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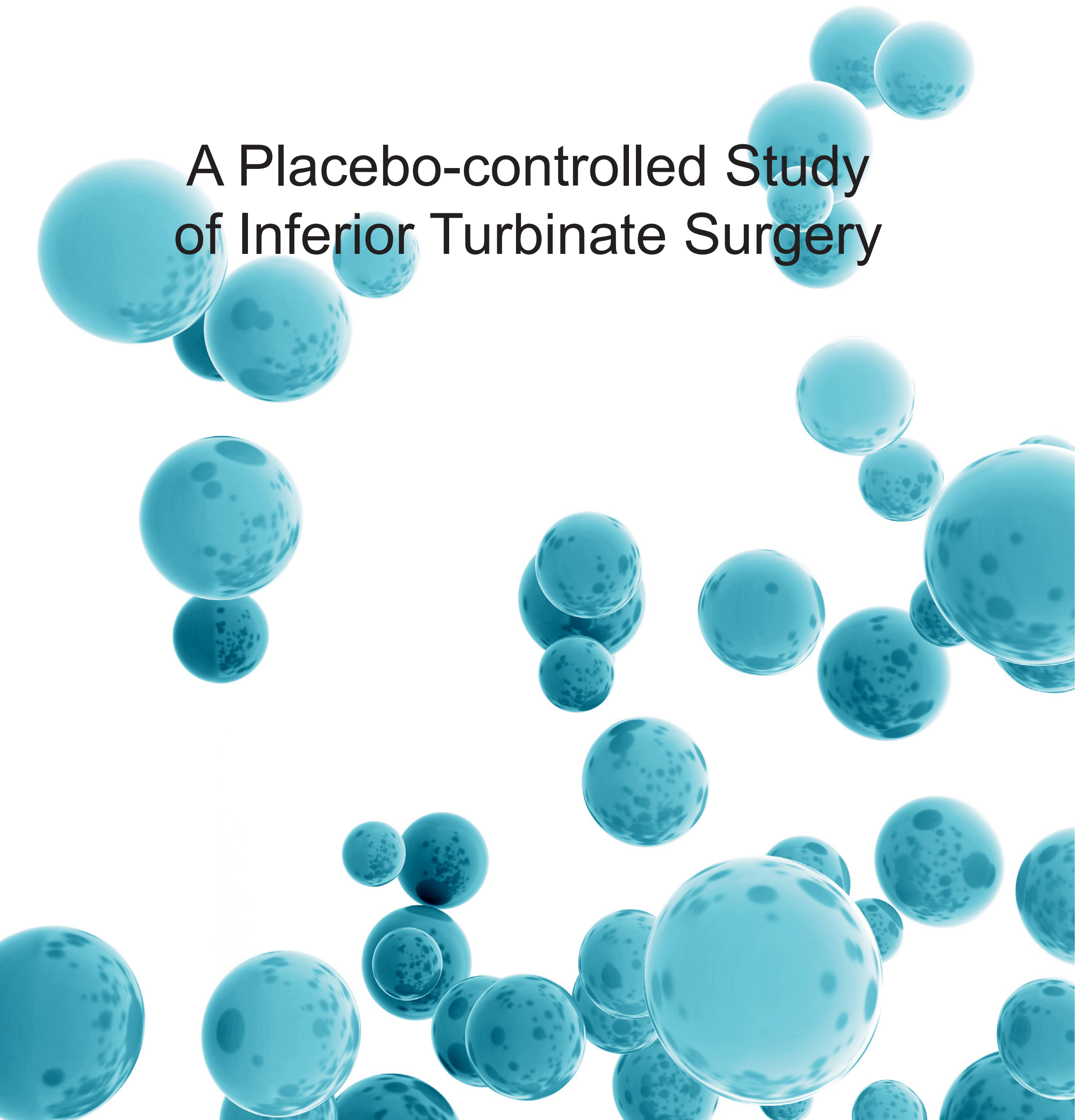
TEEMU HARJU

A Placebo-controlled Study of Inferior Turbinate Surgery



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A Placebo-controlled Study of Inferior Turbinate Surgery

ACADEMIC DISSERTATION
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UNIVERSITY OF TAMPERE

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ACADEMIC DISSERTATION
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To my dear wife Pauliina and my three sweet daughters Elli, Iida, and Aliisa who have tolerated me and laughed at my even more than usual absent-mindedness during the months I spent writing this doctoral thesis.

ABSTRACT

Inferior turbinate enlargement is one of the main causes of chronic nasal obstruction. There are various techniques available for the surgical treatment of inferior turbinate enlargement. Only three of the previous studies of inferior turbinate surgery have been placebo-controlled and, based on them, the placebo effect seems have a role in the results of the surgery. The relationship between Eustachian tube dysfunction (ETD) and inferior turbinate enlargement or inferior turbinate surgery has never been studied before. Furthermore, most of the studies that have evaluated the effect of inferior turbinate surgery on ciliated epithelium have only been descriptive and lacked statistical analysis. This thesis deals with inferior turbinate enlargement and its surgical treatment paying attention to all the above-mentioned aspects.

A total of 104 inferior turbinate enlargement patients were consecutively blinded and randomized into placebo, radiofrequency ablation (RFA), diode laser or microdebrider-assisted turbinoplasty (MAIT) groups in a ratio of 1:2:2:2. Prior to the operation, 6 patients withdrew from the study leaving a total of 98 patients who underwent one of the four alternative procedures. All the patients were evaluated prior to operation and three months subsequent to the operation.

The results of all 98 treated patients were assessed when the effect of inferior turbinate surgery techniques on nasal obstruction was evaluated. At the end of the three-month follow-up, all the procedures, including placebo, decreased the Visual Analog Scale (VAS) score of the severity of nasal obstruction significantly. However, all three active treatments decreased the symptom score of severity of nasal obstruction significantly more than the placebo procedure.

For the first time, we evaluated the relationship between inferior turbinate enlargement and ETD-related symptoms using the Eustachian Tube Dysfunction Questionnaire (ETDQ-7) as an assessment method. We compared the first 40 consecutive patients aged < 45 years from the total 104 patients with inferior turbinate enlargement with 40 healthy controls and found that the ETDQ-7 score was significantly higher in the inferior turbinate enlargement group.

The first 72 consecutive patients out of a total of 98 were evaluated for the effect of inferior turbinate surgery techniques on ETD-related symptoms and examined with the ETDQ-7. All the active treatments decreased the total ETDQ-7 score significantly, but there were no significant differences in the results between the placebo procedure and active treatments.

Samples for scanning electron microcopy (SEM) were taken in the form of mucosal biopsies from 66 consecutive patients in the RFA, diode laser and MAIT groups preoperatively and at the control visit. After SEM, image series of 44 patients were of a technically acceptable quality to be further evaluated. The number of cilia was found to increase significantly after RFA and MAIT treatments and the amount of squamous metaplasia increased significantly after diode laser treatment.

From the above-mentioned findings, we conclude that 1) the placebo effect has a large role in the overall reduction in the severity of nasal obstruction in inferior turbinate surgery. However, all three examined techniques provide a statistically significant additional reduction in the severity of nasal obstruction compared with the placebo procedure. 2) Patients with inferior turbinate enlargement have more symptoms related to ETD than healthy controls. 3) The improvement of ETD-related symptoms due to inferior turbinate surgery as a sole procedure is equal to placebo. 4) RFA and MAIT are more mucosal preserving techniques than diode laser, which seems to increase squamous metaplasia. The number of cilia seems to even increase after RFA and MAIT procedures.

TIIVISTELMÄ

Nenän alakuorikoiden liikakasvu on yksi yleisimmistä kroonisen nenän tukkoisuuden aiheuttajista. Sen kirurgiseen hoitoon on tarjolla useita erilaisia menetelmiä. Alakuorikkokirurgiaa on tähän mennessä tutkittu kolmessa lumekontrolloidussa tutkimuksessa ja niiden perusteella lumeella on vaikutusta kirurgian tuloksiin. Korvatorven toimintahäiriön ja alakuorikoiden liikakasvun tai alakuorikkokirurgian välistä yhteyttä ei ole aiemmin tutkittu. Alakuorikkokirurgian vaikutuksia nenän limakalvojen värekarvalliseen epiteeliin on aiemmin arvioitu, mutta suurin osa tutkimuksista on ollut luonteeltaan kuvailevia eivätkä ole sisältäneet tilastollisia analyyseja. Tämä väitöskirja keskittyy käsittelemään alakuorikkojen liikakasvua ja sen kirurgisia hoitomenetelmiä pyrkien täydentämään aiempaa tutkimustietoa asiasta.

Yhteensä 104 potilasta sokkoutettiin ja satunnaistettiin suhteessa 1:2:2:2 neljään eri ryhmään, jotka olivat lumetoimenpide, radiotaajuushoito (RFA), diodilaserhoito ja imuleikkuriavusteinen turbinoplastia (MAIT). Potilaat tutkittiin korva-, nenä- ja kurkkutautien poliklinikalla ennen toimenpidettä ja jälkikontrollissa kolme kuukautta toimenpiteen jälkeen.

Toimenpide toteutui 98 potilaalle kuuden potilaan keskeytettyä tutkimuksen ennen toimenpiteen ajankohtaa. Tutkimustulosten perusteella arvioitiin eri alakuorikkokirurgisten menetelmien vaikutusta potilaan kokemaan nenän tukkoisuuteen. Kaikkien toimenpiteiden, myös lumetoimenpiteen, havaittiin laskevan tilastollisesti merkitsevästi visual analog scale-mittarilla (VAS) arvioitua nenän tukkoisuuden voimakkuutta. Kaikki kirurgiset hoitomuodot vähensivät oiretta kuitenkin tilastollisesti merkitsevästi lumetoimenpidettä enemmän.

Alakuorikoiden liikakasvun ja korvatorven toimintahäiriön suhdetta arvioitiin tutkimuksessa ensimmäistä kertaa käyttäen korvatorven toimintahäiriökyselyä (ETDQ-7). Tätä tutkimuksen osaa varten valittiin 40 ensimmäistä iältään alle 45-vuotiasta alakuorikoiden liikakasvupotilasta ja heitä verrattiin 40 terveeseen verrokkiin. Oirekyselyn pistemäärä oli tilastollisesti merkitsevästi korkeampi alakuorikoiden liikakasvu-ryhmässä. Korvatorven toimintahäiriön oireita arvioitiin

ETDQ-7-oirekyselyllä 72 ensimmäisen hoidetun potilaan osalta myös alakuorikkojen liikakasvun hoitotoimenpiteen jälkeen. Oirepisteet laskivat tilastollisesti merkitsevästi kaikissa kolmessa kirurgisesti hoidetussa ryhmässä, mutta millään ryhmällä ero verrattuna lumetoimenpiteeseen ei ollut tilastollisesti merkitsevä.

Kirurgisesti hoidettujen ryhmien 66 ensimmäiseltä potilaalta otettiin limakalvonäytteet alakuorikosta ennen toimenpidettä ja jälkikontrollin yhteydessä kolme kuukautta toimenpiteen jälkeen. Näytteet tutkittiin pyyhkäisyelektronimikroskooppitutkimuksella (SEM) ja 44 potilaan näytteiden havaittiin olevan teknisesti onnistuneita arviointia varten. Jälkikontrollin yhteydessä otetuissa näytteissä havaittiin värekarvojen lisääntymistä verrattuna toimenpidettä edeltävään määrään RFA- ja MAIT-ryhmissä. Diodilaser-ryhmässä vastaavaa lisääntymistä ei havaittu, mutta levyepiteelimetaplasian todettiin lisääntyneen.

Väitöskirjan yhteenvetona todetaan: 1) Lumevaikutuksella on suuri rooli alakuorikkokirurgian jälkeisessä nenän tukkoisuusoireen paranemisessa. Kaikki kolme tutkittua kirurgista tekniikkaa vähentävät tukkoisuutta kuitenkin merkitsevästi lumetoimenpidettä tehokkaammin. 2) Alakuorikoiden liikakasvusta kärsivillä potilailla on enemmän korvatorven toimintahäiriön oireita kuin terveillä verrokeilla. 3) Alakuorikoiden liikakasvupotilailla alakuorikkokirurgia ei paranna korvatorven toimintahäiriön oireita lumekirurgiaa enemmän. 4) RFA ja MAIT ovat alakuorikkokirurgiassa limakalvoja säästävämpiä toimenpiteitä kuin diodilaserhoito.

CONTENTS

LIST OF ORIGINAL COMMUNICATIONS

I Harju T, Kivekäs I, Numminen J, Rautiainen M. 2017. Eustachian tube dysfunction related symptoms in chronic nasal obstruction caused by inferior turbinate enlargement. Ann Otol Rhinol Laryngol 126(12):798-803.

II Harju T, Kivekäs I, Numminen J, Rautiainen M. 2018. The effect of inferior turbinate surgery on ear symptoms. Laryngoscope 128(3):568-572.

III Harju T, Kivekäs I, Numminen J, Rautiainen M. 2018. A Prospective, randomized, placebo-controlled study of inferior turbinate surgery. Laryngoscope doi: 10.1002/lary.27103. [Epub ahead of print]

IV Harju T, Honkanen M, Vippola M, Kivekäs I, Rautiainen M. 2018. The effect of inferior turbinate surgery on ciliated epithelium: A randomized, blinded study. Laryngoscope doi: 10.1002/lary.27409. [Epub ahead of print]

ABBREVIATIONS

ANCOVA	analysis of covariance
ANOVA	analysis of variance
AR	allergic rhinitis
ATP	adenosine triphosphate
ATPase	adenosine triphosphatase
cAMP	cyclic adenosine monophosphatase
CBCT	cone beam computed tomography
CBF	ciliary beat frequency
CFD	computational fluid dynamics
cGMP	cyclic guanosine monophosphatase
CI	confidence interval
CO_2	carbon dioxide
CRS	chronic rhinosinusitis
CT	computed tomography
ENS	empty nose syndrome
ET	Eustachian tube
ETD	Eustachian tube dysfunction
ETDQ-7	Eustachian Tube Dysfunction Questionnaire
HMDS	hexamethyldisilazane
Ho:YAG	holmium:yttrium-aluminum garnet
IgE	immunoglobulin E
IQR	interquartile range
KTP	potassium titanyl phosphate
MAIT	microdebrider-assisted inferior turbinoplasty
NAR	non-allergic rhinitis
Nd:YAG	neodymium:yttrium-aluminum garnet
IR	idiopathic rhinitis
MCA	minimal cross-sectional area
MRI	magnetic resonance imaging
NOSE	Nasal Obstruction Symptoms Evaluation scale
OME	otitis media with effusion

PCD	primary ciliary dyskinesia
PNEF	peak nasal expiratory flow
PNIF	peak nasal inspiratory flow
RCT	randomized controlled trial
RFA	radiofrequency ablation
SEM	scanning electron microcopy
STT	saccharin transit time
TEM	transmission electron microscopy
TPP	tympanometric peak pressure
TRPM8	transient receptor potential melastin family member 8
VAS	Visual Analog Scale
V2-5 cm	anterior nasal cavity volume

1 INTRODUCTION

Chronic nasal obstruction is a common nasal symptom that has many adverse effects, including mouth breathing, dryness of the oropharynx, nasal speech, disordered sleep, restlessness, malaise, reduced lung volume, and overall descended quality of life. In chronic year-round allergic (AR) or non-allergic rhinitis (NAR), long standing swelling may become irreversible leading to inferior turbinate enlargement, which is one of the main causes of chronic nasal obstruction (Willatt 2009). Conservative treatment of inferior turbinate enlargement is based on intranasal corticosteroids, and medical management is considered mandatory before surgery can be undertaken (Rice et al. 2003). If the topical treatment fails, inferior turbinate surgery can be considered (Jackson and Koch 1999; Chang and Ries 2004).

Various surgical techniques have been described for the reduction of enlarged inferior turbinates. Microdebrider-assisted inferior turbinoplasty (MAIT) and radiofrequency ablation (RFA) are called mucosal sparing techniques that are widely used and the most commonly studied in the recent literature (Bhandarkar and Smith 2010). Diode laser treatment has also gained popularity during recent years due to its ease of use in an office setting (Janda et al. 2000). Previous studies that have compared RFA and the diode laser (Rhee et al. 2001; Kisser et al. 2014) and MAIT and the diode laser (Kassab et al. 2012) have not found significant differences between the techniques in the treatment of chronic nasal obstruction. A systematic review and meta-analysis by Acavedo et al. compared RFA and MAIT. They concluded that inferior turbinate reduction produces a significant subjective and objective improvement in nasal airflow in the short term that is not related to the technique used (Acavedo et al. 2015). No previous studies have compared all three techniques together.

Thus far, three placebo-controlled trials have been published regarding RFA. These studies have evaluated the influence of the treatment on the subjective scores of nasal obstruction, and they have found that the placebo effect seems to have a role in the results of inferior turbinate surgery (Powell et al. 2001; Nease and Krempl 2004; Bran et al. 2012).

Eustachian tube dysfunction (ETD) usually refers to a problem with the ventilatory function of the Eustachian tube (ET) and is defined by symptoms and signs of pressure dysregulation in the middle ear (Schilder et al. 2015). It has been presented that sinonasal problems, such as viral upper respiratory infections (Doyle et al. 2000), allergic rhinitis (Ohrui el al. 2005), and chronic rhinosinusitis (Stammberger 1986; Stoikes and Dutton 2005), can cause mucosal inflammation leading to dilatory ETD. However, the relationship between chronic nasal obstruction caused by inferior turbinate enlargement and ETD and the effect of turbinate surgery on ETD have not previously been evaluated in the literature.

The beating cilia are the driving force of mucociliary clearance, which is the primary means by which the airway clears pathogens, allergens, debris, and toxins (Gudis et al. 2012b). Various factors can affect cilia and mucociliary function. Mucociliary disorders can be primary, caused by an inherited defect resulting in abnormal cilia structure or, more commonly, secondary, caused by environmental, infectious, or inflammatory factors, such as chronic rhinosinusitis (Toskala et al. 1995a; Gudis 2012b), AR and NAR (Watanabe an Kiuna; 1998, Gindros et al. 2009), and infections (Rautiainen et al. 1992; Gudis 2012b). Most of the previous studies that have evaluated the effect of inferior turbinate surgery on ciliated epithelium have only been descriptive and lacked statistical analysis with relatively small numbers of specimens examined.

This thesis summarizes the main aspects of chronic nasal obstruction and inferior turbinate surgery, and also goes though the basics of ETD as well as cilia and mucociliary disorders. Above all, the thesis describes a prospective randomized placebo-controlled study, the main objective of which was to compare RFA, diode laser, and MAIT techniques in the treatment of chronic nasal obstruction caused by inferior turbinate enlargement, and to compare these techniques with a placebo procedure (III). In addition, the study also evaluated the relationship between chronic nasal obstruction caused by inferior turbinate enlargement and ETD-related symptoms and the effect of RFA, diode laser, MAIT and placebo procedures on ETD-related symptoms (I, II). Furthermore, the study also compared the effects of RFA, diode laser, and MAIT techniques on ciliated epithelium and mucociliary function (IV).

2 REVIEW OF THE LITERATURE

2.1 Nasal cavity and nasal airflow

2.1.1 Nasal cavity

The nasal cavity is an epithelial lined passageway bounded by the paranasal sinuses, oral cavity, and intracranial vault (Moche and Palmer 2012). The external nose surrounds the nostrils and one-third of the nasal cavity, which in its entirety consists of a 5 cm high and 10 cm long dual chamber. The total surface area of both nasal cavities is about 150 cm2 and the total volume is about 15 ml (Dahl and Mygind 1998). The nasal septum separates the right and left nasal airway, beginning at the columella and extending to the nasopharynx. The septum has both an anterior cartilaginous component and a posterior bony component covered with mucosa. The entrance area to the nose on both sides is called the nasal vestibule. Posterior to the vestibule, the lateral wall of the nasal cavity has three bony projections known as the inferior, middle, and superior turbinates. Each turbinate extends the length of the nasal cavity and is covered with a submucosal layer and respiratory mucosa (Moche and Palmer 2012). Inferior and lateral to each turbinate are passages called the inferior, middle, and superior meatus. The inferior meatus receives the openings of the nasolacrimal duct and the middle meatus the openings of the paranasal sinuses. The middle meatus is an important anatomic area in the pathophysiology of sinus disease. It has a complex anatomy of bones and mucosal folds and is referred to as the osteomeatal complex. The olfactory region is located in the upper part of the nasal cavity (Dahl and Mygind 1998).

2.1.2 Functions of the nose

The main functions of the nose are the filtering, warming, and humidifying of inspired air, the condensation of exhaled water, directing airflow up into the olfactory area, and protecting the host with mucosal IgA and mucociliary clearance

(Dahl and Mygind 1998; Willatt 2009). The nose is well suited to its air-conditioning function. The shape of the nasal cavity assures close contact between the inhaled air and the mucous membranes. The width of the cavity can adapt quickly to changing needs by alteration in mucosal swelling. Heat exchange is facilitated by the large amount of arterial blood flowing in arteriovenous anastomoses. The nasal mucosa also has a high secretory capacity (Dahl and Mygind 1998).

2.1.3 Inferior turbinate

The inferior turbinate is the largest of the three turbinates. It runs parallel to the floor of the nose (Moche and Palmer 2012). The normal turbinate is composed of an outer layer of respiratory mucosa, a submucosal layer, an inner periosteal layer, and the turbinate bone. The submucosal layer is largely venous sinusoids, capable of engorgement with blood, that cause swelling of the nasal mucosa and largely regulate the width of the nasal cavity. The distension of the venous sinusoids is controlled mainly by the sympathetic nervous system. The inferior turbinate plays a major role in the main functions of the nose (Dahl and Mygind 1998; Berger et al. 2006; Willatt 2009).

2.1.4 Nasal cycle

The physiologic alternating of vascular congestion and decongestion of the turbinates and nasal mucosa is referred to as the nasal cycle. It is a physiologic process caused by selective autonomic innervation by the hypothalamus. The alternating swelling of the inferior turbinates is found in 80% of the normal population. The turbinates on one side are filled with blood, whereas the opposite turbinates are decongested, with total nasal resistance remaining constant (Moche and Palmer 2012). The duration of this cycle is 2 to 4 hours (Dahl and Mygind 1998). It has also been observed that when a person is in the lateral decubitus position, the turbinates in the same nasal cavity side are filled with blood. It has been thought that the purpose of this alternating positional obstruction is to cause a person to turn from one side to the other while sleeping (Moche and Palmer 2012).

2.1.5 Internal nasal valve

The internal nasal valve, which is traditionally referred to as the nasal valve, is the two-dimensional opening formed by the caudal edge of the upper lateral cartilage, the nasal septum, and the anterior head of the inferior turbinate. The nasal valve is the narrowest part of the nasal cavity, and its angle should ideally be between 15 and 20 degrees. It comprises up to 50% of the total airway resistance (Moche and Palmer 2012).

