according to standard cochlear implantation procedures. After retro auricular incision a mastoidectomy and posterior tympanotomy was performed to reach the middle ear space. Depending on randomization, entry to ST was achieved with either an anteroinferior CO (i.e. relative and <1 mm to RW membrane) or a pure RW approach. In addition, either a Midscala (PM array; length from electrode contact at tip to proximal blue marker: 18.5 mm) or SlimJ array (LW array; length from electrode contact at tip to proximal blue marker: 23 mm) was implanted. These arrays were supplied by the manufacturer (Advanced Bionics®). The PM arrays were prior to implantation straightened with a stylet. The arrays have blue markers for gauging the insertion depth of the array. The LW array has one proximal (i.e., basal) blue marker, and it was inserted until this marker reached the CO or RW site. The PM array has in addition to proximal marker also a distal blue marker (i.e., apical): the array with stylet is inserted first until the distal blue marker. Subsequently, the array is pushed over the stylet into the cochlea, while holding the stylet in place (i.e. so called 'advance off technique') until reaching the proximal blue marker for full insertion. Duration of array insertion was approximately 20 seconds. If any resistance was encountered during insertion, the array was carefully and slightly withdrawn, subsequently insertion was continued as normal until full insertion was achieved (if possible). The arrays were fixed with an instant adhesive at posterior tympanotomy site after reaching full insertion. The majority of implantations was performed by the first author (SJ), and the remainder were done by the senior author (HT) who is an experienced otologist. The first author had half year of extensive training in cochlear implantation surgery with fresh frozen cadaveric heads under supervision of senior otologist before commencing these experiments.

Cone beam CT protocol

All cadaveric heads were scanned within 1 hour after implantation. Cone beam CT scanner (3D Newtom, NNT, Italy, 2018) was used for all scans. The tube voltage was 110 kV, with tube charge 30 mC with total scan time of 20 s. The field of view was 8x8 cm. Left and right temporal bones were scanned separately. The 3-D volumetric data was reconstructed with isometric 150 µm voxels.

The images were analyzed with software that is supplied by the same CB-CT manufacturer (3D Newtom, NNT, Italy, 2018). Multiplanar reconstructions were made using this software.

Radiological analysis

Fig. 2 illustrates the cochlear view, defined as the plane perpendicular to the basal turn of the cochlea and parallel to the modiolar axis, that was acquired to assess distance A (Koch et al. 2017). Distance A is defined as the length of the line between site of entry (CO or RW) through the modiolus to the contralateral wall. This is an indirect measure of cochlear size, proportional to the cochlear duct length. In addition, the Verbist et al. 2010 method was used for determining insertion depth, which was advised in a consensus meeting (Verbist et al. 2010). To compute the insertion angle and distance A, the images were analyzed with ImageJ software (U. S. National Institutes of Health, USA).

STL was assessed using two types of multiplanar reconstructions. First, after tilting the coronal plane to an oblique plane, the cochlear view image was acquired. Subsequently, conventional multiplanar axial and sagittal reconstructions (MPRs) were created and used for assessment of STL (Fig. 3). Secondly, the cochlea with implanted electrode array was uncoiled using curved multiplanar reconstructions, as introduced by de Seta et al. (2016). The curved cochlear structure was traced using the trajectory of the electrode array in the cochlear view plane, with a thickness of 2 mm to include also the width of the cochlea (Fig. 4A). Subsequently, these reconstructions generated a planar two-dimensional image, the uncoiled cochlear reconstruction (UCR; see Fig. 4B), which cross-cuts the uncoiled tubular cochlear structure perpendicular along its long axis (De Seta et al. 2016).

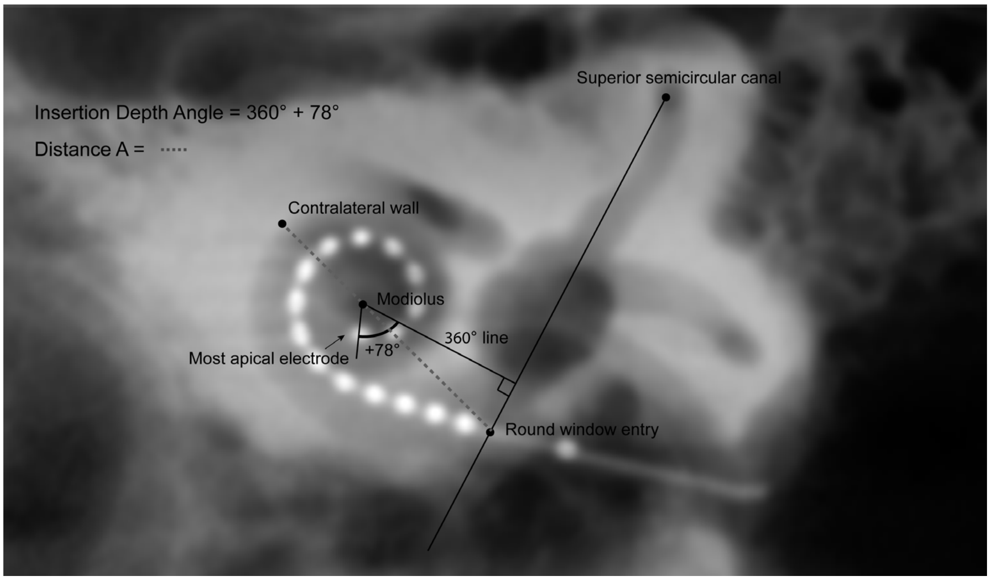

Figure 2. In the cochlear view reconstruction of CB-CT scan both insertion depth angle and distance A can be measured. The 360° line is drawn perpendicular to a line between round window entry and middle of upper part of the posterior semicircular canal. The insertion depth angle is measured by adding 360° to the angle between the apical electrode and the 360° line. Distance A (dashed line), an indirect measure proportional to cochlear duct length, is measured as the length of the line from the point of the array entering the RW or CO, through the modiolus to the contralateral cochlear wall.

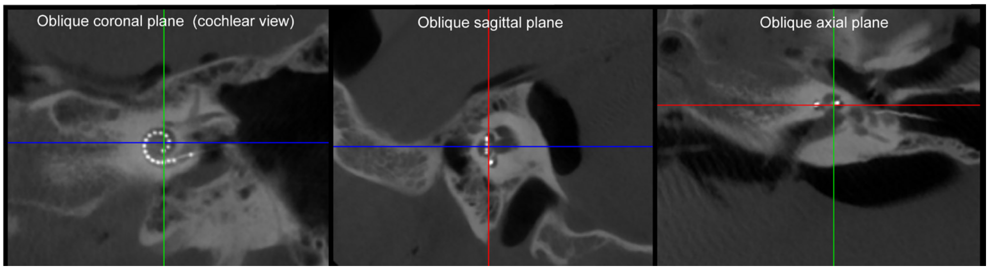

Figure 3. Method for conventional multiplanar reconstructions. The lines in the images represent the position of the shown images relative to the planes. Oblique planes were reconstructed by aligning the red line in sagittal and axial plane to the basal turn of the cochlea, and the blue and green line were aligned to the course of the cochlear modiolus. This resulted in multi reconstructions of three oblique planes: oblique coronal plane, oblique sagittal plane or 'cochlear view', and oblique axial plane.

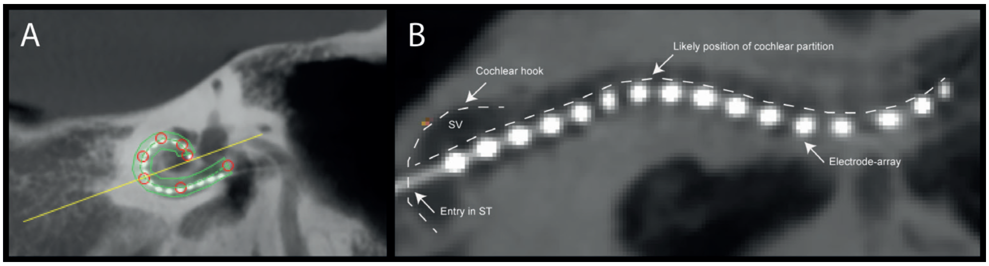

Figure 4. Method for uncoiled cochlear reconstructions (UCR). A: line is drawn along the implanted array in the oblique 'cochlear view' reconstruction with 2 mm thickness. The red circles depict the manually selected points that were used to trace the array. The yellow line shows the cross section perpendicular to this tracing line. B: Subsequently, these reconstructions generated a planar two-dimensional image with implanted array, UCR. The cochlear structure is therefore viewed from the side, with upper half being the scala vestibuli (SV) and lower part scala tympani (ST). The first basal segment is characterized by the cochlear hook.

Histology

The temporal bones with implanted arrays were extracted from cadaveric heads using a large diamond band saw (Exakt-Apparatebau, Norderstedt, Germany), and fixated with formaldehyde (2%). Subsequently, the temporal bones were carefully reduced to small cubes of approximately 1x1x1 cm^3 with a smaller diamond band saw (Exakt-Apparatebau, Norderstedt, Germany). We used the posterior tympanotomy site and the internal auditory canal as anatomical boundaries for the region of interest (i.e. cochlea with inserted array). The tissue blocks were dehydrated over two weeks in increasingly higher concentrations of ethanol, starting with 70% ethanol, and finishing with 99%. After dehydration the blocks were embedded for 24 h in butyl methacrylate. Within this period, the blocks were put for 1 h in a vacuum desiccator. After this 24 h period, the blocks were put in an oven at 35°C for two days for polymerization. Modiolar sections of 400 µm thickness were acquired from polymerized blocks using a saw microtome (RMS-16G3; REHA-tech engineering; The Netherlands). The sections were stained with methylene blue and glued with ultraviolet adhesive (Ber-Fix Klebstoffprodukte, Berlin, Germany) on microscope slides. Several non-implanted temporal bones (n=6) underwent the same procedures. This was done to rule out any structural trauma to cochlear structures arising from the histological procedures (i.e. histological artifacts).

Arrays embedded in butyl methacrylate can increase in size due to swelling of the silicone of the electrode array. Non-implanted arrays were cut in small pieces, and were embedded in butyl methacrylate for 24 h, showing under the microscope (magnification: 2.5x) a maximum increase 30%-40% in size. This increase was directly visible after embedding. The cochlear tissue was fixated with formaldehyde (first step in tissue processing) before embedding in butyl methacrylate, to make it unlikely that swelling induced secondary damage to cochlear structures such as osseous spiral lamina, stria vascularis and basilar membrane.

Assessment of scalar translocation

The scalar position of each electrode of the array was assessed both using histology and radiology. STL of an array was noted if at least one electrode was in either SV or in SM. Direct SV insertions were also rated as STL. Histology was used to validate the radiological STL scores.

To assess inter-observer reliability regarding both UCRs and MPRs, two assessors independently assessed occurrence of STL. Assessors were blinded for case number and treatment in order to allow for independent assessment. In addition, the case order was shuffled between the two types of images, to avoid further linkage between UCR and MPR images. A third assessor (SJ) decided the final outcome if the first two assessors disagreed. SJ assessed the histological sections for STL. To assess the inter-method agreement, the final outcomes of the third assessor were compared with histological outcomes. The histological sections were assessed without knowledge of the radiological outcomes of scalar array position.

Statistical analysis

STL scores based on histology were compared between the four groups using Fisher's exact test. Insertion depth differences were assessed with ANOVA test. Pearson's correlations were used to assess relationship between cochlear size and insertion depth angle. Inter-observer agreement was measured as percent agreement between the two assessors (agreement score divided by total number of observation). Similarly, the inter-method agreement between radiological and histological assessments was measured as percent agreement. The 32 observations for this study are sufficient to assess reliability of these agreements with kappa coefficient. This is according to $y=2a^2$ with a being 3 (3 outcomes possible: SV, ST or SM), resulting in need for at least 18 observations (Landis and Koch 1977).

4

To determine whether the kappa coefficient values significantly differed we used the following formula (Martens, Versnel, and Dejonckere 2007):

$$z = \frac{\kappa_1 - \kappa_2}{\sqrt{(\sigma_{\kappa 1}^2 - \sigma_{\kappa 2}^2)}}$$

κ_1 and κ_2 denote the kappa values and $\sigma_{\kappa 1}$ and $\sigma_{\kappa 2}$ denote the corresponding standard deviations. The P value was calculated two-sided on the assumption of z being a standardized normal distribution.

Results

Histological analysis of scalar translocation

Thirty-two samples were sectioned and used for assessment of STL. One sample was excluded, because the sections were not cut in the midmodiolar plane (i.e. no midmodiolar sections were available). Careful analysis comparing histology and radiology showed no signs of swelling influencing STL outcomes. The radiological images were acquired <1 h after implantation, and before histology. In Fig. 5, the array position of the midmodiolar histological sections and corresponding CT images were compared for a case with non-STL PM array (Fig. 5A/B), STL PM array (Fig. 5 C/D), non-STL LW array (Fig. 5E/F), and STL LW array (Fig. 5G/H). The positions in histological and radiological images were similar: array swelling due to histological processing induced no change of array position or severe trauma to cochlear structures, although minor not visible trauma due to swelling cannot be excluded.

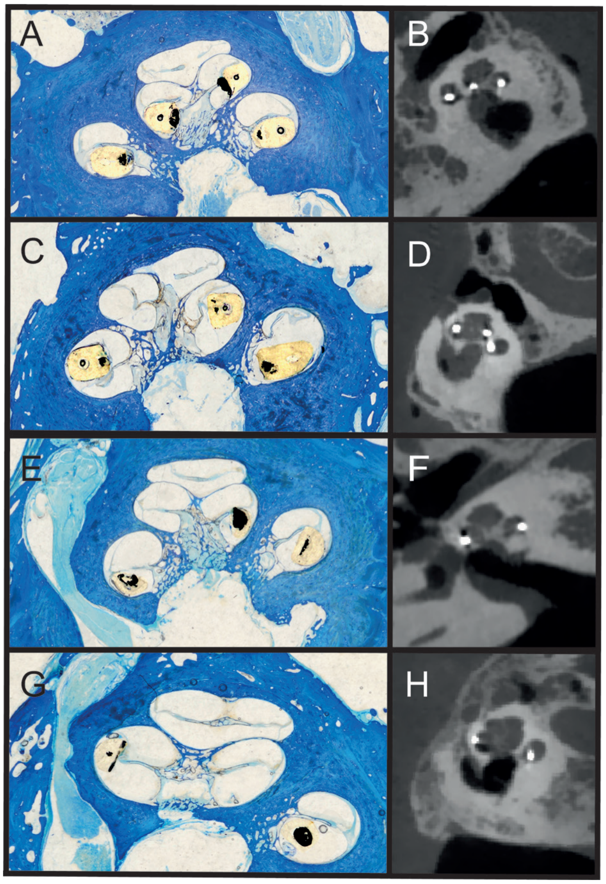

Figure 5. Histological modiolar plane sections and corresponding CT images were compared. Similar array positions were observed between histology and radiology. In A/B: non-STL PM array. In C/D: non-STL LW array. In E/F: STL PM array. In G/H: STL LW array. Note: the diameter of the array was increased 30-40% due to swelling of the silicon layer after processing with butyl methacrylate. Contrast of array was increased for visibility reasons.

4

In total, 12 out of 31 arrays (39%) were fully located in ST, and 19 out of 31 arrays (61%) had at least one electrode in either SV (n=12) or SM (n=7). Very similar outcomes were observed between two surgeons: 7/11 (63%) and 12/20 (60%) had at least one electrode in either SM or SV (i.e. STL) for respectively HT and SJ.

Fig. 6. shows the scalar position distribution for the 4 groups. The RW approach with PM array had a STL rate of 87% (7/8), CO approach with LW array 75% (6/8), RW approach with LW array 50% (4/8) and CO approach with PM array 29% (2/7). This is significant difference (p=0.016, Fisher's Exact test). The PM-CO group had the smallest STL rates, while the PM-RW group had the largest STL rates. Comparing these two PM groups shows a significant difference (p=0.041, Fisher's Exact test). Comparing the RW groups we also see a significant difference (p=0.01, Fisher's Exact test). No statistical differences were observed between array types with CO approach (i.e. LW-CO vs PM-CO) and between surgical approaches with LW array (i.e. RW-LW vs CO-LW).

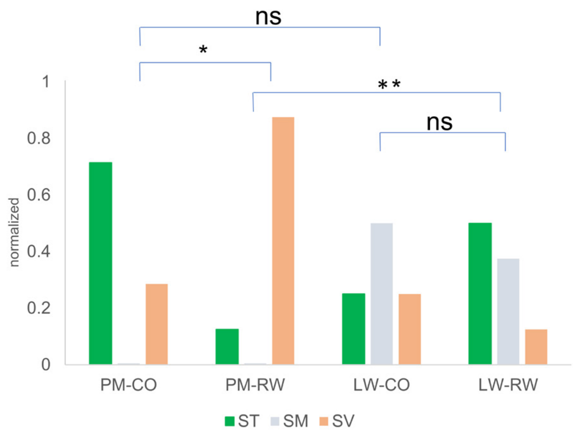

Figure 6. Group comparison of array scalar positioning. Scala media or scala vestibuli position is assigned if at least one electrode-contact was located in the respective compartment. *: p<0.05, **: p<0.01. ST: scala tympani; SM: scala media; SV; scala vestibuli.

The two types of arrays have different positions in ST (as schematically depicted in Fig. 1). On the one hand, the PM array is located medially towards Rosenthal's canal and beneath the osseous spiral lamina (Fig. 7A). On the other hand, the LW array is, as intended, located more laterally towards the stria vascularis (Fig. 7C). When STL occurred, the kind of inflicted trauma differed between LW and PM arrays. In PM arrays, if translocated, the array always fractured the osseous spiral lamina (Fig. 7B). In contrast, in LW arrays, SM was in several cases (n=7/10, 70%) severely crushed and pushed towards SV, including stria vascularis and basilar membrane trauma but without osseous spiral lamina fracture (Fig. 7D).

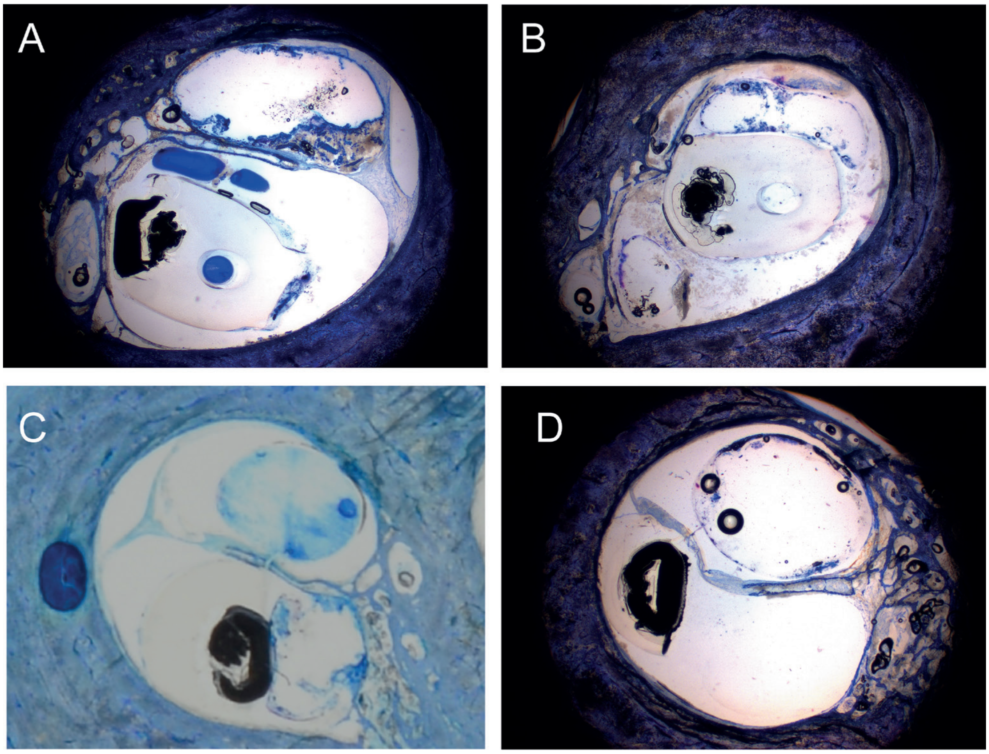

Figure 7. Histological modiolar plane sections. A: non-STL PM array. B: STL array with fracture of osseous spiral lamina. C non-STL LW array. D STL LW array to scala media with displacement of stria vascularis, basilar membrane and spiral ligament.

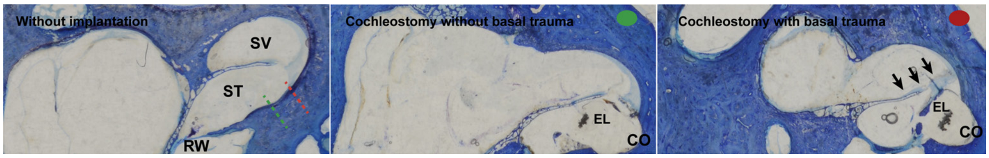

Figure 8. Histological modiolar plane sections. On the left a non-implanted basal turn of the cochlea. The green and red dotted lines depict angles of cochleostomy site of respectively the middle and right image. Green dotted line represents an antero-inferiorly placed cochleostomy, the red dotted line represents slight displacement of cochleostomy to anterior. In middle image, corresponding to the green line, no basal trauma is observed. In right image, corresponding to the red line, basal trauma is observed: displacement of stria vascularis, basilar membrane and osseous spiral lamina resulting in a crushed scala media compartment. RW: round window; ST: Scala tympani; SV: Scala vestibuli.

Cochleostomy burr hole that is too anteriorly placed can lead to trauma around the site of cochleostomy, thus in the very most basal part of the cochlea, as illustrated in Fig. 8. This trauma affects the osseous spiral lamina, and can result in direct insertion into SV, resulting in an unintended complete insertion of the array into SV. In total, of 16 insertions using the CO approach, four cases had such trauma. In two of these cases, the array was indeed completely located in SV, and in the other two cases the arrays were completely located in ST. In remainder of the CO cases no direct basal trauma around the CO site could be objectified.

Radiological analysis of scalar translocation

The 32 ears were imaged with CB-CT scanner. All scans were of sufficient quality, and thus included in this study. For STL analysis, two types of reformatted CB-CT scans were used, uncoiled cochlear reconstructions (UCR) and multiplanar reconstructions (MPR), for both of which four example cases are illustrated in Fig. 9, with the UCR on the left and the MPR on the right. In cases with the PM array a STL event could be easily identified as a jump of the array to SV (see Fig. 9C vs 9A). In contrast, LW arrays can be situated in an intermediate position at SM, and therefore show a more subtle scalar jump (see Fig. 9G vs 9E).

In the MPRs, the normal non-STL positions of LW vs PM arrays are clearly different (Fig. 9B vs 9F). Both these positions are in ST, with the PM array being closer to cochlear modiolus, and the LW array lying towards the lateral wall of the cochlea. Fig. 9D shows that an electrode of the PM array is located in the upper half of the cochlea, therefore located most likely in SV, clearly different from non-STL (Fig. 9B). In contrast, for LW arrays, it is more challenging to differentiate between STL and non-STL arrays (see Fig. 9H vs 9F). The array is located in both cases laterally and towards the SM, with a subtle difference showing the non-translocated array located lower than the translocated array.

Array fold-over occurred in 4 cases (4/32=12%), illustrated in Fig. 10 with for every case a UCR (left) and oblique coronal plane image of the cochlea (right). In three cases a tip fold-over had occurred with a PM array (A-C). Two tip fold-overs occurred at similar position (see Fig. 10 A/B), approximately at insertion depth of 180°, while the other tip fold-over occurred deeper at around 270° (Fig. 10C). In the first two cases tip fold-over had occurred most likely because of a too shallow insertion of the array with stylet. After removing the stylet, the array bumped against the modiolar wall, rather than following the curvature of the cochlear duct. For the third case, with a deeper insertion, it seems that the electrode contacts were slightly tilted away from

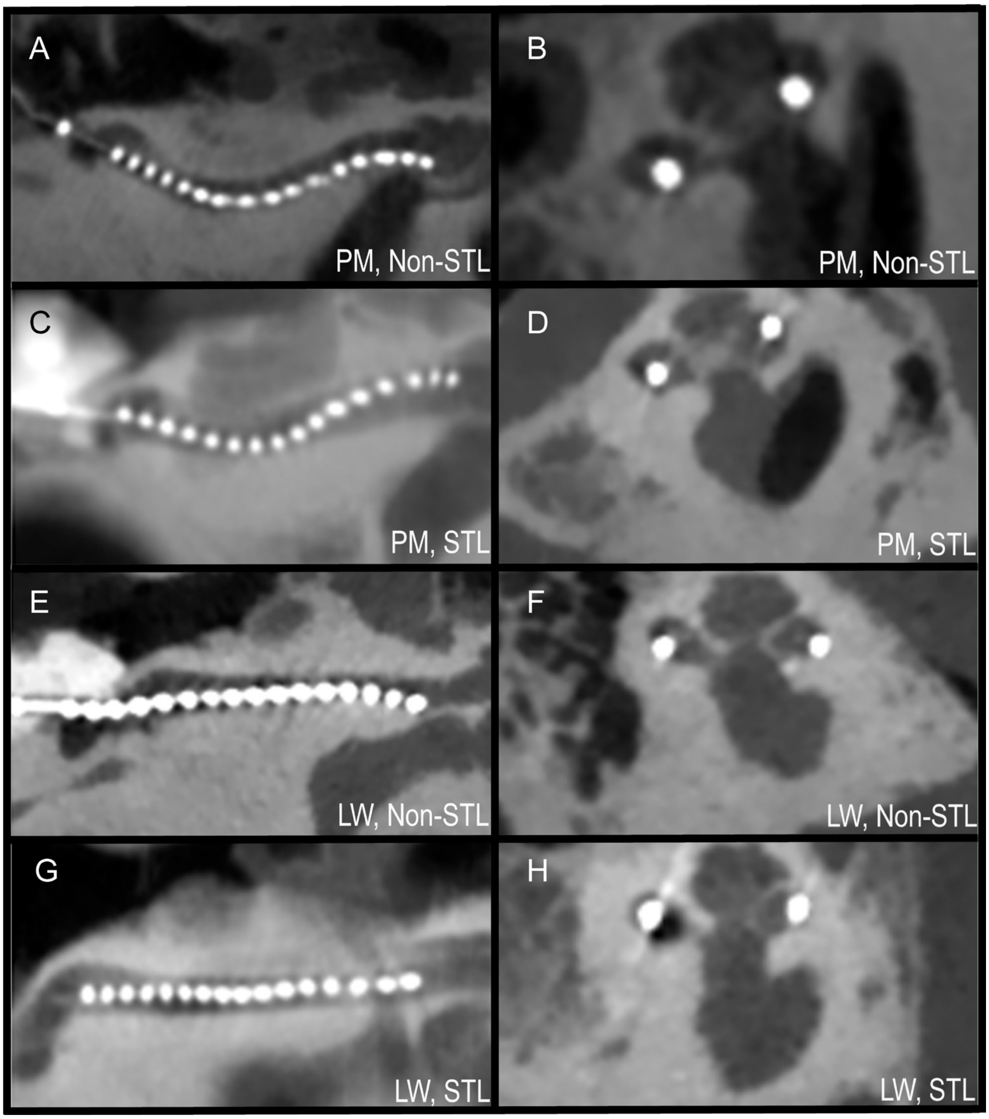

Figure 9. Assessment examples between uncoiled cochlear reconstructions (on the left) and conventional multiplanar reconstructions (on the right). In 9A the PM array is neatly following the scala tympani, which is located in lower half of the uncoiled cochlea. In 9C, however, clear kinking of the PM array results in STL from scala tympani to scala vestibuli. This difference of PM non-STL vs STL is also seen in conventional reconstructions in 6B/D, with the array, the white dots, located in STL case of 9D more towards the upper half of the cochlea than in 6B. In 6E the LW array follows the scala tympani without interruption, in contrast in 6G, the LW array shows an subtle, but still clear kink towards scala vestibuli (i.e., STL). The different position of the LW array is difficult to observe in conventional reconstructions, see 9F vs 9H.

