

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

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Abstract

Background: Several methods of imaging the Eustachian tube have been tested in the last century, although neither has led to an established method. The introduction of balloon Eustachian tuboplasty (BET) has revived the request for Eustachian tube (ET) visualization in patients with chronic Eustachian tube dysfunction. Many institutions perform preoperative computed tomography (CT) scans of the temporal bone and epipharynx before BET.

Purpose We hypothesize that the injection of a contrast medium into the tympanic cavity is safe and feasible and can evolve the CT scan by visualizing the ET lumen and, potentially, the level of obstruction. This study is the initial feasibility study for such a human application.

Material and Methods Ten minutes before a CT scan, diluted iodixanol was injected into the middle ear in 18 patients planned for BET due to otitis media with effusion. Five patients with Meniere's disease were controls. Any immediate or delayed adverse events were recorded. Masking of adjacent bony structures in the middle ear on the CT images was evaluated and the most caudally visible contrast medium between the middle ear and epipharynx recorded.

Results There were no serious adverse events. One patient reported transitory vertigo. The contrast medium did not mask middle ear structures, apart from the tympanic membrane. The level of contrast medium passage could be assessed.

Conclusion Visualizing the ET lumen in humans using intratympanic contrast medium is feasible and safe and does not obscure other valuable image information in a preoperative CT scan.

Keywords

Ear nose and throat, Eustachian tube, computed tomography, contrast agents, balloon insertion

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Introduction

Eustachian tube (ET) function is complex and two-directional. It protects the middle ear from reflux of microorganisms and secretions and from the body's own sounds coming from the oral cavity and pharynx. It assists in maintaining the middle ear pressure equal to the atmospheric pressure in the epipharynx by the passing of small gas boluses in the direction necessary. It assists in draining excess fluids from the middle ear and simultaneously ciliated epithelial cells clear away contaminants by beating towards the epipharynx. Loss or reduction in one or more of these functions leads to dysfunction. According to consensus by an international forum of scientists and physicians with expertise in

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the field of Eustachian tube (Schilder et al. (1)), there are three subtypes of Eustachian tube dysfunction (ETD): dilatory ETD; baro-challenge-induced ETD; and patulous ETD. Here, we focus on dilatory ETD, for which balloon Eustachian tuboplasty (BET) has recently become a treatment option. However, not all patients benefit from BET (2–4). As the method usually demands general anesthesia and is resource-intensive, it would be beneficial with optimized preoperative patient selection. Visualizing the ET lumen could perhaps provide information on its patency and even on the level of obstruction.

An air-filled ET lumen during Valsalva's maneuver seems to be an ideal option to image the ET. There are several publications on this method on patulous ETD (4–6). However, for patients with dilatory ETD, many are unable to perform Valsalva's maneuver (7,8).

The application of iodine-based contrast mediums (CM) to visualize the Eustachian tube (ET) is not a novel idea. In 1927, Spielberg (9) already described roentgenograms of the ET using an iodinated oil. Further publications of studies on living humans have been performed with conventional X-ray (10–12). Most studies have administered the CM in the torus area, and defined patency of the ET upon the arrival of CM in the tympanic cavity. Based on the results of our study on human cadavers and rabbits (13), we aimed to visualize the ET lumen in human patients using intratympanic iodixanol for computed tomography (CT) imaging. We hypothesize that the method is feasible and safe in humans, that adjacent, bony structures in the ME are not masked by the CM and that the CM can be observed at the torus tubarius if the ET is patent.

To ensure that the method showed CM passage to the epipharynx in individuals with assumed healthy ETs, we included a small control group. Patients with Meniere's disease can experience a reduction of vertigo after installation of tympanostomy tube (14,15) despite the fact that this patient group does not have middle ear disease. Thus, patients with Meniere's disease with tympanostomy tubes and normal ET function made a suitable control group.

Material and Methods

Two senior otologists and two senior radiologists experienced in temporal bone radiology conducted the study. Eighteen adult patients diagnosed with OME and referred to BET (9 women, mean age = 46 years) were included consecutively. On clinical examination, fluid in the middle ear without inflammatory signs and inability to perform Valsalva's maneuver were confirmed. Inclusion and exclusion criteria are listed in Table 1. All patients had previously been treated with

nasal steroids and tympanostomy tubes without satisfactory results or relapsing symptoms after tube extrusion. One male patient was excluded due to previous major temporal bone surgery, leaving 17 included patients. Five adult patients with Meniere's disease (3 women, mean age = 58 years) who had a tympanostomy tube due to Meniere symptoms, but a healthy middle ear with normal tympanic membrane position, normal Valsalva's procedure, and no visible fluid in the ME, 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 before 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.