2.1.6 Nasal airflow

During recent years, the mechanics of nasal airflow have been studied with experimental measurements, such as digital particle image velocimetry and with numerical simulations using computational fluid dynamics (CFD) (Doorly et al. 2008). In particle image velocimetry, a geometric model, based on a computed tomography (CT) scan or magnetic resonance imaging (MRI) image of a patient's nasal cavity, is created. Then a fluid is circulated inside it with aim of measuring the local and instantaneous fluid velocity. This is achieved by illuminating a plane of interest by a high-energy pulsed laser sheet (Quadrio et al. 2014). In CFD, a CT scan or MRI image of the actual nasal cavity is reconstructed into a three-dimensional computer model. Then a three dimensional mesh of the inner surface of the nasal cavity is constructed using a variety of software. The simulation, which usually takes days or weeks, is carried out in the resultant model. The results of the simulation are derived from the complex calculations of the Navier-Stokes equation (Leong et al. 2014).

The aerodynamics of the airflow alters significantly from the relatively laminar profile at the nasal vestibule to the high turbulent kinetic energy at the nasal valve region (Leong et al. 2010). Furthermore, > 50% of the total nasal airflow pressure-drop happens at the nasal valve region. Nasal resistance and wall shear stress are also highest at the nasal valve region. After the nasal valve, the turbulent energy decreases to zero. Nasal resistance and wall shear stress also decrease as the nasal airway expands (Zhao and Jiang 2014).

It is generally agreed that nasal airflow at a restful breathing rate (< 200 ml/s) is predominantly laminar, although strong sniffing can cause turbulent flow (Zhao and Jiang 2014). The shape of the flow downstream from the nasal valve varies markedly (Doorly et. al. 2008). The most obvious variation is the formation of an anterior dorsal vortex immediately after the nasal valve. The forming of the vortex likely depends on the angle of the nasal valve and the abrupt volume increase after the nasal valve. The formation of such vortices is quite common, especially in narrower and taller noses. The relevance of these vortices is unclear (Zhao and Jiang 2014). In sniffing, however, the gradual growth of the vortex has been found to entrain and mix the inspired air before releasing it into the jet to the olfactory cleft (Doorly et al. 2008).

There is considerable variation across individuals in the main nasal flow pathways posterior to nasal valve region. They appear in the inferior meatus, the middle meatus and the common meatus (between the turbinates and septum), but never in the superior meatus (Zhao and Jiang 2014). In recent CFD studies, healthy individuals have been found to have significantly higher middle airflow (level of the middle turbinate), which correlates with the sensation of nasal patency (Zhao and Jiang 2014; Casey et al. 2016).

Areas of high temperature increase, such as the nasal valve and the head of the inferior turbinate, are associated with turbulent airflow with vortices of low velocity that indicate increased contact between the air and the mucosa. Heating of the respiratory air depends on both heating the air during inspiration and heat recovery during expiration. During inspiration, the greatest increase in air temperature occurs at the nasal valve region. Smaller temperature increments occur distally (Leong et al. 2010).

2.1.7 Sensation of nasal airflow

The mechanism of the perception of airflow is not fully understood. In particular, the presence of airway receptors in the mucosa has been the subject of controversy (Willatt 2009). Earlier studies suggested that the nasal vestibule is the primary area for sensing nasal airflow (Jones et al. 1987; Jones et al. 1989). However, more recent literature suggests that menthol-sensitive cold reseptors are uniformly distributed throughout the nasal cavity (Meusel et al. 2010). Based on the current literature, the primary physiological mechanism that produces the sensation of ample nasal airflow is the activation of trigeminal cool thermoreceptors, specifically transient receptor potential melastin family member 8 (TRPM8), by nasal mucosal cooling. The dynamic change in temperature is ultimately sensed. Nasal mucosal cooling is therefore the result of conductive heat loss, driven by temperature gradient, and evaporative heat loss, driven by humidity gradient (Sozansky and Houser 2014). In a study by Zhao et al., peak nasal mucosal heat loss occurred posterior to the nasal vestibule and correlated with nasal patency (Zhao et al. 2014). Sullivan et al. concluded that the sensation of nasal patency was due to the stimulation of cold receptors throughout the nasal mucosa rather than a single site where heat flux is maximal (Sullivan et al. 2014). Casey et al., in turn, concluded that reduced middle airflow correlates with the sensation of nasal obstruction, possibly due to a reduction in mucosal cooling in this region (Casey et al. 2016).

2.2 Chronic nasal obstruction

Chronic nasal obstruction is a common nasal symptom that has many adverse effects, including mouth breathing, dryness of the oropharynx, nasal speech, disordered sleep, restlessness, malaise, reduced lung volume, and an overall reduction in quality of life (Willatt 2009). Chronic nasal obstruction has several different anatomic and physiologic causes. For example, AR and NAR, inferior turbinate enlargement, chronic rhinosinusitis (CRS), septum deviation, septal body hypertrophy, and internal/external valve collapse or stenosis can all lead to nasal obstruction (Willatt 2009; Moche and Palmer 2012; Ye and Zhou 2015).

On the other hand, the sensations of nasal obstruction and patency are complex parameters. Although nasal obstruction is commonly associated with increased nasal airway resistance, the objective measurements do not always correlate with the subjective degree of nasal obstruction. Damaged or by-passed trigeminal nerve endings can create the sensation of nasal obstruction without an objective increase in nasal airway resistance. Furthermore, stimulation of the menthol receptors can cause a subjective sensation of nasal patency without decreasing airway resistance (Willatt 2009).

2.2.1 Chronic allergic and non-allergic rhinitis

The prevalence of chronic rhinitis is estimated to be as high as 30% of the total population. Chronic rhinitis is defined as a symptomatic inflammation of the inner lining of the nose, leading to nasal obstruction, rhinorrhea, sneezing, or nasal/ocular itch. To define chronic rhinitis, two of the abovementioned nasal symptoms should be present for at least one hour daily for a minimum of 12 weeks per year. Patients with occasional or physiological nasal symptoms and those with rhinosinusitis are excluded from this definition. It is important, however, to realize that rhinitis symptoms are also present in those individuals with CRS (Hellings et al. 2017). The two major classifications of chronic rhinitis are AR and NAR (Greiner et al. 2011; Hellings et al. 2017).

2.2.1.1 Allergic rhinitis

AR, an inflammatory condition of the nasal mucosa mediated by an immunoglobulin E (IgE)-associated response to environmental allergens, has traditionally been classified as being seasonal or perennial, depending on whether an individual is sensitized to cyclic pollens or year-round allergens. In most parts of the world, AR is mainly triggered by inhalant allergens, such as grass and tree pollens and house dust mite. Allergen-specific IgE and eosinophilic nasal inflammation are typical features of AR (Greiner et al. 2011). The diagnosis of AR is based on the correspondence between the history of induction of symptoms by allergen contact and the positive results of a skin prick test or allergen-specific IgE in the blood.

Local allergic rhinitis or entopy is a subgroup of AR, where an allergic reaction is confined to the nasal mucosa with negative results in the above-mentioned tests. The pathophysiology is characterized by local production of IgE and a Th2 cytokine pattern of mucosal cell infiltration. The diagnosis of local AR can be confirmed by the detection of nasal IgE, a positive nasal provocation test, or both (Hellings et al. 2017).

2.2.1.2 Non-allergic rhinitis

There are many patients suffering from persistent rhinitis who are defined as NAR patients. NAR is defined as an inflammation of the nasal mucosa with the presence of a minimum of two nasal symptoms, such as nasal obstruction, rhinorrhea, sneezing, and/or itchy nose, without clinical evidence of endonasal infection and without systemic signs of sensitization to inhalant allergens. The symptoms of NAR may have a wide range of severity and be either continuously present and/or induced by exposure to unspecific triggers, also called nasal hyperresponsiveness. Nasal hyperresponsiveness represents a clinical feature of both AR and NAR patients. The inflammatory pathway is found in a subgroup of NAR patients. However, several patients with NAR do not have an influx of inflammatory cells in the nasal mucosa, and a neurogenic mechanism is believed to be involved (Hellings et al. 2017). NAR comprises different subgroups: drug-induced rhinitis, (non-allergic) occupational rhinitis, hormonal rhinitis (including pregnancy rhinitis), gustatory rhinitis, senile rhinitis, non-allergic rhinitis with eosinophilia, and idiopathic rhinitis (IR). Up to 50% of patients are included in the IR subgroup. NAR and local allergic rhinitis should be distinguished from each other (Tran et al. 2011; Hellings et al. 2017).

2.2.1.3 Conservative treatment of allergic rhinitis

The conservative treatment of AR includes allergen avoidance, antihistamines (oral or intranasal), intranasal corticosteroids, intranasal chromones, leukotriene receptor antagonists, and immunotherapy. Occasional systemic corticosteroids and decongestants (oral and topical) are also used. Intranasal corticosteroids are the most effective medications for improving all allergic rhinitis symptoms. Their onset of action is from 3 to 12 hours. Their use on an as needed basis is not as effective as continual use (Tran et al. 2011). The clinical effects of intranasal corticosteroids are based on a broad mechanism of action that leads to a reduction of inflammation in the nasal mucosa (Greiner et al. 2011).

2.2.1.4 Conservative treatment of non-allergic rhinitis

In the conservative treatment of NAR, avoidance of environmental triggers, such as strong odors and air pollutants that are respiratory irritants, is recommended in those who find such triggers worsen their rhinitis symptoms. Intranasal corticosteroids have been found to be effective for some non-allergic rhinitis and should be considered as a first-line therapy. Topical antihistamines (e.g., azelastine) have been found to be effective for the overall treatment of NAR and should also be considered as a first-line therapy (Tran et al. 2011). Ipratropium bromide is an anticholinergic drug that is effective in reducing the severity of rhinorrhea in senile rhinitis. There have also been studies published showing that the repeated administration of nasal capsaicin leads to a significant long-term reduction in symptoms in patients with IR (Hellings et al. 2017). Decongestants may be used in the treatment of NAR for symptomatic improvement as occasional adjunctive therapy (Tran et al. 2011).

2.2.2 Inferior turbinate enlargement

Inferior turbinate enlargement has not been very accurately defined in the previous literature. Enlargement can be unilateral or bilateral (Willatt 2009). Unilateral enlargement occurs in association with a congenital or acquired anatomical deviation of the septum into the contralateral nasal passage. In unilateral enlargement, there is some increase in the thickness of the mucosa and a significant doubling in the thickness of the conchal bone (Berger et al. 2000). Bilateral enlargement is due to AR or NAR and is thought to be one of the main causes of chronic nasal obstruction. In chronic perennial rhinitis, long standing swelling may become irreversible. This may be the result of dilated submucosal venous sinuses becoming atonic and varicose and losing their ability to vasoconstrict with sympathetic nervous system stimulation or medical treatment or because of fibrosis (Willatt 2009).

The pathologically hypertrophied inferior turbinate is quantitatively significantly wider, with a medial mucosal layer doubling in width and making the greatest contribution to the hypertrophy of the inferior turbinate, the bone changing very little in size. The increase in the width of the mucosa is predominantly due to an increase in the thickness of the lamina propria, which houses inflammatory cells, venous sinuses, and submucosal glands. The hypertrophied inferior turbinate shows dilated, engorged thin-walled venous sinusoids, marked subepithelial inflammatory cell infiltrate beneath the basement membrane, and fibrosis of the lamina propria, suggesting a progressive and irreversible course and representing the end point of inflammation. At this point, supportive treatment usually fails (Berger et al. 2006; Willatt 2009).

The aerodynamic patterns of the nasal cavity are changed in inferior turbinate enlargement. The streamlines of the airflow are redirected into the upper part of the nasal cavity. Both total negative pressure and maximum shear stress are increased by more than three and two times compared with healthy noses. The intensity of turbulent airflow is increased and moved upward into the upper and superior nasal cavity (Chen et al. 2010).

2.3 Examination of chronic nasal obstruction

2.3.1 History and clinical examination

Patient history and clinical examination are important aspects in the assessment of the significance and the etiology of the nasal obstruction. Patients often complain of a long-standing inability to breathe either through one or both nostrils. They may also describe other symptoms, such as rhinorrhea, postnasal drip, sneezing, and iching. Provocative factors, such as allergens and irritating factors, should be identified. Patients may describe an alternating congestion occurring every several hours, which refers to the nasal cycle. It is therefore important to separate what is likely a normal physiologic process from disease. Patients should be asked about prior nasal surgeries, traumas, and their use of medications, such as nasal corticosteroids and topical decongestants. An abundant use of topical decongestants may refer to rhinitis medicamentosa. In addition, a history of trauma may refer to a fracture or displacement of the nasal septum, and symptoms of purulent nasal drainage or facial pain may refer to sinusitis. Patients should be asked about unilateral or bilateral epistaxis. Unilateral nasal bleeding with obstruction may be a sign of a nasal or sinus mass. Patients should also be asked about loss of smell or taste and any inflammatory or collagen diseases they or their family members have (Moche and Palmer 2012; Ottaviano and Fokkens 2016).

On inspection, a patient with severe nasal obstruction often shows mouth open posturing. A patient with chronic rhinitis may have an irritated upper lip and nasal vestibule due to repetitive nasal blowing and an irritated junction of the nasal tip and dorsum due to repetitive wiping. Deviations along the nasal dorsum and depressions of the lateral sidewalls at rest and during inspiration should be recorded. Patients with longer noses often have an extended cartilaginous middle vault and, as a result, are more predisposed to internal valve collapse. In such cases, a narrow nasal base and nostril may limit nasal airflow. A depression above the nasal alae may indicate external valve collapse (Moche and Palmer 2012).

In anterior rhinoscopy, the caudal internal valve should be noted, and the angle between the nasal septum and upper lateral cartilage should be evaluated. A Cottle maneuver can be performed unirateraIly by occluding first the other nostril and with the opposite hand extending the facial soft tissues laterally to open the contralateral internal and external valve. A modified Cottle maneuver may also help identify internal nasal valve collapse by placing a head of a cotton tip applicator in the nasal valve between the upper lateral cartilage and and septum. If collapse in either is present, the patient responds to a dramatic improvement in airflow. Septal deviations, spurs, and perforations should be identified. The swelling of the inferior turbinates should also be evaluated. The inferior turbinate should generally not be in contact with the nasal septum. The addition of a topical decongestant, such as oxymetatsoline, helps remove any swelling and allows a large open view of the nasal anatomy. It also helps in assessing whether the cause of nasal obstruction is anatomical or mucosal. The region of the middle turbinate should be examined for any signs of purulence or nasal polyps (Moche and Palmer 2012).

Nasal endoscopy allows inspection of the full nasal cavity, with a wider range of view and increased detail in comparison with anterior rhinoscopy. Rigid endoscopy is, however, considered to be more patient-friendly and provides a better image than a flexible endoscope (Ottaviano and Fokkens 2016).

2.3.2 Allergy testing

If AR is suspected, allergy testing is recommended to identify those patients with allergic sentisization. In most cases, this is carried out with skin prick testing or determination of allergen-specific IgE in the blood (Jutel et al. 2014). Skin testing provides results within 15 minutes of doing the test, whereas results of the allergen-specific IgE can take several days to arrive, and the test can therefore be less cost effective than skin prick testing. Test results must be interpreted along with the patient´s history, since both false-positive (sentisization without clinical disease) and false negative results can arise (Greiner et al. 2011).

An allergen provocation test is most commonly performed when occupational allergy is suspected. It can be performed in the form of a placebo-controlled nasal provocation test or an allergen challenge chamber test (Numminen 2017). Immunospot and microcell are special tests that are not routinely used in the allergy diagnostics. Immunospot shows allergen IgE against the patient's own allergen samples or laboratory allergens in the patient's serum. Microcell is an allergen component IgE test, which can test sensitization to over 100 allergen components at the same time. (Numminen 2017; HUS 2018).

2.3.3 Measurement of nasal obstruction

The measurement of nasal obstruction is essential for both patient selection for surgery and for the assessment of surgical techniques in research (Leong and Eccles 2010). Objective and subjective evaluation give different information that together optimizes the diagnosis and treatment of the patients (Ottaviano and Fokkens 2016).

2.3.3.1 Subjective methods

In previous studies, the most commonly used instrument in the subjective assessment of the outcomes of turbinate surgery has been the Visual Analog Scale (VAS) (Batra et al. 2009). The Nasal Obstruction Symptom Evaluation (NOSE) scale was developed by Stewart et al. to measure the burden of nasal obstruction. It is a disease-specific questionnaire for the assessment of nasal obstruction that has been validated solely in septoplasty patients (Stewart et al. 2004).

2.3.3.2 Visual Analog Scale

VAS is a measurement instrument that tries to measure a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured. For example, the severity of nasal obstruction that a patient feels ranges across a continuum from none to an extreme severity of nasal obstruction. From a patient's perspective, this spectrum appears continuous - their nasal obstruction does not take discrete jumps, as a categorization of none, mild, moderate, and severe would suggest. Operationally, a VAS is usually a horizontal line, 100 mm in length, that is anchored by word descriptors at each end. The patient marks on the line the point that they feel represents their perception of their current state. The VAS score is determined by measuring in millimeters from the left-hand end of the line to the point that the patient marks. The validity of the 10 cm VAS has been established, and there is evidence that the 10 cm scale graded into one cm intervals with small markings on the horizontal line is more reliable (Bradley et al. 1989; Wewers and Lowe 1990).

2.3.3.3 Objective methods

Commonly used methods in the objective assessment of nasal obstruction are peak nasal expiratory flow (PNEF), peak nasal inspiratory flow (PNIF), rhinomanometry, and acoustic rhinometry. All these methods provide values before and after decongestion. The differences in these values can be attributed to nasal mucosal congestion. The values obtained after nasal decongestion allow the evaluation of anatomical factors (Grymer 2000; Ottaviano and Fokkens 2016).

Based on the literature, it seems that objective methods roughly correlate with each other and that all of them can be alternatively used in research as well as in clinical practice (Numminen et al. 2003; Ottaviano and Fokkens 2016). However, the subjective sense of nasal patency and the outcomes found with objective methods do not always correlate. It seems that the chance of a correlation is greater when each nasal passage is assessed individually and when obstructive symptoms are present (André et al. 2009). One possible explanation for the poor correlation is that the nasal valve region primarily determines nasal resistance, while the sensation of nasal obstruction may be related to the congestion in other areas of the upper airway (Ottaviano and Fokkens 2016).

2.3.3.4 Peak nasal expiratory and inspiratory flow

Peak nasal flows can be measured during expiration (PNEF) and inspiration (PNIF) by means of flow meters. Both of the measurements have been shown to be valid for the measurement of nasal airflow and are well tolerated. PNIF correlates better with nasal resistances than PNEF. PNIF is also an inexpensive, fast, and simple technique with good reproducibility. As an inspiratory maneuver, PNIF can cause alar collapse and when the nose is completely blocked, it is not possible to obtain a PNIF measurement (Ottaviano and Fokkens 2016).

2.3.3.5 Rhinomanometry

Rhinomanometry involves the measurement of nasal airflow and the pressure gradient required to achieve a flow from which nasal airway resistance can then be calculated. Active anterior rhinomanometry is the most commonly used method of rhinomanometry. Nasal airway resistance is normally determined at a fixed pressure gradient of 150 Pa. The reference interval for normal total nasal airway resistance under congested nasal mucosal conditions is found to be at 0.25 $Pa/cm^3/s$ (95% RI 0.10 - 0.40 $Pa/cm^3/s$) for adults (Ottaviano and Fokkens 2016).

2.3.3.6 Acoustic rhinometry

Acoustic rhinometry allows the determination of the cross-sectional area and volume of the nasal cavity as a function of the distance into the nasal cavity. The method is based on a comparison/analysis of the amplitude (representative for the area) of sound waves as reflections by the nasal cavity of an incident sound wave, and this as a function of time (representative for the distance into the nasal cavity (Hilberg et al. 1989; Hilberg and Pedersen 2000; Hilberg 2002). The method provides values before and after decongestion, which allows evaluating whether the cause of the nasal obstruction is mainly mucosal or anatomical. The majority of the publications dealing with acoustic rhinometry in nasal surgery are related to septoplasty and inferior turbinate surgery (Grymer 2000).

In acoustic rhinometry, the narrowest part of the nasal cavity is usually situated within a distance of 3 cm from the nares and moves anteriorly during decongestion (Grymer et al. 1991). Two minima have been described in this region. The first deflection reflects the nasal valve (I-notch representing the Isthmus nasi), the second the anterior end of the inferior turbinate (C-notch representing the head of the inferior turbinate) (Lenders and Pirsig 1990). The third deflection reflects the middle - posterior portion of the middle turbinate (Corey 2006). One of the two first minimum areas is the absolute minimum of the curve. In some subjects, the minimal cross-sectional area (MCA) corresponds to the nasal valve, while in others it corresponds with the head of the inferior turbinate (Hilberg and Pedersen 2000). For mucosal changes, the anterior nasal cavity volume (V2-5 cm) is an important value. Measurement of V2-5 cm rather than MCA is the most sensitive measure for changes in mucosal swelling during decongestion (Straszek et al. 2007).

Acoustic rhinometry will in most instances give a valid result at least for the first 5 cm to 6 cm into the nasal cavity (Hilberg 2002). The accuracy of the technique decreases as the distance from the beginning of the nasal cavity increases. Areas measured in the posterior part of the nasal cavity may be affected by the openings to the paranasal sinuses, especially the maxillary sinuses (Hilberg and Pedersen 2000). When evaluating nasal patency, it is important to have an estimate of the normal variation in nasal mucosal congestion. The nasal cycle may contribute to the variation, but in the case of classical nasal cycle, the total congestion sum of the two sides is usually constant (Hilberg 2002). For the nose, it is difficult to define normal values that can separate normal from pathological conditions. In some patients, the nose may be almost totally occluded without subjective notice. The nostril is generally considered obstructed if the MCA value is below 0.35 cm^2 (Hilberg and Pedersen 2000).

Acoustic rhinometry is a simple technique that requires minimal patient cooperation (Ottaviano and Fokkens 2016). Most of the variability in the measurements is usually caused by the unsatisfactory coupling of the nose to the nosepiece of the equipment. In order to avoid error, the operator of the measurement should be well trained and follow a standard procedure. Environmental conditions (temperature, noise), which may also affect the results, should be controlled (Hilberg Pedersen 2000).

