Neurosurgical interventions at the cochlear nerve & nucleus for treatment of tinnitus

Minke J.C. van den Berge

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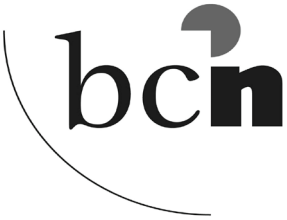

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Aan mijn ouders en Fenna

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General introduction and aims of the thesis

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Tinnitus – definitions, prevalence and impact

Tinnitus aurium literally means 'ringing in the ears' and is defined by the perception of sound or noise in the absence of an external physical sound source.[1] Nearly every adult experiences transient tinnitus at some point in his or her live. Persistent or permanent tinnitus is a common condition as well. In the Western population, the estimated prevalence of tinnitus is 8-20%[1], however estimations of incidence and prevalence are probably varying across studies due to lack of consistent methods to identify tinnitus. This makes it difficult to specify tinnitus and to study its epidemiology. There is however widespread consensus that tinnitus is highly common and it is anticipated that in the near future, the incidence of tinnitus will rise due to increasing amount of patients with disabling hearing loss[2], which is considered a main risk factor for developing tinnitus.[3]

Commonly, two types of tinnitus are defined: subjective and objective tinnitus. Objective tinnitus is a rare form of tinnitus and is by definition a sound that can be perceived not only by the patient, but also by an external observer. It often causes an intermittent or pulsatile sound, which in some cases can be influenced by craniocervical manipulations. Objective tinnitus may for instance be caused by (intracerebral) vascular or muscular spasms, e.g. a vascular murmur caused by a carotid stenosis; an arteriovenous malformation or myoclonic contractions of the middle ear muscles or soft palate. Treatments for objective tinnitus are regularly available and often imply an invasive treatment strategy such as surgery or embolization. Subjective tinnitus is the far more common form of tinnitus, which by definition can only be observed by the patient in the absence of an identifiable sound source. Subjective tinnitus is therefore regarded as a phantom sound.[4] It can be perceived in one or both ears, or centrally in the head. Since this type of tinnitus cannot be identified objectively, physicians can only rely on the patient's own description of his or her tinnitus. This is comparable with, for example, the symptom of pain.

Tinnitus is clinically heterogeneous and may have a severe impact on quality of life. The degree of impact varies from one to another and can also vary over time within a person. Tinnitus burden also depends on a patient's general state of wellbeing. Patients often present with various accompanying symptoms, such as psychiatric disorders (i.e. depression and anxiety), sleep disturbance and insomnia, irritability and annoyance, and cognitive impairment due to concentration disorders.[5] Tinnitus can even result in suicidal thoughts in some patients.[6,7] In addition, tinnitus is often accompanied by hearing difficulties and hyperacusis. All these factors are highly important in determining the severity of tinnitus and impact on quality of life.

With growing attention and awareness for tinnitus by different types of media and patients' platforms, together with the appearance of specialized 'tinnitus clinics', it has now become clear that the health burden from tinnitus is rapidly increasing, as is the economic burden to society.[8] It is estimated that approximately 13 million people in Western Europe and the USA seek medical advice for tinnitus.[9] Therefore, the resulting socioeconomic burden is substantial. In the Netherlands, which has 17 million inhabitants in 2019, the total mean societal costs of tinnitus

were estimated €6.8 billion in 2009.[8] This amount is expected to increase as the prevalence of tinnitus is expected to increase with the rise in prevalence of hearing loss.[2]

Pathophysiology of tinnitus

Although the pathophysiologic process of tinnitus is still not fully understood, there is consensus that the central nervous system plays an important role. Tinnitus is often referred to as a phantom sound, which is the unwanted result of abnormal functioning of the central auditory system caused by deprivation of auditory input.[10]

One theory of the neural substrate of tinnitus is that cochlear hearing loss leads to a diminished cochlear nerve activity, which results in down regulation of inhibitory cortical processes. This in turn leads to spontaneous hyperexcitability of central auditory structures, such as the primary auditory cortex.[11] The abnormal cortical neuronal activity, or 'pathological reorganization', can be perceived as tinnitus. Also, neural synchrony is thought to play a role in tinnitus perception. Neural synchrony is a physiological phenomenon of nearly simultaneous firing of individual neurons, which causes synchronized oscillations of membrane potentials in a network of neurons. However in tinnitus patients, as a result of deafferentation in hearing loss, a maladaptive process in neural synchronization is thought to play a role in the perception of tinnitus.[12,13] In patients who experience tinnitus, increased or abnormal neural synchrony might occur in the absence of a physical auditory stimulus, which leads to the percept of a phantom sound.[14] Tinnitus-related activity is not limited to central auditory structures, also non-auditory structures such as the somatosensory system[13,15] and 'awareness networks' such as the cingulate cortices, thalamus, amygdala, (para)hippocampus, prefrontal and parietal cortex and anterior insula, play a role in conceiving tinnitus.[13,16]

A major issue in understanding the pathophysiology of tinnitus is that tinnitus may not be a solitary disorder with one underlying pathophysiology, but a heterogeneous disorder with various underlying pathologies, depending on the type of damage and the anatomical location (i.e. cochlear, cochlear nerve or other parts of the brain).

Overview of tinnitus treatments

In search for a treatment for tinnitus, a range of treatments has been developed and investigated over the years. Different treatments, from conventional to more experimental treatment methods, are outlined below.

Current conservative treatments
When causes for tinnitus amenable for medical treatment have been excluded after thorough examination, the recommended treatment strategy according to the Dutch tinnitus guidelines consists of: 1) counseling and explanation of tinnitus and influencing factors; 2) sound therapy (hearing aids and/or sound generators); and 3) psychological guidance in the form of cognitive

behavioral therapy. The majority of patients have sufficient benefit from counseling and conventional, non-invasive treatments. However, not all patients are sufficiently treated and a subgroup of patients still has severe complaints of tinnitus despite these first-line treatment options. For patients not responding to these standard, non-invasive strategies, treatment in the form of (neuro)surgical implants are under investigation.

Neuro-otological and neurosurgical treatments

Over the past years, several studies have been performed that investigated the role of microvascular decompression surgery and surgical placement of active implants on peripheral and central auditory level. In fact, several levels of the auditory pathway have been investigated as target for surgery or stimulation in order to decrease tinnitus (see overview in Figure 1). Below, the targeted levels of the auditory pathway are described from cochlea tot cortex.

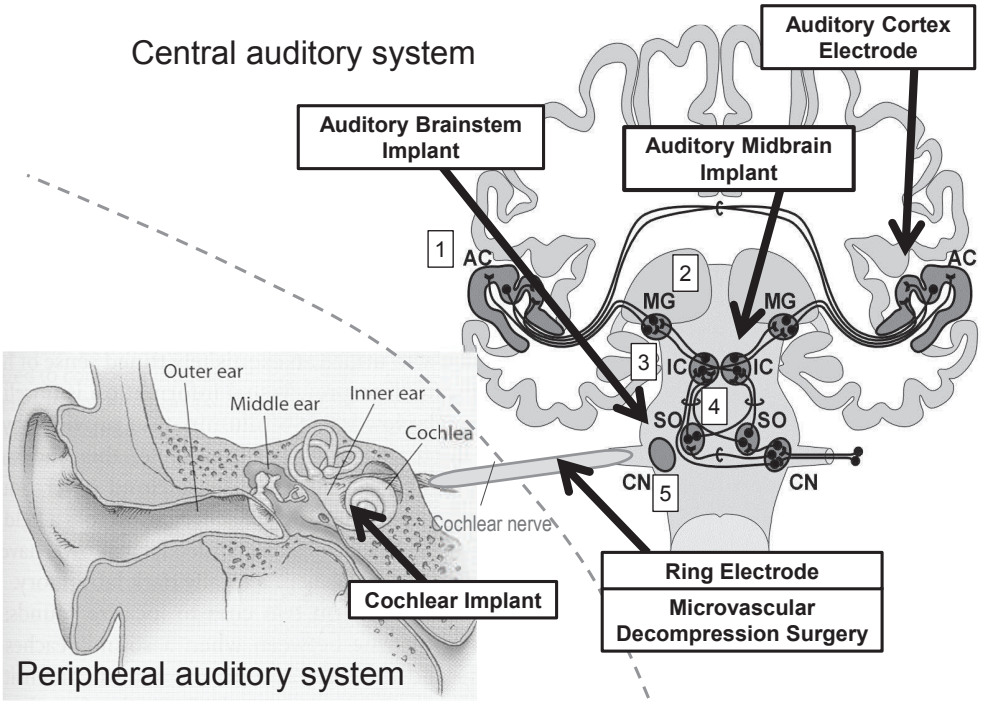

Figure 1. *Overview of various surgeries or implants which are being investigated as treatment option for intractable tinnitus*

AC: auditory cortex; 2) MG: medial geniculate body; 3) IC: inferior colliculus 4) SO: superior olivary complex); 5) CN: cochlear nucleus.

Cochlea

Since many forms of tinnitus are suggested to be the result of auditory deprivation, restoring auditory input might be a solution to provide relief for tinnitus. A well-known example is the use of hearing aids, which are often advised in common practice. However, for patients with severe sensorineural hearing loss and tinnitus, hearing aids are not a viable option.

For those patients with severe sensorineural hearing loss, a **cochlear implant** (CI) is a well-established treatment option for hearing rehabilitation. Studies in patients with profound sensorineural hearing loss who have been implanted with a CI in order to restore hearing, demonstrate a beneficial effect on tinnitus symptoms in 25-93% of the patients.[17] Prospective investigation in CI recipients for regular indication (i.e. severe sensorineural hearing loss) showed that 25% of patients reported tinnitus cessation after cochlear implantation and 50% reported at least partial tinnitus reduction.[18] Furthermore, in an experimental prospective study with 26 patients with single-sided deafness accompanied by tinnitus, implantation of a CI resulted in a subjective benefit on tinnitus and a significant long-time reduction in tinnitus loudness.[19] Thus, by restoring auditory input, tinnitus reduction can be achieved. Suggested mechanisms for this beneficial effect are[20]:

1) restoring input to the auditory nerve by electrical stimulation may reverse pathologic reorganization associated with peripheral deafferentation (e.g. by causing an inhibitory effect on central hyperactivity causing tinnitus);
2) a masking effect by acoustic input, comparable to sound therapy, that masks or draws the attention away from the patient's own tinnitus sound.[21,22]

Although the majority of patients in these studies were reported to have improvement in tinnitus symptoms, aggravation and new-onset tinnitus after cochlear implantation have also been described in 8.2% and 19.6% of CI patients, respectively.[23] An explanation for this finding is that the insertion of the electrode may damage intracochlear structures.[20,21] Today, a CI is only a potential option for those tinnitus patients with profound sensorineural hearing loss. Thus, only tinnitus patients without residual hearing abilities are potential candidates for CI. This means that there is a large population of tinnitus patients who have (any) hearing function left, for whom a CI is not a treatment option.

Cochlear nerve

Tinnitus has several similarities with neuropathic pain, which is also regarded as a hyper excitability disorder.[4] Direct stimulation on the spinal cord is a technique that is often successful in the treatment of severe neuropathic pain.[24,25] In analogy to this technique, the University Medical Center Groningen developed a cuff electrode for **direct stimulation of the cochlear nerve** in patients with intractable, unilateral tinnitus. Six patients had been implanted with this cuff electrode, showing a promising effect in terms of reducing tinnitus.[26,27] However, extension of this research to a larger patient group and with long-term follow-up data was warranted.

Another example of interventions at the cochlear nerve is the relief of a neurovascular conflict. A neurovascular conflict is the phenomenon of a blood vessel, either a vein or an artery, compressing a cranial nerve that may cause symptoms related to the affected nerve. Well known types of a neurovascular conflict are trigeminal neuralgia and hemifacial spasms.[28] A neurovascular conflict of the cochleovestibular nerve has been suggested to cause tinnitus, vertigo, and sometimes sensorineural hearing loss, which is also referred to as the 'cochleovestibular nerve compression syndrome'.[29] A neurovascular conflict can be diagnosed on magnetic resonance imaging (MRI), although its diagnostic value remains uncertain as not all patients with an neurovascular conflict on MRI experience tinnitus.

Conservative treatment of a neurovascular conflict such as trigeminal neuralgia or hemifacial spasms comprises treatment with carbamazepine and/or Botox injections.[30,31] Another option is surgical treatment in the form of **microvascular decompression surgery** (MVD). For trigeminal neuralgia, the long-term success rate of this type of surgery was previously reported to be 83%.[30] For hemifacial spasms, the reported success rate was even higher, i.e. 91%.[32] However for tinnitus and/or vertigo in case of a neurovascular conflict of the cochleovestibular nerve, there is however no general acceptance of MVD since its success rates vary widely. The estimated success rate of MVD for tinnitus varies between 28 and 100% and for vertigo between 75 and 100%.[33] More research on the success rate and possible predictors for success for this latter type of surgery is warranted.

Cochlear nucleus

The fibers of the cochlear nerve enter the brainstem at the cochlear nucleus. The cochlear nucleus can be divided in the dorsal cochlear nucleus (DCN) and ventral cochlear nucleus. Especially the DCN seems to play an important role in generating and modulating noise- induced tinnitus.[34,35] Hyperactivity of the cochlear nucleus has been demonstrated following damage of peripheral auditory pathways by noise-exposure.[36] This hyperactivity in turn causes reduced intrinsic inhibition and elevating excitability.[14] The DCN is the location where the auditory system converges with the ipsilateral somatosensory inputs and it has been clinically observed that tinnitus can be modulated by certain head positions or for example jaw-clenching.[15] Hence, the DCN may also play a critical role in mediating in the auditory- somatosensory interaction.[34,37]

In 1979, House and Hitselberger successfully implanted the first **auditory brainstem implant** (ABI). The ABI is an electrical active implant that is comparable to a CI, yet is specifically designed to bypass the cochlea and the auditory nerve and to directly stimulate the cochlear nucleus in the brainstem.[38] The purpose of the ABI, similar to the CI, is to improve hearing ability in patients with profound sensorineural hearing loss. The ABI was developed in extension to the CI especially for patients with neurofibromatosis type II (NF2). These patients often have severely damaged cochlear nerve(s) because of growth of vestibular schwannomas and/or surgical removal of these tumors. Therefore, cochlear implantation is usually not an option for hearing rehabilitation.[38,39]

The ABI received FDA-approval in 2000. The ABI was initially only indicated for hearing rehabilitation in adult patients with NF2 and concomitant bilateral vestibular schwannomas. More recently, the indications for ABI were expanded to patients with: total ossification of both cochleae following meningitis; severe retrocochlear otospongiosis; cochlear trauma or cochlear nerve disruption; young congenitally deaf patients with cochlear nerve aplasia or hypoplasia and/or severe cochlear malformations. However, these expanded indications are still subject of debate.[40]

With the positive effects of a CI on tinnitus symptoms in mind, it was suggested that the ABI may also have a positive effect on tinnitus. The first to report on the clinical effect of electric stimulation on the cochlear nucleus for tinnitus were Soussi and Otto. In their study in 10 ABI recipients (NF2 patients), 7 out of 10 patients reported a decrease in tinnitus loudness during stimulation.[41] More recently, this finding was also demonstrated in clinical studies from Behr et al., McSorley et al. and Roberts et al., who all described a reduction of tinnitus during stimulation with the ABI in patients who suffered from tinnitus before the implantation.[42-44] An animal study by Luo et al. demonstrated that electrical stimulation of the DCN suppressed behavioral evidence of tinnitus in rats.[45] Suppression of tinnitus was noted during stimulation in the high frequency regions, and tinnitus suppression persisted after stimulation withdrawal.[45] In conclusion, both experimental and clinical studies suggest that electrical stimulation of the DCN may play an important role in the generation and/or modulation of noise-induced tinnitus. Future experiments should be performed to examine if electrical stimulation, for instance with ABI, indeed results in suppression of tinnitus.

Inferior colliculus

The inferior colliculus is located in the midbrain, halfway up the central auditory pathway, and is an important convergence center in the auditory system, as bilateral ascending and descending input is integrated in the inferior colliculus. Also, the inferior colliculus is known to show tinnitus related activity, especially in the central nucleus.[46] The **auditory midbrain implant** (AMI) is designed to stimulate the central nucleus of the inferior colliculus in order to improve hearing in profoundly deaf NF2 patients with such a distorted anatomy that would make adequate ABI placement challenging.[47,48] The AMI consists of one or two shanks with up to 20 electrodes.[47] The implant is placed along the tonotopic axis of the central nucleus of the inferior colliculus. A clinical pilot study described 3 patients that were implanted with the AMI and these patients have shown improvement in lip-reading capabilities and environmental awareness with some speech perception in one patient.[47]

The possibility of suppressing tinnitus through deep brain stimulation of the inferior colliculus using the AMI was investigated in guinea pigs.[49] In this study, the feasibility of the AMI for tinnitus treatment was successfully demonstrated, considering that plastic changes were shown in the central nucleus of the inferior colliculus by stimulating the dorsal cortex of the inferior colliculus.[49] In another more recent experimental study, it was demonstrated that deep brain stimulation of the inferior colliculi was effective in reducing behavioral signs of tinnitus in rodents.[50] Results of the AMI on tinnitus reduction in humans have not yet been described.

Auditory cortex

The auditory cortex is usually considered to be the end station of the auditory tract and is also thought to be involved in the pathological functioning of neural networks that generate tinnitus.[51] In search of finding an optimal place for electrical stimulation, **auditory cortex implants** have been investigated as well.[51] Transcranial magnetic stimulation is a non- invasive method which causes depolarization and changes excitability of cortical neurons by delivering oscillating magnetic fields and a small electrical current from an electrical coil. When used for tinnitus suppression, the efficacy varies over different studies from 53-100% and is often temporarily.[51] An invasive alternative for this method has been investigated, in order to provide chronic stimulation, in placing an auditory cortex electrode extradurally[52-54] of intraparenchymal.[55] However, in a recent double-blind randomized cross-over study with 8 patients with severe tinnitus who underwent chronic epidural stimulation of the auditory cortex showed that this was not efficient in treating severe and resistant tinnitus.[56]

Aims and outline of this thesis

Aims

Surgical treatment may be an option for patients who have intractable tinnitus that is not manageable with conventional treatment options. The aim of this thesis is to explore the possibilities, feasibility and effect of various neurosurgical treatment options for tinnitus at the level of the cochlear nerve and cochlear nucleus.

Outline of the thesis

There is a tendency to search for an individual, patient-tailored strategy instead of a 'one size fits all' approach to tinnitus treatment.[57] It can be speculated that specific subgroups of tinnitus patients, require specific treatment. In order to design phenotype-specific treatments, more insight in the heterogeneity of tinnitus is needed. Therefore, in **Chapter 2** a cluster analysis was performed on a large database of tinnitus patients of the University Medical Center Groningen with the aim to identify recognizable subgroups of tinnitus patients.

One proposed surgical treatment for tinnitus is MVD surgery. However, general acceptance of MVD surgery for tinnitus by a neurovascular conflict is lacking and the success rates of this type of surgery for tinnitus relief are varying. In order to gain more insight in the effectiveness, complication rate and prognostic factors for success of MVD surgery for tinnitus, a systematic review and meta-analysis using individual patient data was conducted (**Chapter 3**).

The causal relation between a neurovascular conflict and tinnitus is complicated. The clinical value of a neurovascular conflict on MRI is unclear, since not all patients with a neurovascular conflict of the cochleovestibular nerve on MRI experience tinnitus. In fact, close contact between the cochleovestibular nerve and surrounding blood vessels is often observed in tinnitus patients (25-53%), but this percentage does not differ from asymptomatic patients.[58,59] In **Chapter 4**, we hypothesize that the type or degree of compression of the cochleovestibular nerve may have

diagnostic value in tinnitus patients with an neurovascular conflict and may yield more insight into whether a neurovascular conflict is causative for tinnitus symptoms. Therefore, we performed a retrospective study in tinnitus patients who underwent an MRI to investigate the type and degree of compression of the cochleovestibular nerve and related this to clinical tinnitus parameters.

The remaining chapters of this thesis consider electrical brain stimulation for the treatment of tinnitus. A previous pilot study by our colleagues Bartels et al. showed that direct stimulation of the cochleovestibular nerve with an implanted cuff electrode in patients with intractable, unilateral tinnitus is a safe procedure and generated promising results in terms of tinnitus reduction.[26] In **Chapter 5**, a long-term follow-up of this study was described together with the results of an additional five patients who were implanted with a cuff electrode. Since this study showed a moderate success rate with an important unwanted complication of induced hearing loss, stimulation of the auditory tract using the ABI was suggested as a next and better step in searching for a solution. The ABI has been reported to have a positive effect on tinnitus in NF2 patients who received the implant for hearing rehabilitation.[41-44] An advantage of the ABI over a CI in tinnitus treatment might be that the ABI does not harm auditory structures. Therefore, patients with residual hearing ability and tinnitus may benefit from this option. In order to investigate the safety and effect of direct stimulation of the cochlear nucleus with the ABI in patients with intractable tinnitus, a prospective study was designed. In **Chapter 6** the protocol of this interventional pilot study is described in detail. In **Chapter 7**, the preliminary results of the first patients of this ongoing trial are presented.

Finally, in **Chapter 8** the main findings and conclusions of this thesis are discussed and future directions in the ongoing search for surgical treatment options for tinnitus are suggested.

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2

Cluster analysis to identify possible subgroups in tinnitus patients

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Abstract

Introduction

In tinnitus treatment, there is a tendency to shift from a "one size fits all" to a more individual, patient-tailored approach. Insight in the heterogeneity of the tinnitus spectrum might improve the management of tinnitus patients in terms of choice of treatment and identification of patients with severe mental distress. The goal of this study was to identify subgroups in a large group of tinnitus patients.

Methods

Data were collected from patients with severe tinnitus complaints visiting our tertiary referral tinnitus care group at the University Medical Center Groningen. Patient- reported and physician-reported variables were collected during their visit to our clinic. Cluster analyses were used to characterize subgroups. For the selection of the right variables to enter in the cluster analysis, two approaches were used: (1) variable reduction with principle component analysis and (2) variable selection based on expert opinion.

Results

Various variables of 1,783 tinnitus patients were included in the analyses. Cluster analysis (1) included 976 patients and resulted in a four-cluster solution. The effect of external influences was the most discriminative between the groups, or clusters, of patients. The "silhouette measure" of the cluster outcome was low (0.2), indicating a "no substantial" cluster structure. Cluster analysis (2) included 761 patients and resulted in a three-cluster solution, comparable to the first analysis. Again, a "no substantial" cluster structure was found (0.2).

Conclusion

Two cluster analyses on a large database of tinnitus patients revealed that clusters of patients are mostly formed by a different response of external influences on their disease. However, both cluster outcomes based on this dataset showed a poor stability, suggesting that our tinnitus population comprises a continuum rather than a number of clearly defined subgroups.

Introduction

Tinnitus is a prevalent condition (estimated to affect 5-18% of the adult population,[1] that may lead to severe impairment in quality of life. Although many trials on tinnitus therapies have been conducted, hardly ever a treatment effect is demonstrated. A potential explanation for the lack of effectivity of these treatments might be the underlying heterogeneity of the disease. Therefore, consensus on the optimal treatment of tinnitus gradually shifts from a 'one size fits all' approach to a more patient-tailored approach. Possibly, a particular group of patients would be more likely to respond to treatment, if a selection is made on etiology, tinnitus characteristics or patient characteristics. It might be the case that in a specific subgroup a particular treatment is successful that is not successful in another subgroup. Thus, insight in the heterogeneity of the tinnitus spectrum might improve the management of these patients.

Identification of tinnitus subgroups is also important with regard to concomitant mental distress. Hoekstra et al. demonstrated that patients that express certain characteristics (i.e. high percentage of tinnitus during the day, self-reported depression and/or anxiety and subjective experience tinnitus loudness) are more at risk for a high tinnitus burden.[2] This subgroup of patients with high tinnitus distress needs more extensive counseling and follow- up in order to prevent mental breakdown.

In an attempt to identify subgroups of tinnitus patients, cluster analysis was used in this study. Cluster analysis is a statistical technique that divides data into groups, or clusters, that are meaningful and/or useful. It is an explorative analysis that assigns patients to clusters based on certain characteristics, so that patients look very much alike within a cluster (high within- group homogeneity) and at the same time are very different from the other clusters (low between-group homogeneity).[3] In research, this cluster analysis method it is not only used in medicine studies to identify groups of patients, but also in i.e. marketing for finding customer segments.

In 2008 Tyler et al. performed a preliminary cluster analysis on 153 patients with tinnitus.[4] The cluster analysis of Tyler et al. identified distinct cluster characteristics, which were described as: (1) 'constant distressing tinnitus'; (2) 'varying tinnitus that is worse in noise'; (3) 'tinnitus patients who are copers and whose tinnitus is not influenced by somatic modulation'; and (4) 'tinnitus patients who are copers but whose tinnitus is worse in quiet environments'. Tyler et al. did not report a statistic value to identify the degree to which patients clustered in these groups.

In this paper, we report on an exploratory cluster analysis of patients from the tinnitus database of the University Medical Center Groningen (n=1783 patients). We initially attempted to replicate the cluster analysis reported by Tyler et al.[4], however this was not possible as many of the variables used in their analysis were not identical or not available in our database. Instead, we report on two further cluster analyses. In the first analysis, the choice of variables that were entered in the cluster analyses was fully guided by the statistical techniques. In the second analysis, the selection of variables was based on the expert opinions in our tinnitus clinic. The aim of this study was to identify subgroups of tinnitus using cluster analysis, based on a very large dataset of tinnitus patients.

Methods

Tinnitus population

This study was performed at the Otorhinolaryngology department of the University Medical Center Groningen (The Netherlands), which has a specialized multidisciplinary care group for tinnitus patients since 2007. Patients with severe complaints of tinnitus can be referred to this care group for medical consultation and psychological support. Almost all patients who visit this care group, have consulted an audiologist and/or otorhinolaryngologist earlier. However, these patients were referred to our specialized tertiary care group by these specialists, because of the severity and impact of the complaints. Consultation at our clinic consists of thorough evaluation by an otorhinolaryngologist, an audiologist, radiologist, a medical social worker and/or a psychologist.

Variables

The variables that were available for this cluster analysis were demographic characteristics (e.g. sex and age), tinnitus characteristics (e.g. duration of tinnitus, onset, lateralization, pitch, variable loudness), factors of influence on their tinnitus (e.g. influence of loud sounds, noisy environment, movement of head and neck), tinnitus and quality-of-life related questionnaires (e.g. Tinnitus Handicap Index [THI], Visual Analogue Scale [VAS] and Hospital Anxiety and Depression Scale [HADS]) and audiological characteristics (e.g. frequency matching, pure tone averages [PTA], loudness matching of tinnitus). Hearing loss was divided into categories based on the pure tone audiogram: (1) no or slight hearing loss (both ears thresholds <30dB on PTA thresholds at 0.25-0.5-1-2-4-8 kHz); (2) asymmetrical hearing loss (≥30dB difference between both ears on the mean PTA thresholds at 2-4-8 kHz); (3) bilateral high tone hearing loss (both ears thresholds ≥30dB on PTA thresholds at 2-4-8 kHz); (4) bilateral severe hearing loss (PTA thresholds >30dB on 0.25-0.5-1-2-4-8 kHz); and (5) other. The available variables are all listed in a Table in Appendix 1. All patient-reported variables were completed by the patients in booklets during the visit at the tinnitus outpatient clinic. Physician reported data, such as audiological characteristics, were also reported in booklets by the physician. All these routinely collected data were anonymized and entered in a database. For the current analysis, this data was retrospectively analyzed. The collection of data was approved by the Institutional Reviewer Board of the UMCG. No full review was needed due to the retrospective nature of this study.

Selection of variables for cluster analysis

All variables that were collected, were entered in the database. However, not all of these variables could be entered in the cluster analysis. In cluster analysis, it is important to keep the sample size in mind when deciding how many variables to enter in the analysis. Formann et al. recommends a number of variables (m) of 2^m=sample size.[5] In our study, the sample size is n=1783, implying that the number of variables should be 10 or 11. There are two ways to select appropriate variables for cluster analysis: (1) a statistical approach with the use of Principal Component Analysis and (2) selection of variables based on 'expert opinion', i.e. variables that are presumed to be clinically relevant and thought to be discriminative in the total group. Both selection procedures were performed in this study, resulting in two different cluster analyses.

(1) Variable reduction by Principal Component Analysis

A Principal Component Analysis is a dimension reduction technique that condenses variables that are highly correlated into a set of factors, thereby removing overlap and redundancy. Principal Component Analysis (PCA) with Varimax rotation was performed on all variables with missing values ≤20%. The PCA revealed several factors, and for each factor the variable with the highest loading was selected for inclusion in the cluster analysis.

(2) Variable reduction by 'expert opinion'

After excluding variables with missing values >20%, variables were selected by a group of tinnitus care professionals and investigators (MB [otolaryngology resident, PhD-candidate in tinnitus research], PD (medical physicist, audiologist, involved in the tinnitus care group) and EK (medical physicist, audiologist, involved in the tinnitus care group)].Based on clinical experience and knowledge, those variables were selected that were deemed important in discriminating subgroups of tinnitus.

Cluster analysis

The 'two-step' cluster analysis method was used as the analyses contained both categorical and continuous variables.[6] Continuous variables were standardized by default. For distance measures, the log-likelihood method was used, as both continuous and categorical variables were entered in the analysis. The number of clusters to be formed was not specified in advance. The 'Silhouette measure of cohesion and separation' is a measure for the overall goodness-of-fit of the cluster structure that was found. It ranges from -1 to 1 (<0.25: no substantial structure has been found; 0.26-0.50: weak structure and could be artificial; 0.51- 0.70: reasonable structure; 0.71-1.0: strong structure).[7]

Differences in characteristics between clusters were compared according to the cluster membership variable, using one-way ANOVA for continuous variables and Pearson Chi- square tests for categorical variables. SPSS version 23.0 (Chicago, Illinois) was used for all tests. The significance level was set at α=0.05 and all tests were two-tailed.

Results

Subject characteristics

For this study, data from 1783 consecutive patients who visited the UMCG tinnitus clinic between July 2007 and June 2016 were collected. The baseline characteristics of this study population are shown in Table 1. Variables that had >20% missing values are not shown in this table. In this population, 39.3% was female and the mean age was 53.6±13.5 years. Tinnitus was unilateral in 50.7% of the cases and bilateral or central in 48.2%. The mean THI in the total patient group was 42.5±23.2.

