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The Human Cochlea and Cochlear Implantation

Morphological Characteristics and Clinical Correlations

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Abstract
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The most common sensory deficit in the world is sensorineural hearing loss. Cochlear implantation (CI) can majorly contribute to restore hearing, not only in patients with severe to profound hearing loss, but also in hearing-impaired patients with residual low-frequency hearing. The overall aims of the present thesis were to study human cochlear anatomy in order to improve structural preservation during CI surgery. An archival collection of temporal bones underwent micro-computer tomography and synchrotron radiation phase-contrast imaging (SR-PCI) with 3D reconstructions, new techniques to digitally image and reproduce the human inner ear. Studying the anatomy of the facial nerve and its interaction with the cochlea revealed that a fusion of the two was found in 1.4 % of the specimens (cochlear-facial dehiscence). This may cause facial nerve excitation after CI. CT-scans and intraoperative electrically auditory brainstem response (e-ABR) measurements were analyzed in patients with cochlear-facial dehiscence. A large evoked late myogenic potential at low stimulation levels during intraoperative e-ABR measurements, can foresee excitation at CI activation. The 3D anatomy of the fundus of the inner acoustic canal was also studied, helping to interpret preoperative imaging of the VIIIth nerve before CI. In a subsequent study, SR-PCI reproduced the soft tissue anatomy at the round window region. Results indicated a high risk for trauma at cochleostomy. For optimal preservation, the round window approach was recommended. In a long-term follow-up the first 21 consecutively operated patients in Uppsala, that underwent hearing preservation CI-surgery, data could be retrieved in 15 patients. Pure tone audiometry was assessed preoperatively and at one, three and >5 years following surgery. Insertion angle, number of electrodes inside the cochlea, user-time of the processor, and stimulation strategies were documented. Results showed that long-term preservation of hearing is possible in most cases. There was a high correlation between insertion depth and preservation of residual hearing. Also, patients with complete hearing loss experienced good performance in speech discrimination and user time.

Keywords: cochlear implantation, micro-CT, synchrotron, facial nerve stimulation, hearing preservation, round window

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Panta rei. Alles fliesst.

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Schart-Morén N, Sune L, Rask-Andersen H, Li H. Anatomical Characteristics of Facial Nerve and Cochlea Interaction. *Audiol Neurootol.* 2017;22(1):41-49.

II Schart-Morén N, Hallin K, Agrawal SK, Ladak HM, Eriksson PO, Li H, Rask-Andersen H. Peri-Operative Electrically Evoked Auditory Brainstem Response Assessment of Facial Nerve/Cochlea Interaction at Cochlear Implantation. *Cochlear Implants Int.* 2018; 19(6): 324-329.

III Schart-Morén N, Sune L, Rask-Andersen H, Li H. Three-Dimensional Analysis of the Fundus of the Human Internal Acoustic Canal. Ear Hear. 2018;39(3):563-572.

IV Schart-Morén N, Agrawal SK, Ladak HM, Li H, Rask-Andersen H. Effects of Various Trajectories on Tissue Preservation in Cochlear Implant Surgery: A Micro-Computed Tomography and Synchrotron Radiation Phase-Contrast Imaging Study. *Ear Hear.* 2018 Jun26. Epub ahead of print.

V Schart-Morén N, Erixon E, Li H, Rask-Andersen H. Cochlear Implantation and Residual Hearing Preservation. Long-term Follow-up of the First Consecutively Operated Patients Using the Round Window Approach in Uppsala. Submitted manuscript.

Contents

Abbreviations

ACO	Anterior cochleostomy
AICO	Anterior-inferior cochleostomy
BM	Basilar membrane
CD	Distance between the cochlea and the facial nerve
CFD	Cochlear-facial dehiscence
CI	Cochlear implant(ation)
CO	Cochleostomy
CT	Computed tomography
EAS	Electro-acoustic stimulation
e-ABR	Electric auditory brainstem response
FNS	Facial nerve stimulation
HP	Hearing preservation
IAC	Internal acoustic canal
ICO	Inferior cochleostomy
LLFP	Lateral wall/ligament fusion point
LP	Labyrinthine portion
MRI	Magnetic resonance imaging
OSL	Osseous spiral lamina
PCI	Phase-contrast imaging
PTA	Pure tone average
RW	Round window
SL	Spiral ligament
SNC	Saccular nerve canal
SR-PCI	Synchrotron radiation phase-contrast imaging

Introduction

The sense of hearing is essential for the performance of our daily life. Worldwide, approximately half a billion people suffer from disabling hearing loss. According to a survey performed between 2014–2016 by the government agency Statistics Sweden, 18.5 % of the Swedish population (> 16 years) suffer from some kind of hearing loss. Thirty to fifty children are born each year in Sweden with deafness, of which approximately 70 % have a genetic predisposition; however, the most common cause of hearing loss is age-related, which can, in moderate cases, be treated with hearing aids. In more severe cases surgery with cochlear implantation may be needed. More than 250 cochlear implant (CI) surgeries are performed each year in Sweden, with a total of more than 4,000 surgeries nationwide since the beginning of the 1980s, and approximately half a million individuals have been treated worldwide. Due to the size of multielectrode devices, a so-called cochleostomy (CO) is often used to insert the electrode. This trajectory pathway makes it possible to insert the electrode array beyond the narrow, curved portion of the basal turn of the cochlea.

A new era in CI surgery began over 10 years ago. The concept was introduced to combine electric and acoustic stimulation (EAS) of the same ear in patients with residual low-frequency hearing (von Ilberg et al. 1999). This type of surgery initiated a new soft atraumatic approach and technique. Electrodes are now inserted through the round window (RW) instead. This technique was combined with softer implants to limit inner ear trauma during surgical implantation. The vision to create more compliant and softer electrode arrays placed within the scala tympani without interfering with any associated structures is still on-going. An important obstacle is the many anatomic variations of the human cochlea. It requires a more individualized design of the electric array in the future to avoid trauma and induced inflammation (Nadol et al. 2014). A broad knowledge, based on the structure and function of the human inner ear, is therefore key for further enhancement of modern hearing implants for a wide range of patients. This includes patients with residual hearing and those with profound sensorineural hearing loss or total deafness.

This thesis aims to further examine and broaden our understanding of human cochlear anatomy, associated cranial nerves and their relevant variations for CI. For this, we took advantage of novel imaging techniques, such as micro-computerized tomography (micro-CT) and synchrotron radiation phase-contrast imaging (SR-PCI), as well as computer-based 3D reconstructions.

Background

Anatomy of the cochlea and VIIIth nerve

A thorough knowledge of the anatomy of the human cochlea and the VIIIth cranial nerve is essential for CI surgeons, as a correct placement of the electrode inside the scala tympani may yield better functional results (Aschendorff et al. 2007). Moreover, it is important to verify the existence of a patent cochlear nerve in the internal acoustic canal (IAC) and cerebellar-pontine angle before CI surgery. To preserve hearing, it is necessary to perform CI surgery with meticulous care. In addition, the facial nerve lies close to the cochlea and can be a challenge as in most types of ear surgery. Its position near the cochlear turn can lead to the spread of electrical currents of the CI and unwanted side effects. In this thesis, anatomic variations and the topography of the facial nerve were analyzed in more detail. Its visualization via CT scans, possible use of 3D reconstructions, and clinical decisions on alternate electrodes are discussed together with possibilities for avoiding and alleviating these complications.

The present study focused on the variable cochlear anatomy using new imaging techniques such as micro-CT and synchrotron radiation. Particular interest was paid to the structure of the basal turn of the cochlea and the RW. This portion is often named the "hook" due to its fishhook-like structure and is trajectory pathway during most CIs. Since imaging can reproduce soft tissues as well, it may offer unique possibilities in viewing the effects of several types of surgical procedures. The research may also provide more knowledge about optimal trajectory pathways for electrode insertion.

The thesis also included analyses of the intricate anatomy of the fundus of the IAC using micro-CT. These results culminated later in an investigation of the cranial nerve anatomy using synchrotron imaging (Mei et al. 2018).

