The effect of cochlear implantation on the auditory and vestibular function

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Introduction

Given the changing criteria for cochlear implant (CI) candidates, an increasing number of people with preoperatively residual hearing and vestibular function are qualified for cochlear implantation. It is known that during surgery, the electrode that is placed into the cochlea might cause damage to the auditory and vestibular system. There is a lack of knowledge about the impact of structural damage in CI patients in the Radboudumc. Therefore, there is a need for a complete database, which includes data of both vestibular as auditory measurement. The purpose of the present study is to determine the impact of surgery to the vestibular and auditory function. The influence of age and cause of deafness will be determined, to optimize preoperative counseling of patients' risks and benefits of a CI. Up to now, it seemed that the only way to assess the vestibular function was the velocity step test (VST) or irrigation. Because of the increasing knowledge of vestibular physiology, the video Head Impulse Test (vHIT) became more important since it can investigate all semicircular canals of the vestibular system. Not only the influence of the CI on objective tests will be evaluated, subjective measurement through Dizziness Handicap Inventory (DHI) is also evaluated.

Chapter 1 Hearing and vestibular system in human

1.1 Hearing in human

In humans, the auditory organ consists of several parts which each have their own function in the hearing process (see Figure 1). Before the function of the inner ear is discussed, information about hearing will be provided. Sound waves that are captured by the ear shelf, go through the auditory external auditory canal and reach the eardrum, which results in quick or slow vibrations of the eardrum (Pickles, 2012). Due to these vibrations, the auditory ossicles are set in motion (first hammer, then anvil and stapes) and they transfer the vibrations towards the end of the stapes. The stapes is connected to the bony labyrinth through the oval window and it sends vibrations into the cochlea (Møller, 2012). Here, hair cells are triggered to send information to the auditory cortex that will be interpreted as sound (Goutman, 2012).

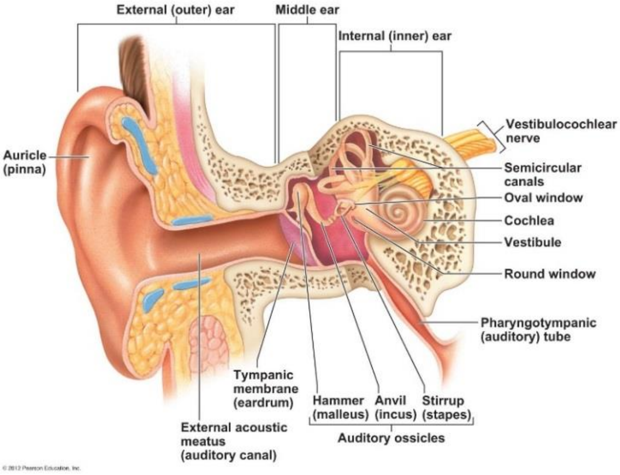


Figure 1: Anatomy of the ear, pointing out the separate but connected parts; the external, middle and inner ear. Further on, beyond the inner ear, the nervous system passes on the auditory information towards the auditory cortex. Copyright © 2009 Pearson Education, Inc., publishing as Benjamin Cummings.

The human inner ear consists of both auditory and vestibular components (Schrauwen et al., 2016), which have a connection with the brainstem, cerebellum and the cortex, the ocular system and postural muscles. Information provided from the vestibular system in the inner ear, along with vision and propriocepsis is sent to the central neural system (Wuyts, Furman, Vanspauwen & Van De Heyning, 2007). All these sources share the same function: sending information about balance/equilibrium to the central neural system. The organs of the vestibular system will be discussed now. The vestibular labyrinth in the inner ear contains of three semicircular canals and two otolith organs, utricle and saccule (Connor & Sriskandan, 2014; Schrauwen et al., 2016; Bronstein, Patel & Arsquad, 2015; Cullen, 2012). The vestibular system perceives head motion and forces of gravity on the body. The semicircular canals respond to angular acceleration and the saccule and utricle respond to linear and gravitational acceleration (Connor & Sriskandan, 2014; Schrauwen et al., 2016; Bronstein et al., 2015; Cullen, 2012). The sensory systems in these structures are referred to as the macula and crista ampullaris, in which the hair cells are embedded. To understand the function of the vestibular system, information about the function of the hair cells is provided.

1.2 Hair cells

Both the crista ampullaris (in semicircular canals) and macula (in utricule and saccule) are equipped with hair cells. In general, a hair cell contains of one big cilia, called kinocilium and 70-100 small cilia, called stereocilia (Figure 2). These stereocilia are placed as a staircase from large to small, with the largest standing next to the kinocilium (Engström, Ades & Hawkins, 1962). Due to motion, the cilia can bend towards or away from the kinocilium (Connor & Sriskandan, 2014; Cullen, 2012). Bending the stereocilia towards the kinocilium results in an opening of the potassium channel and therefore depolarizes and opens the calcium channel. The release of neurotransmitter is stimulated and therefore the vestibular nerve firing rate is increased. On the other hand, in case stereocilia are bent away from the kinocilium, channels are closed and hyperpolarization arises. Less neurotransmitter is released and the firing rate of the vestibular nerve is decreased (Khan & Chang, 2013).

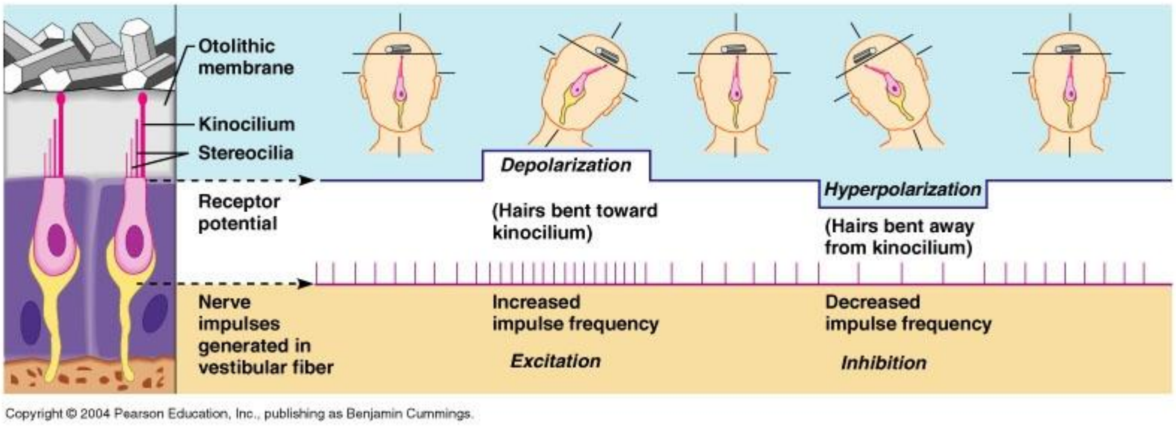


Figure 2: Movement of the head results in bending hair cells. Depending on the direction of the movement, hairs bent toward or away from the kinocilium. Increased or decreased impulse frequency are processed in the corresponding part of the brain. Copyright © 2004 Pearson Education, Inc., publishing as Benjamin Cummings.

1.3 Utricle and saccule

The two otolith organs, saccule and utricle, are situated in the inner ear (Khan & Chang, 2013; Bronstein et al., 2015). The sensory system in the saccule and utricle responds to linear and gravitational acceleration and tilting of the head. The saccule and utricle both contain hair cells, of which the nerve endings are clustered in a macula. The utricle and saccule are orthogonal, which means that the macula of the saccule are oriented in the vertical plane and the macula of the utricle are oriented in the horizontal plane (Wuyts et al., 2007). Therefore, linear movements in the horizontal plane will be perceived by the hair cells of the utricular macula and linear movement in the vertical plane in the hair cells of the saccular macula. During acceleration of the head, the organs in both ears will simultaneously be triggered. The static tilt of the head can also be detected by the saccule and utricle. This is due to the so-called otoliths or otoconia, which are embedded in a gelatinous membrane on top of the macula (see Figure 2, top left). Due to the tilting of the head, the otoconia get in motion by the difference in density and therefore trigger the hair cells to de- or hyperpolarize (Khan & Chang, 2013). Information from these hair cells are sent to the vestibular nuclei in order to sustain balance (Cullen, 2012).

1.4 Semicircular canals

Both ears contain 3 semicircular canals situated in the horizontal, anterior and posterior direction (Figure 3, top). Each canal is sensitive to movement in line with the corresponding angular acceleration. Due to a specific alignment, the directions RALP (right anterior left posterior) and LARP (left anterior right posterior) respond to the same movement. For example, both the anterior canal in one ear and the posterior canal in the other ear are triggered by the same movement. At the end of each semicircular canal, a thickening called the ampulla is embedded in the utricle. The ampulla is filled with one crista ampullaris, an arch-wise structure in which the hair cells are situated (Figure 3, bottom).

A closer look at the crista ampullaris shows that the hair cells are covered by cupula, a gelatinous substance. Due to rotational acceleration of the head, the endolymph gets in motion and therefore displaces the cupula. Displacement of the cupula as an effect of angular acceleration or rotation of the head triggers the hair cells. These hair cells will bend in the opposite direction of the rotation (Khan & Chang, 2013), see Figure 4. As a result of the bending hair cells, ion channels can either open or close with depolarization or hyperpolarization as result. The de- or hyperpolarization effects the firing rate of its afferent nerve fibers de- or increasing. Semicircular canals in both ears are aligned in such a way that the endolymph flow that causes excitation in one semicircular canal, will inhibit the hair cells of the contralateral canal in the other ear it is paired with (Khan & Chang, 2013). This principle is also known as the ‘push-pull’ system of the semicircular canals.

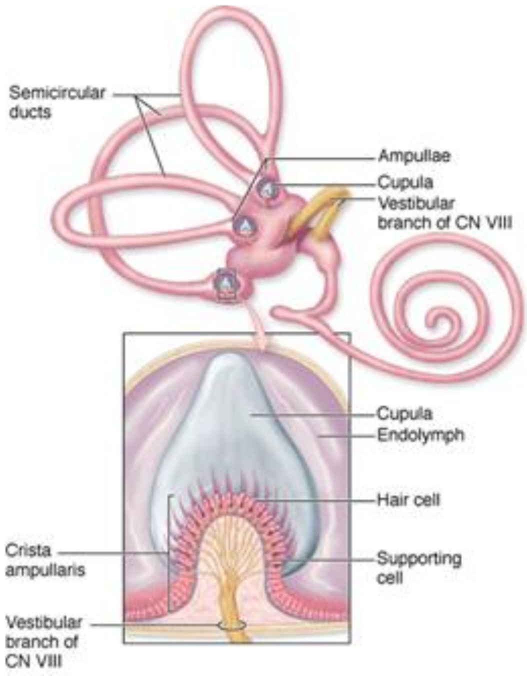


Figure 3: The vestibular system and a closer look at one of the ampullae. Obtained from http://www.accessmedicine.com. Copyright © The McGraw Hill Companies, Inc.

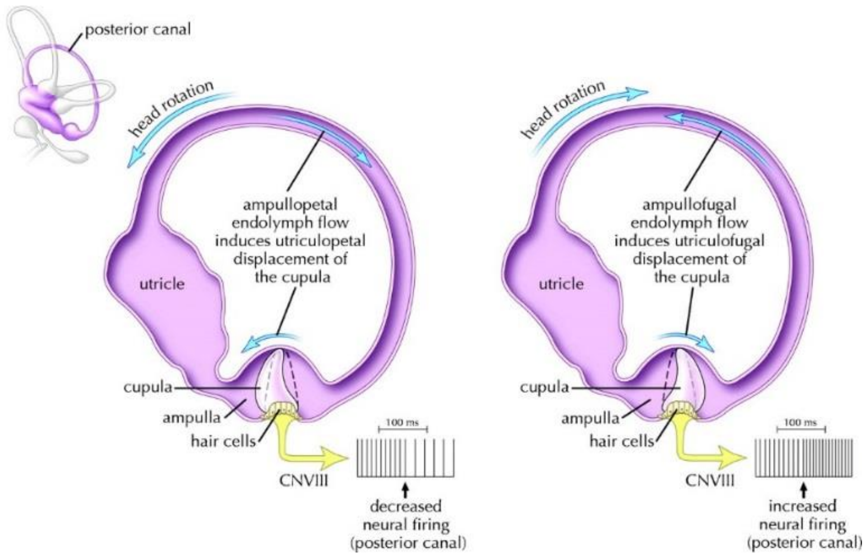


Figure 4: The influence of endolymph flow, caused by head rotation, to the cupula in the posterior canal. Obtained from http://alfa-img.com/show/cupula-of-ear.html

The information about the movements of the head and body that is transferred to the vestibular nerve leads to adjustments in order to remain balanced. Not only body position, but also visual adaption is needed, otherwise blurry vision occurs. In the next section, more information about natural and pathological adaptions of the eyes due to visual perception of self-motion will be discussed.

1.5 VOR, OKN and nystagmus

In vision, only a small piece of the retina is designed for clear images. During displacement of the head, a natural response of the eyes occurs to obtain visual acuity (Waddington & Harris, 2015; Bronstein et al., 2014). In healthy humans six ocular pairs of muscles collaborate to prevent vision from getting blurred (Agarwal et al., 2015). These involuntary reflexes to stabilize are essential and indispensable (Ranjbaran, Smith, Galiana, 2016). The extraocular muscles can generate saccades, smooth pursuit eye movements, gaze fixation, accommodation, optokinetic nystagmus (OKN) and vestibulo-ocular reflexes (VOR) (Agarwal et al., 2015). In case the head is moving during fixation on a target, vestibulo-ocular reflexes (VOR) prevent the image from getting blurry. Sometimes, in case the object of interest is moving while the head is kept steady, the eyes might not be able to move as fast as the object moves. Visual distortion is caused due this moving object, but optokinetic nystagmus (OKN) is able to compensate for this. OKN consists of slow movement in the direction of the object, and rapid movement to a new object of interest (comparing with looking at objects while sitting in a train/car) (Agarwal et al., 2015). Smooth pursuit eye movements occur when the object of interest is smoothly moving, because the eye velocity needs to be adapted to maintain clear vision (Spering & Montagnini, 2011; Agarwal et al., 2015). Saccades have the task to rapidly fixate on the visual target of interest and move it onto the retina (Spering & Montagnini, 2011; Agarwal et al., 2015), as in reading. During self-motion, vestibulo-ocular reflex (VOR) and optokinetic nystagmus (OKN), act synergistically to stabilize gaze (Waddington & Harris, 2015; Gorges, Pinkhardt & Kassubek, 2014). The collaboration between these 2 features is coordinated by an internal mechanism, called the “velocity storage mechanism”. In general, OKN is provoked in motions with a low-frequency and VOR in high-frequency motions (Fadaee & Migliaccio, 2016).