Table 1. Demographic and tinnitus related characteristic of included tinnitus patients (n=1783)

	Total N	
Demographic characteristics		
Mean age ±SD	1783	53.6±13.5
Female gender – no.(%)	1783	701 (39.3)
Tinnitus characteristics		
Mean duration of tinnitus ±SD – in y	1635	6.8±8.7
Onset tinnitus – no.(%)	1685	
Acute		813 (48.2)
Gradual		872 (51.8)
Lateralization of tinnitus – no.(%)	1496	
Bilateral/Central		738 (49.3)
Unilateral		758 (50.7)
Description of tinnitus – no.(%)	1607	
Tonal		715 (44.5)
Noise		708 (44.1)
Other		184 (11.4)
Experience of tinnitus – no.(%)	1645	
Continuous		1512 (91.9)
Intervals		133 (8.1)
Pitch of tinnitus – no.(%)	1620	
Low		79 (4.9)
Moderate		403 (24.9)
High		997 (61.5)
Other		141 (8.7)
Variable loudness of tinnitus – no.(%)	1762	
Yes		1271 (72.1)
No		491 (27.9)
Mean % of burden during awake time ±SD	1671	74.7±28.0
Preference for silence or noise – no.(%)	1559	
Silence		697 (44.7)
Noisy environment		862 (55.3)
Highest burden at time of the day – no.(%)	1522	
Waking up		131 (8.6)
Morning		38 (2.5)
Afternoon		34 (2.2)
Evening		282 (18.5)
Night		149 (9.8)
Other		888 (58.3)
Sound unpleasant – no.(%)	1446	
Never		137 (9.5)
Seldom		192 (13.3)
Some times		590 (40.8)
Most of the time		357 (24.7)
Always		170 (11.8)

Table continues on the next page

Factors of influence on tinnitus		
Influence of noisy background – no.(%)	1551	
Tinnitus louder		212 (13.7)
No effect		753 (48.5)
Tinnitus less loud		586 (37.8)
Influence of loud sounds – no.(%)	1539	
Tinnitus louder		693 (45.0)
No effect		523 (34.0)
Tinnitus less loud		323 (21.0)
Influence of head and neck – no.(%)	1559	
Tinnitus louder		479 (30.7)
No effect		995 (63.8)
Tinnitus less loud		85 (5.5)
Influence of nap in the afternoon – no.(%)	1419	
Tinnitus louder		233 (16.4)
No effect		1003 (70.7)
Tinnitus less loud		183 (12.9)
Influence of stress – no.(%)	1508	
Tinnitus louder		937 (62.1)
No effect		552 (36.6)
Tinnitus less loud		19 (1.3)
Influence of sleep deprivation – no.(%)	1491	
Tinnitus louder		847 (56.8)
No effect		629 (42.2)
Tinnitus less loud		15 (1.0)
Audiological characteristics		
PTA (1-2-4 kHz) (mean±SD)	1764	29.7±18.0
Difference in PTA (1-2-4 kHz) between both ears (mean±SD)	1764	11.5±18.1
Frequency matching of tinnitus – no. (%)	1469	
0-2000 Hz		378 (24.0)
2000-4000 Hz		239 (15.5)
4000-6000 Hz		287 (18.6)
6000-8000 Hz		275 (17.9)
>8000 Hz		290 (23.4)
Type of hearing loss – no. (%)	1782	
No/Slight hearing loss		989 (55.5)
Asymmetrical hearing loss		265 (14.9)
Bilateral high tone hearing loss		243 (13.6)
Bilateral severe hearing loss		246 (13.8)
Other		39 (2.2)
Tinnitus Questionnaires		
VAS tinnitus loudness* (mean±SD)	1615	66.7±20.9
VAS tinnitus annoyance* (mean±SD)	1641	69.1±22.6
THI-score (mean±SD)	1505	42.5±23.2
HADS-depression score ±SD	1676	5.4±4.3
Indication HADS-depression** – no.(%)	1676	
No indication depression		1321 (78.8)
Indication depression		355 (19.9)

Table continues on the next page

HADS-anxiety score ±SD	1690	6.9±4.3
Indication HADS-anxiety** – no.(%)	1690	
No indication anxiety		1103 (65.3)
Indication anxiety		587 (34.7)

** on VAS range from 0-100%*

*** range 0-21, indication for depression/anxiety with score >8. Range is 0-100 unless indicated otherwise*

dB: decibel; SD: standard deviation; PTA: pure tone audiometry; THI: Tinnitus Handicap Inventory; HADS: Hospital Anxiety and Depression Scale; VAS: visual analogue scale

Outcome of cluster analysis with variables selected by Principal Component Analysis

The Principal Component Analysis was performed to obtain eigenvalues for each factor. The Kaiser-Meyer-Olkin measure of sampling adequacy was 0.681. The Bartlett's test of sphericity was significant ($\chi 2$ (6127)=325, $p<0.001$), both indicating an appropriate factor model. A total of eight factors was extracted (based on the eigenvalue >1 rule), which together explained 55% of the total variance. Variables with the highest loading on each factor was selected. Subsequently, these variables (n=8) were entered in the cluster analysis. The clustering revealed a four-cluster solution. As the analysis excludes every case when there is any variable with a missing value (listwise exclusion), the analysis was based on n=976 patients. The cluster outcome showed a 'Silhouette measure of cohesion and separation' of 0.20, indicating that it is a "no substantial" cluster solution7. Characteristics of these four identified clusters are shown in Table 2. The variables in the table are ranked from most discriminative between groups (top of the table) to less discriminative (bottom of the table). All variables differed statistically significant between the four clusters, except for the variables 'VAS tinnitus annoyance' and 'Frequency of the tinnitus' (p=0.925 and p=0.478 respectively).

Cluster 1 (n=293) is characterized by the fact that tinnitus is not easily influenced: loud sounds, sleep deprivation and nap in the afternoon have no effect on their tinnitus. These patients have a relatively high difference between hearing loss in the right and left ear. These patients have relatively low HADS-depression scores.

Cluster 2 (n=259) is distinguished by a gradual onset of the tinnitus. Also in this group, tinnitus is easily negatively influenced, especially by loud sounds and sleep deprivation. Both make their tinnitus louder.

Cluster 3 (n=197) is a group of patients that report that their tinnitus is less loud when they hear loud sounds. Sleep deprivation and a nap in the afternoon mostly have no effect on their tinnitus.

Cluster 4 (n=227) is typically a group with tinnitus of acute onset. They report that their tinnitus is easily negatively influenced by loud sounds or sleep deprivation. They show relatively high HADS-depression scores.

Table 2. Characteristics of the four clusters identified by clustering with variable selection based on Principal Component Analysis

	Cluster 1 (n=293)	Cluster 2 (n=259)	Cluster 3 (n=197)	Cluster 4 (n=227)	p-value
Influence of loud sound (%)					**<0.001***
Tinnitus louder	37.5	54.4	0	68.7	
No effect	62.5	39.4	0	30.0	
Tinnitus less loud	0	6.2	100	1.3	
Influence of sleep deprivation (%)					**<0.001***
Tinnitus louder	0	89.2	47.2	86.8	
No effect	100	10.8	49.7	11.5	
Tinnitus less loud	0	0	3.0	1.8	
Onset (%)					**<0.001***
Acute	48.1	0	49.2	100	
Gradual	51.9	100	50.8	0	
Influence of nap afternoon (%)					**<0.001***
Tinnitus louder	0	27.0	11.2	22.9	
No effect	100	56.8	84.3	52.4	
Tinnitus less loud	0	16.2	4.6	24.7	
HADS depression scale (mean)	4.6	5.6	5.5	6.0	**0.001†**
Difference in mean PTA ADS (dB)	13.1	10.8	7.9	11.9	**0.015†**
Frequency of tinnitus (%)					0.478*
0-2000 Hz	23.2	23.2	21.8	25.1	
2000-4000 Hz	14.7	13.9	21.3	15.0	
4000-6000 Hz	18.8	20.5	20.3	15.0	
6000-8000 Hz	19.5	17.0	12.7	19.4	
>8000 Hz	23.9	25.5	23.9	25.6	
VAS tinnitus annoyance (mean)	69.2	69.4	68.2	69.6	0.925†

** Pearson Chi-square test, † one-way ANOVA*

ADS: both ears; PTA: pure tone audiometry; VAS: visual analogue scale

Outcome of cluster analysis with variables selected by expert panel

For the alternative method of choosing variables for clustering, 11 variables were selected by a panel of experts. The selected variables (see Table 3) were entered in the cluster analysis. The outcome was a three-cluster solution, with a 'Silhouette measure of cohesion and separation' of 0.20, again indicating a poor solution. Because of listwise exclusion as described earlier, this analysis was based on n=761 patients. 527 Of these patients were also included in cluster analysis 1. Also in this table, variables are ranked according to their degree of discriminative value. All variables differed significantly between the clusters (all p-values <0.001).

Cluster 1 (n=287) is a group of patients whose tinnitus is not easily influenced: loud sounds, stress or movement of head and neck have no effect on their tinnitus loudness. Patients prefer a noisy environment. Sounds are never to seldom experienced as uncomfortably loud. The tinnitus is mostly unilateral. Although most patients in this group have no or slight hearing loss, other types of hearing loss are present in this group as well. They are not very much bothered or depressed by their tinnitus, as the THI and HADS-depression scores are low.
Cluster 2 (n=247) is a predominantly male group, whose tinnitus gets worse by stress, loud sounds and movement of head and neck. These patients prefer to be in a noisy environment. Sometimes, sounds are experienced as uncomfortably loud. Most of the patients have no or slight hearing loss. Tinnitus is bilateral and the loudness of the tinnitus is variable.

Cluster 3 (n=227) is a characterized by the fact that their tinnitus is easily negatively influenced: loud sounds and stress clearly make their tinnitus louder. These patients prefer a silent environment. Often, patients find sounds uncomfortably loud. Tinnitus is often bilateral with most patients having no or slight hearing loss or asymmetrical hearing loss. The loudness of the tinnitus is variable.

Table 3. Characteristics of the four clusters identified by clustering with variables selected by expert opinion

	Cluster 1 (n=287)	Cluster 2 (n=247)	Cluster 3 (n=227)	p-value
Influence of loud sound (%)				**<0.001***
Tinnitus louder	16.0	27.9	96.9	
No effect	56.1	38.5	3.1	
Tinnitus less loud	27.9	33.6	0	
Influence of stress (%)				**<0.001***
Tinnitus louder	24.4	87.4	78.4	
No effect	74.9	9.7	21.6	
Tinnitus less loud	0.7	2.8	0	
Preference for silence or noise (%)				**<0.001***
Silence	28.2	25.5	89.9	
Noisy environment	71.8	74.5	10.1	
Are sounds uncomfortably loud? (%)				**<0.001***
Never	18.8	6.9	0.4	
Seldom	28.9	13.4	3.1	
Sometimes	31.4	61.5	31.7	
Most of the time	14.6	13.4	43.2	
Always	6.3	4.9	21.6	
Lateralization of tinnitus (%)				**<0.001***
Bilateral/central	31.0	84.2	38.3	
Unilateral	69.0	15.8	61.7	
Hearing loss category (%)				**<0.001***
No hearing loss	51.9	72.5	44.9	
Asymmetrical hearing loss	15.7	2.4	35.2	
Bilateral high tone hearing loss	17.4	8.9	9.7	
Bilateral flat hearing loss	12.9	16.2	6.2	
Other	2.1	0	4.0	
Variable loudness (%)				**<0.001***
No	49.8	15.0	18.1	
Yes	50.2	85.0	81.9	
THI-score (mean)	32.6	48.0	46.9	**<0.001†**
Influence of movement of head and neck (%)	8.4	40.1	39.2	**<0.001***
Tinnitus louder	84.3	55.5	55.9	
No effect	7.3	4.5	4.8	
Tinnitus less loud				
HADS depression scale (mean)	4.2	5.9	5.4	**<0.001†**
Gender (%)				**<0.001***
Male	59.9	74.1	55.9	
Female	40.1	25.9	44.1	

** Pearson Chi-square test, † one-way ANOVA*

THI: Tinnitus Handicap Inventory; HADS: Hospital Anxiety and Depression Scale

Discussion

In this study, we performed cluster analysis with the aim to identify subgroups in a population of tinnitus patients. Variable selection for cluster analysis was performed in two ways: by a strict methodological approach based on principal component analysis, and by expert opinion, respectively. These analyses identified four and three patient clusters, where the clusters showed clearly different characteristics. However, the clustering solution was in both analyses not substantial, as indicated by a poor cluster solution quality.

Although both cluster analyses gave different outcomes, there were also interesting similarities. In both cluster solutions, the effect of 'stress' and 'loud sounds' on tinnitus have a relatively high discriminative value between groups. In each analysis, a group was revealed in which patients report that their tinnitus gets louder from loud sounds, and there was a group that reported that their tinnitus got less loud. In their earlier cluster analysis, Tyler et al., also describe that their clusters differed by the effect of external factors on tinnitus: some patients are easily negatively influenced by external factors and in others this has no effect.[4] On the contrary, Tyler et al. describe a group that is characterized by high scores on tinnitus questionnaires and the HADS depression and anxiety scale. However, this was not reflected in our cluster solutions.

In the cluster analysis based on variables selected by experts, there was a clear distinction between a group that preferred a silent environment for their tinnitus and another group that had a preference for a noisy environment. The fact that there some patients with tinnitus prefer noise and other silence for their tinnitus, has been described earlier.[8] This is interesting, as one might speculate that the latter group may have a higher change of responding well to sound therapy than the other group.

When interpreting these results, it must be kept in mind that the 'Silhouette measure' of both analyses was only 0.2. This is lower than the critical boundary of 0.25, which implies that there was no substantial clustering in this patient cohort. A lack of clustering indicates that the transition from one cluster to another is relatively smooth, without clear-cut boundaries. As a comparison, consider a group of cities, where the coordinates of the cities would go into a cluster analysis. If one group of cities is clearly separated from another group by a stretch of open land, the silhouette value will be large (when viewed from a distance, the cities will have a distinct silhouette of their skyline). However, if there is no such open land between the clusters, the silhouette value is low, consistent with the absence of substantial clustering. In our patient cohort, there were clearly no distinct 'open stretches of land' between the clusters, suggesting that patient form a continuum rather than a clear clustering. As discussed above, the cluster analysis of Tyler et al., identified clusters with characteristics that show some resemblance to the clusters reported here. Unfortunately, Tyler et al do not report a Silhouette value or another measure of clustering. Hence, it is at present no possible to discuss the clustering strength in their cohort.

Cluster analysis has been upcoming in medical research. Recently, an interesting cluster analysis on bilateral Meniere disease was published to define clinical subgroups with potential similar etiologies. In this study, five clinical variants of bilateral Meniere disease were found based on six clinical variables and with a high Silhouette measure of 0.8.[9] This study is not only beneficial to improve the selection of patients, but can also explain the negative treatment effects of several treatment trials, as results can be biased by a heterogeneous patient group based on etiology.[9] The difficulty in cluster analysis is that it is a type of analysis that is very sensitive to change of variables. The selection of variables is critical for the outcome of the cluster analysis.6 Generally, highly correlated variables should be avoided and it is important to select variables that can make a clear-cut differentiation between clusters.[6] The systematic statistical approach of selecting variables using the highest factor loading on extracted factors by Principal Component Analysis is often used and has the advantage of choosing variables in a reproducible, transparent way. A downside of this technique is that the factor solution only explains a certain amount of variance and therefore, much information is discarded. Eliminating factors with low loadings on the extracted factors, has the same effect.[10] This may lead to a reduced success of a subsequent cluster analysis. On the other hand, a disadvantage of selecting variables based on clinical knowledge or 'gut feeling' is that it is less transparent. Also, unrecognized highly discriminating variables may remain undiscovered.

Strengths of the study

For this study, a very large database of tinnitus patients was used with almost 1800 patients. Even after exclusion of patients with missing values, still n=976 and n=761 could be included in the cluster analyses. We expect, that if clear clustering would have existed with these variables, we would have been able to find it in these groups. There was an overlap of 527 patients who were included in both the first cluster outcome and the second cluster outcome. This is a substantial overlap, pointing out that it does not seem likely that the differences between both cluster analyses are caused by the differences in included patients.

Limitations

This study explored the patient cohort of a tertiary tinnitus referral center. Thus, the population described here, consists of a group of tinnitus patient who were persistent in their search for treatments for their tinnitus. Our patient cohort may therefore be biased with a certain type of tinnitus patients. Potentially, a study including also less-persistent help seeking and non-help-seeking subjects would have identified a clearer clustering.

Although we had access to a large database of tinnitus patients (n=1783), over the years there were changes in the variables that were collected because of changes made to the diagnostic protocol. Since the cluster analyses required a complete set of data for each patient, not all 1783 patients could be included in the analysis, but 976 and 761 respectively.

Furthermore, it is debatable internationally whether tinnitus is a disease or a symptom. One can look at it in both ways: when tinnitus is a result of an acoustic neuroma, then tinnitus can be a symptom. However, if we look at tinnitus as the result of defect on a cellular level of the auditory cortex, then tinnitus can be regarded as a disease. In most patients visiting our clinic, the etiology of the tinnitus in unclear. The fact is that these patients included in our dataset experience bothersome tinnitus. Within this group, we aimed to find subgroups such as for example: patients with continuous central, loud tinnitus, tend to have a high score on THI and VAS and find that their tinnitus gets worse in noisy environments. If we are able to find such patterns, maybe we can adjust our treatment strategy to that (in this example, hearing aids might not be successful). Although the raised issue about tinnitus being a symptom or disease is important, we believe that this analysis looking for clusters of patients based on tinnitus characteristics, transcends this issue.

Finally, the low silhouette value indicates that this patient cohort represents a heterogeneous group without clear clustering. Obviously, any cluster analysis outcome highly depends on the variables that we entered into the clustering algorithm. Our patient data consisted of mainly audiometry and questionnaire metrics. In these cluster analyses, tinnitus patients appear to represent a continuum rather than clearly defined subgroups, based on a low silhouette measure. However, it is possibly that other metrics (e.g. fMRI/EEG, genetic data) is able to identify tinnitus subgroups. In other words, the lack of clustering in our analyses, does not imply that clusters do not exist. However, if clusters exist, they cannot be identified with the variables the were considered here.

Conclusion

Two cluster analyses of a large patient cohort identified three and four groups of tinnitus patients, respectively. The clustering was not substantial, as a low Silhouette measure of the cluster solutions was found, indicating that in this particular cohort, tinnitus patients appear to represent rather a continuum than clearly defined subgroups. This finding may have consequences for future treatments: if clear subgroups would have been present, clearly distinct treatment might be developed in the future. However, for a continuum of patients, it may be necessary to use a number of treatments to find the optimum for each individual patient. Obviously, our conclusion is based on the set of variables that were at our disposal. Possibly, new future ways to characterize tinnitus patients may be able to find distinct subgroup in tinnitus patients.

Appendix 1. List of available variables

	Variable name	Source of data	Data type	Description of variable
Demographics	Gender	PR	Binary	Male/Female
	Age	DD	Continuous	In years
Tinnitus characteristics	Duration of tinnitus	PR, DD	Continuous	In years
	Onset of tinnitus	PR	Binary	Acute / Gradual
	Lateralization of tinnitus	PR	Categorical	Unilateral / Bilateral or Central
	Description of tinnitus	PR	Categorical	Tonal / Noise / Other
	Experience of tinnitus	PR	Binary	Continuous / Intervals
	Pulsating tinnitus	PR	Categorical	Not pulsating / Pulsating synchronous with heartbeat / Pulsating not synchronous with heartbeat
	Pitch of tinnitus	PR	Categorical	Low / Moderate / High / Other
	Variabele loudness of tinnitus	PR	Binary	Yes / No
	Percentage of burden during awake time	PR	Continuous	Range 0-100%
	Preference for silence or noise	PR	Binary	Silence / Noisy environment
	Daytime with highest burden	PR	Categorical	Awaking / Morning / Afternoon / Evening / Night / Other
	Is sound unpleasant?	PR	Categorical	Never / Seldom / Sometimes / Most of the time / Always
Audiological characteristics	Etiology of hearing loss	CR	Categorical	Presbyacusis / Noise exposure / Otosclerosis / Congenital / Otitis Externa / Sudden hearing loss / Otitis Media / Cholesteatoma / Lyme disease / Other or Unknown
	Frequency matching	CR	Categorical	0-2000 Hz / 2000-4000 Hz / 4000-6000 Hz / 6000-8000 Hz / >8000 Hz
	Loudness matching	CR	Continuous	In dB
		CR	Continuous	In dB (mean thresholds 2-

CR: clinician reported; DD: derived data (calculated); HADS: hospital anxiety and depression scale; HQ: hyperacusis questionnaire; PR: patient reported; PTA: pure tone audiometry; THI: tinnitus handicap inventory; VAS: visual analogue scale

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3

Microvascular decompression of the cochleovestibular nerve for treatment of tinnitus and vertigo: a systematic review and meta-analysis of individual patient data

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Abstract

Objective

Microvascular decompression (MVD) is regarded as a valid treatment modality in neurovascular conflicts (NVC) causing e.g. trigeminal neuralgia and hemifacial spasms. NVC the cochleovestibular nerve might cause tinnitus and/or vertigo, however general acceptance of MVD for this indication is lacking. We aimed to investigate the effectiveness, safety and prognostic factors for success of MVD of the cochleovestibular nerve.

Methods

A systematic review and meta-analysis with individual patient data (IPD) was conducted according to the PRISMA-IPD guidelines. With a comprehensive search (January 2016) in MEDLINE, EMBASE and Google Scholar, eligible studies were identified. The collected outcome was a global measurement of improvement of (1) tinnitus, (2) vertigo and (3) tinnitus combined with vertigo. For the meta-analysis, IPD was collected from the papers and/or from the authors. IPD was analysed with logistic regression analysis while accounting for study clustering.

Results

Thirty-five studies (527 patients) were included. The level of evidence provided by these studies was low. In 28% of tinnitus patients and 32% of vertigo patients complete relief following MVD was reported. Patients with both tinnitus and vertigo had complete relief in 62%. In 11% of the patients ≥1 complications were reported. Meta-analysis of IPD (165 patients) demonstrated that patients with both tinnitus and vertigo had higher chance of success (OR: 3.8, 95% CI: 1.45-1.10) than patients with tinnitus alone. No other variables related significantly to success.

Conclusions

Due to low success rates, MVD cannot be considered as a standard treatment method for tinnitus or vertigo. Moreover, a substantial complication rate was found. However, patients with combined symptoms had a higher chance of success. When symptoms occur combined, it is more likely that an NVC is the underlying pathology and MVD might be appropriate. Due to the low level of evidence in the included studies, this conclusion must be taken with caution and further validation is necessary to evaluate whether patients with combined symptoms indeed are better candidates for MVD.

Introduction

A neurovascular conflict (NVC) is a well-known neurological phenomenon in which the root entry zone of a cranial nerve is compressed by an artery or vein. As such, a NVC may cause symptoms related to the affected nerve. In 1932, neurosurgeon Walter Dandy (Baltimore, USA) was the first to propose this concept, describing a NVC of the trigeminal nerve in the posterior fossa as the cause of trigeminal neuralgia.[1] In the late 1960s, the theory of NVC received more attention after the publication by Peter Jannetta (Pittsburgh, USA) of a large series of microvascular decompression (MVD) surgery as treatment for symptomatic NVC of various cranial nerves.[2] Today, MVD surgery is a widely accepted treatment for a symptomatic NVC of the trigeminal nerve (i.e. trigeminal neuralgia), facial nerve (i.e. hemifacial spasms) and glossopharyngeal nerve (i.e. glossopharyngeal neuralgia).[3-5] It has been suggested that NVC of the cochleovestibular nerve could be a cause of unilateral tinnitus and vertigo.[2] A NVC of the cochleovestibular nerve may cause a heterogeneous symptomatology, since the nerve is composed of the superior vestibular nerve, the inferior vestibular nerve and the cochlear nerve. Therefore, compression of the cochleovestibular nerve has the potential to cause symptoms of tinnitus and/or vertigo, sometimes accompanied by sensorineural hearing loss, which in the literature is also referred to as the cochleovestibular nerve compression syndrome.[6]

Unlike MVD for e.g. trigeminal neuralgia, general acceptance of MVD for tinnitus and/or vertigo is lacking. For trigeminal neuralgia, the success rate of long-term follow-up is 83%.[3] For hemifacial spasms (91%) and glossopharyngeal neuralgia (92-98%), the success rates are even higher.[4,5] In contrast, the estimated success rate of MVD for tinnitus lies between 28 - 100% and for vertigo between 75-100%.[7] This dissimilarity in success rates may be caused by the lack of sufficient diagnostic criteria for tinnitus and/or vertigo caused by a NVC, resulting in inadequate patient selection.

To tackle the ongoing controversy regarding this type of surgery, more insight is needed. Many reports in which MVD is performed for tinnitus and/or vertigo have been published since 1975. However, to our knowledge no meta-analysis of this data has been performed so far. Therefore, we conducted a systematic review and meta-analysis of individual patient data (IPD) on all studies assessing the effectiveness of MVD of the cochleovestibular nerve for patients with complaints of tinnitus and/or vertigo. In addition, complication rates and prognostic factors of success were reviewed, in order to gain more insight in safety and adequate patient selection.

Materials and Methods

This systematic review and IPD meta-analysis were conducted according to the methods of the Cochrane Collaboration[8] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Individual Participant Data (PRISMA-IPD) guidelines.[9] A protocol of this systematic review was specified in advance and published in the PROSPERO database (CRD42015017437) (www.crd.york.ac.uk/PROSPERO).

Eligibility criteria and information sources

A systematic search in MEDLINE (PubMed) and EMBASE was conducted on February 18th 2015 and was updated on January 27th 2016. The search strategy was developed using the PICO method. The "P" (participants) were patients with a NVC of the cochleovestibular nerve and symptoms of tinnitus and/or vertigo. The "I" (intervention) was MVD surgery of the cochleovestibular nerve, "C" (comparison), "O" (outcome) were left open to ascertain a broad search. The peer-reviewed search strategy was designed using the following search indexing terms: "tinnitus", "vertigo", "cochleovestibular nerve compression syndrome", "microvascular decompression", "cochleovestibular nerve" and other variations (see Appendix 1). An additional search was conducted in Google Scholar, to avoid missing articles that lacked one of the search terms in the title, abstract or index terms. In addition, the Cochrane Central Register of Controlled Trials was searched for relevant articles. Furthermore, references of all included studies and relevant reviews on this topic were screened for potentially eligible studies.

Study selection

Eligible articles consisted of studies that: (1) included patients with a NVC of the cochleovestibular nerve with symptoms of tinnitus and/or vertigo, (2) investigated the effectiveness of MVD of the cochleovestibular nerve, (3) included a measure of recovery as outcome and (4) presented the results in a quantitative way. Only full text peer reviewed papers were included in the systematic review. No restrictions were made with regard to the design of the study. Publications written in languages other than English, Dutch or German were excluded. The study selection was performed by two reviewers (MB&IP) independently. Disagreements between reviewers were resolved in a consensus meeting. All retrieved titles were screened for eligibility, followed by screening of the remaining abstracts. Subsequently, a final selection based on the full text papers. When it was suspected that papers were based on the same study population (i.e. same study or same study center), the paper with the most complete patient data or, if papers were evenly complete, the paper presenting the longest follow-up data was included. Other overlapping studies were excluded.

Data-extraction and methodological quality assessment

A predesigned form was used to extract data from the included studies. Data extraction was performed by one reviewer (MB) and was cross-checked by another (IP). The following information was extracted both on study level and individual patient level (if available): (1) patient characteristics (age, sex, symptoms, duration of symptoms before surgery, specification of

symptoms, auditory brainstem response [ABR], preoperative use of carbamazepine for symptom relief); (2) inclusion criteria, type of intervention, causative vessel identified perioperative; (3) length of follow-up, recurrence of symptoms, necessity of re-surgery; (4) primary outcome (i.e. global measurement of improvement of preoperative symptoms) indicating the treatment success; and (5) complications. For each study, information on complications was registered and categorized into minor complications (e.g. transient facial palsy, cerebral spinal fluid leak, wound infect, transient hearing deficit) and major complications (permanent facial palsy, permanent hearing deficit, meningitis, stroke, death). If no IPD was reported in the article, the corresponding author of the included study was contacted by email with a request to provide the (additional) IPD. After two and four weeks, a reminder was sent.

The methodological quality of all included studies was assessed by two reviewers (MB&IP) independently, using the "Quality Assessment Tool for Case Series Studies" (adjusted for the research topic) from the National Institute of Health.[10] Follow-up was regarded as "adequate" if the mean follow-up was ≥1 year. Disagreements between the reviewers were discussed and resolved in a consensus meeting. In necessary, the final decision was made by a third reviewer (NS). The overall percentage of agreement and Cohen's kappa were calculated to evaluate inter-rater agreement on the methodological quality of the included studies. To provide insight in possible publication bias, a scatterplot of sample size of study against percentage of complete relief of symptoms was constructed.

Statistical analysis

Aggregate data analysis

For all included studies, the mean data on study level ("aggregate data") was presented using descriptive statistics. In order to quantitatively analyze the data, the postoperative outcome (i.e. global measurement of improvement) was categorized four groups: "complete relief" (i.e. symptom free), "improvement" (i.e. defined as any variation of improvement), "no change" and "worsening". The outcome was related to change in preoperative symptoms of (1) tinnitus and (2) vertigo. As there was also a proportion of patients in which both symptoms occurred combined, a subgroup analysis was conducted for patients with (1) tinnitus, (2) vertigo and (3) vertigo and tinnitus. The overall treatment outcome was presented as percentage, calculated by the number of patients with e.g. "complete relief of tinnitus" divided by the total number of patients who underwent MVD for, in that case, tinnitus.

Individual patient data meta-analysis

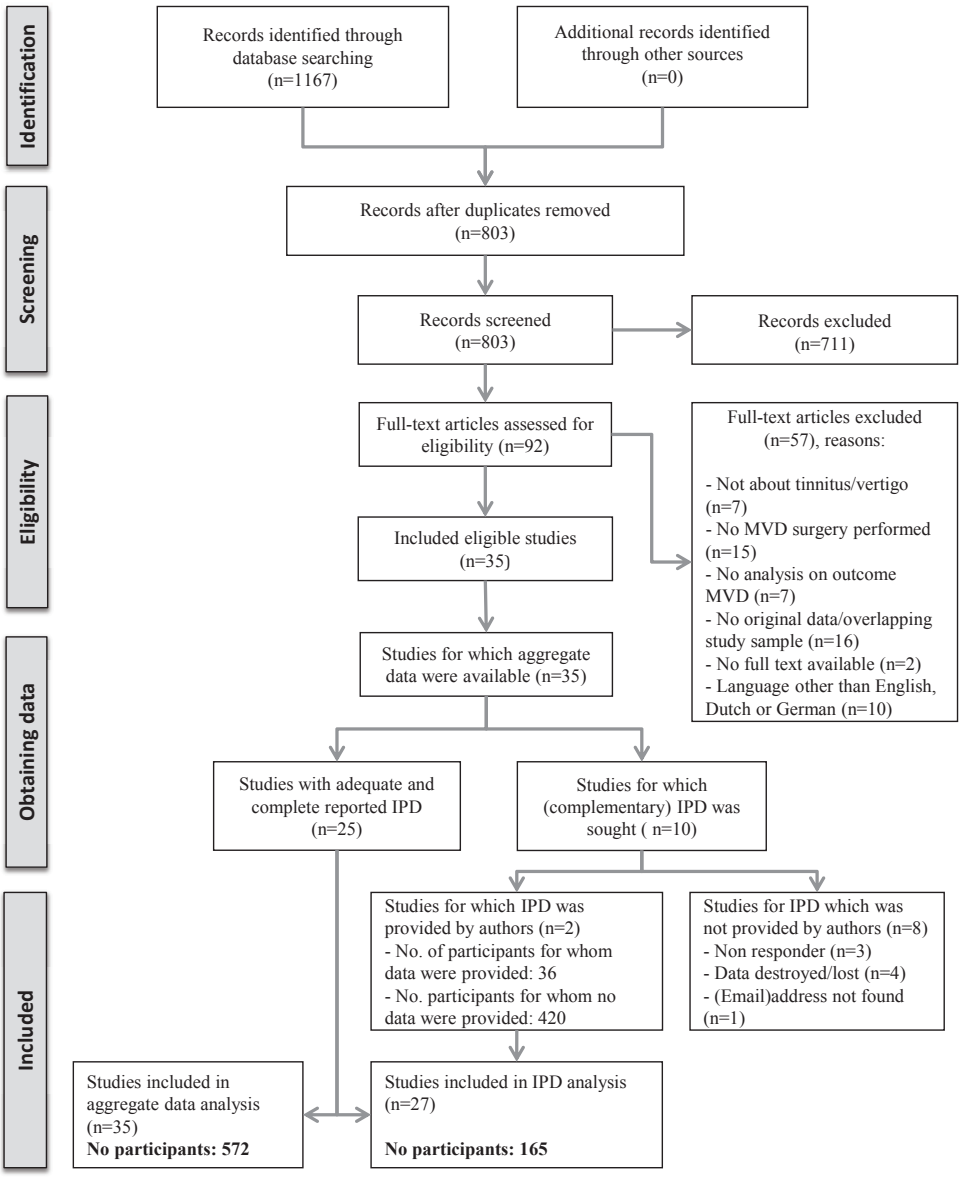
Continuous variables (e.g. age, follow-up) were described using means with standard deviation for normal distributed data and median and interquartile range (IQR) for skewed distributed data. Categorical variables were presented as numbers with percentages. In order to investigate prognostic variables of success of MVD, a meta-analysis of IPD was performed. For this purpose, the primary outcome (i.e. success of MVD surgery) was dichotomized into two categories: (1)

"Success" (defined as: complete relief of symptoms and marked improvement of symptoms); and (2) "No Success" (defined as: minimal improvement of symptoms, no change, or worsening). The IPD from all studies were analyzed using a binary logistic regression model (one-stage approach), while accounting for clustering among patients within the same study by including random study effects.9,11 Odds ratio's (OR), 95% confidence intervals (95% CI) and overall p-values were presented. An OR>1 indicates increased odds for "Success" of the intervention. All statistical analyses were performed using IBM SPSS Statistics (version 22). Differences were regarded as significant with a p-value <0.05.