History

In an overview, Van De Water 2012 described the historical aspects of inner ear anatomy and biology that underlie the design of hearing and balance prosthetic devices. He stated that Vesalius 1543 and Eustachi 1564 were the first to describe the anatomy of the human cochlea. At first, it was thought that the inner ear was filled with some type of gas (Galen 1542) until Cotugno 1761 found that the cochlea and vestibular organs contain liquid, later called perilymph. Antonio Scarpa published his studies in 1789 on the inner ear membranous labyrinth and endolymph space (Scarpa 1789). He described the innervation of the three ampullae, and the maculae of the utricle and the saccule via fibers that originate from the acoustic nerve. He also published anatomical observations of the RW in 1772 and showed that Fallopia was the first to describe both the oval and the RWs (Scarpa 1772).

Thanks to the development of compound microscopes and improved histological techniques, the organ of Corti was discovered together with several other inner ear cell types (Claudius 1856, Deiters 1860, Hensen 1863).

Retzius and Brödel provided aesthetic illustrations of the inner ear anatomy in the 19th century, that are still valid and valuable today giving us important insight into the structure of the inner ear.

Electron microscopy made it possible to analyze the microstructures of the inner ear in more detail. Lim 1969 and Engstrom and Engstrom 1972 are some of the pioneers in this field, using both transmission and scanning electron microscopy. Over the last several decades, new imaging techniques like micro-CT and SR-PCI have been introduced that provide clinicians with new insights in temporal bone anatomy and pathology, increasing diagnostic and surgical precision.

Cochlear implantation and hearing preservation

A CI is a hearing implant that is used when conventional hearing aids can no longer amplify acoustic hearing in patients with severe or profound hearing loss. It consists of a sound processor that is worn behind the outer ear and captures sound, transforms it into a digital code, then sends it through the coil to the internal receiver. The implant converts this digitally coded information into electrical impulses conveyed to an electrode array placed in the cochlea. The electrodes electrically stimulate the neurons within the spiral ganglion in the cochlea. It is important that the oto-surgeon is well acquainted with the inner ear anatomy to avoid harming the fine structures of the cochlea. Recently, patients with more residual hearing have been operated upon with shorter and softer electrodes. The aim of these implantations is to preserve the natural residual low-frequency hearing and compensate the high frequency loss by electric stimulation.

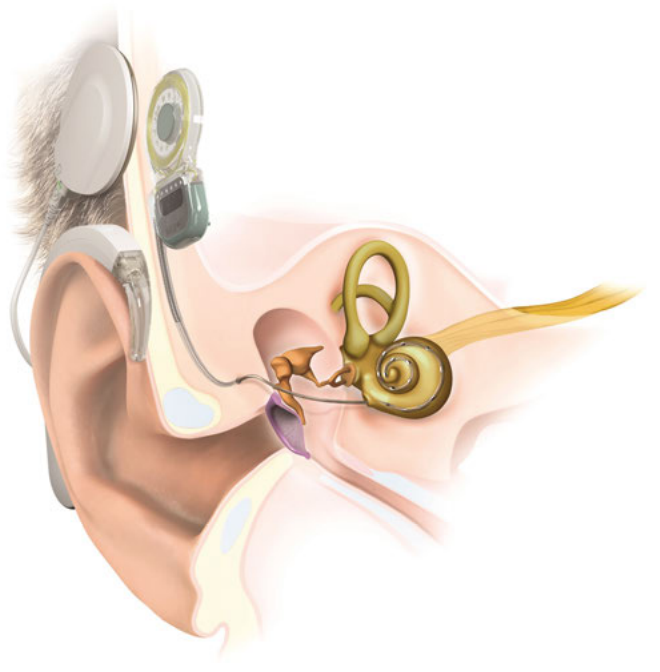

Figure 1. Cochlear implant. Reprinted with kind permission from MED-EL GmbH Innsbruck, Austria.

Cochlear-facial dehiscence

Cochlear-facial dehiscence (CFD), a fusion between the basal part of the cochlea and the labyrinthine portion (LP) of the facial nerve canal, is a rare condition. The LP of the facial nerve and the otic capsule of the cochlea are anatomical neighbours (see Figure 2). This is why, in rare cases, electric currents can spread from the cochlear electrodes and lead to adverse stimulation of the facial nerve. This phenomenon occurs typically in otosclerosis, malformations of the inner ear and after temporal bone fractures. An opening, or dehiscence, between the facial nerve and the cochlea occured in 0.6 % of samples in the temporal bones collection, as previously described by Fang et al. 2016. Blake et al. 2014 were the first to describe this condition in a case report. They reported two cases with hearing loss, tinnitus and autophony. A combination of family history, physical examination, and high resolution computer tomography supported their diagnosis.

Imaging techniques

Our knowledge of the micro-anatomy of the inner ear is mainly based on conventional histology on two-dimensional sections, imaged by optical microscopy. However, this source has several major deficits and limitations compared to 3D imaging. Apart from the risk of slicing or staining artifacts, it is extremely time consuming to record the entire organ.

Conventional clinical computed tomography and magnetic resonance imaging (MRI) typically have resolution capabilities in the 0.5 mm range. For resolving microanatomy of the cochlear structures, a resolution is necessary that is at least two orders of magnitude higher. Micro-CT and SR-PCI are capable of assessing the native 3D structure of tissues in the range of several microns.

In micro-CT, a micro-focused X-ray source illuminates the object and a planar X-ray detector collects magnified projection images. Based on hundreds of angular views acquired while the object rotates, a computer synthesizes a stack of virtual cross section slices of the object. Due to the size of the machine and the high intensity of radiation over a long period, it is only suitable in experimental conditions. While CT imaging is absorption-contrast based, phase-contrast imaging (PCI) can be combined with synchrotron radiation to give an improved contrast of soft tissue while maintaining precise visualization of bone.

Micro-CT and SR-PCI, therefore, have the potential to replace histology as the gold standard for evaluating intra-cochlear structures in human specimens, as well as motivate further optimization for translation into the clinic setting.

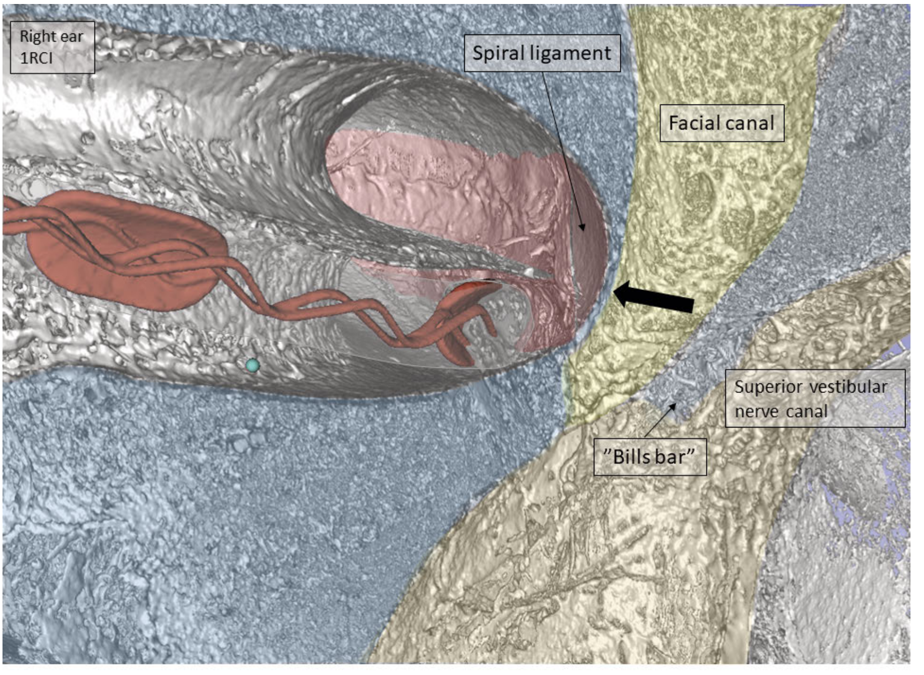

Figure 2. Synchrotron radiation phase-contrast imaging (SR-PCI) and 3D rendering of a right human temporal bone, implanted with a 28 mm flexible lateral wall electrode. There is a cochlear-facial juxtaposition at the upper basal turn of the cochlea corresponding to the inferior-medial aspect of the labyrinth segment of the facial nerve canal. A 3D reconstruction program was used with scalar opacity mapping thresholds to improve visualization of the surface anatomy.