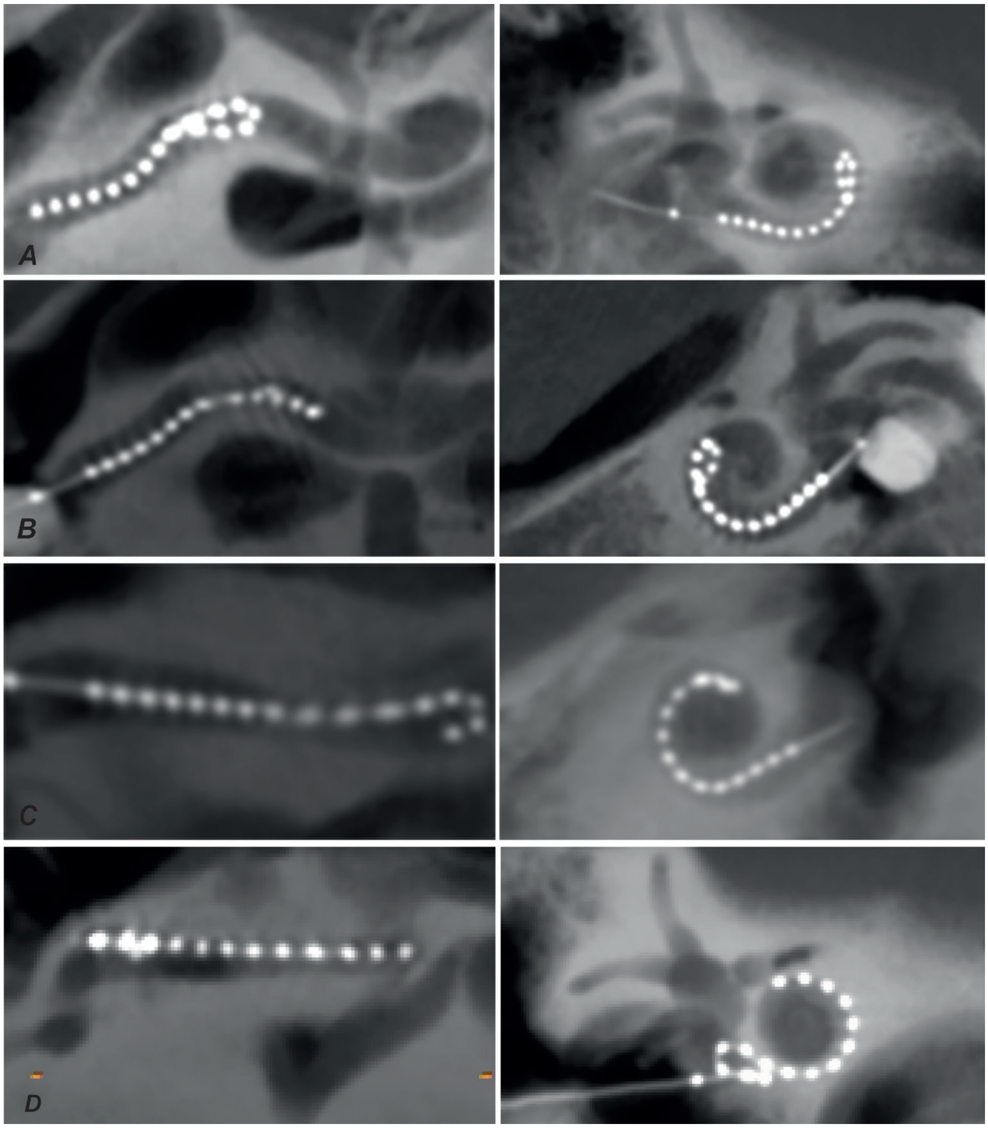

Figure 10. Four fold-overs were observed, depicted on the left with uncoiled cochlear reconstructions and on the right with conventional reconstructions. In Fig. 10A-C a PM array was used. Two tip fold-overs occurred at similar position (see Fig. 10 A/B), approximately at insertion depth of 180°, while the other tip fold-over occurred deeper at around 270° (Fig. 10C). Finally, in Fig.10D a case with a basal fold-over had occurred using the LW array. In both reconstruction techniques the fold-overs were clearly seen. PM; perimodiolar. LW; lateral wall.

the modiolar wall. Finally, one case with a LW array had a fold-over in the basal end of the cochlea (Fig. 10D). In this case, the surgeon continued array insertion to reach full insertion even though resistance occurred early during insertion. This was an exception: normally array insertion is not continued when resistance is encountered, however in this case the resistance occurred at the basal turn (i.e., very shallow insertion).

Inter-observer and inter-method agreement

Table 1 (left side) shows the inter-observer agreement for both UCRs and MPRs. The agreement between the two assessors for UCR images was very high: 91%, 29 out of 32, had the same score (κ=0.85). In 2 out of 3 cases the two assessors disagreed whether it was SV or SM, thus they agreed on STL, resulting in an agreement score of 97% for STL. The assessors were not in agreement regarding occurrence of STL for just one case, which had a tip fold-over according to histology. The assessors were in agreement when using MPRs for 22 out of 32 cases, resulting in an inter-observer agreement score of 69% (κ=0.45). Two of the 10 cases of disagreement had tip fold-overs. For the remaining cases, the assessors mostly disagreed regarding LW arrays (6 out of 8, 75%). The two κ values differed significantly (z value 2.01; p=0.04).

Table 1. Scalar translocation event evaluation after cochlear implantation (n=32)⁑

Inter-observer agreement UCR*: reviewer 1 vs. reviewer 2		Inter-observer agreement MPR#: reviewer 1 vs. reviewer 2		Inter-method agreement: CB-CT vs Histology			
				UCR† vs Histology§		MPR† vs Histology§	
Observed agreement	κ ¶	Observed agreement	κ	Observed agreement	κ	Observed agreement	κ
91%	0.85	69%	0.45	94%	0.89	74%	0.57

⁑: scalar translocation event: minimal of one electrode-contact in scala vestibuli or scala media, including direct scala vestibuli insertions
*: UCR: uncoiled cochlear reconstruction CB-CT images
#: MPR: axial and sagittal multiplanar reconstructions
†: if observations by reviewer 1 and 2 were different, consensus was achieved by final decision of reviewer 3.
§: based on observations of reviewer 3
¶: magnitude of kappa coefficient: <0: poor, 0.00-0.20 = slight, 0.21-0.40 = fair,
0.41-0.60 = substantial, 0.81-1.00 = excellent agreement.

Table 1 (right side) also shows inter-method agreements between radiological assessment options and histology. The inter-method agreement between UCR and histology was very high: 94% (κ=0.89). In two cases the histology did not match the UCR outcome. In one of these cases a tip fold-over had occurred, which was according to histology a non-STL insertion and was rated in UCR by the assessors as STL in SV. The inter-method agreement between conventional MPR assessment and histology was lower: 74% (κ=0.57), almost reaching a statistically significant difference (z value -1.81; p=0.06). In half of the wrongly assessed cases (4 out of 8), differentiating between SM and SV position proved to be difficult. In addition, 3 STs proved to be false positive (i.e. translocated according to histology), and one STL case was false negative (non-translocated).

Insertion depth

Insertion depth angles were similar for the four groups when assessing all implanted arrays, with group means ranging from 322 to 374 degrees (Table 2). Three more analyses were performed (see Table 2). 1) Excluding the 4 fold-over cases, array type and surgical approach had significant effect on insertion depth (ANOVA, p=0.01 and p=0.046 respectively). PM arrays reached higher insertion depths than LW arrays (mean 392° vs 342°), and CO approach reached higher depths than RW approach (mean 387° vs 348°). 2) In addition, 6 arrays had electrodes outside the cochlea, all LW arrays, ranging from 11 to 15 inserted electrode-contacts (from 16 electrode-contacts in total). Excluding these not fully implanted arrays still shows a main effect of array type (ANOVA, p=0.01), favoring PM arrays with higher insertion depths (mean 402° vs 370°). 3) Furthermore, according to the manufacturer, not only the functional 16 electrodes-contacts should be inside the cochlea, but also the stop non-functional electrode-contact should be at RW or CO site. For 11 arrays, all electrodes were inside the cochlea, however, the stop electrode was 1-2 mm outside RW or CO, resulting in a total of 11 full insertions according to the manufacturer. No effect of array type or surgical approach on insertion depth was seen in this last analysis.

Regarding these 11 fully implanted arrays we found that insertion depth was inversely correlated with distance A, which reflects the size of the cochlea (R^2 = 0.39, p=0.04), i.e. a small cochlea leads to a larger insertion depth angle (Fig. 11). Insertion depth for all 22 arrays that had all 16 electrode-contacts inside the cochlea (see aforementioned analysis 2) does not change when these arrays translocate to SV (unpaired t-test, p=0.11; Fig. 12).

Table 2. Insertion depth angles

Group	Mean PM-CO (n)	Mean PM-RW (n)	Mean LW-CO (n)	Mean LW-RW (n)	Main effect approach	Main effect array	Interac-tion
All	374 (8)	357 (8)	354 (8)	322 (8)	p=0.31	p=0.25	p=0.74
1) Minus TFs	410 (6)	375 (7)	365 (7)	322 (8)	**p=0.046**	**p=0.01**	p=0.83
2) Minus TFs and <16E inserted	410 (6)	395 (6)	383 (5)	357 (5)	p=0.09	**p=0.01**	p=0.63
3) Full inser-tion (accord-ing to manu-facturer)	412 (3)	398 (4)	407 (3)	372 (1)	p=0.29	p=0.46	p=0.92

TF: tip fold-over; PM: perimodiolar; LW: lateral wall; CO: cochleostomy; RW: round window; E: electrode-contacts.

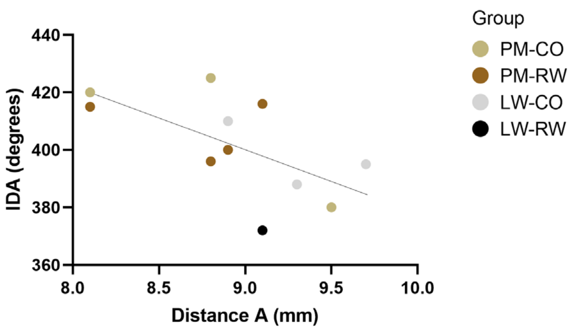

Figure 11. The insertion depth angles and corresponding cochlear distance A are plotted of the 11 full insertions according to the manufactures guidelines. An inverse correlation is observed between insertion depth angle and distance A (R2 = 0.39, p<0.05). Distance A is an indirect measure of cochlear duct length. IDA: insertion depth angle; PM: perimodiolar; LW:lateral wall; CO: cochleostomy; RW: round window.

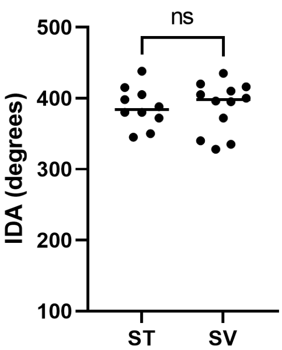

Figure 12. Insertion depth angle is compared between fully scala tympani located arrays and arrays with at least one electrode in scala vestibuli. All insertion depth angles were plotted of arrays with the stop electrode within 2 mm distance from the CO or RW site (n=21). Median of both groups are shown. IDA: insertion depth angle. CO: cochleostomy; RW: round window.

Discussion

We have investigated cochlear implantation in cochleas of fresh frozen cadaveric heads comparing the two types of arrays (LW and PM), and using the two commonly used surgical approaches (CO and RW). We showed that STL, considered as severe cochlear trauma, is frequently occurring and affected by choice of array and surgical approach. In addition, assessment of LW array positioning by conventional CT analysis appeared to be difficult. An adaptation of a reconstruction CT technique using curved reconstructions (Achenbach et al. 1998; Stimpel et al. 2018) showed superior results, correlating significantly better with histological outcomes than the conventional technique. This technique, which is readily available in clinical medical care, might be useful for radiological assessment of pathologies concerning the cochlea and vestibular organ, and other pathologies involving complex shaped bony tube-shaped structures (e.g. facial nerve canal integrity assessment in human temporal bone trauma)(Kurihara et al. 2020).

Our study showed a mean STL occurrence rate of 61%, which is higher than shown in a review study with both temporal bones and CI recipients (mean of 18% trauma; Hoskison, Mitchell, and Coulson 2017). This discrepancy might be due to methodological differences. In this study, implantation was performed solely in human cadaveric heads, not in vivo, which might affect STL outcomes in two ways. Use of human cadaveric heads allows for histological assessment, and therefore more thorough investigation of scalar position (De Seta et al. 2017). In addition, implantation in human cadaveric heads is more prone to friction and resistance during insertion as dead tissue is less flexible, leading to higher insertion forces (De Seta et al. 2017; Schuster, Kratchman, and Labadie 2015). Both these factors might explain higher STL rates found in our study than in other studies. Another important factor is difficulty in assessing trauma when LW arrays are used. The LW arrays lie laterally in the scala tympani, and are enveloped by the basilar membrane and spiral ligament. In our study displacement of these structures, albeit partially to scala media, was seen as STL. However, in literature these cases are not always seen as STL, e.g. one study (Rivas et al. 2019) judges pushing of basilar membrane as minimal insertion trauma (see also (De Seta et al. 2016; Sipari et al. 2018; Du et al. 2021)). The complex anatomy at LW array site might also have led to underestimation of LW array STLs in previous studies, which in most cases relied solely on conventional MPRs for STL diagnosis. The STL rate of our study is more in line with previous studies when accounting for these differences, i.e. without SM cases: our study had STL rate of 39% vs 42% in another similar histological temporal bone study (De Seta et al. 2017), and 24% STL rate in review study with live CI recipients (Jwair et al. 2021).

We showed that if opting for RW approach more STLs were observed with PM arrays than LW arrays. A recent systematic review showed similar results with PM arrays in general (i.e. including other brands) translocating more often than LW arrays when using a RW approach (41% vs 7%) (Jwair et al. 2021). Considering also that PM-RW combination leads to more STLs than PM-CO, these findings point to an interaction effect between RW and PM arrays. It is likely that RW and PM array combination leads to more insertion forces, resulting in severe trauma (Kaufmann et al. 2020; De Seta et al. 2017). Another study also showed more STLs with PM-RW combination in temporal bones using an older generation PM array (Jeyakumar, Pena, and Brickman 2014). Several factors might be responsible. Firstly, the cochlear hook region may lead to more resistance during insertion (Avci et al. 2017; Rask-Andersen et al. 2012). The cochlear hook region is directly adjacent to RW, and has a complex anatomical shape with varying width and height along its course (Avci et al. 2017; Rask-Andersen et al. 2012). The cochlear hook region can be an issue with RW entry, while a CO approach uses a different insertion angle that bypasses largely the cochlear hook region with a more straight insertion approach (Richard et al. 2012). Another factor is the size and shape of the RW membrane, which can vary greatly in roundness with sizes ranging from 0.9 to 2.1 mm diameter for the shortest diagonal (Atturo, Barbara, and Rask-Andersen 2014; Rask-Andersen et al. 2012). The cross section of the largest basal part of the PM and LW arrays of Advanced Bionics, used in this study, is approximately the same, around 0.49 mm2, with PM arrays having square cross sections and LW arrays having larger flat side and smaller rounded side. The largest part of these cross sections is smaller than the smallest dimensions of the RW membrane (~0.7 mm versus 0.9 mm), and therefore these arrays should fit through the RW membrane. In addition, often the crista fenestra, a bony crest structure within the RW niche, can form an obstacle that further decreases the surface area of the RW membrane (Angeli et al. 2017). The different shape and varying size of the RW membrane in conjunction with crista fenestrae can be more an issue with the rigid more square cross-sectional shaped PM array that requires a stylet for insertion. Therefore, PM arrays should be used in conjunction with a CO approach. In our study indeed less STLs were observed with PM-CO approach. However, this is contradicted by a study with CI recipients that showed RW approach leading to less STLs than CO approach when opting for PM arrays (Wanna et al. 2014). The discrepancy with our study could lie in that they investigated different type of PM arrays within their study. In addition, their results were based solely on imaging, making it harder to correctly assess array position. It is also worth considering that studies have shown surgeons often preferring different CO sites (Iseli, Adunka, and Buchman 2014). In our study the CO was antero-inferiorly placed relative to RW membrane, in order to avoid the osseous spiral lamina during array insertion and to achieve ST placement. However, if the CO is placed entirely anteriorly, the osseous spiral lamina can form an obstacle for electrode insertion, resulting in an SV translocation. In our study, we have shown that even a small displacement of the CO site can result in trauma to the osseous spiral lamina.

Previous studies showed that shorter arrays lead to better hearing preservation, at least on the short term, and argued that less mechanical trauma occurred with these arrays (Suhling et al. 2016; Causon, Verschuur, and Newman 2015). However, some studies showed that deeper insertion depth is correlated with better speech perception outcomes (Finley et al. 2008; O'Connell et al. 2017; Canfarotta et al. 2021). In contrast, other studies, showed no clear effect of insertion depth on speech perception (van der Jagt et al. 2016; Wanna et al. 2015). Both insertion depth and speech perception are influenced by a myriad of factors, making it difficult to investigate this topic accurately, as shown by a relatively recent review with inconclusive results on this subject (Heutink et al. 2019). In this study, comparable insertion depths for CO and RW approach were found. This is expected as the CO site is very close (<1 mm) to the RW membrane. Regarding array type we also found comparable insertion depths for the fully implanted arrays, and in line with another study using the same arrays (Lenarz et al. 2020). In addition, we observed that in general, LW arrays were more often not fully inserted, even though full insertion was intended for all implantations. This might indicate that more friction occurred with LW arrays, leading to more detrimental insertion forces. The reason for more friction with LW arrays is unclear, as it might be inherent to the design, or to differences of resistances between modiolar and lateral wall regions. Insertion depth, however, had in general no effect on STL events in our study. A large study of 220 implants in patients showed similar results with no effect of insertion depth on STLs (O'Connell et al. 2016). However, an older study (Adunka and Kiefer 2006), and a more recent study (Zelener et al. 2020) showed that deeper insertions are associated with insertion trauma in temporal bones and patients. Although that latter study (Zelener et al. 2020) is relatively recent, an older generation PM model (Helix of Advanced Bionics) was investigated. Comparing those studies with our study, which uses the latest PM array (Midscala), is therefore somewhat limited. Importantly, in our study, tip fold-overs were only observed for PM arrays, which were always accompanied with STL. This agrees with the general observation that tip fold-overs mainly occur with PM arrays (Jwair et al. 2021), although, the fold-over rate of CI recipients is reported lower than what we found (i.e. ~2% vs ~18%). The difference in rate might be due to several reasons. We used the advance-off-stylet method instead of the insertion tool for inserting PM arrays, however currently no difference between these techniques regarding tip fold-over have been reported. Another factor, related also to the insertion technique, is cochlear implantation experience. Indeed, a previous study has shown that increased experience can lead to less insertion trauma (Aschendorff et al. 2011), although that is not always the case (Kant et al. 2022). We consider a more likely reason that in prior clinical studies possible fold-overs might have been overlooked. In our study, in one case, as described, the array tip fold-over can be easily missed if not adequately assessed with both axial and coronal views. So even with adequate type of CT, with high resolution and less metal scattering artefacts, a tip fold-over can be overlooked.

Studying intra-cochlear structures in CI patients remains very difficult due to technical limitations of CT-scanners. Metallic 'bloom' artifacts can obscure intra-cochlear structures, and CT resolution is still too low to adequately visualize intra-cochlear structures (Barrett and Keat 2004). In the current study whole cadaveric heads were used for scanning, which limits these artefacts, which are more present in isolated temporal bones (Guldner et al. 2012). Another advantage of scanning the whole cadaveric head is that our images are more similar to images of live patients, and therefore our results are translational to the clinical care. Still, because of the technical limitations, in vivo assessment of array position in the cochlea can only be based on approximate estimates of cochlear structure sites. A study using curved multiplanar reconstructions found similar to our study high interobserver agreement score (93%) for electrode position at 180° (De Seta et al. 2016). However, a 72% agreement score was found between radiology and histological outcomes. The images in that study had considerable metallic artefacts probably due to scanning isolated temporal bones. This is possibly the reason for the discrepancy with our study that has a higher histological agreement score (94%).

Some studies (Teymouri et al. 2011; Wanna et al. 2011) have focused on other methods to estimate the location of intra-cochlear structures, such as basilar membrane, using both pre- and postoperative images. Computer modeling has been used to estimate basilar membrane position (Wanna et al. 2011). The model was created using high resolution micro CT images that can depict intra-cochlear structures in cadaveric temporal bones. No data on observer agreement was reported. Another research group used different preoperative micro-CT atlases to find the most fitting atlas for the patient's cochlea (Teymouri et al. 2011). These atlases are then used as a template for the postoperative CT scans to determine if a translocation had occurred. They found 97% agreement between assessors, and 95% agreement with histology, however, this was based on a small sample size of 9 cadaveric temporal bones. These methods are, in contrast to our methods, not readily applicable in every medical center and might be difficult to implement in a large population with great temporal bone anatomy variability. The CB-CT images used in the present study were relative fast and straightforwardly reconstructed, without needing predetermined atlases, using only the postoperative scans. Although the osseous spiral lamina and basilar membrane are not visible on CB-CT scans (nor on conventional CT scanners), highly accurate assessment of scalar position is possible for both type of arrays.

The benefits of using methyl acrylates are short processing time, high resolution and clear histological sections and low costs, especially when compared to more laborious methods using decalcifying techniques (Nageris and Gazit 1995). Although histological processing with methacrylates has been used for many similar studies investigating histological trauma (Gstoettner et al. 1999; Adunka et al. 2004; Adunka et al. 2005; Teymouri et al. 2011; Nageris and Gazit 1995; De Seta et al. 2016; De Seta et al. 2017), it has its downsides. Methacrylates lead to swelling of the silicone layer of the array, possibly causing (micro)trauma unrelated to cochlear implantation. In our study it was therefore not possible to use grading trauma scales such as the Eshraghi scale (Eshraghi, Yang, and Balkany 2003). Macroscopic severe trauma, such as STL, is very unlikely to be related to array swelling. The tissue was fixated with formaldehyde before histological processing, and larger structures such as osseous spiral lamina, which is often fractured in cases with STL, are unlikely to be affected by silicone swelling. A previous study, reviewing 21 papers, showed that STL from ST to SV is observed in 85% of the cases with trauma present (Hoskison, Mitchell, and Coulson 2017). In other words, isolated trauma that is less severe than STL is in the minority of CI cases present. Of course, there might be a bias: severe trauma is easier to detect than minor trauma. Still, it is questionable whether a more in depth trauma grading scale is necessary to judge trauma severity of individual CI cases.

Conclusion

We show that the choice for surgical approach to the cochlea should be based on the planned use of type of array, and the other way round: the choice of array type should be based on the surgical approach. Lateral wall arrays were preferred when a round window approach was used, and cochleostomy approach was preferred when a perimodiolar array was used. In addition, we found that conventional CT reconstruction technique can lead to misinterpretation of lateral wall array position. This has probably led to underestimation of lateral wall array translocations in literature. We show for the first time that a relative easy to implement CT reconstruction method can be used in the clinic to accurately assess translocations for both type of arrays, and is herein superior to conventional CT reconstruction techniques. Radiological assessment of pathologies involving the inner ear, and pathologies involving complex shaped bony tubular structures, might also benefit from this technique.

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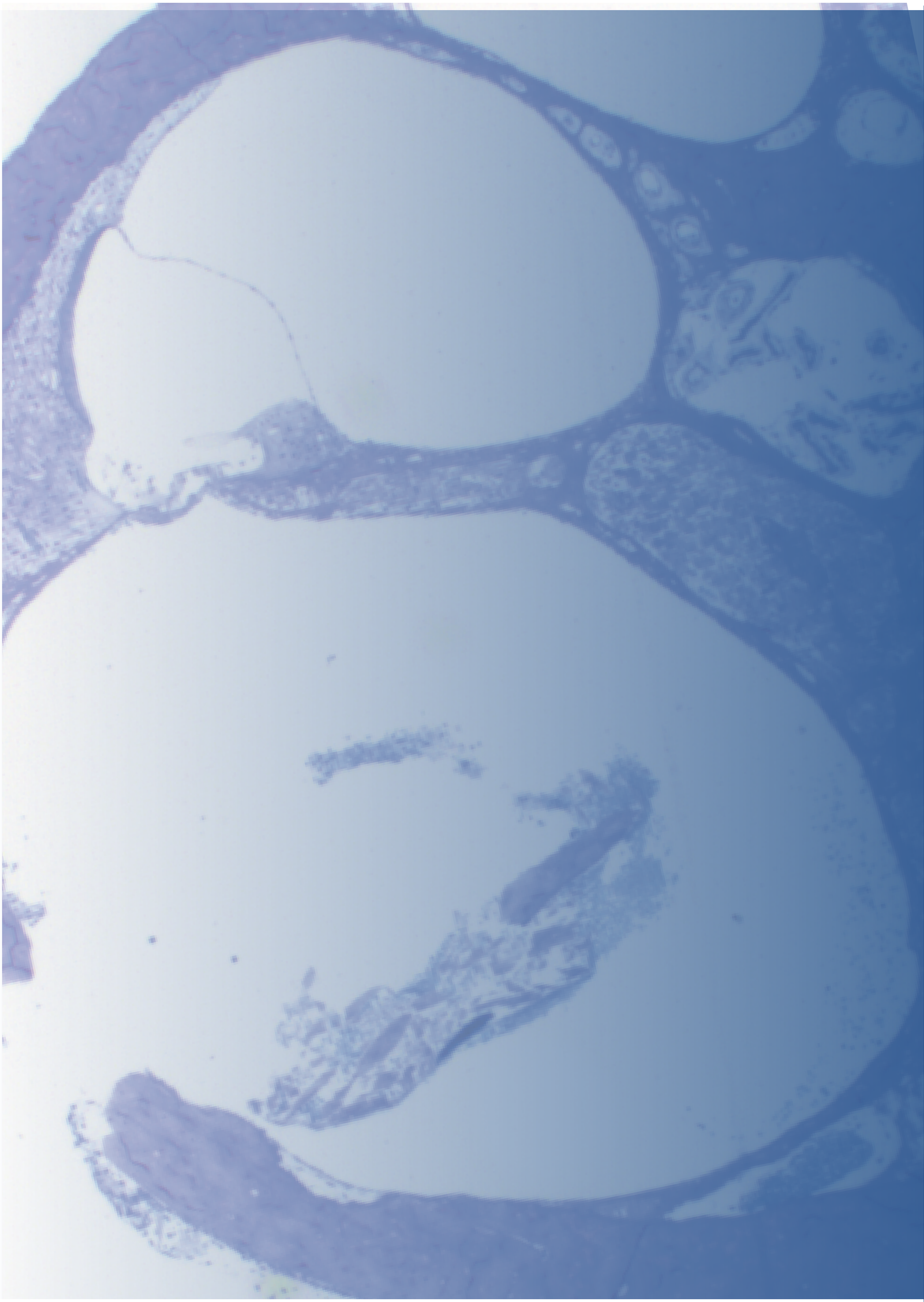

Chapter 5

Radiological and surgical aspects of round window visibility during cochlear implantation:

a retrospective analysis

Saad Jwair, Job van Eijden, Esther Blijleven, Jan Willem Dankbaar,
Hans G.X.M Thomeer

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Abstract

Objectives

The round window (RW) approach has become the most preferred option for cochlear implant (CI) insertion, however, sometimes it may not be possible due to the (in) visibility of the RW membrane. The feasibility of the RW approach and radiological markers of RW membrane visibility were assessed.

Methods

This study retrospectively analysed the operative reports and preoperative high resolution axial computed tomography (CT) scans of a CI recipients cohort between January 2015 to May 2020. The main outcomes were feasibility of the RW insertion and occurrence of intraoperative events.