Results

Study selection

The initial search retrieved 1167 articles (MEDLINE: 550, EMBASE: 610, Google Scholar: 7, Cochrane Central Register of Controlled Trials: 0). Duplicate articles were removed. Reviewing 803 titles, 255 abstracts and 92 full text articles resulted in the inclusion of 35 articles.[2,6,7,12-43] Special care was taken to avoid including studies with potentially overlapping study participants (16 studies were excluded for this reason). For an overview of the selection process, see the PRISMA-IPD flow diagram (Figure 1). An update of the search using the identical search strategy and selection process was performed on January 27th 2016 and identified 34 additional articles. None of these articles were eligible for inclusion.



PRISMA: Preferred Reporting Items for Systematic Review and Meta-analysis, IPD: individual patient data, No.: number

Adapted from: Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. JAMA 2015 Apr 28;313(16):1657-1665.

Figure 1. *Flow diagram of inclusion process according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) and individual patient data (IPD)*

Study characteristics and characteristics of total study population

Details regarding the study characteristics of the included studies are presented in Table 1. The 35 studies that were included in this review were published between 1980 and 2015 and originated from various countries. The included studies were case reports or case series and the number of enrolled patients per study varied from 1 to 163. In total, 572 patients were included in this review, of which 313 (55%) were females. As main symptom, 207 (36%) patients had tinnitus, 222 (39%) had vertigo and 143 (25%) had both tinnitus and vertigo. The mean age at surgery was 52±6.7 years. The median duration of symptoms prior to surgery was 48 months (IQR 26-74) and median follow-up was 19 months (IQR 9-38). Abnormal ABR measurements preoperatively were reported in 312 out of 398 patients (78%). Not all studies specified the criteria for abnormality of ABR, however most studies reported a prolonged wave I-III interval. Indications for performing MVD varied between the studies, as shown in Table 1. Recurrence of preoperative complaints were described in 35 of 446 patients (8%), followed by revision MVD in 31 patients (7%) (data not shown in Table). The vessel that was most often reported as the cause of the NVC, was the anterior inferior cerebellar artery in 16% of the cases, however in 60% the causative vessel was not reported (data not shown in Table).

Assessment of study quality

The inter-rater agreement on the methodological quality assessment was substantial (overall agreement 81% [227/280]; Cohen's kappa 0.63).[44] Results of the methodological quality assessment of the included studies are presented in Figure 2. Two studies were conducted prospectively[24,34] and 33 retrospectively. The majority of the studies were case series (n=22) and the other studies were case reports (n=13), i.e. a description of only one patient. The most frequently encountered flaw was that the "outcome measure was not clearly defined, valid, reliable and/or implemented consistently" (question V5, see Figure 2). Only four studies (11%) scored positive on this item.[16,20,24,41]

Regarding Table 1, opposite page:

a: mean with [range]
b: number/total number (%)
**: individual patient data available and included in meta-analysis*
†: only unilateral MVD included
§: one patient lost from follow up
¥: only patients with proven NVC included
Ω: only patients who underwent MVD included

No: number; MVD: microvascular decompression; CMP: carbamazepine; NR: not reported; CNCS: cochleovestibular nerve compression syndrome; ABR: auditory brainstem responses; DPV: disabling positional vertigo; HFS: hemifacial spasm; VA: vertebral angiogram; CT: computed tomography; MRI: magnetic resonance imaging; MRA: magnetic resonance angiography; NVC: neurovascular conflict.

Table 1. Characteristics of included studies (n=35) on microvascular decompression surgery for tinnitus and/or vertigo

Author, Year, Originating country	No. of patients included	Female n(%)	Surgery period	Age at MVD (yrs[a])	Duration of symptoms, (months[a])	Use of CMP, success	Abnormal ABR pre-surgery[b]	Follow-up (months[a])	Study inclusion criteria
Artz et al., 2008, *USA*	1*	1 (100%)	NR	NR	NR	NR	NR	2	Anamnestic CNCS
Bayazit et al., 2010, *Turkey*	6*	NR	1999-2008	NR	NR	NR	4/6 (80%)	6	Abnormal ABR, NVC on MRI, tinnitus
Bejjani et al., 1997, *USA*	1*	1 (100%)	NR	59	NR	NR	NR	5	NVC on MRI, episodic dizziness
Borghei-Razavi et al., 2014, *Germany*	1*	1 (100%)	NR	40	48	Yes, not successful	1/1 (100%)	24	NVC on MRA, vertigo & tinnitus
Brackmann et al., 2001, *USA*	20	16 (80%)	1990-1999	46 [30-71]	64 [4-132]	NR	NR	82 [5-117]	NVC on CT/MRI, diagnosis DPV
Brookes et al., 1996, *UK*	9*	5 (56%)	NR	48 [31-76]	63 [19-120]	NR	8/9 (89%)	35 [16-60]	Anamnestic tinnitus and/or vertigo, abnormal ABR, vascular loops on CT/MRA
Fries et al., 1998, *Germany*	1*	0	NR	49	24	NR	NR	NR	Tinnitus and vertigo, NVC on MRI
Fuse et al., 1996, *Japan*	1*	1 (100%)	1985	52	0.8	Yes, not successful	Normal ABR	96	Episodes of vertigo & constant tinnitus
Guevara et al., 2008, *France*	15*	8 (53%)	1994-2001	57 [31-71]	38 [12-96]	NR	15/15 (100%)	72 [60-84]	Incapacitating tinnitus unilateral, abnormal ABR, NVC on MRI (T2 CISS)
Herzog et al., 1997, *USA*	2*	0	NR	63 [63]	15 [12-18]	NR	NR	NR	Vertigo & hearing loss, NVC on MRI
Isu et al., 1985, *Japan*	1*	0	NR	55	240	NR	NR	12	Paroxysmal tinnitus & nystagmus, loop on VA
Jannetta et al., 1980, *US*	38*	24 (63%)	1971-1979	NR [17-69]	NR	NR	NR	NR	Intractable vertigo & tinnitus (various diagnoses)
Ko et al., 1997, *Korea*	59	24 (41%)	1996-1997	49 [27-73]	70 [2-240]	NR	44/59 (75%)	7 [1-14]	Incapacitating refractory tinnitus, <80 years old

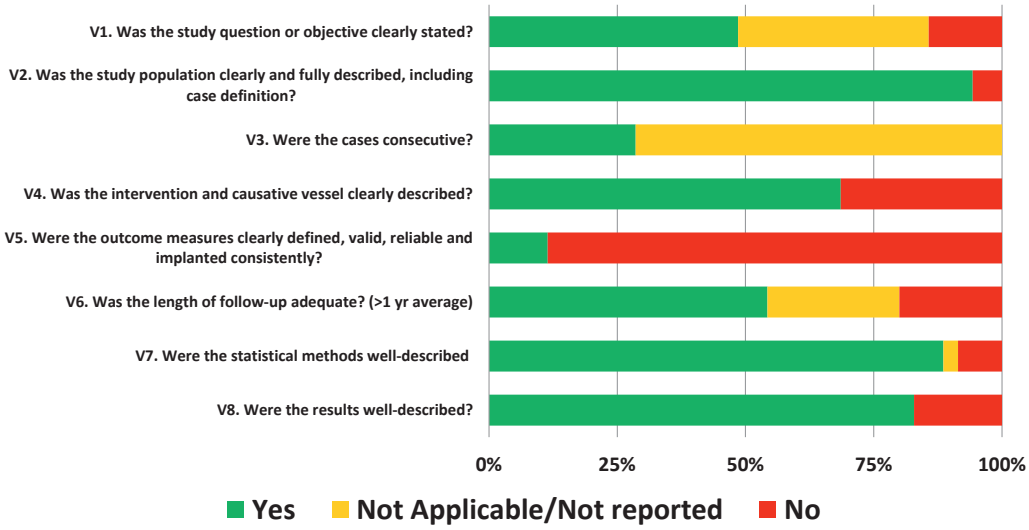


Figure 2. Assessment of study quality for included studies using the National Institute of Health: Quality Assessment Tool for Case Series Studies (adjusted for this topic)

Treatment success of MVD: aggregate data analysis

The outcomes of MVD on study level are described in the outcome table (Appendix 2) and summarized in Figure 3. The aggregate data analysis shows that complete relief of symptoms following MVD was achieved in 28% of the patients with tinnitus and in 32% of the patients with vertigo (Figure 3a). In a second analysis the outcomes were split to "tinnitus", "vertigo" and "tinnitus and vertigo". In this analysis, there was treatment success in 62% of the patients who had both tinnitus and vertigo, in 22% of the patients with tinnitus and in 27% of the patients with vertigo (Figure 3b).

Meta-analysis of individual patient data

IPD was adequately reported in 25 studies.[2,7,12,14,15,17-22,25-30,33,35-42] From the remaining ten studies, IPD was requested. This resulted in the inclusion of IPD from two more studies in the IPD analysis (Figure 1).[13,34] Finally, IPD from 165 patients was available originating from 27 studies (marked with an asterix in Table 1). In Table 2, patients' characteristics are shown for the "Success" group (n=108) and "No Success" (n=57) group. In Table 3, for every individual study it was shown which terminology was defined as "Success" and "No Success". For several variables, little data was available (e.g. "Type of tinnitus symptoms" [n=21], "Type of vertigo symptoms" [n=24], "Successful use of carbamazepine" [n=69]). For these variables an univariate analysis was not appropriate and therefore, they were excluded from the analysis. In the univariate binary logistic regression analysis of the remaining variables (Table 4), it is demonstrated that patients with both tinnitus and vertigo

had higher chance of "Success" compared to patients with only tinnitus (p=0.00, OR: 3.8, 95% CI: [1.45-10.10],). Patients who underwent the translabyrinthine route of surgery had a lower change of treatment success (p=0.01, OR: 0.14, 95% CI: [0.04-0.50],) compared to the most frequently used retrosigmoidal approach. No other variables were significantly related to treatment "Success" or "No Success". No multivariate logistic regression analysis could be performed because of too many missing values for the total of variables and sample size.

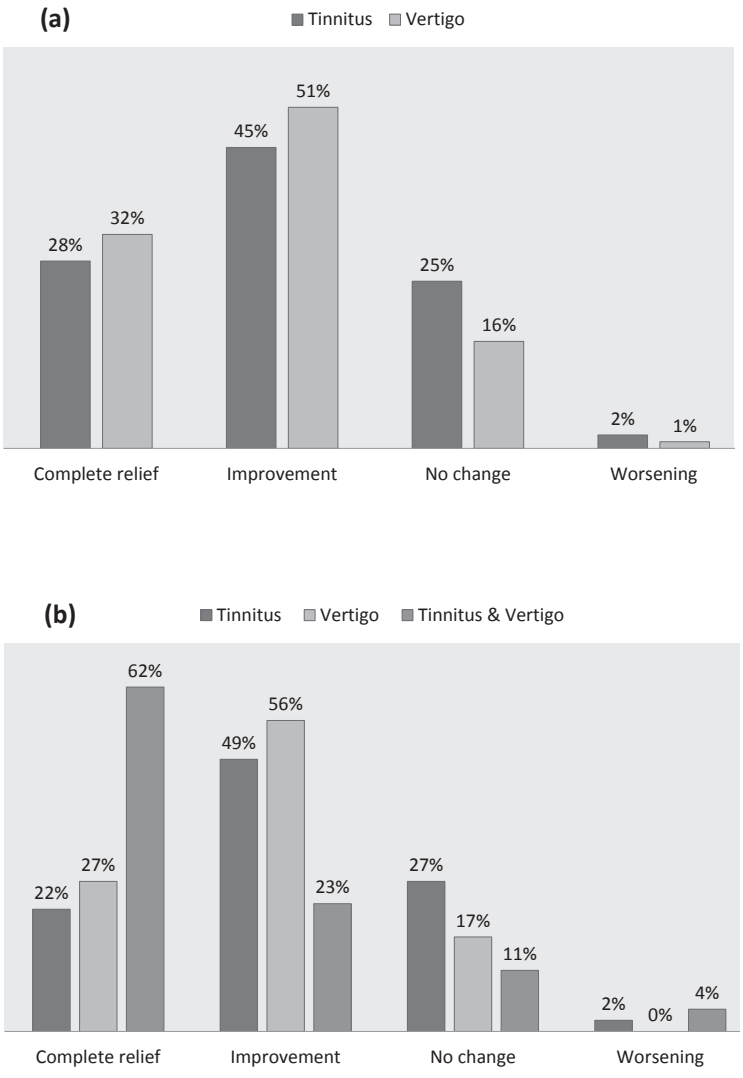


Figure 3. Overview of surgical outcome for tinnitus and vertigo after microvascular decompression surgery of the cochleovestibular nerve, (a) for "tinnitus" and "vertigo" and (b) for "tinnitus", "vertigo" and "tinnitus and vertigo"

Table 2. Patient characteristics in the "Success" and "No Success" group following microvascular decompression surgery of the cochleovestibular nerve

Characteristics	Total population (n=165)	Success (n=108)	No Success (n=57)
Gender – no.(%) (n=149)			
Male	71/149 (48)	49/104 (47)	22/35 (49)
Female	78/149 (52)	55/104 (53)	23/35 (51)
Mean age ±SD – years (n=148)	52±12	51±12	53±10
Preoperative symptoms – no./total no.(%) (n=165)			
Tinnitus	75/165 (46)	35/108 (32)	40/57 (70)
Vertigo	16/165 (10)	16/108 (15)	0
Tinnitus and vertigo	74/165 (45)	57/108 (53)	17/57 (30)
Type of tinnitus symptoms – no./total no.(%) (n=21)			
Pulsatile	6/21 (28)	6/18 (33)	0
Non-pulsatile	9/21 (43)	6/18 (33)	3/3 (100)
Paroxysms	6/21 (28)	6/18 (33)	0
Type of vertigo symptoms – no./total no.(%) (n=24)			
Paroxysms	8/24 (33)	6/22 (27)	2/2 (100)
Constant	1/24 (4)	1/22 (5)	0
DPV	13/24 (54)	13/22 (59)	0
Other	2/24 (8)	2/22 (9)	0
Duration of symptoms – no./total no.(%) (n=114)			
0-2 years	36/114 (32)	26/76 (34)	10/38 (26)
2-4 years	29/114 (25)	20/76 (26)	9/38 (24)
>4 years	49/114 (43)	30/76 (40)	19/38 (50)
Successful use of carbamazepine – no./total no.(%) (n=69)			
Successful use	3/69 (4)	3/40 (8)	0
No successful use	33/69 (48)	26/40 (65)	7/29 (24)
Success not reported	2/69 (3)	1/40 (2)	1/29 (3)
No usage	31/69 (45)	10/40 (25)	21/29 (73)
Route of surgery – no./total no.(%) (n=111)			
Retrosigmoidal	48/111 (43)	36/77 (47)	12/34 (35)
Retrolabyrinthine	4/111 (4)	3/77 (4)	1/34 (3)
Retromastoidal	37/111 (33)	28/77 (36)	9/34 (26)
Translabyrinthine	17/111 (15)	5/77 (6)	12/34 (35)
Suboccipital	5/111 (5)	5/77 (6)	0
Causative vessel – no./total no.(%) (n=151)			
AICA	78/151 (52)	51/100 (51)	27/51 (53)
PICA	11/151 (7)	7 /100 (7)	4/51 (8)
Vertebral artery	11/151 (7)	8/100 (8)	3/51 (6)
Combination	39/151 (26)	25/100 (25)	14/51 (27)
Other	12/151 (8)	9/100 (9)	3/51 (6)

SD: standard deviation; DPV: disabling positional vertigo; IQR: interquartile range; ABR: auditory brainstem response; AICA: anterior inferior cerebellar artery; PICA: posterior inferior cerebellar artery.

All values are reported as the number of patients (%), unless otherwise indicated.

Table 3. Definition of "Success" and "No Success" for every individual study

Author	"Succes"	"No Success"
Artz et al.	"resolved"	-
Bayazit et al.	"complete relief" and "partial relief"	"worsening of tinnitus"
Bejjani et al.	"complete relief"	-
Borghei-Razavi et al.	"complete relief"	-
Brookes et al.	"complete abolishment", "cured" and "reduction in objectified tinnitus loudness"	"No benefit" and "no significant reduction in tinnitus loudness"
Fries et al.	"persistent relief from vertigo" and "partial relief from tinnitus"	-
Fuse et al.	-	"First improved, than increasing symptoms of vertigo and tinnitus"
Guevara et al.	"totally free" and "improved"	"no change" and "worse"
Herzog et al.	"symptoms resolved", "symptoms subsided"	-
Isu et al.	"completely relieved"	-
Janetta et al.	"no symptoms", "no vertigo, slight tinnitus"	-
Kudo et al.	"much reduced, returned to work"	-
Leclerq et al.	"good result" and "returned to work"	"-returned to preoperative level"
Mathiesen et al.	"relief from attacks"	-
Meaney et al	"complete resolution"	-
Meyerhoff et al.	"almost totaly subsided" and "marked improvement"	-
Ohashi et al.	"symptoms disappeared"	-
Okamura et al.	"free of vertigo", "recovered tinnitus with low pitched tinnitus", "marked recovered of vertigo"	"remained low pitched tinnitus", "improvement of vertigo and remained tinnitus"
Pirayesh Islamian et al.	"symptoms alleviated" and "completely free of symptoms"	-
Roland et al.	"almost complete relief" and "improved markedly"	-
Ryu et al.	"improved" and "resolved" *	"symptoms present"
Sakaki et al.	"free", "markedly improved" and "moderately improved" *	"mildly improved" and "unchanged"
Strupp et al.	"no symptoms"	-
Tanrikulu et al.	"symptoms diminished"	-
Vasama et al.	"totally free" and "markedly improved"	"slightly improved", "unchanged" and "worse"

Table 4. Univariate logistic regression analysis with prognostic factors for "Success"

	OR	95% CI	p-value
Gender			0.77
Male	Ref		
Female	1.07	0.65 – 1.76	
Age – years	0.99	0.96 - 1.01	0.25
Preoperative symptoms			**0.000**
Tinnitus	Ref		
Vertigo	NA	NA	
Tinnitus and vertigo	**3.83**	**1.45 – 10.10**	
Duration of symptoms			0.30
0-2 years	Ref		
2-4 years	0.86	0.38-1.92	
>4 years	0.61	0.29-1.28	
Route of surgery			**0.01**
Retrosigmoidal	Ref		
Retrolabyrinthine	1.00	1.00 -1.00	
Retromastoidal	1.04	0.37 – 2.90	
Translabyrinthine	**0.14**	**0.04 – 0.50**	
Suboccipital	NA	NA	
Causative vessel			0.89
AICA	Ref		
PICA	0.93	0.31 – 2.75	
Vertebral artery	1.42	0.36 – 5.55	
Combination	0.95	0.36 – 2.50	
Other	1.59	0.39 – 6.43	
Preoperative ABR			0.43
Normal	Ref		
Abnormal	1.53	0.46 – 5.05	
Follow-up –years	0.97	0.86 – 1.09	0.59

NA = not available; Ref = reference
Overall p values are presented

Complications

Thirteen of the 35 included articles did not report on complications. Analysis of the complications from the remaining 22 studies (representing 492 patients) is presented in Figure 4. Minor complications were reported in 3% and major complications in 6%. The most common complication was permanent hearing deficit after surgery (5%). Overall, 11% of the patients had complications following MVD. No stroke or death was registered.

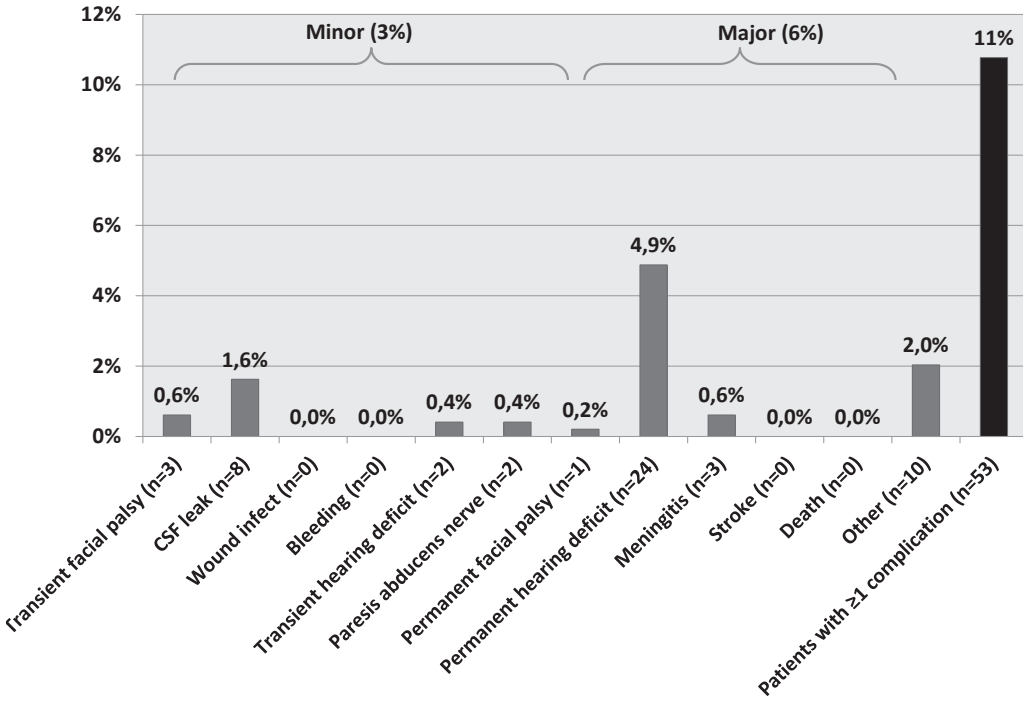


Figure 4. Complication rates of MVD surgery of the cochleovestibular nerve. Only 22 of 35 articles (representing 492 patients) reported if there were complications and, if so, which ones. The "Other" category included epidural hematoma (n = 1), temporary vagal nerve paresis (n = 1), herpes zoster (n = 1), loss of vestibular function (n = 1), temporary vocal cord weakness (n = 1), temporary trochlear nerve paresis (n = 1), temporary bulbar paresis (n = 1), temporary swallowing problems (n = 1), transient cerebellar sign (n = 1), and cerebellar hematoma (n = 1).

CSF: cerebrospinal fluid

Assessment of publication bias

Figure 5 shows a scatterplot of "sample size of study" vs. "complete relief (of all symptoms)" with the mean percentage (vertical line) of patients who had complete relief. In the smaller studies (i.e. n<40), high as well as low success rates were published. This suggests that there is no severe risk on publication bias. However, no formal statistical tests for publication bias could be performed on this data.

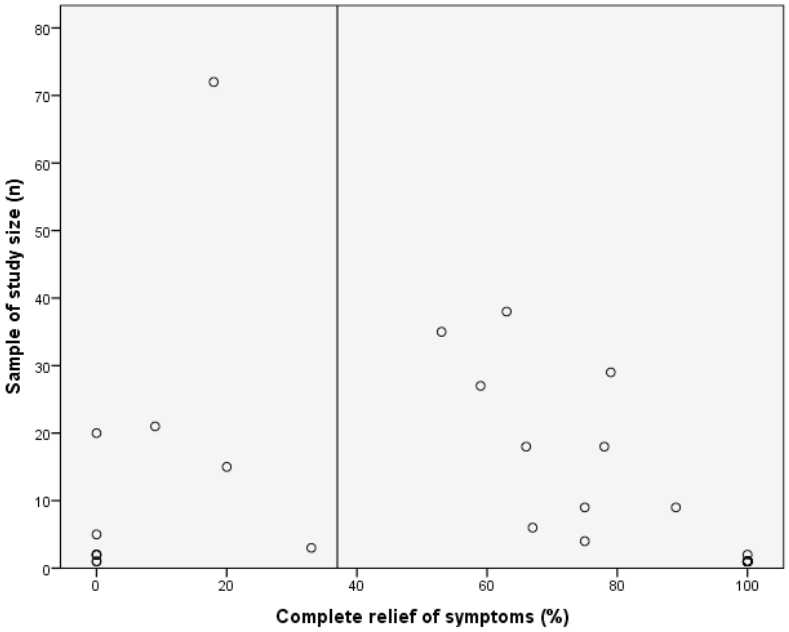


Figure 5. Scatterplot of sample size of study vs. percentage of complete relief assessing publication bias

Discussion

This systematic review and meta-analysis assessed the treatment success of MVD of the cochleovestibular nerve for tinnitus and/or vertigo. The success rate, defined as percentage of patients who had complete relief, was 28% for patients with tinnitus and 32% for patients with vertigo. If patients had both tinnitus and vertigo, treatment success was 62%. The meta- analysis of IPD also showed that patients with tinnitus combined with vertigo had a higher change of treatment success than patient with solitary tinnitus or solitary vertigo. Moreover, a substantial complication rate was encountered. No other prognostic factors related to age, sex, preoperative ABR, duration of symptoms, symptoms specification or use of carbamazepine could be identified.

In 2008, Yap et al. attempted to identify the success rate of MVD of the cochleovestibular nerve in a systematic review and found a very wide range of success (defined as "complete relief and/or marked improvement") of 28-100% for tinnitus and 75-100% for vertigo.[7] Yap et al. included 22 studies without guidance of PRISMA, whereas our systematic review comprises 35 studies. Our review provides a more specific analysis of treatment success, subdivided into four outcome categories. By evaluating the percentage of "complete relief" instead of "complete relief and/or marked improvement", we are able to make a comparison with success rates of MVD for other cranial nerves, such as trigeminal neuralgia. In this review, a complication rate of 11% was encountered, which is more specific than that of Yap et al. who reported that "morbidity was minimal".[7]

The rate of "complete relief" of MVD for tinnitus or vertigo is low when compared to the success rates of MVD for other cranial nerves.[3,4,5] One of the reasons for this rather low success rate might be the fact that a NVC of the cochleovestibular nerve can cause a wide variety of symptoms, sometimes resembling other diagnoses such as Ménière's disease. Therefore it is challenging to correctly assign tinnitus and/or vertigo complaints to a NVC. Several studies have attempted to specify a typical patient group with tinnitus and/or vertigo that would benefit from MVD.[6,27,31,32,45] However, presenting symptoms of NVC of the cochleovestibular nerve are not as distinct as in trigeminal neuralgia for example, which makes it difficult to determine adequate selection criteria. Nevertheless, this review showed that if patients had both tinnitus and vertigo, the success rate increased to 62%. This remarkable difference, compared to the success rate of solitary tinnitus or vertigo, suggests that when both symptoms occur in one patient, the underlying pathology is more likely to be of a NVC and thus MVD is an appropriate treatment method. The cochleovestibular nerve contains of a vestibular and cochlear branch and conflict of a vessel might therefore affect both nerves and may cause both related symptoms. This hypothesis is supported by findings of Ryu et al., who correlated the complaints of a NVC to the exact location of compression on the nerve.[37] It must be noted that other inner ear disorders may cause tinnitus combined with vertigo, such as Ménière's disease. Therefore, other likely causes must be excluded and additional information is needed to make the presumption that a NVC is the cause of the complaints. For example, an MRI with a NVC on the ipsilateral side of the complaints would point to the direction of a NVC, although it has been reported that some patients have a NVC on MRI but do not have any complaints.[46] However, the likelihood of a NVC as cause of the complaints might increase when several clues add up. Clinical findings such as changes in ABR, anamnestic unilateral, paroxysmal attacks of tinnitus or vertigo and responsiveness to carbamazepine have been suggested as other selection criteria.[27,45,47,48] Unfortunately, in our IPD analysis, none of these suggested selection criteria could be confirmed.

The patient group included in the IPD analysis was representative for the total MVD population from the aggregate data analysis, in terms of sex, age, duration of symptoms and follow-up. In accordance to the outcomes of our aggregate data analysis, the IPD analysis showed that if MVD was performed in patients with both tinnitus and vertigo, there was a significant higher change of treatment success compared to patients with tinnitus alone. Also, it was shown that the translabyrinthine approach for MVD resulted in statistically significant less treatment success, which suggests that this surgical approach should not be used. Indeed this approach seems obsolete to use in tinnitus and vertigo patients, as in this approach the vestibule and semicircular surgically removed and complete sensorineural hearing loss is induced, which in turn may cause tinnitus and vertigo.

It was found that 78% of the reported preoperative ABR measurements were abnormal. De Ridder et al. proposed a pathophysiological mechanism for tinnitus resulting from NVC of the cochleovestibular nerve, describing that if a blood vessel causes a NVC with the auditory part of the nerve, a disorganized signal transmission occurs, objectified by peak II decrease in ABR testing, resulting in tinnitus.[45] However, although ABR abnormalities have been suggested to result from a

NVC of the cochleovestibular nerve, our IPD analysis did not demonstrate that abnormality of ABR is a prognostic factor for treatment success. The preoperative duration of symptoms has also been suggested to be related to the outcome of the MVD.[31,49] De Ridder et al. argued that in a NVC of the cochleovestibular nerve, tinnitus is initially the result of impaired signal transmission at the level of the vascular contact. The longer the compression exists, the more damage is done to the auditory nerve, which may lead to demyelination of the nerve. In turn, this may relate to differentiation of auditory input into the central auditory cortex, leading to tinnitus. Therefore, De Ridder et al. suggest that surgical decompression should be performed within four years after the onset of symptoms.[49] In our IPD analysis no statistically significant relationship between the preoperative symptom duration and a successful outcome could be demonstrated. Finally, several authors have suggested that the specification of symptoms is essential in diagnosing a symptomatic NVC, e.g. so called "typewriter tinnitus". Typewriter tinnitus is a clicking or ticking noise which may occur in paroxysms of tinnitus and may be combined with ipsilateral vestibular symptoms, and it is suggested to result from a NVC.[48,50] Unfortunately, the specification of preoperative symptoms was underreported in this IPD and therefore, this information could not be included in a statistical model. In future research, more attention must be paid to this topic, as specification of symptoms might be essential in identifying these patients that may benefit from MVD.

Limitations

This systematic review has limitations that merit emphasis. First, an important finding is that there were only low level of evidence (level 4) studies available that addressed our research topic. This must be kept in mind when interpreting the presented results. On the other hand, this is the best available evidence and a sham-controlled study with MVD would raise serious ethical concerns. Because of included case reports and small case series, there is a possibility of publication bias, which may have resulted in an overestimation of the success rate that was found in this study. Unfortunately, the data did not allow formal statistical tests to assess publication bias. Second, in this review a global measurement of improvement was extracted from the included papers. This outcome is subjective (patient assessed) and it was not standardized in the vast majority of the included studies, as shown by our quality assessment. Unfortunately we had to rely on these unstandardized self-assessed outcomes, however this is a significant limitation of the presented study. Obviously, standardized outcome measurement should be used in future research, such as validated tinnitus questionnaires, in order to gain better evidence of the true success rate. Although De Ridder et al. published an article describing the results of MVD for tinnitus using pre- and postoperative questionnaires (e.g. visual analogue scale and tinnitus questionnaire), these outcome measures could not be included in our analysis, because these could not be translated to global measurement of improvement, as used in all the other studies. Third, all included patients had an objectified NVC during surgery and all patients underwent MVD of the cochleovestibular nerve. However, inclusion criteria for surgery varied considerably across the studies. Some patients were operated based primarily on their disease history (e.g. intractable tinnitus/vertigo) with or without the suspicion of NVC on imaging or abnormal ABR, while others were operated based on more specific diagnoses (e.g. typewriter tinnitus or disabling position

vertigo). Considering that asymptomatic NVCs are not seldom reported[46], one should keep in mind that a proportion of patients might have undergone MVD for an incorrect indication, leading to a lower overall success rate. Finally, an important limitation is that we were not able to collect IPD of the two largest studies describing MVD for tinnitus patients (n=72) and MVD for disabling vertigo patients (n=163).[31,32] Due to these missing data (varying from 6-85%) we were not able to perform a multivariate logistic regression analysis. Therefore, the conclusions from our IPD meta-analysis are based only on a univariate analysis and should be interpreted with caution. A larger sample size is needed to perform a multivariate logistic regression analysis and to gain more insight in the prognostic factors for successful surgery.