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Aims of Present Studies

The overall aims of the present studies were to analyze the human cochlear anatomy that is relevant for cochlear implantation, as well as to broaden our understanding of the anatomic variations using new imaging techniques such as micro-CT and SR-PCI.

The specific aim of each paper was:

(I): To study the relationship between the labyrinthine portion of the facial canal and the cochlea in human inner ear molds and temporal bones using micro-CT and 3D rendering.

(II): To describe how electrically evoked auditory brainstem response (e-ABR) and radiological investigations may assist in identifying patients with cochlear-facial dehiscence, a rare condition that causes abnormal facial nerve stimulation (FNS) after activation of the cochlear implant.

(III): To describe the anatomical variations of the IAC and their clinical implications using micro-CT and 3D rendering.

(IV): To describe the architecture of the basilar membrane (BM) and RW in the basal part of the human cochlea and to see how it relates to different CI trajectory pathways by using micro-CT and SR-PCI.

(V): To perform long-term follow-up of patients operated with CIs and hearing preservation.

Materials and Methods

Papers I, III, and IV

Uppsala archival temporal bone collection

The Uppsala archival temporal bone collection consists of 113 unselected human temporal bones from autopsies and 334 plastic and silicone molds made from the labyrinth. The collection of temporal bones was established by Herman Wilbrand, Jan Stahle, Karin Wadin, and Helge Rask-Andersen during the 1970s and 1980s at the Department of Diagnostic Radiology and Otolaryngology at the Uppsala University Hospital, Sweden. Seventy-eight bones were micro-dissected in order to expose the vestibular and cochlear aqueducts. After maceration, the roof of the internal acoustic canal was drilled away and the fundus was exposed. Thirty-five bones were left un-dissected. Data from this collection was previously published by Wilbrand 1975, Rask-Andersen et al. 1977, and Wadin and Wilbrand 1987. Recently, this unique collection has formed the basis for new publications on the anatomy of the cochlea, RW, and vestibular aqueduct (Erixon et al. 2009, Atturo et al. 2014, Nordstrom et al. 2016).

The plastic and silicone molds in the collection were prepared in the 1970s. The temporal bones were soaked and cleaned in potassium hydroxide (KOH), boiled and then treated with 2 % hydrogen peroxide (H2O2) and trypsinized. The bones were positioned in a wax form with the cavities of the inner ear canals left open. Next, a polyester resin or silicone rubber material was poured into the wax form. The forms were placed in a low pressure chamber to improve the dispersion of the molding material into the tiny, bony canals of the temporal bones. The bone was suspended with hydrochloric acid after hardening.

In Paper I, 282 out of 334 molds could be analyzed for cochlear-facial dehiscence (CFD). The distance between the cochlea and the facial nerve (CD) was measured in 48 out of 59 randomly chosen silicone molds and in 49 out of 51 resin molds. All 113 temporal bones underwent micro-CT. Eighty bones could be analyzed for superior semicircular canal dehiscence (SSCD) (see Table 1).

Table 1.

	Uppsala archival bone collection
334 molds	282 were analyzed for CFD
	CD was measured in 48 out of 59 silicone molds
	CD was measured in 49 out of 51 resin molds
113 temporal bones	113 underwent micro-CT
	80 bones could be analyzed for SSCD

In Papers III, which is more descriptive, we analyzed 113 temporal bones and 334 plastic and silicone molds.

In Paper IV, we drilled out different conventional COs using a 1mm diamond burr in 17 out of the 78 micro-dissected bones. Afterwards, the bones underwent micro-CT.

Papers I, III, and IV

Micro-computed tomography

The type of clinical CT used today suffers from a fairly low image contrast resolution. In experimental situations, micro-CT allows high-intensity irradiation and offers a resolution down to the micrometer level with greatly improved image contrast. X-rays are emitted from a generator and travel through a sample, in our cases temporal bones or corrosion casts, which are detected on the opposite side to produce radiograph imaging. The X-ray tube and the detector rotate around the sample by a fraction of a degree, and another projection image is taken at the new position. This procedure is repeated until a 360-degree rotation is achieved. The projection images are processed using a computer software (Slicer 4.6) to visualize the internal structures of the samples. The reconstructed images are transferred and modelled into a 3D volumetric object for quantitative analysis or visualization. However, one disadvantage is the low reproduction of soft tissues, such as the BM and spiral ligament (SL). Our micro-CT reproduction allowed for edge enhancement by accentuating the contrast between the boundaries of structures.

Paper II

Patients

In 2017, a short time after publishing our first micro-CT study on the relationship between the cochlea and the facial nerve, two patients with the precise clinical condition of a CFD were diagnosed in our clinic. Two surgeons had operated on them at different times, and there was no other medical condition, like otosclerosis or skull base fracture to explain the facial excitation during the devices' activation. Both patients were operated with lateral wall electrodes. In the first patient a MedEL flexsoft 28 mm was used. In the second patient a MedEl flexsoft 31 mm long electrode was inserted via the RW.

Clinical scan procedures

All CI-patients in Uppsala routinely undergo preoperative CT scans and MRI to confirm normal inner ear anatomy. Perioperative conventional X-rays confirm the correct position of the electrode after insertion. In both patients, a postoperative cone beam CT scan and 3D reconstructions were analyzed and compared to preoperative images for description of the labyrinthine portion of the facial nerve and its relationship to the cochlea.

Electrical evoked auditory brainstem responses

Auditory brainstem response (ABR) measurements during CI surgery allows us to test the auditory nerve function objectively. We use it routinely in our clinic to better predict hearing outcomes with CI. Normally, the ear is stimulated acoustically, but during CI, it is possible to electrically stimulate the cochlear nerve via the electrode. The principle of ABR recording is stimuli presented to the ear and registry of the voltage changes from the skin electrodes on the scalp surface. A computer program filters and removes the background noise. Normally, waves I-V are analyzed. However, wave I is missing in e-ABR because the electrode stimulates the cochlea directly where wave I is normally generated. Wave I is often shadowed by a stimulation artifact (Abbas and Brown 1988, Firszt et al. 2002).

Two separate systems were used, one for stimulation and one for recording. In this study, we used the Med El programming device and the recording system was an evoked potential, triggered from the stimulating system to initiate recording. The system for the evoked potential was the Otometrics Chartr 200 (GN Otometrics, Taastrup, Denmark). We recorded e-ABRs through stimulation channels 1, 7, and 11 on the electrode.

Paper IV

Temporal bone preparation

The technique used in our studies was recently described by Elfarnawany et al. 2017 and Koch et al. 2017. Sixteen freshly frozen and then fixed adult cadaveric temporal bones were used in this study. All specimens were obtained with approval from the body bequeathal program at Western University, London, Ontario, Canada, in accordance with the Anatomy Act of Ontario and

Western's Committee for Cadaveric Use in Research. Following thawing, a cylindrical cutter was used to core a sample (40 mm in diameter and 60 mm in length) of the middle ear from each temporal bone. The samples were fixed in a 4F1G (3.7 % formaldehyde and 1 % glutaraldehyde in phosphate buffer) bath for 5 days. The samples were rinsed twice and dehydrated using an ethanol series (50 %, 60 %, 70 %, 80 %, 90 %, 95 %, and 100 %). No additional processing (i.e., staining, sectioning or decalcification) was performed on the samples. Sample fixation eliminated the risk of degradation during the two-month time difference between imaging sessions and scanning. Samples were transported to the synchrotron facilities in motion-proof boxes to prevent the risk of damage during shipping.

Synchrotron radiation phase-contrast imaging

The SR-PCI on the 16 temporal bones was performed by our collaborating research team at Western University, Ontario, Canada. The setup is comparable to conventional radiography. It comprises an X-ray source, a sample, and a detector with no extra optical elements. The detector stands at a distance from the sample. This permits the phase shifted beam to interfere with the original beam and produce measurable fringes.

