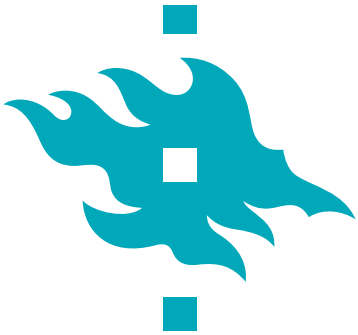

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VEERA LUUKKAINEN

BALLOON EUSTACHIAN TUBOPLASTY — TECHNIQUE, OUTCOME, AND INDICATIONS

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BALLOON EUSTACHIAN TUBOPLASTY – TECHNIQUE, OUTCOME, AND INDICATIONS

Veera Luukkainen

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To my family

The important thing is not to stop questioning.
Curiosity has its own reason for existing.
- Albert Einstein

ABSTRACT

Normal middle ear function is based on the air-filled middle ear (ME) cleft. The air in the ME is derived from the nasopharynx through the Eustachian tube (ET) and from the mastoid air cell system through transmucosal gas exchange. In chronic ear diseases, aeration is usually impaired because of ET dysfunction (ETD) or because the aeration routes from the mastoid are blocked or both. Balloon Eustachian tuboplasty (BET) aims at improving the function of the ET, thereby facilitating the prevention and treatment of chronic ear diseases.

Only individual reports mention performing BET under local anesthesia (LA). However, BET under LA can offer several advantages, including reduced anesthesia-related risks and decreased time needed in the operation room. Although short-term outcomes of BET are promising, more studies focusing on the long-term outcomes of BET, subjective and objective, are warranted. Establishing accepted indications for BET is also necessary.

In Study I, we investigated the feasibility of BET under LA by comparing it with endoscopic sinus surgery (ESS) that is routinely performed under LA. The study focused on safety of the procedure and the patients' experience. The balloon dilation device was Acclarent Aera (Acclarent Inc., Menlo Park, CA, USA) but its import to the EU ceased and, therefore, in Study II, we decided to examine if BET was feasible under LA with other BET devices (TubaVent and TubaVent Short, Spiggle & Theis Medizintechnik GmbH, Overath, Germany). In Study II, we also compared lidocaine-prilocaine cream and cocaine-adrenaline solution in anesthetizing the ET.

No adverse effects occurred among the patients treated with BET under LA. Intraoperatively, those treated with Acclarent Aera and TubaVent Short had similar visual analog scale (VAS) scores for pain to those of the ESS group. Compared with ESS patients, TubaVent patients reported significantly more pain and discomfort during BET. No differences emerged between the effects of lidocaine-prilocaine cream and cocaine-adrenaline solution.

In Study III, we examined the long-term outcomes of BET in our institution, focusing on the patients' perspective. The questionnaire

study showed that pain in the ears, feeling of pressure in the ears, and feeling that ears are clogged reduced the most, in 75% or more of the patients who had suffered from these symptoms preoperatively. Of all patients, 77% had milder overall ear symptoms after the mean follow-up of 3.1 years.

In Study IV, a systematic literature review revealed that the studies on the long-term outcomes of BET were heterogeneous in definition of ETD, selection of patients, duration of follow-up, additional treatments, and chosen outcome measures. Together, data from the studies suggested that BET has a positive long-term effect on chronic ETD symptoms and objective findings. Study IV also presented national indications for BET in adults as proposed by the Finnish Otosurgical Society: chronic bothersome symptoms referring to ETD, ETD symptoms when atmospheric pressure changes rapidly, or recurring serous otitis media.

We conclude that BET is safe and feasible under local anesthesia. In addition to regular nasal nerve block anesthesia, both lidocaine-prilocaine cream and cocaine-adrenaline solution are suitable for local anesthesia although room for improvement regarding the anesthesia method still exists. Pain and discomfort scores were similar between the three different BET devices. However, patients treated with TubaVent experienced significantly more pain and discomfort during the operation than patients undergoing ESS.

With the knowledge of which symptoms of chronic ETD respond best to BET and with the national consensus on indications for BET, patient counseling and selection can be enhanced. However, more long-term studies – with uniform criteria – on the effect of BET are still needed.

TIIVISTELMÄ

Välikorvan normaali toiminta perustuu hyvin ilmastoituihin välikorvaonteloon ja kartiolisäkkeen lokerostoon. Ilma pääsee välikorvaan joko korvatorven kautta nenänielusta tai kartiolisäkkeen lokeroston limakalvon läpi tapahtuvan kaasujenvaihdon seurauksena. Kroonisissa korvataudeissa ilmastoituminen on kuitenkin yleensä vaillinaista kartiolisäkkeen lokeroston ja välikorvan välisten ilmastointireittien tukkeutumisen, korvatorven vajaatoiminnan tai molempien vuoksi. Korvatorven pallolaajennus tähtää korvatorven toiminnan parantamiseen ja siten kroonisten korvasairauksien ehkäisyyn ja hoitoon.

Vain yksittäisissä julkaisuissa on raportoitu korvatorven pallolaajennuksen suorittamista paikallispuudutuksessa. Paikallispuudutustoimenpiteellä voidaan olettaa olevan kuitenkin useita etuja yleisanestesiatoimenpiteeseen verrattuna. Näitä ovat esimerkiksi nukutukseen liittyvien riskien poistuminen ja lyhyempi leikkaussaliaika. Vaikka lyhytaikaiset seurantatulokset ovat lupaavia, korvatorven pallolaajennuksen subjektiivisiin ja objektiivisiin pitkäaikaishyötyihin keskittyviä tutkimuksia tarvitaan lisää. Myös yhtenevät toimenpideindikaatiot puuttuvat.

Ensimmäisessä osatyössä tutkittiin, soveltuuko korvatorven pallolaajennus paikallispuudutuksessa tehtäväksi toimenpiteeksi vertaamalla sitä paikallispuudutuksessa tehtävään poskionteloaukon avarrukseen. Tutkimuksessa selvitettiin toimenpiteen turvallisuutta sekä potilaan kokemusta paikallispuudutustoimenpiteestä. Ensimmäisessä osatyössä korvatorven pallolaajentimena käytetyn Acclarent Aera -laitteiston (Acclarent Inc, Menlo Park, CA, USA) maahantuonti kuitenkin loppui, ja sen vuoksi päätimme toisessa osatyössä selvittää, sopivatko muut saatavilla olevan korvatorven pallolaajentimet – TubaVent ja TubaVent short (Spiggle & Theis Medizintechnik GmbH, Overath, Saksa) – paikallispuudutustoimenpiteessä käytettäviksi. Lisäksi vertailimme lidokaiiniprilokaiinivoidetta ja kokaiiniadrenaliiniliuosta korvatorven puuduttamisessa.

Paikallispuudutuksessa tehdyissä korvatorven pallolaajennuksissa ei ilmaantunut haittavaikutuksia. Acclarent Aeralla ja TubaVent Shortilla

hoidettujen potilaiden arvio toimenpiteen aikaisesta kivusta vastasi poskionteloaukon avarruksella hoidettujen potilaiden kokemuksia. Sen sijaan TubaVentillä hoidetut potilaat kokivat merkitsevästi enemmän kipua ja epämukavuutta toimenpiteen aikana kuin poskionteloaukon avarrusleikkauksella hoidetut potilaat. Lidokaiiniprilokaiinivoiteen ja kokaiiniadrenaliiniliuoksen puudutustehossa ei havaittu eroja.

Kolmannessa osatyössä selvitimme korvatorven pallolaajennuksen pitkäaikaistuloksia klinikassamme keskittyen erityisesti potilaan kokemukseen hoidon tehosta. Kyselytutkimuksen perusteella korvatorven pallolaajennus helpotti eniten korvakipua, paineen tunnetta korvassa sekä korvien lukkoisuutta. Nämä oireet lievittyivät vähintään 75 %:lla niistä, jotka olivat kärsineet kyseisestä oireesta ennen toimenpidettä. Kaiken kaikkiaan korvaoireet olivat nyt leikkausta edeltäneeseen tilanteeseen verrattuna vähäisempiä 77 %:lla kaikista tutkimukseen osallistuneista potilaista. Seuranta-aika oli keskimäärin 3,1 vuotta.

Neljännessä osatyössä tehtiin systemaattinen kirjallisuuskatsaus, jossa todettiin korvatorven pallolaajennuksen pitkäaikaistuloksia selvittävien tutkimusten olevan kovin heterogeenisiä potilasvalinnan ja käytettyjen mittareiden suhteen. Tutkimukset kuitenkin osoittavat, että korvatorven pallolaajennuksella on hyvä pitkäaikaisteho kroonisen korvatorven vajaatoiminnan hoidossa. Lisäksi osatyössä esitettiin Suomen Korvakirurgiyhdistyksen muodostamat kansalliset indikaatiosuositukset korvatorven pallolaajennukselle aikuispotilailla: pitkäaikaiset korvatorven vajaatoiminnan oireet ja löydökset, nopeisiin paineenvaihteluihin liittyvät paineentasausongelmat sekä toistuva liimakorva.

Korvatorven pallolaajennus on turvallinen myös paikallispuudutuksessa tehtynä. Nenän johtopuudutuksen lisänä sekä lidokaiiniprilokaiinivoide että kokaiiniadrenaliiniliuos ovat sopivia korvatorven puudutukseen, vaikka paikallispuudutusmenetelmän lisäkehittely on vielä tarpeen. Korvatorven pallolaajentimista Acclarent Aera ja TubaVent Short sopivat käyttöön paikallispuudutustoimenpiteissä.

Tämän tutkimuksen perusteella tiedämme, mitkä korvatorven vaajatoiminnan oireista lievittyvät parhaiten korvatorven pallolaajennuksella. Lisäksi on luotu korvatorven pallolaajennuksen

kansalliset indikaatiot. Nämä tiedot ovat tärkeitä potilasohjauksessa ja potilaiden valinnassa toimenpiteeseen. Silti tarvitaan vielä lisää yhtenäisillä kriteereillä tehtyjä pitkäaikaistutkimuksia korvatorven pallolaajennuksen tehosta.

CONTENTS

Abstract 4

Tiivistelmä 6

Contents 9

List of Original Publications 14

Abbreviations 15

1 Introduction 16

2 Review of the literature 18

2.1 Eustachian Tube (ET) 18

2.1.1 Anatomy, Physiology, and Pathophysiology 18

2.1.1.1 Mucosa 19

2.1.1.2 Tubal Muscles 21

2.1.1.3 Muscle Action 22

2.1.1.4 Eustachian Tube Function 24

2.1.1.5 Gas Exchange 24

2.2 Eustachian Tube Dysfunction (ETD) 28

2.2.1 Definition 28

2.2.1.1 Dilatory ETD 28

2.2.1.2 Baro-challenge-induced ETD 29

2.2.1.3 Patulous ETD 29

2.2.2 Epidemiology 30

2.2.3 Diagnosis 31

2.2.3.1 Otoscopy or Otomicroscopy 32

2.2.3.2 Tympanometry 33

2.2.3.3 Valsalva and Toynbee Maneuvers 34

2.2.3.4 Tubomanometry 35

2.2.3.5 Eustachian Tube Dysfunction Questionnaire (ETDQ-7) 36

2.2.3.6 Eustachian Tube Score (ETS) and ETS-7 37

2.2.3.7 Differential Diagnosis Between Dilatory ETD and Patulous ETD 38

2.3 Concervative Treatment of Dilatory ETD 39

2.3.1 Medication 39

2.4 Operative Treatment of Dilatory ETD 41

2.4.1 Myringotomy and Tympanostomy 41

2.4.2 Laser Tuboplasty 42

2.4.3 Microdebrieder Tuboplasty 42

2.5 Balloon Eustachian Tuboplasty (BET) 43

2.5.1 History 43

2.5.2 Technique 45

2.5.3 Preoperative Investigations 47

2.5.3.1 Imagining 47

2.5.4 Indications 48

2.5.5 Outcome 49

2.5.5.1 Short-term Outcome 49
2.5.5.2 Long-term Outcome 50
2.5.6 Complications 51
3 Aims of the Study 52
4 Materials and Methods 53
4.1 Ethical Considerations 53
4.2 Patients 53
4.3 Surgical Procedures 54
4.3.1 Local Anesthesia (LA) 54
4.3.2 Surgical Technique 56
4.3.3 Questionnaires 57
4.3.4 Systematic Literature Review 58
4.3.5 Formulating Indications for BET 59
4.4 Patient Demographics (Studies I-III) 60
4.4.1 Statistics 62
5 Results 63
5.1 Local Anesthesia (Studies I & II) 63
5.1.1 Comparison of Devices 63
5.1.1.1 Pain and Discomfort During and After BET 63
5.1.1.2 General Responses 64
5.1.2 Comparison of LA Methods 65
5.2 Complications of BET under LA (Studies I & II) 65

5.3 Long-term Outcome of BET in Helsinki University Hospital (Study III) 66
5.4 Long-term Outcome of BET in the Literature (Study IV) 70
5.5 Diagnostics of ETD (Study IV) 73
5.6 Indications for BET (Study IV) 73
6 Discussion 75
6.1 Local Anesthesia (Studies I & II) 75
6.2 Differences Between BET Devices (Studies I & II) 77
6.3 Long-term Effects of BET (Studies III & IV) 79
6.4 Indications for BET (Study IV) 83
6.5 Future Perspectives 85
7 Conclusions 89
Acknowledgments 90
References 93
Appendices 106
Appendix 1. Questionnaire for Study I 106
Appendix 1a. Questionnaire in Finnish 106
Appendix 1b. Questionnaire in Swedish 108
Appendix 1c. Questionnaire in English 110
Appendix 2. Questionnaire for Study II 112
Appendix 2a. Questionnaire in Finnish 112
Appendix 2b. Questionnaire in Swedish 115
Appendix 2c. Questionnaire in English 117

Appendix 3. Questionnaire for Study III 119
Appendix 3a. Questionnaire in Finnish 119
Appendix 3b. Questionnaire in Swedish 125
Appendix 3c. Questionnaire in English 130
Original Publications 135

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I Luukkainen V, Kivekäs I, Hammarén-Malmi S, Rautiainen M, Pöyhönen L, Aarnisalo A, Jero J, Sinkkonen ST. Balloon Eustachian tuboplasty under local anesthesia: Is it feasible? Laryngoscope. 2017 May;127(5):1021-1025.

II Luukkainen V, Jero J, Sinkkonen ST. Balloon Eustachian tuboplasty under monitored anaesthesia care with different balloon dilation devices: A pilot feasibility study with 18 patients. Clin Otolaryngol. 2019 Jan;44(1):87-90.

III Luukkainen V, Vnencak M, Aarnisalo AA, Jero J, Sinkkonen ST. Patient satisfaction in the long-term effects of Eustachian tube balloon dilation is encouraging. Acta Otolaryngol. 2018 Feb;138(2):122-127.

IV Luukkainen V, Kivekäs I, Silvola J, Jero J, Sinkkonen ST. Balloon Eustachian Tuboplasty: Systematic Review of Long-term Outcomes and Proposed Indications. J Int Adv Otol. 2018 Apr;14(1):112-126.

The publications are referred to in the text by their Roman numerals.

ABBREVIATIONS

15D	15-dimensional measure of health-related quality of life
AAO-HNSF	American Academy of Otolaryngology – Head and Neck Surgery Foundation
ABG	air-bone gap
BET	balloon Eustachian tuboplasty (Eustachian tube balloon dilation)
BPM	beats per minute
CT	computed tomography
ENT	ear, nose, and throat
ESS	endoscopic sinus surgery
ET	Eustachian tube
ETD	Eustachian tube dysfunction
ETDQ-7	validated seven-item Eustachian Tube Dysfunction Questionnaire
ETS	Eustachian Tube Score
LA	local anesthesia
LVP	levator veli palatini muscle
MAC	monitored anesthesia care
ME	middle ear
MRI	magnetic resonance imaging
OME	otitis media with effusion
SEM	standard error of the mean
TM	tympanic membrane
TMM	tubomanometry
TMR	tympanic membrane retraction
TVP	tensor veli palatini muscle
VAS	visual analog scale

1 INTRODUCTION

The Eustachian tube (ET), also called the auditory tube or pharyngotympanic tube, connects the tympanum to the nasopharynx. The structure is named after the Italian anatomist Bartolomeus Eustachius who was the first to describe it in detail in 1562. Despite several researchers studying the ET since, some of its functions, its importance to the healthy middle ear (ME) cleft, and treatment methods of its dysfunction remain unclear. ET ventilates and equalizes the pressure in the ME, clears secretions from it by mucociliary clearance, and protects the ME from sounds, pathogens, and nasopharyngeal secretions (Schilder et al., 2015).

The prevalence of ET dysfunction (ETD) in the general population is approximately 1% (Browning and Gatehouse, 1992). ETD is involved in the pathogenesis of most chronic ME diseases such as otitis media with effusion (OME), chronic suppurative otitis media, retraction pocket of the tympanic membrane (TM), and cholesteatoma (Tysome, 2015). The most common consequence of failure in opening of the ET valve is otitis media (Bluestone et al. 1972).

A recent treatment method for ETD is balloon Eustachian tuboplasty (BET). It aims at improving the function of the ET by dilating its diameter at rest and crushing diseased submucosal tissue (Kivekäs et al., 2015). BET is a safe procedure, and its short-term results are promising (Schilder et al., 2015; Huisman et al., 2018). However, only few studies evaluating its long-term outcome exist (Silvola et al., 2014; Schröder, Lehmann, Ebmeyer et al., 2015; Dalchow et al., 2016; Xiong et al., 2016; Leichtle et al., 2017).

During BET, the patients are usually under general anesthesia. Catalano and co-workers (2012) performed BET under local anesthesia (LA) in office, but it led to shorter durations of dilation and lower inflation pressures than regularly used. Commonly, patients are under LA during endoscopic sinus surgery (ESS), and from the patient's point of view BET is technically very similar to ESS. Therefore, BET should also be feasible under LA.

The greatest challenge with analyzing BET studies is the different criteria used to even define ETD and the variability of measures selected

for assessing the outcome in any given study. In a systematic review on treatments for ETD, Norman and colleagues (2014) even recommended that researchers should refrain from any new studies until these aspects are defined in consensus. Systematic review from UK National Institute for Health Research Health Technology Assessment Programme (Llewellyn et al., 2014) also reached the same conclusion: consensus on definition and diagnostic criteria of ETD is necessary (Llewellyn et al., 2014). Given these shortcomings, no international or national indications for BET had been published before this thesis project. After the above-mentioned critical review, an international panel published a consensus statement on ETD and BET but not on indications for BET (Schilder et al., 2015).

2 REVIEW OF THE LITERATURE

2.1 EUSTACHIAN TUBE (ET)

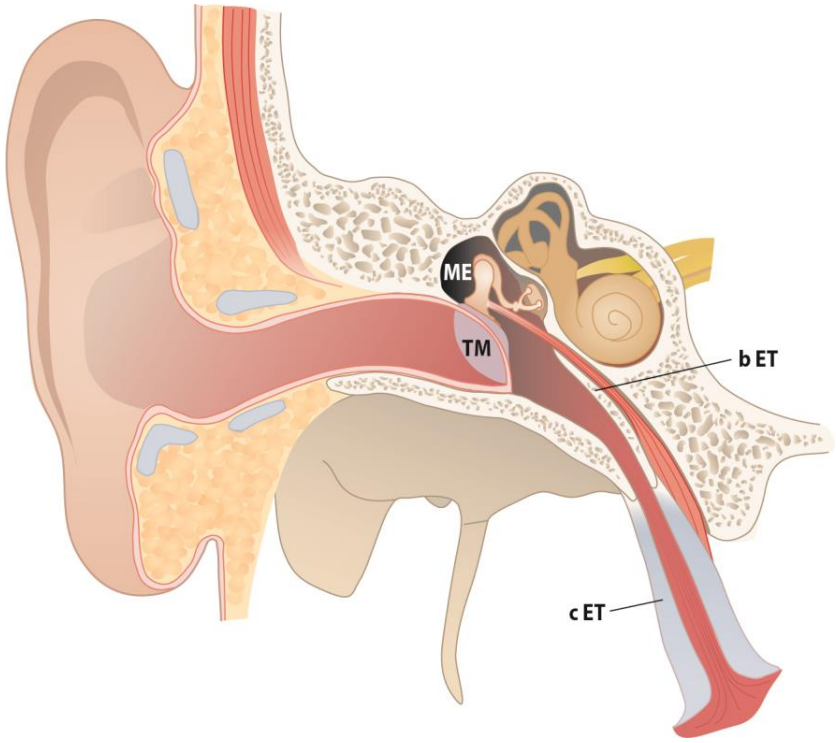

Figure 1. *Location of the Eustachian tube, right side. Adapted from Standring et al., 2008. Artist: Helena Schmidt. b ET, bony ET; c ET, cartilaginous ET; ME, middle ear; TM, tympanic membrane.*

2.1.1 ANATOMY, PHYSIOLOGY, AND PATHOPHYSIOLOGY

The ET connects the ME to the nasopharynx (Figure 1). It has three functions: i) to equalize pressure and to ventilate the ME, ii) to clear secretions from the ME through mucociliary and peristaltic clearance, and iii) to protect the ME from sounds, pathogens, and nasopharyngeal secretions.

The ET has a posterolateral bony part and an anteromedial fibrocartilaginous part. Its total length is approximately 31–38 mm in

adults. (Proctor, 1973) However, large variations exist between measurements from different studies: Graves and Edwards (1944) reported the osseous portion to be 11–12 mm in length but Sudo and colleagues (1997) measured it to be approximately half of that at 6.4 mm. The first study measured the lengths in histologic specimens whereas the latter used computer-aided three-dimensional reconstruction. Sudo and colleagues (1997) reported the length of the cartilaginous part to be 23.6 mm on average and the junctional part to be 3.0 mm. However, the tubal cartilage overlaps with the bony ET, so it is longer than the fibrocartilaginous part of the ET at approximately 31.4 mm (Sudhoff et al., 2017). In infants, the length of the ET is approximately half (18 mm) of that in adults. In the early childhood, the ET lengthens rapidly, and by four years of age, its length is 30.5 mm on average (Ishijima et al., 2000). By seven years of age, it reaches the length of the ET of an adult (Sadler-Kimes et al., 1989).

From the nasopharynx toward the ME, the ET courses posteriorly and laterally in a shape of a gently sloping inverted S. On average, the angle between the ET and the parasagittal plane is 42° and between the ET and the axial plane (the palatine bone) is 34°–36° (Robert et al., 1994; Prades et al., 1998).

The two parts of the ET resemble two cones that join and overlap in their narrower ends (Bluestone, 2005). However, the narrowest part of the ET, the isthmus, is distinct from the junction: it lies in the cartilaginous part, at 20.5 mm from the nasopharyngeal orifice and a few millimeters medial to the junction, and has a cross-sectional area of 0.65 mm^2 on average (Sudo et al., 1997; Poe et al., 2000; Poe et al., 2001).

The main compartments of the ET orifice are the cartilage, the lumen, the ligaments, the Ostmann's fat pad, and the muscles (Figure 2). The cartilage resembles an inverted J with the medial lamina longer (5.1 mm) than the lateral lamina (1.8 mm) (Dornhoffer et al., 2014). Torus tubarius is the name for the medial end of the ET which protrudes into the nasopharynx under the mucosa (Bluestone, 1996).

2.1.1.1 *Mucosa*

The ET forms the ME cleft together with the tympanic cavity and the mastoid air cell system. The posterosuperior part of the ME cleft is lined

by abundantly vascularized cuboidal epithelium (Ars et al., 1997). In the protympanum, the mucosa comprises a cylindrical-cuboidal epithelium on a basal membrane with little lymphoid infiltration. The epithelium of the osseous ET is cuboidal and respiratory. In the cartilaginous portion of the ET, the mucosa is composed of ciliated pseudostratified respiratory epithelium and includes mucus cells. Near the pharyngeal orifice, the undulating basal membrane forms pseudodiverticular invaginations, which sometimes act as micro-turbinates in protection and clearance. The mucosa of the cartilaginous ET contains also lymphoid cells, mastocytes, and histiocytes. In the lamina propria, the number of submucosal accessory glands increases toward the pharyngeal orifice. The epithelium of the ET at the pharyngeal orifice is histologically identical with the epithelium of the nasopharynx. (Martin et al., 2017) Mucosa-associated lymphatic tissue is present in the ET mucosa (Matsune et al., 1996).

The clearance action of the ET is ciliary and muscular. Ciliary clearance is dominant with highly viscous fluid, whereas mainly muscular pumping action expels mucous secretion of high volumes. However, only ciliary clearance expels small volumes of ME effusion whether low or high viscosity. (Honjo et al., 1985)

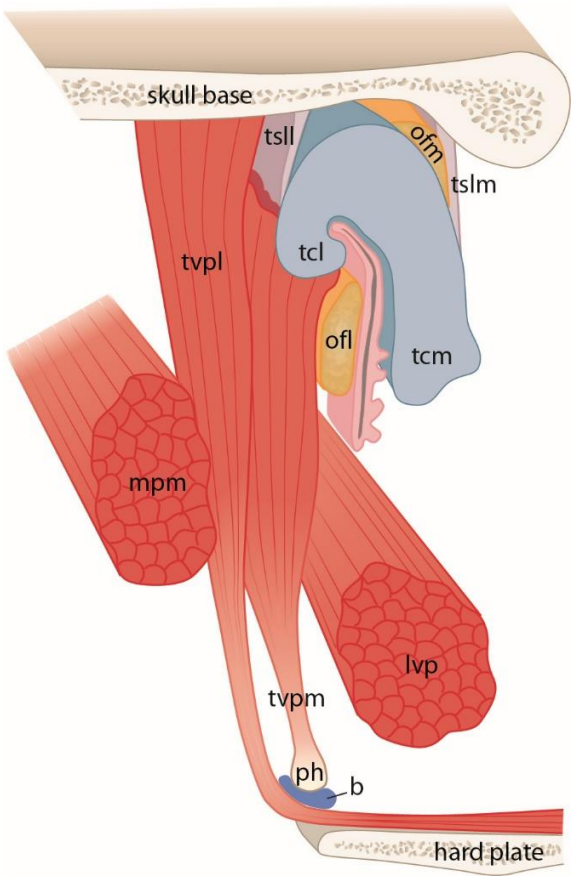

***Figure 2**. Cross-section of the Eustachian Tube, right side. Adapted from Leuwer, 2016. Artist: Helena Schmidt. b, bursa; lvp, levator veli palatini; mpm, medial pterygoid muscle; ofl, lateral Ostmann's fat pad; ofm, medial Ostmann's fat pad; ph, pterygoid hamulus; tcl, lateral tubal cartilage; tcm, medial tubal cartilage; tsll, lateral tubal suspensory ligament; tslm, medial tubal suspensory ligament; tvpl, lateral part of tensor veli palatini; tvpm, medial part of tensor veli palatini.*

2.1.1.2 *Tubal Muscles*

There are four tubal muscles: tensor veli palatini (TVP), levator veli palatini (LVP), salpingopharyngeus, and pterygoideus medialis (Rood and Doyle, 1978). The TVP originates from the scaphoid fossa of the pterygoid process and from the spine of the sphenoid bone. It also attaches to the anterolateral surface of the fibrocartilaginous part of the ET at the level of the isthmus. Distally, the tendon of the TVP courses

around the pterygoid hamulus to the palatine aponeurosis and the palatine bone. The medial pterygoid branch of the mandibular nerve innervates the TVP. The ascending palatine branch of the facial artery and the greater palatine branch of the maxillary artery provide its vascular supply. (Proctor, 1973; Standring et al., 2008)

The origin of the LVP is on the inferior surface of the petrous part of the temporal bone, anterior to the orifice of the carotid canal (Standring et al., 2008). Loose connective tissue is its only contact to the ET (Sudo et al., 1998). The LVP courses from inferior to the ET and reaches medially to the soft palate and the palatine aponeurosis. The LVP receives its innervation from the cranial part of the accessory nerve from the pharyngeal plexus and its vascular supply from the ascending palatine branch of the facial artery and the greater palatine branch of the maxillary artery. (Standring et al., 2008)

The salpingopharyngeus muscle's origin is on the inferior surface of the fibrocartilaginous ET, near the nasopharyngeal orifice. It runs inferiorly and blends with the palatopharyngeal muscle at the posterolateral border of the soft palate. The cranial part of the accessory nerve innervates the salpingopharyngeus, and its vascular supply is derived from the ascending palatine branch of the facial artery, the greater palatine branch of the maxillary artery, and the pharyngeal branch of the ascending pharyngeal artery. (Standring et al., 2008)

One head of the medial pterygoid muscle arises from the medial surface of the lateral pterygoid plate of the sphenoid bone. The smaller head originates from the pyramid process and the maxillary tuberosity of the palatine bone. The muscle runs inferiorly to the medial surface of the ramus and angle of the mandible. It is innervated by the medial pterygoid branch of the mandibular nerve, and its vascular supply is mainly from the pterygoid branches of the maxillary artery. (Standring et al., 2008)

2.1.1.3 *Muscle Action*

The bony part of ET is always open. The active function of the ET takes place in the cartilaginous part, which is closed at rest. The functional valve – the portion that opens and closes – lies a few millimeters medial to the junction of the cartilaginous and bony ET sections and is 5–10 mm in length (Poe et al., 2000; Poe et al., 2001).

