CT imaging of the cartilaginous Eustachian tube

Benedicte Falkenberg-Jensen

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Faculty of Medicine, University of Oslo

Division of Radiology and Nuclear Medicine

Oslo University Hospital, Rikshospitalet

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To Emil and Marius

“Neither blame or praise yourself”

Plutarch
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2 Abstract of the thesis

Middle ear disease is common. Chronic otitis media has a prevalence of 4.1% in the adult population (1) which gives an estimated 180,000 Norwegian adult patients with chronic middle ear disease. In many, the problem is bilateral. Although silent and invisible to the observer, middle ear disease induces hearing loss, pressure sensations, pain, sound phenomena such as popping, crackling or ringing, and recurrent infections. Over time, scarring, atelectasis and cholesteatoma and may develop, sometimes leading to extensive surgery.

As the Eustachian tube (ET) is the only macroscopic channel of ventilation of the middle ear, dysfunction of the ET is a major contributor to middle ear disease. Tympanic tubes were up until recent years the best treatment option and have provided a relief of symptoms without addressing the cause. Over the past few years, balloon Eustachian tuboplasty (BET) has emerged as a treatment option, addressing dysfunction in the cartilaginous portion of the ET. Indications for BET can be otitis media with effusion, recurrent pressure equalizing problems after pressure changes or chronic symptoms believed to be caused by ET dysfunction, such as muffled hearing, popping sounds and pressure sensations.

The ET serves not only as a pressure equaliser, but is lined with ciliated epithelium, transporting mucus and contaminations such as microorganisms and pollution out from the middle ear to the epipharynx.

In this thesis, we tested the feasibility and safety of letting diluted contrast medium (iodixanol) pass through the ET from the tympanic cavity to the epipharynx and visualising it with CT imaging, both in an animal model and in humans. In addition, we determined the level of contrast medium passage in the human study. We also described a new method to measure the length of the cartilaginous ET, and tested the accuracy of the measurements. Finally, we tested whether the length of the cartilaginous ET predicts disease development and treatment outcome after BET.

Our results demonstrate that the use of the contrast medium iodixanol in the middle ear and ET is safe, and that it fills the ET after approximately 10 minutes in an animal model. Furthermore, the technique can be used in humans, but larger studies are needed to determine
if it has diagnostic value. The measurement study showed excellent inter and intra observer correlation and good correlation to endoscopic measurements. The length of the cartilaginous ET does not seem to have prognostic value. However, females have shorter cartilaginous ETs than men do.
3 Acknowledgements

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perspective. I love you for always offering to do the job for me, when the going gets tough, no matter how unqualified you might be.

To my parents, siblings and extended family. I love you.
4 Abbreviations

AE Adverse events
BET balloon Eustachian tuboplasty
CBCT cone beam computed tomography
CT computed tomography
DFOV display field of view
ENT ear nose and throat
ET Eustachian tube
kV kilo Volt
mAs milliampere second
MDCT multi detector computed tomography
OME otitis media with effusion
SAE Serious adverse events
5 List of papers

This thesis is based on the following publications, which will be referred to by their roman numerical.

I.

CT imaging of the Eustachian tube using focal contrast medium administration: a feasibility study

Falkenberg-Jensen, Benedicte; Silvola, Juha; Laurvik, Helene; Lervik, Andreas; Kristiansen, Joanna Fenn; Jablonski, Greg; Hopp, Einar


II.

CT imaging of the Eustachian Tube using focal contrast medium administration: a feasibility study in humans

Falkenberg-Jensen B, Jablonski G, Silvola J, Kristiansen JF, Hopp E.

Submitted: JT. Am J Otolaryngol. 2018 August 13th

III.

The cartilaginous Eustachian tube: Reliable CT measurement and impact of the length.

Falkenberg-Jensen B, Hopp E, Jablonski GE, Pripp AH, Silvola JT.

6 Introduction

This project and PhD thesis is a result of my desire to know a lot in a narrow field. The goal was not to achieve a PhD (actually, it was a criterion on my part that it would not lead to one). Nevertheless, as science got under my skin and the enthusiasm from my otology colleagues rubbed off on me, I was caught. They had so many ideas and a drive to improve patient care, and I was believed to have the means to contribute. One would think that such a small structure as the ET would be well documented and categorized by now, but there is still a lot we do not know and many science projects will follow mine.

The ET is also called the auditory tube and the pharyngotympanic tube.

6.1 History

6.1.1 Early descriptions and publications

The first known mention of the ET was by Alcaeon of Sparta approximately 500 BC who identified a tube between the ear and the throat through dissection of goats, and thought the tube enabled the animal to breathe through its ears as well as its nose. This was later contradicted by Aristotle who acknowledged the ET’s role in transportation of air and in hearing. The anatomy of the ET was more precisely described by Bartomoleus Eustachius who held the chair of anatomy in Rome, and who described the pharyngotympanic tube in his Epistola de auditus organis 1562. Here he described the structure quite detailed, including the levator veli palatini and tensor veli palatini muscles. He wrote (translated by Graves and Galante in 1944):

From the cavity of the petrous bone, there in which the auditory passage called concha such a passage toward the nasal cavity is perforated … Others would perhaps think that this passage about which this dissertation is being written, ends in that place; this is not so, however, for it is augmented by a substance of different nature and is carried on between two muscles of the pharynx … and it ends in either cavity of
the nose near the internal part of the root of the apophysis of the bone that is shaped like the wings of the bat, and is inserted in a thick revestment of the palate near the root of the uvula. Its substance, where it touches the extremity of the fissure which is common to the temporal and wedge-shaped bones, is cartilaginous, and quite thick; but the substance of the opposite part is not exactly cartilaginous, but is somewhat membranous and becomes thinner gradually; but the internal end of the passage facing the middle of the nasal cavity has a strong cartilage which is very thick and is covered by the mucous membranes of the nares, and is seen at the end of the same meatus as if it were a guardian. It is not round, but is some way depressed and makes two angles. It is as large as a writing cane, but is twice as large at the end as at the beginning, which is eaully invested by a mucous membrane, which is, however, thinner.

It was his colleague Antoni Valsalva, who named the tube after Eustachus 150 years later, and who described the Valsalva manoeuvre in Tractus Aure Humana 1704, which is now used worldwide.

6.1.2 History of Eustachian tube catheterisation.

Stevenson and Guthrie summarize early descriptions of catheterisations (4). The first record of instrumentation of the ET is from 1724 by the French postmaster in Versailles Edmé Gilles Guyot (5, 6) who reported improvement of hearing after inserting a curved metal instrument through his mouth and behind the palate. During the same time, British army surgeon A. Cleland described and published a catheter, which could be passed through the nose. About a century later, Joseph Toynbee did many studies on the ET, including a catheter of hard rubber, which could be inserted into the ET through the nose. In the following period many surgeons (Wathen, Douglas, Saissy, Itard) describe pouring lukewarm water through an instrument into the ET to evaluate the sensation the patient had (or did not have) in the middle ear. Cleland did not mention Guyot in his publication. A decade later, the Frenchman A. Petit and Englishman J. Wathen mentioned neither Guyot, Cleland nor each other, when they both claimed to be first with an instrument to treat blocked ETs. It may very well be that they were unaware of the earlier and concurrent works.
A different approach was applied by N. Deleau (1799-1862) who constructed a tube attached to an inflator (air douche), forcing air into the ET and middle ear (7). After Deleau, catheterisation of the ET has been performed on a small scale up until recent years, with the introduction of the balloon dilation tuboplasty (BET). Nevertheless, it is fair to say that the idea of forcing the ET open has been there since the French postmaster.

6.1.3 Historical development of x-ray methods and of views on radiation.

Methods:

There has been a vast development since Willhelm Conrad Roentgen discovered the x-ray wave in 1895. Only six months after his discovery, surgeons were using his technique in the battlefield to search for bullets in wounded soldiers. In the following decades, much work was put in by engineers to improve the stability of the vacuum tubes in which the rays were generated. These often broke when high voltages were used. As higher tube currents were achieved, fluoroscopy developed and with it the first dynamic examinations of the gastrointestinal tract after orally administered barium were performed in the 1920s. Fluoroscopy is still widely used today, both in diagnostics but also to monitor medical equipment and to locate pathology in angiolabs and operating theatres. Tomography was introduced in the 1940s, where the x-ray tube was rotated to allow tomograms / slices to be imaged without the blurrings of the underlying and overlying tissue. CBCT and CT are further developments of this technique (for discrepancies between CBCT and MDCT see section 6.6). The first CT scanner was developed by Houndsfield and Cormack in 1972, and the first clinical scanners installed between 1974 and 1976. Initially they were used for head imaging exclusively, but after a few years the scan opening / gantry size was increased, and other parts of the body could be scanned. In 1976 it took 5 seconds to scan one 8 mm slice with the Searle Pho/Trax 4000 scanner. Over time, scan time has been considerably reduced. Today, the entire head can be captured in one rotation, taking less than a second. Less scan time, means less movement artefacts from patient movements, pulsations or peristalsis. Along with faster scan time, evolvement of reconstruction algorithms, increased number of detectors, reduction of slice thickness
etc. has increased image quality, contrast and spatial resolution. The latter being the ability to differentiate tissues with different densities in the same area.

One of the most recent developments in CT imaging is Dual energy CT. The technique is based on the principle that each element has its own K-edge, which is the energy required to "knock" an electron out of the K-shell and emit photoelectric energy. Using two different tube voltages, where one is specific for e.g. iodine, one can create virtual non-contrast images and subtraction reformats. Several combinations of two voltages can be chosen. The scanners either have two separate tubes with different voltages or one tube that quickly shifts between two voltages.

Radiation:

As opposed to what is known today, in the first decades of the 1900s, it was thought that x-rays, which could not be detected by any of the human sense organs, were safe or rather beneficial for the body. Because adverse effects from x-rays often appeared long after exposure, it took time before the link was made between the harmful ray and its effects. The first three to report their suspicion of such, were Thomas Edison, Nicola Tesla and William J. Morton, who all reported eye irritations after experimenting with x-rays (8). Since then, enormous amounts of data has been gathered on radiation exposure and disease development, both due to use of radiography in imaging and of radiation in cancer treatment, but also due to the large amount of people exposed to radiation in Hiroshima and Nagasaki in August 1945. We now possess tables over different tissues’ sensitivity to radiation. Medical use of x-rays today are performed after the “ALARA-principle” (as low as reasonable achievable) which basically means that one uses the lowest dose possible that gives the image quality necessary to address the clinical matter.

In temporal bone imaging, radiation doses are usually low, and most patients do not have to repeat their examinations many times. However, the dose should still be kept low, both because the eyes are often partially in the field of view, and the eye’s lens is sensitive to radiation and because every examination contributes to the patient’s accumulated dose.
6.1.4 Historical and current use iodinated of contrast media

The first use of contrast media was published in 1896, only a year after the discovery of the x-ray. Haschek and Lindentahl used lead, bismuth and barium to perform an angiogram of an amputated hand (9). These salts are toxic, and before one succeeded in developing a safe solution of them, in the early 1920s Osborne et al. discovered that the urine of patients who had received iodine treatment for syphilis was radiopaque. In other words, the discovery of iodine as a contrast medium was accidental. After this the quest for making the optimal contrast medium began, several salt combinations were made, most with one or two iodine atoms per molecule. As the radiopacity increases with the number of iodine atoms, the beginning of modern contrast media was in 1933 when the chemist Wallingford discovered the non-toxic properties of paraaminohippuric acid which could bind three iodine atoms per molecule. The following contrast media were safe, but painful due to their viscosity and ionic character. More water soluble contrast media were developed in the 1950s and 60s. The only water insoluble iodine based contrast medium today is ethiodized poppy seed oil (Lipoidol™), which is used for embolo / sclerotherapy and hysterosalpingography. The water soluble contrast media can be divided into high osmolality and low osmolality (< 3 x the osmolality of human serum). The first group is used in gastrointestinal and cystourethral imaging and coat surfaces well, while the latter is less viscous and is used intravenously, intraarterially and for imaging of almost all natural and acquired spaces of the human body. Iodixanol, which we have used in the studies in this thesis, is the only contrast medium which is isoosmolar to human serum.

All iodinated contrast media can aggravate a reduced kidney function with severity proportional to the given dose (10).

6.1.5 Historical radiologic imaging of the Eustachian tube

As early as 1927 dr. Spielberg described visualisation of the ET using an iodinated solution which he pumped into a silk catheter inserted through the nose (11). His
radiograms demonstrate the ET coated with iodine in healthy middle ears, and the lack of iodine in the middle ear in a patient with chronic otitis media. Through the 20\textsuperscript{th} century several authors published results on contrast medium aided visualisation of the ET (12-16), with the first transtympanic approach in 1947 (15). Winther et al. published the first study on CT in 2005 (16), demonstrating that contrast media distributed in the epipharynx reached the tympanic cavity while the patients yawned. Before we conducted our studies (paper I & II) there were no publications on the level of obstruction using the combination of contrast medium and CT imaging.