2.3.3.7 Imaging

CT scans and MRI images can be used in the measurement of the cross-sectional area of the nasal passage as well as in the measurement of nasal cavity volume. In previous studies, the imaging techniques have been used for assessing the effects of different treatment options and for validitating measurement methods, such as acoustic rhinometry (Ottaviano and Fokkens 2016). Recently, CT scans and to a lesser extent, MRI images have been used in CFD studies in the modeling of airway boundaries (Doorly et al. 2008). In clinical practice, CT scans and Cone Beam Computed Tomography (CBCT), the radiation intensity of which is notably lower than in normal CT (Hodez et al. 2011), are normally used in the evaluation of the paranasal sinuses. MRI, in turn, is commonly used in sinonasal tumor diagnostics.

2.4. Principles of inferior turbinate surgery

2.4.1 Indications for inferior turbinate surgery

Medical treatment, which is based on intranasal corticosteroids, is considered to be mandatory before inferior turbinate surgery can be undertaken (Rice et al. 2003). If topical treatment fails, inferior turbinate surgery can be considered (Jackson and Koch 1999; Chang and Ries 2004). However, the duration and exact nature of the medical treatment is not well defined. There is a need for studies to define what sufficient medical treatment is and how long it should be administered before surgery is considered (Willatt 2009). Surgery is also often preferred to avoid the side effects of the long-term use of medicines and because patients prefer not to have long-term use of medicines.

The feeling of nasal patency is an individual and complex parameter that influences the decisions about treatment. Single variables of objective methods do not provide enough information for the diagnosis of nasal obstruction. For example, in the single individual, it is not known which change in the internal dimension of the nasal cavity is necessary to change the feeling of nasal patency. Therefore, when a decision about the treatment is made, the results of the objective measurements should be interpreted together with rhinoscopy findings and subjective complaints (Grymer et al. 1991).

2.4.2 Role of the vasoconstriction test

Chronic bilateral mucosal swelling can be identified with the vasoconstriction test. The effect of topical vasoconstrictor use can be evaluated subjectively using VAS or objectively using rhinometric methods (Jones et al. 1989; Yilmaz 2006; Volk et al. 2010). In normal subjects, the increase in nasal cavity volume after vasoconstriction has been reported to be between 30% and 55%. Studies of rhinomanometry, in turn, have shown decreases in nasal resistance after decongestion of around 25% to 40% (Fisher 1997). These values should be taken into account when defining how much the nasal cavity volume must increase or the resistance decrease due to the shrinking of the turbinates after vasoconstriction in order to diagnose chronic bilateral inferior turbinate enlargement.

There have been studies that show that response to topical vasoconstriction is predictive of a favorable response to various inferior turbinate surgery techniques (Jones et al 1989; Yilmaz et al. 2006; Volk et al. 2010). In a study by Yilmaz et al., an improvement due to surgical treatment seemed to depend more on how much the patients' turbinates responded to topical vasoconstrictor than how much they complained of nasal obstruction (Yilmaz et al. 2006).

2.4.3 Site of the surgery and surgical extension

Based on their findings, Berger et al. suggest the targets for inferior turbinate surgery are the medial and inferior mucosal layers. The medial layer shows the greatest thickening and obstructs the airway. The inferior layer contributes less to the increase in width but is rich in sinusoids, poor in glandular elements, and lacks major arteries. Hence, surgical reduction of the inferior layer will help congestion, will not increase the risk of nasal dryness nor increase the risk of perioperative hemorrhage. The lateral mucosal layer should be spared because it does not encroach on the airway and plays an important role in humidifying the inspired air and maintaining mucociliary clearance (Berger et al. 2006).

The nasal valve is the narrowest part of the nasal cavity. The anterior portion of the inferior turbinate is the predominant structure in this part of the nose and therefore plays a major role in nasal obstruction. The main strategy of turbinate surgery is to reduce the volume of the inferior turbinate, especially in its anterior portion (Apaydin 2011; Moche and Palmer 2012). In a study by Civalek et al., treatment applied to the anterior 1/3 of the inferior turbinate was equally as effective in decreasing obstruction as treatment to the whole turbinate (Civalek et al. 2010). In a CFD simulation study by Lee et al. based on the total pressure field distribution and the need to maintain olfaction, the 1/3 resection seemed to be better than total turbinectomy and front-end surgery (Lee et al. 2013). However, in their recent review, Ye and Zhou suggest that the resection range of the inferior turbinate should be based on the severity of the nasal obstruction (Ye and Zhou 2015).

Recent studies have reported that mucosal cooling correlates with subjective feeling of nasal patency. This finding should also be taken into account when performing inferior turbinate surgery (Sullivan et al. 2014; Zhao et al. 2014; Casey et al. 2016). A too wide nasal passage with the bulk of the airstream having little contact with the mucosal wall may produce a weak mucosal cooling and the sensation of congestion. A slightly narrower nasal valve, in turn, would benefit patency by creating strong regional mucosal cooling (Zhao and Jiang 2014).

2.5 Inferior turbinate surgery techniques

Various surgical techniques have been described for the reduction of enlarged inferior turbinates, such as total or partial turbinectomy, submucous resection, various lasers, cryosurgery, RFA, and outfracture (Willatt 2009; Sinno et al. 2016). No clear consensus exists in the literature, however, on the exact role of the surgery or the most optimal method for surgical treatment (Batra et al. 2009). Generally, techniques that remove the turbinate most, such as total or partial turbinectomy and submucosal resection, have the greatest and longest lasting effects, but they are also accompanied by a higher likelihood of adverse effects, most commonly bleeding, postoperative pain, crusting, and synechia (Passali et al. 2003, Willatt 2009; Sinno et al. 2016). In addition, treatments such as cryotherapy, electrocautery, and some laser types have failed to provide long-term results (Passali et al. 2003; Sinno et al. 2016).

In recent years, surgical procedures have concentrated on minimal disturbance towards the nasal mucosa. The aim of inferior turbinate surgery is to carry out reduction of the turbinate with an improvement in nasal obstruction while maintaining nasal function and minimizing complications (Bhandarkar and Smith 2010). MAIT, which is a powered subtype of submucosal resection (Sinno et al. 2016), and RFA are called mucosal sparing techniques that are widely used and most commonly studied in the recent literature (Bhandarkar and Smith 2010). The diode laser has also gained popularity in recent years for its ease of use in the office setting (Janda et al. 2000).

2.5.1 Partial turbinectomy

Partial turbinectomy means selective trimming of the inferior turbinate (Sinno et al. 2016). Any enlarged tissue of the inferior turbinate can be excised with turbinate scissors. The resection may include mucosa, submucosal tissue, and a small resection of bone. The extent of the resection depends on the degree of enlargement. The procedure can be carried out under general or local anesthesia and short nasal packing is indicated (Romano et al. 2015). Crusting has been reported to be the most common adverse effect (Sinno et al. 2016). Bleeding risk has been found to be higher compared with submucosal techniques (Romano et al. 2015). Partial turbinectomy has been found to be effective in treating inferior turbinate enlargement compared with other old and modern techniques (Sapci et al. 2003; Salzano et al. 2009; Romano et al. 2015). However, trimming remains a controversial procedure regarding the preservation of nasal mucosa and physiology (Willatt 2009; Romano et al. 2015; Garzaro et al. 2012).

2.5.2 Total turbinectomy

Total turbinectomy involves the removal of the entire inferior turbinate. Previous studies have shown a decrease in nasal resistance and an improvement in nasal obstruction in about 80% of patients (Sinno et al. 2016). However, 20% of patients have been found to complain of recurrent nasal obstruction two years after the procedure (Wight et al. 1990). Total turbinectomy is also associated with higher rates of crusting, postoperative pain, and bleeding compared with the other techniques. Moreover, the huge postoperative increase in nasal airflow corresponds to a decrease in the humidifying activity of the nasal mucosa resulting in excessive drying and crust formation (Passali et al. 2003).

2.5.2.1 Atrophic rhinitis and 'empty nose' syndrome

Traditionally, there has been a concern that total removal of the turbinates may result in rhinitis sicca, atrofic rhinitis, and/or ozaena. These processes have been attributed to excessive drying from the loss of mucosa, the destruction of cilia secondary to scarring, atrophy, and endstage infection (Willatt 2009). However, the previous literature regarding the role of excessive turbinate resection as an etiology for secondary atrophic rhinitis has been controversial (Moore and Kern 2001).

Some patients may have symptoms of nasal obstruction after turbinectomy in the absence of anatomic obstruction. This has been termed the "empty nose syndrome" (ENS), which has been associated with the patient's inability to recognize the normal nasal sensation of breathing. An extreme lack of nasal resistance may paradoxically be perceived as nasal obstruction (Willatt 2009). ENS patients have been found to have a significantly smaller inferior turbinate volume than healthy controls (Hong and Jang 2016). The precise pathogenesis of ENS has, however, remained unclear. Various factors, such as nasal aerodynamics and sensorineural dysfunction, have been suspected. In a recent study, CFD analysis showed that, paradoxically for all ENS patients, inferior turbinate reduction did not draw more airflow to the airway surrounding the inferior turbinates but rather resulted in nasal airflow forming into a narrow jet toward the middle meatus region, leaving the airway surrounding the inferior turbinate with significantly reduced airflow intensity and air-mucosal interactions. ENS patients also had significantly impaired trigeminal sensorineural sensitivity compared with healthy controls (Li et al. 2017).

For the reasons mentioned above, total turbinectomy is no longer recommended. Nowadays, otorhinolaryngologists believe that turbinate reduction should be performed as conservatively as possible (Rice et al. 2003).

2.5.3 Outfracture

Outfracture is performed by medially infracturing the turbinate, crushing it with a flat bladed instrument, then forcing it laterally and holding it in position with nasal packing (Willatt 2009). The procedure is recommended in combination with tissue-reduction surgery (Sinno et al. 2016) because it has been reported to improve the results (Passali et al. 2003).

2.5.4 Electrocautery

Electrocautery can be performed with either linear mucosal or submucosal contact. For surface cautery, a wire or needle electrode can be used to streak the turbinate mucosal surface. Submucosal cautery can be performed with either a unipolar or bipolar electrode to induce fibrosis and wound contracture and resultant volume reduction. High tissue temperatures (up to 800 °C) are achieved (Salzano et al. 2009). Electrocautery has the highest percentage of patients that suffer from postoperative crusting compared with other techniques (Passali et al. 2003; Sinno et al. 2016). Also, more synechiae have been reported after electrocautery compared with other older techniques (Passali et al. 2003). In addition, electrocautery has not been shown to provide long-lasting results (Passali et al. 2003; Sinno et al. 2016).

2.5.5 Cryotherapy

Cryotherapy is a minimally invasive procedure used to treat lesions by causing necrosis from the freezing and thawing of cells (Sinno et al. 2016). The treatment is well tolerated and is not associated with significant adverse effects (Willatt 2009). However, the procedure has been shown to provide only short-term benefit in the treatment of inferior turbinate enlargement (Passali et al. 2003; Sinno et al. 2016).

2.5.6 Lasers

Since the early 1980s, various types of lasers have been used for the reduction of enlarged inferior turbinates. Laser-assisted turbinate surgery causes limited submucosal scarring and obliteration of the venous sinusoids shrinking the turbinate and relieving nasal obstruction (Cakli et al. 2012). Laser surgery is a minimally invasive procedure with a controllable ablation of tissue causing few complications and almost never requires nasal packing. It is also easy to perform as an outpatient procedure (Janda et al. 2001). Lasers that have been used to treat enlarged inferior turbinates include Nd:YAG (neodymium:yttrium-aluminum garnet), Ho:YAG (holmium:yttrium-aluminum garnet), argon, CO_2 (carbon dioxide), KTP (potassium titanyl phosphate), and diode lasers (Janda et al. 2001; Huttenbrink 2005). The basic differences between these laser types depend on the emitted laser wavelength, output power, whether the laser emission is applied in pulsed or continuous wave mode, and whether it is a contact or non-contact application (Janda et al. 2001). Various contact techniques have been described for the lasers including linear vaporization, where parallel strips are coagulated along the length of the inferior turbinate, cross-hatching of the mucosa, contact cautery along the free inferior edge of the turbinate, diffuse application using non-contact technique, and spot application on the head of the turbinate (Huttenbrink 2005).

With the exception of the CO_2-laser, the other lasers can be delivered using a flexible quartz fiber in contact or non-contact mode (Cakli et al. 2012).

After follow-ups of up to one year, laser treatment seems to be as or even more effective than most of the conventional techniques such as electrocautery (Janda et al. 2001) or even as effective as newer techniques such as RFA (Rhee et al. 2001; Sapci et al. 2003). More invasive techniques, such as submucosal resection, have been found to achieve better results in most cases, especially in the long-term (Janda et al. 2001; Passali et al. 2003). There are, however, also some previous studies where high success rates using various lasers have been reported in longer follow-ups (Sroka et al. 2007; Iwasaki et al. 2010; Raja et al. 2017). In a comparative review by Janda et al., the authors concluded that due to the variety of application modes with very different results in several studies, it is neither meaningful to compare laser systems, nor to determine the best system for turbinate surgery. Depending on the parameters chosen and the knowledge and experience of the physician, it is possible to induce very similar tissue effects with laser emissions of different wavelengths (Janda et al. 2001).

2.5.6.1 Diode laser

Today, the diode laser is the most portable and least expensive of the lasers available for rhinologic applications. The laser has gained increasing popularity for its ease of use under local anesthesia in the office setting (Janda 2000 et al; Volk 2010 et al; Caffier et al. 2011). The used wavelengths are 940 nm, 980 nm, and 1470 nm (Janda et al. 2000; Cakli et al. 2012; Havel et al. 2011). In previous studies, the diode laser has been described to provide significant improvement in nasal airflow subjectively and also in objective measurements at one-year (Janda et al. 2000; Cakli et al. 2012), two-year (Caffier et al. 2011), and three-year (Sroka et al. 2007) follow-ups. The most common adverse effects are nasal edema and crusting, which usually resolve in 2 to 4 weeks (Janda et al. 2000; Sroka et al. 2007).

2.5.7 Submucosal resection

The goal of submucosal resection is to reduce bulky submucosal tissue, while maximally preserving the overlying mucosa, and thereby maintaining ciliary function (Chabra and Houser 2012). Submucosal resection can be accomplished with either manual or powered instrumentation. Inferior turbinoplasty is a classical form of submucosal resection. In this method, a vertical part of the conchal bone and a wedge of soft tissue attached to the lateral and inferior aspects are resected. The remaining flap is rolled up to form a neoturbinate (Mabry 1982; Willatt 2009). Passali et al. indicated that submucosal resection was superior to various forms of surgery in relieving nasal obstruction, rhinorrhea, sneezing, and postnasal dripping postoperatively (Passali et al. 1999), and that it resulted in the highest long-term degree of nasal patency and mucociliary clearance (Passali et al. 2003). Joniau et al. described extraturbinal turbinoplasty in which a powered microdebrider with oscillating blade is used to remove the tissue as in inferior turbinoplasty. Using this technique, they demonstrated the long-term subjective and objective relief of nasal obstruction in five-year follow-up (Joniau et al. 2006).

2.5.7.1 Microdebrider assisted inferior turbinoplasty

Intraturbinal power-assisted submucosal turbinate reduction can be carried out with small (2.0 mm or 2.9 mm) microdebrider blades with an elevator. Under local anaesthesia, a microdebrider tip is pushed into the turbinate, and a submucosal pocket is created by tunneling the elevator tip in a sweeping motion on the medial side of the bony turbinate. Debridement of the submucosal tissue from the inferior turbinate is performed in the medial submucosal plane at speeds of up to 3000 rpm. No postoperative packing is necessary (Willatt 2009), and postoperative complications are considered minor. Nasal congestion can occur up to one month (Yanez and Mora 2008). However, notable intraoperative bleeding (Kassab et al. 2012) or postoperative bleeding during the early days after MAIT (Cingi et al. 2010) has been reported. Chen et al. showed that the intraturbinal microdebrider technique is at least as effective as traditional submucous resection in reducing subjective complaints and improving nasal airflow. Also, operation time and blood loss are significantly less with MAIT compared with traditional submucous resection (Chen et al. 2008). Huang and Cheng found a significant decrease in nasal resistance and an increase in quality of life at one year postoperatively. They suggested that the rhinorrhea, sneezing, and postnasal discharge in allergic patients were the result of the removal of the large number of inflammatory cells in the medial submucosal tissue (Huang and Cheng 2006). In addition, submucosal turbinectomy cuts the branches of the postnasal nerve arising from the sphenopalatine foramen that may have a role in decreasing sneezing and hypersecretion (Mori et al. 2002). Yanez and Mora treated 350 non-allergic patients with MAIT in study with 10-year follow-up. At 10 years postoperatively, 91% of patients were completely symptom free and rhinomanometry revealed also long-term improvement (Yañez and Mora 2008).

2.5.8 Radiofrequency ablation

Since described by Li et al. in 1998 (Li et al. 1998), RFA has probably become the most used inferior turbinate reduction technique. In general, RFA is an electrosurgical medical procedure in which the operated tissue is ablated using the heat generated from low to medium frequency alternating current (in the range of 100 to 500 kHz) (Bäck 2002; Courtney and Townsend 2012). RFA utilizes a probe or an electrode inserted directly into the inferior turbinate that is used to deliver ionic energy. The procedure creates a submucosal lesion, inducing tissue volume reduction. The submucosal lesion results from friction between ions that rapidly change direction because of the alternating current produced by the electrode. A temperature of less than 85 °C is generated as opposed to the 800 °C temperature brought about by electrocautery. The lesion is therefore controlled, and the overlaying mucosa and the underlying turbinate bone are preserved. Postoperative wound contracture and fibrosis induces tissue volume reduction (Willatt 2009). There are two RFA techniques, monopolar and bipolar, which have been reported to be equally efficient (Cavaliere et al. 2007). Moreover, RFA is reported to be a safe procedure, and complications are rare and minor. The most common adverse effects are pain during the procedure, bleeding, crusting, and postoperative edema causing blockage of the nose during the first weeks after the procedure (Hytönen et al. 2009). The procedure can be performed on an outpatient basis under local aneshesia without nasal packing, and it can be repeated if necessary (Bäck et al. 2002). In a systematic review by Hytönen et al., most of the studies reported an improvement in subjective symptoms after treatment and the number of serious adverse effects was small. However, most of the published studies were observational and had a relatively short follow-up (Hytönen et al. 2009). The evidence of the long-term effect of RFA is controversial. Liu et al. treated patients with allergic rhinitis and enlarged inferior turbinates. They found an improvement in VAS and rhinomanometry at six months that was only sustained to one year with a gradual return to baseline from two to three years postoperatively (Liu et al.

2009). There are other studies, however, where the clinical benefit of the procedure has persisted for up to five years (Lin et al. 2010; Cukurova et al. 2011).

2.5.9 Comparative studies of inferior turbinate surgery techniques

During recent years, comparative studies involving diode laser, MAIT, and RFA have been published. Kizilkaya et al. conducted a prospective trial with 30 patients who underwent simultaneous RFA and MAIT on consecutive sides. Both procedures resulted in improvements in both VAS score of nasal obstruction and acoustic rhinometry results, with no significant difference in six-month follow-up (Kizilkaya et al. 2008). Liu et al. prospectively studied 120 patients with enlarged inferior turbinates caused by persistent allergic rhinitis who received MAIT or RFA. The outcome measures were VAS score of nasal obstruction and rhinomanometry. MAIT resulted in an improvement of all parameters at six months with sustained improvement to three years. RFA also resulted in improvement at six months but was sustained only to one year with a return to baseline from two to three years (Liu et al. 2009). Cingi et al. compared MAIT and RFA in a prospective study with 268 patients. The severity of nasal obstruction grades improved significantly in the microdebrider group in the first week, the first month and the third month post-operatively, compared with the radiofrequency group. The severity of nasal discharge, headache, and hyposmia grades improved significantly in the first week of the operation both in the microdebrider and the radiofrequency group and persisted to the third month of the operation. At three months, the rhinomanometric measurements were also significantly lower in the MAIT group (Cingi et al. 2010). A systematic review and meta-analysis by Acavedo et al. compared RFA and MAIT. The median follow-up of the included studies was 6 months. There was no difference in outcome by technique, allergic rhinitis, or quality score. They concluded that inferior turbinate reduction produces a significant subjective and objective improvement in nasal airflow in the short term, which is not related to the technique used (Acavedo et al. 2015).

Rhee et al. compared RFA and diode laser in a prospective randomized study with 24 patients. At 8 weeks, the severity of nasal obstruction as well as nasal volume and resistance improved significantly in both groups. The significant subjective improvement occurred within two to three days after RFA and within four weeks after diode laser (Rhee et al. 2001). In their prospective randomized single-blinded clinical trial with 26 patients, Kisser et al. compared RFA and diode laser (940 nm wavelength). In the trial, one side of the nose was treated with RFA and the other with diode laser. After three months, a significant reduction in nasal obstruction was observed for both groups with no significant difference between them. Objective parameters did not improve significantly (Kisser et al. 2014). Kassab et al. compared MAIT and diode laser (980 nm wavelength) in a prospective randomized study with 40 patients. After six months, 90% of the MAIT group patients and 85% of the diode laser group patients were completely relieved of their nasal obstruction. There were no significant differences between the groups regarding success rate, acoustic rhinometry results, complications, or operation time (Kassab et al. 2012). Veit et al. compared anterior turbinoplasty (submucosal resection), RFA, and diode laser (1470 nm), each in combination with standard septoplasty, in a prospective single-blinded randomized trial with 60 patients. A significant subjective improvement in nasal breathing and nasal volume was observed at three months, one year, and two years in the anterior turbinoplasty and RFA groups. In the diode laser group, a significant improvement in nasal breathing was only observed at three months. Furthermore, the diode laser group also failed to reach significant improvement in nasal volume at all follow-up visits (Veit et al. 2015). To date, no studies have compared the diode laser, MAIT, and RFA techniques together.

2.5.10 Placebo-controlled studies of inferior turbinate surgery

So far, there have only been three placebo-controlled trials evaluating the influence of treatment on the subjective scores of nasal obstruction. In a double-blinded placebo-controlled trial by Powell et al., 22 patients were randomly assigned to either an RFA (n = 17) or placebo (n = 5) group. The beneficial effect of treatment on nasal obstruction with RFA was demonstrated, but it did not reach statistical significance, probably due to the small sample size (Powell et al. 2001). A single-blinded placebo-controlled trial with a crossover option by Nease and Krempl included 32 patients who were randomized to either an RFA (n = 16) or placebo (n = 16) group. Improvement was shown in the frequency of nasal obstruction, severity of nasal obstruction, and overall ability to breathe for both the placebo and RFA treatment arms at 8 weeks. However, the effects of RFA were significantly better than those of placebo in the severity of nasal obstruction and the overall ability to breathe (Nease and Krempl 2004). In a single-blinded placebo-controlled crossover trial by Bran et al. with 22 patients, the first group received RFA first followed by a placebo treatment 6 to 8 weeks later. In the second group, the order was reversed. Nasal obstruction only decreased significantly after RFA in both groups. There was a tendency of improvement after placebo in both treatment arms. However, the observed trends of a placebo effect were not statistically significant (Bran et al. 2013).