The involuntary movements of the eyeball that occur during fixation in horizontal, vertical or rotatory direction are called nystagmus (Gupta & Mundra, 2015). Several types of nystagmus exist, however the one which is mostly observed in clinical settings is the ‘jerk nystagmus’. Nystagmus is defined as ‘jerk nystagmus’ in case a slow phase towards one side is followed by a fast saccade returning to midline in order to re-fixate (Gupta & Mundra, 2015; Hussain, 2016), see Figure 5. A nystagmus is named after the direction of the fast phase movement (left or right) and this phase is quantified and referred to as ´maximum slow phase velocity´ (Starčević, Velepič & Bonifačić, 2014). The presence of pathologic nystagmus causes blurred images on the retina and can therefore lead to vestibular symptoms (Stahl & Leigh, 2001). Information about nystagmus (the direction, the amplitude and frequency) can lead to information about the vestibular system. This will be explained in chapter 3.

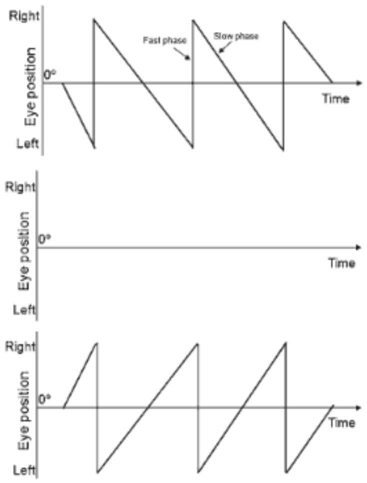


Figure 5: Pattern of a nystagmus to the right (upper nystagmus) and to the left (lower nystagmus). As this Figure shows, nystagmus is named after the fast-phase. Obtained from Stanford Medicine and adapted (http://ophthalmology.stanford.edu) on 21th of October, 2016.

Chapter 2 Cochlear implantation

2.1 Pros and cons

Since the inner ear is responsible for appropriate hearing, loss of auditory neurons or hair cells may lead to congenital or neurosensory hearing loss (Goutman et al., 2012). In case hearing-aids do not provide enough benefit, a cochlear implant can be useful to improve auditory perception. A cochlear implant can be beneficial and therefore improve quality of life. An investigation of the quality of life in post 1 year CI-users showes an improvement of the quality of life (Rumeau et al., 2015). Clinical effectiveness of CI is confirmed in a systematic review regarding children (Forli et al., 2011) as well as adults (Berrettini et al., 2011). The cochlear implant consists of an electrode, speech processor, microphone, transmitter and receiver (see Figure 6). The electrode is placed in the inner ear, where it functions as an artificial replacement along the basilar membrane of the cochlea. Acoustic signals are captured by the microphone of the cochlear implant and is transformed into electric impulses. These electric impulses are transferred to the auditory nerve and the stimulated fibers of the auditory nerve causes hearing (Petersen, Gjedde, Wallentin & Vuust, 2013). The cochlear implant is normally placed in the ear with more hearing deterioration, but anatomical alternations are taken into account. Vestibular function is also one of the influencing factors in deciding in which ear the CI will be implanted (Parmar et al., 2012; Robard, Hitier , Lebas & Moreau, 2015; Thierry et al., 2015). Implantation of the CI is done in the side with the least amount of vestibular function in case other factors (hearing loss, anatomy e.g.) are equal (Parmar et al., 2012).

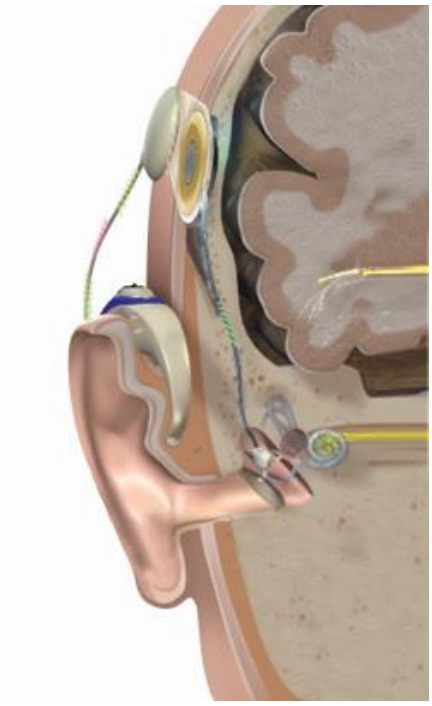


Figure 6 (right): The components of a cochlear implant, showing that the electrode is placed in the inner ear. Obtained from www.hoorzaken.nl/hoorverbetering/cochleair-implantaat on 22 November 2016, created by Advanced Bionics Benelux B.V.

Despite the well-known hearing benefits, several risks and cons can be experienced due to the cochlear implantation. Complications of the soft tissue in the cochlea is mentioned as one of the risks of cochlear implantation (Janssens de Varebeke et al., 2012). In a systematic review on cochlear implantation and complications, the most commonly reported post-operative complications are device failure, skin infections and vestibular problems (Terry, Kelt & Jeyakumar, 2015). Due to insertion of the electrode into the cochlea, hair cells can deteriorate to a certain amount. Considering the tonotopy of the cochlea, the electrode first reaches the hair cells that are responsible for the higher frequencies, expecting these frequencies to deteriorate (Podskarbi-Fayette, Pilka & Skarzynski, 2010). In further insertion towards the apex of the cochlea lower frequencies are expected to be damaged.

2.2 Criteria

Hearing preservation becomes more realistic because of the development of invasive surgical techniques and electrodes in different lengths and diameters (Usami et al., 2011; Nguyen et al., 2016). In the last couple of years criteria for CI candidacy expanded in a way, that patients with an increasing amount of residual hearing and younger patients are implanted due to advanced technological and surgical developments (Sampaio, Araújo & Oliveira, 2011; Kuang, Haversat & Michaelides, 2015). The requirements for cochlear implantation are extended due to the postoperative hearing results which suggested that an increasing number of patients, both adults and children, with residual hearing should be fitted with a cochlear implant (Havenith et al., 2013; Carlson et al., 2014; Gifford, Dorman, Shallop & Sydlowski, 2010). Due to these shifting criteria, more and more studies are aimed at pointing out the least harmful aspects of surgery and electrodes in cochlear implantation to achieve complete hearing preservation.

The definition of hearing preservation is still controversial (Hunter et al., 2016). In order to cope with this problem a classification of hearing preservation was proposed by Skarzynski et al. (2013), see Table 1. This definition is used in several studies (Santa Maria, Domville-Lewis, Sucher, Chester-Browne & Atlas, 2013; Mertens, Punte, Cochet, De Bodt & Van de Heyning, 2014; Hunter et al., 2016).

Table 1: Classification of hearing preservation based on the percentage of residual hearing suggested by Skarzynski et al. (2013).

Percent of residual hearing preserved	**Classification**
0-10 dB HL	Complete hearing preservation (HP)
11-29 dB HL	Partial HP
> 30 dB HL	Minimal HP
No measurable hearing	Loss of hearing/No hearing

On one hand the risk of hearing loss is due to the cochlear implantation, one the other hand vestibular problems are mentioned. Due to the anatomical proximity of the vestibular system and the cochlea (Parietti-Winkler, Lion, Montaut-Verient, Grosjean & Gauchard, 2015), vestibular function can also be impaired after cochlear implantation (Katsiari et al., 2013; Robard et al., 2015; Chen, Chen, Zhang & Qin, 2016; Devroede, Pauwels, Le Bon, Monstrey & Mansbach, 2016). Several aspects of cochlear implantation can influence preservation of both hearing and vestibular functions (Brown, Hullar, Cadieux & Chole, 2010), for example type of the electrode, type of surgery, type of insertion and the use of corticosteroids in the cochlea (Zanetti, Nassif & De Zinis, 2015). These variables concerning cochlear implantation are shortly mentioned in the following sections.

2.3 Surgical techniques

The main surgical techniques that are used in the Radboudumc, are cochleostomy and round window insertion. Classic cochleostomy consists of drilling into the mastoid (mastoidectomy), finding a way to the posterior scala tympani. This technique is seen as the standard for cochlear implantation (Postelmans et al., 2014; Nguyen et al., 2016). To decrease facial recess and leaking perilymph, the round window insertion technique is mentioned as an alternative surgery technique (Zanetti et al., 2015). This technique is described as the approach in which the electrode is placed via the round window in the inner ear. An electrode can be placed into the scala tympani without drilling. In another surgery technique, the extended round window approach, the area of the round window is enlarged by drilling into the bony structure (Wanna et al., 2015).

Soft surgery refers to another type of surgery, which was described by Lehnhardt (1993) and after him many other authors (Friedland & Runge-Samuelson, 2009). The aim of soft surgery is to reduce the damage of the cochlea and also to prevent unforeseen factors that might cause undesirable reactions in the cochlea (Friedland & Runge-Samuelson, 2009; Havenith et al., 2013). More explicitly, soft surgery is known for its drilling a minimal cochleostomy in order to avoid damage to the cochlea and keep suctioning of the perilymph to a minimum (Nguyen et al., 2016; Havenith et al., 2013). Discrete insertion of the electrode in combination with the administering of corticosteroids are important features that make soft surgery an important aspect in the preservation of residual hearing (Nguyen et al., 2016). Nowadays, the Radboudumc aims to maintain these discrete aspects in cochlear implantation.

2.4 Electrodes

Electrodes differ in shape, length and flexibility (Zanetti et al., 2015). Still, no consensus is reached about the most favorable insertion depth or electrode length for preserving residual hearing as much as possible (Nguyen et al., 2016). To prevent further deprivation of hearing, deep insertion is recommended (Usami et al., 2011), but on the other hand, deep insertion might damage the hair cells that still respond to low frequencies and therefore a short electrode is proposed (Gantz et al., 2016).

2.5 Electric and acoustic stimulation (EAS)

Part of the CI candidates are able to cope with hearing aids and other CI candidates with the least amount of hearing can benefit from the electrical stimulation of the cochlear implant. However, a third group can benefit from CI as a hearing aid in combination with the use of electric acoustic stimulation (EAS) (Podskarbi-Fayette et al., 2010). In patients with residual hearing in the lower frequencies, electric and acoustic stimulation (EAS) is used (Usami et al., 2011). Electric and acoustic stimulation consists of an electrode array into the cochlea hence providing high frequencies by electrical stimulation and acoustic stimulation for the low frequencies. In the operated ear, a hearing aid (HA) conveys low frequency information (Incerti, Ching & Cowan, 2013).

2.6 Plasticity

Cochlear implantation and hearing aids are known for their reorganization of the frequency mapping in the primary auditory cortex (Piotrowska, Lorens, Jedrzejczak & Skarzynski, 2010). In children, this reorganization seems superior compared to adults. Profound deafness seems partially reversible due to auditory rehabilitation after cochlear implantation (Thai-Van, Veuillet, Norena, Guiraud & Collet, 2010). In a tomography study of Petersen et al. (2013), cortical reactivation of the brain and therefore plasticity of the neural system was examined. The authors concluded that in CI-patients speech and speech-like stimuli activate brain areas which are normally activated in normal hearing people. Notable is, that this activation was only seen in post-linguals; no brain areas which are associated with speech comprehension were activated in pre-lingual cochlear implanted patients.

Plasticity due to cochlear implantation can occur with the auditory cortex, but also the vestibular system can be reorganized after loss of function (MacDougall & Curthoys, 2012). Due to cochlear implantation, unilateral vestibular loss can occur, in which case a patient can experience vertigo and postural unsteadiness. However, a study of MacDougall & Curthoys (2012) showed that in 70-80% of the patients with unilateral vestibular loss, vestibular compensation solved their symptoms. Despite the initial loss of the vestibular function, symptoms could be reduced by this reorganization.

Chapter 3 Measuring the auditory and vestibular function

3.1 Methods to examine auditory function

The type, degree and configuration of hearing loss are the components that provide information about hearing loss (ASHA, 2005). Based on the location of lesion, sensorineural (organ of Corti, pathways or higher auditory centers) and conduction (mechanical part of the ear) hearing loss can be defined. Mixed hearing loss is a combination of both (Baiduc, Poling, Hong & Dhar, 2013). The auditory function can be measured with pure-tone air and bone conduction audiometry, executed by an audiologist to establish the amount and type of hearing loss. Before the audiometry can be done, physical inspection of the outer ear is needed to exclude the patient from having any abnormalities of the ear drum and auditory canal (Campbell, Hammill, Hoffer, Kil & Le Prell, 2016; Baiduc et al., 2013). During conventional audiometry, the patient is exposed to several sounds through a headphone. These sounds vary in their frequency, in order to measure all frequencies that appear in the cochlea. Measuring air conduction contains of a headphone that will represent the conduction of the sound from the outer, to the middle and inner ear up to the nervous system (Causon, Verschuur & Newman, 2015; Mattingly, Uhler & Cass, 2016). Pure tone threshold is tested for each frequency, i.e. the least amount of dB the patient needs to 'hear' the sound at that frequency (ASHA, 2005; Campbell et al., 2016). In this behavioural test, the patient is requested to respond in case the sound is heard. Each frequency should be tested using the Hughson Westlake procedure, in which each frequency is measured in steps of 10 dB (Carhart & Jerger, 1959). In an audiogram, using the verbal responses of the patient to each sound heard, the pure-tone threshold average (PTA) can be noted. Skarzynski et al. (2013) defines PTA as the pure-tone average for unaided frequencies between 125–8000 Hz. PTA is the mainly used standard for the assessment of pre- and post-operative hearing preservation (Causon et al., 2015).

3.2 Methods to examine vestibular function

No single vestibular test can assess the complete vestibular labyrinth (Wuyts et al., 2007) However, a combination of available tests can obtain information about the vestibular system. The requirement for vestibular testing is that healthy patients can be distinguished from pathologic patients with a high sensitivity and acceptable specificity (Shupak, Kaminer, Gilbey & Tal, 2010). Not only the deficit, but also localization of the vestibular problems can be detected using vestibular testing (Eza-Nuñez, Fariñas-Alvarez & Fernandez, 2016). The methods to examine vestibular function can be distinguished based on the part of the inner ear that is being measured. Another distinguishing factor is the frequency domain in which the vestibular function is stimulated (Eza-Nuñez et al., 2016). Caloric irrigation is the method with the lowest frequency, followed by the Velocity Step Test (VST). In this study the method with the highest frequency is the video Head Impulse Test (vHIT). Although Vestibular Evoked Myogenic Potential (VEMP) is not included as a clinically available vestibular method in the current study, this method will be mentioned briefly.

3.2.1 Objective methods

3.2.1.1 Video Head Impulse Test (vHIT)

After the 'bed-side' head impulse test (HIT/head thrust test) is considered to be a non-sensitive instrument to examine and identify deficits in the peripheral vestibular function (Mantokoudis et al., 2016b), the video HIT provides attention as an appropriate alternative in vestibular diagnosis. The measurement of the vHIT is based on the VOR, which in case of high acceleration head movements or impulses can generate slow-phase eye movements with high velocity in order to gaze (Bronstein et al., 2015). During the vHIT, a patient is asked to fixate on a target during a quick movement of the head by the examiner. These movements are in the directions of the semicircular canal pairs, see Figure 7.

