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Imaging of temporal bones.

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Abstract: (200 words)

Multidetector computed tomography (MDCT) has been the benchmark for visualizing bony changes of the ear but has recently been challenged by cone-beam computed tomography (CBCT). In both methods with 2D or 3D imaging all inner ear bony structures can be visualized satisfactorily. Both of these imaging methods produce ionizing radiation and induce adverse health effects, especially among children. In 3T magnetic resonance imaging (MRI) the soft tissue can be highly accurately imaged. Use of gadolinium chelate (GdC) as a contrast agent allows the partition of fluid spaces to be visualized, such as the bulging of basilar and Reissner's membranes.. Both intravenous and intratympanic administration of GdC has been used. The development of the positive endolymph imaging method, which visualizes endolymph as a bright signal and the use of image subtraction seems to allow more easily interpretable images. This long-awaited possibility of diagnosing endolymphatic hydrops in living human subjects has enabled the definition of Hydropic Ear Disease, encompassing typical Meniere's disease as well as its monosymptomatic variants and secondary conditions of endolymphatic hydrops. The next challenge in imaging of the temporal bone is to perform imaging at the cellular and molecular level. This chapter provides an overview of current temporal bone imaging methods and a review of emerging concepts in temporal bone imaging technology.

Introduction.

Rapid development of radiological equipment over the last several decades has significantly promoted the role of imaging in otology. Computed tomography (CT) and magnetic resonance imaging (MRI) have become an integral part of the evaluation of children and adults with hearing loss and diseases associated with temporal bone. The currently used Multi Detector CT (MDCT) techniques allow bony tissue determination with an accuracy of 0.1 mm. Recently cone-beam computed tomography (CBCT) technology has become particularly attractive for temporal bone imaging as CBCT imaging reduces the exposure to ionizing radiation when compared with traditional MDCT. However, changes in inner ear fluid spaces became possible only with 3T or higher MRI equipment in combination with contrast agents and special imaging techniques.

Abnormalities on CT or MRI are found in 20% to 50% of children with sensorineural hearing loss and correlate with the degree of hearing loss(1). Imaging of the temporal bone by using both MRI and MDCT is likely the future gold standard for temporal bone imaging (2). Some recent and novel imaging methods used experimentally in temporal bones have not yet been applied clinically such as optical coherence tomography imaging (3) (4) (5), microtomography (μCT) (6) and endoscopes using coherent anti-Stokes Raman spectroscopy (CARS) technique (7) these (7), development of advanced of contrasting agents (8) and these may provide additional imaging benefits in the future. This chapter provides an overview of current temporal bone imaging methods and a review of emerging concepts in temporal bone imaging technology.

CT

CT is the most common modality for assessing the bony anatomy of the temporal bone. CT can detect signs of perilymphatic fistulae (i.e. pneumolabyrinth) but fails to detect subtle traumatic lesions within the inner ear, such as labyrinthine haemorrhage or axonal damage along central auditory pathways (9). Many anatomic structures of the middle and inner ears are not optimally depicted using conventional CT with image reconstruction in the standard axial and coronal planes. In early development of CT, cochlear partitioning and soft tissue membranes were not adequately visualized (10) (11). Recent advances in MDCT, including the development of scanners with 32 detector rows (64 effective sections) for depiction of normal anatomy and pathologic states in the temporal bone, allow the acquisition of isotropic voxels that can be reconstructed and used in the multiplanar reconstructions of volumetric CT images (12). This technique gives radiologists the opportunity to visualize the anatomic structures of the middle and inner ears accurately (table 1) (13). Recent reconstruction methods in MDCT may also allow

Legend for table 1: Synopsis of the anatomically important structures and the respective primary criteria for image quality assessment. Rated as: -= not visible, += poorly, ++= moderately and +++= good visible. (6) (54)

Structure/Condition	**Review Criteria**	**MDCT**	**CBCT**	**MRI**
Cochlea	Normal contour, 2.5 turns	+++	+++	+++
Intracochlear calcification	Ability to discern intracochlear ossifications	++	+++	+\-
Osseous spiral lamina	Presence, integrity	-	-	-
Modiolus	Presence, integrity	++	++	+
Vestibule	Contour, density	+++	+++	+
Semicircular canals	Contour, density, Hypo-/Aplasia, dehiscence	+++	+++	++
Vestibular aqueduct	Contour, density	+++	+++	+
Cochlear aqueduct	Contour, density	++	+++	+++
Cochlear nerve	Presence	+	+	+++
Bony lamella at auditory canal fundus	Presence, integrity of bony lamella separating the internal auditory canal from the cochlea	+	+	+++?
Internal auditory canal	Contour	+++	+++	+++?
Facial nerve canal, cochlear segment	Contour, course	++	+++	-
Facial nerve canal, tympanic segment	Contour, course	+++	+++	-
Facial nerve canal, mastoid segment	Contour, course	+++	+++	-
Middle ear cavity	Aeration	+++	+++	+++
Malleus	Presence of all parts	++	+++	-
Incus	Presence of all parts	++	+++	-
Stapes	Presence of all parts	++	+++	-
Round window	Presence, aperture	++	+++	-
Round window niche	Borders, aeration	++	+++	-
Oval window	Presence, borders, footplate position	++	+++	-
Internal carotid artery canal	Borders, osseous wall dehiscence	+++	+++	-
Jugular foramen / jugular bulb	Borders, osseous wall dehiscence	+++	+++	-
Mastoid	Bony borders, aeration	+++	+++	-
Perilymphatic space	Gadolinium contrasted,	-	-	+++
Endolymphatic space	Not contrasted	-	-	+++
Stria vascualris	If leaking and contrasted	-	-	+++
Cochleo-vestibular nerve	Tissue growth > 1 mm	-	-	+++
Canal for subarcuate artery	Course and contour visualized by CT and MRI	+++	?	+++
Singular canal	Course and contour visualized by CT and MRI	+++	?	+++

visualization of the cochlear partitioning (9). A recent paper by Maillot et al. (12) indicated that MDCT allows radiologists to examine the complex anatomy of the temporal bone with sub-millimeter resolution and is the first

modality of choice. Indeed, it is capable of revealing a broad spectrum of ossicular lesions that may not be apparent on the basis of clinical findings alone.

For MDCT the slice thickness is a critical point and detailed anatomical evaluation as small as 0.2 mm slice intervals have been used (12). The MDCT technique may help to overcome the limitations long imposed by restrictions in gantry angle and patient positioning and improves diagnostic accuracy. The main advantages of MDCT for temporal bone imaging are shorter acquisition times, a decrease in tube current load and better spatial resolution. The short acquisition time is an advantage especially when dealing with younger patients, or those with claustrophobia or severe pain that often need sedatives for appropriate image acquisition. The ability of MDCT to obtain images of temporal bones bilaterally in one scan is another reason why MDCT is effective for imaging the temporal bone. Additional techniques such as virtual otoscopy with 3-D reconstructions of MDCT images can provide a different view on ossicular chain anomalies in traumatic conditions (14). CT has been considered the gold-standard method for postoperative imaging of the electrode position after cochlear implantation (CI),although plain X-ray films have been used (15, 16).

In detecting a thin bony coverage of a superior semicircular canal, digital volume tomography (DVT) scans seem to be superior to MDCT scans (13). Giesemann and Hofmann (9) indicated that CT is the gold standard in imaging diagnosis of semicircular canal dehiscence syndrome (SCDS).; however, it has a high false-positive rate and may be misleading in terms of diagnosis because it overestimates the size of the dehiscence and the prevalence (17). In addition, many patients with imaging findings of superior canal dehiscence do not suffer from a clinical dehiscence syndrome. In those with SCDS there is no clear linear relationship between the size of the dehiscence and the extent of clinical symptomatology, however the dehiscence length does correlate positively with the maximal air-bone gap (17). Nevertheless, a definite diagnosis of SCDS is difficult with any radiologic imaging technique (18). It has been reported that subarcuate venous malformations cause audio-vestibular symptoms similar to those of SCDS and should be excluded in temporal bone imaging (19).