Results

The operative reports showed that RW insertion was feasible in 151 out of 153 patients. The most frequent serious intraoperative events were lesions of the chorda tympani nerve (CTN) (8%), posterior canal wall (8%) and fallopian canal (6%). In patients with an intraoperatively difficult view of the RW membrane, the largest distance from the facial to chorda tympani nerve (FN-CTN) on the axial CT scan was considerably smaller than in cases with an easy view of RW intraoperatively (1.5 mm vs 2.3 mm). In addition, a 'prediction' line towards the anterolateral side of the RWM was found to be more prevalent in these patients' CT scans (sensitivity 81%, specificity 63%).

Conclusion

The round window approach is feasible in almost all patients undergoing CI surgery in our cohort. However, the CTN had to be lesioned in some patients. Difficult cases had a smaller FN-CTN distance, and a more anterior position of the FN relative to the RW. These radiological markers can be used to plan a safer insertion approach.

Introduction

Cochlear implants (CIs) provide a solution for patients of all ages with severely impaired hearing. The classical surgical method of implantation is performed by way of a retro-auricular approach with a mastoidectomy-facial recess technique, followed by a CI insertion via either the round window membrane (RWM) or an anteroinferiorly (relative to the RWM) placed cochleostomy (Adunka et al., 2010; Mangus et al., 2012). This surgical method is standard care in most CI centers worldwide (Gazibegovic & Bero, 2017). The RW approach can be preferred over a cochleostomy because it might be less traumatic (Mangus et al., 2012; Richard et al., 2012).

Although the RW approach is widely adopted, only few studies reported its feasibility and complications (Gazibegovic & Bero, 2017; Gudis et al., 2012). The RW approach is not always possible, presumably because of the sometimes difficult visualisation of the RWM (Adunka et al., 2010; Gazibegovic & Bero, 2017; Leong et al., 2013). Intraoperatively, trying to improve visibility of the RWM can lead to an increased chance of intentional or unintentional damage to important structures like the chorda tympani nerve (CTN), the fallopian canal, posterior canal wall or tympanic membrane. Although this damage does not necessarily lead to postoperative complications, it is preferred to leave these structures intact (Hansen et al., 2010). To avoid these situations, it might be beneficial to assess the RWM visibility before surgery.

In current medical practice RWM visibility is not assessed beforehand. A preoperative high resolution computed tomography (HRCT) is used to assess medical contraindications for a RW approach (e.g. otosclerosis or cochlear malformations) (Vaid & Vaid, 2014). In addition, surgeons use this scan to be adequately prepared for surgery, by assessing important surgical landmarks such as the sigmoid sinus, incus and lateral semicircular canal (Harnsberger et al., 1987; Vaid & Vaid, 2014). Previous studies have shown that these scans can also be used for investigation of the RWM visibility (Chen et al., 2019; Karkas et al., 2018; Kashio et al., 2015; Park et al., 2015).

For this study we outlined two goals regarding cochlear implantation surgery: 1) to identify the feasibility of the RW approach in our adult CI recipients population, and 2) to assess the prevalence, consequences and radiological markers of intraoperative difficult RWM visibility.

Materials and Methods

Study design

The operative reports and preoperative HRCT scans of a cohort of adult patients that received a CI at our tertiary referral centre between January 2015 and March 2020 were retrospectively examined. These patients were consecutively operated by one surgeon. The data were collected from the patient files. The eligibility criteria were as follows: 1. age ≥ 18 years, 2. no inner ear deformities, 3. primary cochlear implantation, 4. no prior mastoid or middle ear surgery on the implanted side, 5. no signs of (chronic) otomastoiditis, 6. patent RWM and scala tympani (ST) of implanted side on preoperative HRCT scan. The first five items were assessed with the operative and medical report data. If discussion on the eligibility criteria was encountered, consensus was obtained between the authors.

Operative report

The operative report of every patient of the database was evaluated by two investigators (SJ and JvE). The following variables were extracted: age, gender, medical diagnosis, side of implantation, type of middle ear and insertion approach, mastoid pneumatisation, view of RWM (easy or difficult), facial recess size (normal or small), other notable issues (e.g. overhanging posterior wall or bulging jugular bulb), and lastly intraoperative events (e.g. lesions of the CTN, posterior wall, facial nerve (FN) and fallopian canal). In addition, the postoperative medical reports of cases with an intraoperative event involving the FN or CTN were reviewed for related complaints (e.g. tongue sensitization or face paralysis).

High resolution CT scan

High resolution temporal bone images (axial and coronal plane reconstructions) with a slice thickness of 1.0mm were obtained using a Siemens-force CT scanner at 120kV and 150mAs or a Philips scanner at 120kV 300mAs. Two investigators (SJ and JvE) analysed and gathered the HRCT scans. These investigators were not involved in any of the surgeries, and were blinded for the operative findings during the analysis of the HRCT scans. Beforehand, the investigators were trained by an ENT surgeon (HT) and neuroradiologist (JWD) in the analysis of the mastoid, with an extra focus on the course of the FN and CTN.

The CTN was identified by three points:

1. Origin of the FN at mastoid tip
2. Mastoidal course until tympanic annulus (bony rim of the tympanic membrane)

3. Re-appearing again at the anterior wall of the middle ear cavity and entering thepetrotympanic fissure.

The authors drew a line between the FN and the CTN on the axial HRCT scan, see Figure 1. The measurement of the FN-CTN distance was defined by the shortest distance (inner margin) between two points on the axial HRCT reconstructions with the posterior canal wall/mastoid and the middle ear space within the same plane:

1. The CTN, as close as possible to its entry in the middle ear space, but still in the mastoid.
2. FN, at the point of the second genu.

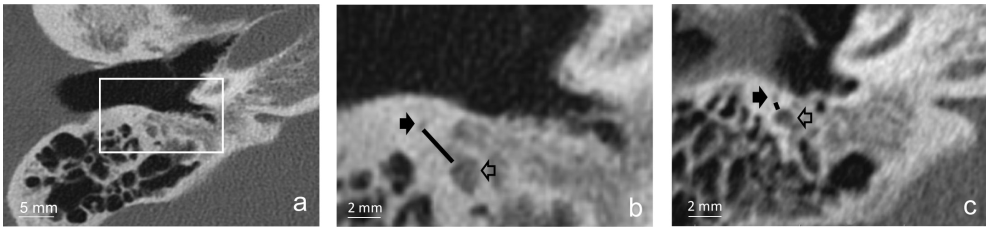

Figure1.
a Overview of the preoperative axial high resolution CT scan of the right temporal bone. **b** Magnification (2.5x) of the same axial high resolution CT scan of the right temporal bone. Black arrow depicts the chorda tympani nerve (CTN), and the unfilled arrow the facial nerve (FN). The yellow line between these two nerves is the FN-CTN distance. This case had a FN-CTN distance of 2.9 mm. **c** Axial high resolution CT scan of the right temporal bone of another patient. This case had a small FN-CTN distance of 0.6 mm.

The second last axial HRCT section of the mastoid segment of the CTN, before entering the middle ear space, proved to be the most optimal section to measure the FN-CTN distance. This measurement enabled us to confidently state the near maximal distance of the facial recess opening between the FN and CTN.

The authors established a second measurement, partly based on a previous study (Kashio et al., 2015), that indicated the anterior position of the FN relative to the RWM. A prediction line was drawn from the anterior part of the mastoid course of the FN on the axial planes, towards the lower side of the basal turn of the cochlea. Subsequently, the intersection point between the RWM and the prediction line is categorized in being either anterolateral or posteromedial, see Figure 2. All intersection points below the middle of the RWM were classified as posteromedial, and the intersection points above this middle were classified as anterolateral.

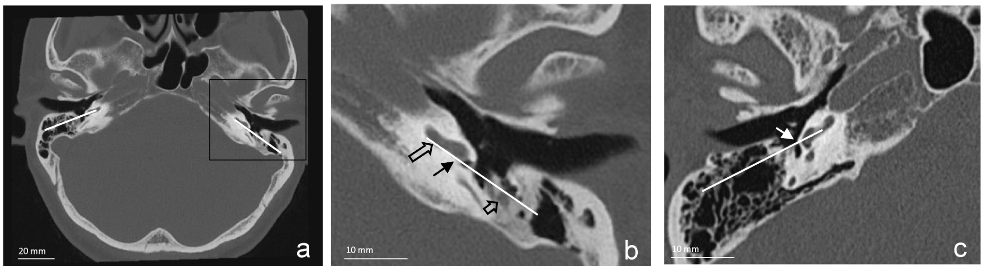

Figure 2.

a Prediction line drawn on the axial high resolution scan of both temporal bones.

b Close up view of the prediction line. The prediction line was drawn on the preoperative axial high resolution CT scans between the anterolateral mastoid facial nerve and the lower side of the basal turn of the cochlea. The intersection point lies on the posteromedial side of the round window membrane in this example. Large unfilled arrow = lower side of basal turn, filled black arrow = posteromedial intersection point, small unfilled arrow = facial nerve.

c Example of an intersection point on the anterolateral side of the RWM. White arrow = anterolateral intersection point.

Analysis

Based on the operative reports we established whether the intended RWM insertion was successful. The operative reports were also used to assess the intraoperative visibility of the RWM. Two groups were identified: cases with normal identification of the RWM and cases with difficult visibility of the RWM. Cases with difficult RW niche visibility were also included in the latter group. After excluding all cases with inadequate scans we compared the radiological measurements between the normal and difficult cases. For the second radiological measurement (i.e. prediction line) 20 cases of the normal group, at random, were selected for the comparison analysis. All radiological analyses were done blinded for the operative report and outcomes.

Results

The patient cohort, January 2015 – May 2020, was screened for the in- and exclusion criteria (see Figure 3). After applying these criteria, 153 cases were included for the operative report analysis. Regarding the HRCT analyses, we had to exclude 33 from 153 cases, 30 from the normal group and 3 from the difficult group, because in those cases the only available scan was of a low-quality CT with inadequate image resolution or with severe motion artefacts. In total, 120 HRCTs were analysed.

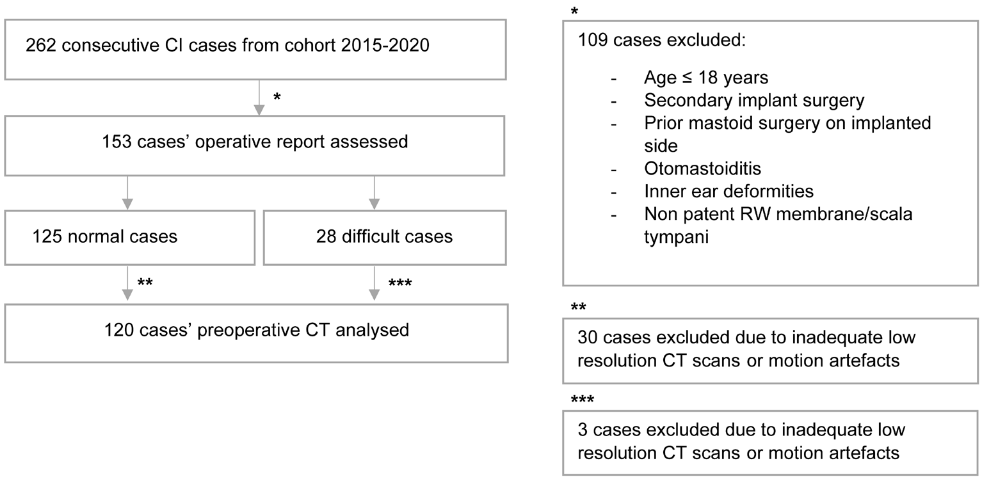

Figure 3. Flow chart of the in- and excluded cases for both the operative report and preoperative computed tomography scan analyses.

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Operative report

In 151 out of 153 patients (99%) a RWM insertion was realized and successful, the other two patients received a cochleostomy. An example of the intraoperative view is depicted in Figure 4. That example would classify as a normal case, as the surgeon is able to identify the RWM with intact anatomical borders (i.e. FN, CTN, incus buttress and posterior canal wall). The intraoperative findings were evenly spread over time (during the included period of investigation) and side of implantation, indicating no relationship of these findings with either of these factors. The patient characteristics and intraoperative events are summarized in Table 1.

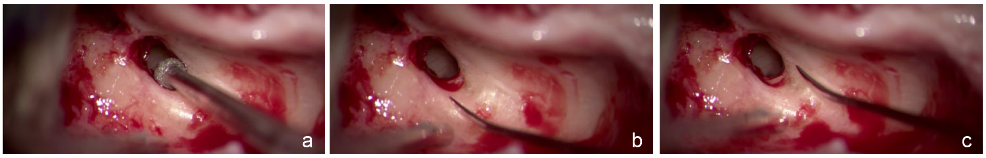

Figure 4.
a Intraoperative view of the facial recess opening, a 2 mm burr fits easily in the facial recess opening.
b Facial nerve is clearly identifiable, with an intact posterior canal wall.
c Chorda tympani nerve is also clearly identifiable, the round window is seen posteroinferiorly in the facial recess opening.

Table 1.

Patient characteristics and outcomes, n=153 (%)		
Age at implantation, mean (SD)		62 (16)
Gender		
	Male	80 (52)
	Female	73 (48)
Diagnosis		
	Bilateral IPSNHL	151 (99)
Side of implantation		
	Right	72 (47)
	Left	80 (52)
	Bilateral	1 (<1)
Mastoid pneumatization		
	Sclerotic	14 (9)
Type of middle ear approach		
	Mastoidectomy-facial recess	153 (100)
Type of insertion approach		
	Direct RW	151 (99)
	Cochleostomy	2 (1)
Intraoperative events[a]		
	Facial nerve exposure	10 (6)
	Chorda tympani nerve lesion	13 (8)
	EAM/TM lesion	12 (8)
	Other[b]	14 (9)

Abbreviations: EAM, External auditory meatus; IPSNHL, idiopathic progressive sensorineural hearing loss; TM, Tympanic membrane; RW, Round window; SD, Standard deviation; a, some patients had more than one event; b, includes venous bleeding and tegmen tympani lesions.

In total, in 28 patients (18% from total), the RWM and niche detection was difficult, mostly due to a small facial recess (26/28). In one case, the posterior canal wall was hindering the surgeons view, while another case had a high riding jugular bulb obstructing the RWM access. Interestingly, all these patients had at least one intraoperative event. The chorda tympani nerve (CTN) was sacrificed in 13 cases (8%), posterior canal wall lesions in 12 cases (8%) and fallopian canal uncovering in 10 cases (6%). The CTN had to be sacrificed in order to provide adequate visualisation of the RWM and niche. Postoperative medical reports showed no complaints related to the CTN sacrifice (e.g. taste disturbance or tongue sensitization). Furthermore, to improve the visibility through the facial recess opening, a small part of the bony cover of the FN canal had to be removed. No FN weakness direct postoperatively or long term was noted in any case. Finally, no complaints were detected for patients with the partial uncovering of the bony posterior wall of the external auditory canal or tympanic membrane annulus.

High resolution CT scan

In total, 120 HRCT scans were analysed for the FN-CTN distance, and divided in two groups based on the operative reports: 95 scans of the normal cases, and 25 scans of the difficult cases. For the prediction line, 20 cases of the normal group, at random, were selected for comparative analysis with the difficult cases. A sclerotic mastoid was seen in 10% of the patients (in concordance with the operative reports), no difference was observed between both groups.

Facial-chorda tympani nerve distance

The mean FN-CTN distance was 2.2mm (SD: 0.5, confidence interval 2.12 – 2.32) for the normal cases (n=95), in contrast, the mean distance was 1.5mm (SD: 0.4, confidence interval 1.31 – 1.68) for cases with difficult view of the RWM (n=23), which is a significant difference (t-test, $p<0.001$). The FN-CTN distance of ≤ 1.5mm was applicable for 9 patients (9%) of the normal group, and for 17 patients (74%) of the difficult cases group, resulting in a sensitivity of 65% and a specificity of 93%. Two cases with a difficult view of the RWM were left out of this analysis, because the visibility of the RWM was hindered by other factors than the facial recess opening. The FN-CTN distance was 2.9mm for one case with an overhanging posterior canal wall, and the other case had a high riding jugular bulb with a FN-CTN distance of 2.2mm.

Prediction line

Axial HRCT reconstructions showed that the anterolateral FN and the basal turn of the cochlea could not be reliable identified in 3 out of 23 cases with a difficult view of the

RWM and niche. Those cases were therefore excluded, resulting in 20 included cases with difficult view of the RWM. Analysis showed that in group A (difficult cases) 9 out of 20 had an anterolateral intersection point, and 11 out of 20 had a posteromedial intersection point. For group B (normal cases) 3 out of 20 had an anterolateral intersection point, and 17 out of 20 had a posteromedial intersection point. See Figure 5 for a summary of these results. The sensitivity was 81%, and specificity 63%, with a posteromedial intersection point being favourable for easy or normal detection of the RWM. No differences were observed between both sides within cases.

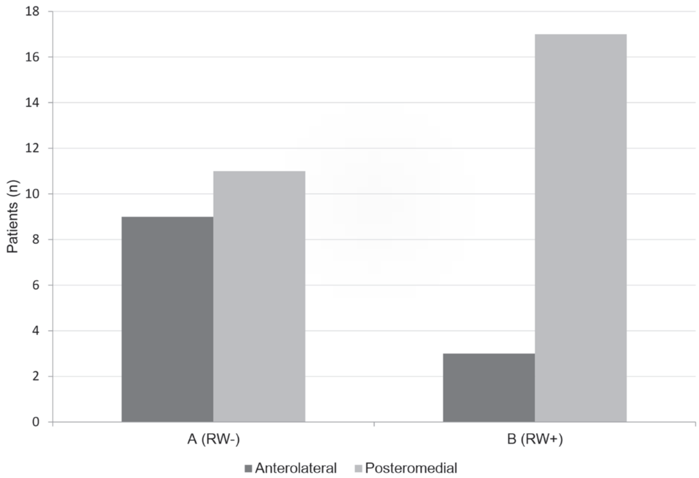

Figure 5. Comparison between group A (difficult visualisation of RW; RW-) and B (easy visualisation of the RW; RW+) of the intersection point of the prediction line. The intersection point was on the anterolateral part of the RW in most patients in group B. Both groups consisted of 20 patients. Abbreviation: RW (round window).

Discussion

Operative report

Our study shows that a direct RW approach is feasible in almost all cases (99%). In addition, the RWM was difficult to visualize in 18% of the cases, usually because of a small facial recess (n=26/28). In 13 cases (8% of total), the CTN had to be sacrificed in order to visualize the RWM. Clearly, in those cases, the CTN was limiting the viewing angle through the facial recess. In the remaining cases with a narrow facial recess the surgeon presumably succeeded in retaining the CTN, while implanting via the RWM. The retrospective design of this study, however, meant that we were limited to the retrospective operative reports, introducing possible bias. In addition, only crude estimations of the relevant outcomes were possible, i.e., we were only able to discern between easy and difficult cases.

Another study showed that direct RWM insertion is almost always possible, however, without reporting intraoperative events to important landmarks (Bae et al., 2019). In contrast, other studies indicate that a direct RWM insertion is not always possible (Gazibegovic & Bero, 2017; Gudis et al., 2012; Jang et al., 2019; Kashio et al., 2015; Leong et al., 2013). In these studies, the rate of unsuccessful direct RWM insertion ranges between 7-15%, often necessitating a conventional cochleostomy.

The surgical approach in our study involved maximal exposure of the facial recess, while preserving the integrity of the FN (fallopian canal), CTN, posterior canal wall and bony tympanic annulus whenever possible, followed by drilling of the bony overhang of the RW niche to expose the RWM. The posterior canal wall was often thinned as much as possible. Subsequently, if needed, the CTN was sacrificed to visualize the RWM, potentially explaining the higher success rate of this study.

Other causes that can obscure the RWM visibility have been described in previous studies, such as a 'high riding' jugular bulb or an overhanging posterior canal wall (Hamamoto, Murakami, & Kataura, 2000; Kashio et al., 2015; Leong et al., 2013; Xie et al., 2018). In this study, there was one case with an overhanging posterior wall, and one with a high riding jugular bulb. In our cohort and in previous studies, the obscuration of the facial recess opening by the posterior wall or sigmoid sinus and jugular bulb is a rare phenomenon (<1%) (Bae et al., 2019; Lee et al., 2012). Some surgeons advocate in cases of an overhanging posterior wall, to "green stick fracture" the posterior wall medially (just lateral from the FN and push it forward) providing improved exposition of the RWM, access to the middle ear and perform implantation of the electrode array; then replace the (partly mobile) canal wall to its previous position where bone will regrow.

Lastly, we identified no cases with postoperative complaints related to the CTN or FN, although patients with CTN lesions only mention their taste disturbances postoperatively if they are asked for it (Ziylan et al., 2018). Other studies also showed that FN paralysis occurs infrequently (<1%) following cochlear implantation procedure with a mastoidectomy-facial recess approach (Hansen et al., 2010; Jeppesen & Faber, 2013). In contrast, postoperative complications related to the CTN seem to occur more often (>2%), although rates vary widely between studies (Hansen et al., 2010; Ziylan et al., 2018).

Facial-chorda tympani nerve distance

Comparison of the radiological measurements of the FN-CTN distance between cases with normal and difficult visibility of RWM showed a smaller FN-CTN distance (difference of 0.7 mm) for the cases with difficult visibility. Therefore, the FN-CTN measurements corresponded to the subjective outcome of the operative reports (i.e. small facial recess). These results show that the FN-CTN distance indeed provides a realistic estimate of the size of the 'window' to the middle ear structures (Hamamoto et al., 2000). A previous study also showed that the FN-CTN distance in the mastoid is important for the viewing angle through the facial recess opening (Lee et al., 2012). Two other studies in adults showed no effect of the facial recess width on the visibility of the RW (Chen et al., 2019; Kashio et al., 2015). These studies, however, measured the width of the facial recess using the posterior canal wall and FN. A correct facial recess opening, in our opinion, is the distance between the FN and CTN. By opting for the posterior wall, the mentioned study could have measured a facial recess width that was larger than what was actually possible intraoperatively.

Prediction line

Our study shows that the prediction line between the basal turn of the cochlea and the FN can be important in indicating the visibility of the RWM intraoperatively. A different study showed that the RWM visibility, classified into three types (invisible/nearly invisible, partially visible, fully visible), was predicted by a line drawn parallel to the external auditory canal and the FN (Chen et al., 2019). The basal turn of the cochlea was in our experience more reliably and easier determined than a line parallel to the canal.

Previous studies have shown that the course of the FN can be highly heterogeneous, and might play a role in RWM visibility. In addition, the angle of rotation of the RWM plays an important role as well. These two aspects both heavily influence the outcome (anterolateral vs posteromedial intersection point) of our prediction line, confirming indeed their importance in determining the viewing angle of the RWM.

Clinical perspectives

In this study, a RWM insertion approach was chosen for all patients if the ST and RWM were patent on the preoperative CT scan. The CTN was sacrificed if the RWM was difficult to recognize, achieving a high rate of direct RWM insertions. Other studies chose in such cases to convert the RWM approach to a conventional cochleostomy (Chen et al., 2019; Leong et al., 2013). It is unclear which of these two options is the best choice for patients when the RWM is not or barely visible. On the one hand, opting for a conversion of insertion access to the cochlea by a conventional cochleostomy has its own potential downsides. An important rationale for direct RWM insertion, is that the RWM forms a natural gateway to the ST of the cochlea thereby preserving as much as possible the cochlear anatomy and inner ear microstructures. A cochleostomy also might lead to increased chance of translocation of the electrode array, or missing the ST altogether, leading to a direct scala vestibuli insertion, potentially negatively impacting the overall hearing outcomes of the CI user (O'Connell et al., 2016; Wanna et al., 2014). Some surgeons, however, advocate that the vector of insertion angle might be more parallel and in line with the ST direction in the basal turn in contrast with RWM insertion. On the other hand, sacrificing the CTN can lead to symptoms such as a dry mouth and taste disorders (McManus, Stringer, & Dawes, 2012; Ziylan et al., 2018). However, these symptoms might not always lead to persistent and troublesome complaints, and the recovery rate can be as high as 79% after CTN lesion (Ziylan et al., 2018). Probably the rate of postoperative complaints related to the CTN is underestimated, because most patients with CTN lesions only mention their taste disturbances postoperatively if they are asked for it. The high recovery rate of the CTN can be potentially explained by improved functioning of the ipsilateral glossopharyngeal nerve, re-innervation via contralateral or ipsilateral glossopharyngeal nerve and CTN, and by subjective adaption of patients (McManus et al., 2012; Ziylan et al., 2018). Of course, both these options' advantages and disadvantages should be weighed against the specific clinical characteristics of the patient, e.g., in a patient with preoperative taste disturbances sacrificing the CTN would be contraindicated.

Conclusion

The RW approach is feasible for most patients. Difficult visualization of the RW membrane leads to intraoperative events such as CTN damage, (minor) exposure of the FN epineurium and lesions of the posterior canal wall. In patients with difficult visualization of the RW membrane during surgery, the preoperative CT showed a small facial recess and anterior position of the FN relative to the RW niche. These factors can be used to plan an insertion approach, potentially leading to less iatrogenic damage of especially the CTN during cochlear implantation surgery.

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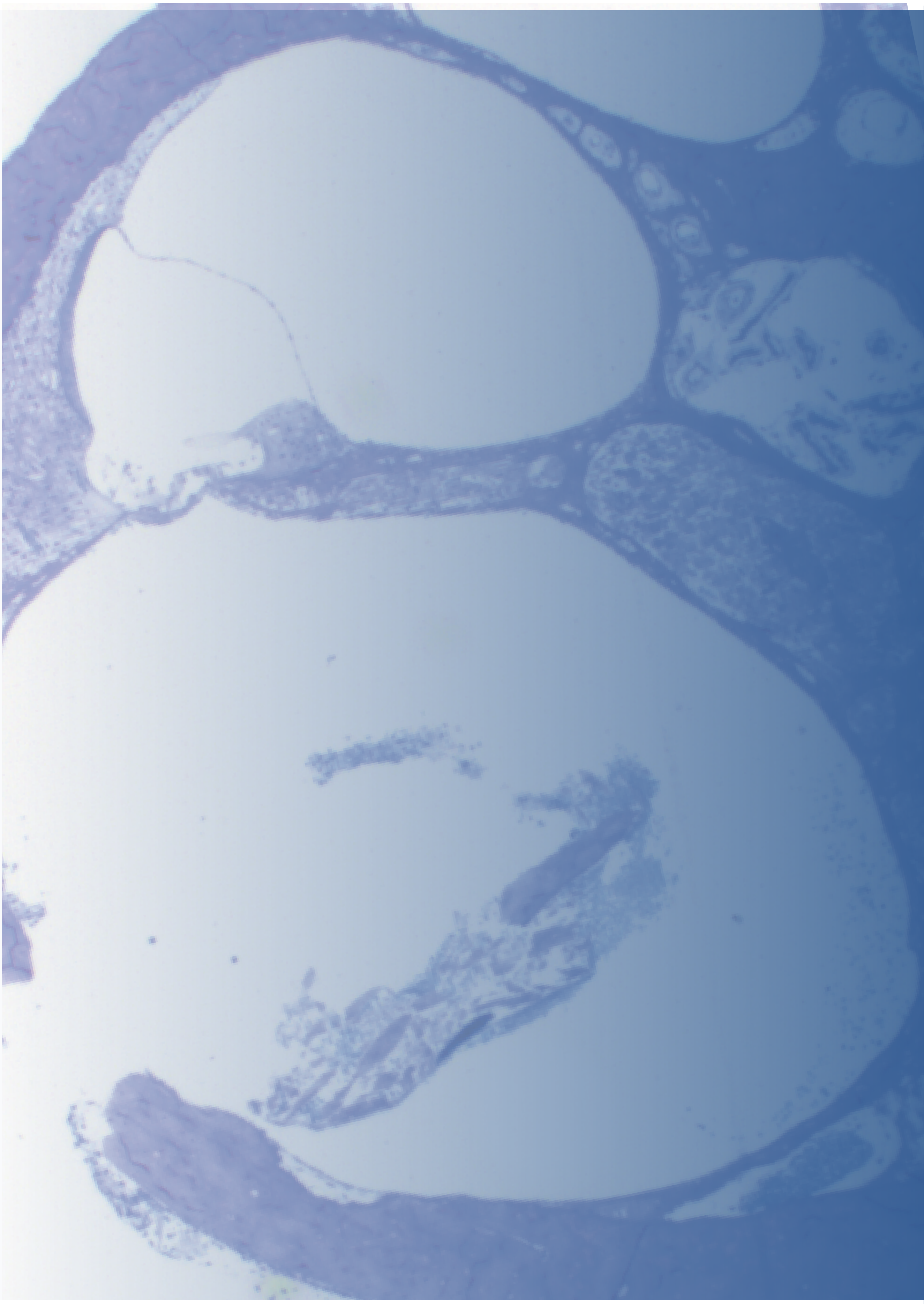

Chapter 6

Acute effects of cochleostomy and electrode-array insertion on compound action potentials in normal-hearing guinea pigs

Saad Jwair, Dyan Ramekers, Hans G.X.M Thomeer, Huib Versnel

Under review in Frontiers Neuroscience

Abstract

Objectives

Electrocochleography (ECochG) is increasingly used in cochlear implant (CI) surgery, in order to monitor the effect of insertion of the electrode array aiming to preserve residual hearing. Here we aim to relate changes in ECochG responses to acute trauma induced by different stages of cochlear implantation by performing ECochG at multiple time points during the procedure in normal-hearing guinea pigs.