When the LVP contracts, the soft palate rises, helping to close the nasopharynx, and the medial cartilaginous lamina of the ET rotates anteromedially (Proctor, 1973). However, using sonotubometry and endoscopy, Handzel and colleagues (2012) discovered that although contraction of the LVP rotates the posterior cushion of the ET and the posteromedial wall of the ET dilates, the tube stays closed. Alper and co-workers (2012) made a similar observation when using electromyography in addition to sonotubometry and endoscopy. They also noted that the LVP contracts prior to the contraction of the TVP and thus before opening of the ET (Alper et al., 2012). Gyanwali and colleagues (2016) showed in an animal model that disconnecting the TVP caused inflammation of the ME but LVP excision did not affect the ME, indicating that the LVP seems to be unimportant for the function of the ET.

The TVP contracts during yawning and swallowing. Its lateral part tenses the soft palate and participates in raising it together with the LVP and flattens the arch of the soft palate. Contraction of the medial part of the TVP pulls the lateral lamina of the tubal cartilage and further the lateral wall of the ET laterocaudally, which opens the valve. (Proctor, 1973; Rood and Doyle, 1978; Ghadiali et al., 2003; Standring et al., 2008) Conversely, the relaxed TVP bulges into the ET lumen from the anterolateral wall, thereby facilitating its closure (Ishijima et al., 2002; Takasaki et al., 2002).

When TVP contracts, the medial pterygoid muscle relaxes and moves anterolaterally, away from the ET. When TVP relaxes, the medial pterygoid contracts and moves towards the ET, assisting in its closure (LeuwerR. et al., 2003). The significance of the salpingopharyngeus muscle to the opening and closing of the ET is unclear (Sudhoff et al., 2017).

The tubal suspensory ligament attaches the cartilaginous ET to the skull base at the temporal and sphenoid bones. Distally, the ligament attaches to the medial and lateral laminas of the cartilage in a plate-resembling manner. Between this ligament is the medial Ostmann's fat pad, which divides the ligament into medial and lateral parts. Th lateral Ostmann's fat pad lies between the membranous ET and the medial band of the TVP. (Sudhoff et al., 2017)

2.1.1.4 *Eustachian Tube Function*

Using videoendoscopy, Poe and colleagues (2000) discovered four phases in the opening of the ET in healthy individuals:

1) Elevation of the soft palate, medial rotation of the medial lamina, and medial movement of the lateral pharyngeal wall.
2) With the palate elevated and the medial lamina rotated, lateral movement of the lateral wall and laterovertical dilation of the orifice of the ET.
3) Spreading of the tension of the lateral wall proximally as the lateral wall moves laterally, further dilating the lumen.
4) Dilation of the resting convexity of the lateral wall of the ET to an almost round shape. Strong swallows or yawns can also depress the floor of the ET, which widens the lumen further.

During the closure of the ET, stages 3 and 4 are repeated in reverse order. Then, stages 1 and 2 occur in variable order or even simultaneously. (Poe et al., 2000)

In patients with ETD, several pathologic changes were visible on videoendoscopy. The lateral wall movement was reduced for several reasons, the most common of which was mucosal edema. Muscle functions could be abnormal so that the dilatory wave of the lateral wall was disorganized or absent. Other dysfunctional patterns were present as well, such as relaxation of the medial lamina during the dilation of the lateral wall or even fasciculating muscle movements. (Poe et al., 2001)

2.1.1.5 *Gas Exchange*

The normal function of the tympano-ossicular system requires the ME pressure to be equal to the pressure of the ambient atmosphere. The mucosa of the ME cleft is mainly responsible for maintaining pressure equilibrium between the ME cleft and the outside of it. Opening of the ET plays a major role in rapid changes of atmospheric pressure. (Martin et al., 2017)

The ME cleft is a closed bony-walled compartment and its only direct contact to the ambient air is the ET. As approximately 80% of swallows

start during the expiratory phase of breathing (Hergils and Magnuson, 1998), the air that enters the ME from the nasopharynx through the ET is mostly exhaled air and therefore contains more carbon dioxide and less oxygen than the ambient air (Table 1). However, gases also diffuse between the ME cleft and the surrounding structures, including the blood (through the mucosa), the inner ear (through the round window), the external ear canal (across the TM), and the nasopharynx (through the ET). (Elner, 1976; Nishino et al., 1985; Naito et al., 1987; Luntz and Sadé, 1993; Tideholm et al., 1996; Hergils and Magnuson, 1998; Ars et al., 2012)

Normally, gas diffusion through the round window and through the TM is very limited. Diffusion trough the ME mucosa and the change in the atmospheric pressure are the main intrinsic and extrinsic factors affecting the pressure gradient between the ME and the environment. The gas exchange through the ME mucosa is directly related to the blood flow in it and to gradients in partial pressures of gases between different compartments. (Doyle, 2017)

According to the ideal gas law, the volume of a gas is dependent on the pressure of the gas, the number of moles of the gas, the ideal gas constant, and the temperature. The ME cleft can adjust its volume only through swelling/decongestion of the mucosa. The amount of the gas or the diffusion of the gas may also change. (Ars et al., 2012)

The capacity of the mastoid air cell system to act as a pressure buffer corresponds to its volume (Doyle, 2007; Csakanyi et al., 2014). Therefore, in diseased ears with poorly pneumatized mastoid cells, the absence of the pressure regulating mechanism of the mastoid likely promotes increasingly negative pressure in the ME. (Sadé et al., 1995)

Diffusion rates of oxygen, carbon dioxide, and water vapor are high and that of nitrogen low, and blood flow in the ME mucosa is supposedly slow. Therefore, partial pressures of oxygen, carbon dioxide, and water vapor may nearly reach a steady state. Nitrogen constantly has higher partial pressure in the ME cleft than in the ambient air because it diffuses slowly. (Ars et al., 2012) The differences in partial pressures of gases between the ME cleft and venous blood (Table 1) lead to decrease in pressure in the ME as there is a net absorption of gases to circulation (Sadé et al., 1995; Ars et al., 2012; Csakanyi et al., 2014). The opening of the ET equalizes the pressure in the ME with the pressure in the

nasopharynx and the ambient air, changes the balance of the partial pressures of gases, and promotes net diffusion away from the ME. (Ars et al., 2012; Csakanyi et al., 2014)

Table 1. *Partial pressures of gases in various locations (Sadé et al., 1995; Ars et al., 2012; Csakanyi et al., 2014).*

	P_{tot}	P_{O2}	P_{CO2}	P_{N2}	P_{H2O}
ET	760	103	37	573	47
ME cleft	757	43	50	620	47
Blood	706	40	46	573	47
Inner ear	706	40	46	573	47
External ear canal	760	158	0.3	596	5.7

ET, Eustachian tube; ME, middle ear; P_{CO2}, partial pressure of carbon dioxide; P_{H2O}, partial pressure of water vapour; P_{N2}, partial pressure of nitrogen; P_{O2}, partial pressure of oxygen; P_{tot}, total pressure of gases.

The distance between the basal lamina and the centers of the blood vessels is significantly shorter in the epitympanum, aditus ad antrum, antrum, mastoid process, and the highest part of the retrotympanum than in the protympanum, mesotympanum, the lowest part of the retrotympanum, and hypotympanum. This implies faster gas exchange between the ME and the blood in the posterosuperior ME cleft than in the anteroinferior part. Also, the epithelium of the posterosuperior ME cleft is better suited for gas diffusion than the epithelium of the rest of the ME cleft: it is cuboidal, single-layered, and richly vascularized, and its mucociliary function is reduced. The mucosa in the tympanum – except the epitympanum – has ciliated pseudostratified epithelium and thick and tight connective tissue. (Matanda et al., 2006) In the rats, the mucosa in the bulla that corresponds to mastoid is one-layered without cilia and contains abundant blood vessels. It also has a short distance between blood vessels and the basal lamina through loose connective tissue. Together, these findings suggest that the posterosuperior part of the ME cleft is dedicated to gas exchange whereas in the anteroinferior part is devoted to the clearing function. (Sadé et al., 2004; Matanda et al., 2006; Ar et al., 2007)

During inflammation, the distance between the blood vessel's centers and the basal lamina shortens even more enabling faster and more abundant gas exchange. In the inflamed mucosa, blood flow increases, thereby further increasing diffusion of gases away from the ME. This leads to more rapidly developing and more severe negative pressure in the ME. (Ars et al., 1997; Sadé et al., 2004; Bluestone, 2005; Matanda et al., 2006; Ar et al., 2007) Negative pressure contributes to the development of ME diseases (Bluestone, 2005).

Air that enters the ME during tubal opening usually is expiratory air from the nasopharynx. Its composition resembles that of the air in the ME, and therefore, the gas composition in the ME changes very little with each opening. (Hergils and Magnuson, 1998) When the ET is obstructed, the pressure gradient between the ME and the blood approximately equals the partial pressure gradient of nitrogen between the ME and the venous blood. (Doyle, 2017)

One opening of the ET lasts for 0.1–0.9 s, and 0.79–2.79 µl of air passes through it at a time (Mondain et al., 1997; Mover-Lev et al., 1998; Padurariu, 2012; Gaihede et al., 2013). A voluntary opening of the ET lasts longer than a spontaneous opening (Mondain et al., 1997). The ET opens 1–2 times per minute on average (Mondain et al., 1997). However, reaching the steady state in the gas exchange through the mucosa takes 10^5–10^6 s. Therefore, changes in total pressure and gas composition in the ME when the ET stays closed are modest (Ostfeld and Silberberg, 1991). Pressure reaches an equilibrium in 10^{-4}–10^{-3} s, which is clearly a shorter time than what the ET stays open (Ostfeld and Silberberg, 1991).

The gas exchange through the ME cleft mucosa is continuous. Although the ME pressure changes only a little between ET openings, the net absorption of gases, especially the slow absorption of nitrogen, drives it toward an increasingly negative pressure (Ostfeld and Silberberg, 1991; Tideholm, 2003; Pau et al., 2009). Because of these factors, prolonged failure of the ET to open causes pathological negative pressures, leading to retraction or atelectasis of the TM or OME (Falk and Magnuson, 1984; Bluestone, 2005).

Measuring ET function is complicated as ET opening is a poor marker for its physiological function: patulous ET is an example of this. In healthy individuals, the ET opens only at 63%–92% of swallows in adults (Avoort Van Der et al., 2005; 2006; Smith and Tysome, 2015) and at

37%–80% of swallows in children (Avoort Van Der et al., 2005; 2009). Peristaltic opening of the ET might explain why not every swallow lets sound pass from the nasopharynx to the ME in healthy ears. A bolus of air might be able to travel through the ET with its fast peristaltic movement even if sound might not. (McDonald et al., 2012) Therefore, false negative findings in ET function tests are possible. (Smith and Tysome, 2015)

The healthy ear is very sensitive to changes in the atmospheric pressure. Stretch receptors of the TM may be responsible for this as pathologies of the TM impair the ear's sensitivity to pressure. (Rockley and Hawke, 1992) The tympanic plexus seems to transmit information of the ME pressure to the ipsilateral respiratory subnuclei of the nucleus of the solitary tract. This might be a sensory pathway for brain to monitor aeration of the ME. Efferent pathways of ME pressure regulation may reach from the ipsilateral trigeminal motor nucleus and nucleus ambiguous to TVP and LVP muscles, respectively. (Eden and Gannon, 1987)

2.2 EUSTACHIAN TUBE DYSFUNCTION (ETD)

2.2.1 DEFINITION

The definition of ETD varies greatly can be witnessed in an earlier review (Smith and Tysome, 2015). Strictly speaking, ETD is the failure of the ET to perform any of its functions, and abnormalities of opening, dilating, or closing of the ET may be involved. However, in clinical practice, the term ETD commonly refers to disorders of ET's ventilatory function. Therefore, the definition of clinical ETD is the presence of symptoms and signs of impaired regulation of pressure in the ME. Three subtypes of ETD exist: i) dilatory ETD, ii) baro-challenge-induced ETD, and iii) patulous ETD. (Schilder et al., 2015; Sudhoff et al., 2017)

2.2.1.1 *Dilatory ETD*

Dilatory ETD – also called obstructive ETD – refers to situation in which the opening of the ET is limited or absent. Symptoms of dilatory ETD include aural fullness, popping, discomfort or pain, feeling of pressure,

clogged or 'under water' sensation, crackling, ringing, autophony, and muffled hearing (Schilder et al., 2015). ETD is acute if symptoms and signs have persisted for less than three months and chronic if they last over three months. Acute ETD often associates with an upper respiratory tract infection and sometimes an exacerbation of allergic rhinitis. (Schilder et al., 2015) However, it may be present without any other aerodigestive tract disorder (Seibert and Danner, 2006). Dilatory ETD has three subtypes: i) functional obstruction, ii) dynamic obstruction, i.e., muscular failure, and iii) anatomical obstruction (Schilder et al., 2015).

2.2.1.2 *Baro-challenge-induced ETD*

Baro-challenge-induced ETD exhibits similar symptoms to dilatory ETD, but the symptoms occur during ambient pressure changes, such as landing of airplanes or scuba diving, and may continue after equalization of pressure. Typically, patients are asymptomatic and clinical examination is normal at other times. Although ME effusion or hemotympanum is sometimes visible also at the ground level after a significant baro-challenge, the diagnosis of baro-challenge-induced ETD is solely based on patient history. (Schilder et al., 2015)

2.2.1.3 *Patulous ETD*

Aural fullness and autophony are typical symptoms of patulous ETD. Symptoms may be alleviated by supine position or upper respiratory tract infection and worsened by exercise. Recent large weight loss, stress (might cause TVP contraction), and rheumatologic or other chronic diseases may trigger patulous ETD. However, in most cases, a precipitating factor remains nonexistent. Some patients alleviate their symptoms by habitual sniffing. (Adil and Poe, 2014; Schilder et al., 2015) Movement of the TM with nasal respiration suggests patulous ETD (Tucci et al., 2019). The movement of the TM can be observed with otomicroscopy and tubomanometry (TMM).

2.2.2 EPIDEMIOLOGY

In the clinic, ETD is usually seen as a part of diagnostic spectrum of ME pressure equalization problems from retraction of the TM (TMR) to OME to cholesteatoma rather than as a separate entity. According to Browning and Gatehouse (1992), the prevalence of ETD is 0.9% in adult British population. Their criteria for ETD diagnosis was concurrent existence of three signs: i) intact TM, ii) flat tympanogram or showing ME pressure more negative than -100 mmH_2O (-98 daPa), and iii) air-bone gap (ABG) ≥15 dB in the pure tone audiometry. (Browning and Gatehouse, 1992) On the other hand, Shan and colleagues (2019) reported that the prevalence of ETD in US adults is 4.6%. They defined ETD more broadly as peak pressure less than -100 daPa in tympanometry when the person had been free of cold, sinus problems, or ear ache for 24 h and of head and chest cold for 30 days.

Browing and Gatehouse (1992) discovered that 2.6% of adults had dry perforation of the TM without mucosal edema. Active chronic otitis media – perforation with evidence of inflammation caused by mucosal disease or cholesteatoma – was present in 1.5%. In the USA, ETD, TMR, and OME together led to 1.6 million annual visits to the doctor among people over 20 years old in 2005–2012. In children and adolescents (0-20 years of age), the number was even higher at 2.1 million annual visits. Including chronic suppurative otitis media and cholesteatoma raised the numbers further: 2.2 million and 2.7 million visits, respectively. (Vila et al., 2017)

McCoul and colleagues studied health care utilization and prescribing patterns for adult patients with ETD by database search from Truven Health MarketScan Research Databases (Commercial and Medicare) during 2010–2014. They searched adult patients with a diagnosis of OME, ETD, or TMR. They found 1.3 million patients with acute ETD (less than three months from the primary diagnosis) or chronic ETD (at least two instances of a primary diagnosis with at least three months between the diagnoses and continuous enrollment for 15 months after the index diagnosis). Of these patients, 1.2 million (89%) suffered from acute ETD. The most common comorbidity was allergic rhinitis. However, comorbidities such as allergic rhinitis, chronic rhinitis, chronic sinusitis, and mixed or conductive hearing loss were more common among patients with chronic ETD than with acute ETD. (McCoul et al., 2019) In

one study, 49% of 101 patients with chronic rhinosinusitis had codiagnosis of ETD but whether it was acute or chronic ETD remained unclear (Tangbumrungtham et al., 2018).

One randomized placebo-controlled study (Gluth et al., 2011) on intranasal corticosteroid treatment of ETD revealed that tympanogram normalized in approximately 21% of the treatment group and in 35% of the placebo group during six weeks of follow-up. The results of the placebo group may be seen as approximation of natural course of OME or negative pressure in the ME. Animal studies suggests that exposure to tobacco smoke and gastroesophageal reflux predispose to ETD (White et al., 2002; Dubin et al., 2002).

2.2.3 DIAGNOSIS

Different studies have used different diagnostic methods and criteria, and no gold standard method for diagnosing ETD exists (Smith and Tysome, 2015). Although many have aimed at developing an objective test for ETD, none of the current ET function tests alone can serve as a diagnostic measure (Llewellyn et al., 2014; Holmquist and Olén, 2019).

The international consensus statement on ETD (Schilder et al., 2015) recommends the following diagnostic measures:

i) Otomicroscopy or otoscopy
ii) Tympanometry
iii) Tuning fork tests (Rinne's and Weber's tests) or pure tone audiometry
iv) Nasopharyngoscopy.

The American Academy of Otolaryngology – Head and Neck Surgery Foundation (AAO-HNSF) gathered a panel to compose a clinical consensus statement on ETD (Tucci et al., 2019). The panel reached a consensus that otoscopy and tympanometry are essential, but they considered pure tone audiometry to not be replaceable by tuning fork tests. AAO-HNSF consensus also emphasized the necessity of nasal endoscopy instead of mirror nasopharyngoscopy in assessing the feasibility of BET and in excluding other possible causes of symptoms. (Tucci et al., 2019) Comprehensive audiometry might reveal findings that suggest endolymphatic hydrops or superior semicircular canal

dehiscence and these findings should lead to reconsideration of the diagnosis (Poe et al., 2011; Teixeira et al., 2018; Poe et al., 2018).

Symptoms suggestive of ETD are nonspecific: aural fullness, pressure, hearing loss, and pain can be present in many otologic disorders. Differential diagnosis includes Ménière's disease (endolymphatic hydrops), dehiscence of the superior semicircular canal, disorders of the temporomandibular joint, patulous ET, and sporadic otitis media. (Llewellyn et al., 2014; Schilder et al., 2015) Autophony, audible breathing, or pulsatile tinnitus as additional symptoms suggest patulous ET whereas baro-challenge-induced symptoms might indicate obstructive ETD (Schilder et al., 2015). Although symptoms are vital in the diagnosis of ETD, symptom scores alone are inadequate diagnostic tool (Tucci et al., 2019).

For diagnosis of dilatory ETD, the patient should report symptoms suggestive of ETD and, additionally, the examiner should verify signs of negative pressure. Negative ME pressure is identifiable as a TMR in otoscopy/otomicroscopy or as negative ME pressure in tympanogram. (Schilder et al., 2015) However, the clinician should assess the patient history also beyond otorhinolaryngological symptoms as for example weight loss might induce patulous ETD (Muñoz et al., 2010).

ICD-10 (International Classification of Diseases, 10th Revision) offers only following diagnoses related to ETD:

H68.1 Obstruction of the ET

H69.8 Other specified disorders of the ET

H69.0 Patulous ET

H69.9 ET disorder, unspecified

Challenges with ET function tests include that many of them are indirect or based on passive opening of the ET instead of active opening through contraction of the peritubal muscles (Tysome and Sudhoff, 2018). Most importantly, a clinician should secure he diagnosis of ETD only after comprehensive history taking and examination as none of the diagnostic tools is alone sufficient to diagnose ETD (Tucci et al., 2019).

2.2.3.1 *Otoscopy or Otomicroscopy*

Otoscopy or otomicroscopy is an essential part of clinical examination of patients with ETD. Otoscopic findings that suggest ETD include TMR and

ME effusion (Smith and Tysome, 2015). Sensitivity and specificity of pneumatic otoscopy in diagnosing ME effusion are 94% and 80%, respectively, but the investigation is dependent on examiner and is only an indirect measure of ET function (Shekelle et al., 2002).

2.2.3.2 *Tympanometry*

Tympanometry describes changes in compliance of the TM with respect to different air pressures in the external ear canal. It is a method to investigate, the mobility of the TM and the ossicles, the presence of fluid in the ME, and the volume of the external ear canal. (Jerger, 1970) However, pressure in the ME may vary greatly for a few hours. Thus the value of the tympanometry measurement in ETD diagnosis is limited (Falk, 1981).

Type A tympanogram is a normal result. It reflects normal pressure in the ME and normal mobility of the TM and the ossicles. However, also otosclerotic ears result in type A tympanogram. The chart shows a quite sharp peak between -100 daPa and +100 daPa – usually at or close to zero – and compliance between 0.3 ml to 1.5 ml.

Type B tympanogram presents as a flat line at a low compliance level. It might be a sign of fluid in the ME. The graph has no peak but the ear canal volume is normal. A perforation of the TM or a patent grommet might result in type B-high tympanogram in which a straight line on the horizontal plane, with no peak, is high on the x-axis and the volume of the ear canal is larger than normally, i.e., clearly larger than 1.5 cm^3.

Type C tympanogram reflects negative pressure in the ME. The shape of the graph is similar to that of type A tympanogram but type C lies on the left side of the chart as the peak is below -100 daPa. Compliance is normal, 0.3–1.5 ml. ETD is a possible cause of type C tympanogram.

Although tympanometry is sensitive and specific for OME, its accuracy in the diagnostics of ETD is limited as it measures the ME pressure at a single moment and not the direct opening or function of the ET (Bluestone et al., 1973; Grøntved et al., 1989). However, its sensitivity markedly increases when it measures pressure changes over performing maneuvers such as Valsalva and Toynbee even though changes in nasopharyngeal pressure during the tests vary considerably between patients (Kumazawa et al., 1977; 1993; Finkelstein et al., 1988). The

decrease or increase of pressure is related to the ET opening frequency (Swarts et al., 2011). Repeatability of tympanometry regarding the ME pressure is good, and as the ME pressure can change considerably over the course of hours, changes in the ME pressure in tympanometry reflect true variations of pressure (Grøntved et al., 1989; Gaihede and Ovesen, 1997). However, repeatability of tympanometry regarding the compliance of the TM is limited (Gaihede and Ovesen, 1997).

2.2.3.3 *Valsalva and Toynbee Maneuvers*

Valsalva maneuver, named after Italian Antonio Maria Valsalva (1666–1723), can help to identify a properly functioning ET. In the maneuver, forced expiration, while keeping the nose and the mouth closed, forces air toward the nasopharyngeal orifices of the ETs. In normal situation, the maneuver results in positive pressure in the ME. Subjective Valsalva maneuver is positive when the subject feels air passing to the ME or hears a sound indicating it (usually the movement of the TM). Positive objective Valsalva requires an examiner to record – with the help of otoscopy or otomicroscopy – the TM moving laterally when the subject performs the maneuver. (Bluestone, 2005) The maneuver is nonphysiologic.

In the Toynbee maneuver (named after the English clinician Joseph Toynbee (1815–1866)), the subject swallows while keeping the nose manually compressed (Bluestone, 2005). TVP contracts during swallowing and therefore the maneuver should open the ET. Tympanometry before and after performing the Toynbee maneuver registers the possible change of pressure. (Bluestone, 2005) Similar to the Valsalva maneuver, the Toynbee maneuver also has subjective and objective versions. The Toynbee maneuver is closer to the physiologic function of the ET than the Valsalva maneuver as it involves swallowing.

Both Valsalva and Toynbee maneuvers become positive only when the ET opens at least partially. However, even when positive, the Valsalva maneuver is an unsure sign of ET function as it can become positive with enough positive pressure from the nasopharynx even if the ET would stay closed during swallowing and other physiologic situations. Furthermore, a negative result in Valsalva maneuver is an unreliable sign of ETD as it might be challenging to find the right technique to perform the maneuver. It is also impossible for the examiner to ensure that the

individual's technique to perform the Valsalva maneuver is correct in case the maneuver remains negative.

Positive objective Valsalva or Toynbee maneuvers, evaluated by the examiner during ot oscopy or otomicroscopy, together with the patient's subjective assessment of the maneuvers suggests that the ET is patent at least to some degree (Elner et al., 1971). However, false negative results in these tests appear in up to 30% (Finkelstein et al., 1988).

2.2.3.4 *Tubomanometry*

Tubomanometry (TMM) studies the latency of ET opening after a swallow. A nasal applicator delivers pressures of 30, 40, or 50 mbar to the nasopharynx while the subject swallows a sip of water. During swallowing, the soft palate closes the nasopharynx-oropharynx border. If the ET opens successfully during the swallowing, the pressure applied to the nasopharynx through the nasal applicator passes via the ET to the ME. Then, a pressure receptor probe, placed tightly in the external ear canal, measures movements of the TM caused by the increase of pressure in the ME. (Ars and Dirckx, 2003; Schröder, Lehmann, Korbmacher et al., 2015) TMM describes if ET opens during swallowing and if so, at what pressure level and how fast (Estève, 2003).

