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Current diagnosis and treatment

Heidi Oehlandt

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To my family

UNIVERSITY OF TURKU
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HEIDI OEHLANDT: Obstructive Eustachian tube dysfunction - Current diagnosis and treatment
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ABSTRACT

The Eustachian tube (ET) connects the middle ear (ME) to the nasopharynx and has a vital role in ME health. Functional obstructive Eustachian tube dysfunction (OETD) is a result of an inadequate opening of the ET. The symptoms of OETD, however, are unspecific, posing a need for objective ET measurements. One of the most objective methods to test ET opening is tubomanometry (TMM), which has been shown to have sufficiently high specificity and sensitivity to OETD. Nevertheless, information on the technical success rate and factors affecting the results is almost nonexistent. Proper diagnosis has high significance nowadays, as there is a surgical treatment option for OETD, balloon Eustachian tuboplasty (BET). BET has in many studies proven to be effective and safe. Despite this, more studies are needed on its use in different patient groups.

We studied the clinical use of TMM in OETD diagnostics by assessing the technical success rate of the TMM measurements in a retrospective cohort from Helsinki University Hospital in 2016–2020. The success rate (91%) was evaluated to be sufficiently high for clinical diagnostics. In addition, we evaluated factors affecting the TMM results; the only patient-related characteristic to have an effect seemed to be a pollen allergy.

We also examined the efficacy and safety of BET in different patient groups: children, baro-challenge-induced ETD patients, OETD patients, and as part of other ear surgery. Therefore, all consecutive patients from Turku University Hospital during 2013–2016 and baro-challenge-induced ETD patients from Helsinki University Hospital during 2011–2020 treated with BET were retrospectively evaluated. Questionnaires showed long-term improvement in all these groups. No major complications were encountered. An additional systematic review revealed that studies on baro-challenge-induced ETD were heterogeneous, with a small study sample and varying improvements in outcome measures.

In conclusion, TMM appears to be a reliable and practical diagnostic tool for OETD patients. Our results on BET compliments the existing studies suggesting long-term efficacy and safety also in different patient groups.

KEYWORDS: Eustachian tube, functional obstructive Eustachian tube dysfunction, baro-challenge-induced Eustachian tube dysfunction, tubomanometry, balloon Eustachian tuboplasty

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Kliininen laitos
Korva-, nenä- ja kurkkutautioppi
HEIDI OEHLANDT: Korvatorven obstruktiivinen vajaatoiminta – nykyinen diagnostiikka ja hoito
Väitöskirja, 140 s.
Turun kliininen tohtoriohjelma
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TIIVISTELMÄ

Korvatorvi yhdistää välikorvan nenänieluun ja ylläpitää välikorvan terveyttä. Korvatorven vajaatoiminta (obstructive Eustachian tube dysfunction, OETD) on seurausta riittämättömästä korvatorven avautumisesta. OETD:n aiheuttamat oireet ovat kuitenkin epäspesifejä, joten korvatorven toiminnan mittaaminen on tarpeellista. Yksi objektiivisimmista testeistä korvatorven avautumisen tutkimiseen on tubomanometria (tubomanometry, TMM). TMM:n on osoitettu olevan riittävän spesifinen ja sensitiivinen käytettäväksi OETD:n diagnostiikassa. Kuitenkaan tietoa mittauksien teknisestä onnistumisesta ja tuloksiin vaikuttavista tekijöistä ei juurikaan ole. Luotettavalla diagnoosilla on nykyään suuri merkitys, kun OETD:n hoitoon on olemassa kirurginen hoitovaihtoehto, korvatorven pallolaajennus (balloon Eustachian tuboplasty, BET). BET on tutkimuksissa osoittautunut tehokkaaksi ja turvalliseksi. Lisää tutkimusta BET:n käytöstä eri potilasryhmien hoidossa kuitenkin tarvitaan.

Tutkimme TMM:n käyttöä OETD:n diagnostiikassa arvioimalla mittauksien teknistä onnistumista Helsingin yliopistollisessa keskussairaalassa tutkituilla potilailla (2016-2020). Kliinistä käyttöä varten mittauksien todettiin onnistuvan riittävän usein (91 %). Selvitimme TMM:n tuloksiin vaikuttavia tekijöitä, joista ainoastaan siitepölyallergialla todettiin olevan vaikutusta. Tutkimme myös BET:n tehoa ja turvallisuutta eri potilasryhmissä: lapset, vain paineentasausongelmista kärsivät potilaat, OETD-potilaat ja BET:n ollessa osa muuta korvakirurgiaa. Potilasaineisto kerättiin retrospektiivisesti Turun (2013-2016) ja Helsingin (2011-2020) yliopistollisista keskussairaaloista. Kyselytutkimuksien perusteella oireet vähenivät pitkäaikaisesti kaikissa näissä ryhmissä. Merkittäviä haittavaikutuksia ei todettu. Systemaattisessa kirjallisuuskatsauksessa todettiin paineentasausongelmia selvittävien tutkimuksien olevan heterogeenisiä, pieniä aineistokooltaan ja niissä raportoitiin parantumista vaihtelevin mittarein.

Yhteenvetona voidaan todeta, että TMM vaikuttaa olevan luotettava ja käyttökelpoinen testi OETD-potilailla. Tuloksemme BET:sta täydentävät jo olemassa olevia tutkimuksia, joiden perusteella BET vaikuttaa tehokkaalta ja turvalliselta eri ryhmien hoidossa.

AVAINSANAT: korvatorvi, korvatorven obstruktiivinen vajaatoiminta, tubomanometria, korvatorven pallolaajennus

Table of Contents

Abbreviations

BET	Balloon Eustachian tuboplasty (Eustachian tube balloon dilation)
BMI	Body mass index
CI	Confidence interval
CT	Computed tomography
ET	Eustachian tube
ETD	Eustachian tube dysfunction
ETDQ-7	7-item Eustachian tube dysfunction questionnaire
ETS	Eustachian tube score
ETS-7	7-item Eustachian tube score
IQR	Interquartile range
ME	Middle ear
OETD	Functional obstructive Eustachian tube dysfunction
OME	Otitis media with effusion
OR	Odds ratio
P-value	Probability value
R-value	Tubomanometry value indicating opening latency of Eustachian tube
SD	Standard deviation
TM	Tympanic membrane
TMM	Tubomanometry
ρ	Spearman's rank correlation coefficient

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Lindfors OH, Oehlandt H, Sinkkonen ST. Tubomanometry Measurement Success Rate in Clinical Practice. *Otology & Neurotology*, 2021; 42(5):e552-e558.

II Oehlandt H, Lindfors O, Sinkkonen ST. Tubomanometry correlations with patient characteristics and other diagnostic tests of Eustachian tube dysfunction: a cohort study of 432 ears. *European Archives of Oto-Rhino-Laryngology*, 2022; 279(11):5153-5160.

III Oehlandt H, Pulkkinen J, Haavisto L. Balloon Dilation of the Eustachian Tube in Chronic Eustachian Tube Dysfunction: A Retrospective Study of 107 Patients. *Journal of International Advanced Otology*, 2022;18(6):495-500.

IV Oehlandt H, Laakso J, Lindfors O, Toivonen J, Poe D, Sinkkonen ST. Efficacy of Balloon Tuboplasty for Baro-Challenge-Induced Eustachian Tube Dysfunction: A Systematic Review and a Retrospective Cohort Study of 39 Patients. *Otology & Neurotology*, 2022; 43(6):611-618.

1 Introduction

The Eustachian tube (ET) is a tubular structure connecting the middle ear (ME) to the nasopharynx. Its anatomy was first described in detail in 1562 by Bartolomeus Eustachius. The ET's main functions are to equalize the pressure of the ME, clear secretions from the ME, and protect the ME from nasopharyngeal sounds and pathogens (Schilder, et al., 2015). Failure of these functions is known as Eustachian tube dysfunction (ETD). Functional obstructive ETD (OETD) is a result of insufficient ET opening and causes symptoms such as aural fullness, 'popping', and discomfort (Schilder, et al., 2015). As the ET has a vital role in ME health, OETD can contribute to chronic ME diseases such as otitis media with effusion (OME), perforation of the tympanic membrane (TM), and cholesteatoma (Seibert & Danner, 2006). Baro-challenge-induced ETD means insufficient ME pressure equalization in situations where ambient pressure changes rapidly (Schilder, et al., 2015). It typically causes symptoms similar to OETD but which occur mainly during a sudden change in ambient pressure. The prevalence of OETD in adults has been estimated to be between 1% and 5% (Browning & Gatehouse, 1992; Shan, et al., 2019), which translates to 34,000–170,000 OETD patients over the age of 15 years in Finland. For comparison, 130,000 patients over the age of 15 years were entitled to asthma reimbursement in Finland in 2013 (Kankaanranta, et al., 2017).

OETD patients typically have symptoms that negatively impact their quality of life (Teklu, et al., 2020) but which are unspecific, requiring ET function measurements (Tucci, et al., 2019). Of the many tests currently in use, no single test has proven to be superior (Smith, Takwoingi, et al., 2018; Tucci, et al., 2019). Tubomanometry (TMM) was first described by Esteve in 2001 (Esteve, et al., 2001). Since then it has demonstrated relatively high sensitivity and specificity for OETD (Schröder, Lehmann, Korbmacher, et al., 2015; Liu, et al., 2016; Smith, Cochrane, et al., 2018; Smith, Takwoingi, et al., 2018). It aims to detect the ET opening with different predefined nasopharyngeal pressures. The technical success rate of TMM has not been studied prior to this dissertation project. Data on possible patients' characteristics affecting TMM results are also limited, consisting of one study on dust-mite allergic rhinitis and another on nasal septum deviation, both found to have an association with poorer TMM results (Ma, et al., 2020; Lima, et al., 2022).

Balloon Eustachian tuboplasty (BET) has been used since 2010 to treat OETD patients (Ockermann, et al., 2010a). In Finland, on average 236 BET operations were performed annually between 2013 and 2021 (THL, 2022). There are already several case series and four randomized controlled trials on the efficacy and safety of BET (Meyer, O'Malley, et al., 2018; Poe, et al., 2018; Froehlich, et al., 2020; Choi, et al., 2021; Krogshede, et al., 2022). Based on these studies, BET seems to be effective in the treatment of adult patients with OETD and adverse effects have been mild (Huisman, et al., 2018; Froehlich, et al., 2020). There are fewer published studies of BET in children, patients with chronic ME disease, and baro-challenge-induced ETD patients, although it is used in all of these patients (Tucci, et al., 2019; Saniasiaya, et al., 2022; Sandoval, et al., 2023). Most of the studies of BET are also short-term and currently there are only six studies reporting results from follow-ups longer than 2 years (Silvola, et al., 2014; Schröder, Lehmann, Ebmeyer, et al., 2015; Luukkainen, Vnencak, et al., 2018; Cutler, et al., 2019; McMurran, et al., 2020; Sandoval, et al., 2023).

This dissertation project aimed to evaluate TMM in clinical practice, its technical success, and possible patient characteristics affecting the results. This information would be useful in the interpretation of TMM results. Another aim was to evaluate the long-term efficacy and safety of BET in different patient groups.

2 Review of the Literature

2.1 Eustachian tube (ET)

2.1.1 Anatomy

The Eustachian tube (ET) is a functional structure connecting the middle ear (ME) to the nasopharynx (Figure 1). It consists of a proximal cartilaginous part and a distal bony part (Proctor, 1967). These two sections overlap in their narrowest part, called the junctional portion (Proctor, 1967; Sudo, et al., 1997). The narrowest point of the ET, the isthmus, is located in the cartilaginous part near this junction (Bluestone & Doyle, 1988; Sudo, et al., 1997). The total length of the ET in adults varies between 30 and 43 mm (Bluestone & Doyle, 1988; Takasaki, et al., 2007). From the nasopharynx, the ET points laterally and posterosuperially toward the ME (Proctor, 1967). In adults, the average angle of the ET axis to the horizontal plane is 36° and to the sagittal plane 42° (Prades, et al., 1998).

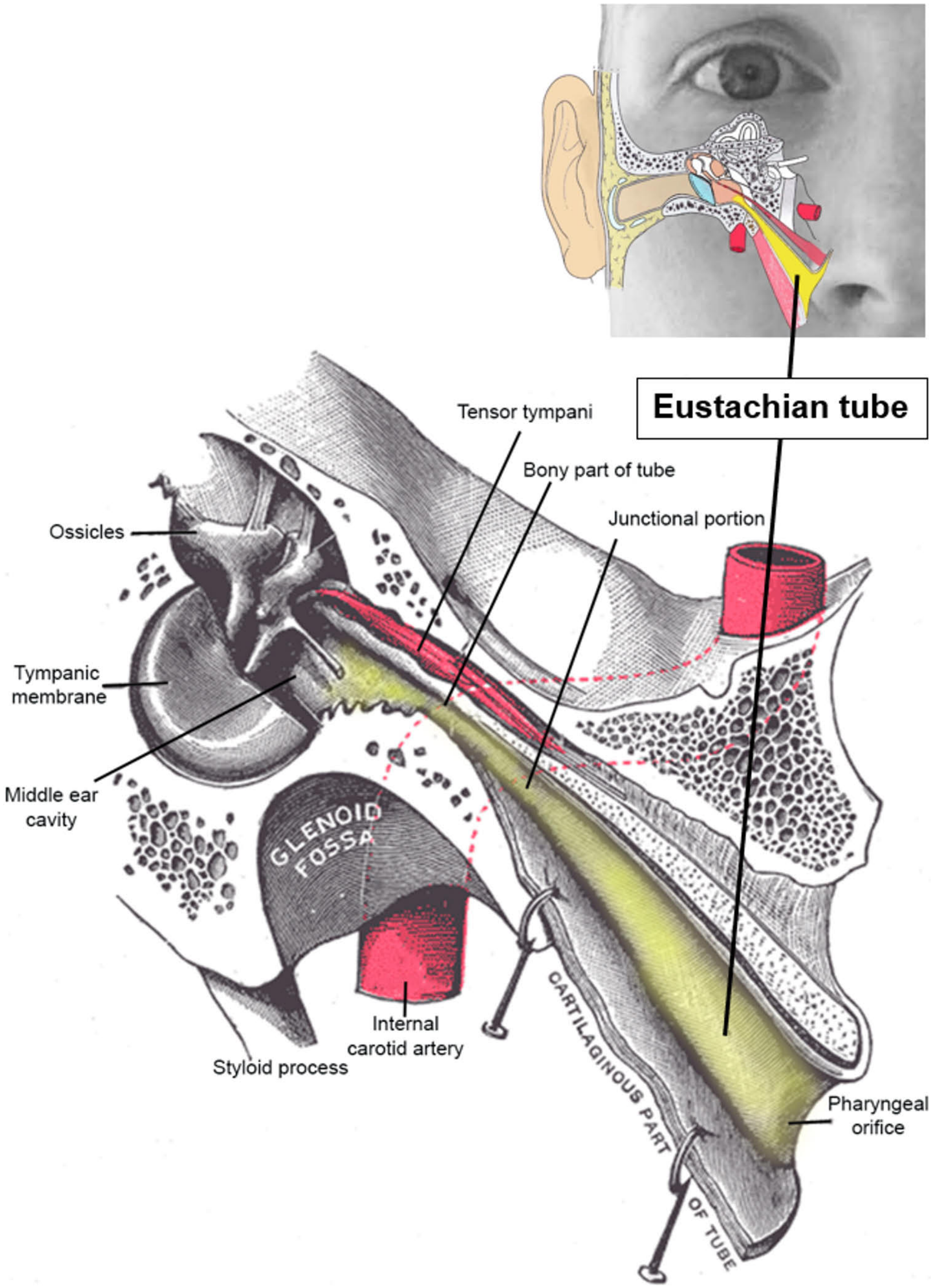


Figure 1. Location of the Eustachian tube (illustrated in yellow). Above: position in the head; below: cut along its long axis, right side. Image: Oehlandt H. and modifications from Gray, Anatomy of the Human Body, 1918 and Descouens D, Wikimedia Commons, 2009, licence: CC BY-SA 3.0.

2.1.1.1 Cartilaginous part of the ET

The length of the cartilaginous part of the ET is approximately 24 to 25 mm, even though the cartilage is longer (Proctor, 1967). Normally it is closed at rest (Bluestone & Doyle, 1988). It runs curved between the greater wing of the sphenoid bone and the petrous part of the temporal bone (Bluestone & Doyle, 1988). The cartilage forms the framework for the cartilaginous part of the ET, the medial lamina being considerably higher than the lateral lamina (Bluestone & Doyle, 1988). However, a broad variety of shapes have been found (Oshima, et al., 2008). In addition, accessory cartilage may be present (Proctor, 1967). The inferolateral part of the cartilaginous ET is formed by Ostmann's fat pad and the levator veli palatini muscle (Proctor, 1967). (Figure 2)

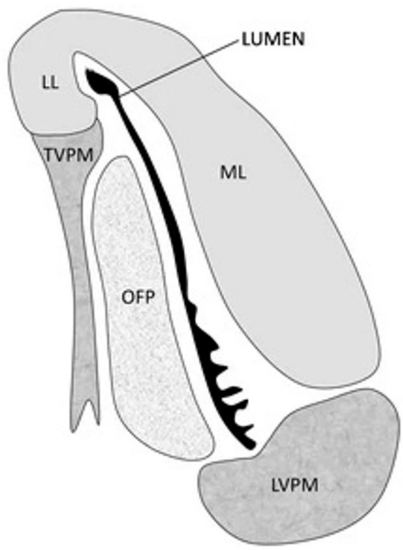


Figure 2. Cross section of the cartilaginous part of the ET, right side. Collapsed lumen shown in black. ML, medial lamina of the cartilage; LL, lateral lamina; OFP, Ostmann fat pad; TVPM, tensor veli palatini muscle; LVPM, levator veli palatini muscle. Image: Smith, et al., Imaging of the Eustachian tube and its function: a systematic review, 2016, licence: CC BY 4.0.

The cartilaginous part of the ET protrudes into the nasopharynx forming an elevation, the torus tubarius (Proctor, 1967). The torus tubarius is a mobile posterior cushion which, together with a smaller and immobile anterior lip, forms the orifice of the ET (Proctor, 1967). The orifice is located behind the inferior turbinate, above the palatine tonsil, and in front of the fossa Rosenmüller (Figure 3) (Bluestone & Doyle, 1988).

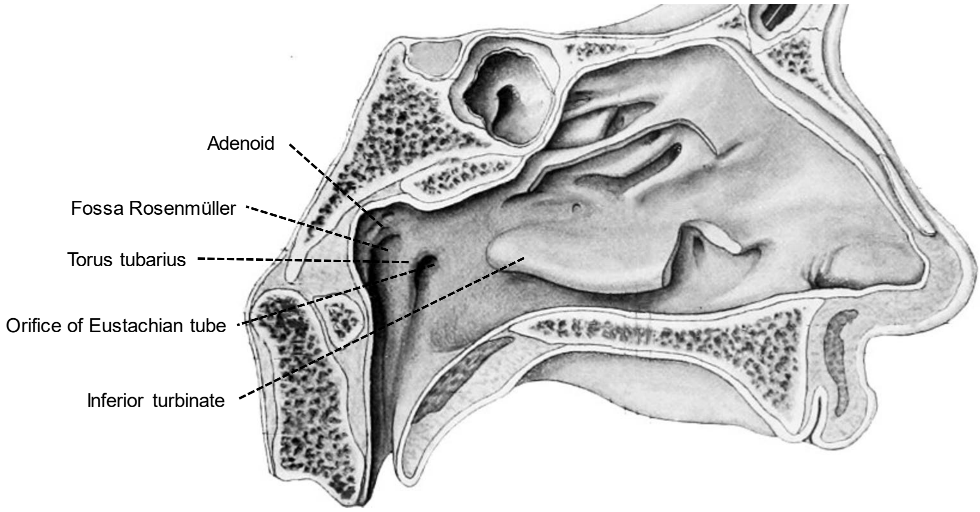


Figure 3. Location of the Eustachian tube orifice in the nasopharynx, left side. Image: modified from Schultze, et al., Atlas and text-book of topographic and applied anatomy, 1905.

The mucosa in the cartilaginous part consists of ciliated pseudostratified columnar epithelium containing both mucus and cilia cells (Martin, et al., 2017). The mucosa also contains lymphoid cells, mastocytes, and histiocytes, the number increasing toward the nasopharyngeal orifice (Martin, et al., 2017). The mucosa of the orifice is identical to the mucosa in the nasopharynx (Martin, et al., 2017).

2.1.1.2 Bony part of the ET

The bony part of the ET, also known as the protympanum, runs within the petrous part of the temporal bone and terminates in the anterior part of the attic (Proctor, 1967; Bluestone & Doyle, 1988). In adults, the average length is 11 mm (Djerić & Savić, 1985). The lumen of the bony part is triangular or quadrangular and is normally always open (Djerić & Savić, 1985; Bluestone & Doyle, 1988). Pneumatized petrous apex cells typically communicate directly with the bony part of the ET (Jen, et al., 2004). In this part, the mucosa consists of cylindrical-cuboidal epithelium containing little lymphoid infiltration (Martin, et al., 2017). The carotid artery is in close proximity to the bony part of the ET (Proctor, 1967). Arterial dehiscence may even be present adjacent to the ET (Abdel-Aziz, et al., 2014).