Materials and Methods

Eleven normal-hearing guinea pigs received a gold-ball electrode that was fixed in the round-window niche. ECochG recordings were performed during the four steps of cochlear implantation using the gold-ball electrode: (1) Bullostomy to expose the round window, (2) hand-drilling of 0.5 – 0.6 mm cochleostomy in the basal turn near the round window, (3) insertion of a short flexible electrode array, and (4) withdrawal of electrode array. Acoustical stimuli were tones varying in frequency (0.25 - 16 kHz) and sound level. The ECochG signal was primarily analyzed in terms of threshold, amplitude, and latency of the compound action potential (CAP). Midmodiolar sections of the implanted cochleas were analyzed in terms of trauma to hair cells, modiolar wall, osseous spiral lamina (OSL) and lateral wall.

Results

Animals were assigned to cochlear trauma categories: minimal (n=3), moderate (n=5) or severe (n=3). After cochleostomy and array insertion, CAP threshold shifts increased with trauma severity. At each stage a threshold shift at high frequencies (4-16 kHz) was accompanied with a threshold shift at low frequencies (0.25 – 2 kHz) that was 10-20 dB smaller. Withdrawal of the array led to a further worsening of responses, which probably indicates that insertion and removal trauma caused affected responses rather than the mere presence of the array. In two instances, CAP threshold shifts were considerably larger than thresholds of cochlear microphonics, which could be explained by neural damage due to OSL fracture. A change in amplitudes at high sound levels was strongly correlated with threshold shifts, which is relevant for clinical ECochG performed at one sound level

Conclusion

Basal trauma caused by cochleostomy and/or array insertion should be minimized in order to preserve the low-frequency residual hearing of CI recipients.

Introduction

Cochlear implants (CIs) have been tremendously successful in restoring speech perception in severely hearing impaired patients (Carlson 2020). The CI converts sound into electrical current pulses that stimulate the auditory nerve, thereby bypassing affected and degenerated hair cells. However, for most CI recipients, speech perception is suboptimal and requires considerable listening effort, especially in situations with background noise (Gifford & Revit 2010). Residual hearing, i.e threshold <80 dB hearing level at 125 – 500 Hz, is present in around 50% of CI recipients (Kant et al., 2022), and can be used to improve speech perception, e.g. with use of electro-acoustical stimulation (Gstoettner et al., 2004; Dhanasingh et al., 2021). Preservation of residual hearing after cochlear implantation has been reported by several studies (see for reviews Miranda et al., 2014; Snels et al., 2019). However, Kant et al. (2022) have shown that in one CI center residual hearing was (partially) lost in most CI recipients (90%) 3 months after implantation.

Residual hearing can be acutely affected by cochlear implantation in several ways. The cochlear structures can be directly damaged by insertion of the electrode array, such as with scalar translocation of the array (Jwair et al., 2021). In addition, the basal cochlear turn can also be damaged by the drill that is used for surgically approaching the cochlea (Richard et al., 2012). Mechanical trauma to hair cells and auditory nerve fibers by drilling and/or array insertion directly impacts the residual hearing. In addition, trauma to cochlear structures can lead to mixture of endolymph, located in the cochlear duct, and perilymph, which is located in the scala tympani and scala vestibuli. This mixture abolishes the endocochlear potential (Reiss et al., 2015). Acute structural trauma might also alter the mechanics of the basilar membrane, impeding the travelling wave, thereby potentially impacting cochlear areas located more apically to the site of trauma. Residual hearing can also deteriorate by sudden changes in intra-scalar pressure (Gonzalez et al., 2020), blood and bone dust entering the cochlea (Radeloff et al., 2007), and noise-related trauma associated with drilling of the bone (Pau et al., 2007).

It is clear that electrocochleography (ECochG) has the potential to detect physiological changes and trauma intracochlearly (Giardina et al., 2019). ECochG has emerged as a promising tool that might aid the surgeon in minimizing acute trauma, thereby preserving residual hearing of CI patients (Bester et al., 2017). ECochG refers to the recording of electrical potentials generated by hair cells and auditory nerve in response to acoustic stimuli. ECochG research has been performed since the sixties to assess

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cochlear pathologies as endolymphatic hydrops in Ménière's disease (Eggermont 2017). The resurgence of research regarding ECochG is linked to relatively new ability to record cochlear potentials using the intracochlear electrode array (Calloway et al., 2014, Bester et al., 2017). ECochG can provide feedback about the cochlear structures during electrode insertion, based on which the surgeon can adapt the insertion to potentially reduce trauma (Weder et al., 2020). In addition, ECochG can shed light on which aspects of cochlear implant surgery are detrimental for hearing preservation (Weder et al., 2021, Lenarz et al., 2022).

Currently, however, ECochG responses during cochlear implantations show large variability. This variability can be caused by several factors, such as trauma to cochlear structures, physiological changes without trauma, and due to movement of the electrode during insertion (Dalbert et al., 2021). Often there is a discrepancy seen between intraoperative ECochG responses and postoperative audiometric thresholds in CI recipients, probably due to this large variability (Adunka et al., 2016).

To understand the ECochG better during cochlear implantation, several animal studies investigated the relationship between ECochG and acute trauma in normal-hearing and noise-induced hearing loss gerbils and guinea pigs. Smaller compound action potentials (CAP) and cochlear microphonics (CM) responses were seen after electrode insertion. In addition, even though small responses were in most cases associated with histological trauma, some cases showed no association with histological trauma, i.e. to osseous spiral lamina (OSL), basilar membrane, spiral ligament (Choudhury et al., 2011; DeMason et al., 2012; Choudhury et al. 2014; Honeder et al., 2016; Honeder et al., 2019). In addition, ECochG responses to low frequencies (associated to the apical cochlear turn) can be affected by basal trauma such as OSL and basilar membrane damage (Choudhury et al., 2011; Choudhury et al., 2014; Smeds et al., 2015), although electrode insertion was not affecting low frequencies in some studies (Robertson & Irvine 1989; Chambers et al., 2019; Andrade et al., 2020). A recent study in CI recipients showed that insertion of a short electrode array can preserve the ECochG responses to the lower frequencies, indicating that basal trauma is not necessarily affecting apical areas (Dalbert et al., 2021). To our knowledge, just one study has described ECochG results after solely cochleostomy, i.e. without electrode insertion (Andrade et al., 2022). To our knowledge, just one study has described ECochG results after solely cochleostomy, i.e. without electrode insertion (Andrade et al., 2022). They recorded CAPs for frequencies between 2 and 32 kHz, and they found that cochleostomy did not affect the responses, whereas array insertion caused threshold shifts of around 20 dB at higher frequencies. In the current study we investigated ECochG over a wide range of frequencies from 250 Hz to 16 kHz. Additionally, histological analysis of the cochlea was conducted after the ECochG experiments, allowing for more thorough analysis of cochlear structures (including hair cell counts) than the micro-computed tomography system used in the Andrade et al. paper (2022).

We tested the degree to which cochlear potentials, in terms of primarily CAP thresholds, amplitudes and latencies, are affected by acute trauma during separate stages of the cochlear implantation procedure, i.e. cochleostomy and array insertion. We conducted ECochG at the round window (RW) varying stimulus frequencies from 250 Hz to 16 kHz in normal-hearing guinea pigs in order to be able to detect effects of trauma to both high and low frequencies. Cochlear implantation was performed with flexible electrode arrays (similar to those in humans). Subsequently, ECochG responses were evaluated in relation to cochlear structural trauma.

Materials and Methods

Animals and experimental design

Thirteen female albino guinea pigs (Dunkin Hartley; Hsd Poc:DH; ~350 g) were obtained from Envigo (Horst, the Netherlands) and kept under standard laboratory conditions (food and water ad libitum; lights on between 7:00 a.m. and 7:00 p.m.; temperature 21 °C; humidity 60%). The same procedures were followed for all animals. ECochG was performed at four separate stages of surgery: before cochleostomy (PRE), after cochleostomy (POST1), after CI insertion (POST2), and after CI withdrawal (POST3), see Figure 1. In all four stages ECochG was performed with a custom-made gold-ball electrode that was fixated in the round window niche.

All surgical and experimental procedures were approved by the Animal Experiments Committee of Utrecht University (4315-1-01) and the Central Authority for Scientific Procedures on Animals (AVD1150020174315).

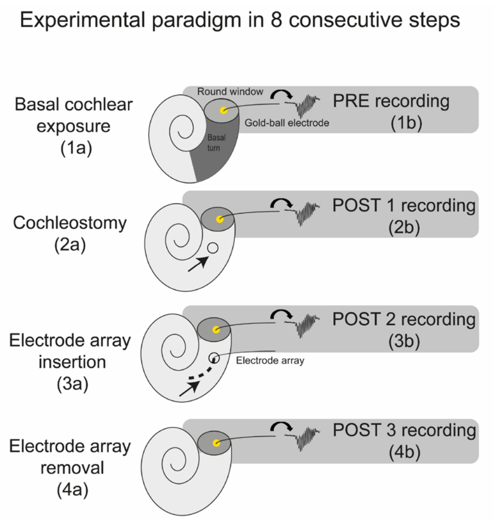

Figure 1. A schematic overview of the experimental paradigm. The electrocochleography was performed using the gold-ball electrode in the round window niche. The experiments consisted of 8 consecutive steps, with electrocochleography at 4 separate stages of the procedure, i.e. at PRE (before cochleostomy), POST1 (after cochleostomy), POST2 (after electrode-array insertion) and POST3 (after electrode-array removal).

Surgical procedures

The animals were anesthetized by intramuscular injection of dexmedetomidine (Dexdomitor; Vetoquinol, Breda, the Netherlands; 0.13 mg/kg) and ketamine (Narketan; Vetoquinol, Breda, the Netherlands; 20 mg/kg). The animals were tracheostomized, and artificially ventilated with 1-2% isoflurane in O2 and N2O (1:2) throughout the experiment. Subsequently, needle electrodes were used for ABR recordings, with the active electrode placed subcutaneously behind the right ear, and the reference electrode subcutaneously at the midline of the frontal skull. The skull and the neck muscles overlying the bony bulla were exposed with one surgical incision along a line from the anterior medial side of the skull to retro-auricular right-ear region. One transcranial screw was placed on the skull, 1 cm anterior from bregma (ECochG reference electrode). After pushing the neck muscles aside, a bullostomy was performed to expose the right basal turn of the cochlea (PRE). To perform ECochG, a gold-ball electrode was used which consisted of an isolated stainless steel wire (diameter 0.175 mm; Advent, Halesworth, UK) with a 0.5 mm diameter gold-ball micro-welded to the tip (Unitek 80 F, Unitek Equipment, Monrovia, CA). The steel wire was curled near the gold-ball tip, which then was positioned in the RW niche, and the steel wire was subsequently fixed with an electrode holder. Subsequently, a cochleostomy was manually performed with a 0.5 mm human-powered drill, just below (~0.5 mm) the round window (POST1). After the cochleostomy, a custom-made electrode array (Advanced Bionics; diameter 0.5 mm, length basal electrode to tip 3.5 mm, inter-electrode distance 1.0 mm) was inserted ~4 mm into scala tympani (POST2) with all 4 electrodes of the array positioned intracochlearly. The diameter of the scala tympani at 5 mm from the round window is about 0.5 mm (Wysocki and Sharifi 2005), which allows for the insertion depth of 4 mm. Lastly, the electrode array was removed (POST3).

Electrophysiology

Auditory brainstem response

After tracheostomy the ABRs were recorded using subcutaneously positioned needle electrodes (active electrode behind the right pinna; reference electrode on the skull, rostral to the brain on the midline; ground electrode in left hind limb). Broadband acoustic clicks (20 µs monophasic rectangular pulses; inter-stimulus interval 99 ms) were synthesized and attenuated using a TDT3 system (Multi-I/O processor RZ6; Tucker-Davis Technologies, Alachua, FL, USA), and presented in free field using a Bowers & Wilkens speaker (CCM683; 8 Ω; 25 - 130 W) at 10 cm distance from the right ear.

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The signal was pre-amplified using a Princeton Applied Research (Oak Ridge, TN, USA) 5113 pre-amplifier (amplification ×5000; band pass filter 0.1–10 kHz). The amplified signal was digitized by the same TDT3 system for analysis (100 kHz sampling rate, 24-bit sigma-delta converter). The responses were averaged over 500 repetitions (maximum) and stored on a PC for offline analysis with custom MATLAB software. The sound level was attenuated in 10 dB steps, starting with maximum sound level at approximately 105 dB peak equivalent SPL (average of maximum sound level of 2, 4, 8 and 16 kHz tones), until 10 dB below the sound level with no visible ABR response. The threshold was defined as the interpolated sound level at which the ABR N1–P2 peak was 0.3 μV. Preoperative threshold dB peak equivalent SPL of <55 dB were considered to indicate normal hearing. See for further details (Ramekers et al., 2014).

Electrocochleography

ECochG was performed using the gold-ball electrode as active electrode (situated in round window niche), a screw on the skull for reference electrode, and a needle in the left hindlimb muscle as ground electrode.

All recordings were performed in a sound-attenuated room. Stimuli were presented in a free-field 10 cm from the right pinna, using the same Bowers & Wilkens speaker as for the ABRs. The stimuli consisted of pure tone pips ranging from 0.25 kHz to 16 kHz in octave steps, that were presented with alternating polarity.

Our stimulus parameters are chosen to be long enough to measure the CM, and to have sufficient rise and fall times to avoid spectral splatter. Therefore, we applied 2 or more periods of rise-fall time and 2 or more periods of plateau (Stronks, Aarts et al. 2010, Havenith, Klis et al. 2013). Durations of the tones was 8 ms for the high frequencies (4 - 16 kHz) with rise/fall time of 1 ms. The 1 kHz and 2 kHz stimuli had duration of 8 ms, and rise/fall time of respectively 2 ms and 1.5 ms. The 500 Hz tone had a duration of 12 ms, with rise/fall time of 4 ms. And lastly, the 250 Hz tone had a duration of 24 ms with rise/fall time of 8 ms.

Sound levels were chosen sufficiently high to assess amplitudes and latencies at the same level at each stage, and with sufficiently small step sizes to assess the threshold. Stimuli were presented at maximum sound level, which differed across frequencies (in dB SPL): 99 at 250 and 500 Hz, 103 at 1 kHz, 98 at 2 kHz, 104 at 4 kHz, 110 at 8 kHz, and finally 107 at 16 kHz. The sound level was attenuated in 10 dB steps, starting with maximum sound level, until 10 dB below the sound level with no visible CAP and CM response.

The signal was pre-amplified using the same preamplifier as for the ABRs (amplification 5000x; band-pass filtered 1Hz – 30 kHz). The amplified signal was digitized by the same TDT3 system for analysis. The responses were averaged over 500 repetitions (maximum). Sometimes less repetitions were needed to achieve a reliable response, with typically smaller responses with low signal-to-noise ratio needing more repetitions.

Tissue fixation and histological processing

After completing all ECochG measurements the animals were terminated with an overdose of pentobarbital injection intracardially. The right cochlea was then harvested for histological analysis. Intra-labyrinthine cochlear fixation was done with a fixative of 3% glutaraldehyde, 2% formaldehyde, 1% acrolein and 2.5% dimethyl sulfoxide (DMSO) in a 0.08 M sodium cacodylate buffer, as described by a previous study (de Groot, Veldman et al. 1987). The cochleas were decalcified in 10% EDTA for around 10 days, secondarily fixed in 1% osmium tetroxide and 1% potassium ruthenium cyanide, and embedded in Spurr's low-viscosity resin. Staining was done with 1% methylene blue, 1% azur B, and 1% borax in distilled water. Tissue was sectioned using LeicaRM2265 microtome. From each cochlea, 5 midmodiolar sections of 1 µm were obtained in sequential manner and put on a slide with coverslip. Data analysis

Data Analysis

Histology

Macroscopic cochlear trauma was assessed with light microscopy in standardized midmodiolar sections. The following items were used for trauma severity rating: fracture of modiolar wall (yes or no), OSL fracture (yes or no), and lateral wall damage around cochleostomy (as expected = +, more traumatic= ++). A more traumatic cochleostomy is considered to have fractured the lateral wall at different place than the site of cochleostomy (see Fig. 2). Additional features of traumatic cochlestomy are more blood cells, and splintered smaller pieces of bone. In addition, the midmodiolar sections were used for quantification of inner and outer hair cells from base to apex, and the structural integrity of these hair cells was also evaluated. Animals with affected structural integrity of inner or outer hair cells (e.g. dislocated or abnormally shaped), or loss of these hair cells were rated in general as having hair cell damage (yes or no).

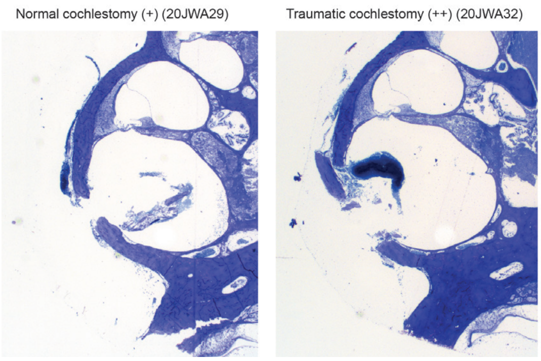

Figure 2. Two examples of the cochleostomy site: 20JWA29 shows a normal cochleostomy site, with no additional fracture of the lateral wall besides the intended cochleostomy. 20JWA32 shows a traumatic cochleostomy with an additional fracture of the lateral wall, splintered bone and blood cells near the cochleostomy site.

Electrocochleography

The ECochG was analyzed using custom-written MATLAB scripts. See Figure 3 for example ECochG, with analysis of the response to one low-frequency (1 kHz) and one high-frequency (4 kHz) tone. To extract the compound action potential (CAP) and the cochlear microphonics (CM), alternating polarity stimulation (condensation-leading and rarefaction-leading) was used. The compound action potential (CAP) was analyzed by summation of the two responses, i.e. the SUM response. For frequencies 2 – 16 kHz, the N1-P1 peak-to-peak amplitude was determined. For the other frequencies ranging between 0.25 kHz – 1 kHz, because of the ongoing auditory nerve response (also known as auditory nerve neurophonic), the largest peak-to-peak amplitude was determined, which was not always at the start of the response. Note that we simply refer to the nerve responses at low frequencies as CAP rather than neurophonic, as each peak represents a sum of action potentials. The amplitudes vary among animals as it depends on electrode positions of both the gold-ball and reference. Therefore, we examined the change of amplitude relative to the PRE stage by computing the ratio (POST/PRE). The CAP threshold criterion was an amplitude of 3 μV for high frequencies (4 – 16 kHz), and an amplitude of 1 μV for low frequencies (0.25 – 2 kHz). Thresholds were assessed by interpolation of the two datapoints around threshold (one above, one below). In case no data were acquired below threshold, we applied extrapolation of the datapoints at the lowest two sound levels. Threshold shifts (in dB) per POST stage, were determined with PRE values as reference for statistics, unless stated otherwise. The latency assessment was based on the N1 peak for all frequencies, and again shifts per POST stage (in ms), with PRE as reference, were used for analysis. Figure 4A shows an example of CAP for a 4 kHz tone at different attenuated sound levels, starting at maximal sound level, and an I/O curve is obtained to derive the interpolated threshold (Fig. 4C). These recordings were performed before cochleostomy (PRE stage).

To analyze the CM the two responses (condensation-leading and rarefaction-leading) were subtracted, i.e. the DIF response. The CM threshold criterion was 1 μV for all frequencies. However, speaker artefacts were also present during measurements, which was evident in the click-evoked responses as an isolated peak at stimulus onset. Based on the magnitude of that peak, thresholds of the speaker artefacts were obtained for every measurement. Only CM data were included in our analyses that were larger than artefact. Figure 4B shows an example of CM for a 4 kHz tone at different attenuated soundlevels, starting at maximal sound level, and an I/O curve is also obtained to derive the interpolated threshold (Fig. 4C).

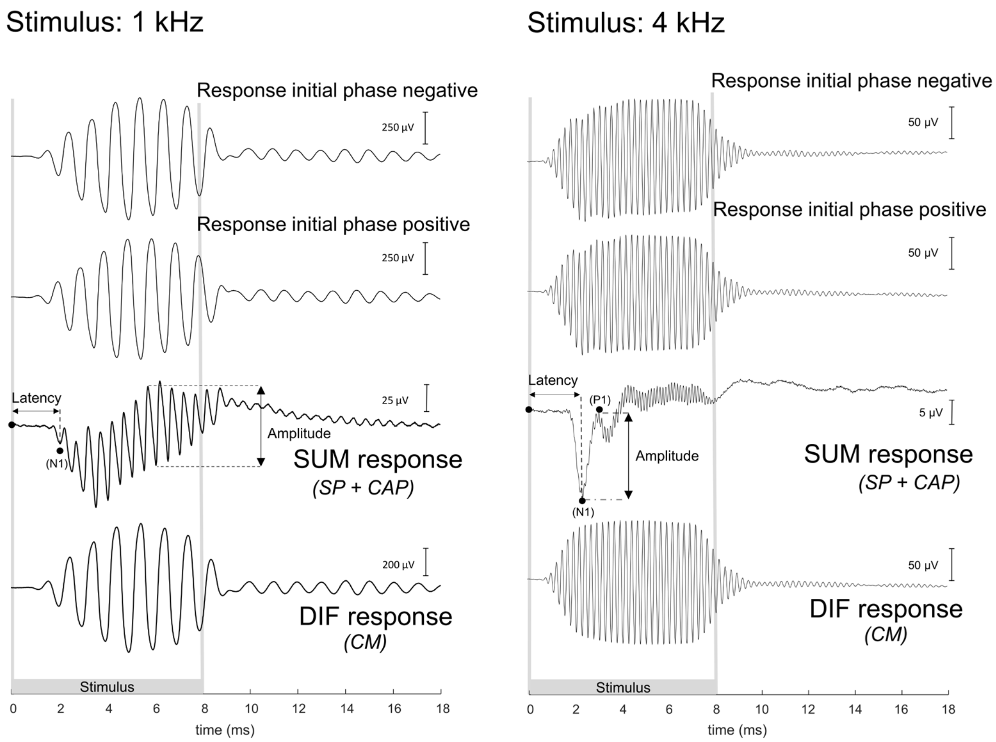

Figure 3. These are example electrocochleography responses using the gold-ball electrode, before cochleostomy, to a low and high frequency tone. Duration of the stimulus differed between the different frequencies, and the stimuli were presented in alternating polarity. The compound action potential is derived from the SUM response by adding the two initial responses together. At frequencies between 0.25 – 1 kHz, in this instance at 1 kHz, the CAP latency is derived from the N1 peak, and the CAP amplitude was derived from the largest peak-to-peak amplitude of the ongoing response. At the other frequencies of 2 – 16 kHz, in this instance at 4 kHz, the CAP latency was similarly extracted with the N1 peak, and the CAP amplitude as the N1P1 peak-to-peak at the onset of the response. The cochlear microphonics (CM) is derived from the difference (DIF) response by subtracting the initial responses from each other. For high stimulation levels the SUM response will contain some CM in addition to the CAP since the CM at those levels may not be symmetric (Fontenot et al., 2017). For low frequencies the DIF response will contain some neural responses in addition to CM since the phase-following responses to opposite polarity have opposite phase. Note: the late responses after stimulus offset may be evoked by echoes, 20-30 dB below the actual stimulus level, caused by reflections of the experimental chamber.

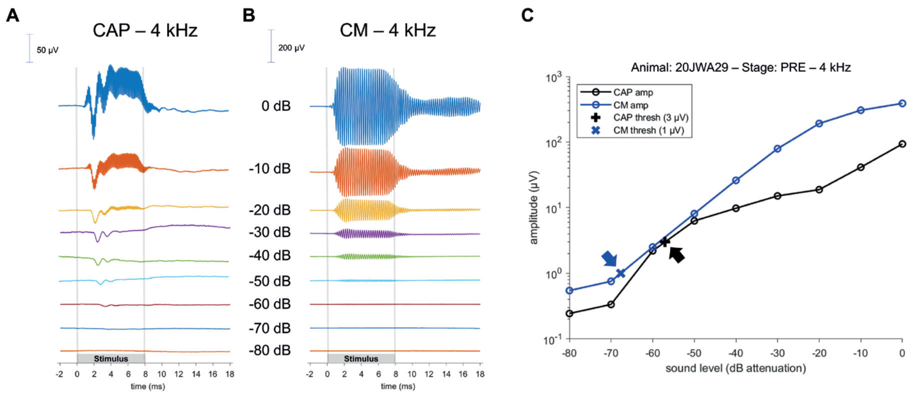

Figure 4. Example of a compound action potential (CAP; A) and a cochlear microphonics (CM; B) response to a 4 kHz tone across different sound levels. Stimulus started with maximum sound level (in this instance of 4 kHz, at 104 dB SPL) and was attenuated in 10 dB steps until the CAP or CM response was not visible anymore. Subsequently, an input/output curve was constructed, and the threshold was interpolated using pre-defined threshold criteria (C).

Results

Animals

All animals had normal preoperative click-evoked ABR thresholds (mean 43 dB peSPL, range 36 – 50). Two out of 13 animals were excluded because their PRE stage CAP threshold values were ~20 dB more than the average threshold on at least 2 out of 7 tested frequencies. The standard deviation of the mean CAP threshold of the remaining 11 animals at every separate frequency (0.25 – 16 kHz, octave steps) was ~5 dB (range: 4.5 – 5.6).

Histology

Midmodiolar sections were assessed for trauma. Based on these assessments, three groups of animals were identified: with minimal trauma (n=3), moderate trauma (n=5) or severe trauma (n=3). See Figure 5. for one histological example for each trauma group, and Table 1 for an overview of the results of all animals. In addition to the cochleostomy, the severe group had OSL fracture and a fracture of the modiolar wall. Two of the moderately affected animals had more severe damage to the lateral wall near cochleostomy, and the other three animals had OSL fracture, but no fracture of the modiolar wall. In cases with trauma, it was always located at the site of cochleostomy and electrode insertion, i.e. at the basal turn of the cochlea.

Additionally, both inner and outer hair cells were counted in the midmodiolar sections (see Table 2). All three cochlear turns were assessed, i.e. basal, middle and apical. The minimal trauma animals had no damage to either inner or outer hair cells across all three turns. However, hair cells were affected for both the moderate and severe trauma animals. In the moderate trauma group, one animal (20JWA11), had damage to both inner and outer hair cells at the basal turn, and loss of these cells at the middle and apical turn. Another moderately affected animal (20JWA21) also had basal damage to both inner and outer hair cells, and intact hair cells at the other turns. In addition, animal with moderate trauma (20JWA18) had a patchy loss of outer hair cells, i.e. some hair cells were missing in both the basal turn and middle turn, although the section was not entirely cut in the midmodiolar plane. The other two animals (20JWA32 and 33) had no damage or loss of any hair cells. Finally, in the severe trauma group, animal 20JWA15 and 16 had damaged inner and outer hair cells at all turns, and 20JWA17 only damaged inner and outer hair cells at the basal turn.

