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SURGICAL TREATMENT OF OBSTRUCTIVE EUSTACHIAN TUBE DYSFUNCTION

Joonas Toivonen

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To my family

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ABSTRACT

Obstructive Eustachian tube dysfunction is the inability of the Eustachian tube to sufficiently open in order to ventilate the middle ear and can result in acute otitis media, or even chronic otitis media with or without cholesteatoma. Treatment of obstructive Eustachian tube dysfunction has traditionally been targeted at the tympanic membrane or the adenoid. Balloon dilation of the Eustachian tube has been shown to be safe and effective. However, the procedure has mostly been performed in adults and under general anesthesia.

In this study, we first studied the efficacy of balloon dilation of the Eustachian tube in pediatric patients. Next, we studied performing balloon dilation under local anesthesia in adults with a comprehensive anesthesia protocol. We examined the possibility of recanalization to restore normal function in patients with total obliteration of the Eustachian tube. Finally, in a multicenter study, we studied the risk of patulous dysfunction after dilation and determined risk factors for developing symptoms of patulous dysfunction.

We found that balloon dilation was a safe procedure in pediatric patients. The need for additional procedures was significantly lower in children treated with balloon dilation than with tympanostomy tube placement. In adults, the procedure was feasible under local anesthesia with significant improvement in middle ear ventilation. A procedure to recanalize a totally obliterated Eustachian tube was shown to be effective. After balloon dilation, the rate of patulous dysfunction symptoms was 7%. Pediatric patients, patients undergoing repeat dilation and patients with severe Eustachian tube mucosal inflammation were at a greater risk for patulous dysfunction after balloon dilation.

Balloon dilation of the Eustachian tube is safe and effective in pediatric patients and feasible under local anesthesia in adults. Total obstruction of the Eustachian tube can be surgically opened. There is a small risk for developing patulous dysfunction symptoms after the dilation procedure.

KEYWORDS: Eustachian tube, Eustachian tube dysfunction, obstructive dysfunction, balloon dilation, reconstruction of the Eustachian tube, patulous dysfunction

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TIIVISTELMÄ

Korvatorven vajaatoiminnassa välikorvan ilmastointi ei toimi normaalisti. Pitkittyessään vajaatoiminta voi aiheuttaa muun muassa äkillisiä tai kroonisia korvatulehduksia, ja kolesteatooman kehittymisen. Korvatorven vajaatoimintaa on perinteisesti hoidettu tärykalvoputkituksella ja kitarisaleikkauksella. Korvatorven pallolaajennus on osoitettu turvalliseksi ja tehokkaaksi toimenpiteeksi vajaatoiminnan hoidossa. Toimenpide on tehty pääasiassa yleisanestesiassa aikuisille.

Tämän tutkimuksen ensimmäisessä työssä selvitimme korvatorven pallolaajennuksen tehoa lapsilla pitkäaikaisen korvatorven vajaatoiminnan hoidossa. Toisessa työssä tutkimme pallolaajennusta paikallispuudutuksessa aikuisilla. Lisäksi tutkimme korvatorven muovausleikkausta normaalin toiminnan palauttamiseksi korvatorven täystukkeuman hoitona. Neljännessä työssä tutkimme riskiä avoimen korvatorven oireiluun pallolaajennuksen jälkeen sekä sille altistavia tekijöitä.

Pallolaajennus todettiin turvalliseksi toimenpiteeksi lapsipotilailla. Riski joutua uuteen toimenpiteeseen oli merkittävästi matalampi lapsilla, jotka hoidettiin pallolaajennuksella verrattuna lapsiin, jotka hoidettiin tärykalvoputkituksella. Korvatorven pallolaajennus on mahdollista tehdä paikallispuudutuksessa aikuisilla. Korvatorven pallolaajennuksella hoidetuilla potilailla todettiin merkittävä paraneminen välikorvan ilmastoitumisessa. Korvatorven muovausleikkaus osoittautui toimivan täysin tukkeutuneen korvatorven hoidossa. Pallolaajennuksen jälkeen avoimen korvatorven oireita todettiin 7 %:ssä hoidetuista korvista. Riski oli suurin lapsilla, uusintatoimenpiteen jälkeen ja potilailla, joilla on voimakkaat korvatorven tulehduslöydökset.

Korvatorven pallolaajennus on turvallinen ja tehokas toimenpide lapsipotilailla ja voidaan tehdä aikuisille paikallispuudutuksessa. Täysin tukkeutunut korvatorvi voidaan muovausleikkauksella saada toimivaksi. Riskinä korvatorven pallolaajennuksessa on avoimen korvatorven oireiden esiintyminen osalle potilaista.

AVAINSANAT: korvatorvi, korvatorven toimintahäiriö, korvatorven vajaatoiminta, korvatorven tukkeutuminen, pallolaajennus, avoin korvatorvi

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Abbreviations

ATM	standard atmosphere
BDET	balloon dilation of the Eustachian tube
CT	computed tomography
daPa	decaPascal (pressure unit)
ET	Eustachian tube
ETD	Eustachian tube dysfunction
ETDQ-7	seven-item Eustachian tube dysfunction questionnaire
ETS	Eustachian tube score
FDA	Food and drug administration
GA	general anesthesia
ICA	internal carotid artery
LA	local anesthesia
LVP	levator veli palatine -muscle
mbar	millibar
ME	middle ear
OETD	obstructive Eustachian tube dysfunction
OME	otitis media with effusion
PETD	patulous Eustachian tube dysfunction
RCT	randomized controlled trial
SSCD	superior semicircular canal dehiscence
TM	tympanic membrane
TMR	tympanic membrane retraction
TT	tympanostomy tube
TVP	tensor veli palatine -muscle

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 Toivonen J, Kawai K, Gurberg J, Poe D. Balloon Dilation for Obstructive Eustachian Tube Dysfunction in Children. *Otology & Neurotology,* 2021 Apr 1;42(4):566-572.

II Toivonen J, Dean M, Kawai K, Poe D. Comparison of Outcomes for Balloon Dilation of the Eustachian Tube Under Local vs General Anesthesia. *Laryngoscope Investigative Otolaryngology*, 2022; Jun 24;7(4):1120-1128.

III Toivonen J, Poe D. Reconstruction of the Obliterated Eustachian Tube: A Pilot Case Series. *The Laryngoscope*. 2023 Aug;133(8):1970-1975.

IV Hubbell RD, Toivonen J, Kawai K, Kim HJ, Nieman CL, Ward BK, Poe DS. Patulous Eustachian Tube Dysfunction Symptoms Following Balloon Dilation. *The Laryngoscope*. 2023 Nov;133(11):3152-3157.

1 Introduction

The Eustachian tube (ET) connects the middle ear (ME) with the nasopharynx. Pressure equalization between the middle ear and ambient pressure requires proper function of the ET. At rest, the ET is closed and opens with active muscular contraction. The active part of the ET is the functional valve located in the cartilaginous nasopharyngeal portion of the tube. In addition to pressure equalization, a normally functioning ET provides clearance of secretions from the middle ear and protection from sounds and material from the nasopharynx (Bluestone & Bluestone, 2005).

Eustachian tube dysfunction (ETD) is a spectrum of disorders ranging from obstructive ETD (OETD) to patulous ETD (PETD) (Bluestone & Bluestone, 2005). OETD is the inability of the ET to sufficiently open in order to adequately ventilate the ME. Obstructive Eustachian tube dysfunction (OETD) can become chronic causing acute otitis media (AOM), persistent or recurrent otitis media with effusion (OME), tympanic membrane retraction (TMR), hearing loss, chronic otitis media and ultimately cholesteatoma (Schilder et al., 2015). A severe form of OETD is complete obliteration of the ET. In patients with a lesser degree of OETD in barochallenge-induced dysfunction, difficulty ventilating the ME only occurs when subjected to rapid changes in ambient pressure. At the other end of the spectrum is PETD with a constantly open ET. In PETD, the abnormally open ET results in the inability of the ET to protect the ear from sounds causing the hearing of one's own voice and breath unusually loudly (autophony).

Treatment of OETD has traditionally been targeted indirectly at the adenoid or the tympanic membrane (TM) with tympanostomy tube (TT) placement. In children, given the potential of improvement of ET function with growth, adenoidectomy and TT placement are still the primary treatment methods (Rosenfeld et al., 2022). Any underlying inflammatory condition such as allergic rhinitis and laryngopharyngeal reflux disease should be recognized and addressed (Mills & Hathorn, 2016). In PETD, symptoms are often relatively mild and manageable with counselling and medical or behavioral management, but operative treatment methods, such as mass loading of the TM, are available for difficult cases (Ward et al., 2019).

Balloon dilation of the Eustachian tube (BDET) was introduced in 2010 as a treatment directly addressing the site of pathology and has since gained popularity among physicians treating OETD. Several studies including randomized controlled trials (RCT) have shown BDET to be a safe and effective procedure (Meyer et al., 2018; Poe et al., 2018). However, there is limited experience with BDET in children, although some studies have been published (Tisch et al., 2017). In children, the anatomy and responsiveness to treatment may differ from adults and these need to be carefully contemplated when considering treatment with BDET. As BDET has become more familiar, interest in performing the procedure in the office setting under local anesthesia has been increasing. Studies on the feasibility and different anesthesia protocols for performing BDET have had variable success. However, given the possible advantages of improved patient safety and reduced costs, performing BDET under local anesthesia could be beneficial (Catalano et al., 2012; Dean & Pynnonen, 2019). In patients with total obliteration of the ET, reopening and establishing an open ET between the nasopharynx and the ME is the only way to potentially restore normal function (Ward et al., 2013). However, long-term results on ET reconstruction have not been reported in the literature. BDET, like any surgical intervention, carries risks for complications. Most commonly reported risks include local bleeding and subcutaneous emphysema (Huisman et al., 2018). The risk of developing PETD is often mentioned but there are no reports on the incidence of patulous dysfunction after BDET.

In this study, we investigated the feasibility of BDET in children, BDET under local anesthesia, and recanalization of the obliterated ET. Furthermore, we studied the risk of developing symptoms of patulous Eustachian tube after BDET.

2 Review of the Literature

2.1 Anatomy of the Eustachian tube

The ET functions as a valve between the ME cavity and the nasopharynx. The length of the ET in adults is approximately 31 to 38 mm and the length of the cartilaginous portion is approximately 25 mm (Proctor, 1973). In infants, the length of the ET is approximately half of that in adults and full length is typically reached at the age of seven (Sadler-Kimes et al., 1989). The anteromedial nasopharyngeal two-thirds contains a cartilaginous skeleton while the posterolateral one-third, a continuation of the protympanum of the middle ear narrowing towards the bony-cartilaginous junction, is surrounded by bone. The body of the cartilaginous ET is formed by an inverted J-shaped cartilage with a longer medial and shorter lateral lamina. A complex arrangement of peritubal muscles responsible for tubal function is attached to the cartilage. A submucosal layer of lymphatics and Ostmann's fat pad form the thickness and convexity of the lumen (Bluestone & Bluestone, 2005; Proctor, 1973).

From the nasopharynx, the ET courses initially posteromedially, then posterolaterally and superiorly towards the middle ear (ME) in the shape of a slowly curving inverted S. The angle related to the horizontal plane is about 45 degrees in adults but only 10 degrees in infants (Proctor, 1973). The bony portion is always open while the cartilaginous ET is closed at rest and opens actively with muscular exertion. The actively opening part, the functional valve, extends from within a centimeter from the nasopharyngeal orifice to a few millimeters distal to the bony-cartilaginous junction. The narrowest portion of the ET, the isthmus, is located at the proximal end of the cartilaginous portion just distal to the bony-cartilaginous junction (Poe et al., 2000). (**Figure 1**)

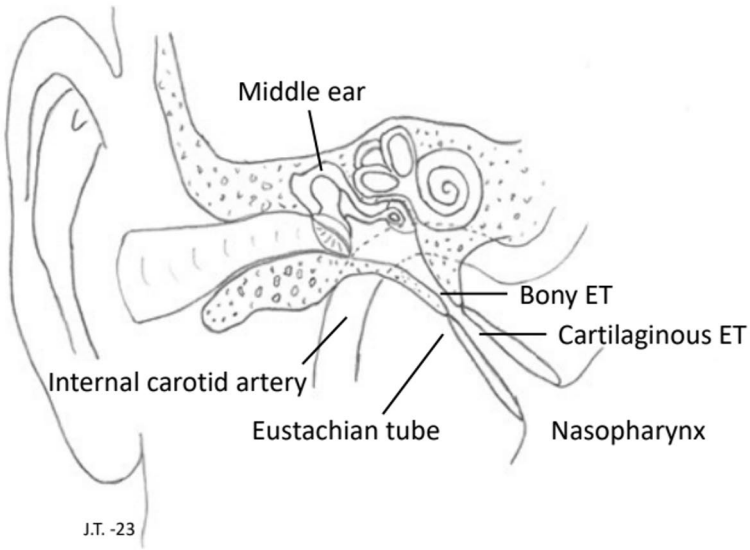

Figure 1. Anatomy of the Eustachian tube, right ear. ET, Eustachian tube. Author's own drawing.

Mucosa of the Eustachian tube

The bony portion of the Eustachian tube is lined by a thin layer of columnar respiratory epithelium. The nasopharyngeal two-thirds, the cartilaginous portion, is lined by pseudostratified columnar ciliated respiratory epithelium also containing mucoid and lymphoid cells (Honjo et al., 1985). The mucus-producing goblet cells are concentrated in the inferior aspect of the lumen. At the pharyngeal orifice of the ET, the epithelium is histologically identical with that of the nasopharynx (Martin et al., 2017).

Muscles connected to the Eustachian tube

There are four muscles connected to the functioning of the Eustachian tube; levator veli palatini (LVP), tensor veli palatini (TVP), salpingopharyngeus and pterygoid medialis. The LVP originates from the inferior part of the petrous apex of the temporal bone. It passes inferomedially to the ET paralleling and lying beneath the tubal cartilage and the floor of the lumen inserting into the soft palate. LVP is connected to the medial cartilage of the ET by loose connective tissue. LVP is not a primary dilator of the ET but adds to the support and contributes to the function by elevating the medial arm of the cartilage at the nasopharyngeal end. It serves as a scaffold against which the inefficiently arranged TVP muscle can contract (Bluestone & Bluestone, 2005; Ishijima et al., 2002; Poe et al., 2000).

The TVP is formed of a lateral and medial bundle. The lateral bundle originates from the scaphoid fossa and the greater wing of the sphenoid bone forming an

inverted triangle. It descends anteriorly, laterally and inferiorly forming a tendon that rounds the hamulus of the pterygoid bone to insert into the palatine bone and the palatine aponeurosis of the velum. The medial bundle lies immediately medial to the lateral membranous wall of the cartilaginous ET originating from the posterior part of it. This inner bundle, also called the dilator tubae muscle, is primarily responsible for the active dilation of the ET. The fibers descend to blend with the fibers of the lateral bundle (Bluestone & Bluestone, 2005; Ishijima et al., 2002).

The salpingopharyngeus muscle originates from the medial and inferior borders of the tubal cartilage. It is fixed to the tubal cartilage via strings of muscular and tendinous fibers. It inserts into the posterior pharynx wall with the palatopharyngeal muscle. Consisting of only a few muscle fibers it is likely unable to perform physiologically (Bluestone & Bluestone, 2005).

One part of the medial pterygoid muscle originates from the lateral pterygoid plate of the sphenoid bone and the second part from the pyramid process and the maxillary tuberosity of the palatine bone. The muscle affects the muscular compliance of the ET by interaction with the TVP (Leuwer et al., 2002).

2.2 Physiology of the Eustachian tube

The three main functions of the ET include:

1) Ventilation and pressure equalization of the ME facilitating optimal surroundings for TM vibration and sound transmission
2) Clearance of secretions from the ME by gravity and active mucociliary function
3) Protection of the ME from reflux of sounds and nasopharyngeal contents.

Certain functions of the ET require it to open and others to remain closed. Opening occurs beginning from the nasopharyngeal orifice and progating towards the middle ear, then closing in the reverse direction. Middle ear pressure is maintained by middle ear mucosal gas exchange and opening of the ET. In the healthy middle ear, pressure slowly decreases and periodic openings of the ET equilibrate toward ambient pressure. Equilibration of middle ear pressure with ambient pressure occurs during brief dilations of the Eustachian tube lumen as a result of actions of principally the LVP and TVP muscles during swallowing or yawning (Sade, 1984).

2.2.1 Muscular action of the Eustachian tube

The bony portion of the ET is always open and active functions occur in the cartilaginous portion of the ET. At rest, the cartilaginous two-thirds is closed. The

segment in which the active opening takes place is 5-15 mm in length, extending proximally to within a few millimeters from the bony isthmus, and acts as the functional valve of the ET (Poe et al., 2000).

Contraction of the LVP muscle elevates the soft palate and rotates the medial cartilaginous lamina and the torus tubarius medially (Proctor, 1973). This provides a stable platform for the subsequent TVP muscle contraction that lateralizes the lateral membranous wall opening the ET lumen (Alper et al., 2012; Honjo et al., 1979). One opening sequence takes about 0.4 seconds (Mondain et al., 1997).

Closure of the valve occurs in reverse order beginning from the isthmus valve in the direction of the nasopharynx. Relaxation of the TVP moves the lateral wall medially closing the ET followed by relaxation of the LVP. This order of closure functions as the muscular pumping action aiding in clearing secretions from the ET in addition to the mucociliary function (Cantekin et al., 1983; Honjo et al., 1983).

2.2.2 Middle ear gas exchange

For optimal hearing and function of the tympano-ossicular chain, middle ear pressure needs to be equivalent with the atmospheric pressure. Under normal conditions there is a steady gas exchange between the tympanic cavity and the blood compartment while the ET supplies an intermittent transfer of gas between the tympanic cavity and the nasopharynx to maintain a healthy balance.