The National Cancer Institute of United States estimates that approximately 5 to 9 million CT examinations are performed annually on children all over the country (20). Despite the many benefits of CT, a disadvantage is the inevitable radiation exposure. Although CT scans comprise approximately12 per cent of diagnostic radiological procedures in large U.S. hospitals, it is estimated that they account for approximately 49 per cent of the U.S. population's collective radiation dose from all medical x-ray examinations (20). An association between increased

risk of cancer and CT scans has been reported especially in children (21), (22) (23). The National Cancer Institute of United States estimates that a radiation dose of 50 mSieverts (mSv) increases of the risk of cancer by threefold, particularly in children (20, 22, 24). This dose reflects CT imaging performed in 5-10 head CT scans. The lifetime cancer mortality risk is estimated to be approximately 14% per Sv for a 1-year-old child, 5% per Sv for a middle-aged adult, and based on current models less than 2% per Sv for an individual older than 60 years (23).

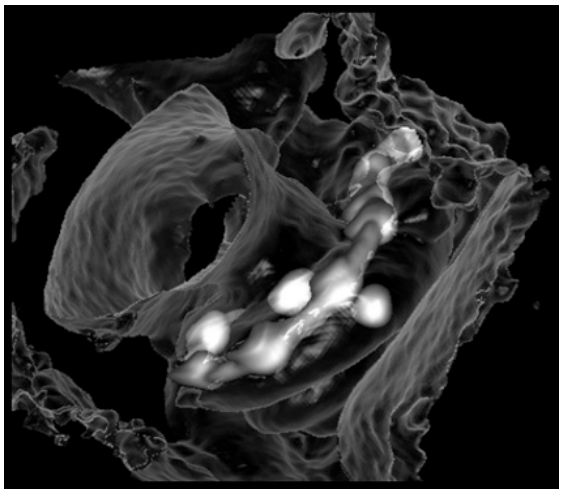
To avoid high radiation dose the novel "low dose protocols" of MDCT have been developed and a compromise between dose and resolution has been made (25) (26). The tube current-time product and voltage can be reduced by 50% without increasing artefacts. (26) Low-dose postoperative MDCT scans are sufficient for localizing the CI electrode (26) and reduce metal artefacts (25). The application of conventional CT in otolaryngology might be replaced by cone-beam computed tomography (CBCT) in the future (27, 28). For congenital malformations of the inner ear MDCT has a long history and is an outstanding tool to visualize anatomical changes. Ultra-high resolution CT (UHR-CT) with collimation of 0.25mm is coming to clinical field soon (29). Future study is warranted to compare the ability of CBCT and UHR-CT, although CBCT might have the advantage in terms of radiation dose reduction.

CBCT

In CBCT, a pulsed cone shaped X-ray beam performs a single rotation around a patient simultaneously acquiring all of the necessary volumetric data for the reconstruction of separate images in the sagittal, coronal, and axial planes. In the temporal bone any interface between two materials (as from fluid to the bone), is a step in tissue anatomy, but like a ramp in the CBCT image. The width of the ramp depends on factors such as detector pixel size, image acquisition geometry and radiation source focal spot size. This process differs from traditional MDCT that reconstructs images using a series of axial slices. CBCT creates less streak artefacts and offers higher spatial resolution than MDCT (cubic voxel size of approximately 0.07 mm versus 0.1 –0.6 mm, respectively). Erovic et al. (27) promoted the use of CBCT in intraoperative monitoring of the temporal bone. CBCT has a smaller footprint compared with MDCT, which makes it more feasible for use in outpatient departments or operating theatres. CBCT is reportedly capable of demonstrating fine structures of the middle and inner ears as well as pathological diseases within temporal bone, such as otosclerosis (30). In the assessment of SCDS, CBCT is suggested to be more reliable than MDCT (31).

CBCT appears to provide sufficient spatial accuracy for intraoperative usage during temporal bone surgery (32) (27). Identifying the location of implants is becoming increasingly important in modern otology, which involves applications such as the Vibrant Soundbridge implant and CI (6, 33) (34). With regard to monitoring the electrode array location during CI surgery, there is an emerging need to improve the imaging quality to better assess electrode trauma to the fine structures of the cochlea, such techniques include low-dose iterative reconstruction, scatter correction, lag correction, and metal artifact reduction (35) (36) (37) (38). Gupta et al. (39) refined the technology for temporal bone imaging using a smaller detector element and acquired a total of 900 cone-beam projections under a field of view of 15.5 cm; however, the image quality was not perfect. Furthermore, metal electrodes tend to cause artifacts that may blur the images (40). In assessment of the location of the cochlear implant with CBCT Pearl et al (41) could not clearly detect the basilar membrane to designate exact scalar location, which is consistent with previous reports. Zou et al (6) used the osseous spiral lamina of cochlea to assess the location of cochlear implant and to delineate between the scalae (Fig. 1). The scalar position, has also been evaluated by Ruivo et al. (42) and Verbist et al. (43), and in their study the osseous spiral lamina was visible in all sections.

Figure 1. A cochlear implant electrode located in the cochlea imaged with CBCT. Osseous spiral lamina is visible in all turns and the locations of electrodes are typically leaning on the lateral wall in the scata tympani. With permission of Acta Otolaryngol (Stokh.) (32).

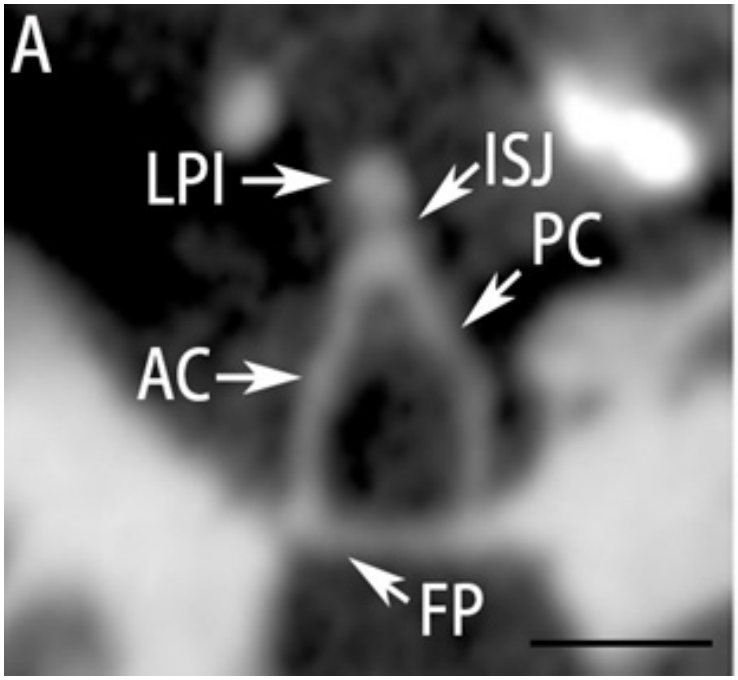


Ruivo et al (42) concluded that CBCT provides high-resolution and almost artefact-free multiplanar reconstruction images allowing assessment of the precise intracochlear position of the electrode and visualization of each of the individual contacts; the CBCT visualization consisted of 23 middle and inner ear structures using a 5-point scale.

They showed that insufficient image-quality scores were more frequent in low-dose scans versus high-dose scans, however, the difference was only statistically significant for otologists but not for neuroradiologists. Image quality was critical for small structures (such as the stapes or lamella at the internal auditory canal fundus). The CBCT images can discern individual electrode contacts, often not possible on MDCT (44) (45). In addition, Pearl et al (41) demonstrated that CBCT improved imaging of the cochlea and facial nerve canal, enabling identification of electrode contacts in close proximity to the fallopian canal and therefore most prone to induce inadvertent stimulation of the facial nerve.