2.1.1.3 Muscles related to the ET

Four muscles are related to the ET: the tensor veli palatini, the levator veli palatini, the salpingopharyngeus, and the tensor tympani (Figure 4) (Bluestone & Doyle, 1988). The tensor veli palatini originates widely from the sphenoid bone and membranous wall of the ET (Rood & Doyle, 1978; Bluestone & Doyle, 1988). It runs under the pterygoid hamulus inserting into the soft palate (Proctor, 1967) and has two distinct bundles of muscles (Bluestone & Doyle, 1988). Part of the medial bundle, which originates from the tubal wall, is known as the dilator tubae (Rood & Doyle, 1978; Licameli, 2002) and is considered the main dilator of the ET (Alper, et al., 2012). When contracting, it pulls the lateral lamina inferolaterally, opening the cartilaginous part of the ET (Bluestone & Doyle, 1988). Tensor veli palatini is innervated by the mandibular nerve, a branch of the trigeminal nerve (Proctor, 1967).

The levator veli palatini originates from the petrous apex, runs posterolaterally to the cartilaginous part of the ET, and inserts into the soft palate (Sudo, et al., 1998). It has no direct origin from the ET and is only attached to it by loose connective tissue (Simkins, 1943). It constricts the soft palate and rotates the ET cartilage (Alper, et al., 2012). The levator veli palatini is innervated by the pharyngeal plexus formed by branches from the vagus nerve, glossopharyngeal nerve, and cervical sympathetic trunk (Proctor, 1967).

The salpingopharyngeal muscle originates from the inferior and medial aspects of the cartilaginous ET (Bluestone & Doyle, 1988). It runs downwards along with the palatopharyngeal muscle into the pharyngeal wall (Bluestone & Doyle, 1988; Licameli, 2002). It is poorly formed and seems to have an insignificant role in ET function (Bluestone & Doyle, 1988; Licameli, 2002).

The tensor tympani originates from the posterior part of the tensor veli palatini, mainly from the cartilaginous part of the ET (Bluestone & Doyle, 1988). It inserts into the malleus and does not seem to have a role in ET function (Bluestone & Doyle, 1988).

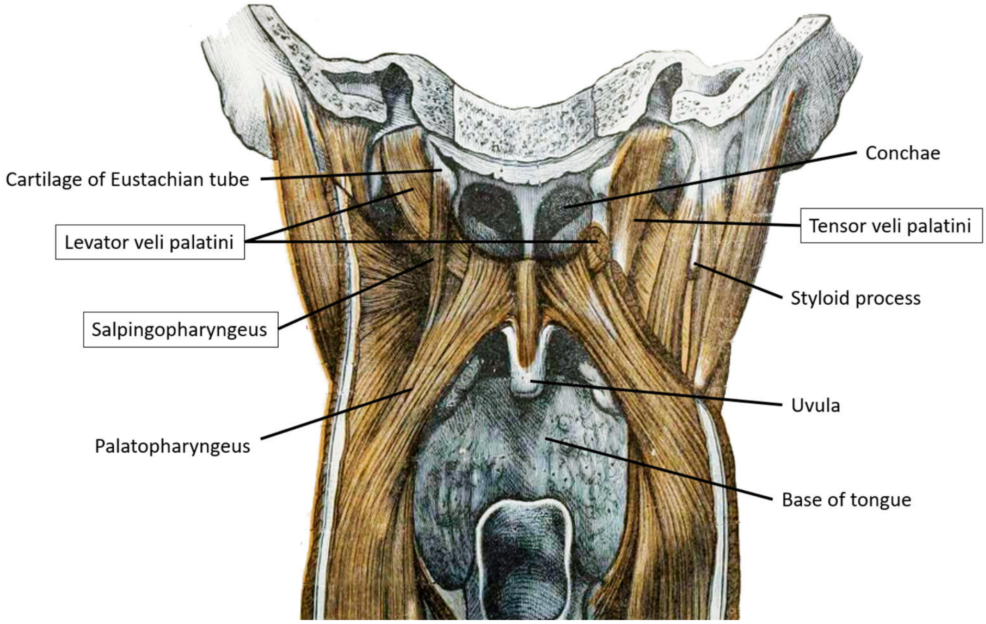


Figure 4. Muscles related to the Eustachian tube. Pharynx from behind with a median longitudinal incision. Image: modified from Told C., An atlas of human anatomy for students and physicians, 1919.

2.1.1.4 Special features in children

The ET in children is shorter and its orientation closer to horizontal (Ishijima, et al., 2000; Takasaki, et al., 2007). ET length in infants is around 21 mm, attaining almost full length by 7 years of age (Ishijima, et al., 2000). The lumen is also more circular and the isthmus may be underdeveloped (Oberascher & Grobovschek, 1987). Due to these morphological differences the relative position of the tensor veli palatini also differs, leading to a weaker muscular opening of the ET (Bylander, et al., 1983; Sadler-Kimes, et al., 1989). Young adolescents have a closely similar morphology to adults (Magro, et al., 2021).

2.1.2 Physiology

The ET has three known functions: to equalize pressure and ventilate the ME, drain secretions from the ME, and protect the ME from sounds, pathogens, and secretions from the nasopharynx (Bluestone, et al., 1972; Schilder, et al., 2015). These functions are involved in maintaining a healthy and aerated ME, which is essential for optimal sound transmission from the outer to the inner ear (Ars, et al., 2012).

2.1.2.1 Pressure equalization

The pressure in the ME fluctuates constantly (Martin, et al., 2017), for example due to changes in posture, hypo- or hyperventilation, or during sleep, which can alter the pressure notably (Hergils & Magnuson, 1985). The ME pressure balance is a complex system comprising gas exchange via passive pathways and active ET opening (Figure 5) (Alper, et al., 2011). Mastoid cells increase the volume of the ME and have a significant role in the pressure balance (Gaihede, et al., 2010; Alper, et al., 2011). The mucosa of the ME acts as a semipermeable membrane between the ME and blood vessels (Alper, et al., 2011). Normally, there is a constant exchange of gas: oxygen and nitrogen pass out of the ME and carbon dioxide and water into it (Martin, et al., 2017). Oxygen and carbon dioxide transfers are fast while nitrogen transfer is slow (Martin, et al., 2017). Partial pressures of oxygen and carbon dioxide quickly reach a steady state in the mucosa, whereas the nitrogen gradient is constant (Hergils & Magnuson, 1990). This nitrogen gradient and slow transfer of nitrogen between the ME and blood vessels slowly lead to negative ME pressure (Ars, et al., 2012; Csakanyi, et al., 2014). The capillary perfusion and thickness of the mucosa can vary and thus regulate gas exchange and pressure (Magnuson, 2003; Martin, et al., 2017). An inflammatory process increases vascularization of the mucosa, resulting in increased gas flow away from the ME and greater negative pressure in the ME (Ars, et al., 2012).

The TM has some ability to buffer pressure changes by deforming inwards or outwards, altering the size of the ME cavity (Padurariu, et al., 2016). There is also a limited diffusion of gases, mostly carbon dioxide, through the TM (Yuksel, et al., 2009). Limited gas exchange also occurs through the round window (Alper, et al., 2011).

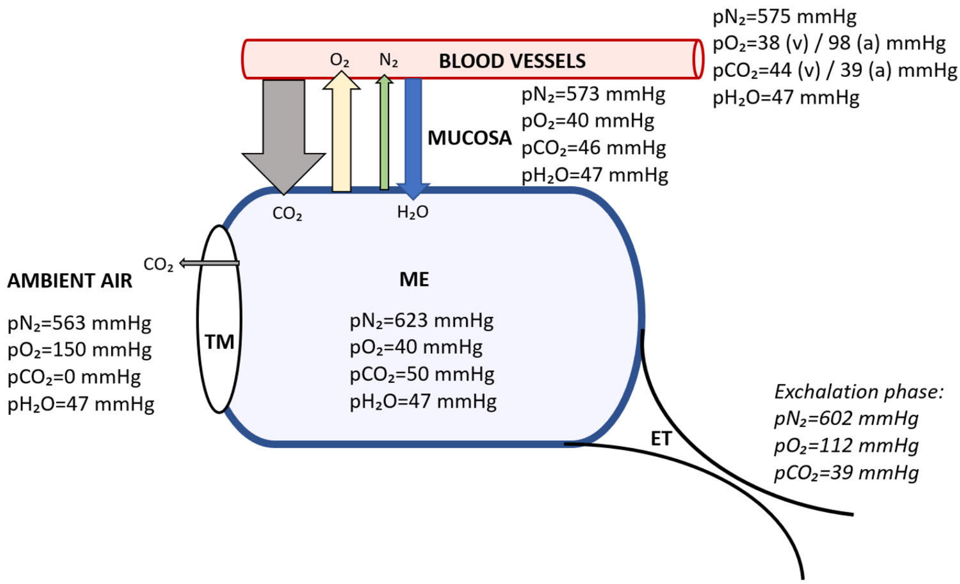


Figure 5. Illustration of middle ear gas exchange. Partial pressures of oxygen (O_2), carbon dioxide (CO_2), nitrogen (N_2), and water vapour (H_2O). Arrows indicate the direction and approximate speed difference of gas transfer. ET, Eustachian tube; ME, middle ear; TM, tympanic membrane; Vessels: a, artery; v, vein. Image: Oehlandt H. Information from Hergils & Magnuson, 1998; Ars, et al., 2012; Csakanyi, et al., 2014.

The ET plays the most prominent role in rapid changes in ambient pressure, allowing rapid transfer of a gas bolus (Martin, et al., 2017). The ET needs to open periodically to equalize negative ME pressure caused by the aforementioned nitrogen gradient (Pau, et al., 2009; Ars, et al., 2012; Csakanyi, et al., 2014). ET is normally closed at rest and opens by active muscle contraction, which allows gas exchange between the ME and the nasopharynx (Bluestone & Doyle, 1988). Typically, actions such as swallowing, yawning, and yaw movements open the ET (Bluestone & Doyle, 1988), but not every time a person swallows (Mondain, et al., 1997). The ET can be opened more forcefully with techniques to increase pressure in the nasopharynx, such as the Valsalva manoeuvre (Bluestone & Doyle, 1988). Video endoscopy of the ET has shown that opening usually occurs in consecutive order: 1) the palate elevates, which causes passive and active rotation of the medial cartilaginous lamina, 2) the lateral pharyngeal wall excurses laterally, 3) the lumen dilates, caused primarily by tensor veli palatini muscle movement beginning distally and inferiorly, then opening proximally and superiorly, and 4) the tubal valve at the isthmus opens as a result of dilator tubae muscle contraction (Poe, et al., 2000). Normally ET closure occurs in the reverse order, but stages one and two can take place simultaneously or in variable order (Poe, et al., 2000). On average, the ET opens every 41 s in healthy adults (Mondain, et al., 1997). The duration of an individual's ET opening is constant, thus multiple consecutive openings may be needed for sufficient pressure equalization (Gaihede, et al., 2013). The mean opening time is 0.34–0.43 s (Mondain, et al., 1997; Gaihede, et al., 2013). The gas transferring to the nasopharynx is expiratory, as 80% of swallowing occurs during the exhalation phase (Hergils & Magnuson, 1998). As a result, it contains a higher level of carbon dioxide and nitrogen and less oxygen than in ambient air (Hergils & Magnuson, 1998). The pressure gradient needed to open the ET is constant in healthy subjects but varies between individuals (Martin, et al., 2017).

ME pressure equalization and ET opening depend on a reflex mechanism (Martin, et al., 2017). The ME, TM, and nasopharynx contain mechanoreceptors and the ME also has chemoreceptors (Shupak, et al., 1996; Salburgo, et al., 2016; Songu, et al., 2019). From these originate the afferent system. The afferent pathway continues as the tympanic plexus to the ipsilateral respiratory subnuclei of the nucleus of the solitary tract (Eden & Gannon, 1987). From there it continues to the cerebellum (Sami, et al., 2009) and cortex (Job, et al., 2011). The efferent pathway forms a neural system innervating the muscles of the ET and the autonomous nervous system related to the ME capillaries (Martin, et al., 2017). The motoneurons of the efferent system have been observed in the ipsilateral trigeminal motor nucleus and nucleus ambiguus (Eden & Gannon, 1987). The trigeminal motor nucleus contains nerves that innervate the tensor veli palatini and tensor tympani and the nucleus ambiguus innervates the levator veli palatini (Eden & Gannon, 1987).

2.1.2.2 Secretion drainage

There are three ways to clear fluids from the ME: muscular pumping action through the ET, mucociliary transport via the ET, and absorption into blood vessels through the ME mucosa (Honjo, et al., 1985; Li, et al., 2005). A large volume of fluids is drained by muscular action and active ET opening (Honjo, et al., 1985). Its effectiveness is dependent on the viscosity of the fluid, as muscular action mainly drains fluids with low viscosity (Honjo, et al., 1985). Ciliary cells continually transport mucus towards the nasopharynx (Honjo, et al., 1985). These cells are mainly situated in the anteroinferior part of the ME and the inferomedial wall of the ET (Martin, et al., 2017). The transport velocity depends on the location of the ciliary cell and possible underlying ear pathology; even a 1.5 mm-per-second velocity has been measured (Sadé, 1967). A study of healthy ears found three main ciliary pathways, and on average it took 7 minutes for the dye to reach the nasopharyngeal orifice of the ET from the mucosa of the promontory (Ilomäki, et al., 2016). Absorption through the mucosa involves osmosis and active Na^+ transport (Li, et al., 2005; Petrova, et al., 2007). The absorption rate depends on the osmotic pressure and amount of the liquid (Petrova, et al., 2007).

2.1.2.3 ME protection

A closed ET protects the ME from endogenous sounds such as a person's own voice and sounds originating from the pharyngeal muscles (Martin, et al., 2017). The ET also prevents reflux from the nasopharynx into the ME. Several factors contribute to reflux such as mechanical features like length, angle, and compliance of the ET (Bluestone & Doyle, 1988). For these reasons, children's anatomy (shorter and more horizontal ET) makes them more vulnerable than adults to otitis media with effusion (OME) (Bluestone & Doyle, 1988).

The ET also plays a part in immune defence. It is covered with a thick mucus layer and a thin serous layer containing immune components such as antimicrobial proteins, pathogen recognition receptors, and surfactant proteins (Abdel-Razek, et al., 2022). These form the first line of defence, the innate immune response (Abdel-Razek, et al., 2022). The adaptive immune response takes place in the mucosal-associated lymphoid tissue of Waldeyer's ring, which surrounds the orifice of the ET (Abdel-Razek, et al., 2022). Mucosal-associated lymphoid tissue may also be found in the ET and ME, especially in the presence of OME (Kamimura, et al., 2001). The main component induced by the mucosal-associated lymphoid tissue is antigen-specific immunoglobulin A (Abdel-Razek, et al., 2022).

2.2 Eustachian tube dysfunction (ETD)

2.2.1 Definition

ETD means a failure in any of the ET's three known functions. In clinical practice, mainly the ventilation function is tested. An expert panel has agreed on three subtypes of ETD: dilatory ETD, baro-challenge-induced ETD, and patulous ETD. (Schilder, et al., 2015)

Dilatory ETD is a result of insufficient or absent ET opening and has three types: functional obstruction, dynamic dysfunction (muscular failure), and anatomical obstruction (Schilder, et al., 2015). Functional obstructive ETD is referred to here as obstructive ETD (OETD), as it is by far the most common form. Thus, in this dissertation OETD means insufficient or absent ET opening in the absence of specific muscular or anatomical reason. Based on the duration of symptoms, OETD can be either acute (less than 3 months) or chronic (more than 3 months). Baro-challenge-induced ETD symptoms and sequelae occur or initiate when ambient pressure changes rapidly. It is a result of insufficient pressure equalization between the ME and the changed ambient pressure. Patulous ETD means an abnormally patent ET. (Schilder, et al., 2015)

2.2.2 Dilatory ETD

2.2.2.1 Epidemiology

Dilatory ETD prevalence in adults has been estimated to be between 0.9% and 4.6% (Browning & Gatehouse, 1992; Shan, et al., 2019). Both studies used tympanometry as diagnostic criteria (ME pressure less than -100 daPa or a flat tympanogram) with slight variations in additional criteria (Browning & Gatehouse, 1992; Shan, et al., 2019). The prevalence of ETDQ-7 scores higher than 14 was 42% in a study of the Saudi Arabian population aged above 10 years (Alshehri, et al., 2020). This result presents a surprisingly high incidence of ear symptoms but cannot be used as a prevalence of dilatory ETD. The prevalence of dilatory ETD in the elderly population is estimated to be 5.4% (Fischer, et al., 2020). In adolescents, it is estimated to be 3.7% in those aged 16 to 19 years and 5.0% in those aged 12 to 15 years (Kim, et al., 2020). In addition, OME is a frequent childhood disease affecting 50% to 90% of children by the age of five (Rosenfeld, et al., 2016). The point prevalence of OME in children is estimated to be between 7% and 13% with emphasis on the youngest (Rosenfeld, et al., 2016). The visits annually related to ETD, OME, or TM retraction have been approximately 2.0 million in adults and 2.6 million in children and adolescents (aged 0-20 years) in the United States (Vila, et al., 2017). The study revealed also that most visits are not related to concomitant infection (Vila, et al., 2017). Another study estimated that chronic ETD accounted for 11% of annual visits in adults related to ETD, OME, or TM retraction in the United States (McCoul, et al., 2019).

2.2.2.2 Aetiology

The causes and risk factors of dilatory ETD are variable from obvious anatomical obstruction to multifactorial issues. Most commonly, upper respiratory infection is related to OETD (Juszczak, et al., 2019). For anatomical reasons, dilatory ETD is more common in children and frequently leads to OME (Bluestone & Doyle, 1988).

In children, the main non-anatomical risk factors for OME are gastroesophageal reflux and allergies (Simon, et al., 2018). Nonetheless, there is no convincing evidence of causation or benefit of treatment (Simon, et al., 2018). Likewise in adults, an association between allergic rhinitis and OETD has been found in large studies (Lazo-Sáenz, et al., 2005; Juszczak, et al., 2019). In patients with chronic rhinosinusitis, OETD occurred in 47% of patients (Chen, et al., 2022). Another external risk factor is tobacco smoking, which has been linked to OETD in a few studies (Pezzoli, et al., 2017; Altalhi, et al., 2022). Tobacco smoke has also been found to relate to ME diseases in children (Adair-Bischoff & Sauve, 1998). A study has shown improvement in ET function in adults after significant weight loss from bariatric surgery (Eravci, et al., 2022). In children, obesity has been linked to OME in several studies (Jung, et al., 2019). Obstructive ET function has been shown with high frequency in patients with obstructive sleep apnoea, even in patients without visible nasopharyngeal abnormality (Magliulo, et al., 2018).

Dilatory ETD can also be a consequence of either a congenital or an acquired anatomical deformity. Adenoid enlargement is a well-known risk factor for OME, and the benefit of adenoidectomy has been shown in several studies (Mashat, et al., 2022). Improvement in ET function after adenoidectomy has also been shown in children with OME or adhesive TM as a sign of dilatory ETD (Manno, et al., 2021). However, routine adenoidectomy in young children with OME was not found useful compared to tympanostomy alone in a randomized controlled trial (Casselbrant, et al., 2009). In addition, children with dental overbites are more likely to have OETD (McDonnell, et al., 2001). In adults, nasal septum deviation has been found to cause OETD, and symptoms have been alleviated after septal surgery (Lima, et al., 2022). A common congenital malformation leading to dilatory ETD is a cleft palate due to abnormal anatomy of the tensor veli palatini (Heidsieck, et al., 2016; Kraus, et al., 2022). Congenital malformations associated with Down syndrome also lead to dilatory ETD (Shibahara & Sando, 1989).

Nasopharyngeal tumours, either benign or malignant, can cause dilatory ETD either by obstructing the ET or by destructing the significant muscles (Mills & Hathorn, 2016). In adult-onset OME, the prevalence of malignancy has been 4.7% (Glynn, et al., 2006). Furthermore, surgical resection of the tumour and radiotherapy can lead to dilatory ETD, and there seems to be a correlation between radiation dose and subsequent ETD (Redaelli de Zinis, et al., 2013; Akazawa, et al., 2018).

2.2.2.3 Symptoms and sequelae

The main symptoms of OETD are aural fullness, 'popping', and discomfort. Other symptoms include pressure and clogged sensations, sounds of cracking or ringing, otalgia, and hearing impairment. Patients may also have a need to repeatedly perform the Valsalva manoeuvre. (Schilder, et al., 2015) Hence, OETD decreases the quality of life and has been estimated to have similar health burden as gastroesophageal reflux disease or moderate asthma (Teklu, et al., 2020).

However, OETD symptoms are nonspecific. Similar symptoms may occur in patients with patulous ETD, Meniere's disease, temporomandibular disorders, migraine, superior semicircular canal dehiscence, sinus disease, and dental problems (Moshtaghi, et al., 2018; Smith, Cochrane, et al., 2018; Tucci, et al., 2019; Newman, et al., 2020).