The eye response occurs due to the high velocity (over 150°/second) and a frequency of 1-16 Hz (Eza-Nuñez et al., 2016). The vHIT is the first potential measurement to evaluate the function of the six semicircular canals in a simple way (McGarvie et al., 2015; Hamilton, Zhou & Brodsky, 2015). The rotation response of the eye following an abrupt head rotation can be evaluated by quantification of the VOR gain and detection of corrective saccades. Normal eye movements are almost equal in velocity with a minimum difference in time (Agrawal et al., 2014). Therefore, in healthy patients no deviation is expected between eye and head velocity after quickly moving the head and gain is still focused on the target (MacDougall & Curthoys, 2012). The vHIT detects the so-called 'catch-up' saccade in patients with pathological VOR which occurs if the slow-phase vestibular eye movements are not able to preserve the fixation (MacDougall & Curthoys, 2012; Bronstein et al., 2015). These compensating re-fixating saccades can be covert or overt in the opposite direction of the head, which can be detected with an advanced high frequency (> 100 Hz) video-camera (Heuberger et al., 2014; Weber, MacDougall, Halmagyi & Curthoys, 2009). Corrective saccades are a sign of loss of semicircular canal function (MacDougall & Curthoys, 2012).

The vHIT is an appropriate and effective test to detect semicircular canal dysfunction in both unilateral and bilateral peripheral vestibular losses, not only in children < 20 years (Hamilton et al., 2015) but also in adults (MacDougall, McGarvie, Halmagyi, Curthoys & Weber, 2013). In an attempt to validate the vHIT, no significant differences were found with the scleral search coil, which had been the golden standard for measuring vestibular dysfunction so far (MacDougall et al., 2013; Agrawal et al., 2014). Test-retest and interrater reliability of the vHIT in both adults and pediatrics was established (Ross & Helminski, 2016). Examining healthy subjects resulted in small decreases of VOR gain in increased head velocity. In the vertical planes, the variability of VOR gain was concluded to be higher. Age did not seem to be a significant factor in VOR gain in horizontal and anterior canals; only a small significant effect was measured for the posterior canal, in which a small decrease of VOR gain was measured (McGarvie et al., 2015). For a complete description of the vHIT, see Bronstein et al. (2015) or McGarvie et al. (2015).

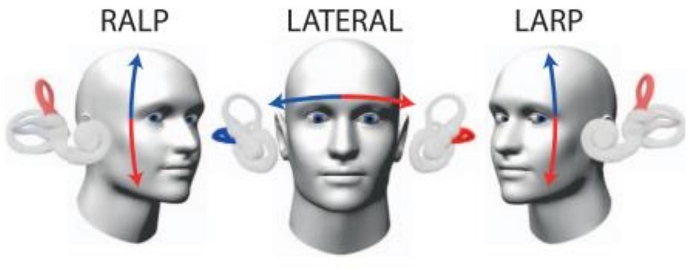


Figure 7: Testing the six semicircular canals with the vHIT by moving the patient's head in the direction of both red and blue arrows in the direction towards the right and left anterior and posterior canal. Movements are based on the anatomy of the semicircular canals. Obtained from MacDougall et al. (2013)

3.2.1.2 ENG

Registration of eye movements can obtain information about the vestibular system. The scleral search coil method is often seen as the golden standard as a method for recording eye movements, based on electrical information measured with a small coil of wire (Wuyts et al., 2007), but is clinically not acceptable. Videonystagmography (VNG) is an alternative that is used for the recording of eye movements (Wuyts et al., 2007). In the Radboudumc, electronystagmography (ENG) is used. ENG is also known as electro-oculography (EOG) and one of the most common and cost-effective method for the registration of eye movements (Stewart et al., 1999; Wuyts et al., 2007; Ganança, Caovilla & Ganança, 2010). ENG relies on the variation of the corneal-retinal potential, that is measured by electrodes placed around the eyes (Ganança et al., 2010; Siddiqui & Shaikh, 2013). Maximum slow-phase velocity (SPV) of the nystagmus can be calculated (see Figure 8) which provides information about vestibular asymmetry (unilateral weakness) and directional preponderance. ENG is an important, indispensable research tool to assess eye movements during vestibular testing (Gupta & Mundra, 2015; Szirmai & Keller, 2013). During the assessment of vestibular function, mental alertness of the patient is preferred since greater nystagmus occur in this condition (McGovern & Fitzgerald, 2008). ENG can be used during several objective vestibular tests, that will be described in the sections below.

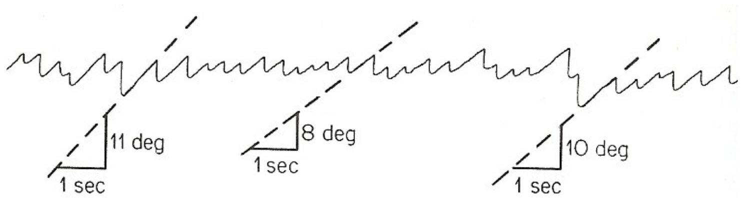


Figure 8: Calculation of the maximum slow-phase velocity (SPV) of nystagmus (Baloh, Lyerly, Yee & Honrubia, 1984). Maximum SPV is the parameter used in ENG.

3.2.1.3 Oculomotor tests

The oculomotor movements previously mentioned, which are executed by the extraocular eye muscles, are triggered by moving objects or movement of the head or body. Visual acuity can be measured recording the OKN response to moving stripes in the patient's field of vision (Spering & Montagnini, 2011). Smooth pursuit eye movements are provoked using a moving object on a screen while the responses of the eye are recorded. The efficiency of the saccades and smooth pursuit is confirmed for central lesions with accurate sensitivity (83%). It is preferable to use the results of both movements over testing only one of them (Tirelli et al., 2011). Oculomotor tests provide information about the patient's ability to make these involuntary eye movements. Results of these tests are gathered prior to the tests that are mentioned below.

3.2.1.4 Velocity Step Test (VST)

The Velocity Step Test (VST), sometimes called the rotatory chair test, is a commonly used test in vestibular examination, providing information about both ears due to the simultaneously rotating of a chair (Eza-Nuñez et al., 2016). The VST can be used to precisely measure the VOR response due to physiologic stimulation of the horizontal canals (Chan, Galatioto, Amato & Kim, 2016). The patient is seated on a chair that can be controlled by the examiner. After the chair is rotated with a sustained, constant velocity, post-rotatory nystagmus (PRN) occurs in healthy patients immediately after this rotation stops

(Mantokoudis et al., 2016a). Eye movements are measured and provide information about the neurophysiologic interaction of the vestibular system via brainstem pathways (Cullen, 2012). In a clockwise chair rotation, a nystagmus towards left occurs after the chair stopped. Counterclockwise results in a nystagmus towards right. For both sessions, information about the nystagmus is gathered. In VST, the maximum slow phase velocity of the nystagmus at time of the stop is examined (v, in degrees/sec) as well as the time constant tau (t, in sec). Gesamtamplitude is the multiplication of v and t and can be seen as an extra parameter to diagnose nystagmus.

3.2.1.5 Caloric testing

Stimulating the vestibular organs with cold (30° Celsius) or hot (44° Celsius) water induces the perilymph in the semicircular canals and therefore causes a flow to or from the utricle (De Barros & Caovilla, 2012). Bithermal irrigation evaluates the horizontal semicircular canal and the superior vestibular nerve (Andrade, Santos-Perez, Diz, Caballero & Soto-Varela, 2013). The flow of perilymph provokes polarization or depolarization, depending on the temperature of the water (see Figure 9). The VOR occurs due to this flow of perilymph (Adams, Telian, Kane & Butler, 2016; Eza-Nuñez et al., 2016). During irrigation, eye movements are recorded with electronystagmography. Irrigation can be done using water or air (De Barros & Caovilla, 2012). In the Radboudumc, water is used unless the eardrum is perforated.

In the binaural bithermal test, 4 ear irrigations with both hot and cold water take place while eye movements are recorded (Adams et al., 2016). Each ear can be examined independently (Eza-Nuñez et al., 2016) and information of the horizontal semicircular canal can be obtained (Kuang et al., 2015) if the chair with the patient in supine position is tilted 30° (degrees) backwards. Binaural bithermal caloric testing is considered to be the only available test to detect the side of peripheral vestibular problems (Shupak et al., 2010). During irrigation with cold water, the endolymph shrinks and a decreased vestibular afferent firing rate results in a nystagmus towards the contralateral ear (see Figure 9). Irrigation with warm water results in an increased rate of vestibular afferent firing and nystagmus occurs towards the ipsilateral ear (De Barros & Caovilla, 2012; Jacobson, Newman & Peterson, 1993). A systematic review reveals that irrigations with only one temperature (monothermal caloric test) does not seems proficient in detecting patients with slightly abnormal vestibular function (Adams et al., 2016). In a study by Eza-Nuñez et al. (2016), the authors compared the results of irrigation results, VST and vHIT. The accordance among the three diagnostic tests was low due to the difference in stimulus frequency and structures and processes that are involved in each test. The difference between sensitivity and specificity among the three tests was low (difference in sensitivity 0.026 and specificity 0.073). Although the caloric test was defined as best based on the statistical power, the discomfort and duration of the caloric test loses from the convenience and sufficiently powerful vHIT.

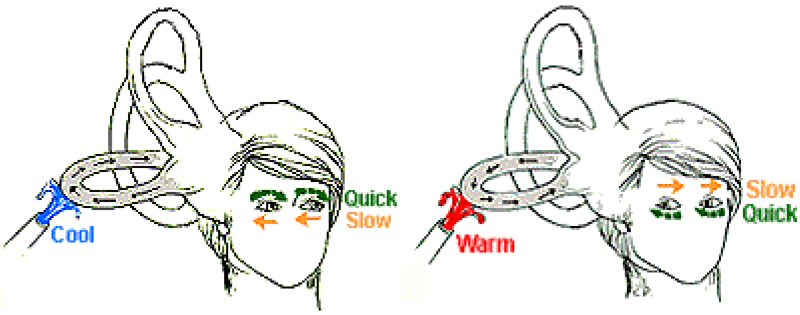


Figure 9: Depending on the water temperature, the endolymph flows to or from the ampulla of the horizontal canal. This causes the VOR to create nystagmus to the right or to the left. Warm irrigation in the right ear evokes nystagmus to the right. Cold water in the right ear evokes nystagmus to the left. For the left ear this is vice versa. Adapted and obtained from Brookler et al. (1986).

3.2.1.6 VEMP

Disorders of the vestibular system can cause impairment of the descending and ascending tracts in the brainstem (Oh, Kim & Kim, 2016). Vestibular Evoked Myogenic Potential (VEMP) is a technique that is able to detect this impairment due to evaluation of these descending and ascending tracts (Andrade et al., 2013). Nowadays, VEMPs are not only used in peripheral neurovestibular disorders, but are also assessable for central neurological disorders (Venhovens, Meulstee & Verhagen, 2016). VEMPs cannot only test the function of the otolithic end organs (saccule or utricule), also the vestibulospinal and vestibulo-ocular pathways can be examined (Oh et al., 2016). Stimulation with air or bone conduction results in reactions of the utricular and saccular maculae, which are connected to the corresponding vestibular area in the brainstem. Due to this stimulation, action potentials are evoked and presented in waveforms (Oh et al., 2016; Venhovens et al., 2016). During the assessment of VEMPs, stimuli are presented into the ear and the activation of the responding organ can be recorded (Psillas et al., 2014; Venhovens et al., 2016). In cVEMP, the evoked potential is measured from the sternocleidomastoid muscle to examine the function of the saccule and the inferior vestibular nerve function (Papathanasiou, Murofushi, Akin & Colebatch, 2014; Meyer, Vinck & Heinze, 2015). oVEMP is mostly used for the examination of responses from the otolith end-organ (utricle) to the brainstem vestibular nuclei through the superior vestibular nerve (Venhovens et al., 2016).

No correlation was found in their ability to test the vestibular function due to the complementary function of caloric testing and cVEMPs (Andrade et al., 2013). Caloric testing can examine the function of the horizontal semicircular canal whereas the cVEMPs is able to examine the function of the saccule and inferior vestibular nerve. VEMP, both oVEMP and cVEMP, could be extensions to the currently available diagnostic measurements in the clinical procedure of the Radboudumc. At the time of writing this study, the implementation of VEMPs in the measurement of balance is examined.

3.2.2 Subjective/behavioural methods

3.2.2.1 DHI

Dizziness remains a subjective symptom that is challenging to assess (Mutlu and Serbetcioglu, 2013). Sense of spinning motion, loss of balance or feelings of lightheadedness can be perceived by the patient to a greater or lesser extent (Bisdorff, Von Brevern, Lempert & Newman-Toker, 2009). In this study the Dizziness Handicap Inventory (DHI) is used in an attempt to measure the subjective dizziness. The DHI contains 25 questions that is a selfassessment measure for dizziness, subdivided into three categories (Jacobson & Newman, 1990). In the categories physical, functional and emotional, patients can select the most appropriate answer choosing “yes” (4 points), “sometimes” (2 points) or “no” (0 points) (McCaslin, Jacobson, Grantham, Piker & Verghese, 2011). According to Jacobson & Newman (1990), the total DHI score should at least drop 18 points per individual, to interpret this as a genuine change. In a systematic review, Mutlu & Serbetcioglu (2013) concluded that the Dizziness Handicap Inventory is the most widely used self-reported measurement for evaluating the effect of vestibular problems on the self-perceived handicap. This conclusion was based on the reliability, validity, internal consistency and correlation between objective vestibular assessment and the DHI. Moderate correlation existed between DHI and the rotation chair however, no correlation was found between DHI and caloric responses and DHI and cVEMP (Mutlu & Serbetcioglu, 2013). No effect of age on the self-perceived handicap was reported in the scores of the subcategories or total score of the DHI (Mutlu & Serbetcioglu, 2013). The loss of vestibular function that occurs due to aging was not always measurable with the DHI, although the prevalence of abnormalities in objective measurement was high (Davalos-Bichara & Agrawal, 2014). This conclusion however, was based on outcomes of the outdated methods HIT and the modified Romberg test, none of which are described in the vestibular examination protocol of the Radboudumc.

3.3 Audio function pre-operative versus post-operative

Earlier studies about hearing preservation after cochlear implantation were conducted. Post-operative hearing was preserved in 39% of the CI patients in a study by Zanetti et al. (2015). More preservation was seen in the lower frequencies than in the higher frequencies. In Hunter et al. (2016), preservation of hearing was measured at 125, 250 and 500 Hz pre- and post-operative. The author reported deterioration of hearing function with a mean threshold difference of 20.2 dB post-operative. In the study of Havenith et al. (2013) post-operative low frequency hearing loss ranged from 10 to 30 dB at 125, 250 and 500 Hz, regardless of surgical technique. No benefit regarding preservation of hearing in CI patients was reported for either cochleostomy or round window approach. For the frequencies 250 to 4000 Hz, significant deterioration for air conduction threshold was found (Raveh, Attias, Nageris, Kornreich & Ulanovski, 2015) with a mean of 10-21 dB. No significant deterioration was found for the bone conduction thresholds. These results only applied to a selected group of patients. Further investigations concerning a large number of patients with preserved hearing in low frequencies were recommended by the author.