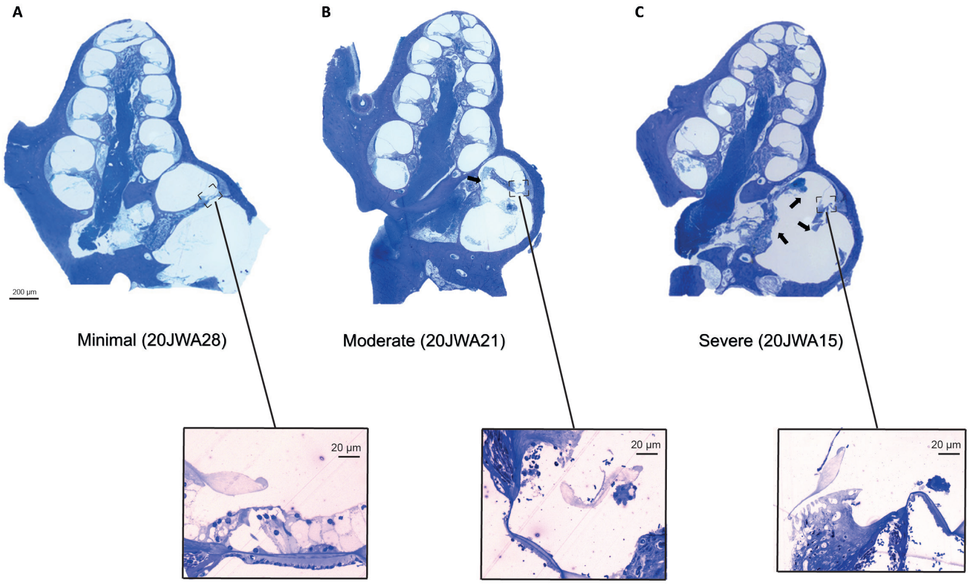

Figure 5. Three midmodiolar section examples (2.5x, light microscopy) are shown of each trauma group. In the minimal trauma group (A), no other trauma than the cochleostomy was observed. In the moderate trauma group (B), a fracture of the osseous spiral lamina is clearly seen in the basal turn (arrow). In the severe trauma group (C), in addition to fracture of OSL, the modiolar wall is damaged at the basal turn. Additionally, the organ of Corti of B1 region is shown at greater magnification (25x): A: intact organ of Corti with 3 outer hair cells and one inner hair cell; B: absent inner and outer hair cells; C: absent inner and outer hair cells.

Table 1. Trauma severity assessment based on histology.

Animal	Hair cell damage	OSL Fracture	Modiolar wall fracture	LW damage at cochleos-tomy	Trauma rating
20JWA15	+	+	+	++	severe
20JWA16	+	+	+	++	severe
20JWA17	+	+	+	++	severe
20JWA11	+	+	-	++	moderate
20JWA18	+	+	-	++	moderate
20JWA21	+	+	-	++	moderate
20JWA32	-	-	-	++	moderate
20JWA33	-	-	-	++	moderate
20JWA28	-	-	-	+	minimal
20JWA29	-	-	-	+	minimal
20JWA30	-	-	-	+	minimal

OSL, osseous spiral lamina; LW, lateral wall.

Table 2. Hair cell count in one midmodiolar section for every animal.

Animal number	IHC Basal	OHC Basal	IHC Mid	OHC Mid	IHC Apex	OHC Apex	Trauma severity
20JWA11	1	3	0	0	0	0	MO
20JWA15	0	0	0	0	0	0	SE
20JWA16	0	0	0	0	0	0	SE
20JWA17	0	0	2	6	2	6	SE
20JWA18	1	3	2	5	1	6	MO
20JWA21	1	3	2	5	2	6	MO
20JWA28	2	6	2	5	1	6	MI
20JWA29	2	6	2	6	2	6	MI
20JWA30	2	6	2	6	2	6	MI
20JWA32	2	6	2	6	2	6	MO
20JWA33	2	6	2	6	2	6	MO

IHC: inner hair cell; OHC: outer hair cell; MI: minimal trauma; MO: moderate trauma; SE: severe trauma; Basal: lower and upper basal semiturns; Mid: lower and upper middle semiturns; Apex: lower and upper apical semiturns. Two IHCs and six OHCs are present normally in normal-hearing guinea pigs for each of the three cochlear areas (basal, mid and apex).

Electrocochleography

Individual animals

To determine the relationship between ECochG and trauma severity we primarily analyzed the CAP. Figure 6 shows an overview of the trauma groups (based on histology), by providing an example of one individual SUM response to a high frequency (8 kHz) and low frequency (500 Hz) tone. It shows the responses for these three animals at ~90 dB SPL across all 4 stages, and the respective CAP amplitudes and latencies as function of sound level. The PRE stage showed roughly equal CAP thresholds for these three animals at 8 kHz (range: 27-36 dB SPL, i.e. ~80 dB attenuation) and at 500 Hz (range: 44-53 dB SPL, i.e. ~50 dB attenuation).

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At POST1, the CAP responses are in line with histological outcomes, i.e. the severe trauma animal (Figure 6A) having the smallest amplitudes (e.g. at ~90 dB SPL: 5 μV) at 8 kHz; while the moderate trauma animal (Figure 6B) had larger responses (at ~90 dB SPL: 30 μV), and the minimal trauma animal (Figure 6C) had the largest responses (at ~90 dB SPL: 115 μV). The threshold shifts were 55 dB, 45 dB and 5 dB for the severe, moderate and minimal trauma animal respectively. Similarly, the CAP latency

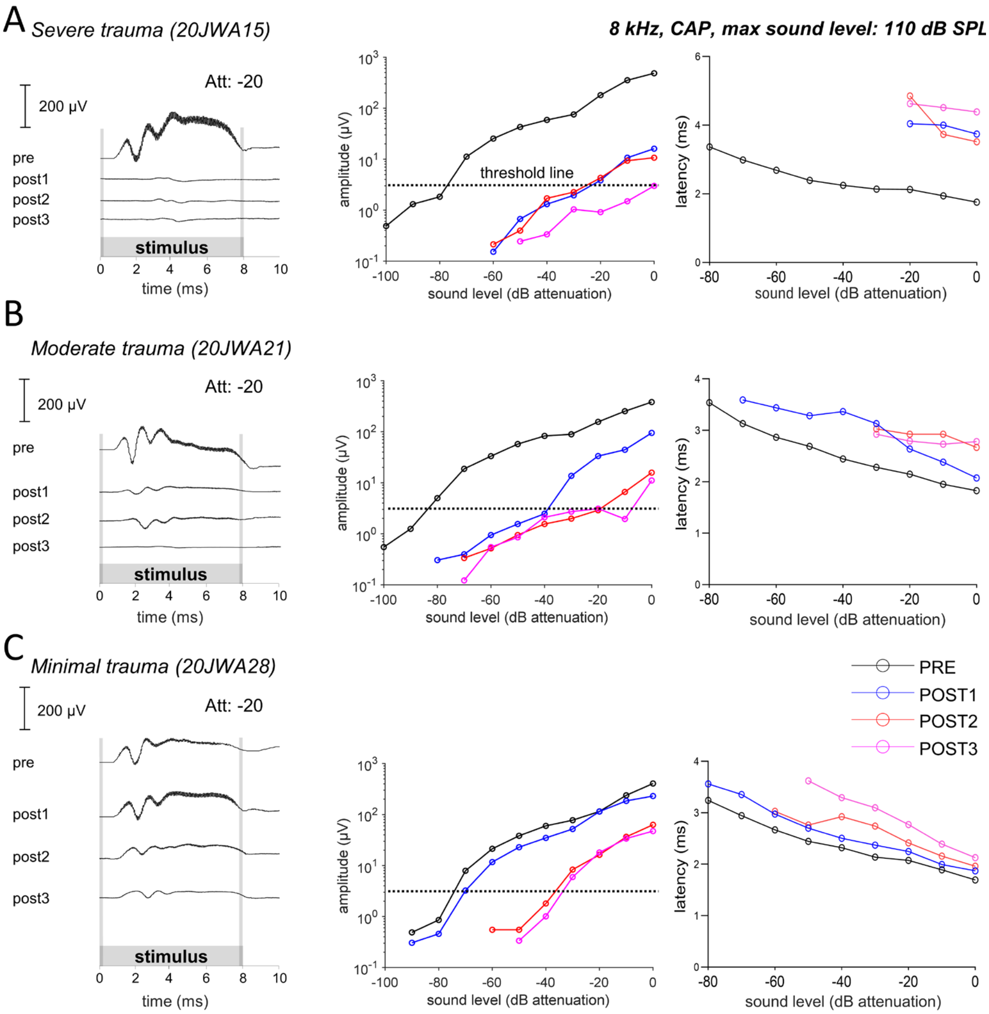

Figure 6. The compound action potential responses to a 8 kHz (A-C) and 500 Hz (D-F) tone of three individual animals is shown for all 4 stages. In the upper row (A/D), the responses of a severely affected animal are shown. It is clear that after cochleostomy the responses were severely affected (high threshold and latency shifts), to both a high and low frequency tone. In the middle row (B/E), the responses of a moderately affected animal are shown. In this animal, the responses are less severely affected, but still both responses to a low and high frequency were affected. In the lowest row (C/F), the responses of a minimally affected animal are shown. In this animal, the responses to a high frequency tone are especially affected after electrode-array insertion.

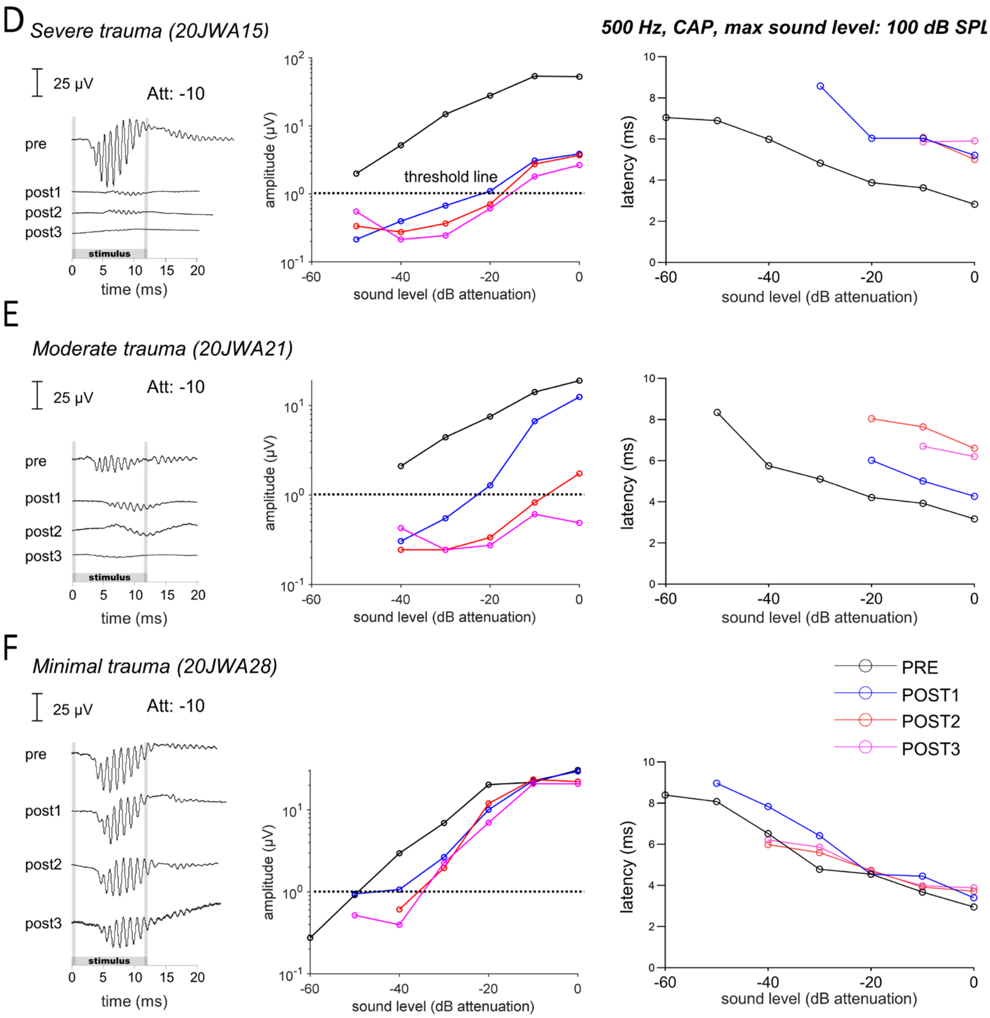

Figure 6 - continued

(at 90 dB SPL) increased most for the severe trauma animal with a latency shift of 2 ms, followed by 0.5 ms for the moderate trauma and 0.2 ms for the minimal trauma animal. In addition, not only higher frequencies were affected at POST1, but also lower as illustrated here for 500 Hz (see Figure 6 D-F). CAP thresholds, amplitudes and latencies, showed similar results to 8 kHz tone, with smallest responses, largest threshold and latency shifts for the severe trauma animal (5 μV amplitude; 30 dB threshold shift and 2.6 ms latency shift), and largest responses and smallest threshold and latency shifts for the minimal trauma animal (25 μV amplitude; 5 dB threshold shift and 0.01 ms latency shift).

The POST2 and POST3 stages are described together, as they showed largely similar responses. At these two stages, the CAP threshold, amplitude and latency were similar to the POST1 responses for the severe trauma animal (Figure 6. A/D). The moderate trauma animal had bigger differences between the CAP thresholds at POST2/POST3, than at POST1 (Figure 6. B/E). The threshold and latency increased at POST2 for both 8 kHz and 500 Hz, and also, albeit less, at POST3. For the minimal trauma animal, the CAP thresholds and latencies increased, of all the stages, the most at POST2, for both 8 and 0.5 kHz. At POST3, the responses were mostly similar to POST2 for the minimal trauma animal, except for latencies.

Groups

CAP threshold

Figure 7 shows the mean CAP thresholds (in dB SPL) plotted for each of the three trauma groups across all tested frequencies (range: 0.25 – 16 kHz). The largest threshold increases occurred at POST1 for the severe group, with a mean of 37 dB increase (across all frequencies), followed by 23 dB for the moderate group, and just 4 dB for the minimal group. A difference in CAP thresholds was observed between the higher frequencies (4 - 16 kHz), and lower frequencies (0.25 - 2 kHz). The mean shift of the higher frequencies was higher with 43 dB (SD:9), 28 dB (SD:14) and 3 dB (SD:4) for respectively the severe, moderate and minimal group at POST1. The lower frequencies had mean shifts of 26 dB (SD:9), 17 dB (SD:8) and 1 dB (SD:4) for respectively the severe, moderate and minimal group at POST1.

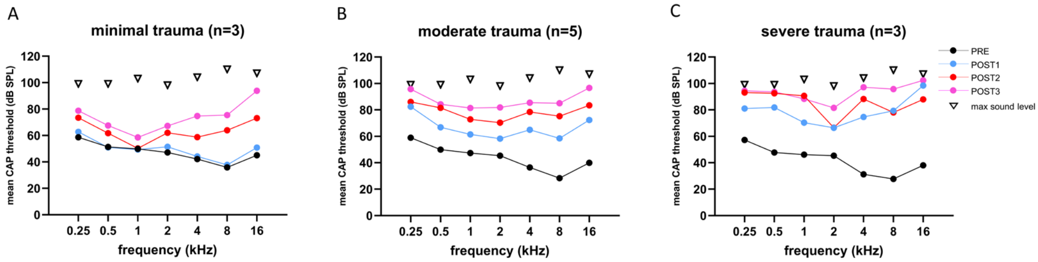

Figure 7. The mean CAP thresholds of all three trauma groups are shown across all tested frequencies (0.25 – 16 kHz), and the 4 stages. The PRE values were comparable between the three groups. Threshold shifts in all three groups were observed across all frequencies, and increased with every POST stage, except for the minimal trauma group (A), in which barely any threshold shift was observed across all tested frequencies at POST1.

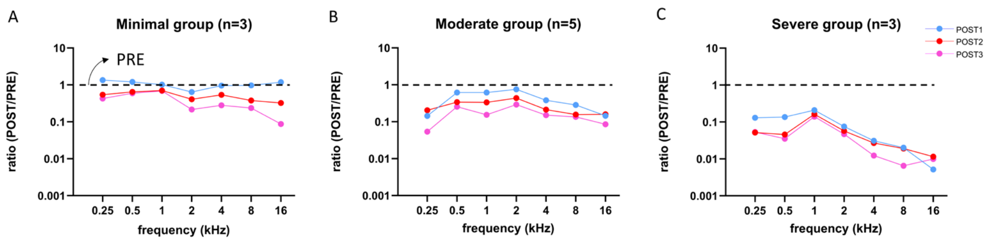

Figure 8. Mean compound action potential amplitude ratios (POST/PRE) at ~90 dB SPL of all three trauma groups are shown for each stage. After each stage, the amplitudes decreased for all three groups, except at POST1 stage in the minimal trauma group (A). Responses to high frequency tones were severely affected, however also responses to low frequency tones were affected, especially in the severe trauma group (C).

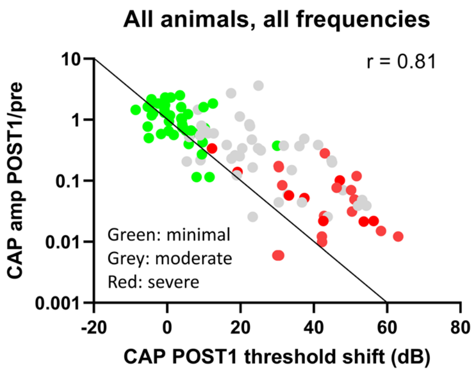

Figure 9. The compound action potential (CAP) amplitude ratios (POST1/PRE) at ~90 dB SPL were plotted against CAP threshold shifts at POST1. Data points represent all individual responses of all animals to the tested frequencies (0.25 – 16 kHz, octave steps). The data points are dispersed according to trauma group, with minimal trauma animals having less decline of amplitude and threshold shift increase. The line represents the 1 dB amplitude decrease with 1 dB threshold shift. A decrease of these amplitudes at 90 dB SPL was strongly correlated with threshold shifts (Spearmans's rho -0.81, $p<0.0001$).

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At POST2, the minimal group had the largest threshold increase regarding the higher frequencies, i.e. additional shift of 27 dB (SD:16), while the moderate group had an additional shift of 14 dB (SD:21), and the severe group an additional shift of 14 dB (SD:13). The additional threshold shifts for the lower frequencies were comparable between the groups, i.e. 11 dB (SD:14), 10 dB (SD:13) and 9 dB (SD:10) for respectively the severe, moderate, and minimal group. At POST3, the additional threshold shift of ~20 dB increase for the higher frequencies was comparable for all three groups. The thresholds at the lower frequencies increased at POST3 less than the higher frequencies, ~7 dB.

Repeated measure ANOVA confirms that frequency, stage and trauma group all had a significant effect on CAP threshold shifts (see Table 3), with respectively p values of <0.0001; <0.001 and 0.006. In addition, no interaction effects were observed between frequency, stage and trauma group for all possible combinations (p>0.2). Lastly, post hoc analysis showed that between pairs of stages the CAP threshold shifts were significantly different between all combinations (i.e. POST1 vs POST2, p=0.007; POST1 vs POST3, p<0.001; POST2 vs POST3, p=0.002).

Table 3. Results from the repeated measure ANOVAs.

CAP		Main effects			Interaction effects[2]			Between pairs analysis[3]		
		Frequency[1]	Stage	Group	Freq × Stage[1]	Freq x Group[1]	Stage × Group	Post1 vs Post2	Post1 vs Post3	Post2 vs Post3
Threshold	F	15.86 (2.60)	38.10 (2.00)	10.47 (2.00)	1.36 (4.11)	1.12 (5.21)	0.71 (4.00)	-	-	-
	P	<0.001	<0.001	0.006	0.27	0.38	0.60	0.007	<0.001	0.002
Amplitude	F	10.34 (3.26)	21.95 (2)	14.33 (2.00)	1.15 (3.96)	1.94 (6.53)	1.04 (4)	-	-	-
	P	<0.001	<0.001	0.002	0.35	0.11	0.42	0.22	0.01	0.004
Latency	F	16.72 (1.21)	5.29 (1.21)	7.79 (2.00)	3.53 (2.13)	0.79 (2.42)	0.90 (2.41)	-	-	-
	P	0.002	0.040	0.013	0.05	0.51	0.46	0.06	0.03	0.03

[1]Greenhouse-Geisser corrected

[2]Interaction of Freq × stage × group was not significant for all three variables

[3] Bonferroni correction

Degrees of freedom (df) given in bracket

CAP amplitude

We examined the change of amplitudes relative to the PRE stage by computing the amplitude ratio. Figure 8 shows the log10 of the mean amplitude ratios at ~90 dB SPL for POST1-3 stages for every trauma group. Across all frequencies the CAP amplitude decreased with each consecutive surgical procedure. As expected, high frequencies (4 – 16 kHz) were affected, however also low frequencies (0.25 – 2 kHz), e.g. at 16 kHz, the mean amplitude ratio of all animals at POST1 was 0.44, and at 500 Hz the mean ratio was 0.65. Every subsequent stage had lower amplitude ratios. Repeated measure ANOVA shows that frequency, stage and trauma group all had a significant effect on CAP amplitude (see Table 3), with p values of <0.001; <0.001 and 0.002, respectively. No interaction effects were observed between frequency, stage and trauma group for all possible combinations (p>0.1).

We analyzed the correlation between CAP threshold shifts and CAP amplitudes ratio (at 90 dB SPL) at POST1 for all frequencies (Figure 9). In general, as shown before, the amplitude ratio values and thresholds are corresponding to histology grouping (i.e. minimal, moderate or severe trauma), with the minimal group animals having largely the same amplitude as in the PRE stage, with small threshold shifts, and the severely affected animals having amplitude magnitudes of around 1% of the PRE stage amplitudes, and thresholds shifts of ~60 dB. The increased threshold and decline in amplitudes at POST1 of all three groups was correlated (Spearman's r of 0.81, p<0.0001). Analysis of the trauma groups separately also showed significant correlation for minimal group (Spearman's r of 0.466, p=0.033), for moderate group (Spearman's r of 0.550 p=0.001) and for severe group (Spearman's r of 0.475, p=0.029). Lastly, post hoc analysis showed that between pairs of stages the CAP amplitude shifts were significantly different between POST1 vs POST3, p=0.01; POST2 vs POST3, p=0.004, however not for POST1 vs POST2 (p>0.2).

6

CAP latency

The mean latency at ~90 dB SPL for each group across all tested frequencies was plotted in Figure 10. At each stage, the latency was dependent on trauma severity, with more trauma leading to longer latencies. The CAP latencies for all frequencies were affected by the surgical interventions, but the degree differed between the lowest frequencies (0.25 kHz and 0.5 kHz) and the higher frequencies (1 kHz – 16 kHz). This latter finding is due to the much longer period lengths of the lower frequencies (period = 1/f). The severe trauma group reached maximum latencies at POST1 (i.e. mean of 10 ms and 6 ms for 0.25 kHz and 0.5 kHz; and mean ~3 ms for the higher frequencies). In contrast, the minimal trauma animals showed a gradual increase of

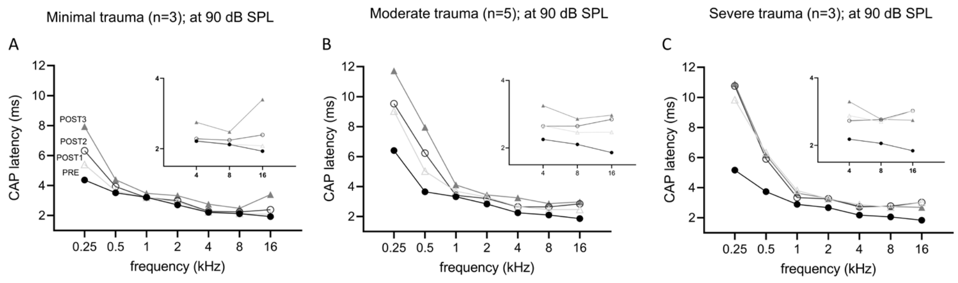

Figure 10. The mean CAP latencies at 90 dB SPL of the three trauma groups are shown for all stages, with insert graphs highlighting the differences at the higher frequencies (4 - 16 kHz). The PRE values were comparable between the three groups. In addition to high frequencies (4 – 16 kHz), the lower frequencies (0.5 – 2 kHz) were also affected in all three groups. The minimal trauma group had the lowest latency shifts, followed by the moderate trauma group (B), and the highest shifts were observed for the severe trauma group (C).

latency with each consecutive stage. The low frequencies' mean latency increased starting with 3.9 ms in PRE stage, to 4.5 ms at POST1, 5.1 ms at POST2 and finally 6.1 ms for POST3. The higher frequencies also showed a trend of latencies becoming longer, with mean latency from 2.3 ms at PRE to 2.5 ms at POST1, 2.7 ms at POST2, and 3.0 ms for POST3. The moderate trauma group showed similar to the mild group gradual increases wit each stage, but with larger steps. Repeated measure ANOVA showed that frequency, stage and trauma group all had an significant effect on CAP latency shift (see Table 2), with p values of 0.002, 0.040 and 0.013 respectively. No interaction effects were observed between frequency, stage and trauma group for all possible combinations. Lastly, post hoc analysis showed that between pairs of stages the CAP latency shifts were significantly different between POST1 vs POST3, p=0.03; POST2 vs POST3, p=0.03, however not for POST1 vs POST2 (p>0.05).

Cochlear microphonics

In Figure 11 an example of CM responses (DIF) is shown for a sound level of ~90 dB SPL for a 8 kHz tone (Figure 11A) and a 500 Hz tone (Figure 11B), and I/O curves for an animal with minimal trauma (animal 20JWA28). For both frequencies the CM was affected by the surgical phases. In addition, as was observed for the CAP responses, the CM responses declined the most at POST2 (i.e. after electrode insertion). In general, threshold shifts were similar for CAP and CM at POST1. Figure 12 shows two exceptions: two moderately affected animals with OSL fracture had much higher CAP threshold shifts (~40 dB) than CM threshold shifts (~18 dB) at 8 kHz. This effect was also seen at 4, and 16 kHz (not shown). In contrast, the remaining two animals in the moderate trauma group, without OSL fracture, had slightly more CM threshold increases (~20 dB) than CAP threshold increases (~15 dB). The animals with minimal trauma had the lowest CAP and CM threshold shifts, with approximately equally affected CAP and CM thresholds. At a lower frequency, at 1 kHz, the CAP and CM threshold shifts were highly correlated for both moderate and minimal group animals (Spearmans's r 0.947, p=0.004), without any outliers.

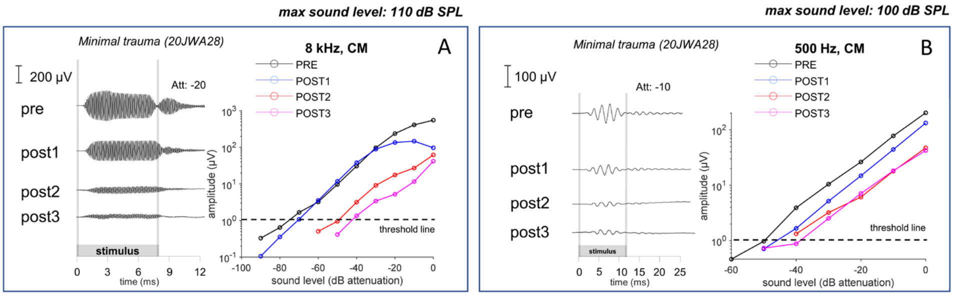

Figure 11. The cochlear microphonic responses to a 8 kHz (A) and 500 Hz (B) tone of one individual minimal trauma animal are shown for all 4 stages at ~90 dB SPL. The graphs show the input/output curve, with threshold criterium of 1 µV amplitude (peak-to-peak). The highest threshold shifts are seen after electrode insertion (POST1) to a 8 kHz tone, however also threshold shifts occurred for the responses to a low frequency tone.