ET has a vital role in ME physiology. Therefore, a common sequela of OETD is OME (Simon, et al., 2018). Negative ME pressure caused by OETD can also lead to TM retraction and atelectasis. This is believed to contribute to cholesteatoma formation. (Holt, 2003; Seibert & Danner, 2006; Ku, et al., 2022)

2.2.3 Baro-challenge-induced ETD

2.2.3.1 Epidemiology

Baro-challenge-induced ETD can be considered a milder form of OETD. Its estimated prevalence varies and its manifestation is related to flying and diving activities. Nonetheless, ME barotraumas are the most common problem related to diving and aviation (Taylor, et al., 2003; Lindfors, Ketola, et al., 2021). Most of the studies evaluating the incidence focused on a specific study population and may not be representative of the general population (Landolfi, et al., 2009; Tseng, et al., 2018; Lindfors, Ketola, et al., 2021). The estimated incidence of diving-related ME barotrauma varies widely and has been reported to be anywhere between 10% and 81% (Uzun, 2005; Tseng, et al., 2018; Lindfors, Räisänen-Sokolowski, Suvilehto, et al., 2021). Tseng et al. conducted a retrospective cohort review of 3608 navy recruits subjected to a pressure chamber test, 10% of whom were found to have ME barotrauma (Tseng, et al., 2018). In a prospective study of 31 scuba divers and a total of 774 dives, symptomatic ME barotrauma occurred in 45% of divers and 3% of dives (Uzun, 2005). In this study and a previous study from the same author, small mastoid cells were associated with ME barotraumas (Uzun, et al., 2002; Uzun, 2005). A survey study of professional and recreational divers by Lindfors et al. found that ME barotrauma had affected 81% of the 1881 responders (Lindfors, Räisänen-Sokolowski, Suvilehto, et al., 2021). Of those, 95% had symptoms sporadically or occasionally and 5% almost always or always (Lindfors, Räisänen-Sokolowski, Suvilehto, et al., 2021). Factors associated with ME barotrauma were unsuccessful Valsalva and Toynbee manoeuvres, female sex, and a high number of upper respiratory tract infections (Lindfors, Räisänen-Sokolowski, Suvilehto, et al., 2021). Inner-ear barotraumas are rare; however, the incidence has not been properly studied and it varies depending on diving conditions (Lindfors, Räisänen-Sokolowski, Hirvonen, et al., 2021).

A similar highly variable ME barotrauma incidence range has been reported in aviation (Lindfors, Ketola, et al., 2021). In a hypobaric chamber test, ME barotrauma occurred only in 2.4% of 335 Italian military pilots (Landolfi, et al., 2009). In a prospective study, 41% of airplane passengers reported pain during flight, and in 32% of them was it possible to identify barotraumas at otoscopy (Stangerup, et al., 2004). A survey study involving 44% of all commercial aircrew operating in Finland found that ME barotrauma had affected up to 85% of the 1789 responders, and 48% had been on sick leave because of it (Lindfors, Ketola, et al., 2021). Of those affected by ME barotrauma, 2.4% had symptoms on every or almost every flight (Lindfors, Ketola, et al., 2021). Upper tract respiratory infections and unsuccessful Valsalva and Toynbee manoeuvres were strongly associated with ME barotraumas (Lindfors, Ketola, et al., 2021). The progression of symptoms was inconsistent in commercial aircrew, as 18% felt they had less symptoms and 15% had more symptoms compared to earlier in their career (Lindfors, Ketola, et al., 2021). However, a similar study of divers found that symptoms decreased over time, as 38% had less symptoms and only 6% had more compared to earlier (Lindfors, Räisänen-Sokolowski, Suvilehto, et al., 2021). In both studies, progression was in connection with Valsalva manoeuvre performance (Lindfors, Ketola, et al., 2021; Lindfors, Räisänen-Sokolowski, Suvilehto, et al., 2021).

2.2.3.2 Symptoms and sequelae

Symptoms of baro-challenge-induced ETD such as aural fullness, 'popping', and otalgia resemble those of OETD but typically only occur when the ambient pressure fluctuates (Schilder, et al., 2015). Flying and diving, and the associated significant changes in ambient pressure, are typical reasons for symptoms of baro-challenge-induced ETD, but even the smaller fluctuations in a train or elevator can cause symptoms for some patients. Failure of pressure equalization can lead to barotrauma from mechanical damage due to a pressure gradient in accordance with Boyle's law (Lechner, et al., 2018). Barotraumas can occur in the ME or inner ear (Lechner, et al., 2018). ME barotraumas are more frequent and commonly presents as otalgia and hearing loss (Lechner, et al., 2018). The TM can show signs of barotrauma and occasionally perforation (O'Neill & Weitzner, 2015). Other manifestations are alternobaric vertigo and facial baroparesis (Molvaer & Eidsvik, 1987; Klingmann, et al., 2006).

Inner ear barotraumas include rupture of the oval or round window (Rozycki, et al., 2018). These perilymphatic fistulas can be caused by two mechanisms: In the first, an external rise in pressure pushes the TM inwards and then the stapes into the oval window, raising the pressure in the cochlea. The pressure is amplified if an unsuccessful and forceful Valsalva manoeuvre raises the intracranial pressure, further impacting the cochlea and possibly leading to rupture of the round window. In the second mechanism, the ET opens after a forceful and successful Valsalva manoeuvre raising the ME pressure quickly and causing the TM and the bones attached to it to move outward. This causes negative pressure on the cochlea and may lead to rupture of the oval window, round window, or internal membrane of the cochlea. (Rozycki, et al., 2018) Symptoms include hearing loss, tinnitus, nausea, vomiting, vertigo, and nystagmus (Rozycki, et al., 2018; Lechner, et al., 2018). In severe cases, baro-challenge-induced ETD may cause hazardous situations for divers and pilots (Klokker & Vesterhauge, 2005; Lechner, et al., 2018).

2.2.4 Patulous ETD

Patulous ETD results from an abnormally patent ET and can thus be considered the opposite of OETD (Schilder, et al., 2015). Despite the different pathophysiology, many symptoms resemble those of OETD, such as aural fullness, tinnitus, and cracking sounds (Ward, et al., 2017). However, in patulous ETD, autophony and voice distortion play a greater role in patient discomfort (Ward, et al., 2017). The prevalence of patulous ET is less studied; in a study of 97% of the Korean population estimated from the Korean health database, the prevalence was around 0.01% (Choi, et al., 2018). Female sex is associated with a higher prevalence (Ward, et al., 2017; Choi, et al., 2018). Weight loss, mucosal atrophy, pregnancy, neurological disorders and muscular dysfunction, radiotherapy, and surgical complications are some known risk factors for patulous ETD (Shambaugh, 1938; Pulec & Simonton, 1964; Plate, et al., 1979; Young, et al., 1997; Ward, et al., 2017). A classic sign of patulous ET is synchronous TM movement with nasal breathing, visible on otomicroscopy (Schilder, et al., 2015). TM movements may, however, be absent, especially in a supine position (Ward, et al., 2017). Otherwise, most patients have no abnormal findings on otomicroscopy (Ward, et al., 2017). However, TM retraction and even OME may be present (Ward, et al., 2017). These findings result from habitual sniffing, a mechanism that patients have developed to alleviate their symptoms (Ikeda, et al., 2011). This sniffing habit creates negative pressure on the ME and may lead to other ME diseases such as TM retraction, OME, and even cholesteatoma (Ohta, et al., 2009; Ikeda, et al., 2011).

2.3 Diagnosis

As stated above, OETD symptoms are nonspecific, posing a clear need for ET function tests. Currently, there is no gold standard test for OETD and expert recommendations differ on the best protocol (Table 1) (Schilder, et al., 2015; Smith, Takwoingi, et al., 2018; Tucci, et al., 2019; Plaza, et al., 2020). All recommendations emphasize the need for a thorough clinical history of patients.

In baro-challenge-induced ETD patients, clinical signs and findings are typically absent in normobaric situations (Schilder, et al., 2015). For these patients, no single test can be recommended for clinical use (Tailor, et al., 2018).

Table 1. Recommended test protocols in addition to clinical history for use in the diagnosis of OETD or for preoperative to BET.

TUCCI 2019	SMITH 2018	PLAZA 2020
Otolaryngological examination	Otolaryngological examination	ETDQ-7
Nasal endoscopy	Tympanometry (if ME pressure lower than -50 daPa no further testing required)	Otoscopy/otomicroscopy including Valsalva and Toynbee manoeuvres
Audiometry	Tubomanometry and/or sonotubometry (Valsalva manoeuvre if those are not available)	Tympanometry
Tympanometry		Audiometry
		Nasal endoscopy
		Tubomanometry and CT optional

2.3.1 Eustachian Tube Dysfunction Questionnaire (ETDQ-7)

ETDQ-7, a survey designed for OETD diagnostics, assesses the severity of OETD symptoms and measures the treatment response (McCoul, Anand & Christos, 2012). The questionnaire contains seven questions regarding OETD-related ear symptoms (Table 2), the severity of which patients are asked to grade over the past month (McCoul, Anand & Christos, 2012). The ETDQ-7 results vary from 7 to 49 points. A total score of 14.5 has been used as a cut-off, which had preliminary exceptional sensitivity and specificity to OETD (McCoul, Anand & Christos, 2012) The ETDQ-7 has been translated and validated in several languages (Andresen, et al., 2021), including Finnish, although the latter has not been validated. Despite good discrimination results in early studies, recent studies implicate a poor value of ETDQ-7 as a diagnostic tool (Andresen, et al., 2021). ETDQ-7 was unable to differentiate between patients with OETD and patulous ETD (Van Roeyen, et al., 2015). Among studies in which ETDQ-7 was administered before objective ET testing, the specificity varied between 24% and 89% and the sensitivity between 37% and 80% (Smith, Takwoingi, et al., 2018; Teixeira, et al., 2018; Herrera, et al., 2019; Moon, et al., 2022). In several studies, ETDQ-7 results have improved after BET (Froehlich, et al., 2020), suggesting its significance as a patient-reported outcome measure.

Table 2. Questions in the ETDQ-7 (McCoul, Anand & Christos, 2012)

PRESSURE IN THE EAR
PAIN IN THE EAR
FEELING THAT THE EAR IS CLOGGED OR ’UNDER WATER’
EAR SYMPTOMS WHEN SUFFERING FROM A COLD OR SINUSITIS
CRACKLING OR POPPING SOUNDS IN THE EAR
RINGING IN THE EAR
A FEELING THAT HEARING IS MUFFLED

2.3.2 Otomicroscopy

Otomicroscopy or otoscopy is the foundation of ETD diagnostics. TM retraction and ME effusion are typical signs of OETD visible on otomicroscopy (Smith & Tysome, 2015). The use of pneumatic otoscopy can improve test accuracy. The sensitivity and specificity of pneumatic otoscopy for ME effusion were 94% and 81%, respectively (Shekelle, et al., 2002). Pneumatic otoscopy can also differentiate between adhesive and non-adhesive retraction (Tucci, et al., 2019). As discussed later, during otomicroscopy, results of the Valsalva and Toynbee manoeuvres can be objectively witnessed. In addition, otomicroscopy has a significant role in differential diagnostics. For example, TM movement with breathing may be observed, suggesting patulous ETD (Tucci, et al., 2019). However, otomicroscopy is an insensitive and indirect measure of the ET (Smith & Tysome, 2015).

2.3.3 Tympanometry

Tympanometry is a fast and objective method to test the status of the TM and ME. It measures the acoustic impedance of the ME, not the actual ET opening. Still, tympanometry has been used to test ET function for decades (Bluestone & Cantekin, 1981), and in a recent study it was evaluated to have the highest specificity for OETD (Smith, Takwoingi, et al., 2018). Unfortunately, tympanometry has poor sensitivity to OETD and must be followed by other ET tests (Smith, Takwoingi, et al., 2018).

Tympanometry results, tympanograms, are traditionally categorized into three types of curves based on shape (Jerger, 1970). The type A tympanogram is considered normal and has a sharp peak pressure near zero (between -100 daPa and +100 daPa). Type B has a flat line; fluid in the ME and TM perforation are typical reasons for this curve. Type C has a peak like type A but is shifted to negative (under -100 daPa), indicating negative pressure in the ME possibly resulting from ET dysfunction. Sniffing can also lead to negative intratympanic pressure (Falk, 1981).

The use of an unconventional lower tympanometric peak pressure cut-off may improve sensitivity (Parsel, et al., 2021).

2.3.4 Nine-step test

The nine-step inflation/deflation tympanometric test assesses ET function and can be used when the TM is intact and the ME dry (Bluestone, 1975). The test is performed by measuring the ME compliance after swallowing-triggered ET opening while varying positive and negative pressure applied to the ear canal (Bluestone, 1975). There are modifications to the test, some of which allow nonintact TM patients to be tested (Bluestone & Cantekin, 1981). Different pressures applied to the ear canal may lead to different results on ET opening (Seifert, et al., 1979). Dry swallowing has been found to be more effective than water swallowing (Adali & Uzun, 2005). In healthy adults, the detectable ET opening rate has varied between 81% and 94% (McBride, et al., 1988; Smith, Blythe, et al., 2017). The sensitivity and specificity for OETD vary depending on the applied ear canal pressure and the measured pressure change, but overall, the nine-step test is not considered a reliable diagnostic tool (Smith, Takwoingi, et al., 2018). However, it has been found to be a good predictor of ME barotrauma (Uzun, et al., 2000; Hussein & Abousetta, 2014). Thus, it may be the most useful test for baro-challenge-induced ETD (Tailor, et al., 2018).

2.3.5 Valsalva manoeuvre

The Valsalva manoeuvre is performed by exhaling with a closed mouth and pinched closed nostrils (Valsalva, 1704). The aim is to increase the pressure in the nasopharynx, which will forcefully open the ET. The manoeuvre tests non-physiological ET opening. The test is positive if the subject reports a sensation or sound, typically from TM movement. Objective assessment involves observing TM movement on otoscopy or otomicroscopy, or detection of a pressure change on tympanometry. The objective Valsalva manoeuvre has been shown to have specificity and sensitivity of over 60% for OETD and has been recommended for ET diagnosis, especially if special instrumentation is not available (Smith, Takwoingi, et al., 2018). Nonetheless, around 20% of healthy adults fail this test (Elner, et al., 1971; Swarts, et al., 2011; Smith, Blythe, et al., 2017). Success is dependable on the technique and achieved nasopharyngeal pressure (Swarts, et al., 2011; Smith, Blythe, et al., 2017). Pressure equalization has been found to be more effective in the sitting position compared to supine (Groth & Tjernström, 1980). Despite this, most studies have not reported patients' body posture during manoeuvres. Compared to other manoeuvres, such as Toynbee manoeuvre, the Valsalva manoeuvre is the most effective for opening the ET (Smith, Blythe, et al., 2017). In addition, poor success with the Valsalva manoeuvre has been associated with barotrauma during diving or flying (Lindfors, Ketola, et al., 2021; Lindfors, Räisänen-Sokolowski, Suvilehto, et al., 2021).

2.3.6 Toynbee manoeuvre

In the Toynbee manoeuvre, the subject swallows while pinching the nostrils closed (Toynbee, 1853). ET opening occurs due to decreased pressure in the nasopharynx and active pharyngeal muscle movement. As with the Valsalva manoeuvre, a positive Toynbee manoeuvre can be determined by either a subjective sensation or objective TM movement. In healthy adults, the ET opening rate is 73% to 83% with the Toynbee manoeuvre (Elner, et al., 1971; Finkelstein, et al., 1988; Smith, Blythe, et al., 2017). The objective Toynbee manoeuvre has been reported to have 74% sensitivity and only 54% specificity (Smith, Takwoingi, et al., 2018). Dry swallowing has been found more effective than wet (Smith, Blythe, et al., 2017). Like the Valsalva maoeuvre, a negative Toynbee manoeuvre has been linked to barotrauma when diving or flying (Lindfors, Ketola, et al., 2021; Lindfors, Räisänen-Sokolowski, Suvilehto, et al., 2021).

2.3.7 Nasal endoscopy

Nasal endoscopy has a substantial role in the clinical assessment of ETD patients. It can be used to evaluate the nasal cavity, ET orifice, and ET patency (Figure 6) (Di Martino, et al., 2005; Tucci, et al., 2019). Primarily, with nasal endoscopy, nasopharyngoscopy, or posterior rhinoscopy, anatomical obstruction such as malignancy causing OETD and OME may be identified (Tucci, et al., 2019). In addition, slow-motion video endoscopy has successfully been used to evaluate ET movements in patients with OME (Poe & Pyykkö, 2011). Secondly, nasal endoscopy provides information on the feasibility and accessibility of BET. This may be helpful when BET is indicated in deciding local vs. general anaesthesia and the need for additional septoplasty (Tucci, et al., 2019).

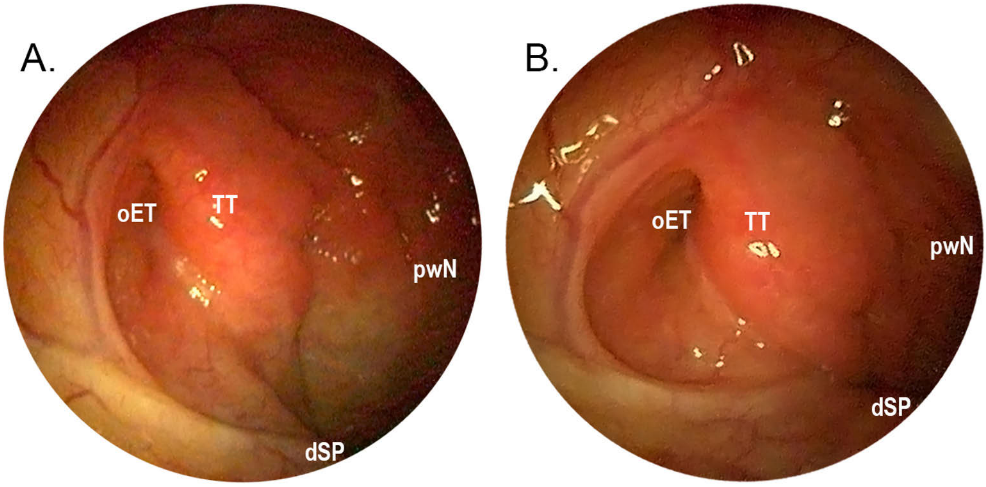


Figure 6. Endoscopic view of the Eustachian tube orifice (right side). **A**) Resting/closed position. **B**) Active/open position. dSP, dorsal soft palate; oET, orifice of Eustachian tube; pwN, posterior wall of the nasopharynx; TT, torus tubarius. Image: Oehlandt, H.

2.3.8 Tubomanometry (TMM)

2.3.8.1 Technique

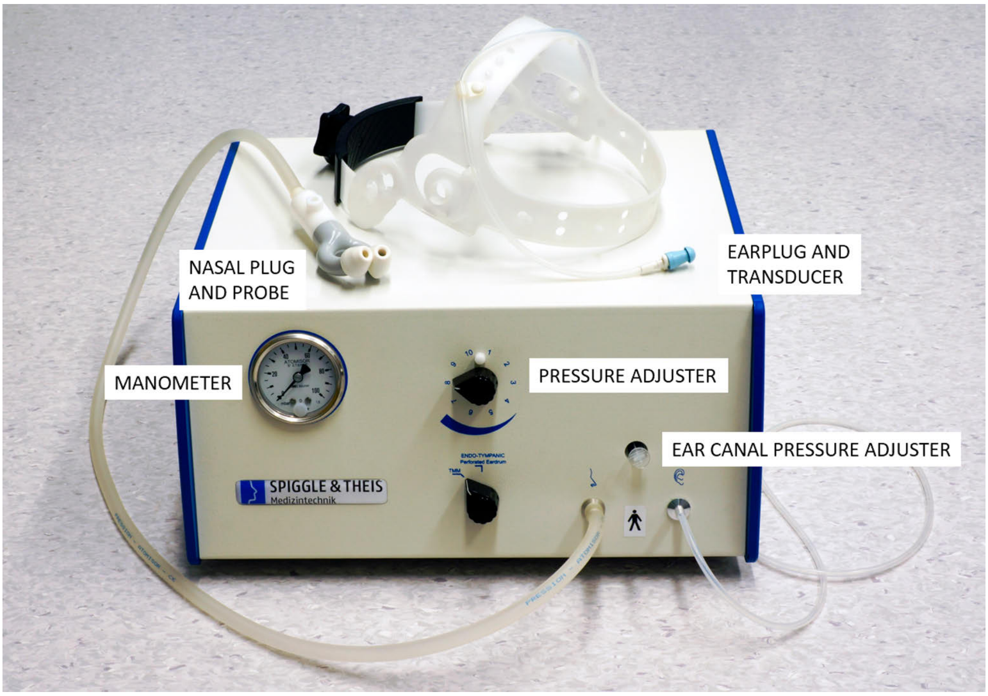


Figure 7. Tubomanometer (Spiggle & Theis, Overath, Germany). Image: Oehlandt H.