In a retrospective analysis of studies from 2000 till 2014, factors that significant influenced the hearing preservation were mentioned (Causon et al., 2015). Aspects of electrodes (insertion angle of the electrode, electrode array type), surgery (the site of insertion, use of steroids during surgery) and hearing etiology (progressive versus stable hearing loss and cause) were considered to be of significant influence on hearing preservation. In Hunter et al. (2016), age, surgical technique and the use of steroids during the surgery was not correlated with the hearing preservation outcomes at the time of activation and 6 months post-operative. In Zanetti et al. (2015), no significant correlation was found between age, side of implant, type of electrode or type of surgery and the preservation of residual hearing. Only a small trend was seen in the comparison between children and adults.

3.4 Vestibular function pre-op versus post-operative in cochlear implantation

Cochlear implantation can impair the saccule, horizontal semicircular canals and utricle; however, researchers disagree about which component has the highest risk of impairment.

Fujimoto et al. (2015) states that the vestibular organs that are closest to the cochlear seemed more at risk due to the anatomical proximity. The amount in which the horizontal canal and the saccule suffer from cochlear implantation was equal according to Katsiari et al. (2013). On the other hand, some researchers stated that the saccule is damaged more than the horizontal canal function (Devroede et al., 2016; Krause, Louza, Wechtenbruch & Gürkov, 2010). In another study, horizontal semicircular canals seemed to be more at risk than the saccule (Chen et al., 2016). Differences in these conclusions may be attributed to the number of patients selected, types of implant and surgical techniques.

Using variable types of measurement (objective, subjective or both), several conclusions were drawn about the influence of the cochlear implant on the vestibular function. For example, Katsiari et al. (2013) used cVEMP and caloric measurement to examine the saccule and horizontal canal before and after implantation. Significant deterioration of the horizontal canal ($p = 0.01$) and the saccule ($p = 0.002$) was found in the implanted ear, but not in the non-implanted ear. In a study by Chen et al. (2016), significant decrease of caloric results in 93% of the implanted ears was found. Also, oVEMPs and cVEMPs waveforms decreased significantly or vanished completely in the implanted ear. In 30% of the patients examined in Batuecas-Caletrio et al. (2015), the results of the vHIT show post-operative decline to a gain below 0.8, which is defined as insufficient. Tsukada, Moteki, Fukuoka, Iwasaki & Usami (2013) examined the vestibular function pre- and postoperatively in cochlear implantation, through the results of cVEMP- and caloric-outcomes. The participants for this study received the EAS (electric acoustic stimulation) procedure, since their hearing loss is mostly preserved in the lower frequencies. No significant difference was found in the pre- and post-operative cVEMP and caloric outcomes. In a study of Jacot, Van Den Abbeele, Debre & Wiener-Vacher (2009), vestibular function was examined pre- and post-operative in cochlear implanted children. Based on caloric test and cVEMP, in 50% of the cases, vestibular function was affected. In 10% of the patients (n = 224), vestibular loss was diagnosed post-operative.

Vestibular dysfunction influences the accurate perception of the environment and the balance (Le Nobel, Hwang, Wu, Cushing & Lin, 2016). During processing by the brainstem and cerebellum, discrepancies in the information received can result in dizziness, sense of vertigo or imbalance. Despite the significant deterioration of the horizontal canal and saccule reported by Katsiari et al. (2013), no correlation was found in the vestibular symptoms of the patients. Age, sex, implant side, preoperative caloric results and pre-operative cVEMP status and changes in both caloric testing and cVEMP testing did not seem to correlate with the vestibular symptoms. Therefore, a change in postoperative vestibular function that is measured with objective measurements, does not always result in post-operative vestibular symptoms. No specific manner of investigation of the dizziness symptoms was mentioned. In Chen et al. (2016), significant decrease of post-operative vestibular function was reported, based on oVEMP, cVEMP and caloric results compared with the pre-operative status. This deterioration did not correlate significantly with age, gender, side of the implantation or vertigo symptoms. However, no clarity exists about the exact questionnaire that was used assessing the vertigo symptoms.

Sometimes, when subjective dizziness is present, the symptoms cannot always be measured objectively. Examination of objective measurement using caloric tests and vHIT and subjective measurement using DHI did not reveal a significant correlation (Batuecas-Caletrio et al., 2015). Based on a questionnaire, no correlation between subjective symptoms and the objective measurement cVEMP was found in Krause et al. (2010). For the subjective symptoms, no significant influence of the factors gender, implant type, side of implant, surgeon, cause of deafness and pre-operative vertigo was concluded. In a study of Le Nobel et al. (2016) vestibular symptoms were examined pre- and post-operative in 1 week and 1 month. No significant difference between pre- and post-operative DHI-scores were examined, but results were based on a small group. Therefore, subjective dizziness might also be absent in post-operative cochlear implanted patients.

Also in healthy people, vestibular function can be influenced by aging (Maheu, Houde, Landry & Champoux, 2015). The effect of normal aging on the vestibular symptom is examined in a systematic review by Zalewski (2015). The author reported that the majority of the studies did not find any correlation between decline in vestibular function and their histological reports. In case abnormalities were present, these differences were usually subtle and fell within normal range. In a study by Maes et al. (2010), no main effect of aging in irrigation were reported, although an increase of slow-phase velocity was found with advancing age. This was especially seen in warm irrigation. In VST, only subtle decreased values with advancing age were found.

Similar studies about auditory and vestibular functions were performed at the Radboudumc Nijmegen. In the study of Kieft (2010), postoperative horizontal semicircular canal dysfunction was examined using caloric tests and VST. Risk factors such as cause of deafness, age at implantation, surgical procedure, type of electrode, surgeon, time between surgery and vestibular examination and postoperative deterioration in PTA were examined in order to find any correlation between these factors and vestibular deterioration. The author concluded that 25.7% of the subjects lost vestibular function to a certain amount. The predictors age and cause of deafness seemed of significant influence on this deterioration in vestibular function. One of the limitations of this study and the benefit of the current study is the amount of pre-operative data of the vestibular function.

3.5 Aim of the present study

Shifting criteria for cochlear implantation resulted in patients who have preserved residual hearing in low frequencies. More information is needed about the effect of unilateral cochlear implants on the auditory and vestibular function of these patients. Therefore, data of the available audiograms and objective and subjective vestibular tests of patients receiving a cochlear implant between 2010 and 2016 in the Radboudumc will be investigated. Point of interest is whether the vestibular function, according to both subjective and objective vestibular methods, changes due to the cochlear implant and if any change in vestibular function correlates with changes in auditory function. Additionally, the influence of age and cause of deafness on the auditory function will be examined. Therefore, the following questions are to be answered:

Research question 1: Can the change in the ipsilateral auditory function of CI patients be predicted based on age and cause of deafness?

Research question 2: How does the vestibular function examined by objective vestibular techniques change due to the cochlear implantation?

Research question 3: How does the subjective vestibular function change due to the implantation, measured by the DHI?

Research question 4: Are changes in auditory and vestibular function related to each other?

Chapter 4: Method

4.1 Test-protocol and norm-values

This study was a follow-up study of previous comparable studies, although the current study involved different research questions, with a more detailed database. This database existed of the results of audiometric and vestibular tests. Standard protocol in the Radboudumc for patients that were considered for cochlear implantation involved audiometric and vestibular testing.

4.2 Audiometric testing

Audiometric testing included the examination of thresholds up to 125 Hz, 250 Hz, 500 Hz, 1000 Hz, 2000 Hz and 4000, 6000 Hz and 8000 Hz. The average pure tone threshold (PTA) was calculated for these frequencies. Only unaided data, which was measured with air conduction, was selected. The difference between pre- and postoperative provided information about loss, improvement or equality of hearing. Examination of the threshold 125 Hz did not provide sufficient subjects. The frequencies 250 and 500 Hz were the frequencies of interest, representing the low frequencies of the auditory function. Data were collected of unaided air conduction in which masking occurred based on the clinical opinion of the audiologist. These data were obtained from Audiologicx, the software of the Radboudumc which is an audiogram database.

4.3 Vestibular examination

Complete vestibular testing included bilateral examination of the VST, bithermal caloric test for both ears, vHIT for each canal and DHI. A fixed order of vestibular testing (see Table 2) was used. All patients that were evaluated for their vestibular function at least had the VST and caloric test. In some cases, also the DHI and the vHIT were completed. Eye movements were registered using electronystagmography, results were analyzed using ´BalanceLab´ version 2.0.0 (Maastricht Instruments B.V., 2004). Based on the norm values, conclusions about the vestibular function of the patient were described by the vestibular examiner. Raw scores and conclusions were interpreted in consultation with an experienced clinician. The norm values for the VST, caloric test and vHIT are mentioned in Table 3. For the patients tested with DHI, scores were categorized (see Table 4). The etiology of deafness was hereditary, acquired and unknown.

Table 2: Fixed order of the vestibular examination and their parameters

Fixed order	**Parameters**
Anamneses	Cause of deafness, medicines
vHIT	Mean gain of the horizontal ipsilateral canal
DHI	Total score
Oculomotor tests	Calibration horizontal and vertical, smooth pursuit, saccade random, gaze, OKN
VST	Velocity in start (ν) and duration (τ)
Caloric test	Ipsilateral warm and cold

Table 3: Norm values for VST, caloric test and vHIT

Subtest	**Norm values**
VST	
Gain	33-72
Velocity in start (ν)	30-65 °/s
Time constant (τ)	11-26 seconds
Gesamtamplitude	485-1135°
Directional preponderance	< 25%
Caloric test	
Cold water (30^0)	7-31
Warm water (44^0)	10-52
Directional preponderance	< 30%
Unilateral weakness	< 20%
vHIT	
VOR gain	> .8

Table 4: The amount of points as a results of the DHI shows the category of the subjective symptoms, based on Whitney, Wrisley, Brown & Furman, (2004)

DHI result	**Category**
0	No handicap
1 – 30	Mild handicap
31-60	Moderate handicap
> 60	Severe handicap

4.3.1 Anamneses

Clinical vestibular subjective anamneses took place. The vestibular examiner noted the cause of deafness and the use of medications.

4.3.2 vHIT

During the vHIT, the patient was seated on a regular chair. During all sudden movements of the head during the examination, eye movements were recorded with a camera using the Synapsys system (Synapsys SA, France.) While remaining seated, the patient was requested to gaze at a point straight ahead. The examiner was seated behind the patient and his/her hands held the patient's head. For examination of the horizontal semicircular canal, the head was quickly moved in lateral direction. The camera calculated the mean gain of the movements in one direction. An average gain of > .8 is established as normal, with a minimum of 5 reliable measurements of the canal, according to the Synapsys system.

4.3.3 DHI

The Dutch version of the DHI was used to assess the amount of dizziness that the patient experienced (Appendix I). The patient was asked to fill in the DHI in a way that the answers were only based on the amount of dizziness they experienced. The total score was analyzed, which represented the subjective complaints of the patient.

4.3.4 Oculomotor tests

Before the vestibular test procedure was started, the oculomotor movements were tested to ensure the patient was able to show the expected nystagmus. The parameters gaze, smooth pursuit, OKN and other abnormalities of the vestibulo-ocular reflex were checked.

4.3.5 VST

Patients were seated upright in a chair in complete darkness. Complete VST was conducted on both sides. Eye movements of both eyes were analyzed using ENG. Maximum slow-phase velocity of the nystagmus was calculated for each nystagmus and averaged for each eye. Maximum at time of deceleration (ν) and time constant (τ) of the nystagmus was determined.

4.3.6 Caloric tests

Caloric tests were conducted with cold and warm water in both ears. The temperature of the water was 30° Celsius for cold and 44° Celsius for warm caloric testing. The water was infused in the external auditory canal for 20 seconds. A fixed order in which the ears are examined was pursued: right warm (RW) – left warm (LW) – left cold (LC) – right cold (RC). Only irrigation with water was analyzed. For each irrigation, slow phase velocity maximum and fixation suppression were measured by Balance Lab.

Pathological upper and lower limits for hypo-/hyperreflexia and areflexia in irrigation values are noted in Table 5.

Table 5: For both cold as warm irrigation, the lower and upper limit are mentioned.

Temperature	Lower limit	Upper limit
Warm	10	52
Cold	7	31

When values are beneath the lower limit, hyporeflexia is diagnosed. When the upper limit is exceeded, hyperreflexia is diagnosed. Values between 0 and 2 in both warm as cold in both ears are diagnosed as areflexia.

4.4 Correction for contralateral change between pre- and post-operative status

To discuss the amount of de- or melioration of balance in the ipsilateral, the contralateral is needed as a control function. Patients were excluded when their diagnosis of the contralateral side changed to a lower level, i.e. that patients who were pre-operatively diagnosed with hyperreflexia (warm or cold) and post-operatively become 'normal'. Patients having pre-operatively normal balance function and changed to hypo or areflexia postoperatively were also marked. At last, patients who start hypo and have areflexia post-operatively were also excluded.

The parameters of the VST, both time of deceleration (ν) as time constant (τ), represent the variables for bilateral balance function and come from the same measurement. Excluding patients with contralateral deterioration, based on 'ν' and 'τ', isn't meaningful, since the results that are measured can come for either ipsi- or contralateral side. To analyze the presence of a vestibular symmetry or asymmetry, Gesamtamplitude was used as variable that represents the vestibular function, since this variable is based on the multiplication of 'ν' and 'τ'.

In the analysis of DHI results, all patients with pre- and post-operative results will be analyzed. A second analysis will be executed, in which only patients with objectively seen contralateral deterioration are included.

4.5 Subjects

Patients that received a unilateral cochlear implant between January 2010 and June 2016 in the Radboudumc were considered for analysis. Of all these patients, data of their pre- and post-operative audio and vestibular examination were collected. Based on the available data, patients were selected for auditory and vestibular research, see Appendix II. In case a patient was tested another time (in the pre- or post-operative stage), the results of the measurements closest to the surgery were selected, unless these results were incomplete. Of this patient group, which totals 626 patients, not everyone received vestibular testing or auditory testing. To select the appropriate patients, groups were made to assess if the patients received both vestibular as auditory examination (see Table 6)

Table 6: The number of patients with auditory and/or vestibular examination, based on the examination the patient underwent.

	Auditory examination	Vestibular examination	Number of patients
Group 1	Yes	Yes	491
Group 2	Yes	No	100
Group 3	No	Yes	11
Group 4	No	No	24
Total			**626**

Of each patient in group 1 & 2, results on the PTA were established pre- and post-operative. For the correlation between these data and age and cause of deafness, multivariate regression was used. This was repeated for the threshold on 500 Hz and 250 Hz. Data of the selected participants were checked for the amount of hearing loss on their contralateral side. In case the difference between pre- and post-operative for the contralateral side was more than 10 dB (deterioration or melioration), these participants were excluded for the analysis. Eventually, 420 participants were selected and after correction for the contralateral side, 321 patients remained.

For the vestibular analysis, data of groups 1 & 3 resulted in 168 patients that received both pre- as post-operative vestibular analysis. Not all patients were tested in the vHIT and/or DHI (see Table 7).

Table 7: Results of the mentioned vestibular tests were collected of all the selected patients who underwent vestibular examination. Oculomotor tests were examined in all 168 patients.