2.6 Nasal epithelium and cilia

2.6.1 Nasal epithelium

The vestibulum of the nose is covered by a squamous epithelium that contains sebaceous glands, sweat glands, vibrissae, and finer hair. The upper part of the cavity is covered by an olfactory epithelium. The remaining portion of the nasal cavity as well as the paranasal sinuses, Eustachian tube, and middle ear are covered by a typical respiratory epithelium, which is ciliated, pseudostratified and columnar. The upper part of the nasopharynx is covered by ciliated epithelium and the lower part by squamous epithelium. Respiratory epithelium is composed of four major cell types: basal cells, ciliated and non-ciliated columnar cells, and goblet cells (Mygind et al.1982; Dahl and Mygind 1998; Gudis et al. 2012a).

2.6.1.1 Basal cells

Basal cells, which are progenitors of the other cells types, lie on the basement membrane and do not reach the airway lumen. The basal cells may develop into columnar cells with or without cilia or goblet cells via intermediate cells. The epithelium rests upon a layer of collagen fibrils, which in the light microscope is referred to as 'basement membrane'. Currently, basal cells are also believed to help in the adhesion of columnar cells to the basement membrane (Mygind et al. 1982; Dahl and Mygind 1998).

2.6.1.2 Ciliated and non-ciliated columnar cells

Columnar cells are approximately 25 μm long and 7 μm wide, tapering from 2 μm to 4 μm at the base. They are connected to neighboring cells by tight junctions apically and in the uppermost part by interdigitations of the membrane. All the cells are in contact with the basement membrane, but only part of the cells reach the surface of the epithelium (Mygind et al.1982; Dahl and Mygind 1998). All the columnar cells, with or without cilia, are covered with 300 to 400 microvilli. These are finger-like expansions of the cell membrane up to 2 μm long and about 0.1 μm wide that increase the surface area of the epithelium and probably retain the moisture essential for ciliary function (Mygind et al.1982; Petruson et al. 1984).

A ciliated cell contains about 50 to 200 cilia (Gudis et al. 2012a). The anterior one-third of the nasal cavity is non-ciliated. On the lateral wall, the density of the ciliated cells increases in the antero-posterior direction. Cilia start occurring just behind the front edge of the inferior turbinate. More posteriorly, the density of the ciliated cells ranges from 50% in the 1/3 middle to 100% in the posterior part of the inferior turbinate. Similar density patterns are present on the septum side and on the medial turbinate. In all the paranasal sinuses, the density is very high. The distribution pattern of ciliated cells corresponds well with a map of nasal airflow, indicating that the density of ciliated cells is inversely proportional to the linear velocity of inspiratory air in the nasal cavity. It is also assumed that other physical properties of the nasal airflow, such as low temperature, low humidity, and contamination, contribute to the reduced number of ciliated cells (Halama et al. 1990). Understandably, the anterior part of the nasal cavity hit by strong currents of cold, dry, and polluted air has a lower density of ciliated cells (Dahl and Mygind 1998).

2.6.1.3 Goblet cells

Goblet cells contain mucous granules that give the cells their goblet shape. The surface of the goblet cells is covered with microvilli. The goblet cells constitute between 5% and 15% of the mucosal cells in the nasal inferior turbinate (Petruson et al. 1984). The goblet cell contribution to the volume of nasal secretion is probably small when compared to that of the submucosal glands. The release mechanism from goblet cells is not under the control of the parasympathetic nervous system. Goblet cells probably respond to the physical and chemical irritants in the microenvironments (Dahl and Mygind 1998).

2.6.2 Respiratory cilia and mucociliary function

2.6.2.1 Ciliary ultrastructure

The human respiratory cilium is an extension of the columnar cell. Cilia are 5 μm to 6 μm long and about 0.2 μm wide (Mygind 1975; Rautiainen et al. 1984). The longitudinal fibrils of the ciliary shaft form a tubular complex called the axoneme. The axoneme is composed of two central microtubules in the middle of the cilium and nine peripheral microtubule doublets around the central tubules. The peripheral double tubules are arranged regularly near the ciliary membrane. Each doublet comprises one complete A microtubule and one partial B microtubule that is attached laterally to the A microtubule (Warner 1974; Sleigh 1977).

There are inner and outer adenosine triphosphatase (ATPase) containing dynein arms projecting from microtubule A of each doublet toward microtubule B of the adjacent doublet. The outer one is longer and has an extra segment at its tip. The peripheral doublets are connected to each other by nexin links. The radial spokes, ending in a spoke head, connect microtubule A to the central sheet around the central tubules (Sleigh 1977).

2.6.2.2 Mucociliary function

Mucociliary function describes the process by which cilia transport the mucus overlying the respiratory mucosa to the gastrointestinal track for ingestion. Mucociliary function is the primary means by which the airway clears pathogens, allergens, debris, and toxins (Gudis et al. 2012b). Effective mucociliary function is based on an interaction between the three components: moving cilia, periciliary fluid, and mucus.

2.6.2.3 Ciliary activity

The beating cilia are the driving force of mucociliary transport. Ciliary beat usually begins with a recovery phase, where the cilium swings about 180 degrees backward being in periciliary fluid. Then, the cilium is streched and goes directly through its effective stroke. During the effective phase, the tip of the streched cilia moves the mucus layer towards the larynx (Satir 1974; Sanderson and Sleigh 1981). The movement of cilia is highly syncronized, producing metachronical waves that pass over the epithelial surface. The mechanism by which the metachronal waves are coordinated seems to be based on mechanical impulses between adjecent cilia: one cilium swinging backwards from its resting state stimulates adjecent cilia to go into the recovery phase (Sanderson and Sleigh 1981). In humans, the spontaneous beating of the cilia can range from ~ 9 Hz to 15 Hz (Gudis et al. 2012a).

According to the sliding filament theory, the ciliary movement is based on the sliding of the axonemal microtubules without there being any change in their length (Satir 1974). The sliding of the doublet microtubules is accomplished by successive detachment - reattachment of the ATPase containing dynein arm to the adjecent microtubule B containing adenosine triphosphate (ATP). Each detachment requires binding of new ATP, which is then hydrolyzed at some point in the subsequent cycle, providing energy for directional force generation (Satir 1980).

CBF changes in response to several chemical, thermal, mechanical, and hormonal stimuli (Gudis et al. 2012a). The stimulation of beating is mediated and controlled by an intricate signaling network that relies on interplay between calcium and cyclic nucleotide pathways (Cohen 2006; Braiman and Priel 2008). The ciliary machinery can work in at least two different modes: a low rate of beating that requires only ATP and a high rate of beating involving not only ATP but an acceletory modification regulated by secondary messengers, such as cAMP, cGMP, and Ca++ (Braiman and Priel 2008). Extracellular nucleotides as well as adrenergic, cholinergic, and peptidergic stimulation have also been demonstrated to stimulate ciliary motility (Gudis et al. 2012b).

2.6.2.4 Mucus

Airway mucus is composed of water (95%), glycoproteins (2%), other proteiinia including albumin, immunoglobulons, lysozyme and lactoferin (1%), inorganic salts (1%), and lipids (<1%). The submucosal glands, and to a lesser degree the goblet cells, are the main source of mucus glycoproteins that provide mucus with its viscoelastic properties (Kaliner et al. 1984). The mucus lining is about 5 micrometers thick and comprises two layers. The periciliary layer (sol) is about 4 micrometers thick and the overlying layer (gel) from 1 to 2 μm thick. The upper layer is composed of mucus of high viscosity and the lower layer of fluid with low viscosity (Dudley and Cherry 1980). In the effective phase of the ciliary beat, the tips of the cilia penetrate into the upper gel layer and propel the mucus forward. In the recovery phase, the cilia sweep back without touching the upper layer (Sleigh 1983).

2.7 Methods for studying cilia and mucociliary function

2.7.1 Ciliary beat frequency

The sample is typically obtained via brushing of the nasal epithelium and then observed under a microscope. Ciliary beat frequency (CBF) has been analyzed previously in ex vivo specimens using a variety of methods including photodiode detectors and conventional video recording (Schipor et al. 2006). More recently, high-speed digital video analysis has become increasingly popular in the evaluation of ciliary motion and CBF (Chilvers and O'Callaghan 2000).

2.7.2 Mucociliary transport

Mucociliary transport can be evaluated with the radioisotopic method (Kärjä et al. 1982) or with the saccharin transit time (STT) test (Anderson and Lundqvist 1977).

In the STT test, a particle of saccharin is placed just behind the anterior end of the inferior turbinate and the patient is asked to sit quietly with their head tilted forward and not to sniff, sneeze, eat, or drink. The time taken to the first perception of the sweet taste is the STT. The average STT for an adult free from nasal disease would be 7 to 15 min. Patients who have a saccharin clearance time greater than 20 min have disturbed nasal mucociliary transport (Anderson and Lundqvist 1977; Lale et al. 1998). Also, a blue dye can be included in the saccharin. When the patient tastes the saccharin, the test is stopped, and the transfer can be confirmed by direct viewing of the blue color on the pharyngeal wall. This is called a saccharin-dye test (Dahl and Mygind 1998).

2.7.3 Electron microscopy

Transmission electron microscopy (TEM) is widely used for studying the ultrastructure of cilia. Tubulus anomalies, compound cilia, dynein defects, radial spoke defects, and disorientation of the cilia can all be investigated using TEM. Much larger populations of cilia can be studied with scanning electron microscopy (SEM). SEM reveals a three-dimensional impression of mucosal surfaces, and it is a suitable method when ciliary orientations or lengths are evaluated (Toskala et al. 1994).

2.7.3.1 Scanning electron microscopy

Two major components of SEM are the electron column and the control console. The electron column comprises an electron gun and electron lenses that influence the path of the electrons traveling down an evacuated tube. The control console comprises a cathode ray tube, a viewing screen, knobs, and a computer keyboard. (Goldstein et al. 2003).

The electron gun accelerates electrons to energy in the range of 0.1 keV to 30 keV. Electron lenses are used to demagnify the spot size of the electron beam to get better image resolution. The beam emerges from the final lens into the specimen chamber and interacts with the specimen generating signals used to form an image. The deflection system, which comprises two pairs of electromagnetic scan coils, causes the beam to move to a series of discrete locations along the line and then another line below, and so on, until a rectangular raster is generated on the specimen. Simultaneously, the same scan generator creates a similar raster on the viewing screen. The magnification is also controlled by the deflection system. The electron detector collects the signals and converts them to point-to-point intensity changes on the viewing screen and produces an image (Goldstein et al. 2003).

2.7.3.2 Sample preparation for scanning electron microscopy

Samples from the nasal mucosa are first taken in the form of mucosal biopsies with forceps and then washed. The fixation of the samples is usually carried out using solutions that contain glutaraldehyde (Karnovsky 1965). The water in the biological samples must be removed before SEM. The removal of water must be achieved with minimal extraction (difficult) and minimal distortion of the specimen (possible). There are several ways to dehydrate the specimens (Goldstein et al. 2003). The most common method of dehydrating specimens for SEM is critical point drying (Cohen 1979). A highly volatile liquid, hexamethyldisilazane (HMDS), is a time-saving and inexpensive alternative to critical point drying. Tissues prepared with HMDS are fixed in 1% glutaraldehyde, dehydrated through a graded ethanol series, immersed in HMDS for 5 to 15 minutes, and then air dried (Nation 1983). The specimens are then attached on supporting specimen stubs, for transfer to and examination in SEM, using various glues, such as carbon glue. The stubs must be conductive and are made of metal. It is important to mark the stub with a code to identify the sample. The stub is then dried over night. Finally, the specimen is coated in a sputter coater with a thin layer of conductive material, such as gold, to avoid sample charging during SEM (Goldstein et al. 2003).

2.7.3.3 Findings of respiratory epithelium in scanning electron microscopy

Epithelial metaplasia, loss of ciliated cells, ciliary disorientation, microvilli, and short cilia are all possible epithelial findings in SEM. These findings have all been found to correlate with poor mucociliary transport rate (Toskala et al. 1995b).

2.7.3.4 Epithelial metaplasia

The epithelium in the nasal mucosa can change as a reaction to external stimuli (Hilding 1932). Among these stimuli are the flow of inspired air, its humidity and temperature, the inhalation of dust particles, chemical products, and trauma. Pseudostratified epithelium is replaced by fully developed stratified squamous epithelium through a sequence of epithelial alterations (Boysen 1982). Metaplasia is mainly found in those parts of the nasal mucosa exposed to external agents. The substitution of one type of epithelium for another is an indication that one type is better adapted to certain circumstances (Augusto et al. 2001). Squamous metaplasia starts at an early age and becomes more prominent with increasing years. The changes in surface features during metaplastic transformation include an increase in the number and shortening of the microvilli, the appearance of microridges in squamous epithelium, and alterations in mucus secretion (Boysen 1982).

2.7.3.5 Ciliary disorientation

The parallel beat direction of cilia is important for effective mucociliary function. Internationally accepted normal values for ciliary disorientation are < or = 20 degrees; values of 20 to 35 degrees indicate increased disorientation; and values > 35 degrees represent a random orientation (Jorissen and Willems 2004). Ciliary disorientation is common in primary ciliary dyskinesia (PCD) (Rautiainen et al. 1990), but it can also be secondary due to inflammation (Rayner et al. 1995).

2.8 Various factors affecting cilia and mucociliary function

PCD, or immobile cilia syndrome, is an inherited disorder of dysfunctional cilia that appears as severely impaired muciliary clearance. In most cases, the inherited defect of the disorder is in the dynein arms of the axonemal microtubules, which may result in the absence of the outer dynein arms, the inner dynein arms, or both. PCD patients typically have chronic airway and recurrent middle ear infections, and approximately 50% of PCD patients have situs inversus. Many PCD patients, both male and female, also suffer from infertility. Kartagener syndrome is a subgroup of PCD marked by the triad of chronic sinusitis, situs inversus, and bronchiectasis (Gudis et al. 2012a).

The nasal mucosa of the patients with CRS shows loss of ciliated cells, ciliary disorientation, and epithelial metaplasia (Toskala et al. 1995a). Mucociliary clearance is decreased in CRS resulting in stasis of sinonasal secretions and subsequent chronic infection and/or persistent inflammation (Chen et al. 2006).

The literature is contradictory regarding mucus viscosity and basal ciliary beat frequency in CRS. (Gudis et al. 2012b) For example, recent studies have suggested that a subset of patients with CRS have a blunted ciliary response to environmental stimuli (Chen et al. 2006).

There have been previous studies that show the loss of cilia is more common in both AR and NAR compared with healthy controls (Watanabe and Kiuna 1998; Gindros et al. 2009). Also, abnormalities of ciliary ultrastructure have been observed in both conditions (Maurizi et al. 1984). Patients with septal deviation have decreased mucociliary activity on both sides of the deviation, the least activity being on the side opposite the deviation (Kamani et al. 2006). More severe loss of cilia has also been reported on the concave side (Jang et al. 2002).

Common bacterial pathogens, such as pseudomonas aeruginosa, haemophilus influenza, streptococcus pneumoniae, and staphylococcus aureus, produce specific toxins that impair ciliary motion and destroy cilia and ciliated cells (Gudis et al. 2012b). Viral infections can cause a reduction in mucociliary transport rate that lasts for weeks. This reduction is due to the loss of cilia and ciliated cells, rather than to ultrastructural anomalies in the cilia (Wilson et al. 1987; Rautiainen et al. 1992). Studies of cilia from the airways of smokers have consistently showed a decreased number of cilia (Gudis et al. 2012b). Nasal mucociliary clearance has also been shown to be reduced in smokers (Stanley et al. 1986).

Topical corticosteroids have been found to reduce ciliary beat frequency in vitro, but short-term use of these drugs does not affect mucociliary transport in vivo (Stanley et al. 1985; Duchateau et al. 1986). The clinical concentration of the topical nasal decongestant oxymetazoline, 0.05%, has no obvious inhibitory effect on human nasal CBF in vitro, but higher concentrations induce a significantly lower CBF (Zhang et al. 2008). Prolonged application of nasal vasoconstrictors causes rhinitis medicamentosa, which causes epithelial damage and loss of ciliated cells (Knipping et al. 2007).

In cystic fibrosis, ciliary activity and ultrastructure are normal, but abnormal viscous mucus seriously affects mucociliary clearance and results in chronic infections (Rossman et al. 1984). In Sjögren's syndrome, the drying of mucous membranes results in poor mucociliary function (Takeuchi et al. 1989).

2.9 The effect of inferior turbinate surgery on cilia and mucociliary function

2.9.1. The effect of inferior turbinate surgery on ciliated epithelium

There have been some previous electron and light microscopy studies that have evaluated the effect of inferior turbinate surgery on ciliated epithelium. Most of them have been only descriptive lacking statistical analysis with relatively small numbers of specimens examined.

Talaat et al. treated non-allergic hypertrophic rhinitis patients with submucosal electrocautery and found restoration of normality for the epithelium with reappearance of cilia in small areas of the epithelium one month postoperatively (Talaat et al. 1987). Elwany et al. treated non-allergic patients with hypertrophic rhinitis with bipolar submucosal diathermy using a radiofrequency unit. In TEM examination one year postoperatively, the specimens showed intact ciliated epithelium with goblet cells (Elwany et al. 1999). Inoye et al. investigated patients with perennial allergic rhinitis. In SEM examination before the KTP laser operation, they found a decrease of ciliated cells, a shortening of cilia, and an increase of goblet cells. After 4 to 10 weeks postoperatively, the mucosas had no ciliated cells or goblet cells and were covered with squamous epithelium. Findings suggestive of regeneration of squamous epithelium were also recognized (Inoye et al. 1999). Bergler et al., in turn, examined the effect of argon plasma laser coagulation. After three months of treatment, electron microscopic findings showed a totally regenerated ciliary epithelium, which was already present preoperatively (Bergler et al. 2001). In a study by Coste et al., ciliated cells were the most abundant epithelial cell type before and after RFA surgery, although in five cases, moderate numbers of squamous cells were detected on either day 7 or day 60 (Coste et al. 2001). Sargon et al. found no ultrastructural pathology in the number and morphology of the cilia in SEM and TEM examinations either preoperatively or 2 months after the RFA treatment (Sargon et al. 2009). Recently, Neri et al. treated 18 patients carrying out a total removal of the mucosa of the medial and inferior portions of the inferior turbinate with the microdebrider. A complete re-epithelisation of nasal mucosa with well differentiated columnar ciliated epithelium was detected at 4 months postoperatively (Neri 2016).

Cassano et al. compared laser-assisted turbinoplasty and endoscopic turbinoplasty. At both one and three-month postoperative visits, the number of altered ciliated cells had increased in the laser-assisted turbinoplasty-treated group but had decreased in the endoscopic turbinoplasty-treated group (Cassano et al. 2010). Garzaro et al. compared RFA and partial inferior turbinectomy. In preoperative samples, findings by TEM showed a normal appearance of the epithelium with a preserved number of cilia. Six months postoperatively, however, ultrastructural analysis revealed a loss of ciliated cells in the partial inferior turbinectomy group, whereas normal ciliated epithelium was found in the RFA group (Garzaro et al. 2012). Gindros et al. compared ultrasound turbinate reduction, submucosal monopolar electrocautery, and RFA and their effects on mucosa. In preoperative TEM examination, they found severe metaplasia of the nasal epithelium, evident stratification in the epithelium, loss of cilia, and an increased number of goblet cells. After electrocautery and RFA, metaplastic epithelium was observed in most specimens. Only after the use of ultrasound did the specimens show islands with ciliated cells at six months postoperatively. They concluded that epithelial changes due to chronic hypertrophic rhinitis do not significantly improve after turbinate reduction, and that only after ultrasound procedure does some regeneration of ciliated epithelium occur (Gindros et al. 2008).

2.9.2 The effect of inferior turbinate surgery on mucociliary function

There have been many previous inferior turbinate surgery studies where the effect of the techniques on mucociliary transport has been evaluated with STT. The results of the studies in up to 12 months follow-up are presented in **Table 1**.

There have also been some previous comparative studies and studies with longer follow-ups that are not shown in the table. Passali et al., for example, compared the older techniques of turbinectomy, CO_2-laser, cryotherapy, electrocautery, submucosal resection, and submucosal resection with lateral displacement over a six-year follow-up period. Only the patients with submucosal resection with or without lateral displacement achieved normalized STT (Passali et al. 2003). Chen et al. evaluated the long-term efficacy of MAIT with lateralization compared with submucosal resection. In both groups, STT was significantly decreased compared with preoperative values at 1, 2, and 3 years after surgery (Chen et al. 2008). Kizilkaya et al. compared RFA and MAIT. In their study, STT showed no significant post-treatment variation between the groups three and six months postoperatively. Preoperative values were not reported in the study (Kizilkaya et al. 2008). Liu et al. compared MAIT and RFA over a three-year follow-up period. Compared with preoperative values, the STT for the MAIT group significantly decreased from six months to three years after surgery. In the RFA group, the STT significantly improved from six months to one year postoperatively compared with the preoperative levels. However, in the RFA group, no improvement in the STT from two to three years was noted (Liu et al. 2009). In a study by Neri et al. where the inferior and medial portions of the inferior turbinate above the periostium were shaved using the microdebrider, STT was found to decrease compared with preoperative values at 4 months and 4 years after the procedure (Neri et al. 2016).

Table 1. Postoperative changes in STT in the previous studies in up to 12 months follow-up.

Author	Technique	Follow-up time (months)				
		1	2	3	6	12
Sapci 2003	Partial turbinectomy			+/-		
Salzano 2009	Partial turbinectomy		+/-			
Garzaro 2012	Partial turbinectomy				+	
Romano 2015	Partial turbinectomy			+/-		
Cavaliere 2005	Submucosal resection	+/-				
Veit 2016	Submucosal resection			-		-
Salzano 2009	Electrocautery		+			
Bergler 2001	Argon plasma coagulation	+/-				
Sapci 2003	CO2-laser			+		
Vijayakumar 2016	KTP-laser	+		+/-		
Min 1996	Diode laser				+/-	
Janda 2000	Diode laser					+/-
Parida 2013	Diode laser			+	+/-	
Veit 2016	Diode laser			+		-
Coste 2001	RFA		-			
Rhee 2001	RFA		+/-			
Sapci 2003	RFA			+/-		
Cavaliere 2005	RFA	+/-				
Salzano 2009	RFA		+			
Garzaro 2012	RFA				+	
Rosato 2016	RFA	+/-	+/-	+/-		
Veit 2016	RFA			-		-
Romano 2015	MAIT			+/-		

STT = saccharin transit time; +/- = preserved; + = prolonged; - = decreased.