Zou et al (42) (28) evaluated the effects of filters, voltage and frame numbers in visualization of the inner ear using CBCT among isolated human temporal bones; each temporal bone was independently analysed by two imaging engineers and 3 otologists; each investigator had at least 15 years of experience with temporal bone CT and were blinded to the dose-relevant scan parameters during the review of the scan. In 2D imaging in all temporal bones the land marks of modiolus, osseous spiral lamina, and bony wall of cochlear duct that isolate scala vestibuli from scala tympani were demonstrated at a level in that the anatomic structures were fully assessable in all parts and acceptable image quality (table 1). Basilar membrane was not visualized in the cochlea. Changes in the tube current from 8 mA to 12.5 mA resulted in a minimal change of the temporal bone image quality. The tube voltage of 80 kV provided best images using 900 frames. In 3D images contrasts adjustment allowed very high quality of imaging of inner ear (fig. 2). The low X-ray dose is mostly a result of the small region scanned and the low kV used in CBCT (79 kV). The reason why the artefacts in the work of Zou et al. (6) were relatively minor in comparison of a previous work is that a suitable adjustment on the "γ curve" of the original images that suppresses the metal artefacts on the images was employed, and in addition improved imaging sharpness was achieved by using a pause during each exposure (e.g., start-stop-expose-start-stop-expose) together with high frames of two dimensional images, which was not previously reported (38).

Figure 2. CBCT imaging using 900 frame numbers and 1.72 magnification factor on a temporal bone. A sharp image of the stapes was demonstrated in the temporal bone. Abbreviations: AC: anterior crus; FP: footplate; PC: posterior crus. ISJ: incudo-stapedial joint; LPI: lenticular process of incus. The black scale bar in the right lower corner = 2.5 mm. With permission of Annals of Otology, Rhinology & Laryngology (49).



With CBCT the full course of the subarcuate canal from the subarcuate fossa to the mastoid antrum can be accurately visualized, and the accompanying air cells were distinguished from the subarcuate canal in a temporal bone with a pneumatized superior semicircular canal wall (46) (47). The novel high-resolution CBCT system potentially has the power to detect changes associated with SCCD.

A comparison of low-dose MDCT and CBCT image quality after cochlear implantation revealed that the visibility of cochlear inner and outer walls and overall image quality were positively correlated with radiation dose on MDCT; image quality was better with clinical MDCT than with CBCT protocols (48). In other comparisons, differences between systems were found, but a distinction between CBCT and MDCT could not be made (48). The effective radiation dose of the CBCT protocols was 6 to 16% of the clinical MDCT dose.

Yamane et al. (49) evaluated the diagnostic properties of 3D CBCT images among 25 patients with Meniere's disease (MD) and 13 healthy patients. They developed algorithms to determine the optimal 3D-CBCT window settings for the detection of water, muscle, calcium carbonate, and bone (48). It was suggested that 3D CBCT imaging changes in the membranous labyrinth may be useful for the objective diagnosis of MD, that dislodged saccular otoconia may have an important role in MD, and that CBCT may be useful even in inner ear membrane imaging (48).

In CBCT the total radiation dose of the work in Zou et al (46) was 13 μSv in male phantom head... The most

dominant contributor to the effective dose was bone marrow (36%-37%) followed by brain (34%-36%), remainder tissues (12%), extra-thoracic airways (7%), and oral mucosa (5%) (46). It is important to note that in this study the dose was measured with an anthropomorphic model with controlled error marginal. These results were in accordance with results of a previous study that demonstrated effective doses between 35.2 – 137.6 µSv (50). In some reports there is estimation of even lower dose of radiation in CBCT imaging (30) but the estimated values may significantly deviate from the measured values (51). In a comparable study Erovic et al. (27) reported that the radiation dose of CBCT per scan is ~10 mGy (~0.35 mSv) to a dosimetry head phantom at 100 kVp and 170 mA, and was low compared with a typical 2 to 5 mSv diagnostic head CT and as high as 4.8 mSv have been reported (42) (52).

MRI

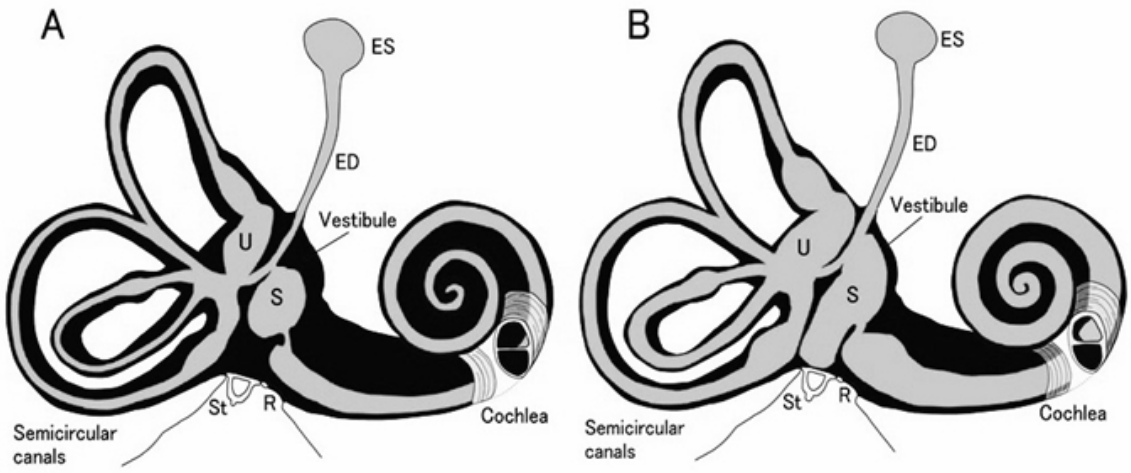
High resolution MRI imaging has an advantage over all types of CT imaging of the temporal bone as it provides better characterization of soft tissue and fluid-filled partitions. Despite several advantages, the major limitations of this method are the lack of bony details. Even with the recently developed ultra-short echo time pulse sequence, middle ear ossicles are only partly visualized (53{Naganawa, 2016 #1182). This is due to the lack of water containing material in the dense cortical bones. Another major disadvantage of using this method in temporal bone imaging is the high cost of the examination and the sedation needed for younger patients or patients in severe pain. In addition, this method cannot be used for implant imaging or intra-operative imaging where metal objects are involved in the operations as the superconducting magnets will attract the metals and electronic devices. For patients who are allergic to certain contrast agents, another type of contrast agent that may be more costly is required.

MRI is the modality of choice when investigating the inner ear and suspecting soft tissue growth such as vestibular schwannoma, vascular malformations, endolymphatic hydrops or pathology of the cochlear aqueduct (54). Naganawa et al. (55) (56) (57) developed specific algorithms using Fluid Attenuation Inversion Recovery sequences (FLAIR) that will demonstrate minute amounts of contrast agent in the inner ear (56) (58). The use of MRI in temporal bone imaging is dependent on the area to be visualized, the patient's age, the pathology involved and its severity level. MRI is the gold standard in radiologic evaluation of soft tissue changes in the temporal bone and may serve as a complementary method when CT is used to characterize the bony structures.

MRI diagnosis of MD has been challenging until recent years (59) The first efforts to demonstrate visualization of fluid spaces in the inner ear with GdC were carried out in animal studies by using animal MRI equipment of 4.7 T scanner (60). After demonstrating the contrasting of perilymph, Zou et all (61) (62) were the first to demonstrate that in the guinea pig endolymphatic hydrops could be visualized accurately and that the changes respected the histological verification of the degree of endolymphatic hydrops. These findings were followed by Niyazov et al. (63) who showed similar results using a clinical 1.5 T machine. In humans using 1.5T MRI, the passage of GdC delivered transtympanically, was shown to accumulate in the inner ear after 12 h post injection and fully contrasted the labyrinth after 24 h post injection. However 1.5T MRI equipment was not sensitive enough to demonstrate the delicate details of the perilymph and endolymph borders (64). Figure 3 demonstrates the cochlear fluid spaces and endolymphatic hydrops (59).