The TMM device displays pressure diagrams both in the nasopharynx and in the external ear canal. The diagrams show pressure (mbar) on the y-axis and time (s) on the x-axis. The device then allows the examiner to calculate the opening latency index (R-value) which describes the latency of ET opening after pressure application to the nasopharynx. A normally functioning ET opens while pressure is rising and receives R-value >1. R≤1 denotes late opening after the nasopharyngeal pressure has reached its maximum and suggests somewhat restricted function of the ET. If the ET is completely obstructed and no opening occurs, R is negative or nonmeasurable. The device might show patulous ET as fluctuating pressure in the external ear canal. TMM may also be used in cases of TM perforation or grommet. (Ars and Dirckx, 2003; Schröder, Lehmann, Korbmacher et al., 2015)

Alper and colleagues (Alper et al., 2017) investigated sensitivity and specificity of TMM in relation to the magnitude of pressure change in the ME during the test. They made 280 measurements in 249 ears (136

individuals). Before TMM, the average pressure in the ME was -19.9 ± 39.5 daPa, and after TMM it was 37.7 ± 78.6 daPa. The increase in the ME pressure was over 5 daPa in 72% of measurements and over 10 daPa in 69%. By comparing the change in the ME pressure during TMM, they discovered that TMM has high sensitivity of 93% in detecting ET opening with over 5 daPa increase in the ME pressure but specificity is low, 44%. For ET opening with pressure increase of over 10 daPa, sensitivity and specificity are 93% and 41%, respectively. (Alper et al., 2017) In TMM, the ET stays closed in 7% of healthy persons but, in the absence of otologic problems, it may be seen as a physiologic feature without any clinical significance (Estève, 2003).

2.2.3.5 *Eustachian Tube Dysfunction Questionnaire (ETDQ-7)*

Seven-item Eustachian tube dysfunction questionnaire (ETDQ-7) is the first and, so far, also the only validated disease-specific instrument for assessing ETD. It comprises of seven symptoms, and the patient rates on a scale from 1 (no problem) to 7 (severe problem) the level of problem each symptom has caused over the past month. The ETDQ-7 is fast and easy to use and burden to respondents is minimal. In the validation study (McCoul et al., 2012), it showed excellent ability to discriminate between patients with ETD and those without ETD. Also test-retest liability was good among untreated participants (McCoul et al., 2012).

The ETDQ-7 covers the following symptoms:

i) Pressure in the ears
ii) Pain in the ears
iii) Feeling that ears are clogged or “under water”
iv) Ear symptoms during a cold or sinusitis
v) Crackling or popping sounds in the ears
vi) Ringing in the ears
vii) Feeling that hearing is muffled

Mean item score is the total score divided by seven. A total score ≥ 14.5 and a mean item score ≥ 2.1 signify ETD. This borderline was chosen because having an optimal total item score cutpoint at ≥ 14.5 instead of < 14.5 presented with 100% sensitivity and 100% specificity. (McCoul et al., 2012) However, in the evaluation of the German version of ETDQ-7, sensitivity and specificity were 91% and 95%, respectively (Schröder et

al., 2014). In the German validation study, the patients with ETD had type B or C tympanogram and/or recurring OME, and/or subjectively and objectively negative Valsalva maneuver.

As validation studies of ETDQ-7 have been case–control studies, it is uncertain if the questionnaire is able to select patients with ETD from a population of patients representing a variety of otological symptoms. Also, its correlation with objective ET function tests is unclear. (Schröder, Lehmann, Sauzet et al., 2015) McCoul and Anand found that a decrease in ETDQ-7 score correlated with reduced symptoms (McCoul and Anand, 2012). ETDQ-7 has later received validation also in Spanish (Herrera et al., 2019) and Brazilian Portuguese (Gallardo et al., 2019).

Van Roeyen and colleagues (Roeyen Van et al., 2016) discovered that ETDQ-7 is excellent at discriminating healthy persons from patients with baro-challenge-induced ETD. In their study, ETDQ-7 was also substantially responsive to changes in patients who had received BET.

2.2.3.6 *Eustachian Tube Score (ETS) and ETS-7*

A German research group developed a summation point score, Eustachian tube score (ETS), for evaluation of the function of the ET (Ockermann et al., 2010a; Schröder, Lehmann, Sauzet et al., 2015). ETS combines objective and subjective parameters for ET function:

i) Clicking noise by swallowing (subjective)
ii) Clicking noise by Valsalva (subjective)
iii) TMM 30 mbar
iv) TMM 40 mbar
v) TMM 50 mbar

Every parameter gives 0–2 points with a total score of 0–10. The first two questions, the subjective ones, give zero points if the patient never hears a clicking noise by swallowing or by Valsalva, one point if the clicking noise appears only infrequently, and two points if the clicking noise is always audible. For TMM, $R < 1$ gives two points, $R \geq 1$ one point, and no opening of the ET zero points. (Ockermann et al., 2010a) The subjective aspects of the ETS should relate to at least the previous two months. Sensitivity of ETS to detect ETD is 91% and specificity 86% in patients with typical ETD symptoms and minimum of two of the following: ETDQ-

7 mean item score >2.1, type B or C curves in tympanometry, or ETD according to expert opinion. (Schröder, Lehmann, Sauzet et al., 2015)

Schröder and colleagues (Schröder, Lehmann, Sauzet et al., 2015) added tympanometry and objective Valsalva to the ETS in order to increase its predictive value. The extended score, ETS-7, has a range of total points from 0 to 14. Immediately objectively recordable Valsalva or type A tympanogram yield two points, weak and slow objective Valsalva or type C tympanogram one point, and Valsalva objectively negative or type B tympanogram zero points. ETS ≤ 5 and ETS-7 ≤ 7 are suggestive of chronic ETD. Sensitivity and specificity of ETS-7 each are 96%. (Schröder, Lehmann, Sauzet et al., 2015)

2.2.3.7 *Differential Diagnosis Between Dilatory ETD and Patulous ETD*

As symptoms of ETD are nonspecific, differential diagnosis between dilatory and patulous ETD is often challenging in the clinic. However, it is necessary to differentiate these two types of ETD as target of their treatments are opposite.

The Japan Otological Society proposed the following diagnostic criteria for patulous ET (Kobayashi et al., 2018):

1. Subjective symptoms

   At least one of the following: voice autophony, aural fullness, breathing autophony
2. Either of the tubal obstruction procedures provide clear improvement of symptoms:
   a. Assuming a supine or prone position
   b. Obstructing the nasopharyngeal orifice of the ET with a swab, gel, etc.
3. At least one of the objective signs of patulous ET:
   a. TM movement upon respiration
   b. Changes in nasopharyngeal pressure causes variations in pressure in the external auditory canal
   c. Probe tone sound pressure level < 100 dB or an open plateau pattern in sonotubometry

According to the Japan Otological Society, the diagnosis of patulous ET is definite, if the patient fulfills all three criteria. If, in addition to

symptoms suggesting patulous ET, the patient fulfills either criteria 2 or 3, the diagnosis is possible but indefinite. (Kobayashi et al., 2018)

Aural fullness and autophony are also possible symptoms of dilatory ETD (Schilder et al., 2015). However, assuming a supine or prone position closes the ET and should relieve the symptoms of patulous ET but not those of dilatory ETD. Forced nasal breathing in the sitting position is supposed to cause synchronous movement of the TM in case of patulous ET, and the examiner can observe it under the microscope. However, examining forced breathing in the supine position might give false negative results for patulous ET as the ET closes in the recumbent position. (Sudhoff et al., 2017)

Because this thesis focuses on BET, which is a treatment modality for dilatory ETD and baro-challenge-induced ETD but not patulous ETD, patulous ETD is not addressed later in this text.

2.3 CONCERVATIVE TREATMENT OF DILATORY ETD

2.3.1 MEDICATION

No scientifically proven or standard medical treatment has been indicated for nonspecific dilatory ETD (Adil and Poe, 2014). However, as allergic rhinitis, rhinosinusitis, and laryngopharyngeal reflux might cause ETD, diagnosing and treating these conditions before proceeding to operative treatment is important. (Poe et al., 2000; Poe et al., 2001; Mills and Hathorn, 2016; Tucci et al., 2019) Adil and Poe (2014) noticed that 83% of the ETs with dilatory ETD were edematous and that 74% of the patients had decreased anterolateral wall motion probably resulting from increased thickness of the inflamed mucosa. Mucosal inflammation correlates with laryngopharyngeal reflux and allergies (Edelstein et al., 1994; Poe et al., 2001). Therefore, it is crucial to recognize and treat the conditions that cause inflammation. Granulomatous diseases also require special treatment and possibly consultation of another specialty (Adil and Poe, 2014).

A randomized controlled double-blind trial found that intranasal triamcinolone as effective in treating ETD as a placebo. The study population was a mixture of adults and children who had OME or

negative ME pressure with intact TM. The study assessed the efficacy of triamcinolone after six weeks by otoscopy, tympanometry, and questionnaires on severity and frequency of symptoms. (Gluth et al., 2011)

Another double-blind placebo-controlled trial indicated that spraying xylometazoline directly to the pharyngeal ET orifice significantly improved Valsalva maneuver 30 min later. However, it had no effect on the aspiration/deflation test. (Jensen et al., 1990)

Oral antihistamine-ephedrine tablets had a positive effect on 58% (11 of 19 ears) in a double-blind study. The effect was significant compared with placebo. (Holmquist and Larsson, 1976)

McCoul and colleagues (2019) studied prescription medication use among adults diagnosed with TMR, OME, or ETD. They found that 50% of 1.2 million patients with acute ETD and 75% of 144 000 patients with chronic ETD received a prescription. The most often prescribed medications were antibiotics (over 22% of all acute ETD encounters and up to 6% of chronic ETD encounters) followed by intranasal corticosteroids (over 22% of all acute ETD encounters and up to 3% of chronic ETD encounters), oral corticosteroids (12% of all acute ETD encounters and up to 2% of chronic ETD encounters), and analgesics (6% of all acute ETD encounters and up to 2% of chronic ETD encounters). (McCoul et al., 2019)

Patients with acute ETD received prescriptions of antibiotics and oral corticosteroids more frequently if they had the co-morbidity of chronic rhinosinusitis than the co-morbidity of allergic rhinitis or neither. Patients with chronic ETD received antibiotics or oral corticosteroids more often if they had co-morbidity of chronic rhinosinusitis than those without chronic rhinosinusitis or allergic rhinitis. The prescription types varied according to whether the care provider had been otolaryngologist, physician from another specialty, or nurse. For acute ETD, otolaryngologists prescribed mostly antibiotics and intranasal corticosteroids followed by oral steroids, and less analgesics, antihistamines, and decongestants. The study excluded patients who had suffered acute rhinosinusitis, acute otitis media, or upper respiratory infection within three months before the diagnosis of ETD. (McCoul et al., 2019)

Regardless of the care provider type, patients with chronic ETD received most often a prescription of antibiotics. Otolaryngologists prescribed antibiotics almost twice as often as intranasal corticosteroids (approximately 17% vs. 9%) in cases of chronic ETD. Amounts of prescriptions for oral steroids and analgesics were little less than those for intranasal corticosteroids. Only approximately 2% of their patients with chronic ETD received a prescription for antihistamines and approximately 1% for decongestants. In this study, the indications for antibiotic prescriptions remained unclear. (McCoul et al., 2019)

According to the studies mentioned above, triamcinolone has no effect on ETD and decongestants have little effect. However, the duration of the effect of decongestants is short and generally they are recommended only for a maximum of 10 days. Therefore, decongestants might be beneficial in acute ETD but are unsuitable for chronic ETD. As antibiotics target bacterial infection, they may be suitable only in the presence of an upper respiratory tract infection such as rhinosinusitis. In treatment of chronic dilatory ETD, no medication has proved successful. Therefore, operative treatment modalities are needed.

2.4 OPERATIVE TREATMENT OF DILATORY ETD

2.4.1 MYRINGOTOMY AND TYMPANOSTOMY

Myringotomy or tympanostomy help to aerate the ME, and they are appropriate means of alleviating symptoms of ETD (BMJ Best Practice, n.d.). The AAO-HNSF panel (Tucci et al., 2019) considered myringotomy and tympanostomy as alternative to BET, not an essential prerequisite. Depending on the individual clinical situation, the surgeon might also decide to perform myringotomy or tympanostomy concurrently with BET. However, failure of open myringotomy or tympanostomy to alleviate the ETD symptoms indicate that the cause of the symptoms is other than ETD. (Tucci et al., 2019)

Klopp-Dutote and co-workers (2018) investigated risks of tympanostomy by following up 215 children under 12 years of age for 6–10 years after bilateral tympanostomy tube insertion. Otorrhea appeared in 5%, retraction pocket in 2%, and perforation of the TM in 1% of the study population after the first tympanostomy. At the last follow-up,

tympanosclerosis and perforation of the TM each were present in approximately 7% and these were the most common complications. With long-term ventilation tubes, the risk of permanent perforation is 19%, that of one episode of otorrhea 24%, and recurrent otorrhea 29% (Heerbeek Van et al., 2002).

2.4.2 LASER TUBOPLASTY

Laser tuboplasty of the ET aims to reduce hyperplastic mucosa, submucosa, and sometimes cartilage in the nasopharynx and in the area of the ET orifice. It can be performed endonasally with a combined instrument with different shafts for optics, laser fiber, and suction, or with a separate endoscope and laser. With separate instruments, also combined transoral and endonasal approach is possible by inserting the endoscope through the nose and the laser through the mouth. Laser may be carbon dioxide, diode, or argon. (Poe et al., 2003; 2007; Kujawski and Poe, 2004; Miller et al., 2017; Sudhoff and Mueller, 2018)

Kujawski and Poe (2004) treated 108 ETs of 56 patients with laser Eustachian tuboplasty. At one year, 69% of MEs were normally aerated. At two years, 71% were normally aerated, and at three years or later 65%. Only 6% of the ears required tympanostomies because of unsuccessful operation. Another study (Poe et al., 2007) followed 13 patients with OME up to two years after laser Eustachian tuboplasty. OME was absent in 40% at one year and 38% at two years. No major complications emerged with laser Eustachian tuboplasty (Kujawski and Poe, 2004; Poe et al., 2007; Miller et al., 2017).

2.4.3 MICRODEBRIEDER TUBOPLASTY

Microdebrieder Eustachian tuboplasty aims to reduce the damaged mucosa and submucosa of the posterior cushion and the posteromedial wall of the ET (Adil and Poe, 2014). Metson and colleagues (2007) studied 20 patients who also had sinonasal disease in addition to ETD and received sinus surgery concurrently with Eustachian tuboplasty. Subjective symptoms improved in 70% in follow-up of 3–34 months (mean 13 months). Mean pure tone average in audiogram improved by 6 dB HL. No major complications appeared.

2.5 BALLOON EUSTACHIAN TUBOPLASTY (BET)

2.5.1 HISTORY

After its establishment in vascular, cardiac, urologic, and gastrointestinal procedures, the first studies presented balloon dilation of paranasal sinus ostia in cadavers (Bolger and Vaughan, 2006) and then in patients in 2006 (Brown and Bolger, 2006). The expected advances included improved safety, reduced risk of complications, and reduced expenses compared with surgery. The cadaver study proved the technique feasible, and postoperative CT scan, endoscopy, and anatomic dissection revealed no trauma to the surrounding structures. Moreover, mucosal trauma was smaller than in standard ESS. (Bolger and Vaughan, 2006) No technical difficulties emerged in the study with patients, either, and also in that study bleeding and trauma to the soft tissue were less than with ESS and no adverse events appeared (Brown and Bolger, 2006). In two-year follow-up, paranasal sinus balloon dilation showed its long-term efficacy as measured using symptom scores and CT (Weiss et al., 2008).

Two preliminary studies of BET on cadavers came out in 2010. However, in one of them (Ockermann et al., 2010b), the technique included dilating both the cartilaginous and the osseous part of the ET whereas in the other (Poe and Hanna, 2011) only the cartilaginous portion. Ockermann and colleagues (2010a) were the first to publish a study on BET on patients in 2010. Since then, many studies have added to our understanding of the procedure.

Ockermann and co-workers (2010a) performed BET with a device called Bielefeld balloon catheter (Spiggle & Theis, Overath, Germany), which was specifically designed for the ET. Later, the same device got a name TubaVent. The device was used already in 2009 for the first time (Sudhoff et al., 2013). However, in the early years of BET, surgeons in some countries used sinuplasty device Relieva Solo (Acclarent, Menlo Park, CA, USA) (Poe et al., 2011; McCoul and Anand, 2012; Miller and Elhassan, 2013; Silvola et al., 2014). In the US, the Food and Drug Administration permitted marketing of first BET device, Acclarent Aera, in 2016 (FDA, 2016). However, Acclarent Aera is currently unavailable in Europe but Spiggle & Theis have developed a new catheter, TubaVent Short. The original TubaVent is still on the market. Recently, a new BET device, XprESS-ENT Dilation System (Entellus Medical, Menlo park, CA,

USA), became available in Europe. Table 2 presents BET devices previously and currently available in Europe. They are different in length (16–24 mm), and the width (3–7 mm) of the balloon varies. Figure 3 shows the Spiggle & Theis TubaVent balloon dilation device as an example of a BET device.

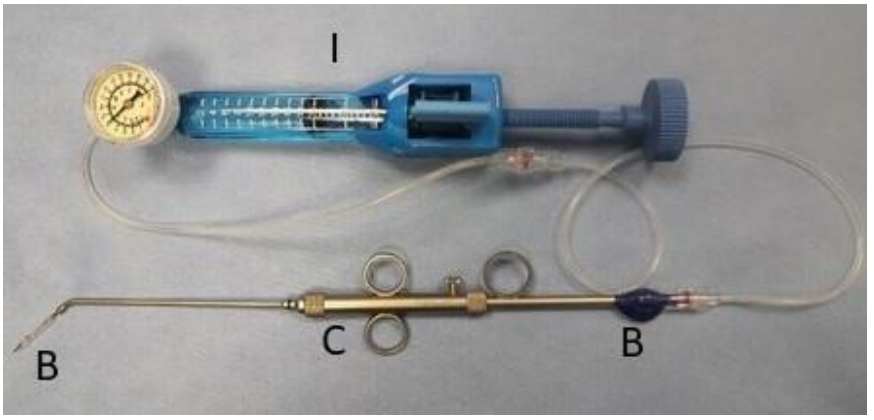

Figure 3. *Spiggle & Theis TubaVent Balloon Dilation Device. Photo: Veera Luukkainen. B, balloon dilation catheter; C, combined insertion instrument; I, inflation pump. The Spiggle & Theis TubaVent balloon dilation device includes the balloon dilation catheter, the TubaVent combination insertion instrument, and the inflation pump. Here, the balloon dilation catheter is inserted in the combination insertion instrument and connected to the inflation pump.*

Table 2. *BET Devices Previously and Currently Available on the European Market.*

Instrument	**Balloon Size (mm x mm)**
Acclarent Relieva Solo	5 x 24, 7 x 16, or 7 x 24
Acclarent	5 x 16
Acclarent Aera	6 x 16
Spiggle & Theis TubaVent (Bielefeld)	3 x 20
Spiggle & Theis TubaVent Short	3 x 20
Entellus XprESS LoProfile	5 x 20, 6 x 20, or 7 x 20

2.5.2 TECHNIQUE

Three approaches are possible when performing BET with current balloon dilation systems: ipsilateral, contralateral, and pharyngeal – also called combined endonasal and transoral – approach (Ockermann et al., 2010b; McCoul et al., 2011; Poe and Hanna, 2011). Usually, preoperative decongestant to the nose is used, e.g., naphazoline 0.1%, to reduce swelling of the mucosa. Nasal nerve block anesthesia with cocaine and adrenaline decongests the mucosa even more.

If no pathology is visible in either of the nostrils or in the epipharynx in nasoendoscopy, the surgeon places a rigid nasal endoscope to the ipsilateral nostril to visualize the ET. An endoscope of 0°–45°is suitable for ipsilateral or contralateral approach and a 70°–90° endoscope for the combined approach. In the ipsilateral approach, the surgeon places a 30°–70° applicator system along the floor of the nose to the ET orifice and then inserts a balloon catheter along the applicator into the ET. Depending on the device, the correct insertion depth is reached when a mark on the catheter is at the ET orifice or mild resistance prevents further entry without force. The resistance appears usually 13–16 mm into the lumen from the orifice. (Ockermann et al., 2010a; Schröder et al., 2013; Tisch, Maier and Maier, 2013; Tisch, Maier, Hecht et al., 2013; Miller and Elhassan, 2013; Jenckel et al., 2014; Dalchow et al., 2016)

The inflation pressure for the balloon is 10–12 atm and time usually 1–2 min (Poe and Hanna, 2011; McCoul and Anand, 2012; Silvola et al., 2014; Schröder, Lehmann, Ebmeyer et al., 2015; Dalchow et al., 2016; Xiong et al., 2016; Liang et al., 2016; Bowles et al., 2017). The balloon is inflated through an inflation pump that is filled with saline. The pump has a scale with which the pressure can be controlled. After the target inflation pressure has been kept for desired time the balloon is deflated and removed together with the applicator. The surgeon always has direct visibility to the operational field during the procedure. After the removal of the balloon and the applicator system, it is obligatory to inspect the operational field to exclude damage to the mucosa and bleeding. (Ockermann et al., 2010a; Schröder et al., 2013; Tisch, Maier and Maier, 2013; Tisch, Maier, Hecht et al., 2013; Miller and Elhassan, 2013; Jenckel et al., 2014; Dalchow et al., 2016) The devices from different manufacturers also offer applicators with different angles so that the surgeon can optimize the approach to the ET orifice.

In contralateral approach, the surgeon inserts the optics through the contralateral nostril and in combined approach through the mouth. Each approach has its advantages and disadvantages. In the ipsilateral approach, the insertion of the applicator and the balloon happens under direct visual control but it is unsuitable for a narrow nose. The contralateral approach is suitable for a nose that is too narrow for both the endoscope and the applicator system on the side of the dilation. However, it provides no visual control for inserting the applicator system through the nose. The combined approach offers great visibility to the oropharynx in addition to the nasopharynx and the ET orifice. It is also suitable for a narrow nose. However, it requires the use of an oral retractor and provides no visual control for inserting the applicator system through the nose. All approaches offer good visibility to the nasopharynx and the ET orifice. (Ockermann et al., 2010a; Schröder et al., 2013; Tisch, Maier and Maier, 2013; Tisch, Maier, Hecht et al., 2013; Jenckel et al., 2014; Dalchow et al., 2016)

The first published study on BET on patients (Ockermann et al., 2010a) presented a technique that involved dilating both cartilaginous and osseous parts of the ET. However, it later become known that dilating the bony part relieves the patients' symptoms no more than dilating only the cartilaginous part and moreover, it contains a risk of damage to the internal carotid artery. (Miller and Elhassan, 2013)

In 2012, Catalano and co-workers (2012) were the first to report BET under LA. LA was 0.05% oxymetazoline and 1% lidocaine sprays to the nostrils and 1.5 ml of 2% lidocaine gel to the ET. However, the inflation pressure was a little lower and the dilation time shorter than commonly under general anesthesia: 6 atm (time unspecified) for the first five ears and, after improvement in the LA technique, 8 atm for 10 s for 20 ears and 8 atm for 30 s for the remaining 16 ears. These inflation pressures were clearly lower and times much shorter than what is currently used when patients are under general anesthesia (10–12 atm and 2 min).

Histopathologic studies on cadavers showed that the ET stays largely unaffected by BET: only microtears were visible in the cartilaginous portion of the ET, significant microfractures were absent, and the mucosa of the ET and the wall of the internal carotid artery was intact (Ockermann et al., 2010b). However, one study (Kivekäs et al., 2015) focusing on histology before, immediately after, and 5–12 weeks after

BET discovered that inflammatory changes, mainly lymphocytic infiltrates, in the mucosa reduced significantly immediately after BET. In the end of the 5–12-week follow-up, biopsies revealed that a thinner layer of fibrous tissue had replaced the crushed lymphocytic infiltrates and that healthy ciliated pseudocolumnar epithelium had restored.

2.5.3 PREOPERATIVE INVESTIGATIONS

In many studies, preoperative examinations include tympanometry, otoscopy/otomicroscopy, Valsalva and computed tomography (CT) of paranasal sinuses (Miller and Elhassan, 2013). The international consensus panel recommended the following preoperative investigations: otoscopy or otomicroscopy, tympanometry, tuning fork tests or pure tone audiometry, and nasopharyngoscopy (Schilder et al., 2015). The clinical consensus statement of AAO-HNSF was of the same opinion as they considered otoscopy, nasal endoscopy, tympanometry, and comprehensive audiometry to be essential preoperative investigations (Tucci et al., 2019). Nasal endoscopy enables identifying extrinsic causes of ET obstruction as well as evaluation of the ET lumen and feasibility of BET regarding anatomy of the nasal airway. Nasal endoscopy also reveals patient's tolerance to nasal manipulation and therefore the feasibility of operation under LA instead of general anesthesia. (Poe et al., 2011; Teixeira et al., 2018; Poe et al., 2018; Tucci et al., 2019) Known pathologies that could affect nasal or ET function should receive medical or surgical management before BET (Tucci et al., 2019).

2.5.3.1 *Imagining*

CT and magnetic resonance imaging (MRI) scans have offered a method to investigate the anatomy and function of the ET, e.g., to visualize anatomic obstruction or to predict postoperative aeration of the ME (Tarabichi and Najmi, 2015a; Smith et al., 2016). However, CT is a poor means for diagnosing ETD because of its weakness in assessing soft tissues (Kanzaki et al., 1985). After the expulsion of fluid by tympanostomies, it is possible to localize mucosal thickening in some patients (Kanzaki et al., 1985). According to two studies, cross-sectional

diameter of the bony ET was smaller in persons suffering from ETD than in controls (Conticello et al., 1989; Yoshida et al., 2007). The angle of the ET might also be reduced in persons with obstructive ETD (Tsai et al., 2010).

Although one reason behind preoperative CT scan has been to detect carotid canal dehiscences or anomalies of the internal carotid artery and thereby prevent complications related to them, such findings are rare: Tisch and colleagues (Tisch, Störrle et al., 2013) studied 1000 head CT scans (2000 carotid canals) and noted that internal carotid artery anomalies were absent in all of 2000 carotid canals. They concluded that the necessity of a preoperative CT scan deserves critical discussion.

On the other hand, Abdel-Aziz and colleagues (2014) discovered that 18 out of 284 patients (6.3%) undergoing BET had uni- or bilateral dehiscence of the carotid canal in CT (3.5% unilateral and 6.3% bilateral). However, CT scan results were poor predictors of technical difficulties or of complications in that study. No complications related to the internal carotid artery appeared in the study, and all complications (three patients, 1.1%) occurred to patients with normal CT scans.

According to the international consensus statement, CT is a measure to be taken if patient history or examination raises suspicion of additional or alternate pathology but is unessential as a routine for everyone (Schilder et al., 2015). The members of AAO-HNSF panel reached no consensus on whether a preoperative CT is essential or not (Tucci et al., 2019).

2.5.4 INDICATIONS

During this thesis work, no published or widely accepted indications for BET existed. However, according to the recent clinical consensus statement of AAO-HNSF (Tucci et al., 2019), obstructive ETD that is unresponsive to appropriate medical treatment for an identifiable cause is an indication for BET. Patients with barochallenge-induced ETD that causes considerable discomfort might benefit from BET. However, the benefit of repeating BET when the initial BET proved ineffective is unclear and no recommendations for a repeat-BET exists. Patulous ETD is a contraindication for BET. Patients with a known carotid artery

dehiscence should receive BET only with a device that has a depth marker limiting insertion in to the ET. (Tucci et al., 2019)

2.5.5 OUTCOME

Ockermann and colleagues (2010a) published the first follow-up study on BET in 2010. In that study, the follow-up time was eight weeks. Still, approximately 10 years later, long-term outcome studies are only few in literature. In this study, we define long-term follow-up as at least 12 months.