VST	Caloric test	vHIT	DHI	Number of patients
X	X	X	X	75
X	X	X		9
X	X		X	45
X	X			39
				168

4.6 Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS), version 22 (SPSS Inc., Chicago, IL, USA). The reported p-values were two-sided, significance was established in case p values were less than 0.05. Descriptive statistics were mentioned for each analysis to provide an overview of the number of participants in each variable.

Multivariate regression was used for the research questions in which the influence of the predictors on the dependent variable was measured. Paired t-test was used to analyze the data of pre- and post-operative vestibular measurement. Two paired samples t-tests were conducted for ν and τ regarding VST. Results of warm and cold irrigations were analyzed and for the vHIT the lateral canal was analyzed. The total score of the DHI was compared pre- and post-operative, for which paired samples t-test was used.

4.7 Assumptions

For multiple regression, several assumptions needed to be considered before reliable interpretation was allowed (Field, 2013). The assumption for sample size was that for each independent variable, 20 samples were needed. For research question 1, this assumption was checked. For research question 4, in the regression of vHIT only 39 patients were available. Regression regarding caloric results involved 70 patients, data of 83 patients was used for the VST. Multicollinearity was checked within the output of VIF statistics. The assumption for multicollinearity states that no perfect linear relationship between two or more predictors should exist (Field, 2013). VIF values quantify the severity of multicollinearity and values lower than 3 show that the assumption of multicollinearity was checked. For the multiple regressions in research question 4, all values of variance inflation factors (VIF) statistics were less than 3. The normal P-P plot showed outliers, and for some variables the Cook's distance gave sufficient reason to exclude them. For each statistical test, outliers were detected and removed, based on the P-P plot and Cook's distances. Cook's distance is a calculated value for each data point to estimate the influence of this item (Field, 2013).

Conducting a paired samples test, several assumptions should be met. Firstly, sampling distribution of the differences between scores should be normally distributed (Field, 2013). Secondly, data must be at interval level. For each variable of any paired samples t-test, a boxplot was executed. For research questions 2 and 3, the paired samples t-test was used since the same patients were tested in one pre-operative stage and post-operative stage. A new variable was created, which was a calculation of pre- minus the post-operative result, to test normality of the sampling distribution of the differences. These variables showed normal distribution and therefore, assumption of normality was met. All dependent variables in research questions 2 and 3 were at interval level, so both assumptions for paired samples t-tests were met.

Chapter 5 Results

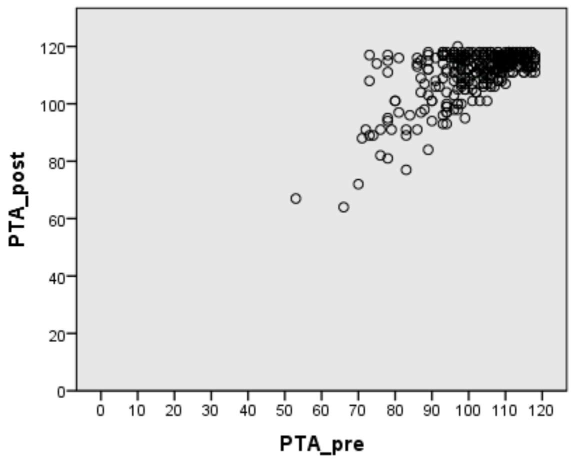
5.1 Can the change in the ipsilateral auditory function of CI patients be predicted based on age at implantation and cause of deafness?

Of the patients that were selected for this analysis, deterioration/melioration in the contralateral hearing was established. Of the 420 patients with pre- and post-operative results of hearing thresholds, 99 patients showed deterioration in their contralateral ear. Of the remaining 321 patients, the difference between the threshold of PTA, 500 Hz and 250 Hz was examined pre-operative versus post-operative, using 3 paired t-tests. In Table 8, these thresholds and their number of patients are mentioned. Outliers of each variable were removed, as described in Chapter 4.7.

Table 8: Mean, minimum, maximum, standard deviation in dB HL and number of patients of the pre- and post-operative hearing variables

Variable	**Mean (dB HL)**	**Minimum threshold (dB HL)**	**Maximum threshold (dB HL)**	**Standard deviation (dB HL)**	***N***
PTA_pre	102	53	118	11	317
PTA_post	112	64	120	9	317
Difference_PTA	10	-7	44	9	317
500Hz_pre	91	5	120	20	315
500Hz_post	109	10	120	16	315
Difference_500Hz	18	-5	60	14	315
250Hz_pre	78	0	110	24	311
250Hz_post	93	5	110	21	310
Difference_250Hz	15	-10	60	14	310

On average, the threshold of PTA was significantly higher in post-operative stage (M = 112, SE = .5), compared to the pre-operative stage (M = 102, SE = .6), $t(316)$ = -17.93, p = .001. For the threshold of 500 Hz, the post-operative results were significantly higher (M = 91, SE = 1.2) compared to the pre-operative results (M = 109, SE = .9), $t(314)$ = -22.93, p = .000. Regarding the threshold of 250 Hz, post-operative results of the threshold were significantly higher (M = 78, SE = 1.2), $t(314)$ = 17.82 , p = .000.
Measurement of the pre- and post-operative thresholds in PTA, 500 Hz and 250 Hz of the patients can be seen in Figure 11, 12 and 13.



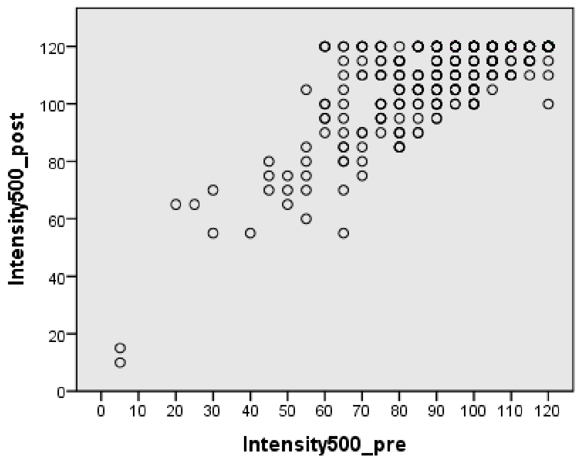


Figure 11 (left): The threshold on PTA pre- and post-operative (N = 317), p = .000.

Figure 12 (right): The threshold on 500 Hz pre- and post-operative stage (N = 315), p = .000.

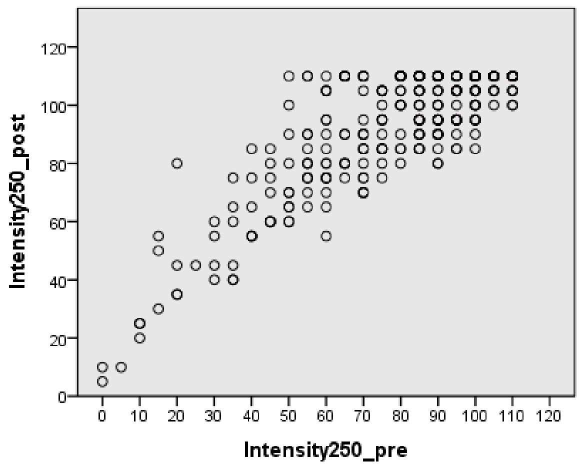


Figure 13: The threshold on 250 Hz pre- and post-operative (N = 310), p = .000.

Referring to the classification mentioned in Chapter 2.2, hearing preservation can be classified based on the amount of preserved dB. In Table 9, results of the patients in the present study are classified, based on their amount of deteriorated dB regarding PTA. The same classification is presented, based on the amount of deterioration in dB regarding 500 Hz and 250 Hz, see Table 10 and 11.

Table 9: The category of hearing preservation for the selected patients in this study, based on PTA

Classification	**Amount of patients (percentage)**	**Range (average)**
Complete hearing preservation (0-10 dB)	205 patients (65%)	-7 – 10 (4)
Partial hearing preservation (11-29 dB)	104 patients (33%)	11 - 29 (18)
Minimal hearing preservation (> 29 dB)	8 patients (2%)	30 – 44 (37)
Total	317 patients	-7 - 44

Table 10: The category of hearing preservation for the selected patients in this study, based on 500 Hz

Classification	**Amount of patients (percentage)**	**Range (average)**
Complete hearing preservation (0-10 dB)	121 patients (38%)	-5 – 10 (5)
Partial hearing preservation (11-29 dB)	123 patients (39%)	15 - 25 (20)
Minimal hearing preservation (> 29 dB)	71 patients (23%)	30 – 60 (40)
Total	315 patients	

Table 11: The category of hearing preservation for the selected patients in this study, based on 250 Hz

Classification	**Amount of patients (percentage)**	**Range (average)**
Complete hearing preservation (0-10 dB)	149 patients (48%)	-10 – 10 (4)
Partial hearing preservation (11-29 dB)	106 patients (34%)	15 - 25 (19)
Minimal hearing preservation (> 29 dB)	55 patients (17%)	30 – 60 (39)
No results available	2 patients (1%)	
Total	310 patients	

The average age at implantation, as one of the variables, for each moment of measurement in the process is mentioned in Figure 14. On average, patients were tested 55 days after their cochlear implantation.

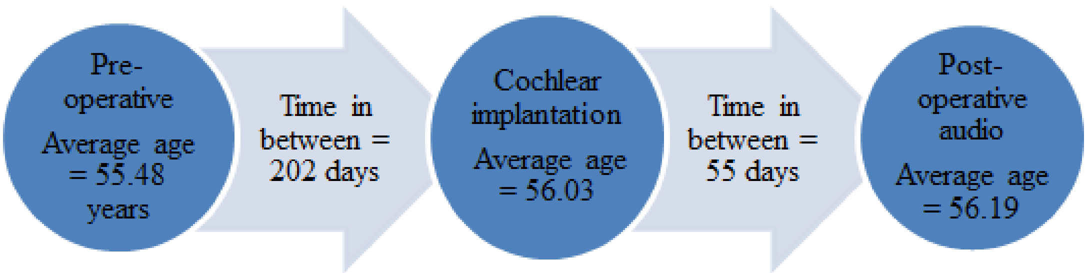
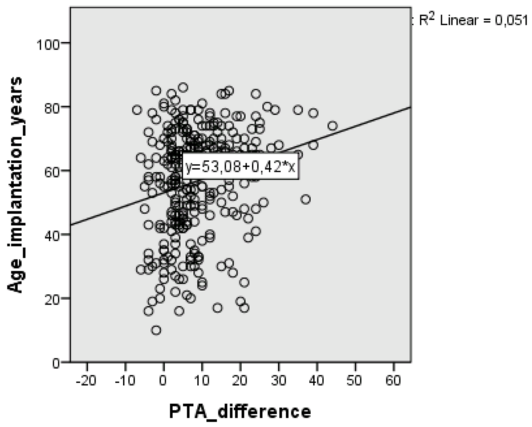


Figure 14: The average age of the patients at implantation (n = 321) is displayed for each part of the process concerning cochlear implantation.

To examine the influence of implantation age and cause of deafness on the 3 hearing variables, regression analyses were used. The average age at implantation of the included patients is 56 years (*SD* = 16.6), with the youngest patient 10 years of age and the oldest patient 86 years of age.

On average, predictor age at implantation (*M* = 56.8 years, *SD* = 16.6) had a significant influence on the difference in PTA (β = .21, *p* = .000). With increasing age at implantation, the difference in PTA increased significantly, showed in Figure 15. R square (R^2) was .05.

The effect of age at implantation (*M* = 56.9 years, *SD* = 16.6) on the 500 Hz threshold was significant (β = .24, *p* = .000). With increasing age at implantation, the difference in threshold on 500 Hz increased significantly, showed in Figure 16, R^2 = .066.
The effect of age at implantation (*M* = 56.7 years, *SD* = 16.7) had a significant influence on the 250 Hz threshold ((β = .26, *p* = .000). With increasing age at implantation, the difference in threshold on 250 Hz increased significantly, showed in Figure 17, R^2 = .095.



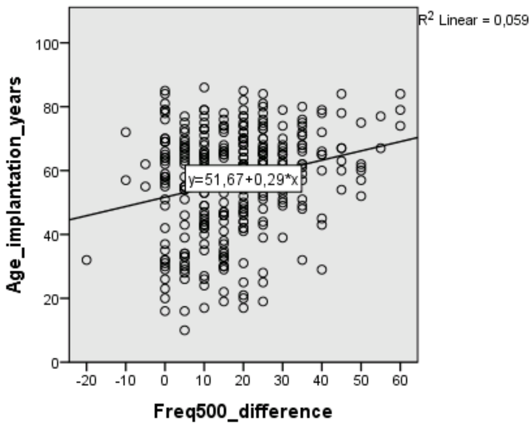


Figure 15 (left): The influence of age at implantation on the difference in PTA, p = .000.
Figure 16 (right): The influence of age at implantation on the threshold on 500 Hz, p = .000.

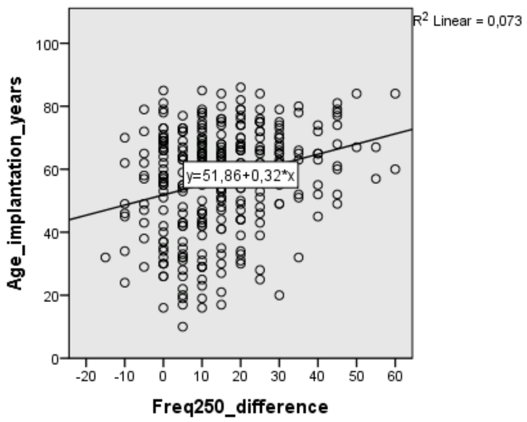


Figure 17: The influence of age at implantation on the threshold on 250 Hz, p = .000.

For all regressions, one can see that as age at implantation increases, greater difference between the threshold of 250 Hz, 500 Hz and PTA were found. On average, for each of these dependent variables, cause of deafness showed no significant change in any of the thresholds.

5.2 How does the vestibular function examined by objective vestibular techniques change due to the cochlear implantation?

In all patients, oculomotor tests were executed prior to the vestibular examination. Based on the oculomotor tests, no abnormalities were observed in the included patients. This result shows that in all patients, both eyes were able to make ocular movements, for example in order to focus. The anamneses of the patients did not show any abnormalities that could be influencing the vestibular results.

For the cold caloric test results, patients were excluded due to their contralateral change in balance function, shown below (Table 12).

Table 12: The number of patients of which the post-operative diagnosis changed, based on cold caloric test results

Diagnosis pre-operative	Diagnosis post-operative	Number of patients
Hyperreflexia	Normal	6
Normal	Hyporeflexia	12
Normal	Areflexia	2
Hyporeflexia	Areflexia	2
Total deterioration of the contralateral ear		22

Table 13 shows these numbers for the warm caloric test results, in which the same protocol was maintained.