Conclusions

This systematic review and meta-analysis demonstrated a low success rate of MVD of the cochleovestibular nerve for treatment of tinnitus and vertigo. Also, a surgical complication rate of 11% was encountered. Therefore, this surgery cannot be considered a standard treatment method for tinnitus, nor vertigo complaints. However, in patients with both tinnitus and vertigo, there was a substantial higher chance of treatment success. It is the combination of symptoms that suggests that an NVC is the underlying pathology and thus MVD might be appropriate. However, this systematic review was based on low level of evidence studies and hence no definite recommendations can be made. Further validation is necessary to evaluate whether patients with combined symptoms indeed are better candidates for MVD.

Appendix 1. Search strategy for MEDLINE (Pubmed)

("Tinnitus"[Mesh] OR "Vertigo"[Mesh] OR "Hearing Loss"[Mesh] OR tinnitus[tw] OR vestibular*[tw] OR cochlear[tw] OR neurovascular*[tw] OR vascular[tw] OR cochleo*[tw] OR vertigo*[tw] OR hearing[tw]) AND ("Microvascular Decompression Surgery"[Mesh] OR compression*[tw] OR decompression[tw]) AND ("Vestibulocochlear Nerve"[Mesh] OR Vestibulocochlear nerve*[tw] OR vestibulo cochlear nerve*[tw] OR (Cranial Nerve*[tw] AND (VIII*[tw] OR eight*[tw] OR 8th[tw])) OR cochlear nerve*[tw] OR vestibular nerve*[tw] OR vestibulo*[tw] OR cochleovestibular nerve*[tw] OR cochleo vestibular nerve*[tw] OR cochlear vestibular nerve*[tw] OR vestibulo cochlear nerve*[tw] OR VIIIth nerve*[tw] OR VIII nerve*[tw] OR eighth nerve*[tw] OR eight nerve*[tw] OR 8th nerve*[tw] OR auditory nerve*[tw])

		Outcomes			
Author	**Symptoms** N	**Complete relief** N/total N(%)	**Improvement** N/total N(%)	**No change** N/total N(%)	**Worse** N/total N(%)
Artz et al	**T+V**: 1	**T+V**: 1/1 (100%)	**T+V**: -	**T+V**: -	**T+V**: -
Bayazit et al.	**T**: 4 **V**: 2	**T**: 2/4 (50%) **V**: 2/2 (100%)	**T**: 1/4 (25%) **V**: -	**T:** - **V**: -	**T** : 1/4 (25%) **V**: -
Bejjani et al.	**V**: 1	**V**: 1/1 (100%)	**V**: -	**V**: -	**V**: -
Borghei-Razavi et al.	**T+V** : 1	**T+V:** 1/1 (100%)	**T+V**: -	**T+V**: -	**T+V**: -
Brackmann et al.*	**V**: 4 **T+V**: 16	**T**: - **V**: -	**T**: 7/16 (44%) **V**: 16/20 (80%)	**T**: 8/16 (50%) **V**: 3/20(15%)	**T**: 1/16 (6%) **V**: 1/20 (5%)
Brookes et al.*	**T**: 5 **T+V**: 4	**T**: 3/9 (33%) **V**: 3/4 (75%)	**T**: 4/9 (44%) **V**: 1/4 (25%)	**T**: 2/9 (22%) **V**: -	**T**: - **V**: -
Fries et al.*	**T+V**: 1	**T:** - **V** : 1/1 (100%)	**T**: 1/1 (100%) **V:** -	**T:** - **V:** -	**T:** - **V:** -
Fuse et al.	**T+V**: 1	**T+V:** -	**T+V:** -	**T+V:** -	**T+V:** 1/1 (100%)
Guevara et al.	**T** : 15	**T**: 3/15 (20%)	**T**: 5/15 (33%),	**T**: 7/15 (47%)	**T**: -
Herzog et al.	**V**: 2	**V**: 2/2 (100%)	**V**: -	**V**: -	**V**: -
Isu et al.	**T+V**: 1	**T+V**: 1/1 (100%)	**T+V**: -	**T+V**: -	**T+V**: -
Jannetta et al. (1980)	**T**: 11 **V**: 7 **T+V**: 20	**T**: 5/11 (45%) **V**: 6/7 (86%) **T+V:** 13/20 (65%)	**T**: 0/11 **V**: 1/7 (14%) **T+V**: 0/20 (0%)	**T**: 6/11 (55%) **V:** 0/7 **T+V:** 6/20 (30%)	**T**: 0/11 **V**: 0/7 **T+V:** 1/20 (5%)
Ko et al.*	**T**: 32 **T+V**: 27	**T**: NR$^{\alpha}$ **V**: NR$^{\alpha}$	**T**: 55/59$^{\alpha\beta}$ (93%) **V**: NR$^{\alpha\beta}$	**T**: 4/59$^{\alpha\beta}$ (7%) **V**: NR$^{\alpha\beta}$	**T**: - **V**: -
Jannetta et al. (1984)	**T**: 3 **T+V**: 6	**T**: 3/3 (100%) **T+V**: 5/6 (83%)	**T**: - **T+V**: 1/6 (17%)	**T**: - **V**: -	**T**: - **V**: -
Kudo et al.	**T**: 1	**T**: -	**T**: 1/1 (100%)	**T**: -	**T**: -
Leclerq et al.	**T**: 1 **V**: 1 **T+V**: 3	**T**: - **V: -** **T+V: -**	**T**: 1/1 (100%) **V**: 1/1 (100%) **T+V:** 3/3 (100%)	**T**: - **V: -** **T+V: -**	**T**: - **V: -** **T+V: -**

T: tinnitus, V: vertigo, T+V: tinnitus and vertigo

** outcomes of T+V were split to outcomes for T and outcomes for V*

α: no discrimination was made between 'complete relief' and 'improvement'

β: no discrimination between outcome of T and T+

- : zero percent of the patients

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The relation between tinnitus and a neurovascular conflict of the cochleovestibular nerve on magnetic resonance imaging

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Abstract

Introduction

Magnetic resonance (MR) imaging is often used in diagnostic evaluation of tinnitus patients. Incidental findings like a neurovascular conflict (NVC) in the cerebellopontine angle are often found, however the diagnostic value of this finding remains unclear. The aim of this study is to investigate whether the type or degree of compression of the vestibulocochlear nerve is of diagnostic value in patients with a NVC.

Methods and materials

A retrospective study was performed in 111 tinnitus patients with available MR imaging between 2013 and 2015. Clinical and audiometric variables were gathered and MR imaging was re-evaluated by two neuroradiologists. NVCs were analyzed using a grading system based on previous research by Sirikci et al.

Results

In total, 220 ears were available for assessment. In patients with unilateral tinnitus a loop compression and an indentation of the cochleovestibular nerve were more frequent than in patients with bilateral tinnitus. However, there was no significant difference in distribution of the type of compression between tinnitus and non-tinnitus ears. Patient with unilateral tinnitus had a significantly higher degree of hearing loss in the symptomatic ear, compared to the asymptomatic ear and to the bilateral tinnitus group. Also, it was found that the degree of hearing loss did not differ between the various types of compression.

Conclusions

This study did not find a diagnostic value of specific types of compression in patients with a NVC. Although the distribution of NVC classification was different in patients with unilateral and bilateral tinnitus, there was no definite relation between the type of NVC and the presence of ipsilateral tinnitus. Also, the degree of hearing loss was not related to specific types of NVC.

Introduction

Tinnitus is a common condition, affecting 5-15% of the adult population.[1] When an otorhinolaryngologist is consulted for tinnitus complaints, a targeted patient history, physical and audiological examination is performed. In case of for example unilateral tinnitus, pulsatile tinnitus, focal neurological abnormalities or an asymmetrical hearing loss, further diagnostic evaluation often includes routine magnetic resonance imaging (MRI).[2] The most important purpose of using MRI in tinnitus patients is to exclude pathology in the cerebellopontine angle (CPA), such as a vestibular schwannoma. In 41% of the MRI studies an incidental finding is reported, such as the presence of a vascular loop in the CPA with close contact to the vestibulocochlear nerve[3], which is often referred to as a neurovascular conflict (NVC). This is a phenomenon in which a cranial nerve is compressed by a nearby artery or vein, which presumably causes ectopic excitation and thereby symptoms related to the affected nerve.[4] For example, a NVC is a well-known cause of hemifacial spasms in case of facial nerve compression and trigeminal neuralgia in case of trigeminal nerve compression.[5,6] A neurovascular conflict of the vestibulocochlear nerve visible on imaging is suggested to cause a 'vestibulocochlear nerve compression syndrome' consisting of ipsilateral symptoms of unilateral tinnitus, hearing loss and/or vertigo.[7] However, the diagnostic value of finding an NVC on MRI remains unclear, as not all patients with an NVC on MRI experience tinnitus and not all patients with tinnitus have an NVC on MRI. In fact, tinnitus has multiple etiologies.

Previous studies investigating the relationship between the vestibulocochlear nerve and the anterior cerebellar inferior artery (AICA) show that close contact between the two was observed in 25-53% of patients with tinnitus.[8,9] In both studies, the percentages of NVCs in tinnitus patients did not significantly differ from the percentage that was found in asymptomatic patients.8,9 Several previous studies were aimed at finding characteristics of a NVC that predicted that the NVC was indeed symptomatic. For example, it is suggested that the root entry zone (REZ) of a cranial nerve, which is the transition zone of the peripheral nerve segment to the central nerve segment, is more susceptible to injury and therefore a NVC in the REZ possibly is more likely to be symptomatic then when the NVC is located at the peripheral nerve segment.[10,11] Also, the type of symptoms or the type of compression might be an indicator that a NVC is symptomatic. In trigeminal neuralgia and hemifacial spasms, it has been demonstrated that the degree or severity of compression and atrophy of the nerve correlate with good clinical outcome after decompression surgery. This suggests that in these more profound compression cases, a neurovascular contact is the correct underlying pathology.[12,13,14] This might also be the case for patients with NVC of the vestibulocochlear nerve. Siricki et al. developed a classification system for types of compression of the vestibulocochlear nerve.[15] In this study we hypothesize that the type or degree of compression can be of diagnostic value in tinnitus patients with a neurovascular compression. The goal of this study is to investigate whether there is a correlation between the type of neurovascular compression and the presence of tinnitus.

Materials and Methods

Patients

All consecutive patients referred to the tertiary specialized outpatient clinic for patients with tinnitus in the University Medical Center Groningen between September 2013 and November 2015 were analyzed. Baseline data and questionnaires were gathered prospectively into an anonymized database and analyzed retrospectively. All patients 18 years and older with an available MRI scan of the CPA were included. This research was submitted to the Institutional Review Board of the University Medical Center Groningen, who decided that no full review was needed due to the retrospective nature of this study.

Clinical variables

All tinnitus patients in our specialized outpatient clinic were evaluated by a multi-disciplinary group of medical professionals including an otolaryngologist, audiologist and psychologist. Information is gathered structurally and includes demographics, clinical complaints related to tinnitus (e.g. presence of vertigo, lateralization of the tinnitus, type of tinnitus), audiometric information and results from questionnaires, i.e. the Hospital Anxiety and Depression Scale (HADS) and the Tinnitus Handicap Index (THI). The HADS is divided in no anxiety or depression (score ≤8) versus indication for anxiety or depression (score >8). The THI is divided in slight tinnitus (grade 1: 0-16 points), mild tinnitus (grade 2: 18-36 points), moderate tinnitus (grade 3: 38-56 points), severe tinnitus (grade 4: 58-76 points) and very severe tinnitus (grade 5: 78-100 points). Audiological information from tone audiogram was classified into four categories based on PTA (Pure Tone Average at 1,2 and 4 kHz in decibel): minimal (10-30 dB), moderate (30-55 dB), severe (55-90 dB) and very severe (>90 dB) hearing loss.

Radiological analysis of MR imaging

All patients with available MRI were re-evaluated by a highly experienced neuroradiologist and a last-year radiology resident specializing in neuro- and head and neck radiology. Both, were blinded for clinical information. Although there were differences in interpretation in this re-evaluation, overall consensus was reached in all cases. Most patients had already had a scan in secondary hospitals, the indications for scanning were mostly unknown. Re-evaluation included: scoring of the presence of a vascular compression of the vestibulocochlear nerve in the CPA; the specific anatomical vessel causing the compression; whether compression occurred in the REZ and if there was any other CPA pathology. The type of compression of the vestibulocochlear nerve was classified based on the grading system Sirikci et al.[15] The classification divides NVC on MRI into five categories: no neurovascular conflict on imaging (no NVC), point compression (grade 1), longitudinal compression (grade 2), loop compression (grade 3) and indentation (grade 4). The NVC classification was determined on the left and right cochleovestibular nerve. For unilateral tinnitus, the results were stratified with respect to the symptomatic tinnitus side and to the asymptomatic non-tinnitus side. In patients with bilateral tinnitus, the classifications were stratified as left and right-sided.

Statistical analysis

Comparison between categorical groups was performed with the Pearson chi quadrate test and univariate logistic regression analysis. In the logistic regression analysis, the dependent variable THI was split into two groups (THI grade 1 & 2 versus THI grade 3, 4 & 5). Continuous data was analyzed using the Students' t-test. A P-value of <0.05 was considered statistically significant. SPSS software version 22 (SPSS Inc., Chicago, Illinois, USA) was used for all analyses.

Results

Patient characteristics

The consecutive cohort consisted of 297 tinnitus patients. In 182 of these patients, no MRI was available and in four patients, the MRI was of inadequate quality to properly evaluate the CPA. In the remaining scans, one left ear and one right ear could not be reliably assessed due to insufficient quality of MRI, leaving 111 patients with 220 ears available for radiological assessment (Figure 1). The MRI was also evaluated for other pathologies: there was one patient with dehiscence of the superior semi-circular canal. There were no patients with a tumor or other pathology in the CPA or petrous bone.

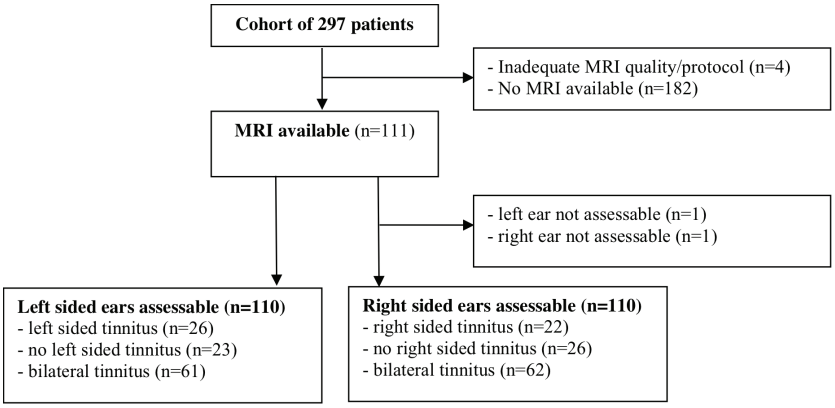

Figure 1. *Flow chart of included patients with tinnitus*

MRI: magnetic resonance imaging

The characteristics of included patients are summarized in Table 1a. The total percentage of women was 41% and the age distribution ranged from 23-77 years with an average of 55 years. Most patients (83%) had complaints of subjective non-pulsatile tinnitus, the other 17% i.e. pulsatile. Tinnitus was unilateral, i.e. either only in the right or in the left ear, in 49 patients (44%) and bilateral in 62 patients (56%). When stratified with respect to severity of the hearing loss, a mild hearing loss (PTA 10-30dB) was most frequently present (48%).

Table 1a. Characteristics of included patients (n=111)

	Total (n=111)	Unilateral tinnitus (n=49)	Bilateral tinnitus (n=62)	p-value
Age (n=111) (years) Mean [range]	55 [23-77]	52 [23-76]	58 [30-77]	0.01
Gender (n=111) (%)				
Male	65 (59%)	24 (49%)	41 (66%)	0.07
Female	46 (41%)	25 (51%)	21 (34%)	
Type of tinnitus (n=111) (%)				
Subjective non-pulsatile tinnitus	92 (83%)	40 (82%)	52 (84%)	0.76
Other	19 (17%)	9 (18%)	10 (16%)	
Neurovascular conflict (n=111) (%)				
No NVC present	14 (13%)	3 (6%)	11 (18%)	0.23
Left NVC	25 (23%)	13 (27%)	12 (19%)	
Right NVC	21 (19%)	8 (16%)	13 (21%)	
Bilateral NVC	51 (46%)	25 (51%)	26 (42%)	
Vertigo (n=110) (%)				
Vertigo/dizziness	34 (31%)	16 (33%)	18 (30%)	0.72
No vertigo/dizziness	76 (69%)	33 (67%)	43 (70%)	
THI grade (n=107) (%)				
Grade 1	12 (11%)	5 (11%)	7 (11%)	0.71
Grade 2	29 (27%)	16 (34%)	13 (22%)	
Grade 3	32 (30%)	12 (20%)	20 (33%)	
Grade 4	19 (18%)	8 (13%)	11 (18%)	
Grade 5	15 (14%)	6 (10%)	9 (15%)	
HADS-Depression* (n=106) (%)				0.75
No indication depression	79 (75%)	35 (76%)	44 (73%)	
Indication depression	27 (25%)	11 (24%)	16 (27%)	
HADS-Anxiety* (n=106) (%)				0.25
No indication anxiety	72 (68%)	34 (74%)	38 (61%)	
Indication anxiety	34 (32%)	12 (26%)	22 (37%)	
Hearing loss in tinnitus affected ear(s) (n=111)(%)				0.13
Mild (10-30 dB)	53 (48%)	22 (37%)	31 (50%)	
Moderate (35-55 dB)	37 (33%)	13 (27%)	24 (38%)	
Severe (60-90 dB)	15 (14%)	10 (20%)	5 (8%)	
Very severe (>90 dB)	6 (5%)	4 (8%)	2 (3%)	

dB: decibel; HADS: Hospital Anxiety Depression Scale; THI: Tinnitus Handicap Inventory; NVC: neurovascular conflict on imaging

** Cut-off score for HADS-depression/anxiety: indication for depression or anxiety is present when scores ≥8*

Vascular compression of the vestibulocochlear nerve

Characteristics of the evaluated MRI scans (per ear, n=220) are depicted in Table 1b. In 146 ears (67%) a NVC was found by radiological assessment. Regarding the type of compression, loop compression (grade 3) was most frequently found (28%), followed by point compression (grade 1; 24%), longitudinal compression (grade 2; 14%) and nerve indentation (grade 4; 1%). Of those NVCs, the AICA was the compromising vessel found most frequently (80%).

Table 1b. Characteristics of the contact between cochleovestibular nerve and a compressing vessel on evaluated MRI scans (per ear total, n=220)

Variable	Number (%)
Classification of compression (n=219) (%)	
No NVC	73 (33%)
Grade 1	52 (24%)
Grade 2	30 (14%)
Grade 3	61 (28%)
Grade 4	3 (1%)
Compromising vessel (n=144) (%)	
AICA	115 (80%)
PICA	1 (1%)
Venous	28 (20%)
Root entry zone on ipsilateral side of complaints (n=143) (%)	
Yes	21 (15%)
No	122 (85%)

AICA: Anterior Inferior Cerebellar Artery; PICA: Posterior Inferior Cerebellar Artery; NVC: neurovascular conflict on imaging

Table 2 compares patients with unilateral and bilateral tinnitus. For patients with unilateral tinnitus, the NVC on the tinnitus side (symptomatic side) and non-tinnitus side (asymptomatic side) was recorded. For bilateral tinnitus, also the NVC was evaluated on both sides (left and right ear). Table 2 shows a cross tabulation of: the classification of compression; the degree of hearing loss (PTA in dB); the compromising vessel; and compression in the REZ; in relation to these two groups (unilateral tinnitus vs. bilateral tinnitus). The distribution of NVC classification on the tinnitus side (symptomatic side) of unilateral cases was significantly different from that in bilateral cases (p=0.014), with loop compression (grade 3) and indentation (grade 4) being more common in the group of unilateral cases. The distribution of NVC classification in the asymptomatic ears was not significantly different from bilateral tinnitus (p=0.099). There was no significant difference in NVC classification within the unilateral tinnitus group (asymptomatic vs. symptomatic ears) (p=0.80).

The degree of hearing loss was significantly higher (p=0.042) in the unilateral tinnitus group (44dB), compared to the bilateral tinnitus group (36 and 32 dB for left and right ear, respectively). The compromising vessels did not significant differ between unilateral and bilateral tinnitus (p=0.227). Also, whether or not there was compression in the REZ did not significantly (p=0.839) differ among the two groups (unilateral symptomatic vs. bilateral).

Table 2. Neurovascular conflicts in the CPA and their characteristics on MRI related to unilateral tinnitus versus bilateral tinnitus ears

		Unilateral tinnitus (n=97)		Bilateral tinnitus (n=122)				
	Total n(%)	Symptomatic side, n(%)	Asymptomatic side, n(%)	Left, n(%)	Right, n(%)	Total, n(%)	*	**
Classification of compression NVC (n=219)							0.01	0.10
No NVC	73	12 (25%)	14 (29%)	23 (38%)	24 (39%)	47 (39%)		
Grade 1	52	8 (17%)	11 (22%)	20 (33%)	13 (21%)	33 (27%)		
Grade 2	30	8 (17%)	5 (10%)	5 (8%)	12 (20%)	17 (14%)		
Grade 3	61	18 (38%)	18 (37%)	13 (21%)	12 (20%)	25 (20%)		
Grade 4	3	2 (4%)	1 (2%)	0	0	0		
PTA (dB)	33	44	21	36	32	34	0.04	0.00
Compromising vessel (n=147)							0.23	0.02
AICA	115	27(75%)	28 (80%)	32 (84%)	27 (71%)	59 (78%)		
Venous	28	7 (19%)	4 (11%)	6 (16%)	11 (29%)	17 (22%)		
PICA	1	1 (3%)	0	0	0	0		
Unclear	4	1 (3%)	3 (9%)	0	0	0		
Compression in the root entry zone (n=143)							0.84	0.31
No	122	31 (86%)	28 (80%)	34 (90%)	29 (85%)	63 (88%)		
Yes	21	5 (14%)	7 (20%)	4 (11%)	5 (15%)	9 (13%)		

** Unilateral symptomatic vs. total bilateral p-value. ** Unilateral asymptomatic vs. total bilateral p-value.*

The two rightmost columns shows the statistical significance of the difference in grade distribution between the symptomatic (p= 0.01) and asymptomatic side (p=0.10) in unilateral patients and the combined left and right sides of the bilateral patients.

AICA: Anterior Inferior Cerebellar Artery; NA: not available; NVC: neurovascular conflict on imaging; PICA: Posterior Inferior Cerebellar Artery; PTA: pure tone audiometry (mean over 1, 2 and 4 kHz).

Figure 2 shows a boxplot with the different types of compression in relation to the degree of hearing loss (PTA) for tinnitus ears (symptomatic ears) vs. asymptomatic ears. For each type of compression, asymptomatic ears had less hearing loss than tinnitus ears. No significant difference in degree of hearing loss was found between any grade of NVC versus 'no NVC'.

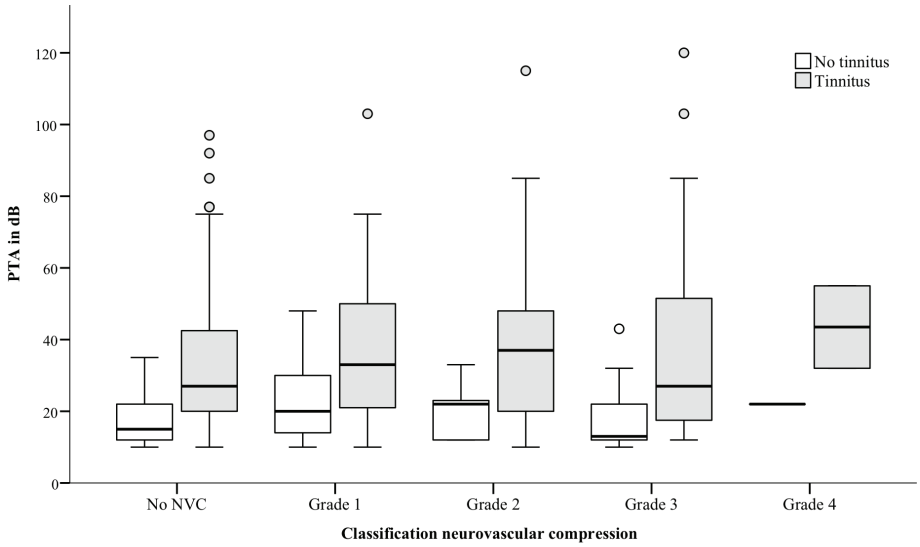

Figure 2. *Boxplot with classification of the neurovascular conflict versus pure tone audiometry thresholds (mean 1-2-4 kHz) in symptomatic versus asymptomatic tinnitus ears*

The boxplot in Figure 3 shows the relation between the type of compression and the degree of hearing loss on the side of the compression, regardless of any tinnitus symptoms. The degree of hearing loss does not significantly differ between the various types of compression, indicating that there is no causal relation between the type of compression and the degree of hearing loss.

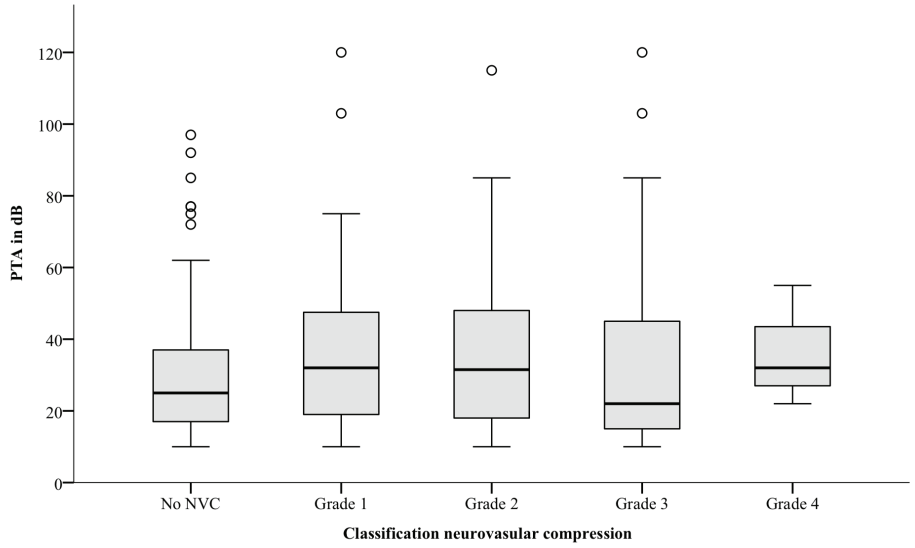

Figure 3. *Boxplot showing the type of compression in relation to degree of hearing loss on the ipsilateral side*

Univariate analysis of different clinical factors influencing tinnitus severity

A univariate logistic regression related various variables to tinnitus handicap (Table 3). For this analysis, the patients were divided in 2 groups: group 1: THI 0-35, mild tinnitus, and group 2: THI 36-100, moderate to very severe tinnitus. There was no significant relation between the presence of a NVC or the type of compression and the tinnitus handicap. Univariate analysis within the patient groups revealed no significant links between age, gender, severity of hearing loss, type of tinnitus and tinnitus handicap. However, there was a significant association for both anxiety and depression in relation to severity of tinnitus (p=0.012, OR3.62 CI: 1.33-9.82 and p=0.003, OR 1.45 CI: 0.50-4.86 respectively), showing that patient with moderate to very severe tinnitus more often have an indication for anxiety and depression.

Table 3. *Univariate analysis of different factors in relation to tinnitus handicap (Group 1: THI 0-35 vs. Group 2: THI 36-100)*

Variable	Odds ratio [CI]	P value
Age group		0.52
18-40 years	1 (reference)	
40-60 years	1.04 [0.28-3.83]	
Older than 60 years	1.80 [0.77-4.24]	
Gender		0.88
Male	1 (reference)	
Female	0.94 [0.42-2.10]	
HADS anxiety		**0.01**
No anxiety	1 (reference)	
Anxiety	3.62 [1.33-9.82]	
HADS depression		**0.00**
No depression	1 (reference)	
Depression	9.55 [2.11-43.18]	
Severity of hearing loss		0.75
Minimal	1 (reference)	
Moderate	0.97 [0.16-5.82]	
Severe	0.63 [0.10-3.94]	
Very severe	1.83 [0.22-15.3]	
Type of tinnitus		0.45
Subjective non-pulsatile tinnitus	1 (reference)	
Subjective pulsatile tinnitus	1.45 [0.50-4.68]	
NVC		0.93
No	1 (reference)	
Yes	1.03 [0.56-1.87]	
Type of compression		0.94
No NVC, grade 1 or 2 compression	1 (reference)	
Grade 3 or 4 compression	0.98 [0.55-1.73]	

Severity of tinnitus was measured with the THI and was divided into two groups (THI 0-35 vs. 36-100). Tinnitus related findings (neurovascular conflict and type of compression) were analyzed in 220 separate ears; patient related variables were analyzed in 111 separate patients.

CI: confidence internal; HADS: hospital anxiety depression questionnaire; NVC: neurovascular conflict on imaging; THI: Tinnitus Handicap Inventory.

Discussion

Summary of findings

In this retrospective study, we evaluated the relation between the type of contact between the cochleovestibular nerve and a nearby blood vessel (using the grading system of Sirikci et al[115]) and the presence of unilateral tinnitus. We found that loop compression and indentation of the cochleovestibular nerve were more common in the patient group who had unilateral tinnitus, however there was no significant difference in distribution of NVC classification between symptomatic (tinnitus) and asymptomatic (no tinnitus) ears. The degree of hearing loss did not differ between the various types of compression. The vessel causing the compression or the fact that the compression was found in the root entry zone, was not significantly related to the presence of unilateral tinnitus. Finally, we found that the severity of tinnituswas not related to the presence of a NVC, the type of hearing loss or the type of tinnitus.

Interpretation of results

In concordance with other studies, this study demonstrated that when an NVC of the vestibulocochlear nerve is found, this does not necessarily correlate with tinnitus symptomatology.[8,9] This phenomenon is also seen in NVCs of the trigeminal nerve: a study by Miller et al. showed that an arterial NVC of the trigeminal nerve without symptoms of trigeminal neuralgia was seen in 17% of patients.[1,4] In trigeminal neuralgia and hemifacial spasms, a significant predictor of symptomology was compression of the proximal nerve and nerve indentation or displacement.1[3,14] In our study we found that in the group of patients with unilateral tinnitus, loop compression and nerve indentation (grade 3 and 4) were significantly more present and the point compression and longitudinal compression (grade 1 and 2) were less often found, as compared to the bilateral tinnitus group. We hypothesized that specific types of compression are more likely to have a causal relation with tinnitus when it causes unilateral symptomatology, as seen in the 'vestibulocochlear nerve compression syndrome'.[7] It may be that when there is compression by a loop around the nerve (grade 3), a larger contact surface with the nerve exists, causing more disruption of neuronal transmission. The same theory applies for nerve indentation (grade 4), as it is plausible that an indentation in the nerve causes local irritation and ectopic excitation. This is in line with a recently published study of Bae et al, who found that a NVC of the cochlear nerve (with >50% extension of contact in the internal auditory canal) was more frequently detected on symptomatic sides of patients with typewriter tinnitus.[16] In our study, although loop compression and indentation were more frequently found in the unilateral tinnitus group, the distribution in types of NVC did not significantly differ between within the unilateral tinnitus group (asymptomatic side vs. symptomatic side), which does not affirm our hypothesis. Possibly the presence of a higher graded NVC is more of a risk factor for development of (unilateral) tinnitus rather than a cause. Unfortunately, the indentation type of NVC was rare in our patient sample (n=3), therefore firm conclusions are not possible.