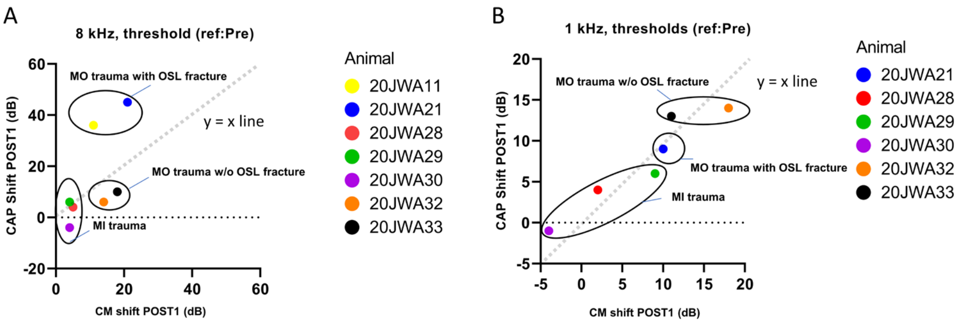

Figure 12. The correlation between the compound action potential (CAP) shift and cochlear microphonics (CM) shift at POST1 stage was assessed. 20JWA11 CM threshold at 1 kHz was near the artefact threshold and therefore omitted. The threshold shifts are shown for responses to 8 kHz (A), and 1 kHz (B) tone. Individual datapoints are shown. Animals with osseous spiral lamina (OSL) fracture had higher CAP threshold shifts than CM threshold shift at 8 kHz (A). However, at 1 kHz, the CAP and CM threshold shift were strongly correlated, with Spearmans's rho of 0.947, with p=0.004.

Discussion

EcochG is a promising tool that might aid the surgeon in minimizing acute trauma during cochlear implantation. To understand the relationship between ECochG and the separate stages of cochlear implantation, we investigated primarily CAP thresholds, amplitudes and latencies before cochleostomy, after cochleostomy, after electrode-array insertion and after withdrawal of the electrode array. We show that ECochG can be affected by both cochleostomy and subsequent insertion of an array, and that these responses declined even further with withdrawal of the array. Additionally, basal trauma, inflicted by cochleostomy, array insertion and/or withdrawal of array, affected not only high frequency regions, but also more apical lower-frequency regions.

In general the induced damage was more substantial than we had anticipated. In only 3 out of 11 cases threshold shifts were mild and correspondingly histological damage in those cases was limited, and similar to the results of Andrade et al. (2022). In an acute ECochG study in guinea pigs they showed minimal effects of cochleostomy and thresholds shifts of around 20 dB after array insertion only for high frequencies mainly corresponding to the location of the electrode array. We think that the moderate and severe cases we observed may be typical for the clinical situation in which the cochlear implantation surgery is performed, also when minimal invasive procedures are conducted. Our data show that without the explicit hearing preservation approach moderate to severe trauma leads to substantial loss of low-frequency hearing.

Cochl y

The CAP changes after cochleostomy correlated with the severity of trauma that was inflicted at the basal turn. The largest CAP changes were probably cause by modiolar wall fracture. Less severe CAP changes occurred with OSL fracture, and almost no CAP changes. The only CAP changes in animals without structural trauma were minor latency increases. In animals with structural trauma, a threshold shift at high frequencies (4 - 16 kHz) was always accompanied with a threshold shift at low frequencies (0.25 – 2 kHz) that was 15 dB smaller. Apparently, (severe) local basal trauma due to the cochleostomy, can affect CAP responses of the apical turn.

The high-frequency loss in animals with trauma, both moderate and severe, might be related to OSL fracture at the basal turn that lesioned the peripheral processes of the basal SGCs. In the severely affected animals, fracture of the modiolar wall at the basal turn, probably caused additional trauma to the cell bodies of the basal SGCs. The low-frequency loss can be related to the basal trauma to the basilar membrane, which potentially impacted its sensitivity and its passive contribution to the traveling wave (Nuttall & Dolan 1996), hereby reducing the sensitivity at the apical turn.

Local basal trauma in guinea pigs can affect SGCs more than the basilar membrane in some instances (Figure 11). We observed that CAP threshold shifts were larger than CM threshold shifts at 8 kHz in animals with OSL fracture at the basal turn. This can be explained by the relatively large OSL, that crosses the space between the modiolus and the organ of Corti. Therefore, the OSL can be damaged without violating the borders of the scala media. In addition, considering the angle of the cochleostomy, the OSL was fractured near the modiolar side (more medial) rather than near the basilar membrane (i.e. more lateral). In a human study, it has been shown that, indeed, a change of position of the cochleostomy site, i.e. more anteriorly than inferiorly, might damage the OSL more easily (Iseli et al., 2014). If the discrepancy of CAP and CM thresholds at higher frequencies is indeed related to local trauma of the OSL, agrees with the CAP and CM thresholds being equally affected at a low frequency (Figure 12).

Chronic experiments in normal-hearing guinea pigs have shown that CAP responses to lower frequencies can be affected after array insertion (Honeder et al., 2016; Honeder et al., 2019). Their cochleostomy position was similar to our study (0.5 – 1 mm from the RW in both studies), and similar CAP recordings were conducted with gold electrode wire on the RW (Honeder et al., 2018). However, because these studies measured only after insertion, the effect of cochleostomy is not entirely clear. In addition, those experiments were chronically performed, as opposed to our acute experiments. This raises important differences. Timepoint of measurement is delayed in the chronic experiments, raising the possibility of additional trauma that is not related to cochleostomy nor electrode insertion. Also, the (in)reversibility of the CAP responses could not be tested with withdrawal of array for obvious reasons in a chronically implanted animal. Still, these studies showed mean CAP threshold shifts of 20-30 dB for low frequencies (0.5 – 2 kHz) postoperatively after electrode insertion through a cochleostomy. These threshold shifts were similar to our study. We have shown in the present study that insertion trauma causes these changes, and in addition that trauma due to cochleostomy might enhance these changes even more. The responses improved approximately 10 dB after one month in the Honeder studies, which raises the question whether the acute effects, as observed in our study, are temporarily. It is likely that the acute effects, that are caused by structural trauma, such as in our study with the moderate and severe group, are long lasting. In contrast, the threshold shifts in the minimal trauma group, even though threshold shifts occurred after array insertion, might be more of temporarily fashion. Progressive deterioration after cochleostomy affecting the cochlear responses is unlikely to have occurred in this study considering the short time intervals between the different stages (1-2 hour), although it cannot be excluded.

Electrode insertion

In our study, the electrode array reached approximately the upper basal semiturn of the cochlea in guinea pigs (depth of 4 – 5 mm). Based on the Greenwood function, the directly affected frequency range would be around 10 – 30 kHz (Greenwood 1990; van Ruijven et al., 2005), which is near to or at our high frequency range of 4 -16 kHz. Thus, changes to the CAP at the high frequencies are expected. However, in all trauma groups, electrode insertion trauma occurred also at low frequencies (threshold shift of 10 dB, ~10 dB less than high frequencies).

Previous animal studies investigated mainly insertion trauma by measuring responses at the RW, and subsequently during electrode insertion through the RW. These studies were performed in normal-hearing, or high-frequency deafened gerbils, in which RW insertion is more feasible than in guinea pigs (Adunka et al., 2010; Choudhury et al., 2011; DeMason et al., 2012). They all showed higher CAP and CM thresholds for lower frequencies upon electrode insertion. Recordings performed with RW or intracochlear array electrodes, showed that the CAP and CM responses to low frequencies deteriorated after array insertion limited to the basal turn. These measurements correlated in most instances with anatomical damage to basilar membrane or OSL (or both).

Various factors might play a role in local basal turn trauma affecting the function of the apical cochlear areas. The array touching the basilar membrane changes its position, which affects the mechanical response. Other factors are reduction in blood flow volume, due to disruption of capillaries or small blood vessels around the basilar membrane and osseous spiral lamina, and additional disruption of the homeostasis when the stria vascularis is damaged (Nakashima et al., 2002; Shi, 2016). Red blood cells, which are ototoxic, at the basal region might be pushed more apically by the array during insertion. Trauma to cochlear structures can lead to mixture of endolymph, located in the SM, and perilymph, which is located in the ST and SV, abolishing the endocochlear potential (Reiss et al., 2015). It has also been reported that intracochlear shift of pressures upon cochleostomy and/or array insertion can affect the general function of the cochlea acutely (Greene et al., 2016; Gonzales et al., 2020). The array with its diameter of 0.5 mm is inserted for 4 mm into the scala tympani, reaching the location where the scala tympani has a width of about 0.5 mm (Wysocki and Sharifi, 2005). This may have caused increased pressure changing the basilar membrane position. Conversely, leakage of perilypmh may reduce the pressure, thereby also negatively affecting the basilar membrane response (Todt et al., 2017). It is likely that the above mentioned mechanisms all contribute to the (negative) effect of basal trauma on apical cochlear areas.

The damage is correlated to the size and stiffness of the electrode array. Studies have shown that lower threshold shifts occurred, at both low and high frequencies, with smaller and flexible arrays (Choudhury et al., 2014; Drouillard et al., 2017). Similar to the present study, insertion trauma was not always accompanied with (severe) structural trauma in those studies.

Interestingly, a study using ABR recordings in normal-hearing guinea pigs showed that at 1 week after cochlear implantation no difference in ABR threshold shifts was found between animals with and animals without OSL fracture at 2 - 32 kHz (Chambers et al., 2019). They did find increased thresholds of 20 - 30 dB in general. This discrepancy with our study might be due to methodological differences. The ABRs might be less sensitive to trauma, compared to CAP, since they are much smaller. In addition, they measured one week after surgery, which is possibly enough time for the non-trauma group to develop other traumas related to chronic implantation (e.g. tissue inflammation).

Withdrawal of the array led to a further worsening of responses, which indicates that trauma caused by insertion, rather than the mere presence of the array, affects the responses. We reason that the presence of the array can affect the ECochG temporarily by touching the basilar membrane and/or increasing the scalar pressure. It can affect ECochG permanently by damaging structures. In the former case removal might have caused recovery of responses. On the other hand, removal may cause additional mechanical trauma. It has been shown that the endocochlear potential might be affected by presence of the electrode array (Oshima et al., 2014; McClellan et al., 2021). However, those studies also suggest that the role of the endocochlear potential is delayed after cochlear implantation, and might affect predominantly the area with direct trauma. It is therefore likely that the increased thresholds observed in this acutely performed study were not caused by a reduced endocochlear potential.

Conclusion

We found that cochleostomy can be performed without causing cochlear structural damage and effect on the responses, but that subsequent insertion leads to deterioration of the responses for each of the included 11 animals. The extent of deterioration of ECochG was associated with the severity of trauma by cochleostomy or electrode insertion. In addition, even though the cochleostomy is drilled in the basal turn and the electrode array does not reach beyond the basal turn, ECochG responses to the lower frequencies can be significantly affected as well. This implies that basal trauma should be minimized in order to preserve the low-frequency residual hearing of CI recipients. Even though minimal invasive procedures are conducted, the surgeon should be aware of the negative impact of this surgical procedure.

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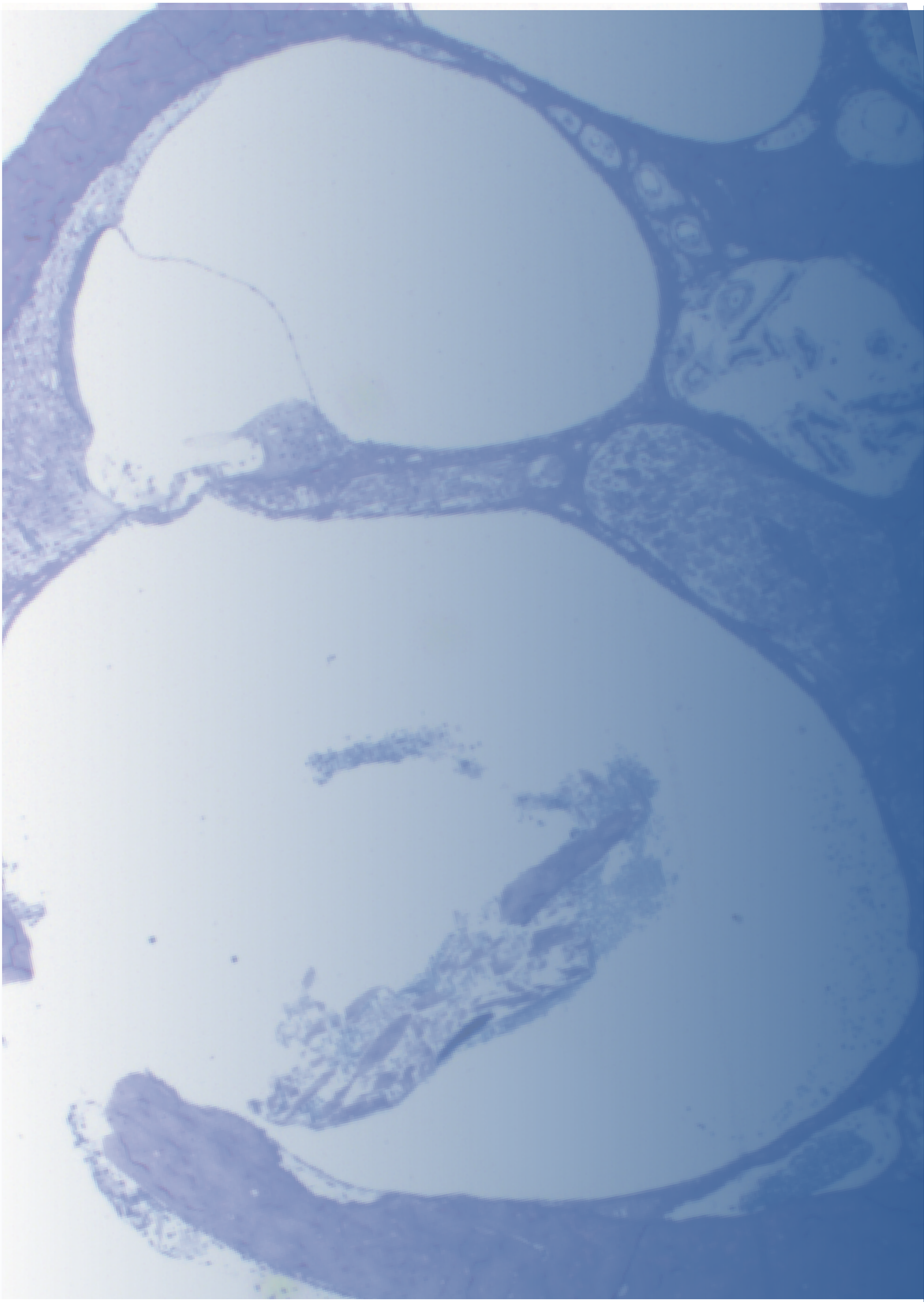

Chapter 7

Evaluating cochlear insertion trauma and hearing preservation after cochlear implantation (CIPRES):

A study protocol for a randomised single-blind controlled trial

Saad Jwair, Ralf A. Boerboom, Huib Versnel, Robert J. Stokroos, Hans G.X.M Thomeer

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Abstract

Objectives

In order to preserve residual hearing in patients with sensorineural hearing loss (SNHL) who receive a cochlear implant (CI), insertion trauma to the delicate structures of the cochlea needs to be minimized. The surgical approach comprises the conventional mastoidectomy-posterior tympanotomy (MPT) to arrive at the middle ear, followed by either a cochleostomy (CO) or the round window (RW) approach. Both techniques have their benefits and disadvantages. Another important aspect in structure preservation is the design of the electrode array. Two different designs are used: a 'straight' lateral wall lying electrode array (LW), or a 'pre-curved' perimodiolar lying electrode array (PM). Interestingly, until now, the best surgical approach and design of the implant is uncertain. Our hypothesis is that there is a difference in hearing preservation outcomes between the four possible treatment options.

Methods

We designed a monocenter, multi-arm, randomized controlled trial to compare insertion trauma between four groups of patients, with each group having a unique combination of electrode array type (LW or PM) and surgical approach (RW or CO). In total, 48 patients will be randomized into one of these four intervention groups. Our primary objective is comparison of postoperative hearing preservation between these four groups. Secondly, we aim to assess structure preservation (i.e., scalar transposition, with basilar membrane disruption or tip fold-over of array) for each group. Thirdly, we will compare objective outcomes of hearing and structure preservation by way of electrocochleography (ECochG).

Discussion

Cochlear implantation by way of a cochleostomy or round window approach, using different electrode array types, is the standard medical care for patients with severe to profound bilateral sensorineural hearing loss, as it is a relative simple and low-risk procedure that greatly benefits patients. However, loss of residual hearing remains a problem. This trial is the first randomized controlled trial that evaluates the effect of cochlear insertion trauma of several CI treatment options on hearing preservation.

Trial registration

This trial ('CIPRES') is registered in the Netherlands Trial Register (www.trialregister.nl).

Introduction

In people with severe sensorineural hearing loss or deafness, hearing can be (partially) restored with a cochlear implant (CI). A CI bypasses the sensory hair cells and directly stimulates the auditory nerve via electrical current pulses, allowing deaf patients to hear again. Cochlear implantation has become a standard and accepted treatment for severely hearing impaired patients throughout the years in high income countries. Hearing with a CI has seen a tremendous development in auditory perception, from only sound detection in the 1980s to speech understanding in the last decades (Eshraghi et al., 2012). However, speech understanding is far from optimal, especially in difficult situations where background noise is present, and perception of other sounds as music can also be quite troublesome. Several studies have shown that preserving residual hearing can lead to better hearing outcomes, especially in noisy environments (Gfeller et al., 2006; Buechner et al., 2008; Gifford et al., 2013; Skarzynski et al., 2014). In order to preserve residual hearing, trauma to the delicate structures of the cochlea needs to be minimized during the surgical implantation procedure.

The surgical procedure commonly starts with the conventional mastoidectomy-posterior tympanotomy (MPT) approach to the middle ear, and is followed by accessing the cochlea, either through a cochleostomy (CO) or the round window (RW). Several papers, including systematic reviews comparing CO and RW approaches in literature, concluded that evidence lacks regarding preference for one or the other approach with respect to hearing preservation (Havenith et al., 2013; Wanna et al., 2014; Wanna et al., 2015; Fan et al., 2018; Snels et al., 2019). Both techniques of accessing the cochlea have their potential pros and cons (e.g., cochleostomy leads to a smaller angle of insertion and by definition induces damage to outer bony wall and spiral ligament, while the RW approach ensures a correct positioning of the electrode array and leaving outer bony wall and spiral ligament intact). The extended round window (ERW) approach will not be tested in this study. The ERW approach is a combination of the direct RW and cochleostomy approach, and is generally considered to be a variant of the cochleostomy approach. It is therefore unlikely that the ERW approach would be significantly different than the cochleostomy approach. One may also argue a preference for a certain approach based on individual cochlear structures. Several studies for example have clearly shown that each human cochlea has a different 'cochlear hook' in parallel with one's unique fingerprint (Avci et al., 2017; Escude et al., 2006; Rask-Andersen et al., 2011).

Correct insertion, for both cochleostomy and round window approach, ensures that the implant is in the scala tympani of the cochlea (O'Connell et al., 2016). If during insertion, the CI translocates to the scala vestibuli or scala media, the basilar membrane with the organ of Corti (the physiological receptor organ that transduces the acoustic energy) is damaged. Scalar translocation can negatively influence the final hearing outcome and hearing preservation of CI patients (Holden et al., 2013; Shaul et al., 2018).

Another aspect relevant for minimizing insertion trauma, is the design of the electrode array. There are two fundamentally different designs: a 'straight' lateral wall lying electrode array (LW), or a 'precurved' perimodiolar lying electrode array (PM). No evidence has been provided that one design outperforms the other in terms of hearing with a CI and structure preservation (Holden et al., 201; Wanna et al. 2014; Snels et al., 2019). On the one hand, lateral wall positioning might be the best way to preserve structures as the osseous spiral lamina, and basilar membrane; on the other hand, perimodiolar positioning might provide better hearing with a CI (which is the ultimate objective for deaf patients with a CI), as the electrodes are situated closer to the medially situated spiral ganglion cells which form the auditory nerve and need to be electrically stimulated. In addition, the perimodiolar array has the potential to minimize contact between the array and the lateral wall, leading to structure preservation of the lateral wall and stria vascularis.

According to one study, speech perception scores were better for the LW group (O'Connell et al., 2016). On the contrary, other studies report better speech perception outcomes for the PM group (Holden et al. 2013; Wanna et al. 2014). The majority of the studies, however, showed no difference between both groups (Doshi et al., 2015; van der Marel et al., 2015; van der Jagt et al., 2016; Fabie et al., 2018; Moran et al., 2019). However, all these studies had a high risk of bias. In addition, the studies failed to differentiate between the surgical approaches, inducing a major confounding factor. Additionally, an interaction effect may be present with the effect of the electrode array type on surgical approach and other outcomes being different for the two surgical approaches.

It is unclear which surgical approach and electrode design is most suited to achieve minimal insertion trauma, and thereby preserving residual hearing in cochlear implantation surgery. Therefore, it is not surprising that worldwide both type of approaches and electrode designs are used.

Considering the surgical approach and electrode array design, it is important to note that during insertion no reliable feedback is provided regarding the array tip position in relation to the intracochlear structures. After inserting the tip of the electrode array in the round window perforation or cochleostomy, only tactile feedback is available which might not be sufficient to distinguish whether the implant is correctly inserted.

One of the possibilities to view the intracochlear structures and thereby discern the scalar location of the array in relation to the micro-anatomical structures (thus providing postoperative feedback), is by applying imaging techniques after surgery such as cone beam computed tomography (CB-CT), which has been proven to be reliable in differentiating the different scalae and exact electrode array position (Saeed et al., 2014; Zou et al., 2015; Mosnier et al., 2017). Another possibility to detect insertion trauma is by intraoperative electrophysiological measurements, providing indirect feedback: intracochlear electrocochleography (ECochG) which measures responses of residual functioning hair cells and spiral ganglion cells to acoustic tone stimuli. During insertion, ECochG measures can be used to assess the probability of insertion trauma, thus providing feedback of the insertion (Choudhury et al., 2012; Dalbert et al., 2015; Giardina et al., 2019; Fontenot et al., 2019).

Objectives

The primary objective of this study is to compare hearing preservation after cochlear implantation between the four possible combinations of surgical approaches (CO and RW) and electrode array designs (LW and PM). Hearing preservation will be measured postoperatively with pure tone audiometry. Secondary objectives are to compare the effect of these interventions on scalar position and ECochG measures. Furthermore, we aim to assess the relationship between the outcome measures for hearing preservation (audiometry, ECochG and postoperative CT).

Trial design

This study concerns a single-blind, mono-center, multi-arm randomized trial. All four treatment options are implemented interchangeably in standard medical care. Our hypothesis is that there are differences in hearing preservation between these four treatment options. Participants will be blinded for surgical approach/type of electrode. In total, 48 participants will be included, all groups carry the same equal weight (allocation ratio 1:1:1:1). In case of a drop out, a replacement will be included to ensure 48 participants who completed the study.

Methods

Study setting

This is a mono center study performed at the department of Otorhinolaryngology in the University Medical Center Utrecht, an academic hospital, and is expected to run for approximately three years.

Eligibility criteria

All participants will undergo the usual standard medical care of work-up before, during and after cochlear implantation. The work-up includes a pure tone audiogram (PTA), a speech audiogram, a preoperative CT, and interviews with speech therapist, audiologist, ENT surgeon and social worker. In a multidisciplinary meeting, the Cochlear implantation team of the UMC Utrecht will assess all results and decide whether a patient is eligible for a CI. A patient is eligible if phoneme score (based on CVC words) with hearing aids ≤ 60% and/or speech perception with noise is insufficient according to criteria adopted by Snel-Bongers et. al (2018). In addition, the personal expectations, beliefs and motivation of the patient play an important role. In addition, according to standard medical care, participants will receive corticosteroids before and after surgery.

Inclusion Criteria

- Dutch language proficiency
- 18 years or older
- Choice for Advanced Bionics implant
- No signs of acute or chronic middle ear infections and/or mastoiditis

Exclusion Criteria

- Prior otologic surgery in the implanted ear (excluding tympanostomy tube placement)
- Inner ear malformation (i.e. ossification, Mondini malformation)
- Retrocochlear pathology
- Neurocognitive disorders
- Acute or Chronic otomastoiditis

Who will take informed consent?

Participants ENT-physician or audiologist during visits to the outpatient clinic will asks whether the patient would be interested to participate in the study. Additional verbal and written information about the study will be provided to all participants by an investigator. An investigator will also provide and obtain the informed consent (IC) form, which is also co-signed by the investigator. There will be ample opportunity (at least 1 week) for the participants to consider participation and discuss their questions with one of the investigators before the participants may decide to sign the IC form in order to participate. Participation in the study is entirely voluntary. If a subject wants to participate, several appointments for the audiological follow-up will be scheduled. If a patient does not want to participate, contact with the investigator will be terminated.

Additional consent provisions for collection and use of participant data and biological specimens

Not applicable, no additional consent is required for use of participant data and biological specimens.

Explanation for the choice of comparators

Four groups of participants will be included, which all have a different combination of electrode type, and surgical insertion approach. These treatment options are all standard care in cochlear implants centers worldwide.

Intervention description

The electrode type consists of either a lateral wall electrode array, or a perimodiolar electrode array, specifically, respectively the SlimJ and Midscala electrode arrays. Both these arrays are developed by Advanced Bionics. Two surgical approaches are used, a round window or cochleostomy approach. The cochleostomy is placed antero-inferiorly from the round window niche.

Criteria for discontinuing or modifying allocated interventions

It is only possible to change the allocated intervention via a second surgery, by removing the cochlear implant. A second surgery increases potential harm for the patient, outweighing potential benefits. Therefore, removal of the cochlear implant is only performed if medically necessitated, e.g. in instances of malfunctioning device, wound infection or persisting pain. Such rare cases will be discussed in a plenary session dedicated for cochlear implant patients, in line with normal standard medical care.

Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

Strategies to improve adherence to interventions

To improve adherence to the study protocol, the follow-up measurements for the study are planned simultaneously with the standard medical rehabilitation appointments. Apart from showing up for the follow-up appointments, participants do not need to adhere to specific tasks.

Relevant concomitant care permitted or prohibited during the trial

Not applicable, there is no relevant concomitant care that is permitted or prohibited.

Provisions for post-trial care

The sponsor has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research participants through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

Outcomes

At intake baseline data will be collected, including gender, age, duration of deafness, pre- or post-lingually deafened, cause of deafness and side of implantation. In addition, the most recent pure tone thresholds (250 Hz, 500 Hz and 1, 2, 4, and 8 kHz) and speech reception thresholds (SRT) for consonant-vowel-consonant (CVC) word lists in quiet for both ears will be collected. See figure 1. time schedule of all outcomes

Hearing preservation (primary outcome)

Hearing preservation is calculated by comparing pure-tone thresholds after and before CI surgery using the following equation (Skarzynski et al. 2013), Eqn. 1:

$$\text{HP} = 1 - \frac{PTApost - PTApre}{PTAmax - PTApre}$$

In this equation, HP is hearing preservation, *PTApre* is the average pure-tone (unaided) hearing threshold of 125, 250 and 500 Hz measured preoperatively, *PTApost* is the same average pure-tone hearing threshold measured postoperatively, and *PTAmax* is the maximum sound intensity generated by a standard audiometer (usually between 90 and 120 dB HL). With full preservation of hearing, HP=1, and with complete loss of hearing HP=0. The postoperative tone audiometry will be measured at 1, 3, 6 and 12 months after activation of the cochlear implant. Primary outcome measure is the average hearing preservation over the four follow-up measurements.