Compared to a conventional radiogram, the fringes correspond to surfaces and structural boundaries of the sample (edge enhancement). Each sample was scanned using the Bio-Medical Imaging and Therapy 05ID-2 beamline at Canadian Light Source Inc. in Saskatoon, Saskatchewan, Canada. It provides an SR beam produced by a superconducting wiggler source (Wysokinski et al. 2015). A monochromator, yielding an energy bandwidth of $\Delta E/E = 10^{-3}$ over an energy range of 25-150 keV, was used to filter the beam. The imaging setup is installed at the beamline length of 55 m from the source. It is made up of a sample stage and a charge-coupled device-based detector system. Both are positioned on a vibration isolation table. The distance between the sample and detector was 2 m, and the photon energy was 47 keV. Motorized alignment stages were used to align the sample and detector for high-resolution tomography. The detector (an AA-60 beam monitor coupled with a C9300-124 camera, Hamamatsu Photonics, Shizuoka, Japan) has a 12-bit resolution and an effective pixel size of 9 x 9 μm^2. The imaging field of view was set to 4000 x 950 pixels, corresponding to 36.0 x 8.6 mm, and 3000 projections over 180° rotations were acquired per view. The 3D image volume had an isotropic voxel size of 9 µm. The acquisition time to capture all projections per view was approximately 30 minutes. While CT imaging is absorption-contrast based, phase-contrast imaging (PCI) can potentially be combined with synchrotron radiation to improve soft-tissue contrast while maintaining an accurate visualization of bone. Conventional absorption-contrast based CT depends on the attenuation of X-rays, whereas in PCI, the phase shift caused by the sample is transformed into detectable variations in X-ray intensity. PCI can provide edge enhancement by emphasizing the contrast between the boundaries of different structures in the image.

Paper V

Patients

Erixon et al. 2012 presented our results on hearing preservation (HP) CI surgery in the first 21 consecutively operated on patients using the RW approach in Uppsala. One patient died during the follow-up period and was therefore excluded. Data from 15 of these patients was available for our long term follow-up, showing how hearing is affected over a period of more than 5 years. The mean age at operation was 59 years (range: 19¬87 years), nine women, eleven men.

Surgery

All 21 patients were operated on by the same surgeon between September 2008 and October 2010. In 20 cases, a MedEl flex EAS electrode (24 mm long) with an insertion depth of 17.5-23.5 mm was used in 20 cases and in one case a MedEl flex soft electrode (31 mm long) with an insertion depth of 28.5 mm. The surgical approach was via the RW after gentle drilling of the bony overhang and insertion of the electrode after a vertical incision of the membrane. Corticosteroids (Triamcinolon solution 40 mg/ml) were installed in the middle ear while inserting the electrode slowly by free hand. The correct electrode position was checked and confirmed by postoperative radiology.

Audiometry

Hearing thresholds were evaluated at frequencies of 250, 500, 1000, 2000, 3000, 4000, 6000 and 8000 Hz preoperatively, as well as at 1, and 3 years postoperatively with one long-term follow-up after more than 5 years (mean 86 months, range: 61-103 months) in both ears of each patient.

Additionally, the percent of HP over the whole frequency range (125- 8000 Hz) was calculated as stated by the HEARRING group consensus in 2013, according the following formula:

$$HP = \left(1 - \frac{PTApost - PTApre}{PTAmax - PTApre}\right) * 100\ [\%]$$

In this equation, PTApre is pure tone average measured preoperatively, PTApost is pure tone average measured postoperatively, and PTAmax is the maximum sound intensity generated by a standard audiometer, usually 120 dB hearing level.

In accordance with this groups' suggestion, >75 % of the preserved residual hearing can be classified as complete HP, >25-75 % as partial HP and 0-25 % as minimal HP (Skarzynski et al. 2013).

Fitting of speech processor

One month after surgery, the patients were fitted with their speech processor. Different stimulation strategies were carefully evaluated by the patient and the engineers. We documented user-time of the processor, and whether the patients were fitted with full-frequency stimulation (e-only), cut-off frequency stimulation strategy with acoustic stimulation in the lower frequencies (a+e), or natural hearing (n+e), both during the first year and at the long-term follow-up. The user-time of the processor was recorded (full-time user > 8 hours per day, part-time user < 8 hours per day, and non-user).

Results

Paper I

In the first paper we studied the relationship between the labyrinthine portion (LP) of the facial canal and the cochlea in human inner ear molds and temporal bones. We measured the cochlea-facial distance in silicon and polyester resin molds in our archival collection of human temporal bones. The association between the labyrinthine portion and the upper basal turn of the cochlea was analyzed (see Figure 3). The mean distance in the axial-pyramidal direction (vertical plane) was 0.20 mm (range 0-0.46 mm) in the plastic resin group and 0.22 mm (range 0.06-0.45 mm) in the silicone group. The relative portion of the cochlea exposed on either side of the nerve canal was calculated. The mean percentage located laterally from the nerve was 8 % (range 0 %-26 %) and that located medial to the nerve was 62 % (range 39 %-79 %). Local thinning of the otic capsule and local anatomy may explain the development of CFD. It was found in 1.4 % of the molds. A reduced cochlea-facial distance was noted in one bone with a superior semicircular canal dehiscence but not in bones with superior semicircular canal "blue line". The otic capsule often impinged upon the LP of the facial nerve canal and caused narrowing. We used micro-CT and 3D rendering with multi-planar sectioning for the first time in our temporal bone collection to add and visualize information about the interaction between the LP and cochlea.

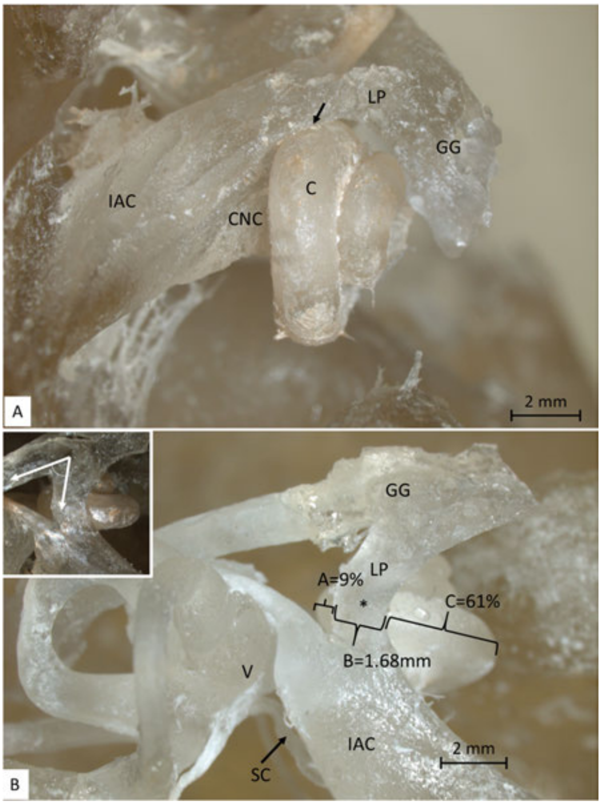

*Figure 3. Plastic corrosion casts of two left human temporal bones. **A** Axial-pyramidal projection. The cochlea and the facial canal are fused (arrow). **B** Cranio-caudal projection. The axial view shows the projection of the labyrinthine portion over the cochlea. **Inset** Measured angle between the labyrinthine and tympanic portions of the facial canal. C, cochlea; CNC, cochlear nerve canal; GG, geniculate ganglion; IAC, internal acoustic canal; LP, labyrinthine portion; SC, canal of the singular nerve.*

Paper II

CFD is a very rare condition. In our second paper we analyzed the clinical, radiological, and electrophysiological conditions of our two patients with the suspected CFDs. In both cases, e-ABR measurements showed a very specific pattern. A prominent response was observed after 7.5 ms in case one and an uncommon late wave V, and a larger late potential after 6 ms in case two.