Table 13: The number of patients of which the post-operative diagnosis changed, based on warm irrigation test results

Diagnosis pre-operative	Diagnosis post-operative	Number of patients
Hyperreflexia	Normal	3
Normal	Hyporeflexia	10
Normal	Areflexia	0
Hyporeflexia	Areflexia	3
Total deterioration of the contralateral ear		16

All patients with deterioration in either cold and/or warm caloric test results of their contralateral side were excluded. Regarding overlap in results of cold and warm irrigation in 2 patients, not 38 but 36 patients were excluded. So, of the 168 selected patients, data of 132 patients was analyzed.

For each parameter of the vestibular objective tests, paired t-tests were used to examine the pre- versus post-operative results. For the difference of each variable, outliers were identified and excluded. Descriptive analyses of the parameters for the ipsilateral side of the remaining patients are mentioned in Table 14. The numbers of patients for each variable are less than 132 due to outliers and due to the fact that not all patients received all vestibular tests.

Table 14: Mean, number of patients, standard deviation and standard error for all parameters of the used objective vestibular tests

Test	Variable	Mean	Std. deviation	*N*
VST	ν_ pre	58.2 degrees	22 degrees	129
VST	ν_ post	57.1 degrees	23 degrees	129
VST	τ_ pre	12.2 sec	4 sec	128
VST	τ_ post	11.3 sec	4 sec	128
Caloric test	warm_ pre	16.3 degrees/sec	9 degrees/sec	122
Caloric test	warm_ post	14.7 degrees/sec	10 degrees/sec	122
Caloric test	cold_ pre	15.7 degrees/sec	8 degrees/sec	105
Caloric test	cold_ post	12.2 degrees/sec	7 degrees/sec	105
vHIT	lateral_pre	.98 gain	.1 gain	59
vHIT	lateral_post	.97 gain	.1 gain	59

The analysis showed that one variable of the VST (time constant ‘τ’) and one variable of the irrigations (maximum velocity of the cold irrigation) showed significant deterioration. On average, values of ‘τ’ were significantly lower post-operative (M = 11.2 sec, SE = .3 sec) compared to the pre-operative values (M = 12.1 sec, SE = .3 sec), $t(127) = 2.91$, $p = .000$. Also for the values of cold caloric, results were post-operative significant lower (M = 15.71 degrees/sec, SE = .73 degrees/sec) than the pre-operative values (M = 12.19, SE = .74), $t(104) = 6.45$, $p = .000$. Other parameters showed no significant change between pre- and post-operative.

Additional analyses were conducted for the pre- and post-operative outcomes of the Gesamtamplitude in VST, the multiplication of ‘ν’ and ‘τ’. Descriptive analyses of the Gesamtamplitude are shown Table 15.

Table 15: Mean, number of patients and standard deviation of the Gesamtamplitude pre- and post-operative

Variable	**Mean**	**Std. Deviation**	***N***
Gesamtamplitude pre-operative	722.3	342.8	130
Gesamtamplitude post-operative	664.5	347.9	130

The Gesamtamplitude significantly deteriorated post-operative (M = 664.485, SE = 30.5), compared to pre-operative (M = 722.3, SE = 30.1), $t(129) = 2.09$, $p = .039$. Means of both pre- as post-operative measuring were within the normal range of Gesamtamplitude.

First, an overview of the diagnoses based on warm irrigation results are shown in Table 16. Pre- and post-operative diagnoses based on raw data of warm caloric tests are presented. It can be observed that the diagnoses deteriorated, meliorated (Table 17) or did not change (Table 18) post-operatively compared to the pre-operative diagnose.

Table 16: The number of patients for each diagnosis in pre- and post-operative stage are mentioned concerning warm irrigation test results

	Warm_pre		**Warm_post**	
Diagnosis	**Frequency**		**Frequency**	
Areflexia	4	3%	7	5%
Hyporeflexia	27	20%	34	26%
Normal	95	72%	85	64%
Hyperreflexia	0	0%	2	2%
Missing	6	5%	4	3%
Total	**132**	**100%**	**132**	**100%**

Table 17: The number of patients of which the post-operative diagnosis deteriorated or meliorated, based on warm irrigation test results of the ipsilateral ear

Diagnosis pre-operative	**Diagnosis post-operative**	**Number of patients**	**Diagnosis pre-operative**	**Diagnosis post-operative**	**Number of patients**
Hyporeflexia	Areflexia	1	Areflexia	Hyporeflexia	1
Normal	Hyporeflexia	16	Hyporeflexia	Normal	9
Normal	Areflexia	2	Areflexia	Normal	0
Hyperreflexia	Normal	0	Normal	Hyperreflexia	2
Total patients with deterioration		**19**		**Total patients with melioration**	**12**

Not all patients had a different diagnoses post-operative compared to pre-operative. In Table 18, the amount of patients for which the same diagnoses was concluded are mentioned.

Table 18: Diagnoses based on the irrigation results of patients that did not show change post-operatively.

Diagnosis	**Number of patients**
Areflexia	3
Hyporeflexia	16
Normal	74
Missing	8
Total	**101**

In 3 patients (2%), post-operative diagnoses changed to areflexia and in 17 patients (13%) to hyporeflexia.

Similar analyses were performed for the cold irrigation outcomes. An overview of the diagnoses based on cold irrigation results are shown in Table 19. In Tables 20 and 21, frequency of deterioration and no change in the post-operative diagnosis are shown. Based on the diagnosis of the cold irrigation results, only one patient meliorated from 'hyporeflexia' to 'normal'.

Table 19: The number of patients for each diagnosis in pre- and post-operative stage are mentioned concerning cold irrigation test results

	Cold_pre		**Cold_post**	
Diagnosis	**Frequency**		**Frequency**	
Areflexia	4	3%	8	6%
Hyporeflexia	9	7%	18	14%
Normal	103	78%	87	66%
Hyperreflexia	4	3%	0	0%
Missing	12	9%	19	14%
Total	**132**	**100%**	**132**	**100%**

Table 20: The number of patients of which the post-operative diagnosis deteriorated, based on cold irrigation test results

Diagnosis pre-operative	**Diagnosis post-operative**	**Number of patients**
Hyperreflexia	Normal	3
Hyporeflexia	Areflexia	1
Normal	Hyporeflexia	13
Normal	Areflexia	2
Total patients with deterioration		**19**

Table 21: The number of patients of which the post-operative diagnosis did not change, based on cold irrigation test results

Diagnosis	**Number of patients**
Areflexia	4
Hyporeflexia	5
Normal	78
Missing	25
Total	**112**

In 3 patients (2%), post-operative diagnoses changed to areflexia and in 13 patients (10%) to hyporeflexia.

The same procedure was carried out for the results of Gesamtamplitude. In Table 22, the frequency of diagnoses is shown for pre- and post-operative results. In Table 23, the diagnoses pre- and post-operative are compared and therefore melioration, deterioration or no change was concluded.

Table 22: The number of patients for each diagnosis in pre- and post-operative stage are mentioned concerning results of the Gesamtamplitude

	Gesamtamplitude_pre		**Gesamtamplitude_post**	
Diagnosis	**Frequency**		**Frequency**	
Areflexia	1	1%	2	2%
Hyporeflexia	35	26%	38	28%
Normal	78	59%	79	60%
Hyperreflexia	18	14%	12	9%
Missing	0	0%	1	1%
Total	**132**	**100%**	**132**	**100%**

Since one patient was pre-operatively diagnosed with ‘areflexia’ and one patient did not have post-operative VST results, the diagnoses of 130 patients were analyzed.

Table 23: The number of patients of which the post-operative diagnosis deteriorated or meliorated, based on Gesamtamplitude

Diagnosis pre-operative Gesamtamplitude	**Diagnosis post-operative Gesamtamplitude**	**Number of patients**	**Diagnosis pre-operative Gesamtamplitude**	**Diagnosis post-operative Gesamtamplitude**	**Number of patients**
Hyperreflexia	Normal	9	Normal	Hyperreflexia	10
Hyperreflexia	Hyporeflexia	3	Hyporeflexia	Hyperreflexia	0
Normal	Hyporeflexia	11	Hyporeflexia	Normal	10
Normal	Areflexia	0	Areflexia	Normal	0
Hyporeflexia	Areflexia	1	Areflexia	Hyporeflexia	0
Total number of patients with deterioration		24	**Total number of patients with melioration**		20

Results show that post-operatively, 1 patient (.7%) changed in diagnoses to areflexia and 14 patients (11%) to hyporeflexia. However, also in the range of the Gesamtamplitude, patients received the same diagnoses both pre- as post-operative. These patients and their diagnoses are mentioned in Table 24.

Table 24: The number of patients of which the post-operative diagnosis did not change, based on Gesamtamplitude

Diagnosis in Gesamtamplitude	**Number of patients**
Hyporeflexia	24
Normal	60
Hyperreflexia	1
Areflexia	1
Total number of patients with no change	**86**

Based on the parameter of vHIT, gain of the lateral canal, 25 patients (42%) meliorated in their results, with gain ranging from 0.01 to 0.21, with an average of 0.048. 6 patients (10%) showed no change post-operative compared to pre-operative. In 28 patients (47%), deterioration of the results was seen, ranging from 0.01 to 0.2, with an average of 0.07. Despite these 28 patients with deterioration, only three patients had a gain below .8 post-operatively, ranging from .63 to 0.75. None of the patients were diagnosed with areflexia, considering the results of vHIT.

5.3 How does the subjective vestibular function change due to the implantation, measured by the DHI?

In the analysis, 91 patients were included after the exclusion of patients with established contralateral deterioration (based on irrigation results). Descriptive statistics of the variables of DHI are mentioned in Table 25. The total score of the DHI, the parameter of the subjective method of vestibular testing, resulted in a mean difference between pre- and post-operative of .46.

Table 25: Pre- and post-operative mean, number of subjects and standard deviation of the parameters of subjective vestibular testing

	Mean	**Standard deviation**	***N***
DHI pre-operatively	8.00	12.79	91
DHI post-operatively	8.46	14.18	91

The DHI score in post-operative stage (M = 8.46, SD = 14.18) did not change significantly compared to the pre-operative stage (M = 8.00, SD = 12.79), $t(90) = -.33$, $p = .743$, $r = .03$. Although not being significant, some patients do experience post-operative subjective complaints compared to their pre-operative status. Therefore, the shift of the subjective scores and the frequencies of pre-operative and post-operative DHI scores are shown in Figure 18 and 19.

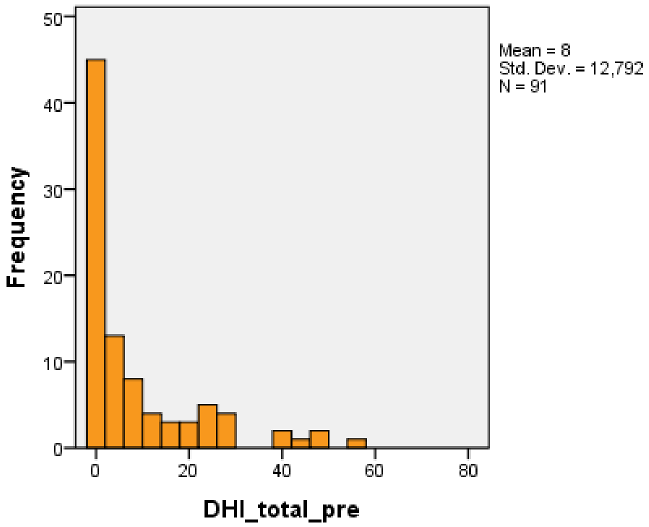


Figure 18: The amount of points in pre-operative DHI results and their frequency

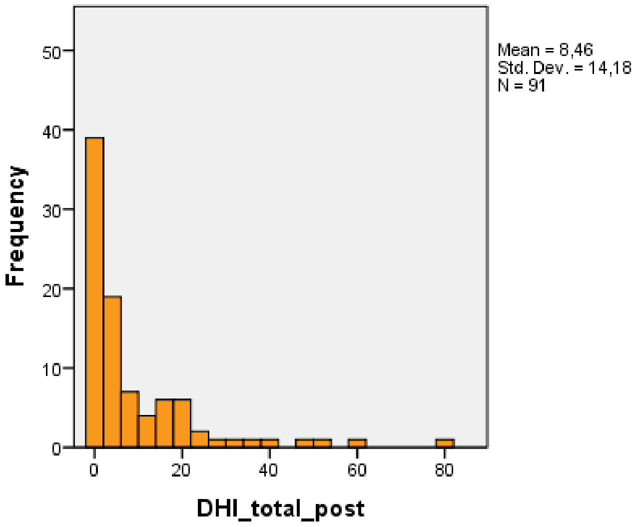


Figure 19: The amount of points in post-operative DHI results and their frequency

According to the categorization of Whitney et al. (2004), the pre- and post-operative DHI score can be assigned to a category. Table 26 shows the frequencies of the categorized DHI scores and in Figure 20, the difference between pre- and post-operative DHI score and the frequencies are displayed.

Table 26: The number of patients for each category, based on their amount of points in DHI

DHI result	**Category**	**Pre-operative**	**Post-operative**
0	No handicap	45	39
1 – 30	Mild handicap	40	45
31-60	Moderate handicap	6	6
> 60	Severe handicap	0	1

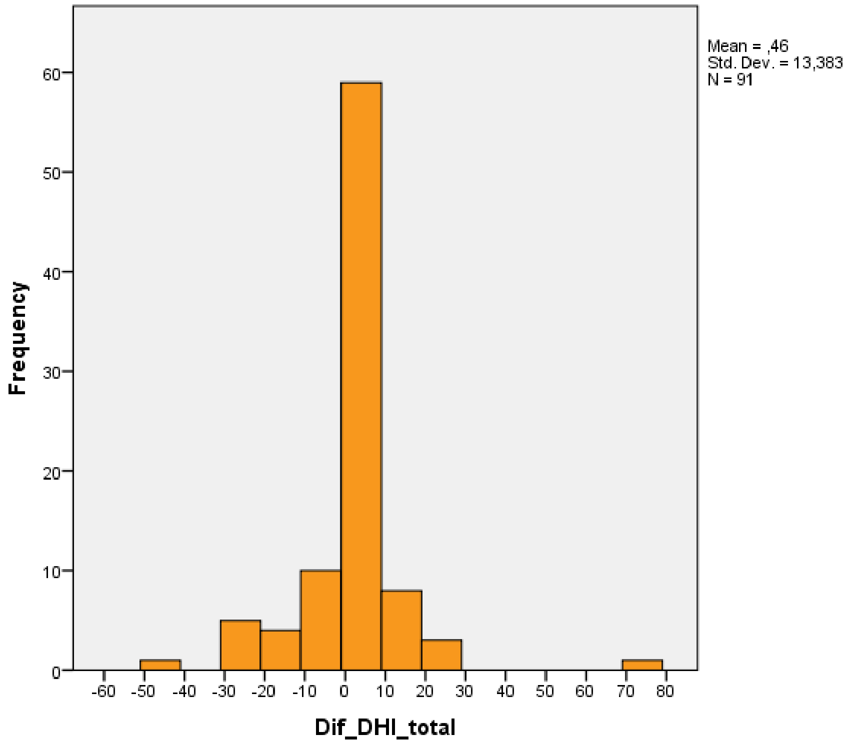


Figure 20: Frequencies for the difference in DHI total score.