For 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 study (13), a 20% iodixanol (Visipaque™ 320 mg/mL) solution diluted with saline (NaCl 9 mg/mL), was slowly injected into the middle ear through the tympanostomy tube using a 22-G suction needle. The injection was carefully delivered by hand from a 1 mL 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 nasopharyngeal 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 for optimal gravity effect. This position was held for 10 min before the CT scan was performed.

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

Table 1. Inclusion and exclusion criteria in the patient and control groups.

Inclusion	Exclusion
<p><i>Patient group</i></p> <p>Patients aged > 18 years</p> <p>Referred to our ENT clinic for evaluation and treatment of OME, tympanic membrane perforation, or tympanic membrane retraction</p> <p>Dysfunction of the ET is suspected by the ENT surgeon</p> <p>The patient is a candidate for balloon dilation of the ET</p> <p><i>Control group</i></p> <p>Patient aged > 18 years</p> <p>Referred to the ENT clinic for evaluation and treatment of Mb Meniere</p> <p>CT of the temporal bone is required</p> <p>Patient has or is considered to benefit from a tympanic tube</p>	<p><i>Patient group</i></p> <p>Previous serious allergic reaction to iodine-based CM</p> <p>Increased risk of bleeding</p> <p>Serious heart disease</p> <p>Diabetes I</p> <p>Previous ENT surgery (t-tubes excluded)</p> <p>Middle ear disease, which requires other type of treatment</p> <p>Chronic rhinosinusitis or nasal polyposis</p> <p>Anatomical variations in the temporal bone or skull base that contraindicates balloon dilation</p> <p>Women who are pregnant or breast feeding</p> <p><i>Control group</i></p> <p>Same as for the patient group</p>

CM, contrast medium; ENT, ear, nose and throat; ET, Eustachian tube; OME, otitis media with effusion.

Table 2. Serious AEs and expected AEs as reported to the Norwegian Medicines Agency before the study.

Serious AE	Expected AE
<ul style="list-style-type: none"> • Results in death • Is immediately life-threatening • Requires inpatient hospitalization • Results in persistent or significant disability or incapacity 	<ul style="list-style-type: none"> • Taste of metal • Brief hearing impairment in the treated ear, immediately after CM deposition lasting < 60 min • Vertigo • Nausea

AE, adverse event; CM, contrast medium.

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, such as edema and erythema, and removed any excess CM in the external auditory canal with suction. All patients and controls were specifically asked for immediate reactions or discomfort and encouraged to report any complaints, both immediate and delayed directly to the lead investigator. Any serious adverse events (AEs) and expected AEs were recorded (Table 2), as well as immediate or delayed complications. We addressed the level of CM passage, aware that our study population was too small to draw conclusions on this point. The radiologists carefully evaluated the CT images with regard to how far the CM had passed along 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: 2 min dilation with Acclarent Aera (Irvine, CA, USA) 6 mm balloon catheter, within 10 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 examined the patients and specifically checked for any chronic or late inflammatory changes. All patients were carefully interrogated about any signs of dizziness, nausea, tinnitus, or hearing loss since the procedure.

An external monitor, with no personal interest in the study, monitored the complete study. The 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

No serious AEs were detected. One of the control patients reported transient dizziness during CM administration. Dizziness was classified as an expected AE in the study protocol. The symptoms resolved before the examination was over for this particular patient and we assumed the event to be a caloric reaction. There were



Fig. 1. Levels of contrast medium passage. Four tilted coronal CT images after focal contrast medium injection, demonstrating four levels of passage. Top left: Patient with remaining fluid in the middle ear; the CM pooled in the hypotympanum (white arrow) and did not pass to the bony ET (black circle). Top right: The CM reached and filled the bony portion of the ET (open white arrow). Bottom left: The CM passed to the cranial portion of the cartilaginous ET. Bottom right: The CM coats the cartilaginous ET and has also reached the torus Tubarius (white circle). CM, contrast medium; ET, Eustachian tube.

no other AEs. No signs of worsened or acute inflammation were found in the clinical exams.