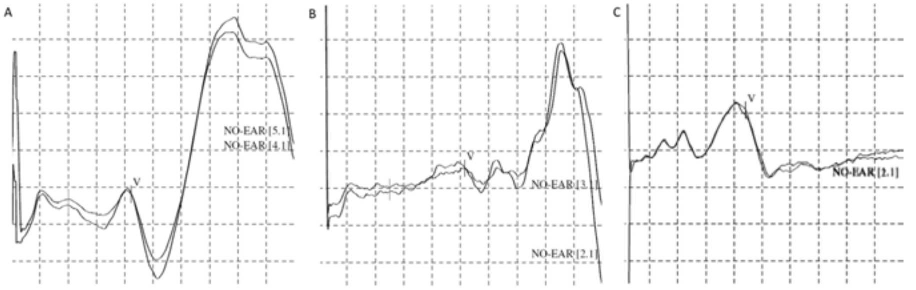

Figure 4. Illustration of peri-operative e-ABR curves. A prominent response was observed after 7.5 ms in case 1 (A). Uncommon late wave V after 5 ms and a larger late potential after 6 ms in case 2 (B). Normal e-ABR curve (C).

The clinical CT scans of the patients were analyzed pre- and postop. In case one, the radiologists suspected the dehiscence between the facial nerve and the cochlea, but in case two, the radiological imaging was not clear enough to make a determination.

Patient one could reach an open speech discrimination after switching off channels four and five and increasing the pulse width. In patient two, facial nerve stimulation occurred on a majority of channels. Even after several attempts to reprogram, it was not possible for him to gain an open speech discrimination.

Paper III

We used micro-computed tomography and analyzed the fundus bone channels in the archival collection of 113 macerated human temporal bones and 325 plastic inner molds. Data were subsequently processed by volume-rendering software using a bony tissue algorithm. Three-dimensional reconstructions were made and, through orthogonal sections, the topographic anatomy was established. The technique provided information regarding the anatomy of the nerve foramina/channels of the human fundus region including variations and destinations. Channel anastomosis were found beyond the level of the fundus, as well as anastomosis between the vestibular and facial nerve. An incomplete separation after the division of the superior vestibular nerve canal into the ampulla nerve canals and utricle nerve canals with a fenestrated bony crest could be observed. Not infrequently, there were two saccular nerve canals (SNC1 and SNC2) running to the saccule. Micro-CT scans of inner ear molds also suggested that utricle and saccule nerves may also anastomose more centrally, also known as the Voit's nerve anastomosis (Voit 1907). A foramen of the transverse crest was identified in 77 % of the studied temporal bones. The channel ran to the cribriform region of the utricle. Other anatomical variations like Oort's anastomosis (Oort 1918) and Hardy's nerve (Hardy 1934), were also described together with their clinical implications. Three-dimensional reconstructions and cropping outlined the bone canals and demonstrated the highly variable VIIIth nerve anatomy at the fundus of the human inner acoustic canal (see Figure 5). A myriad of channel interconnections suggested an intricate system of neural interactive pathways in humans.

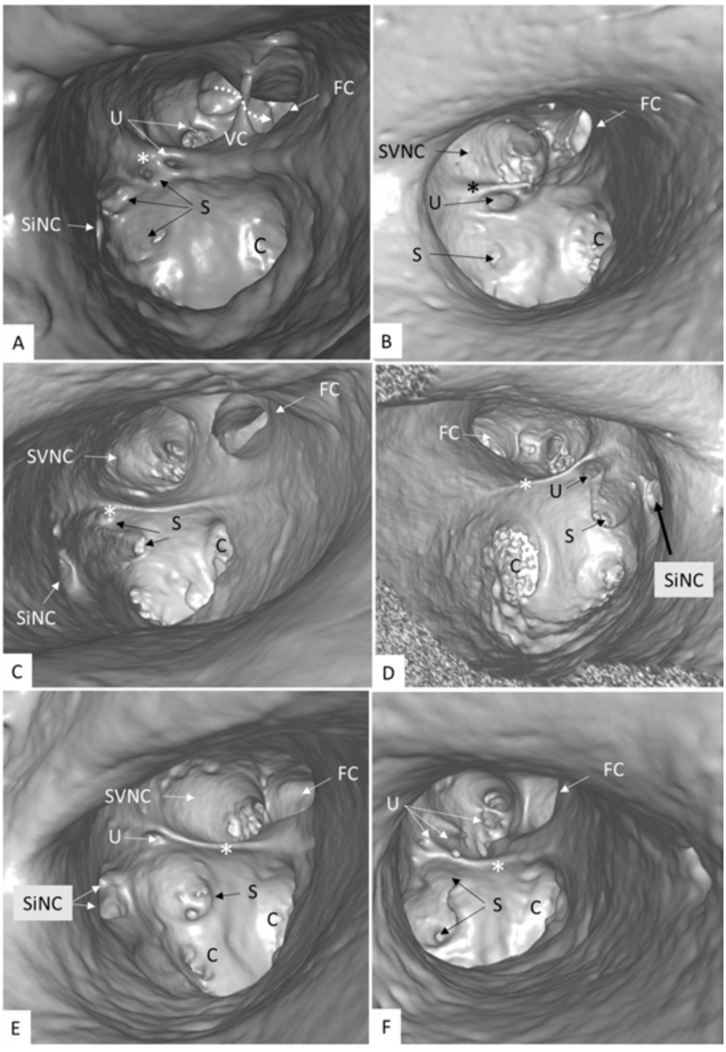

Figure 5. Varied anatomy of the human fundus (left ears). Each channel was followed to the labyrinth with the help of cropping. Foramen of the transverse crest (*) ran to the utricule (U) while those situated beneath ran to the saccule (S). Two or even three cibriform plates of the saccule are seen. The location of the singular nerve channel (SiNC) varies. The wall between the facial nerve canal (FC) and superior vestibular nerve canal (SVNC) is fenestrated in (A). The vertical crest (VC) is poorly defined in (D). C indicates cochlea.

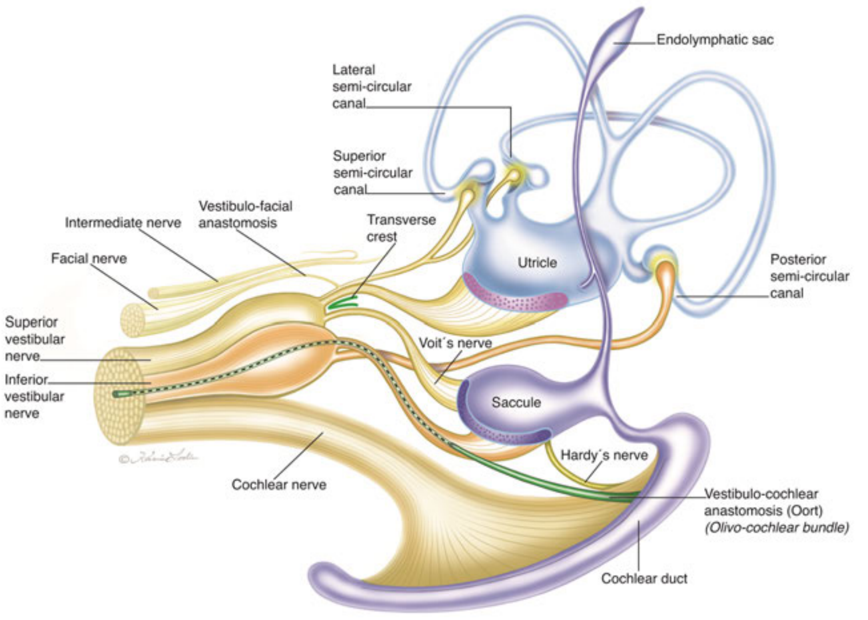

Figure 6. Schematic illustration of the principal organization of the nerve anatomy in the human IAC (adapted from Ort 1918 and de Burlet 1924).

Paper IV

In our fourth paper, the anatomy of the RW and the effects of various cochleostomies during CI surgery are described. Micro-computed tomography with 3D rendering revealed the anatomy of the RW and osseous spiral lamina (OSL), whereas synchrotron imaging made the soft tissues, such as the BM and its suspension around the RW membrane, visible.