This study also showed that the severity of hearing loss was significantly higher in the symptomatic ears in patients with unilateral tinnitus. Also, in our analysis the degree of hearing loss was equal in relation to the different types of NVC, including 'no NVC'. No specific relation between degree of hearing loss and a specific type of compression could be found. In our patient sample, it could not be confirmed that hearing loss is a symptom of the cochlear nerve compression syndrome and a result of compression and thereby irritation of the auditory nerve.[17,18] The significant difference in degree of hearing loss in the unilateral symptomatic tinnitus vs. bilateral tinnitus ears can be explained by the fact that hearing loss is a known risk factor for the development of tinnitus. In conclusion, lateralization of tinnitus (i.e. unilateral tinnitus) was the result of asymmetry in hearing loss (caused by other etiologies) and the degree of hearing loss could not to be related to a specific type of NVC.

Interestingly, in this study a rather high percentage of NVCs were found (67%). Other studies demonstrated percentages of tinnitus patients with an NVC caused by an AICA loop varying from 14-65%.[3,9,15] Possibly, the rather high percentage of NVCs in our study can be partially explained by the fact that not only the AICA was scored in our study, but also other compromising vessels such as the posterior inferior cerebellar artery and venous vessels.

Limitations of the study

As the patients included in this study visited a tertiary outpatient clinic, more severe tinnitus symptoms can be expected in comparison to the general tinnitus population. This selection bias may have influenced our data, especially in terms of severity of tinnitus burden.

The current study has one of the largest sample sizes in comparison to previous studies investigating the relation between symptoms and NVC on MRI. However, still a larger number of patients would be preferable, mainly because some types of NVCs (i.e. loop compression and especially indentation) are only present in small numbers. Moreover, a standardized protocol of imaging should be used in a prospective study as our study consisted of MRI scans from different hospitals, preferable in higher quality imaging such as 3 Tesla MRI. Also, a control group would be recommendable, as a NVC is known to also be present in patients without tinnitus.

Moreover, tinnitus is a subjective complaint and description by patients is difficult to interpret objectively. For some patients, the difference between unilateral and bilateral tinnitus can be difficult to distinguish, which may have influenced our data. Future research should therefore concentrate on prospectively gathering standardized clinical and imaging data to confirm the results that were found in this study.

Conclusions

The mere presence of an NVC on MRI or the involvement of the REZ does not correlate with symptoms of tinnitus. Although the distribution of NVC classification is different in patients with unilateral and bilateral tinnitus, there was no definite relation between the type of NVC and the presence of ipsilateral tinnitus or the degree of hearing loss. Further prospective research is warranted to confirm these findings in order to assess and confirm the clinical relevance of NVC on MRI.

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Effect of direct stimulation of the cochleovestibular nerve on tinnitus: a long-term follow-up study

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Abstract

Objective

Tinnitus is a common entity that may lead to severe impairment in quality of life. An adequate treatment modality for severe tinnitus is currently lacking. Neurostimulation of the auditory tract may serve as a promising adjunct in tinnitus treatment. The aim is to investigate the effect of direct stimulation on the cochleovestibular nerve for intractable tinnitus.

Methods

This study was conducted at the University Medical Center Groningen, The Netherlands. We studied ten patients with severe, unilateral, intractable tinnitus, who were implanted with a cuff electrode around the cochleovestibular nerve between 2001 and 2013. All patients were preoperatively known with ipsilateral hearing loss. Tinnitus Handicap Inventory (THI) scores and audiometric values were collected. Treatment success was determined based on the self-assessment of satisfactory usage by each patient.

Results

The mean preoperative tinnitus duration was 8.0±5.9 years. The preoperative THI score was 71±18 points. During mean follow-up of 49 months, the mean THI-reduction was 24±26 points (p=.02). Treatment was regarded successful in six patients (60%). In these patients tinnitus did not disappear, but transformed into a more bearable sound. In four patients, transient complications occurred and one patient experienced permanent vertigo postoperatively. Furthermore, hearing deterioration was seen as a result of implantation in 86% of the patients.

Conclusions

Direct neurostimulation resulted in treatment success in a small majority of the patients with a significant decrease in THI score. However, because of a high risk of additional hearing damage, this technique seems not viable for patients with moderate hearing loss.

Introduction

Tinnitus is the perception of sound or noise in the ear or head in the absence of an external physical sound source. With a prevalence of 5-18%, it is a common disorder.[1] It can lead to a substantial impairment in quality of life and additional symptoms such as anxiety, depression, insomnia and irritability are often reported.[2] Conventional treatment methods for tinnitus include sound therapy and/or cognitive behavioral therapy. Unfortunately, not all patients benefit from these measures and for those patients an adequate treatment modality is currently lacking.

Although tinnitus is still not completely understood, it is generally accepted that tinnitus is caused by an imbalance between excitatory and inhibitory input to auditory neurons.[3,4] This imbalance may occur at multiple levels of the auditory system and can be elicited by deprivation of auditory stimuli, such as the absence of normal auditory stimuli in patients with hearing loss. The loss of input can evoke plastic readjustments in the central auditory system and even in the non-auditory system, which include hyperactivity, bursting discharges and increases in neural synchrony, leading to the percept of tinnitus.[3] For several years, electrical stimulation of the auditory system has been investigated as a treatment option for intractable tinnitus. This is based on the idea that restoration of peripheral sensory input may result in reorganization of the central auditory system and subsequently in a reduction of tinnitus.[5] Also, a masking effect on tinnitus may be achieved by electrical stimulation.[6] Several techniques of permanent invasive stimulation of the auditory tract have been investigated, such as auditory and frontal cortex stimulation, round window stimulation[7], promontory stimulation[8] and cochlear implants (CI).[9] Additionally, previously our center developed a cuff electrode for direct stimulation of the cochleovestibular nerve (CVN) for patients with intractable tinnitus.[10] This technique had not been explored before in tinnitus treatment. It was based on an existing treatment of direct stimulation of the nerve system for intractable neuropathic pain, as it has been demonstrated direct stimulation on the spinal cord can successfully treat neuropathic pain syndroms.[11,12] Neuropathic pain in fact shows similarities in pathophysiology with other hyperexcitability disorders, such as tinnitus.[13] Previously, we have treated six tinnitus patients with such cuff electrode, proving safety and showing promising results in terms of tinnitus reduction.[10,14] To further investigate this supposedly beneficial effect, a larger study population is warranted. The aim of the present study is to investigate the long-term effects of direct stimulation of the CVN on therapeutically intractable tinnitus.

Material and Methods

Inclusion criteria

In this case series, 11 adult patients with severe, intractable, and unilateral tinnitus were included. Patients were recruited from our tertiary referral outpatient clinic. An additional inclusion criterion was sensorineural hearing loss at the side of the tinnitus (defined as mean ≥ 80 dB over 1-2-3-4-8 kHz for the latter five patients in a protocol amendment). Patients were excluded if there was a treatable cause of tinnitus (e.g., glomus tumor, otosclerosis or vestibular schwannoma)

and/or if tinnitus was lateralized to the better hearing ear. Other exclusion criteria were previous cerebellopontine angle pathology and/or surgery or the presence of another electronic implant. All patients were screened for psychiatric pathology and were excluded in case of e.g., depression. This study has been performed according to the Declaration of Helsinki and approval was obtained by the ethical committee of the University Medical Center Groningen. All patients gave written informed consent.

Cuff electrode & surgical technique

A custom-made cuff electrode designed for placement around the CVN was manufactured by Medtronic (Medtronic Bakken Research Center, Maastricht, The Netherlands). The full configuration of the implanted system is depicted in Figure 1a. The quadripolar cuff electrode has a circular distal housing with a slit, two opening levers and four radial positioned electrodes for placement around the CVN as close to the brainstem as possible (Figure 1b and 1c). The cuff electrode was connected via an extension cable (model 37083, Medtronic) to the pulse generating device (model 37702, Medtronic) that was placed subcutaneously in the subclavicular or paraumbilical region. Programming of the system was performed using the MyStim-programmer (model 37742, Medtronic), which communicates transcutaneously with the implanted pulse generator. The use of the cuff electrode for the treatment of tinnitus was considered 'off-label'. All implant components, except from the custom-made cuff electrode, were European Conformity approved.

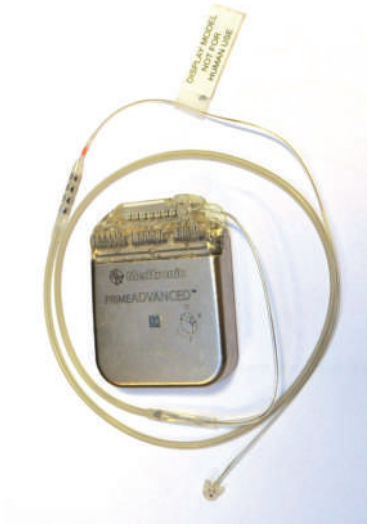

Figure 1a. *The total implant system*

The total implant system consists of the pulse generator, extension cable and cuff electrode at the distal end of the electrode. In the latter cohort, an updated version of the pulse generator was used ('Activa'-version). Reproduced with permission of Medtronic

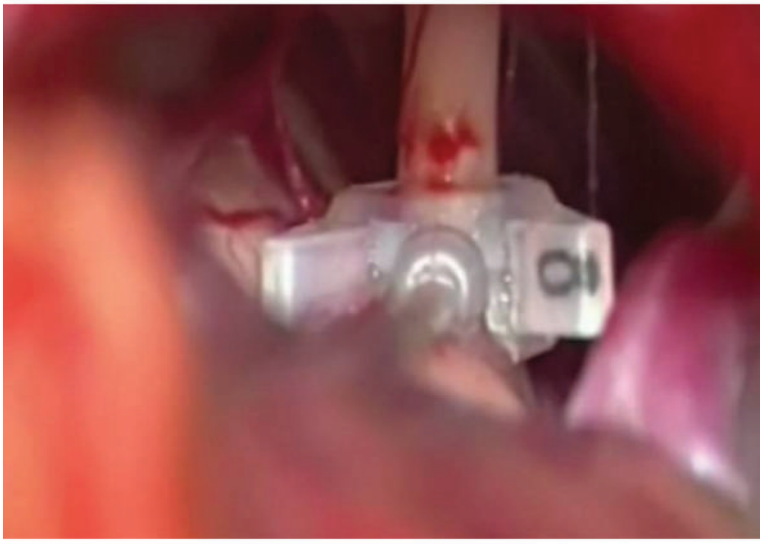

Figure 1b. *Details of the quadripolar cuff and the lead of the electrode (custom-made by Medtronic)*

Numbers 0 to 3 indicate the four different electrodes. The inside diameter of the cuff was variable from 2.50, 2.75, 3.00 to 3.50 mm. Reproduced with permission of Medtronic

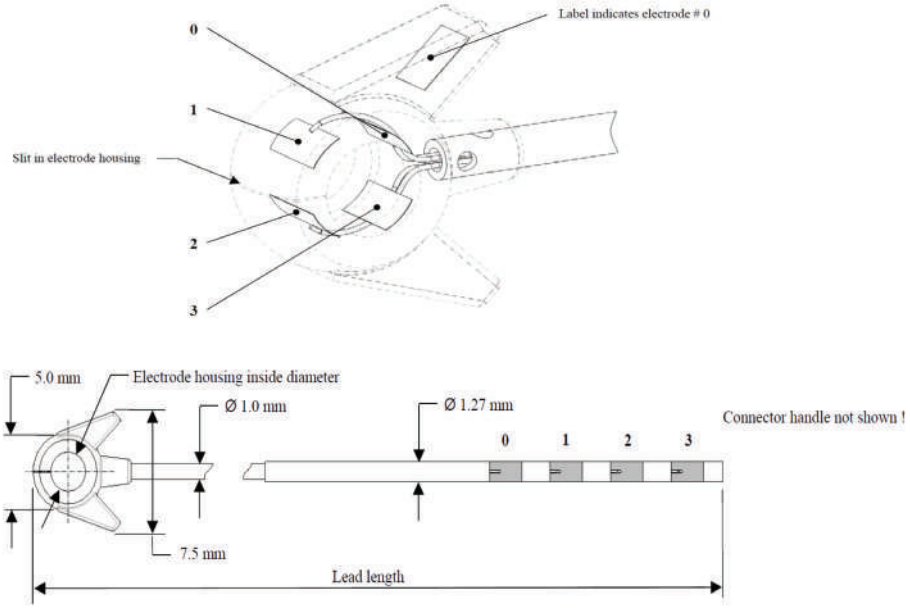

Figure 1c. *Implantation of the cuff electrode*

The cuff electrode is placed around the cochleovestibular nerve, as close to the brainstem as possible

Surgeries were performed at the University Medical Center Groningen, The Netherlands. In all patients, the cuff electrode was surgically positioned around the CVN via a retrosigmoid craniotomy. Depending on the diameter of the CVN, an electrode with appropriate internal cuff diameter between 2.50 and 3.50 mm was chosen peroperatively.

Stimulation after implantation

The neurostimulator was activated as soon as the patient recovered from the surgery. The stimulation parameters were adjustable: active electrodes (0-4), amplitude, frequency and pulse width. Stimulation parameters ranged from 60-450 μs for pulse width, 0-4.0 V for amplitude; and 2-250 Hz for frequency. Stimulus pulse amplitudes and frequencies were unmodulated and monophasic. Programming of optimal stimulation settings was performed in multiple consecutive visits with a technical physician specialized in neuromodulation. During these visits, in each individual patient, optimal stimulation parameters were found by the following procedure: every visit, the pulse generator was programmed with four programs with different stimulation strategies. First, the pulse width was determined: the highest pulse width that was accepted without side effects, was chosen. Consequently, the amplitude and frequency were adjusted. Patients received a patient programmer, which enabled them to switch between programs and turn the implant on and off. The patient was instructed to use all four programs during a couple of weeks and find out, which one suited best to reduce or mask their tinnitus. The most favorable program was selected in the next visit and fine-tuned into four slight variation of this program. In subsequent sessions following the implantation, fine- tuning of the stimulation strategies was performed, to maximize the response in terms of effect and subjective comfort. These steps were repeated until a (subjective) preferable program was found.

Follow-up and evaluation

Baseline characteristics, e.g. age, sex, duration of tinnitus and standard pure tone audiometry (PTA) were collected. Treatment success was considered as satisfactory, when a patient used their device on a daily basis and when they were satisfied with the effect that the device had on their tinnitus. Tinnitus severity was measured using the validated Tinnitus Handicap Inventory (THI) and change in the THI was used as primary outcome. Total scores vary from 0-100 points and a reduction of >7 points was considered a clinically relevant change.[15] The last five patients were also asked to classify their tinnitus on a Visual Analogue Scale (VAS). The VAS-tinnitus annoyance (VAS-TA) was labeled from 0 (not annoyed by tinnitus) to 10 (worst possible annoyance by tinnitus). The VAS-tinnitus loudness (VAS-TL) was labeled from 0 (no tinnitus) to 10 (loudest tinnitus ever).[16] All assessments were collected preoperative and during repetitive postoperative evaluation. The effect on hearing was measured by postoperative PTA during 'off'-condition of the implant and presented as the mean pure tone audiometry (PTA), i.e. mean dB over 1-2-4 kHz. In all patients, follow-up was obtained at least three months after implantation. In the latter five patients, a standard one-year assessment was performed additionally. In 2015, all patients with a functioning neurostimulator in situ were evaluated to obtain the most recent follow-up.

Statistical analysis

Continuous variables are presented as mean ± standard deviation for normal distributed data and median and interquartile range (IQR) for skewed distributed data. Paired-samples t-test was performed to compare differences within groups. A p-value of <.05 was considered statistically significant. SPSS software version 22 (Chicago, Illinois, USA) was used for all analyses.

Results

Participants

From 2001 until 2013, 11 patients were implanted with the cuff electrode. One patient withdrew consent shortly after implantation and was therefore excluded from the analysis. Over the course of the study, two patients died (Case 1 and 3), respectively 14 and 7 years after implantation, as a result of unrelated causes. In one patient, the pulse generator was removed on the patient's request, due to lack of benefit of the implant. Implants were replaced in two satisfied users, because of end-of-life of the battery.

Patient characteristics

Patient characteristics are presented in Table 1. All patients had severe, intractable and unilateral tinnitus. Five patients were female (50%) and the mean age at implantation was 56.6±5.9 years. The mean preoperative duration of tinnitus was 8.0±5.9 years. The causes of tinnitus are outlined in Table 1. Postoperatively, all patients underwent a tailored stimulation strategy in several programming sessions. The most favorable stimulation strategy for every individual patient is presented in Table 2.

Table 1. Patient characteristics of the total cohort (n=10) and postoperative complications

Case #	Age, Sex	Duration of tinnitus (y)	Cause of tinnitus	Side of implantation	Complications
1	51M	22	None specific	L	-
2	51F	1	Sudden deafness	R	CSF leakage
3	69F	6	None specific	L	-
4	51F	8	Sudden deafness	L	CSF leakage
5	61F	6	Morbus Ménière, after drainage saccus endolymfaticus	R	CSF leakage
6	62F	10	Sudden deafness	R	Temporary paralysis right sided larynx, temporary swallowing problems
7	57M	4	After a skull base fracture	R	-
8	57M	6	None specific	R	Permanent vertigo
9	54M	4	Sudden deafness	R	-
10	53M	13	After sudden deafness/ neuritis vestibularis	R	-

F: female, M: male; L: left, R: right; CSF: cerebrospinal fluid

Table 2. Individual stimulation parameters

Case #	Mode of stimulation	Amplitude (V)	Frequency (Hz)	Pulse width (ms)
1	2- C+ (monopolar)	0.5	50	90
2	1- 3+ (bipolar)	2.60	60	240
3	2- 0+ (bipolar)	0.95	60	120
4	2- 0+ (bipolar)	2	60	60
5	3- C+ (monopolar)	0.55	18	60
6	0+1- (bipolar)	2.0	95	60
7	0- 1+ (bipolar)	0.55	175	270
8	0+ 1- 2+ (tripolar)	1.20	210	60
9	0+ 1- (bipolar)	2.4	210	70
10	0- 1+ (bipolar)	1.10	180	180

The four electrodes of the cuff are numbered from 0 to 3. Negative poles are marked with – and positive electrodes with +. The electrical current flows from – to +. C indicates the 'case' of the pulse generator device, which was programmed as the positive pole in monopolar stimulation

Outcomes

The treatment outcome in terms of change in THI and PTA are presented in Table 3. Preoperatively, the mean THI score was 71±18 points. At mean follow-up of 49 months (range 3-168 months), the THI score decreased by an average of 24±26 points (p=0.016). The modification in the THI of all cases is shown in Figure 2, with a differentiation in 'Users' and 'Non Users'. At the latest follow-up available, six patients (60%) still used their neurostimulator on a daily basis. In these patients tinnitus did not disappear, however it was transformed into a more bearable sound. In these 'Users', the mean reduction in THI score was 35±25 points (p=0.018). In the remaining four 'Non Users' (Case 3, 8, 9 and 10) patients regarded the treatment as not successful. None of the patients reported an increase of their tinnitus. For Case 6 to 10, the change in VAS-scores for each case is presented in Figure 3. All patients, except Case 7, showed a postoperative decrease in VAS-scores.

Table 3. *Overview of the outcomes of the total cohort (n=10) implanted with the cuff electrode*

Preoperative					Postoperative						
Case #	Age*, Gender	Side†	THI	PTA (dB)‡	THI 3mo	THI 1 y	THI latest FU	Duration of latest FU (mo)§	PTA (dB)‡	Daily use of NS? Satisfied?	Course
1	51M	L	62	>120	58	-	56	42	>120	Yes, until 2008	Satisfied 4 y later, 25-35% reduction of tinnitus. Stopped using NS after 7y. Patient deceased in February 2015.
2	51F	R	100	70	100	-	56	168	80	Yes, satisfied up till latest FU	NS brought reduction of tinnitus after ~1 y. Up till latest FU moment very satisfied with NS. Replacement NS (battery end of life) 11 y after implantation.
3	69F	L	90	37	52	-	-	3	NA	No	Slight reduction of tinnitus. Stopped using NS after 2 y. Patient deceased in April 2008.
4	51F	L	88	98	4	-	10	42	>120	Yes, satisfied with NS up till latest FU	Satisfied. Direct tinnitus reduction, replacement with a pleasant sound.
5	61F	R	58	95	58	-	26	150	100	Yes, satisfied with NS up till latest FU	Very happy with the NS, experiences no tinnitus burden. NS replacement (battery end of life) 10 y after implantation.
6	62F	R	68	75	38	24	46	25	120	Yes, replaced by more pleasant sound	Improvement of tinnitus distress with NS. Temporary vocal cord paralysis and alteration of taste.
7	57M	R	40	117	42	32	-	12	>120	No	Little effect at first, implant was removed on patients request 2 y after implantation.
8	57M	R	60	85	62	66	-	12	98	No	No satisfying effect. Postoperative vertigo with afunctional right labyrinth.
9	54M	R	80	78	54	50	54	26	92	Yes, satisfied with NS	Subjectively moderate improvement, NS always on.
10	53M	R	66	95	62	72	-	12	93	No	At first light improvement with NS, permanently turned off 2 y after implantation.

**Age at implantation; † side of implantation; ‡ pure tone audiometry (mean over 1-2-4 kHz) of the ipsilateral ear; § last follow-up available during functioning neurostimulator was in situ; -: not available, F: female; FU: follow-up; M: male; mo: months, PTA: pure tone audiometry; L: left; NS: neurostimulator; R: right*

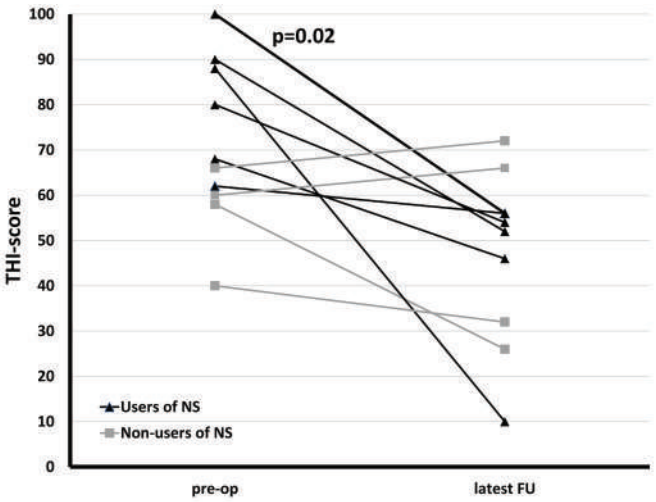

Figure 2. Change in THI in ' Users' vs. 'Non Users'. A statistically significant decrease of the THI (p=0.02) was seen in the total patient group (n=10)

FU: follow-up; NS: neurostimulator

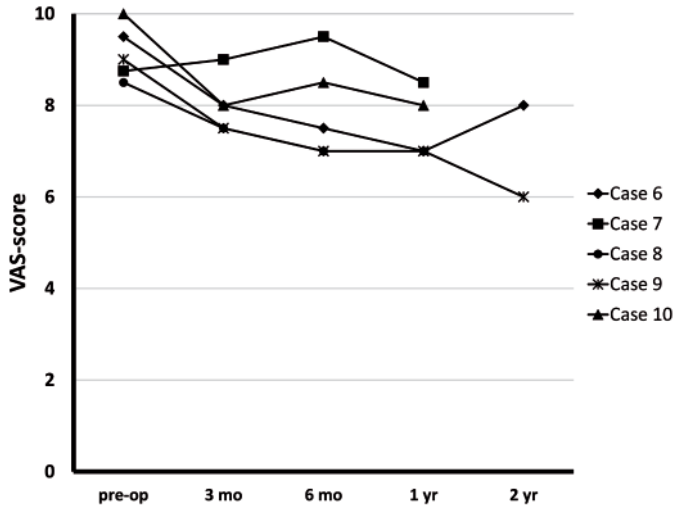

Figure 3. Change in VAS scores from Case 6 to 10

VAS-score was calculated as the average of "VAS-tinnitus annoyance" and "VAS-tinnitus loudness". VAS: visual analogue scale, mo: months, yr: year

Complications

In three patients cerebrospinal fluid leakage occurred postoperatively, which in all cases was adequately treated with temporary drainage. One patient had postoperative swallowing problems and dysphonia due to a right-sided paresis of the larynx, which resolved spontaneously within three months. Another patient experienced permanent vertigo postoperative with related absence of the caloric response from the vestibule on the operated side. Dysfunction of the facial nerve was not observed in any patient. Uneventful surgery was reported in five patients (50%).
Eight of 10 patients had residual hearing preoperatively (i.e., mean PTA <115 dB). For one patient, there was missing data of a postoperative PTA. In six patients with preoperative residual hearing (86%) a deterioration of hearing was seen postoperatively, defined as a ≥5 dB decrease on PTA. Over all, there was a mean decrease of 13±14 dB on PTA.

Discussion

Key results

This study provides the long-term follow-up of 10 patients implanted with a cuff electrode around the cochleovestibular nerve with the aim to reduce tinnitus. We demonstrated that six patients (60%) reported to have a beneficial effect of the stimulation on their tinnitus and used the neurostimulator on a daily basis, which was reflected by a clinically significant reduction in their THI scores. Stimulation transformed their tinnitus into less disturbing sounds. However, several complications were encountered, varying from transient cerebrospinal fluid leakage to permanent ipsilateral vertigo and hearing deterioration

Interpretation of results

To our knowledge, our series is the only experience with direct electrical stimulation of the cochleovestibular nerve for the treatment of tinnitus. Although data of the first five patients have been reported earlier, the larger sample and longer follow-up period of this unique patient group provides a relevant contribution to the existing literature. Our study is in line with previous attempts to investigate permanent electrical stimulation of neural auditory pathways to reduce tinnitus, such as extradural auditory cortex stimulation, which showed similar suppression effects on tinnitus in 51% of 43 patients.[17] Implants originally aimed at rehabilitation of hearing are also investigated for their effect on tinnitus. Seo et al. demonstrated that middle-ear implants can reduce tinnitus.[18] Also, auditory brainstem implant recipients, mainly neurofibromatosis type II patients, report a beneficial effect on tinnitus in 62-70% of cases.[19-21] However, the most frequently reported and the most promising implant is the CI.5 Kleine Punte et al. showed a beneficial effect of CI implantation in unilaterally deaf patients for the primary aim of tinnitus reduction.[9] In a long-term follow-up of 26 patients, tinnitus disappeared completely in 15% and improved in 85% of the cases.9 It is not yet clear what the exact underlying mechanism is that explains the reduction of tinnitus percept by these types of stimulation. Current hypotheses are that it is due to restoration of auditory input and thereby recovering disorganized central auditory pathways[22], an attention-shift from the tinnitus[23], or a masking effect.[6]

This study yielded a moderate success rate. A possible explanation for the rather disappointing effect is that in our study, stimulation was used with pulses that were generated irrespective of environmental sounds, unlike stimulation with a CI. It is hypothesized that tinnitus may be more effectively reduced with a stimulation strategy of meaningful stimuli which are aimed at hearing rehabilitation.[9] Alternatively, studies have also demonstrated that tinnitus can be reduced in CI patients using stimuli that are independent of external acoustic sounds, although the optimal stimulation strategy seems to be very subject-specific.[23,24] In our study, we demonstrated similar findings: the individual stimulation parameters comprised a wide range and were highly subject-specific. The results of our study support the hypothesis that tinnitus reduction is possible with non-meaningful stimuli. However, as none of our study participants experienced complete disappearance of tinnitus, the outcomes of CI implantation for tinnitus reduction seem to be superior to our study. Furthermore, our neurostimulator had only a limited array of stimulation strategies, whereas a CI has the advantage of more possibilities in altering stimulus settings over multiple electrodes, increasing the possibility to create a successful stimulation strategy. Lastly, it was striking that in 86% of the patients with residual hearing, deterioration of hearing was found postoperatively. This is most likely explained by mechanical damage caused by placement of the cuff electrode around the fragile cochleovestibular nerve. Hearing deterioration is the most common reported complication in cerebellopontine angle surgery, indicating the vulnerability of the nerve.[25] Therefore, the neurostimulator would not serve as a favorable treatment option in normally hearing patients or patients with moderate hearing losses. Mechanical damage to the cochleovestibular nerve is also the most plausible explanation for the permanent ipsilateral vertigo reported by one of the patients.

Limitations

This study has some limitations that merit emphasis. The moderate success rate of this study is partially imputed to technical aspects as described earlier. Furthermore, although the pulse generator is a regular medical device used to treat neuropathic pain, this study was the first to use it for direct CVN stimulation. No predefined stimulation algorithm could be used, because of little knowledge on stimulation for this indication. Second, we were able to report on only a small group of 10 patients. Although there are many patients with intractable tinnitus, it was difficult to include eligible and motivated participants for this experimental study. Third, the data for the 'on' and 'off' condition of the implant during audiometry were not collected consistently, which hinders a firm conclusion on the question if hearing loss is truly attributable to mechanical aspects. Also, in future research, one should perform vestibular tests in pre- and postoperative setting, to investigate the vestibular effects of stimulation and/or implantation. Lastly, tinnitus is a complex entity that cannot be objectified. Our patients joined an experimental study and underwent an invasive surgical procedure for their tinnitus. This effort undertaken by the patients may have contributed to a positive effect, leading to a bias based on effort justification. Due to the lack of a control group, internal validity of this study is low. An intervention study with a placebo would be recommended, although this would raise ethical concerns. This is a problem in almost all neurosurgical intervention studies for tinnitus.

Conclusion

Long-term results show that direct stimulation of the cochleovestibular nerve resulted in significant decrease in THI score and treatment success in small majority of patients. However, because of a high risk of additional hearing damage, this technique seems not viable for patients with normal hearing or with moderate hearing loss. For tinnitus patients with severe hearing loss, recent studies show that CIs are a superior treatment option. Thus, at present there is no patient category for which this method of direct electrical stimulation is recommended.

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6

An auditory brainstem implant for treatment of unilateral tinnitus: protocol for an interventional pilot study

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Abstract

Introduction
Tinnitus may have a very severe impact on the quality of life. Unfortunately, for many patients, a satisfactory treatment modality is lacking. The auditory brainstem implant (ABI) was originally indicated for hearing restoration in patients with non-functional cochlear nerves, for example, in neurofibromatosis type II. In analogy to a cochlear implant (CI), it has been demonstrated that an ABI may reduce tinnitus as a beneficial side effect. For tinnitus treatment, an ABI may have an advantage over a CI, as cochlear implantation can harm inner ear structures due to its invasiveness, while an ABI is presumed to not damage anatomical structures. This is the first study to implant an ABI to investigate its effect on intractable tinnitus.

Methods and analysis
In this pilot study, 10 adults having incapacitating unilateral intractable tinnitus and ipsilateral severe hearing loss will have an ABI implanted. The ABI is switched on 6 weeks after implantation, followed by several fitting sessions aimed at finding an optimal stimulation strategy. The primary outcome will be the change in Tinnitus Functioning Index. Secondary outcomes will be tinnitus burden and quality of life (using Tinnitus Handicap Inventory and Hospital Anxiety and Depression Scale questionnaires), tinnitus characteristics (using Visual Analogue Scale, a tinnitus analysis), safety, audiometric and vestibular function. The end point is set at 1 year after implantation. Follow-up will continue until 5 years after implantation.

Ethics and dissemination
The protocol was reviewed and approved by the Institutional Review Board of the University Medical Centre Groningen, The Netherlands (METc 2015/479). The trial is registered at www.clinicialtrials.gov and will be updated if amendments are made. Results of this study will be disseminated in peer reviewed journals and at scientific conferences.

Trial registration number
NCT02630589

Introduction

Tinnitus, which literally means 'ringing in the ears', is defined by the perception of sound or noise in the absence of an external physical sound source.[1] It is a very common condition (prevalence 5-18% in Western population) and, in a subgroup of patients, it causes extreme distress with far-reaching consequences for daily activities and quality of life.[1-3] Conventional treatment methods, e.g. sound generators and cognitive behavioral therapy, seem not to reduce the loudness of tinnitus, but may improve related depression and quality of life.[4,5] However, not all patients benefit from these treatments and there is a remaining group of patients with severe tinnitus for whom there is no conventional treatment modality available.[6]

During the ongoing search for causal treatment methods, it has been demonstrated that a cochlear implant (CI) may be a potential treatment option. In a prospective study, CI implantation in patients with single-sided deafness and tinnitus resulted in significantly reduced tinnitus loudness in the long-term.[7] However, insertion of an electrode into the cochlea often leads to mechanical damage of intracochlear structures and subsequent, additional hearing loss. Therefore, CI is only indicated in cases where there is severe to profound hearing loss. This means that CI is not an option for the large group of tinnitus patients who still have usable hearing. To fill this gap, the auditory brainstem implant (ABI) might be an option.