6.2 Eustachian tube anatomy, physiology and function

The ET is a tubular structure connecting the middle ear cavity to the pharynx. It consists of a bony and a cartilaginous portion, which are connected with a slight overlap (junctinal portion). The bony portion is funnel shaped, exiting the protympanon and narrowing towards the junctional portion. The bony portion is shorter than the cartilaginous, with an average of 6.4 ± 2.6 mm and 23.6 ± 4.3 mm respectively. The junctonal portion measures 3.0 ± 1.9 mm. Lengths are according to Sudo et al.’s computed measurements on human cadavers (17). In our studies on CT images of living patients, we find the cartilaginous portion to be longer than Sudo’s findings. The cartilaginous portion consists of a long almost triangular fibrocartilage which folds upon itself, but does not cover the whole circumference (this was described by B. Eustachi already in 1566, see 6.1.1). Thus, the anterolateral surface is fibrous without cartilage (Figure 1). Ostmann’s fat pad lies directly laterally to it, and is considered important for complete closure of the ET. The Ostmann’s fat pad is shown to decrease in size with old age (18).
At the pharyngeal end, the opening is slit like, and the cartilage end slightly lifts the mucus membrane to a small bulge, named the torus tubarius. The mucus membrane is lined with pseudostratified ciliated epithelium, and goblet cells. The cartilaginous ET is rich in seromucinous glands. The cilia beat in the direction of the pharynx, transporting mucus, contaminations and microorganisms out from the middle ear. Rather than the entire lumen being air filled at once, tubal opening is a peristaltic like motion, allowing an air bolus to pass. The major contributor is the tensor veli palatini.
muscle (also called dilator tubae) which attaches to the lateral lamina. Its contraction pulls the lamina laterally causing the tube to open (Figure 2).

![Cross section of the ET](image)

*Figure 2. Cross section of the ET. On the left (A) the ET is closed and the tensor veli palatini muscle relaxed. On the right (B) the tensor veli palatini contracts, pulling the lateral wall, and opening the ET. Diseases of the ear, nose and throat. P L Dhingra (20). Reprinted with permission.*

The levator veli palatini muscle runs parallel to the cartilaginous ET (Figure 3). As the name implies, it elevates the soft palate, and at the same rotates the ET cartilage. However, studies have shown that disabling the muscle does not lead to OME. Hence, ET function is less likely important for ET function (21, 22). The salpingopharyngeus muscle assists in opening the pharyngeal orifice. The tensor tympani muscle does not contribute (23).
The ET has three functions (24)

- pressure equalisation and ventilation of the middle ear
- mucociliary clearance of secretions from the middle ear
- protection of the middle ear from sounds, and from pathogens and secretions from the nasopharynx

6.3 Middle ear disease and Eustachian tube dysfunction

The dynamics in middle ear pressure equalization are widely studied and discussed, but still partially understood (24-26). Opening of the ET and subsequent transportation of an air bolus to or from the middle ear is, along with middle ear mucous membrane gas exchange believed to be the two main contributors to normal middle ear pressure. It is shown that larger and rapid pressure changes are few during a 24-hour monitoring (27). These pressure changes are considered related to ET opening and the infrequency of rapid pressure changes led to the assumption that mucosal gas exchange plays an important role in maintaining middle ear pressure. However, the difference in nitrogen concentration in the middle ear and in the mucosa / blood is substantial, which is indicative for the ET playing a large role, since the
transport of nitrogen is believed to be passive (diffusion) and the difference would indicate an active transport if gas transport would play the largest role (28, 29).

The causes of ET dysfunction (ETD) are complex and the mechanisms are not fully understood (30). The most common types of dysfunction function involve the ventilation and the drainage of the middle ear. These functions may be compromised by structural or functional blockage. Structural blockage includes conditions such as inflammation and consequent mucosal swelling due to infections, allergic rhinitis or rhinosinusitis, and extrinsic obstruction of the ET due to tumours, scars or a large adenoid. Failure of the muscles involved in the ET opening cause functional blockage (see section 6.2). Even septal deviation is described as a cause or contributor to ETD, since septal corrective surgery relieved ETD symptoms in scuba divers and submarine personnel (31). The pathophysiology often includes a combination of these conditions.

Depending on whether ETD results in compromised ventilation with negative pressure, drainage problems in the middle ear or both, symptoms of ETD include muffled hearing, pain, tinnitus, reduced hearing, a feeling of fullness in the ear or problems with balance. Both acute and chronic middle ear disease are common. Children have shorter and more horizontal ETs than adults, and often have difficulties performing Valsalva’s manoeuvre. This is thought to be one of the reasons why they have a higher incidence of both acute otitis media and OME (2). The most common middle ear diseases in childhood is acute otitis media, defined as middle ear effusion concurrent with signs of inflammation, such as fever, otalgia, redness and swelling. It stands for 2.5% of all outpatient visits in the USA (2). Otitis media with effusion (OME) is defined as presence of fluid in the middle ear without clinical inflammatory signs (32), although studies using polymerase chain reaction (PCR) have shown that DNA and RNA of microorganisms are often present in middle ear fluids in OME patients (33).

ETD can lead to negative pressure in the middle ear, and retraction of the tympanic membrane. A spectrum of subsequent disease may develop from tympanic membrane retractions, such as atelectasis, adhesive otitis, perforation, and in worst-case cholesteatoma. Cholesteatoma is a rare, but potentially dangerous and destructive complication to ET dysfunction. Cholesteatomas are benign accumulations of keratinized epithelium in the middle ear. There are two main types. The congenital type, where keratinized epithelial cells are trapped within the middle ear during foster development, and the acquired type. In the
acquired type, there are several theories on how these epithelial cells find their way into the middle ear, the most common of which comprise retraction of a thinned tympanic membrane, a constant vacuum in the middle ear, trauma, or surgical manipulation. Retractions are believed to be associated with ETD since their origin has been suggested to be negative middle ear pressure combined with thinning of the tympanic membrane. The retraction pocket gradually becomes deeper and narrower (Figure 4). The outer layer of keratinized epithelium loses its capacity to clean itself into the external ear canal and keratin becomes trapped. Hence, the name retraction pocket cholesteatoma. It is also postulated that habitual sniffing can cause the negative middle ear pressure and tympanic membrane retraction (34-36). Even though they are benign, cholesteatomas grow and cause severe destruction of bone and ossicles in the middle ear. It is therefore important to prevent them. Improving ET function could help prevent the retraction of the tympanic membrane.

Figure 4. Schematic illustration of the development of a retraction pocket cholesteatoma.

Case courtesy of A.Prof Frank Gaillard, Radiopaedia.org, rID: 9672
6.4 Eustachian tube dysfunction

By dysfunction, we understand a failure in one or more of the functions listed above (section 6.2). In 2014, a consensus group established a definition on ET dysfunction (24). They separated acute dysfunction (< 3 months) from chronic dysfunction (> 3 months), and segregated the chronic dysfunction into three subtypes (bullet points and Figure 5.)

1. dilatory Eustachian tube dysfunction,
2. baro-challenge-induced Eustachian tube dysfunction,
3. patulous Eustachian tube dysfunction.

The subtype addressed in our studies is chronic dilatory ET dysfunction.

![Figure 5: Eustachian tube dysfunction: consensus statement on definition, types, clinical presentation and diagnosis. Clinical Otolaryngology, Volume 40, Issue 5, October 2015 (24). Reprinted with permission.](image)

To diagnose dysfunction the patient’s symptoms are combined with clinical findings, where the position of the tympanic membrane and the results of the tympanogram are the most important. The ability to perform Valsalva’s manoeuvre can be indicative of the ET’s patency, but failure to do so is not reliable to alone diagnose dysfunction (24).
6.5 Balloon dilation and its effects

Until recent years, tympanic tubes have been the most common treatment for OME. The tubes have a certain life expectancy and usually fall out after a few months. They may dislocate on the wrong side of the tympanic membrane, and cause obstruction in the bony part of the ET. Usually they fall out into the external ear canal, without any complications, but do occasionally leave behind a scar in the tympanic membrane. As the tympanic membrane heals and closes, a new fluid collection can form, given that the ET is still dysfunctional. Repeated scarring can lead to hearing deficits.

During the recent years, the option of BET has developed from an experimental to a planned procedure. It is performed in many clinics around the globe, and although the type of catheter, balloon size and pressure used may vary, the essence of the procedure is the same: Guided by endoscopy, a balloon catheter is led into the ET through the torus tubarius (Figures 6. and 7.). The balloon is inflated to a certain pressure for a certain time, and sometimes the balloon is re-inflated and the procedure is repeated before the balloon is deflated and removed.

![Figure 5. Left: Balloon catheter inserted in the cartilaginous ET. Right: Inflated balloon. Figure reprinted with permission. Wanscher JH, Svane-Knudsen V. Promising results after balloon dilatation of the Eustachian tube for obstructive dysfunction. Danish medical journal. 2014;61(4):A4818.](image-url)
There is no international consensus on indications for BET (37). The most frequently described indications for BET in adult patients are:

- symptoms and clinical findings of OME; hearing loss, hearing sensations, tinnitus, feeling of muffled ear, inability to perform Valsalva’s manoeuvre, fluid accumulation in the middle ear, retraction of the tympanic membrane and pathological tubomanometry. Most patients have recurrence of symptoms after several attempts to relive symptoms with tympanic drainage tubes. Some institutions, including ours, have as a criterion for BET that the patient has tried tympanic drainage tubes without remission.
- ETD-related symptoms in conjunction with rapid pressure changes
• Some institutions perform BET in patients with ETD symptoms (as described above) but without clinical findings (38)

There are several publications both on the method and on results (39-49) and few reported moderate complications (39, 50). A histopathological study has shown that the treatment is not only a mechanical one, but that the cellular composition in the adjacent tissue actually changes (51).

Approximately 50% of the patients benefit from BET (49). As the procedure usually is performed in general anaesthesia, it is costly both in hospital resources and expenses. It is of interest to determine which patients will most likely benefit from the treatment, and to determine if there are common factors within the non-responder group. This was part of our study aim in Paper III.

The number of treated patients varies from centre to centre. In Norway approximately 240 BET catheters were sold in 2017 (source Kebomed, Norway and Entellus Medical, Norway), indicating a similar number of treated ETs.

6.6 Computed Tomography

In CT imaging, tissues are assigned a shade of grey based on their permeability to x-rays, measured on the Hounsfield scale. As bone and air are on opposite ends of the scale and are the two main components in the temporal bone, CT generates a good depiction of the temporal bone structures with high spatial resolution. Hence, CT is often used in temporal bone diagnostics, and the majority of scans are performed without intravenous or focal contrast media. OME is a clinical diagnosis, and there is no academic consensus on whether a preoperative CT is required before balloon dilation (52). However, a CT scan can help reveal conditions that will complicate BET such as a cholesteatoma, or be the direct source of OME such as an epipharyngeal mass. In addition, the CT images will provide information regarding the anatomical conditions, which may vary from patient to patient.

After the introduction of multi detector CT (MDCT) the quality of the images has improved,
image resolution has increased and the scan time (which equals the time the patient has to lie still) has been reduced. However, unless there is air in the cartilaginous ET lumen it will not be visible in a traditional CT scan.

Another CT technique, which can give excellent imaging of the temporal bone, is cone beam CT (CBCT). Both MDCT and CBCT use a conventional x-ray source. MDCT uses a fan shaped x-ray beam and detectors located opposite the source, which rotate together along the axis of the patient, recording a 2D slice for each rotation or a volume. The scan is recorded in a helical manner with a slight overlap and the slices stacked to record an intact volume of the scanned field. CBCT on the other hand uses a pyramidal or cone shaped x-ray source, covering the entire FOV in one-half or full rotation (Figure 8.). The word “cone” refers to the shape the source has if the collimators are cylindrical which was common in the first generations of machines. Now most machines have rectangular collimators, which generate a pyramidal source and FOV. As opposed to MDCT where all the beams are oriented perpendicular on the detector, CBCT beams are divergent in their projection angle and the image quality is optimal in the centre of the FOV. In general, the received patient radiation dose is lower with CBCT than with MDCT. This is due to lower tube output (kV and mAs) and to horizontally collimated FOV. Small detector pixels and hence, image voxels, give high spatial resolution, and makes CBCT superior in imaging structures with high anatomical contrast such as the temporal bone. When soft tissue differentiation and characterisation is needed, however, MDCT is superior due to better contrast resolution and a lower signal to noise ratio.

Both MDCT and CBCT can be subject to metal artefacts. Modern machines of both kinds have software to reduce these, and differences between scans can be assigned to scanner type and manufacturer, beam hardening, grey scale values etc. more than to the two different scanning techniques. In temporal bone imaging, metal artefacts are less frequent than in maxillofacial imaging, but occur in patients with hearing aids such as cochlear implants and BAHAs, and with ossicular prosthesis of metal. For MRI, the device may be conditional or unsafe and the importance of artefact reduction in CT high. With the advancement of the multi detector technique and an increasing number of detector rows, a large amount of image slices can be recorded in one rotation. For a temporal bone examination, this means that the whole FOV can be captured in one rotation. Scan time is as low as less than a second, making MDCT less exposed to movement artefacts.
Figure 8. Left: conventional MDCT. Right: Cone beam CT.
7  Aims of the thesis

7.1 General aims

The overall aim has been to investigate whether adjustments in the preoperative CT examination, such as focal contrast medium application, and measurements made on specific image reformats are feasible and if it can generate reliable and valuable information. Furthermore, if this information can help select patients for surgery in a patient group, which at the current date is difficult to segregate.