We could visualize the BM, the SL, and the OSL. The secondary spiral lamina is a plate that arises at the posterior rim of the RW by the scala tympani wall of the lower part of the SL. It attaches the BM laterally and reaches the caudal end of the RW where it contacts with the OSL. We defined a fusion point of the SL and the OSL near the posterior margin of the RW membrane, the lateral wall/ligament fusion point (LLFP) (see Figure 7).

We performed different conventional COs and showed that anterior cochleostomies (ACOs) and anterior-inferior cochleostomies (AICOs) consistently destructed the area of the spiral lamina. Even inferior cochleostomies (ICOs) sometimes ended up in this vulnerable region.

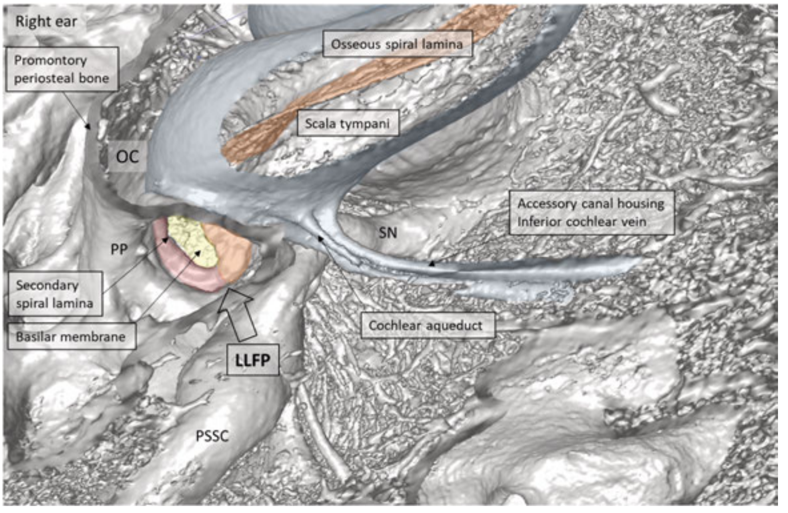

Figure 7. Magnification of hook region of the cochlea. The twisted osseous spiral lamina (brown) is shown after cropping. The secondary spiral lamina is viewed (red) through the RW. LLFP defines the beginning of the BM. The cochlear aqueduct and inferior cochlear vein channels can be seen. PSSC; posterior semicircular canal. SN; singular nerve. OC; otic capsule. PP; postis posterior.

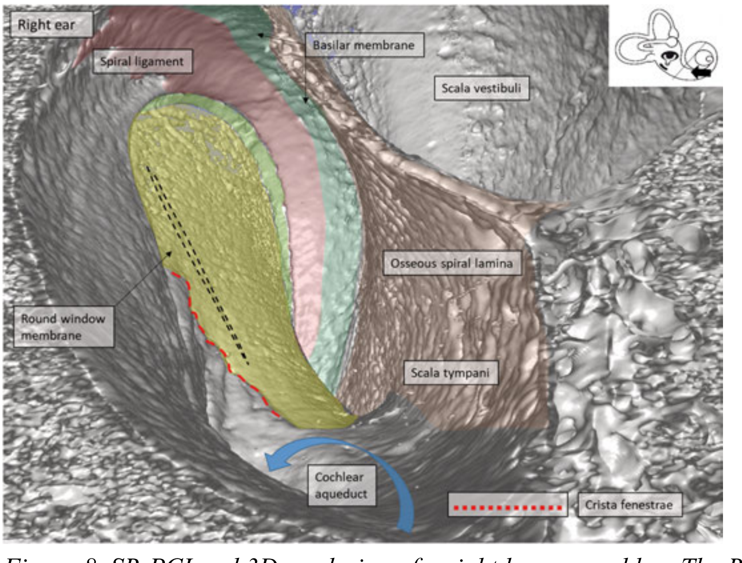

Figure 8. SR-PCI and 3D rendering of a right human cochlea. The RW membrane is viewed from the scala tympani (inset). The spiral ligament/secondary spiral lamina (red) suspends the BM laterally. The opening of the cochlear aqueduct is located in the floor of the scala tympani at the interior surface of the crista fenestrae (red interrupted line).

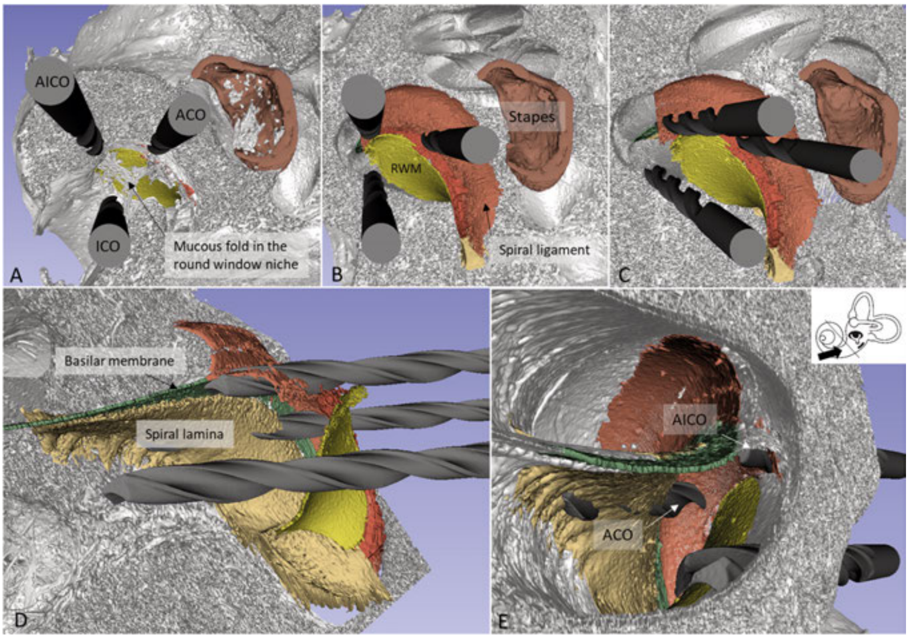

Figure 9. SR-PCI of different surgical approaches (facial recess view) and how they wind up inside the cochlea. The soft tissues of the basal part of the cochlea were traced and color-labeled on serial sections for reconstruction. The data were fed into the 3D software program and models were made using the threshold paint tool in the editor module. A. Cropping of the bony overhang was made to define the margins of the round window membrane (RWM) and different COs as defined by the authors. ACO; anterior cochleostomy, AICO; anterior-inferior cochleostomy, ICO; inferior cochleostomy. B and D. Deeper sections expose the spiral ligament which is crossed by ACO and AICO trajectories. D. Lateral view. E. Anterior view after cropping of the cochlea (inset).

Paper V

Nineteen of the 20 evaluated patients had preserved residual hearing after one and three years post-operatively, as previously described by Erixon et al. 2012. We could collect data for long-term follow-up from more than five years post-operatively in 15 patients. Out of these 15 patients, 12 still had residual hearing after a follow-up period of over five years (mean: 86 months, range: 61-103 months). Another 4 out of 15 patients had complete HP (>75 %), 8 had partial HP (25-75 %), and 3 patients had complete hearing loss. There was a high correlation between insertion angle and HP rate (Pearson test, $p < 0.002$). The patients with complete HP had a relatively smaller insertion angle compared to the patients with partial or complete hearing loss. Most patients that could be followed-up with in the long-term used their implants full time (13 out of 15 patients). The patients experienced noticeable benefits from the devices. One patient was a non-user (probably due to dementia) and one patient a part-time user (three hours/day).