The recent development of 3T MRI provides a tool for visualizing endolymphatic hydrops with GdC as the contrast agent (65) (66) (67) (fig. 3). MRI especially in Japan ,Germany and just recently in USA has become a clinically useful tool for the diagnosis of atypical cases as well as typical cases of MD. Methodological development in imaging techniques and increase of the magnetic field strength have allowed separation of bone from fluid and contrast agent, and have improved spectral resolution, signal-to-noise ratio and contrast intensity and reduced scan acquisition times (55) (56) (68). These properties are particularly helpful in the attempt to resolve details between the minute fluid filled spaces within the inner ear (approximately50 µl for endolymph and 150 µl for perilymph!).

Figure 3. Endolymph and perilymph in the inner ear. (A) normal, (B) endolymphatic hydrops. The endolymph (gray) is surrounded by the perilymph (black) except for endolymphatic duct (ED) and endolymphatic sac (ES). U: utricle, S: saccule, St: stapes, R: round window. With permission of Auris Nasus Larynx (70)



A grading scale for the degree of endolymphatic hydrops has been proposed for use in research settings that was validated using identical histologic criteria and has also been applied also to clinical evaluations (61) *(69)* (70). The normal limit of ratio of the endolymphatic area over the vestibular fluid space (sum of the endolymphatic and perilymphatic area) is 33 % and any increase in the ratio would be indicative of EH (70) (71). According to the criteria, *mild endolymphatic hydrops* in the vestibule covers the ratio of 34% to 50% and *significant endolymphatic hydrops* covers the ratio of more than 50% in the vestibule (70). The respective evaluation of the ratio of the endolymphatic area over the total fluid space in the cochlea is correlated to displacement of Reissner's membrane. Normally the Reissner's membrane remains in situ and is shown as a straight border between the endolymph containing scala media and the perilymph containing scala vestibuli. *Mild endolymphatic hydrops* displays an extrusion of the Reissner's membrane towards the scala vestibuli and results in an enlargement of the scala media with an area of less than that of the scala vestibuli. *Severe endolymphatic hydrops* causes an increase of the scala media with an area larger than that of the scala vestibule (70). A similar grading system on the ordinal level, with three degrees of severity for cochlear hydrops (mild, marked, extreme), has also been proposed (72). In cadavers without symptom history, the ratio of the endolymphatic space to the total vestibular fluid space ranged from 26.5 % to 39.4 % (70) (73)

The perilymphatic space facing the vestibule is sealed by the annular stapedial ligament and the perilymphatic space of scala tympani is sealed by the round window membrane. Animal and human experiments indicated that on

MRI the perilymphatic space in the vestibule is filled with GdC earlier and more intensively than the perilymphatic space of scala tympani (74) (75). Thus the cochlear perilymph space was often poorer filled with GdC than the vestibular part. Zou et al. performed a series of experiments by sealing either the round or oval windows and demonstrated that the permeability of the round window was poorer than that of the oval window (76) (77) (78). This explains also why treatment of severe Meniere's disease with low dose gentamicin infrequently causes deafness (less than 5% with two gentamicin injections) (79, 80) but is effective in ablation of vestibular complaints. For the visualization of inner ear membranes therefore it is important to fill the upper posterior part of the middle ear cavity with GdC so that the contrast agent has the possibility to be transported also via the oval window as the annular ligament is quite porous. Intratympanic administration of GdC provided efficient loading of the contrast agent in the inner ear perilymph and reduced the risk of systemic toxicity but raised concerns of local toxicity, as it is off label and requires puncture of the tympanic membrane. Such local toxicity was not observed during short, medium or long-term follow-up (81) (82) (83). In addition, image quality might be compromised owing to impaired GdC penetration of the round and oval window membranes (78) (84) and only the injected side of the inner ear can be evaluated (58). To evaluate both ears simultaneously, it is necessary to inject GdC into both sides (85) (68) (86). These drawbacks hinder the widespread use of this procedure (87). The development of more sensitive MRI techniques facilitates endolymphatic hydrops imaging using a single dose of intravenous GdC (56, 88) ; this method has become intensively used as clinical research method (89) (90) (91). To establish the normal range of endolymph ratio, healthy volunteers were scanned after intratympanic (70) (73) and intravenous (92) GdC applications. Figure 4 demonstrates visualization of endolymphatic hydrops with different MRI protocols.

Figure 4. Fig. 1 a 72-year-old man with the clinical suspection of left Meniere's disease. Images are obtained 4 hours after IV-SD-GBCM. Conceptual diagram for the image generation of HYDROPS-Mi2 and HYDROPS2-Mi2. Upper row images indicate the generation of HYDROPS-Mi2. HYDROPS image, which is the subtraction of positive endolymphatic image (not shown) from positive perilymphatic image (heavily T2-weighted 3D-FLAIR, not shown) is multiplied by T2-weighed MR cisternography. Note that black areas (arrows) represent endolymphatic space in labyrinth and white areas represent perilymphatic space on HYDROPS-Mi2. Contrast between endo- and perilymphatic space is very strong, while the back ground signal is quite uniform on HYDROPS-Mi2. Lower row images indicate the generation of HYDROPS2-Mi2. HYDROPS2 image, which is the subtraction T2-weighed MR cisternography from positive perilymphatic image (heavily T2-weighted 3D-FLAIR, not shown) is multiplied by T2-weighed MR cisternography. Note that black areas (arrows) represent endolymphatic space in labyrinth and white areas represent perilymphatic space on HYDROPS2-Mi2 similar to HYDROPS-Mi2. Contrast between endo- and perilymphatic space is very strong, while the back ground signal is quite uniform on HYDROPS2-Mi2 similar to HYDROPS-Mi2. With permission of Jpn J Radiol (58).