2.10 Eustachian tube

ET is responsible for maintaining aeration, clearing secretions, and preventing gastroesophageal and sound reflux within the middle-ear cavity. The ET courses from the middle-ear cavity (proximally) to the nasopharynx (distally). The distal two thirds comprise a cartilaginous skeleton, whereas the proximal one third has an osseous skeleton. The osseous portion is normally patent and does not open and close dynamically as does the cartilaginous portion. The cartilaginous portion of the ET remains closed in its resting state and only opens for brief periods of time. When the ET is closed, gases diffuse out of the middle-ear into the mucosal lining and capillaries forming negative pressure that continues to build until the ET periodically opens. The ET remains closed until the peritubular musculature dilates the tube open during deglutition or yawning. There are four peritubular muscles. The most important muscle for the opening of the ET is the tensor veli palatini. When the ET opens, nasopharyngeal air, generally at atmospheric pressures, is exchanged with the middle-ear gases allowing for an equalization of pressure on both sides of the tympanic membrane. The closure of the cartilaginous tubal lumen proceeds progressively toward the nasopharyngeal orifice. When the tensor veli palatine muscle relaxes it forms a muscular pumping mechanism that, together with mucociliary function, removes the secretions from the middle-ear (Kivekäs et al. 2015). Small amounts of liquid placed into the middle ear are transported to the nasopharynx by mucociliary function, whereas large amounts are transported both by the mucociliary system and muscular function (Seppä 1993).

2.11 Eustachian tube dysfunction

ETD usually refers to a problem with the ventilatory function of the ET and is defined by symptoms and signs of pressure dysregulation in the middle ear (Schilder et al. 2015). The prevalence of chronic ETD in Western countries has been evaluated to be 1% in the adult population (Browning and Gatehouse 1992). A recent consensus statement by Schilder et al. defined three subtypes of ETD: dilatory ETD, baro-challenge-induced ETD, and patulous ETD (Schilder et al. 2015). In most cases, the problem is dilatory ETD caused by mucosal inflammation and edema in the ET lumen (Poe et al. 2001). It has been reported that viral upper respiratory infections (Doyle et al. 2000), allergic rhinitis (Ohrui et al. 2005), chronic sinusitis (Stammberger 1986; Stoikes and Dutton 2005), and upper gastroesofageal reflux disease (Brunworth at al. 2014) can cause mucosal inflammation leading to dilatory ETD. Dilatory ETD can also be caused by muscular problems leading to dynamic obstruction or result from anatomical obstruction caused by adenoid hypertrophy, nasopharyngeal cysts, and malignant masses (Kivekäs et al. 2015; Schilder et al. 2015). Typical symptoms of ETD include 'aural fullness' or 'popping' or discomfort/pain. Patients may also report pressure, a clogged or 'under water' sensation, crackling, ringing, autophony, and muffled hearing. In baro-challenge-induced ETD, symptoms of aural fullness, popping, or discomfort/pain occur or are initiated under conditions of alteration to the ambient pressure. Patients are typically asymptomatic once they return to ground level. Patulous ETD presents with symptoms of aural fullness and autophony and is thought to be caused by an abnormally patent ET (Schilder et al. 2015). In dilatory ETD, the negative middle-ear pressure may also lead to other sequelae, such as retraction pocket formation, tympanic-membrane perforation, atelectasis, cholesteatoma, serous otitis media, and chronic otitis media (Kivekäs et al. 2015).

2.12 Examination of Eustachian tube dysfunction

Many subjective and objective methods have been reported in the assessment of ET function that include otoscopic appearance, Valsalva and Toynbee tests, tympanometry, endoscopic examination of the nasopharyngeal orifice, the forced response test, the inflation-deflation test (Kivekäs et al. 2015; Schilder et al. 2015), tubomanometry (Liu et al. 2016), and sonotubometry (van der Avoort et al. 2005). Due to the complexity of the functional anatomy and physiology of the ET, however, there is still no diagnostic "gold standard" for ETD (McCoul et al. 2012; Smith and Tysome 2015).

2.12.1 Tympanometry

In tympanometry, middle ear pressure is measured with an electroacoustic impedance meter that allows the precise evaluation of eardrum mobility and helps to assess ET function. The tympanometric curves are traditionally classified as follows (Liden 1969; Jerger 1970): type A, normal ET function; type B, flat tympanogram characteristic of the presence of fluid in the middle ear or eardrum perforation; or type C, peak at very negative pressure, typically 150 dPa, which may be indicative of eardrum retraction and ETD. Tympanometric peak pressure (TPP) is the peak admittance in the tympanogram and an indirect measurement of middle ear pressure.

2.12.2 Eustachian Tube Dysfunction Questionnaire

McCoul et al. have developed the Eustachian Tube Dysfunction Questionnaire (ETDQ-7), which is an instrument for the assessment of symptoms related to the obstructive dysfunction of the ET and treatment outcome. The ETDQ-7 comprises 7 questions and a 7-item Likert-type scale, with a response of 1 indicating no problem and 7 indicating a severe problem. The total score is divided by 7 to give an overall score ranging from 1.0 to 7.0 (**Table 2**). The ETDQ-7 is the only patient-reported outcomes tool to have undergone initial validation studies. It can provide a more precise estimate of a disease burden and may yield information not readily identified by traditional clinical methods (McCoul et al. 2012).

2.13 The role of sinonasal factors in Eustachian tube dysfunction

In a prospective series of 167 patients with adult-onset otitis media with effusion (OME), Finkelstein et al. found evidence of CRS, particularly in the ethmoids, in 66% of cases (Finkelstein et al. 1994). In a retrospective study by Stoikes et al., symptoms of ETD were found to improve or resolve in the majority of patients undergoing endoscopic sinus surgery (Stoikes et al. 2005).

Low and Willatt evaluated the relationship between middle ear pressure and a deviated nasal septum. They found that middle ear pressure ipsilateral to the obstructed nasal passage was negatively correlated with the degree of asymmetry of the patencies of the two nasal passages. Middle ear pressure improved in both ears after septal surgery. They postulated that the postnasal airflow turbulence associated with a deviated nasal septum may lead to ETD (Low and Willatt 1993). Deron et al., in turn, found that septum deviation has as much influence on the passive opening pressure of the ET on the deviated side as on the non-deviated side (Deron et al. 1995).

In AR, nasal mucosal oedema can affect the ET by direct expansion to the nasopharyngeal ET orifice or through nasal obstruction. Nasal obstruction can then lead to an increase in negative pressure in the nasopharynx, resulting secondarily in decreased ET patency, disturbance of its ciliary epithelium function, and obstruction of the ET, with a subsequent increase in the negative pressure of the middle ear cavity (Pelikan 2008). There have been many studies that support the role of AR in the development of ETD and OME, whereas there have only been a few reports on the role of NAR (Quaranta et al. 2014). Most of these studies deal with children and evaluate the relationship between AR and OME among them (Kreiner-Möller et al. 2012, Roditi et al. 2016). In a recent large American retrospective analysis of cross-sectional national databases, the presence of AR was found to significantly increase the odds of OME, ETD, or tympanic membrane retraction (odds ratio = 4.2) in children aged 6 years or older (Roditi et al. 2016). In a prospective Mexican study, both children and adults with mostly perennial AR had more negative values of tympanometric peak pressure than the controls, indicating a higher risk of ETD (Lazo-Saenz et al. 2005). Ohrui et al. explored whether there is an association between AR and ear pain experienced in hypobaric chamber training in the Japanese Air Self-Defense Force. They hypothesized that the increased incidence of ear pain may be due to the increased incidence of ETD associated with AR. Trainees with AR complained of ear pain significantly more often during the allergy season than trainees without AR (Ohrui et al. 2005).

There have been a few previous studies that have compared the incidence of ETD between patients with an allergic cause of nasal obstruction and patients with a non-allergic cause of nasal obstruction. In a Danish birth cohort study of 291 children in the sixth year of life, OME was associated with AR (odds ratio = 3.4), but not with NAR or mucosal swelling (Kreiner-Möller et al. 2012). Bakhshaee et al. investigated the ET function of patients with nasal obstruction due to nasal polyposis. The ET function in the patients with polyposis was disturbed. However, regression analysis revealed that the infection and allergic inflammation associated with polyposis have more important roles in ET function than the obstructive nature of the disease (Bakhshaee et al. 2016).

In their randomized prospective placebo-controlled trial, Gluth et al. evaluated the efficacy of nasal steroid spray in treating the tympanometric signs and symptoms of ETD. They found no statistically significant difference in the normalization of abnormal tympanometric signs or in the overall post study symptom score between the active treatment arm and placebo (Gluth et al. 2011).

The relationship between the chronic nasal obstruction caused by inferior turbinate enlargement and ETD and the effect of inferior turbinate surgery on ETD have not been evaluated in the previous literature.

2.14 Placebo effect

Based on recent studies of the neurobiology of placebo and nocebo effects, the psychosocial context around the patient and the therapy, which represents the ritual of the therapeutic act, may change the biochemistry and the neuronal circuitry of the patient's brain. This context includes the physical properties of the treatment, the characteristics of the healthcare setting, the sight of health professionals (words, attitudes, and behaviours), medical instruments, and the interaction between patient and physicians. The nocebo effect is the opposite to the placebo effect because it involves the pathogenic consequences of placebo administration within a negative psychosocial context (Frisaldi et al. 2015).

The placebo effect can be triggered by a variety of psychological mechanisms, such as expectation, conditioning, and reward, which can, in turn, be modulated by other factors, such as anxiety, desire, motivation, memory, self-efficacy, and reinforcing feedback. During medical treatment, the patient has different expectations about the therapeutic outcome. The patient also anticipates the possible positive or negative effects of the therapy (Frisaldi et al. 2015). This anticipatory process, in turn, triggers internal changes that result in such experiences as placebo analgesia, where the mere belief that one is receiving an effective analgesic treatment can reduce pain in itself or enhance the analgetic benefit of a real treatment. In contrast, negative treatment expectancy can abolish the analgesic effect (Bingel et al. 2011; Frisaldi et al. 2015). Put simply, a positive expectation creates a positive response and vice versa.

Placebo analgesia is based on the activation of the endogenous opioid system (Benedetti and Amanzio 2013). It has been shown in many neuroimaging studies that placebo analgesia activates the same brain region as opioids (Petrovic et al. 2002; Bingel et al. 2011). Cholecystokinin has been found to have an inhibitory effect on opioids, and thus inhibiting placebo analgesia. Cholecystokinin is also involved in nocebo hyperalgesia (Frisaldi et al. 2015). In addition to pain, the placebo has also been studied in Parkinson's disease where it induces the release of dopamine in the striatum (Benedetti and Amanzio 2013).

Taking into account the whole ritual of the therapeutic act associated with surgical procedures, it can be thought that surgery has the potential to produce powerful placebo effects, which has also been proven in previous studies (O'Malley et al. 2002; Sihvonen et al. 2013).

Overall, the placebo effect highlights the important role of therapeutic rituals as well as the expectations and experiences of patients in the overall therapeutic outcome.

2.15 A placebo-controlled study

Randomized controlled trials (RCT) are scientific studies that try to reduce bias when testing a treatment (Zwarenstein et al. 2008). RCTs are considered to be the best way to evaluate healthcare interventions. The subjects in the RCT are randomly allocated to either the group receiving the treatment under examination or to a control group. The subjects then receive either a previously tested treatment (positive-control study) or a placebo treatment (placebo-controlled study).

The majority of RCTs are parallel group trials, where each participant is randomized to one of the intervention arms. Crossover trials, where each participant is exposed to each intervention in a random sequence, are the second most common trial design (Hopewell et al. 2010). RCTs can also be classified as "explanatory" or "pragmatic." Explanatory RCTs test efficacy in a research setting with highly selected participants and under highly controlled conditions. As a result, explanatory RCTs have a high internal quality. In contrast, pragmatic RCTs test effectiveness under usual practice circumstances, and therefore they have high generalizability or external validity (Zwarenstein et al. 2008).

The use of placebos is a standard control component of most clinical trials. In placebo-controlled studies, the placebo is used to find out the true treatment effect of the examined treatment. The true treatment effect is the difference in improvement between the intervention group and the control group (placebo effect) (Powell et al. 2001). Common examples of inert placebo treatments are a pill containing only sugar and sham surgery where no efficacious surgical procedure is really done. In a single-blinded study (Bran et al. 2013), the subjects do not know whether they are treated actively or not. In a double-blinded study, in addition to patients, the physicians are also unaware of which treatment is given to the patients (Powell et al. 2001). This prevents the physicians from affecting the expectations of the patients, or inadvertently informing the patients of their group with their own behaviour (Bran et al. 2013).

The placebo effect is very important in surgery. During recent years, in ortopaedics for example, placebo-controlled trials have been published that have shown that placebo/sham surgery is as effective as certain common arthroscopic procedures, and have therefore questioned the use of such procedures in clinical practice (O'Malley et al. 200; Sihvonen et al. 2013). The presence of the placebo effect has already been shown in inferior turbinate surgery (Powell et al. 2001; Nease and Krempl 2004; Bran et al. 2012). These facts highlight the further need for randomized, placebo-controlled studies to adequately examine the true treatment effects of inferior turbinate surgery techniques.

3 AIMS OF THE STUDY

1. To evaluate the relationship between chronic nasal obstruction caused by inferior turbinate enlargement and ETD-related symptoms using the ETDQ-7 as an assessment method (I).

2. To evaluate the effects of RFA, diode laser, MAIT, and placebo procedures on ETD-related symptoms using the ETDQ-7 as an assessment method (II).

3. To compare RFA, diode laser, and MAIT techniques in the treatment of chronic nasal obstruction caused by inferior turbinate enlargement, and to compare these techniques with a placebo procedure (III).

4. To evaluate the effects of RFA, diode laser, and MAIT techniques on ciliated epithelium and mucociliary function (IV).

4 MATERIALS AND METHODS

4.1 Patient selection

The study was carried out at Tampere University Hospital, Tampere, Finland, between February 2014 and September 2017. A total of 104 consecutive adult patients with enlarged inferior turbinates due to persistent year-round rhinitis were enrolled in this study. An additional 40 subjects were enrolled for healthy controls in Paper I. The patients with enlarged inferior turbinates presented symptoms of bilateral nasal obstruction related to inferior turbinate congestion that had not responded to a three-month trial of appropriate treatment with intranasal corticosteroids. Patients with significant nasal septum deviation affecting the nasal valve region, internal/external valve collapse/stenosis, chronic rhinosinusitis with or without polyposis, previous nasal surgery, sinonasal tumor, severe systemic disorder, severe obesity, or malignancy were excluded.

CBCT imaging (Planmeca Max, Planmeca, Helsinki, Finland) was used to exclude patients with chronic rhinosinusitis from the study. Serum-specific IgE level measurements were used to identify patients with allergic sensitization. Allergic sensitization was defined as a specific IgE > 0.35 for any common airborne allergen (cat, dog, horse, birch, grass, mugwort, D. pteronyssinus, and molds).

The definition of inferior turbinate enlargement was based on persistent bilateral symptoms, a finding of bilateral swelling of the inferior turbinate in nasal endoscopy, and the evident shrinking of both turbinates in a decongestion test. The nasal response to the topical vasoconstrictor 0.5% xylometazoline hydrochloride (Nasolin, Orion, Finland) in both nasal cavities 15 minutes before obtaining the second measurement was evaluated objectively using acoustic rhinometry (Acoustic rhinometer A1, GM instruments Ltd, Kilwinning, UK). An improvement of less than 30% in anterior nasal cavity volume (V2–5 cm) in one or both nasal cavities was considered normal and those patients were excluded from the study. The limit value of 30% was chosen according to the previous literature (Grymer et al. 1991; Tomkinson and Eccles 1996; Fisher 1997).

4.2 Eustachian tube dysfunction-related symptoms in chronic nasal obstruction caused by inferior turbinate enlargement (I)

The first 40 consecutive patients aged < 45 years from the total 104 patients with inferior turbinate enlargement formed Group 1 (inferior turbinate enlargement). Group 2 (controls) were 40 healthy subjects without any clinical signs or history of persistent nasal obstruction or other nasal problems. The group comprised volunteer medical students and health care personnel. The appearance of their inferior turbinates was normal in nasal examination. The subjects in Group 2 did not undergo rhinometric evaluation or CBCT. Otherwise, the clinical exclusion criteria were the same as in Group 1. The groups were matched by age and sex. After signing the informed consent, all the subjects underwent an otorhinolaryngologic examination with tympanometry included and then filled out the ETDQ-7.

4.3 Randomization (II, III, IV)

Patients were consecutively blinded and randomized into placebo, RFA, diode laser, and MAIT groups in a ratio of 1:2:2:2 using Minim, a free MS-DOS program that randomizes patients to treatment groups by the method of minimization. Proportional numbers of patients with allergic sensitization were kept similar in each group. Age and sex distributions were also kept similar for each group.

4.4 Surgical procedures (II, III, IV)

Before surgery, 6 patients withdrew from the study, and so a total of 98 patients underwent the placebo, RFA, diode laser, or MAIT procedure. All procedures were performed in similar circumstances at the day surgery department of the hospital's ENT clinic. All the procedures were performed by the same surgeon (T.H). The staff of the day surgery department was instructed to avoid all communication before and during the operation, as well as during post-operative care, that might reveal the group of the patient. All the alternative surgical devices were available in the operation room. The procedures were carried out under local anesthesia with the patient's eyes covered.

First, the inferior turbinate was topically anesthetized using cotton strips with a mixture of lidocaine 40 mg/ml (Lidocain, Orion, Finland) and 2 to 3 drops of epinephrine 0.1 % in 5 to 10 ml of lidocaine. The local anesthetic (Lidocain 10 mg/ml c. adrenalin 10 μg/ml, Orion, Finland) was then applied to the medial portions of both inferior turbinates. Before the procedures, small (2 mm to 3 mm in diameter) nasal mucosal biopsies were taken from the anterior medial portions of the inferior turbinates of all the patients in the placebo group and from the first 66 patients in the treatment groups, who formed a study population in Paper IV. All the procedures were performed under the direct vision of a straight, 4 mm-diameter, 0-degree endoscope (Karl Storz, Germany). In all the groups with every technique, the treatment was given to the medial sides of the anterior halves of the inferior turbinates. Short-term (until next morning) nasal packing (Ivalon, Fabco, New London, Connecticut) was applied only if active bleeding developed during the surgery.

4.4.1 Radiofrequency ablation

The RFA treatment was carried out with a radiofrequency generator (Sutter RF generator BM-780 II). A “Binner” bipolar needle electrode was inserted into the medial submucosal tissue of the inferior turbinate. The upper and lower parts of the medial side of the anterior half of the inferior turbinate were treated for 6 s at 10 W output power in three areas.

4.4.2 Diode laser

The diode laser treatment was performed with a FOX Laser (A.R.C. LASER GmbH, Nuremberg, Germany). The settings were as follows: wavelength of 980 nm, output power of 6 W in continuous-wave mode, and laser delivery by a 600 μm fiber using “contact” mode. Four parallel stripes were made on the mucosa by drawing the fiber from the posterior to the anterior direction along the medial edge of the anterior half of the inferior turbinate.

4.4.3 Microdebrider assisted inferior turbinoplasty

In the MAIT treatment, a 2.9 mm-diameter rotatable microdebrider tip (Medtronic Xomed, Jacksonville, Florida) was firmly pushed toward the turbinate bone until it pierced the mucosa of the anterior face of the inferior turbinate. Next, a submucosal pocket was dissected by tunneling the elevator tip in an anterior-to-posterior and superior-to-inferior sweeping motion. Once an adequate pocket had been created, resection of the stromal tissue was carried out by moving the blade back and forth in a sweeping motion, with the system set at 3000 rpm using suction irrigation.

4.4.4 Placebo

In the placebo procedure, small (2 mm to 3 mm in diameter) nasal mucosal biopsies were first taken from the anterior medial portions of the inferior turbinates, causing minor bleeding. Next, a radiofrequency tissue ablation device was turned on repeatedly near the patient, but without the needle electrodes of the device touching the patient; the patient could only hear the acoustic tone of the device. During this sound deception, a suction tube and a nasal endoscope were moved lightly in both sides of the nose for a couple of minutes in order to convince the patients that they had undergone surgery.

4.5 The effect of inferior turbinate surgery on ear symptoms (II)

Of the 98 patients who underwent one of the 4 alternative procedures, 72 patients formed the population in Paper II, which evaluated the effect of various inferior turbinate surgery techniques on ETD-related symptoms. All the patients were evaluated prior to surgery and three months subsequent to the surgery. All clinical examinations were performed by the same examiner (T.H.), who was also the operator and not blinded to the patients' groups. The patients filled out the

ETDQ-7 and tympanometry was also performed both before the procedure and during the control visit at three months. During the control visit, the patients filled out the questionnaire before meeting the examiner.

4.6 A prospective, randomized, placebo-controlled study of inferior turbinate surgery (III)

All 98 patients who underwent one of the 4 alternative procedures formed the population in Paper III, which compared RFA, diode laser, and MAIT techniques in the treatment of chronic nasal obstruction caused by inferior turbinate enlargement and compared these techniques with a placebo procedure. After the operation, none of the patients were given medical treatment, such as analgesics, nasal steroids, and nasal decongestants. The patients were given a 100 mm visual analogue scale (VAS) questionnaire that had first been filled out during the preoperative visit. They were asked to mark on the line the point that they felt represented their perception of their current state regarding post-operative nasal symptoms that included severity of nasal obstruction (not obstructed – very obstructed), discharge (no discharge – much discharge), crusting (no crust – much crust), and pain (no pain – much pain). The questionnaire was to be filled out daily for the first week, and then after two, three, and four weeks post-operatively. They were instructed to return the questionnaire by post one month after the operation.

All the patients were evaluated prior to surgery and three months subsequent to the surgery. All clinical examinations were performed by the same examiner (T.H) who was also the operator and not blinded to the patients' group. The patients filled out the VAS questionnaire regarding nasal symptoms during both visits. They were asked to mark on the line the point that they felt represented their perception of their current state. Acoustic rhinometry was also performed both before the surgery and during the control visit at three months. During the control visit, the patients filled out the questionnaire before meeting the examiner.

4.7 The effect of inferior turbinate surgery techniques on ciliated epithelium and mucociliary function (IV)

Before the procedures, preoperative samples for SEM were taken in the form of small (2 mm to 3 mm in diameter) nasal mucosal biopsies from the anterior medial portion of the left inferior turbinate of the first 66 consecutive patients in the RFA, Diode laser, and MAIT groups. These patients formed a study population in Paper IV that evaluated the effects of the three examined techniques on ciliated epithelium and mucociliary function. All the patients were evaluated prior to surgery and three months subsequent to the surgery. During both visits, nasal mucociliary transport was evaluated with STT by placing a saccharine particle on the anterior portion of the inferior turbinate, and the time until the patient tasted sweetness was measured. Postoperative samples for SEM were taken under local anesthesia from the anterior medial portion of the left inferior turbinate of every patient at the control visit.