Apart from the tympanic membrane with its borders, no bony anatomical structures or landmarks in the middle ear were masked by the diluted CM.

The CM could be assessed in the images of all individuals. 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.

Discussion

Our study is the first controlled patient study with transtympanic CM administration visualized with CT imaging. We investigated the feasibility and safety of the procedure. In addition, we addressed whether the

CM passed to the epipharynx and, if not so, at which level it was seen. This might be the site of obstruction. The five individuals in our study—patients with no CM passage to the cartilaginous part of the ET—represent an interesting group. We consider it an advantage to identify the patients who will not benefit from BET. Patients with the obstruction localized in the ME or in the bony ET may be one such group, as the target of BET is the cartilaginous part of the ET. However, this feasibility study was not designed to distinguish responders from non-responders based on CM passage level. It is not given that the level of CM passage represents an actual obstruction or even the correct level as such.

Other authors have demonstrated visualization of the ET with air and Valsalva's maneuver (6,16,17). This is a less-invasive method, and the attenuation difference between air and soft tissue is larger than for our CM and soft tissue. The method, however, requires the ability to perform Valsalva's maneuver, which our patients could not. The CM procedure visualizes the

passive clearance of CM from the ME towards the epipharynx and demonstrates the direction of mucosal secretion clearance. An air-filled ET during Valsalva's maneuver demonstrates the patency of passing an air bolus from the epipharynx to the ME. It remains to be proven that the ability to perform Valsalva's maneuver alone is enough to maintain all of the ET's functions.

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 visualization in itself; 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 (18), where the study patients had pathological TM, ME, and Valsalva's. Our control patients all had normal tympanic membrane position, MEs, and Valsalva maneuvers upon inclusion in the study, indicating normal ET function.

Iodixanol is a widely used CM and can be administered intravenously, intraarterially, orally, or in acquired cavities such as abscesses. In many countries, it is also approved for intrathecal use. Use in the middle ear is not listed as an area of administration, and such use is off label. In addition to inflammatory reactions in the middle ear and ET, ototoxicity is a possible complication to all substances administered to the middle ear. Nevertheless, we considered the risk of ototoxicity to be extremely low. Substances such as CM and antibiotics can pass through the round window membrane (19–21) and the oval window membrane (20,22,23), but also diffuse into the labyrinth from the blood stream (20,22). We chose iodixanol (Visipaque™) as the CM, both in our animal study (13) and in this human study, due to its properties. It is a non-ionic CM with an osmolality of 0.29 osmol/L which is isoosmolar with blood and assumed isoosmolar with perilymph (24). This should in theory reduce the risk of diffusion across membranes. Although no studies have been done with ototoxicity or hearing loss as specific endpoints after administration of iodixanol, there are no reports on hearing loss after intravenous, intrathecal, or intratympanic use. As it is used daily and worldwide, the common clinical experience is, in itself, an argument for its safety. In addition, the fact that no study participant experienced worsened hearing speaks against a clinically relevant ototoxic effect in this sample.

By including patients with a recent CT of the temporal bone, a larger study sample would have been achievable. However, for this feasibility study, we found it controversial to repeat a recent CT examination, due to both radiation dose and possible AEs.

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

The CM procedure was meant to add information that could be read from the routine preoperative CT; thus, 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 make them good reference points to monitor specific and overall masking. We addressed inflammatory changes and subjective reactions, both directly after the CM administration and after 4–6 months, without any positive findings. Given that this study was off-label, we believe this was an important aspect and supports the findings in our animal trial (13).

CT imaging with air-soft tissue contrast during Valsalva's maneuver is a less invasive and time-consuming method compared to ours. We did not consider it suitable for our patient group. Nevertheless, the two methods have not been compared directly and the potential benefits and discrepancies have yet to be clarified.

In conclusion, imaging the ET lumen using diluted iodixanol is safe and feasible. It is feasible to detect passage of CM to the epipharynx. The dilution of iodixanol to 20% visualizes the ET lumen without masking vital bony middle ear structures. Further studies are recommended to confirm that the method adds information about the ET to the preoperative CT.

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