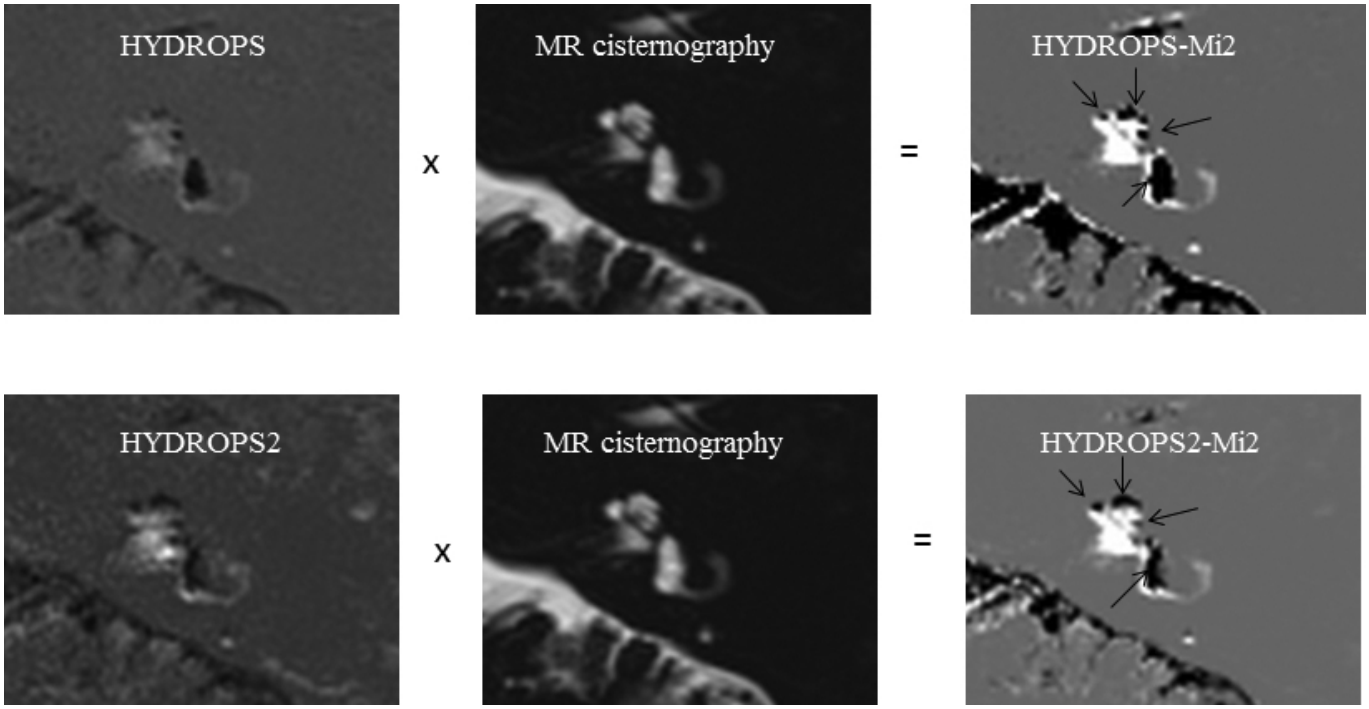
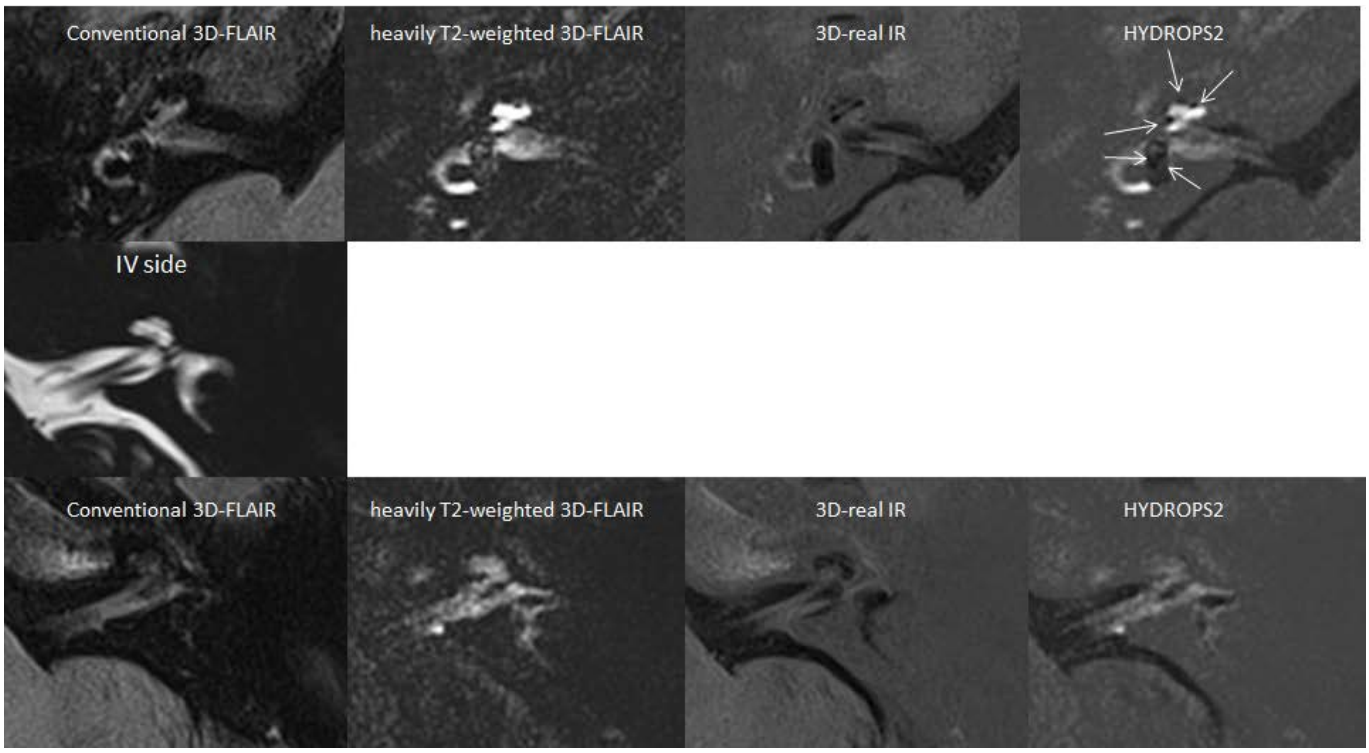


Fig. 5 A 42-years-old man with the clinical diagnosis of right sided definite Meniere's disease. Images are obtained 24 hours after IT-GdC in the right ear and 4 hours after IV-SD-GBCM. The right ear shows IT+IV-GdC effect and the left ear shows only IV-GdC effect. Note that conventional 3D-FLAIR and 3D-real IR shows the sufficient enhancement of perilymph to recognize endolymphatic space only in the IT+IV side, however heavily T2-weighted 3D-FLAIR and HYDROPS2 allows the differentiation between peri- and endolymphatic space on both IV side and IT+IV side. Significant endolymphatic hydrops (arrows) is seen in cochlea and vestibule in the right side and no endolymphatic hydrpos is seen in the left cochlea. Absence of endolymphatic hydrops in the left vestibule is confirmed in lower level slices (not shown). With permission of Jpn J Radiol. (58)