7.2 Specific aims

Paper I
To establish safety of inserting iodixanol into the middle ear, and the feasibility of the contrast medium filling the ET in an animal model.
To estimate the time delay between contrast medium and CT and the optimal contrast medium dilution.

Paper II
To test if the methods from paper I are feasible in humans.

Paper III
To establish a reproducible method of length measurement of the cartilaginous portion of the ET, and to examine whether the length predicts development of disease or treatment outcome.
8 Summary of papers

8.1 Paper I

8.1.1 Title and status


8.1.2 Purpose

To establish a safe and feasible model for visualizing the ET lumen on CT examinations using cadaver and animal models.

8.1.3 Material and Methods:

Detailed description of the protocol is found in paper I.

Models:

Cadaver: A frozen human cadaver model was used to determine the optimal contrast medium dilution and CT parameters. The model type was chosen in order to achieve the correct anatomical circumstances without having to consider radiation dose or length of anaesthesia. Contrast medium (Visipaque 320 mg/ml) was diluted with saline (NaCl 9 mg/ml) to solutions of 5, 10, 15, 20 and 25%. Starting with the lowest concentration, each dilution was separately inserted into the middle ear through a needle in the tympanic membrane. CT scans were performed, before the middle ear was flushed with saline, and the next dilution was installed. This was repeated until all concentrations had been scanned. The CT scans were evaluated by two radiologists, who reached a consensus on optimal degree of contrast medium dilution and CT tube current, based on differentiation of soft tissues contrast medium and bone structures.

Animal: Based on the results of the cadaver study we designed an animal study. Ten New Zealand white rabbits were bought through the Centre of comparative medicine, from Charles Rivers Laboratories Inc. The animals were given an individual letter from A to J. Two of the animals were kept as controls. Over a period of a few weeks, each of the remaining eight was
examined once or twice in general sedation (table 2). Anesthesia was administered through an intravenous catheter in each auricular vein. Premedication consisted of fentanyl and fluanisone (Hypnorm, VetaPharma, Leeds, UK), followed by a slow intravenous injection of propofol (Propofol-Lipuro, B. Braun, Melsungen, Germany), which was maintained at a constant rate using a syringe driver. Dexmedetomidine (Dexdomitor, Orion Corporation, Turku, Finland) was also given using a syringe driver. By monitoring respiratory rate and spontaneous movement in response to stimulation, combined with pulse rate and arterial oxygen saturation of hemoglobin on a pulse oximeter, adequate anesthetic depth was maintained.

An ENT surgeon examined the tympanic membrane and middle ear through a 3 mm examination tube aided by otomicroscopy. Lidocaine (Lidokain 10 mg/ml, PharmaPlus, Oslo, Norway) was dripped into the distal auricular canal, and the tympanic membrane was perforated with a 22 G needle attached to a syringe with 20% contrast dilution by a flexible connection tube with Luer Lock ends. The contrast medium was slowly injected into the middle ear until it was visually full but unexpanded. Injection volume was 0.3–0.4 ml. CT scans of the temporal bone and epipharynx were performed 3, 6, 9, and 12 minutes after the contrast medium injection, to evaluate the optimal scan point of time, where the contrast medium has reached the epipharyngeal orifice, but still lines the ET lumen (figure 8). After the last CT scan, the propofol, dexmedetomidine and oxygen delivery were discontinued, and the animal was brought back to the department of comparative medicine. All animals were reexamined in sedation after a minimum of one week, to identify any signs of inflammation, after which a non-contrast enhanced CT was done. Most animals repeated the contrast medium procedure with new CT scans in the same sedation before euthanasia (table 2).

CT examination: All examinations were performed on a Toshiba, Aquilion One CT scanner. In the cadaver study the CT was done with two different tube currents; one at 120 kV and one at 135 kV, employing a constant mA of 200, and with display field of view (DFOV) 8 cm and 16 cm. In the animal study the CT parameters were 200 mA, 120 kV and 10.3 cm DFOV, based on the cadaver study results.

All CT evaluations were carried out by the two radiologists using MPR reconstructions.

The two control animals also underwent a CT examination without contrast medium before euthanasia to exclude any middle ear pathology. Histopathology from three of the animals
examined with contrast medium was evaluated regarding inflammation and tissue changes, and the two last animals were used as controls.

8.1.4 Results paper I

The contrast medium dilution with clearest differentiation towards both bone and soft tissue in the cadaver study was the 15% solution. After evaluating the images with different tube currents and DFOV, there was consensus between the two radiologists that 120 kV and 8 cm DFOV gave the best results.

Eight animals (A-H) were in the contrast medium group, and the procedure was repeated on four of the animals (Table 1.) after one or two weeks. In total 23 ETs were examined with contrast medium. Of these, three ears (of two animals) were excluded. Of the 20 remaining ears, the contrast medium passed through the ET in 19 of the cases. In some of the cases, the contrast medium coated the ET lumen in its full length (Figure 9.). The optimal time for CT scan was found to be between 9 and 12 minutes. No remnants of contrast medium were found on the CT scans on the day of euthanasia. Clinical inspection was performed one or two weeks after the first examination. All of the animals had normal ME status upon clinical inspection one or two weeks following the first procedure.

Figure 9. Oblique coronal MIP image demonstrating the cartilaginous ET lumen filled with contrast medium bilaterally. The MIP reconstruction is meant as an illustration only, and was not used in the evaluation of passage.
Gross histopathological samples and microscopic examination (Figure 1. Section 6.2) samples were taken from both sides in three contrast medium exposed animals. The samples showed no sign of inflammatory reaction or tissue changes in the eardrum, ME or ET.

The optimal contrast medium dilution in the animal study was considered to be 20%.

Table 1. Showing animals A-J, the number of contrast-enhanced CT examinations (procedures) conducted on each animal, the number of successful contrast medium passages, and number of ears excluded.

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>I</th>
<th>J</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td># Procedures</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>23</td>
</tr>
<tr>
<td># Contrast medium passages to epipharynx</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>19</td>
</tr>
<tr>
<td># Ears examined with CT without contrast</td>
<td>2</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td># Ears excluded</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td># Ears sent to histopathology</td>
<td>2</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>2</td>
<td>10</td>
</tr>
</tbody>
</table>
Figure 10. Dr. Silvola inspecting the tympanic membrane and middle ear in one of the animals before the contrast medium injection.

8.1.5 Correction paper I

In the published article, it is stated that the animals were acclimatised at the Charles River Laboratories Inc. in France. This is incorrect. They were acclimatised in the Department of Comparative Medicine, Oslo hospital services, Norway, after arrival from France and before the study began.
8.2 **Paper II**

8.2.1 Title and status


*Submitted:* JT Am J Otolaryngol. 2018 August 13th

8.2.2 Purpose

To further develop and test the method used in paper I, in humans, by addressing level of contrast medium passage in the ET and record any complications.

8.2.3 Material and methods

Detailed description of the protocol is found in paper II.

Seventeen adult patients with otitis media with effusion (OME) and five control patients with healthy middle ears were included consecutively. For inclusion and exclusion criteria, see Table 2. All patients and controls had a drainage tube in the tympanic membrane, which for the patients was installed two weeks in advance to drain any middle ear fluid. Through this tube, diluted Visipaque (20%, 320 mg/ml) was injected into the middle ear using a 22G suction needle. After 10 minutes on the CT table in a lateral recumbency position, a CT scan was performed. Two radiologists evaluated the level of contrast medium passage in the ET.

Any signs of adverse events (AE), serious adverse events (SAE) including inflammation were recorded immediately, and again after 4-6 months.
Table 2. Inclusion and exclusion criteria as sent to and approved by the Norwegian Medicines Agency

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Group</strong></td>
<td><strong>Patient Group</strong></td>
</tr>
<tr>
<td>Patients &gt; 18 years old</td>
<td>Previous serious allergic reaction to iodine based contrast medium</td>
</tr>
<tr>
<td>Referred to ENT clinic at RH for evaluation and treatment of OME, tympanic membrane peroration or tympanic membrane retraction</td>
<td>Increased risk of bleeding</td>
</tr>
<tr>
<td>Dysfunction of the ET is suspected by the ENT surgeon</td>
<td>Serious heart disease</td>
</tr>
<tr>
<td>The patient is a candidate for balloon dilation of the ET</td>
<td>Diabetes I</td>
</tr>
<tr>
<td></td>
<td>Previous ENT-surgery (t-tubes excluded)</td>
</tr>
<tr>
<td></td>
<td>Middle ear disease, which requires other type of treatment</td>
</tr>
<tr>
<td></td>
<td>Chronic rhino sinusitis or nasal polyposis</td>
</tr>
<tr>
<td></td>
<td>Anatomical variations in the temporal bone or skull base that contraindicates balloon dilation</td>
</tr>
<tr>
<td></td>
<td>Females who are pregnant or breast feeding</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Control group:</strong></th>
<th><strong>Control group</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient &gt; 18 years old</td>
<td>Same as for the patient group</td>
</tr>
<tr>
<td>Referred to the ENT clinic for evaluation and treatment of Mb Meniere</td>
<td></td>
</tr>
<tr>
<td>CT of the temporal bone is required.</td>
<td></td>
</tr>
<tr>
<td>Patient is has or is considered to benefit from a tympanic tube</td>
<td></td>
</tr>
</tbody>
</table>

8.2.4 Results paper II

Of the seventeen patients, four had contrast medium passage to the epipharynx, eight had passage to the cartilaginous ET, two had passage to the bony ET (Figure 11.) and three did not have contrast medium in the ET at all. In the control group, three of five had contrast medium in the epipharynx and in two the contrast medium passed to the cartilaginous portion.
There were no signs of inflammation in the clinical exam following the CT or after 4-6 months.

We did not record any SAE. One patient in the control group reported a mild dizziness at the CT table, which resolved within a few minutes. This was recorded as an expected AE, and interpreted as a likely caloric response.

*Figure 11. Oblique coronal MPR after contrast medium injection in the right middle ear where the contrast medium reached the isthmus (open arrow) but did not pass into the cartilaginous ET. Contrast medium filling the bony ET marked in red in the right image (II).*
8.3 Paper III

8.3.1 Title and status


8.3.2 Purpose

To create a simple method to measure the length of the cartilaginous ET on CT images and validate the measurement.

To examine whether the length of the cartilaginous ET is influenced by gender or age, and whether it influences disease development or treatment outcomes.

8.3.3 Material and methods

Detailed description of the protocol is found in paper III.

The paper consists of three parts, each with its individual material and method:

Retrospective CT measurement

Retrospectively 29 consecutive, adult patients with CT images of the temporal bone, which included the torus tubarius, were included. Oblique coronal images, displaying both the bony ET end and the torus lip, were reconstructed from the thin axial images. We defined the length of the cartilaginous ET to extend from the medial border of the bony ET’s end to the tip of the torus tubarius (figure 12). Quote from the methods chapter in the paper: “In consensus, two radiologist and two otologists determined the cranial and caudal limits of the cartilaginous ET. The cranial limit was defined as the bony eminence at the medial side of the bony ET’s caudal end. This eminence is formed by a thickening of the bone separating the carotid canal from the bony ET. The caudal limit was defined as the tip of the soft tissue lip of the torus tubarius on one, single CT image.” Based on these two points the length of the cartilaginous ET was measured on both sides in each patient by one radiologist (Figure 12.)
On a copy of the oblique coronal stack, a second radiologist repeated the measurements, blinded from the first examiners results. Finally, the first examiner repeated the measurements on a new stack copy after two weeks. All measurements were recorded in mm with one decimal. Intraobserver and interobserver variability was calculated. To ensure the reproducibility of the reformats and results, new oblique coronal reformats were made for repeated measurement of ten of the patients, comparing the first measurements to the new.

Figure 12. Upper left: The angle and area of reformatting.
Upper right: The oblique coronal image plane from which measurements were made.
Bottom: Same image as above with magnification of the bony eminence at the caudal medial end of the bony ET (long arrow) and short arrow pointing to the tip of the torus lip. Measurement as it was made on the contralateral side.
Prospective CT and endoscopic measurement

In this prospective study, 10 patients were included consecutively. All patients had OME and were planned for BET regardless of our study. A preoperative CT of the temporal bone was performed and reformats as described in the retrospective study above were made. Both sides’ cartilaginous ET were measured, but not reported to the surgeons. At the time of balloon dilation, the catheter was inserted until resistance was felt at the assumed transition between cartilaginous and bony ET. After balloon dilation, a guide catheter was placed outside the balloon catheter to the tip of the torus tubarius. The whole catheter with emptied balloon and guide were simultaneously pulled out and the length of the disposed catheter was measured from the tip of the guide catheter to the tip of the balloon catheter.