TMM was described by Esteve in 2001 (Esteve, et al., 2001). Its purpose is to objectively detect the ET opening at different nasopharyngeal pressures. The TMM device (Figure 7) delivers a defined pressure to the nasopharynx through a nasal probe. The subject is then asked to swallow, either dry or with a small amount of water, which closes the nasopharynx. If the ET opens during swallowing, the pressure change is transmitted to the ME, leading to deflection of the TM. The movement of the TM changes the pressure in the outer ear canal, which is registered by the ear transducer of the TMM device. (Esteve, 2003)

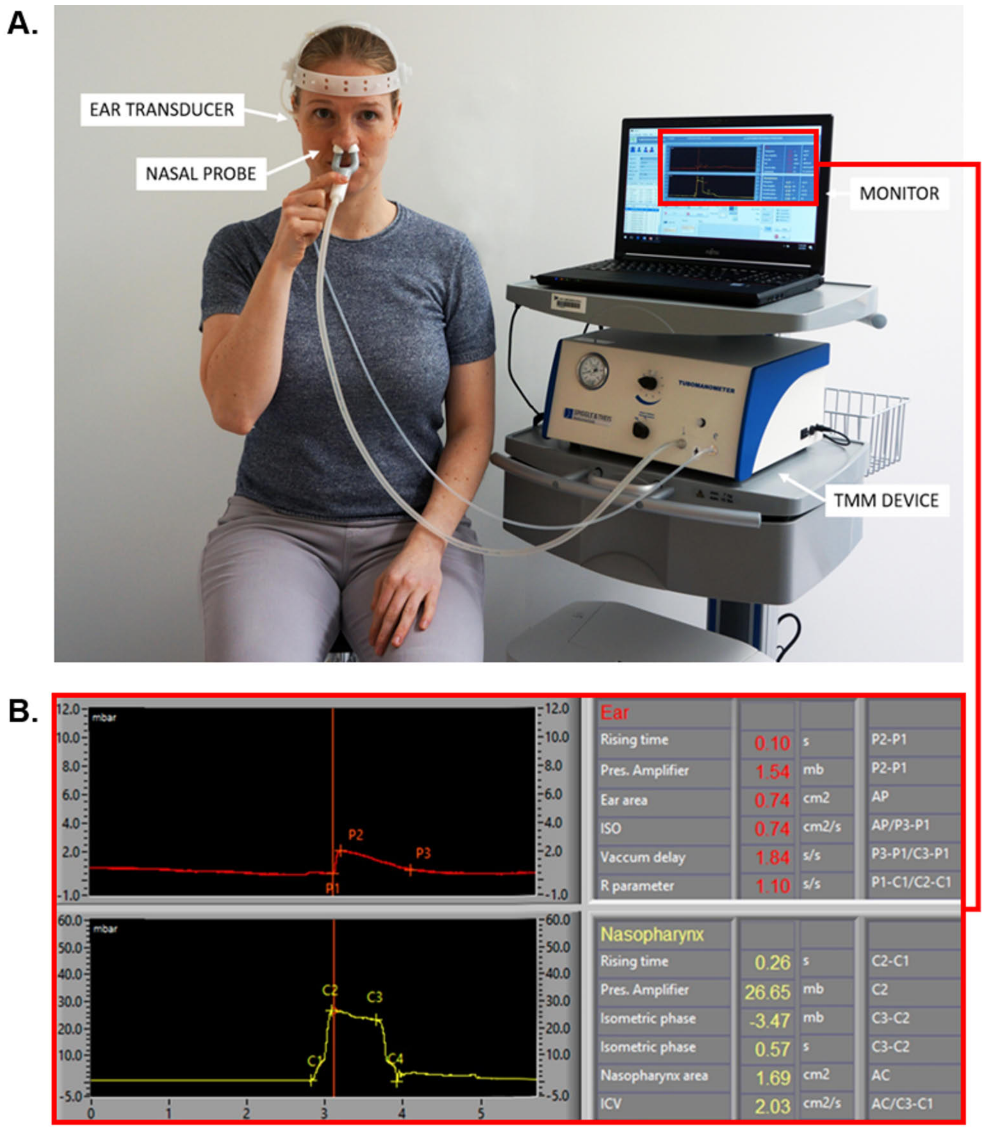
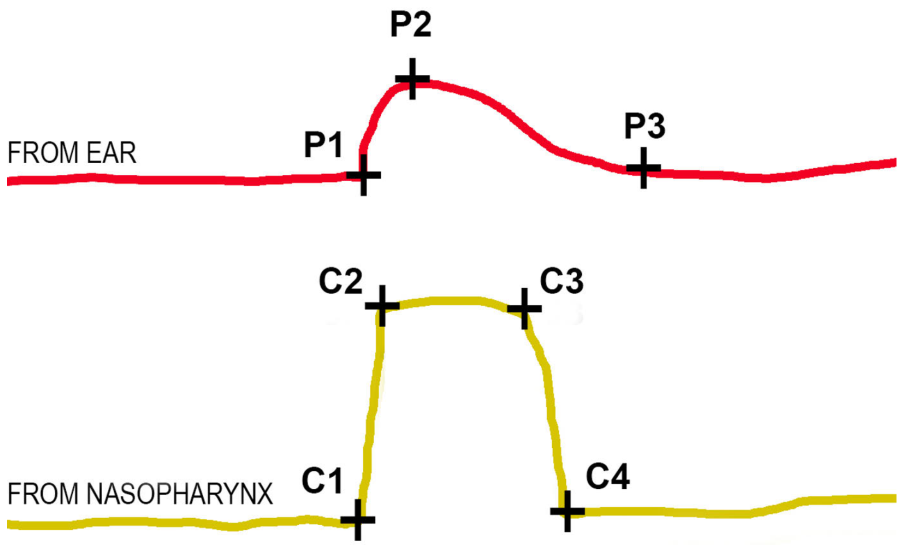


Figure 8. **A**) Performance of tubomanometry measurement. **B**) TMM measurement curves at 30 mbar. Image: Oehlandt H.

At the end of the test, the TMM device displays the pressure curves of the nasopharynx and outer ear canal (Figure 8). These curves display changes in the pressure, and the location points of changes are used in the analysis (Figure 9).



P1: Onset of pressure increase/ET opening point
P2: Achieved maximum pressure in the ear
P3: End of increased pressure
C1: Onset of swallow/pressure increase
C2: Achieved maximum pressure in nasopharynx
C3: End of maximum pressure/start of pressure decrease
C4: End of increased pressure/pressure returning to baseline

Figure 9. Pressure curves from the ear (above) and the nasopharynx (below) displaying the locations of the pressure changes. Image: Oehlandt H.

Using these values, the R-value is calculated (R = P1 – C1 / C2 – C1) reflecting the ET opening latency (Alper, et al., 2017). At R-value <1, the pressure change in the ear canal is detected before maximum pressure is reached in the nasopharynx and is considered normal. At R-value >1, the pressure changes in the ear canal after maximum pressure is reached in the nasopharynx and indicates restricted ET function. If no pressure change is detected in the ear canal, the ET is considered to be obstructed (Schröder, Lehmann, Korbmacher, et al., 2015). The usefulness of the other parameters received has not been studied (Alper, et al., 2017).

The pressure delivered to the nasopharynx can be widely adjusted on the TMM device. The minimum pressure at which a normally functioning ET should open has not been determined. Lower pressure has been found to have higher sensitivity and lower specificity for OETD compared to higher pressure and vice versa (Table 3) (Schröder, Lehmann, Korbmacher, et al., 2015; Liu et al., 2016; Smith, Takwoingi, et al., 2018). Typically, TMM is conducted with three pressures, 30 mbar, 40 mbar, and 50 mbar (Schröder, Lehmann, Korbmacher, et al., 2015; Alper, et al., 2017). A pressure of 20 mbar has also been evaluated but was found to have lower repeatability and opening detection rate in healthy adults (Smith, Zou, et al., 2017). Conversely, some patients struggle with high pressure (Smith, Zou, et al., 2017).

TMM measurements require patient cooperation. The process is generally well tolerated and causes only minor discomfort. TMM with three pressures takes approximately 8 minutes to complete (Smith, Takwoingi, et al., 2018). The measurement can be carried out with either an intact or perforated TM (Schröder, Lehmann, Korbmacher, et al., 2015). TMM has also successfully been used in children from the age of 5 years, but its significance in children requires further research (Jenckel, et al., 2015; Leichtle, et al., 2017). A recent study found TMM feasible for children aged 6 to 15 years and an R-value cut-off of 1.12 was recommended (Kuhlmann, et al., 2023).

Tubomanometers (Spiggle & Theis, Overath, Germany) have previously been available in Europe, the unit price in Finland being around €10,000 in 2017 (J. Oikarainen, Otoplug, personal communication, August 8, 2023). All parts, including ear and nasal plugs, are reusable. Currently, the device is unavailable in Europe because it has not yet been approved under the new European Union medical device regulation (J. Oikarainen, Otoplug, personal communication, August 8, 2023).

2.3.8.2 Sensitivity and specificity

TMM is a reasonably objective method and is suggested as the most reliable one for testing OETD (Smith, Takwoingi, et al., 2018). In healthy adults, the ET opening rate has been around 95% at 50 mbar pressure, with high repeatability (Schröder, Lehmann, Korbmacher, et al., 2015; Smith, Zou, et al., 2017; Ruan, et al., 2020). Sensitivity and specificity for OETD are generally high, varying in different studies and depending on the pressure used (Table 3). Measurement at all three pressures (30, 40, 50 mbar) is recommended to gain the most reliable result (Schröder, Lehmann, Korbmacher, et al., 2015). TMM can also be combined with other ET tests for better sensitivity and specificity.

Table 3. Sensitivity and specificity of tubomanometry for OETD diagnosis.

STUDY	SENSITIVITY	SPECIFICITY	STUDY SAMPLE
ESTEVE 2001	49%	93%	111 healthy ears compared to 109 ears with OME
SCHRÖDER, LEHMANN, KORBMACHER 2015			215 healthy subjects compared with 171 OETD patients (type B/C tympanogram and/or recurrent OME and/or negative Valsalva)
30 MBAR	82%	73%	
40 MBAR	80%	73%	
50 MBAR	74%	80%	
LIU 2016			60 healthy ears compared with 63 ears with OME
30 MBAR	68%	90%	
40 MBAR	62%	95%	
50 MBAR	53%	100%	
SMITH, TAKWOINGI 2018			116 patients with possible OETD. Diagnosis evaluated by a panel of experts.
30 MBAR	68%	60%	
40 MBAR	49%	70%	
50 MBAR	47%	72%	
SMITH, COCHRANE 2018	63%	79%	33 healthy subjects compared with 60 OETD patients (symptoms and pressure disequilibrium or tympanometry pressure < -100 daPa)

2.3.9 Sonotubometry

The principle of sonotubometry, which evaluates sound transmission through the ET, was introduced by Polizer in the 1860s (Virtanen, 1978). After further developement, the present-day procedure was described by Virtanen in 1978 (Virtanen, 1978). A sound source is inserted into the nostril and a microphone placed in the external ear canal. The patient is then advised to swallow. If this opens the ET, the increase in sound is recorded in the ear canal. (Virtanen, 1978) The advantage of sonotubometry is its ability to test ET function under physiological conditions without having to alter the pressure in the nasopharynx or ear canal. Measurement can be performed during dry or wet swallowing or, for example, during the Valsalva manouevre (Smith, Blythe, et al., 2017). In addition to infrequent ET opening, differences in amplitude and duration of opening have been found in impaired ears (Asenov, et al., 2010).

ET openings can be detected in approximately 90% of healthy adults (Van der Avoort, et al., 2005). However, the opening rate has varied in studies between 63% and 92% (Mondain, et al., 1997; Van der Avoort, et al., 2006). In one study, ET opening was detected in 88% of patients with OETD but in only 47% of all manoeuvres performed by them (Asenov, et al., 2010). The sensitivity was 56% and specificity 60% to OETD when a 5 dB increase was used as the cut-off (Smith, Takwoingi, et al., 2018). Sonotubometry is also feasible in children with slightly lower opening rates (Van der Avoort, et al., 2005).

2.3.10 Pressure chamber tests

A pressure chamber test for ET function was first described by Ingelsted (Ingelstedt, et al., 1967). Using a continuous impedance recording from the ME under hypo- and hyperbaric pressure allows dynamic evaluation of ET function (Meyer, et al., 2017). Both passive and active opening of the ET can be evaluated (Meyer, et al., 2017). In particular, a pressure chamber test may be useful in identifying patients with baro-challenge-induced ETD (Meyer, Korthäuer, et al., 2018). The pressure chamber test has even been suggested for use in the selection of flight personnel (Groth & Tjernström, 1984). Other testing methods have also been performed in connection with the pressure chamber test, such as sonotubometry (Swarts, et al., 2015). Pressure chamber tests are, however, expensive and time-consuming, precluding their use in routine diagnostics (Meyer, et al., 2017).

2.3.11 Eustachian tube score (ETS) and 7-item Eustachian tube score (ETS-7)

The ETS was first introduced as an outcome measure of BET in 2010 (Ockermann, et al., 2010a). Originally it included subjective Valsalva and Toynbee manoeuvres and the results of TMM at 30, 40, and 50 mbar pressure. The score was extended by adding the results of the objective Valsalva manoeuvre and tympanometry, creating the ETS-7 (Table 4) (Schröder, Lehmann, Sauzet, et al., 2015).

Table 4. 7-item Eustachian tube score (Schröder, Lehmann, Sauzet, et al., 2015)

TEST	2 POINTS	1 POINT	0 POINTS
ABILITY TO PERFORM VALSALVA MANOEUVRE	Always	Occasionally	Never
ABILITY TO PERFORM TOYNBEE MANOEUVRE	Always	Occasionally	Never
OBJECTIVE VALSALVA MANOEUVRE	Immediate	Weak/slow	Negative
TYMPANOMETRY	A	C	B
TUBOMANOMETRY AT 30 MBAR	R ≤ 1	R > 1	No R
TUBOMANOMETRY AT 40 MBAR	R ≤ 1	R > 1	No R
TUBOMANOMETRY AT 50 MBAR	R ≤ 1	R > 1	No R

Initially, using an ETS-7 score of 7 as a cut-off point for OETD, the sensitivity and specificity were found to be 96% (Schröder, Lehmann, Sauzet, et al., 2015). The study used ETDQ-7, tympanometry, and expert evaluation as comparisons (Schröder, Lehmann, Sauzet, et al., 2015). In another study by an expert panel, the ETS-7 sensitivity was 68% and specificity 47% for OETD (Smith, Takwoingi, et al., 2018).

2.3.12 Imaging

Computed tomography (CT) of the temporal bone is the most widely used imaging method in OETD patients (Smith & Tysome, 2015). CT and magnetic resonance imaging respectively allow the bony and soft anatomy of the ET to be assessed (Smith, et al., 2016). Suggestive signs of OETD on imaging are a narrower bony channel (Yoshida, et al., 2007) and a more horizontal angle of the ET (Tsai, et al., 2010). However, evaluation of ET function is not possible, and the usefulness of imaging is limited in routine diagnostics (Smith, et al., 2016). Imaging was also found to be inadequate for predicting intraoperative or postoperative complications (Abdel-Aziz, et al., 2014). For those reasons, recent consensus does not see imaging as a necessity before BET (Tucci, et al., 2019; Plaza, et al., 2020). Imaging is recommended if acute or previous temporal bone disease is suspected (Plaza, et al., 2020).

Other imaging modalities have been developed for ET function assessment but are currently mainly used in study settings (Smith, et al., 2016). For example, scintigraphy examines the mucociliary function and clearance of radioactive tracer from the ME (Paludetti, et al., 1992; Pöyhönen, et al., 2019); Valsalva CT allows visualization of the lumen (Tarabichi & Najmi, 2015); and optical coherence tomography produces high-resolution images of the lumen (Schuon, et al., 2019).

2.4 Treatment of OETD and baro-challenge-induced ETD

2.4.1 Conservative treatment

2.4.1.1 Medication

Intranasal corticosteroids, nasal decongestants, and antihistamines have commonly been used as initial treatment for OETD (Mehta, et al., 2022). A randomized, blinded, placebo-controlled study of intranasal corticosteroids including both adults and children with OME or type B or C tympanogram revealed no differences in subjective symptoms or tympanometry (Gluth, et al., 2011). Intranasal corticosteroids were also used as treatment in a control group of adult patients with OETD in three randomized controlled trials, with symptom improvement reported in 11% to 18% of patients (Meyer, O'Malley, et al., 2018; Poe, et al., 2018; Zeng, et al., 2019). Two of these studies aimed to assess the efficacy of BET (Meyer, O'Malley, et al., 2018; Poe, et al., 2018) and one looked at Buteyko breathing (Zeng, et al., 2019). A recent meta-analysis of intranasal corticosteroids found improvement in 50% of adult OETD patients, but the mean improvement in the ETDQ-7 score was less than one point from a mean pretreatment score of above 30 (Mehta, et al., 2022). This change was considered clinically insignificant (Mehta, et al., 2022). Thus, medical treatment is concluded to be ineffective for chronic OETD in adults (Mehta, et al., 2022). In addition, the latest clinical practice guideline states that intranasal corticosteroids and decongestants are strongly discouraged for treating OME in children (Rosenfeld, et al., 2016). In subacute symptoms, the benefit of medical treatment remains uncertain (Mehta, et al., 2022). Medical treatment may play a role in preventing or treating problems relating to baro-challenge-induced ETD (Lechner, et al., 2018).

2.4.1.2 Non-surgical therapies

Non-surgical treatments include therapies such as the Valsalva manoeuvre and Buteyko breathing, and mechanical devices such as a Politzer or N-300 (Mehta, et al., 2022). Evidence for these treatments is very limited, consisting of a few studies with small study samples, short follow-up time, and high risk of bias (Norman, et al., 2014; Mehta, et al., 2022). Despite the known association between an unsuccessful Valsalva manoeuvre and OETD, there is no high-quality evidence for the use of repeated Valsalva manoeuvres as a treatment method. One study recommends it as first-line treatment for adults with OME (Han, et al., 2019). The Buteyko breathing technique aims to reduce hyperventilation with periods of shallower breathing through the nose and breath holding (Zeng, et al., 2019). It was first developed for the treatment of asthma, but some studies have shown a possible effect in treating OETD patients (Zeng, et al., 2019). A Politzer device applies positive pressure to the nasopharynx during the act of swallowing. A study of 28 adult patients showed improvement on tympanometry (Silman & Arick, 1999). The Cochrane review concluded that although the evidence is limited, it is reasonable to consider Politzerization as a treatment option for children with OME (Perera, et al., 2013). The N-300 is a device creating mild negative pressure in the external ear canal; only one study found improvement in symptoms during a follow-up time of 1 week (Alpini & Mattei, 2009).

2.4.2 Surgical treatment

2.4.2.1 Myringotomy and tympanostomy

Myringotomy, with or without tympanostomy tube insertion, effectively alleviates OETD symptoms (Tucci, et al., 2019). If symptoms persist with an open tympanostomy tube, other diagnoses should be considered (Tucci, et al., 2019). However, tympanostomy provides only a temporary solution due to excursion of the tympanostomy tubes, and repeated surgery is often required (Monsell & Harley, 1996). On average, tubes extrude after 6 to 9 months (Monsell & Harley, 1996). Long-term tubes have been developed, but their use increases complication rates (Monsell & Harley, 1996). Complications of tympanostomy include otorrhea (17%), tympanosclerosis (32%), retraction pocket (3%), perforation (2% with short-term tubes and 17% with long-term tubes), and cholesteatoma (0.7%) (Kay, et al., 2001). Tympanostomy was not considered a necessity prior to BET by a recent expert panel (Tucci, et al., 2019), and in some patients, such as divers, it is an unsuitable treatment choice. In contrast, the Finnish Society of Ear Surgery has recommended tympanostomy prior to BET for patients with OETD or OME as a good predictor of the possible benefit of BET (Luukkainen, Kivekäs, et al., 2018). In some cases, tympanostomy may be beneficial to perform concomitantly with BET (Tucci, et al., 2019; Li, et al., 2021).

2.4.2.2 Laser tuboplasty

In laser ET tuboplasty, a laser is used to ablate the nasopharyngeal orifice of the ET, generally debulking the mucosa and submucosa of the posteromedial wall (Poe, et al., 2003; Miller, et al., 2017). Surgeries have been performed under general or local anaesthesia (Poe, et al., 2003; Kujawski & Poe, 2004; Sedlmaier, et al., 2009). In the literature, either carbon dioxide, a diode, or an argon laser has been used with either an endonasal or combined transoral approach (Poe, et al., 2003; Sedlmaier, et al., 2009). Evidence on laser tuboplasty is limited, as only case series have been published (Miller, et al., 2017; Jamil & Izzat, 2020). The patients in these studies were heterogeneous, including patients with OETD, OME, and baro-challenge-induced ETD (Miller, et al., 2017). A study of OME patients found resolution of effusion in 38% at 2-year follow-up (Poe, et al., 2007). In another study of patients with OME or TM atelectasis, otomicroscopic status was normal in 61% at 3-year follow-up (Kujawski & Poe, 2004). In one prospective study of OETD patients, subjective symptoms improved in 92% of treated patients (Yañez, 2010). Laser tuboplasty has also been used to treat baro-challenge-induced ETD patients, and in one study of divers, pressure equalization improved in all patients (9/9) and 78% (7/9) were able to dive again (Jumah, et al., 2013). In addition, some improvements have been reported in the Valsalva manoeuvre, tympanometry, and otomicroscopic findings (Miller, et al., 2017; Jamil & Izzat, 2020). A total complication rate of 4.4% was computed in a systematic review of laser tuboplasty, and complications were mainly minor (Miller, et al., 2017).