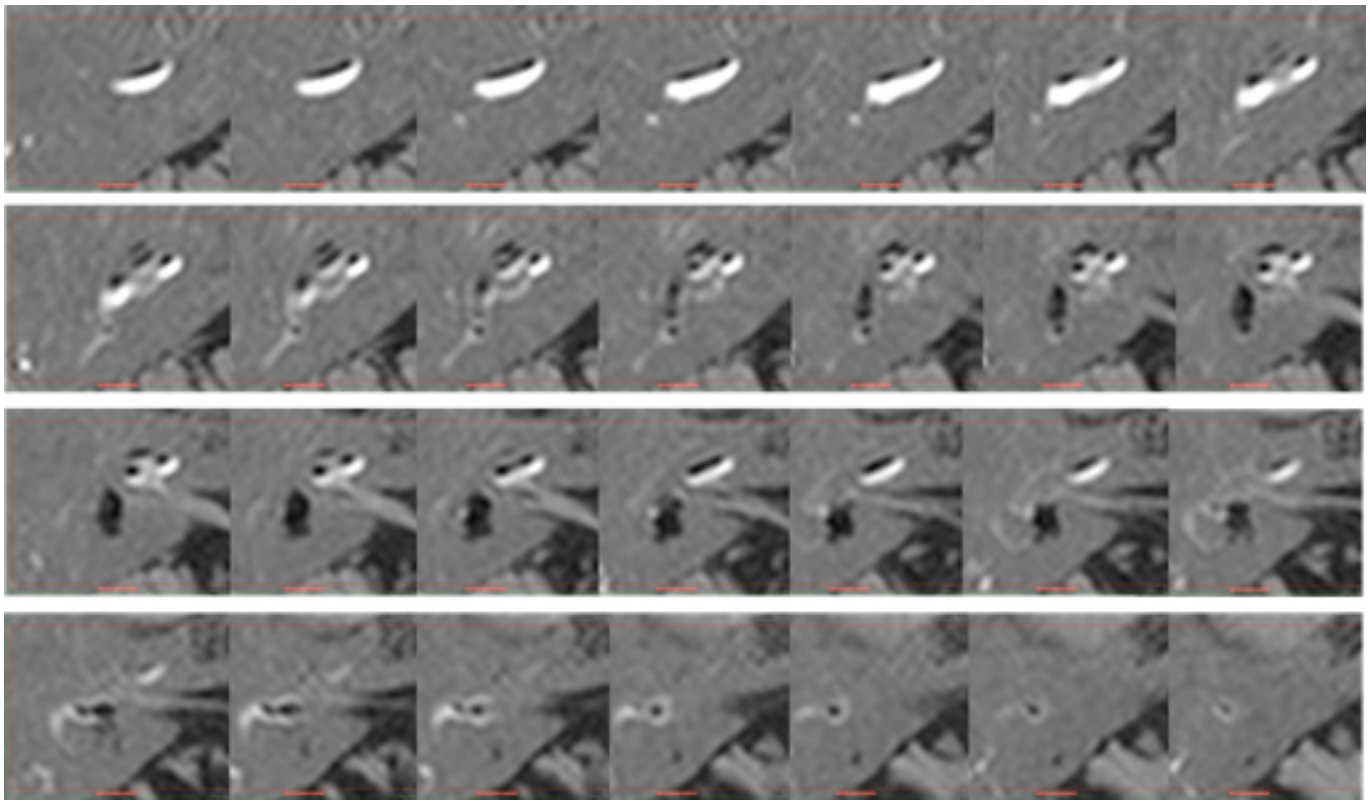


The measurement of endolymph volume ratio following 3D-real inversion recovery images obtained 24 hours after intratympanic GdC using machine learning and automated local thresholding segmentation algorithms has been reported with highly reproducible results and a highly significant correlation between hearing loss and cochlear endolymphatic hydrops (93). Semi-automated volume ratio measurement of endolymph from images obtained 4 hours after single dose intravenous GdC using short (8 minutes) and long (18 minutes) acquisition times (57) has been recommended. The correlation of the volume ratio between the long and short acquisition time images was high ranging from 0.77 (endolymphatic hydrops in the cochlea) to 0.99 (endolymphatic hydrops in the vestibule); the Pearsson's correlation coefficients were all statistical significant ($p<0.001$). Later they demonstrated that 3-Inversion-recovery turbo spin echo with real reconstruction (3D-real IR) showed higher contrast between the non-enhanced endolymph and the surrounding bone (94) (fig. 6). Regular contrast 3D-FLAIR cannot readily visualize cochlear hydrops after single dose IV-Gd, especially in apical turn. Recently Naganawa et al. developed the positive endolymph image method, which visualizes endolymph as bright signal as well as subtraction images (HYDROPS images, HYbriD of Reversed image Of Positive endolymph signal and native image of positive perilymph Signal images) and allowed more easily interpretable images (85) (95). In our experience, using heavily T2-weighted 3D-FLAIR positive perilymph image (PPI) and positive endolymph image (PEI) and subtracted images (HYDROPS technique) is useful to compensate for the lower concentration of Gd by IV. A further developed technique for generating improved HYDROPS (i-HYDROPS) images allows for a higher contrast to noise ratio per unit time compared to conventional HYDROPS imaging; this is accomplished by elongating the repetition time and increasing the refocusing flip angle(96). In the study the size of the endolymphatic space was comparable in both the i-HYDROPS and 3D-real IR images.. The 3D-real IR does not require postprocessing for subtraction and might be more robust toward slight compositional alterations in endolymph than i-HYDROPS imaging-based on magnitude reconstruction and the scan time for 3D-real IR images was 10 min.

Figure 4 (after IV. injection of GdC) and fig. 5 (after intratympanic injection of GdC) demonstrates the inner ear fluid compartments, anatomical structures and endolymphatic hydrops. Nakashima et al. (59), Pyykkö et al. (71) and Fiorino et al. (97) have demonstrated, with MRI, that endolymphatic hydrops was present in all living patients with definite MD, which is different from the reports by Shi et al. in which endolymphatic hydrops was absent in some definite MD (98). Recently it has been demonstrated that endolymphatic hydrops can affect the cochlear and

vestibular compartments differently and cause different complaints (71). However, the association between clinical symptoms and endolymphatic hydrops in individual patients is not yet clarified, as hearing can be relatively well preserved despite prominent endolymphatic hydrops (67) (99) and the extent of endolymphatic hydrops seems to vary along the course of the disease: it may increase, decrease or remain stable (100, 101) (102). With new imaging techniques, endolymphatic hydrops can be demonstrated in vivo and can confirm the diagnosis. Furthermore, it has become possible to evaluate MD using new functional tests, such as VEMP frequency tuning measurements, in patient populations with clinically and morphologically (by MRI detection of endolymphatic hydrops) confirmed diagnosis of MD (101) (103).

Figure 6.. 3D Real reconstruction inversion recovery MRI of the right ear illustrates high signal-to-noise ratio and severe cochleovestibular endolmyphatic hydrops in a patient with Meniere's disease 24 hours after intratympanic GdC application (Magnevist 1:8 diluted). Section thickness 0.3 mm. Siemens Verio scanner, 32-channel head coil. Endolymph appears black, perilymph appears white, temporal bone appears grey. The sections are positioned from left to right and from top to bottom so that they move through the inner ear in a caudal-to-cranial direction. The cochlea displays endolymphatic hydrops in all three turns. The vestibulum displays severe endolymphatic hydrops, with only a weak perilymph signal at its outer borders. The horizontal semicircular canal is completely visualized by its perilymph signal. (With kind permission of Prof. B. Ertl-Wagner, Institute of Clinical Radiology, University of Munich)



The current challenges in inner ear imaging are to improve the delivery of the contrast agent so that the concentration of GdC in the inner ear will exceed the detection limit. The transtympanic and intravenous administrations have different indications (66). If the aim is to demonstrate an endolymphatic hydrops, then transtympanic injection of GdC is preferred. Usually the transtympanic administration provides stronger uptake and is easier to assess than intravenous injection. In principle, the sensitivity of the intravenous and the transtympanic method to demonstrate endolymphatic hydrops in the inner ear should be similar based on sufficient uptake of GdC in the inner ear, as both methods measure the same phenomenon (87). A technique in which the images of inverted grey-scale positive endolymph are subtracted from images with native positive perilymph images is useful when inner ear loading of GdC is low. This subtraction significantly improves the contrast noise ratio and assists in separation of endolymph, perilymph and bone (104) or when combining intravenous injection with transtympanic injection (68).

The development of dynamic imaging techniques of the inner ear has provided several important new insights into MD; 1) the cochlear and vestibular compartments can be differently affected, and 2) in about 24 -75% of the cases the disease is bilateral (71) (105). 3) The extent of endymphatic hydrops can vary during time in individual patients (102). 4) the extent of the endolymphatic hydrops does not correlate with complaints (86). The variable latency between complaints in MD (71) and bilateral nature of the disease confirms (106) (107) the observations in MRI (71) Unilateral disease was reported to progress to bilateral disease in up to 35% of patients within 10 years and in up to 47% within 20 years of follow up (108, 109). The vestibule showed endolymphatic hydrops more frequently than did the cochlea although most commonly the endolymphatic hydrops was found in both cochlea and vestibule (71). Patients with sudden deafness and in spontaneous tinnitus often had endolymphatic hydrops (71). Whether endolymphatic hydrops will develop in all forms of tinnitus is not known but is worth studying. The application of endolymphatic hydrops imaging in patients with various inner ear symptoms and disorders has shown that endolymphatic hydrops is not only present in cases of typical MD, but also in its monosymptomatic variants and in the conditions of secondary endolymphatic hydrops. These observations have coined the term “Hydropic Ear Disease”, allowing for a logic and comprehensive classification of these disorders (110).