The samples for SEM were first immersed in 1% glutaraldehyde for fixation. Then, the samples were dehydrated in a graded alcohol series. Finally, the samples were immersed in hexamethyldisilazane for 15 min at room temperature and air-dried overnight. The samples were glued on the SEM specimen stubs with carbon glue. To avoid sample charging during the SEM studies, the specimens were coated for 3 min with gold using Edwards S150 sputter coater in an argon atmosphere. In total, 4 to 8 randomly selected fields per sample were viewed and imaged with a Philips XL30 SEM at primary magnification of x2000.

After SEM, the quality of both the pre- and postoperative SEM image series of 44 patients, out of 66, were of a technically acceptable quality to be further evaluated. The main reasons for sample rejection were fibrin or other impurity covering the surface, glue covering the surface, broken sample and sample wrong side up, and a charged sample. The pre- and postoperative image series of every patient were put into separate folders. Then, the folders were coded and evaluated by five examiners (T.H., I.K., M.H., M.V., M.R.), who did not know which technique had been used or whether the pictures were pre- or postoperative and were therefore blinded. The evaluated parameters were the number and amount of cilia, non-ciliated pseudostratified columnar cells, squamous metaplasia, microvilli, goblet cells, and disorientation of the cilia. The parameters were graded as follows:

0 = no; 1 = a little; 2 moderately; 3 = a lot. The mean of the grades given to an image series by the five examiners was used as a score of one image series.

4.8 Statistical analysis

IBM SPSS Statistics 22.0 was used for the statistical analyses. Non-parametric data was statistically processed using the Wilcoxon signed-rank test, Mann-whitney *U* test, and Kruskal-Wallis test. In the cases of parametric data, the analysis of the differences between the groups was carried out by a one-way ANOVA and a three-way ANCOVA. Chi-square test was used to calculate the associations between various categorical variables. Correlations were evaluated using Pearson's correlation and Spearman's rho.

4.9 Ethical considerations

The study protocol (R13144) was approved by the Ethics Committee of Pirkanmaa Hospital District. All subjects provided written informed consent. The work was carried out according to the Helsinki declaration.

5 RESULTS

5.1 Eustachian tube dysfunction-related symptoms in chronic nasal obstruction caused by inferior turbinate enlargement (I)

There were no significant differences found regarding sex or age between the groups. Abnormal tympanometry results (two type B with middle ear effusions were also found in the otoscopies, and one type C with tympanic membrane retraction was also found in the otocopy) were observed in 3 ears (3.8%) in Group 1 (inferior turbinate enlargement). Only A curves were found in Group 2 (controls). The differences were not statistically significant.

The results of the ETDQ-7 are shown in **Table 2**. The median total scores in Groups 1 and 2 were 1.9 (IQR 1.4 to 2.8) and 1.1 (IQR 1.0 to 1.7), respectively. The differences were statistically significant ($p < 0.001$). Overall, the score was significantly higher in six of the seven question categories in the inferior turbinate enlargement group.

Table 2. Results of the ETDQ-7

Question, Median (IQR)	Group 1[a]	Group 2[a]
1. Pressure in the ears?	2.0 (1.0–3.0)	1.0 (1.0–1.0)[b]
2. Pain in the ears?	1.0 (1.0–2.0)	1.0 (1.0–1.0)[c]
3. A feeling that your ears are clogged?	3.0 (2.0–3.8)	1.0 (1.0–2.0)[b]
4. Ear symptoms when you have a cold or sinusitis?	3.0 (1.0–4.0)	1.0 (1.0–2.0)[b]
5. Crackling or popping sounds in the ears?	1.0 (1.0–3.0)	1.0 (1.0–2.0)[d]
6. Ringing in the ears?	2.0 (1.0–2.8)	1.0 (1.0–2.0)[d]
7. A feeling that your hearing is muffled?	2.0 (1.0–2.8)	1.0 (1.0–1.0)[e]
Total score, Median (IQR)	1.9 (1.4–2.8)	1.1 (1.0–1.7)[b]

The distribution of the data is non-parametric, hence medians and interquartile ranges (IQR: Q25–Q75) are used in statistical testing.
[a]Group 1: inferior turbinate enlargement; Group 2: healthy controls.
[b]P < 0.001, Mann–Whitney *U* test.
[c]Not significant.
[d]P < 0.05, Mann–Whitney *U* test.
[e]P < 0.01, Mann–Whitney *U* test.

Of the subjects in Group 1, 23% had a total score of 3.0 or more. The maximum score in Group 1 was 4.9. Of the subjects in Group 2, 88% had a total score of less than 2.0. The maximum score in Group 2 was 2.4.

Some 48% of the subjects in Group 1 had positive values in serum- specific IgE level measurements for common airborne allergens, but there was no significant difference in the ETDQ-7 total score between the subjects with allergic sensitization and other subjects. There was no significant correlation between the ETDQ-7 total score and the improvement in V2–5 cm after vasoconstriction in Group 1.

5.2 The effect of inferior turbinate surgery on ear symptoms (II)

In the active treatment groups, there were abnormal tympanometry curves in six (five type B and one type C) ears preoperatively and seven (six type B and one type C) ears postoperatively. The difference was not statistically significant. In the placebo group, there was an abnormal tympanometry curve in only one ear (type C) preoperatively, and there were no abnormal findings postoperatively. This difference was not significant either. There were no significant changes in preoperative and postoperative TPP values among either the actively treated patients or the placebo group patients.

The results of the ETDQ-7 are shown in **Table 3**. Some 45% of the patients had a preoperative ETDQ-7 total score of 1.0 to 1.9, 33% had a score of 2.0 to 2.9, and 22% had a score of 3.0 or more (range 3.1 to 4.4). In the evaluation of all patients, RFA, MAIT, and placebo procedures decreased the total score significantly. When only patients with a preoperative score of 2.0 or more were evaluated, all the active treatment procedures decreased the total score significantly.

A three-way ANCOVA was run on the sample of 72 patients to examine the effect of sex, allergy status, and procedure group on the ETDQ-7 score change. Age was added to the model as a continuous covariate. In the evaluation of all patients, none of the factors had a significant individual main effect on the change in ETDQ-7 total score. There were no significant differences in the change in ETDQ-7 total score between the procedure groups, nor were there significant differences in the results between the placebo and any of the active treatment procedures. Allergic sensitization, sex, and age had no effect on the results either. The analysis was repeated for the patients with a preoperative total score of 2.0 or more, and the same results were found.

Table 3. Results of the ETDQ-7.

All patients				
	Preoperative ETDQ-7 Median (IQR)	Postoperative ETDQ-7 Median (IQR)	ETDQ-7 change Mean (95% CI)	p-value
Procedure				
All active treatments, n = 61	2.1 (1.4–2.9)	1.7 (1.2–2.1)	-0.4 (-0.6–-0.2)	<0.001*
RFA, n = 20	2.5 (1.3–3.3)	1.7 (1.5–2.3)	-0.4 (-0.8–-0.02)	0.03*
Diode laser, n = 18	1.6 (1.3–2.4)	1.4 (1.1–1.9)	-0.3 (-0.6–0.01)	0.06
MAIT, n = 23	2.4 (1.6–3.3)	1.9 (1.3–2.4)	-0.5 (-0.9–-0.2)	0.006*
Placebo, n = 11	2.1 (1.4–2.9)	1.4 (1.3–2.1)	-0.5 (-0.9–-0.1)	0.04*
Preoperative ETDQ-7 total score 2.0 or more				
Procedure				
All active treatments, n = 34	2.9 (2.4–3.4)	2.0 (2.43.4)	-0.8 (-1.0–-0.5)	<0.001*
RFA, n = 12	2.9 (2.6–3.7)	2.1 (1.6–3.4)	-0.8 (-1.4–-0.2)	0.02*
Diode laser, n = 7	2.6 (2.1–2.9)	1.9 (1.3–2.3)	-0.7 (-1.3–-0.2)	0.02*
MAIT, n = 15	3.1 (2.4–3.3)	2.0 (1.6–2.4)	-0.8 (-1.3–-0.3)	0.01*
Placebo, n = 6	2.8 (2.1–3.6)	2.1 (1.7–2.6)	-0.7 (-1.4–-0.02)	0.08

The distribution of the data is non-parametric, hence medians and interquartile ranges (IQR: Q25–Q75) are used in the statistical testing. *Statistically significant, Wilcoxon Signed-rank test.

5.3 A prospective, randomized, placebo-controlled study of inferior turbinate surgery (III)

The operation time for the MAIT procedure was statistically significantly longer compared with the other procedures. The operation time for the diode laser, in turn, was statistically significantly longer than the time for the RFA. The VAS score for pain during the operation was highest in the MAIT group, but there were no statistically significant differences between the groups. Five patients in the MAIT group and one patient in the diode laser group had moderate bleeding that required short-term (until next morning) nasal packing. Four patients in the MAIT group complained of notable bleeding during the first post-operative day and three of them had to be treated at the outpatient clinic with short-term (until next morning) nasal packing.

The changes in nasal symptoms reported by the patients after the operation are described in **Figure 1**. The severity of nasal obstruction started to decrease immediately after MAIT and continued up to four weeks. In the diode laser and RFA groups, the response appeared slightly slower. In the placebo group, the response also started immediately and reached its final level after two weeks.

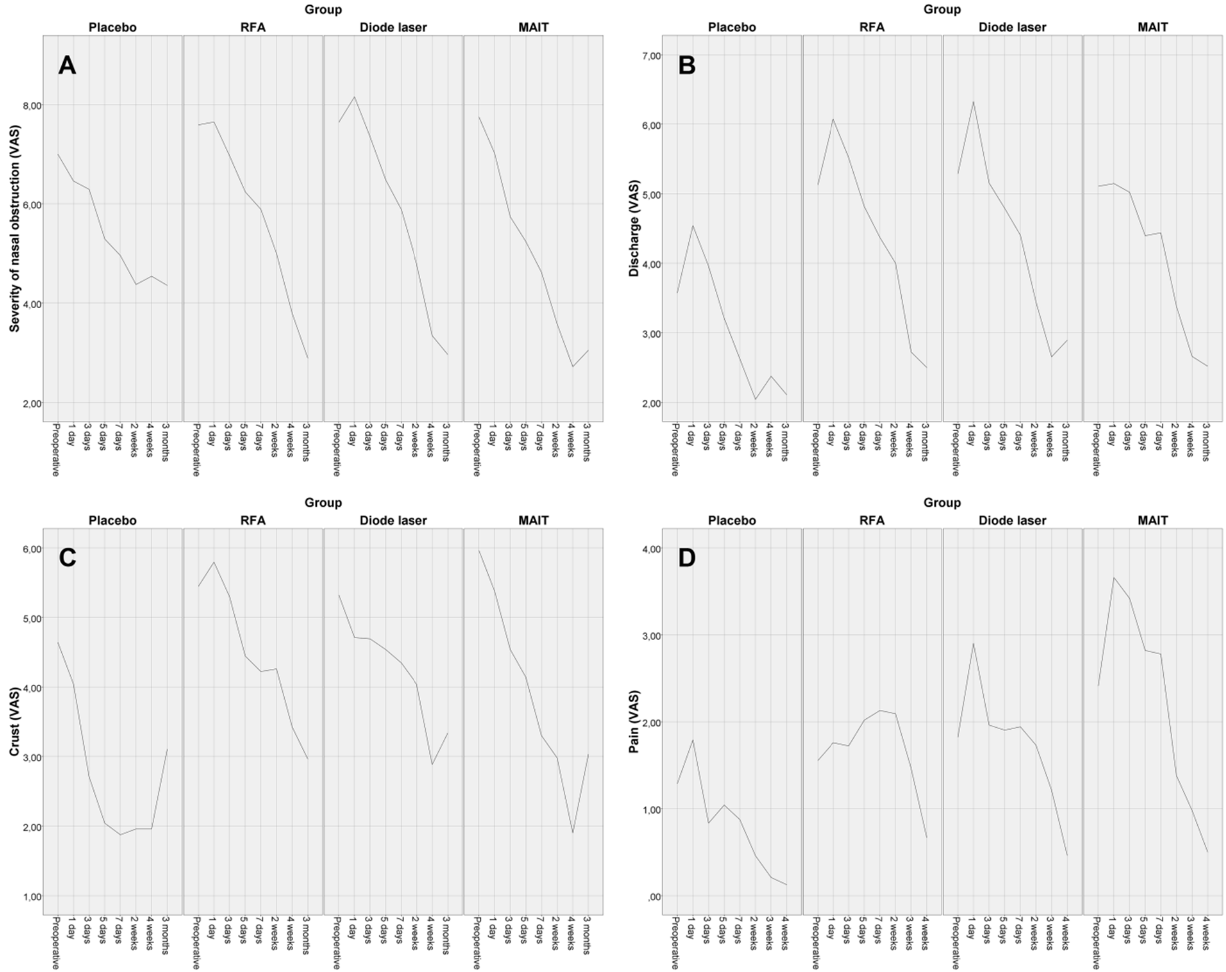

Figure 1. Mean changes in the severity of nasal obstruction (A), discharge (B), crust (C) and pain (D) after the operation; VAS = visual analog scale.

At the three-month control visit, minor crusting was seen in the nasal cavities of one patient in the placebo group, in 12 patients in the RFA group, in six patients in the diode laser group, and in two patients in the MAIT group. One patient in the MAIT group had a small synechia. Atrophy was not found in any of the cases.
The changes in the VAS scores for nasal symptoms at three months are described in **Table 4.** The severity of nasal obstruction decreased statistically significantly in all the groups. All the techniques used were compared separately with placebo using the Mann–Whitney *U* test. RFA ($p = 0.02$), diode laser ($p = 0.03$), and MAIT ($p = 0.04$) all decreased the symptom score for the severity of nasal obstruction statistically significantly more compared with the placebo.

In all the groups, nasal discharge and crusting decreased statistically significantly, but there were no statistically significant differences between the groups, including the placebo group **(Table 4)**.

Table 4. Change in the VAS scores for nasal symptoms at three months.

	Placebo	RFA	Diode laser	MAIT	p-value†
Severity of nasal obstruction, median (IQR)					
Preoperative	7.0 (5.8–8.0)	8.0 (6.3–8.9)	8.0 (7.0–8.0)	8.0 (7.0–9.0)	NS
Post-operative	4.0 (2.0–6.3)	2.0 (1.0–3.8)	3.0 (1.6–4.0)	3.0 (1.6–4.0)	
Change, median	-2.5 (-5.0–-0.8)	-5.0 (-7.0–-3.3)	-5.0 (-6.0–-3.0)	-5.5 (-6.4–-3.0)	0.04*
Change, mean (95% CI)	-2.6 (-4.0–-1.3)	-4.7 (-5.6–-3.8)	-4.7 (-5.4–-4.0)	-4.7 (-5.7–-3.7)	
p-value‡	0.004*	<0.001*	<0.001*	<0.001*	
Change compared to placebo, mean (95% CI)		-2.1 (-4.0–-0.1)	-2.1 (-4.0–0.1)	-2.1 (-4.1–-0.1)	
p-value§		0.03*	0.02*	0.04*	
Discharge, median (IQR)					
Preoperative	3.5 (1.8–5.3)	6.0 (2.3–7.8)	5.5 (3.3–7.0)	5.0 (3.3–7.0)	NS
Post-operative	2.0 (0.9–3.0)	2.0 (0.0–4.8)	2.0 (1.0–4.1)	2.0 (1.0–4.5)	
Change, median	-1.5 (-4.0–- 0.3)	-2.0 (-5.0–-0.6)	-2.5 (-4.0–-1.0)	-2.0 (-4.8–-0.4)	NS
p-value‡	0.06	<0.001*	<0.001*	0.001*	
Crust, median (IQR)					
Preoperative	4.6 (3.0–6.3)	5.4 (4.6–6.3)	5.3 (4.6–6.0)	6.0 (5.1–6.8)	NS
Post-operative	3.1 (1.6–4.6)	3.0 (2.1–3.8)	3.3 (2.4–4.3)	3.0 (2.1–4.0)	
Change, median	-2.0 (-3.3–-0.4)	-2.0 (-5.0–-1.0)	-2.0 (-3.8–0.0)	-3.0 (-4.0–-1.3)	NS
p-value‡	0.08	<0.001*	<0.001*	<0.001*	

The distribution of the data is non-parametric, hence medians and interquartile ranges (IQR: Q25–Q75) are used in the statistical testing. †Kruskal–Wallis test; ‡Wilcoxon signed-rank test; §Mann–Whitney *U* test with Bonferroni correction; NS = not significant; *statistically significant.

All three techniques improved the V2–5 cm acoustic rhinometry values significantly, but there were no statistically significant differences between the groups, including placebo **(Table 5)**.

Table 5. Change in V2–5 cm acoustic rhinometry values (one side of the nasal cavity).

	Placebo	RFA	Diode laser	MAIT	*p*-value†
V2–5 cm (cm^3)					
Preoperative					
Median (IQR)	3.60 (2.82–4.94)	4.39 (3.02–5.65)	3.47 (2.71 4.36)	3.57 (2.52–4.58)	NS
Post-operative					
Median (IQR)	3.94 (2.82–5.33)	5.39 (4.29–6.48)	4.37 (3.56–5.60)	4.27 (3.37–5.41	
Change					
Median (IQR)	0.39 (-0.21–0.96)	1.12 (-0.38–2.39)	0.84 (-0.41–1.66)	0.64 (-0.27–1.56)	NS
Mean (95% CI)	0.13 (-0.51–0.77)	1.14 (0.51–1.78)	0.85 (0.43–1.26)	0.86 (0.30–1.41)	
p-value‡	NS	<0.001*	0.001*	0.003*	

The distribution of the data is non-parametric, hence medians and interquartile ranges (IQR: Q25–Q75) are used in the statistical testing. † Kruskal–Wallis test; ‡ Wilcoxon signed-rank test; NS = not significant; * statistically significant

5.4 The effect of inferior turbinate surgery techniques on ciliated epithelium and mucociliary function (IV)

The total loss of cilia was detected in 52% and squamous metaplasia in 61% of the preoperative samples. The median preoperative scores of the number and amount of cilia and squamous metaplasia of all the patients were 0.0 (IQR 0.0 to 1.0) and 0.2 (IQR 0.0 to 0.8), respectively **(Table 6)**. There were no significant differences in the preoperative scores of the number and amount of cilia and squamous metaplasia between the patients with and without allergic sensitization. The preoperative scores of the number and amount of cilia and squamous metaplasia did not have significant correlations with age either.

In the RFA group, the pre- and postoperative numbers of cases with the total loss of cilia were 10 and 2, respectively. The difference was statistically significant (p = 0.01). In the MAIT group, a decrease in the number of cases was also detected. The result was at the borderline regarding statistical significance (p = 0.05). In the diode laser group, there was no significant difference between the pre- and postoperative numbers of the total loss of cilia cases. In the diode laser group, the pre- and postoperative numbers of the cases where the squamous metaplasia was detected were 4 and 12, respectively. The difference was statistically significant (p = 0.004). There were no significant differences between the pre- and postoperative numbers of squamous metaplasia cases in the RFA and MAIT groups.

The score of the number of cilia increased statistically significantly in the RFA (*p* = 0.03) and MAIT (*p* = 0.04) groups but not in the diode laser group. The score of the squamous metaplasia increased statistically significantly in the diode laser group (*p* = 0.002). No significant changes in the score were found in the RFA and MAIT groups. The score of the microvilli increased statistically significantly in all three groups **(Table 6) (Figures 2-4)**.

Table 6. The scores of the number of cilia, metaplasia, and microvilli.

	All patients	RFA	Diode laser	MAIT
Number of cilia				
Preoperative	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.6 (0.0–1.8)	0.0 (0.0–0.5)
Postoperative	1.0 (0.2–1.6)	0.8 (0.2–2.1)	1.0 (0.3–1.5)	0.8 (0.2–1.9)
Change	0.2 (-1.0–1.2)	0.2 (-0.1–1.9)	0.6 (-1.3–1.2)	0.2 (0.0–1.2)
p-value†	0.01*	0.03*	NS	0.04*
Metaplasia				
Preoperative	0.2 (0.0–0.8)	0.2 (0.0–0.8)	0.0 (0.0–0.3)	0.6 (0.3–1.0)
Postoperative	1.0 (0.5–1.4)	1.0 (0.5–1.4)	1.0 (0.6–1.4)	0.9 (0.6–1.3)
Change (95% CI)	0.5 (0.2–0.8)	0.5 (-0.2–1.1)	0.9 (0.5–1.3)	0.2 (-0.3–0.7)
p-value†	0.002*	NS	0.002*	NS
Microvilli				
Preoperative (IQR)	0.8 (0.4–1.8)	0.6 (0.4–1.5)	0.8 (0.3–1.8)	0.8 (0.4–2.1)
Postoperative (IQR)	2.1 (1.2–2.6)	2.0 (1.3–2.5)	2.2 (1.5–2.8)	2.0 (0.9–2.5)
Change (95% CI)	0.8 (0.5–1.1)	0.9 (0.3–1.5)	0.9 (0.1–1.7)	0.6 (0.1–1.1)
p-value†	< 0.001*	0.008*	0.04*	0.04*

Medians and interquartile ranges (IQR: Q25–Q75) are used due to non-parametric data if not otherwise mentioned.
†Wilcoxon signed-rank test; NS = not significant; *statistically significant.

The preoperative mean score of the non-ciliated pseudostratified columnar cells was 1.6 (95% CI 1.3 to 1.9) and the median score of the goblet cells was 0.4 (IQR 0.1 to 0.6). Regarding these parameters, there were no significant differences found between the pre- and postoperative values in any of the treatment groups.

The median preoperative score of ciliary disorientation was 2.6 (IQR 2.1 to 3.0). There was a statistically significant negative correlation found between the preoperative scores of the ciliary disorientation and the number of cilia (Spearman's rho -0.6; *p* = 0.007). There was no statistically significant correlation found between the postoperative values. Cilia were found in both the pre- and postoperative samples of 16 patients. These samples were used in the paired comparison of the ciliary disorientation. There were no significant differences found in ciliary disorientation between the pre- and postoperative values in any of the treatment groups.

There were no significant changes found between the pre- and postoperative STT values in any of the treatment groups. There were no significant differences in the change in STT values between the treatment groups either.