2.4.2.3 Balloon Eustachian tuboplasty (BET)

2.4.2.3.1 Technique

The first study of BET performed on adult patients was published in 2010 by Ockermann and colleagues (Ockermann, et al., 2010a). Since 2016, the U.S. Food and Drug Administration has granted approval to BET devices (FDA, 2016). Currently, only dilation of the cartilaginous part of the ET is conducted, as dilation of the bony part has been found to increase complication risks and has had no additional benefits (Miller & Elhassan, 2013).

BET is typically performed transnasally through either the ipsilateral or contralateral nasal cavity (Poe, Silvola & Pyykkö, 2011). Topical decongestion, such as xylometazoline, may be used for nasal cavities (Poe, Silvola & Pyykkö, 2011; Tisch, et al., 2013; Dalchow, et al., 2016). The orifice of the ET is visualized with a 30° to 45° nasoendoscope (Ockermann, et al., 2010a; Poe, Silvola & Pyykkö, 2011; Schröder, et al., 2013; Tisch, et al., 2013; Dalchow, et al., 2016). Under visual control, the applicator containing the balloon catheter is passed into the lumen with minimum resistance (Poe, Silvola & Pyykkö, 2011; McCoul, Singh, et al., 2012; Dalchow, et al., 2016). Insertion depth depends on the device used. The correct position is marked on the device and is attained when encountering mild resistance (Poe, Silvola & Pyykkö, 2011; Miller & Elhassan, 2013; Bowles, et al., 2017). The balloon is then inflated with saline (Miller & Elhassan, 2013; Schröder, et al., 2013; Dalchow, et al., 2016). Typically inflation pressure of 10 to 12 atm is used for 1 to 2 minutes, after which the balloon is deflated and removed (Ockermann, et al., 2010a; Poe, Silvola & Pyykkö, 2011; Schröder, et al., 2013; Tisch, et al., 2013; Dalchow, et al., 2016; Bowles, et al., 2017). The entire operation should be performed under visual control to ensure the correct position and detect any mucosal damage and bleeding (Miller & Elhassan, 2013; Schröder, et al., 2013). The reported operation time has been approximately 15 minutes (Tisch, et al., 2013).

Initially, all BETs were performed under general anesthesia (Schröder, et al., 2013; Tisch, et al., 2013; Dalchow, et al., 2016), but local anaesthesia later became feasible using a nasal nerve block and numbing of the ET lumen with lidocaine-prilocaine cream (Catalano, et al., 2012; Luukkainen, et al., 2017; Luukkainen, et al., 2019). In early studies by Luukkainen and colleagues including a total of 31 adult patients who underwent BET under local anaesthesia, all the operations were technically successful and no adverse effects occurred (Luukkainen, et al., 2017; Luukkainen, et al., 2019).

Several different devices are currently available, but comparative data is limited (Luukkainen, et al., 2019; Plaza, et al., 2020). The balloon size of the instruments available in Finland varies in length from 16 to 20 mm and in diameter from 3.28 to 7 mm (TubaVent 20 x 3.28 mm and TubaVent wide 20 x 4.94 mm, Spiggle & Theis, Overath, Germany; NuVent Eustachian 16 x 6 mm, Medtronic, Minneapolis, USA; and XprESS LoProfile 20 x 5/6/7 mm, Stryker, Plymouth, USA). Some devices previously used in Finland are currently unavailable in Europe (such as the Acclarent AERA 16 x 6 mm, Menlo Park, USA). The size of the balloon affected the tissue deformation created in a study on cadavers (Smith, et al., 2020).

The mechanism behind the clinical improvement of BET is not thoroughly understood (Smith, et al., 2020). Studies on cadavers have had inconsistent results. One study observed microtears in the cartilaginous part of the ET and no tears in the mucosa (Ockermann, et al., 2010b). Another study found lacerations to the mucosa and no tears in the cartilage (Poe & Hanna, 2011). Kivekäs and colleagues studied patients with biopsies taken from the ET mucosa preoperatively, immediately after operation, and 5 to 12 weeks postoperatively (Kivekäs, et al., 2015). Biopsies showed preoperatively inflammatory changes in the epithelium and submucosa; crush injury and lacerations to the mucosa and submucosa immediately afterward; and healthy pseudo-columnar epithelium and a thinner layer of fibrous tissue postoperatively (Kivekäs, et al., 2015). Similarly, a reduction in mucosal inflammation in the nasopharyngeal orifice of the ET on endoscopy has been found after BET (Silvola, et al., 2014). A study on rats observed damage to the epithelium and cartilage immediately after BET, which recovered within 12 weeks (Kim, et al., 2022). Postoperative submucosal fibrosis increased in addition to the depth and neovascularization of the submucosa (Kim, et al., 2022).

2.4.2.3.2 Indications

The Finnish Society of Ear Surgery agreed in 2016 on possible indications for BET: 1) chronic OETD symptoms and findings in adults, 2) baro-challenge-induced ETD in adults, and 3) recurrent OME in adults (Luukkainen, Kivekäs, et al., 2018). A similar consensus was reached in 2019 by the American Academy of Otolaryngology – Head and Neck Surgery Foundation panel (Tucci, et al., 2019). Accuracy of diagnosis is emphasized, as symptoms of OETD are nonspecific (Luukkainen, Kivekäs, et al., 2018; Silvola, et al., 2019; Tucci, et al., 2019). In children, the evidence is more limited, but BET may be considered after failed standard treatment (Silvola, et al., 2019; Saniasiaya, et al., 2022). OME has been the main indication in children for BET (Leichtle, et al., 2017; Tisch, et al., 2020; Saniasiaya, et al., 2022). The minimum age of the children has varied in studies, even a 28-month-old having undergone BET (Tisch, et al., 2017). In addition, BET is used as a concomitant surgery in the treatment of chronic ME diseases, but due to limited data, no consensus has been reached regarding its benefits (Tucci, et al., 2019). Evidence on the cost-effectiveness of BET with any indication is limited.

Contraindications include patulous ETD and malformation of the temporal bone and carotid artery (Silvola, et al., 2019). Other suggested contraindications include previous radiation of the nasopharynx, cleft palate, Down syndrome, and substantial scar tissue in the nasopharynx (Plaza, et al., 2020). Tympanostomy is not considered obligatory prior to BET. Nevertheless, if symptoms are not alleviated after tympanostomy, BET is not recommended (Luukkainen, Kivekäs, et al., 2018; Tucci, et al., 2019).

2.4.2.3.3 Outcome

There are several original studies on the efficacy and safety of BET, most of them being case series (Tucci, et al., 2019; Froehlich, et al., 2020). To date, only four randomized control studies on the efficacy of BET in the treatment of OETD patients and one of OME patients have been published (Table 5) (Liang, et al., 2016; Meyer, O’Malley, et al., 2018; Poe, et al., 2018; Choi, et al., 2021; Krogshede, et al., 2022). The overall conclusion of recent systematic reviews is that BET appears to improve subjective symptoms and objective findings of OETD (Luukkainen, Kivekäs, et al., 2018; Huisman, et al., 2018; Tucci, et al., 2019; Froehlich, et al., 2020). Different outcome measures have been used in studies, including ETDQ-7 scores, the Valsalva manoeuvre, otomicroscopic findings, tympanometry, and TMM (Huisman, et al., 2018; Froehlich, et al., 2020). Of these, patient-reported scores such as ETDQ-7 and the ability to perform the Valsalva manoeuvre are suitable for evaluating the outcome of BET according to the American Academy of Otolaryngology – Head and Neck Surgery Foundation panel (Tucci, et al., 2019).

The ETDQ-7 score decreased by 2.9 points in the BET group compared to a 0.6-point decrease in the control group at a 6-week follow-up in a randomized trial of 60 patients (Meyer, O'Malley, et al., 2018). In a meta-analysis of ETDQ-7, the mean decrease was 2.1 points in 111 patients (6-week follow-up) and 2.2 points in 123 patients (3 to 12-month follow-up) (Froehlich, et al., 2020). Furthermore, ETDQ-7 scores improved in 93% and normalized in 54% of the 113 patients after BET (Froehlich, et al., 2020).

A randomized trial of 323 patients found an increase in the ability to perform a modified Valsalva manoeuvre after BET in 33% compared to a 3% increase in the control group at a 6-week follow-up (Poe, et al., 2018). A meta-analysis including 153 operations by Huisman et al. showed an increase in the ability to perform the Valsalva manoeuvre from 7% to 90% (Huisman, et al., 2018). Likewise, another meta-analysis by Froehlich et al. showed an increase from 13% preoperatively to 71% at 6-week follow-up in 356 patients and to 81% at 3 to 12-month follow-up in 337 patients (Froehlich, et al., 2020).

Otomicroscopic findings have typically been classified in studies as normal or abnormal; abnormal findings include TM retraction, TM perforation, tympanostomy tubes, and OME (Huisman, et al., 2018). Meta-analysis revealed that abnormal otoscopy was less common after BET: preoperatively 76% and postoperatively 46% at 6-week follow-up including 166 patients and 21% at 3 to 12-month follow-up including 179 patients (Froehlich, et al., 2020). Two randomized trials also show a favorable change in otomicroscopic findings after BET and a significant difference compared to the control group (Liang, et al., 2016; Meyer, O'Malley, et al., 2018). One study of patients with TM retraction showed improvement in 62% of the 43 ears in a 2-year follow-up (Sandoval, et al., 2023).

Tympanometry has typically been reported as a distribution of type A, B, and C tympanograms or improvement in tympanometry results (from type B to type A or C, or from type C to type A tympanogram) (Froehlich, et al., 2020). In two meta-analyses, a type A tympanogram was found prior to BET in only 20% of 255 patients and in 14% of 606 patients; improvement was reported in 55% and 53% of patients, respectively (Huisman, et al., 2018; Froehlich, et al., 2020). In a randomized trial where only 1% of the patients had a type A tympanogram preoperatively, at 6-week follow-up 52% of the patients in the BET group had a type A tympanogram compared to 14% of patients in the control group (Poe, et al., 2018).

Some studies have reported TMM results as an outcome measure separately and some as part of the ETS or ETS-7. One study of 38 patients showed improvement on TMM in 81% of cases (Schmitt, et al., 2018). Another study of 40 patients showed a change in distribution in the TMM results; an R-value <1 was measured preoperatively in 36% of the patients and at 12-month follow-up in 79% of the patients (Xiong, et al., 2016). Pooled ETS increased by 3.9 points in the meta-analysis containing 670 procedures (Huisman, et al., 2018).

The above-mentioned outcomes include results mainly from OETD patients. Few studies have been conducted on baro-challenge-induced ETD alone. They show improvement primarily in subjective symptoms and in the ability to perform the Valsalva manoeuvre, as this patient group typically has no other clinical findings (Van Roeyen, et al., 2016; Giunta, et al., 2019; Ungar, et al., 2020; Utz, et al., 2020). One retrospective study had a subgroup of 107 ears diagnosed with baro-challenge-induced ETD and found improvement in ETDQ-7 scores, Valsalva manoeuvre performance, and tympanogram in a 2-year follow-up period (Sandoval, et al., 2023). A pressure chamber test has also been used as an outcome measure in study settings (Jansen, et al., 2020).

Some studies have been carried out on children with OETD or OME mainly after conventional therapy has failed (Saniasiaya, et al., 2022). A retrospective study of 52 children aged from 3 to 15 years diagnosed with recurrent or persistent otitis media, adhesive TM, persistent TM perforation, or cholesteatoma demonstrated an increase in type A tympanograms from 14% to 50% (Leichtle, et al., 2017). In addition, improvement was reported in subjective symptoms, in the ability to perform the Valsalva manoeuvre, and in TMM 50 bar results (Leichtle, et al., 2017). A study of 26 patients aged between 7 and 17 years and a retrospective control group (only tympanostomy performed) showed that after BET the risk of needing further tympanostomies was lower during a 2-year follow-up time (Toivonen, et al., 2021). In a pooled systematic review of 408 children, the distribution of type B tympanograms decreased from 64% to 16% and the air-bone gap decreased by 15 dB (Aboueisha, et al., 2022).

The results appear to be long-term. A retrospective study of 130 patients including adults and children with baro-challenge-induced ETD, OME, or adhesive otitis media during a 2-year follow-up showed lasting improvement in otoscopic findings, Valsalva manoeuvre, and tympanometry (Sandoval, et al., 2023). ETDQ-7 scores even decreased over time (Sandoval, et al., 2023). Comparing those three subgroups, patients with baro-challenge-induced ETD benefited the most based on this study (Sandoval, et al., 2023). Another prospective study of 47 adult patients with OETD showed stable improvements at a follow-up of at least 18 months (mean 29 months) in ETDQ-7 scores, otomicroscopic findings, Valsalva manoeuvre, and tympanometry (Cutler, et al., 2019).

Table 5. Randomized control trials of BET.

STUDY	NUMBER OF PATIENTS BET + CONTROL GROUP	INCLUDED PATIENTS / NOTABLE	FOLLOW-UP TIME	ETDQ7 IMPROVEMENT	OTOMICROSCOPIC IMPROVEMENT	VALSALVA MANOEUVRE IMPROVEMENT	TYMPANOMETRY IMPROVEMENT
LIANG 2016	30+30	Adults with OME The control group underwent tympanostomy. The study also had a group of BET + tympanostomy.	6 months	NA	80% vs. 7%	NA	83% vs. 13%
POE 2018	162+80	Adults with OETD symptoms and abnormal tympanogram Randomization terminated after 6 weeks, follow-up continued for 24 weeks.	6 weeks	56% vs. 9%	NA	33% vs. 3%	63% vs. 26%
MEYER 2018	28+27	Adults with ETDQ-7 score ≥21 Randomization terminated after 6 weeks, follow-up continued for 1 year.	6 weeks	Mean decrease of 2.9 vs. 0.6 point	67% vs. 0%	47% vs. 14%	57% vs. 10%
CHOI 2021	16+15	Adults with OETD symptoms or recurrent OME or adhesive otitis media.	2 weeks	Mean decrease of 1.3 vs. 0 point	NA	32% vs. 16%	37% vs. 16%
KROGSHEDE 2022	13+11	Adults with unilateral abnormal tympanogram and otomicroscopy (OME or TM retraction)	6 months	Mean decrease approx. 8 vs. 2 points	69% vs. 0%	NA	69% vs. 27%

Improvement reported in change from baseline, BET group vs. control group.
NA, data not available

2.4.2.3.4 Complications

Complications have mainly been self-limiting and mild. In a systematic review including a total of 1155 patients and 1830 operations, the complication rate was 2% (Huisman, et al., 2018). The most prevalent complication was crush injury or local bleeding of the mucosa at the site of the ET, accounting for 56% of all reported complications (Huisman, et al., 2018). Other encountered complications include acute otitis media, self-resolving subcutaneous emphysema, transient rhinitis, transient increase in tinnitus, hemotympanum, minor lacerations of the mucosa, epistaxis, self-limiting otorrhea, and mild vertigo (McCoul & Anand, 2012; Wanscher & Svane-Knudsen, 2014; Schröder, Lehmann, Ebmeyer, et al., 2015; Gürtler, et al., 2015; Sandoval, et al., 2023). Most of these have been self-limiting, but hemotympanum has required myringotomy and epistaxis nasal packing (McCoul & Anand, 2012; Sandoval, et al., 2023). One study of 182 patients reported symptoms from patulous ETD in 9% of patients who underwent BET, most of which were self-limiting (Hubbell, et al., 2023). Similar complications have been encountered in children; a systematic review of 408 children reported a pooled 5% complication rate (Aboueisha, et al., 2022). The American Academy of Otolaryngology – Head and Neck Surgery Foundation panel has stated that relevant risks that patients should be informed about include bleeding, scarring, infection, development of patulous ETD, and the need for additional procedures (Tucci, et al., 2019). In the literature, injury to the carotid artery has been considered a possible complication of BET; fortunately, such a major event has not yet been reported (Tucci, et al., 2019).

3 Aims

The purpose of this study was to evaluate the use of TMM in ETD diagnostics and the efficacy of BET in different patient groups. Thus, the aim was to improve the treatment of OETD and baro-challenge-induced ETD patients.

The specific objectives of the four studies were:

1. To assess the technical success rate of TMM measurements and identify common errors in TMM use in clinical practice (I).
2. To examine whether patient characteristics affect TMM results and how TMM results correlate with those of other diagnostic tests (II).
3. To study the outcome and safety of BET in patients with OETD or ME disease (III).
4. To evaluate the efficacy of BET in baro-challenge-induced ETD patients (IV).

4 Materials and Methods

4.1 Ethical considerations

Studies I, II, and IV were approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa (I and II: 68/HUS/356/2017; IV: 69/HUS999/2021). For Study III, approval was received from the Clinical Research Centre of the Hospital District of Southwest Finland (TO6/055/17). Written informed consent was obtained in connection with a questionnaire from the patients in Study IV. Each study followed the guidelines of the Declaration of Helsinki.

4.2 Patients

All studies were retrospective patient cohort series. Otological patients with OETD symptoms evaluated at a specific ET clinic without the need for a specific diagnosis were included in the TMM series (I-II). Furthermore, ETD patients who had undergone BET were reviewed (III-IV). Available data on the patients' characteristics, clinical history, and ear-specific symptoms and findings were retrieved retrospectively from patient charts. Information on the operation performed and postoperative symptoms and findings was also collected (III-IV). (Table 6)

Patients with ETD symptoms referred to tertiary care are evaluated at Helsinki University Hospital at a specific ET outpatient clinic, where a comprehensive otological evaluation is conducted. All consecutive adult patients (age >16 years) visiting this ET clinic and having a TMM performed from November 2016 onwards were retrieved. Patients diagnosed with patulous ETD and cleft palate were excluded (I-II). In addition, one patient with meningioma treated with radiation therapy was excluded, along with patients who had previously undergone BET (I). Study I continued until November 2018 with 114 patients (228 ears), and Study II until October 2020 with 219 patients (432 ears).

All consecutive BET operations performed between 2013 and 2016 at Turku University Hospital were evaluated. One patient was excluded because of ME squamous cell carcinoma. Finally, 84 adults (age >16 years) and 23 children were included. In addition to a patients' chart review, a paper questionnaire was sent to all the patients and 45 (42%) of them returned the questionnaire. (III)

The efficacy of BET in baro-challenge-induced ETD patients was studied by conducting a systematic literature search and reviewing a patient cohort from Helsinki University Hospital. In the literature search, eight articles (74 baro-challenge-induced ETD patients) met the inclusion criteria. For the patient cohort, all adult patients (age > 18 years) with baro-challenge-induced ETD who had undergone BET at Helsinki University Hospital between February 2011 and October 2020 were identified, including 39 patients. In addition to the aforementioned retrieved patient data, attention was paid to the patients' flying and diving habits. Additionally, a paper questionnaire was sent to all Helsinki University patients and was returned by 28 (72%) patients. (IV)

Table 6. Summary of patient characteristics in all the studies.

	STUDY I	STUDY II	STUDY III	STUDY IV
NUMBER OF PATIENTS	114	219	107	39
AGE (YEARS)	42 (15)	43 (15)	34 (19)	42 (14)
MALE, **FEMALE**	52 (46%), 62 (54%)	90 (41%), 129 (59%)	44 (41%), 63 (59%)	19 (49%), 20 (51%)
BMI (KG/M²)	26 (5.3)†	26 (5.1)†	26 (5.7)	25 (4.2)
ALLERGY	37 (32%)*	79 (36%)*	24 (22%)	19 (49%)
SMOKING	17 (15%)*	34 (16%)*	8 (8%)*	4 (10%)*

Categorical data are presented as numbers (%) and continuous data as mean (*SD*). Allergy, patients with only drug or food allergies are excluded. BMI, body mass index. *: data missing on 2-4 patients; †: data missing on 6-10 patients.

4.3 TMM examinations (I-II)

All TMM examinations were performed with a tubomanometer (Spiggle & Theis, Overath, Germany). A predefined nasopharyngeal pressure of 30, 40, and 50 mbar was used in consecutive order for each ear. The examination was always started with 30 mbar pressure and in some cases, higher pressure was used only if a normal ET opening was not detected. Measurement was considered to be successful if a sufficient rise in the nasopharynx was followed by either a detectable pressure rise in the outer ear canal (ET opening) or an unchanged pressure curve of the outer ear canal (no ET opening). The ET's opening was further assessed with an R-value. The reason for unsuccessful measurements was analysed (I). Examples of successful and unsuccessful measurements are shown in Figure 10. For evaluating TMM results in a single value, we used a seven-step score ranging from 0 (normal ET function) to 6 (no detectable ET opening at any measured pressure) (Table 7) (II).