A constant gas exchange normally occurs in the middle ear and mastoid due to diffusion across a gradient (Ostfeld & Silberberg, 1991). Oxygen, carbon dioxide, and nitrogen equilibrate with the venous blood, which has lower partial pressures of these gases (**Table 1**), causing the pressure in the middle ear space to become progressively lower than ambient atmospheric pressure as long as the Eustachian tube remains closed (Pau et al., 2009). Under physiologic conditions, diffusion of gases through the round window and the tympanic membrane is very limited (Doyle, 2017).

Table 1. Partial gas pressure values in different locations. (mmHg, Csakanyi 2014; Harell 1996; Sade 1995)

	P_{tot}	P_{O2}	P_{CO2}	P_{N2}	P_{H20}
Atmospheric air	760	150	0	563	47
Venous blood	704	38	44	575	47
Nasopharynx	760	112-120	27-32	557-569	47
Middle ear	760	40	50	623	47

P_{tot}=total pressure, P_{O2}=partial pressure of oxygen, P_{CO2}=partial pressure of carbon dioxide, P_{N2}=partial pressure of nitrogen, P_{H2O}=partial pressure of water vapor.

Opening of the ET is the result of a neural feedback reflex mechanism where mechano- (and possibly chemo-) receptors of the TM and middle ear cavity report pressure changes to respiratory brain stem centers which results in the activation of the muscles responsible for opening the ET (Eden et al., 1990). The mean opening time of the ET has been measured to be between 0.34 s and 0.43 s (Gaihede et al., 2013; Mondain et al., 1997) while the full duration of muscular activity during openings is 0.995 s (Poe & Pyykkö, 2011). The pressure gradient between the middle ear and ambient air has not been shown to affect the duration of each opening but rather stimulates a series of openings instead (Elner et al., 1971; Gaihede et al., 2013).

The average middle ear gas volume is 0.5 to 0.6 ml. The mastoid air cell system adds between 1 ml to 30 ml to this volume and acts as a pressure buffer adding volume to the middle ear cavity (Doyle, 2007; Sadé & Ar, 1997). Poor mastoid pneumatization in diseased ears likely increases the effects of negative middle ear pressure in the absence of the buffer mechanism (Sadé & Ar, 1997).

The antero-inferior part of the tympanomastoid cavity, more specifically the protympanum, mesotympanum, hypotympanum and retrotympanum, are lined by ciliated epithelium. The ciliated epithelium, either secretory or non-secretory together with goblet cells, is principally responsible for the clearance function. The distance between the center of the blood vessels and the basal membrane is greater in the ciliated epithelial area which adds to the resistance thus diminishing the possibilities for gas exchange. The epitympanum, aditus ad antrum, mastoid antrum and the mastoid cavity, comprising the postero-superior part of the tympanomastoid cavity are covered by a highly vascularized cuboidal epithelium. The distance between blood vessels and basal membrane is smaller, characteristic of respiratory epithelium performing the specific function of gas exchange. Overall, these characteristics distinguish two separate areas of the tympanomastoid cavity, the antero-inferior part devoted to mucociliary cleareance and the postero-superior part mainly devoted to gaseous exchange (Ars et al., 1997; Csakanyi et al., 2014; Gaihede et al., 2010).

During inflammation, blood flow increases enabling a faster diffusion of gases from the ME. In addition, the distance between the blood vessels and the basal membrane shortens which further increases gas flow. These factors contribute to the development of more severe negative ME pressure that can lead to middle ear diseases such as otitis media with effusion (Ars et al., 1997; Bluestone & Bluestone, 2005; Sadé & Ar, 1997).

2.3 Eustachian tube dysfunction

Eustachian tube dysfunction (ETD) is a spectrum of disorders that ranges from obstructive ETD (OETD) to patulous ETD (PETD) (Bluestone & Bluestone, 2005). OETD is the inability to open the lumen of the ET adequately in order to ventilate the ME and PETD occurs with difficulty closing the lumen. A milder form of obstructive dysfunction and a separate entity is barochallenge-induced ETD with symptoms of obstructive dysfunction only when subjected to sudden pressure changes. ETD can be further defined as acute when lasting for up to three months and chronic when signs and symptoms persist for over three months (Schilder et al., 2015).

In a previous study, the prevalence of Eustachian tube dysfunction among adults in the United States was estimated to be 4.6% (Shan et al., 2019). The definition of ETD was tympanometric middle ear pressure less than -100 daPa in either ear. Subjects were required to not have had a cold, sinus problems or earache during the last 24 hours and head cold or chest cold during the last 30 days. According to the study, ETD would affect a total of 11 million individuals in the U.S. Using the same criteria, in another study, the prevalence of ETD in adolescents was estimated to be 6.1% in the United States (Patel et al., 2016). Health care visits related to ETD, OME or TMR account for over 2.6 million visit yearly in the United States in patients 0 to 20 years of age and for another 2 million visits in patients over 20 years of age (McCoul et al., 2019). The visits for ETD were more frequent in children, for every 1 visit in children, 0.77 visits occurring in adults. Annual cost of medication for ETD was reported to be over $8.5 million in the U.S. with a mean of $80 per patient.

There are no studies estimating the prevalence in the Finnish population. However, with the prevalence of 4.6% ETD would affect 250000 individuals in Finland.

2.3.1 Obstructive dysfunction

With obstructive Eustachian tube dysfunction, the ET fails to adequately perform its ventilatory function. The ET opens either insufficiently often or does not open sufficiently. The underlying reason for OETD may be anatomical obstruction or physiologic failure (Tucci et al., 2019). Possible etiologies for OETD include mucosal inflammation in the ET causing functional obstruction or failure of dilation, muscular issues resulting in dynamic dysfunction, hereditary factors and true anatomical obstruction due to neoplasms, scarring, or other mass lesions. The resulting inadequate ventilation of the ME and insufficient clearance of secretions can lead to secondary ear pathology. Due to the constant gas absorption from the ME, negative pressure can progressively develop until tissue transudates fill the vacuum, creating a middle ear effusion (Pau et al., 2009). Tympanic membrane

retraction or ME effusion can be observed on otoscopy or otomicroscopy with insufflation or as a type B or type C tympanogram. One of the most important clinical findings in the diagnostics of OETD is the negative pressure persisting within the middle ear.

The most common cause of OETD is mucosal inflammation within the cartilaginous Eustachian tube. Any history of inflammatory disease including environmental and seasonal allergies, adenoid hypertrophy, reflux disease and chronic rhinosinusitis should be considered along with exposure to tobacco smoke when diagnosing OETD (Takahashi et al., 1996). The torus tubarius contains adenoid-like lymphoid follicles called the tubal tonsil of Gerlach and glandular tissue that can enlarge in inflammatory conditions. This swelling can cause obstruction at the nasopharyngeal orifice and also extend into the lumen of the ET (Emerick & Cunningham, 2006). Adenoid hypertrophy with associated hypertrophy of the torus tubarius causes OETD in both children and adults (Nistico et al., 2011; Paradise et al., 1990).

A less common cause for OETD is muscular dysfunction involving the muscles responsible for ET opening, the two most important being the levator veli palatini and the tensor veli palatini muscles (Poe et al., 2001). In case of muscular disease or craniofacial anomalies, the muscles may be inherently weak, underdeveloped or unfavorably oriented. The most common symptomatic abnormality is the decreased action of the tensor veli palatini muscle. This results in reduced strength in lateralizing the anterolateral wall therefore possibly limiting the final opening of the ET valve (Poe et al., 2000). Cleft palate repair surgery may result in superior suspension of the levator veli palatini muscle resulting in functional limitation of tubal opening (Bluestone, 2008).

Anatomical obstructions caused by neoplasms are uncommon, but must be suspected especially in adult patients presenting with persistent unilateral middle ear effusion (Rohde et al., 2022). Total obstruction of the ET, unilateral or bilateral, is rare but causes chronic middle ear effusions and hearing deficiency (Ward et al., 2013). Surgery, trauma or diseases resulting in nasopharyngeal scarring can affect the ET orifice and result in total obstruction of the ET. A surgical procedure, such as adenoidectomy or turbinectomy, may cause unexpected scarring (Abdel-Aziz et al., 2019). ET obstruction after orthognathic surgery has been reported as a consequence of altered anatomy or scarring (Jędrzejewski et al., 2015; Wong et al., 2002; Yaghmaei et al., 2009). Primary mucosal diseases such as granulomatosis with polyangiitis and sinonasal sarcoidosis have been shown to cause scarring resulting in total obstruction (Braun et al., 2004).

2.3.2 Barochallenge-induced dysfunction

Symptoms of barochallenge-induced ETD may only occur during rapid or significant changes in ambient pressure, for example when flying or diving (Lynch & Deaton, 2014; Wright, 2015). The effort needed to open the ET valve is increased during rapid pressure changes. Typical symptoms of difficulties in pressure equalization are aural fullness, decreased hearing and otalgia that can persist for hours or days (Ryan et al., 2018). More severe complications include middle ear effusion, hemotympanum or tympanic membrane perforation (Livingstone et al., 2017). In rare extreme situations, the pressure may be transmitted to the inner ear, causing round window rupture, sensorineural hearing loss or vestibular dysfunction (Raymond et al., 2022).

At ambient pressure, patients with barochallenge-induced ETD are asymptomatic and present with normal otoscopic and tympanometric findings. They may also have little or no endoscopically visible pathology along the spectrum of tubal disease on endoscopic evaluation. The diagnosis is based on the consistent history of barochallenge-induced symptoms in combination with the observation of potential pathology on endoscopic examination (Oehlandt et al., 2022; Poe et al., 2001).

2.3.3 Patulous dysfunction

With patulous dysfunction, the ET is unable to fully close when relaxed. This is caused by a concave defect that is typically located longitudinally in the anterolateral wall of the Eustachian tube instead of the normal convex bulge that aids in closing the functional valve (Poe et al., 2001). Incomplete closure results in the inability of the ET to protect the middle ear from sounds and secretions from the nasopharynx.

The anterolateral wall consists of mucosa, submucosa, the lateral cartilaginous lamina, Ostmann's fat and the tensor veli palatini muscle. Conditions affecting these structures can predispose to patulous dysfunction. Comorbidities commonly associated with patulous dysfunction are allergic rhinitis, laryngopharyngeal reflux and weight loss (Ward et al., 2017). Atrophy of the mucosa and submucosa has been observed in patients in the nasal and sinus mucosa with chronic nasal allergies and laryngopharyngeal reflux. Chronic increased tension in the lateral wall has been associated with stress and anxiety, which is possibly due to chronic contraction of the tensor veli palatini and medial pterygoid muscles. A congenitally small lateral cartilaginous lamina can also be a contributing factor for the development of PETD. Other reported risk factors of PETD include radiation therapy, pregnancy, and hormone replacement therapy (Plate et al., 1979; Young et al., 1997). Symptomatic patulous dysfunction is often multifactorial.

2.4 Diagnostics of Eustachian tube dysfunction

The diagnosis of Eustachian tube dysfunction is based on both patient reported symptoms and objective findings (Smith et al., 2019). Neither subjective symptoms nor any current single test alone is enough to determine diagnosis. Several tests measuring Eustachian tube function have been developed but they have not gained widespread acceptance because of either poor reliability, impracticality, or lack of correlation with clinical presentation (Doyle et al., 2013). An international consensus statement recommended the following to be included in the assessment of ETD depending on availability: 1) otoscopy or otomicroscopy, 2) tympanometry, 3) Rinne's and Weber's tuning fork tests or pure tone audiometry, and 4) nasopharyngoscopy to inspect the opening of the Eustachian tube (Schilder et al., 2015). The clinical consensus statement by the American Academy of Otolaryngology – Head and Neck Surgery Foundation on balloon dilation of the Eustachian tube agreed on the necessity of otoscopy, tympanometry, pure tone audiometry, and endoscopic investigation of the nasopharynx prior to considering BDET (Tucci et al., 2019).

Symptoms consistent with ETD are nonspecific and may also be present in several other otologic conditions. Typical complaints include aural fullness, pressure in the ear, hearing loss, discomfort or pain, popping, clicking and clogging of the ear, and autophony (Schilder et al., 2015). Possible causes of these symptoms include obstructive Eustachian tube dysfunction, patulous Eustachian tube dysfunction, temporomandibular disorders, superior semicircular canal (otic capsule) dehiscence, endolymphatic hydrops (Ménière's disease), and otologic migraine (Lopez-Escamez et al., 2015; Minor, 2005; Moshtaghi et al., 2018; Riga et al., 2010).

Typical symptoms of negative middle ear pressure with obstructive dysfunction are aural fullness, pressure in the affected ear, hearing loss, or pain in the ear (Huisman et al., 2018). A history of otitis media and either recurrent or persistent middle ear effusion is common (McCoul et al., 2019). Hearing loss is often associated with retraction of the tympanic membrane or middle ear effusion. In barochallenge-induced ETD, the lead complaint is difficulty or inability to clear the ears during rapid pressure changes (Livingstone et al., 2017; Ryan et al., 2018). A myringotomy or a tympanostomy tube should relieve the symptoms for the duration of the perforation in the tympanic membrane or a diagnosis other than OETD should be considered. The negative pressure in the middle ear should be confirmed by examination, testing, or in the case of barochallenge-induced ETD, by a consistent history.

On examination, a retracted tympanic membrane or effusion in the middle ear are suggestive of obstructive Eustachian tube dysfunction. Pneumatic otoscopy with negative pressure insufflation is 94% specific and 80% sensitive in recognizing ME effusion, but does not inform measurement of the ME pressure (Smith & Tysome,

2015). Tympanogram will typically be type C or B indicating negative pressure or middle ear effusion, respectively. A fixed retraction pocket, an atelectatic tympanic membrane or even cholesteatoma may, however, be due to previous obstructive ET dysfunction and not necessarily be indicative of active dysfunction. Patients with barochallenge-induced ET dysfunction, while asymptomatic in normobaric conditions, usually have a normal otoscopic examination and tympanogram (Tucci et al., 2019).

With patulous Eustachian tube dysfunction, typical symptoms are autophony of voice and breathing sounds together with symptoms of aural fullness or pressure. Autophony of pulse may also be experienced (O'Connor & Shea, 1981). Symptoms may present continuously, but in a study of demographics by Ward et al. only 35% of patients were persistently symptomatic (Ward et al., 2017). More often symptoms are intermittent and can be triggered by physical activities like exercising, prolonged talking or singing, dehydration, caffeine, diuretics and decongestants (Schilder et al., 2015; Ward et al., 2017). Symptoms are often relieved in the supine position or during upper respiratory infections (Oshima et al., 2007). Patulous symptoms may be relieved with inducing negative pressure towards the middle ear by sniffing. The Eustachian tube may in this way close temporarily with negative pressure but the negative pressure can also cause progressive TM retraction or effusion that can be mistaken for OETD (Sakakihara et al., 1993).

In patients with symptomatic patulous ETD, movement of the tympanic membrane with breathing may be observed during otoscopy while autophony is active. Examination should be done with the patient in seated position to avoid venous congestion and temporary closure of the valve. Excursions of the TM are best observed with ipsilateral nasal breathing (contralateral nostril and mouth closed) (Oshima et al., 2007). Ward et al. found that 82% of patients with patulous dysfunction had TM excursions with nasal breathing during otoscopy and 96% had a defect consistent with patulous dysfunction in the ET on nasopharyngoscopy (Ward et al., 2017). A continuous column of air in the ET may be visible on CT imaging in some patients with PETD. Cone beam CT that is performed in the sitting position increases the possibility of detecting a long column of air within the lumen of the ET (Oonk et al., 2014). Findings on tympanometry may be normal or show either negative middle ear pressure or hypermobility of the TM (Poe, 2007). Fluctuation between obstructive and patulous dysfunction may also occur depending on exacerbation of contributing factors which may make the diagnosis challenging. Such fluctuations are particularly common in patients with chronic allergic rhinitis, depending on whether their allergic condition is active or quiescent.

2.4.1 Differential diagnosis

Otic capsule dehiscence, typically superior semicircular canal dehiscence (SSCD), can present with aural fullness and auditory symptoms such as conductive hearing loss and autophony with or without the classic signs of oscillopsia and pressure- or sound-induced vertigo (Minor, 2005). Symptoms may also be improved with supine position making differentiation from patulous Eustachian tube challenging (Zhou et al., 2007). Autophony from dehiscence usually involves voice, footsteps, eye-movements and other bone-conducted noises instead of breath, which is usually prominent in patulous dysfunction (Zhou et al., 2007). Imaging with computed tomography (CT) and vestibular evoked myogenic potential testing are used to confirm the diagnosis (Belden et al., 2003).

Temporomandibular disorders, including temporomandibular joint dysfunction and disorders of the muscles of mastication, can cause symptoms commonly attributed to obstructive Eustachian tube dysfunction including aural fullness, clicking and popping sounds, and pain and pressure in the ears (Schilder et al., 2015). Adding to the challenge of the differential diagnosis, temporomandibular disorders commonly occur concurrently with obstructive and patulous Eustachian tube dysfunction (Riga et al., 2010). The medial pterygoid muscle may serve as an auxiliary dilatator of the valve of the ET and may be associated with PETD (Ward et al., 2017).

2.4.2 Audiometry

Audiometry is routinely performed when evaluating for ETD since patients with ETD commonly report hearing loss. With obstructive Eustachian tube dysfunction, conductive hearing loss is common as a result of negative pressure or effusion in the middle ear (Huisman et al., 2018). With patulous dysfunction, subjective hearing loss may result from autophony and voice distortion affecting hearing. The autophony of breathing may cause a masking effect that can increase auditory thresholds (Ward et al., 2017).