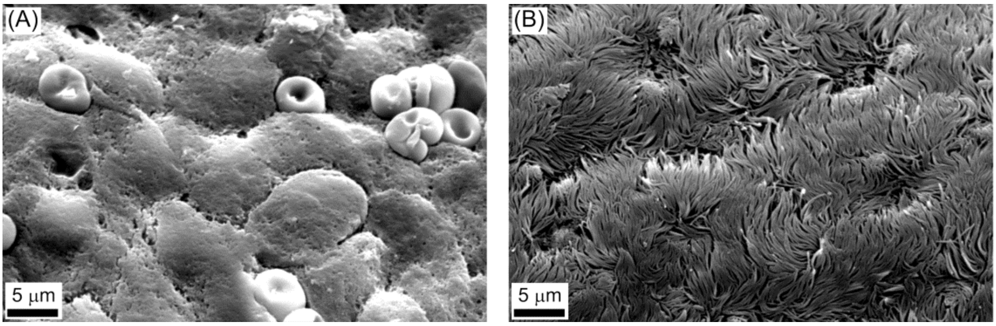

Figure 2. A pre-operative SEM image from a patient in the RFA group showing squamous metaplasia **(A)**. A post-operative image from the same patient showing oriented ciliated epithelium **(B)**.

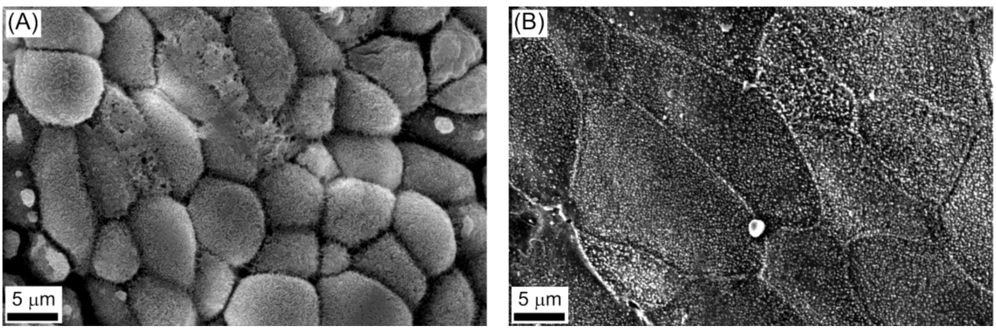

Figure 3. A pre-operative SEM image from a patient in the diode laser group showing non-ciliated columnar epithelium with microvilli **(A)**. A post-operative image from the same patient shoving squamous metaplasia with microvilli **(B)**.

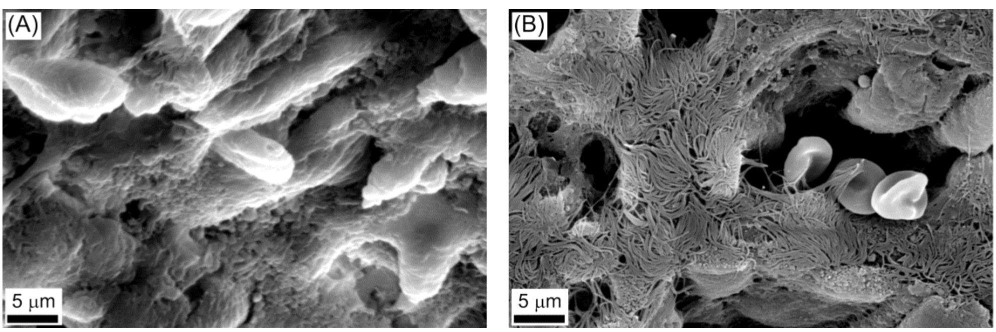

Figure 4. A pre-operative SEM image from a patient in the MAIT group showing non-ciliated columnar epithelium **(A)**. A post-operative image from the same patient showing that cilia have emerged on the epithelium **(B)**.

6 DISCUSSION

6.1 Inferior turbinate enlargement and Eustachian tube dysfunction-related symptoms

6.1.1 The evaluation of ear symptoms using Eustachian Tube Dysfunction Questionnaire

In the present study, patients with nasal obstruction due to inferior turbinate enlargement were found to have significantly more symptoms related to ETD compared with the healthy controls (I). In previous studies, the relationship between ETD and nasal factors has been evaluated using different methods, including symptom questions (Ohrui et al. 2005; Stoikes and Dutton 2005), tympanometry (Lazo-Sáenz et al. 2005), and Toynbee and Valsalva tests (Bakhshaee et al. 2016). In the study, the relationship between ETD-related symptoms and nasal obstruction was evaluated for the first time using the ETDQ-7. The main problem for the patients in the inferior turbinate enlargement group was nasal obstruction; ear symptoms were not their major concern in the first place. Their median ETDQ-7 score was higher than healthy subjects but not very high. Only three abnormal tympanograms were found among them, and the difference was not significant compared with the healthy subjects. Based on the findings of our study, the ETDQ-7 may be a useful tool in detecting patients with a mild level of ETD without clear objective findings, such as tympanic membrane retraction or middle ear effusion (I).

In the study by McCoul et al., the ETDQ-7 was able to discriminate between patients with ETD and those without. The mean ETDQ-7 total score for the ETD group was 4.0 (SD 1.1). In our study, taking into account the relatively low median of the ETDQ-7 total score in the inferior turbinate enlargement group, the lack of significant difference in the number of abnormal tympanometry results between the groups may cause a doubt as to whether the ear symptoms of the patients were just symptomology related to the nasal obstruction itself but not ETD. However, almost one fourth of the subjects in the inferior turbinate enlargement group had an ETDQ-7 total score of 3.0 or more (range 3.0 to 4.9) (I), representing the same severity of symptoms as the patients with ETD in the study by McCoul et al. (McCoul et al 2012).

The weakness of ETDQ-7 is that it cannot discriminate between the three subtypes of ETD (van Royen et al. 2015). In cases of patulous Eustachian tube, patients often complain about similar symptoms as patients with dilatory ETD, but there is also otoscopic or tympanometric evidence of excursion of the tympanic membrane with breathing, and patients often report autophony (Schildrel et al. 2015).

6.1.2 Possible mechanisms behind the Eustachian tube dysfunction-related symptoms

Almost half of the patients in the inferior turbinate enlargement group had a positive result in allergy testing. However, there was no significant difference in ETD-related symptoms between the subjects with allergic sensitization and other subjects in the group. This finding supports the idea that nasal obstruction in itself may have a predisposing role in ETD. It is also possible that in some cases of chronic inferior turbinate enlargement, the nasal mucosal oedema – which can originally be caused by environmental allergens or non-allergic and non-specific triggers – can expand to the nasopharyngeal ET orifice, disturbing ET function. The degree of mucosal oedema in the anterior part of the nose does not seem, however, to correlate directly with the degree of disturbances in the ET which is supported by the finding that there was no correlation between the ETDQ-7 total score and improvement in V2–5 cm after vasoconstriction (I).

6.1.3 Eustachian tube dysfunction-related symptoms and objective findings

The consensus statement by Schildrel et al. agrees that to diagnose dilatory ETD patient-reported symptoms should go together with evidence of negative pressure in the middle ear as assessed by clinical assessment (Schildrel et al. 2015). In our study, tympanometry was the objective examination method for detecting possible dilatory ETD. The finding that there was no significant difference in the number of abnormal tympanometry results between the groups can be partly explained by the inadequate power of the study. 40 subjects in both of the groups were estimated to be enough for the evaluation of the differences in the ETDQ-7 score. Regarding the tympanometry results, a larger sample size might have been needed. Overall, the added value of tympanometry in this study was low. In any case, that is why we are not able to definitely say that dilatory ETD and not just ETD-related symptoms is more common among inferior turbinate enlargement patients (I). The ETDQ-7 cannot be used as a sole criterion for the diagnosis of dilatory ETD because it cannot discriminate between the subtypes of ETD (van Royen et al. 2015). It is, however, sometimes very difficult to detect the signs of negative pressure by clinical methods. In mild or fluctuating cases, the patients may have symptoms suggestive of ETD, but the clinical tests can be within normal limits, whereas in more severe cases the tympanic membrane findings are usually abnormal (I). For example, in cases of baro-challenge-induced Eustachian tube dysfunction tympanometry may be normal (Schildrel et al. 2015).

6.1.4 The effect of inferior turbinate surgery on Eustachian tube dysfunction-related symptoms

In the present study, the ETD-related symptoms were found to improve due to inferior turbinate procedures. However, the placebo procedure improved the symptom score as effectively as real surgery. Furthermore, in the subgroup with more preoperative ear symptoms, there were no significant differences in the ETDQ-7 total score changes between the active treatments and the placebo procedure (II). There were no significant changes in the pre- and postoperative numbers of abnormal tympanometry curves or in the pre- and postoperative TPP values among actively treated patients and the placebo patients. Possible changes in TPP values may have indicated minor changes in middle ear pressure as a result of the operation (II).

Based on the findings of our study, the surgical treatment of the anterior part of the inferior turbinate did not have any real effect on the nasopharyngeal ET orifice and possible ETD (II). The posterior part of the turbinate, which is anatomically located very close to ET orifice, was not operated on in the present study. The main aim of the larger study setting was to compare the efficacy of various inferior turbinate surgery procedures in the treatment of chronic nasal obstruction, which was the patients' main problem. Surgical treatment of the anterior part of the inferior turbinate, in turn, has been found to be effective in decreasing nasal obstruction (Civelek et al. 2010). In addition, to make the procedures as comparable as possible, we treated the same length of the turbinate with every technique. The easiest way to guarantee that was to limit the operation to the anterior part of the inferior turbinate because in some cases it can be difficult to operate the posterior part of the turbinate under local anesthesia.

More than half of the patients had an ETDQ-7 score of 2.0 or more, and more than one fifth of the patients had a score of 3.0 or more (II). This represents the same severity of symptoms as patients found to have ETD in the study by McCoul et al. (McCoul et al. 2012). However, fewer than 10% of the enrolled patients had an abnormal tympanogram (type B or C) confirming the diagnosis of ETD. As a result, we are not able to generalize the results of our study to ETD. Therefore, we can only talk about the effect of inferior turbinate procedure on patient symptoms suggestive of ETD (II).

6.2 Placebo-controlled comparison of inferior turbinate surgery techniques

6.2.1 The operations and side-effects

Some studies have reported notable intraoperative bleeding (Kassab et al. 2012) or post-operative bleeding in the early days after MAIT (Cingi et al. 2010), and this was also the case in our study. During the operation, the mean VAS score for pain was the highest in the MAIT group, but there was no statistical difference between the groups. Post-operatively, there was an increase in the VAS score for pain in the MAIT group that lasted up to one week. This can possibly be explained by the direct surgical tissue trauma caused by the operation. Short-term nasal packing, which was most common in the MAIT group, may also partly explain the increase of pain during the first days of the follow-up. Increased pain was also reported during the first two days after diode laser treatment. This can possibly be explained by the higher temperature and therefore the more severe tissue damage caused by the laser compared with the RFA (III).

In the present study, a temporary increase in the symptom of nasal discharge and a minor increase in the symptom of crusting during the first post-operative days after RFA was noted (III). A similar finding has been reported in previous studies (Coste et al. 2001; Bäck et al. 2002). Some patients treated with RFA complained of crust formation for as long as three months (III). In a study by Janda et al., patients showed moderate-to-severe nasal obstruction, crusting, and nasal secretion in the first four weeks following diode laser treatment (Janda et al. 2000). In our study, however, patients in the diode laser group on average reported a decrease in crusting immediately after the operation and an increase in nasal discharge only during the first two days. In some cases, however, crust formation continued up to three months (III).

6.2.2 The effect of inferior turbinate surgery procedures on the severity of nasal obstruction

In recent years, studies have been published that compare RFA and MAIT in the treatment of nasal obstruction. There are studies where the results of MAIT have been better in the short follow-up (Cingi et al. 2010) and also in the longer follow-up (Liu et al. 2009). There are also studies where the techniques have been found equal in efficacy (Kizilkaya et al. 2008). In their systematic review and meta-analysis comparing RFA and MAIT, Acavedo et al. concluded that inferior turbinate reduction produces a significant subjective and objective improvement in nasal airflow in the short term, which is not related to the technique used (Acavedo et al. 2015). There are also studies that have compared RFA and the diode laser (Rhee et al. 2001; Kisser et al. 2014) and MAIT and the diode laser (Kassab et al. 2012) but no significant differences between the techniques have been found in any of these studies. Furthermore, no previous studies have compared all three techniques together.

In our study, the decrease in the VAS score for severity of nasal obstruction started faster after MAIT (III). In MAIT, the submucosa of the turbinate is emptied immediately during the operation, whereas in the RFA and diode laser procedures the heat caused by the device creates a submucosal lesion, inducing scarring and tissue volume reduction during the following weeks (Willatt 2009; Cakli et al. 2012). The post-operative nasal packing, which was most common in the MAIT group, squeezes the mucosa of the emptied turbinate against the bone and may therefore contribute to the faster response. Based on this conclusion and the higher rate of post-operative bleeding in the MAIT group, nasal packing can be recommended in the MAIT procedures (III).

At the end of the three-month follow-up, all three techniques decreased the VAS score for the severity of nasal obstruction and V2–5 cm values statistically significantly compared with the preoperative values, and they were equal in efficacy regarding both parameters (III).

There have been no previous placebo-controlled studies involving the three different techniques, or studies where the diode laser and MAIT have been compared with placebo treatment. In the present study, RFA, diode laser, and MAIT all improved the VAS score for the severity of nasal obstruction statistically significantly better than placebo (III). This finding is in line with the previous study by Nease and Krempl regarding RFA (Nease and Krempl 2004).

6.2.3 The effect of inferior turbinate surgery procedures on nasal discharge and crusting

In the present study, all the techniques decreased the symptom scores of nasal discharge and crusting statistically significantly compared to the preoperative values at the end of the three-month follow-up, but none of them statistically significantly compared with placebo. In addition, minor crusting was still found in some noses at three months, especially in the RFA and diode laser groups. Therefore, most of the improvement in these symptoms can be explained by the placebo effect (III).

6.2.4 Objective examination

V2–5 cm in acoustic rhinometry was used as a parameter for objective examination. It represents well the operated anterior half of the inferior turbinate and describes the possible nasal cavity volume changes due to the operation at that region. In the three-month follow-up, RFA, diode laser, and MAIT techniques all improved the V2–5 cm values statistically significantly compared with the preoperative values. Due to the lack of a real operation, there was understandably no statistically significant change in the V2-5 cm values in the placebo group. This supports the conclusion that the improvement in the VAS score for severity of nasal obstruction in the placebo group was due to placebo effect. However, none of the techniques improved the volume statistically significantly compared with placebo. This finding can be partly explained by the relatively small number of patients in the placebo group. A larger number might have led to statistical significance (III). In addition, environmental conditions and technical difficulties in measurement may have an influence on the volume values (Hilberg and Pedersen 2001). Furthermore, the symptom of nasal obstruction and objective parameters do not always correlate very well (André et al. 2009). On the other hand, it is wise to remember that the increase in the nasal cavity volume should be optimal instead of too large in order to avoid making the nose too wide, which might lead to problems, such as nasal dryness, crusting, atrophy, worsening of the symptom of nasal obstruction, and "empty nose syndrome" (Willatt 2009; Hong 2016).

6.2.5 Economical aspects

One aspect that should be noted when comparing these techniques is cost-efficiency. The cost-efficiency depends on, for example, whether the equipment is multi-use or disposable, and whether the procedure is carried out in the office setting or in the operation room setting. There are also many devices available from different manufacturers and their prices vary. The RFA electrode (purchase price 419 euros) that was used in the present study is a multi-use (instrument cleaning price 1.5 euros) instrument. RFA treatment is a fast procedure, which was also found in the present study (III). It is also usually carried out in the office setting (Nease and Krempl 2004; Cavaliere et al. 2005). Therefore, it can be considered cost-effective. The diode laser fiber (purchase price 122 euros) that we used is disposable (III). The diode laser treatment can also be easily carried out in the office setting (Sroka et al. 2007), which increases its cost-efficiency. The microdebrider blade (purchase price 179 euros) that we used is disposable, which decreases its cost efficiency (III). It is commonly used in the operation room setting, although the treatment can be carried out in the office setting as well. The final conclusion about cost-efficiency should be based on the long-term effect of the treatments, and for that our study cannot give answers.

6.3 The effect of inferior turbinate surgery techniques on mucosal epithelium and mucociliary function

6.3.1 The meaning of the biopsy site

In previous light and electron microcopy studies of inferior turbinate surgery, the preoperative findings regarding cilia have been controversial. There have been studies reporting preoperative findings of epithelial metaplasia and loss of ciliated cells (Inoye et al. 1999; Gindros et al. 2009; Neri et al. 2016). On the other hand, there have also been studies that have shown normal appearance of the epithelium with a preserved number of cilia (Sargon et al. 2008; Garzaro et al. 2012). In the present study, there were squamous metaplasia and total loss of ciliated cells found in the majority of the preoperative samples (IV). This may partly be explained by the chronic rhinitis behind the inferior turbinate enlargement taking into account previous studies showing that the loss of cilia is more common in both allergic and non-allergic rhinitis compared with healthy controls (Watanabe et al. 1998; Gindros et al. 2009). In our study, however, the biopsies were taken from the anterior portion of the inferior turbinate approximately 1 cm behind the anterior edge, and this is the most likely explanation for the high incidence of squamous metaplasia and total loss of ciliated cells in the preoperative samples (IV). The density of ciliated cells increases in the nasal cavity in the antero-posterior direction (Halama et al. 1990). Augusto et al. reported that ciliated epithelium with goblet cells (normal respiratory epithelium) was found in only half of the samples taken from the anterior portions of the inferior turbinates of normal noses and various degrees of epithelial metaplasia was found in half of the samples taken from the same sites. The anterior part of the inferior turbinate is more exposed to external elements, such as strong air flow, and therefore prone to metaplatic transformation (Augusto et al. 2001).

6.3.2 The effect of inferior turbinated surgery techniques on mucosal epithelium

There have been some previous light and electron microscopy studies that have evaluated the effect of inferior turbinate surgery on ciliated epithelium. Based on the previous studies, RFA (Coste 2001, Gindros 2008, Sargon 2009, Garzaro 2012) and submucosal electrocautery (Talaat 1987, Elwany 1999, Gindros 2008) do not have a significant effect on ciliated epithelium. After endoscopic turbinoplasty, some improvement has been described (Cassano 2010). Regarding lasers, however, the findings have been controversial (Inoye 1999, Bergler 2001, Cassano 2010). Ultrasound reduction, in turn, may have an improving effect on ciliated epithelium (Gindros 2008), whereas a worsening effect has been previously described for partial inferior turbinectomy (Garzaro 2012). Interestingly, in a recent study by Neri et al., a complete re-epithelisation of nasal mucosa with columnar ciliated epithelium was detected 4 months after the total removal of the mucosa of the medial and inferior portions of the inferior turbinate with the microdebrider (Neri 2016).

In the present study, the effect of various inferior turbinate surgery techniques on ciliated epithelium was for the first time evaluated with a statistical analysis using a score based on the mean of the grades given to the image series by the blinded examiners. Based on the score, the number of cilia increased significantly after RFA and MAIT treatments. The number of cases with total loss of cilia was also found to decrease after these treatments. No similar changes were found after diode laser treatment. On the other hand, the score of metaplasia seemed to increase significantly after diode laser treatment as well as the overall number of cases where metaplasia was detected. No similar findings were found after RFA or MAIT. Regarding the diode laser, the findings can be explained by the damage the laser causes to the mucosal surface during the treatment. RFA and MAIT are more clearly submucosal techniques that do not notably harm the mucosal surface. In some cases, however, mucosal surface changes can also occur after these submucosal procedures due, for example, to vascular alterations of the turbinate. Inferior turbinate surgery creates more airspace at the level of the anterior part of the inferior turbinate, which decreases the nasal airway resistance, causes changes in the airflow patterns, and likely decreases the shear stress on the mucosa of the anterior part of the inferior turbinate. This could be a possible explanation for the increase in the number of cilia after RFA and MAIT treatments (IV).

In human nasal epithelial cells, the number of microvilli has been found to increase before the ciliogenesis starts (Jorissen et al. 1990). In chronic rhinosinusitis, an increased number of microvilli and short cilia are thought to indicate the regeneration of epithelium and ciliated cells (Toskala and Rautiainen 2003). In the present study, the number of microvilli increased significantly in all three groups. This finding can be interpreted to be related to a regeneration of the mucosal epithelium after the damage caused by the surgery (IV).

The degree of ciliary disorientation was relatively high both pre- and postoperatively in all three groups and there were no significant differences in disorientation between the pre- and postoperative samples (IV). The disorientation can be explained mainly by the inflammation caused by chronic rhinitis (Rayner et al. 1995) and the shear stress caused by the airflow (Augusto et al. 2001). Preoperatively, there was also a negative correlation found between the scores of the ciliary disorientation and the number of cilia indicating that the smaller the number of cilia is the more disorientated they are (IV). This finding is in line with a previous study by Rautiainen, where a few cilia or small groups of cilia were found in most fields that differed dramatically from the main orientation (Rautiainen 1988).

6.3.3 The effect of inferior turbinate surgery techniques on mucociliary function

The effect of various techniques of inferior turbinate surgery on mucociliary function has been examined in several studies using STT. Based on the previous studies, the diode laser technique may worsen the mucociliary transport during the first three months after operation, but in longer follow-up it returns to normal (Parida et al. 2013, Veit et al. 2016). In most of the studies regarding RFA, the STT has either been preserved (Sapci et al. 2003; Cavaliere et al. 2005; Rosato et al. 2016) or improved (Coste et al. 2001; Veit et al. 2016) after the operation in one- to three-month follow-ups. However, there are also studies where STT has been prolonged at two (Salzano et al. 2009) and six (Garzaro et al. 2012) months after the operation. There is also one study where the STT significantly improved from six months to one year postoperatively compared with the preoperative levels. However, no improvement in the STT from two to three years was noted (Liu et al. 2009). Regarding MAIT, there are studies where STT has been preserved after three months (Romano et al. 2015) or decreased in a longer, up to three years, follow-up (Liu et al. 2009).

In the present study, there were no significant changes found between the pre- and postoperative STT values in any of the treatment groups. There were also no significant differences in the change of STT values between the treatment groups. The findings are in line with the previous studies on RFA and MAIT. Although the amount of squamous metaplasia was found to increase in the diode laser group, the STT was not found to increase. One possible explanation for this could be the contact technique used, where parallel stripes were made on the mucosa along the turbinate leaving lanes on the mucosal surface with preserved mucociliary function between them. Moreover, STT itself might also be too rough a measurement to find out slight differences (IV).

6.4 The significance of the study setting in the results

6.4.1 Randomization

Possible biases caused by confounding factors, such as patient biases, natural course of the disease, and regression to the mean (Benedetti et al. 2013) can be controlled with proper randomization. In our study, the randomization was carried out just before the procedure in consecutive order by the method of minimization. The only parameters that were inputted to the program were age, sex, and allergic sentisization. The distributions of these parameters were kept similar in each group to prevent the possible confounding effect of the parameters on the results.