Furthermore, clinical imaging of endolymphatic hydrops has shown that 1) endolymphatic hydrops progresses with time, both on the cross-sectional level (72) and on the individual level (101), 2) the severity of cochlear and vestibular function deficits are generally correlated with the severity of endolymphatic hydrops (72), 3) the hydropic herniation of vestibular endolymphatic spaces into the semicircular canal can be visualized in-vivo (111) and - with the advent of accurate measurements of the vestibule-ocular reflex (VOR) at high frequencies (Video Head Impulse Test) offers a possible explanation for the well-known paradox of horizontal semicircular canal dysfunction in MD: while the (low-frequency) caloric response is impaired, the (high frequency) head impulse test is typically normal (112)(113) (114).

Legend for table 2. Inner ear pathology with MRI with different application routes of contrast agent used for visualizing different nature of the disorder.

Disease	**Membranous labyrinth injury**	**Delivery route of Gd**
Ménière's disease	Reissner's membrane bulging, rarely a rupture	Transtympanic delivery /Intravenous delivery
Inner ear immune disorder	Stria vascularis pathology/ Endolymphatic hydrops	Intravenous delivery or Intratympanic delivery
Circulatory disturbances	Stria vascularis pathology	Intravenous delivery
Spontaneous membrane rupture	Reissner's membrane	Intravenous delivery or Intratympanic delivery
Perilymphatic fistula	Round window membrane rupture or semicircular canal injury	Intravenous delivery or Intaratympanic delivery
Trauma (mechanical and noise)	Stria vascularis pathology	Intravenous delivery

In clinical practice, the question is often pending, which GdC delivery pathway should be taken; the intratympanic or the intravenous delivery? Table 2 demonstrates the alternative strategies to visualize inner ear disorders in different disease and suspected pathologies. The benefit of intratympanic delivery is that most often the GdC concentration is greater in transtympanic delivery than in intravenous delivery and the pathology is easier to assess

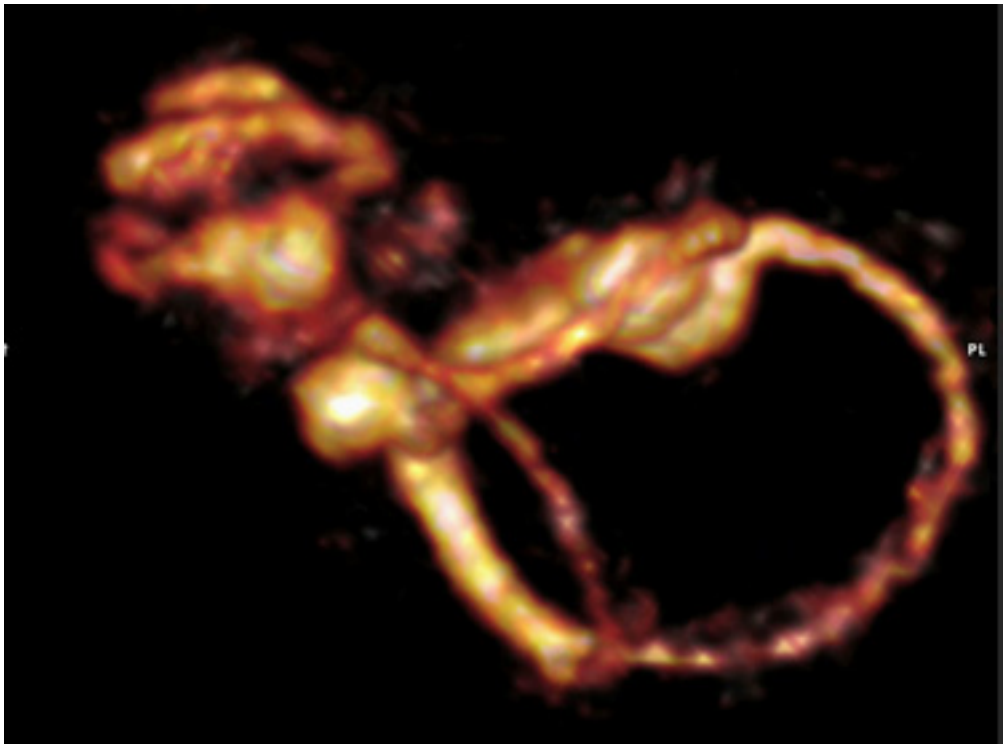
(Figure 5). However, even with this delivery route in our hands, occasionally the inner ear shows insufficient concentration of GdC in the perilymph and assessment of the disorder may be difficult.

Future development

1. ***Novel contrast agents:***

Novel highly sensitive, specific, and low-toxicity contrast agents for MRI and MDCT are in urgent need in the clinic. For MRI manganese-containing contrast agents would be most suitable as these can demonstrate the calcium metabolism that is inherent in disease processes in the inner ear (115) (116) (117) (118). Nanoparticle based GdC carrier can be are an effective MRI T1 contrast agent and have been used in high resolution MRI for tracing apoptosis and gene transcription in animal models of cerebral ischemia and brain tumours(119)(120). A novel type of super-paramagnetic iron oxide nanoparticles (SPIONs) that is water soluble, a characteristic that can be invaluable for medical applications has been designed (Fig. 7) (121, 122). It is constructed from iron oxide nanoparticle cores with a hierarchical coating consisting of a surface layer of Pluornic® F127 copolymer (PF127, approved by the Food and Drug Administration) that overlays a layer of oleic acid on the surface of the iron oxide nanoparticles (POA@SPIONs). POA@SPIONs is a promising T2 negative contrast agent that is detectable within the inner ear by MR imaging (123). Functionalization of POA@SPIONs can be performed and will make it targetable to inflammatory cytokines in the inner ear; however, the POA@SPIONs did not enter the inner ear efficiently after the transtympanic injection (106). Another novel highly hydrophilic anti-aggregative super-paramagnetic maghemite (γ-Fe_2O_3) nanoparticles (NPs) was developed using ceric ammonium nitrate (CAN)-mediated oxidation of starting magnetite (Fe_3O_4) NPs (CAN-γ-Fe_2O_3 NPs), which were highly stable aqueous suspensions/ferrofluids due to a unique ultrasound-mediated doping process of the Fe_3O_4 NP surface using lanthanide $Ce^{3/4+}$ cations (124). Zou et al. have also demonstrated that the novel CAN-γ-Fe_2O_3 NPs is a strong T_2 MRI contrast agent and penetrates both round and oval windows, which has potential applications in molecular imaging of the inner ear (125).

Figure 7. Super-paramagnetic iron oxide nanoparticles (*SPION) contrasted inner ear in rat. The SPION administered into the perilymph will extinguish the signal from the perilymph and only endolymphatic spaces are visible on MRI. Reprinted with permission of Europ J nanomed (122). Cochlea, vestibule and the semicircular canals are shown.*



By developing a novel nanomaterial to be used as contrasting agent for example encapsulation of metals and metal clusters in fullerenes (endohedral metallofullerenes) opens additional vistas for inner ear imaging (126) (127) (128). The carbon cage has inherent advantages because of its high stability and characteristic resistance to any potential metabolic cage-opening process. This prevents the release of toxic metal ions from endohedral metallofullerenes into surrounding tissue, serum, and other biologic components (126). Water-soluble endohedral gadolinium-lutetium fullerene is generating considerable interest because of the possibility of using these novel nanomaterials as both MRI and MDCT imaging contrast agents. It is possible in the future medicine that specific molecular MRI and MDCT imaging can be performed after single injection of the targetable dual contrast agent.