2.4.3 Function tests

Several tests have been developed to objectively measure Eustachian tube function. Due to issues with reliability, impracticality or lack of correlation with clinical outcomes, none of the tests have been adopted into widespread use (Alper et al., 2017; Casselbrant et al., 2014; Doyle et al., 2013). Smith et al. published a comprehensive review of Eustachian tube function testing and concluded that since ETD occurs from a variety of etiologies, no single currently available test adequately evaluates function. Therefore, it is best to employ a battery of tests that in

combination with the history and physical examination, can lead to an accurate diagnosis (Smith et al., 2018).

Valsalva and Toynbee maneuvers

In the Valsalva maneuver, the nose is blown against a closed mouth and nose generating positive pressure in the nasopharynx. Subjective Valsalva is positive when the air is felt passing through the ET into the ME resulting in an increase in ME pressure in a positive direction. The result can be objectively evaluated with either noting lateralization of the TM via otoscopy or recording a change in pressure with tympanometry (Bluestone & Bluestone, 2005). The maneuver is nonphysiological and even if positive, it does not necessarily reflect ET opening in physiological circumstances.

In the Toynbee maneuver, the subject swallows while holding the nose closed. A swallow should initiate ET opening and the resulting pressure change in the ME can be noticed either by the subject or objectively by the examiner via otoscopy or tympanometry. As there is no positive pressure being generated by a nose blow in this maneuver, it usually creates a negative change in ME pressure (Bluestone & Bluestone, 2005).

Tympanometry

Tympanometry measures ET function by indirectly measuring middle ear pressure as a response to changes in TM compliance when applying varying air pressure in the ear canal (Jerger, 1970). The ME has a theoretical normal pressure of zero (ambient atmospheric pressure) with 95% of healthy subjects ranging between -20 daPa and +20 daPa. Tympanometry is effective in detecting ME effusion with a sensitivity of 94% and a specificity of 95% (Shekelle et al., 2002). A normal tympanogram result is type A with a high peak between -100 daPa and +100 daPa. Obstructive ET dysfunction is usually noted as a type B tympanogram indicating middle ear effusion with a flat tympanogram or type C with negative middle ear pressure showing a sharp peak below -100 daPa. With patulous dysfunction, the tympanogram is often normal (Bluestone & Bluestone, 2005). However, variations in compliance synchronous with breathing can be seen while autophony is active using the reflex decay mode to generate a continuous measurement of ear canal pressure. Testing for breathing-synchronous compliance of the TM with tympanometry was found to be 75% sensitive and 97% specific in detecting PETD (McGrath & Michaelides, 2011).

A single tympanometry measurement provides no information on ET opening and tympanogram results can vary over the course of a few hours (Grøntved et al.,

1989). In a test-retest study by Gaihede et al., it was shown that although TM compliance might be increased with repeated testing over a short period of time (in the absence of opening of the ET during that interval), fluctuations then represent true middle ear pressure changes (Gaihede & Ovesen, 1997).

Forced response test

Performing the forced response test requires either a TM perforation or a patent tympanostomy tube. Air is delivered through a sealed probe in the external ear canal into the middle ear until the ET opens at the tubal opening pressure. Air flow is continued to find a steady state of pressure that keeps the ET open. The pressure at which the ET closes is recorded. The measurements can also be performed during swallowing in order to acquire information on active ET function and tubal resistance (Cantekin et al., 1979; Swarts et al., 2011).

Inflation-Deflation test

The inflation-deflation test measures active ET function. It is performed with a probe in the ear canal through which first positive pressure is applied and pressure changes during repeated swallows are recorded until reaching a plateau. Next, the procedure is repeated with similar negative pressure. The residual pressure and the number of swallows required to reach it are recorded (Bluestone & Bluestone, 2005). In a previous study, healthy adults were able to equilibrate 83% of the applied positive inflation pressure and 67% of the deflation pressure (Swarts et al., 2011).

Tubomanometry

Tubomanometry is performed with a pressure transducer in the ear canal and a nasal applicator delivering pressure to the nasopharynx. While the patient swallows, a defined pressure ramping up to 30, 40, or 50 mbar is delivered in the nasopharynx. Pressure changes within the external auditory canal from movement of an intact TM or through a perforation are recorded. The pressure at which the ET opens in response to a change in the ear canal pressure is considered the opening pressure. In addition to the opening pressure, the latency of the ET opening from the swallow-triggered pressure build-up in the nasopharynx until the resultant opening of the ET is measured. An R value is calculated from the latency measurements and $R \leq 1$ indicates normal ET function (Alper et al., 2017). Schröder et al. compared tubomanometry results between healthy subjects and patients with chronic OETD. They found immediate opening in 94% in healthy subjects and delayed opening in 58% of OETD patients, with a pressure of 30-50 mbar concluding that

tubomanometry can be used to support the diagnosis of OETD (Schröder et al., 2015).

Sonotubometry

Sonotubometry measures opening of the ET placing a sound source into the nostril and a microphone into the external ear canal. If the ET opens during a swallow, an increased sound volume can be detected in the ear canal. Detection of an increase of ≥ 10 dB over baseline during a swallow is consistent with opening of the ET. Testing is usually performed in atmospheric pressure and sonotubometry is one of the few tests testing ET function under physiological pressure conditions (van der Avoort et al., 2006). With sonotubometry, the rate of detectable ET openings is reported to be 63-92% in healthy adults, 37-80% in healthy children, 47% in adults with ETD, and 27-29% in children with OME (van der Avoort et al., 2005, 2009).

2.4.4 Patient reported outcome measures

ETDQ-7

The seven-item Eustachian tube dysfunction questionnaire (ETDQ-7), published in 2012 by McCoul et al., was the first validated instrument for assessment of ETD and it remains the most widely used (McCoul et al., 2012). It is a questionnaire comprising of seven questions, each scored on a scale from 1 (no problem) to 7 (severe problem). A total score of <14.5 or a mean item score of <2.1 is considered normal. The ETDQ-7 is a useful tool in measuring the effect of treatment and correlates with symptoms but not with objective measures of ET function (Teixeira et al., 2018). Symptoms such as tinnitus, ear pain and muffled hearing can also be present with other pathologies such as semicircular canal dehiscence and temporomandibular joint disorders. Therefore, it cannot be used for diagnosis.

Eustachian Tube Score (ETS) and ETS-7

The Eustachian tube score (ETS) was introduced by Ockerman et al. in 2010 (Ockermann et al., 2010) and the ETS-7 with two additional items by Schröder and colleagues in 2015 (Schröder et al., 2015). The ETS combines subjective estimates of Valsalva and Toynbee maneuvers and three separate tubomanometry results at varying pressures, while the ETS-7 additionally has tympanometry and objective Valsalva measured. The tests are scored from 0 (no function) to 2 (normal function) points per item with a total score of 0-10 for the ETS and 0-14 for the ETS-7. The ETS has a reported sensitivity of 91% and specificity of 86% in detecting chronic

OETD while for the ETS-7, a sensitivity and specificity of 96% has been reported (Schröder et al., 2015).

2.4.5 Endoscopy of the Eustachian tube

Advancements in endoscopic technology during the 1970s and 1980s increased interest in endoscopy of the Eustachian tube, first to better understand physiology and later to advance knowledge on pathophysiology (Jaumann et al., 1980; Takahashi et al., 1996; Wang et al., 1992). Further improvements in both camera technology and the use of high definition video have led to better image resolution and the ability to observe Eustachian tube action in slow motion (Poe et al., 2001). With microendoscopy of the bony portion of the Eustachian tube it has been shown that the obstructive pathology in OETD is usually in the cartilaginous portion. Even in cases with middle ear effusion, the bony Eustachian tube was seen free of obstruction and pathology was commonly observed as inflammation of the mucosa in the cartilaginous ET (Linstrom et al., 2000).

Endoscopy of the nasopharynx and Eustachian tube orifice is considered essential in the evaluation of suspected ETD (Schilder et al., 2015; Tucci et al., 2019). The anatomy and dynamic function can be evaluated with an angled endoscope or a flexible nasopharyngoscope. With a view of the ET lumen, including the anterolateral and posteromedial walls, pathology of the ET can be observed together with the quality of the opening and closing of the functional valve. The size of the adenoid and possible contact to the torus tubarius are evaluated together with the tubal tonsil tissue and any potential scarring. The fossa of Rosenmuller is inspected for masses (Chen et al., 2019). Possible lymphoid hypertrophy or cobblestoning of the torus mucosa obstructing the orifice should be noted. Static findings do not necessarily indicate pathophysiology and therefore a dynamic examination is valuable (Poe et al., 2000).

A series of actions from the closed resting state to actively dilated open position are observed. The convex bulge of the anterolateral wall closes the ET lumen at rest. First, the contraction of the LVP muscle results in the elevation of the soft palate and medial rotation of the torus tubarius. The contraction holds through the opening process. Second, the TVP within the anterolateral wall contracts causing the anterolateral wall to take a concave form, opening the lumen of the ET beginning from the nasopharyngeal orifice and progressing towards the isthmus. Closure of the ET occurs in reverse order from the isthmus to the nasopharynx (Poe et al., 2000). The muscular actions visible by endoscopy correlated with measurements of simultaneous muscular activity in a study by Alper et al. who recorded electromyographic potentials from the levator and tensor muscles during swallows

along with verification of the resulting tubal opening by sonotubometry (Alper et al., 2016).

2.4.6 Pathology on endoscopy

Causes of OETD include intrinsic pathology from inflammatory mucosal disease or extrinsic pathology from adenoid hypertrophy or adenitis. Potential associated conditions that may be causative include allergic rhinitis, chronic rhinosinusitis and laryngopharyngeal reflux among others (McCoul et al., 2019; Vila et al., 2017).

A grading scale for the degree of ET inflammation and functional impairment has been validated by Kivekäs et al. as follows: (Kivekäs, Pöyhönen, et al., 2015)

Grade 1: Normal mucosa and normal dilation

Grade 2: Mildly inflamed mucosa, no apparent compromise of dilation

Grade 3: Moderately inflamed mucosa or some compromise of dilation

Grade 4: Severely inflamed mucosa, unable to dilate open

Blockage caused by nasopharyngeal neoplasms is uncommon, but should be evaluated by endoscopy and with imaging if suspected (Tsunoda et al., 2019). Muscular discoordination or muscular deficiency causing loss of opening function can result from anatomical abnormalities in conditions such as trisomy 21 or cleft palate, or neuromuscular conditions (Shott, 2006).

Dynamic endoscopic evaluation can show hypertrophy of the adenoid, tubal tonsil, and torus tubarius that can cause OETD in children and adults (Paradise et al., 1990). A hypertrophic adenoid may cause impingement of the torus during dilatory effort. During dilation the torus should rotate medially but a hypertrophic adenoid or torus tubarius can restrict this movement, forcing it instead to move anteriorly obstructing the ET lumen. This is called anterior thrusting and it is commonly encountered with OETD (Nguyen et al., 2004; Poe et al., 2001).

Patulous dysfunction resulting in the inability to close the ET valve completely is usually a result of a concave defect in the normally convex anterolateral wall that extends the full length of the valve. A concave defect limited to the ET orifice is common and is not diagnostic for patulous dysfunction (Poe, 2007; Poe et al., 2001).

Chronic allergic disease can result in bulky inflammatory mucosa in combination with mucosal atrophy. However, inflammation at the tubal orifice may not be present within the valve region of the lumen. Atrophy of the mucosa and or submucosa in the anterolateral wall of the ET can make them translucent through which the yellow coloration of the Ostmann's fat pad or the appearance of the tensor veli palatini muscle may be visible. This patchy atrophy may predispose to patulous dysfunction (Ward et al., 2017).

2.5 Treatment of Eustachian tube dysfunction

2.5.1 Medical management

2.5.1.1 Medical management of obstructive dysfunction

Several studies have concluded that medical management alone is not effective in treating primary OETD and OME with systemic decongestants, antihistamines, nasal topical decongestants, or nasal corticosteroids in the absence of identifiable treatable causes (Norman et al., 2014; Tucci et al., 2019). However, the presence of any underlying condition such as laryngopharyngeal reflux, allergic rhinitis, and rhinosinusitis that could predispose to OETD should be recognized and managed before other interventions are considered (Mills & Hathorn, 2016; Sone et al., 2011). All aforementioned conditions cause mucosal inflammation which has been shown to be a frequent finding with OETD with 83% of patients seen with mucosal edema and 74% with secondary decreased ET anterolateral wall mobility (Adil & Poe, 2014). Smoking has been shown to reduce ciliary motility in adult patients with OME and cessation of smoking should be recommended (Agius et al., 1995). Targeted treatment for any predisposing condition or factor may result in improvement of associated symptoms of OETD (Tucci et al., 2019).

Gluth et al. conducted a placebo-controlled trial of 91 subjects aged 6 to 95 years. They found no significant difference in groups of patients with OME or negative middle ear pressure treated with intranasal corticosteroids compared to placebo in terms of tympanogram normalization (Gluth et al., 2011).

In a randomized controlled trial (RCT) by Jensen and colleagues, 36 patients with OETD aged 12 or older were assigned to two groups. Either a nasal decongestant spray with xylometazoline chloride or placebo with saline was sprayed directly to the nasopharyngeal ET orifice. No significant difference between the active treatment and the placebo group was detected (Jensen et al., 1990).

In a RCT by Cengel et al., children between 3 and 15 years of age diagnosed with chronic OME waiting for tympanostomy tube placement or adenoidectomy were randomized to receive either intranasal mometasone furoate or no treatment for six weeks. A significant difference in clearance of the ME fluid was noticed in favor of the treatment group with 42.2% resolution compared to 14.5% in the control group (Cengel & Akyol, 2006).

A meta-analysis by Mehta et al. examined the combined results of publications on medical management of adult ETD (Mehta et al., 2022). They concluded that with medical management only, significant improvement in patient reported outcome measures (ETDQ-7) was not achieved. Also, while tympanogram results were improved in patients with ETD, the likelihood of improvement of tympanogram was

moderate from 27-33%. The results of potential benefits of intra-nasal corticosteroid treatment were consistent with the earlier published RCTs, finding no improvement either in symptoms or in tympanogram results. This is also consistent with the most recent update to the American Academy of Otolaryngology Clinical Practice Guidelines on otitis media with effusion (OME) in children with a Grade A recommendation against the use of topical corticosteroids in addition to antibiotics, decongestants or antihistamines (Rosenfeld et al., 2016).

McCoul et al. studied the prescription patterns and health care utilization for ETD in the U.S. on patients with ETD, OME or TMR (McCoul et al., 2019). Patients with an acute upper respiratory infection within three months, previous head and neck cancer, or radiation therapy were excluded. ETD was diagnosed in 1.3 million patients with 11% having chronic ETD. Medical management was frequent with 54% of patients receiving at least one prescription. Prescriptions included antibiotics for 22% of the patients with acute ETD and 6% with chronic ETD, oral corticosteroids for 12% of the patients with acute and 2% with chronic ETD, intranasal corticosteroids for 22% of the patients with acute and 3% with chronic ETD, and analgesics for 6% with acute and 2% with chronic ETD.

Since there is no effective medical management for chronic OETD in which no underlying treatable etiology has been identified, in addition to the need for education on appropriate use of medical management, there is a need for other treatment modalities (McCoul et al., 2019).

2.5.1.2 Medical management of patulous dysfunction

The aim in the treatment of patulous dysfunction is to restore functional closure of the Eustachian tube. Use of any substances that cause patulous symptoms including decongestants, antihistamines, topical nasal steroids, caffeine, or diuretics should be minimized. Even though weight loss is a risk factor and associated with onset of patulous symptoms, only 14% of patients were noted to have minor symptom alleviation with weight gain making it an ineffective treatment modality and can only be recommended if the patient is undernourished and underweight (Ward et al., 2017). Sufficient hydration especially when exercising should be encouraged. Medications stimulating mucus production such as saturated solution of potassium iodide (SSKI) three times a day is well tolerated (Dyer & McElveen, 1991). Hydrochloric acid, boric acid, silver nitrate, salicylic acid and phenol as topical irritants have been used in the past to induce mucosal edema and increase mucus production. More recently, commercially available topical ascorbic acid drops have been employed (Adil & Poe, 2014). Topical estrogen drops have had some effectiveness in causing mucosal hypertrophy, thus relieving symptoms. With all

medical options the effect or duration of symptom relief is individual and lasts usually for only a limited time (Adil & Poe, 2014; Poe, 2007).

2.5.2 Surgical treatment

Surgical intervention can be considered if appropriate medical management has failed to adequately treat persistent ETD. In the event that other predisposing conditions including chronic rhinosinusitis, turbinate hypertrophy, nasal septal deviation or adenoid hypertrophy are present, symptomatic and possibly contributing to OETD, operative treatment of those conditions can be considered if indicated (Adil & Poe, 2014). Adenoid hypertrophy, especially of the lateral portion against or near the torus tubarius, can interfere with the rotation of the torus during ET opening. If the endoscopic evaluation demonstrates that the primary difficulty in opening of the ET valve is due to the effects of adenoid or tubal tonsil hypertrophy, adenoidectomy (possibly including light cauterization of the tubal tonsil tissue in the medial one-half of the torus) may be the only intervention needed (Nguyen et al., 2004).

Tympanostomy tubes have been the principal procedure used for management of chronic OETD. Either a myringotomy or tympanostomy tube is expected to relieve the symptoms of obstructive dysfunction by providing pressure equalization, bypassing the ET entirely. If the symptoms and signs return after closure of the tympanic perforation, a repeat procedure or an alternative procedure, such as balloon dilation of the Eustachian tube, may be considered. An alternative procedure may also be indicated without prior myringotomy or tube. Importantly, failure of a tube to resolve symptoms thought to be due to chronic obstructive dysfunction is an indication for consideration of a different diagnosis. The symptoms of OETD should be improved with a myringotomy or tube while the perforation remains open (Tucci et al., 2019). Tympanostomy tube placement for pediatric patients remains the first line treatment for chronic OETD given the potential of anatomical and physiological growth contributing to maturation of the ET with time (Rosenfeld et al., 2022).