Secondary outcomes

Scalar positioning of the electrode array

We will use the CB-CT scanner (Newtom VGi EVO, Cefla Italy) to postoperatively assess the scalar location of the electrode array in cochlea's of all four groups. The CB-CT has been proven to be the best imaging modality to date, for assessing the scalar location postoperatively, as it has low radiation artefacts (caused by the metal parts of the cochlear implant) and high spatial resolution needed to image the cochlea and its internal parts. Other advantages of this modality are amongst others that it has relatively low radiation exposure, is less likely to trigger claustrophobic events and requires shorter scanning durations compared to traditional CT scanners (Li 2013; Nardi et al., 2018; Casselman et al., 2013). CB-CT imaging postoperatively leads to exposure of low-dose radiation (effective dose: 0.18 mSv), and is therefore considered to be of low-risk.

We will assess CI translocation by making multiplanar midmodiolar reconstructions of the CB-CT images, which is validated (Mosnier et al., 2017; Zou et al., 2015; Saeed et al., 2014). These multiplanar reconstructions will allow us to systematically indicate for every electrode contact of the electrode array the exact scalar position (i.e. scala tympani or scala vestibuli).

Electrocochleography

Electrocochleography (ECochG) is a method for recording the electrical potentials of the cochlea. The ECochG is composed of several components: the compound action potential (CAP), auditory nerve neurophonic (ANN), cochlear microphonics (CM) and the summating potential (SP). In essence, the CAP and ANN reflect auditory nerve activity, the CM and SP are generated by the hair cells of the organ of Corti. The CM is an alternating current response following the tone, and the SP is a direct current response. Outcome measures include the total ECochG amplitude. Potentially, the difference in the amplitude of the total ECochG response after and before insertion might contain information about insertion trauma, i.e. damage to the basilar membrane, stria vascularis or other structures.

Intraoperatively we will use the most apical contact point of the electrode array to measure these outcomes during insertion. The acoustic pure tones stimuli will be delivered via an earphone (earplug) on the operated ear. This will be coupled to the measurement equipment (active insertion monitoring system, Advanced Bionics) that is provided by the manufacturer. The amplifier in the implant will be used for amplification of the response. Apart from prolonged surgery time (estimate of 10 mins), there will be no added risk for the participant. Postoperatively ECochG measurements will be repeated. We will perform recordings at each of the 16 electrodes for the following frequencies: 125, 250, 500 Hz and 1, 2, 3, 4 kHz. In addition, acoustic tone thresholds will be indirectly estimated by measures of the total ECochG responses.

Speech perception

One year after activation of the CI, a conventional speech perception test in quiet and in noise will be performed with CVC words from the 'Nederlandse Vereniging voor Audiologie' (NVA: Dutch Society of Audiology) word-list. Speech reception thresholds will be registered. Also, the clinical spectral ripple test, which uses ripples instead of words, can be used to complement speech perception scores in noise (Drennan et al. 2014). The extra ECochG measurements and tone/speech tests are not considered to be of any risk for the participants.

Participant timeline

Schedule of enrolment, interventions, and assessments is depicted in Figure 1. Participants will be screened and enrolled two weeks before the surgery. On the day of surgery the participant will be allocated to one of the four groups (A-D). During surgery intraoperative ECochG measure will be conducted. The CB-CT scan will be performed on the same day after surgery. Activation of the CI is approximately 4-6 weeks after surgery. After activation of the CI, the first audiometry and postoperative ECochG measures will be conducted. These measurements will be repeated at approximately 2, 5 and 12 months after activation of the CI.

CIPRES TRIAL	STUDY PERIOD							
	Enrol-ment	Allo-cation	Post-allocation					Close-out
TIMEPOINT	-2 wk.	0	Day 0	wk. 4-6	mo. 3-4	mo. 6-7	mo. 13-14	mo. 14
ENROLMENT:								
Eligibility screen	■							
Informed consent	■							
Allocation		■						
Surgery (including ECochG)			■					
Cone beam CT			■					
Activation of Cochlear Implant				■				
1st audiometry/ECochG				■				
2nd audiometry/ECochG					■			
3rd audiometry/ECochG						■		
4th audiometry/ECochG							■	■
INTERVENTIONS:								
Intervention A, (RW/LW)	←	—	—	—	—	—	—	→
Intervention B, (RW/PM)	←	—	—	—	—	—	—	→
Intervention C, (CO/LW)	←	—	—	—	—	—	—	→
Intervention D, (CO/PM)	←	—	—	—	—	—	—	→
ASSESSMENTS:								
Baseline variables	■							
Primary Outcome: PTA thresholds				■	■	■	■	
Secondary Outcomes:								
Intraoperative ECochG			■					
CI position			■					
Post-op ECochG				■	■	■	■	
Speech perception							■	

Figure 1.
Schedule of enrolment, interventions, and assessments adapted from the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)

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Sample size

Hearing preservation as computed according to Eqn. 1 is the primary outcome variable. Sample size calculation was based on a comparison of the means between the four treatment groups using the overall F-test for an ANOVA. Based on three studies in literature (Manjaly et al., 2018; Rader et al., 2018; Sierra et al., 2019) we expect a large range of hearing preservation within each group, from 0 (no preservation, i.e., loss of all hearing) to 100 (full preservation, hearing stable), and occasionally above (improved hearing). In a single group with mean score of 50, we expect 60% of observations to lie between 25 and 75 points yielding a within-group standard deviation of 30 points assuming a normal distribution. A clinically relevant difference was defined as a difference of 40 points between means in the intervention group with lowest and highest mean hearing preservation. Assuming means in groups are equally spaced (e.g. 30, 43.3, 56.7, and 70 points) between-group standard deviation is anticipated to be approximately 17.2 points. The corresponding effect size f, found by dividing between-group by within-group standard deviation, equals 0.57. To detect this effect size with 90% power when testing at the 5% significance level, 12 participants need to be included in each of the four treatment groups. The total sample size is set at 14 per intervention group to account for a 10% drop-out rate. Smaller effects can likely be detected because the primary outcome is measured at four different time points for each participant. Assuming a within-subject correlation of 0.5, then the four follow-up measurements per participant will allow detection of effect sizes of $f = 0.45$ and larger. We used G*power (version 3.1.9) to calculate the power.

Recruitment

No particular strategies were developed to increase the likelihood of participant enrolment. However, in developing the protocol, efforts were made to limit the extra burden for participants participating in this study. For example, follow-up measurements are planned on the same days of rehabilitation appointments. Also, based on previous experience and data, we expect to achieve adequate participant enrolment to reach our targeted sample size.

Sequence generation

A separate independent department, the Julius Research and Epidemiology Department of the University Medical Center Utrecht, will handle the method of generating the allocation sequence. Randomisation will be stratified by age, with two subgroups: 18-50 years and more than 50 years. Every participant will be allocated randomly a number, that is generated with a computer, from 4 numbers that are possible (each referring to a unique treatment group). The research tool software of the Julius center and Epidemiology department will be used to generate the random sequences. Random sequences will be generated separately for the two age strata. In each age stratum, block randomisation is used.

Concealment mechanism

The allocation will be done before surgery, and after IC approval and screening. Participants will no be informed about the treatment group to which they have been allocated.

Implementation

The Julius centre and epidemiology department will generate the allocation sequence with their own developed research tool for randomisation. A participant can be included by every member of the research team, when in doubt, the inclusion will be judged by the whole research team. Subsequently, based on the allocation, the patient is assigned to one of the groups by a member of the research team.

Who will be blinded

This study is single-blind, meaning that only participants are blinded for the treatment allocation. Because of the nature of the intervention (type of surgery and intracochlearly placed electrode array), it is impossible for the patient to discover the allocation. The research team is not blinded. The audiology assistants, however, who will perform the audiometry, are blinded. In addition, the offline outcome data will be blindly analysed.

Procedure for unblinding if needed

In rare cases in which the device has to be removed via surgery unblinding may be permissible. Before the second surgery, the subject will be unblinded by a member of the research team, who will discuss the treatment options with the subject. If needed, the surgeon will also be informed about the exact intervention, as is standard in medical practice.

Plans for assessment and collection of outcomes

All data will be collected using an electronic data capture (EDC) tool (Castor EDC). The UMC Utrecht healthcare data of the participants, including baseline outcomes, CT images and results of the audiometry will be derived from the electronic patient file. The assessors are specialized in otorhinolaryngology, and therefore they are trained in assessing the audiology, CT images and electrophysiology data of this study.

Plans to promote participant retention and complete follow-up

Once a participant is enrolled and randomized, the study site will make every reasonable effort to follow the subject for the entire study period. Participants can leave the study at any time for any reason if they wish to do so without any consequences. Participants who withdraw from the study or who terminate the recording sessions prematurely, in the absence of any adverse event, will not be followed. Participant retention will be increased by schedule strategies, e.g. by planning the follow-up measures on the same day of clinical rehabilitation. Participants will also be reminded of the study via e-mail between sessions, including information of any published results (if they are interested).

Data management

All data will be handled confidentially and research data will be coded by using a unique patient identification number. To be able to reproduce the study finding and to help future users to understand and reuse the data all changes made to the raw data and all steps taken in the analysis will be documented. The database files will be kept for 15 years after the study has ended.

Confidentiality

The key to the code will be safeguarded by the investigators. All data will be stored on the research network disc of the UMC Utrecht in a secured research folder structure. Only the team of investigators will have access to the database files.

Statistical methods

Statistical methods for primary and secondary outcomes

We will use linear mixed models to compare the primary outcome measure (hearing preservation) between the four treatment groups. Linear mixed models will include a random effect for participant and fixed effects for intervention group and follow-up visit. In case the overall F test for comparing the intervention groups is significant, we will compare means in intervention groups pairwise through posthoc tests using a Bonferroni correction. Fisher's exact test will be used to compare the proportion of patients with correct electrode location within the scala tympani (correct location after insertion) between the four intervention groups. If the test compare four groups is significant, then proportions will be compared between each pair of treatment groups separately by means Fisher's exact tests and accounting for multiple testing through use of a Bonferroni correction.

Secondary analyses will include testing of main effects of surgery type and electrode array type and their two-way interaction. For hearing preservation outcomes this will be done using linear mixed models. For scalar translocation outcomes we will use logistic regression. We will also use linear mixed model analysis to identify independent additional predictors for hearing preservation. Among the factors to examine are insertion depth and cochlear volume.

We will use a Pearson correlation test to quantify the strengths of association between ECochG responses and hearing preservation at the various time points (during and after cochlear implantation). All analyses will be done on an intention-to-treat basis. A two-sided significance level of 5% will be used. The normality assumption for the residuals will be assessed visually using normal-probability plots. In case normality assumption does not hold, we will use either a transformation of the outcome or an appropriate non-parametric test for comparing the continuous outcomes between treatment groups.

Interim analyses

Independent analysis of the Institutional Review Board (IRB) or in Dutch 'Medisch Ethische Toetsing Commissie' (METC) classified this study as a low risk, not needing a data safety monitoring committee (DSMC), mainly because all interventions are standard medical care. Therefore, no interim analyses will be conducted during this trial.

Methods for additional analyses (e.g. subgroup analyses)

Participants age might play an important role in outcomes, however the randomization procedures is stratified for age which minimizes confounding by age. We will test for an interaction effect of the electrode type and surgical approach using multivariable linear and logistic regression.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data

Participants who withdraw from the study or who terminate the recording session prematurely will be considered as lost and will be replaced. Reasons for withdrawal or premature termination will be documented. We expect a withdrawal rate of participants of no more than 10% (since N=48, this is 2 per group). The number of replacements will be limited to two persons per treatment group. Missing at random assumption will be made for the linear mixed model analyses. Depending on the missing values, multiple imputation or simply list wise deletion will be conducted for the missing values in linear and logistic regression analysis.

Plans to give access to the full protocol, participant level-data and statistical code

Data sharing, including full protocol, participant datasets and statistical codes will be considered upon reasonable request.

Composition of the coordinating centre and trial steering committee

Trial quality will be independently monitored by a local monitor (UMC Utrecht) once a year. The local monitor will check at least 10% of the signed ICs. From the first five participants the in- and exclusion criteria will also be checked. The monocenter study file will be also monitored. This study has no public involvement group.

Composition of the data monitoring committee, its role and reporting structure

Not applicable, a data monitoring committee is not appointed for this study.

Adverse event reporting and harms

Adverse events (AE) will be recorded; serious adverse events (SAE) will be reported to the local IRB, and centrally stored in a digital database. Serious adverse events are not expected, but in case they do occur, the research group can decide to terminate prematurely the study.

Frequency and plans for auditing trial conduct

The investigators will submit a summary of the progress of the trial to the accredited IRB once a year. Information will be provided on the date of inclusion of the first subject, numbers of participants included and numbers of participants that have completed the trial, serious adverse events/serious adverse reactions, protocol violations, other problems, and amendments.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees)

Amendments are changes made to the research after a favourable opinion by the accredited IRB has been given. All protocol amendments will be notified to the IRB for approval. Non-substantial amendments will not be notified to the accredited IRB and the competent authority, but will be recorded and filed by the sponsor.

Dissemination plans

The trial results will be made accessible to the public in a peer-review journal, preferable in an open access-study journal. In addition, key trial results will be presented in national and international conferences and other relevant meetings. There are no publication restrictions

Discussion

Cochlear implantation by way of a cochleostomy or round window approach, using different electrode array types, is the standard medical care for patients with severe to profound bilateral sensorineural hearing loss, as it is a relative simple and low-risk procedure that greatly benefits patients. Despite the increased interest in hearing preservation, loss of residual hearing remains an important problem in cochlear implantations. This might be caused by a lack of adequate, randomized, and blinded prospective studies, investigating hearing preservation in CI patients. There are studies that investigated hearing preservation in CI patients, however these studies have a high risk of bias. Therefore, the level of evidence for many aspects of hearing preservation is low. This trial is the first prospective, randomized controlled trial that evaluates the effect of cochlear insertion trauma of several CI treatment options on hearing preservation. Another strength of this study, is evaluation of insertion trauma by three separate assessment tools: audiometry, electrophysiology and CT imaging. These tools can complement each other, potentially leading even to detection of minimal insertion trauma. In addition, the multiple outcome measures allow us to investigate insertion trauma on the short and long term.

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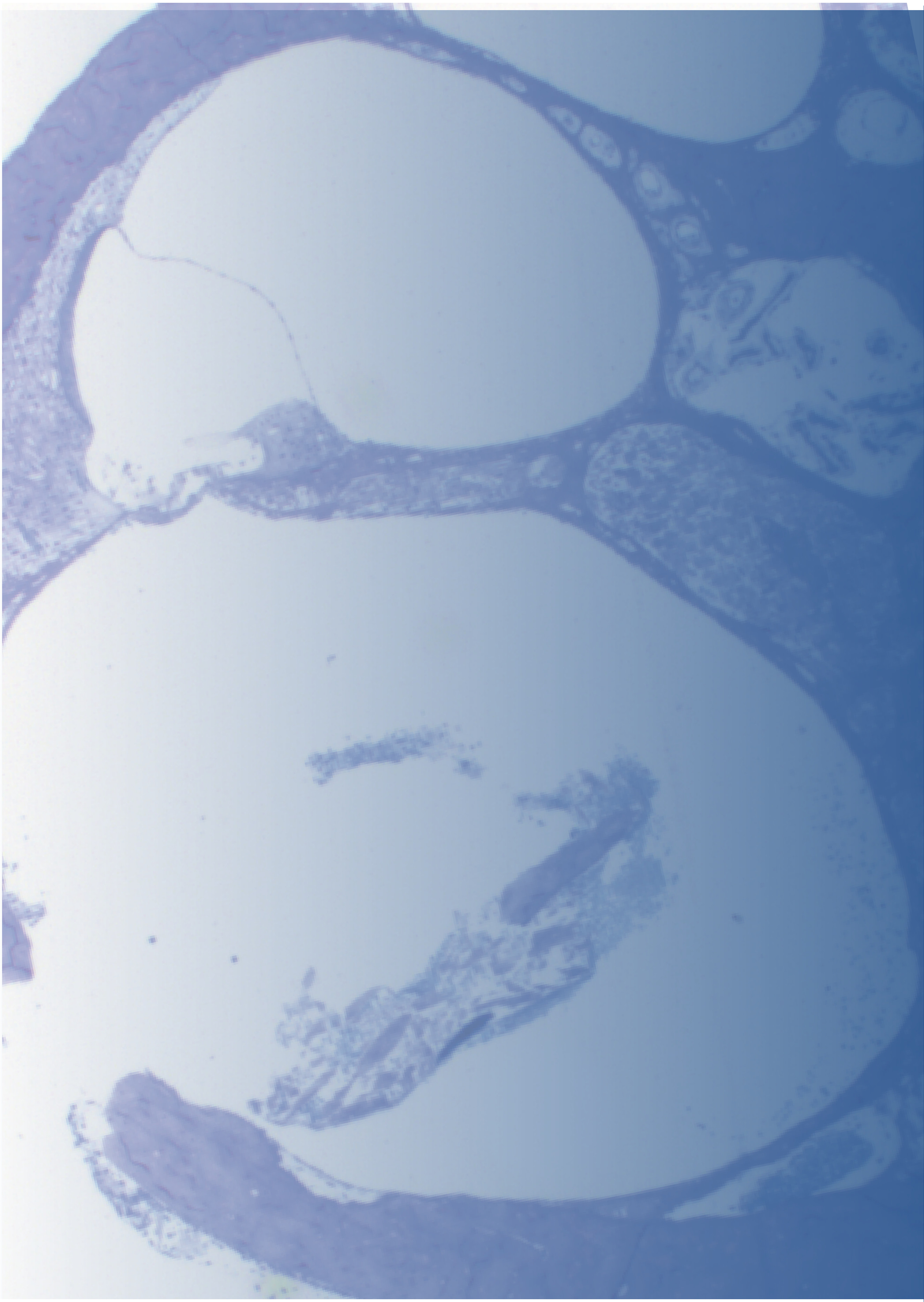

Chapter 8

General discussion

General discussion

Patients with severe-to-profound hearing loss and patients who struggle to understand speech with hearing aids during normal listening conditions are eligible for a cochlear implant (Carlson 2020; Wilson et al. 2017). The cochlear implant bypasses the non-functioning or absent hair cells, and stimulates the auditory nerve directly with electrical pulses, allowing severely hearing-impaired patients to hear again. In these patients, cochlear implants are considered successful in restoring speech perception performance to high levels that are otherwise not achievable with bilateral acoustical sound amplification.

Since a couple of decades it is priority to preserve the natural hearing, or residual hearing, of CI recipients during cochlear implantation surgery (Carlson 2020). Great strides have been made in electrode-array design, cochlear implant surgery and speech processing techniques (such as combined utilization of both the natural 'acoustical' hearing and 'electrical' hearing with cochlear implant). Studies show large variability in hearing preservation rates: range 0 - 68% (Causon, Verschuur, and Newman 2015; Iso-Mustajarvi et al. 2020; Mamelle et al. 2020). In our retrospective cohort study, in Chapter 2, we observed that residual hearing is present in approximately 50% of the CI recipients, and completely preserved in approximately 10% of the cases after cochlear implantation. This broad range is among others probably caused by the usage of different classification criteria for hearing preservation, and differences in timing of hearing tests after cochlear implantation. Although the variability in hearing preservation rates is large, it is evident that often the residual hearing is lost in CI recipients in current medical practice.

Because the natural hearing is usually lost after cochlear implantation, cochlear implant treatment is currently mainly reserved for a select group of patients. Assessment of CI candidates is based on pure tone thresholds as assessed with tone audiograms, and speech perception using speech audiometry with e.g. words or sentences. Currently, patients eligible for a CI have profound hearing loss at high frequencies (thresholds > 90 dB HL; at 1 – 8 kHz), and sentence recognition scores <60% using both ears with hearing aids. CI treatment for patients with less severe hearing loss is therefore somewhat hindered. Some hearing-impaired patients with considerable residual hearing fall in between two stools: hearing aids are not sufficient, but their hearing is too good to be eligible for a CI. A patient with hearing up to 1500 Hz for example might benefit from a CI but is currently not eligible (Skarzynski et al. 2007). CI treatment might also benefit patients with other diseases than hearing loss, such as patients with severe tinnitus, who can have considerable residual hearing (van der Straaten et al. 2021; Van de Heyning et al. 2008).

Additionally, preserving the natural hearing of CI recipients has added benefits. Already in 2004, a paper by Turner et al. showed the benefits of preserving the natural hearing of CI recipients (Turner et al. 2004). Based on electrical hearing only, with use of a CI, due to limited spectral resolution and high spectral smearing, perception of pitch is especially difficult (i.e. frequency discrimination), but also musical elements such as melody and timbre (or tone color) is poor in CI users (Fu and Nogaki 2005; Reiss et al. 2007; Brockmeier et al. 2010). The use of the residual hearing at the lower frequencies, by way of acoustical stimulation, combined with electrical hearing, i.e. electrical-acoustical hearing (EAS), can improve the aesthetic qualities of sound that a CI user perceives (Gifford et al. 2017). The improved sound quality also aids speech perception performance in conditions with background noise, especially with other talkers in the background as opposed to steady noise, in which a higher spectral resolution is needed than in quiet conditions (Imsiecke et al. 2020).

The preserved residual hearing might also be relevant for the overall performance with a CI, even in cases without the benefits of acoustical stimulation. Important herein is the auditory nerve health. Duration of deafness is one of the strongest predictors of CI performance, with longer durations leading to worse outcomes (Blamey et al. 2013). Although (auditory) cerebral cortex reorganization and adaption upon prolonged deafness plays a major role in the worsened speech perception outcomes of CI recipients, it has been shown that reduced auditory nerve size (i.e. auditory nerve degeneration) is also important (Kim et al. 2013). It is therefore paramount to preserve and maintain a healthy auditory nerve for a high level of performance with CI. An important hypothesis is that damage to hair cells might lead to degeneration of the SGCs, and therefore the functionality (and excitability) of the auditory nerve. The auditory nerve for example can be indirectly affected by damaging residual hair cells and/or supporting cells, which promote survival of the SGCs, leading to accelerated degeneration of the SGCs (Ramekers et al. 2012).

In Chapter 2, surprisingly no beneficial effect was observed of preserved hearing on speech perception scores with CI. However, in that study, speech perception tests, in the form of word recognition, were conducted without background noise. Using speech perception tests with background noise is more suitable to detect effect of hearing preservation, because it is a more difficult task, although to a degree these tests can also overestimate the performance (Badajoz-Davila and Buchholz 2021). Another important factor that might explain the same speech perception performances for CI candidates with and without residual hearing is the timing of hearing tests. In Chapter 2 the average timing of speech perception test, and the tone audiograms was approximately 3 months after surgery, at which trauma and inflammation caused by cochlear implantation affected the hair cells (i.e. loss of residual hearing), but auditory nerve function might still be relatively unaffected.

Type of array

The design of arrays is aimed at achieving minimal cochlear trauma during array insertion. The so called 'hybrid' arrays were designed to achieve structure preservation. These hybrid arrays were shorter than conventional arrays (Miranda et al. 2014). The idea is to minimize trauma to the functional apical areas by implanting the array only in the non-functional basal turn of the cochlea. In chapter 6, however, we showed that basal cochlear trauma, due to a cochleostomy and short array insertion, can affect the more apical areas in guinea pigs. Another issue with the hybrid arrays turned out to be the gradual loss of residual hearing over time, i.e. the loss of acoustical stimulation of the mid-to-low frequencies (~2 kHz). This loss couldn't be compensated with the electrical hearing part, because the short array covers only the basal cochlear areas (Kopelovich et al. 2014). Over time this meant poor speech perception performances for hybrid array recipients. Upon reimplantation with a normal-length arrays, the speech perception performance was improved (Fitzgerald et al. 2008).

Residual hearing can deteriorate over time irrespective of trauma by a myriad of factors, more related to progress of hearing loss, or more chronically related issues can arise after initially preserving the residual hearing, such as new bone formation (Seyyedi and Nadol 2014; Heutink et al. 2022). Acute trauma might lead to new bone formation on the longer term (Heutink et al. 2022). That study showed that avoiding trauma by implanting the array completely in the ST leads on the long term to less new bone formation, but array position was not significantly related to new bone formation. However, there are also reports that residual hearing can be stable on the long-term (at least 25 years), although this was based on audiograms of non-implanted hearing impaired patients (Yao, Turner, and Gantz 2006). This makes it likely that the deterioration of residual hearing is based on secondary causes arising from array implantation. A more conventional standard-length array has better stimulation coverage of the cochlea, and is suitable in both CI recipients with and without residual hearing. A relatively recent study showed that EAS is beneficial for speech perception performance in CI recipients with standard-length arrays (Gifford et al. 2017). Although hybrid arrays are still used, the focus of array design in the last decade shifted to these conventional standard-length arrays (reaching mostly around the second turn of the cochlea, at ~400 degrees insertion depth) that should be as atraumatic as possible (Carlson 2020).

Electrode arrays have been developed not only to minimize insertion trauma, but also for optimization of the electrode-nerve interface. Two types of standard-length arrays are distinguished: the LW and PM arrays. The PM arrays are pre-curved arrays, in contrast to the straight LW arrays, developed to intracochlearly lower the distance to the centrally located modiolus with the auditory nerve. In theory, PM arrays achieve better frequency resolution by lessening the spread of excitation across electrodes. Studies investigating electrically evoked compound action potential (eCAP) thresholds, which is a measure of stimulation efficacy of the separate electrode contacts, show indeed lower eCAP thresholds for PM arrays than LW arrays (Gordin et al. 2009; Lee et al. 2019; Tilton and Hansen 2019). Additionally, PM arrays have reduced battery consumption as lower currents are needed to activate the nerve. However, most studies find similar speech perception outcomes between CI recipients with LW and PM arrays (Doshi et al. 2015; van der Marel et al. 2015; van der Jagt et al. 2016; Fabie et al. 2018; Moran et al. 2019). In contrast, fewer studies showed better speech perception outcomes if the array is closer to the modiolus (Gordin et al. 2009; Holden et al. 2013). Apparently, the improved stimulation of the auditory nerve by PM arrays shows no clear improvement of CI performance compared to LW arrays.

Our retrospective cohort study in Chapter 2 shows clearly that array type is an important variable that can affect hearing preservation rates. CI recipients with LW arrays had significantly better hearing preservation rates than with PM arrays; complete hearing preservation was achieved in 6% with PM arrays, and in 14% with LW arrays. Other factors such as corticosteroids, hyaluronic acid and surgical experience had no effect on hearing preservation rates. In a small subset of patients local application of corticosteroids in the round window (RW) niche during surgery showed improved hearing preservation rates. However, because these implantations were performed with LW arrays in just 8 patients, the added benefit of corticosteroids was unclear. Still, it is clear that the choice for array type plays an major role in preserving the residual hearing of CI recipients.

Important difference between both type of arrays lie in STL, i.e an array translocating from the scala tympani to the SV or SM during insertion. The PM arrays were much more often linked to STL than LW arrays (43% vs 7%) as shown in the meta-analysis in Chapter 3. This difference in STL rate is probably caused by the stylet that is needed to insert the PM arrays into the cochlea. The stylet is semi-rigid and can penetrate intra-cochlear structures like the osseous spiral lamina thus causing STLs. In addition, insertion with PM arrays probably requires more experience than with LW arrays. A study by Aschendorff et al. showed that STL rate using two different PM arrays decreased significantly for all three surgeons with more experience (overall STL reduction of ~50%), and between surgeon comparison showed individual learning curves (Aschendorff et al. 2011). Surgical experience is needed with PM arrays to assess the correct insertion depth before retracting the stylet, allowing the PM array to follow the curvature of the cochlea. Additionally, it is important that before release, the electrode contacts are facing towards the cochlear modiolus, i.e. the surgeon needs to be aware of the angle of the basal turn of the cochlea. Both aspect are still relevant for the newer PM arrays, which either use a stylet or a sheath to straighten the array before insertion. The position of the cochleostomy relative to the RW, and obtaining a wide enough facial recess opening can also be troublesome, although this is relevant for both array types. For instance, too anteriorly of the RW leads to scala vestibuli insertion, and obtaining a small facial recess opening hinders the view of the RW membrane.