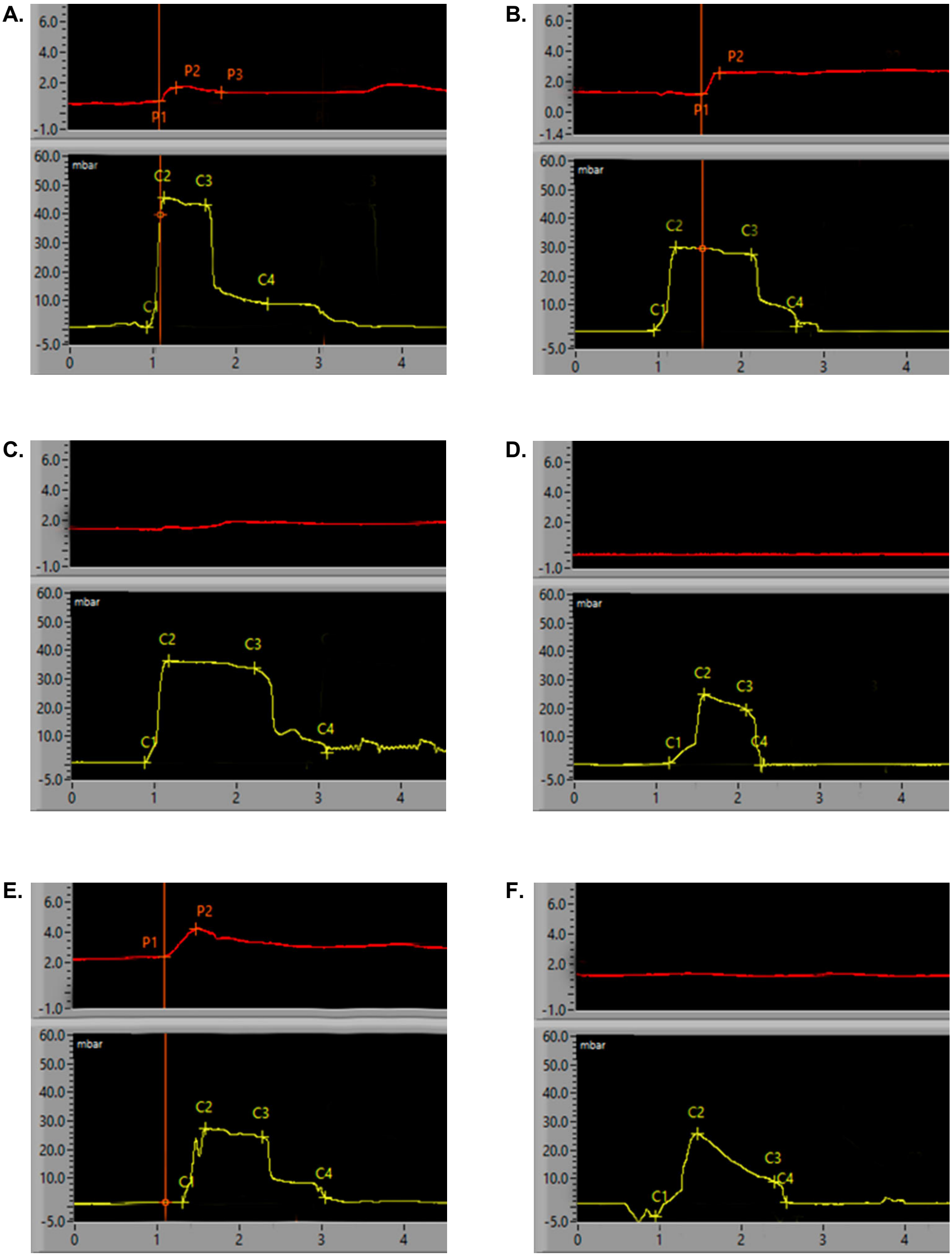


Figure 10. Successful (**A**–**C**) and unsuccessful (**D**–**F**) TMM measurements. **A**) R-value <1, **B**) R-value >1, **C**) no detectable ET opening, **D**) air leakage from the ear canal; this is easiest to detect at the time of measurement when a pressure level higher than zero cannot be maintained, **E**) R-value negative; typically result from movements other than swallowing, **F**) sufficient pressure not reached in the nasopharynx (set pressure was 50 mbar). Image: Oehlandt H.

Table 7. TMM score used (II). From Study II.

TMM SCORE	RESULT AT 30 MBAR	RESULT AT 40 MBAR	RESULT AT 50 MBAR
0	R<1		
1	R>1		
2	No definable R-value	R<1	
3	No definable R-value	R>1	
4	No definable R-value	No definable R-value	R<1
5	No definable R-value	No definable R-value	R>1
6	No definable R-value	No definable R-value	No definable R-value

4.4 BET (III-IV)

BET was performed for altogether 123 adults and 23 children (age < 16 years). The mean age of adults was 39 years (SD 16, ranging from 16 to 77 years) and of children 13 years (SD 1.8, ranging from 9 to 16 years). All children had undergone other operations before BET. (Table 8)

Table 8. Operations and follow-up conducted (III-IV).

	STUDY III, 107 PATIENTS	STUDY IV, 39 PATIENTS HELSINKI COHORT
INSTRUMENTATION		
SPIGGLE & THEIS TUBAVENT OR TUBAVENT SHORT	107 (100%)	17 (44%)
ACCLARENT AERA		21 (54%)
ENTELLUS XPRESS		1 (3%)
BILATERAL, UNILATERAL	60 (66%), 47 (44%)	29 (74%), 10 (26%)
CONCURRENT OPERATION	76 (71%)	0 (0%)
TYMPANOSTOMY	35 (33%)	
MYRINGOPLASTY	28 (26%)	
ATTICO/TYMPANOTOMY	15 (14%)	
ADENOIDECTOMY	6 (6%)	
SINONASAL OPERATION	5 (5%)	
MASTOIDECTOMY	4 (4%)	
OTHER	5 (5%)	
FOLLOW-UP		
VISIT (NUMBER OF PATIENTS, TIME)	88 (82%), 8 months (*SD* 4)	27 (69%), 15 months (*SD* 22)
QUESTIONNAIRE (NUMBER OF PATIENTS, TIME)	45 (42%), 33 months (*SD* 12)	28 (72%), 56 months (*SD* 26)
COMPLICATIONS	4 (4%)	1 (3%)

4.4.1 Surgical technique (III)

All operations were performed under general anesthesia by the same ENT surgeon (J. Pulkkinen). At the start of the operation, nasal cotton pads soaked in epinephrine solution (1%) were applied to decongest the mucosa and minimize bleeding. A rigid 45° angle Hopkins endoscope or Hopkins endoscope with an adjustable angle between 0° and 70° was used to visualize the orifice of the ET. Dilation was performed with Spiggle & Theis instrumentation with a balloon size of 3.3 × 20 mm (Medizintechnik GmbH, Overath, Germany). The balloon catheter was inserted into the cartilaginous part of the ET, then inflated with saline to 10 bar for 2 minutes. BET ended after the balloon was deflated and carefully removed. In some cases, other surgery was performed simultaneously, such as tympanostomy, myringoplasty, mastoidectomy, or adenoidectomy (Table 8).

4.4.2 Questionnaires (III-IV)

A paper questionnaire was sent in March 2018 to all patients who had undergone BET at Turku University Hospital from 2013 to 2016 (Appendix 1). Patients were asked about their present symptoms, the effect of the BET on the symptoms, possible adverse effects, and if they would have undertaken the operation in retrospect. They were also asked to complete the ETDQ-7 (unvalidated translation into Finnish). (III)

Two questionnaires were sent to all adult patients with baro-challenge-induced ETD who had undergone BET between February 2011 and October 2020 first in May 2021 and again in June and August 2021 to non-responders. These were a validated Ear Outcome Survey (EOS-16) (Laakso, et al., 2021) and a separate paper questionnaire developed for this study (Appendix 2). The questionnaire developed for this study included questions on patients' symptoms and problems during rapid changes in ambient pressure, ability to perform the Valsalva manoeuvre, changes in diving or flying habits, and whether they would undergo re-dilation if their symptoms returned. (IV)

4.4.3 Systematic literature search and meta-analysis (IV)

We performed a systematic literature search in PubMed, the Cochrane library, and Scopus on November 2, 2020. The search terms ("balloon dilation" OR "balloon dilatation" OR "balloon tuboplasty") AND ("Eustachian tube" OR "tuba auditiva" OR "auditory tube") were used. Inclusion criteria were at least one adult patient with baro-challenge-induced ETD who had undergone BET. Results had to be specified for baro-challenge-induced ETD patients. Therefore, if necessary, we asked for more data from the corresponding authors by email. If there were no specified results available on baro-challenge-induced patients even after the data request, articles were excluded. Other exclusion criteria were articles not written in English and articles including only children, cadavers, animals, or patients who underwent other surgery. Likewise, review articles, editorial articles, and other short correspondence were excluded.

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. The level of evidence was evaluated using the Oxford Centre for Evidence-Based Medicine (OCEBM) 2011 Levels of Evidence guidelines (Howick, et al., 2011) and the quality of studies using the National Institute of Health (NIH) Study Quality Assessment Tool for Before-After (Pre-Post) studies with no control group (NHLBI, 2021).

From the included articles we collected all available data on patients' characteristics, information on the operation performed, follow-up time, all reported pre- and postoperative examinations, reported outcomes, and flying or diving habits. Meta-analysis was conducted with the available results from the included articles and the results from our Helsinki University patient cohort. Pooled meta-analysis was done for the Valsalva manoeuvre, ETDQ-7 score, and subjective improvement in symptoms.

4.5 Statistics

Categorical data on descriptive characteristics were analysed using Fisher's exact test (I) and Pearson's chi-square test (II). Continuous data on descriptive characteristics were tested for skewness, which was found, thus nonparametric tests were used such as the Mann–Whitney U test or the Kruskal–Wallis test (I-II). Logistic regression was used to analyse parameters affecting the success rate of TMM (I) and the association between patient characteristics and diagnostic tools (II). In addition, ordinal regression for ordinal scale data was applied (II). Associations between different diagnostic tests were analysed using Spearman's rank correlation and the difference in means using the Mann–Whitney U test (II).

Nonparametric data on pre- and postoperative symptoms and clinical findings were compared using McNemar's test or the Wilcoxon signed-rank test for matched samples (III-IV). Spearman's rank correlation was used to evaluate the correlation between nonparametric ordinal scale data (IV).

Meta-analyses were conducted for three findings: the Valsalva test, the ETDQ-7 score, and subjective improvement in symptoms. A random effects model was used due to the heterogeneity of the included studies. Relative risk was calculated with a 95% confidence interval (*CI*). (IV)

Statistical analyses were conducted using SPSS Statistics software for Windows, version 25.0 (I), version 27.0 (II and IV), and version 28.0 for additional analysis in the dissertation (IBM SPSS Statistics, Armonk, NY). Meta-analyses were conducted using RevMan 5.3. (Cochrane, London, UK) (IV). Statistical analyses for Study III were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). A statistician was consulted when needed.

5 Results

5.1 TMM in clinical use

5.1.1 Measurement technical success rate (I)

The overall technical success of all 626 TMM measurements was 91%, ranging from 87% to 94% at different pressures. Similar results were obtained when measurements from the patients from Study II were added (Figure 11). With a larger number of subjects and TMM measurements, measurements at 50 mbar had a statistically lower success rate compared to measurements at lower pressures (30 vs. 50 mbar $P = 0.025$ and 40 vs. 50 mbar $P = 0.013$).

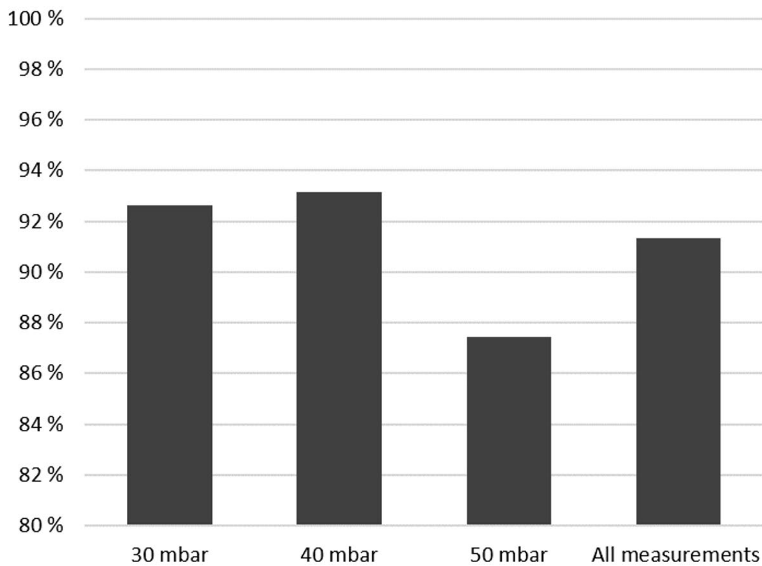


Figure 11. Percentage of technically successful tubomanometry measurements at different pressures.

The reasons for unsuccessful measurements were evaluated. The most common reason for failure was air leakage from the external ear canal, accounting for 40% (24/59) of the unsuccessful measurements. Air leakage was the single most common reason for failure at 30 and 40 mbar. At 50 mbar the most common reason for unsuccessful measurements was that sufficient nasopharyngeal pressure was not reached (62%, 16/26): this problem was not observed at lower pressures. Patients' characteristics were not associated with the technical success of TMM measurements (Table 9).

5.1.2 Correlations with patient characteristics (II)

An association between pollen allergy and a lower opening rate in TMM measurements (higher TMM score) was detected (*OR* 1.74, 95% *CI* 1.15–2.63, $P = 0.009$, $N = 362$). The median TMM score in pollen-allergic and non-allergic patients was 2 (*IQR* = 5) and 1 (*IQR* = 3), respectively. Other patient characteristics (age, gender, BMI, smoking, or sinonasal disease) and TMM score were not related (Table 9). Associations between other diagnostic tests and patient characteristics are discussed in detail in Study II.

Table 9. Correlations between patient characteristics and technical success of TMM measurements and TMM score.

	MEASUREMENT UNSUCCESSFUL	**TMM SCORE** (HIGHER SCORE)
AGE (*OR*/YEAR)	*OR* 1.02 (1.00-1.05) *P* = 0.083	*OR* 1.01 (1.00-1.02) *P* = 0.145
GENDER (REF. MALE)	*OR* 0.81 (0.38-1.71) *P* = 0.579	*OR* 0.74 (0.51-1.07) *P* = 0.108
BMI (*OR* / KG/M²)	*OR* 1.01 (0.94-1.08) *P* = 0.852	*OR* 1.02 (0.98-1.05) *P* = 0.426
SMOKING (REF. NO)	*OR* 0.35 (0.08-1.50) *P* = 0.155	*OR* 1.53 (0.94-2.48) *P* = 0.087
POLLEN ALLERGY (REF. NO)	*OR* 1.14 (0.50-2.56) *P* = 0.759	*OR* 1.74 (1.15-2.63) *P* = 0.009
ANIMAL ALLERGY (REF. NO)	*OR* 0.81 (0.24-2.78) *P* = 0.735	*OR* 1.20 (0.68-2.11) *P* = 0.522
SINONASAL DISEASE (REF. NO)	*OR* 1.46 (0.60-3.53) *P* = 0.412	*OR* 0.83 (0.50-1.37) *P* = 0.462

The analysis was conducted with patients from Study II. The number of ears in individual analysis varied from 346 to 399. TMM measurement success at 30 mbar nasopharyngeal pressure. BMI, body mass index; *OR,* odds ratio (95% *CI*); *P*, *P*-value; TMM score, tubomanometry score (ranging from 0 to 6). Statistical analysis was conducted using logistic regression (TMM measurement success) and ordinal regression (TMM score). Partly from Study II.

5.1.3 Correlations with other diagnostic tests (II)

The strongest correlation between TMM score and other diagnostic tests was noted with performance of the Valsalva manoeuvre ($\rho = 0.306$, $P < 0.001$, $N = 349$). The TMM score also correlated with TM status ($\rho = 0.283$, $P < 0.001$, $N = 366$) and independently with ME effusion ($\rho = 0.139$, $P = 0.008$), TM perforation ($\rho = 0.131$, $P = 0.012$), pars tensa retraction ($\rho = 0.181$, $P = 0.001$), and pars flaccida retraction ($\rho = 0.119$, $P = 0.022$). (Figure 12)

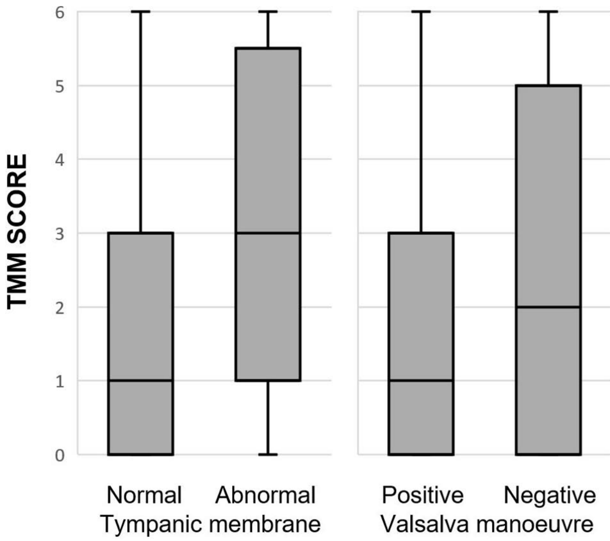


Figure 12. Box plot of the association between TMM score and other diagnostic tests (otomicroscopy and objective Valsalva manoeuvre). TMM score, tubomanometry result (values from 0 = normal ET opening to 6 = no ET opening at 30–50 mbar pressure). Partly from Study II.

Interestingly, no correlation was found between the ETDQ-7 score and any other diagnostic test, including with the TMM score ($\rho = 0.086$, $P = 0.217$, $N = 207$).

5.2 Outcome of BET

5.2.1 Dilatory ETD (III)

OETD symptoms such as aural fullness ($P < 0.001$), otalgia ($P < 0.002$), and symptoms when the ambient pressure changes rapidly ($P < 0.001$) improved significantly in the whole group at mean 7-month follow-up. Significant improvement was also found in patients' ability to perform the Valsalva manoeuvre ($P < 0.001$), recurrent acute otitis media ($P < 0.001$), and OME ($P < 0.001$). Patients were further divided into subgroups, the BET-only group and the children group. In the BET-only group, reduction was found in recurrent acute otitis media ($P < 0.01$), OME ($P < 0.001$), aural fullness ($P < 0.05$), and symptoms with sudden changes in ambient pressure ($P < 0.001$). In the children group, reduction was found in recurrent acute otitis media ($P < 0.001$) and OME ($P < 0.002$). Postoperative status was available for 88 patients (82%). A significant change was found in the ME effusion ($P < 0.005$) and TM perforation ($P < 0.005$) in the whole group. When divided into subgroups, no significant change was found in status findings. Of the 28 patients who underwent BET and concomitant myringoplasty, eight (29%) had postoperative perforation. Pre- and postoperative findings of all patients are shown in Figure 13.

At mean 33-month follow-up, symptoms had resolved in 13 (29%) patients and improved in 23 (51%). In hindsight, five (11%) patients would not have had the operation. In the BET-only, concomitant surgery with BET, and children subgroups symptoms had resolved or improved in 83% (15/18), 78% (21/27), and 100% (6/6) of patients, respectively. Evaluation of differences between patients who returned the questionnaires and those who did not showed a statistically significant difference in age and smoking status. Those who returned the questionnaire were older (P = 0.004), mean age 41 years (*SD* 18) vs. 30 years (*SD* 18), and fewer of them smoked, 2% vs. 11% (P = 0.032), respectively. Other parameters showed no statistical difference, including sex, preoperative findings, prior operations, and concomitant ear surgery.