A myringotomy or tympanostomy tube placement has also showed some benefit in relieving symptoms of patulous dysfunction, possibly by the effect of mass loading altering the impedance of the middle ear system or by helping with the sensation of the TM moving during breathing (Poe, 2007; Smith et al., 2019).

2.5.2.1 Surgical treatment of obstructive Eustachian tube dysfunction

Laser Eustachian tuboplasty (LETP) was the first procedure to treat ETD targeted to the cartilaginous portion of the ET and it was limited to the region at and adjacent to the nasopharyngeal orifice (Kujawski, 2000). The procedure aims to reduce

hyperplastic mucosa, submucosa and in more severe cases, part of the cartilage of the posteromedial wall in order to achieve a functioning ET. Either diode, carbon dioxide or argon laser have been used to ablate excess tissue with an endonasal or a combined transoral and endonasal approach (Kujawski & Poe, 2004; Poe et al., 2007). In a preliminary study on ten patients with refractory OME, the safety and potential efficacy with 60% clearance of ME effusion at 12 months was shown (Poe et al., 2003). Kujawski and Poe performed laser Eustachian tuboplasty for a total of 108 ears and reported achievement of normal ME aeration for 69% of ears at 12 months, 70% at 24 months, and 60% at 36 months (Kujawski & Poe, 2004). In another study by Poe et al. on thirteen patients, laser Eustachian tuboplasty resulted in 38% clearance of ME effusion at 1 year and 40% at 2 years. There was a strong correlation between failure to clear ME effusion and other risk factors like reflux and allergic disease (Poe et al., 2007). Caffier and colleagues performed LETP successfully under local anesthesia on 31 patients. They also included patients with TM perforations resulting from chronic otitis media in addition to OME patients. Successful Valsalva, verified with either otomicroscopy or tympanometry, was achieved in 66% of patients at 1 year (Caffier et al., 2011). In a review on laser Eustachian tuboplasty, Miller et al. concluded that while the procedure seemed safe, the data on efficacy, especially long-term, was limited (Miller et al., 2017).

Microdebrider Eustachian tuboplasty was introduced by Metson et al. as a procedure to similarly remove inflamed tissue from the posteromedial wall of the ET (Metson et al., 2007). Debulking of the hypertrophic mucosa and submucosa from the luminal side should allow regrowth of a healthy uninflamed mucosa (Adil & Poe, 2014). All patients were also diagnosed with sinonasal disease and underwent concurrent sinus surgery. There were no complications related to surgery. With a mean follow-up of 13 months, subjective ear blockage improved in 70% and tympanogram improvement was documented in 65% of the patients. However, the authors concluded that since concurrent sinus surgery was performed, it was not possible to determine the proportion of each procedure on ETD symptom improvement.

2.5.2.2 Balloon dilation of the Eustachian tube

Balloon dilation of the cartilaginous portion of the Eustachian tube (BDET) has been established as a safe and effective treatment for chronic obstructive Eustachian tube dysfunction during recent years. Clinical studies have shown the pathology of the ET to usually be situated within the cartilaginous portion (Poe et al., 2001; Takahashi et al., 1996). The ability to dilate the cartilaginous lumen of the ET with an inflatable balloon was first shown in cadaver studies (Poe & Hanna, 2011). The bony portion should not be dilated because of the close proximity of the internal carotid artery.

There is the risk of damaging the internal carotid artery especially in the case of a bony dehiscence along the lumen of the ET.

The clinical consensus statement on balloon dilation of the Eustachian tube from the American Academy of Otolaryngology – Head and Neck Surgery by Tucci et al. requires the following symptoms or findings for BDET to be indicated (Tucci et al., 2019) (Requires both 1 and 2):

1) Requires each of the following:
    a. Chronic symptoms of obstructive Eustachian tube dysfunction (defined as ≥3 months duration)
    b. Symptoms persistent despite appropriate directed medical therapy (if indicated)
    c. Objective pathological findings on dynamic endoscopic examination of the Eustachian tube

2) Requires at least one of the following:
    a. Persistent OME or TM retraction with negative pressure on insufflation AND type B or C tympanogram
    b. Consistent history of barochallenge

The most commonly used devices employ a guide catheter through which the balloon catheter is inserted. The guide catheter containing the balloon is delivered under direct endoscopic view through the nasal cavity to the ET opening. Both the guide catheter and the endoscope can be passed through the same nasal passage when the anatomy is favorable, or the endoscope can be passed through the contralateral side. The balloon catheter is advanced carefully into the Eustachian tube lumen along the anterolateral wall, which initially curves medially. The balloon catheter may be advanced the full length of the cartilaginous portion of the ET. Some devices with a sufficiently wide tip will yield a palpable stop upon contact with the isthmus. A calibrated mark on the balloon catheter should indicate the maximum length that should be inserted into the lumen (≤ 25 mm in adults). The balloon is then inflated to the pressure of 10-12 atmospheres (ATM) depending on the device. The duration of inflation is a maximum of 2 minutes and the duration can be reduced commensurate with associated factors such as the degree of inflammation or patient age. After the desired duration, the balloon is deflated, retracted from the ET lumen and removed. The ET is inspected for the effect and for possible injury.

Balloon dilation for obstructive dysfunction

Ockermann and colleagues first published the results of balloon dilation of the Eustachian tube in 2010 demonstrating improvement in tubomanometry scores in all eight patients with a 2-month follow up (Ockermann et al., 2010). In 2011, a study by Poe et al. on 11 patients found dilation of the cartilaginous ET to be safe and feasible with improvements in the ability to perform a Valsalva maneuver and tympanogram results with at least 6 months follow-up (Poe et al., 2011). Since then, the knowledge on safety and efficacy of BDET has accumulated along with increasing interest and research as surgeons have adopted the procedure in the treatment of OETD.

In a multicenter randomized controlled trial (RCT), balloon dilation of the Eustachian tube with medical management was compared with medical management alone (nasal steroids) on 323 patients assigned to either group (Poe et al., 2018). Patients were required to have OETD refractory to medical management and either C or B tympanograms to enter the trial. At 6 weeks after the procedure, normalization of tympanograms to type A was observed in 51.8% of the patients in the balloon dilation group and 13.9% of the patients in the control group. Improved scores in ETDQ-7 were seen in 90.6% and 45.1% in the BDET and control groups, respectively. Due to the cross-over trial design, between group comparisons could not be done beyond 6 weeks since there was a high rate of cross-over. At 24 weeks the ETDQ-7 improvement in the treatment arm was sustained at 59.8%, but comparisons could not be done since 82% of patients in the control arm had crossed over to the BDET group. A follow-up report on the treatment group at 12 months showed sustained results in terms of ETDQ-7 and tympanogram normalization indicating clinically relevant durability through 12 months (Anand et al., 2019).

In another multicenter RCT, patients were assigned to either the BDET group or the control group. ETDQ-7 scores and the rate of improvement of tympanograms between groups were compared at the 6-week timepoint with statistically significant improvement in both favoring the BDET group. The results of ETDQ-7 and middle ear function (TM position, Valsalva, tympanogram) improvements in the BDET group endured at the 12 month follow-up (Meyer et al., 2018). A long-term follow-up study on the treatment arm with a mean follow-up of 29 months showed statistically significant durable improvement compared to baseline in all measures including ETDQ-7 improvement, TM position, tympanogram and the ability to Valsalva (Cutler et al., 2019).

A third RCT comparing BDET with medical management for OETD was performed by Krogshede et al. (Kjær Krogshede et al., 2022). They compared 24 patients undergoing BDET or medical management for up to 6 months. Patients with OME or retraction of the TM and C or B tympanogram were included. In the BDET group, with 9 of 13 patients, normal TM and ME status was achieved compared to 0

out of 11 in the control group. A statistically significant improvement was also documented in tympanogram results. ETDQ-7 and audiogram results did not reach statistical significance which may be due to the small study population.

Several studies have reported improved outcomes after balloon dilation (Catalano et al., 2012; Dean, 2019; Satmis & van der Torn, 2018; Xiong et al., 2016). Studies assessing long-term outcomes with a follow-up time of 12 months or more are however limited (Cutler et al., 2019; Luukkainen et al., 2018). Sandoval et al. reported on results at two years after BDET with improvement in tympanogram for 74% in the chronic otitis media group, 69% in the adhesive otitis media group and 88% in the barochallenge-induced ETD group (Sandoval et al., 2023). A study on BDET with a mean follow-up of 2.5 years noted improvement from the preoperative inability to the postoperative ability to perform Valsalva in 80% of patients (Silvola et al., 2014). In a retrospective report with the Eustachian tube score (ETS) as the main outcome measure, statistically significant improvement for 82% of subjects at two years was reported, but the follow-up rate at two years was only 10% in the study (Schröder et al., 2015). Systematic reviews have concluded that while studies have documented improved results with success rates between 50%-98%, all of the retrospective studies reporting long-term results have been case series with several limitations and high risk of bias (Froehlich et al., 2020; Huisman et al., 2018; Luukkainen et al., 2018). Also, the studies have had heterogeneous inclusion criteria and different outcome measures making comparison difficult.

The mechanism of benefits caused by balloon dilation are not fully established. The extent of effect may vary between balloon size used, duration of inflation and depth of insertion. Additionally, dilation pressure could play a role although, in a biomechanical study, most tissue deformation was shown to occur well below the pressures that are in clinical use and repeat dilation did not increase effect (Smith et al., 2020). Balloons in current use are either non-compliant or semi-non-compliant. In a histopathology study by Kivekäs et al., biopsies were taken from the area of dilation immediately before and after the procedure. Before dilation, disordered epithelium with loss of cilia and submucosa containing inflammatory infiltrate with thick lymphoid follicles was found. Immediately after dilation, there was diffuse crush injury in the mucosa and submucosa with cases of partly stripped off epithelium down to the basal layer. The crush effect was severe in the lymphocytes and lymphoid follicles, but the submucosal glands located just deeper appeared intact. Follow-up biopsies taken 5-12 weeks later showed restoration of normal pseudocolumnar ciliated epithelium with the lymphoid follicles replaced with a thin layer of fibrous tissue reducing the overall inflammatory conditions in the ET (Kivekäs et al., 2015).

Balloon dilation for barochallenge-induced dysfunction

Balloon dilation for barochallenge-induced dysfunction was reported by Utz et al. on military divers and aviators unable to perform their work duties (Utz et al., 2020). Following treatment, 11/12 patients (92%) successfully returned to their operational duties with an average return time of 8.5 weeks. Mean ETDQ-7 scores improved from 4.33 preoperatively to 2.19 postoperatively (p=0.0063). In a questionnaire-based retrospective study with a mean follow-up time of 4 years and 8 months, 79% of patients who underwent BDET for barochallenge-induced ETD were able to resume flying normally and 93% of patients working in an occupation requiring flying were able to resume work free from symptoms (Oehlandt et al., 2022). A systematic review concluded that there is data only from retrospective reviews along with their inherent risk of bias and the studies are not necessarily comparable. However, BDET seems effective in treating barochallenge-induced ETD with an 83% improvement in the ability to Valsalva, 79% ability to return to work, and 79% having statistically significant decrease in ETDQ-7 scores (Raymond et al., 2022).

Balloon dilation in pediatric patients

Balloon dilation of the ET has been less commonly performed in children than in adults. Possible reasons for this include the efficacy of tympanostomy tubes for majority of children, lack of treatment recommendations and approval of balloon device use with pediatric patients, absence of pediatric size balloon devices, the risk of injury to the carotid artery, and the lack of scientific data on safety and efficacy of the procedure in children. For these reasons, in most studies, BDET has been performed on children with recalcitrant disease (Aboueisha et al., 2022). The first study on balloon dilation of the ET in children was published in 2015 and reported 80% improvement in ETD symptoms (Maier et al., 2015). Retrospective reports have since demonstrated significant improvement after BDET in clinical symptoms, TM appearance, tympanogram results, and hearing (Jenckel et al., 2015; Tisch et al., 2017; Tisch et al., 2020). Demir and Batman compared the effect of either BDET or tympanostomy tube insertion as first line treatment on the quality of life in children with a mean age of 7 years (Demir & Batman, 2020). Significant improvement was seen in both groups at the six week and one year follow-ups, but not to the advantage of either group. BDET was seen as a possibly safe alternative as first line treatment but not superior to tympanostomy tubes. Howard et al. analyzed the safety of BDET in a pediatric cohort of 42 patients. In their study, two children had a minor complication with a complication rate of 4.7%. One child had self-limiting epistaxis and one had vertigo which was later diagnosed as vestibular migraine. In a meta-analysis, Aboueisha et al. found a decrease in type B tympanograms from 64.2% preoperatively to 16.1% postoperatively after BDET, concluding BDET to be

comparable, if not superior, to ventilation tube insertion when treating chronic otitis media with effusion (Aboueisha et al., 2022).

Balloon dilation under local anesthesia

Performance of balloon dilation under local anesthesia has drawn interest among surgeons for reasons including avoiding the risks of general anesthesia to the patient, convenience of an in-office procedure, operating-room restrictions, and reduced treatment costs (Catalano et al., 2012; Meyer et al., 2018; Sheppard et al., 2023). Luukkainen et al. performed a feasibility study comparing BDET and endoscopic sinus surgery under local anesthesia (Luukkainen et al., 2017). In the BDET group, 77% found the pain relief to be sufficient, demonstrating a need for improvement in local anesthesia techniques. The majority of patients reported BDET more painful than sinus surgery. In another study on 33 patients, full dilation was performed on 31 (94%) patients with one patient experiencing significant discomfort during dilation and one patient aborting before the procedure. The other procedures were carried out uneventfully and 87% had normalized tympanograms at their 6 week postoperative visit (Dean, 2019). Chen et al. compared BDET under local anesthesia versus general anesthesia in 49 patients (X. Chen et al., 2020). There were no complications reported. Normalization of ETDQ-7 -scores was observed for 72% in the local anesthesia group and for 81% in the general anesthesia group at the 12 week timepoint. At 52 weeks, the results persisted in 63% and 80% in the local anesthesia and general anesthesia groups, respectively. A similar pattern was observed with Valsalva results with 94% in the general anesthesia group and 66% in the local anesthesia group being able to Valsalva at 12 weeks. A remarkable reduction in duration and costs of treatment was also observed when BDET was performed under local anesthesia compared to general anesthesia.

2.5.2.3 Reconstruction of the obliterated Eustachian tube

Reconstruction of the ET may be considered when the nasopharyngeal orifice or the lumen of the cartilaginous portion is totally obliterated. Obliteration can result from various etiologies such as external or iatrogenic trauma or systemic diseases causing scarring in the nasopharynx (Mills & Hathorn, 2016; Young, 2019). When the lumen is totally obliterated, pressure equalization or clearance of secretions from the middle ear through the ET is impossible. The chronic negative pressure in the ME results in retraction of the TM and accumulation of fluid in the ME necessitating pressure relief usually with tympanostomy tubes. However, repeat tympanostomies often result in a chronic TM perforation. Additionally, complete obliteration may be associated with thick viscous mucoid effusions that can repeatedly clog tympanostomy tubes.

Normal function of the obliterated Eustachian tube cannot be restored by medical management or balloon dilation. Restoring a patent lumen could give the Eustachian tube the possibility to function normally. Reconstruction can be performed with an illuminated guidewire inserted transtympanically to act as a guide while the reopening of the nasopharyngeal orifice is performed (Ward et al., 2013). Stenting the newly formed lumen is necessary in order to prevent re-scarring of the mucosal raw surfaces. Steroid-eluting stents have been used in sinus surgery to reduce the risk of re-scarring and could be beneficial in the ET also (Luong et al., 2018).

2.5.2.4 Surgical treatment of patulous dysfunction

Surgical treatment of patulous dysfunction can be considered when medical or behavioural management is not effective. Tympanostomy tube placement has been shown to be effective in 53% of patients with patulous dysfunction (Chen & Luxford, 1990). It can reduce the movement of the TM but usually does not help with the autophony. Symptoms have also been shown to alleviate with mass loading of the TM thus reducing the movement with breath. Temporary means have been studied and found effective with paper, tape and clay-like adhesive (Blu Tack™) (Bartlett et al., 2010; Boedts, 2014). If temporary measures are effective, a more permanent solution for TM stiffening has been achieved with tympanoplasty and cartilage grafting (Si et al., 2016). Treating the patulous Eustachian tube can be done by addressing the ET directly. Plugging the ET with the Kobayashi silicone plug from the middle ear via a myringotomy or a tympanotomy has been reported to be effective in up to 85% of patients (Ikeda et al., 2020; Kikuchi et al., 2017). Other surgical methods address the ET from the nasopharynx. Stenting the ET from the nasopharyngeal orifice with an angiocatheter filled with bone wax as a shim was shown to be effective in 75% of patients at 12 months from insertion (Ward et al., 2019). The shim is inserted the full length of the bony and cartilaginous ET and is therefore contraindicated in cases of bony dehiscence of the internal carotid artery (ICA) into the ET. The plug or the stent are removable if necessary. Augmentation of the ET lumen with injectable fillers in order to facilitate full closure of the valve has been studied. Calcium-hydroxyapatite is a non-permanent filler that Vaezeafshar et al. noted to be effective in 57%-63% of patients with PET symptoms (Vaezeafshar et al., 2014). Ward et al. reported on a high symptom reappearance rate with 68% of patients starting to have patulous symptoms again within a year from treatment (Ward et al., 2019). Other potential materials include polydimethylsiloxane elastomer (Vox) (Schröder et al., 2015), autologous fat and cartilage (Doherty & Slattery, 2003; Oh et al., 2016). Patulous Eustachian tube reconstruction surgery aims to narrow the ET lumen without totally occluding it. Techniques have included transposition of the medial cartilaginous lamina or insertion of graft material

including fat, cartilage or acellular dermal matrix (Alloderm) into a submucosal pocket (Poe, 2007). As a last resort, if debilitating patulous symptoms persist despite previous efforts, an option is to permanently obliterate the lumen of the ET. This will result in resolution of patulous symptoms but tympanostomy tubes will likely be needed due to chronic middle ear effusion. There can be production of thick mucoid effusions that clog tympanostomy tubes in some cases such that elective obliteration should be a treatment of last resort (Ward et al., 2019). Systematic reviews of surgical treatment of patulous dysfunction have concluded that comparison between methods is difficult since there is a wide range of experimental procedures with moderately successful outcomes (Hussein et al., 2015; Luu et al., 2015).