In 2014, the Health Technology Assessment Programme of the UK National Institute for Health Research published a report on interventions for ETD in adults (Llewellyn et al., 2014). The report stated that evidence is insufficient for assessing the effect of any intervention or even for recommending a trial of any intervention. The Health Technology Assessment Programme then commissioned a review on treatment modalities for ETD and the review also found evidence of BET insufficient (Llewellyn et al., 2014).

The AAO-HNSF panel reached no consensus on the overall short-term or long-term effectiveness of BET because high-level evidence is lacking. They considered patient-reported symptom scores and the ability to perform a modified Valsalva maneuver to be suitable measures for assessing outcome of BET but stated that it is unclear whether they alone suffice in determining the outcome of the operation. (Tucci et al., 2019)

Tympanostomy tube placement concurrently with BET is beneficial in cases with ME effusion (Liang et al., 2016; Ashry et al., 2017). The effect of BET remains unclear in following situations: performing BET concurrently with middle ear operations such as tympanoplasty, treating patients who have previously undergone ME surgery, and performing repeat BET after ineffective initial BET. The AAO-HNSF panel urges the clinician to reconsider the diagnosis in case BET proves to be ineffective. (Miller and Elhassan, 2013; Tucci et al., 2019)

2.5.5.1 *Short-term Outcome*

The only randomized studies on BET had randomization time of six weeks after which the control patients could choose to cross over from

the group treated with medical management to the group treated with BET and medical management (Poe et al., 2018; Meyer et al., 2018). Poe and colleagues (2018) enrolled 323 patients (462 ETs) including 81 patients treated prior to the actual study (115 ETs). The 242 patients of the actual study included 162 patients (234 ETs) randomized to BET and medical treatment, and 80 patients (117 ETs) randomized to medical management alone. At six weeks, tympanogram had normalized in 52% of the BET group and 14% of the controls ($p < 0.0001$). ETDQ-7 normalized in 56% and 9%, respectively ($p < 0.001$). The BET group clearly improved in mucosal inflammation and Valsalva maneuver compared with the control group.

In a randomized controlled study with 60 patients, Meyer and co-workers (2018) compared change in ETDQ-7 in treatment arm patients ($n = 31$) that received BET and medication with control arm patients ($n = 29$) on only medication. Medication was, supposedly, intranasal corticosteroid. The overall ETDQ-7 score decreased significantly more in the treatment arm than in the control arm (by 2.9 (±1.4) points (mean, SD) and 0.6 (±1.0) points, respectively, $p < 0.0001$). Moreover, TMR reduced significantly more in the treatment group than in the control group (66% vs. 0%, respectively, $p < 0.001$) and tympanograms improved significantly more (57% vs. 10%, respectively, $p = 0.006$). However, the difference in improvement of Valsalva maneuver between the groups was not significant.

2.5.5.2 *Long-term Outcome*

Long-term evidence comes from prospective and retrospective case series. Overall, the trend of improvement is visible in long-term follow-up after BET. However, how much each outcome measure improved was inconsistent as Valsalva maneuver improved in 27%–98% (Silvola et al., 2014; Xiong et al., 2016; Leichtle et al., 2017; Meyer et al., 2018), tympanogram normalized in 9%–54% (Silvola et al., 2014; Xiong et al., 2016; Leichtle et al., 2017; Meyer et al., 2018), and otomicroscopic findings in 90% (Silvola et al., 2014).

Some studies have used TMM as part of the ETS but did not report TMM results separately (Schröder, Lehmann, Ebmeyer et al., 2015; Dalchow et al., 2016). In two case series, TMM improved in 40%–64%

(Xiong et al., 2016; Leichtle et al., 2017). Overall, symptoms improved in 73%–98% (Silvola et al., 2014; Schröder, Lehmann, Ebmeyer et al., 2015; Xiong et al., 2016).

2.5.6 COMPLICATIONS

No study reported major complications associated with BET. Minor, transient complications have arisen in many studies (Poe et al., 2011; Catalano et al., 2012; Schröder, Lehmann, Ebmeyer et al., 2015; Leichtle et al., 2017) but they rarely required any interventions. Reported complications were minor bleeding, mucosal lacerations, emphysema in the parotid region, temporary worsening of tinnitus, hemotympanum, unilateral hypoglossal paresis (oral approach), and contralateral C6-7 radiculopathy (Poe et al., 2011; Catalano et al., 2012; Abdel-Aziz et al., 2014; Schröder, Lehmann, Ebmeyer et al., 2015; Leichtle et al., 2017). Most of the complications resolved with time. Leichtle and colleagues (2017) reported that minor nasal bleeding resolved with intranasal xylometazoline. Reported complication rates varied from 0.3% to 21% (Poe et al., 2011; Schröder, Lehmann, Ebmeyer et al., 2015; Leichtle et al., 2017). The clinical consensus statement of AAO-HNSF states that risks important to patient counseling are bleeding, scarring, infection, development of patulous ETD, and the need for additional procedures (Tucci et al., 2019).

Even though an injury to the carotid artery during BET is possible, no reports of such cases exist in literature. An injury to the internal carotid artery might occur, in rare cases, if dilation is incorrectly performed in the bony part of the ET canal and the patient has a dehiscence of the carotid canal (Tisch, Störrle et al., 2013). A few case reports describe epistaxis originating from a petrous internal carotid artery aneurysm in the ET, but that was unrelated to BET (Busby et al., 1968; Willinsky et al., 1987).

3 AIMS OF THE STUDY

The aim of the study was to improve the treatment of patients with ETD by investigating the feasibility of performing BET under LA by using different balloon dilation devices, by defining long-term outcome of BET, and by presenting a proposal for indications for BET.

The specific objectives were the following:

1. To investigate whether BET is feasible under LA with Acclarent Aera balloon dilation device by comparing BET with ESS that is routinely performed under LA. The focus was on safety of the procedure and the patients' experience of the operation. (Study I)

2. To examine if BET is feasible under LA also with Spiggle & Theis TubaVent and TubaVent Short devices. We also intended to compare the two devices with each other and with the Acclarent device as well as to compare the two different LA methods. (Study II)

3. To study the long-term outcomes of BET in our clinic and to determine which symptoms of ETD respond to BET the best. (Study III)

4. To explore the long-term outcomes of BET in the literature by performing a systematic literature review and to present a proposal for indications for BET as outlined by the Finnish Otosurgical Society. (Study IV)

4 MATERIALS AND METHODS

4.1 ETHICAL CONSIDERATIONS

The Ethics Committee of Helsinki and Uusimaa Hospital District approved Studies I-III (I: reg. no. 226/13/03/02/2015; II: 2270/2016; III: 60/13/03/02/2015), and all patients signed informed written consent. As Study IV was a literature review and a description of outlining indications for a procedure, assessment of the Ethics Committee was unnecessary. A research permit was obtained for each study from the Department of Otorhinolaryngology – Head and Neck Surgery at the Helsinki University Hospital. The studies followed the guidelines of the Declaration of Helsinki.

4.2 PATIENTS

In Study I, the patients were from departments of Otorhinolaryngology – Head and Neck Surgery in two Finnish tertiary hospitals: Helsinki University Hospital and Tampere University Hospital. We recruited 13 consecutive adult patients with ETD who were to receive BET under LA and 12 adult patients with sinus problems who were to undergo ESS of the maxillary ostium to serve as controls.

The patients in Study II were from the department of Otorhinolaryngology – Head and Neck Surgery in Helsinki University Hospital. Eighteen consecutive adult patients underwent BET under LA.

The diagnostic workup was similar in Studies I and II and included the following: otomicroscopy, nasoendoscopy, pure tone audiometry, and ETDQ-7. Part of the patient population underwent also tubomanometry preoperatively. The operating surgeon assessed the suitability of the patient for an operation under LA in the preoperative visit. Nasal anatomy and co-operation were decisive factors.

In Study III, we retrospectively identified 51 consecutive patients who had received BET in 2011–2013 in the department of Otorhinolaryngology – Head and Neck Surgery in Helsinki University Hospital. Exclusion criteria were simultaneous otologic operation (other

than myringotomy and tympanostomy) and previous operation of the ET. We mailed a questionnaire to all 46 patients who met the inclusion criteria, and 34 of them (74%) participated the study by returning the questionnaire. Preoperative studies included otomicroscopy and nasoendoscopy or anterior and posterior rhinoscopy.

4.3 SURGICAL PROCEDURES

4.3.1 LOCAL ANESTHESIA (LA)

We performed BET under LA in Studies I and II and under general anesthesia in Study III. The ESS patients were also under LA in Study I. As ESS under LA is a routine operation, we presumed that the LA method as similar as possible to that used for ESS would be suitable for BET too. When performing BET under general anesthesia, we had applied nasal nerve block anesthesia to decongest the mucosa and minimize bleeding. For the BET LA procedure, we only had to add LA of the ET.

In Study I, we applied following nasal LA to every BET patient (Table 3): first, xylometazoline drops and then 50 mg cocaine in 1 ml of 0.01% adrenaline in small cotton pads to both nares to induce nasal nerve block anesthesia. We removed the cotton pads after 15–20 min. We anesthetized the ETs with 25/25 mg/g lidocaine-prilocaine cream (EMLA; AstraZeneca, London, UK, or Tapin; Orifarm Generics, Odense, Denmark). To connect a 2.5-ml syringe with the proximal end of the Acclarent Aera balloon catheter EU-55 shaft we cut a 2-cm piece from a CH16 tracheal suction catheter. This piece of suction catheter connected the syringe tightly to the catheter shaft. (I: Fig. 1). With the help of this instrument, we inserted 1 ml of lidocaine-prilocaine cream into the ET under endoscopic control (II: Fig. 1C). After 5 min, we suctioned away the excess anesthetic cream and started the balloon dilation.

Table 3. *Local anesthesia, Studies I & II.*

	Study I/BET	**Study I/ESS**	**Study II**
Xylometazoline drops	Yes	Yes	No
Nasal nerve block anesthesia	50 mg cocaine in 1 ml of 0.01% of adrenaline	50–250 mg cocaine in 1 ml of 0.1% adrenaline	200 mg cocaine in 1 ml of 0.1% adrenaline
Anesthesia of the ET	1 ml of 25/25 mg/g lidocaine-prilocaine cream	NA	Either (a) 25/25 mg lidocaine-prilocaine cream or (b) 20 mg cocaine in 0.1% adrenaline solution soaked in a cotton pad
Anesthesia of the middle meatus	NA	Infiltration of 1% lidocaine cum adrenaline solution	NA

BET, balloon Eustachian tuboplasty; ESS, endoscopic sinus surgery; ET, Eustachian tube; NA, not applicable.

Every patient in Study II received nasal nerve block anesthesia with 200 mg cocaine in 1 ml of 0.1% adrenaline. Those who underwent unilateral operation were anesthetized with 1 ml of 25/25 mg lidocaine-prilocaine cream to the ET. In case of bilateral operation, we randomized the ETs so that one ET received 1 ml of 25/25 mg lidocaine-prilocaine cream and the other 20 mg cocaine in 0.1% adrenaline solution. We placed cocaine-adrenaline solution to the ETs with the help of cotton pads immersed in the solution. To insert lidocaine-prilocaine cream into the ET we assembled a device similar to that in the previous study: when using TubaVent, a 5-ml syringe fit tightly to the distal part of the Combined Insertion Instrument (Spiggle & Theis Medizintechnik GmbH, Overath, Germany) but when using TubaVent Short we needed to

connect a 5-ml syringe and TubaInsert instrument (Spiggle & Theis Medizintechnik GmbH, Overath, Germany) with a 1-cm piece of CH14 tracheal suction catheter (II: Fig. 1A, 1B). Moreover, in this study, the substances for the nasal nerve block anesthesia were in place for 15–20 min and the LA substances were in the ET for 5 min.

The patients received oral premedication according to the common practice of the hospital where the patients were treated. Most patients received oral paracetamol 1–2 g, and oral 5–10 mg diazepam or 7.5 mg midazolam was added if needed. In the OR, the patients received intravenous fentanyl (25–50 μg) if necessary during both the application of LA and the operation itself (I: Table I). Some patients also required intravenous midazolam, diazepam, or propofol. One of the ESS patients in Study I needed intravenous atropine during the application of LA, and one ESS patient received intravenous atropine and etilephrine during the operation.

4.3.2 SURGICAL TECHNIQUE

We performed BET with Acclarent Aera 6 x 16 mm balloon dilation catheter in Study I and with Spiggle & Theis TubaVent and Spiggle & Theis TubaVent Short in Study II. Rigid nasoendoscopes with diameter of 3–4 mm and angles from 0° to 45° provided the view to the operational field. With the two-hands technique, we inserted the nasoendoscope to the ipsilateral nostril with the BET catheter if possible. If nostrils were too narrow, a 45° endoscope was inserted in the contralateral nostril. We inserted the BET catheter into the ET lumen as instructed by the manufacturer and then inflated the balloon with saline to 10–12 atm for two minutes. Several experienced ear, nose and throat (ENT) surgeons performed the operations. The duration of BET from the application of LA to the end of the operation was 40 ± 3 min (mean ± SEM) in Study I. During the operation, blood pressure, heart rate, and blood oxygen saturation were under monitoring in Studies I-III.

Several experienced ENT surgeons performed the ESS operations. The ESS operation included removing the uncinatus and enlarging the maxillary ostium and, in three cases, opening the bulla ethmoidalis. Five patients received self-absorbable tamponade to the middle meatus, one patient received removable tamponade, one patient both self-absorbable

and removable tamponade, and for five patients tamponade was unnecessary.

In Study III, the patients were under general anesthesia and received also nasal nerve block anesthesia with cocaine-adrenaline solution. The balloon dilation catheter was sinus balloon dilation device Acclarent Relieva Solo 7 mm x 16 mm. The inflation of 10–12 atm lasted for two minutes at once or for one minute twice. Otherwise, the BET technique was as in Studies I and II.

4.3.3 QUESTIONNAIRES

The patients in Studies I and II filled in questionnaires on their experience of operation under LA. In Study I, the questions covered both sides together if the operation was bilateral but in Study II the questionnaire had separate questions for right and left sides when the operation was bilateral. Other than that, the questionnaires were similar in both studies. The questionnaires examined pain and discomfort the patients experienced during the operation and 2 h after the operation, i.e., at the time of discharge. The patients marked their experience on the Visual Analog Scale (VAS). Furthermore, we also asked whether they felt pain relief had been sufficient or not and whether, based on their current knowledge and experience, they would prefer LA over general anesthesia if they were to undergo BET anew at a later time point. The questionnaires are in Appendices 1 and 2.

The questionnaire in Study III investigated the level of ETD symptoms in long-term follow-up of 2–4 years. McCoul and colleagues (2012) published ETDQ-7 in 2012, and approximately half of the patients in Study III had received treatment with BET by then. Therefore, ETDQ-7 had not been a part of preoperative investigations, and thus, we were unable to use it in its original form for the follow-up but had to modify it.

First, ETDQ-7 questionnaire was translated from English to Finnish and Swedish (the two official languages of Finland). Then, the questions were modified to compare the current level of each symptom presented in ETDQ-7 to the preoperative level of the given symptom on a scale from 1 to 5 (clearly less, somewhat less, the same, somewhat worse, or clearly worse than preoperatively; III: Table 2). In addition to the symptom questions derived from ETDQ-7, we asked if they can perform Valsalva

better now than preoperatively, if swallowing releases pressure in the ears better compared with preoperative situation (III: Table 2), and how they would evaluate the severity of their overall ear symptoms (III: Table 3) and disturbance caused by the current symptoms (III: Table 4). We also asked if the patients had visited a doctor because of ear symptoms and possibly received treatment for them after BET. The patients also answered the question whether they would consider re-treatment with BET in case their symptoms returned to the preoperative level (III: Table 5). With this questionnaire we assumed to gain an understanding of long-term outcome of BET and which symptoms respond the operation the best. The questionnaire is in Appendix 3.

4.3.4 SYSTEMATIC LITERATURE REVIEW

The first literature review was made in the early 2016 and presented in the annual meeting of the Finnish Otosurgical Society in April 2016. We updated the literature review with a database search on May 24th, 2017 when beginning to work with the manuscript. We searched Scopus and PubMed with the following keywords: 'Eustachian tube' AND 'balloon', 'Eustachian' AND 'balloon dilation', 'Eustachian' AND 'balloon dilatation', and 'balloon Eustachian tuboplasty' (Study IV: Fig 1). To be included in the review, a study had to be available in full text in English and include at least 12-month follow-up after BET. From 100 articles that formed the result of the search, we excluded 95 based on following exclusion criteria: article in other language than English (n=24), articles unrelated to ET (4), cadaver or animal studies (18), reviews (5), editorial or other short correspondences (4), transtympanic BET (3), case reports (3), studies with no follow-up (16), and follow-up <12 months or unclear (18). Because we had only five articles left, we also included studies with 6–11 months of follow-up (five more articles) as supportive information. The information gathered from the studies is presented in Table 4.

Table 4. *Information Gathered from Studies in the Literature Review, Study IV.*

Study setting
Number of patients and ears treated
Age of patients
Inclusion and exclusion criteria
Preoperative investigations
Surgical technique
Type of balloon dilation catheter
Type of anesthesia
Other interventions performed simultaneously with BET or during follow-up
Conservative treatment given preoperatively or postoperatively
Outcome measures
Duration of follow-up
Numbers of drop-outs
Complications

4.3.5 FORMULATING INDICATIONS FOR BET

The annual meeting of the Finnish Otosurgical Society in April 2016 (Pallas, Finland) included a session concerning ETD and BET. The session consisted of lectures on ET physiology, aeration mechanisms of the ME, transmucosal gas exchange in the ME and the mastoid, review of the BET outcome studies published in English until then, and the consensus statement of the ET (Schilder et al., 2015).

After reviewing and discussing above mentioned topics we agreed on diagnostic criteria. Thereafter, we reviewed 14 imaginary patient cases of adults and children with different signs and symptoms suggestive of ETD. The members of the Society voted on their personal mobile phones with Kahoot application (https://kahoot.it) on each case whether they considered that the case presented indications for BET or not or whether they were unable to decide. The members based their votes on their personal experience and current literature, and we divided voters into three categories according to their experience level: ENT specialists routinely performing BET (n=15), ENT specialists irregularly performing BET (n=6), and ENT residents (n=5).

First, everyone voted whether they would perform BET or not or if they were unsure. Second, we discussed the result of the vote and the case in question. We then reached a consensus on each case before moving to the next case. Based on the voting results and discussion on the cases and our knowledge of literature, the members of the Society finally agreed on a proposal for indications for BET. The cases are in IV: Supplementary File 1, and the results of the vote are in IV: Supplementary Table 1.

4.4 PATIENT DEMOGRAPHICS (STUDIES I-III)

In Study I, the 13 patients with ETD included both chronic dilatory ETD (62%) and baro-challenge-induced ETD (38%). One patient (8%) was a smoker. Preoperative ETDQ-7 scores ranged from 8 points to 42 points with a mean of 25 points.

In Study II, 18 consecutive adult patients with either chronic dilatory ETD (61%) or baro-challenge-induced ETD (39%) underwent BET under LA. We treated the first eight patients with Spiggle & Theis TubaVent and the next 10 patients with TubaVent Short. Of the TubaVent group, 13% and of the TubaVent Short group 22% were smokers, and 38% and 60% had allergies, respectively. No differences in demographics existed between the three BET groups and the ESS group regarding age and sex in Studies I-III (Table 5).

The patient characteristics of Study III are displayed in Table 6. From the medical charts, we recorded patient demographics, preoperative clinical findings, given treatment, and possible subsequent treatment after BET. We investigated the factors that might predict the need of re-BET or other surgical intervention during the successive years. However, no such distinguishing factor in the patient demographics emerged.

Table 5. *Patient demographics, Studies I & II.*

	Study I/ BET	**Study I/ ESS**	**Study II/ TV**	**Study II/ TVS**
Patients (n)	13	12	8	10
Age, mean ± SEM (range), years	48 ± 4 (19–75)	44 ± 3 (35–65)	35 ± 5 (19–66)	44 ± 4 (29–62)
Male, n (%)	8 (62)	6 (50)	3 (38)	7 (70)
Dilatory ETD (%)	62	NA	63	60
Baro-challenge-induced ETD (%)	38	NA	38	40
ETDQ-7 (mean ± SEM (range))	25 ± 3 (8–42)	NA	25 ± 3 (11–36)	30 ±2 (22–36)
Smokers, n (%)	1 (8)	0 (0)	1 (13)	2 (22)
Allergies	-	-	3 (38)	6 (60)
Previous nasal cortico-steroid treatment *n* (%)	-	-	4 (50)	3 (30)

BET, balloon Eustachian tuboplasty; ETD, Eustachian tube dysfunction; ETDQ-7, 7-item Eustachian tube dysfunction questionnaire; ESS, endoscopic sinus surgery; NA, not applicable; SEM, standard error of mean; TV, TubaVent; TVS, TubaVent Short; -, information not available. One-way ANOVA for age and sex.

Table 6. *Patient demographics, Study III.*

	All patients	**All respondents**	**Received no treatment after BET**	**Received treatment after BET**
Patients, n (%)	46 (100)	34 (74)	25 (74)	9 (26)
Age, mean (range), years	38 (16–70)	41 (16–70)	-	-
Male, n (%)	23 (50)	17 (50)	-	-
Ears treated, n	69	52	38	14
Preoperative diagnosis, *n (%)*				
OME	32 (79)	23 (68)	16 (64)	7 (78)
ETD	11 (24)	9 (26)	7 (28)	1 (8)
Chronic otitis media	3 (7)	2 (6)	2 (8)	0 (0)

BET, balloon Eustachian tuboplasty; ETD, Eustachian tube dysfunction; OME, otitis media with effusion; -, not available.

4.4.1 STATISTICS

In Studies I and II, we analyzed differences between parametric variables with unpaired *t*-test and between nonparametric variables with chi-square test. In Study III, generalized estimating equation, Fischer's exact test, and chi-square test were used to calculate differences in prevalence of the different symptoms and to evaluate the effect of BET on different symptoms. GraphPad Prism software (version 6, GraphPad Software Inc., La Jolla, CA, USA) was used in Studies I and II and SAS software (SAS Institute Inc., Cary, NC, USA) in Study III. In Study IV, the sample sizes for different variables were so small that statistical calculations were unreasonable, and we performed only qualitative analysis.

5 RESULTS

5.1 LOCAL ANESTHESIA (STUDIES I & II)

5.1.1 COMPARISON OF DEVICES

5.1.1.1 *Pain and Discomfort During and After BET*

Experience of intraoperative pain was similar among patients treated with Acclarent Aera, TubaVent Short, and ESS (Table 8). The Aera patients experienced significantly more discomfort during the operation than the ESS group (4.2 ± 0.6 and 2.5 ± 0.3, respectively; $p < 0.05$). This difference emerged in the Study I when comparing only Aera and ESS. When we added the results of Study II and compared all three BET devices and ESS, no significant difference between Aera and ESS appeared. TubaVent Short patients felt more pain than the ESS patients during the operation (7.0 ± 0.7 vs. 3.2 ± 0.7). Furthermore, intraoperative discomfort was greater among the TubaVent patients than the ESS patients (6.1 ± 0.8 vs. 2.5 ± 0.3). Results of TubaVent Short were similar to those of ESS.

At the time of discharge, no difference in VAS scores for pain existed between Aera and ESS (0.8 ± 0.2 and 1.4 ± 0.3, respectively). Contrary to the intraoperative situation, the Aera patients had lower VAS scores for discomfort than the ESS group at that time point (0.9 ± 0.2 and 1.9 ± 0.4, respectively; $p = 0.041$). Furthermore, the significance of this difference appeared only in Study I. No significant differences emerged in pain or discomfort during or after the operation when comparing TubaVent and TubaVent Short devices with lidocaine-prilocaine anesthesia. Table 7 shows the comparison of all three BET devices and the ESS procedure.

Table 7. *Outcome, lidocaine-prilocaine as local anesthetic, Studies I & II.*

	TV (*n* = 8)	**TVS** (*n* = 10)	**Aera** (*n* = 13)	**ESS** (n = *12*)
During operation, *mean ± SEM*				
Maximal pain, VAS (0–10)	7.0 ± 0.7[a]	4.5 ± 1.0	5.0 ± 0.7	3.2 ± 0.7[a]
Maximal discomfort, VAS (0–10)	6.1 ± 0.8[b]	4.0 ± 0.9	4.2 ± 0.6	2.5 ± 0.3[b]
Heart rate, BPM (range)				
Minimum	69 ± 5 (50–95)	73 ± 4 (60–93)	65 ± 4 (39–90)	76 ± 4 (38–96)
Maximum	98 ± 9 (68–130)	87 ± 4 (72–105)	72 ± 5 (45–105)	93 ± 4 (68–114)
Change	28 ± 7 (10–58)[c]	14 ± 2 (6–28)	8 ± 2 (2–22)[c,d]	17 ± 4 (5–53)[d]
At discharge, *mean ± SEM*				
Pain, VAS (0–10)	1.1 ± 0.5	0.6 ± 0.3	0.8 ± 0.2	1.4 ± 0.3
Discomfort, VAS (0–10)	1.4 ± 0.6	1.2 ± 0.7	0.9 ± 0.2	1.9 ± 0.4

BPM, beats per minute; ESS, endoscopic sinus surgery; SEM, standard error of the mean; TV, TubaVent; TVS, TubaVent Short; VAS, visual analog scale. a, p = 0.0118 for the difference between TubaVent and ESS groups; b, p = 0.0036 for the difference between TubaVent and ESS groups; c, p = 0.0120 for the difference between TubaVent and Aera groups; d, p = 0.0302 for the difference between Aera and ESS groups. One-way ANOVA and Tukey's multiple comparison test used for pain and discomfort, and chi-square test used for the other parameters.

5.1.1.2 *General Responses*

Anesthesia and intraoperative pain relief were sufficient according to 77% of the patients in the Aera group, 63% of the TubaVent group, 90% of the TubaVent Short group, and 92% of the ESS group (Table 8). Differences were not significant. One patient from each of all other groups than TubaVent Short assessed the operation to be too uncomfortable under LA. Three TubaVent Short patients were of that opinion. However, this level of discomfort stayed unrevealed in any of the cases during the operation, and all operations were carried out successfully under LA. All ESS patients and all but one of the Aera and TubaVent patients,

respectively, stated that they would prefer LA instead of general anesthesia if they were to undergo the same operation later again. Two patients treated with TubaVent Short would choose general anesthesia over LA in case of re-operation.

Table 8. *General questions, Studies I & II.*

	TV (*n* = 8)	**TVS** (*n* = 10)	**Aera** (*n* = 13)	**ESS** (n = *12*)
Operation too uncomfortable, *n* (%)	1 (13)	3 (30)	1 (8)	1 (8)
Pain relief sufficient, *n* (%)	5 (63)	9 (90)	10 (77)	11 (92)
Would choose LA again, *n* (%)	7 (88)	8 (80)	12 (92)	12 (100)

ESS, endoscopic sinus surgery; LA, local anesthesia; TV, TubaVent; TVS, TubaVent Short.