Continuous variables are described as mean ± standard deviation. The Pearson correlation coefficient between measurements was calculated. Difference between left and right ET was tested with paired Student’s t-test. Inter- and intrarater reliability between CT measurements and internal consistency between CT and endoscopic measurements were tested with reliability tests, e.g. Bland-Altman plots and the intraclass correlation coefficient (figure 11).

Length versus treatment outcome and disease development

In this third study section we compared the measurements to disease development and treatment result by including all patients who had been treated with BET from February 2013 through June 2016 and who also had a CT examination of the temporal bone which included the torus tubarius. Previous to the BET, all patients had tympanic drainage tubes for one or more periods, without satisfactory symptom relief. In total 69 patients with 97 treated ETs were included. The control group consisted of 34 patients, without middle ear disease, with CT examinations of the temporal bone during the same period. Both the patient group and the control group were measured on both sides, giving 138 and 68 measurements respectively. We kept two columns in the data set separating the controls from the patients, and the treated ETs from the healthy, so that both categories could be compared. Treatment outcome was collected from the postoperative follow up approximately 3 months after surgery, based on three factors: positive Valsalva, position of the eardrum and presence of fluid in the middle ear. One point was given for each normal finding, creating a scale between 0 and 3 points. All
patients had a preoperative score of 0 or 1. This is not a validated method, but since there is no international consensus on testing the results of BET (37) we chose three objective parameters which are always part of the pre and postoperative clinical examinations in our clinic.

In addition we recorded age, gender, time between CT and operation, and tubes ≤25 mm. Correlation was analysed between the following:

- length and development of disease (length in control group vs. treated ETs)
- length and treatment outcome (only treated ETs)
- age and disease development
- age and treatment outcome
- gender and disease development
- gender and treatment outcome
- short tubes (≤25 mm) and treatment outcome
- time between CT and operation and treatment outcome

In the clinical measurements, both sides were measured in the same patient. These clustered data within the same patients were therefore assessed by using generalized estimating equations with an unstructured working correlation matrix.

8.3.4 Results paper III

ET length as measured by CT was 26.7 ± 2.1 mm for all summarized measurements, with a range from 21.7 to 32.6 mm, and no statistical significant difference between left and right side (p = 0.32). For measurement on similar CT sets, the Pearson correlation coefficient between measurements was 0.93 between observers and 0.92 for repeated measurements of one observer. Inter- and intrarater reliability between CT measurements was excellent with an intraclass correlation coefficient of 0.93 and 0.92. The repeated measurements on new reformats had a Pearson correlation coefficient between measurements of 0.92. Interrater reliability after renewed reconstruction was excellent with an intraclass correlation coefficient of 0.92. Based on results from analysis before and after renewed dataset reconstruction, the standard error of mean and minimal detectable change were estimated to 0.013 mm and 0.036 mm, respectively.
ET length of the smaller sample was 26.2 ± 1.6 mm as measured by endoscopy and 26.0 ± 1.6 as measured by CT. The Pearson correlation coefficient between endoscopic and CT measurements was 0.64. The internal consistency between endoscopic and CT measurement was adequate with a Cronbach’s alpha of 0.78.

A Bland Altman plot with a regression analysis revealed no bias dependent on ET length (Figure 13).

Figure 13. Bland Altman plot on difference versus mean of CT and endoscopic measurements of ET length, measurements in mm. Mean difference is 0.00 mm (read line), green lines define ± 1.96 SD. Regression analysis confirms mean difference is not dependent of mean (β = -0.31, p = 0.90).

The results for our clinical measurements are summed up in Table 3. ET length was found not to be predictive for development of disease or for treatment outcome. Females had shorter ET lengths. However, there was no correlation between gender and treatment result. Furthermore, no correlation was found between age and length. Time between CT and BET did not influence treatment outcome. Seven of the 97 sick ears had a poor treatment outcome.
with a score of 0 or 1 of the possible 3 points. One patient had a poor result bilaterally, while the other five were treated unilaterally.
<table>
<thead>
<tr>
<th>Problem</th>
<th># ears</th>
<th>Mean in mm</th>
<th>Mean difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Length vs. outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90 good</td>
<td></td>
<td>27.4</td>
<td>-.11</td>
<td>.482</td>
</tr>
<tr>
<td>7 poor</td>
<td></td>
<td>26.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Length in ears with OME vs. control gr</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>97 OME</td>
<td></td>
<td>26.8</td>
<td>-.53</td>
<td>.266</td>
</tr>
<tr>
<td>68 control</td>
<td></td>
<td>26.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Length in patient gr vs. control gr</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>138 patient*</td>
<td></td>
<td>26.8</td>
<td>-.44</td>
<td>.349</td>
</tr>
<tr>
<td>68 control</td>
<td></td>
<td>26.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Length vs. age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>206 all</td>
<td></td>
<td>26.7</td>
<td>.01</td>
<td>.270</td>
</tr>
<tr>
<td><strong>Length vs. gender</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>108 female</td>
<td></td>
<td>25.8</td>
<td>-1.88</td>
<td>.000</td>
</tr>
<tr>
<td>98 male</td>
<td></td>
<td>27.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Outcome vs. age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90 good</td>
<td></td>
<td>27.4</td>
<td>.01</td>
<td>.637</td>
</tr>
<tr>
<td>7 poor</td>
<td></td>
<td>26.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Outcome vs. gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90 good</td>
<td></td>
<td>27.4</td>
<td>-1.69</td>
<td>.128</td>
</tr>
<tr>
<td>7 poor</td>
<td></td>
<td>26.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>outcome vs. short tubes ≤25mm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90 good</td>
<td></td>
<td>27.4</td>
<td></td>
<td>.084</td>
</tr>
<tr>
<td>7 poor</td>
<td></td>
<td>26.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Outcome vs. timespan between CT and op.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90 good</td>
<td></td>
<td>27.4</td>
<td>-.01</td>
<td>.817</td>
</tr>
<tr>
<td>7 poor</td>
<td></td>
<td>26.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*the healthy ears in the patient group are included
9 Ethical considerations

The use of animals as models in clinical trials should be well founded and necessary. In the trials described in paper I, we followed the principles of replacement, reduction and refinement (the three Rs) described by Russell and Burch in 1959 (53). We aimed for our sample size to be as small as possible, but as large as necessary. Using the cadaver heads (replacement) to establish the range of CM dilution and the CT parameters meant less testing on animals, minimizing sample (reduction). Repeating the tests on both ears and again on the same animal also contributed to a smaller sample size. Discomfort was minimized by examining the animals under general anaesthesia (refinement).

The remaining questions, which we addressed with rabbits, were timing and safety of the CM. The radiation burden of repeated CT scans would ethically have been too high to test on humans, since each individual would not benefit from the results, but rather future patients would.

In line with the ALARA principle, radiation dose was also the reason we excluded patients with recent CT exam of the temporal bone. As a direct result, our sample size in paper II was smaller than it might have been, and our statistical power weaker. On a larger scale, and for future perspectives, one can discuss which the lesser evil is; repeating the CT on patients who had a recent CT scan of the temporal bone, providing more study data on the cost of a higher radiation dose for individual patients, or the other way around.

The insertion of tympanic drainage tubes in the patients who did not already have one, gives room for ethical considerations. Even if the tympanic membrane was anesthetized, the procedure may still give some discomfort. However, it is a procedure with which all patients were familiar and had previously undergone. The discomfort of the procedure is brief, while the relief of symptoms lasts as long as the tube is in place.
10 Discussion

10.1 Contrast media and ototoxicity

Even though iodixanol is approved for use in any other cavity in the human body, and many authors have described the use of iodine based CMs in the middle ear (see 6.1.4 for references), our study was still off label, and the safety important to establish. By registering the study through EudraCT and the Norwegian Medicines Agency, with registration of AEs and SAEs, any events were reported in a standardized manner and will be accessible to future study groups. The risk of allergic reactions was considered to be equal to the risk when iodixanol is injected intravenously or applied to other mucous membranes. We considered the risk of ototoxicity to be extremely low. However, substances such as contrast media and antibiotics can indeed pass through the round window membrane (54-56) (lately, passage through the oval window has also been reported (55, 57)), but they can also diffuse into the labyrinth from the blood stream (55, 58). Ototoxicity due to this transport is both a feared complication, and a desired effect. The latter for example when aminoglycosides are applied in the middle ear to treat symptoms in patients with Meniere’s disease (56).

Iodixanol (Visipaque) was chosen as contrast medium both in the animal trail and in the human study. It is a non-ionic contrast medium, which is also isoosmolar with blood, with an osmolality of 0.29 osmol/l. This is also the osmolality in perilymph in guinea pig (59) and expected osmolality in human perilymph. Our intension by choosing iodixanol, was to reduce the risk of diffusion across the round window as well as across the mucous membranes, as the osmolality would be equal on both sides. Even though the concentration of iodixanol used was 64 mg/ml, and the maximum recommended intravenous dose is 150 ml of iodixanol 320 mg/ml, which would give a concentration of 9.6 mg/ml in an average adult with a 5000 ml blood volume. As stated in the introduction of this thesis (6.1.4), many scientific publications before us have used iodine-based contrast media to image the ET and documented its presence in the middle ear. Most of them were undiluted. Although no study specifically aimed to test safety, none have reported unexpected adverse events. One can also argue that since contrast media can reflux to the middle ear when swallowing (16), any orally administered contrast medium (which are often iodine based or barium based) could end up undiluted in the middle ear. One could expect that case reports would have been published, had the frequently used non-ionic contrast media such as iodixanol been ototoxic through an undamaged round window. Iodixanol is also approved for intrathecal use, and hence
neurotoxicity is tested for that indication (60-62). Maximum recommended dose of iodixanol intratechally is 10 ml, which in an average CSF volume of 125-150 ml would give a concentration of 21.3-25.6 mg/ml. It is also published that concentration of a substance is not in its self the most crucial factor in ototoxicity (63).

Iodixanol was originally produced by Nycomed and is now produced by GE pharmaceuticals. Through their documentation of premarketing trials, side effects and adverse events, I have not come across any documentation or reports on hearing loss, transitory deafness or deafness. There have however been reports on transitory blindness, seizures and loss of consciousness (64).

The ototoxic / neurotoxic effect of iodine is only documented for iodine dissolved in chemical solutions such as chlorhexidine or alcohol (65) and showed no such effects when dissolved in distilled water (66). Hence, it is probably not the iodine itself, but rather the complexes it is dissolved in or the molecules it is bound to, which are the hazardous components. This could explain why iodine based ionic contrast media used in myelographies have led to SAE (67, 68).

MR contrast media are also used “off label” intratympanically and “on label” intravenously to image endolymphatic hydrops. Both methods are dependent on diffusion of gadolidium based contrast media to the perilymph, which will then stand in contrast to the non-attenuating endolymph. The first trials published on this method in humans reported “no side effects” (69) and “no adverse effects” (70) in their results chapters, without reporting any method of registering side effects / adverse effects or what effects would be considered as side effects / adverse effects. Gadolinium based contrast media have later proved to have an ototoxic effect on guinea pigs when diluted 1:7 (71), which does not seem to have had an effect on the use or dosage (55). However, what is true for one gadolinium product is not necessarily true for another. The weight of clinical experience and lack of actual reported adverse effects is also an argument in its self.
10.2 Discussion Paper I

Our hypothesis was that we could visualise the lumen of the cartilaginous ET using intratympanic contrast medium, and that the method was safe. We have conducted a study on both a human cadaver model and on an animal model, neither of which truly mimic humans. Both models have less soft tissue and bone, a fact that in turn influences the differentiation and image perception on CT. However, when conducting an off-label study, one has to sacrifice certain factors in order to address the main aims, which in this study were feasibility and safety. Given what is known about rabbits’ ET anatomy and tissue composition (72), we can assume that inflammatory changes would have appeared if iodixanol caused focal tissue irritation. Given that iodine based contrast media are well documented and approved for use on many other mucus membrane covered areas, the likelihood of inflammation was probably low in the middle ear and ET. Varying the CT parameters also sorts under the safety label, as it gave important information on which parameters give the best image result, preventing unnecessary radiation in human studies.

There have been certain previous studies that supported the feasibility (9-13). However, none with tympanic contrast medium administration in live subjects examined with CT. Since this was the method intended for our future studies, it was important to establish the specific method’s feasibility and parameters that would otherwise lead to excess human trails. This includes the contrast medium dilution grade and delay between contrast medium administration and CT scan.

As stated in the paper, the relatively low number of animals is a limitation. Subjective discomfort could not be recorded. Results cannot directly be transferred to human use. Finally, this study confirmed the potential use of contrast medium to explore whether the ET was patent.

10.3 Discussion Paper II

We conducted the study based on our results in Paper I. Inclusion of patients was lower than expected and this resulted in a low number of results. Consequently, we could not conclude on whether the level of obstruction could be established. However, we did not experience any complications, and believe the method to be safe.