In 1979, the first ABI was implanted by House and Hitselberger for the purpose of restoring hearing in a patient with neurofibromatosis type II (NF2).[8,9] The implant hardware is comparable to that of the CI, however the ABI was specifically designed to bypass both the cochlea and the auditory nerve to directly stimulate the cochlear nucleus in the brainstem. It is thought that the dorsal cochlear nucleus (DCN) plays an important role in modulation and generation of tinnitus. For example, as a result of increased noise exposure, hyperactivity, expressed as an increased spontaneous activity, can be found in DCN; this in turn reduces residual inhibition and increases excitability.[10] In an animal model, it was demonstrated that there is behavioral evidence of tinnitus in conditions of increased hyperactivity in the DCN.[11] Thus electrical stimulation of the cochlear nucleus in rats led to suppressed behavioral evidence of tinnitus.[12] This effect might be explained by the possibility that stimulation of DCN compensates the loss of peripheral input caused by e.g. noise damage and thereby restores the disturbed balance between excitatory and inhibitory processes. Also, hyperactivity in the DCN might be modulated by direct stimulation of the neuronal circuit and interrupt pathways of hyperactivity to higher regions, such as the inferior colliculus, or it may induce a masking effect.[12] Several clinical studies have also shown a positive effect of ABI implantation on tinnitus. Soussi et al. published a study with patients who were implanted with an ABI for the indication of hearing loss. Seven out of ten patients with tinnitus before the implantation reported a decrease in their tinnitus loudness during stimulation with the ABI.[13] This finding was confirmed in several other clinical studies, showing a reduction of tinnitus in patients who suffered from tinnitus before ABI implantation after removal of vestibular schwannoma.[14-16]

Together, the preclinical and clinical studies suggest that electrical stimulation of the cochlear nucleus with the ABI may be an effective method to suppress tinnitus. The potential advantage of the ABI over a CI is that it can be implanted without causing hearing damage. Therefore, we designed a pilot study. The objective of this study is to study the effect of the ABI on the suppression of unilateral, incapacitating and intractable tinnitus. We hypothesize that stimulation of the cochlear nucleus by the ABI can reduce tinnitus and, thereby, decrease the tinnitus burden and enhance the quality of life.

Methods & Analysis

Study design

This is a single-center, nonrandomized, interventional pilot study. The goal is to include 10 patients. There is no control group. The study site is a tertiary academic hospital (University Medical Center Groningen, The Netherlands).

Inclusion criteria

Adults with unilateral, incapacitating tinnitus that is refractory to conventional treatment methods, are included in this study. Lateralization (either left or right ear) and the assessment of tinnitus as unilateral was based on patients perception. The patients must have tinnitus for more than one year, with a stable situation over the last year. For the ipsilateral ear, the pure tone audiometry (PTA) thresholds averaged between 1, 2 and 4 kHz must be between 40 and 90dB. The contralateral ear should have functional hearing ability with PTA thresholds of <35dB (average between 1, 2 and 4kHz), with a minimum of 25dB (average between 1, 2 and 4kHz) difference compared to the tinnitus (ipsilateral) ear.

Exclusion criteria

Patients with a detectable cause for tinnitus that requires causal therapy, e.g. vestibular schwannoma or glomus tumor, are excluded from this study. Also, patients with psychiatric pathology or an unstable psychological situation as declared by a psychiatrist, are excluded. Patients with a life expectancy <5 years, a history of blood coagulation pathology, an ASA (American Society of Anesthesiologists) score >2, as well as pregnant women, are also excluded from participation. Additionally, anatomic abnormalities that prohibit appropriate placement of the implant, or a history of intolerance to materials used in the implant, are exclusion criteria. An overview of inclusion and exclusion criteria is presented in Table 1.

Table 1. Inclusion and exclusion criteria

Inclusion Criteria
Unilateral tinnitus
Severely incapacitating tinnitus
Men or women, Age >18 years
Tinnitus that is present >1 year and was stable during the last year
Tinnitus that is not responsive to indicated conventional existing treatments (hearing aids and cognitive behavioral therapy). If a psychologist has indicated cognitive behavioral therapy, the patient should have tried this therapy for long enough to reasonably argue that these treatments were not successful. The same applies to the use of hearing aids
Ipsilateral ear: pure tone audiometry thresholds >40dB and <90dB (mean over 1-2-4 kHz)
Functional hearing in the contralateral ear with pure tone audiometry thresholds <35dB (mean over 1-2-4 kHz) and with a minimum Δ25dB compared to the ipsilateral ear.
Informed consent after extensive oral and written information about the surgery, complications and uncertain effect of the Auditory Brainstem Implant on tinnitus
Exclusion Criteria
Detectable cause for tinnitus that requires causal therapy (e.g. vestibular schwannoma, glomus tumor, otosclerosis, arteriovenous malformation) as investigated by radiological and otologic examination
Psychiatric pathology and/or an unstable psychological situation as declared by a psychiatrist
Unrealistic expectations as declared by the investigator and/or psychiatrist
Life expectancy <5 years
History of blood coagulation pathology
ASA >II
Pregnancy
Anatomic abnormalities that would prevent appropriate placement of the stimulator housing in the bone of the skull
Anatomical abnormalities or surgical complications that might prevent placement of the Auditory Brainstem Implant Active Electrode Array
Known intolerance to the materials used in the implant (medical grade silicone, platinum, iridium and parylene C)

ASA: American Society of Anesthesiologists[26]

Study device

The device used in this study is the Mi1200 SYNCHRONY Auditory Brainstem Implant, manufactured and supplied by MED-EL® (Innsbruck, Austria). The ABI is an implantable, electrically active device that consists of a stimulator, a coil with a removable magnet in its center and an active electrode array that is permanently attached to the stimulator (Figure 1). The electrode array stimulates the cochlear nucleus using 12 independent surface electrodes (Figure 2). The stimuli are controlled by an external processor that uses stimulation strategies similar to CI.

Figure 1. *The auditory brainstem implant consists over several components (from left to right): the speech processor (consisting of transducer, microphone and connecting cable) which is the external and visible part of the implant; the receiver-stimulator with electrode (implantable component); and close-up of the electrode paddle. Reproduced with permission of Med-EL*

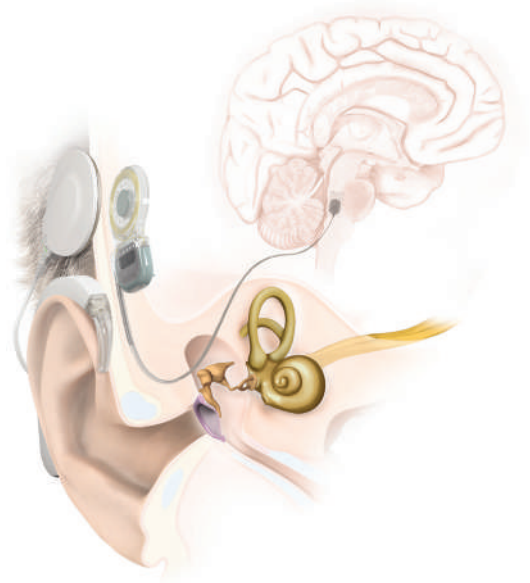

Figure 2. *Overview of the position of the implant and placement of the electrode on the cochlear nucleus on the brainstem. Reproduced with permission of Med-EL*

The intended use of the ABI device is for the electrical stimulation of the cochlear nucleus via an implanted stimulator and a specially designed electrode array to evoke auditory sensations in patients with non-functional cochlear nerves. In this study, the ABI will be primarily investigated for its ability to reduce tinnitus in patients having moderate to severe hearing loss despite having a functional cochlear nerve. This is regarded as an off-label use of the ABI, although the surgical method of implantation, the equipment and stimulation strategies are the same as for regular indications.

Recruitment

Potentially eligible patients are recruited from our outpatient clinic, as well as from our tinnitus database, collected during several years of clinical practice in tertiary tinnitus care. Furthermore, advertisements were placed in magazines and on websites of patients' associations and on the research website of the University Medical Center Groningen. Awareness of this study was created by presenting this study protocol at various scientific meetings.

Patient and public involvement

A plan for organization of the recruitment of eligible patients was made in consultation and collaboration with a national patients' association. Patients were not involved in the development of the research question or in the design of the study. Patient materials, such as information about the study, was screened by the Institutional Review Board (IRB) for understandable not-medical language and approved. Results of this study will be disseminated to study participants and patients via a personal newsletter and via the patients' association website.

Study description

Preoperative phase

After extensive information on the nature, possible risks and benefits of this study, informed consent is obtained by the study coordinator from eligible patients (for informed consent form, see supplementary file). When informed consent is obtained, a diagnostic work-up is performed. This includes otologic examination, cranial MRI, psychiatric assessment, audiometric and vestibular tests, tinnitus analysis, preoperative assessment by an anaesthesiologist, tinnitus- and quality of life-related questionnaires and a pregnancy test (if applicable). Whenever an exclusion criterion arises during this diagnostic work-up, the patient will be excluded. Otherwise, surgery is scheduled.

Implantation

Participants are admitted to the neurosurgical ward of the University Medical Center Groningen for ABI implantation by a trained neurosurgeon. The neurosurgeons are experienced in cerebellopontine angle surgery and were specifically trained for ABI placement. The implant is subperiostally fixated on the parietal skull. Access to the cochlear nucleus is made via retrosigmoid craniotomy. The electrode array is inserted in the lateral recess of the fourth ventricle in the direct vicinity of the cochlear nucleus. The most optimal position of the electrode is determined

using a probing electrode with four contact points, applying bipolar stimulation in transverse, longitudinal and oblique directions while recording evoked auditory brainstem responses. After determining the best stimulation site, the active and definitive electrode is placed. With the definite electrode in position, all electrodes are checked for optimal responses. The estimated duration of hospitalization is 4 to 6 days.

Postoperative phase

Shortly postoperative, a CT-scan is made to determine the position of the electrode and to screen for intracranial complications. The ABI will be switched on at 6 weeks postoperatively. This happens under monitoring of vital functions, as cranial nerves, such as the vagal nerve, may be stimulated unintentionally. The switch on is performed by a trained medical physicist, using MED-EL software (Maestro 7.0) and hardware (MAX interface). At this stage, patients receive the external audio processor. At first, the fitting and settings of the ABI will be aimed at optimizing hearing performance, since this approach had given favourable results on tinnitus in earlier implant surgeries for deafness.[13] Later in the process, other stimulation strategies might be attempted. In the fitting procedure, pitch scaling and consecutive pitch ranking is performed. Electrodes are switched off if they give unwanted side effects during stimulation, e.g. facial twitching or dizziness. If electrode stimulation is without complications, further adjustments and fittings can safely take place at the outpatient clinic. Several repetitive fitting sessions will be necessary to find an individual optimal stimulation strategy. In order to get the patient acquainted with the ABI and to improve their hearing ability, each fitting session is combined with training by a specialized speech therapist.

Outcome measures

Primary outcome measures

The primary outcome measure of this study is the change in the score of the Tinnitus Functional Index (TFI) questionnaire. We compare the preoperative (baseline) TFI-score to postoperative TFI-scores at several time points (see Figure 3), with the primary end point set at one year after initial stimulation with the ABI. The TFI consists of 25-items and scores range from 0 (no tinnitus complaints) to 100. The validated Dutch TFI-version is used to detect changes in tinnitus outcome after the intervention and its psychometric properties are in line with the original version.[17] For the Dutch version, no minimal clinical important difference (MCID) was calculated. The MCID in the US version is determined at a 13 point reduction[18], however the smallest detectable change in TFI is still debated.[19]

Secondary outcome measures:

Audiometric function

- *When:* preoperatively (baseline) and several time points postoperatively. Audiometric function is determined with the ABI switch on and switched off.
- *Measure:* determining PTA thresholds and speech audiometry, performed according to guidelines from the Nederlandse Vereniging van Audiologie (Dutch Association of Audiology, www.audiologieboek.nl).
- *Important change scores:* a change of more than 5dB is considered as clinically relevant (±5 dB is considered measurement error).

Vestibular function

- *When:* preoperatively (baseline) and at 3 months postoperatively.
- *Measure:* videonystagmography, rotation tests and calorisation tests of both labyrinths performed according to local hospital protocol.
- *Important change scores:* clinical relevant changes in vestibular function, i.e. newly arisen asymmetrical function during calorisation.

Tinnitus burden

- *When:* preoperatively (baseline) and several time points postoperatively.
- *Measures:*
  - Hospital Anxiety and Depression scale (HADS)20: scores for anxiety/depression range from 0 to a maximum of 21, with a score >8 indicating a possible anxiety/depression.
  - Tinnitus Handicap Inventory (THI): scores range from 0 (no tinnitus complaints) to 100 (catastrophic complaints).
  - Visual analogue scale (VAS) for tinnitus loudness and tinnitus annoyance: patients are instructed to draw a vertical line on a 10cm horizontal scale as to how they would rate their tinnitus loudness and annoyance. With 0 being not loud/not annoyed by tinnitus and 100 most thinkable loud/ annoyed by tinnitus.
- *Important change scores:*
  - HADS: not calculated for the Dutch version.
  - THI: 6-7 points21, although not calculated for the Dutch version.
  - VAS: between 10 and 15 points22.

Tinnitus analysis

- *When:* preoperatively (baseline) and several time points postoperatively.
- Measure: by tone matching at the contralateral ear (in intensity and frequency), according to guidelines from the Nederlandse Vereniging van Audiologie (Dutch Association of Audiology, www.audiologieboek.nl). ABI-related outcomes
  When: several time points after ABI is implanted and switched on.

- *Measure:*
  - Number of electrodes evoking auditory sensation (out of a total of 12 electrodes).
  - Pitch matching: frequency matching per electrode using a tone stimulus on the contralateral ear, based on the method for pitch mapping in single sided deafness with unilateral cochlear implants23.
  - Tonotopic organisation: tonotopical electrode ordering according to subjective tonal perception, this is performed using the Bubblesort procedure.
  - Hours of usage, based on data logging and patient interview. o
  - Preferred program (in percentage, out of 4 programs).

Safety

- *When:* during the complete course of the study
- *Measure:* safety in terms of (serious) adverse events, (serious) adverse device effect.

Follow-up

Follow-up will take place at three and 6 months after switching on the ABI. The endpoint of this study is set at 12 months. Follow-up will, however, continue yearly, up to 5 years after initial stimulation. An overview of the assessments and their timeline is provided in Figure 3.

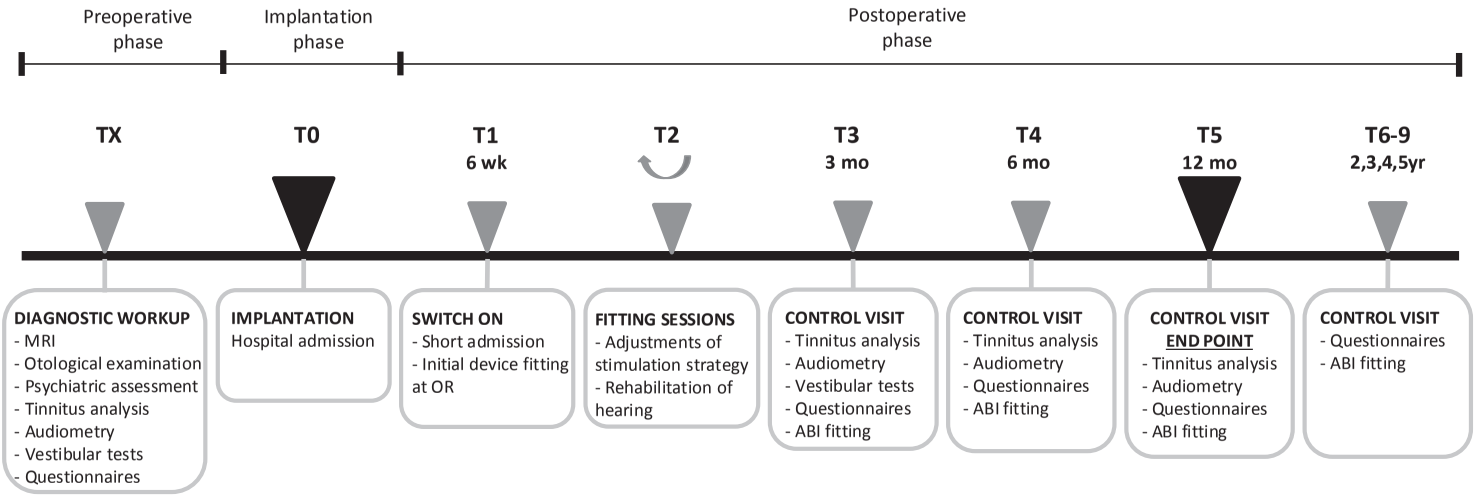

Figure 3. Study timeline

ABI: auditory brainstem implant; OR: operating room; mo: months; MRI: magnetic resonance imaging; T: time point, wk: weeks; yr: years

Data analysis & Statistical Analysis

All collected data are entered into predesigned electronic case report forms (eCRF) in an Open Clinica® database (www.openclinica.com) by a trained investigator. Data in this database are anonimyzed and contains range checks. Stored data in this database are anonymized and password-protected. The database is only accessible by the study coordinator and assigned investigators. All changes made in the database are logged. Hard-copy data will be stored in a locked cabinet. The handling of personal data will comply with the Dutch Personal Data Protection Act. The final dataset will be available to the authors only.

Statistical analysis

The analysis of data is mainly descriptive. Mean and standard deviations are calculated in case of normally distributed data and median and interquartile range in case of skewed- distributed data. Differences in the primary outcome measure (i.e. TFI) as well as the secondary outcome measures (i.e. VAS, THI, HADS) are checked for significance using a paired t-test (if data are normally distributed), although the outcome will be interpreted with caution, since no power calculation was instituted. SPSS (IBM, newest available version) will be used. A p-value <0.05 is regarded as statistically significant. If needed, analysis will be adjusted for multiple comparisons.

Sample size

This is a pilot study. Due to the experimental nature of the study, no power analysis was performed. It was empirically decided to select a cohort of 10 patients for this study.

Ethics & Dissemination

Ethics

Tinnitus can be very incapacitating, with a large impact on quality of life. Previous reports have shown that the ABI is a promising method to reduce tinnitus in these patients. Although the major complication rate is low when performed by experienced surgeons24, potential complications can be severe. This study imposes a significant risk on the study participants; it is, however, likely that the potential to ameliorate severely debilitating tinnitus outweighs these risks. The study is approved by the IRB of the University Medical Center Groningen and by the Dutch Health Care Inspectorate. It is performed according to the quality standards of Good Clinical Practice. Participation in the study is completely voluntary. Patients can withdraw at any time, without giving any reason. It is stressed that withdrawal does not affect standard clinical care. Written informed consent is obtained from all participants and they are informed when new information arises that may affect their willingness to participate.

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO (Wet Medisch-wetenschappelijk Onderzoek met mensen, i.e. Dutch Act for Medical Research

Involving Human Subjects) . 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 subjects through injury or death caused by the study.

Study monitoring

This study is monitored by a certified monitor from the Trial Coordination Center, which is independent from the sponsor. Study monitoring includes for example: checking in- and exclusion criteria for included patients, sample-wise data checking, correctness of data handling, storage, correctness and completeness of documentation in trial master file, etc. Monitoring will take place after every 2-3 included patients and after that, once a year for another 4 years.

Safety considerations

We do not expect a deterioration of hearing due to the implantation. However, because this aspect has not yet been studied, it was decided as a first step to include patients with severe ipsilateral hearing loss (i.e. 40 till 90dB mean over 1, 2, and 4kHz in PTA). In this patient group, a small loss of hearing sensitivity would not affect daily functioning. Yet, by excluding patients with profound hearing loss (>90 dB), our study would still be able to quantify unforeseen negative effects on hearing loss. Also, these patients might be eligible for a cochlear implant.

Possible complications are mostly related to the ABI surgery. In a study describing such complications, 78 non-tumor patients were analyzed.[25] These patients were not diagnosed with NF2, and therefore are comparable to our patient group. Major complications (meningitis, hydrocephalus, cerebellar contusion) occurred in 6.4% of cases. No mortality was observed. Minor complications (e.g. cerebrospinal fluid leakage, transient hydrocephalus, wound seroma) occurred in 18%. In 30% of the patients, non-auditory side effects occurred as a result of electrical stimulation. These side effects diminished over time and could be modulated by changing the stimulation settings.[25] It was concluded that ABI implantation is a safe procedure with a low major complication rate when performed by experienced surgeons.[25] Inclusion in the study and ABI-implantation are performed consecutively, allowing adequate monitoring of any unforeseen critical event related to the surgery or to the stimulation with the ABI. Stopping rules are predefined and are described later on in this protocol.

Patients are intensely monitored during the first year following implantation. Patients receive a remote control to switch between 4 preset stimulation programs. All of these actions are logged, as well as hours of usage of the implant. Nonauditory side-effects and disappointing results on hearing and/or tinnitus will be managed by altering stimulation strategy or, if necessary, by turning off the device. All Adverse Events (AE) will be assessed and recorded at each clinical visit. AEs are followed-up until they have abated, or until a stable situation has been reached. In case of a Serious Adverse Event (SAE) or Unanticipated Serious Adverse Device Effect (USADE), this will be reported to the IRB 15 days (SAE) or 7 days (USADE) after the first knowledge of the event. Also, a report will be made to the Dutch Health and Youth care Inspectorate.

Stopping rules
A Data Safety Monitoring Board is not required, due to the small-scale nature of this pilot study and consecutive patient inclusion. Instead, the following 'stopping rules' were predefined:

- If >1 major complication occurs in the implanted study population (i.e. meningitis, transient hydrocephalus, symptomatic cerebellar contusion).
- If in >2 cases unacceptable worsening of tinnitus is experienced and it is decided to permanently switch off the ABI.

In case one of the stopping rules occurs, the study will be suspended and the risk/benefit balance would be reassessed in accordance with the IRB and/or Dutch Health and Youth care Inspectorate, before considering pursuing the study.

Dissemination and data sharing statement
The final manuscript will be written by the authors as named above. The results of this study will be published in peer-reviewed journals. Also, findings will be presented at national and international conferences for widespread dissemination of the results. When the trial is finished, data will be available upon request.

Author Contribution

PD, RF, JD, AM and MB conceived and designed the study and participated in logistical planning of the study. MB and AM are responsible for data acquisition. JD, JM and RF perform surgical implantation of the auditory brainstem implants and AM takes care of the perioperative and postoperative fitting sessions. All authors made significant contributions to the development and conceptualization of the protocol. MB wrote the manuscript with input from all co-authors. All co-authors reviewed the draft versions of this paper and have read and approved the final manuscript.

Funding statement

This study is investigator-initiated. Funding is provided by Med-EL elektromedizinische Geräte GmbH. All study materials used in this study, i.e. implants, software, hardware, monitoring devices, are supplied by Med-EL.

Competing interest statement

Competing interest is not declared.

Disclaimer

Med-el has had an advisory role in designing the study. The funding party has no role in the study design and conduct; the collection, management, analysis and interpretation of the data; or the preparation and final approval of the manuscript(s). The final manuscript(s) will be send to Med-el prior to publication for notification.

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7

Auditory brainstem implantation for the treatment of incapacitating tinnitus - preliminary results

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Introduction & Methods

Introduction and Methods of this study are described in detail in Chapter 6. In brief, for many patients suffering severe tinnitus, a satisfactory treatment is lacking. The auditory brainstem implant (ABI) is a hearing implant that is originally indicated for the restoration of hearing in patients with non-functional cochlear nerves, e.g. neurofibromatosis type II (NF2). Similar to a cochlear implant (CI), it has been demonstrated that an ABI may reduce tinnitus as a beneficial side effect. In terms of tinnitus treatment, an ABI may have an advantage over a CI, as cochlear implantation can harm inner ear structures due to its invasiveness into the cochlea, while an ABI is presumed not to damage anatomical structures.

The aim of this study is to investigate the effect of auditory brainstem implantation on intractable tinnitus. For this pilot study, the goal is to implant an ABI in 10 patients with unilateral incapacitating tinnitus with ipsilateral moderate to severe sensorineural hearing loss. The ABI is switched on six weeks after implantation, followed by several fitting sessions aimed at finding an optimal stimulation strategy based on preference of the patient.

The primary outcome of this study is the change in the Tinnitus Functioning Index (TFI) questionnaire. Secondary outcomes are: safety; signs of anxiety and depression (Hospital Anxiety and Depression Scales [HADS]); other tinnitus related questionnaires such as the Tinnitus Handicap Inventory (THI) and visual analogue scales (VAS); and audiometric and vestibular function. The end point of the study is set at one year after implantation, follow-up will continue up till five years postoperatively.

Results

Patient characteristics

Patient recruitment started in July 2016, after approval of the local Institutional Review Board was obtained. Eligible patients were recruited from: a patients database; advertisements on a patients platform (www.stichtinghoormij.nl); advertisements on the website of the University Medical Center Groningen; via referrals from colleagues (otorhinolaryngologists and audiologists) throughout the Netherlands; and via www.clinicaltrials.gov. From July 2016 to November 2019, four patients signed informed consent. One patient was excluded from the study after psychiatric screening during the diagnostic work-up.

Up till November 2019, three patients were included and two patients have been implanted with an ABI. The third implantation is scheduled for the near future. Characteristics of the first two included patients are demonstrated in Table 1.

Table 1. Baseline characteristics of included patients

	Age (yr)*/ Gender	Tinnitus side	Cause of tinnitus/ hearing loss	Duration of tinnitus*	Preoperative PTA		Side of implant-ation
					Ipsi-lateral	Contra-lateral	
Case 1	54/F	Right	Possibly Menière's disease	5 years	75dB	25dB	Right
Case 2	75/M	Left	Unknown	25 years	83dB	23dB	Left

** At inclusion. F: female, M: male, mean PTA: pure tone audiometry over 1-2-4 kHz*

Surgery

Both patients were implanted with an ABI (Mi 1200 Synchrony, Med-el®). Via a retrosigmoidal craniotomy, access to the cerebellopontine angle was created (Figure 1A). The lateral recess was identified. In both patients, the placing electrode was able to identify an optimal position for the permanent electrode. No complications occurred intraoperatively. Postoperative hospitalization was 6 and 5 days in the first and second patient, respectively. A CT-scan was made postoperatively to verify the correct position of the ABI electrode patch (Figure 1B). After surgery, both patients experienced vertigo and instability for several weeks, which is an expected postoperative course given the type of surgery with manipulation of the cerebellum and cochleovestibular nucleus. No postoperative complications occurred.

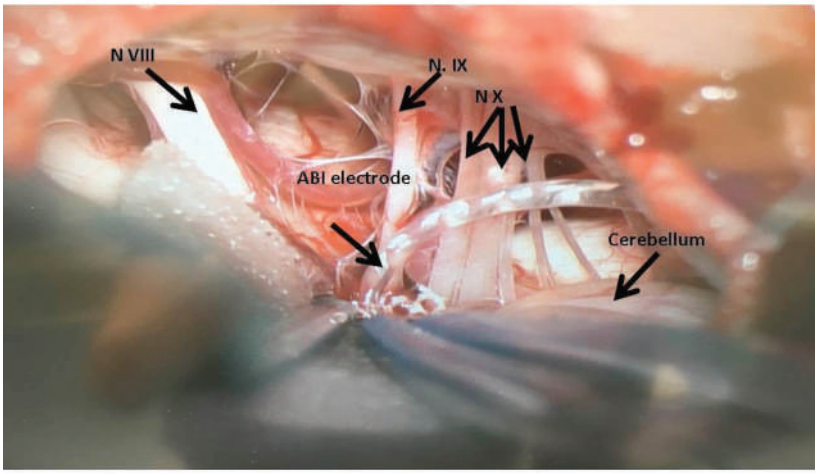


Figure 1A. *Intraoperative view of the cerebellopontine angle (view from posteriolateral on the pons, the cranium is on the left side) with (from left to right): cochleovestibular nerve (n.VIII); ABI electrode; accessory nerve (n.IX); vagal nerve (n.X); and cerebellum*

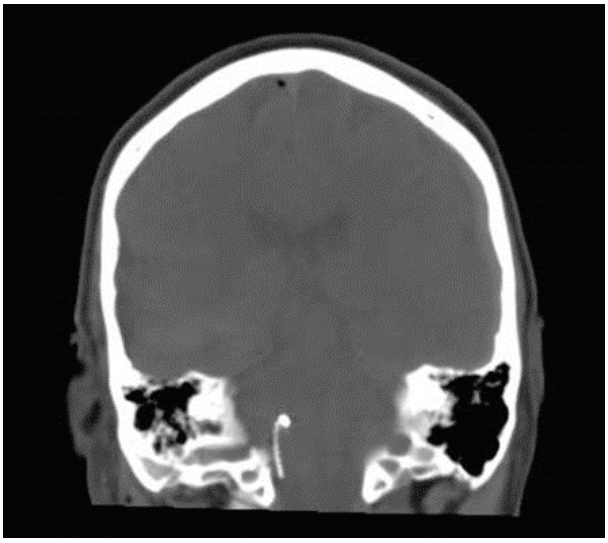


Figure 1B. *Postoperative CT-scan of Case 1 with coronal view of the cranium, showing the position of the ABI electrode on the brainstem*

Activation and rehabilitation

- ABI activation

In both patients, activation of the implant took place at a controlled setting in the presence of an anesthesiologist while monitoring vital functions. Activation of the implant was uneventful in both patients. In Case 1, one electrode evoked vertigo and one electrode did not evoke auditory sensations. Both electrodes were deactivated. All other electrodes evoked auditory sensations and maximum comfortable loudness (MCL) levels per electrode were established. In Case 2, four of 12 electrodes were deactivated because stimulation-initiated complaints of vertigo and nystagmus. All other electrodes were activated and MCL levels were established.

- Fitting and rehabilitation strategy

After activation of the implant, both patients had ABI-rehabilitation with regular follow-up visits. During these visits, the patients consulted our audiologist who performed the ABI fitting according to the steps described below in Table 2. Also, however less frequent, patients visited a speech therapist for training of hearing rehabilitation with the ABI after Stage 1 was completed.

Table 2. Stepwise approach of ABI fitting

Stage 0	Determining subjective tonotopic organization (using the Bubblesort-procedure[1]).
Stage 1	Starting with functional settings, i.e. settings aimed at speech understanding (intended use of the ABI).
Stage 2	Adding a program with low stimulus rate and low current rate (around threshold stimulation, not functional for speech understanding).
Stage 3	Adding a 'night program' with continuous, sub threshold stimulation.
Stage 4	Follow-up and optimization of preferred programs/settings. Re-evaluating tonotopic organization, combined with frequency matching

In the first year after activating the implant, Case 1 visited the audiologist 14 times for evaluation and adjustments of ABI-settings and hearing rehabilitation with a speech therapist (2 sessions). Case 2 has visited the audiologist 10 times following activation of the implant and 3 sessions of hearing rehabilitation.

Tinnitus outcomes

- Tinnitus and quality of life questionnaires

The baseline score of TFI was 66 points (Case 1) and 57 points (Case 2). The baseline TFI measurement was repeated two weeks after the first measurement to verify a stable and reliable baseline for the primary outcome, which was the case in both patients. A reduction of TFI-score (i.e. an improvement in tinnitus) was seen in both patients after three months, six months and one year after activation of the implant: postoperative TFI-scores for these time points were respectively 49, 48, 49 points in Case 1 and 29, 41, 41 in Case 2. One year postoperatively, the TFI was reduced with 17 points (Case 1) and 16 points (Case 2). These and other outcome measures are present in Figure 2. The other tinnitus-related questionnaires such as the THI and VAS tinnitus loudness also showed a stable reduction after surgery. Only the VAS tinnitus annoyance (VAS-TA) remained unchanged in Case 2. In Case 1, HADS- depression score was reduced from 11 (i.e. indication for depression) to a stable 5 (i.e. no indication for depression). The HADS-anxiety score remained stable after baseline. In Case 2, HADS depression was unchanged after 1 year (6 points, i.e. no indication for depression) and there was a slightly reduced HADS anxiety score.