2.5.2.5 Complications of Eustachian tube procedures

As with all surgery, procedures involving the Eustachian tube have the risk of complications. Usually complications are mild and self-limiting such as nasal bleeding or local bleeding from the ET orifice due to mucosal injury in approximately 1% of cases (Huisman et al., 2018). Hemotympanum after dilation requiring myringotomy has been reported (McCoul & Anand, 2012) as well as acute otitis media (Wanscher & Svane-Knudsen, 2014).

Subcutaneous emphysema has been reported as a rare complication after BDET in case reports and one retrospective analysis with a complication rate of 0.3% (Jang & Yuen, 2022; Skevas et al., 2018). Subcutaneous emphysema is likely to occur due to mucosal injury during BDET. This can be caused by trauma to the mucosa or by creating a false passage during balloon insertion. In the reported cases the emphysema has mostly been limited to the parotid and cervicofacial area, but a case of mediastinal emphysema has also been reported (Shah et al., 2018).

The most feared complication is injury to the internal carotid artery which is located in close proximity with the bony ET (Olander et al., 2017). Jeoung et al. reported on a case of carotid dissection presenting with a stroke seven days after BDET (Jeoung et al., 2023). The patient made a full recovery after stent placement. Treble and colleagues studied the risk of entering the middle ear with a 3 x 20 mm balloon catheter in a cadaver model (Treble et al., 2023). They were able to enter the middle ear in all 16 ETs showing that with certain devices entering and potentially damaging middle ear structures is possible and caution regarding insertion depth is necessary. Computed tomography (CT) has been used to identify potential dehiscence in the carotid canal but CT scans have not shown relation in predicting difficulties intra- or postoperatively (Abdel-Aziz et al., 2014). Experience with BDET and knowledge of the anatomy is important when performing balloon dilation. With procedures extending closer to the bony portion such as ET

reconstruction, the risk should be taken into account and preoperative imaging performed.

In one study, self-limiting intensification of pre-existing tinnitus has been reported in three subjects (Skevas et al., 2018). In another study, hearing loss was reported after BDET in 0.3% of patients and permanent hearing loss in 0.08% of patients (Todt et al., 2021).

The onset of patulous symptoms after BDET is mentioned in single studies as a minor self-limiting complication without the need for additional interventions (Oehlandt et al., 2022; Satmis & van der Torn, 2018). A meta-analysis on pediatric BDET reported on two cases of self-limiting patulous symptoms after dilation (Aboueisha et al., 2022).

With surgery for PETD, minor complications of middle ear effusion, pain, epistaxis, and tinnitus have been reported (Hussein et al., 2015). Plug insertion transtympanically has been reported to have a 14% risk of TM perforation and a 17% risk of developing middle ear effusion (Ikeda et al., 2020). With shim insertion, 52% of patients and with hydroxyapatite injections, 11% of patients needed subsequent tympanostomy tube insertion (Ward et al., 2019). The use of Teflon as an injection agent has been abandoned after past incidents of cerebral embolism and death, possibly due to injection into the internal carotid artery. With improvements in endoscope technology and knowledge in surgical anatomy the safety of injections has improved (Poe, 2007).

3 Aims of the study

The aims of this study were to investigate the efficacy and safety of surgical treatment of obstructive Eustachian tube dysfunction including balloon dilation of the Eustachian tube in pediatric patients, balloon dilation of the Eustachian tube under local anesthesia, reconstruction of the obliterated Eustachian tube, and to assess the rate of patulous Eustachian tube dysfunction symptoms after balloon dilation.

The specific aims of this study were:

1. To study the efficacy, safety and long-term results of balloon dilation of the Eustachian tube in pediatric patients compared to matched controls treated with tympanostomy tubes. (Study I)
2. To investigate the feasibility and long-term results of BDET under local anesthesia compared to general anesthesia and to present a comprehensive and effective local anesthesia protocol. (Study II)
3. To study the effectiveness and long-term results of reconstruction of the totally obliterated ET and to describe the technique for reconstruction. (Study III)
4. To assess the incidence and risk factors for patulous ETD symptoms following BDET. (Study IV)

4 Materials and Methods

4.1 Patients and outcome measures

4.1.1 Pediatric patients (I)

In Study I, pediatric patients aged 7 to 17 years undergoing balloon dilation of the ET at Boston Children's Hospital, Boston, USA, between 2013 and 2017 were included. Requirements for BDET were persistent symptoms of ETD or non-fixed tympanic membrane retraction that had failed to improve with optimal medical therapy as indicated and treatment of any identified underlying conditions such as allergy or reflux. All patients were previously treated with tympanostomy tube placement according to guideline suggestions. Patients with conditions increasing susceptibility for recurrent ear infections including trisomy 21 and other syndromes, craniofacial anomalies, cleft palate, chronic inflammatory diseases, chronic ear disease except for OME or AOM or immunodeficiency were excluded.

The control group was collected from pediatric patients treated at Boston Children's Hospital between 2010 and 2017 for chronic or recurrent OME or non-fixed TM retraction with tympanostomy tube placement. The subjects in the BDET treatment group and the control group were matched by number of prior tympanostomy tubes, age, gender, and history of adenoidectomy as closely and consecutively as possible in order to minimize the risk of bias. Exclusion criteria were the same for the tympanostomy tube placement group as for the BDET treatment group.

Outcomes measured were the ability to perform modified Valsalva, otomicroscopy findings, tympanometry, audiometry, and ET mucosal inflammation score. Clinically successful outcomes after BDET were defined as: 1) normal or mildly retracted TM by otomicroscopy and 2) tympanogram type A or type C with normal hearing. Failure was defined as the absence of clinically successful findings including: 1) OME, moderate or severe TM retraction, atelectasis, or retraction pockets by otomicroscopy or 2) type B or type C tympanogram with decreased hearing (as for example after cartilage graft tympanoplasty, tympanogram may be type B because of the stiffness of the TM with an aerated middle ear and no hearing loss), or 3) the need for tympanostomy tube placement.

4.1.2 Patients undergoing dilation under local or general anesthesia (II)

Retrospective review was done of 191 consecutive adult patients aged ≥18 years with persistent OETD who underwent BDET between 2013-2018 at Ear and Sinus Institute, Baylor Surgical Hospital, Fort Worth, USA either under general anesthesia (n=133) or local anesthesia (n=58). Indications for surgery were 1) persistent symptoms of aural fullness and hearing loss with type B or C tympanograms or 2) consistent symptoms of aural fullness with pain when barochallenged with type A tympanogram for over three months. All patients were treated with medical therapy for at least four weeks including a trial of nasal steroid spray unless medically contraindicated. Additionally, in case of evidence of allergic rhinitis or laryngopharyngeal reflux, antihistamines or proton pump inhibitors (PPIs) were prescribed for a minimum of four weeks. Patients with type A tympanograms and normal otoscopic findings were required to have significant and consistent barochallenge complaints. All patients had inflammatory pathology on preoperative transnasal endoscopy in the cartilaginous portion of the ET.

The decision to perform BDET under local or general anesthesia depended on the anesthetic requirements of possible adjunctive procedures, patient or surgeon's preferences and financial aspects. Adjunctive procedures were performed when indicated, with balloon dilation of the paranasal sinuses being most common in the local anesthesia group and functional endoscopic sinus surgery (FESS) in the general anesthesia group.

The primary outcome of the study was change in tympanogram. Tympanogram improvement was defined as improvement from type B or C tympanogram preoperatively to type A tympanogram postoperatively, or improvement from type B to C tympanogram with normal hearing. Failure was defined as no change or worsening in the tympanogram. Patients with a minimum of 6 months of follow-up and a preoperative type B or C tympanogram were included in the analysis. Secondary outcome was change in otoscopic findings defined as persistence or worsening of middle ear effusion or significant non-fixed tympanic membrane retraction. A third outcome was the need for additional surgical intervention, which was considered a failure. In case the first procedure failed to resolve symptoms or findings, revision surgery was considered 6 months later. In addition to the same indications as for primary surgery, significant improvement with the first procedure was required including: 1) symptoms and findings had initially resolved but returned or 2) symptoms and findings had improved, but not to the expected extent.

4.1.3 Patients with total obstruction of the ET (III)

In this pilot study, all seven patients who underwent reconstruction to re-canalize the full length of the ET at Boston Children's Hospital and Massachusetts Eye and Ear Infirmary between 2011 and 2019 were included in the study. To be considered for candidacy for the surgery, total obliteration of the nasopharyngeal orifice or cartilaginous portion of the ET and mucoid ME effusion that could not be adequately handled with tympanostomy tubes were required. All patients previously had tympanostomy tubes for intractable effusions, but were not satisfied with repeated reaccumulation of viscous mucoid effusions despite the tubes in place due to occlusion of the lumen or from early extrusion of the tubes.

During follow-up, patients were evaluated for their symptoms of ET dysfunction including ear examination with otomicroscopy, flexible fiberoptic or rigid nasopharyngoscopy and tympanometry if the tympanic membrane was intact. Outcome measures were presence or absence of middle ear effusion, TM status, and visible patency of the lumen of the cartilaginous ET.

4.1.4 Multicenter BDET study (IV)

Consecutive patients undergoing BDET for OETD between 2014 and 2019 were included from Georgetown University Medical Center, Washington DC; Johns Hopkins University School of Medicine, Baltimore, MD; Massachusetts Eye and Ear Infirmary, Boston, MA, and Boston Children's Hospital, Boston, MA, USA. Altogether 182 patients were studied for patient reported symptoms of patulous ETD after BDET.

Any postoperative symptoms of PETD, including breath or voice autophony or aural fullness, were documented from medical records. Characteristics assessed were age, sex, ET mucosal inflammation score, and common risk factors predisposing to ETD including laryngopharyngeal/gastroesophageal reflux, environmental allergies, and chronic rhinosinusitis. Additionally, the effect of balloon diameter, duration of balloon inflation, repeat BDET, and concurrently performed adjunctive procedures on the risk of developing PETD were analyzed.

4.2 Procedures and anesthesia

4.2.1 Balloon dilation of the Eustachian tube

Study I

All procedures in Study I were performed under general anesthesia. A 3.5 x 10 mm, 3.5 x 12 mm, 5 x 16 mm or 6 x 16 mm sinuplasty balloon (off-label use, Acclarent,

Irvine, CA, USA) was used for dilation of the cartilaginous ET depending on the age and size of the patient. For subjects of adult size, the 6 x 16 mm balloon was used, including the AERA balloon specifically designed for ET dilation (off-label use for pediatric patients, Acclarent, Irvine, CA, USA) which was used for 6 patients after 2016 when the US Food and Drug Administration (FDA) approved the device for clinical use. A 45 degree, 3 mm ear endoscope (Karl Storz, CA, USA) was used for viewing. For balloon insertion, with the sinuplasty balloon catheter, a 70-degree guide catheter was used and for the AERA balloon the 52 degree guide catheter. A yellow marker 31 mm from the balloon catheter's distal end was used for estimation of the depth of insertion. Balloon inflation was done up to 12 ATM and the pressure maintained for 2 minutes in most cases and for 1-1.5 minutes in subjects with milder inflammatory disease. For some of the younger children, due to the angle and length of the guide catheter, nasal anatomy did not allow for direction of the balloon catheter into the tubal orifice transnasally. For those cases, a transoral approach was used with the balloon catheter passed through an olive tipped suction into the lumen of the ET with the endoscope in the nasal cavity for viewing.

Study II

For viewing, a 45-degree 2.7 mm diameter sinus endoscope (Karl Storz, Tuttlingen, Germany) was used. Before 2016, balloon dilation was performed with a 6 x 16 mm sinuplasty balloon with a 70 degree guide catheter (off-label use, Acclarent, Irvine, CA, USA) and after FDA approval in 2016, with the Acclarent AERA balloon (6 x 16 mm, Acclarent, Irvine, CA, USA). The balloon insertion into the ET orifice was done under direct endoscopic view in order to avoid mucosal trauma or false passage. For the dilation, the balloon was advanced to the isthmus, indicated by feeling resistance with the catheter while keeping the yellow mark in the catheter visible outside the ET orifice. Balloon inflation was performed at the pace of 1 ATM per second to 12 ATM. Pressure was maintained for 2 minutes before deflation. Finally, the balloon catheter was slowly retracted back into the guide catheter in order to avoid additional mucosal damage. The procedure was performed identically for the patients undergoing BDET under local anesthesia and the patients undergoing BDET under general anesthesia.

Study IV

A 6 x 16 mm balloon was used for dilation after FDA approval of the device (AERA, Acclarent, Irvine, CA, USA). Prior to FDA approval of the AERA dilation system, off-label use of sinuplasty balloons with informed consent from the patients was performed in altogether 26 procedures using 7 x 16 mm, 5 x 16 mm, and 3.5 x 12

mm balloons. Procedures with balloon size of 5 x 16 mm and 3.5 x 12 mm were mostly performed on pediatric patients. All procedures in Study IV were performed under general anesthesia. The most common duration of balloon dilation was 2 minutes, but durations ranged from 30 seconds to 4 minutes.

4.2.2 Local vs. general anesthesia

Study II

For the BDET group undergoing the procedure under local anesthesia, a precise anesthesia protocol was utilized. Patients were medicated with 10 mg of diazepam before the operation adjusting the dose if needed due to comorbid conditions, age, and size. Oxymetazoline 4% solution was used for decongestion sprayed into each nostril. Five drops of 7% tetracaine / 7% lidocaine compounded into an otic solution was used as topical anesthetic placed on the ipsilateral intact tympanic membrane because pain had been reported during insertion of the balloon due to pressure changes in the middle ear (Luukkainen et al., 2017). Cottonoids with 2% tetracaine solution were used for topical anesthesia of the nasal cavity bilaterally for 10 minutes. The cottonoids were then removed and 0.5 cc of compounded 7% tetracaine / 7 % lidocaine cream applied to the ET orifice and the ET through a Weiss catheter (Grace Medical, Memphis, TN, USA). The cottonoids with tetracaine were replaced in each nasal passage for an additional 10-15 minutes.

For the group undergoing BDET under general anesthesia, a laryngeal mask or endotracheal intubation were used depending on anesthesiologist preference. Oyxmetazoline 4% solution was used for decongestion and cocaine 4% pledgets in the nasal cavity for topical anesthesia but nothing in the ET.

4.2.3 Reconstruction of the Eustachian tube

Study III

Reconstruction was performed in patients diagnosed with complete obliteration of the ET lumen across the entire nasopharyngeal orifice. Preoperatively, a CT scan was performed for all patients. Intact anatomy of the bony portion of the ET and absence of any bony dehiscence of the internal carotid artery were a criteria for surgery.

All procedures were performed under general anesthesia with a combined transtympanic and endoscopic transnasal or transoral approach. Oxymetazoline nasal spray was used for decongestion.

A myringotomy was made anteriorly over the location of the orifice of the bony ET unless a pre-existing favorably located anterior perforation was present in the tympanic membrane. An illuminated 0.9 mm diameter sinuplasty guidewire (Luma, Acclarent, Irvine, CA, USA, off-label use) was introduced through the TM into the middle ear and advanced through the protympanum into the orifice of the bony ET. Advancement was continued along the bony ET into the cartilaginous part until meeting resistance at the site of the obstruction. The guidewire was taped in place in order to hold its position.

A 45-degree, 4 mm rigid endoscope (Karl Storz, El Segundo, CA, USA) was used for viewing. A navigation system was used in the cases of suspected significant alteration of anatomy or obstruction located proximally within the cartilaginous ET and therefore in closer proximity to the internal carotid artery. A Crowe-Davis retractor was used to hold the mouth open. The palate was retracted with a flexible catheter placed through the contralateral nostril. The endoscope in the ipsilateral nasal cavity was secured in place with an endoscope holder (Karl Storz, El Segundo, CA, USA). The procedure was then mostly performed transorally with dedicated endoscopic nasopharyngeal angled instruments (Karl Storz, El Segundo, CA, USA). Constant inspection of the ET orifice was done in order to notice the light from the guidewire through the obstruction. If the obstruction was sufficiently limited in thickness, a glow could be seen and would serve as a guide indicating the location of the ET lumen.

After infiltrating lidocaine with epinephrine into the ET orifice, advancement in the direction of the illumination from the guidewire with endoscopic scissors was done. In case there was no light visible to follow, the dissection was proceeded using available landmarks as guidance. Remnants of the torus tubarius and the underlying medial cartilaginous lamina, the roof of the ET (basi-sphenoid), medial pterygoid plate, and tensor veli palatine (TVP) muscle would serve as possible guiding structures. In case of severe anatomical deformation, the navigation system was used to assist in staying on the right course toward the remaining ET. For hemostasis, monopolar cautery (Karl Storz, El Segundo, CA, USA) was used. Dissection toward the isthmus was carried out, occasionally turning down light from the endoscope, until identification of the red glow from the guidewire was seen. The dissection was continued until contacting the guidewire, after which the lumen was widely opened, advancing through the obstruction until uncompromised ET lumen was identified. As soon as the ET lumen was reached, mucus was typically encountered confirming the correct location.