Patients with Meniere’s disease were chosen as a control group because they already had a tympanic drainage tube, which reduced the invasiveness of our procedure. As a control group,
they would not benefit from the contrast medium visualisation in its self, and it was therefore of importance to avoid inserting tympanic drainage tubes in patients who would not benefit from one, which would also have been difficult to argue for ethically. Reduced ET function in Meniere patients has been published (73). Our control patients all had normal tympanometry, tympanic membrane position, MEs and Valsalva manoeuvres upon inclusion in the study, indicating normal ET function.

We could have included an audiometry (Paper II) at a given time after the CT examination where iodixanol was injected intratympanically, to register any sensorineural hearing loss and perhaps we should have. This would have resulted in an objective measurement of sensorineural hearing loss, which, in the patient group could indicate ototoxicity. Our control group of Meniére patients would however not be as suitable, since they have sensorineural hearing loss as part of their disease development. In addition, apart from the contrast medium and questionnaire, we intended the patient stream to be equal to the existing stream for patients referred to our hospital for BET. These patients are examined with audiometry prior to the BET, but not systematically after. Biopsy and microscopy of the organ of Corti is naturally not an option in patients. However, we have conducted an animal trial (paper I) where the cochlea was present in the histopathologic slides. In retrospect, we could have included the organ of Corti in the histopathological evaluation, even though a normal microscopy would not exclude damaged cell function, pathological findings would indicate toxic effect.

10.4 Discussion Paper III

We developed a method to measure the cartilaginous ET that was reproducible and reliable. The definition of our chosen measurement points may very well not represent only the cartilage, but likely includes some other soft tissues at the tip of the torus. However, the medial border of the isthmus and the torus tubarius are identifiable structures and therefore the method becomes reproducible. One can also argue that the tip of the torus is the entry point for balloon catheters, and hence the distance in a surgeon’s eye would start for here. As we have shown that the length of the cartilaginous ET probably does not influence development of disease or treatment outcome, it is for future studies to investigate whether other factors do. One limitation of this latter part, is the retrospective study design, and the
lack of a control group not receiving treatment. With our method of measurement, the surgeon can calculate the desired position and avoid dilating the balloon catheter in the bony ET, and reduce the risk for complications.

10.5 General discussion

In our institution, most preoperative CT imaging today is performed with MDCT, while intraoperative images (if done) often are performed on cone beam CT scanners (CBCT). This is mostly due to the actual localisation of the machines. CBCT scanners are few and located in labs intended for conventional interventions and angiographic diagnostics, or in operating theatres. Hence, planning a study and scheduling patients to a specific time for the examination is challenging, since these labs often are occupied due to acute medical procedures that can be very time consuming. Studies of the temporal bone can be performed with high resolution with both techniques, and we see no reason why our described techniques should not be transmissible to CBCT in other studies. In our particular studies though, we aimed to make the examination as similar as the one we would have performed if the patient had not been included in the study.

Imaging of the ET has been described for a century. Most studies demonstrate patency, and none of the described methods have led to established diagnostic procedures. Nevertheless, preoperative CT imaging is performed in many institutions, and in the images lies information beyond what is used today. Not all patients benefit from BET, and if information from the images could help select the patients most likely to respond to BET, it would not only be beneficial for the patients, but socioeconomically as well.
11 Conclusions and future aspects

Our studies on animals and humans demonstrate that visualization of the ET is feasible, safe and can be combined with the preoperative CT. It is beneficial with a time delay between the CM administration and the CT scan. The procedure was simple. This may form the basis of future studies. Measurements of the cartilaginous ET, made on reformatted oblique coronal CT images, are precise. The measurements can be used preoperatively to plan insertion depth and balloon calibre, but do not seem to predict disease development or treatment outcome.

Our study sample in the contrast media study is low, and it will take additional, larger studies to determine its clinical value. It could be interesting to combine other imaging techniques with a contrast medium. Cine imaging might add valuable information on ET dynamics. Dual energy CT will likely offer new possibilities, also in terms of other substances (with higher K-edge than atoms found in human tissues) which could serve as contrast agents. MRI has a superb differentiation between different soft tissues, and hence one could perhaps image the ET without contrast medium, on the other hand, this would not visualize the lumen. Gadolinium contrast media are already in use in the middle ear for other purposes, and MR imaging of a contrast filled ET would give a better definition of the cartilage against the contrast medium. Here the options of contrast media are many, since fluids containing water give high signals in T2 weighted series. For our technique, it would however be a more complicated process, as the otomicroscope and ENT instruments are not MRI compatible. One would have to prepare the patients outside the lab.

When we first started planning this project in 2013 there were few publications on treatment results. Today the use and experience of BET has increased considerably and several manuscripts on treatment results have been published. The questions we asked then are not necessarily the ones we would ask today. However, the project has its roots in the clinical experience of my ENT co-authors and in their hypothesis on how certain parameters might interact with each other. Some of our findings are negative findings. We did not find a correlation the ET’s length and treatment outcome or disease development. However, it contributes knowledge and allows us and other researches to focus on other parameters that might fully or partially explain why some patients benefit from BET and some do not.
As the procedure of BET becomes more common, I believe the quest to identify the patients who will benefit will go on, and that radiology will play a role in the identification process.
12 Reference List


64. VISIPAQUE 270 and 320 mg I/ml Solution for Injection SmPC UK [Internet]. 2018. Available from: www3.gehealthcare.co.uk/~/uk/.../uk%20spc%20visipaque.pdf.


13 PAPERS I-III
CT Imaging of the Eustachian Tube Using Focal Contrast Medium Administration: A Feasibility Study

Benedicte Falkenberg-Jensen, MD; Juha Silvola, MD, PhD; Helene Laurvik, MD; Andreas Lervik, DVM, Dipl. ECVVA; Joanna Fenn Kristiansen, MSc; Greg Jablonski, MD, PhD; Einar Hopp, MD, PhD

**Objectives:** We aim to develop an imaging technique for visualization of the Eustachian tube (ET) lumen.

**Study Design:** A prospective, experimental study in an animal model and in human cadaver specimens.

**Methods:** Applying iodixanol to the middle ear in two human temporal bone specimens, followed by computed tomography (CT) examinations, we optimized contrast dilution, CT algorithm, and head positioning for visualization of contrast passage through the ET.

Myringotomy was performed on eight rabbits. Based on the cadaver study, a 20% iodixanol solution was applied to the middle ear, and subsequent CT scans were performed to observe iodixanol in the epipharynx. For some animals, the procedure was repeated on the contralateral ear. We performed the procedure twice on four subjects. Twenty examinations were included.

Iodixanol appearance in the ET and the epipharyngeal orifice was assessed qualitatively on CT scans. The tympanic membrane was inspected after 1 or 2 weeks, and histopathological examination of six contrast-exposed temporal bones was performed.

**Results:** The cadaver study provided information on imaging technique and contrast dosage. In rabbits, iodixanol passed through the ET in 19 of the 20 ears. Qualitatively, optimal visualization was seen after 9 to 12 minutes. Clinical inspection after 1 or 2 weeks revealed normal middle ear status. Histopathological samples showed no sign of inflammatory reaction in the tympanic membrane, middle ear, or ET.

**Conclusion:** Iodixanol application to the middle ear is feasible, safe, and demonstrates patency of the ET.

**Key Words:** Eustachian tube, contrast medium, CT, balloon dilation, rabbit.

**Level of Evidence:** N/A.

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**INTRODUCTION**

Middle ear ventilation problems are connected to infectious, inflammatory, or even destructive disease of the middle ear (ME). Dysfunction of the Eustachian tube (ET) is considered to be one of the main reasons for ME ventilation problems.

The ET consists of a bony part leading from the tympanic cavity and connecting to a cartilaginous part, which is considered the functional part and leads to the epipharynx. The point of connection between the two parts, the isthmus, is anatomically the narrowest portion. However, pathological processes such as inflammation, tissue hyperplasia, and malignancies can lead to stenosis along the lumen. The ET’s explicit manner of function is still discussed, but studies have shown an opening of a more peristaltic character rather than a simultaneous opening of the entire lumen. Muscles levator veli palatini, tensor veli palatini, and the medial pterygoid are all involved in the opening process. Because the lumen is only open one portion at a time in healthy subjects, diagnostic radiologic imaging is challenging. With computed tomography (CT) imaging, soft tissue is homogeneously gray. Magnetic resonance imaging (MRI) may define muscle and cartilage of the ET. Both on CT and MR images, sporadic air can be seen along the expected course of the ET’s cartilaginous portion, but most of the lumen is closed. Thus, the lumen is not visualized and the ET’s patency cannot be evaluated. As Smith et al. conclude, there is a need for refined imaging methods.

In recent years, balloon catheter dilation of the cartilaginous part of the ET has emerged as a treatment option with beneficial effect on ET dysfunction. According to Schröder et al., balloon dilation has a positive effect on ET function in more than 70% of cases. Nevertheless, it is a challenge for the otologist to select...
patients for the treatment, not knowing whether the pathology is in the cartilaginous part of the ET. At present, predilation CT is performed to reveal any anatomical variants contraindicating dilation, or on rare occasions to reveal an epipharyngeal mass causing compression of the ET. Imaging has not yet contributed to existing knowledge regarding the functional cause of obstruction or the obstruction level. The question remains whether preoperative selection could be improved if the level and origin of pathology was known. This would require visualization of the ET lumen on radiologic images.

Our main hypothesis is that contrast medium (CM) applied to the ME will drain into the ET and be visible in a subsequent CT examination of the temporal bone and epipharynx, providing clinically important information before ET balloon dilation.

Although studies using CM to validate the function of the ET have been performed, no systematic studies have been conducted. Before performing studies on humans, we needed to assess possible negative effects of the CM to determine a CM dilution that would be distinguishable from both bone and soft tissue, and to confirm that CM does pass from the ME to the epipharynx in assumed healthy individuals.

To address all of these aspects, we conducted an animal trial with the opportunity to perform multiple CT examinations. The project had the following objectives: 1) To determine the ideal parameters regarding contrast dilution, CT algorithm, and head positioning for visualization of the ME anatomy and contrast passage through the ET; and 2) to explore the feasibility and safety of CM injection into the ME.

To achieve this, we combined two methods in our study design. The first objective was assessed through studies on human temporal bone cadaver specimens and the second objective through a study on live rabbits. Sucheston has described the ET in rabbit as similar to the human ET on both a gross and microscopic level. We believe the method to be applicable to humans with tympanostomy tubes. The animal study was approved by the national animal research authority and was conducted according to European Communities Council Directive of November 24, 1986 (86/609/EEC) and the guidelines of Animal Research: Reporting In Vivo Experiments.

MATERIALS AND METHODS

Two human temporal bone cadaver specimens that had been preserved by freezing were used. In the initial preparation, the auricules were removed; in one specimen, part of the ET’s epipharyngeal orifice was missing. Iodixanol (Visipaque, GE Healthcare, Oslo, Norway) was chosen as CM due to its isosmolar properties. Dilutions of 5%, 10%, 15%, 20%, and 25% were made in advance by using NaCl 9 mg/mL (B. Braun Melsungen AG, Melsungen, Germany) as a diluant. To avoid movement, the temporal bone specimens were fixed to a plastic tray with Play-Doh (Hasbro Inc., Pawtucket, RI) in what would have been an oblique, decubitus position. Aided by otomicroscopy, an experienced otologist performed the myringotomy. Starting with the lowest iodine concentration, contrast medium was applied to the ME, succeeded by two CT (Aquilion One, Toshiba, Minato, Japan) scans employing a constant mA of 200: one at 120 (kilovolt) kV and one at 135 kV. Following scan acquisition, the ME cavity was flushed with saline (NaCl 9 mg/mL), and the procedure repeated with each contrast dilution in turn. Images were reconstructed with both 8-cm and 16-cm display field of view (DFOV).

Two experienced radiologists subjectively evaluated image quality with respect to the optimal contrast medium dilution and the optimal spatial and contrast resolution. The contrast dilution that was most easily distinguishable from soft tissue without masking bone tissue was deemed the best choice (Figure 1).

Ten rabbits (New Zealand White, female) were purchased through the Centre for Comparative Medicine at Charles River Laboratories Inc. (Chatillon-sur-Chalaronne, France) and were kept in individual cages in a separate room in the Centre for Comparative Medicine. All animals had identification ear tattoos in one ear and in addition were given an individual letter (A–J). Each cage was marked with both identifiers. Before the experiments started, the animals were acclimatized in the Centre for Comparative Medicine (Charles River Laboratories Inc.) for 2 weeks. Every animal had a healthy appearance and a good appetite during this period.

All animals had access to food and water until premedication was given. Premedication consisted of fentanyl and Fluanisone (Hynorm, VetaPharma, Leeds, UK). The animals were instrumented with an intravenous catheter in each auricular vein. Anesthesia was induced with a slow intravenous injection of propofol (Propofol-Lipuro; B. Braun Melsungen AG) and maintained by propofol infusion at a constant rate using a syringe driver. Dexmedetomidine (Dexdomitor, Orion Corporation, Turku, Finland) was administered as a constant rate infusion using a syringe driver. All animals were monitored for signs of inadequate anesthetic depth, which included an increase in pulse rate, respiratory rate, and spontaneous movement in response to stimulation. Arterial oxygen saturation of hemoglobin and pulse rate were monitored using a pulse oximeter.