5.1.2 COMPARISON OF LA METHODS

We compared lidocaine-prilocaine cream with cocaine-adrenaline solution as LA in BET by comparing the results of bilaterally treated patients who had different LA in each ET. Our study revealed no significant differences between the anesthesia methods (Study II: Table 3). Intraoperative pain with TubaVent and lidocaine-prilocaine cream was 7.7 ± 0.6 and with TubaVent and cocaine-adrenaline 6.8 ± 1.3. With TubaVent short and lidocaine-prilocaine cream, pain was 6.0 ± 1.5 and with TubaVent short and cocaine-adrenaline it was 4.8 ± 1.0.

5.2 COMPLICATIONS OF BET UNDER LA (STUDIES I & II)

We monitored the heart rate intraoperatively as a safety measure and also as a sign of experience of pain. Change in heart rate during the procedure was significantly greater in the TubaVent group than in the ESS group (Table 8). Furthermore, the Aera group experienced significantly greater fluctuations in the heart rate than ESS group. This is in line with differences in pain and discomfort levels as we considered the range of

heart rate as a measure of pain or discomfort, with larger range reflecting more negative feelings.

While the surgeon applied LA, one ESS patient experienced a drop in the heart rate. Atropine restored heart rate to the previous level. Another patient's heart rate and blood pressure dropped during ESS operation. These incidents resolved with atropine and etilephrine. No other intraoperative or immediate postoperative complications appeared in this study.

5.3 LONG-TERM OUTCOME OF BET IN HELSINKI UNIVERSITY HOSPITAL (STUDY III)

We analyzed the results in three groups: all respondents (n = 34, 52 ears), those who had undergone only BET during the study period (n = 25, 38 ears), and those who had received additional operations (n = 9, 14 ears). First, we calculated the preoperative prevalence of the symptoms, and the here presented percentages regarding changes in the intensity of symptoms are calculated of the preoperatively symptomatic patients. Feeling that ears are clogged was the most prevalent symptom among all respondents (in 92%). Muffled hearing (92%), ear symptoms during a cold (77%), crackling or popping sounds in the ears (77%), and pressure in the ears (73%) were also among the five most common symptoms (Fig. 4). The two most common symptoms were significantly more prevalent than any of the other symptoms in the questionnaire ($p \leq 0.0390$; III: Table 2a).

Among the patients that had undergone only BET, the order of the four most common symptoms was the same as among all respondents (Fig. 5). Feeling that ears are clogged had significantly higher prevalence than any other symptom (95%, $p \leq 0.0493$). Among the patients that required additional procedures during the follow-up, all had experienced feeling that ears are clogged, feeling that hearing is muffled, and feeling of pressure (III: Table 2b).

BET had the best effect on pain in the ears among all respondents (Fig. 4; III: Table 2a). Pain, pressure in the ears (improvement in 79%), clogged feeling (76%), and ear symptoms when having a cold (66%)

diminished significantly more than ringing in the ears (40%) ($p \leq 0.0346$).

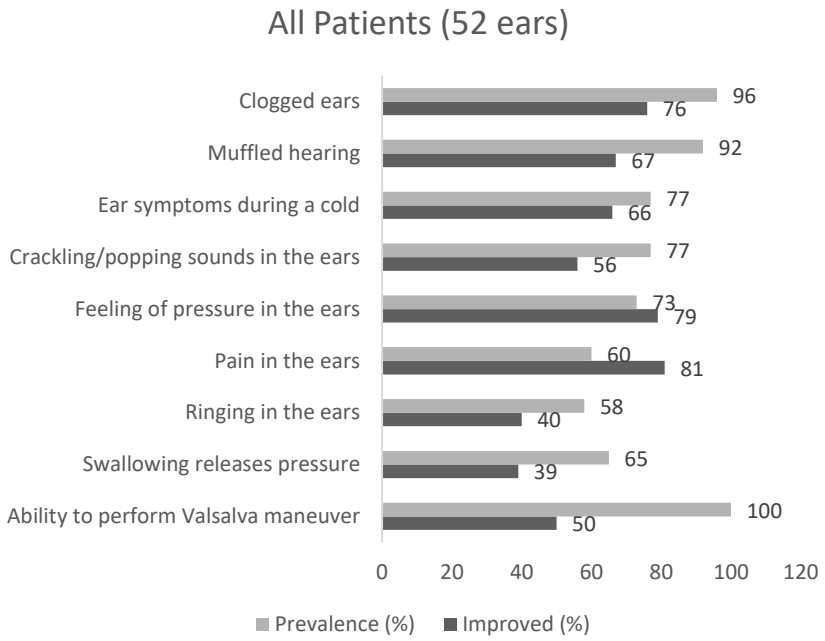

Figure 4. *Symptoms and their improvement in all patients (Study III).*

Among patients undergone only BET, feeling of pressure in the ears improved the most (Fig. 5). BET had significantly better effect on ear symptoms during a cold (improvement in 83%) than on ringing in the ears (50%) or on releasing pressure in the ears by swallowing (48%) ($p \leq 0.0155$). (III: Table 2b)

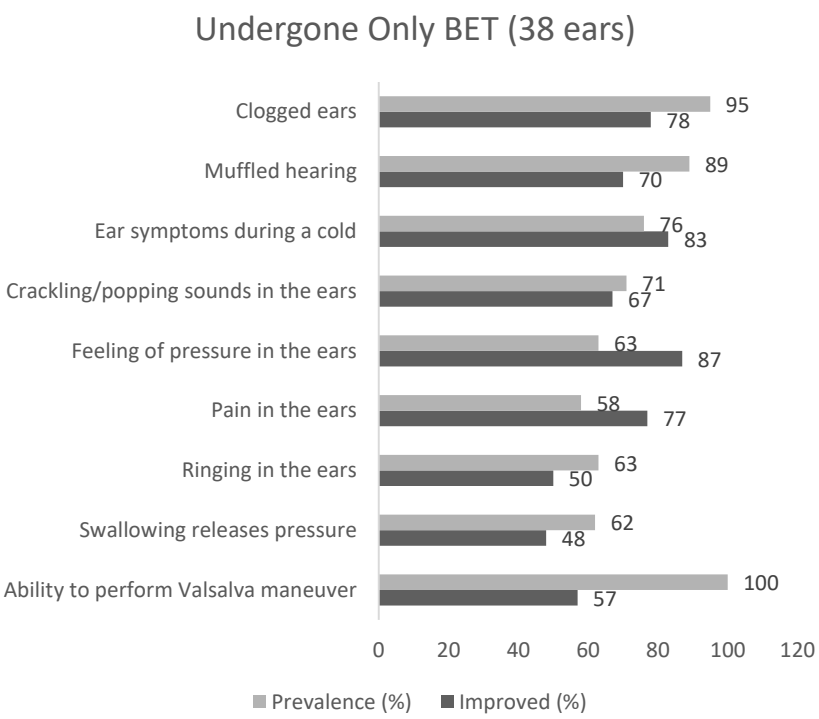

Figure 5. *Symptoms and their improvement in patients undergone only BET (Study III).*

In the group that had undergone additional operations during the follow-up, ringing in the ears remained unaffected by BET (Fig. 6). Reduction of pain (89%) and clogged feeling (71%) were significantly greater than improvement in Valsalva (28%), in ability to release pressure in the ears by swallowing (20%), in ear symptoms when having a cold (18%), or in ringing in the ears (0%) ($p \leq 0.0423$). (III: Table 2c)

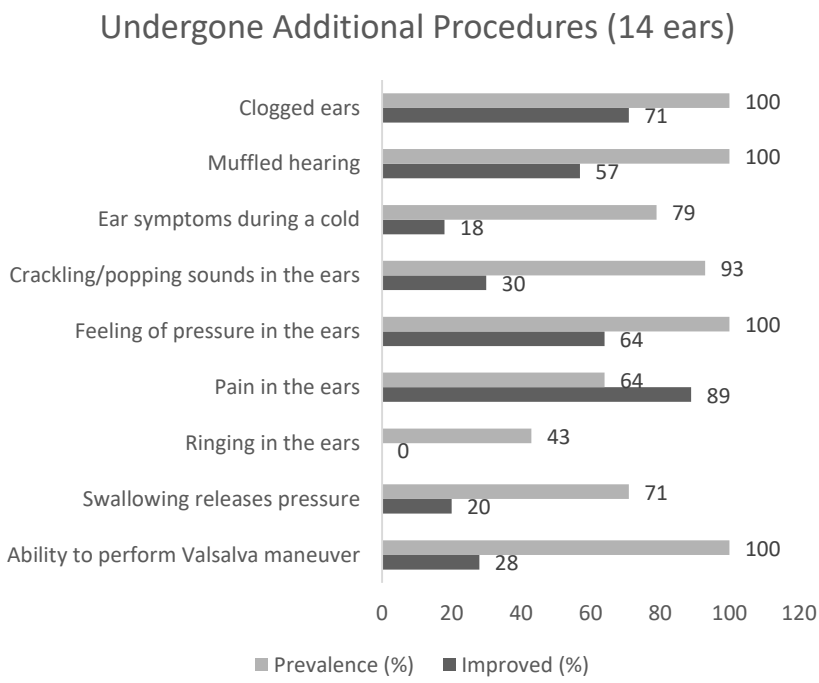

Figure 6. *Symptoms and their improvement in patients undergone additional procedures (Study III).*

Overall, 77% of all respondents felt their symptoms were milder at the end of the follow-up than preoperatively (III: Table 3). This was significantly greater percentage than the number of those who reported that symptoms remained unimproved (23%) (p = 0.0060). Of all respondents, 67% felt that their current ear symptoms caused no disturbance, very little disturbance, or little disturbance (III: Table 4).

We were also interested in if the patients, considering their current knowledge on BET and its effects on their symptoms, would choose BET again if their symptoms returned to the preoperative level. Of all respondents, 82% would choose BET again. Also 86% of those who required no additional interventions and 75% of those who needed to undergo additional procedures would choose BET again in that situation. (III: Table 5)

5.4 LONG-TERM OUTCOME OF BET IN THE LITERATURE (STUDY IV)

Results of different studies were very difficult to compare as every study had used different sets of outcome measures (Table 9). Outcome measures chosen varied so much that none of the measures was included in the results of all the five studies with long-term follow-up or all the five additional studies. Dalchow and colleagues (Dalchow et al., 2016) even developed their own ETS even though McCoul and colleagues (McCoul and Anand, 2012; McCoul et al., 2012) already had introduced their ETS.

Even preoperative workup included notable variations. Four of the analyzed studies mentioned clinical examination as part of preoperative investigations without details of what the term includes in their routines (McCoul and Anand, 2012; Bast et al., 2014; Schröder, Lehmann, Ebmeyer et al., 2015; Leichtle et al., 2017). Supposedly, otorhinolaryngological clinical examination includes otoscopy or otomicroscopy and inspection of the nasopharynx either with mirrors or with endoscopes. In that case, six (McCoul et al., 2012; Bast et al., 2014; Schröder, Lehmann, Ebmeyer et al., 2015; Dalchow et al., 2016; Bowles et al., 2017; Leichtle et al., 2017) of the 10 studies applied all preoperative investigations recommended by the international consensus statement (Schilder et al., 2015) and the clinical consensus of AAO-HNSF (Tucci et al., 2019). The remaining four studies (Poe et al., 2011; Silvola et al., 2014; Xiong et al., 2016; Liang et al., 2016) all examined the ears but 1–2 of the following were missing preoperatively: tympanometry, tuning fork tests/audiometry, and nasopharyngoscopy/nasoendoscopy.

In the studies with a follow-up of at least 12 months, tympanometry improved in 24%–54% (Silvola et al., 2014; Xiong et al., 2016; Bowles et al., 2017; Leichtle et al., 2017), otoscopic findings normalized in 90% (Silvola et al., 2014), Valsalva improved in 60%–98% (Silvola et al., 2014; Xiong et al., 2016; Leichtle et al., 2017), and tubomanometry in 40%–64% (Xiong et al., 2016; Leichtle et al., 2017). Subjective symptoms improved in up to 90% (Silvola et al., 2014; Schröder, Lehmann, Ebmeyeret al., 2015; Xiong et al., 2016; Leichtle et al., 2017). ETS was as outcome measure in two studies (Schröder, Lehmann, Ebmeyeret al., 2015; Dalchow et al., 2016), but one of them was Dalchow and colleagues' own ETS, which was impossible to compare to the ETS by Ockermann and colleagues that Schröder and co-workers used.

The studies with follow-up of 6–11 months provided similar results as the long-term studies: tympanometry, otomicroscopy, and Valsalva improved (Poe et al., 2011; McCoul and Anand, 2012; Liang et al., 2016; Bowles et al., 2017). None of the short-term studies reported change in overall symptoms or in ETS. However, two studies (McCoul and Anand, 2012; Bowles et al., 2017) used ETDQ-7 and both reported improvement. Bast and colleagues (2014) applied only Glasgow Benefit Inventory (GBI) as outcome measure and reported improvement in its subscores 'general health' and 'physical health'.

In studies with 6–14 months' follow-up, Valsalva improved in almost all patients (96%–100%) (Poe et al., 2011; Bowles et al., 2017). Tympanogram normalized in 36%–97% (Poe et al., 2011; McCoul and Anand, 2012; Liang et al., 2016; Bowles et al., 2017) and otomicroscopic findings in 54% (Poe et al., 2011). In otomicroscopy, effusion reduced in 87% of patients treated with BET only and in 93% of those who received myringotomy in addition to BET (Liang et al., 2016). ETDQ-7 score reduced from 4.5 to 2.8 (McCoul and Anand, 2012) and 4.9 to 2.0 (Bowles et al., 2017) in two prospective studies.

TMM normalized in 40%–64% at 50 mbar (Xiong et al., 2016; Leichtle et al., 2017), and mean ETDQ-7 score decreased by 2.5 points (Meyer et al., 2018). Schröder and colleagues (Schröder, Lehmann, Ebmeyer et al., 2015) followed 622 patients (1076 ETs) for two months to four years after BET. At one, two, and three years after BET, ETS improved. Two years postoperatively, 89 patients (154 treated ETs) received a questionnaire to which 34% responded, and 60% of the responders were satisfied with the result. (Schröder, Lehmann, Ebmeyer et al., 2015)

In some studies, all patients had abnormal baseline assessment of the ME, but in other studies, even the major part of the patients had normal baseline measurements, e.g., in tympanogram. In cases of abnormal initial measurements, otomicroscopy normalized in 79%–90% (Silvola et al., 2014; Meyer et al., 2018) and Valsalva in 63%–98% (Silvola et al., 2014; Xiong et al., 2016; Meyer et al., 2018), and tympanogram improved in 55% (Meyer et al., 2018).

Table 9 summarizes the results of the systematic literature review. First, it shows the wide variation in chosen outcome measures between studies. Bast and colleagues (2014) investigated only the effect of BET on the quality of life. Therefore, the study reported no parameters generally

chosen to illustrate the outcome of BET and presented in other analyzed studies in the review. Most of the parameters show improvement in over 50% of any study population. However, improvement in a given outcome measure varies between studies: for example, tympanometry showed improvement in over 75% of the patients in two studies (McCoul and Anand, 2012; Liang et al., 2016) but in under 50% in three studies (Poe et al., 2011; Xiong et al., 2016; Leichtle et al., 2017). Nevertheless, the studies with at least one year of follow-up show positive trend in the outcome of BET, and the studies with follow-up of 6–11 months support this result.

Table 9. *Long-term results of BET, Study IV.*

Publication	Tympanometry	Oto(micro)scopy	Symptoms	Valsalva	TMM	ETS	ETDQ-7
Silvola et al, 2014	++	+++	+++	+++	-	-	-
Schröder, Lehmann, Ebmeyer et al., 2015	-	-	++	-	-	+++	-
Dalchow et al. 2016	-	-	-	-	-	+*	-
Xiong et al., 2016	+	0	+++	+++	+	+++	-
Leichtle et al, 2017	+	-	+	++	++	-	-
Poe et al., 2011	+	+	-	+++	-	-	-
McCoul et al., 2012	+++	-	-	-	-	-	++
Bast et al. 2013	-	-	-	-	-	-	-
Liang et al., 2016	+++	+++	-	-	-	-	-
Bowles et al., 2017	++	-	-	+++	-	-	++

*BET, balloon Eustachian tuboplasty; ETDQ-7, Eustachian Tube Dysfunction Questionnaire; ETS, Eustachian Tube Score; TMM, tubomanometry. +, improvement in under 50% of cases; ++, improvement in 50%–75% of cases (or ETDQ-7 mean value significantly improved but not normalized); +++, improvement in over 75% of cases (or ETS mean score normalized); 0, no change; *, own ETS score from 1 to 4, clinical significance of the improvement of the mean value unclear; -, not reported.*

5.5 DIAGNOSTICS OF ETD (STUDY IV)

After reviewing literature and voting and discussing imaginary patient cases the members of the Finnish Otosurgical Society formed a consensus on diagnostic workup for ETD and indications for BET. The society's members mostly agreed with the international consensus statement (Schilder et al., 2015) on definition of ETD and on its diagnosis. In addition to the criteria on the international consensus statement, the society's members agreed to consider also ME effusion as a sign of potential chronic dilatory ETD.

According to the Finnish Otosurgical Society, the diagnosis of ETD requires both

i) Ear symptoms referring to ETD (feeling of fullness, popping, discomfort or pain, pressure, clogged feeling, crackling, ringing, muffled hearing), and
ii) Clinical signs of negative ME pressure in the ME (negative pressure in tympanogram or serous effusion in the ME)

In baro-challenge-induced ETD, clinical findings are usually normal in the office. Therefore, its diagnosis is based solely on patient history.

5.6 INDICATIONS FOR BET (STUDY IV)

Before considering BET, the clinician should address the treatable conditions that might cause ETD, including allergies, chronic rhinosinusitis, nasal polyposis, adenoid hypertrophy, and gastric reflux. Even though smoking is not considered a contraindication for BET, the clinician should encourage patients to quit smoking before proceeding to BET. The Finnish Otosurgical Society agreed that a positive response to tympanostomy suggests that BET might relieve the patient's symptoms and that unsuccessful treatment with tympanostomy tubes implies that BET is unlikely to benefit the patient. Therefore, in our recommendation, patients with non-baro-challenge-induced dilatory ETD should undergo tympanostomy prior to BET.

The Society published the indications on its web page and delivered them to the Finnish ENT colleagues by e-mail. The members of the Society suggest treating only adult patients until more evidence on safety

and efficacy of BET in children is available. The Finnish Otosurgical Society proposes the following indications for BET in adults:

i) Persistent and troublesome symptoms of ETD
ii) Recurring OME
iii) Difficulties in equalizing pressure in the ears related to rapid changes in atmospheric pressure.

6 DISCUSSION

BET is a relatively new treatment method for ETD. Despite increasing amount of publications since 2010, the current evidence of BET remains insufficient (Llewellyn et al., 2014; Norman et al., 2014; Tucci et al., 2019). As no gold standard for diagnosis of ETD or outcome for BET exists, researchers have used a wide variety of diagnostic and inclusion criteria as well as outcome measures. Therefore, the comparison of studies and the power of the existing evidence is limited.

6.1 LOCAL ANESTHESIA (STUDIES I & II)

In rhinology, procedures under LA are common, but few studies have analyzed BET under LA. Catalano and colleagues (2012) reported BET under LA in cases with no adjunctive procedures. They used three sprays of both 0.05% oxymetazoline and 1% lidocaine to the nares combined with 1.5 ml of 2% lidocaine gel to the ET. However, the anesthesia seemed to be insufficient as the dilation lasted only 30 s at maximum and the inflation reached only 6–8 atm in contrast to 2 min and 10–12 atm common under general anesthesia.

Dean and Pynnonen (2019) presented a diagnostic workup and a LA protocol but presented no results of its use. Later, Dean (2019) retrospectively reported a series of in-office BET with 33 patients using the LA protocol. Dean and Pynnonen (2019) suggested 10 mg diazepam 90 min before the operation to suppress the vestibular system and 5 mg hydrocodone 30 min before the operation. The LA was as follows: four sprays of oxymetazoline into both nostrils, five drops of 7% tetracaine/7% lidocaine in an otic solution onto the ipsilateral TM through the external ear canal, and two cottonoids soaked in 2% tetracaine bilaterally on the nasal floor. Cottonoids should be removed after 10 min, and then, 0.5 ml of 7% tetracaine/7% lidocaine cream is applied to the nasopharyngeal opening of the ET with the help of a cannula. Then, the tetracaine in cottonoids are replaced for 10–15 min. The reasoning behind the protocol was the hypothesis that the mechanical receptors in TM, promontory, and nasopharynx control the pressure in the ME and the function of the

ET through a neuronal reflex arc. (Songu et al., 2009; Dean and Pynnonen, 2019)

In the study on in-office BET (Dean, 2019), 31 of 33 patients (94%) completed the procedure. One patient experienced severe discomfort, and the dilation was stopped early. Another patient got so severe cough that the procedure had to be finished before dilation. Since then, Meyer and colleagues (2018) have mentioned performing BET under LA even in the office, but they left their LA method unreported.

In our studies, we noticed that oxymetazoline, nasal block anesthesia with cocaine-adrenaline, and cocaine-adrenaline or lidocaine-prilocaine to the ET orifice provided acceptable anesthesia that allowed performing BET in full in all the study patients under LA. However, the patients still experienced some pain and discomfort even though it was bearable and comparable to pain and discomfort levels the ESS patients reported in Study I. We performed all the operations in the OR with the possibility of intraoperative intravenous medication. In order to confidently perform BET in the office, our protocol should be further improved.

The benefits of performing BET under LA even in the OR versus under general anesthesia include diminished anesthesia-related risks to the patient, less time required in the OR, faster recovery, and reduced costs of the treatment. The cost reduction results mainly from the less time needed in the OR without general anesthesia. In our studies, we still applied LA in the OR for monitoring purposes. One ESS patient experienced a drop of the heart rate to 38/min during the application of LA. Thus, the rate of complications related to the LA was 1/43 patients, i.e., 2.3%, in Studies I & II combined.

In Study II, the LA method was very similar to the LA method in Study I. In Finland, we use the term LA quite broadly, i.e., in cases in which the patient is awake and not heavily sedated. If the patient is under LA in the OR, an anesthesiologist is on stand-by. However, the American Society of Anesthesiologists defines monitored anesthesia care (MAC) as LA along with sedation and analgesia, still preserving spontaneous breathing and airway reflexes. In fact, the definition of MAC applies to what we often call LA in the OR. Therefore, after a discussion with the reviewers, the term used in Study II is MAC although the anesthesia method was very close to that in Study I.

In our clinic, ESS patients often receive LA in a separate preparation room where heart rate and blood pressure monitoring is available. Therefore, also BET patients may be able to receive nasal nerve block anesthesia in the preparation room in the future, which would further cut the time spent in the OR by approximately 20 min. The total duration of the operation, including LA, was 40 ± 3 min in Study I. After further improving the LA method, we envision performing BET in office in the future.

Although we could perform all the operations as planned in Studies I & II, the patients still reported pain and discomfort. Study II aimed to improve the LA method from Study I, but lidocaine-prilocaine cream and cocaine-adrenaline solution proved to be equally effective in our studies. However, the patient cohorts were small, which might have affected the results. We still need to improve the LA method before proceeding to in-office BET. In Study I, two ESS patients experienced adverse effects requiring intravenous medication. Larger patient cohorts might have shown adverse effects on heart rate and blood pressure also in the BET group. Therefore, we still are cautious in proceeding to perform BET in office.

However, even with the current LA methods, 12 of 13 BET patients from Study I and 15 of 18 patients from Study II would choose LA again. With these results, we feel that BET under LA is feasible and safe in the OR but proceeding to in-office procedures requires further studies on pain control and possible vagal reactions.

6.2 DIFFERENCES BETWEEN BET DEVICES (STUDIES I & II)

Pain and discomfort scores of patients treated with Acclarent Aera and Spiggle & Theis TubaVent Short were similar to those of the ESS patients. However, TubaVent patients experienced significantly more pain and discomfort than the ESS patients (7.0 ± 0.7 vs 3.2 ± 0.7 [$p = 0.0118$] and 6.1 ± 0.8 vs 2.5 ± 0.3 [$p = 0.0036$], respectively; II: Table 2). Even though no difference in these outcome measures existed between TubaVent and TubaVent Short, the operating surgeon made a personal note that the

patients treated with TubaVent seemed to be in more pain than TubaVent Short patients.

According to our clinical experience, insertion of the catheter is the most painful phase of the procedure. The inflation seems to be mostly uncomfortable or cause deep dull pain that is easier to tolerate than the pain during insertion. The catheters have marked differences in the shapes of their tips (Fig. 7). Aera's tip is round and blunt, TubaVent has a small and sharp tip, and TubaVent Short's tip is olive-shaped and blunt. The olive-shape is specifically designed to protect the mucosa (Spiggle & Theis, n.d.). According to our experience, the shape of the tip is crucial when performing BET under LA, and the olive shape of TubaVent Short seems to be gentler to the mucosa than the sharper tip of TubaVent.

In Studies I & II, the numbers of patients were small. Therefore, the relevance of the statistical analysis is questionable, and only larger cohorts can confirm the findings.

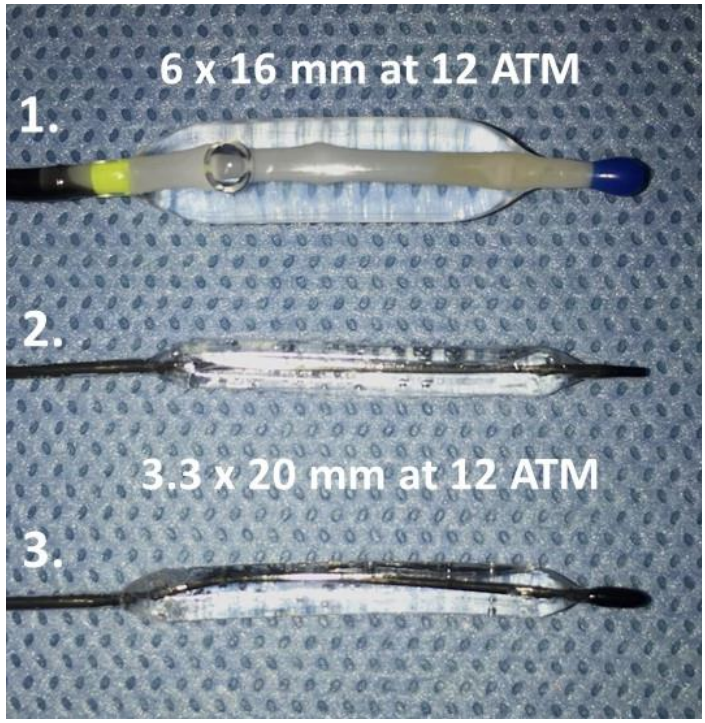

Figure 7. *Catheter tips and balloon sizes. Photo: Saku Sinkkonen. From top to bottom: 1. Acclarent Aera, 2. Spiggle & Theis TubaVent, 3. Spiggle & Theis TubaVent Short. When inflated to 12 atm, the balloon in Aera has a diameter of 6 mm and a length of 20 mm. TubaVent and TubaVent Short are of the same size when inflated to 10–12 atm: 3.3 mm x 20 mm.*

6.3 LONG-TERM EFFECTS OF BET (STUDIES III & IV)

We studied the long-term effects of BET in our department with a questionnaire modified from the ETDQ-7. As McCoul and colleagues published ETDQ-7 in 2012 (McCoul et al., 2012), it was unavailable at the start of our retrospective study period. Therefore, we had no baseline ETDQ-7 and were unable to use the validated form of the questionnaire in the follow-up. However, McCoul and Anand (2012) found that a decrease in ETDQ-7 correlated with reduction in patient-reported symptoms. Thereby we conclude that our questionnaire assessing current

ETD symptoms compared with the preoperative situation would reflect a respective change in ETDQ-7.