A 14 gauge angiocatheter stent was prepared by filling it with melted bone wax. In order for the stent to cover the full length of the ET from the bony part to the nasopharyngeal orifice allowing it to be sutured to the anterior pillar, the stent was cut to 40mm to 44mm in length. A 4-0 nylon suture was passed through the

nasopharyngeal end of the catheter and the catheter was loaded into an insertion tool (Karl Storz, El Segundo, CA, USA). The insertion tool was passed transorally and delivered to the opening of the ET lumen. The guidewire was then withdrawn out of the ET and the catheter was inserted through the entire length of the newly established lumen of the ET. Resistance would be noticed as the catheter passed through the isthmus into the bony portion of the ET. Inspection of the ear with a 0-degree endoscope was done to ensure that the catheter was not visible within the middle ear. If that was the case, the catheter was withdrawn further into the nasopharynx. A single suture was used to secure the catheter to the anterior pillar using endoscopic instruments (Karl Storz, El Segundo, CA, USA).

In the more recent procedures, in order to lower the risk of scarring and improve the chances of preserving a lumen, a Propel mini steroid-eluting stent (Intersect ENT, Menlo Park, CA, USA, off-label use) was placed into the ET lumen in addition to the angiocatheter stent.

An adhesive Steri-Strip (3M, St. Paul, MN, USA) patch cut into appropriate size was placed on the myringotomy. The adhesive would aid in keeping the patch in place and preventing displacement in case of pressure build-up from the middle ear.

As for the angiocatheter stent, the intention was to leave it in place for a minimum of six months with the option of removal after twelve months, or even later if not causing symptoms.

4.2.4 Adjunctive procedures (Studies I, II, IV)

Adjunctive procedures were performed in addition to BDET in studies I, II and IV when indicated. Separate subgroup analyses were performed comparing subjects undergoing BDET alone and BDET with adjunctive procedures within the studies in order to analyze their effect on each endpoint.

Myringotomy was done in cases of partial middle ear effusion and to release non-fixed TM retraction to the incus or promontory for facilitation of early middle ear aeration. Tympanostomy tube insertion was performed when there was effusion that filled the middle ear and when lysis of middle ear adhesions was done in order to mobilize the TM when retractions were fixed by the adhesions.

Adenoidectomy or in some cases lateral adenoidectomy, also addressing the tubal tonsil tissue with light cautery if indicated, was performed if anterior thrusting of the torus tubarius was noticed to interfere with the opening of the ET valve preoperatively. Turbinate reduction or septoplasty were done in cases of chronic anatomical obstruction when appropriate medical management was not sufficient. Tympanoplasty and ossicular chain reconstruction were performed in selected cases when indicated.

In study I, in cases with suspected obstruction within the bony ET, an illuminated sinuplasty guide-wire was used to probe and clear the lumen (Luma, Acclarent, Irvine, CA, USA, off-label use). If the use of a guidewire probe was planned, high resolution computed tomography (HRCT) was performed, unless already available, to exclude dehiscence of the internal carotid artery adjacent to the bony ET. CT could also reveal opacification within the bony ET if the middle ear were aerated (eg. by a perforation or tympanostomy tube). CT was particularly indicated in the absence of pathology on preoperative endoscopy. CT was obtained for 17 patients and guidewire probing done for four of them.

Adjunctive sinus surgery, either balloon dilation or functional endoscopic sinus surgery (FESS), was performed for patients with chronic rhinosinusitis, when indicated, after failing to improve with medical management.

4.3 Statistical analyses

All analyses were performed using SAS version 9.4 (SAS Institute, NC, USA) and R statistical software.

Study I

Longitudinal data analysis comparing data before and after surgery was conducted using generalized linear models. A three-level hierarchical model using a generalized estimating equations (GEE) approach was employed to account for the correlations between repeated measures over time and between each pair of ears. Any change in outcomes between the pre-operative period (baseline) and post-operative period with months of follow-up time as a continuous variable were evaluated. For otomicroscopic findings, tympanogram, and Valsalva, a logistic regression model using a GEE approach was used. For mucosal inflammation, a model with a gamma distribution and log link function was used. Kaplan-Meier survival plots were constructed to compare the failure-free survival probability between patients who received BDET vs. matched patients who received TT insertion. Cox proportional hazards model with frailty term to account for matched pairs of BDET and TT patients adjusted for age, gender, and number of prior tympanostomy tubes was used. The gamma distribution was specified for the frailty term. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated. Model diagnostics were performed to assess the fit of the model and the proportional hazards assumption.

Study II

Any changes in the outcomes between pre-operative period and post-operative period were examined using the mixed effects regression model. A three-level random-effects model was used to account for the correlations between repeated measures over time and between each pair of ears. The mixed effects logistic regression model was used to examine the post-operative changes in otomicroscopic findings and tympanograms. Patients with an intact healthy TM or healthy TM graft or a type A tympanogram at pre-operative period were not included in the analysis. The linear mixed effects model was used for audiogram data. Kaplan-Meier survival plots were constructed to examine the failure-free probability with failure defined as no change or worsening in tympanogram. Cox proportional hazards model with frailty term was used to compare the risk of failure between BDET under local anesthesia vs. general anesthesia. The log-normal distribution was specified for the frailty term, which accounts for the correlation between paired ears. HRs and 95% CIs were estimated.

Study III

Surgical outcomes of ET reconstruction with presence or absence of middle ear effusion, otomicroscopic findings, tympanogram and visible patency of the cartilaginous ET as outcomes were examined. Due to the small population, only descriptive statistics were reported.

Study IV

The risk of developing PETD was examined by patient and procedure characteristics. To examine predictors of PETD, a regression analysis using a generalized estimating equations (GEE) approach was conducted to account for the correlation between each pair of ears. All analyses were performed with the ear as the unit of analysis. Laterality of symptoms were documented in the majority of patients who developed PETD (15/17 patients); however, laterality was unknown in two patients and they were included as probable unilateral PETD cases in the analysis. A sensitivity analysis was performed including patients with unknown laterality as bilateral cases. Risk ratios (RR) and 95% CIs were estimated from the binomial regression model with a log-link function or Poisson regression model. The multivariable regression model was built using backward selection criteria with $p<0.05$ as the retention criteria.

4.4 Ethical aspects

All studies were approved by the Institutional Review Board (IRB) at Boston Children's Hospital, Boston, USA (IRB-P00010256). Data collection for retrospective surgical data was performed at each participating center and approved by the local Institutional Review Boards. A data transfer agreement was signed between the participating centers: Boston Children's Hospital and Texas Tech Health Care (Study II) and Boston Children's Hospital, Georgetown University Medical Center and Johns Hopkins University School of Medicine (Study IV). All data were de-identified prior to sharing. All analyses were performed at Boston Children's Hospital, Boston, USA. The studies complied with the Declaration of Helsinki.

5 Results

5.1 Balloon dilation in pediatric patients (I)

Twenty-six pediatric patients undergoing balloon dilation of the ET at Boston Children's Hospital between 2013 and 2017 were included in the study. One patient with trisomy 21 was excluded from the analysis. Patients' ages ranged from 7 to 17 years. A total of 46 BDETs were performed in 26 patients (38% females) with a mean age of 12.5 years (SD 3.3; range 7 to 17 years). Mean duration of symptoms before the procedure was 9.2 years (SD 3.8 years). All patients had previously undergone tympanostomy tube (TT) placement with a mean of 3.7 (SD 1.4) tympanostomy tubes per patient. Mean duration of follow up was 2.3 years ranging from 6 months to 5 years.

Statistically significant improvement in otomicroscopic findings including normalization of TM status, tympanogram improvement, audiogram improvement and Valsalva performance was observed following BDET. The tympanic membrane status improved to healthy in 38% of the cases at 6 months, 55% at 12 months, and 93% at 36 months postoperatively. Gradual improvement in tympanograms to type A during the follow-up was seen in 50% of cases at 6 months, 59% at 12 months, and 85% at 36 months. Improvement was observed in audiogram findings with air/bone (A/B) gap significantly decreasing from 17.5dB (± 11.9) pre-operatively to 10.8dB (± 10.8) at 6 months and 5.7dB (± 4.8) at 36 months postoperatively. Significant improvement was also observed in the ability to successfully aerate the middle ear with a Valsalva maneuver (p=<0.001). The mucosal inflammation score declined from a pre-operative mean of 3.2 (± 0.6) to 2.5 (± 0.7) at 6 months postoperatively and 1.7 (± 0.6) at 36 months postoperatively.

Adjunctive procedures were performed on all patients in conjunction with BDET. Most common procedures were revision adenoidectomy for 20 (77%) patients and tympanostomy tube placement for 13 (26%) patients. Cartilage tympanoplasty was done for 6 patients.

Comparison of patients undergoing BDET vs. TT insertion

The risk of failure was defined as the need for an additional procedure including a second BDET or tympanostomy tube placement, type B or C tympanogram with decreased hearing, OME, or severe or moderate TM retraction. The characteristics of patients in the BDET group and the tympanostomy tube group are described in **Table 2**. A total of five ears failed treatment in patients who underwent BDET. One patient (two ears) required re-dilation, one patient (two ears) had recurrent effusion, one patient (one ear) developed recurrence of middle ear effusion requiring tympanostomy tube placement.

Table 2. Characteristics of patients undergoing balloon dilation and matched patients undergoing tympanostomy tube insertions. Modified from Study I.

	Procedure	
	Balloon dilation	**Tympanostomy tube**
Total number of patients, n	26	26
Total number of procedures, n	46	46
Gender, female, n (%)	10 (38%)	12 (46%)
Mean age at surgery, years (SD)	12.5 (± 3.3)	12.2 (± 3.3)
Prior adenoidectomy done	22 (85%)	25 (96%)
Mean number of prior tympanostomy tubes (SD)	3.6 (± 1.5)	3.3 (± 1.4)

SD, standard deviation.

In the control group undergoing TT insertion, 19 ears failed treatment. Type B tympanogram with effusion, recurrent acute otitis media (AOM) or TM retraction requiring additional TT placement was diagnosed during follow up. Patients in the BDET group had a lower risk of failure than patients in the TT treatment group (adjusted HR: 0.26; 95% CI: 0.10, 0.70; p=0.007; **Table 3** and **Figure 2**). The probability of being failure free at two years was 87% (95% CI: 70, 94%) in the BDET group and 56% (95% CI: 40, 70%) in the TT treatment group (p=0.007).

In a subgroup analysis of 21 patients (34 ears), the risk for failure in patients undergoing BDET without adjunctive tympanoplasty or turbinate reduction was lower when compared to matched controls undergoing TT insertion (HR 0.30; 95% CI: 0.10, 0.92; p=0.04).

Table 3. Risk of failure requiring revision surgery during the two-year follow-up in patients undergoing balloon dilation and matched patients undergoing tympanostomy tube insertion. Modified from Study I.

Procedure	Failures/ procedures, n	2-year failure-free probability (95% CI)	Adjusted HR (95% CI)	*p*
Balloon dilation of the Eustachian tube	5/46	87% (70, 94%)	0.26 (0.10, 0.70)	0.007
Tympanostomy tube insertion	19/46	56% (40, 70%)	Reference	

Adjusted hazard ratio (HR) and 95% confidence interval (CI) were analyzed using the Cox proportional hazards model with frailty term accounting for matched pairs.

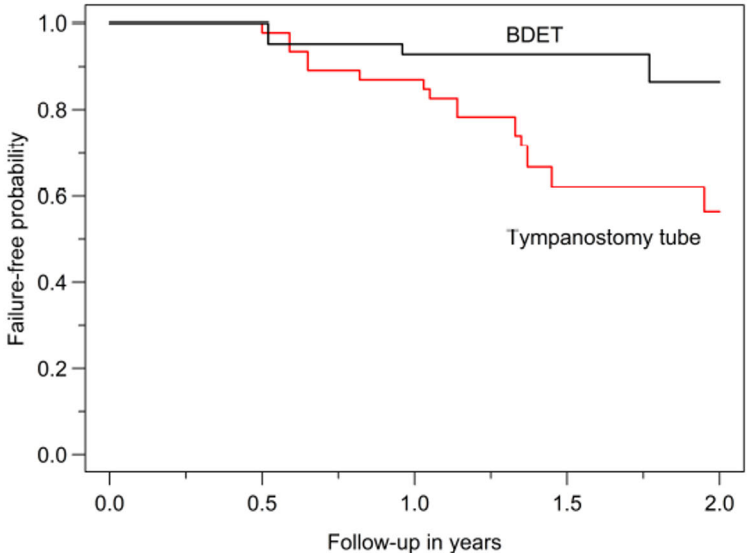

Figure 2. Kaplan-Meier curve for failure-free probability comparing patients treated with balloon dilation of the Eustachian tube versus matched patients treated with tympanostomy tube placement (p=0.007). BDET, balloon dilation of the Eustachian tube. From Study I.

5.2 Local vs. general anesthesia (II)

BDET was done for 191 patients (112/191, 59% female) of whom 58 had the procedure under local anesthesia and 133 under general anesthesia. Mean age at the time of surgery was 58.0 years (SD 15.8; range 18 to 88 years). In total, 332 BDET procedures were performed, 107/332 (32.2%) under local anesthesia and 225/332 (67.8%) under general anesthesia (**Table 4**). In the local anesthesia group, adjunctive procedures were performed for 84.1% (90/107) of the patients and in the general anesthesia group for 43.1% (97/225) of the patients. The mean duration of follow-up was 3.1 years (SD 1.9; range 6 months to 6.6 years).

Table 4. Characteristics of patients undergoing balloon dilation under local anesthesia vs. general anesthesia. Modified from Study II.

	BDET under local anesthesia	BDET under general anesthesia
Patients (n = 191)	58	133
Procedures (n=332)	107	225
Gender		
Female	34 (58.6%)	78 (58.7%)
Male	24 (41.4%)	55 (41.3%)
Age (years), mean (SD)	57.2 (± 14.2)	58.3 (± 16.5)
Comorbidities		
Chronic rhinosinusitis	41 (70.7%)	41 (30.8%)
Allergies	26 (44.8%)	64 (48.1%)
Reflux disease	16 (27.6%)	39 (29.3%)
Asthma	6 (10.3%)	10 (7.5%)
Side of the procedure		
Bilateral	49 (84.5%)	92 (69.2%)
Unilateral	9 (15.5%)	41 (30.8%)
Indication for the procedure		
Chronic otitis media	86 (80.4%)	200 (88.9%)
Recurrent otitis media	8 (7.4%)	4 (1.8%)
Barochallenge-induced ETD	13 (12.2%)	21 (9.3%)
Follow up (years), mean (SD)	3.6 (± 2.0)	2.9 (± 1.7)

Numbers are n (% of the patients) unless otherwise stated. BDET, balloon dilation of the Eustachian tube; ETD, Eustachian tube dysfunction; SD, standard deviations.

Statistically significant change was seen in tympanogram improvement from B and C preoperatively to A postoperatively at the one year follow up in 88% in the local anesthesia group and 74% in the general anesthesia group. In patients with abnormal otomicroscopic findings including middle ear effusion and/or TM retraction preoperatively, significant improvement was seen. Otomicroscopic status improved to healthy (no ME effusion, no TM retraction) in 90% of cases in the local anesthesia group and in 85% in the general anesthesia group at one year (**Table 5**).

Table 5. Outcomes after balloon dilation under local anesthesia vs. general anesthesia. Modified from Study II.

	Time-point				
	Pre-operative	**1 mo**	**6 mo**	**1 yr**	***p***
BDET under local anesthesia					
Tympanogram	(n=50)	(n=21)	(n=7)	(n=17)	
A	0 (0%)	15 (71%)	5 (71%)	15 (88%)	<0.001
B	13 (26%)	1 (5%)	2 (29%)	1 (6%)	
B/tube, perforated	4 (8%)	1 (5%)	-	-	
C	33 (66%)	4 (19%)	-	1 (6%)	
Otomicroscopy	(n=31)	(n=23)	(n=21)	(n=20)	
Healthy	0 (0%)	21 (91%)	19 (90%)	18 (90%)	0.01
Retracted	25 (81%)	-	-	-	
Tube, perforated	4 (13%)	2 (9%)	2 (10%)	2 (10%)	
Effusion	2 (6%)	-	-	-	
BDET under general anesthesia					
Tympanogram	(n=164)	(n=114)	(n=90)	(n=96)	
A	0 (0%)	75 (64%)	54 (60%)	71 (74%)	<0.001
B	50 (31%)	15 (13%)	14 (15%)	16 (17%)	
B/tube, perforated	19 (11%)	11 (10%)	7 (8%)	1 (1%)	
C	95 (58%)	15 (13%)	15 (17%)	8 (8%)	
Otomicroscopy	(n=121)	(n=98)	(n=80)	(n=85)	
Healthy	0 (0%)	88 (90%)	71 (89%)	72 (85%)	<0.001
Retracted	72 (60%)	-	-	6 (7%)	
Tube, perforated	20 (16%)	10 (10%)	7 (9%)	5 (6%)	
Effusion	28 (23%)	-	-	1 (1%)	
Graft	1 (1%)	-	2 (3%)	1 (1%)	

P-value based on any change in the outcome between pre-operative period and post-operative period (months of follow-up as a continuous variable) using the mixed effects regression model. BDET, balloon dilation of the Eustachian tube.

Failures, defined as no change or worse in tympanogram, occurred in 14/50 (28%) of the patients treated under local anesthesia and in 49/164 (30%) of the patients treated under general anesthesia. There was no difference in the risk of failure between the two groups in the multivariable Cox model accounting for age, sex, comorbidities, and adjunctive procedures (adjusted HR = 0.60; 95% CI: 0.27 to 1.31; p=0.20). The probability of being failure-free at 5 years was 70% (95% CI: 52

to 82%) in the local anesthesia group vs. 65% (95% CI: 55 to 73%) in the general anesthesia group (p=0.20, **Table 6** and **Figure 3**).