2. Targeted contrast agents:

Contrast agents to enhance or darken fluid or tissue signals help to visualize regions of interest and efforts are now being made to create biological tags using these agents for molecular imaging at the level of cellular processes. Aimed to visualize liposome nanoparticles in the inner ear, GdC-encapsulated liposomes were developed and distribution of the nanoparticles in the cochlea was detected *in vivo* using MRI after either intracochlear injection or intratympanic injection (129-131). These studies open a window in specific visualization

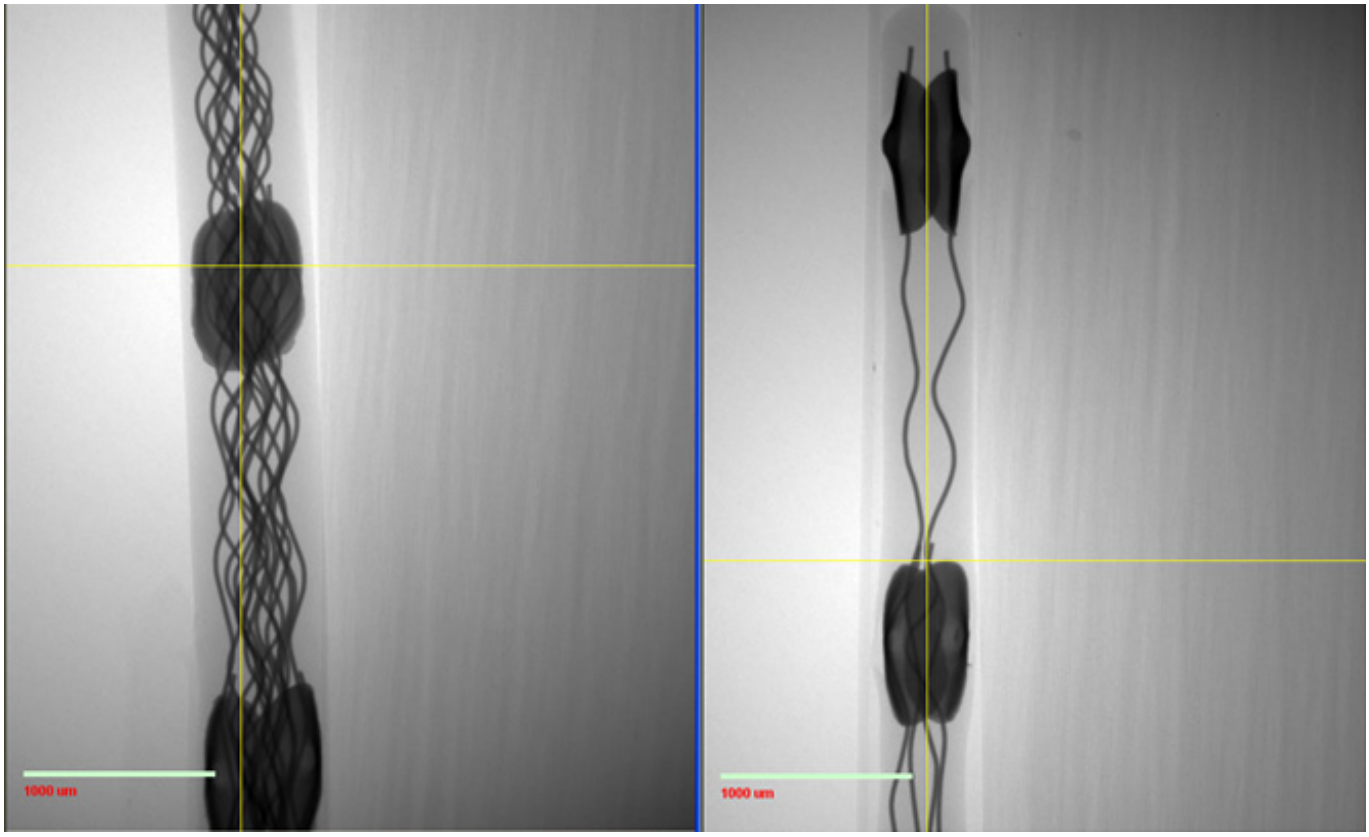
of inner ear pathology using MRI. GdC-encapsulated liposomes pass through both the oval and round windows and was not toxic in in-vivo experiments. Potential molecular imaging in the inner ear using the novel CAN-γ-Fe_2O_3 NPs was also demonstrated in an animal study (132)The novel NPs are especially useful for molecular imaging of the inner ear to detect molecular changes in pathological conditions.

3. *Microtomgraphy (μCT)*

In CT the cochlear partition and soft tissue as membranes are not adequately visualized (10) (11). The gray levels in a CT slice image correspond to X-ray attenuation, which reflects the proportion of X-rays scattered or absorbed as they pass through each voxel, and is affected by the density and composition of the material being imaged. Non-destructive X-ray microtomography (μCT) has proven its utility in 3D assessment of mineralized and soft tissue morphology (133) (134). The cochlear partition and the basilar membrane could not be distinguished and reconstructed with μCT (134) Recently Poznyakovskiy et al. presented an algorithm for cochlear segmentation, which resulted in the reconstruction of scala tympani (135). μCT has been engaged in middle and inner ear imaging of animals and implicated to be a useful tool to trace distribution of drugs in the inner ear. However, it can only be used for *ex-vivo* imaging due to the extremely high dose of exposure and the close imaging distance which is only suitable for the head (136). The contrast enhanced μCT methodology is further developed for *ex-vivo* cochlear imaging (28). It can demonstrate the position of Reissner's membrane and basilar membrane if a contrast agent is used (136). Figure 8 demonstrates CI imaged with μCT. However, μCT produces extremely high radiation dose and in present form cannot be applied in humans.

Recently this technique has been advanced in animal experiments by revealing the inner ear compartment with simultaneous 9T MRI scanner and μCT (2). The combined MRI-μCT imaging techniques were complementary, and provided high-resolution dynamic and static visualization of the morphological features of the normal mouse inner ear structures.

Figure 8. Imaging of CI electrode with μCT, Left figure shows the base electrodes stimulating areas close to the round window, The right figure shows the first and second tip electerodes aimed to stinmulate apex of the cochlea. The bars indicate distance of 100 μm,



4. High-resolution coherent anti-Stokes Raman spectroscopy (CARS)

Raman spectroscopy is a powerful tool to generate a characteristic signature of specific tissues and operates by detecting energy with the molecular bond vibration of incident photons. The process results in non-elastically scattered light, also known as Raman scattering(137) Raman spectroscopy is capable of discerning molecular pathology of differential proliferative middle ear lesions and may provide an aid in assessment of the borders of the pathological process in order to improve surgical outcome of the middle ear diseases (138)(139)(140)(141)(7). CARS occurs when a target molecule is irradiated using two laser beams simultaneously at different frequencies, a pump beam and a Stokes beam. When the difference between the higher frequency (pump beam) and the lower frequency (Stokes beam) equals the vibrational frequency of the target bond of the molecule, a CARS signal is generated (139) (140) (141). Zou et al (7) has recently demonstrated the feasibility of using CARS microscopy to display the specific molecular morphology of cholesteatoma that has the potential to be integrated in a novel endoscope for cholesteatoma imaging in the clinic. There are reports on developing CARS endoscopes, although the system needs further improvement (142, 143).

Conclusions.

Temporal bone imaging should be sensitive enough to reveal functional disorders after trauma, inflammatory diseases, space occupying lesions such as cholesteatoma or vestibular schwannoma, changes in bone density such as otoscleosis, disruption of ossicular chain, various congenital anomalies, vascular malformations and position and insertion depth of cochlear implants. MDCT and CBCT have the benefit that they accurately describe the bony structures of the temporal bone. During CBCT imaging, the dose is applied to a very narrow section of the body with minimum exposure of the non-targeting area to radiation, and the total X-ray dose is lower compared with MDCT. In addition, CBCT's rapid data acquisition means that only a low dose of radiation is created during the imaging. MRI, especially at a field strength of 3T, is excellent in revealing changes of the soft tissues and fluid spaces in the temporal bone. The 3T MRI allows relatively accurate visualization of endolymphatic hydrops and even the membranous structures of the inner ear. Modern trends with targeted imaging of the inner ear may provide possibilities to visualize inner ear pathologies that can be assessed today only on histology. The recent imaging possibilities to explore inner ear fluid spaces are especially encouraging and contribute to clinical practice by defining Hydropic Ear Disease as a new entity.

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