The tympanic membrane was visualized through a 3-mm examination tube. Lidocaine (Lidokain 10 mg/mL, PharmaPlus, Falkenberg-Jensen et al.: Contrast Medium CT of the ET...
Oslo, Norway) was administered locally into the distal auricular canal. Aided by otomicroscopy, an experienced otologist perforated the tympanic membrane with a 22-G needle attached to a syringe with contrast dilution by a flexible connection tube with Luer lock ends. The CM was slowly injected into the ME until achieving a visual impression of the ME being full but not expanded. The injected volume was 0.3 to 0.4 mL for all animals.

The CM was slowly injected into the ME until achieving a visual impression of the ME being full but not expanded. The injected volume was 0.3 to 0.4 mL for all animals.

With the animal in a lateral decubitus position, CT scans of the temporal bone and epipharynx were performed with 200 mA, 120 kV, and 10.5 cm DFOV at 3-minute intervals for 12 minutes. After the experimental procedure, propofol, dexmedetomidine, and oxygen delivery were discontinued. Monitoring continued until the rabbits were sitting in sternal recumbency.

The first rabbit (A) was given a 15% CM solution in its left ear based on the results of the human cadaver study. However, the contrast medium appeared less dense than desired. The concentration was therefore increased to 20% for the remaining ears. In spite of the increased CM concentration, bone was easily distinguishable.

The animals were followed for 1 or 2 weeks to explore whether the procedure induced inflammation. Before euthanasia, all animals underwent a noncontrast CT scan, and the CM application was repeated and new CT scans acquired for most of the subjects.

In total, the eight animals underwent the CM procedure 23 times, with a maximum of two procedures per ear (Table 1).

Euthanasia was performed in continuity with the final sedation by an intravenous injection of 20-mL potassium chloride (1 mmol/mL; Kaliumklorid B. Braun, B. Braun Melsungen AG) or by blood drainage through the jugular vein.

The two remaining animals (I and J) had not undergone the procedure and were euthanized on the last day of the experiments to serve as control animals in the histopathological evaluation. In total, three of the animals given CM and the two controls were dissected for histopathological purposes after euthanasia. The latter two underwent a CT examination of the temporal bones (without myringotomy and CM injection) before euthanasia to exclude any ME effusion.

After the animals were sacrificed, the left and right temporal bones and surrounding tissue were dissected out in one piece. After fixation in 10% buffered formalin, frontal slices were cut by a diamond saw and placed in separate cassettes to decalcify for 36 hours. The decalcification time was kept as short as possible to prevent damage to the morphology in the final microscopic sections. Thirty-six hours proved to be enough time to soften the tissue. The specimens were then paraffin-embedded, and microscopic sections were cut from the paraffin blocks and stained with hematoxylin and eosin.

**RESULTS**

In the cadaver experiment, 15% ioxaglate had a density lower than bone but was easily distinguishable from soft tissue (Figure 1). Twenty percent dilution also provided satisfactory visualization, whereas <15% was too weak and >20% was too dense to distinguish from soft tissue and bone, respectively.

Both radiologists subjectively evaluated image quality by comparing images acquired at 120 kV with 135 kV, and images reconstructed with 8 cm DFOV with 16 cm DFOV. The optimal combination was deemed to be 120 kV and 8 cm DFOV.

In total, eight rabbits (animals A–H) were in the CM group. The procedure was repeated on four of the animals after 1 or 2 weeks (Table 1), resulting in a total of 23 examined ears. Of these, two ears (same animal) were excluded due to aspiration of stomach contents and subsequent pharyngeal edema (following an accidental overdose of dexmedetomidine), and one ear was excluded due to contrast from the contra lateral ear contaminating the ET orifice and ventral ET lumen. Of the 20 remaining ears, the CM passed through the ET in 19 of the cases. In some of the cases, the CM coated the ET lumen in its full length and could be visualized in a single image using thick MIP (maximum intensity projection) reconstruction.

Although CM was seen in the epipharyngeal orifice on the early series (3 and 6 minutes), the course of the ET was seen more clearly on the later series (9 and 12 minutes) (Figure 2).

The CT scans on the day of euthanasia did not reveal remnants of CM in the ME, mastoid, or ET in any of the animals.

Clinical inspection was performed 1 or 2 weeks after the first examination. All of the animals had

### Table 1

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CM = contrast medium; CT = computed tomography.
normal ME status. One animal had the remains of a minor perforation in one eardrum and a small bulla in the other. In the rest of the animals, the perforations had healed (Figure 3).

Gross histopathological samples taken from both sides in three animals showed no sign of inflammatory reaction in the eardrum, ME, or ET. Microscopic examination of the stained slides revealed good representation of the inner part of the auditory canal and the tympanic cavity of all the ears. The tympanic membrane could be appreciated in most cases. Pathological changes were not found in any of the examined structures or the surrounding tissues (Figures 4 and 5).

The optimal contrast dilution in the animal experiment was considered to be 20% when qualitatively evaluated using the criteria described in Material and Methods.

DISCUSSION

In this study, we present a systematic approach to establish an imaging method for evaluation of ET patency by deposition of CM in the ME. The application of ioxaglate in the ME is off-label. The method was proven feasible in anesthetized rabbits, and clinical and histopathological examinations revealed no adverse effects of CM.

The choice of rabbits was, in addition to size and availability, based on our knowledge on ET gross and microscopic anatomy and physiology in rabbits. Suches-ton has shown that the ET in rabbits has the same gross anatomy, with the same type of cartilage, arrangement of goblet cells, and mucoserous glands as humans. Like humans, and unlike some other species, they have lymphoid tissue surrounding the ET.13

Regardless of animal species, the ability to monitor symptomatology is limited, and the low number of subjects is in itself a limitation. We have chosen to present each CM injection as individual experiments—not considering whether the same animal was operated twice—due to the observations that all animals were healthy and there were no signs of inflammation after the first procedure.

Sedation of the animals prevented us from knowing whether the swallowing reflex was intact and, furthermore, whether the appearance of ioxaglate in the epipharynx was due to an active act of swallowing or passive drainage. This will become more evident in future human studies. These will also be the issue regarding the timing of the CM passage through the ET. Not only is the species different, but the physiological conditions will also vary because the animals were sedated. In addition, the human head is composed of more tissue, both soft and bone, than the rabbit head and the temporal bone specimens used. It is therefore...
likely that patient studies will require adjustments to the DFOV, kV, amount and degree of iodine administered, and the time lapse between CM injection and CT acquisition.

In future patient studies, the CM should be deposited through a tympanic tube. Most patients with ME disease and assumed ET dysfunction already have tubes, or tubes are installed during their first visit to the otologist; therefore, unnecessary perforation of the tympanic membrane can be avoided. Long-term complication rate due to tympanic tubes is low.14 Although the study does not predict how the method will work on patients, we believe that imaging in a lateral decubitus position also will be preferable in human studies, with the face slightly rotated toward the CT table and unilateral contrast deposition in the superiorly positioned ear, hence taking advantage of gravity.

Our study demonstrated indirectly that the ET is open by detecting CM in the epipharynx. Nevertheless, it is not given that the absence of CM in the epipharynx is synonymous with stenosis. Neither is it certain that the method will help us differentiate the normal from the pathological, or the level of pathology.

Potential hazards pertaining to the method must be addressed. Although this will be an off-label study, and the method has not been systematically tested before, we do not expect contrast-induced complications. We consider the risk of CM-induced anaphylactoid reactions to be the same as for other examinations using iodine-based CM. Iodixanol is approved and well documented to have a substance exchange with the labyrinthine system. Nevertheless, these contrast agents are approved for intrathecal and intravenous use, systems also known to have a substance exchange with the labyrinthine system. Therefore, we consider the risk of ototoxicity to be minimal.

Finally, the radiation dose with 120 kV will be slightly lower than that of our current temporal bone CT protocol (135 kV, dose-length product 150, effective dose 0.345 mSv).

Previous studies have shown both antegrade and retrograde passage of CM through the ET.8–12 Our study contributes knowledge regarding safety, CT parameters, and CM volume and dilution. A study of patients with chronic ME disease who have tympanic drainage tubes will be conducted based on our findings.

CONCLUSION

In rabbits, diluted iodixanol can fill and visualize the ET on CT images. Contrast medium passes from the ME to the epipharynx in 19 of 20 cases. The risk of mucosal inflammatory changes following the CM injections seems to be small.

BIBLIOGRAPHY

CT imaging of the Eustachian Tube using focal contrast medium administration: a feasibility study in humans

Benedicte Falkenberg-Jensen a,b, Greg E. Jablonski b,c, Juha Tapio Silvola b,d, Joanna F. Kristiansen *, Einar Hopp a

aDepartment of Radiology and Nuclear Medicine, Rikshospitalet
Oslo University Hospital
bThe faculty of Medicine, Oslo University
bDepartment of Otolaryngology, Head and neck Surgery
Oslo University Hospital
cDepartment of Otolaryngology, Head and neck Surgery
Akershus Universitetssykehus

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Abstract:
Purpose: Imaging of the Eustachian tube has been attempted in several ways during the last century, yet no published method has ended up as an established diagnostic tool. However, with the introduction of balloon dilation of the cartilaginous Eustachian tube (BET), the demand for ET visualization in patients with chronic Eustachian tube dysfunction prevails. There is no consensus regarding the aim and necessity of preoperative images. Many institutions perform preoperative computed tomography scans of the temporal bone and epipharynx. We hypothesize that the injection of contrast medium into the tympanic cavity can evolve the CT scan, visualizing the ET lumen and, potentially, the level of obstruction.

Method: To test this, eighteen patients with otitis media with effusion, referred to our hospital for BET of the ET, had diluted iodixanol carefully injected through a tube in the tympanic membrane ten minutes before the CT scan. Five patients with Meniere’s disease served as a control group. The most caudally visible contrast medium between the middle ear and epipharynx was recorded. Results: The contrast medium did not enter the
bony Eustachian tube at all in three patients; the contrast medium reached the bony Eustachian tube in two patients and the cartilaginous Eustachian tube in eight patients, while it passed to the epipharynx in four patients. In the control group, the contrast medium reached the cartilaginous portion in two patients, while contrast medium was seen in the epipharynx in three.

Conclusion: Visualizing the Eustachian tube lumen using intratympanic contrast medium is safe and feasible. A 20% dilution of iodixanol allows distinction of key bony structures.
Introduction:

Background: The application of iodine-based contrast mediums (CM) to visualize the Eustachian tube (ET) is not a novel idea. Already in 1927 Speilberg described roentgenograms of the ET using an iodinated oil \(^1\). Further publications of studies on living humans have been with conventional x-ray\(^2\)-\(^4\). Most studies have administered the CM in the torus area, and defined patency of the ET on the arrival of CM in the tympanic cavity. According to consensus by an international forum of scientists and physicians with expertise in the field of Eustachian tube dysfunction (ETD) (Schilder et al. \(^5\)) there are subtypes of ETD. We focus on chronic dilatory ETD, for which BET has recently become a treatment option. However, not all patients benefit from BET \(^6\)-\(^8\). As the method is both time-consuming and resource-intensive, it would be beneficial with optimized preoperative patient selection. We proposed improved imaging techniques to identify the level of obstruction, not only to demonstrate that there is one. Based on the results in our study on human cadavers and rabbits\(^9\) we aimed to visualize the ET lumen in human patients using intratympanic iodixanol for CT imaging. We determined the level of CM passage. Any adverse and severe adverse reactions were recorded, as well as immediate or delayed complications. Finally, we examined if important anatomical structures were masked by the CM.

Patients with Meniere’s disease can experience a reduction of vertigo after installation of tympanic tubes (tympanostomy tube) \(^10\),\(^11\) despite the lack of middle ear disease. They may therefore serve as a control group for studies that involve transtympanic substance administration.

Material and methods:

Two senior radiologists experienced in temporal bone radiology and two senior otologists conducted the study. Eighteen adult patients (9 female, mean age 46 years) were included. Inclusion criteria in the patient group were age \(>18\) years, chronic otitis media with effusion (OME), planned BET, no previous major middle ear surgery and no recent high resolution CT of the temporal bone. One male
patient was excluded due to previous major temporal bone surgery, leaving seventeen included
patients. Five adult patients with Meniere’s disease (3 female, mean age 58 years) who had a
tympanostomy tube due to Meniere symptoms, but a healthy middle ear, served as a control group.

In the patient group, an ENT surgeon evaluated the referral to BET, performed a clinical examination,
included the patient in the study, and obtained written consent 2-3 weeks prior to the CT examination.
If the patients did not have a tympanostomy tube, one was installed during the same consultation to
allow effusion to drain before the CM injection.