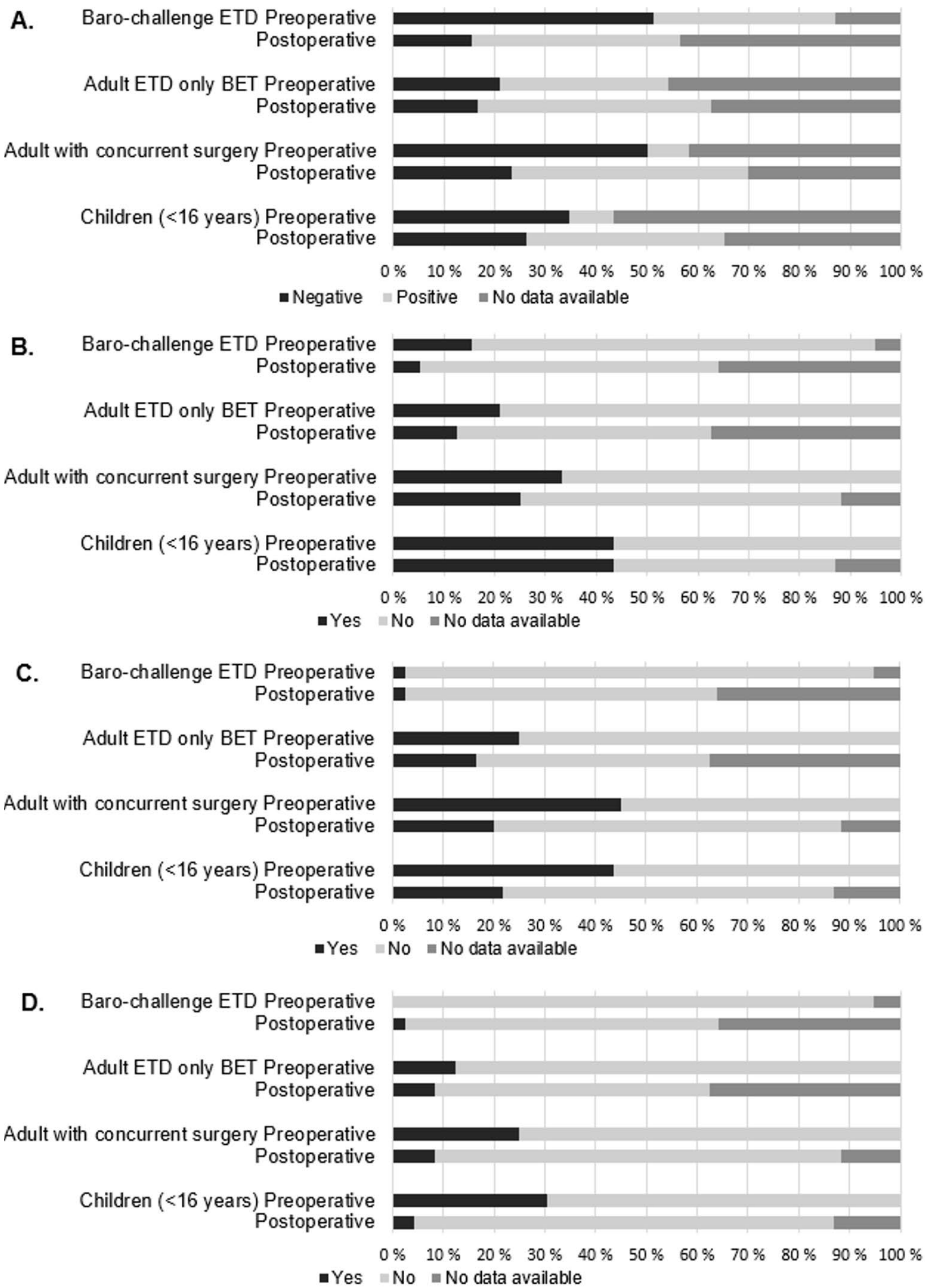


Figure 13. Pre- and postoperative findings (III-IV). **A**) Valsalva manoeuvre, **B**) Tympanic membrane retraction, **C**) Tympanic membrane perforation, **D**) Middle ear effusion

5.2.2 Baro-challenge-induced ETD (IV)

A significant change was found in the ability to perform the Valsalva manoeuvre ($P = 0.008$). Pre- and postoperative findings are shown in Figure 13. At the 4-year, 8-month follow-up, equalization problems had resolved in 18 (64%) patients and improved in seven (25%). Problems with flying or diving had disappeared in 10 (36%) patients and improved in 13 (46%). There were no statistical differences between the group who returned the questionnaire and those who did not; the mean age was 40 years vs. 46 years ($P = 0.167$), females accounted for 54% vs. 55% ($P = 0.956$), and relief was noted in 71% vs. 51% at the follow-up visit ($P = 0.163$), respectively.

In a systematic review, we identified 174 articles of which eight were included in the review. Reported inclusion criteria and surgical outcomes were heterogeneous. Subjective improvement in symptoms was the only outcome reported in all studies, and overall improvement was reported in 80% of patients. Some studies also reported improvement in the Valsalva manoeuvre, ETDQ-7 scores, TMM, tympanometry, ear status, and pressure chamber test (Table 10).

Meta-analysis shows improvement in the ability to perform the Valsalva manoeuvre (five studies, 78 patients), in ETDQ-7 scores (four studies, 34 patients), and in subjective symptoms (nine studies, 113 patients) with P-values < 0.0001.

Table 10. Reported outcomes after BET from the included articles in Study IV.

STUDY	*N*	SUBJECTIVE SYMPTOMS	ETDQ-7 SCORE	VALSALVA MANOEUVRE	OTOSCOPY	TYMPANOGRAM	TMM	PRESSURE CHAMBER TEST
VAN ROEYEN 2016	11	++	+++	NA	+/-	+/-	NA	NA
SCHMITT 2017	6	+++	NA	+	+/-	NA	++	NA
ASHRY 2017	13	+++	NA	+++	+	+	NA	NA
GIUNTA 2019	20	++	NA	+	+/-	+	NA	NA
MCMURRAN 2020	3	++	NA	NA	+/-	+/-	NA	NA
JANSEN 2020	5	+++	+++	++	NA	+/-	NA	+
UTZ 2020	12	+++	+++	+	+/-	+/-	NA	+
UNGAR 2020	4	+++	+	NA	+/-	+/-	NA	NA
OEHLANDT 2022	39	+++	+	+	+	NA	+	NA

ETDQ-7 score, Eustachian tube dysfunction questionnaire; *N*, number of patients; TMM, tubomanometry; Valsalva manoeuvre, objective or subjective positive Valsalva manoeuvre; NA, data not available; +/- indicates no change; +, improvement in 1-49% patients or exact data unavailable; ++, improvement in 50-80% patients; +++, improvement in 81-100% patients

6 Discussion

6.1 ETD diagnostics

The search term ["Eustachian tube" AND dysfunction] generates over 2,000 articles in PubMed dated before the end of 2022. Despite diligent research, no single test for ET function has achieved gold-standard status in clinical use. There is consensus on ETD types (Schilder, et al., 2015). However, these diagnoses lack broadly accepted criteria and even experts in the field may disagree on possible diagnoses (Smith, Takwoingi, et al., 2018). For these reasons, we studied the usefulness of TMM without the diagnostic classification. We demonstrate that TMM has a sufficient, over 90%, technical success rate in clinical use. The most common reason for failed measurement was air leakage from the ear canal, which might be avoided in future by paying attention to proper fit and further developing the earplugs. Another aspect worth noting is telling patients to keep still, as movement can disrupt the measurement and make interpretation more difficult. These technical issues are probably one reason TMM was considered the most difficult test to perform in one study (Smith, Takwoingi, et al., 2018), emphasizing the need for physician training and experience.

To my knowledge, Study I is currently the only study on the technical success of TMM and possible reasons for failed measurements. Other studies on TMM have mainly focused on the ET opening rate in healthy subjects (Schröder, Lehmann, Korbmacher, et al., 2015; Smith, Zou, et al., 2017; Ruan, et al., 2020; Kuhlmann, et al., 2023), specificity and sensitivity between OETD patients and healthy subjects (Esteve, et al., 2001; Schröder, Lehmann, Korbmacher, et al., 2015; Liu, et al., 2016; Smith, Takwoingi, et al., 2018), and its use as an outcome measure of BET (Jenckel, et al., 2015; Xiong, et al., 2016; Leichtle, et al., 2017; Schmitt, et al., 2018). Our aim was not to evaluate the specificity or sensitivity of TMM between OETD patients and healthy subjects. Nonetheless, a difference in TMM score between patients with normal ET function, baro-challenge-induced ETD, and OETD was found. In addition, patients with OME were found to have a lower technical success rate compared to other diagnostic groups.

Previous studies on patient characteristics associated with TMM results are limited. One study found a higher prevalence of abnormal TMM result among patients with dust-mite allergic rhinitis (Ma, et al., 2020). Another has linked nasal septum deviation to poorer TMM results, which even improved after septoplasty (Lima, et al., 2022). Neither of these characteristics was evaluated in our study. However, our data found an association between pollen allergy and poorer TMM results. In the future, it would be interesting to know whether poorer TMM performance is only seen in these patients during allergy season.

In our studies, other patient characteristics (age, sex, BMI, smoking, or sinonasal disease) did not affect the technical success rate or TMM results. This implies that TMM is reliable for different patients regardless of their characteristics. An additional advantage of TMM is that it has no patient-related restrictions such as TM perforation or ME effusion (Smith & Tysome, 2015). In the literature, TMM has also been used successfully with children (Kuhlmann, et al., 2023). It is therefore usable with almost all ear-symptomatic patients irrespective of their history or ear status.

In a previous study, TMM was evaluated as the most reliable test for OETD (Smith, Takwoingi, et al., 2018). Our results agree that TMM is a reliable and useful test for all ET patients. In previous studies, the sensitivity and specificity for OETD have been 49–82% and 60–100%, respectively (Esteve, et al., 2001; Schröder, Lehmann, Korbmacher, et al., 2015; Liu, et al., 2016; Smith, Cochrane, et al., 2018; Smith, Takwoingi, et al., 2018). Possible reasons for the inconsistent results include patients being over-diagnosed with OETD, TMM not being able to detect all ET openings in every measurement, and physicians misinterpreting the results. In conclusion, TMM is a highly valuable tool, but it needs to be combined with other tests and physician experience.

There are several other tests for ET function, all with some advantages and disadvantages as described in the literature review. For example, ETDQ-7 has been found to have poor discriminative ability between OETD and other ear problems (Andresen, et al., 2021), and our results are consistent with this. In our study, abnormal TM status was more frequent in older patients, patients with higher BMI, and smokers. Of those, only smoking was associated with an OETD diagnosis made by the attending physician. Smoking has also in previous studies been linked to ME diseases (Adair-Bischoff & Sauve, 1998; Pezzoli, et al., 2017; Altalhi, et al., 2022). Most tests assess ET function either indirectly or by measuring ventilatory function (Schilder, et al., 2015). The significance in clinical settings of directly testing the other known functions of ET, secretion drainage and protection of sounds and pathogens, is unknown.

Current recommendations regarding diagnostic protocols highlight the need for comprehensive evaluation of these patients, although no unanimous consensus on the necessary tests has been reached (Schilder, et al., 2015; Smith, Takwoingi, et al., 2018; Tucci, et al., 2019; Plaza, et al., 2020). Scores combining different test results, such as the ETS-7, have been developed to grade comprehensive assessments with a single value (Schröder, Lehmann, Sauzet, et al., 2015). A benefit of the ETS-7 is that it compels physicians to use multiple tests when making a diagnosis and includes a relatively objective method, TMM. However, the utility of these combined scores in clinical use and the specificity and sensitivity in diagnostics require further research.

6.2 Outcome of BET

BET has in several studies alleviated symptoms and improved the clinical findings of OETD and baro-challenge-induced ETD, as shown in multiple systematic literature reviews (Huisman, et al., 2018; Luukkainen, Kivekäs, et al., 2018; Froehlich, et al., 2020). Research in this area has, however, been inconsistent, as inclusion criteria, outcome measures, and follow-up time have varied widely. Moreover, only one placebo-controlled study with a small study sample has been published (Laakso, et al., 2023).

Study III included a retrospective case series of all BETs performed at Turku University Hospital up until 2016, without specific inclusion criteria. Thus the patients varied as would be expected in clinical settings. Patients were further divided into subgroups for analysis. In OETD patients who underwent only BET, symptoms had abated at 3-month follow-up in 83% of patients whose data were available. This positive result is consistent with previous studies (Catalano, et al., 2012; Gürtler, et al., 2015; Xiong, et al., 2016).

BET performed concurrently with myringoplasty resulted in an intact TM in 71% of patients. This patient group was challenging, as many of the myringoplasties were re-operations. The success of revision myringoplasty without BET has been between 53% and 93% in previous studies (Berger, et al., 1997; Prinsley, 2017; Karunaratne & Violaris, 2021). Compared to these results, BET does not appear to provide substantial benefit when combined with myringoplasty. However, our results include only 28 patients who had undergone concomitant myringoplasty. Other studies have also included concomitant myringoplasty patients, but postoperative TM status is unavailable (McCoul & Anand, 2012; Dalchow, et al., 2016). One study has compared tympanomastoidectomy with vs. without BET in chronic suppurative otitis media patients (Hsieh, et al., 2020). An intact TM was found in 80% of the BET group but the difference from 69% success in the group without BET was statistically insignificant (Hsieh, et al., 2020). Nevertheless, there are studies suggesting that ET function significantly affects the myringoplasty success rate (Holmquist, 1968; Moneir, et al., 2023). Thus, the benefit of BET combined with other ear surgery in the treatment of chronic ME diseases requires more research, as has also been suggested by the American Academy of Otolaryngology – Head and Neck Surgery Foundation consensus (Tucci, et al., 2019).

The third subgroup in Study III was children aged between 9 and 16 years. Most of the ET’s maturation occurs before the age of 7 years (Ishijima, et al., 2000), thus our results are not applicable to young children. All the children in our study had undergone tympanostomy and 52% also other ear surgery before BET. This is typical, as currently BET is mostly used in children only after conventional therapy has failed (Saniasiaya, et al., 2022). In our study, a significant improvement was found in recurrent acute otitis media and OME in this subgroup. In other studies, improvement has also been found in subjective symptoms, tympanometry results, TMM results, otomicroscopic findings, the ability to perform the Valsalva manoeuvre, and in the need for further tympanostomies (Leichtle, et al., 2017; Tisch, et al., 2020; Toivonen, et al., 2021).

We evaluated BET in baro-challenge-induced ETD patients. We had a retrospective cohort of 39 patients, which at the time was the largest published study on this patient group. Earlier, Giunta et al. had conducted a prospective study with freediving fishermen including 20 patients (Giunta, et al., 2019). Recently, Sandoval et al. published a retrospective multicentre study of BET with a baro-challenge-induced ETD subgroup of 107 ears (Sandoval, et al., 2023). Other published studies have been smaller, or this indication group has been included in a larger patient group (Van Roeyen, et al., 2016; Ashry, et al., 2017; Schmitt, et al., 2018; Jansen, et al., 2020; McMurran, et al., 2020; Ungar, et al., 2020; Utz, et al., 2020; Cheng, et al., 2021). In our cohort, significant improvement was found in subjective and objective Valsalva maoeuvres, subjective symptoms, and the ability to fly. Overall, 84% of patients had subjective improvement in symptoms. In previous studies, subjective improvement has varied between 55% and 100% (Van Roeyen, et al., 2016; Cheng, et al., 2021). The ability to perform the Valsalva manoeuvre is a frequently reported outcome measure in this group; and in our study, the postoperative ability to perform it correlated with the ability to fly and improvement in symptoms. In addition to improvement in the Valsalva manoeuvre, other improved outcome measures have been reported (Schmitt, et al., 2018; Cheng, et al., 2021; Sandoval, et al., 2023). However, results on these outcome measures are more inconsistent, as some studies have required normal preoperative findings to include patients in this subgroup (Van Roeyen, et al., 2016; Utz, et al., 2020).

In addition to the Helsinki University Hospital patient cohort, we conducted a systematic review on baro-challenge-induced ETD patients. In meta-analyses, significant improvement was found in subjective symptoms, Valsalva manoeuvre performance, and ETDQ-7 scores. Altogether, improvement was found in 81% of patients including patients from eight articles and our patient cohort. Around the same time, another similar systematic review was published (Raymond, et al., 2022). Unlike ours, it included case reports of facial baroparesis, laser tuboplasty operations, and patients with concomitant septoplasty (Raymond, et al., 2022). In contrast, our review included unpublished patients and results from authors of the included articles and our Helsinki University Hospital patient cohort. Despite these differences, the conclusions were similar.

Follow-up time was long in both Studies III and IV, with a mean time of 2 years 9 months (*SD* 12 months) and 4 years 8 months (*SD* 26 months), respectively. The results were encouraging, as symptoms had either disappeared or abated in 80% and 89% of the patients, respectively. As these results are from questionnaires, no clinical outcomes are available. In a few other studies with follow-up time longer than 2 years, long-term subjective improvement was reported to vary between 73% and 83% of patients with OETD (Schröder, Lehmann, Ebmeyer, et al., 2015; Luukkainen, Vnencak, et al., 2018; Cutler, et al., 2019). Only one study has reported long-term outcomes for baro-challenge-induced ETD patients with an effectiveness of 95% (Sandoval, et al., 2023). In addition to subjective improvement, long-lasting results have been found in otomicroscopic findings, Valsalva manoeuvre performance, tympanometry, and TMM (Schröder, Lehmann, Ebmeyer, et al., 2015; Cutler, et al., 2019; Sandoval, et al., 2023).

We encountered four patients (10%) who reported initially benefitting from the BET but whose symptoms began to return after a few years. One patient underwent successful reoperation 4 years after the first BET. This phenomenon of symptoms returning after years without them has not been comprehensively addressed in previous studies. Revision surgeries have mainly been performed because of an inadequate initial response (McCoul & Anand, 2012; Keschner, et al., 2022). Keschner et al. concluded that revision surgery is unlikely to be beneficial if the first BET has not produced favourable results, as only 30% show a slight improvement in symptoms after revision BET (Keschner, et al., 2022).

Reported complication rates vary up to 45% (Poe, Silvola & Pyykkö, 2011). According to a systematic review, complications occur in 2% of cases (Huisman, et al., 2018). In Study IV, up to 36% of patients reported some symptoms after surgery, mostly short-term flu symptoms. These were insignificant, and most likely similar symptoms have not been reported in other studies. Otherwise, complications were in line with previously reported adverse events: one self-limiting epistaxis (3%) and one patulous ETD (3%), which resolved within a year. In Study III, 9% of patients reported late adverse effects, half of which were symptoms of patulous ETD. In both studies, we encountered patulous ETD as an adverse effect. Despite what one might think, patulous ETD has not been a frequently reported complication of BET (Huisman, et al., 2018). Only a study from Hubbell et al. has reported symptoms of patulous ETD after BET in 7% of cases (Hubbell, et al., 2023). Fortunately, no severe complications occurred in our studies nor in other studies published so far.

6.3 Study limitations

The most relevant limitation of all these studies is their retrospective nature, which meant that some data were missing. In Study I, a total of 8.6% of all TMM measurements were missing, slightly more of them at higher pressures. Study II had more missing TMM measurements (19%), as recently TMM has been started at 30 mbar pressure and, in many cases, further measurement at higher pressure was conducted only if normal ET opening latency was not detected. To overcome this deficiency, we used a new seven-step TMM score to evaluate the ET function on an ordinal scale. Study II evaluated ears separately. However, in the early stages, ETDQ-7 was not collected separately for both ears. This led to missing ETDQ-7 values in 43% of ears. Although we studied patient characteristics, we were unable to include laryngopharyngeal reflux, septum deviation, and dust-mite allergy, all suspected risk factors for OETD symptoms.

Even though TMM is considered a reasonable objective measure of ET, there is some subjectivity in interpretation. Two cases that are difficult to distinguish, in my opinion, are 1) slight movement in the ear curve simultaneously with swallowing – real opening or background noise from movements associated with swallowing, and 2) a flat line in the ear curve at zero pressure – a closed ET or an air-leakage from the ear canal. To minimize the interpretation risk, TMM results were evaluated by three authors and medical charts examined, although most TMM measurements were conducted by one otologist (S.T. Sinkkonen). All TMM measurements were conducted for ear-symptomatic patients, and no healthy control group was used.

In addition, some patients were lost on follow-up (III-IV). Postoperative information from a follow-up made by visit or phone call was available for all patients (III) and 97% of patients (IV). Follow-ups were mainly conducted by the operating surgeon, causing a risk of bias. Later questionnaires were completed by 42% (III) and 72% (IV) of the patients. Differences between patients who returned the questionnaires and non-responders were minor, but statistical analyses were conducted with this limited number of patients. A questionnaire is a well-suited follow-up method especially for baro-challenge-induced ETD patients, as clinical findings are typically absent in normobaric situations and, for this reason, no additional benefit is gained from follow-up visits.

Study III had a heterogenous cohort including children and adults, and BET performed as the only intervention or as concomitant surgery. For this reason, analyses were conducted with different subgroups. Unfortunately, many subgroups were small and statistical significance could not be attained. All patients had persistent symptoms before the operation; nevertheless, a control cohort was not used either. A control group would have been particularly useful for patients who underwent BET concomitantly with other ear surgery, such as myringoplasty.

Although ours was a large study sample compared to previous studies on baro-challenge-induced ETD, it was still small for statistical analyses. To draw more decisive conclusions on the effectiveness of BET in the treatment of baro-challenge-induced ETD, we conducted a systematic literature review. All studies identified in the literature review had a high risk of bias. The level of evidence in all the included articles was 4, according to the Oxford Centre for Evidence-Based. Patient characteristics, follow-up times, inclusion criteria, and outcome measures varied. This reflects the lack of diagnostic criteria and consensus on suitable outcome measures. For these reasons, the conclusions of the meta-analysis should be treated with caution.

6.4 Future perspectives

There are few randomized controlled trials on the efficacy of BET (Liang, et al., 2016; Meyer, O'Malley, et al., 2018; Poe, et al., 2018; Choi, et al., 2021; Krogshede, et al., 2022). However, to my knowledge, there are currently no blinded studies with sufficient study sample of BET published. A systematic review of placebo-controlled trials involving minimally invasive procedures showed that improvement from sham surgery was found in 74% of studies, and 51% of studies showed no difference between active surgery and sham surgery (Wartolowska, et al., 2014). Included studies in this review were from different medical fields of which the most common intervention was an endoscopic operation to treat gastroesophageal reflux disease (Wartolowska, et al., 2014). Reflecting this result, blinded placebo-controlled trials are needed to gain a more definite evaluation of the benefits of BET. Our study group has conducted a double-blinded placebo-controlled pilot study on the efficacy of BET (Laakso, et al., 2023). We were able to demonstrate the feasible study setting, clear placebo effect, and need for placebo-controlled trials. However, since it was a pilot study with a small study sample, no conclusion on the long-term efficacy can be made.