One disadvantage of using patient-reported symptoms is that the symptoms are entirely subjective, and it may be difficult to remember exactly how disturbing the preoperative symptoms were. However, we think that patients' satisfaction with the long-term result is one valid measure of the efficacy of the procedure along with objective measures of the aeration of the ME. Subjective symptoms have an essential role in the diagnosis of ETD and if patients are satisfied with the current situation they refrain from further doctor's appointments. The original ETDQ-7 is unvalidated in Finnish and our modified questionnaire is also unvalidated, which might have affected the results.

In Study III, the mean follow-up was 3.1 years (range 1.8–4.6 years), which is among the longest of the BET follow-up studies. Even though 74% of the patients returned the questionnaire, 26% refrained from responding. The nonresponding patients might have been those who experienced no benefit from BET in the long term, and in that case, our results are overly optimistic. Of all patients, 77% were less symptomatic at the end of the follow-up than preoperatively, and only 43% of the patients who required additional operations reported improvement. However, 75% of those who underwent additional operations would undertake BET again in case their otologic symptoms increased to the preoperative level. This might reflect that they hope a re-operation would improve their complaints or that the effect of BET initially was better and was now fading.

The long-term results of BET in the Department of Otorhinolaryngology – Head and Neck Surgery in Helsinki University Hospital are similar to those from international literature. In Study III, 10% of all patients were asymptomatic at the end of the follow-up, 42% had clearly less symptoms than preoperatively, 25% had somewhat less symptoms, 15% experienced symptoms as much as before BET, and 8% had more symptoms than preoperatively. In Study IV, overall symptoms improved in up to 98% after minimum of 12 months follow-up (Silvola et al., 2014; Schröder, Lehmann, Ebmeyer et al., 2015; Xiong et al., 2016). Schröder and colleagues (Schröder, Lehmann, Ebmeyer et al., 2015) discovered that 47% were satisfied with the current situation, 26% had experienced some improvement, and 27% were unimproved. In Study III,

33% of patients reported that they could perform Valsalva maneuver better than preoperatively. In Study IV, 0%–28% of patients could perform Valsalva preoperatively and 80%–98% at one year after BET (Silvola et al., 2014; Xiong et al., 2016; Leichtle et al., 2017). Miller and Elhassan (2013) found in their review that 64% of cases could consistently perform Valsalva maneuver postoperatively, compared with 11% of cases preoperatively. Of the patients with abnormal preoperative tympanogram, 78% had normalized at up to six months postoperatively.

We also found in Study IV that it is nearly impossible to define the outcome of BET because the study designs are very different between studies (Llewellyn et al., 2014; Huisman et al., 2018). Differences start with the definition of ETD and affect what type of patients with ETD the given study includes. Every study applies a different set of outcome measures which makes comparison of results difficult.

Valsalva maneuver, ETS by Ockermann and colleagues (2010a), and ETDQ-7 seemed to be the most coherently positive outcome measures. In every study that applied these outcome measures, over 50% or over 75% of the patients improved in respect to them. In other outcome measures, the percentage of improvement was from under 50% to over 75%. TMM seemed to be the least positive measure with improvement in under 50% to 50%–75% of the patients. However, only two studies (Xiong et al., 2016; Leichtle et al., 2017) reported pre- and postoperative TMM, ETS (Schröder, Lehmann, Ebmeyer et al., 2015; Xiong et al., 2016), or ETDQ-7 (McCoul and Anand, 2012; Bowles et al., 2017), respectively. (Table 12)

Although the studies are very heterogenous, every study analyzed in this systematic review presents positive results for BET. This applies to studies with the follow-up of minimum 12 months and 6–11 months. In studies with at least 12 months' follow-up, symptoms, Valsalva maneuver, and ETS improved the most. Only Leichtle and colleagues (2017) found that maximum improvement with respect to every outcome measure was less than 75%. In all other studies with 12-month follow-up, at least one of the parameters showed improvement in over 75%. In studies with 6–11 months' follow-up, only Valsalva and ETDQ-7 showed improvement in over 50% of patients in every study applying them (Poe and Hanna, 2011; McCoul and Anand, 2012; Bowles et al., 2017). (Table 12)

The material in Study IV was so heterogenous that no statistical analysis was reasonable. Therefore, we performed only qualitative analysis. However, Huisman and colleagues (2018) performed statistical calculations for a similar material but they also noticed weaknesses in the analysis because of widely varied outcome measures. Thus, small feasibility studies are critical in investigating the feasibility and safety of a procedure before proceeding to larger studies.

While our manuscript of Study IV was under preparation, Huisman and colleagues (2018) published a systematic review of BET. They found that meta-analysis was possible only for four outcome measures: Valsalva maneuver, otoscopy, tympanometry, and ETS. Other parameters included either too wide variation between studies or only one or two studies were available for meta-analysis. In meta-analysis, five studies showed that the ability to perform Valsalva maneuver increased after BET. Abnormal otoscopic findings in the TM decreased postoperatively in six studies, tympanometry improved in nine studies, ETS improved by 3.94 points on average in three studies. (Huisman et al., 2018) Also, our review found improvement in all these four parameters. Although we performed only descriptive analysis, trends of improvement were clearly visible and it was strongest with the Valsalva maneuver. The inclusion and exclusion criteria of the review performed by Huisman and colleagues different from ours and they included 15 studies in the final analysis whereas we had only five with the original criteria and five additional studies.

BET is a relatively new procedure, and more studies are needed to thoroughly investigate its long-term effects. However, not all commonly used operations in ENT specialty are studied in depth although they have been in use for several decades. This raises the question how much evidence is needed before a new procedure can be adopted in regular clinical practice. At present, the effect of BET seems to be positive, but the magnitude of the effect and the optimal patient selection remain unclear. It should be discussed if this is enough evidence to justify performing BET in clinical work.

An outcome measure for the purpose of evaluating the benefit to the patient must be optimized. Whether this is a reduction in tympanostomies, better tympanoplasty results, or a decrease in the rate of recurrence of cholesteatoma remains to be seen. However, a patient

suffering from continuous ear complaints only dreams of relief of symptoms, and therefore it is critical also to consider this aspect in patient selection.

6.4 INDICATIONS FOR BET (STUDY IV)

The indications for BET proposed by the Finnish Otosurgical Society were the first published indications. The indications are (i) chronic bothersome symptoms referring to ETD, (ii) ETD-related symptoms following rapid pressure changes, or (iii) recurring serous otitis media. Our indications are for adult patients.

Later, a Spanish group published a consensus on BET and stated that the indications are (i) barotrauma, (ii) serous otitis media, (iii) adhesive otitis, (iv) atelectatic ME, and – (v) after confirming obstructive ETD – failure in tympanoplasty (Plaza et al., 2020). Our criteria for baro-challenge-induced ETD considers BET indicated when ETD symptoms present in appropriate situations but the Spanish group requires barotrauma. The Finnish indications mention "symptoms referring to ETD" which include feeling of fullness, popping, discomfort or pain, pressure, clogged feeling, crackling, ringing, or muffled hearing. In the indications proposed by the Finnish Otosurgical Society, the objective findings related to ETD are negative pressure in tympanogram, serous effusion in the ME, or retraction of the TM. The Spanish indications state only specific objective findings that indicate BET.

The Finnish Otosurgical Society reached consensus that relief of symptoms with tympanostomy is a prerequisite for BET. The consensus panel of AAO-HNSF disagreed on the requirement of tympanostomy. However, they stated that if myringotomy or tympanostomy provides no relief, the correct diagnosis is probably something other than obstructive ETD. The AAO-HNSF consensus presented no definite indications for BET but focused more broadly on patient criteria, preoperative considerations, and outcome. (Tucci et al., 2019)

The Finnish Otosurgical Society reached a consensus on BET indications as a part of a two-day meeting. The bases of the indications were a review of ET and ME physiology, a literature review on BET outcomes, and expert opinions on imaginary patient cases. At that time,

no other indication proposals were available in the literature. It remains unclear how these national indications have improved patient care and affected BET outcome in Finland in the 3.5 years after their distribution to all Finnish otolaryngological hospital clinics and 1.5 years after their publication in the research article.

When outlining the indications for BET, we agreed that the information is insufficient on the safety and effect of BET in children. Therefore, the Finnish national BET indications apply only to adult patients. However, internationally, a few reports on BET in children exist. Leichtle and colleagues (2017) studied BET in children aged 3–15 years with chronic obstructive ETD. It was always the second interventional treatment as the patients were resistant to adenotomy with myringotomy or tympanostomy. Statistical analysis was challenging, but trends of improvement were visible. The authors stated that more studies with larger patient cohorts and uniform diagnostic criteria of ETD in children and indications of BET for children are needed.

Maier and colleagues (2015) studied BET in children 4–14 years of age with chronic obstructive ETD. The mean follow-up was three months, and otoscopic findings normalized in 80% of 66 patients. ME effusion reduced from 62% to 13%, and TMR and adhesive processes from 47% to 6%. Valsalva maneuver was preoperatively successful in 4% but postoperatively 39% could pneumatize their ears with it. Eighty-six per cent of the parents were very satisfied or satisfied with the results.

These results give a positive sign that BET might be useful for recurrent or chronic otitis media in children if conventional measures with tympanostomy and possible adenotomy do not work out. No major complications have been reported when treating children with BET (Maier et al., 2015; Leichtle et al., 2017). Maier and colleagues (2015) treated children with the Spiggle & Theis TubaVent without any problems. At seven years of age, children already have an ET that is the same size as that of an adult. In infants, the length of the ET is approximately 18 mm (Sadler-Kimes et al., 1989). However, the ratio of the lengths of the cartilaginous ET and the bony ET is 8:1, whereas it is 4:1 in adults (Ishijima et al., 2000). These facts support the results of Maier and co-workers (2015) in that the BET devices seem to be suitable for children. However, more studies are needed to prove the efficacy of BET in the treatment of children.

6.5 FUTURE PERSPECTIVES

Few studies have explored the accuracy of ET function tests, and most of them are case–control studies. A case–control design will probably show higher sensitivity and specificity than that in an unselected population that is only suspected of having the condition. Applying the test in question and a reference test to a group of patients with unknown disease status would better reflect the situation in which the clinicians use the ET function tests. Even the severity and prevalence of the studied disease can affect sensitivity of a test: a more severe condition or higher prevalence tends to increase sensitivity. (Smith and Tysome, 2015) However, the prevalence's effect on specificity varied, and the severity of the condition seemed to have little effect on specificity in a systematic review (Whiting et al., 2004).

None of the current tests of ET function is optimal, which highlights the need for a gold standard test for ETD. That might be a combination of objective findings and patient-reported measures. (Smith and Tysome, 2015; Tysome and Sudhoff, 2018) Symptoms are an important part of the diagnosis of ETD as they are the cause of inconvenience to the patients. However, as the symptoms of ETD are nonspecific, objective measures are also necessary. ETS and ETS-7 provide combinations of patient-reported measures and objective findings but they omit symptoms. Choosing the optimal parameters for a new combined score requires more studies on the accuracy of the different diagnostic measures.

Directing the patients with suspected ETD to a specialist who is familiar with ETD could improve the standard of diagnostics and care compared with examining these patients in a general otorhinolaryngological clinic. In Helsinki University Hospital Department of Otorhinolaryngology – Head and Neck Surgery, we have so called TMM clinic once a week. In the TMM clinic, a specialist familiar with diagnostic measures and treatment of ETD examines the patients and makes a comprehensive evaluation of the situation of each patient. We take patient history, perform clinical examination including otomicroscopy and anterior and posterior rhinoscopy or nasoendoscopy, TMM with all three pressure levels, objective and subjective Valsalva and Toynbee maneuvers, and, if needed, also tympanometry. The patients come to the TMM clinic by referrals from outside of the hospital or from colleagues in our clinic. Because no single test is sufficient for the

diagnosis of ETD, we believe that this type of comprehensive ETD clinic is the best approach for the moment.

Transtympanic BET is a novel approach. Some computer-aided studies (Sudo et al., 1997; Miura et al., 2002) found that commonly used BET catheters that are 20 mm in length reach the point of the minimum cross-sectional area of the ET in approximately 50% of people. A 24-mm-long catheter would reach the minimum cross-sectional area in 87%. However, longer balloons would be unsafe because the anatomy varies and risk of damage for example to the internal carotid artery increases. Using the transtympanic approach can overcome this problem. Catheters longer than 20 mm can safely be used to dilate the whole cartilaginous portion of the ET as the excess length would exit to the nasopharynx. (Sudo et al., 1997; Miura et al., 2002; Jufas and Patel, 2016)

A cadaver study (Kepchar et al., 2012) revealed significant concerns of safety of the transtympanic BET using microscope but no endoscopes. However, three other cadaver studies utilizing endoscopes found that transtympanic BET is feasible and safe (Jufas et al., 2016; Dean et al., 2016; Kapadia et al., 2017).

One study reported that transtympanic BET was feasible in all but three patients of over 100 dilation procedures (Kapadia et al., 2019). Postoperatively, endoscopic examination showed significant improvement of aperture of the ET in all patients with successful dilation. Moreover, the ET opening pressure lowered in all but one patient after the procedure. (Kapadia et al., 2019) In another study, eight patients underwent transtympanic BET concurrently with surgery for TM perforation or cholesteatoma (Tarabichi and Najmi, 2015b). The ET aperture improved in all patients, seven patients had good myringoplasty results and no signs of chronic ear disease during the mean follow-up of 4 months. One patient was lost to follow-up, but seven were free of the pressure symptom. Postoperatively, five patients could perform subjective Valsalva maneuver, but only three had positive objective Valsalva. (Tarabichi and Najmi, 2015b) Although results of transtympanic BET are promising, its role in chronic ear surgery remains unclear and it requires further studies (Dean et al., 2016; Kapadia and Tarabichi, 2018; Kapadia et al., 2019).

Approach to transtympanic BET is available during ear surgery. We have instructed the patients to perform Valsalva and Toynbee maneuvers

five times twice a day for two weeks after transnasal BET, starting from the first postoperative day. Therefore, we have refrained from combining BET to ear surgery other than myringotomy or tympanostomy. However, only two out of the five long-term outcome studies from Study IV reported postoperative instructions of Valsalva or Politzer maneuvers (IV: Table 1c). The importance of the postoperative pneumatization exercises should be studied. If proved ineffective, BET can be performed concurrently with ear surgery. That combination would simultaneously target the underlying problem and its complication, thereby hopefully improving the results of the operation and decreasing the recurrence rate i.e. of cholesteatoma.

Bast and colleagues (2014) studied the effect of BET on quality of life with GBI questionnaire. Postoperatively, total score as well as categories 'general health' and 'physical health' showed improvement. Further studies on BET's effect on the quality of life applying for example the more widely used 15-dimensional questionnaire for measuring health-related quality of life (15D instrument) (Sintonen, n.d.) would be interesting.

The cost-effectiveness of BET remains unclear. In Helsinki University Hospital, Department of Otorhinolaryngology – Head and Neck Surgery, the cost of BET is approximately 10 times the cost of a doctor's appointment in the outpatient clinic. The Finnish national indications for BET include recurrent OME, the aim being to reduce the need for tympanostomies. In that respect, BET becomes cost-effective only if it will prevent 10 or more tympanostomies. The duration of the positive effect of BET remains unclear, and the needed rate for recurrent tympanostomies varies between patients, thus complicating the preoperative estimation of cost-effectiveness. However, the exact calculations should also consider, for example, the need to be absent from work to visit the clinic for tympanostomies and, in case of BET, the usual sick leave of 1–2 days. Ideally, BET would prevent recurrence of a cholesteatoma or other long-term consequences of the chronic underpressure in the ME, but whether this actually is a long-term effect of BET remains uncertain. Only after the determination of this can the total cost-effectiveness of BET be calculated.

The optimal study design for investigating the outcome of BET is still to be found as the available diagnostic tests are suboptimal. Ideally,

randomized placebo-controlled double-blind trials should be conducted. Preoperatively, thorough confirmation of diagnosis based on symptoms, patient-reported measures, and objective measures is essential. Schröder and colleagues (Schröder, Lehmann, Ebmeyer et al., 2015) found that ETS decreased at four years even though it had improved at one, two, and three years. However, in that study, only two out of 17 patients (12%) were available for follow-up examination at four years, which might have influenced the results. Therefore, follow-up time would ideally be at least four years to investigate if the outcomes deteriorate over time.

7 CONCLUSIONS

BET is a safe procedure under general anesthesia as well as under LA. Our LA method of nasal nerve block anesthesia combined with lidocaine-prilocaine cream or cocaine-adrenaline solution to the ET makes BET feasible under LA. However, further studies are warranted to improve the LA method and to reduce pain and discomfort even though they were acceptable and comparable to ESS in Studies I and II.

In our studies, BET under LA is feasible with Acclarent Aera and Spiggle & Theis TubaVent Short. We found that patients treated with Spiggle & Theis TubaVent experienced significantly more pain and discomfort than ESS patients who served as controls. However, our patient groups were small, so these results need further verification with larger studies.

In Study III, 77% of the patients experienced improvement in overall symptoms after the mean follow-up of three years on average. This is similar to results from literature as seen also in Study IV. We found that in all respondents in Study III, the feeling that ears are clogged reduced the most (76%), followed by muffled feeling (67%) and ear symptoms during a cold (66%). Our study revealed no factor that could preoperatively predict which patients will require additional treatment for ear symptoms even after BET.

The existing studies on BET are heterogenous in their array of diagnostic criteria and outcome measures, which makes the results difficult to compare. Overall, they all show positive long-term effects of BET. However, more long-term studies on outcome of BET with similar inclusion criteria and outcome measures are needed to reach a wider understanding of the long-term effects of BET. Double-blind placebo-controlled studies would be ideal.

The Finnish Otosurgical Society agreed on national diagnostic criteria of ETD, which are in line with the international consensus statement. The first published national indications for BET proposed by the Finnish Otosurgical Society may also encourage others to take similar action and hopefully help to unify indications for BET worldwide and thereby improve patient care.

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REFERENCES

Abdel-Aziz T., Schröder S., Lehmann M., Gehl H.B., Ebmeyer J., & Sudhoff H. 2014. Computed Tomography before Balloon Eustachian Tuboplasty-a True Necessity? *Otol Neurotol* 35 (4): 635–38.

Adil E. & Poe D. 2014. What Is the Full Range of Medical and Surgical Treatments Available for Patients with Eustachian Tube Dysfunction. *Curr Opin Otolaryngol Head Neck Surg* 22 (1): 8–15.

Alper C.M., Swarts J.D., Singla A., Banks J., & Doyle W.J. 2012. Relationship between the Electromyographic Activity of the Paratubal Muscles and Eustachian Tube Opening Assessed by Sonotubometry and Videoendoscopy. *Arch Otolaryngol - Head Neck Surg* 138 (8): 741–46.

Alper C.M., Teixeira M.S., Kim J.H., & Swarts J.D. 2017. Diagnostic Accuracy of Tubomanometry R Value in Detecting the Eustachian Tube Pressure Equalizing Function. *Eur Arch Oto-Rhino-Laryngology* 274 (4): 1865–72.

Ar A., Herman P., Lecain E., Wassef M., Huy P.T.B., & Kania R.E. 2007. Middle Ear Gas Loss in Inflammatory Conditions: The Role of Mucosa Thickness and Blood Flow. *Respir Physiol Neurobiol* 155 (2): 167–76.

Ars B. & Dirckx J. 2003. Tubomanometry. In *Fibrocartilaginous Eustachian Tube Middle Ear Cleft*, edited by Bernard Ars, 151–58. Amsterdam: Kugler Publications.

Ars B., Dirckx J., Ars-Piret N., & Buytaert J. 2012. Insights in the Physiology of the Human Mastoid: Message to the Surgeon. *J Int Adv Otol* 8 (2): 296–310.

Ars B., Wuyts F., Heyning P. Van De, Miled I., Bogers J., & Marck E. Van. 1997. Histomorphometric Study of the Normal Middle Ear Mucosa. *Acta Otolaryngol* 117 (5): 704–7.

Ashry Y., Kawai K., & Poe D. 2017. Utility of Adjunctive Procedures With Balloon Dilation of the Eustachian Tube. *Laryngoscope Investig Otolaryngol* 2 (6): 337–43.

Avoort S.J.C. Van Der, Heerbeek N. Van, Zielhuis G.A., & Cremers C.W.R.J. 2005. Sonotubometry: Eustachian Tube Ventilatory Function Test: A State-of-the-Art Review. *Otol Neurotol* 26 (3): 538–43.

Avoort S.J.C. Van Der, Heerbeek N. Van, Zielhuis G.A., & Cremers C.W.R.J. 2006. Validation of Sonotubometry in Healthy Adults. *J Laryngol Otol* 120 (10): 853–56.

Avoort S.J.C. Van Der, Heerbeek N. Van, Zielhuis G.A., & Cremers

C.W.R.J. 2009. Sonotubometry in Children with Otitis Media with Effusion before and after Insertion of Ventilation Tubes. *Arch Otolaryngol - Head Neck Surg* 135 (5): 448–52.

Bast F., Frank A., & Schrom T. 2014. Balloon Dilatation of the Eustachian Tube: Postoperative Validation of Patient Satisfaction. *ORL* 75 (6): 361–65.

Bluestone C.D. 2005. *Eustachian Tube: Structure, Function, Role in Otitis Media*. Edited by Maria B Bluestone. Raleigh: PMPH-USA Ltd.

Bluestone C.D., Beery Q.C., & Paradise J.L. 1973. Audiometry and Tympanometry in Relation to Middle Ear Effusions in Children. *Laryngoscope* 83 (4): 594–604.

Bluestone C.D. 1996. Pathogenesis of Otitis Media: Role of Eustachian Tube. *Pediatr Infect Dis J* 15 (4): 281–91.

Bluestone C.D., Paradise J.L., & Beery Q.C. 1972. Symposium on Prophylaxis and Treatment of Middle Ear Effusions. *Laryngoscope* 82 (9): 1654–69.

BMJ Best Practice. n.d. Eustachian Tube Dysfunction - Treatment Algorithm. *BMJ Best Practice*. Retrieved from https://bestpractice.bmj.com/topics/en-gb/1142/treatment-algorithm. Accessed December 8, 2019.

Bolger W.E. & Vaughan W.C. 2006. Catheter-Based Dilation of the Sinus Ostia: Initial Safety and Feasibility Analysis in a Cadaver Model. 20 (3): 290–94.

Bowles P.F., Agrawal S., & Salam M.A. 2017. Balloon Tuboplasty in Patients with Eustachian Tube Dysfunction: A Prospective Study in 39 Patients (55 Ears). *Clin Otolaryngol* 42 (5): 1057–60.

Brown C.L. & Bolger W.E. 2006. Safety and Feasibility of Balloon Catheter Dilation of Paranasal Sinus Ostia: A Preliminary Investigation. *Ann Otol Rhinol Laryngol* 115 (4): 293–99.

Browning G.G. & Gatehouse S. 1992. The Prevalence of Middle Ear Disease in the Adult British Population. *Clin Otolaryngol Allied Sci* 17 (4): 317–21.

Busby D.R., Slemmons D.H., & Miller T.F. 1968. Fatal Epistaxis via Carotid Aneurysm and Eustachian Tube. *Arch Otolaryngol* 87 (3): 295–98.

Catalano P.J., Jonnalagadda S., & Yu V.M. 2012. Balloon Catheter Dilatation of Eustachian Tube: A Preliminary Study. *Otol Neurotol* 33 (9): 1549–52.

Conticello S., Saita V., Ferlito S., & Paterno A. 1989. Computed Tomography in the Study of the Eustachian Tube. *Arch Otorhinolaryngol* 246: 259–61.

Csakanyi Z., Katona G., Konya D., Mohos F., & Sziklai I. 2014. Middle Ear

Gas Pressure Regulation: The Relevance of Mastoid Obliteration. *Otol Neurotol* 35 (6): 944–53.

Dalchow C. V., Loewenthal M., Kappo N., Jenckel F., Loerincz B.B., & Knecht R. 2016. First Results of Endonasal Dilatation of the Eustachian Tube (EET) in Patients with Chronic Obstructive Tube Dysfunction. *Eur Arch Oto-Rhino-Laryngology* 273 (3): 607–13.

Dean M. 2019. In-Office Balloon Dilation of the Eustachian Tube under Local Anesthesia: A Retrospective Review. *World J Otorhinolaryngol - Head Neck Surg* 5 (3): 143–47.

Dean M., Chao W.C., & Poe D. 2016. Eustachian Tube Dilation via a Transtympanic Approach in 6 Cadaver Heads: A Feasibility Study. *Otolaryngol - Head Neck Surg* 155 (4): 654–56.

Dean M. & Pynnonen M.A. 2019. In-Office Balloon Dilation of the Eustachian Tube under Local Anesthesia. *Otolaryngol Clin North Am* 52 (3): 509–20.

Dornhoffer J.L., Leuwer R., Schwager K., & Wenzel S. 2014. Clinical Anatomy of the Eustachian Tube. In *A Pract Guid to Eustachian Tube*, 1–11. Berlin, Heidelberg: Springer Berlin Heidelberg.

Doyle W.J. 2007. The Mastoid as a Functional Rate-Limiter of Middle Ear Pressure Change. *Int J Pediatr Otorhinolaryngol* 71 (3): 393–402.

Doyle W.J. 2017. A Formal Description of Middle Ear Pressure-Regulation. *Hear Res* 354 (October): 73–85.

Dubin M.G., Pollock H.W., Ebert C.S., Berg E., Buenting J.E., & Prazma J.P. 2002. Eustachian Tube Dysfunction after Tobacco Smoke Exposure. *Otolaryngol Neck Surg* 126 (1): 14–19.

Edelstein D.R., Magnan J., Parisier S.C., Chays A., Isaacs R.S., Gignac D., Bushkin S., & Han J.C. 1994. Microfiberoptic Evaluation of the Middle Ear Cavity. *Am J Otol* 15 (1): 50–55.

Eden A.R. & Gannon P.J. 1987. Neural Control of Middle Ear Aeration. *Arch Otolaryngol Neck Surg* 113 (2): 133–37.

Elner A. 1976. Normal Gas Exchange in the Human Middle Ear. *Ann Otol Rhinol Laryngol* 85 (Sup.25): 161–64.

Elner A., Ingelstedt S., & Ivarsson A. 1971. The Normal Function of the Eustachian Tube: A Study of 102 Cases. *Acta Otolaryngol* 72 (1–6): 320–28.

Estève D. 2003. Tubomanometry and Pathology. In *Fibrocartilaginous Eustachian Tube Middle Ear Cleft*, edited by Bernard Ars, 159–75. Amsterdam: Kugler Publications.

Falk B. 1981. Negative Middle Ear Pressure Induced by Sniffing. A Tympanometric Study in Persons with Healthy Ears. *J Otolaryngol* 10 (4): 299–305.

Falk B. & Magnuson B. 1984. Eustachian Tube Closing Failure in

Children with Persistent Middle Ear Effusion. *Int J Pediatr Otorhinolaryngol* 7 (2): 97–106.

FDA. 2016, September 16. FDA Permits Marketing of Balloon Device to Treat Persistent Eustachian Tube Dysfunction. *FDA*. Retrieved from https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-balloon-device-treat-persistent-eustachian-tube-dysfunction. Accessed October 7, 2019.