On the day of the CT scan, the patient was placed in a lateral recumbency position on the CT table
with the side of interest superior. An ENT surgeon inspected the tympanic membrane, the position of
the tympanostomy tube and the middle ear, guided by otomicroscopy. Based on our previous animal
study⁹, a 20% iodixanol (Visipaque™ 320 mg/ml) solution diluted with saline (NaCl 9mg/ml), was
slowly injected into the middle ear through the tympanostomy tube using a 22G suction needle. The
injection was carefully delivered by hand from a 1mm syringe, attached to a flexible connection tube
with luer locks, while the ENT surgeon held the needle steady and monitored the procedure through
the otomicroscope. The surgeon gave a signal to cease the injection when the middle ear was full, but
not expanded.

Although some patients were to be treated with BET on both sides, CM was only injected on one side
to prevent CM contamination of the opposite torus tubarius. After CM injection the patient was rotated
to a lateral oblique position with the CM-filled ear still superior. The chin was tilted towards the chest
and rotated slightly towards the table. This position was held for 10 minutes before the CT scan was
performed.

All CT scans were performed on an Aquilion ONE™ CT or Aquilion ONE™ / GENESIS Edition
(Toshiba Medical Systems, Tokyo, Japan) with scan parameters similar to our routine protocol for
temporal bone CT scans. The scan range extended from above the mastoid portion of the temporal
bone to the epipharynx and data was acquired in a single rotation in the volume scan mode with the
following scan parameters: 120 kV, 200 / 270 mA respectively, 0.5 second rotation time and 0.5 mm x
160 detector collimation. Images were reconstructed with a high resolution reconstruction filter, FC81, and 160 mm display field of view.

With the patient still on the CT table, the surgeon inspected the external auditory canal, the tympanic membrane and the middle ear to rule out any acute inflammatory reactions, and removed any excess CM with suction.

We used the ETDQ-7 questionnaire to record ear-specific symptoms immediately before, and six months after, the CT examination. The form was translated from the English version by two native Norwegian speaking physicians. After consensus was reached, the Norwegian version was translated back to English by two native English speaking colleagues, as a simplified validation of the Norwegian version. The final translation was compared to the original version and found almost identical.

All patients were encouraged to report any complaints during the injection of contrast and directly after the CT examination.

The radiologists evaluated the CT images in regard to how far the CM had passed in the ET, and whether the CM masked the demarcation of the tympanic membrane, ossicles, sinus tympani, or the round and oval windows.

BET was performed according to standard procedure, of two minutes dilation with Acclarent Aera (Irvine, CA, USA) 6 mm balloon catheter, within ten weeks after the CT examination.

Four to six months after the BET the patients met for a clinical follow-up examination. One of the otologists checked for any chronic or late inflammatory changes. The patients were also asked to answer the EDTQ-7 again. The first score was subtracted from the second, giving a total score.

The whole study was monitored by an external monitor, with no interest in the study. This study was approved by the institutional review board, the Regional Committees for Medical and Health Research Ethics, the Norwegian Medicines agency, and was registered at clinicaltrials.gov (NCT02282540).
**Results:** In the patient group, the CM did not pass from the middle ear to the ET in three patients. In two patients the CM was seen to reach the bony ET, in eight patients it reached the cartilaginous ET, and in four patients CM was visible in the epipharynx. Fig. 1.

In the control group, the CM passed to the cartilaginous ET in two patients, while CM was seen in the epipharynx in three patients.

![Image](image.png)

**Figure 1. Levels of contrast medium passage**
Three axial CT images after focal contrast medium injection, demonstrating three levels of passage. EAC (external acoustic canal), ICA (internal carotic artery)
**Left:** The contrast medium reached the bony portion of the Eustachian tube (open arrow)
**Middle:** The contrast medium reached the isthmus (white arrow)
**Right:** The contrast medium reached the torus Tubarius (black arrow)

One of the control patients reported transient dizziness during CM administration. This was classified as an expected adverse event in the study protocol and the symptoms resolved before the examination was over for this particular patient. There were no other reports of subjective side effects: no signs of added or acute inflammation were found in the clinical exams.

Seven of seventeen patients and four of five control patients answered the second EDTQ-7 during the follow-up period. The mean overall sum in EDTQ-7 was lower the second time, both in the patient group and the control group (table 1).

Apart from the tympanic membrane, the bony anatomical structures and landmarks in the middle ear were not masked by the diluted CM.
Table 1. EDTQ-7 result before and four to six months after BET, and the sum after subtracting the first result from the second after. Empty cells where the EDTQ-7 was not answered.

<table>
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<th>Individual</th>
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<th>EDTQ-7 after</th>
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(C = control, P = patient, BET = balloon Eustachian tuboplasty)

Discussion:

Our study is the first controlled patient study with transtympanic CM administration visualized with CT imaging. We investigated whether the CM passed to the epipharynx and if not so, at which level of the assumed obstruction occurred. CM passed to the epipharynx in 60% in the control group versus 23.5% in the patient group. It is not given that the level of CM passage represents an actual
obstruction, or even the correct level as such. Nevertheless, there is a clear difference between the control group and the patient group, and between our previous study on rabbits\(^9\) and the present patient group. It would be an advantage to identify the patients who will not benefit from BET. Patients with the obstruction localized in the bony ET is one such group, as the goal of BET is the cartilaginous part of the ET.

As results in the patient group vary and our sample is small, studies with a greater number of participants are required to validate the method. We have however, found the method feasible, as the level of CM passage could be assessed in all patients without serious adverse effects, and the evaluation of the other temporal bone structures was not hindered.

As we only wanted to add information that could be read from the preoperative CT, it was important not to mask structures in, or bordering on, the middle ear. The ossicles, sinus tympani and windows are situated in different locations in the middle ear, which makes them good reference points to monitor specific and over-all masking. We addressed inflammatory changes and subjective reactions, both directly after the CM administration and after 4-6 months, without any positive findings. As an off-label trial, we believe this was an important aspect and supports the findings in our animal trial\(^9\).

Few in the patient group answered the EDTQ-7 the second time. However, we suspect the result in this group to reflect the results from the BET. The score of the control group probably reflects the effects of the CM more directly. As the tympanostomy tubes were installed before the first EDTQ-7, the effect of the tympanostomy tubes should not influence the total sum (table 1). Two patients had an increase in EDTQ-7 score. This is not unexpected in the light of other studies, but we cannot completely exclude individual adverse effects due to the CM.

**Conclusion:**

Imaging the ET lumen using diluted iodixanol is safe and feasible. The level of obstruction may be detected, but this needs to be tested further in a larger study population. In 23.5% of the patients with
OME, CM passed to the epipharynx, compared to 60 % in the control group.

The dilution of iodixanol to 20% visualises the ET lumen without masking vital bony middle ear structures.


The cartilaginous Eustachian tube: Reliable CT measurement and impact of the length

Benedicte Falkenberg-Jensen\textsuperscript{a,b,\*}, Einar Hopp\textsuperscript{a}, Greg E. Jablonski\textsuperscript{b,c}, Are Hugo Pripp\textsuperscript{d}, Juha Tapio Silvola\textsuperscript{e}

\textsuperscript{a} Department of Radiology and Nuclear Medicine, Rikshospitalet, Oslo University Hospital, Norway
\textsuperscript{b} The faculty of Medicine, Oslo University, Norway
\textsuperscript{c} Department of Otolaryngology, Head and Neck Surgery, Oslo University Hospital, Norway
\textsuperscript{d} Oslo Centre of Biostatistics and Epidemiology, Oslo University Hospital, Norway
\textsuperscript{e} Department of Otolaryngology, Head and Neck Surgery, Akershus University Hospital, Norway

\begin{abstract}
Purpose: Balloon dilation of the Eustachian tube is a treatment option for obstructive Eustachian tube dysfunction. The desired balloon position is in the cartilaginous portion. However, the balloon catheter may slide into the bony portion without the surgeon's knowledge. Knowing the length of the cartilaginous portion may improve catheter positioning, but there is no published research on measuring this portion selectively or on whether the length has an impact on development of disease or treatment outcome.

To evaluate whether a measurement obtained from CT images is valuable and accurate, to standardize the manner of which the length is measured, and to compare our radiologic measurements to procedural findings, we designed a combined study. Further, we tested the length's influence on development of disease and treatment outcome.

Methods: Anatomical end points of the cartilaginous part of the Eustachian tube were unambiguously defined. The length was retrospectively measured bilaterally in 29 CT examinations by two radiologists, and repeated by one after two weeks. New reformats and measurements were made after 18 months for 10 of the patients. Prospectively 10 patients were included in a study where the length measured on CT was compared to per-procedural measurements based on catheter insertion depth to isthmus. Various parameters including length and treatment outcome were measured in 69 patients and 34 controls.

Results: Correlation was adequate to excellent in all comparisons. The length of the cartilaginous Eustachian tube did not predict treatment outcome or disease development. The lengths were significantly shorter in females.

Conclusion: Measuring the cartilaginous portion of the Eustachian tube on CT images is precise and reproducible, and reflects the length measured intraoperatively. However, it does not seem have a prognostic value.
\end{abstract}

1. Introduction

Ventilation problems due to Eustachian tube dysfunction are associated with several middle ear conditions. Until the present decade, tympanostomy tubes have been the only option to surgically improve middle ear ventilation.

During the present decade, balloon dilation of the Eustachian tube (ET) has evolved from pioneer testing with the first studies published during 2010 and 2011 \cite{1–4} to a treatment option \cite{5,6}. Even though it is debated, whether dilation in the bony part of the ET can damage vital structures like the carotid artery \cite{7}, complications have occurred with similar methods \cite{8,9} and the desired balloon position is in the cartilaginous portion. The cartilaginous part of the ET is flexible, and therefore it is possible to expand a balloon catheter with a much larger diameter. The bony isthmus is the surgical limiting factor, and therefore an anatomical point of interest. However, there seems to be little focus on the significance of the cartilaginous ET’s length, which is the target in balloon treatments. The length is known to vary considerably \cite{6}. If
it is known to the surgeon in advance, we argue that this will facilitate the choice of balloon length and provide information on how far the catheter needs to be inserted to reach the isthmus. A preoperative measurement can assist the optimization of catheter positioning and contribute to conduct a safe and predictable procedure.

In our hospital, all patients undergo a temporal bone CT to rule out other pathologies including obstruction in the bony portion of the ET before balloon treatment. Hence, if the length of the cartilaginous portion can be derived from the CT, more than one purpose can be served.

Sudo et al. measured the length of the cartilaginous portion using computer reconstructions of cadaver specimens [10], versus both Dinc et al. [11] and Takasaki et al. [12] who measured the ET as one unit reformat and have stable, visible reference points. Our goal was to include the full length of the cartilaginous portion in one reconstructed CT image, one must make oblique coronal reformats and have stable, visible reference points. Our goal was firstly to establish a simple and reproducible CT measuring method for the length of the cartilaginous portion of the ET, and to ensure the quality of the method. Secondly, we intended to examine whether the length has an impact on development of disease, the outcome of treatment and if length differs with gender and age.

2. Material and methods

2.1. CT measurement method

Retrospectively, we included all adult patients who were referred to CT of the temporal bone due to ET dysfunction in 2013. Twenty-nine patients were included, 19–79 years, mean age 48, median age 53, 13 female. In consensus, two radiologist and two otorhinosurgeons determined the cranial and caudal limits of the cartilaginous ET. The cranial limit was defined as the bony eminence at the medial side of the bony ET's caudal end. This eminence is formed by a thickening of the bone separating the carotid canal from the bony ET. The caudal limit was defined as the tip of the soft tissue tip of the torus tubarius on one, single CT image (Fig. 1). From the CT raw data, we made tilted coronal reformats projecting both points in the same image plane. Individually two experienced ENT radiologists measured the cartilaginous part of the left and right ET in each patient. One radiologist repeated the measurements after two weeks. All measurements were blinded to previous results. To examine whether the reformat procedure per se would influence the length measurement, we made new CT reformats and new measurements for ten of the patients after 18 months.

2.2. Comparison to catheter measurement

Prospectively, CT measurements were compared to the actual endoscopic findings. Ten patients (seven female, mean age 33 [median 35, range 23–56]) were included. Blinded for the CT measurements, the surgeons measured the length defined as the catheter insertion depth from the tip of the torus tubarius as the catheter met resistance. All endoscopic measurements were done with Acclarent Aera™ catheter (Acclarent Inc., Irvine, CA, USA). This balloon catheter was specifically designed for ET balloon dilation. The tip is rounded and has a diameter of 2.2 mm, which induces a resistance when it reaches the isthmus. Thus, we defined the depth of registered resistance to represent isthmus.

The balloon catheter was inserted until resistance was felt at the assumed isthmus. After balloon dilation, a guide catheter was placed to the tip of the torus tubarius. The whole catheter with emptied balloon and guide were simultaneously pulled out and the length of the disposed catheter was measured from the tip of the guide catheter to the tip of the balloon catheter.

Two patients were treated unilaterally, and subsequently the two contralateral CT measurements were excluded, resulting in 18 included tube measurements. In this study, we regarded each side as independent.