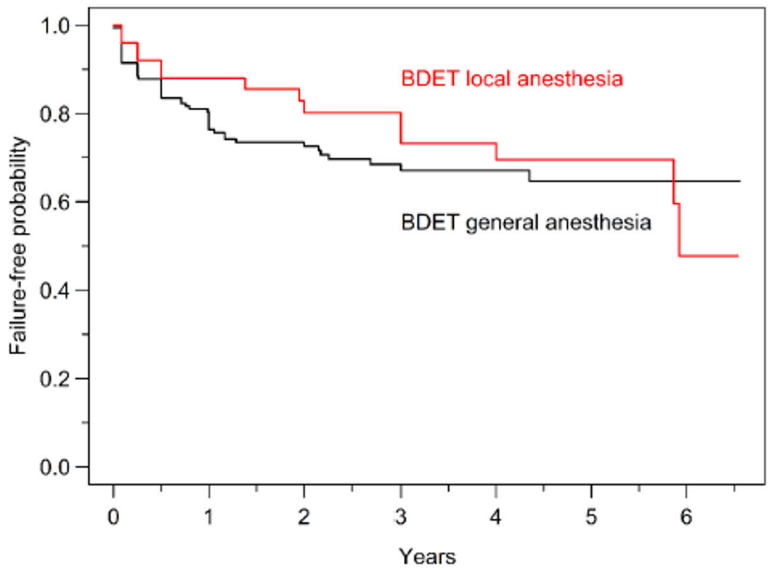

Figure 3. Kaplan-Meier curve for failure-free probability comparing patients who underwent balloon dilation of the Eustachian tube under local versus general anesthesia. Risk of failure was defined as no change or worse in tympanogram. Patients who had type B or type C tympanogram preoperatively were included. BDET, balloon dilation of the Eustachian tube. From Study II.

No improvement or worsening of ME effusion or TM retraction was documented for two ears in the local anesthesia group and eight ears in the general anesthesia group. The risk for persistence or worsening of otomicroscopic findings did not differ between the local anesthesia group and the general anesthesia group (adjusted HR = 0.15; 95% CI: 0.02 to 1.41; p=0.10, **Table 6**).

A second procedure was performed on 33 patients (40 ears). Re-dilation was done on 26 ears, tympanostomy tube placement on 11, tympanoplasty on two ears and myringoplasty on one ear. The need for a second procedure was considered a failure with 13/107 (12%) patients having a second procedure in the local anesthesia group and 27/225 (12%) patients in the general anesthesia group. Risk for a second procedure did not differ between the local anesthesia and the general anesthesia groups (adjusted HR = 0.77; 95% CI: 0.30 to 2.01; p=0.60).

Subgroup analyses were performed with patients having either no adjunctive procedures and with patients having adjunctive procedures done with BDET. In the subgroup analysis, in patients without adjunctive procedures, the risk of failure in

tympanogram improvement (no change or worse) did not differ between local vs. general anesthesia groups (4/17 under local vs. 28/128 general anesthesia; adjusted HR = 1.05; 95% CI: 0.33 to 3.33; p=0.93). There was also no difference in the risk of failure between the groups with adjunctive procedures (10/90 under local anesthesia vs. 26/97 under general anesthesia; adjusted HR = 0.47; 95% CI: 0.17 to 1.30; p=0.15). When comparing the tympanograms in those without adjunctive procedures at 2 years, there was improvement to type A in 75% of the patients in the local anesthesia group and 88% of the patients in the general anesthesia group (p=0.10). In patients undergoing BDET and adjunctive procedures, there was however a difference in favor of the local anesthesia group in normalization of tympanograms at 2 years. Tympanograms improved to type A in 88% in the local anesthesia group and in 56% in the general anesthesia group in those with adjunctive procedures (p=0.03)

One procedure had to be aborted due to significant discomfort during inflation of the balloon while performing BDET under local anesthesia. The patient had the procedure done at a later time under general anesthesia. No other complications or adverse effects were encountered during the procedures.

Table 6. Risk of failure in patients undergoing balloon dilation under local anesthesia vs. general anesthesia. Modified from Study II.

	Failures/ procedures	1-year failure-free probability (95% CI)	2-year failure-free probability (95% CI)	5-year failure-free probability (95% CI)	Adjusted HR (95% CI)	*p*
Tympanogram[1]						
BDET under local anesthesia	14/50	88% (75-94%)	80% (65-89%)	70% (52-82%)	0.60 (0.27-1.31)	0.20
BDET under general anesthesia	49/164	76% (69-82%)	73% (65-79%)	65% (55-73%)	Reference	
Otomicroscopy[2]						
BDET under local anesthesia	2/31	100% (100-100%)	100% (100-100%)	75% (32-93%)	0.15 (0.02-1.41)	0.10
BDET under general anesthesia	8/121	98% (93-99%)	96% (90-99%)	89% (77-94%)	Reference	

[1] Primary outcome (failure) was defined as no change or worse in tympanogram. Patients with preoperative type B or C tympanogram included.
[2] Secondary outcome (failure) was defined as persistence or worsening of effusion or significant non-fixed tympanic membrane retraction.
Adjusted hazard ratio (HR) and 95% confidence interval (CI) were analyzed using the Cox proportional hazards model with frailty term that accounts for pairs of ears. Multivariable model included age, gender, comorbidities, and adjunctive procedures. BDET, balloon dilation of the Eustachian tube

5.3 Reconstruction of the totally obliterated Eustachian tube (III)

In a subspecialty clinic for ET disorders, total obstruction of the ET was diagnosed in 23 (1.2%) of 1829 patients with OETD between 2004 and 2019. Nine totally obstructed Eustachian tubes were reconstructed in seven patients. For two patients, bilateral reconstruction was done. Three patients were female (43%) and four male (57%). Age at the time of surgery ranged from 17 to 68 years (mean 37.9 years). Mean duration of follow-up was 30.9 months. For two patients (3 ETs), a reoperation was done after obstruction recurred during follow-up. In total, for the seven patients, 12 ET reconstruction procedures (9 primary, 3 revisions) were done.

For five patients, the primary reconstruction procedure was successful and ET function was restored. These patients were free from repeat accumulation of mucoid middle ear effusion. For the two patients (3 ETs) having recurrence of obstruction due to scarring, revision surgery was done. In both cases, recanalization of the ET was achieved. Due to an active systemic disease affecting the nasopharynx, a permanent solution was however not achieved for one of these patients (2 ETs).

In three procedures, a steroid-eluting stent was placed in the cartilaginous ET lumen in addition to the angiocatheter stent. No complications directly related to the procedures occurred during or after surgery. For one patient, tympanoplasty was later performed to repair a chronic perforation. Four patients had a TM perforation or a tympanostomy tube at the last follow-up but no further accumulation of middle ear effusion.

5.4 Patulous Eustachian tube symptoms after balloon dilation (IV)

A total of 182 patients underwent 295 BDET procedures (75/182, 41.2% female). Patients were aged between 7 and 78 years at the time of surgery (mean 38.4 years). Bilateral dilations were done for 53.8% (98 patients) and a unilateral dilation for 46.2% (84 patients). In 60% of the operations, adjunctive procedures were performed. Fifteen re-dilations (5.1% of the procedures) were done for eleven patients due to recurrence of symptoms of OETD. Seventeen patients (9.3%) of the 182 patients treated with BDET developed patulous ET symptoms. The rate of development of patulous symptoms after individual BDET procedures was 20/295 (6.8%) (**Table 7**). The risk for patients developing PETD symptoms was the same in each institution. Pediatric patients (age 7-18) were in greater risk of developing patulous symptoms (13.3%) than adult patients (5.6%, age 19-49 years and 2.1%, age ≥50); p=0.01. Repeat dilation increased the risk for developing patulous symptoms with 20.0% of patients having undergone ≥2 dilations vs. 6.1% of patients undergoing one dilation developing patulous symptoms (p=<0.001). Patients with

severe mucosal inflammation preoperatively had a greater risk of developing patulous symptoms after dilation than patients with less inflammation (mucosal inflammation score 4: 19.4% vs. mucosal inflammation score 1-3: 5.4%; *p*=0.007). The risk of developing patulous symptoms after a longer duration of dilation did not reach statistical significance. An association between previous history of environmental allergies, gastroesophageal reflux, or chronic rhinosinusitis and developing patulous symptoms was not observed.

Table 7. Symptoms of patulous Eustachian tube dysfunction in patients undergoing balloon dilation. Modified from Study IV.

	PETD cases / procedures, n (%)	***p***
Overall	20/295 (6.8%)	
Age category		0.01
7-18 years	12/90 (13.3%)	
19-49 years	6/108 (5.6%)	
50-78 years	2/97 (2.1%)	
Gender		0.89
Female	9/128 (7.0%)	
Male	11/167 (6.6%)	
No. of BDET procedure		<0.001
1. BDET	17/280 (6.1%)	
Repeat BDET	3/15 (20.0%)	
Duration of BDET		0.12
0.5 min	0/2 (0%)	
1 min	1/41 (2.4%)	
1.5 min	1/14 (7.1%)	
2 min	15/201 (7.5%)	
3 min	2/16 (12.5%)	
4 min	0/2 (0%)	
Preoperative mucosal inflammation score		0.007
1-3	14/258 (5.4%)	
4	6/31 (19.4%)	

P-values were analyzed using the log-binomial regression model that accounts for the correlation between paired ears. Age, duration of dilation, and mucosal inflammation score were used as continuous variables. BDET, balloon dilation of the Eustachian tube; PETD, patulous Eustachian tube dysfunction.

In the multivariable model, age ≤18 years (adjusted RR = 3.26; 95% CI: 1.24 to 8.54; *p*=0.02), repeat balloon dilation (RR = 3.26; 95% CI: 2.15 to 4.96; *p*=<0.001), and severe mucosal inflammation score (RR = 2.83; 95% CI: 1.10 to 7.28; *p*=0.03)

were significant risk factors associated with developing patulous symptoms (**Table 8**).

Table 8. Factors predicting symptoms of patulous Eustachian tube dysfunction after balloon dilation. Modified from Study IV.

Variable	Univariate RR (95% CI)	*p*	Multivariable-adjusted RR (95% CI)	*p*
Age ≤18 yrs (vs. >18 yrs)	3.13 (1.21, 8.10)	0.02	3.26 (1.24, 8.54)	0.02
Repeat dilation	2.62 (1.89, 3.52)	<0.001	3.26 (2.15, 4.95)	<0.001
Severe mucosal inflammation (score 4)	3.57 (1.40, 9.07)	0.007	2.83 (1.10, 7.28)	0.03
Chronic rhinosinusitis	1.84 (0.72, 4.73)	0.20	-	
Adjunctive adenoidectomy	3.11 (1.20, 8.08)	0.02	-	
Dilation duration ≥ 3 minutes	1.69 (0.44, 6.54)	0.45	-	

Adjusted risk ratios (RR) were analysed using the multivariable regression model including age, repeat dilation procedure, and mucosal inflammation score as covariates and accounting for the correlation between paired ears.

Onset of patulous symptoms was within the first month after BDET in 15/17 (88%) of the patients. In one patient, the symptoms started 5 months after the procedure and later improved during pregnancy. One patient developed symptoms 14 months later after significantly losing weight. In four patients, symptoms were limited to a couple of brief episodes lasting for minutes and in two of these patients, symptoms only occurred after performing the Valsalva maneuver. Sporadic episodes of symptoms lasting for minutes during the first week after surgery were reported by three patients. In one patient, exercising caused patulous symptoms lasting for a month after the procedure. Two patients were symptomatic for 6 months and symptoms lasting for over 6 months were reported by seven patients (41%). Quitting caffeine resolved symptoms for one. All of the patients were treated with behavioral or medical management including hydration, topical nasal drops with saline or hypertonic saline, or diluted ascorbic acid and one underwent mass loading of the TM.

6 Discussion

6.1 Balloon dilation vs. repeat tympanostomy tube placement in children

In this study, children with longstanding chronic obstructive Eustachian tube dysfunction (OETD) that persisted despite prior tympanostomy tube placement were treated with balloon dilation of the Eustachian tube (BDET) and were compared with a matched cohort of patients undergoing tympanostomy tube placement. The patients who underwent BDET needed significantly fewer subsequent tympanostomy tubes or other additional procedures during the follow-up for the treatment of OETD than the matched control group of patients who underwent repeat tympanostomy tube placement alone. BDET was effective in altering the natural history of children who receive more than one set of tympanostomy tubes seen as the control group went on to need significantly more sets of tubes over the follow-up period. We found that in children, BDET, performed in conjunction with other procedures as indicated, resulted in significant improvements in otomicroscopic findings, tympanograms, mucosal inflammation scores, audiometric results and the ability to perform a Valsalva maneuver.

There has long been a shortage of effective treatment methods for obstructive ETD. Efforts to manage OME by treating chronic inflammation in the nasopharynx and ET orifice with nasal steroids have been shown to be ineffective (Gluth et al., 2011). Tympanostomy tube placement has been the first line surgical treatment option, but it does not address the inflammatory disease in the ET and has other potential complications such as development of chronic tympanic membrane perforations (Norman et al., 2014). Balloon dilation of the Eustachian tube has been shown to reduce the inflammatory burden in the ET by crushing the inflamed mucosa and submucosa, including the hyperplastic lymphoid follicles in the submucosa, thus promoting healing and regrowth of a healthy mucosa (Kivekäs et al., 2015). Children are commonly affected by chronic OME and given the growth and maturation potential of the ET with time, tympanostomy tube placement is still considered the first line treatment. Additionally, balloon catheters are considerably more expensive that tympanostomy tubes. In line with previous studies, we show that in complicated cases or when repeat tympanostomy tube placement is ineffective in preventing

recurrence of OETD, BDET could be a feasible treatment option (Leichtle et al., 2017; Tisch et al., 2020).

In a previous study by Leichtle and colleagues, BDET was performed on 52 children (97 ears) refractory to conventional treatment, and the authors found improvement in type A tympanograms from 14% preoperatively to 50% at one year postoperatively. Patients also reported improvement in the ability to perform the Valsalva maneuver from 13% preoperatively to 60% postoperatively (Leichtle et al., 2017). Maier et al. reported the results of BDET on 66 children with improvement in type A tympanograms from 15% preoperatively to 58% postoperatively (Maier et al., 2015). BDET was performed when other treatment modalities, including previous tympanostomy tubes and adenoidectomy, were insufficient. Jenckel et al. reported the results of BDET in 33 children (56 ears) aged 5-14 years (Jenckel et al., 2015). Information was collected by questionnaires and improvement was noted in ear symptoms for 68% and in hearing for 48% of the children. BDET was commonly performed together with either adenoidectomy (55%) or tympanoplasty (42%). Comparison of the results between studies is hindered by the difference between adjunctive procedures since they may affect ETD symptoms. However, the use of adjunctive procedures together with BDET has been studied in adults and significant improvement has been shown both with BDET performed alone as well as along with other procedures depending on overall disease burden (Ashry et al., 2017). A study comparing BDET together with tympanostomy tube placement and tympanostomy tubes alone in children was done by Chen et al. (S. Chen et al., 2020). They found that ETD symptoms resolved in 94% of the children in the BDET group and 89% in the control group with no significant difference between groups.

Most importantly, the studies performed on children have not reported serious adverse effects. Minor complications reported include nasal bleeding, hemotympanum, vertigo, and symptoms of patulous ET. Results of previously reported studies and our findings support that BDET is a safe procedure to perform in pediatric patients. Careful selection of patients for BDET is necessary as the number of studies and understanding of long-term effects is still limited.

In our study as well as in previous reports, the inclusion of adjunctive procedures is a limitation since some of the benefits of treatment may be due to the adjunctive procedure. Also, cartilage tympanoplasty can affect tympanogram results so that with a healthy middle ear and normal ET function, patients may still have type B tympanograms due to the stiffness of the cartilage. The number of subjects was too limited to allow for more specific subgroup analyses. In our study, the patients were seven years of age or older so estimations of effect cannot be made for younger children.

6.2 Balloon dilation under local anesthesia

When BDET was first introduced, it was performed under general anesthesia. Performing procedures under local anesthesia and in the office setting has become more popular during recent years. Earlier studies attempting the procedure under local anesthesia described significant challenges with adequacy of pain control resulting in inability to complete the procedure or self-reporting by patients of inadequate pain control. In this study, we found that BDET is consistently feasible using an effective local anesthesia protocol in appropriately selected adult patients. Our findings are in line with previous studies (X. Chen et al., 2020). A precise anesthesia protocol is necessary for the procedure to be adequately tolerated. Informing patients preoperatively can help in optimizing their cooperation and in minimizing anxiety. In our study, one patient had the procedure discontinued due to discomfort during inflation of the balloon. No compromises in balloon dilation time or pressure were needed for the other patients.

When performing BDET under local anesthesia, improved patient safety, convenience for the patient, and reduced treatment costs can be achieved. Safety with performing other procedures under local anesthesia has been studied especially in older adults given their higher prevalence of comorbidities and risks for postoperative complications (Connors et al., 2020). Increased patient satisfaction has been reported with an option for local anesthesia as they perceived it as being safer with reduced risks and with preservation of some sense of control by allowing for communication and preservation of an open airway (Dietz et al., 2016; Jourdy & Kacker, 2010). Operations in the operating room under general anesthesia compared with procedures in the office setting under local anesthesia have been shown to increase costs by 243% (Locke et al., 2018). One minute in the operating room has been estimated to cost $37 in the U.S. (Childers & Maggard-Gibbons, 2018).

In this study, both the local anesthesia and the general anesthesia groups showed significant improvement in otomicroscopic findings, tympanograms, and the ability to successfully perform a Valsalva maneuver. In the subgroup analysis on patients undergoing adjunctive procedures, tympanogram improvement was more significant in the local anesthesia group at one and two years compared to the general anesthesia group, but this could be due to selection bias because patients with more severe pathology tended to be directed to the operating room. No statistically significant difference was seen between the groups in the need for additional interventions.