Patients with no change in their objective vestibular data were included in the results. In the next comparison, these patients were excluded and only 77 patients with objectively changed irrigation results remained. Of these patients, the post-operative DHI score (*M* = 8.23, *SE* = 1.59) showed no significant difference compared to the pre-operative DHI score (*M* = 7.64, *SE* = 1.41), $t(76) = -.37$, $p = .710$, $r = .04$. Based on the interpretation of Jacobson & Newman (1990), 13 patients showed a change of 18 points between pre- and post-operative score, i.e. 6 patients reported an increase of scores and 7 patients a decrease of scores. Of these 6 patients, the objective test results are mentioned in Appendix III.

5.4 Are changes in auditory and vestibular function related to each other?

Five regression analyses were executed, in which the differences in PTA, threshold on 500 Hz and threshold on 250 Hz were related to the five dependent variables of vestibular objective tests. In each regression, the difference between the pre- and post-operative vestibular objective parameter was used as the dependent variable, in Table 27 highlighted in grey. Descriptive statistics of both dependent and independent variables are presented in Table 27.

Table 27: Mean, standard deviation and number of patients for the variables hearing and difference in balance

Variable	**Mean**	**Std. Deviation**	***N***
Difference_ν_ipsi	1.30	17.58	80
PTA_difference	8.05	11.20	80
Freq500_difference	18.06	15.44	80
Freq250_difference	19.06	18.56	80
Difference_τ_ipsi	.87	3.30	83
PTA_difference	8.25	11.03	83
Freq500_difference	18.55	15.59	83
Freq250_difference	19.34	18.29	83
Difference_warm_ipsi	2.03	8.11	79
PTA_difference	7.71	11.24	79
Freq500_difference	17.85	14.95	79
Freq250_difference	18.42	17.40	79
Difference_cold_ipsi	2.91	5.20	70
PTA_difference	8.07	9.46	70
Freq500_difference	17.86	15.22	70
Freq250_difference	19.07	18.58	70
Difference_lateral_ipsi	.0138	.069	39
PTA_difference	6.79	12.60	39
Freq500_difference	17.69	14.55	39
Freq250_difference	15.64	16.63	39

The difference between maximum slow phase velocity of the nystagmus ‘ν’ (M = 1.3 degrees/sec, SD = 17.5 degrees/sec) could be significantly predicted by variables threshold on 500 Hz (β = .36, p = .04).

The difference between maximum slow phase velocity of the nystagmus ‘ν’ could also be significantly predicted by variables threshold on 250 Hz (β = -.51, p = .007).

However, no the difference in maximum slow phase velocity of the nystagmus ‘ν’ could not significantly predict the difference in PTA (β = .20, p = .104). The R square was .099.

For the other vestibular parameters (i.e. time constant of VST, warm and cold irrigational results and lateral canal of vHIT), no significant influence of the variables 250 Hz, 500 Hz and PTA was found.

Chapter 6 Discussion

6.1 Change in auditory function due to cochlear implantation and the influence of age at implantation and cause of deafness

At first, it was examined whether the results of PTA, threshold on 500 Hz and 250 Hz differed in the pre- and post-operative values. These differences between post- and pre-operative values can be seen in Tables 8 and Figure 11, 12 and 13. Considering the conclusion of several authors, that criteria for CI patients shifted in a way that more patients with preserved hearing in their lower frequencies could receive a cochlear implant (Sampaio et al., 2011; Kuang et al., 2015), more information was needed about this patient group. Therefore, not only PTA was chosen, but also the thresholds on 500 Hz and 250 Hz. Analyses showed that the results of thresholds regarding PTA, 500 Hz and 250 Hz significantly increased after implantation. An increased threshold post-operative showed that it was needed to increase the amount of dB to hear and therefore deterioration of hearing could be concluded. These results are in line with significant increased threshold, reported by Raveh et al. (2015). The increased thresholds can be explained by the damaging effect of the implant, which can destroy the hair cells. Based on the classification on hearing deterioration in PTA, 500 Hz and 250 Hz, respectively 65%, 38% and 48% of the patients are classified with complete hearing preservation. Looking at Figure 11, 12 and 13, one can see that the difference between pre- and post-operative results are smaller in the PTA thresholds than in the 500 Hz and 250 Hz. This is in accordance with earlier studies (Podskarbi-Fayette et al., 2010), reporting deteriorated frequencies of the hair cells closest to the base of the cochlea. Overall, the results are lower than the results reported by Hunter et al. (2016), who reported a difference of 20 dB post-operative. Hunter et al. (2016) used a calculation of PTA including only the frequencies 125 Hz, 250 Hz and 500 Hz. Post-operative, the authors found a threshold elevation of 20 dB, numbers that are comparable to the increased threshold on 500 Hz and 250 Hz in the current study. However, in the study of Hunter et al. (2016), only patients with a mid-scala electrode were included. The authors of the study used their results to demonstrate that mid-scala electrodes provide similar hearing preservation results in CI-users as other studies.

In the current study, the influence of type of surgery and electrode was not examined, but these influences should not be underestimated. The latest technologies launched new electrode designs with the aim to maintain auditory and vestibular function as much as possible. Still no consensus is reached about the most favorable insertion depth or electrode length (Nguyen et al., 2016), follow-up study should include several aspects of electrodes and surgery. Technological improvements and more knowledge about type of surgery might provide new insight into the amount of vestibular and auditory deterioration in following research. At the time of writing, another study in the Radboudumc is being executed, combining information about the electrodes and surgery with speech comprehension scores and hearing thresholds. Combining results of the current study with upcoming results of electrodes, would provide more insight into damaging electrodes and surgery.

Not only significant deterioration in threshold is concluded, also the classification of this hearing deterioration was reported. Complete hearing preservation was established for 65% of the patients in this study. This is way higher compared to the 39% that was reported by Zanetti et al. (2015). The population in Zanetti et al. (2015) involved patients with different electrodes, but concluded that the variations in mean threshold could not be explained by the type of cochleostomy or type of electrode. The lowest frequency that was measured in the study of Zanetti et al. (2015) was 500 Hz, while it is known that the low frequencies are more and more preserved since the criteria shifted. For the current study, it is recommended to investigate whether a specific factor could explain the higher amount of hearing preservation. Despite the fact that only 3% of the included patients had minimal hearing preservation, cochlear implantation should still be considered as a type of surgery that may induce deterioration and patients should be informed preoperatively about possible risks.

Regarding the first research question, the influence of the cause of deafness and age at implantation on these changes in thresholds was examined. The causes of deafness included in this study were hereditary, acquired or unknown. In the current study, the cause of deafness showed no significant influence on any of these thresholds (PTA, 500 Hz and 250 Hz). So, whether the cause of deafness is hereditary, acquired or unknown, these factors cannot predict the post-operative loss of dB. The results are in contrary to the conclusion of Causon et al. (2015) in which cause of deafness was reported to be of significant influence on the post-operative hearing preservation. Causon et al. (2015) reported that the nature of hearing (stable versus progressive) was also a significant factor. In a follow-up study, this aspect of cause of deafness should be taken into account. Separating pre- from post-lingual deaf patients and examining their amount of hearing loss and speech comprehension 12 months post-operative could be an expansion of the current study. This would contribute to the advice given to the patients that consider cochlear implantation.

As the results showed, age at implantation had a significant negative influence on the PTA, the threshold of 500 Hz and 250 Hz. The difference between pre- and post-operative hearing PTA and threshold for 500 Hz and 250 Hz is increased with increasing age at implantation. Despite the significant results, the statistic model that fits the current population is very weak. Some studies reported no significant influence of age (Zanetti et al., 2015; Hunter et al., 2016), while Kieft (2010) did find a significant influence of patients with an age at implantation above 49 years. The model in the current study was limited and therefore follow-up studies should focus on investigating to what extent age at implantation has influence on differences in threshold. Future research should investigate whether other variables have a greater influence considering the amount of deterioration of auditory function.

In the present study, no patients with electro-acoustic stimulation (EAS) were included. EAS stimulates the (preserved) low frequencies by acoustic hearing aid and the high frequencies by electric stimulation (Usami et al., 2011). This electric stimulation might trigger parts in the brain and therefore enhance/facilitate plasticity. It may be interesting to examine whether more plasticity is possible due to EAS compared to only cochlear implants. A follow-up study should also include speech comprehension scores, to investigate the actual benefits of a CI, rather than looking at the acoustic deteriorated scores.

To put results of this first research question in perspective, it should be noted that no conclusion can be drawn about the electric stimulation since results of the auditory thresholds were obtained without the use of CI. The current study was focused on the acoustic stimulation and therefore, the results of the present study include the acoustic stimulation of the hair cells. The actual benefit of the CI relies on the electric stimulation increasing speech comprehension. Follow-up research should include results of speech comprehension, to completely chart the risks and benefits of a CI.

6.2 Change in vestibular function due to cochlear implantation, based on objective vestibular techniques

The second research question involved the change in vestibular function due to cochlear implantation. Significant deterioration was post-operatively found for the cold irrigation results and time constant ('τ') of the VST. Although deterioration was found in two variables, no significant decline was found for the warm irrigation results, velocity 'ν' of VST and the lateral canal of the vHIT.

Significant decrease was found in the results of cold irrigation and time constant (of the VST), showing that the vestibular system can be influenced due to the cochlear implantation. The fact that the vestibular system can be influenced due to cochlear implantation was already confirmed by many authors (Devroede et al, 2016; Chen et al., 2016; Katsiari et al., 2013). Cold irrigation responses deteriorated in post-operative stage and this deterioration was revealed in such manner, that 16 of these patients were diagnosed with hyporeflexia (n = 13) or areflexia (n =3) in their post-operative stage. So, based on cold irrigations, patients with any vestibular function pre-operatively might deteriorate to hyporeflexia or areflexia post-operative. For patients with preoperative areflexia, vestibular function will not change due to the cochlear implantation (since there is no vestibular function at all). Rerunning the analysis after excluding these patients with preoperative vestibular areflexia however, did still not show any change in the results.

No statistics were made on the diagnoses (areflexia, hyporeflexia, normal, hyperreflexia) that the CI patients received due to their vestibular irrigation results. Looking at raw data, deterioration can be concluded that would possibly be invisible when diagnoses are checked. Statistics on the raw data show more valuable results, since patients can also decline in their post-operative raw data but could still be diagnosed as normal. In evaluating the post-operative status of CI patients, this should be kept in mind when looking at the objective deterioration together with the subjective results.

Based on the raw data of the objective vestibular techniques, one parameter of the VST (time constant 'τ') and one parameter of the cold irrigation results (maximum velocity) significantly deteriorated after cochlear implantation. Other parameters also deteriorated, but not significantly. Significant deterioration of the implanted ear in CI-patients based on irrigation was also reported by several authors (Katsiari et al., 2013; Chen et al., 2016).

Regarding the VST, significant deterioration in post-operative time constant ('τ') compared to pre-operative values is concluded. Additional analysis of the Gesamtamplitude can be helpful to interpret this results. Significant deterioration of the Gesamtamplitude was found post-operatively. The post-operative deterioration of Gesamtamplitude resulted in the diagnoses hyporeflexia (n = 14) or areflexia (n = 1). Due to the characteristics of the Gesamtamplitude that both the ipsi- and contralateral side contribute to this significant decline in Gesamtamplitude, no direct deterioration of the ipsilateral side could be concluded based on these results. For the parameter of the vHIT, the lateral canal, deterioration was found (N = 59). Still, values of both pre- as post-operative gains were diagnosed as sufficient. Based on warm irrigation results, areflexia and hyporeflexia were post-operatively diagnosed in 2% and 13% respectively. For the cold irrigation results, again areflexia was concluded in 2% and hyporeflexia in 10%. For all objective variables of the vestibular system, although not all significantly, a trend in decline was seen.

However, not all vestibular parameters of the vestibular system were significantly different pre- versus post-operative, so the conclusion that the vestibular system is definitely deteriorated is too short-sighted. Results of the warm irrigation showed deterioration post-operatively, although not statistically significant. Apparently, triggering the same horizontal canal with either warm or cold water doesn't guarantee equivalent results. Also, despite the deterioration in several vestibular parameters, melioration of the ipsilateral side was seen. With warm and cold irrigation, 12 and 1 patient(s) meliorated in their diagnosis, respectively. For warm irrigation results, this melioration resulted for 9 patients in a diagnosis 'normal', for 2 patients in 'hyperreflexia' and for 1 in 'hyporeflexia' . The patient that meliorated in cold irrigation, was post-operatively diagnosed as normal. The melioration is remarkable since the expectation was to find deteriorated values between pre- and post-operative, based on earlier literature. This implies inconsistency and limited validity of irrigation and should therefore be kept in mind for the conclusion of this study. The limitation of irrigation was already reported being low in the study of Eza-Nuñez et al. (2016). Although irrigation was suggested to be the best method for vestibular examination (Eza-Nuñez et al., 2016), sensitivity and specificity are not optimal. It is recommended to investigate alternatives for caloric testing.

In the present study, contralateral deterioration of the patients for vestibular function is currently based on results of the caloric test. Given the characteristics of this method, deterioration is based on the changes in the horizontal canal. According to Chen et al. (2016), the horizontal canal is the structure that is more at risk than any other structure. Nevertheless, disagreement about the component that is most at risk is still an issue and one cannot simply assume that contralateral deterioration is only present in the horizontal canal. The possibility that the deterioration of vestibular function (in either ipsi- or contralateral side) manifests in the saccule is apparent. This possibility is in accordance with the results of Devroede et al. (2016). Supposing this deterioration is more present in the saccule more than in the horizontal canal, the use of c-VEMP as an objective method might reflect this. At the time of writing, a VEMP study is running at the Radboudumc and will hopefully lead to more information about deterioration of vestibular function after cochlear implantation in future.

Since vHIT is the method that was added to the protocol of the Radboudumc in 2014, only 59 patients were pre- and post-operatively measured with vHIT. In future, more data will be available from both pre- as post-operative vHIT results and new analysis may be worthwhile. In the current study, only the lateral canal is analyzed with vHIT. The lateral canal was chosen because more data was available on it than on the other canals. Examining results of the anterior and posterior canal of these patients might provide insight into the complete post-operative vestibular function. In this study, the contralateral deterioration of the patients was based on data of the caloric test. These results reflect the deterioration of the horizontal canal. The possibility that the deterioration of vestibular function could be reflected in the canals is apparent.

Despite the fact that measurement errors might explain the melioration, other artifacts are considered. In a systematic review of Gonçalves, Felipe & Lima (2008), several artifacts of irrigation are discussed. They reported fear as to be one of the causes of hyperreflexia. Since the patients in the current study are embroiled in a nerve-racking process about their cochlear implantation, anxiety might be one of the influencing variables on their vestibular examination. Hyperreflexia due to anxiety in the pre-operative measurement and a more confident attitude across vestibular examination in the post-operative stage, might be influencing the conclusions in this study. The discomfort and duration of irrigation could attribute to the inconvenience that patients experience during vestibular examination. Perhaps the pre-operative vestibular objective results are biased by the anxiety of the patient whether he/she is eligible for cochlear implantation.