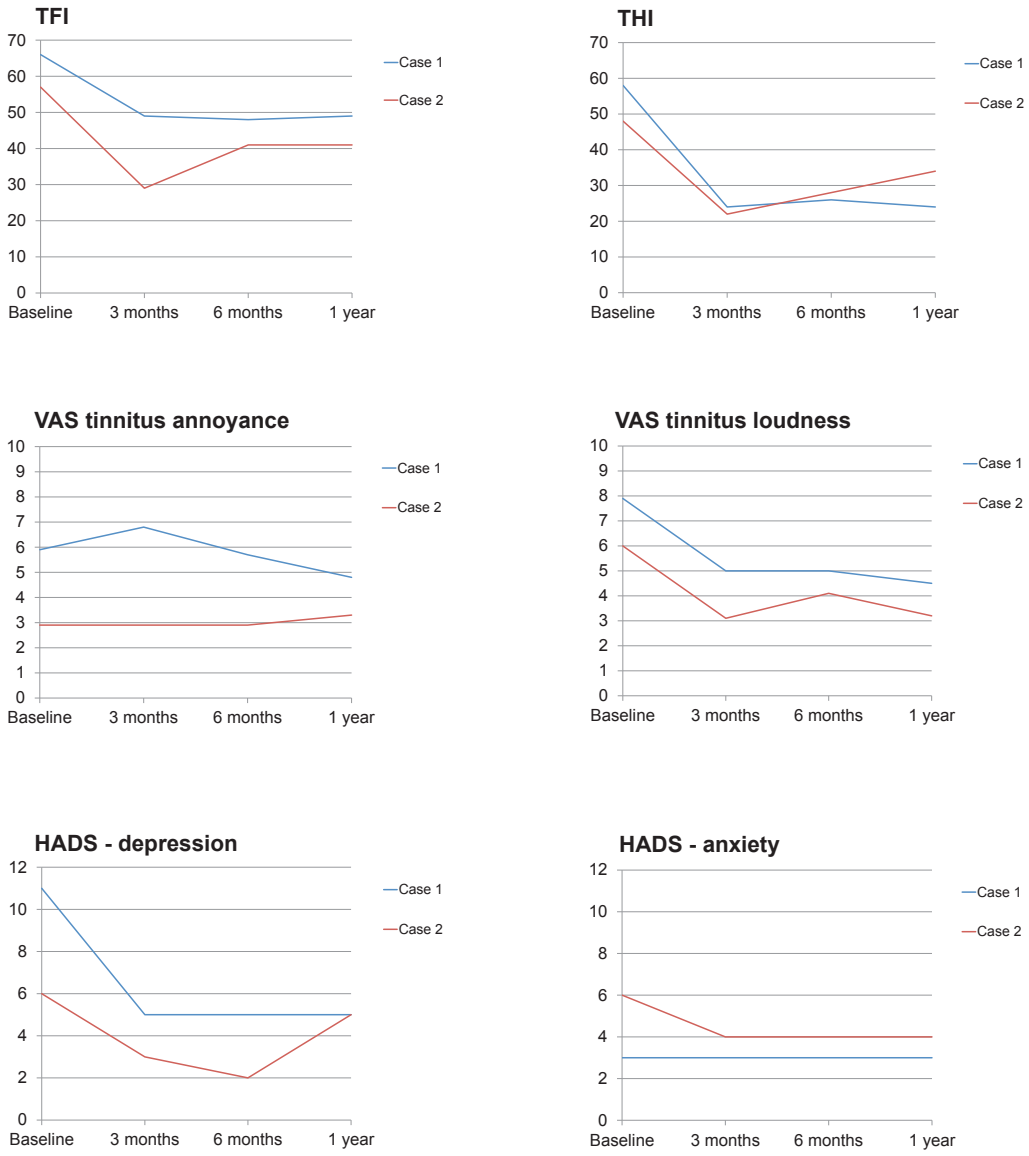


Figure 2. *Outcomes of tinnitus related questionnaires (TFI, THI, VAS) and HADS*

HADS: Hospital Anxiety Depression Scale; THI: Tinnitus Handicap Inventory; TFI: Tinnitus

- Relation to activation strategy and tinnitus

Details of ABI settings at one year after ABI activation are summarized in Table 3. After multiple adjustments, Case 1 preferred a program with a current rate of 291 pps/channel. This is a relatively low current rate. Stimulation is around the auditory threshold, but is independent of environmental speech sounds. Programs aimed at speech perception resulted in an increase of her tinnitus. In fact, she was preoperatively also known with hyperacusis and worsening of tinnitus in relation to loud sounds. The patient uses the implant every day, during most of the day (7 hours on average). The ranges (shown here are ranges over all the activated electrodes, in the most preferred program) of the minimum electrical level the patient can perceive (THR) and maximum level the patient can tolerate (MCL), are listed in Table 3 as well.

Table 3. *Details of ABI settings at 1 year follow-up*

	Average usage (h/day)	Amount of ABI 'switch on/off' (n/day)	Programs (n)	Current rate/ channel*	THR (qu) [range over electrodes]*	MCL (qu) [range over electrodes]*
Case 1	7	1	2	291 pps	[8.29-51.99]	[13.88-74.29]
Case 2	17	4	4	769 pps	[7.71-31.91]	[18.12-49.49]

** of the most preferred program*

h: hours; n: number; MCL: maximum comfortable loudness; pps: pulses per second; THR: threshold level; qu: charge unit

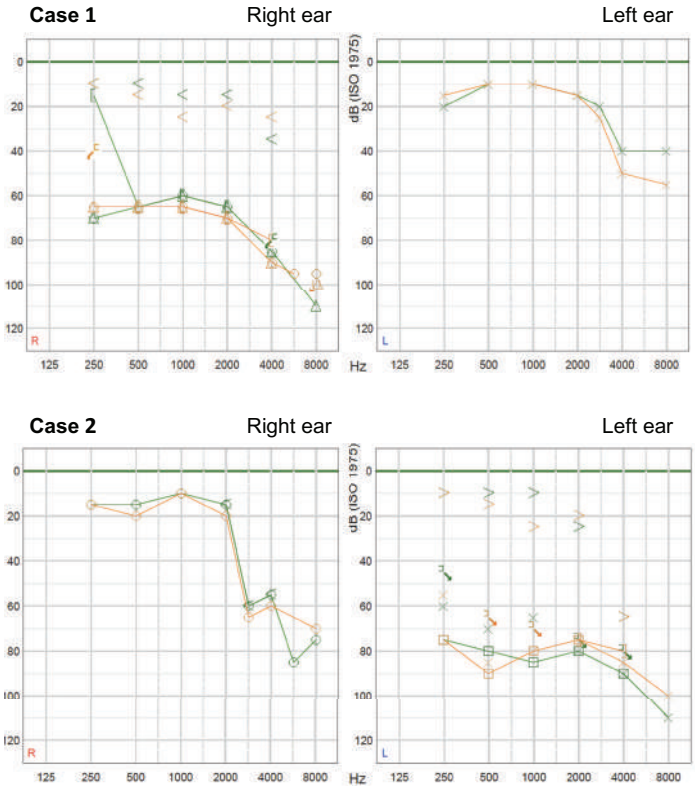
Case 2 describes that regarding his tinnitus, he has more 'good days' than before the ABI activation. His tinnitus remains fluctuating in loudness and in amount of annoyance in relation to stress and tiredness. He uses 4 programs variably: a program with a current rate of 769 pps/channel (stimulation around threshold, independent of environmental speech sounds); a 'night program' with a continuous, sub threshold stimulation and two programs that were fitted for speech perception. The patient uses the latter programs in situations where he benefits from better hearing, such as in meetings or during group conversations, however he describes that the use of both these programs makes his tinnitus temporarily louder.

Other outcomes

- Audiometry

Postoperative pure tone audiometry (PTA) in the implanted ear remained unchanged in both patients (Figure 3) up till one year after activation of the implant, indicating that the surgery with insertion of the electrode did not damage auditory sensitivity.

Figure 3. Pure tone audiometry thresholds at baseline (orange) and 1 year after activation of the ABI (green). In Case 1, ABI was implanted in the right ear, in Case 2 in the left ear



- Binaural speech comprehension

Case 1 did not benefit from the ABI in terms of hearing. When the patient used programs fitted for speech understanding, she reported an increase in her tinnitus. As hearing rehabilitation was not the primary goal of this study, further rehabilitation specific for hearing purposes was not pursued.

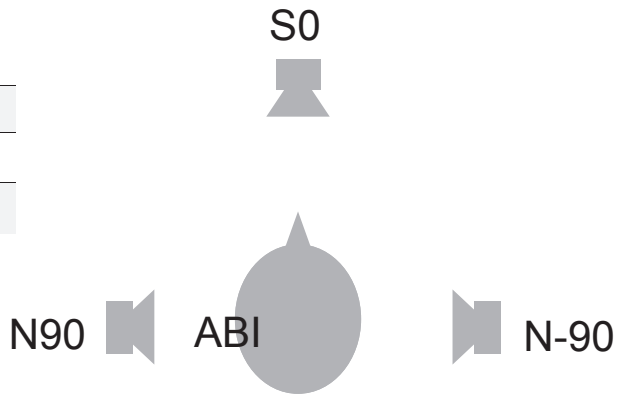
Case 2 was fitted with a program especially for speech understanding, which he uses occasionally when needed. The patient benefits from the ABI in bilateral speech understanding. When measuring phoneme scores at 70dB in the free field, with speech noise (70dB) presented on the side of the good hearing ear, speech understanding on the ABI ear increased from 45% (ABI off) to 63% (ABI on), see Table 4. Free field speech understanding with ABI (phoneme score at 65-75dB) was 20-40%. The patient reports a subjective improvement of speech understanding with the ABI switched on with an improvement of sound localization and therefore experiences a lower listening effort. However, he also reports that the fittings for speech perception are on the verge of being uncomfortable in terms of non-auditory sensations and tinnitus.

Table 4. Free field speech understanding in Case 2 with ABI on and ABI off

Case 2

Phoneme scores at 70 dB SPL, SNR= O dB

	SO	SON90	SON-90
ABI off	100%	72%	45%
ABI on	-	82%	63%



- Vestibular testing

Data from vestibular testing at baseline and three months after ABI activation is listed in Table 5. In Case 1, a new spontaneous nystagmus (1,5 °/s to the right) was found postoperatively. In our test set-up, spontaneous is not considered clinically relevant when >3 °/s. In caloric testing, preoperative and postoperative measurement of vestibular function was unchanged. Normal excitability is defined a.SPV (maximal amplitude of slow phage velocity) >10 °/s during warm stimulation and >7 °/s cold stimulation. Visual suppression was moderate at baseline and was unchanged postoperatively. Visual suppression normal when <50% and reduced when >50%. Testing visual suppression during calorisation yields four outcomes, moderate visual suppression is defined as when four outcomes are both above and beyond 50%.

Table 5. *Outcomes of vestibular testing*

		Baseline	3 months after ABI-activation
Case 1	Spontaneous nystagmus	No spontaneous nystagmus	Spontaneous nystagmus to the right side (ca. 1,5 °/s)
	Calorisation	Symmetrical (unilateral weakness: 7% left side) Normal excitability (a.SPV 126 °/s)	Symmetrical (unilateral weakness: 10% left side) Normal excitability (a.SPV 149 °/s)
	Visual suppression	Moderate visual suppression during fixation (80%, 43%, 48%, 27%)	Moderate visual suppression during fixation (53, 78, 54, 34%)
	Optokinetic nystagmus	Normal horizontal optokinetic nystagmus	Missing data
Case 2	Spontaneous nystagmus	No spontaneous nystagmus	Spontaneous nystagmus to the left (ca. 1,5 °/s)
	Calorisation	Symmetrical (unilateral weakness: 2% left side) Normal excitability (a.SPV 82 °/s)	Symmetrical (unilateral weakness: 4% left side) Normal excitability (a.SPV 62 °/s)
	Visual suppression	Moderate visual suppression during fixation (43, 52, 56, 39%)	Moderate visual suppression during fixation (67,45, 51, 88%)
	Optokinetic nystagmus	Good and symmetric horizontal optokinetic nystagmus (ca. 39 °/s to the left and ca. 42 °/s to the right in case of stimulation with a 50 °/s moving stimulus)	Reduced and asymmetric horizontal optokinetic nystagmus (ca. 12 °/s to the left and ca. 22 °/s to the right in case of stimulation with a 50 °/s moving stimulus)

a.SPV: angular slow phase velocity

In Case 2, also a spontaneous nystagmus (1,5 °/s to the left) was found postoperatively. In caloric testing, there was no change postoperatively compared to baseline. Visual suppression was moderate at baseline and was unchanged postoperatively. A change in optokinetic reflex was found postoperatively (see Table 6): the optokinetic reflex was reduced for both left and right and also asymmetrical (left<right). One year after activation, the patient describes slight instability during movement, for example when riding his bicycle. It is not yet determined if these findings to be expected after retrosigmoidal cerebellopontine angle surgery, for example after manipulation of the cerebellum or (para)flocculus, or have a relation with the ABI placement or activation. Our goal is to gather more data as we expand our patient group and look further into this matter.

- Tonotopy of implant array

Tonotopic electrode ordering (i.e. from low to high frequency) is determined according to subjective tonal perception. Prior to the first stages of ABI-fitting (stage 0), electrode ordering is determined using the Bubblesort procedure.1 During the subsequent ABI-fitting (stage 4), the tonotopic ordering is re-evaluated and combined with pitch-matching to determine the tonotopic organization of the ABI electrode. For this purpose, a tone presented to the contralateral ear (normal hearing ear) is varied in frequency to find the frequency for which the pitch matches that of a single-electrode stimulus via the ABI. This procedure is performed for each ABI electrode to obtain a frequency map of the ABI electrode patch.

The results of the frequency matching per electrode, as obtained 1 year after ABI-activation, are demonstrated in Figure 4. Case 1 repetitively reported the presented electrode ordering as tonotopical in her perception. However, this tonotopical ordering could not be confirmed by frequency matching. Case 2 has a repetitively produced consistent pitch ranking and pitch matching result. Compared to the very first tonotopic ordering, only 2 electrodes (3 and 4) have been interchanged during the subsequent testing in stage 4.

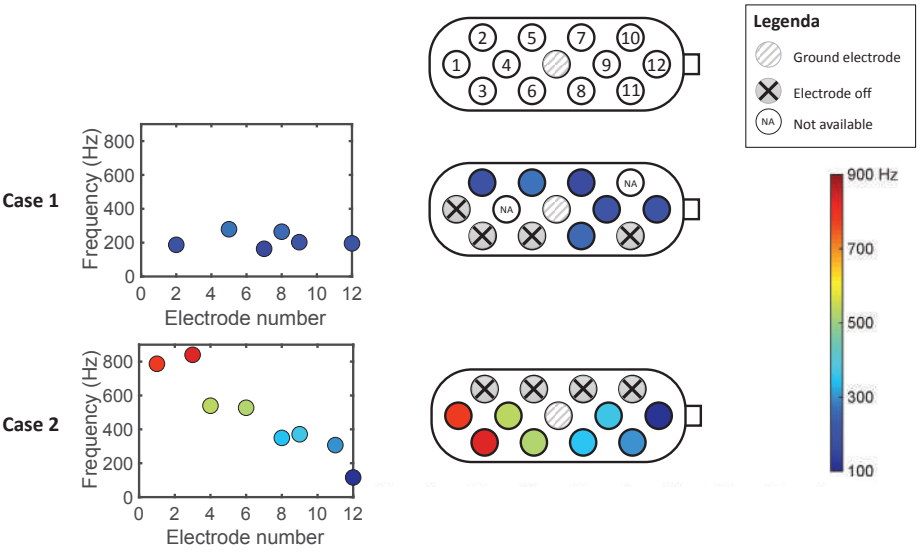


Figure 4. Frequency organization of ABI stimulation. The cochlear nucleus on the implanted side was activated by an electrical stimulus on a single electrode. For each electrode, the frequency of a pitch-matched tone on the contra-lateral ear is shown. Case 1 shows no tonotopic organization. In contrast, there is a clear tonotopic gradient across the ABI electrode in Case 2

NA: not available, patient was not able to pitch match the electrode

Discussion

This study prospectively investigates the effects of an ABI on tinnitus. In this study, patients have partially preserved hearing in the implanted side, therefore the additional aim of this study is to provide more insight in the effect of an implantable hearing device in a relatively good hearing patient. In this chapter, preliminary results of the first two implanted patients are presented and discussed.

ABI & tinnitus

Both patients were successfully implanted with an ABI without major complications. Also, in both patients auditory sensations could be evoked with stimulation of the ABI. A decrease in all tinnitus related questionnaires was observed in both patients, indicating a beneficial effect of the ABI on their tinnitus. One year after activation of the implant, the primary outcome measure TFI was reduced 17 and 16 points (Case 1 and 2, respectively). The THI showed reduction of 34 and 12 points (respectively Case 1 and 2). Statistical analysis does not apply in these two patients, however these results can be interpreted using the minimal important clinical difference (MICD). This is 13 points for the TFI[2,3] and 7 points for the THI.[4] In both patients a reduction was seen that exceeds

these MCIDs, suggesting a clinically relevant effect. This finding is endorsed by the reduction of the VAS tinnitus loudness, a reduction of 3.4 and 2.8 points for Case 1 and 2 respectively. For the VAS-scale in tinnitus patients, MCID is determined to be 1.0-1.5 points.[5]

Interestingly, the VAS tinnitus annoyance has remained roughly unchanged in both patients, although Case 2 reported already a low VAS tinnitus annoyance score (2.9) at baseline. It might be that although the tinnitus loudness is reduced, the tinnitus did not totally subside, leaving the annoyance score at the same level. A shift in the internal reference of the patient might be an explanation for this finding. In other words, a less loud tinnitus can evoke the same annoyance as the previous 'louder' tinnitus. This might also be influenced by psychological factors such as the expectation or hope that the ABI would have led to full disappearance of tinnitus, although we aimed to manage this expectation during the work-up process of the included patients.

In order to compare our findings, we can look at results from the effect of implantation of a CI in patients with single-sided deafness in recent literature. In 2008, Van der Heyning et al. performed a prospectively designed study in which a group of patients with unilateral tinnitus and ipsilateral single-sided deafness was fitted with a CI for the purpose of tinnitus reduction.[6] Long-term evaluation of this cohort showed that all 26 patients reported a subjective benefit from the CI on their tinnitus, as well as significantly reduced VAS loudness scales.[7] A recent systematic review on the effect of CI in tinnitus patients with single-sided deafness showed an overall complete tinnitus suppression in 34.2% of the patients, an improvement of tinnitus in 53.7%, a stable situation in 7.3% and an increase of tinnitus in 4.9% of the tinnitus patients, according to an analysis of the THI questionnaire. Similar results were found by analyzing the VAS-scores, although with a smaller effect.[8] Our preliminary results suggest that we can possibly achieve a similar effect in terms of tinnitus reduction with the ABI as compared to a CI.

In our study, the first two patients both prefer a relatively low current rate for reduction of their tinnitus. When using a program for speech perception, both patients report that their tinnitus becomes louder. This finding is different from the results of the systematic review in single-sided CI patients.[8] Although it is not entirely clear from this study how the CIs were exactly programmed, most studies will have used speech perception settings in their patients. The pathophysiologic mechanisms for tinnitus suppression after CI implantation are not fully understood. As some patients experience direct reduction of tinnitus after activation of the implant, a masking effect is suggested.[9] Also, it is hypothesized that by restoring peripheral input with a CI, reorganization of dysfunctional central auditory pathways is effectuated.[10,11] However, there are also several CI studies that have demonstrated that electrical intracochlear stimulation independent of environmental sounds can also suppress tinnitus both short- and long-term.[12-16] The finding that our first two patients did not prefer a program for speech understanding for optimal reduction of their tinnitus is somewhat surprising, as in the previous studies describing tinnitus reduction in ABI recipients[17-19] the ABI was fitted for enabling speech perception. Possibly, this is related to the presence of acoustic hearing in our subjects, in the ear on the implanted side. For tinnitus reduction, low stimulation rate independent of environmental speech sounds seems to be the most promising stimulation strategy for now.

ABI & hearing

Both patients went through a hearing rehabilitation program after activating the ABI. However, in Case 1, a stimulation program fitted for hearing rehabilitation immediately resulted in a louder tinnitus, possibly because the patient already suffered from hyperacusis at baseline. Also, she did not benefit from better hearing using programs fitted from speech perception. Possibly, this could be related to the tonotopic organization of the implant which, as was shown, only seems to stimulate a small range of low frequencies.

Case 2 also found that the stimulation program fitted for hearing rehabilitation made his tinnitus somewhat louder. Nevertheless, he did experience the beneficial effects of better binaural hearing, indicating that a fusion of the input from the 'normal ear' and the ABI-ear has been made in the auditory pathway.

Recently, more research has been performed in patients with single-sided deafness on the beneficial effect of CI implantation in the profound- hearing loss side. A recent prospective study by Lorens et al. showed clear beneficial effects of the addition of a CI as it enables binaural hearing with positive effect on binaural summation, head shadow and binaural squelch (i.e. signals in competing noise).[20] These findings suggest that the brain is capable of integration of the normal hearing ear with the input from an implanted device. For the ABI, up till now only studies are available on hearing in profoundly deaf patients, mostly NF2 patients. In NF2 patients, speech perception benefits for ABI patients are generally poor when compared to the general population of CI patients[21], although the ABI provides most patients with aid in lip reading as well as awareness of environmental sounds.[22] However, speech perception outcomes appear to be significantly better in non-tumor patients receiving an ABI, such as for indications as head trauma with loss of the cochlear nerves, auditory neuropathy, cochlear malformations or altered cochlear patency.[23] Although with a wide range (average 59%, range 10-100% in open-set speech recognition), non-tumor ABI patients had a significantly better open-set speech performance than NF2 patients (average 10%, range 5 - 31% open-set speech recognition). This shows that if the underlying anatomy is intact, non- tumor patients can receive excellent open-set speech understanding with the ABI.[23] Our study is the first to investigate the effect of the ABI in patients with unilateral partially preserved hearing. Apart from that, our study sample can be best compared to non-tumor patients, as the anatomy of the auditory tract is intact. In the further continuation of our study, more results on open-set speech understanding will be collected and evaluated.

An interesting finding of our study so far is that pre- and postoperative pure tone audiograms on the implanted side (with the ABI off), showed unchanged auditory thresholds. This is in support of our hypothesis that neither implantation nor stimulation with the ABI damages auditory structures. It suggest that an ABI can be used safely in tinnitus patients with residual hearing.

Limitation

The results of these first two patients are promising for the further course of the study, as a stable reduction in all tinnitus related questionnaires was observed, together with rather uneventful surgery in both patients. Firm conclusions, however, cannot be drawn from the data of these two patients only.

Future perspectives

Further inclusion is needed to investigate the effect of the ABI on tinnitus. Finding eligible patients who are motivated for this study is challenging, because of the invasive nature of the study combined with the specific inclusion criteria. Currently, we are actively continuing patient screening.

In the ongoing research, we aim to gain more insight in the effect of the ABI on tinnitus as well as on hearing. Also, we would like to investigate a potential 'placebo-effect' of the ABI, by designing a test setup in which the patients rate their tinnitus on a VAS-scale in the following conditions: (1) with the ABI on; (2) directly after switching the ABI off; (3) after 5 minutes after switching the ABI off; (4) shortly after switching the implant back on. Although a totally blinded test is probably not possible, as patients tend to hear when the ABI is switched on, we can get more insight in the direct effect that the ABI may have on tinnitus. Lastly, the included ABI patients from our study comprise a unique patient group, as they have contralateral good hearing. This enables us to further investigate the tonotopic organization of the cochlear nucleus.

To conclude, results from the first two patients up to one year after ABI implantation show that the ABI has a promising and stable effect on reduction of tinnitus. Implantation and postoperative course were without major complications. Also, auditory sensitivity in the implanted ear remained unchanged in both patients. As the ABI study is ongoing, further valuable data is expected in the near future to validate these preliminary findings.

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8

General discussion and future perspectives

Minke J.C. van den Berge

In the introduction of this thesis the pathophysiology of tinnitus was described. The general consensus is that tinnitus can arise as a result of abnormal neuronal activity in the central auditory pathways, often initiated by cochlear lesions such as hearing loss, noise trauma, or damage by ototoxic drugs. Damage to the cochlear nerve may also lead to tinnitus.

Several conservative and surgical treatment options were discussed in the introduction of this thesis. Tinnitus cannot be cured in most cases, but the majority of patients can be adequately managed with first line treatment options, e.g. counseling, sound therapy with hearing aids or sound generators, and cognitive behavioral therapy. Surgical intervention for tinnitus is becoming increasingly integrated in the list of treatment options. In the present thesis, we aimed to explore the possibilities, feasibility and effect of different (neuro)surgical treatment options for tinnitus at the level of the cochlear nerve and nucleus.

Addressing heterogeneity in tinnitus patients

Tinnitus patients can differ in several dimensions, as proposed by Cederroth et al. First, tinnitus *perception* is variable (e.g. laterality of tinnitus, tinnitus pitch, constant or paroxysmal, pulsatile or non-pulsatile). Second, tinnitus is associated with various *risk factors* (e.g. hearing loss, age) and related *comorbidities* (e.g. hyperacusis, depression, headache). Third, *tinnitus distress* differs largely among patients and lastly, there is a large variation in *treatment responses*.[1] With these large differences in the tinnitus population, we may have to move away from a uniform 'one size fits all' approach to a more personalized treatment depending on the profile of the tinnitus, comorbidities and associated psychological distress. Moreover, subgroups of tinnitus may also explain the many negative treatment effects in several trials, as the results may be biased by the heterogeneity of study groups.

In Chapter 2, we performed a cluster analysis on a large dataset of tinnitus patients (n=1783) with the aim to identify subgroups of tinnitus patients. Two cluster analyses were carried out, one with a variable selection based on a strict methodological approach and one with variable selection based on expert opinion. Both analyses revealed clusters or subgroups of patients that were mostly differentiated by their response on external influences, such as loud sounds. However, both cluster outcomes showed a poor stability, indicating that the tested population comprised a continuum rather than clearly definable subgroups. Cluster analysis is a technique that is very sensitive to the input of variables, hence the selection of variables is critical for the outcome of the analysis. In our dataset, mainly audiometric and questionnaire data were included. As described before, tinnitus comprises several dimensions, leading to a large number of different variables. Other metrics such as structural anatomic data (MRI), functional anatomic data (fMRI), electroencephalography data, genetic components and previous treatment responses should be considered as well, however this would generate even more potential differentiating variables. Although we had a large dataset, clear clustering was not observed in our study, it is possible that subgroups of patients can still by defined by adding these data to a much larger analysis

with multiple variables. First, a standardized, multinational collection of tinnitus-relevant data is a prerequisite for big-data analyses.[2] Addressing tinnitus heterogeneity has recently received special attention as this topic is one of the highlights of a new, EU-funded, European tinnitus collaboration.[1,2] Concluding, in our database study we could not find clear clustering. In our opinion, this does not imply that tinnitus patients form one uniform group. The defining variables need to be further investigated. Tinnitus profiling or subtyping is very important to achieve better understanding of tinnitus and for the selection of the right, personalized treatment.

Surgical interventions and neurostimulation for tinnitus

Microvascular decompression surgery

A neurovascular conflict of the cochleovestibular nerve is reported to be a cause of tinnitus, sometimes in combination with vertigo and/or hearing loss. Consequently, relieving a neurovascular conflict with microvascular decompression (MVD) surgery may be a possible cure for tinnitus. Other well-known neurovascular conflict syndromes are hemifacial spasm and trigeminal neuralgia.[3] For hemifacial spasm and trigeminal neuralgia, MVD surgery is a well-established treatment option with high success rates (91% and 83%, respectively).[4,5] For MVD surgery of the cochleovestibular nerve, well conducted research on the potential treatment success is lacking. In Chapter 3 we performed a systematic review and meta- analysis of individual patient data to investigate the effectiveness, complication rate and prognostic factors for success of MVD surgery of the cochleovestibular nerve for the treatment of tinnitus and/or vertigo. This systematic review showed that the percentage of patients with complete relief after MVD was low (in 28% of patients with tinnitus and in 32% of patients with vertigo). However, when patients had both tinnitus and vertigo, complete relief was achieved much more often (62%). An analysis of individual patient data also showed that patients with tinnitus combined with vertigo symptoms had a higher rate of treatment success than patients with tinnitus or vertigo alone. In Chapter 3, we hypothesized that this novel finding is probably caused by the fact that if a patient has both tinnitus and vertigo, it is more likely that the underlying pathology is a neurovascular conflict, considering that this particular nerve consists of a cochlear and vestibular branch and both branches are likely to be affected in a neurovascular conflict.

The systematic review also showed a substantial complication rate of 11% after MVD surgery. The success rate of MVD surgery of the cochleovestibular nerve was low, especially compared to the success rates of MVD of other cranial nerves. Presumably, this is not due to surgical skills or technique, but because of the difficulty to select the right patient for the surgery. It is challenging to correctly assign symptoms of vertigo and tinnitus to a neurovascular conflict of the cochleovestibular nerve, as it may be hard to distinguish these symptoms from other diseases such as Menière's disease. Correctly diagnosing a symptomatic neurovascular conflict of the cochleovestibular nerve is even more challenging as neuroimaging (with MRI) seems not to be a very reliable diagnostic tool. Several studies have showed that neurovascular conflicts of the cochleovestibular nerve are similarly common in patients with tinnitus as in patient without tinnitus.[6-8]

With the aim to get more insights in the clinical value of a neurovascular conflict detected on MRI, we investigated in **Chapter 4** whether the degree or type of compression that is seen on MRI, such as nerve indentation or loop compression[9], has a diagnostic value in patients with a neurovascular conflict on MRI. In this retrospective study, we analyzed MR-imaging of 220 ears in patients with tinnitus. In concordance with previous literature, we concluded that the mere presence of a neurovascular conflict of the cochleovestibular nerve on MRI did not correlate with ipsilateral tinnitus symptoms.[6,7] Also, there was no definite relation between the type of compression and ipsilateral tinnitus and/or hearing loss. Therefore, the present data do not support the concept of a 'cochleovestibular nerve compression syndrome'.[10] It must be noted that the number of loop compression and indentation type of neurovascular conflicts that were found in our patient group was small and that these findings should be confirmed in a larger sample size than our group.

By summarizing the available evidence on neurovascular conflicts in tinnitus, we conclude that when a neurovascular conflict of the cochleovestibular nerve is found on MRI in a tinnitus patient this rarely relates to tinnitus symptoms, regardless of the type or degree of compression (**Chapter 4**). When MVD surgery is considered as a treatment for a neurovascular conflict, one must keep in mind the low success rate of the procedure at the cost of a substantial complication rate of the surgery, as demonstrated in **Chapter 3**. Despite the poor correlation between tinnitus symptoms and a neurovascular conflict, the positive effect of the MVD surgery in cases with combined vertigo and tinnitus (complete relief in 62%) is remarkable. It suggests that combined tinnitus and vertigo in combination with evidence for a neurovascular conflict on MR-imaging may be a future indication for decompression surgery.

Neurostimulation of the auditory tract

Different neurostimulators at various levels of the auditory tract were discussed in the introduction of this thesis. Stimulation of the auditory tract as a treatment for tinnitus is based on the hypothesis that restoring (peripheral) sensory input can reduce or normalize the pathological organization of the central auditory system and can lead to a reduction of tinnitus perception.