2.3. Clinical measurements

All adult patients who had been treated with balloon dilation of the ET due to OME from February 2013 through June 2016, and had a preoperative CT of sufficient quality to make new reformats, were included. This resulted in 97 ETs in a total of 69 patients (40 female, mean age 45). In the preoperative CT of the temporal bone, the cartilaginous portion of the ET was measured using the CT measurement method. Both sides were measured regarding of whether disease was unilateral or bilateral, but ears with disease were registered separately. As controls, we included 34 (14 female, mean age 50) adult patients with temporal bone CT-examinations without history or findings of middle ear disease. The controls were retrospectively included from the CT examinations performed at our institution over the same time period as the patient group. We recorded gender, age at CT examination, and length of the cartilaginous portion of the ET in both groups, and treatment outcome and time between CT and surgery in the patient group. All patients had a clinical follow up 3 to 6 months after balloon dilation. Valsalva, position of the tympanic membrane and aeration of the ME were evaluated, and each given one point if normal, giving a scale from 0 to 3 points. 0 or 1 point was classified as a poor result, while 2 or 3 points as satisfactory.

The CT examinations in all three studies were conducted on a Toshiba Aquilion One, with 135 kV, 200 mA and 158 dFoV with a slice thickness of 0.67 mm. The tilted coronal reformats were 1/1 mm average intensity projection.

The studies were conducted according to the Helsinki declaration and approved by the National Ethics Committee and Oslo University Hospital's research authorities. Patients in the prospective study gave their informed consent to participate.

3. Statistics

Continuous variables are described as mean ± standard deviation. The Pearson correlation coefficient between measurements was calculated.

Difference between left and right cartilaginous ET was tested with paired Student's t-test. Inter- and intrarater reliability between CT measurements and internal consistency between CT and endoscopic measurements were tested with reliability tests, e.g. Bland-Altman plots and the intraclass correlation coefficient. Standard error of measurement (SEM) and minimal detectable change (MDC) were calculated as shown in eq. 1

$$MDC = 1.96 \times \sqrt{2} \times SEM$$  

(1)

In the clinical measurements, both sides were measured in the same patient. These clustered data within the same patients was therefore assessed by using Generalized estimating equations with an unstructured working correlation matrix.

4. Results

Cartilaginous ET length as measured by CT was 26.8 ± 2.1 mm on the left side, 26.6 ± 2.0 on the right side and 26.7 ± 2.1 mm for all summarized measurements. The complete range was between 21.7 and 32.6 mm. There was no statistical significant difference between left and right side (p = 0.32). For measurement on similar CT sets, the Pearson correlation coefficient between measurements was 0.93 between observers and 0.92 for repeated measurements of one observer. Inter- and intrarater reliability between CT measurements was excellent with an intraclass correlation coefficient of 0.93 and 0.92. CT measurement of 20 cartilaginous ET lengths was repeated after renewed
tilted coronal reconstruction of the datasets in 10 patients and the Pearson correlation coefficient between measurements was 0.92. Interrater reliability after renewed reconstruction was excellent with an intraclass correlation coefficient of 0.92. Based on results from analyses before and after renewed dataset reconstruction, the SEM and MDC was estimated to 0.013 mm and 0.036 mm, respectively.

Cartilaginous ET length of the smaller sample was 26.2 ± 1.6 mm as measured by endoscopy and 26.0 ± 1.6 as measured by CT. The Pearson correlation coefficient between endoscopic and CT measurements was 0.64. The internal consistency between endoscopic and CT measurement was adequate with a Cronbach’s alpha of 0.78.

A Bland Altman plot with a regression analysis revealed no bias dependent on cartilaginous ET length (Fig. 2).

The results for our clinical measurements are summed up in Table 1. We found that cartilaginous ET length was not predictive for development of disease or for treatment outcome. Females had shorter cartilaginous ET lengths. However, there was no correlation between gender and treatment result. Furthermore, no correlation was found between age and length or length and treatment outcome. Time between CT and balloon dilation did not influence treatment outcome. 7 of the 97 sick ears had a poor treatment outcome with a score of 0 or 1 of the possible 3 points. One patient had a poor result bilaterally, while the other five were treated unilaterally.

5. Discussion

We have developed a method to measure the length of the cartilaginous part of the ET on CT images, which is reproducible and comparable to endoscopic finings. The measurement can easily be obtained from the reformatted images acquired from the preoperative CT volume. Our measurements have excellent reproducibility both between observers on similar datasets and after repeated reformattting and measurements. Low MDC confirmed high measurement precision. CT measurement accuracy, especially in 2D, is generally considered high. Although measurement may be influenced by the image plane selected, physical image settings and signal-to-noise ratio, it has been shown that measurements are comparable [13]. For increased relevance, we chose to perform this study on routine temporal bone CT examinations originally not planned for cartilaginous ET length measurement. All examinations had axial high-resolution image stacks with slice thickness of 1 mm or less. In this setting, signal-to-noise ratio is high, measuring the interface between bone and soft tissue cranially and soft tissue and air caudally. In the lack of any measurement gold standard, we compared to endoscopic measurement. For this comparison, precision was reduced. Potential explanations are the complexity of the manual procedure for endoscopic measurement, that resistance of the catheter tip of 2.2 mm is not necessarily met at the point measured, and that the torus tubarius protrusion and epipharyngeal mucous membrane thickness might have changed between CT examination and endoscopy. Given these sources of error, an adequate reproducibility is considered fair. There was a mean difference of 0.00 mm between the methods, suggesting that accuracy of the measurements is good.

Any anatomical measurement is dependent on a precise, unambiguous definition. Although the temporal bone is anatomically complex, the definition in this study served the purpose of a measurement with excellent reproducibility, even though repeat measurements were dependent on sufficiently precise repeat reformattting. We chose to define the caudal ET end at the torus tubarius to strengthen reproducibility in an area of soft tissue with little contrast on CT images. Our study shows a good correlation between the catheter insertion depth...
individual, hence in individuals, but also with time and immune status within the same that the volume of the soft tissue in this area may vary both between
chose the soft-tissue tip of the torus as an endpoint. It can be argued tion of the ET, as this is the target area for balloon treatment. We also work of Takasaki et al., we have only measured the cartilaginous por-
catheter probably straightens the cartilaginous ET. As opposed to the curved and that our measurement is slightly o
junctional portion in vivo. The fact that the cartilaginous ET is slightly
narrowest point found in Sudo's study is in fact more
measuring on human cadaver specimens. One may speculate that the portion, and not at the junction between bone and cartilage, when measuring on human cadaver specimens. One may speculate that the narrowest point found in Sudo's study is in fact more flexible than the junctional portion in vivo. The fact that the cartilaginous ET is slightly curved and that our measurement is slightly off axis of the true ET lumen also seem to have little influence on measurements. The balloon catheter probably straightens the cartilaginous ET. As opposed to the work of Takasaki et al., we have only measured the cartilaginous portion of the ET, as this is the target area for balloon treatment. We also chose the soft-tissue tip of the torus as an endpoint. It can be argued that the volume of the soft tissue in this area may vary both between individuals, but also with time and immune status within the same individual, hence influencing the measurement. On the other hand, the torus is a structure, which is easy to distinguish, given there is no epipharyngeal mass or previous major epipharyngeal surgery.

We did not adjust for smoking in the statistical analysis, as we did not possess such data. Nevertheless one can assume that most patients maintained their smoking habits over the given timespan, and therefore the comparisons made between the radiologic and endoscopic measurements should be uninfluenced on an individual level.

There is a certain bias in measuring both sides in the same patient, as the first length will create an expectancy of the contralateral length; however, we chose to ignore this in the first study. In the second study, we found it more appropriate to address this, as the measurements were compared to other factors.

As a method to determine the level of dysfunction has yet to be established [1-5], the current standard is to insert the balloon catheter to the isthmus, regardless of the length of the cartilaginous portion. The catheter we used should stop at isthmus level. However, as any other anatomical structure, the diameter of the isthmus may vary individually, and all catheters may unintentionally be inserted beyond the isthmus. Regardless of whether inflating the balloon within the bony portion is associated with a risk of complications or not, it is the cartilaginous ET that is the area intended to treat and where results have been documented. Knowing the length of the cartilaginous portion of the ET in advance, may contribute to obtaining the catheter position intended.

Although some variance between machines and algorithms can be expected, we believe the method to be fast and transferrable to any MDCT-volume that includes the middle ear and the torus lip. Thus, it can be used anywhere and be a basis for future studies where the cartilaginous ET length is a factor. The measurement itself can assist the surgeon both in the choice of catheter length and in the positioning of the balloon.

We did not find that the length of the cartilaginous ET influences disease development or treatment outcome, and the scale we used to score treatment outcome is not validated. However, the scale was based on common clinical parameters used for the evaluation of outcome, and should therefore reflect clinical relevance.

Females had significantly shorter cartilaginous portions of the ET. The explanation is likely physiological, however, knowing this the surgeon can adjust the insertion depth. As the length of the cartilaginous ET treatment appears to be independent of outcome, development

Table 1

<table>
<thead>
<tr>
<th>Problem</th>
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<th>Mean in mm</th>
<th>Mean difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length vs. outcome</td>
<td>90 good</td>
<td>27.4</td>
<td>−0.11</td>
<td>0.482</td>
</tr>
<tr>
<td></td>
<td>7 poor</td>
<td>26.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length in ears with OME</td>
<td>97 OME</td>
<td>26.8</td>
<td>−0.53</td>
<td>0.266</td>
</tr>
<tr>
<td>vs. control gr</td>
<td>68 control</td>
<td>26.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length in patient gr vs.</td>
<td>138 patient</td>
<td>26.8</td>
<td>−0.44</td>
<td>0.349</td>
</tr>
<tr>
<td>control gr</td>
<td>68 control</td>
<td>26.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length vs. age</td>
<td>206 all</td>
<td>26.7</td>
<td>0.01</td>
<td>0.270</td>
</tr>
<tr>
<td>Length vs. gender</td>
<td>108 female</td>
<td>25.8</td>
<td>−1.88</td>
<td>0.000</td>
</tr>
<tr>
<td>Outcome vs. age</td>
<td>98 male</td>
<td>27.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome vs. gender</td>
<td>90 good</td>
<td>27.4</td>
<td>0.01</td>
<td>0.637</td>
</tr>
<tr>
<td></td>
<td>7 poor</td>
<td>26.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome vs. short tubes</td>
<td>90 good</td>
<td>27.4</td>
<td>−1.69</td>
<td>0.128</td>
</tr>
<tr>
<td>5 mm</td>
<td>7 poor</td>
<td>26.9</td>
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<td></td>
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<tr>
<td>Outcome vs. timespan</td>
<td>90 good</td>
<td>27.4</td>
<td>−0.01</td>
<td>0.817</td>
</tr>
<tr>
<td>between CT and op.</td>
<td>7 poor</td>
<td>26.9</td>
<td></td>
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</tr>
</tbody>
</table>

* The healthy ears in the patient group are included.

and CT measurements, despite the findings of Sudo et al. [10] where the narrowest point of the ET was found to be within the cartilaginous portion, and not at the junction between bone and cartilage, when measuring on human cadaver specimens. One may speculate that the narrowest point found in Sudo's study is in fact more flexible than the junctional portion in vivo.

There is a certain bias in measuring both sides in the same patient, as the first length will create an expectancy of the contralateral length; however, we chose to ignore this in the first study. In the second study, we found it more appropriate to address this, as the measurements were compared to other factors.

As a method to determine the level of dysfunction has yet to be established [1-5], the current standard is to insert the balloon catheter to the isthmus, regardless of the length of the cartilaginous portion. The catheter we used should stop at isthmus level. However, as any other anatomical structure, the diameter of the isthmus may vary individually, and all catheters may unintentionally be inserted beyond the isthmus. Regardless of whether inflating the balloon within the bony portion is associated with a risk of complications or not, it is the cartilaginous ET that is the area intended to treat and where results have been documented. Knowing the length of the cartilaginous portion of the ET in advance, may contribute to obtaining the catheter position intended.

Although some variance between machines and algorithms can be expected, we believe the method to be fast and transferrable to any MDCT-volume that includes the middle ear and the torus lip. Thus, it can be used anywhere and be a basis for future studies where the cartilaginous ET length is a factor. The measurement itself can assist the surgeon both in the choice of catheter length and in the positioning of the balloon.

We did not find that the length of the cartilaginous ET influences disease development or treatment outcome, and the scale we used to score treatment outcome is not validated. However, the scale was based on common clinical parameters used for the evaluation of outcome, and should therefore reflect clinical relevance.

Females had significantly shorter cartilaginous portions of the ET. The explanation is likely physiological, however, knowing this the surgeon can adjust the insertion depth. As the length of the cartilaginous ET treatment appears to be independent of outcome, development
of disease and age, it remains to be seen whether other factors influence treatment outcome and can be used in patient selection.

6. Conclusion

The length of the cartilaginous portion of the ET can easily be obtained on CT images, and is reproducible and representative for the insertion depth to the isthmus with a balloon catheter. The cartilaginous ET is longer in men. Development of disease and treatment outcome seems to be independent of the length.

The above described studies were approved by the Institutional Board of Ethics.

The authors have no competing interests.

References