Although PM arrays translocated more often, LW array STLs seem to be underestimated, with a much higher STL rate of 75% in Chapter 4 than the pooled 7% STL rate of previous studies in Chapter 3. Part of this discrepancy lies in the methods: use of human cadaveric temporal bones is prone to more friction during insertion than in live CI recipients. Still, the use of histology in Chapter 4 allowed for a much more thorough study of array position compared to the reviewed studies in Chapter 3 that assessed array positioning in vivo using CT scans. To test whether radiological assessment is indeed underestimating the STL rate of LW arrays, a comparison between histology and radiology was conducted in Chapter 4. Histological outcomes of the temporal bone study were compared with the radiological cone beam CT images that were directly obtained after array insertion in the same temporal bones. The cone beam CT (CB-CT) results in comparison to conventional multi-slice high-resolution CTs in less metal artefacts intracochlearly from the in-situ arrays. These CB-CT images were assessed by three independent assessors. What we found was that assessors using conventional analyses of the CB-CT scans were wrong in cases with LW arrays much more often than in cases with PM arrays regarding STL. LW array positions seem to be more difficult to assess. It is probable that in previous studies with CI recipients STLs were underestimated in cases with LW arrays.

Difference in size and electrode contact density along the array is minimal between the PM and LW arrays, so in theory they should be equally difficult or easy to assess. It is more probable that the close relationship of the LW array with its surrounding structures, such as the basilar membrane and the lateral wall, impedes accurate assessment. The type of array not only affected the frequency of trauma, but also the type of structural trauma. STL can cause severe intracochlear trauma by piercing the cochlear partition, affecting important structures such as osseous spiral lamina, basilar membrane, organ of Corti and stria vascularis. If PM arrays translocated, it was always to the SV, accompanied with a fractured osseous spiral lamina. The LW arrays, however, can translocate in addition to the SV also to the SM. In those latter cases the osseous spiral lamina was intact, but the organ of Corti, basilar membrane and stria vascularis were more heavily impacted. LW array translocation towards the SM hampers assessment of array positioning more than a PM array translocating towards the relatively large empty SV.

The use of an adaptation of a CT technique that uses curved reconstructions, i.e. straightened cochlear duct images in Chapter 4, allowed better assessment of STL of both LW and PM arrays than the conventional CT reconstructions. In conventional CT reconstructions midmodiolar plane images are used to assess scalar position of the array, however, the difference between non-translocated and translocated array on these images is difficult to assess. This has mainly to do with difficulty in identifying the basilar membrane and osseous spiral lamina on the midmodiolar sections. Using uncoiled cochlear duct reconstructions, the basilar membrane and osseous spiral lamina position was easier to estimate, resulting in much easier identification of a jump of the array from ST to SM or SV. Indeed, histological outcomes correlated better with the uncoiled cochlear duct reconstructions, and interobserver variability was lower than if the conventional midmodiolar plane reconstructions were used. This technique is readily available in clinical medical care, and might also be useful for radiological assessment of pathologies concerning the cochlea and the vestibular organ, and other pathologies involving complex shaped bony tube-shaped structures (e.g. facial nerve canal integrity assessment in human temporal bone trauma).

Other studies tried to estimate the basilar membrane and osseous spiral lamina by composing an atlas using preoperative micro-CTs that can depict the osseous spiral lamina and basilar membrane (Teymouri et al. 2011; Wanna et al. 2011). Micro CTs have much higher resolution, which can have a resolution of 5 µm, much better than the 70 µm of the best CTs used in clinical practice. Micro CTs achieve higher resolution because the sample is rotating, in contrast to a fixed sample in medical settings, and higher voltages can be more easily obtained. It is because of these reasons that micro CTs are currently only viable in laboratory and industrial settings. Computer models were created using micro-CT images that depicted intra-cochlear structures in cadaveric temporal bones, and used to estimate the basilar membrane position in postoperative CTs of CI recipients (Teymouri et al. 2011). Another research group used different preoperative micro-CT atlases to find the most fitting atlas for the patient's cochlea (Wanna et al. 2014). These methods are, in contrast to our methods, not readily applicable in every medical center and might be difficult to implement in a large population with great temporal bone anatomy variability. The CBCT images used in the present study were relative fast and straightforwardly reconstructed, without needing predetermined atlases, using only the postoperative scans.

Array translocation impacts speech perception outcomes of CI recipients. An array residing in the SV or SM rather than the ST is less effective in stimulating the auditory nerve (Wanna et al. 2014). Our review in Chapter 3 showed that speech perception with CI without background noise is worse in CI recipients with STL than those without STL (weighted mean difference of 14% speech perception scores). These results were primarily based on PM arrays. CI recipients with STL had at least one electrode contact in SV or SM, while those without STL had all electrode contacts in ST. Several factors play a role in STL affecting the speech perception negatively. Firstly, an array residing (partially) in SV or SM has a larger distance to the cochlear modiolus, and therefore also to the auditory nerve, leading to increased spread of excitation (i.e. less effective stimulation) of the auditory nerve (Holden et al. 2013). Secondly, an array residing in SV or SM might lead to more increased overlap of stimulated neural regions (Holden et al. 2013). And thirdly, the trauma associated with STL to the delicate structures of the cochlea might affect the auditory nerve negatively. The auditory nerve can for example be affected by damage to SGCs directly, or indirectly by damaging residual hair cells and/or supporting cells, which promote survival of the SGCs, leading to accelerated degeneration of the SGCs (Ramekers et al. 2012). Interestingly, STL affected speech perception irrespective of the timing of the speech perception test, ranging from 1 to 24 months after surgery. Apparently, the negative effect of STL on speech perception is probably irreversible, although there are means to improve the speech perception in these cases. For example, an audiologist can turn off electrode contacts that are misplaced and have a high threshold for activation, hereby focusing electrode-contact stimulation and reducing channel interaction of the electrode contacts (Bierer and Litvak 2016).

Aside from STL differences, TFs occurred also more frequently with PM arrays

(~8x more frequent) based on our review in Chapter 3. In addition, in Chapter 4, in the temporal bone study, the TFs also occurred predominantly with PM arrays. The advance-off-stylet technique needed to insert the PM array into the cochlea is prone to TF of the array during insertion. The array has to follow the curvature of the cochlea, however, as depicted in Chapter 4, a shallow insertion of the array with stylet can lead to an array that bumps against the modiolar wall during advancement of the array over the stylet. Interestingly, to alleviate TFs and STLs, CI manufacturers have developed other methods to insert the PM array using a removable external sheath. As described in Chapter 3, this new method was associated with 3x higher rate of TF (6% vs 2%, $p<0.05$). It remains to be seen whether this higher TF rate is caused by a (steep) learning curve associated with this new method of insertion, or whether it is inherent to the method itself.

Surgical approach

Currently, two approaches are mostly used for array insertion. Both approaches have their advantages and disadvantages. The RW approach is conducted, after drilling of the bony overhang to expose the RW membrane, through a slit like opening in the RW membrane for entry in the cochlea. In contrast, a cochleostomy approach (CO) uses a burr-hole opening in the cochlea. In order to enter the ST the cochleostomy has to be placed antero-inferiorly from the RW membrane. Important herein is to consider that a cochleostomy placed too anteriorly might lead to an opening to the SV rather than the ST, hereby damaging the osseous spiral lamina (Iseli, Adunka, and Buchman 2014). In Chapter 4 we observed that just a small anterior displacement of the CO can indeed damage the osseous spiral lamina. On the other hand, a cochleostomy placed too inferiorly, might miss the scalae entirely, and can even in rare cases results in damage to the internal carotid artery.

The RW and CO approaches have different insertion angles. An array through the RW entry passes first the cochlear hook region, known for its varying dimension along its course, especially in height (Avci et al. 2017). In contrast, an array through the cochleostomy opening largely bypasses the cochlear hook region, resulting in a less tortuous path with a more straight insertion approach. Another difference between both approaches is the size of entry to the cochlea. Using the CO approach, the size of entry is more controllable and generally larger than the RW. Additionally, often the crista fenestra, a bony crest structure within the RW niche, can form an obstacle that further decreases the surface area of the RW membrane (Atturo, Barbara, and Rask-Andersen 2014). Lastly, a CO approach is more related to new bone formation in the years after CI implantation than a RW insertion (Heutink et al. 2022).

Damage to the osseous spiral lamina with a cochleostomy can affect, in addition to the higher frequencies, the function of more apical areas in which the residual hearing is located, as observed with electrocochleography (ECochG) in Chapter 6. ECochG is a promising tool that might aid the surgeon in minimizing acute trauma during cochlear implantation (Bester et al. 2017). Currently, however, ECochG is poorly understood. The ECochG consists of several electrical potentials that are generated by the cochlea after presenting an acoustic stimulus. The cochlear micophonics (CM) reflects electrical activity of hair cells, mainly outer hair cells, and the compound action potential (CAP) reflects the electrical activity of the SGCs (and therefore the auditory nerve function). To be more precise, the CAP reflects the overall output of the cochlea, therefore, affecting peripheral structures to the SGCs also affects the CAPs, such as hair cell damage. ECochG was used to understand the relationship between primarily the CAP, and the separate stages of cochlear implantation surgery (i.e. cochleostomy, and array insertion) in normal hearing guinea pigs. We found that cochleostomy can be performed without causing cochlear damage, with intact responses, but that subsequent array insertion leads to deterioration of the responses in every case. Trauma severity correlated to the ECochG decline. In addition, even though the cochleostomy is drilled in the basal turn and the electrode array does not reach beyond the basal turn, both CAP and CM responses to the lower frequencies, which originate in the apical turn, can be significantly affected as well. This reinforces the notion that a shorter array to avoid trauma to the apical areas, such as with hybrid arrays, is not necessarily preserving the residual hearing.

Acute structural trauma to the basal turn might alter the mechanics of the basilar membrane, impeding the travelling wave, thereby not only affecting the basal regions but also potentially impacting cochlear areas located more apically to the site of trauma. Additionally, other factors might play a role in local basal turn trauma affecting the function the apical cochlear areas. Such factors are reduction in blood flow volume, due to disruption of capillaries or small blood vessels around the basilar membrane and osseous spiral lamina, and additional disruption of the homeostasis when the stria vascularis is damaged (Nakashima et al. 2002; Shi 2016). Trauma to cochlear structures can lead to mixture of endolymph, located in the SM, and perilymph, which is located in the ST and SV, abolishing the endocochlear potential (Reiss et al. 2015). It has also been reported that intracochlear shift of pressures upon cochleostomy and/or array insertion can affect the general function of the cochlea acutely (Greene et al. 2016; Gonzalez et al. 2020). It is likely that the above mentioned mechanisms all contribute to the (negative) effect of basal trauma on apical cochlear areas.

The interaction between array type and surgical approach was investigated by comparing structural trauma, in the form of STL, between the four possible combinations of array type and surgical approach in Chapter 4. We showed than if opting for RW approach more STLs were observed with PM arrays than LW arrays. Our review in Chapter 3 showed similar results with PM arrays in general (i.e. including other brands) translocating more often than LW arrays when using solely a RW approach (41% vs 7%). In the temporal bone study we also observed that the aforementioned RW-PM approach leads to more STLs than the PM-CO approach. A prior study has also shown that the PM-RW combination can lead to more STLs when using an older generation PM array (Jeyakumar, Pena, and Brickman 2014). In contrast, regarding LW arrays, no difference in STL rate was observed between LW-CO and LW-RW combinations.

It is likely that the PM-RW combination leads to increased friction forces during insertion. Several factors might be responsible. The aforementioned cochlear hook, with its varying dimensions along its course, might increase friction forces. Another factor is the size and shape of the RW membrane, which can vary greatly in roundness with sizes ranging from 0.9 to 2.1 mm diameter for the shortest diagonal, and mean surface area of 2 mm2 (Rask-Andersen et al. 2012; Atturo, Barbara, and Rask-Andersen 2014). The cross section of the largest basal part of the PM and LW arrays of Advanced Bionics, used in Chapter 4, is approximately the same, 0.5 mm2, with PM arrays having square cross sections and LW arrays having a larger flat side and a smaller rounded side than PM arrays. The largest part of these cross sections is smaller than the smallest dimensions of the RW membrane (~0.7 mm versus 0.9 mm), and therefore these arrays should fit through the RW membrane. Its likely that the different shape and varying size of the RW membrane can be more an issue with the rigid and square cross-sectional shaped PM array that requires a stylet for insertion, increasing friction forces during insertion.

It is important to note that the choice for surgical approach, is unlike the choice for array type, not always possible. Prior studies argued that in some cases a surgeon has no other choice than to conduct a cochleostomy, because the RW membrane is not visible through the posterior tympanotomy (Leong et al. 2013). In Chapter 5 we assessed RW visibility retrospectively by analysing the surgical reports of CI recipients of one surgeon of the last five years. In almost all cases the RW approach was feasible (98%). A possible explanation of the discrepancy with prior studies that had lower rates of success with RW approach, might be related to the chorda tympani nerve (CTN). The posterior tympanotomy forms the window of the surgeon to the middle ear structures, and importantly, to the RW membrane. The size of this window is determined by the path of the facial and chorda tympani nerve, forming a v-shaped posterior tympanotomy opening. However, in some instances, we observed that the CTN was sacrificed in order to enlarge the posterior tympanotomy (8%). This latter point probably increased the RW membrane visibility rate in our study compared to other studies. A follow-up analysis with preoperative CT in Chapter 5 showed that the distance between the facial nerve and the CTN can be predictive for the need of sacrificing the CTN, and might help in counselling the CI recipients preoperatively, and preparing the surgeon beforehand.

Concluding remarks

Preserving cochlear structures during cochlear implantation is considered one of the most important steps in improving the hearing performance of CI patients. Minimizing trauma to the cochlea, i.e. preserving the residual hearing, allows for better speech perception performance by the added benefits of acoustical stimulation to the electrical hearing with CI, and probably overall better electrical hearing due to deaccelerated degeneration of the auditory nerve. The differences between PM and LW arrays regarding structure preservation are substantial, and should be carefully considered before commencing cochlear implantation, especially in patients with (substantial) residual hearing.

STL and TF of the array can cause severe intracochlear trauma by piercing the cochlear partition, and it impacts speech perception and the residual hearing of CI recipients. STL and TF were primarily associated with PM arrays. However, studies with CI recipients had a substantial risk of bias, mainly caused by lack of randomization, and lack of standardization of insertion approaches (i.e. RW and CO). Subsequent research with human cadaveric temporal bones showed that the interaction between array type and surgical approach is an important factor regarding insertion trauma. Research showed that scalar localization of LW arrays on CT scans is difficult to interpret, due to LW arrays translocating not only towards SV but also to SM. Therefore, LW array STL rates are probably underestimated in literature. Additionally, PM arrays have in general more efficient stimulation of the auditory nerve than LW arrays, potentially improving speech perception, and lowering battery consumptions. Currently it is not clear which aspect, the preserved cochlear structure or more efficient auditory nerve stimulation, is more important for CI recipients, and how this relates to the surgical approach. This notion should be tested in the clinical practice, particularly the consequences for preservation of residual hearing and hearing with CI in general including speech perception. Although the osseous spiral lamina and basilar membrane are not visible on CT scans, accurate assessment of scalar position is possible for both type of arrays if using an adaption of curved multiplanar reconstruction method (i.e. uncoiled cochlear duct). Lastly, ECochG during several stages of the cochlear implantation procedure showed that acute basal turn trauma in the form of cochleostomy and subsequent short array insertion can affect the apical region of the cochlea.

Future perspectives

Currently it is unclear which combination of treatment of surgical approach and array type can preserve the residual hearing of CI recipients the best. The differences between arrays found in this thesis should be tested in the clinical practice, especially the array interaction with surgical approach. To address this question we set up a randomized controlled trial with CI recipients (CIPRES), as described in Chapter 7. It is the first randomized controlled trial that evaluates the effect of insertion trauma of several CI treatment options on hearing preservation. CI recipients are randomized over 4 groups that have a unique combination of array type (LW vs PM) and surgical approach (RW vs CO). The main outcome is hearing preservation rate as assessed by 4 tone audiograms distributed within one year after CI surgery. Secondary objectives are to compare the effect of the interventions on scalar position on CB-CT, ECochG measures, and speech-in-noise performance.

Minimizing cochlear trauma opens the way for future technologies relying on the intact cochlear structure, e.g. use of corticosteroids or neurotrophin eluting CIs, and hair cell regeneration (Liu and Yang 2022). It is currently unclear how cochlear trauma relates to these future technologies, but it is probable that an intact cochlea might lead to more ways of improving speech perception of severely hearing-impaired patients. For example, damage to organ of Corti might complicate neuroregenerative therapies that are banking on available supporting cells. Additionally, it is likely that drug eluting CIs will achieve better drug distribution inside the cochlea when the normal lymph flow and blood supply of the cochlea is preserved during cochlear implantation. The drug eluting CIs might also reduce new bone formation in the long-term, which can affect long-term residual hearing (Heutink et al. 2022).

Another line of research that can extend the findings of this thesis focuses on the use of diagnostic tools for assessment, and ideally prevention of acute insertion trauma. The use of pre- and peroperative imaging tools that have higher resolution, and even less artefacts, such as with the use of micro CT, might become more feasible for in vivo analysis of cochlear structures such as the basilar membrane and osseous spiral lamina. This might potentially aid in array insertion through especially the cochlear hook region, and through cochlear areas at ~180 degrees insertion depth that are vulnerable for STL. The use of robotics for array insertion to avoid peak forces during insertion is also worth exploring in minimizing trauma to cochlear structures (Torres et al. 2018; Caversaccio et al. 2019). Additionally, the role of ECochG, as remote measurement of cochlear health needs to be explored. ECochG during insertion, although currently difficult to interpret, might aid the surgeon in preventing trauma during array insertion, e.g. by retracting the array or alternating the angle of insertion (Giardina et al. 2019). ECochG postoperatively can be used for objective measurement of CI performance, and can potentially identify areas for improvement during audiological follow-up. To realize this exciting potential of ECochG research into the relationship between structural cochlear trauma indicators (such as with imaging; or array impedance measurements) and ECochG potentials such as the cochlear microphonics, compound action potential and summating potential is needed not only in the acute setting, but also chronically in cases with fibrosis and new bone formation.

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Nederlandse samenvatting

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Nederlandse samenvatting

De prevalentie van gehoorverlies neemt toe. Momenteel lijden meer dan een half miljard mensen wereldwijd aan invaliderend gehoorverlies. Gehoorverlies wordt door het WHO erkend als een belangrijk gezondheidsprobleem, dat kan leiden tot depressie, onzekerheid en sociaal isolement. Perceptief gehoorverlies wordt voornamelijk veroorzaakt door verlies van haarcellen. Het verlies van haarcellen kan door vele factoren worden veroorzaakt, bijvoorbeeld door blootstelling aan lawaai, ototoxische medicatie of erfelijke aandoeningen. Bij de meeste patiënten met ernstig perceptief gehoorverlies kan echter geen oorzaak worden vastgesteld.

De meeste volwassenen met gehoorverlies kunnen goed geholpen worden met hoortoestellen. In gevallen van ernstig gehoorverlies zijn hoortoestellen niet voldoende om spraak goed te verstaan in het dagelijks leven. In die gevallen kan een cochleair implantaat (CI) worden overwogen. In tegenstelling tot hoortoestellen die geluiden versterken, omzeilt een CI de aangetaste haarcellen en stimuleert de gehoorzenuw direct via elektrische stroompulsen. Dit zogenaamde 'elektrisch horen' is in de laatste decennia enorm verbeterd. In de jaren tachtig was alleen perceptie van geluid mogelijk, terwijl CI-gebruikers tegenwoordig spraak kunnen verstaan. Er is echter ruimte voor verbetering, vooral in situaties waar achtergrondgeluid aanwezig is. Muziekperceptie is daarnaast over het algemeen slecht. Het behouden van het restgehoor na cochleaire implantatie kan het spraakverstaan in die moeilijke situaties verbeteren, door bijvoorbeeld een combinatie van het akoestisch horen (m.b.v. het restgehoor) en het elektrisch horen met CI. Helaas is het restgehoor in de huidige situatie vaak verdwenen na cochleaire implantatie. Het beperken van trauma aan het slakkenhuis tijdens de cochleaire implantatie operatie speelt een belangrijke rol in het behouden van het natuurlijke nog aanwezige gehoor van CI-patiënten.

Hoofdstuk 2 betreft een retrospectieve studie naar behoud van restgehoor bij CI-patiënten. Patiënten werden ingedeeld in vier groepen op basis van behoud van restgehoor na cochleaire implantatie. Vervolgens zijn de verschillen tussen de vier groepen bekeken. Uit deze studie is gebleken dat CI patiënten preoperatief restgehoor hebben in ongeveer 50% van de gevallen. Helaas is het restgehoor na cochleaire implantatie in 90% van de gevallen in meer of mindere mate aangetast. Patiënten die een laterale wand elektrode kregen hadden vaker behoud van restgehoor dan patiënten met een perimodiolaire elektrode. In een kleine subset van patiënten had lokaal gebruik van corticosteroïden een gunstig effect op het restgehoor.

Hoofstuk 3 beschrijft een systematische review die de kans op scalaire translocatie vergelijkt tussen de laterale wand en perimodiolaire elektrode. Bij scalaire translocatie verspringt de elektrode van de scala tympani naar scala media danwel scala vestibuli, waarbij cochleaire structuren kunnen beschadigen. Een meta-analyse toonde aan dat scalaire translocatie veel minder vaak voorkomt bij laterale wand elektrodes dan bij perimodiolaire elektrodes. Hetzelfde geldt voor 'tip fold-over', waarbij het uiteinde van de elektrode dubbelklapt bij insertie in de cochlea. Bovendien heeft translocatie van de elektrode een negatief effect op het elektrische horen, en op het natuurlijke restgehoor in de lagere frequenties.

Hoofstuk 4 betreft een studie met experimenten op humane rotsbeenderen. In deze studie is de schade aan het slakkenhuis door cochleaire implantatie in kaart gebracht met behulp van histologie en radiologie. In totaal werden 32 rotsbeenderen geïmplanteerd, verdeeld over 4 groepen, met elke groep een unieke combinatie van type elektrode (laterale wand vs perimodiolair) en chirurgische benadering (ronde venster vs cochleostomie). Deze combinatie bleek een interactie te hebben, waarbij de perimodiolaire elektrode en ronde venster benadering combinatie het vaakst cochleaire structuren beschadigde. Daarnaast is in deze studie de conventionele radiologische beoordeling van scalaire translocatie voor alle groepen vergeleken met een radiologische methode waarbij het slakkenhuis met CI in situ is uitgerold ('uncoiled cochlear reconstructions; UCR). Uit die vergelijking bleek dat beoordelaars met UCRs vaker correct de CI-positie intracochleair beoordeelden, dan met de conventionele manier. Met name translocaties van de laterale wand elektrodes zijn waarschijnlijk vaker over het hoofd gezien door een moeilijk beoordeelbare intracochleaire positie waarbij de elektrode omringd wordt door structuren als de stria vascularis en het basilaire membraan.

In **hoofdstuk 5** is de zichtbaarheid van het ronde venster tijdens cochleaire implantatie onderzocht. Aan de hand van de operatieverslagen is de zichtbaarheid van het ronde venster beoordeeld. In bijna alle gevallen van een vijfjaarscohort was het ronde venster zichtbaar. Echter in 8% van de gevallen werd de posterieure tympanotomie, de toegang naar het middenoor, verruimd door het opofferen van de chorda tympani zenuw. Op de preoperatieve CT scan is de maximale afstand tussen de nervus facialis en chorda tympani zenuw nuttig om te identificeren of ronde venster zichtbaarheid door de posterieure tympanotomie gemakkelijk zal zijn, of dat bijvoorbeeld de chorda tympani hiervoor opgeofferd moet worden.

In **hoofdstuk 6** is het onderzoek beschreven naar het effect van de verschillende stadia van cochleaire implantatie procedure op de elektrocochleografie in normaalhorende cavia's. Met elektrocochleografie kan de elektrische activiteit van de cochlea gemeten worden. Elektrocochleografie wordt in toenemende mate gebruikt bij cochleaire implantaat chirurgie, maar de verkregen resultaten zijn moeilijk te interpreteren. Door elektrocochleografie uit te voeren voor elk stadium van de cochleaire implantatie procedure werden de elektrocochleografie veranderingen gerelateerd aan het acute trauma per stadium. De metingen werden gedaan met behulp van een goudenbal elektrode op het ronde venster van normaalhorende cavia's. Van de elektrocochleografie werden de drempelwaarde, amplitude en latentie van de samengestelde actiepotentiaal (CAP) voornamelijk geanalyseerd. Na cochleostomie en elektrode insertie namen de CAP drempelverschuivingen toe met de ernst van het trauma. Drempelverschuivingen op hoge frequenties gingen samen met drempelverschuivingen op lage frequenties bij elk stadium. Concluderend dient basale trauma veroorzaakt door cochleostomie en/of elektrode insertie geminimaliseerd te worden om het laagfrequente restgehoor van CI-patiënten te behouden.

Hoofstuk 7 beschrijft het protocol voor het gerandomiseerde onderzoek bij CI-patiënten naar de invloed van het type elektrode en chirurgische benadering op het restgehoor. Het restgehoor is de primaire uitkomstmaat. Secundair wordt postoperatief gekeken naar het trauma op cochleaire structuren met behulp van de conebeam CT. Daarnaast wordt de functie van het slakkenhuis met behulp van de elektrocochleografie peroperatief, tijdens elektrode insertie, en postoperatief gemeten.

Tot slot worden in **hoofdstuk 8** de bevindingen van dit proefschrift uitgebreid bediscussieerd. Het minimaliseren van schade aan de cochleaire structuren bij cochleaire implantatie wordt gezien als één van de belangrijkste stappen om het restgehoor van CI-patiënten te sparen. Op dit moment zijn cochleaire implantaties in de meeste gevallen niet gehoorsparend. Het behouden van het natuurlijke gehoor bij cochleaire implantaties zorgt er waarschijnlijk voor dat CIs breder toegepast kunnen worden. Laterale wand elektrodes lijken vaker het restgehoor te sparen dan perimodiolaire elektrodes, waarschijnlijk omdat er minder translocaties optreden bij eerstgenoemde. Echter, translocaties van laterale wand elektrodes worden vaker gemist op CT-scans, vanwege een moeilijk beoordeelbare intracochleaire positie. Daarnaast dient men rekening te houden met de interactie van type elektrode met chirurgische benadering die van invloed kan zijn op het wel of niet ontstaan van scalaire translocatie. Zo leidt bijvoorbeeld de keuze voor een rondevenster benadering met een perimodiolaire elektrode vaker tot een translocatie dan met een cochleostomie benadering. Scalaire translocatie heeft ernstige gevolgen voor belangrijke cochleaire structuren als het basilair membraan en orgaan van Corti. Het eerste gerandomiseerde onderzoek naar behoud van restgehoor bij de verschillende combinaties van type elektrode en chirurgische benadering is opgezet om de bevindingen van dit proefschrift te testen in de klinische praktijk. In de toekomst kunnen de bevindingen van dit proefschrift o.a. gebruikt worden voor neuroregeneratieve toepassingen waarbij een intacte cochlea van belang is.

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Curriculum Vitae

Saad Jwair is a child of Iraqi parents. His family fled during the gulf war to the Netherlands in 1993. Saad grew up in Oost-Souburg in Vlissingen. After graduation from high school (Oostvaarderscollege, Almere), he moved to Rotterdam to study Medicine at the Erasmus University. In addition to his Medicine Master, he studied the Master of Neuroscience, also at the Erasmus University in Rotterdam. After obtaining his medical degree and neuroscience master in 2017, he started working as a neurosurgical resident at the Erasmus Medical Center for one year. During that year he applied for the current PhD project, start date: 01-01-2019, under supervision of prof. dr. Robert Stokroos. Saad starts as a resident at the department of Otorhinolaryngology at the University Medical Center Utrecht from 1 december 2022, under supervison of drs. Ivonne Ligtenberg and prof. dr. Robert Stokroos.

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