Pain has been reported to be a limiting factor when performing BDET under local anesthesia. The first study with BDET under local anesthesia, using oxymetazoline and lidocaine spray in the nose and lidocaine gel topically in the ET for anesthesia, reported pain limiting the dilations to inflation pressures of 6 ATM to 8 ATM and durations from 10 seconds to 30 seconds (Catalano et al., 2012). Luukkainen et al. studied the feasibility of BDET under local anesthesia combined

with monitored anesthesia care and compared it with endoscopic sinus surgery. BDET caused more pain than endoscopic sinus surgery, especially during balloon insertion, but was feasible (Luukkainen et al., 2017). Pain experienced with insertion of the balloon might have been caused by transient inflation of the middle ear with stretching of the TM if air in the proximal lumen was inadequately vented out either through the lumen or beside the catheter. Supporting that hypothesis, the senior author found that topical anesthetic applied to the TM reduced the pain associated with BDET. Chen et al. had patients evaluate their level of pain with the visual analog scale (VAS) from 0 to 10 during BDET. Mean VAS scores were 5.4 during insertion, 6.1 during inflation and 4.9 during maintenance of the pressure. If a second BDET procedure would be needed, 96% (24/25) would choose local anesthesia again over general anesthesia (X. Chen et al., 2020).

Local anesthesia protocols that are in routine use for sinonasal procedures may not provide sufficient pain management for BDET (Catalano et al., 2012; Luukkainen et al., 2017). That may be due to barometric changes caused by BDET in the middle ear. Sudhoff et al. studied pressure changes in the middle ear using a balloon catheter with an inflated outside diameter of 3.28 mm. They reported a mean increase of +58 daPa during insertion and inflation, and a mean decrease of -90 daPa during deflation and retraction (Sudhoff et al., 2018). Mucosal sensory, mechanical, or stretch receptors within the ET, middle ear and TM can be the source of pain and discomfort during insertion and inflation. Vasovagal responses can also be triggered via this neuronal reflex arc (Songu et al., 2009). Early in our experience with BDET, there were two cases of bradycardia during inflation. However, since we began to limit the rate of inflation to no faster than one ATM/second, there have been no episodes of bradycardia or other vasovagal response.

In our study, the anesthesia method was designed to address all aspects of potential discomfort by taking into account local pain management in the nose, nasopharynx, cartilaginous portion of the ET and tympanic membrane. It is important to give the anesthetic adequate time for effect and to take into account the potential pressure change in the middle ear (Dean, 2019). Pain and vagal responses can be minimized with a slow insertion of the balloon catheter into the ET and a slow inflation of the balloon.

Adjunctive procedures were performed in this study if indicated with sinus surgery being the most common. Symptoms of OETD have been shown to improve with FESS (Chang et al., 2020; Wu et al., 2020). However, studies by McCoul et al. and Ashry et al. have shown that BDET with or without adjunctive procedures had comparable rates of improvements (Ashry et al., 2017; McCoul & Anand, 2012).

Limitations to our study include the lack of a control group, unequal and limited numbers of patients in both general and local anesthesia groups, and possible confounding effects of adjunctive procedures. A symptom score such as the ETDQ-

7 questionnaire in addition to objective measures would have given valuable information regarding subjective effects. Sinus procedures were performed with BDET, which has been shown to possibly improve middle ear function (Bowles et al., 2019). However, in a subgroup analysis excluding patients undergoing adjunctive procedures, there was still no difference in the risk of failure, which was similar to outcomes in other studies (Ashry et al., 2017; McCoul & Anand, 2012).

6.3 ET reconstruction

In this study, a novel procedure for reconstruction of the totally obliterated Eustachian tube was described along with a pilot case series with a mean follow-up of over two years. Obliteration can result from various etiologies. Reconstruction of a lumen was achieved in all procedures with no direct complications.

The prevalence of total obstruction of the cartilaginous portion of the ET is unknown. The prevalence of OETD has been reported to be 4.6% in the adult population (Shan et al., 2019) and that likely includes patients with total obstruction the ET that have not been recognized. Patients with total obstruction will be unresponsive to medical treatment and attempts at dilation of the cartilaginous ET. Tympanostomy tube placement often provides limited benefit as repeated tubes are usually necessary with increasing frequency over time. There is a significant incidence of viscous mucoid effusions that repeatedly obstructs tubes. In this study, total obstruction of the cartilaginous portion of the ET was diagnosed in a subspecialty clinic for ET disorders between 2004 and 2019 in 1.2% of patients with obstructive dysfunction (1829 patients with OETD including 23 patients with total obstruction). Endoscopic examination is critical for the diagnosis of obliteration of the cartilaginous ET. The possibility of total obstruction should be considered in cases of intractable mucoid effusions despite tympanostomy tubes and in the presence of persistent OETD together with granulomatous diseases, trauma, and following surgical procedures such as adenoidectomy, sinus surgery and maxillary advancement (Poe et al., 2001).

Obliteration in the nasopharynx as a consequence of systemic inflammatory disease has been reported with sarcoidosis and granulomatosis with polyangiitis (GPA) (Braun et al., 2004). One patient in our cohort had bullous pemphigus causing scarring in the nasopharynx that ultimately obliterated the Eustachian tube orifices. Managing the underlying condition to establish a stable remission is necessary before surgical intervention to achieve success with treatment and long term durability. In one of our cases, a relapse of the primary condition resulted in rescarring of the ET after reconstruction. During reoperation, the tissue in the nasopharynx was so fragile that a stent could no longer be sutured in place resulting in premature stent extrusion.

Failure to maintain remission subsequently caused recurrence of obliterative scarring.

Surgery in the nasopharynx or near the ET orifice can cause scar formation resulting in narrowing or blockage of the ET (Abdel-Aziz et al., 2019). In one patient in our study, repeat surgery for complicated sinus disease resulted in scar formation in the ET orifice. This complication is rare considering the volume of adenoid and sinus surgery, but it should be considered in cases of persistent symptoms of OETD after surgical intervention.

Maxillomandibular advancement (MMA) surgery has been reported to occasionally affect hearing after the procedure. Early changes in auditory function have been hypothesized to be due to surgical edema but long-term effects are possibly a result of compromised ET function (Jędrzejewski et al., 2015). A study on auditory changes after orthognathic surgery on 54 patients reported abnormal findings in tympanograms and performance of the Toynbee maneuver at 8 weeks after surgery for 26% of patients (Yaghmaei et al., 2009). In our study, two patients who underwent ET reconstruction for total obliteration of the ET had undergone prior MMA surgery. In one patient, a postoperative CT scan showed fragments of bone from the medial pterygoid plate that were oriented in such a way as to suggest that they had likely transected the cartilaginous portion of the ET, resulting in scarring and obstruction of the lumen. The ET is potentially at risk when mobilizing the maxillary plate, risking laceration of the ET. If symptoms of OETD persist after orthognathic surgery, the ET should be evaluated for potential evidence of injury.

Only one case of ET reconstruction has been previously reported (Ward et al., 2013) and the authors used the same technique as in our study after having consulted with the present senior author who had been performing these reconstructions, but delayed reporting to allow for long-term follow up data. Their patient had previously undergone an obliteration procedure for patulous dysfunction but the ensuing middle ear effusions, tympanostomy tube blockage, ear pain and pressure were a constant problem even more than the original patulous symptoms.

The most common complaint with patients with total obstruction of the ET was intractable mucoid effusion constantly needing suctioning from the middle ear. Repeated blockage of tympanostomy tubes caused frequent protrusion of the tubes from the TM. In our cohort, two patients had previously had obliteration done for patulous dysfunction and they wanted the procedure to be reversed due to the recurrent mucoid effusions.

When the ET lumen is reconstructed, the mucosal surfaces can scar back together. In order to maintain a patent lumen, stenting is necessary. Placing a stent in the ET after nasopharyngectomy has been shown to significantly reduce the rate of OME (Ho et al., 2014). The largest stent typically accommodated by the ET is a 14 gauge (outside diameter 2.1 mm) angiocatheter. A steroid-eluting stent was

placed alongside the angiocatheter stent for the three most recent patients. Steroid-eluting stents have been shown to be effective in preventing restenosis after sinus surgery (Luong et al., 2018). One patient in our cohort, with restenosis after initial stent removal at 9 months postoperatively, had an additional steroid-eluting stent placed in the ET in addition to the angiocatheter stent during the revision procedure ultimately resulting in a patent lumen.

The study is limited by the small size of the patient cohort, but it is the first case series of reconstruction of the totally obliterated Eustachian tube. Direct comparison between cases is difficult since the operating technique evolved with experience during the timespan of the operations including variation with stent suturing, the time of stent removal, and the use of steroid-eluting stents. Etiologies causing ET obstruction were also heterogenous. A new lumen was successfully re-established in all cases resolving the main complaint of mucoid effusions. Mucoid effusion recurred in one patient with recurrence of obliteration after initial stent removal. After reoperation, a patent ET was established with no recurrence of effusions.

6.4 Patulous symptoms after BDET

BDET has been used as a treatment for OETD since 2010 and has gained increasingly widespread acceptance in Europe (where it was CE marked in 2011) and worldwide. FDA clearance of a balloon device designed specifically for dilation of the Eustachian tube was issued in USA in 2016 and the procedure has gained increasing acceptance since. With OETD affecting almost 5% of adults, many patients could potentially benefit from BDET (Schilder et al., 2016; Shan et al., 2019). Since medical management for OETD from non-specific etiology has been proven to be ineffective and tympanostomy tube placement can be associated with limitations and potential complications as well as failure to address the underlying pathology in the ET, surgeons have increasingly adopted BDET as an optional treatment method. Complications with BDET have been reported including epistaxis, subcutaneous emphysema, otitis media, hearing loss and one case of intimal injury to the internal carotid artery with stroke (Jeoung et al., 2023; Schröder et al., 2015; Todt et al., 2021; Wanscher & Svane-Knudsen, 2014). Patulous ETD after BDET has been reported, but there are no reports on the incidence of the complication (Anand et al., 2019; Jeoung et al., 2023).

In this multicenter study, we found that in 6.8% of all BDETs (20/295 procedures) and in 9.3% of patients (17/182), some patulous symptoms occurred after the procedure. This is much higher than the estimated natural prevalence of 0.01% (Choi et al., 2018). Onset of symptoms was typically shortly after the procedure and the symptoms were usually transient and self-limiting. There were

however cases of delayed presentation months after the procedure for 2/17 (12%) patients and symptoms persisting for over six months for 7/17 (41%) patients.

In this study, we found that younger patients aged eighteen or under were at an increased risk of developing PETD. This may be due to a greater sensitivity of the inflamed mucosa to the effects of dilation, given that inflammatory mediators in the upper respiratory tract are typically upregulated more in pediatric patients than in adults. ET anatomy and ET size relative to the balloon may be a factor contributing to the risk of PETD, but the increased risk was also noticed in patients aged 12 to 18 when the ET should have reached adult size. Dilation time is a potential risk factor for PETD in patients with greater susceptibility for patulous symptoms. In our study no statistical significance between dilation time and the risk for PETD was shown. The majority of dilations (68%) were done for 2 minutes and the study was not powered for the purpose of detecting a correlation between duration and effect. Decreasing the maximum dilation pressure could be an alternative adjustment, but no data on its effectiveness is currently available. Smaller balloon size for younger patients could be considered depending on regional availability and approval for use.

Severe ET mucosal inflammation score was found to be a risk factor for postoperative PETD. This could be due to stronger responsiveness of more inflamed mucosa to dilation. Another possibility is that severe inflammation at the orifice may have obscured the presence of milder inflammation or even atrophy more proximally within the ET lumen. Patchy atrophy with thinning of the mucosa and submucosa in the ET lumen has been recognized with allergic rhinitis, the most common co-morbidity with patulous dysfunction (Ward et al., 2017). Inflammatory findings only on the torus tubarius are not necessarily an indication of inflammation within the ET lumen and careful endoscopic evaluation of the valve area is important. We also hypothesized that patients with severe inflammatory findings may be more likely to have adjunctive procedures, such as sinus surgery, that along with BDET, may result in greater improvement of overall inflammatory burden. However, there are no studies with data to support that possibility.

Repeat dilation was associated with an increased risk of developing patulous symptoms after BDET in this study. Neglecting treatment for any underlying inflammatory disease increases the risk for recurrence of OETD. Awareness of the risk of patulous dysfunction following repeat dilation is important when considering a second procedure.

Limitations of the study included a lack of standardized instruments or measurements to detect PETD, unequal numbers of patients from the participating centers and a lack of a score to quantify the severity of symptoms. In the absence of an instrument for data collection, the participating institutions diagnosed PETD as a part of routine clinical practice based on inquiries to the patients about their symptoms. Since the vast majority of patients were dilated for two minutes, it was

not possible to adequately evaluate the effect of different durations. Even though the majority of dilations were performed at one center, the rates of patulous symptoms following BDET were similar among institutions. The purpose of the study was to detect the incidence of any symptoms, so no attempt was made to assess the severity of the condition.

6.5 Future perspectives

Obstructive Eustachian tube dysfunction affects a significant percentage of the population, but treatment has traditionally been limited to methods that do not directly address pathology within the valve of the ET. Medical management of OETD from non-specific etiology has not been shown to be effective. Previous surgical procedures have targeted the tympanic membrane or the adenoid. Balloon dilation of the Eustachian tube (BDET) has been shown to be effective in adults in randomized controlled trials. The current literature on the effects of BDET in children is promising but there are still several aspects to clarify. The minimum age or size of a patient who may be a candidate for BDET is yet to be determined. Children under the age of four have more reflux of nasopharyngeal contents and pathogens that may contribute to OETD and otitis media. It is possible that BDET could exacerbate such reflux, yet the few studies in young children to date have not shown such a problem. As the ET grows and reaches adult size by approximately the age of seven, it is not yet determined if balloon dilation should be performed using smaller diameter balloons. The robust inflammation seen in patients under the age of seven may potentially be more responsive to BDET than in older patients. However, balloon catheters are significantly more expensive that tympanostomy tubes and growth and maturation often solve the problem. Studies are needed for predicting which patients may be expected to develop chronic OETD needing repeat tympanostomy tube placement thus considering them for earlier treatment with BDET. Further studies with pediatric patients are warranted in order to find the appropriate age group and other factors predicting most benefit from BDET. In this study, we found that pediatric patients are at an increased risk of developing patulous dysfunction after BDET, possibly due to greater sensitivity of the mucosa to the dilation. The optimal dilation time and balloon size for pediatric patients is unknown but should be further studied in order to minimize potential complications while achieving efficient and durable results. RCTs with long-term results are needed for pediatric BDET. There is also a need for animal studies to determine the optimal parameters for balloon dilation such as diameter, length, duration of dilation, inflation pressure and conforming vs semi-non-conforming vs non-conforming balloons.

We presented an efficient and effective local anesthesia protocol for BDET and our results are in line with previous studies showing the results of BDET under local anesthesia comparable with the procedure performed under general anesthesia. A suitable and efficient local anesthesia protocol that provides sufficient pain relief would be essential for surgeons performing the procedure in an office setting.

Total obstruction of the Eustachian tube may be an underdiagnosed condition and awareness of the possibility of total obstruction is necessary. Unless endoscopic evaluation of the nasopharyngeal orifice and the lumen of the ET is performed, it is not possible to recognize obstruction in the cartilaginous ET. This case series and description of the procedure describes a variety of etiologies of obstruction behind the symptom of viscous mucoid effusion unresponsive to treatment. We found that reconstruction of an obliterated ET is safe and effective in restoring a lumen of the ET with a considerable follow-up time of over two years. Studies in larger cohorts and long-term follow up are needed in order to determine if the procedure remains effective in restoring ET function over time.

Knowledge of potential complications when performing surgery is important. First, to be able to avoid them and second, to be able to disclose them to the patient. In this study, we identified that risk factors for developing PETD after BDET include repeat dilation, young age and severe mucosal inflammation of the ET. Chronic allergic rhinitis as a common co-morbidity with PETD could be particularly studied for its potential to be associated with increased risk of developing PETD.

7 Conclusions

In this study, we found that balloon dilation of the Eustachian tube (BDET) is a safe and effective treatment option for children with chronic OETD. We included patients aged seven to seventeen years when the ET has theoretically reached adult dimensions. Results were stable and patients undergoing BDET compared to tympanostomy tube placement needed less additional procedures for the treatment of OETD. When performing the procedure on children, certain safety precautions need to be taken into account including potentially smaller dimensions of the ET, smaller nasal anatomy to accommodate instrumentation and potentially greater responsiveness of the ET mucosa to dilation.

BDET under local anesthesia is feasible in adults with a carefully designed anesthesia protocol. Informing patients on details of the procedure is important so that they can be adequately prepared. Middle ear ventilation, measured by tympanogram, the ability to perform a Valsalva maneuver and otomicroscopic findings, were equally improved in the patients undergoing BDET both under local and general anesthesia.

Total obliteration of the ET is rare, but should be considered in cases of intractable mucoid effusions or persistent OETD in association with granulomatous disease, trauma or surgical procedures including adenoidectomy, sinus surgery and maxillary advancement. In this pilot case series, we show that reconstruction of the ET is safe and effective in re-establishing a patent ET lumen with a considerable follow-up time of at least two years. Further studies in larger cohorts are necessary in order to determine if ET function can ultimately be restored.

When treating OETD with balloon dilation, potential adverse events including patulous dysfunction need to be considered and the patient needs to be appropriately informed. Young age, repeat dilation, and severe mucosal inflammation of the ET were shown to predispose to patulous dysfunction with BDET. A reduction in dilation time should be considered in patients under 18 years of age and patients with any history of patulous dysfunction. A thorough history and a careful preoperative examination of the ET lumen with endoscopy is necessary for recognizing potential risks.

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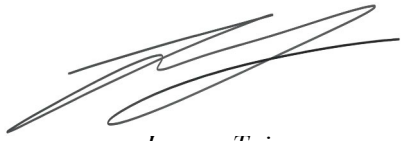

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