Tinnitus has several analogies with other hyperexcitability disorders such as neuropathic pain.[11] Neuromodulation by continuous stimulation of the cochleovestibular nerve in order to reduce tinnitus was therefore proposed[12], in line with the principles of direct spinal cord stimulation in patients with intractable neuropathic pain syndromes.[13,14] A stimulation electrode with four contact points was designed for the purpose of direct stimulation of the cochleovestibular nerve by Staal and Holm et al.[12] In 2014, a long-term evaluation of the first four implanted patients showed promising results in terms of Tinnitus Handicap Inventory (THI) scores and visual analogue scales (VAS).[15] In Chapter 5, we described an extension of this study with the addition of another five implanted participants. In this long-term follow-up study, a significant decrease in THI-score and treatment success in a small majority of the patients was found. An unwanted side effect of the procedure however, was substantial (additional) damage to the sensorineural hearing loss in more than half of the implanted patients. We therefore concluded that this technique is not

a viable treatment option for tinnitus patients with normal hearing or with moderate hearing loss. For patients with severe hearing loss, multiple studies show consistent evidence that single sided deafness patients with a cochlear implant (CI) benefit from both hearing rehabilitation and tinnitus reduction.[16] Combined, these results have led to the conclusion that there is currently no place for direct neurostimulation with a cuff electrode for tinnitus treatment despite the positive effect of electrical stimulation in a subgroup of patients. Further evaluation and exploration of this method was abandoned.

In the ongoing search for the most optimal target for stimulation along the auditory tract for tinnitus reduction, the auditory brainstem implant (ABI) was suggested. The rationale for the use of an ABI in tinnitus is based on previous results in patients with neurofibromatosis type 2 (NF2) who were implanted with an ABI for the purpose of hearing rehabilitation. Several studies described a beneficial 'side-effect' of tinnitus reduction in these patients.[17-19] Based on this direct clinical evidence and on previous preclinical studies[20,21], we designed a prospective interventional pilot study to investigate the effect of stimulation with the ABI in patients with intractable, unilateral tinnitus (**Chapter 6**). This is the first study to prospectively investigate the ABI for the primary goal of tinnitus reduction. Also, to our knowledge it is novel to implant this type of hearing device in patients without complete hearing loss. We hypothesized that the ABI can be implanted without damaging the auditory tract and thus acoustic hearing can be preserved.

The ABI-study is still in progress. In this thesis, we presented the preliminary results of the first two implanted patients in **Chapter 7**. The first two implantations were successfully conducted without major complications. We observed that one year after activation of the ABI, both tinnitus related questionnaires-scores (Tinnitus Functioning Index [TFI] and THI) were reduced (meaning a decline in tinnitus handicap). The absolute reduction in both questionnaires scores exceeded the minimal important clinical difference for both scales. This finding was strengthened by a reduction in VAS-tinnitus loudness score in both patients. Moreover, we found that pure tone audiometry had not changed postoperatively, which indicates that the auditory tract is not damaged by implantation of the ABI. These preliminary results endorse our hypothesis that the ABI may be a beneficial treatment option for patients with (partially) preserved hearing on the side of their tinnitus, as described in **Chapter 7**. Further evaluation and inclusion need to be continued, however these findings might position the ABI as treatment option for patients with (partially) preserved hearing and severe tinnitus complaints. It would complement the CI as a treatment for severe tinnitus, which is currently a (experimental) treatment option but only in those patients with severe to profound sensorineural hearing loss.[22]

Additionally, the beneficial effect of the ABI on the hearing abilities of patients with moderate hearing loss is interesting. In our preliminary results, we have shown that one of the two patients benefitted from binaural hearing with the ABI in terms of free field speech understanding in noise. This finding suggests that in the auditory pathway, there is fusion of the input from the ABI with the input from the normal hearing ear. This phenomenon of beneficial fusion between a normal hearing ear and an 'aided' ear (i.e. the ABI in this study), has also been shown in a recent

study with CI recipients.[23] Although the effect on hearing with the ABI was not the primary goal of investigation in the ABI study, subsequent analyses in our ABI patient group will further investigate this very interesting topic.

Today, it remains inaccurately defined which specific mechanisms are responsible for the observed tinnitus reduction after stimulation with an ABI or with a CI. Potential mechanisms, as described in the introduction of this thesis, are: altering abnormal neuronal activity associated with peripheral deafferentation by inducing an inhibitory effect at the level of the brainstem and/or a masking effect by providing auditory input to the tinnitus ear.[19,24-26]

In our preliminary results, we observed that for tinnitus reduction, both patients preferred a low stimulation rate, independent of environmental speech sounds. This finding was somewhat unexpected as it was described in earlier studies that ABI recipients with NF2 experienced tinnitus reduction while using the ABI for hearing rehabilitation purposes.[19] On the other hand, studies investigating tinnitus reduction using a CI have shown that intracochlear stimulation independent of environmental sounds is able to suppress tinnitus in both the short and long term.[27-32] These studies are in line with the findings in our two patients (i.e. preference of low stimulation levels independent of acoustic stimuli to reduce tinnitus). Possibly, settings for speech understanding require higher stimulation and current rate and this may not be well-tolerated in our patient group, as both patients have partially preserved hearing instead of profound hearing loss. We aim to acquire more information into this matter by further investigating the effect of different stimulation strategies with the ABI in an (enlarged) patient group.

Roberts et al. showed that the ABI had a suppression effect on tinnitus loudness that lasted while the ABI was activated and that continued up to one hour after switching off the device. After one hour of switching off the device, VAS tinnitus loudness returned to baseline.[19] This finding is less supportive for the hypothesis that neurostimulation may induce permanent altering of neural plasticity in the auditory tract. These findings might indicate that it is more plausible that a masking effect is an important mechanism for tinnitus reduction in these patients. Further investigation on this matter is necessary and in our study population, we also intend to evaluate the direct effect of tinnitus suppression in different conditions (e.g. ABI on, ABI off, 1 hour after ABI off, ABI on again) in our (enlarged) patient sample.

Treatment strategies: where do neurosurgical interventions fit in?

In the past years, the field of tinnitus research has been broadened from otorhinolaryngologists, audiologists, and psychologists to neurosurgeons, since it became clear that the brain plays a major role in the generation of tinnitus. Early neurosurgical attempts to treat tinnitus were rather destructive, such as cochlear nerve ligation and frontal lobotomies.[33] After nerve ligation for tinnitus, complaints remained the same or, in a significant number of patients, worsened.[34] This finding led to the understanding that tinnitus is not generated in the peripheral auditory tract,

but more centrally in the auditory system. Transecting the cochlear nerve is now contraindicated as it deprives the auditory system from auditory input. In the 1950-1970s, frontal lobotomies were performed with the goal to disconnect the affective component (i.e. tinnitus distress) from the perceived loudness. This type of surgery has been abandoned. Today, the destructive type of surgery has shifted to functional and preservative types of surgery, using minimally invasive techniques and microscopes. In this thesis, several neurosurgical procedures have been described and evaluated. More neurosurgical stimulation techniques are being developed which are not covered in this thesis, such as the auditory midbrain implant and deep brain stimulation.[35,36]

Invasive neurosurgical procedures inevitably expose tinnitus patients to surgical risks that come with neurosurgery. It has been questioned whether these invasive and expensive procedures should have a place in the treatment for tinnitus, since tinnitus is also accompanied with highly subjective symptoms and is almost inseparable with comorbidities such as anxiety, depression and even personality traits. It could be argued that the chances of long- term and durable tinnitus relief are far better with therapies that are based on disconnecting the negative emotions from the perceived tinnitus, such as psychoeducation, relaxation training, mindfulness, possibly combined with sound therapy.

Patients attending medical care for tinnitus often seek reassurance of the absence of severe pathology or advice on how to cope with their symptoms. The majority of patients is adequately managed with conservative measures. It should be strongly encouraged that all patients with tinnitus are initially treated with first-line, conservative treatments.[37] However, for patients who still suffer from intractable, incapacitating tinnitus despite having tried all of these options, subsequent therapies should become available. From a patient's perspective, a survey showed that the majority of tinnitus patients was willing to have a device implanted in their body if this device would eliminate or reduce their tinnitus perception by half.[38] In addition, there was a strong willingness to pay a considerable amount of money for this treatment.[38] Another recent Dutch study also showed that patients are willing to undergo invasive treatment despite the associate costs and risks.[39] For incapacitating tinnitus, however, neurosurgical interventions should only be an last resort option if there is reasonable evidence for its effect and/or the procedure and the implants are safe.

Over the years, research on neurostimulation along the auditory tract has brought us closer to a solution for tinnitus and moreover, provided critical knowledge of the pathophysiology of tinnitus. Therefore, the search for neurosurgical treatment options should be pursued. It is expected that in the future, when the most useful and most successful treatment methods are sorted out, these interventions or surgical procedures can be performed more routinely as more experience is gained.

Future perspectives

MVD in patients with tinnitus is not a highly recommended procedure, due to the low success rates. As discussed, an explanation for the low success rate is the difficulty of adequate patient selection, i.e. to select those patients who have a symptomatic neurovascular conflict. A recent retrospective study with 1.5 Tesla MRI in multiplanar reconstructions showed that vessels with a large caliber (>0.85mm) in the proximal portion of the internal auditory canal correlated with symptoms of vertigo, tinnitus, and hemifacial spasms.[40] High-resolution thin- section MRI might be useful in providing more detailed information on the cochleovestibular nerve and potential pathological contacts with blood vessels. Future prospective studies with high quality MR Imaging (preferably 3 Tesla) and the possibility of 3D reconstructions should be performed to provide more insight in the status of the cochlear nerve in case of a neurovascular conflict and its relation to auditory symptoms such as tinnitus. With an improved patient selection based on more accurate MR imaging for example, success rates for MVD surgery may improve, however both of these questions must be newly assessed in the future. Additionally, the positive outcomes of MVD surgery in patients with vertigo and tinnitus combined, as found in our study, have to be prospectively investigated under these new MRI conditions.

The dorsal cochlear nucleus (DCN) is suggested to play an important role in the pathophysiology of tinnitus.[20,41-43] A recent study in rodents with noise-induced hearing loss has shown that during high frequency stimulation of the DCN, tinnitus was suppressed. It was suggested that high frequency stimulation of the DCN can block or alter abnormal tinnitus- related neural activity.[44] In 1994, Otto and Soussi were the first to suggest in a clinical study that the ABI, stimulating the cochlear nucleus, might be useful in the treatment of severe tinnitus.[17] The ABI study presented in this thesis is the first study to prospectively investigate this hypothesis and we expect valuable information on the effect on tinnitus. Also, in the near future we expect to get more insight in integration of hearing with the ABI and acoustical hearing in the normal hearing ear. The ABI study is a pilot study, however if the results are promising, further trials need to be conducted to confirm our preliminary findings. We hope that our study will initiate a world-wide interest to further investigate the effect of the ABI on tinnitus.

Numerous studies have investigated the effect of CI stimulation on tinnitus, resulting in increasing general acceptance that CI may be a viable treatment option for tinnitus.[16,25,45,46] Arts and his colleagues recently showed that intracochlear stimulation independent of environmental sounds can provide tinnitus reduction.[28,29,32] They have suggested a 'tinnitus implant': a modified, or simpler, version of the CI, especially for tinnitus sufferers, which could possibly have lower production costs.[29] As already mentioned, future trials investigating the effect of ABI stimulation on tinnitus should be performed. Also, we need to further explore which stimulation strategies are most beneficial for tinnitus reduction. If it is found that a positive effect on tinnitus can be achieved using a stimulation strategy independent of environmental sounds, as is the case in our first two patients, one could propose to develop an ABI-like 'tinnitus implant' for this purpose. Possibly, a simplified version of the speech processor of the ABI could be designed especially for

tinnitus reduction purposes. In the future, when it comes to treatment for patients with severe tinnitus, we might have the choice between a CI-like tinnitus implant for patients with severe hearing loss and an ABI-like tinnitus implant for patients with (partially) intact hearing.

This thesis covered the surgical interventions of the cochlear nerve and nucleus for tinnitus. In the field of tinnitus research, other levels of the auditory tract are targeted as well. The inferior colliculus is known to show tinnitus related activity.[47,48] The auditory midbrain implant (AMI) is currently under investigation as a possible substitute for the ABI for the purpose of hearing rehabilitation in patients with NF2 with severely distorted anatomy.[36] In terms of tinnitus reduction, it has been shown in guinea pigs that stimulation of the inferior colliculus suppresses activity associated with tinnitus in the central nucleus of the inferior colliculus.[49] Appropriate locations for array implantation and stimulation strategies need to be further identified.[49] Up till now, results on tinnitus reduction in humans with the AMI have not yet been published, although a clinical trial in patients with NF2 is planned (ClinicalTrials.gov Identifier: NCT02984202). Another example of invasive surgical procedures for tinnitus is deep brain stimulation (DBS). DBS is known as a treatment option for therapy resistant neurological disorders such as Parkinson's disease.[50] In patients with Parkinson treated with DBS, a positive effect on tinnitus has also been described by Smit et al.[35] Recently, the effect of bilateral caudate nucleus DBS for treatment-resistant tinnitus in six patients was studied, which showed promising results.[51] A clinically significant treatment response was seen in three patients as determined by the TFI (13-point decrease) and four patients as determined by the THI (20-point decrease). Also, the authors concluded that there were no safety concerns.[51] In a phase II study (ClinicalTrials.gov Identifier: NCT01988688) targeting refinement for final DBS lead placement is one of the additional points of interest. In the near future another prospective pilot study investigating the effect of DBS in patients with refractory tinnitus is planned (ClinicalTrials.gov Identifier: NCT03976908). The investigators of this study expect that stimulation of the medial geniculate body of the thalamus inhibits tinnitus perception by altering pathological neuronal activity.

In conclusion, tinnitus research is a very active field and across the world research is conducted to investigate non-invasive treatment methods, such as mindfulness or sound therapy, as well as invasive treatment methods such as the ABI and other neurosurgical implants. It is the hope, and expectation, that this research combined will eventually lead us to finding a cure for tinnitus.

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Appendices

Nederlandse samenvatting

List of publications

Dankwoord

Over de auteur

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Nederlandse samenvatting

Inleiding

Tinnitus, ofwel oorsuizen genoemd, is het fenomeen waarbij een persoon geluid waarneemt in de afwezigheid van een uitwendige stimulus of geluidsbron. Tinnitus komt naar schatting voor bij 8-20% van de Westerse bevolking en is daarmee een veelvoorkomend probleem. Daarnaast verwacht de Wereldgezondheidsorganisatie een toename van het aantal mensen dat tinnitus krijgt, omdat de voorspelling is dat het aantal patiënten met gehoorverlies toeneemt. Gehoorverlies is een bekende risicofactor voor het ontwikkelen van tinnitus. Tinnitus kan zich op verschillende manieren uiten: sommige patiënten horen het geluid in één oor, anderen centraal in het hoofd. Ook kan het type geluid dat patiënten horen variëren, bijvoorbeeld van een hoge toon tot een breedbandige ruis. Tinnitus kan een negatieve impact hebben op de kwaliteit van leven. Regelmatig gaan de klachten samen met psychologische klachten zoals depressie, angst of slapeloosheid. In dit proefschrift evalueerden en onderzochten we verschillende behandelmethoden voor patiënten met ernstige tinnitus.

De grootste groep van tinnituspatiënten heeft *subjectieve* tinnitus, waarbij alleen de patiënt zelf een geluid waarneemt (een fantoomgeluid). Deze vorm van tinnitus wordt dan ook vaak vergeleken met fantoompijn. Dit in tegenstelling tot *objectieve* tinnitus, waarbij het geluid ook kan worden waargenomen door een ander persoon, zoals suizen door een vernauwd bloedvat nabij het oor. Deze vorm van tinnitus is echter zeldzaam en wordt in dit proefschrift niet behandeld.

Men maakt anatomisch onderscheid tussen het perifere auditieve systeem (van trommelvlies, gehoorbeenketen tot en met het slakkenhuis) en het centraal auditieve systeem (van gehoorzenuw, gehoorkern in de hersenstam tot en met hersenschors). Het centrale zenuwstelsel speelt een belangrijke rol in het ontstaan en ervaren van subjectieve tinnitus. De theorie achter het ontstaan van tinnitus is dat de afwezigheid van input vanuit het perifere auditieve systeem, zoals bijvoorbeeld gehoorverlies vanuit het slakkenhuis (cochlea), zorgt voor een afname van remmende processen in het centraal auditieve systeem, wat uiteindelijk leidt tot een hyperactieve staat van het centraal auditieve systeem. Verhoogde spontane activatie en verhoogde synchrone activiteit van neuronen in de hersenschors (cortex) die verantwoordelijk zijn voor het waarnemen van het gehoor zijn factoren die mogelijk leiden tot het waarnemen van tinnitus.

Een genezende behandeling voor tinnitus is er niet. De behandeling van tinnitus in de algemene praktijk bestaat vooral uit voorlichting en uitleg aan de patiënt. Verder kan een onderscheid gemaakt worden tussen behandelingen die beogen tinnitus zelf te verminderen, zoals hoortoestellen of ruismaskeerders, en behandelingen die erop gericht zijn de negatieve gevolgen van tinnitus te verminderen, zoals psychologische ondersteuning in de vorm van bijvoorbeeld cognitieve gedragstherapie. Echter, niet alle patiënten hebben voldoende baat bij deze behandelingen en sommige van deze patiënten hebben een therapieresistente vorm van tinnitus. In de afgelopen jaren zijn daarom ook meer invasieve therapieën onderzocht. Deze therapieën richten zich tot aangrijpingspunten in de cochlea, de gehoorzenuw en –kern (vestibulocochlaire zenuw en

cochleaire nucleus) en de auditieve cortex. In dit proefschrift werden specifiek de mogelijkheden van neurochirurgische interventies op het niveau van de vestibulocochleaire zenuw en nucleus voor de behandeling van tinnitus geëvalueerd en onderzocht.

Variatie in tinnituspatiënten

Een uitdaging in het onderzoek naar de behandeling van tinnitus, is dat de groep met tinnituspatiënten erg gevarieerd is. Verschillende risicofactoren, nevendiagnoses, de mate van stress die iemand ervaart en de reactie op behandelingen maken dat de groep tinnituspatiënten erg heterogeen is. Om meer inzicht te krijgen in deze heterogene groep tinnituspatiënten, hebben we een cluster analyse verricht op een grote dataset van tinnituspatiënten, met als doel om subgroepen te identificeren. De resultaten van deze analyse zijn beschreven in **Hoofdstuk 2.** Voor deze analyse werd patiënt gerelateerde informatie (zoals verschillende tinnituskarakteristieken en scores van vragenlijsten) en door een arts of audioloog vastgestelde informatie (diagnose, gehoortest, nevendiagnoses) gebruikt van 1.783 tinnituspatiënten die het tinnitusspreekuur bezochten in het Universitair Medisch Centrum Groningen. Voor het verrichten van een cluster analyse zijn de definiërende variabelen van groot belang. Zoals beschreven in Hoofdstuk 2 werden de variabelen op twee verschillende manieren geselecteerd. Beide analyses leidden tot verschillende groepen, ofwel 'clusters', van tinnituspatiënten. De groepen waren vooral van elkaar onderscheiden op basis van hoe de tinnitus veranderde in reactie op externe factoren, zoals bijvoorbeeld het effect van hard geluid. Echter in beide analyses liet de clustering een lage stabiliteit zien, wat betekent dat de groepen een significante hoeveelheid overlap hadden en niet voldoende van elkaar verschilden. Een verklaring voor deze bevinding zou kunnen zijn dat: (1) de onderzochte tinnitusgroep meer een continuüm vormt zonder dat er duidelijk afgrensbare subgroepen zijn, of (2) dat de subgroepen in de gebruikte dataset niet geïdentificeerd konden worden omdat niet de juiste variabelen zijn gebruikt. Ten aanzien van het tweede punt: hypothetisch zouden bijvoorbeeld anatomische gegevens van MRI-scans, metingen van hersengolven of genetische data het onderscheid tussen verschillende groepen kunnen versterken. Deze gegevens waren voor de onderzochte patiëntengroep echter niet beschikbaar. Desalniettemin blijft onderzoek naar het vinden van subgroepen in de tinnituspopulatie van groot belang om meer inzicht te krijgen in het mechanisme van tinnitus en voor het ontwikkelen van meer gepersonaliseerde behandelingsstrategieën.

Microvasculaire decompressieoperatie

Tinnitus heeft vele potentiële oorzaken en een neurovasculair conflict van de vestibulocochleaire zenuw, één van de twaalf hersenzenuwen, is één van deze mogelijke oorzaken. Bij een neurovasculair conflict komt een hersenzenuw in contact met een nabijgelegen bloedvat, waardoor druk op en irritatie van de zenuw kan ontstaan. Dit kan leiden tot klachten passend bij de betreffende hersenzenuw. Bekende neurovasculair conflicten zijn bijvoorbeeld trigeminusneuralgie waarbij pijnscheuten in het gelaat optreden (neurovasculair conflict van de gevoelszenuw van het gezicht) en hemifaciale spasmen waarbij trekkingen van het gelaat optreden (neurovasculair conflict van de motorische aangezichtszenuw). Deze ziektebeelden kunnen vaak succesvol worden behandeld door een operatie waarbij het bloedvat wordt losgemaakt van de zenuw, een zogenaamde microvasculaire decompressieoperatie. In wetenschappelijke literatuur wordt

gesuggereerd dat een neurovasculair conflict van de vestibulocochleaire zenuw symptomen kan geven van tinnitus, soms gecombineerd met duizeligheidssymptomen (vertigo) en verminderd gehoor. Microvasculaire decompressieoperaties zijn echter (nog) geen routinematige operatie voor deze symptomen, mede omdat het succespercentage onduidelijk is. Om hier meer inzicht in te verschaffen, verrichtten we een systematische review en meta-analyse van data van individuele patiënten die een microvasculaire decompressieoperatie vanwege tinnitus hebben ondergaan. Deze review wordt beschreven in **Hoofdstuk 3.**

Uit de review bleek dat bij dit type operatie een vrij hoog complicatiepercentage voorkomt, namelijk 11%. De succeskans van de operatie, gedefinieerd als het volledig verdwijnen van symptomen, bij patiënten met alleen tinnitus was laag (28%). Ook bij patiënten met alleen duizeligheidsklachten was het succespercentage laag (32%). Echter, wanneer patiënten beide klachten tegelijk ervaarden, werd een veel hoger succespercentage van de operatie gevonden (62%). Uit de analyse van individuele patiënten data bleek ook dat patiënten met beide symptomen meer kans hadden op succes van de operatie. Deze bevinding kan verklaard worden door het feit dat wanneer een patiënt beide symptomen ervaart, het meer waarschijnlijk is dat een neurovasculair conflict de onderliggende oorzaak is van deze klachten. Immers: de vestibulocochleaire zenuw bestaat uit zowel een bundel met gehoor- en evenwichtsvezels en beide kunnen ten gevolge van irritatie door een bloedvat zijn aangedaan. Het blijft echter een uitdaging om deze symptomen te onderscheiden van andere oorzaken die tinnitus en duizeligheid gecombineerd kunnen geven, zoals de ziekte van Ménière.

MRI en de detectie van een symptomatisch neurovasculair conflict

Op een MRI-scan van de hersenen kunnen onder andere hersenzenuwen en bloedvaten afgebeeld worden. Een MRI-scan zou daarom kunnen helpen om een neurovasculair conflict correct te diagnosticeren als onderliggende oorzaak van tinnitus. Echter, van eerdere onderzoeken is bekend dat een neurovasculair conflict ook gevonden kan worden op een MRI bij patiënten die geen klachten hebben. Er kan daardoor twijfel ontstaan of het neurovasculair conflict wel de oorzaak is van de klachten van de patiënt. Het zou kunnen zijn dat een bepaald type neurovasculair conflict zoals te zien op de MRI, zoals een deukje in de zenuw of een lus van een bloedvat rondom de zenuw, kan helpen om patiënten met een symptomatisch neurovasculair conflict te identificeren. Om dit te onderzoeken, hebben we in een retrospectief onderzoek MRI-beelden van 220 oren van tinnituspatiënten geanalyseerd. Zoals beschreven in **Hoofdstuk 4**, volgde hieruit dat wanneer een neurovasculair conflict van de vestibulocochleaire zenuw op MRI werd gezien, dit niet altijd gerelateerd was met klachten van tinnitus aan diezelfde zijde. Ook werd er geen significant verband gezien tussen het type compressie en symptomen van tinnitus en/of gehoorverlies aan die zijde. Samenvattend concluderen we dat wanneer een neurovasculair conflict van de vestibulocochleaire zenuw op MRI wordt gezien in een patiënt met tinnitus, dit zelden relateert aan tinnitussymptomen, onafhankelijk van het type neurovasculair conflict. Wanneer een patiënt gecombineerde symptomen heeft van zowel tinnitus als duizeligheid en het vermoeden toch bestaat dat dit komt door een neurovasculair conflict, is de succeskans van de operatie het hoogst (Hoofdstuk 3). Men moet hierbij echter rekening houden met een vrij hoog percentage complicaties ten gevolge van de operatie.

Neurostimulatie door middel van een ringelectrode om de vestibulocochlaire zenuw
In het kader van neurochirurgische behandelingen voor tinnitus werden in dit proefschrift verschillende aangrijpingspunten voor neurostimulatie van het auditieve systeem beschreven en onderzocht. Het idee van directe stimulatie van het auditieve systeem als behandeling voor tinnitus is gebaseerd op de hypothese dat het terugbrengen van input in het auditieve systeem de afwijkende organisatie van het centraal auditieve systeem kan verminderen of zelfs normaliseren. Neurostimulatie van de gehoorzenuw met een speciaal ontworpen ringelectrode is één van de behandelingsstrategieën die werd onderzocht. In **Hoofdstuk 5** zijn de langetermijnresultaten beschreven van tien tinnituspatiënten die met een ringelectrode werden geïmplanteerd. Er werd onder andere gevonden dat er in de gehele populatie een significante afname van tinnituslast werd gezien en dat iets meer dan de helft (6/10) van de patiënten zelf de behandeling als 'succesvol' beoordeelde. Echter, de prijs hiervan was dat bij een ruime meerderheid van de patiënten na de operatie een substantiële verslechtering van het gehoor als gevolg van de implantatie werd gevonden. In deze studie werd daarom geconcludeerd dat deze vorm van stimulatie niet geschikt is voor patiënten met een normaal of matig gehoorverlies. Bij patiënten met ernstig gehoorverlies en tinnitus is ondertussen gebleken dat een cochleair implantaat effectief is in het verminderen van tinnituslast in patiënten met enkelzijdige doofheid, met als voordeel dat een cochleair implantaat tevens een positief effect heeft op het herstellen van gehoormogelijkheid. Concluderend, omdat de ringelectrode niet geschikt lijkt voor patiënten met nog (deels) functioneel gehoor en omdat voor patiënten met ernstig gehoorverlies een cochleair implantaat een beter effect op tinnitus heeft en ook gehoorverbeteringseffect geeft, werd geconcludeerd dat neurostimulatie met de ringelectrode geen plaats heeft in de behandeling van tinnitus.

Neurostimulatie met een hersenstam implantaat
Het overgrote deel van de patiënten met tinnitus heeft een redelijk goed gehoor of in ieder geval een resterend gehoor. Voor deze patiënten leek er geen geschikte neurostimulatie behandelingsmogelijkheid in ontwikkeling te zijn. Daarom werd een auditory brainstem implant (ABI) of 'hersenstam implantaat' gesuggereerd als behandeloptie voor tinnitus in **Hoofdstuk 6**. De ABI is een implantaat vergelijkbaar met een cochleair implantaat en is ontworpen voor verbetering van het gehoor in volledig slechthorende patiënten die geen mogelijkheid hebben voor een cochleair implantaat, zoals patiënten met neurofibromatose type II. Daarbij ligt de electrode van de ABI echter niet in de cochlea zoals bij een cochleair implantaat, maar direct op de cochleaire nucleus ter plaatse van de hersenstam. Het idee om de ABI te gebruiken als tinnitusonderdrukker is gebaseerd op bevindingen bij neurofibromatose type II patiënten, waarbij implantatie van de ABI met als doel verbetering van het gehoor, als positief neveneffect had dat eventuele klachten van tinnitus ook verminderden. Tevens hebben dierstudies aanwijzingen laten zien dat stimulatie van de cochleaire nucleus een potentieel gunstig aangrijpingspunt is om tinnitus te verminderen. Omdat bij ABI-implantatie de cochlea niet wordt geopend zoals bij een cochleair implantaat, is de hypothese dat het gehoor bij ABI-implantatie gespaard zou blijven. We hebben een experimentele pilotstudie opgezet om het effect van implantatie met de ABI op tinnitus (primaire uitkomstmaten) en onder andere gehoor en veiligheid van de implantatie (secundaire uitkomstmaten) te onderzoeken. In Hoofdstuk 6 is het studieprotocol beschreven.

Op dit moment is de ABI-studie nog lopende. In **Hoofdstuk 7** zijn de resultaten van de eerste twee patiënten beschreven die een ABI-implantatie hebben ondergaan. Zowel de implantatie als het beloop na de operatie verliep zonder complicaties. Uit tinnitus gerelateerde vragenlijsten afgenomen één jaar na de implantatie bleek dat de ABI een substantieel en stabiel effect had op het verminderen van tinnitus in deze twee patiënten. Ook bleef bij deze patiënten het gehoor in het geïmplanteerde oor onbeschadigd na de operatie. Eén patiënt ervaarde zelfs een positief effect op het verstaan van spraak met de ABI. De ABI-studie is momenteel nog gaande en uit de ABI-implantatie bij andere patiënten moet blijken of deze positieve bevindingen consistent zullen worden gevonden.

Concluderend

Dit proefschrift beschrijft een aantal studies die inzicht geven in neurochirurgische behandelopties voor ernstige tinnitus, zoals microvasculaire decompressie, stimulatie van de gehoorzenuw met een ringelectrode en stimulatie van de gehoorkern met de ABI. Deze laatste behandeloptie lijkt het meest veelbelovend te zijn, echter zal verder onderzoek dit moeten bevestigen. Onderzoek naar tinnitus is een actief veld wereldwijd en vele studies naar invasieve behandelingen worden momenteel opgezet en verricht met als gezamenlijk doel het vinden van een optimale behandeling voor tinnitus. Het is de verwachting dat deze studies in de toekomst zullen leiden tot meer inzicht in de oorzaak van tinnitus en uiteindelijk ook tot goede behandelopties voor patiënten met ernstig invaliderende tinnitus die niet kunnen worden geholpen met conservatieve behandelopties.

List of publications

TTA Peters, **MJC van den Berge**, RH Free, AM van der Vliet, H Knoppel, P van Dijk, R Hofman. *The relation between tinnitus and a neurovascular conflict of the cochleovestibular nerve on magnetic resonance imaging*. Otol Neurotol 2020 Jan, 41: e124–e131

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Over de auteur

Minke Josephine Cornelia van den Berge werd geboren op 22 februari 1989 in Maastricht. Zij groeide op in Leeuwarden, waar zij haar vwo-diploma behaalde aan het Stedelijk Gymnasium in 2007. In dit jaar startte zij de opleiding Geneeskunde aan de Rijksuniversiteit in Groningen en was tijdens de studie een actief lid van studentenvereniging Vindicat. Tussen de bachelor en masterfase van haar studie behaalde zij het Cambridge Proficiency Certificate in Sydney, Australië. In 2011 vervolgde zij haar coschappen in zowel het Universitair Medisch Centrum Groningen (UMCG) als de Isala Klinieken in Zwolle. Tijdens de coschappen werd haar interesse voor het praktische en gevarieerde vak Keel- Neus- Oorheelkunde gewekt. Haar wetenschapsstage en senior coschap deed zij dan ook in het UMCG bij de KNO-afdeling. In april 2014 behaalde zij haar artsendiploma. Na klinische werkervaring te hebben opgedaan als arts op de afdeling cardiologie in het Medisch Centrum Leeuwarden, startte zij in november 2014 haar promotieonderzoek aan de Rijksuniversiteit Groningen op de afdeling Keel- Neus- en Oorheelkunde onder leiding van professor P. van Dijk, professor J.M.C. van Dijk en dr. R.H. Free, initieel vooral om een auditory brainstem implant onderzoek op te zetten. Samen met haar promotieteam breidde zij dit onderzoek uit naar diverse andere neurochirurgische behandelingsopties voor tinnitus. Zij presenteerde haar onderzoeksresultaten op verschillende nationale en internationale congressen. In 2016 startte zij haar opleiding tot Keel- Neus- Oorarts in het UMCG onder leiding van professor B.F.A.M van der Laan met perifere stages in het Martini Ziekenhuis te Groningen en de Isala Klinieken te Zwolle. Minke is verloofd met Thomas Gorter en samen hebben zij een dochter, Fenna.