Finkelstein Y., Zohar Y., Talmi Y.P., & Laurian N. 1988. Study of Toynbee Phenomenon by Combined Intranasopharyngeal and Tympanometric Measurements. *Ann Otol Rhinol Laryngol* 97 (2): 199–206.

Gaihede M. & Ovesen T. 1997. Precision of Tympanometric Measurements. *J Speech, Lang Hear Res* 40 (1): 215–22.

Gaihede M., Padurariu S., Jacobsen H., Greef D. De, & Dirckx J.J.J. 2013. Eustachian Tube Pressure Equilibration. Temporal Analysis of Pressure Changes Based on Direct Physiological Recordings with an Intact Tympanic Membrane. *Hear Res* 301 (July): 53–59.

Gallardo F.P., Onishi E.T., Lira F.I., Suzuki F.B., & Testa J.R.G. 2019. Translation, Validation and Cultural Adaptation of "The Eustachian Tube Dysfunction Questionnaire-7" (ETDQ-7) to Brazilian Portuguese (BR). *Braz J Otorhinolaryngol* 85 (4): 456–64.

Ghadiali S.N., Swarts J.D., & Doyle W.J. 2003. Effect of Tensor Veli Palatini Muscle Paralysis on Eustachian Tube Mechanics. *Ann Otol Rhinol Laryngol* 112 (8): 704–11.

Gluth M.B., McDonald D.R., Weaver A.L., Bauch C.D., Beatty C.W., & Orvidas L.J. 2011. Management of Eustachian Tube Dysfunction with Nasal Steroid Spray: A Prospective, Randomized, Placebo-Controlled Trial. *Arch Otolaryngol - Head Neck Surg* 137 (5): 449–55.

Graves G.O. & Edwards L.F. 1944. The Eustachian Tube: A Review of Its Descriptive, Microscopic, Topographic and Clinical Anatomy. *Arch Otolaryngol - Head Neck Surg* 39 (5): 359–97.

Grøntved A., Krogh H.J., Christensen P.H., Jensen P.O., Schousboe H.H., & Hentzer E. 1989. Monitoring Middle Ear Pressure by Tympanometry: A Study of Middle Ear Pressure Variation through Seven Hours. *Acta Otolaryngol* 108 (1–2): 101–6.

Gyanwali B., Li H., Xie L., Zhu M., Wu Z., He G., & Tang A. 2016. The Role of Tensor Veli Platini Muscle (TVP) and Levetor Veli Platini Muscle (LVP) in the Opening and Closing of Pharyngeal Orifice of Eustachian Tube. *Acta Otolaryngol* 136 (3): 249–55.

Handzel O., Poe D., & Marchbanks R.J. 2012. Synchronous Endoscopy and Sonotubometry of the Eustachian Tube: A Pilot Study. *Otol Neurotol* 33 (2): 184–91.

Heerbeek N. Van, Saar G.M.A.C. De, & Mulder J.J.S. 2002. Long-Term

Ventilation Tubes: Results of 726 Insertions. *Clin Otolaryngol Allied Sci* 27 (5): 378–83.

Hergils L. & Magnuson B. 1998. Nasal Gas Composition in Humans and Its Implication on Middle Ear Pressure. *Acta Otolaryngol* 118 (5): 697–700.

Herrera M., Eisenberg G., & Plaza G. 2019. Clinical Assessment of Eustachian Tube Dysfunction through the Eustachian Tube Dysfunction Questionnaire (ETDQ-7) and Tubomanometry. *Acta Otorrinolaringol Esp* 70 (5): 265–71.

Holmquist J. & Larsson G. 1976. Eustachian Tube Dysfunction: A Preliminary Report of Medical Treatment. *Scand Audiol* 5 (3): 107–11.

Holmquist J. & Olén L. 2019. Evaluation of Eustachian Tube Function. *J Laryngol Otol* 94: 15–23.

Honjo I., Hayashi M., Ito S., & Takahashi H. 1985. Pumping and Clearancefunction of the Eustachian Tube. *Am J Otolaryngol - Head Neck Med Surg* 6 (3): 241–44.

Huisman J.M.L., Verdam F.J., Stegeman I., & Ru J.A. de. 2018. Treatment of Eustachian Tube Dysfunction with Balloon Dilation: A Systematic Review. *Laryngoscope* 128 (1): 237–47.

Ishijima K., Sando I., Miura M., Balaban C.D., & Takasaki K. 2002. Functional Anatomy of Levator Veli Palatini Muscle and Tensor Veli Palatini Muscle in Association with Eustachian Tube Cartilage. *Ann Otol Rhinol Laryngol* 111 (6): 530–36.

Ishijima K., Sando I., Suzuki C., Balaban C., & Takasaki K. 2000. Length of the Eustachian Tube and Its Postnatal Development: Computer-Aided Three-Dimensional Reconstruction and Measurement Study. *Ann Otol Rhinol Laryngol* 109 (6): 542–48.

Jenckel F., Kappo N., Gliese A., Loewenthal M., Lörincz B.B., Knecht R., & Dalchow C. V. 2014. Endonasal Dilatation of the Eustachian Tube (EET) in Children: Feasibility and the Role of Tubomanometry (Estève) in Outcomes Measurement. *Eur Arch Oto-Rhino-Laryngology* 272 (12): 3677–83.

Jensen J.H., Leth N., & Bonding P. 1990. Topical Application of Decongestant in Dysfunction of the Eustachian Tube: A Randomized, Double-Blind, Placebo-Controlled Trial. *Clin Otolaryngol* 15 (3): 197–201.

Jerger J. 1970. Clinical Experience With Impedance Audiometry. *Arch Otolaryngol* 92 (4): 311–24.

Jufas N. & Patel N. 2016. Transtympanic Balloon Dilatation of the Eustachian Tube: Systematic Review. *J Laryngol Otol* 130 (5): 425–30.

Jufas N., Treble A., Newey A., & Patel N. 2016. Endoscopically Guided Transtympanic Balloon Catheter Dilatation of the Eustachian Tube:

A Cadaveric Pilot Study. *Otol Neurotol* 37 (4): 350–55.

Kanzaki J., Taiji H., Kanke H., & Shiga H. 1985. Evaluation of the Eustachian Tube in Normal Subjects and in Patients with Otitis Media with Effusion by High Resolution Computerized Tomography. *Auris Nasus Larynx* 12: S52–54.

Kapadia M., Arsiwala Z., & Tarabichi M. 2019. Endoscopic Transtympanic Eustachian Tube Dilatation: An Overview of Evaluation Methods and Dilatation Technique. *World J Otorhinolaryngol - Head Neck Surg* 5 (3): 152–59.

Kapadia M. & Tarabichi M. 2018. Feasibility and Safety of Transtympanic Balloon Dilatation of Eustachian Tube. *Otol Neurotol* 39 (9): e825–30.

Kapadia M., Tarabichi M., Najmi M., & Hamza M. 2017. Safety of Carotid Canal during Transtympanic Dilatation of the Eustachian Tube: A Cadaver Pilot Study. *Indian J Otolaryngol Head Neck Surg*, January, 1–7.

Kepchar J., Acevedo J., Schroeder J., & Littlefield P. 2012. Transtympanic Balloon Dilatation of Eustachian Tube: A Human Cadaver Pilot Study. *J Laryngol Otol* 126 (11): 1102–7.

Kivekäs I., Chao W.-C., Faquin W., Hollowell M., Silvola J., Rasooly T., & Poe D. 2015. Histopathology of Balloon-Dilation Eustachian Tuboplasty. *Laryngoscope* 125 (2): 436–41.

Klopp-Dutote N., Kolski C., Strunski V., & Page C. 2018. Tympanostomy Tubes for Serous Otitis Media and Risk of Recurrences. *Int J Pediatr Otorhinolaryngol* 106 (March): 105–9.

Kobayashi T., Morita M., Yoshioka S., Mizuta K., Ohta S., Kikuchi T., Hayashi T., et al. 2018. Diagnostic Criteria for Patulous Eustachian Tube: A Proposal by the Japan Otological Society. *Auris Nasus Larynx* 45 (1): 1–5.

Kujawski O.B. & Poe D.S. 2004. Laser Eustachian Tuboplasty. *Otol Neurotol* 25 (1): 1–8.

Kumazawa T., Honjo I., & Honda K. 1977. Aerodynamic Pattern of Eustachian Tube Dysfunction. *Arch Otorhinolaryngol* 215 (3–4): 317–23.

Kumazawa T., Iwano T., Ushiro K., Kinoshita T., Hamada E., & Kaneko A. 1993. Eustachian Tube Function Tests and Their Diagnostic Potential in Normal and Diseased Ears. *Acta Otolaryngol* 113 (S500): 10–13.

Leichtle A., Hollfelder D., Wollenberg B., & Bruchhage K.L. 2017. Balloon Eustachian Tuboplasty in Children. *Eur Arch Otorhinolaryngol* 274 (6): 2411–19.

Leuwer R., Schubert R., Wenzel S., Kucinski T., Koch U., & Maier H. 2003. Neue Aspekte Zur Mechanik Der Tuba Auditiva. *HNO* 51 (5): 431–37.

Leuwer R. 2016. Anatomy of the Eustachian Tube. *Otolaryngol Clin North Am* 49 (5): 1097–1106.

Liang M., Xiong H., Cai Y., Chen Y., Zhang Z., Chen S., Xu Y., Ou Y., Yang H., & Zheng Y. 2016. Effect of the Combination of Balloon Eustachian Tuboplasty and Tympanic Paracentesis on Intractable Chronic Otitis Media with Effusion. *Am J Otolaryngol - Head Neck Med Surg* 37 (5): 442–46.

Llewellyn A., Norman G., Harden M., Coatesworth A., Kimberling D., Schilder A., & McDaid C. 2014. Interventions for Adult Eustachian Tube Dysfunction: A Systematic Review. *Health Technol Assess* 18 (46): 1–180.

Luntz M. & Sadé J. 1993. Dynamic Measurement of Gas Composition in the Middle Ear. I: Technique. *Acta Otolaryngol* 113 (3): 349–52.

Maier S., Tisch M., & Maier H. 2015. Einsatz Der Ballondilatation Der Eustachischen Röhre Bei Chronisch Obstruktiven Tubenventilationsstörungen Im Kindesalter. *HNO* 63 (10): 686–97.

Martin C., Karkas A., & Prades J.M. 2017. Tubotympanic System Functioning. *Eur Ann Otorhinolaryngol Head Neck Dis* 134 (3): 177–84.

Matanda R., Heyning P. Van De, Bogers J., & Ars B. 2006. Behaviour of Middle Ear Cleft Mucosa during Inflammation: Histo-Morphometric Study. *Acta Otolaryngol* 126 (9): 905–9.

Matsune S., Takahashi H., & Sando I. 1996. Mucosa-Associated Lymphoid Tissue in Middle Ear and Eustachian Tube in Children. *Int J Pediatr Otorhinolaryngol* 34 (3): 229–36.

McCoul E.D. & Anand V.K. 2012. Eustachian Tube Balloon Dilation Surgery. *Int Forum Allergy Rhinol* 2 (3): 191–98.

McCoul E.D., Anand V.K., & Christos P.J. 2012. Validating the Clinical Assessment of Eustachian Tube Dysfunction: The Eustachian Tube Dysfunction Questionnaire (ETDQ-7). *Laryngoscope* 122 (5): 1137–41.

McCoul E.D., Lucente F.E., & Anand V.K. 2011. Evolution of Eustachian Tube Surgery. *Laryngoscope* 121 (3): 661–66.

McCoul E.D., Weinreich H.M., Mulder H., Man L.X., Schulz K., & Shin J.J. 2019. Health Care Utilization and Prescribing Patterns for Adult Eustachian Tube Dysfunction. *Otolaryngol - Head Neck Surg (United States)* 160 (6): 1071–80.

McDonald M.H., Hoffman M.R., Gentry L.R., & Jiang J.J. 2012. New Insights into Mechanism of Eustachian Tube Ventilation Based on Cine Computed Tomography Images. *Eur Arch Oto-Rhino-Laryngology* 269 (8): 1901–7.

Metson R., Pletcher S.D., & Poe D.S. 2007. Microdebrider Eustachian Tuboplasty: A Preliminary Report. *Otolaryngol Neck Surg* 136 (3): 422–27.

Meyer T.A., O'Malley E.M., Schlosser R.J., Soler Z.M., Cai J., Hoy M.J., Slater P.W., et al. 2018. A Randomized Controlled Trial of Balloon Dilation as a Treatment for Persistent Eustachian Tube Dysfunction with 1-Year Follow-Up. *Otol Neurotol* 39 (7): 894–902.

Miller B.J. & Elhassan H.A. 2013. Balloon Dilatation of the Eustachian Tube: An Evidence-Based Review of Case Series for Those Considering Its Use. *Clin Otolaryngol* 38 (6): 525–32.

Miller B.J., Jaafar M., & Elhassan H.A. 2017. Laser Eustachian Tuboplasty for Eustachian Tube Dysfunction: A Case Series Review. *Eur Arch Otorhinolaryngol* 274 (6): 2381-7.

Mills R. & Hathorn I. 2016. Aetiology and Pathology of Otitis Media with Effusion in Adult Life. *J Laryngol Otol* 130 (5): 418–24.

Miura M., Sando I., Balaban C.D., Takasaki K., & Haginomori S.-I. 2002. Estimated Locations of the Narrowest Portion of the Eustachian Tube Lumen during Closed and Open States. *Ann Otol Rhinol Laryngol* 111 (3 Pt 1): 255–60.

Mondain M., Vidal D., Bouhanna S., & Uziel A. 1997. Monitoring Eustachian Tube Opening: Preliminary Results in Normal Subjects. *Laryngoscope* 107 (10): 1414–19.

Mover-Lev H., Priner-Barenholtz R., Ar A., & Sadé J. 1998. Quantitative Analysis of Gas Losses and Gains in the Middle Ear. *Respir Physiol* 114 (2): 143–51.

Muñoz D., Aedo C., & Der C. 2010. Patulous Eustachian Tube in Bariatric Surgery Patients. *Otolaryngol Head Neck Surg* 143: 521–24.

Naito Y., Hirono Y., Honjo I., Mori C., Hoshino K., Nishimura K., & Nakano Y. 1987. Magnetic Resonance Imaging of the Eustachian Tube: A Correlative Anatomical Study. *Arch Otolaryngol Neck Surg* 113 (12): 1281–84.

Nishino T., Yonezawa T., & Honda Y. 1985. Effects of Swallowing on the Pattern of Continuous Respiration in Human Adults. *Am Rev Respir Dis* 132 (6): 1219–22.

Norman G., Llewellyn A., Harden M., Coatesworth A., Kimberling D., Schilder A., & McDaid C. 2014. Systematic Review of the Limited Evidence Base for Treatments of Eustachian Tube Dysfunction: A Health Technology Assessment. *Clin Otolaryngol* 39 (1): 6–21.

Ockermann T., Reineke U., Upile T., Ebmeyer J., & Sudhoff H.H. 2010a. Balloon Dilatation Eustachian Tuboplasty: A Clinical Study. *Laryngoscope* 120 (7): 1411–16.

Ockermann T., Reineke U., Upile T., Ebmeyer J., & Sudhoff H.H. 2010b. Balloon Dilation Eustachian Tuboplasty: A Feasibility Study. *Otol Neurotol* 31 (7): 1100–1103.

Ostfeld E.J. & Silberberg A. 1991. Gas Composition and Pressure in the Middle Ear. *Laryngoscope* 101 (3): 297–304.

Padurariu S. 2012. Role of the Mastoid in the Middle Ear Function Histo-Morphometric Analysis of the Mastoid Mucosa versus Middle Ear Mucosa in an Animal Model. Aalborg University, Denmark.

Pau H.W., Sievert U., Just T., & Sadé J. 2009. Pressure Changes in the Human Middle Ear without Opening the Eustachian Tube. *Acta Otolaryngol* 129 (11): 1182–86.

Plaza G., Navarro J.J., Alfaro J., Sandoval M., & Marco J. 2020. Consensus on Treatment of Obstructive Eustachian Tube Dysfunction with Balloon Eustachian Tuboplasty. *Acta Otorrinolaringol Esp* 71 (3): 181-89.

Poe D., Anand V., Dean M., Roberts W.H., Stolovitzky J.P., Hoffmann K., Nachlas N.E., et al. 2018. Balloon Dilation of the Eustachian Tube for Dilatory Dysfunction: A Randomized Controlled Trial. *Laryngoscope* 128 (5): 1200–1206.

Poe D.S., Grimmer J.F., & Metson R. 2007. Laser Eustachian Tuboplasty: Two-Year Results. *Laryngoscope* 117 (2): 231–37.

Poe D. S. & Hanna B.M.N. 2011. Balloon Dilation of the Cartilaginous Portion of the Eustachian Tube: Initial Safety and Feasibility Analysis in a Cadaver Model. In *Am J Otolaryngol - Head Neck Med Surg*, 32:115–23.

Poe D. S., Metson R.B., & Kujawski O. 2003. Laser Eustachian Tuboplasty: A Preliminary Report. *Laryngoscope* 113 (4): 583–91.

Poe D.S., Pyykkö I., Valtonen H., & Silvola J. 2000. Analysis of Eustachian Tube Function by Video Endoscopy. *Am J Otol* 21 (5): 602-607.

Poe D.S, Abou-Halawa A., & Abdel-Razek O. 2001. Analysis of the Dysfunctional Eustachian Tube by Video Endoscopy. *Otol Neurotol* 22 (5): 590–95.

Poe D.S., Silvola J., & Pyykkö I. 2011. Balloon Dilation of the Cartilaginous Eustachian Tube. *Otolaryngol - Head Neck Surg* 144 (4): 563–69.

Prades J.M., Dumollard J.M., Calloc'h F., Merzougui N., Veyret C., & Martin C. 1998. Descriptive Anatomy of the Human Auditory Tube. *Surg Radiol Anat* 20 (5): 335–40.

Proctor B. 1973. Anatomy of the Eustachian Tube. *Arch Otolaryngol* 97 (1): 2–8.

Robert Y., Rocourt N., Gaillandre L., Lemaitre L., & Francke J.P. 1994. Serial Anatomy of the Auditory Tube: Correlation to CT and MR Imaging. *Surg Radiol Anat* 16 (1): 63–69.

Rockley T.J. & Hawke W.M. 1992. The Middle Ear as a Baroreceptor. *Acta Otolaryngol* 112 (2): 816–23.

Roeyen S. Van, Heyning P. Van de, & Rompaey V. Van. 2016. Responsiveness of the 7-Item Eustachian Tube Dysfunction

Questionnaire. *J Int Adv Otol* 12 (1): 106–8.

Rood S.R. & Doyle W.J. 1978. Morphology of Tensor Veli Palatini, Tensor Tympani, and Dilatator Tubae Muscles. *Ann Otol Rhinol Laryngol* 87 (2): 202–10.

Sadé J., Cinamon U., Ar A., & Siefert A. 2004. Gas Flow into and within the Middle Ear. *Otol Neurotol* 25 (5): 649–52.

Sadé J., Luntz M., & Levy D. 1995. Middle Ear Gas Composition and Middle Ear Aeration. *Ann Otol Rhinol Laryngol* 104 (5): 369–73.

Sadler-Kimes D., Siegel M.I., & Todhunter J.S. 1989. Age-Related Morphologic Differences in the Components of the Eustachian Tube/Middle Ear System. *Ann Otol Rhinol Laryngol* 98 (11): 854–58.

Schilder A.G.M., Bhutta M.F., Butler C.C., Holy C., Levine L.H., Kvaerner K.J., Norman G., et al. 2015. Eustachian Tube Dysfunction: Consensus Statement on Definition, Types, Clinical Presentation and Diagnosis. *Clin Otolaryngol* 40 (5): 407–11.

Schröder S., Lehmann M., Ebmeyer J., Upile T., & Sudhoff H. 2015. Balloon Eustachian Tuboplasty: A Retrospective Cohort Study. *Clin Otolaryngol* 40 (6): 629–38.

Schröder S., Lehmann M., Korbmacher D., Sauzet O., Sudhoff H., & Ebmeyer J. 2015. Evaluation of Tubomanometry as a Routine Diagnostic Tool for Chronic Obstructive Eustachian Tube Dysfunction. *Clin Otolaryngol* 40 (6): 691–97.

Schröder S., Lehmann M., Sauzet O., Ebmeyer J., & Sudhoff H. 2015. A Novel Diagnostic Tool for Chronic Obstructive Eustachian Tube Dysfunction-the Eustachian Tube Score. *Laryngoscope* 125 (3): 703–8.

Schröder S., Lehmann M., Sudhoff H., & Ebmeyer J. 2014. Beurteilung Der Chronisch-Obstruktiven Tubenfunktionsstörung: Evaluation Des "Eustachian Tube Dysfunction Questionnaire" in Der Deutschen Übersetzung. *HNO* 62 (3): 160–64.

Schröder S., Reineke U., Lehmann M., Ebmeyer J., & Sudhoff H. 2013. Chronisch Obstruktive Tubenfunktionsstörung Des Erwachsenen Langzeitergebnisse Der Ballondilatation Der Tuba Eustachii. *HNO* 61 (2): 142–51.

Seibert J.W. & Danner C.J. 2006. Eustachian Tube Function and the Middle Ear. *Otolaryngol Clin North Am* 39 (6): 1221–35.

Shan A., Ward B.K., Goman A.M., Betz J.F., Reed N.S., Poe D.S., & Nieman C.L. 2019. Prevalence of Eustachian Tube Dysfunction in Adults in the United States. *JAMA Otolaryngol - Head Neck Surg* 145 (10): 974–75.

Shekelle P., Takata G., Chan L.S., Mangione-Smith R., Corley P.M., Morphew T., & Morton S. 2002. Diagnosis, Natural History, and Late Effects of Otitis Media with Effusion. *Evid Rep Technol Assess*

(Summ), no. 55: 1–5.

Silvola J., Kivekäs I., & Poe D.S. 2014. Balloon Dilation of the Cartilaginous Portion of the Eustachian Tube. *Otolaryngol - Head Neck Surg (United States)* 151 (1): 125–30.

Sintonen H. n.d. *15D Instrument*. Retrieved from http://www.15d-instrument.net/15d/. Accessed March 10, 2020.

Smith M.E., Scoffings D.J., & Tysome J.R. 2016. Imaging of the Eustachian Tube and Its Function: A Systematic Review. *Neuroradiology* 58 (6): 543–56.

Smith M.E. & Tysome J.R. 2015. Tests of Eustachian Tube Function: A Review. *Clin Otolaryngol* 40 (4): 300–311.

Songu M., Aslan A., Unlu H.H., & Celik O. 2009. Neural Control of Eustachian Tube Function. *Laryngoscope* 119 (6): 1198–1202.

Standring S., Ellis H., Healy J.C., Johnson D., & Williams A., eds. 2008. *Gray's Anatomy: The Anatomical Basis of Clinical Practice*. 40th ed. Amsterdam: Elsevier Health Sciences UK.

Sudhoff H., Ars B., Dalchow C., Martino E. Di, Ikeda R., Jumah M.D., Kikuchi T., et al. 2017. *Eustachian Tube Dysfunction*. 2nd ed. Bremen: UNI-MED.

Sudhoff H., Schröder S., Reineke U., Lehmann M., Korbmacher D., & Ebmeyer J. 2013. Therapie Chronisch Obstruktiver Funktionsstörungen Der Tuba Eustachii: Konzepte Im Wandel Der Zeit. *HNO* 61 (6): 477–82.

Sudhoff H.H. & Mueller S. 2018. Treatment of Pharyngotympanic Tube Dysfunction. *Auris Nasus Larynx* 45 (2): 207–14.

Sudo M., Sando I., Ikui A., & Suzuki C. 1997. Narrowest (Isthmus) Portion of Eustachian Tube: A Computer-Aided Three-Dimensional Reconstruction and Measurement Study. *Ann Otol Rhinol Laryngol* 106 (7 II SUPPL. 169): 583–88.

Sudo M., Sando I., & Suzuki C. 1998. Three-Dimensional Reconstruction and Measurement Study of Human Eustachian Tube Structures: A Hypothesis of Eustachian Tube Function. *Ann Otol Rhinol Laryngol* 107 (7): 547–54.

Swarts J.D., Alper C.M., Mandel E.M., Villardo R., & Doyle W.J. 2011. Eustachian Tube Function in Adults without Middle Ear Disease. *Ann Otol Rhinol Laryngol* 120 (4): 220–25.

Takasaki K., Balaban C.D., Sando I., & Miura M. 2002. Functional Anatomy of the Tensor Veli Palatini Muscle and Ostmann's Fatty Tissue. *Ann Otol Rhinol Laryngol* 111 (11): 1045–49.

Tangbumrungtham N., Patel V.S., Thamboo A., Patel Z.M., Nayak J. V., Ma Y., Choby G., & Hwang P.H. 2018. The Prevalence of Eustachian Tube Dysfunction Symptoms in Patients with Chronic Rhinosinusitis. *Int Forum Allergy Rhinol* 8 (5): 620–23.

Tarabichi M. & Najmi M. 2015a. Visualization of the Eustachian Tube Lumen with Valsalva Computed Tomography. *Laryngoscope* 125 (3): 724–29.

Tarabichi M. & Najmi M. 2015b. Transtympanic Dilatation of the Eustachian Tube during Chronic Ear Surgery. *Acta Otolaryngol* 135 (7): 640–44.

Teixeira M.S., Swarts J.D., & Alper C.M. 2018. Accuracy of the ETDQ-7 for Identifying Persons with Eustachian Tube Dysfunction. *Otolaryngol - Head Neck Surg (United States)* 158 (1): 83–89.

Tideholm B. 2003. Middle Ear Cleft Pressure. In *Fibrocartilaginous Eustachian Tube Middle Ear Cleft*, edited by Bernard Ars, 97–112. Amsterdam: Kugler Publications.

Tideholm B., Jönsson S., Carlborg B., Welinder R., & Grenner J. 1996. Continuous 24-Hour Measurement of Middle Ear Pressure. *Acta Otolaryngol* 116 (4): 581–88.

Tisch M., Maier S., Hecht P., & Maier H. 2013. Beidseitige Tubendilatation Beim Kleinkind: Eine Therapiealternative Bei Persistierender Mittelohrfunktionsstörung. *HNO* 61 (6): 492–93.

Tisch M., Maier S., & Maier H. 2013. Die Tubendilatation Mit Dem Bielefelder Dilatationssystem: Klinische Erfahrungen an 320 Interventionen. *HNO* 61 (6): 483–87.

Tisch M., Störrle P., Danz B., & Maier H. 2013. Zum Stellenwert Der Bildgebung Vor Tubendilation Mit Dem Bielefelder Tubenkatheter. *HNO* 61 (6): 488–91.

Tsai L.-T., Wang C.-Y., Lo Y.-C., Lin C.-D., & Tsai M.-H. 2010. Three-Dimensional Image Analysis of the Temporal Bone in Patients with Unilateral Attic Cholesteatoma. *Neuroradiol J* 23 (3): 307–12.

Spiggle & Theis. n.d. TubaVent® Short/TubaInsert®. *Spiggle & Theis*. Retrieved from https://www.spiggle-theis.com/en/products/tuba-eustachii/tubavent-short-tubainsert. Accessed November 10, 2019.

Tucci D.L., McCoul E.D., Rosenfeld R.M., Tunkel D.E., Batra P.S., Chandrasekhar S.S., Cordes S.R., et al. 2019. Clinical Consensus Statement: Balloon Dilation of the Eustachian Tube. *Otolaryngol - Head Neck Surg (United States)* 161 (1): 6–17.