Patient	Age at implantation	Electrode	Degrees	No of electrodes inside the cochlea	User-time	Stimulation	Stimulation (at long-term follow up)	Hearing preservation	MS preop (stimulation level)	MS postop	Long-term follow-up (month)
2	19	Sonata flex EAS	320	9	full-time	a+e	a+e	79%	26% (75dB)	66% (65dB)	97
3	87	Sonata flex EAS	275	9	non-user	a+e	non-user	78%	4% (70dB)	non-user	63
5	50	Sonata flex soft	540	12	full-time	e only	e only	0%	14% (70dB)	70% (65dB)	103
6	71	Sonata flex EAS	335	10	full-time	e only	e only	100%	8% BS (80dB)	46% BS (80dB)	103
8	70	Sonata flex EAS	290	10	full-time	a+e	a+e	50%	34% (65dB)	36% (65dB)	92
9	49	Sonata flex EAS	360	10	full-time	e only	e only	58%	28% (65dB)	70% (65dB)	86
11	69	Sonata flex EAS	320	10	full-time	n+e	n+e	72%	22% (75dB)	54% (65dB)	88
12	27	Sonata flex EAS	280	10	full-time	a+e	no data	95%	no data	no data	72
13	48	Sonata flex EAS	380	11	full-time	a+e	e only	68%	0% (80dB)	64% (65dB)	85
14	68	Sonata flex EAS	390	11	full-time	a+e	e only	48%	0% (70dB)	56% (65dB)	84
16	70	Sonata flex EAS	360	12	full-time	a+e	a+e	70%	42% (70dB)	62% (65dB)	84
18	57	Sonata flex EAS	360	10	full-time	a+e	e only	0%	34% (70dB)	70% (65dB)	82
19	72	Sonata flex EAS	315	10	part-time	e only	e only	55%	26% (70dB)	36% (65dB)	79
20	27	Sonata flex EAS	385	12	full-time	a+e	no data	37%	48% (75dB)	24% (65dB)	80
21	75	Sonata flex EAS	450	11	full-time	e only	e only	0%	44% (70dB)	30% (65dB)	73

Table 2. There were 15 patients with long-term follow-up data. The data included: Degrees = electrode insertion angle verified by radiology; No of electrodes inside the cochlea verified by radiology; Stimulation a+e = acoustic and electrical stimulation, e only = electric stimulation only, n+e = natural hearing in low frequencies, and electric stimulation in the higher frequencies; MS = monosyllables; BS= bisyllables.

Discussion

Cochlear implantation today is routinely performed worldwide to restore hearing in patients with severe sensorineural hearing loss. In the last decade, electrodes have become thinner and more flexible so that even patients with quite usable residual hearing in the low frequencies and losses in high frequency regions can be operated upon and benefit from this technology.

Hearing preservation by inserting the cochlear implant electrode through the RW is now a widely-used surgical technique, but we do not know exactly how this method preserves residual hearing from a long-term perspective. What is the optimal length of an electrode for preserve hearing? How deep do we need to stimulate the cochlea to gain ideal hearing results? Does the size of the cochlea matters? My thesis does not provide answers to all these questions, but it is an attempt to clarify some gaps in our knowledge. First, I focused on the anatomy of the inner ear with new imaging techniques, such as micro-CT and SR-PCI. For this purpose, the Uppsala collection of human temporal bones from the 1970s was an invaluable resource and fortunately we were able to start a collaboration with the Canadian research group. This team had already produced high-quality work in reproducing the human temporal bone and middle ear by synchrotron imaging, and they sought collaborations in order to further interpret the complex inner ear data. It is an exciting development that corrosion anatomy, which took months and even years to execute, can now be done in a few days with the help of these data using 3D reconstructions.

The cochlea and the facial nerve

In Paper I, the close interface between the first segment of the facial nerve canal and upper basal turn of the cochlea is illustrated in man. Micro-CT with 3D rendering offered new possibilities to study this topographic anatomy of the human temporal bone.

A reduced cochlea-facial distance may lead to spread of electric currents from the implant array to the LP of the facial nerve and cause facial nerve stimulation. Influencing factors may be the topographic anatomy and otic capsule properties. In our clinic, just a couple of months after publishing this first paper, two cases with exactly this clinical condition occured. Both patients were operated on with lateral wall electrodes and could initially not reach any open speech discrimination due to an irritating facial stimulation when activating the implant. Smullen et al. 2005 noted 6.5 % FNS in 600 patients where the most common causes were malformations and otosclerosis. The incidence was much lower when using perimodiolar electrodes. This is reasonable since perimodiolar electrodes follow along the medial wall of the cochlea at a slightly longer distance from the facial nerve canal. The second of our patients was recently operated on again, and we altered to a perimodiolar electrode. He is now a full-time user and has a speech understanding rate for monosyllables with 38 % at a 65 dB level (six months after activation). Occasionally he experiences eye twitching, which he is seldom aware of in his daily life.

In both cases, intraoperative e-ABR measurements at low stimulation levels showed a late prominent response due to myogenic activity from the facial nerve. It is debatable whether this will influence our decision to replace an already implanted lateral wall electrode with a perimodiolar one or not the next time this occurs.

The internal acoustic canal

Documentation of the nerve components in the internal acoustic canal is essential before cochlear implantation surgery. Interpretations may be challenged by wide anatomical variations of the VIIIth nerve and their ramifications. Malformations may further distort proper nerve identification. The goal of this study was to describe anatomical variations of the inner acoustic canal and their clinical implications. We used micro-CT and analyzed the fundus bone channels in our archival collection of human temporal bones. Three-dimensional reconstructions were made to visualize the anatomy of the nerve channels of the fundus, including variations and their true destinations using the serial cropping technique. An incomplete separation after the division of the superior vestibular nerve canal into the ampulla nerve canals and utricle nerve canals with a fenestrated bony crest could be observed. Sometimes there were two saccular nerve canals (SNC1 and SNC2) running to the saccule. This could readily be verified using cropping and surface enhancement algorithms. This type of variation may challenge proper identification of the cochlear nerve at MRI before CI, since one of the nerves may be mistakenly interpreted as a cochlear nerve. We found a remarkable variation of the position and size of the singular nerve channel that acts as an important landmark for the prevention of fenestration of the labyrinth in middle fossa surgery, retro-sigmoid vestibular schwannoma surgery, and cochleo-vestibular neurectomy (Gacek 1984, Kos et al. 2006).

A foramen of the transverse crest was identified in 77 % of our temporal bones. The channel ran to the cribriform region of the utricle. In a follow-up study using synchrotron imaging this canal was found to contain a vessel, presumably an artery (Mei et al, 2008).

Micro-CT imaging also reproduced anastomoses between the vestibular and facial nerve. These connections may have clinical importance, for example in Bell's palsy, Ramsey-Hunt syndrome and after treatment of hemi-facial spasms, conditions where patients have a higher incidence of vestibular symptoms (Fisch and Esslen 1972, Wakasugi 1972). We could also see anastomoses between the vestibular and cochlear nerve, such as Oort's anastomosis and Hardy's nerve. These fibers belong to the olivo-cochlear bundle and convey efferent fibers from the brain to the cochlear, as well as some afferent fibers (Rasmussen 1946).

The round window region

There is still much discussion in the literature on how to perform the best CO and preserve hearing. A literature survey on HP surgery shows that there is no general agreement on the optimal trajectory pathway into the cochlea. Both RW, CO and enlarged RW approaches are used. In addition, the COs are placed differently on the promontory with the most accepted placement defined as either ACO, ICO or in between AICO (Atturo et al. 2014). A clear definition of each of these approaches has not been realized, and in a survey investigation by Adunka and Buchman 2007, North American surgeons placed different COs in different places. Their review documented the clear variations for scala tympani at CI. The study seemed to show that there is no clear definition for the surgical anatomy of this region and highlights the need for further investigations of optimal trajectory pathways.

One reason for the different approaches is the highly variable anatomy of the hook region. This part is defined by the curved basal part of the cochlear tube. Near the RW, it dilates and curves laterally at the promontory and turns postero-medial. Another distinct feature is the variable morphology of the RW niche and the bony overhang. It is, therefore, not possible to define the margin of the RW unless the overhang is surgically removed. When performing COs, there is no direct visualization of the spiral lamina, and the surgeon's view does not have a clear indication if the route also passes across the lamina from the scala vestibuli. It was, therefore, pertinent to perform a thorough analysis of the hook anatomy to see the influence of different trajectories for CI on cochlear soft tissue anatomy. Synchrotron imaging and cropping techniques with 3D visualization helped this study to describe the relationship between various COs and cochlear soft tissues, such as OSL, BM, and SL. The results showed that soft tissue in the basal part of the cochlea is seldom preserved after COs. Depending on the size and shape of the cochlea, the soft tissues can, however, sometimes be preserved after ICO. The RW approach seems to be the least traumatic and is recommended in HP surgery.