Patients with ET problems are a heterogeneous group, varying from those whose symptoms appear only when the ambient pressure changes substantially, to those who have persistent symptoms impacting their quality of life, to those with troublesome ME diseases such as cholesteatoma. One study has shown that the outcome differed depending on the indication for BET (Sandoval, et al., 2023). In future research, dividing patients into groups based on their indication would help gain a better understanding of BET in different indications and make the results more comparable. Although OETD is assumed to relate to chronic ME diseases such as OME, TM atelectasis, and even cholesteatoma (Seibert & Danner, 2006; Simon, et al., 2018; Ku, et al., 2022), there is a lack of evidence on the effect of BET in stopping or improving the progression of cholesteatoma. Our Study III and the study from

Hsieh et al. (2020) showed inconclusive results on the benefit of BET as an additional surgery to myringoplasty or tympanomastoidectomy. The use of BET concomitantly with other ear surgeries to treat chronic ME diseases requires more research.

Another patient group for whom further studies are warranted is children, especially younger ones. There is evidence suggesting that BET reduces the need for additional tympanostomies (Toivonen, et al., 2021; Saniasiaya, et al., 2022). Most studies in children have focused on BET after conventional treatment has failed (Saniasiaya, et al., 2022). One study demonstrated the efficacy of BET combined with adenoidectomy as a first-line surgery for children with OME (Demir & Batman, 2020). Knowing that OME is a frequent childhood disease leading to tympanostomies in 9% of children (Bhattacharyya & Shay, 2020) and that after the first tympanostomy as many as 20–37% require revision tympanostomy (Boston, et al., 2003; Choi, et al., 2019), the potential benefit of BET is intriguing. However, more research is needed on adverse effects, efficacy, long-term results, and cost-effectiveness.

Symptoms of OETD are highly important in clinical evaluation, as they are the reason for interventions. These symptoms have typically lasted a long time, 12 years on average in patients from Study III. However, symptoms are unspecific, and even the opposite of dilatory ET, patulous ET, can cause similar symptoms (Tucci, et al., 2019). Patient-reported outcome measures, such as the ETDQ-7, have been designed for diagnostics but unfortunately are unable to discriminate OETD from other ear disorders (Andresen, et al., 2021). For this reason, objective measures are needed to identify patients with abnormal ET functions. Although the need for objective measures has been identified, more research is needed to find the best protocol and validate the ET tests. One possible pathway from symptoms suggestive of OETD or baro-challenge-induced ETD to BET is proposed in Figure 14.

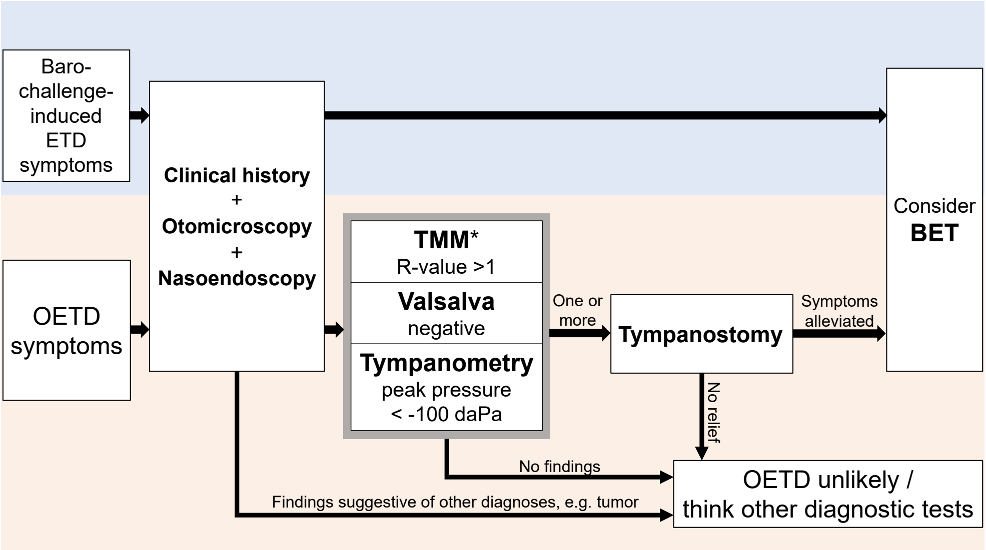


Figure 14. A pathway from symptoms of OETD or baro-challenge-induced ETD to BET. *TMM should be started at 30 mbar pressure and repeated with the same or higher pressure if normal ET opening is not detected. Image: Oehlandt H.

As previously discussed, OETD patients are a heterogeneous group and there is a lack of defined diagnostic criteria. For these reasons, physicians treating these patients should be familiar with ET problems, which can be ensured by referring patients to specific ET outpatient clinics. Directing patients in this way could facilitate access to special instrumentation such as TMM or sonotubometry. These instruments have been evaluated to have the highest accuracy in OETD diagnostics but are not widely available in clinics (Smith, Takwoingi, et al., 2018). The expertise of physicians and adequate diagnostic tools could improve diagnostic accuracy and the selection of appropriate interventions. This would potentially lead to better treatment results, avoiding unnecessary harm and more cost-effective care, and ensuring higher research quality.

Currently, there is no universal consensus on the best protocol for ET diagnostics, however, all proposed approaches include a thorough history of the patient and a combination of measures (Schilder, et al., 2015; Smith, Takwoingi, et al., 2018; Tucci, et al., 2019; Plaza, et al., 2020). At Helsinki University Hospital, patients with ETD symptoms are evaluated at a specific ET clinic. There, an otologist makes a comprehensive evaluation of these patients prior to possible surgical treatment. This includes taking a thorough history, ETDQ-7 on both ears separately, otomicroscopy including Valsalva and Toynbee manoeuvres in the sitting position, tympanometry, TMM, anterior rhinoscopy, visualization of the nasopharynx either with posterior rhinoscopy or nasoendoscopy, and an audiogram. If indicated, tympanostomy is conducted at the same visit. Diagnosis and a decision on appropriate interventions are made in light of all the results, which requires the physician to be familiar with ET measurements and treatments. Smith et al. counted that conducting all objective tests of ET takes about 40 minutes to complete, although they did not recommend conducting all the tests (Smith, Takwoingi, et al., 2018). Tests included in the calculation were tympanometry, the nine-step test, otomicroscopy including Valsalva and Toynbee manoeuvres, different impedance measures (continues, Valsalva and Toynbee manoeuvres and swallowing), TMM, and sonotubometry (Smith, Takwoingi, et al., 2018). Our selection of tests leaves time for informing patients and arranging future interventions with, in our opinion, good diagnostic accuracy. This visit takes around 40 minutes to complete.

Operation under local anaesthesia has proven to be feasible, effective, and to have a high success rate (Luukkainen, et al., 2017; Luukkainen, et al., 2019; Toivonen, et al., 2022). Lukkainen et al. encountered no adverse effects during BET under local anaesthesia, but because of the need for intravenous pain medication they could not recommend in-office procedures (Luukkainen, et al., 2017; Luukkainen, et al., 2019). Recently, two retrospective studies of BET done in an office setting have been published (Dean, 2019; Sheppard, et al., 2023). A study of 33 patients encountered no adverse effects during operations and BET was tolerable in 94% of patients (Dean, 2019). Another study of 30 patients encountered one self-limiting subcutaneous emphysema and BET was tolerable in 97% of patients (Sheppard, et al., 2023). All these operations were conducted without the need for intravenous medication (Dean, 2019; Sheppard, et al., 2023). Nowadays, one company markets its balloon dilation devices as usable in office settings (Medtronic, 2022). In the future, operations entirely in office settings or at least in surgical outpatient clinics with access to heart rate monitoring and intravenous medications may prove a safe and cost-effective way to perform BET. Nonetheless, operation under local anaesthesia reduces the risks associated with general anaesthesia.

BET is a reasonably fast operation; its mean time in an office setting has been approximately 6 minutes (Sheppard, et al., 2023). Thus, possibly in the future both the diagnosis and treatment of OETD patients could be conducted with one or two visits to an ET clinic. At first, an otologist familiar with ET problems would make an accurate diagnosis and would then perform BET if indicated, either at the same or at a follow-up visit.

7 Conclusions

This study found TMM to be a useful and reliable method in ETD diagnostics. For treatment, BET seems to be a safe operation with long-term improvement in symptoms.

The technical success rate of TMM in clinical practice was 91%, which was considered sufficient for use of the test in a routine clinical setting. The most common reason for unsuccessful measurement was air leakage from the ear canal, accounting for 40% of failed measurements. (I)

Patients' characteristics including age, gender, BMI, smoking, and sinonasal disease did not affect the TMM results. The TMM results correlated with otomicroscopic findings and Valsalva manoeuvre performance. (III)

A positive effect was detected in all patient groups after BET. No major complication occurred in any of the 107 operated patients. (III)

The majority of baro-challenge-induced ETD patients gained significant long-term benefits from BET. An additional meta-analysis of baro-challenge-induced ETD patients found a positive effect after BET in ETDQ-7 scores, subjective symptoms, and Valsalva manoeuvre performance. (IV)

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Appendices

Appendix 1. Questionnaire used in Study III.

Appendix 1A. Questionnaire in Finnish.

Tutkimus: **Korvatorven vajaatoiminnan hoito korvatorven pallolaajennuksen avulla/Tuubadilataatio**

Kysely potilaalle

Nimi:______________________________ Henkilötunnus: ______________________

Ennen toimenpidettä

Tärkeimmät kokemanne oireet ennen toimenpidettä

□ korvien lukkoisuus
□ korvakipu
□ äänien kaikuminen
□ kuulonalenema
□ toistuvat äkilliset välikorvatulehdukset
□ toistuva nesteen tai liimaeritteen kertyminen välikorvaan/ välikorviin
□ paineentasausongelmat (esim. lentäessä, sukeltaessa)
□ muu, mikä: ____

Oireiden kesto ennen toimenpidettä ______vuotta ______ kuukautta

Ennen toimenpidettä korvaoireita oli hoidettu seuraavin tavoin

□ allergisten nenäoireiden/ nenän tukkoisuuden hoito
  □ antihistamiinilla
  □ kortisonisuihkeilla
  □ leikkauksella, milloin ja missä? ___________________________________

□ poskiontelotulehdusten hoito
  □ kortisonisuihkeilla
  □ leikkauksella, milloin ja missä? ___________________________________
□ närästyksen hoito happosalpaaja-lääkityksellä
□ tärykalvoon asetetuilla ilmastointiputkilla (”tuubit”)
  □ kerran □ useasti
□ muulla korvaan kohdistuvalla leikkauksella, milloin ja missä?
____
□ muilla tavoin, miten?
____

Tupakointi ennen toimenpidettä: □ en tupakoinut □ kyllä, määrä: _____/ vrk

Tilanne välittömästi toimenpiteen jälkeen (<u>noin 1-2 viikkoa</u> toimenpiteestä)

Miten toimenpide helpotti korvaoireitanne (1-2 vk)
□ korvaoireet poistuivat kokonaan
□ korvaoireet helpottuivat jonkin verran
□ korvaoireet säilyivät ennallaan
□ alkuperäiset korvaoireet pahenivat toimenpiteen jälkeen

Oliko toimenpiteestä Teille haittavaikutuksia
□ ei □ kyllä, millaisia: ____

Tilanne pidemmällä aikavälillä (<u>noin 3 kuukautta</u> toimenpiteestä)

Miten toimenpide helpotti korvaoireitanne (3 kk)
□ korvaoireet poistuivat kokonaan
□ korvaoireet helpottuivat jonkin verran
□ korvaoireet säilyivät ennallaan
□ alkuperäiset korvaoireet pahenivat toimenpiteen jälkeen

<u>Nykyiset</u> korvaoireet
□ minulla ei ole enää minkäänlaisia korvaoireita
□ korvien lukkoisuus
□ korvakipu

□ äänien kaikuminen
□ kuulonalenema
□ toistuvat äkilliset välikorvatulehdukset
□ toistuva nesteen tai liimaeritteen kertyminen välikorvaan/ välikorviin
□ hankalat paineentasausongelmat (esim. lentäessä, sukeltaessa)
□ ilman puhaltaminen korvaan/ korviin ei onnistu
□ muu, mikä: ____

Tarvitsetteko nykyisin lääkityksiä tai muita hoitoja korvaoireiden vuoksi
□ en □ kyllä, millaisia: □ toistuvia ilmastointiputkia
□ nenän säännöllistä hoitoa (kortisonisuihkeet, allergialääkkeet)
□ säännöistä reflux-taudin hoitoa
□ muuta lääkitystä: __________________

Muuta

Olisitteko tullut toimenpiteeseen jälkikäteen arvioiden
□ kyllä □ en, koska: ____

Tupakoitteko nykyisin □ en □ kyllä, määrä: _____/ vrk

Appendix 1B. English translation of the questionnaire.

Study of **Eustachian tube balloon dilation**

Questionnaire for the patient

Name: ______________________________ Social Security number: _______________

Before operation

The main symptoms you had before the operation:

- □ Feeling that the ear is clogged
- □ Ear pain
- □ Reverberation of sound
- □ Hearing loss
- □ Recurrent acute otitis
- □ Recurrent effusion in the middle ear
- □ Equalization problems (e.g., when flying or diving)
- □ Other, what: ____

Duration of the symptoms before operation: ______years ______ months

Before the operation, ear symptoms were treated with the following methods:

- □ Allergic nasal symptoms / nasal obstruction
  - □ Antihistamine
  - □ Nasal corticosteroid spray
  - □ Operation; when and where? ___________________________________
- □ Sinusitis
  - □ Nasal corticosteroid spray
  - □ Operation; when and where? ___________________________________
- □ Proton-pump inhibitor medication used for reflux
- □ Grommet insertion
  - □ once □ multiple times
- □ Another ear operation; when and where?

  ____
- □ Other way, what?

  ____

Smoking before operation: □ No □ Yes, amount of tobacco: _____/ day

Situation immediately after the operation (approximately 1 to 2 weeks after)

Ear symptoms after the operation (1 to 2 weeks)
- □ Ear symptoms were relieved completely
- □ Ear symptoms were relieved slightly
- □ Ear symptoms remained unchanged
- □ Ear symptoms worsened

Did you have any adverse effects from the operation?
□ No □ Yes, what: ____

Situation after a longer time (approximately 3 months after)

Ear symptoms after the operation (over 3 months)
- □ Ear symptoms were relieved completely
- □ Ear symptoms were relieved slightly
- □ Ear symptoms remained unchanged
- □ Ear symptoms worsened

Current ear symptoms
- □ No ear symptoms of any kind
- □ Feeling that the ear is clogged
- □ Ear pain
- □ Reverberation of sound
- □ Hearing loss
- □ Recurrent acute otitis
- □ Recurrent effusion in the middle ear
- □ Equalization problems (e.g., when flying or diving)
- □ Unable to equalize ear pressure by blowing air into the ears
- □ Other, what: ____

Do you currently need medication or other treatments because of your ear symptoms?
□ No □ Yes, what:
- □ Grommet insertions
- □ Nasal treatments (corticosteroid spray, allergy medication)
- □ Ongoing treatment for reflux
- □ Other medication: _________________________________

Other

Would you have had the operation if you could decide again now?
□ Yes □ No, because: ____

Current smoking: □ No □ Yes, amount of tobacco: _____/ day

Appendix 2. Questionnaire used in Study IV.

Appendix 2A. Questionnaire in Finnish

Kysely korvatorven pallolaajennuksen tehosta

Nimi: ____

Henkilötunnus: ____________________________________

Ammatti: ____

Vastauspäivämäärä: ________________________________

Alla on väittämiä, joissa pyydämme vertaamaan **nykyistä** eli pallolaajennuksen jälkeistä tilannetta pallolaajennusta edeltävään tilanteeseen.

1. Onko sinulla korvien paineentasausongelmia?

☐	☐	☐	☐	☐	☐
Ei lainkaan	Selvästi vähemmän	Vähemmän	Saman verran	Enemmän	Selvästi enemmän

2. Onnistuuko korvien paineen tasaus Valsalvan manööverillä (=ilman puhaltaminen korviin sierainten ollessa suljettuna)?

☐	☐	☐	☐	☐	☐
Selvästi paremmin	Paremmin	Saman verran	Huonommin	Selvästi huonommin	Ei lainkaan

3. Lentäminen/sukeltaminen onnistuu?

☐	☐	☐	☐	☐	☐
Selvästi paremmin	Paremmin	Samalla lailla	Huonommin	Selvästi huonommin	Ei lainkaan

4. Käytätkö lääkkeitä korvien paineentasausongelmien vuoksi esim. lentäessä? (Duact, Nasolin, Otrivin tms.)

☐	☐	☐	☐	☐	☐
En aikaisemminkaan	En enää	Vähemmän	Samalla tavalla	Enemmän	Aina

Alla on väittämiä koskien **nykyistä** tilannetta.

5. Pystytkö tasaamaan korvien paineen (Valsalvan tekniikalla tai muuten)?

☐ Lähes aina
☐ Yleensä (en flunssassa)
☐ Maan tasalla (en lentokoneessa tms.)
☐ En pysty

6. Joudutko rajoittamaan lentämistä/sukeltamista korvien paineentasausongelmien vuoksi?

☐ Pystyn lentämään normaalisti
☐ Olen vähentänyt lentämistä
☐ En pysty lentämään

7. Ovatko korvien paineentasausongelmat vaikuttaneet töihisi? (voit jättää vastaamatta, jos et lennä töiden vuoksi)

☐ Jatkoin töissä ilman ongelmia
☐ Jatkoin töissä, mutta ongelmia esiintyy
☐ Olen joutunut vaihtamaan töitä

8. Onko sinulla ollut pallolaajennuksen jälkeen pallolaajennuksen puoleisessa korvassa seuraavia ongelmia? (voit valita useamman vaihtoehdon)

☐ Tärykalvon repeämä
☐ Välikorvatulehdus
☐ Lääkärin tekemä reikä tärykalvolle
☐ Lääkärin laittama putki tärykalvolle
☐ Ei mitään yllä olevista

9. Oliko pallolaajennus mielestäsi hyödyllinen?

☐ kyllä
☐ ei
☐ auttoi vain jonkin aikaa. Kuinka kauan toimenpiteestä oli apua? __________

10. Menisitkö nykytietojesi mukaan korvatorven pallolaajennustoimenpiteeseen uudestaan, jos korvaoireesi palaisivat toimenpidettä edeltäneelle tasolle?

☐ kyllä
☐ en

11. Onko mielessäsi jotain muuta, mitä haluaisit kertoa tutkijoille?

Appendix 2B. English translation of the questionnaire.

Questionnaire after balloon dilation of the tuba auditive

Name:____

Social security number:__________________________

Occupation:___________________________________

Date of answer:________________________________

Below are questions where we ask you to <u>compare your **current** state, meaning after the balloon dilation, to your state before balloon dilation.</u>

1. Do you now have problems with equalizing ear pressure?

☐ Not at all ☐ Significantly less ☐ Less ☐ As much as before ☐ More ☐ Significantly more

2. Can you equalize ear pressure with Valsalva's maneuver (=blowing air to the ears when pinching nose closed)**?**

☐ Significantly better ☐ Better ☐ Same ☐ Worse ☐ Significantly worse ☐ Not at all

3. Can you fly or dive?

☐ Significantly better ☐ Better ☐ Same ☐ Worse ☐ Significantly worse ☐ Not at all

4. Do you use medication for ear pressure problems e.g. when flying? (e.g. Duact, Nasolin, Otrivin)

☐ Never did ☐ Not anymore ☐ Less ☐ Same ☐ More ☐ Always

Below are <u>questions concerning your **current** state.</u>

5. Can you equalize your ear pressure (with Valsalva's maneuver or some other way)**?**

☐ Almost always ☐ Normally (not with the flu) ☐ On ground level (not when flying) ☐ Not at all

6. Do you have to limit your flying or diving because of the problems with ear pressure equalization?

☐ I can fly normally ☐ I have reduced my flying ☐ I cannot fly

7. Have ear equalization problems affected your work? (If you do not fly for work, you can leave this question empty.)

☐ I continued without problems ☐ I continued, but I have problems ☐ I switched jobs

8. Have you had any of the following problems in the operated ear after the balloon dilation? (Choose all that apply)

☐ Eardrum perforation
☐ Middle ear infection
☐ Paracentesis of tympanic membrane
☐ Insertion of a ventilating tube through the tympanic membrane
☐ None of the above

9. Did you benefit from the balloon dilation in your own opinion?

☐ yes
☐ no
☐ only for a while. If so, how long did you benefit from the balloon dilatation: _________

10. With your current knowledge, would you have balloon dilation again if your symptoms returned to the level they were before the operation?

☐ yes
☐ no

11. Do you have something else you would like to share with the researchers?

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