Tysome J.R. 2015. Eustachian Tube Dysfunction Consensus. *Clin Otolaryngol* 40 (5): 406–406.

Tysome J.R. & Sudhoff H. 2018. The Role of the Eustachian Tube in Middle Ear Disease. *Adv Otorhinolaryngol* 81: 146–52.

Vila P.M., Thomas T., Liu C., Poe D., & Shin J.J. 2017. The Burden and Epidemiology of Eustachian Tube Dysfunction in Adults. *Otolaryngol - Head Neck Surg (United States)* 156 (2): 278–84.

Weiss R.L., Church C.A., Kuhn F.A., Levine H.L., Sillers M.J., & Vaughan W.C. 2008. Long-Term Outcome Analysis of Balloon Catheter

Sinusotomy: Two-Year Follow-Up. *Otolaryngol - Head Neck Surg* 139 (3 Suppl. 3): S38–46.

White D.R., Heavner S.B., Hardy S.M., & Prazma J. 2002. Gastroesophageal Reflux and Eustachian Tube Dysfunction in an Animal Model. *Laryngoscope* 112 (6): 955–61.

Whiting P., Rutjes A.W.S., Reitsma J.B., Glas A.S., Bossuyt P.M.M., & Kleijnen J. 2004. Sources of Variation and Bias in Studies of Diagnostic Accuracy: A Systematic Review. *Ann Intern Med* 140 (3): 189–202.

Willinsky R., Lasjaunias P., Pruvost P., & Boucherat M. 1987. Petrous Internal Carotid Aneurysm Causing Epistaxis: Balloon Embolization with Preservation of the Parent Vessel. *Neuroradiology* 29 (6): 570–72.

Xiong H., Liang M., Zhang Z., Xu Y., Ou Y., Chen S., Yang H., & Zheng Y. 2016. Efficacy of Balloon Dilation in the Treatment of Symptomatic Eustachian Tube Dysfunction: One Year Follow-up Study. *Am J Otolaryngol - Head Neck Med Surg* 37 (2): 99–102.

Yoshida H., Takahashi H., Morikawa M., & Kobayashi T. 2007. Anatomy of the Bony Portion of the Eustachian Tube in Tubal Stenosis: Multiplanar Reconstruction Approach. *Rhinol Laryngol* 116 (9): 681–86.

APPENDICES

APPENDIX 1. QUESTIONNAIRE FOR STUDY I

APPENDIX 1A. QUESTIONNAIRE IN FINNISH

Korvatorven pallolaajennus paikallispuudutuksessa.

Kyselykaavake (anestesia)

Nimi: _____
Vastauspäivämäärä: _____
Toimenpide (lääkäri täyttää):

1. Korvatorven pallolaajennus
2. Keskikäytäväantrostomia
3. Poskiontelon aukon pallolaajennus

1. **Kuinka voimakasta kipua koitte toimenpiteen aikana?**
   0_____10

   0 = ei lainkaan kipua
   10 = pahin kuviteltavissa oleva kipu

2. **Kuinka epämukava toimenpide oli?**
   0_____10

   0 = ei lainkaan epämukava
   10 = sietämättömän epämukava

3. **Kuinka voimakasta kipu on 2 tunnin kuluttua toimenpiteestä?**
   0_____10

   0 = ei lainkaan kipua
   10 = pahin kuviteltavissa oleva kipu

4. Kuinka epämukava olo on 2 tunnin kuluttua toimenpiteestä?

0 _____ 10

0 = ei lainkaan epämukava

10 = sietämättömän epämukava

Seuraavien kysymysten osalta ympyröikää sopivin vaihtoehto:

5. Oliko kivunlievitys toimenpiteen aikana riittävä?

Kyllä

Ei

6. Oliko toimenpide paikallispuudutuksessa mielestänne liian epämiellyttävä?

Ei

Kyllä

7. Valitsisitteko uudestaan anestesiamuodoksi paikallispuudutuksen, jos toimenpide tehtäisiin teille toistamiseen?

Kyllä

En

Miksi valitsisitte/ette valitsisi?

APPENDIX 1B. QUESTIONNAIRE IN SWEDISH

Ballongdilatation av örontrumpeten i lokalbedövning.

Frågeformulär (anestesi)

Namn:_____
Datum:_____
Ingrepp (fylls i av läkare): 1.Ballongdilatation av örontrumpeten
2.Bihåleoperation
3.Ballongdilatation av bihåleöppningen

1. **Hur stark smärta upplevde ni under ingreppet?**
   0_____10

   0 = ingen smärta
   10 = värsta tänkbara smärta

2. **Hur obehaligt var ingreppet?**
   0_____10

   0 = inte alls obehagligt
   10 = outhärdligt obehagligt

3. **Hur stark smärta upplever ni 2 timmar efter ingreppet?**
   0_____10

   0 = ingen smärta
   10 = värsta tänkbara smärta

4. **Hur stor är känslan av obehag 2 timmar efter ingreppet?**
   0_____10

   0 = inte alls obehaglig
   10 = outhärdligt obehaglig

För de följande frågor ring in det lämpligaste alternativet:

5. **Var smärtlindring tillräcklig under ingreppet?**

   Ja

   Nej

6. **Var ingreppet för obekväm i lokalbedövning?**

   Nej

   Ja

7. **Skulle ni välja lokalbedövning igen om ni skulle bli behandlat med det samma ingreppet på nytt?**

   Ja

   Nej

   Värför det?

APPENDIX 1C. QUESTIONNAIRE IN ENGLISH

Eustachian tube balloon dilation under local anesthesia.

Questionnaire (anesthesia)

Name: _____
Date: _____
Procedure (doctor fills in):

1. Eustachian tube balloon dilation
2. Endoscopic sinus surgery of the maxillary ostium
3. Balloon dilation of the maxillary ostium

1. **How severe was the pain that you experienced during the procedure?**
   0_____10

   0 = no pain at all
   10 = the most intense pain you can imagine

2. **How severe was the discomfort that you experienced during the procedure?**
   0_____10

   0 = no discomfort at all
   10 = unbearable

3. **How severe was the pain 2 hours after the procedure?**
   0_____10

   0 = no pain at all
   10 = the most intense pain you can imagine

4. **How much discomfort did you have 2 hours after the procedure?**
   0_____10

   0 = no discomfort at all
   10 = unbearable

For the next questions, circle the correct answer:

5. **Was pain relief sufficient during the procedure?**

   Yes

   No

6. **Was the operation under local anesthesia too uncomfortable?**

   Yes

   No

7. **Would you prefer local anesthesia if you had to undergo the operation again?**

   Yes

   No

   Why or why not?

APPENDIX 2. QUESTIONNAIRE FOR STUDY II

APPENDIX 2A. QUESTIONNAIRE IN FINNISH

Korvatorven pallolaajennus paikallispuudutuksessa.

Kyselykaavake (anestesia)

Nimi: _____
Vastauspäivämäärä: _____

1. Kuinka voimakasta kipua koitte toimenpiteen aikana?

oikea puoli
0_____10

vasen puoli
0_____10

0 = ei lainkaan kipua
10 = pahin kuviteltavissa oleva kipu

2. Kuinka epämukava toimenpide oli?

oikea puoli
0_____10

vasen puoli
0_____10

0 = ei lainkaan epämukava
10 = sietämättömän epämukava

3. Kuinka voimakasta kipu on 2 tunnin kuluttua toimenpiteestä?

oikea puoli

0_____10

vasen puoli

0_____10

0 = ei lainkaan kipua

10 = pahin kuviteltavissa oleva kipu

4. Kuinka epämukava olo on 2 tunnin kuluttua toimenpiteestä?

oikea puoli

0_____10

vasen puoli

0_____10

0 = ei lainkaan epämukava

10 = sietämättömän epämukava

Seuraavien kysymysten osalta ympyröikää sopivin vaihtoehto:

5. Oliko kivunlievitys toimenpiteen aikana riittävä?

oikealla: Kyllä Ei

vasemmalla: Kyllä Ei

6. Oliko toimenpide paikallispuudutuksessa mielestänne liian epämiellyttävä?

oikealla: Ei Kyllä

vasemmalla: Ei Kyllä

7. Valitsisitteko uudestaan anestesiamuodoksi paikallispuudutuksen, jos toimenpide tehtäisiin teille toistamiseen ja samalla tavalla kuin nyt?

Oikea puoli:	Kyllä	En
Vasen puoli:	Kyllä	En

Miksi valitsisitte/ette valitsisi?

APPENDIX 2B. QUESTIONNAIRE IN SWEDISH

Ballongdilatation av örontrumpeten i lokalbedövning.

Frågeformulär (anestesi)

Namn:_____
Datum:_____

1. **Hur stark smärta upplevde ni under ingreppet?**

höger sidan
0_____10

vänster sidan
0_____10

0 = ingen smärta
10 = värsta tänkbara smärta

2. **Hur obehaligt var ingreppet?**

höger sidan
0_____10

vänster sidan
0_____10

0 = inte alls obehagligt
10 = outhärdligt obehagligt

3. **Hur stark smärta upplever ni 2 timmar efter ingreppet?**

höger sidan
0_____10

vänster sidan

0 _____ 10

0 = ingen smärta

10 = värsta tänkbara smärta

4. Hur stor är känslan av obehag 2 timmar efter ingreppet?

höger sidan

0 _____ 10

vänster sidan

0 _____ 10

0 = inte alls obehagligt

10 = outhärdligt obehagligt

För de följande frågor ring in det lämpligaste alternativet:

5. Var smärtlindring tillräcklig under ingreppet?

Höger sidan: Ja Nej

Vänster sidan: Ja Nej

6. Var ingreppet för obekväm i lokalbedövning?

Höger sidan: Nej Ja

Vänster sidan: Nej Ja

7. Skulle ni välja lokalbedövning igen om ni skulle bli behandlat med det samma ingreppet på nytt och ingreppet skulle göras som nu

Ja Nej

Värför det?

APPENDIX 2C. QUESTIONNAIRE IN ENGLISH

Eustachian tube balloon dilation under local anesthesia.

Questionnaire (anesthesia)

Name: _____
Date: _____

1. **How severe was the pain that you experienced during the procedure?**

   right side
   0_____10

   left side
   0_____10

   0 = no pain at all
   10 = the most intense pain you can imagine

2. **How severe was the discomfort that you experienced during the procedure?**

   right side
   0_____10

   left side
   0_____10

   0 = no discomfort at all
   10 = unbearable

3. **How severe was the pain 2 hours after the procedure?**

   right side
   0_____10

left side

0 _____ 10

0 = no pain at all

10 = the most intense pain you can imagine

4. How much discomfort did you have 2 hours after the procedure?

right side

0 _____ 10

left side

0 _____ 10

0 = no discomfort at all

10 = unbearable

For the next questions, circle the correct answer:

5. Was pain relief sufficient during the procedure?

Right side: Yes No

Left side: Yes No

6. Was the operation under local anesthesia too uncomfortable?

Right side: No Yes

Left side: No Yes

7. Would you prefer local anesthesia if you were going to undergo the operation again and if the operation was to be performed in the same way as this time?

Right side: Yes No

Left side: Yes No

Why or why not?

APPENDIX 3. QUESTIONNAIRE FOR STUDY III

APPENDIX 3A. QUESTIONNAIRE IN FINNISH

Korvatorven pallolaajennus – kyselytutkimus potilaan kokemasta hoidon vaikutuksesta.

Kyselykaavake

Nimi
Vastauspäivämäärä

Korvatorven pallolaajennus tehtiin (ympyröikää oikea vaihtoehto)
- oikeaan korvatorveen
- vasempaan korvatorveen
- molempiin korvatorviin
- en muista

Verratkaa seuraavien väittämien osalta tämänhetkistä tilannetta pallolaajennusta edeltäneeseen tilanteeseen. Rastittakaa sopivin vaihtoehto sekä oikean että vasemman korvan osalta:

1) Korvissa on paineen tunnetta

	oikea	vasen
selvästi vähemmän kuin ennen pallolaajennusta		
jonkin verran vähemmän kuin ennen pallolaajennusta		
saman verran kuin ennen pallolaajennusta		
jonkin verran enemmän kuin ennen pallolaajennusta		
selvästi enemmän kuin ennen pallolaajennusta		
tätä oiretta ei ollut ennen pallolaajennusta eikä sitä ole nyt		

2) Korvissa on kipua

	oikea	vasen
selvästi vähemmän kuin ennen pallolaajennusta		
jonkin verran vähemmän kuin ennen pallolaajennusta		
saman verran kuin ennen pallolaajennusta		
jonkin verran enemmän kuin ennen pallolaajennusta		
selvästi enemmän kuin ennen pallolaajennusta		
tätä oiretta ei ollut ennen pallolaajennusta eikä sitä ole nyt		

3) Korvissa on lukkoisuuden tunnetta

	oikea	vasen
selvästi vähemmän kuin ennen pallolaajennusta		
jonkin verran vähemmän kuin ennen pallolaajennusta		
saman verran kuin ennen pallolaajennusta		
jonkin verran enemmän kuin ennen pallolaajennusta		
selvästi enemmän kuin ennen pallolaajennusta		
tätä oiretta ei ollut ennen pallolaajennusta eikä sitä ole nyt		

4) Korvaoireita on flunssien yhteydessä

	oikea	vasen
selvästi vähemmän kuin ennen pallolaajennusta		
jonkin verran vähemmän kuin ennen pallolaajennusta		
saman verran kuin ennen pallolaajennusta		
jonkin verran enemmän kuin ennen pallolaajennusta		
selvästi enemmän kuin ennen pallolaajennusta		
tätä oiretta ei ollut ennen pallolaajennusta eikä sitä ole nyt		

5) Korvissa kuuluu rätinää/poksahtelua

	oikea	vasen
selvästi vähemmän kuin ennen pallolaajennusta		
jonkin verran vähemmän kuin ennen pallolaajennusta		
saman verran kuin ennen pallolaajennusta		
jonkin verran enemmän kuin ennen pallolaajennusta		
selvästi enemmän kuin ennen pallolaajennusta		
tätä oiretta ei ollut ennen pallolaajennusta eikä sitä ole nyt		

6) Korvien soimista on

	oikea	vasen
selvästi vähemmän kuin ennen pallolaajennusta		
jonkin verran vähemmän kuin ennen pallolaajennusta		
saman verran kuin ennen pallolaajennusta		
jonkin verran enemmän kuin ennen pallolaajennusta		
selvästi enemmän kuin ennen pallolaajennusta		
tätä oiretta ei ollut ennen pallolaajennusta eikä sitä ole nyt		

7) Kuulo tuntuu tukkoiselta/äänet kuuluvat vaimeampina

	oikea	vasen
selvästi vähemmän kuin ennen pallolaajennusta		
jonkin verran vähemmän kuin ennen pallolaajennusta		
saman verran kuin ennen pallolaajennusta		
jonkin verran enemmän kuin ennen pallolaajennusta		
selvästi enemmän kuin ennen pallolaajennusta		
tätä oiretta ei ollut ennen pallolaajennusta eikä sitä ole nyt		

8) Nieleminen helpottaa paineen tunnetta korvissa

	oikea	vasen
selvästi enemmän kuin ennen pallolaajennusta		
jonkin verran enemmän kuin ennen pallolaajennusta		
saman verran kuin ennen pallolaajennusta		
jonkin verran vähemmän kuin ennen pallolaajennusta		
selvästi vähemmän kuin ennen pallolaajennusta		
tätä oiretta ei ollut ennen pallolaajennusta eikä sitä ole nyt		

9) Valsalvan manööveri (=ilman puhaltaminen korviin sierainten ollessa suljettuna) onnistuu

	oikea	vasen
selvästi paremmin kuin ennen pallolaajennusta		
jonkin verran paremmin kuin ennen pallolaajennusta		
saman lailla kuin ennen pallolaajennusta		
jonkin verran huonommin kuin ennen pallolaajennusta		
selvästi huonommin kuin ennen pallolaajennusta		
en ole koskaan onnistunut tekemään Valsalvan manööveriä		

10) Korvaoireita on nykyään

	oikea	vasen
ei lainkaan		
selvästi vähemmän kuin ennen pallolaajennusta		
jonkin verran vähemmän kuin ennen pallolaajennusta		
yhtä paljon kuin ennen pallolaajennusta		
jonkin verran enemmän kuin ennen pallolaajennusta		
selvästi enemmän kuin ennen pallolaajennusta		

11) Korvaoireet häiritsevät nykyään elämääni

ei lainkaan	
hyvin vähän	
vähän	
kohtalaisesti	
melko paljon	
paljon	

12) Nykyinen yleinen elämänlaatuni on

erittäin hyvä	
hyvä	
kohtalainen	
melko huono	
huono	

Rengastakaa sopivin vaihtoehto

13) Menisittekö nykytietonne mukaan korvatorven pallolaajennustoimenpiteeseen uudestaan, jos korvaoireenne palaisivat toimenpidettä edeltäneelle tasolle?

kyllä
en

14) Suosittelisitteko korvatorven pallolaajennusta muille vastaavista oireista kärsiville?

kyllä
en

15) Oletteko hakeutuneet korvaongelmien vuoksi lääkärin vastaanotolle HYKS Korvaklinikalla vuosina 2011-2013 tehdyn pallolaajennuksen jälkeen?

en
kyllä

Jos vastasitte kysymykseen ”ei”, voitte siirtyä kohtaan 17).

Jos vastasitte kysymykseen ”kyllä”, jatkakaa seuraavaan kysymykseen 16).

16) Onko teille tehty korvaongelmien vuoksi toimenpiteitä HYKS Korvaklinikalla vuosina 2011-2013 tehdyn pallolaajennuksen jälkeen?

ei
kyllä

Mikä toimenpide tehtiin?

Missä toimenpide tehtiin?

Milloin toimenpide tehtiin?

17) Onko mielessänne jotain muuta, mitä haluaisitte kertoa tutkijoille?

APPENDIX 3B. QUESTIONNAIRE IN SWEDISH

Ballongdilatation av örontrumpeten i HUCS Huvud- och halscentrum – Enkät om hur patienten upplever effekten av behandlingen.

Frågeformulär

Namn
Datum

Örontrumpetens ballongdilatation gjordes i (ringa in rätt alternativ)
- höger örontrumpet
- vänster örontrumpet
- båda örontrumpet
- jag minns inte

I följande påstående, jämför den nuvarande situationen till den före ballongdilatation. Kryssa i det lämpligaste alternativet för både höger och vänster öra:

1) Jag har tryckkänsla i öronen

	höger	vänster
mycket mindre än före ballongdilatationen		
något mindre än före ballongdilatationen		
lika mycket som före ballongdilatationen		
något mera än före ballongdilatationen		
mycket mera än före ballongdilatationen		
det här symptomet fanns inte före ballongdilatationen och finns inte nu heller		

2) Jag har smärta i öronen

	höger	vänster
mycket mindre än före ballongdilatationen		
något mindre än före ballongdilatationen		
lika mycket som före ballongdilatationen		
något mera än före ballongdilatationen		
mycket mera än före ballongdilatationen		
det här symptomet fanns inte före ballongdilatationen och finns inte nu heller		

3) Öronen är i lås

	höger	vänster
mycket mindre än före ballongdilatationen		
något mindre än före ballongdilatationen		
lika mycket som före ballongdilatationen		
något mera än före ballongdilatationen		
mycket mera än före ballongdilatationen		
det här symptomet fanns inte före ballongdilatationen och finns inte nu heller		

4) Jag har öronsymptom vid förkylning

	höger	vänster
mycket mindre än före ballongdilatationen		
något mindre än före ballongdilatationen		
lika mycket som före ballongdilatationen		
något mera än före ballongdilatationen		
mycket mera än före ballongdilatationen		
det här symptomet fanns inte före ballongdilatationen och finns inte nu heller		

5) Det hörs knastrande/smällande ljud i öronen

	höger	vänster
mycket mindre än före ballongdilatationen		
något mindre än före ballongdilatationen		
lika mycket som före ballongdilatationen		
något mera än före ballongdilatationen		
mycket mera än före ballongdilatationen		
det här symptomet fanns inte före ballongdilatationen och finns inte nu heller		

6) Det ringer i öronen

	höger	vänster
mycket mindre än före ballongdilatationen		
något mindre än före ballongdilatationen		
lika mycket som före ballongdilatationen		
något mera än före ballongdilatationen		
mycket mera än före ballongdilatationen		
det här symptomet fanns inte före ballongdilatationen och finns inte nu heller		

7) Det är täppt i öronen /ljuden hörs mer dämpade

	höger	vänster
mycket mindre än före ballongdilatationen		
något mindre än före ballongdilatationen		
lika mycket som före ballongdilatationen		
något mera än före ballongdilatationen		
mycket mera än före ballongdilatationen		
det här symptomet fanns inte före ballongdilatationen och finns inte nu heller		

8) Tryckkänslan i öronen lättas genom att svälja

	höger	vänster
mycket mera än före ballongdilatationen		
lite mera än före ballongdilatationen		
lika bra som före ballongdilatationen		
lite sämre än före ballongdilatationen		
mycket sämre än före ballongdilatationen		
det här symptomet fanns inte före ballongdilatationen och finns inte nu heller		

9) Jag lyckas göra Valsalva manövern (=kläm ihop näsborrarna, stäng munnen och blås)

	höger	vänster
mycket bättre än före ballongdilatationen		
lite bättre än före ballongdilatationen		
lika bra som före ballongdilatationen		
lite sämre än före ballongdilatationen		
mycket sämre än före ballongdilatationen		
jag har aldrig lyckats göra Valsava manövern		

10) Nuförtiden har jag öronsymptom

	höger	vänster
inte alls		
mycket mindre än före ballongdilatationen		
något mindre än före ballongdilatationen		
lika mycket som före ballongdilatationen		
något mera än före ballongdilatationen		
mycket mera än före ballongdilatationen		

11) Nuförtiden stör öronsymptom mitt liv

inte alls	
väldigt lite	
lite	
moderat	
ganska mycket	
mycket	

12) Min nuvarande livskvalitet är

väldigt bra	
bra	
rimlig	
dålig	
mycket dålig	

Ring in det lämpligaste alternativet:

13) Skulle ni med nuvarande information genomgå ballongdilatation av örontrumpeten på nytt om era öronsymptom skulle återgå till nivån före ingreppet?

ja
nej

14) Skulle ni rekommendera ballongdilatation av örontrumpeten till andra som lider av liknande symptom?

ja
nej

15) Har ni sökt er till läkarmottagning efter att ballongdilatationen utfördes i HUCS Huvud- och halscentrum år 2011-2013?

nej
ja

Om ni svarade ”nej”, kan ni fortsätta med att svara på fråga nr 17).

Om ni svarade ”ja”, svara också på fråga nr 16).

16) Har det gjorts ingrepp på grund av öronsymptom efter ballongdilatationen utfördes i HUCS Huvud- och halscentrum år 2011-2013?

nej
ja

Vilket ingrepp utfördes?

Var utfördes ingreppet?

När utfördes ingreppet?

17) Finns det något annat som ni vill berätta för forskarna?

APPENDIX 3C. QUESTIONNAIRE IN ENGLISH

Eustachian tube balloon dilation – questionnaire study on how patients experience the effect of the treatment

Questionnaire

Name
Date

Eustachian tube balloon dilation was performed in (circle the right answer)
the right Eustachian tube
the left Eustachian tube
both Eustachian tubes
I do not recall

For the following statements, compare the current situation with the situation before balloon dilation. Check the most appropriate alternative for both the right and the left ear:

1) I feel pressure in my ears

	right	left
clearly less than before the balloon dilation		
somewhat less than before the balloon dilation		
as much as before the balloon dilation		
somewhat more than before the balloon dilation		
clearly more than before the balloon dilation		
I did not have this symptom before the balloon dilation and do not have it now		

2) I have pain in my ears

	right	left
clearly less than before the balloon dilation		
somewhat less than before the balloon dilation		
as much as before the balloon dilation		
somewhat more than before the balloon dilation		
clearly more than before the balloon dilation		
I did not have this symptom before the balloon dilation and do not have it now		

3) My ears feel clogged

	right	left
clearly less than before the balloon dilation		
somewhat less than before the balloon dilation		
as much as before the balloon dilation		
somewhat more than before the balloon dilation		
clearly more than before the balloon dilation		
I did not have this symptom before the balloon dilation and do not have it now		

4) I have ear symptoms when I have a cold

	right	left
clearly less than before the balloon dilation		
somewhat less than before the balloon dilation		
as much as before the balloon dilation		
somewhat more than before the balloon dilation		
clearly more than before the balloon dilation		
I did not have this symptom before the balloon dilation and do not have it now		

5) My ears crackle or pop

	right	left
clearly less than before the balloon dilation		
somewhat less than before the balloon dilation		
as much as before the balloon dilation		
somewhat more than before the balloon dilation		
clearly more than before the balloon dilation		
I did not have this symptom before the balloon dilation and do not have it now		

6) My ears ring

	right	left
clearly less than before the balloon dilation		
somewhat less than before the balloon dilation		
as much as before the balloon dilation		
somewhat more than before the balloon dilation		
clearly more than before the balloon dilation		
I did not have this symptom before the balloon dilation and do not have it now		

7) My hearing is muffled

	right	left
clearly less than before the balloon dilation		
somewhat less than before the balloon dilation		
as much as before the balloon dilation		
somewhat more than before the balloon dilation		
clearly more than before the balloon dilation		
I did not have this symptom before the balloon dilation and do not have it now		

8) Swallowing relieves pressure in my ears

	right	left
clearly more than before the balloon dilation		
somewhat more than before the balloon dilation		
as much as before the balloon dilation		
somewhat less than before the balloon dilation		
clearly less than before the balloon dilation		
I did not have this symptom before the balloon dilation and do not have it now		

9) I can perform the Valsalva maneuver (= to blow air into the ears while keeping both nostrils and the mouth closed)

	right	left
clearly better than before the balloon dilation		
somewhat better than before the balloon dilation		
as well as before the balloon dilation		
somewhat worse than before the balloon dilation		
clearly worse than before the balloon dilation		
I have never been able to perform Valsalva maneuver		

10) Nowadays I have ear symptoms

	right	left
not at all		
clearly less than before the balloon dilation		
somewhat less than before the balloon dilation		
as much as before the balloon dilation		
somewhat more than before the balloon dilation		
clearly more than before the balloon dilation		

11) Currently my ear symptoms disturb my life

not at all	
very little	
little	
moderately	
quite much	
much	

12) My current quality of life is

very good	
good	
adequate	
quite poor	
poor	

Circle the most appropriate alternative:

13) With your current knowledge, would you undergo Eustachian tube balloon dilation again if your ear symptoms returned to the same level as they were before the operation?

yes
no

14) Would you recommend Eustachian tube balloon dilation to others who suffer from similar symptoms?

yes
no

15) Have you visited a doctor because of ear symptoms since Eustachian tube balloon dilation was performed in HUH Department of Otorhinolaryngology – Head and Neck Surgery in 2011–2013?

no
yes

If you answered ”no”, proceed to question 17).

If you answered ”yes”, proceed to question 16).

16) Have you undergone any other operations because of ear symptoms since Eustachian tube balloon dilation was performed in HUH Department of Otorhinolaryngology – Head and Neck Surgery 2011–2013?

no
yes

Which operation was performed?

Where was the operation performed?

When was the operation performed?

17) Is there anything else you would like to tell the researchers?

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