Clinical perspectives on hearing preservation

Documentation of long-term hearing outcomes in cochlear implantation is important. Especially nowadays when companies develop new electrodes that are even more flexible, thinner and are promoted as structure preservative. It is not possible to perform randomized, controlled double-blinded studies in this kind of population. Causon et al. 2015 made a retrospective analysis of the contribution of factors in HP outcomes in CI. Only 12 of 284 papers were approved for evaluation including our original study. Seven factors had a significant effect on HP, namely insertion site, progressive versus stable hearing loss, insertion angle, use of steroids, hearing etiology and electrode array type.

The HEARRING group (Rajan et al. 2018) concludes that, irrespective of the degree of residual hearing present, the concepts of hearing and structure preservation should be applied in every child undergoing cochlear implantation and that HP cochlear implantation is a secure and trustworthy therapy option. Today, even children with residual hearing in the low frequencies are operated on. Wilson et al. 2016 pointed out that children perform better with CIs than with hearing aids, even if their hearing is not fully preserved. They have also found that children need early access to high frequency sound in order to reach their full potential. For the counselling of this pediatric group, it is therefore even more important to follow patients after HP CI surgery over a longer time period.

The results of my study demonstrated that HP is possible when using flexible lateral wall electrode with RW insertion even over a long-term perspective. These outcomes were consistent with results in the literature that demonstrated the preservation of functional hearing after implantation (Moteki et al. 2017, Roland et al. 2018).

A total of 12 out of 15 patients had the same stimulation strategies at long-term follow-up compared to the initial ones at activation. Three patients changed their stimulation strategy from a+e stimulation to e-only over the whole frequency range. Interestingly, two of these patient had quite acceptable low-frequency hearing left even in the long-term follow-up. Long-term follow-up is necessary, particularly for patients using EAS, as changes in hearing may necessitate changes to amplification settings, cross-over frequencies, and their general EAS setup in the future.

In summary, the basic anatomical works performed in the present investigation were highly helpful in the clinical assessment of patients suitable for HP-surgery. In particular, the synchrotron reproduction of soft tissue offered new insights into the intricate anatomy inside the RW membrane. To visualize the micro-structures behind this “curtain” may give surgeons a different view of its great delicacy and the challenges in performing non-traumatizing CI surgery.

Conclusions

Micro-CT with 3D rendering offers new possibilities in studying the topographic anatomy of the human temporal bone. The varied shape of the cross-section of the LP of the facial nerve could often be explained by an "intruding" cochlea. In 1.4 % of our specimens we found a fusion of the LP of the facial nerve and the cochlea, which is a rare condition, called cochlear-facial dehiscence.

Predicting facial nerve stimulation by assessing the distance between the LP of the facial nerve and the cochlea is difficult when using conventional CT-scans. A large evoked late myogenic potential at low stimulation levels during intraoperative e-ABR measurements may foresee FNS at CI activation.

We used micro-CT with 3D rendering to display the anatomy of the fundus of the human inner acoustic canal. We could gain additional information regarding the anatomy of the nerve channels and their destinations from this method. A foramen of the transverse crest was also identified. These results may assist in the interpretation of preoperative imaging of the VIIIth nerve.

SR-PCI reproduced the soft tissues of the human inner ear, including the RW membrane, OSL and SL. The microanatomy of this region should be accounted for when considering cochlear implant surgery. Results suggested that CO approaches often traumatize the soft tissues at the hook region. For optimal structure preservation, the RW approach is recommended.

For our 21 first consecutive patients at our clinic who underwent HP CI surgery, the data of 15 patients was available for a long-term follow-up. Long-term HP was possible in most of these cases. There was a high correlation between insertion depth and HP outcome. Even patients with complete hearing loss experienced good performance in both speech discrimination results and user time.

Future perspectives

In most patients receiving CIs it is possible to preserve residual hearing. A major question, however, is how to preserve these results over a longer period of time. Consequently, further investigations are necessary to better comprehend the essential factors involved in hearing deterioration such as genetic background, surgery techniques, and possible inflammatory intra-cochlear responses. Another possibility is to find more direct medical treatments, such as drug delivery to the inner ear using corticosteroid-diluted and surface-coated electrodes also carrying stem cells or neurotrophins (Li et al. 2017). Other current research focuses on designing an array that brings the electrodes closer to the neurons or other principle stimulation modes such as optical stimulation. Light can be more conveniently defined compared to wide current spread from conventional electrode contacts (Richardson et al. 2017). Eventually, future technologies could be integrated in order to allow individual tailoring of the array design.

Sammanfattning på svenska

Målet med detta avhandlingsarbete var att studera människans komplexa inneröreanatomi med avseende på cochleaimplantat (CI). Detta har ytterligare aktualiserats av s.k. hörselbevarande CI-kirurgi. Patienter med grav hörselnedsättning men bevarad hörsel i de lägre frekvensområdena är idag en viktig målgrupp för CI-behandling. Uppsala har tidigare bidragit till kunskapsutvecklingen inom detta område. I denna avhandling studerades bland annat det unika material av tidigare utförda exakta temporalsbensavgjutningar samt mikrodissektioner.

Med hjälp av Mikro-CT undersöktes varje preparat i detalj. De tomografiska snitten bearbetades digitalt i ett datorprogram varefter benen kunde framställas tre-dimensionellt för analys av anatomiska relationer.

Dessutom användes en ny teknik, s.k. synkrotron avbildning, utförd i London, Canada. Därigenom kunde vi jämföra olika tekniker på vårt material i Uppsala. Synkrotron strålning med faskontrast bildåtergivning (synchrotron radiation with phase contrast imaging, SR-PCI) kan användas för att visualisera intra-cochleära mikrostrukturer och har dessutom hög mjukdelskontrast.

Ansiktsnervens topografiska anatomi studerades med fokus på dess första del (den s.k. intralabyrintära portionen) och förhållandet till hörselsnäckan. CI-elektroder belägna i detta område kan ge upphov till oönskad elektrisk stimulering av ansiktsnerven vid inkopplingen av den yttre processorn. Anatomin studerades i detalj för att öka förståelsen för hur denna komplikation kan uppstå. En avsaknad av den beniga skiljeväggen mellan ansiktsnervens intralabyrintära portion och hörselsnäckan fann vi i 1,4 % av temporalbenen. Detta är ett sällsynt sjukdomstillstånd med namnet ”cochlear-facial dehicence” (CFD). Två patienter med kraftig stimulering av ansiktsnerven efter operation med CI upptäcktes på vår klinik och CFD diagnostiserades. Ett förhöjt sent svar vid de intraoperativa e-ABR mätningarna kan vara en metod att förutse oönskad stimulering av ansiktsnerven.

Dessutom studerades den topografiska anatomin av inre hörselgången med micro-CT och 3D rekonstruktioner. Den 7:e och 8:e kranialnervernas benkanaler analyserades och variationer beskrvs. Studien syftade till att förbättra tolkningen av den preoperativa MR undersökningen vid CI utredning.

I arbetet studerades även hörselsnäckans anatomi i syfte att bevara kvarstående hörsel vid CI-kirurgi. De komplexa anatomiska relationerna i basen av snäckan där elektroden införs kunde analyseras tre-dimensionellt i detalj för första gången med hjälp av synkrotronundersökningar. Vår rekommendation är att elektroden inläggs via runda fönstret för att inte skada känsliga strukturer i hörselsnäckan.

En långtidsuppföljning utfördes av de första opererade patienterna med hörselbevarande CI kirurgi. Patienterna följdes över 5 år och vi fann att 12 av 15 patienter hade bevarad hörsel i det opererade örat. Det förelåg en hög korrelation mellan hur djupt elektroden förts in i hörselsnäckan och kvarvarande hörsel. Även patienter som förlorade resthörsel var heltidsanvändare med goda resultat i taluppfattningstesterna.

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