6.3 Change in vestibular function due to cochlear implantation, based on subjective results

Looking at the subjective results (*N* = 91), DHI scores increased post-operative. An increased DHI score can be interpreted as increased subjective complaints. Despite the fact that a difference was found between pre- and post-operative DHI-score, this difference was not significant. The mean DHI total score changed post-operatively, but still patients were categorized as having a 'mild' handicap. No notable changes could be concluded, considering the frequencies in categories and the difference in DHI score within a range of 0 and 10. Also, a decline in amount of points in DHI was seen. This melioration is remarkable but might be attributed to the reasonable explanation that cochlear implantation might have a placebo effect. Faber & Grøntved (2000) mentioned a possible placebo effect in their study about quality of life after cochlear implantation. The occurrence of a placebo effect could not be determined in the current study based on the total score of the DHI. Follow-up research should also examine the subscale 'emotional' to investigate the occurrence of a placebo effect after cochlear implantation. The current study provided data to set this follow-up research in motion.

Several patients reported post-operative subjective complaints while pre-operatively there were none. Of all patients (*N* = 91), subjective deterioration was reported for a small number of patients (*N* = 32). One patient reported 78 points on the DHI post-operatively, which is diagnosed as a 'severe handicap'. The average post-operative DHI score dropped from 10.13 to 7.93 after removing this patient. Analyzing this specific patient with severe handicap showed that in the subscale 'emotional', a difference of 40 points between post- and pre-operative was seen. Hyporeflexia was diagnosed based on the Gesamtamplitude and areflexia based on irrigation results (warm and cold). The post-operative areflexia might explain the presence of high scores on DHI. Based on this one patient, no statistical conclusion can be drawn about correlation between objective and subjective tests of vestibular function, but scores seem to be in congruency. The other 31 patients were diagnosed with a mild handicap based on their post-operative DHI scores, ranging from 2 to 28 points. To the best of my knowledge, no DHI scores of pre- and post-operative CI patients were examined in other studies.

In the study of Whitney et al. (2004), a correlation was reported for the patients with a severe handicap (based on DHI score) showing greater functional impairment. The study did not focus on CI patients, but similar research can be executed to investigate whether there is a correlation between objective and subjective results. If more deterioration in the objective results is correlated with higher scores in the DHI, it is reflected which component of the vestibular function is associated with higher subjective symptoms. In the present study, only 35% showed reasonable increase in subjective complaints *(N*= 32). Of these 32 patients, only 5 patients showed worsening of more than 17 points, which according to Jacobson & Newman (1990) can be seen as a serious change. Of these patients, no presumptive evidence for their subjective deterioration could be found. In order to examine the correlation between deterioration of subjective complaints and objective vestibular test results, follow-up research should include a larger sample size (i.e. 30 patients) with comparable subjective deterioration.

Of all patients (*N* = 91), a second analysis was executed with the patients showing at least a change in their post-operative objective vestibular irrigational results. In these 77 patients, no significant increased DHI score was concluded as well. Only 13 patients showed a genuine amount of change in DHI score post-operatively. The six patients with deterioration showed an average worsening of 30 points. Considering these 6 patients, objective vestibular tests were assessed in order to find any indication for a cause. No presumptive evidence for assignable vestibular deterioration was found based on the characteristics of these patients (see Appendix III).

One factor, which was not examined in the current study, is vestibular rehabilitation. Vestibular rehabilitation could be of influence on the manner that the vestibular system gets used to the possible (temporary) deterioration in the side of implant. Vestibular rehabilitation is able to set the vestibular system in motion in the non-implanted ear, that might centrally compensate the loss of vestibular function in the implanted ear. Vestibular rehabilitation is one of the factors that might influence the subjective complaints but is currently not involved in the protocol of the Radboudumc. The possibility of including vestibular rehabilitation in the protocol of the Radboudumc should be considered.

6.4 Are changes in auditory and vestibular function related to each other?

The anatomic structure of hearing and the vestibular system are so close to each other, assuming that cochlear implantation in this region might cause damage to both components. Due to the characteristics of cochlear implantation, loss of perilymph and acoustic trauma can occur and the anatomical structure of the cochlea can be damaged and infection might occur. Vestibular problems are listed as one of the most common complications regarding cochlear implantation and the point of interest is whether vestibular problems are in conjunction with the loss of hearing function.

It was examined whether the difference in audiometric thresholds PTA, 500 Hz and 250 Hz were correlated with any of the differences in vestibular parameters. As shown in Table 27, it seemed that only the differences in thresholds are correlated with the difference post-operative versus pre-operative velocity of the nystagmus during VST. However, the R square was so low, that these results are doubtful. The current study provided data to set follow-up research in motion, but the current analysis was limited. Suggestions for follow-up research should confirm any correlation between damage in threshold on PTA, 500 Hz and/or 250 Hz in comparison with other vestibular tests (such as VEMP). Also, computerized tomography (CT) and/or MRI could provide more insight into the anatomic preservation of the cochlea and the vestibular system. Both methods are currently not involved in the standard protocol of post-operative cochlear implanted patients.

7. Conclusions

- Analyses showed that the results of thresholds regarding PTA, 500 Hz and 250 Hz significantly increased after implantation, showing deteriorated hearing thresholds. Based on the classification on hearing deterioration in PTA, 500 Hz and 250 Hz, respectively 65%, 38% and 48% of the patients are classified with complete hearing preservation.
- Although the results show that 65% of the patients had complete hearing preservation (deterioration less than 10 dB hearing loss), cochlear implantation should still be considered as a surgery that may induce deterioration and patients should be informed preoperatively about possible risks.
- The cause of deafness (hereditary, acquired or unknown) showed no significant influence on any of the thresholds (PTA, 500 Hz and 250 Hz). The age at implantation had a significant negative influence on the threshold of PTA, 500 Hz and 250 Hz. The difference between pre- and post-operative hearing PTA, threshold on 500 Hz and 250 Hz was increased with increasing age at implantation.
- Although vestibular deterioration was found in the results of cold irrigation and time constant (of the VST), no significant decline was found in the warm irrigation results, velocity ‘ν’ of VST and the lateral canal of the vHIT. Based on warm irrigation results, areflexia and hyporeflexia were post-operatively diagnosed in 2% and 13% respectively. For the cold irrigation results, again areflexia was concluded in 2% and hyporeflexia in 10%
- Looking at the subjective results (N = 91), mean DHI scores increased post-operatively. The mean DHI total score changed post-operatively, but was still categorized as a ‘mild’ handicap. Of all patients, subjective deterioration was reported for 32 patients (35%).
- Further research might include variables speech comprehension scores, information about surgery and electrode, EAS and vestibular rehabilitation, in order to inform patients that consider cochlear implantation about the specific risks and benefits of a CI.

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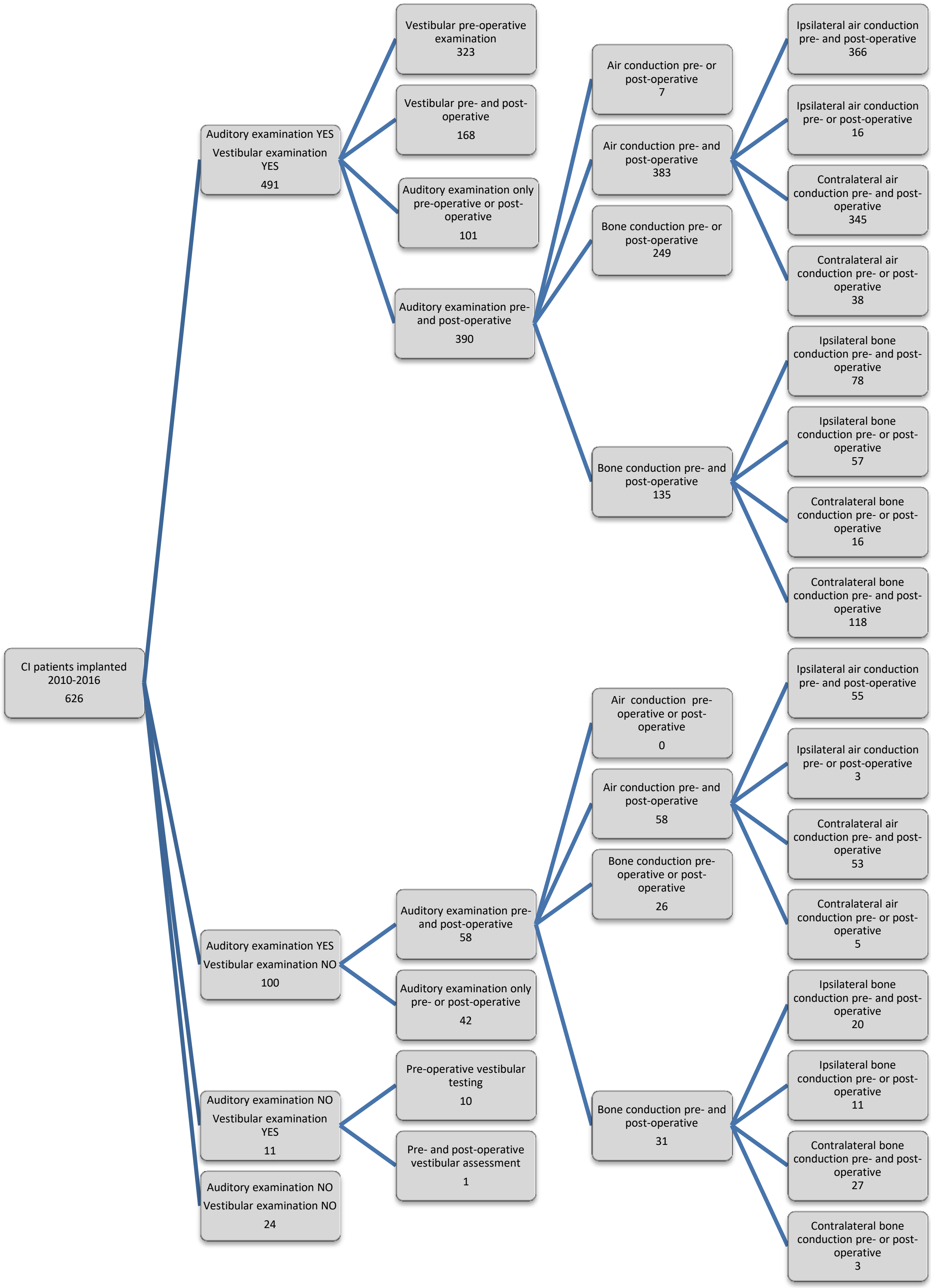
Appendix I: *Dizziness Handicap Inventory (DHI), Dutch version*

		Vaak	Soms	Nooit
P1	Verergeren uw evenwichtsklachten bij omhoog kijken?			
E2	Voelt u zich, vanwege uw evenwichtsklachten, gefrustreerd?			
F3	Worden uw privé- of dienstreizen beperkt door uw evenwichtsklachten?			
P4	Verergeren uw evenwichtsklachten bij lopen door het gangpad van de supermarkt?			
F5	Heeft u, vanwege uw klachten, moeite met het in of uit bed gaan?			
F6	Worden uw sociale activiteiten beperkt door uw evenwichtsklachten? (met sociale activiteiten wordt bedoeld: uit eten gaan, naar de film gaan, dansen, naar verjaardag/feestjes gaan)			
F7	Heeft u, vanwege uw evenwichtsklachten, problemen met lezen?			
P8	Verergeren uw evenwichtsklachten bij meer belastende activiteiten zoals: sport, dansen en huishoudelijke taken?			
E9	Bent u, vanwege uw evenwichtsklachten, bang om zonder metgezel (dus alleen) het huis uit te gaan?			
E10	Bent u bij anderen in verlegenheid gebracht vanwege uw evenwichtsklachten?			
P11	Verergeren snelle hoofdbewegingen uw evenwichtsklachten?			
F12	Vermijdt u hoogtes vanwege uw evenwichtsklachten?			
P13	Verergert omdraaien in bed uw evenwichtsklachten?			
F14	Is het moeilijk voor u, vanwege uw evenwichtsklachten, inspannend werk in huis of tuin te verrichten?			
E15	Bent u bang dat mensen zullen denken dat u dronken bent?			
F16	Is het, vanwege evenwichtsklachten, moeilijk voor u om in uw eentje een wandeling te maken?			
P17	Verergeren uw evenwichtsklachten bij lopen op het trottoir?			
E18	Is het moeilijk voor u om u, vanwege evenwichtsklachten, te concentreren?			
F19	Is het, vanwege evenwichtsklachten, moeilijk voor u om in het donker door het huis te lopen?			
E20	Bent u bang om alleen thuis te zijn vanwege evenwichtsklachten?			
E21	Voelt u zich gehandicapt door evenwichtsklachten?			
E22	Hebben evenwichtsklachten tot stress of spanning geleid in uw relatie met familie of vrienden?			
E23	Bent u depressief vanwege evenwichtsklachten?			
F24	Beïnvloeden evenwichtsklachten uw taken binnen uw werk of huishoudelijke activiteiten?			
P25	Verergeren de evenwichtsklachten als u vooroverbuigt?			

Appendix II: *Of all CI implanted patients between January 2010 and April 2016, subjects for the present study were selected based on the diagram below.*



Appendix III: *Objective vestibular results of the patients that showed deteriorated post-operative subjective results, based on DHI results*

Patient	**1**	**2**	**3**	**4**	**5**	**6**
Side of implant	right	right	left	left	left	left
Cause of deafness	Hereditary	Hereditary	Hereditary	Unknown	n.a.	n.a.
Surgeon	4	2	3	4	4	1
Implant type	1	2	3	4	3	2
Date of birth	11-nov-62	18-aug-50	14-jun-98	26-jul-43	12-dec-73	7-jul-39
Date of OK	15-jan-14	17-aug-15	10-dec-14	30-jun-15	30-sep-13	24-nov-15
Age at implantation (years)	51	65	16	72	40	76
Date pre-operative	14-10-2013	10-03-2015	01-12-2014	27-03-2015	05-04-2013	23-06-2015
Date post-operative	07-03-2014	02-12-2015	10-03-2015	28-08-2015	06-06-2014	18-02-2016
ν ipsi pre	61	89	78	68	47	37
ν ipsi post	60	89	79	49	56	45
Difference ν ipsi	1	0	-1	19	-9	-8
τ ipsi pre	10	13	15	20	21	11
τ ipsi post	6	7	12	18	13	15
Difference τ ipsi	4	6	3	2	8	-4
warm ipsi pre	13	21	18	35	33	13
warm ipsi post	0	18	10	14	7	12
Difference warm ipsi	13	3	8	21	26	1
cold ipsi pre	15	17	25	n.a.	25	6
cold ipsi post	0	9	18	10	10	n.a.
Difference cold ipsi	15	8	7	n.a.	15	n.a.
ipsi lateral pre	1,01	1,12	0,94	1,1	n.a.	0,67
ipsi lateral post	0,36	1,03	0,91	0,93	n.a.	0,88
Difference ipsi lateral	0,65	0,09	0,03	0,17	n.a.	-0,21

N.a. = not available