6.4.2 Blinding

In order to increase feasibility, all clinical examinations and operations in this single-blinded placebo-controlled study were performed by the same physician, who was not blinded to the patient's groups. Unblinding of the examining physician could introduce unintentional bias by causing misinterpretation of data. Blinding of the treating physicians is recommended, even if they are not assessing outcomes, because they may inadvertently affect the expectations of the patients or inform the patients of their treatment group, thus spoiling the placebo control (Powell et al. 2001). However, the examination parameters used in this study were not based on the subjective evaluation of the examining physician. Therefore, from the examining physician's point of view, the study data were objective. In our study, during the preoperative visit, the examining physician did not yet know the patients´ group, and during the control visit the patients filled out the questionnaires regarding nasal symptoms before meeting the physician, which makes the accidental revelation impossible. If the operation is carried out under local anaesthesia, as in our study, there is always a small risk that the operation room staff or the surgeon may accidentally reveal the treatment group no matter if the setting is single- or double-blinded. Taking into account the quality of the inferior turbinate reduction operation, it would have been exaggerated to treat all these adult patients under general anaesthesia.

In the evaluation of the effect of inferior turbinate surgery on the ciliated epithelium, the five examiners who evaluated the SEM images did not know which technique had been used or whether the images were pre- or postoperative. Blinding of the evaluators was extremely important in order to prevent any possible expectations and attitudes of the examiners towards the treatments from affecting their evaluations (IV).

Crossover trials, such as two (Nease and Krempl 2004; Bran et al. 2012) of the three (Powell et al. 2001; Nease and Krempl 2004; Bran et al. 2012) previous placebo-controlled RFA studies, are prone to biases. These include the periodic effect, where the order in which treatments are given may affect the outcome, and the carryover effect, where the effect of the first treatment extends into the time interval between the periods of intervention and has an impact on the outcome of the second treatment (Bran et al. 2013). For these reasons, we did not use the crossover model in our study.

6.4.3 Placebo-control

Inferior turbinate surgery procedures are very common in otorhinolaryngologist's clinical practice. Occasionally, clinicians may be preoccupied by the question whether the procedures are genuinely useful or not. In times like these, when there is a lot of conversation about how to increase effectiveness in the public health care, there is also a general need for the studies, which evaluate the true effectiveness of the given surgical treatment.

In placebo-controlled studies, the placebo is used to find out the true treatment effect of the examined treatment. The true treatment effect is the difference in improvement between the intervention group and the control group (placebo effect) (Powell et al. 2001). In our placebo-controlled comparison of inferior turbinate techniques, the mean true treatment effect in the VAS score change of the severity of nasal obstruction was found to be -2.1 for all three techniques. This indicates that RFA, diode laser, and MAIT are all genuinely effective and useful techniques in decreasing the severity of nasal obstruction in inferior turbinate enlargement. The finding justifies their use in the clinical practice, although, the placebo effect accounted for a large part of the total improvement seen in the intervention groups (III). We also found that the improvement of ETD-related symptoms due to surgery of the anterior half of the inferior turbinate was equal to placebo (II), and that most of the improvements in symptom scores of nasal discharge and crusting can be explained by the placebo effect (III). Without the placebo control, we would have falsely found a greater improvement and significance due to treatment.

6.4.4 Internal quality of the study and generalizability of the results

For the above-mentioned reasons, and despite the mainly single-blinded study setting, the internal quality of our study can be considered high. When we think about the generalizability of the results regarding the treatment of nasal obstruction, we have to take a look at the exclusion criteria of the study. We excluded those patients with obvious anatomical abnormalities, such as severe septum deviation, and patients with chronic sinusitis with or without polyposis. For these patients, inferior turbinate surgery can be carried out in clinical practice.

However, inferior turbinate reduction, as a sole procedure, does not necessarily lead to a satisfactory outcome in these cases, and additional procedures, such as septoplasty or middle meatal antrostomy, are required at the same time. If we think about the indications of inferior turbinate surgery as a sole procedure, the generalizability of this study can be considered to be good.

6.4.5 The significance of the placebo effect in clinical practice

Physicians in general quite often deal with the placebo effect when treating their patients. There are several situations where it is difficult to recognize whether the effect of the treatment is due to the treatment itself or due to the placebo effect. Taking into account how complex the sensations of nasal obstruction and patency are, it is easy to understand the role of the placebo effect in the treatment of nasal obstruction. Probably, physicians most commonly use placebo in their practice when they explain the positive effects of the treatments, which are known and proven to be effective, to their patients. This increases the patients' positive expectations towards the treatment, which is one of the main things behind the placebo effect. When the treatment is proven to be effective, as now seems to be the case with the three inferior turbinate surgery techniques in treating chronic nasal obstruction in short-term follow-up, it is justifiable to make use of all the additional benefits of the placebo effect to increase the improvement of the symptoms that the patients suffer. Regarding inferior turbinate enlargement, the placebo effect can therefore be called an otorhinolaryngologist's best helper.

6.5 Future aspects

In general, there will be need for this kind of placebo-controlled studies, which evaluate the true effectiveness of the given surgical treatment, and in their part, guide the use of economical resources in the health care.

In future, more studies comparing inferior turbinate surgery techniques with long (several years) follow-ups are needed to find out the possible differences in their long-term efficacy in treating the chronic nasal obstruction related to inferior turbinate enlargement. To date, the three-month follow-up period in our study is the longest study of inferior turbinate surgery with a placebo control group. It would also be recommendable to carry out placebo-controlled studies with an even longer follow-up in future to evaluate the true long-term treatment effect of inferior turbinate surgery. However, taking into account ethical aspects, etc., it could be very challenging to carry out a placebo-controlled study with several years follow-up. A placebo-controlled study with one-year follow-up period would probably be the next step.

In the present study, some of the patients in all treatment groups benefitted considerably from the inferior turbinate reduction in the treatment of their chronic nasal obstruction. On the other hand, however, there were also patients who did not benefit from the treatment at all. In future studies, special attention should be paid to the possible factors in the preoperative diagnostics that predict positive or negative outcomes. The use of CFD models in the evaluation of the most optimal nasal airflow concerning the feeling of nasal patency could be a useful in future studies. The definition of inferior turbinate enlargement and the criteria for inferior turbinate surgery also require clarification. This would help otorhinolaryngologists to operate on the patients who, as a result, are likely to benefit from the inferior turbinate surgery.

Conservative treatment of the chronic rhinitis behind the inferior turbinate enlargement is essential before surgical treatment. Therefore, it would be recommendable to carry out controlled trials of medical treatment, where factors such as patient compliance, for example, are taken into account.

It would also be interesting to examine the usefulness of combining inferior turbinate surgery with traditional functional endoscopic sinus surgery in the treatment of those patients with CRS who also have signs of inferior turbinate enlargement.

7 CONCLUSIONS

The present study provides data to support the following conclusions and summary:

After three-month follow-up, there were no statistically significant differences between the RFA, diode laser, and MAIT techniques in their efficacy in treating nasal obstruction. RFA, diode laser, and MAIT were all genuinely effective in treating the chronic nasal obstruction caused by inferior turbinate enlargement. The placebo effect plays a large role in the overall reduction of the severity of nasal obstruction in inferior turbinate surgery, but all three examined techniques provided a statistically significant additional reduction in the severity of nasal obstruction compared with the placebo procedure.

Patients with chronic nasal obstruction caused by inferior turbinate enlargement have more symptoms related to ETD than healthy controls. ETD-related symptoms among the patients are not very severe in most cases and findings, such as abnormal tympanometry, are not common in clinical tests. Whether the patient has allergic sensitization or not does not seem to cause a difference in the symptoms related to ETD.

The improvement of ETD-related symptoms due to surgery of the anterior half of the inferior turbinate as a sole procedure was found to be equal to placebo. The findings of this study do not support the use of reduction of the anterior half of the inferior turbinate as a sole procedure intended to treat the ear symptoms assessed by the ETDQ-7 questionnaire.

RFA and MAIT are more mucosal preserving techniques than diode laser, which was found to increase the amount of squamous metaplasia at three-month follow-up. The number of cilia seemed to even increase after RFA and MAIT procedures, but not after diode laser. Nevertheless, the mucociliary transport was equally preserved in all three groups.

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Eustachian Tube Dysfunction–Related Symptoms in Chronic Nasal Obstruction Caused by Inferior Turbinate Enlargement

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Abstract

Objective: The aim of this study was to evaluate the relationship between chronic nasal obstruction caused by inferior turbinate enlargement and Eustachian tube dysfunction–related symptoms using the Eustachian Tube Dysfunction Questionnaire (ETDQ-7) as an assessment method.

Methods: A total of 80 adults were enrolled. Group 1 comprised consecutive patients with enlarged inferior turbinates and group 2 comprised healthy controls. The ETDQ-7 scores and tympanometry results of both groups were analyzed and compared.

Results: The median total scores of the ETDQ-7 in groups 1 and 2 were 1.9 (interquartile range, 1.4-2.8) and 1.1 (interquartile range, 1.0-1.7), respectively ($P < .001$). There was no significant difference in the abnormal tympanometry results between the groups. There was no significant difference in the ETDQ-7 total score between the patients with allergic sensitization and other patients in group 1.

Conclusions: Patients with inferior turbinate enlargement have more symptoms related to Eustachian tube dysfunction than healthy controls. Most patients with Eustachian tube dysfunction had normal tympanometry and normal otoscopy, which indicates a baro-challenge-induced Eustachian tube dysfunction. Whether the patient has allergic sensitization or not does not seem to cause a difference in symptoms related to Eustachian tube dysfunction.

Keywords

dysfunction, Eustachian tube, nasal obstruction, symptoms, turbinates

Introduction

The prevalence of chronic Eustachian tube dysfunction (ETD) in Western countries has been evaluated to be 1% in the adult population.[1] A recent consensus statement by Schilder et al[2] defined 3 subtypes of ETD: dilatory ETD, baro-challenge-induced ETD, and patulous ETD. In most of the cases, the problem is dilatory ETD caused by mucosal inflammation and edema in the Eustachian tube (ET) lumen.[3] It has been presented that viral upper respiratory infections,[4] allergic rhinitis,[5] chronic sinusitis,[6,7] and upper gastroesophageal reflux disease[8,9] can cause mucosal inflammation leading to dilatory ETD. In baro-challenge-induced ETD, symptoms of aural fullness, popping, or discomfort/pain occur or are initiated under conditions of alteration to the ambient pressure. Patients are typically asymptomatic once they return to ground level. Patulous ETD presents with symptoms of aural fullness and autophony and is thought to be caused by an abnormally patent ET.[2]

The relationship between chronic nasal obstruction caused by inferior turbinate enlargement and ETD has not been evaluated previously. In addition, the relationship between ETD-related symptoms and nasal problems has never been evaluated with a validated questionnaire.

Many subjective and objective methods have been reported for measuring ET function, including otoscopic

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appearance, Valsalva and Toynbee tests, tympanometry, tubomanometry,[10] and sonotubometry.[11] However, due to the complexity of the functional anatomy and physiology of the ET, there is still no diagnostic "gold standard" for ETD.[12,13] McCoul et al[12] have developed the Eustachian Tube Dysfunction Questionnaire (ETDQ-7). Its usefulness has been shown in recent studies.[10,14,15] Thus far, it has not been used in the evaluation of the relationship between ETD-related symptoms and nasal problems.

The aim of this study was to evaluate the relationship between chronic nasal obstruction caused by inferior turbinate enlargement and ETD-related symptoms using the ETDQ-7 as an assessment method.

Methods

This case-control study was carried out at Tampere University Hospital, Tampere, Finland, between February 2014 and August 2016. The institutional review board approved the study design (R13144). A total of 80 adults were enrolled and divided into 2 groups matched by age and sex.

Group 1 (cases) were consecutive patients with enlarged inferior turbinates due to persistent rhinitis. The patients presented with year-round symptoms of bilateral nasal obstruction related to congested turbinate mucosa that had not responded to a 3-month trial of appropriate treatment with topical corticosteroids. When the study was performed, the patients were no longer allowed to use topical corticosteroids or antihistamines. Patients with significant nasal septum deviation affecting the nasal valve region, internal/external valve collapse/stenosis, chronic rhinosinusitis with or without polyposis, previous nasal surgery, sinonasal tumor, Ménière's disease, previous ear surgery, severe systemic disorder, severe obesity, and malignancy were excluded.

All of the patients in group 1 underwent cone beam computed tomography (CBCT) (Planmeca Max; Planmeca, Helsinki, Finland) to exclude patients with chronic rhinosinusitis from the study. Serum-specific IgE level measurements were used to identify the patients with an allergic sensitization, which was defined as a specific IgE > 0.35 for any common airborne allergen.

The definition of inferior turbinate enlargement was based on the persistent bilateral symptom of nasal obstruction, the finding of bilateral swelling of the inferior turbinates in nasal endoscopy, and evident shrinking of both of the turbinates in a decongestion test. The nasal response to the topical vasoconstrictor 0.5% xylometazoline hydrochloride (Nasolin, Orion, Finland) in both nasal cavities 15 minutes before obtaining the second measurement was evaluated objectively using acoustic rhinometry (Acoustic Rhinometer A1; GM Instruments Ltd, Kilwinning, UK). An improvement of less than 30% in anterior nasal cavity volume (V2–5 cm)—the most sensitive measure of change in mucosal swell during decongestion[16]—in 1 or both nasal cavities was considered normal, and those patients were excluded from the study. The limit value of 30% was chosen according to previous literature.[17-19]

Group 2 (controls) were healthy adults without any clinical signs or history of persistent nasal obstruction or other nasal problems. The group consisted of volunteer medical students and health care personnel. The appearance of their inferior turbinates was normal in nasal examination. The participants in group 2 did not undergo rhinometric evaluation or CBCT. Otherwise, the clinical exclusion criteria were the same as group 1.

After signing the informed consent, all participants underwent a complete otorhinolaryngologic examination with tympanometry included. The tympanometric curves were classified following the classification by Liden[20] and Jerger[21]: type A, normal ET function; type B, flat tympanogram characteristic of the presence of fluid in the middle ear or eardrum perforation; or type C, peak at very negative pressure, typically 150 dPa, which may be indicative of eardrum retraction and ETD. Next, the participants completed the ETDQ-7, an instrument for the assessment of symptoms related to obstructive dysfunction of the ET and treatment outcome. The ETDQ-7 consists of 7 questions and a 7-item Likert-type scale, with a response of 1 indicating no problem and 7 indicating a severe problem. The total score is divided by 7 to give an overall score ranging from 1.0 to 7.0.[12]

IBM SPSS Statistics 22.0 was used for the statistical analyses. All the nonparametric data were statistically processed using the Mann–Whitney *U* test. The chi-square test was used in the evaluation of sex distribution and tympanometry results. Correlations were evaluated using Spearman rho.

Results

There were no significant differences found between the groups regarding sex or age. Abnormal tympanometry results (2 type B with middle ear effusions found also in the otoscopies and 1 type C with tympanic membrane retraction found also in the otoscopy) were observed in 3 ears (3.8%) in group 1. Only A curves were found in group 2. The difference was not statistically significant (Table 1).

The results of the ETDQ-7 are shown in Table 2. The median total scores in groups 1 and 2 were 1.9 (interquartile range, 1.4-2.8) and 1.1 (interquartile range, 1.0-1.7), respectively. The difference was statistically significant ($P < .001$). Overall, the score was significantly higher in 6 of the 7 question categories in the inferior turbinate enlargement group.

The distribution of the ETDQ-7 total score is described in Table 3. Of the participants in group 1, 23% had a total score of 3.0 or more. The maximum score in group 1 was 4.9. Of the participants in group 2, 88% had a total score of less than 2.0. The maximum score in group 2 was 2.4 (Table 3).

Table 1. Patients' Characteristics and Tympanometry Results.[a]

	Group 1 (N = 40)	Group 2 (N = 40)	*P* Value
Age			
Median (range), y	32 (24-45)	28 (24-42)	.2[b]
Sex			
Male, No. (%)	23 (57)	22 (55)	.8[c]
Female, No. (%)	17 (43)	18 (45)	
Tympanometry (160 ears)			
Type A, No. (%)	77 (96)	80 (100)	.08[c]
Type B or C, No. (%)	3 (4)	0 (0)	

[a]Group 1: inferior turbinate enlargement; group 2: healthy controls.
[b]Mann–Whitney *U* test.
[c]Chi-square test.

Table 2. Results of the Eustachian Tube Dysfunction Questionnaire.[a]

	Group 1	Group 2
Question		
1. Pressure in the ears?	2.0 (1.0-3.0)	1.0 (1.0-1.0)[b]
2. Pain in the ears?	1.0 (1.0-2.0)	1.0 (1.0-1.0)[c]
3. A feeling that your ears are clogged?	3.0 (2.0-3.8)	1.0 (1.0-2.0)[b]
4. Ear symptoms when you have a cold or sinusitis?	3.0 (1.0-4.0)	1.0 (1.0-2.0)[b]
5. Crackling or popping sounds in the ears?	1.0 (1.0-3.0)	1.0 (1.0-2.0)[d]
6. Ringing in the ears?	2.0 (1.0-2.8)	1.0 (1.0-2.0)[d]
7. A feeling that your hearing is muffled?	2.0 (1.0-2.8)	1.0 (1.0-1.0)[e]
Total score	1.9 (1.4-2.8)	1.1 (1.0-1.7)[b]

[a]Group 1: inferior turbinate enlargement; group 2: healthy controls. Data are presented as median (interquartile range, Q25-Q75).
[b]$P < .001$ (Mann–Whitney *U* test).
[c]Not significant.
[d]$P < .05$ (Mann–Whitney *U* test).
[e]$P < .01$ (Mann–Whitney *U* test).

Table 3. Distribution of the Eustachian Tube Dysfunction Questionnaire Total Score.[a]

Total Score	Group 1	Group 2
1.0-1.9	20 (50)	35 (88)[b]
2.0-2.9	11 (27)	5 (12)[c]
3.0 or more	9 (23)	0 (0)[b]

[a]Group 1: inferior turbinate enlargement; group 2: healthy controls. Data are presented as No. (%).
[b]$P < .001$ (chi-square test).
[c]Not significant.

Some 48% of the participants in group 1 had positive values in serum-specific IgE level measurements for common airborne allergens, but there was no significant difference in the ETDQ-7 total score between the participants with allergic sensitization and other participants (Table 4).

Table 4. Effect of Allergic Sensitization on the Eustachian Tube Dysfunction Questionnaire (ETDQ-7) Total Score in Group 1 (Inferior Turbinate Enlargement).

Allergic sensitization	
Yes, No. (%)	19 (48)
No, No. (%)	21 (53)
ETDQ-7	
Allergic sensitization, median (IQR)	2.1 (1.4-2.7)[a]
No allergic sensitization, median (IQR)	1.9 (1.4-3.0)

Abbreviation: IQR, interquartile range.
[a]Not significant (Mann–Whitney *U* test).

There was no significant correlation between the ETDQ-7 total score and improvement in V2–5 cm after vasoconstriction in group 1.

Discussion

Inferior turbinate enlargement can be unilateral or bilateral. Unilateral inferior turbinate enlargement is associated with septum deviation, and bilateral inferior turbinate enlargement is caused by allergic or nonallergic rhinitis. In chronic rhinitis, long-standing swelling may become irreversible. This may be due to dilated submucosal venous sinuses becoming varicose and unresponsive to sympathetic nervous system stimulation or medical treatment, or because of fibrosis.[22] In the present study, the relationship between ETD-related symptoms and inferior turbinate enlargement was evaluated for the first time. Patients with nasal obstruction due to inferior turbinate enlargement had significantly more symptoms related to ETD compared to the healthy controls.

In previous studies, the relationship between ETD and nasal factors has been evaluated using different methods, including symptom questions,[5,7] tympanometry,[23] and Toynbee and Valsalva tests.[24] In the present study, the relationship between ETD-related symptoms and nasal obstruction was evaluated for the first time using the ETDQ-7, which is the only patient-reported outcomes tool to have undergone initial validation studies. It can provide a more precise estimate of a disease burden and may yield information not readily identified by traditional clinical methods.[12] In the present study, the main problem of the patients in the inferior turbinate enlargement group was nasal obstruction; ear symptoms were not their major concern. Their median ETDQ-7 score was higher than healthy participants but not very high. Only 3 abnormal tympanograms were found among them, and the difference was not significant compared to the healthy participants. Based on the present study, the ETDQ-7 may be a useful tool in detecting patients with a mild level of ETD without clear objective findings, such as tympanic membrane retraction or middle ear effusion.

In the study by McCoul et al, the ETDQ-7 was able to discriminate between patients with ETD and those without. In their study, the mean (standard deviation) ETDQ-7 total score for the ETD group was 4.0 (1.1). In the present study, taking into account the relatively low median of the ETDQ-7 total score in the inferior turbinate enlargement group, the lack of significant difference in the amount of abnormal tympanometry results between the groups may cast doubt on whether the ear symptoms of the patients were just symptomology related to nasal obstruction itself and not ETD. In the present study, however, almost one fourth of the participants in the inferior turbinate enlargement group had an ETDQ-7 total score of 3.0 or more (range, 3.0-4.9), representing the same severity of symptoms as the patients with ETD in the study by McCoul et al.[12]

In the present study, patients with chronic rhinosinusitis and significant nasal septum deviation were excluded. However, the relationship between these nasal factors and ETD has been documented in the previous literature. In a prospective series of 167 patients with adult-onset otitis media with effusion (OME), Finkelstein et al[25] found evidence of paranasal sinus disease, particularly in the ethmoids, in 66% of cases. In a retrospective study by Stoikes et al,[7] symptoms of ET dysfunction were found to improve or resolve in the majority of patients undergoing endoscopic sinus surgery. Low and Willatt[26] evaluated the relationship between middle ear pressure and a deviated nasal septum. They found that middle ear pressure ipsilateral to the obstructed nasal passage was negatively correlated with the degree of asymmetry of the patencies of the 2 nasal passages. Middle ear pressure improved in both ears after septal surgery. They postulated that postnasal airflow turbulence associated with a deviated nasal septum may lead to ETD. Deron et al,[27] in turn, found that septum deviation has as much influence on the passive opening pressure of the ET on the deviated side as on the nondeviated side.

In allergic rhinitis, nasal mucosal edema can affect the ET by direct expansion to the nasopharyngeal ET orifice or through nasal obstruction. Nasal obstruction can then lead to an increase in negative pressure in the nasopharynx, resulting secondarily in decreased ET patency, disturbance of its ciliary epithelium function, and obstruction of the ET, with a subsequent increase in the negative pressure of the ME cavity.[28] There are many studies that support the role of allergic rhinitis in the development of ETD and OME, whereas there are only a few reports on the role of nonallergic rhinitis.[29] Most of these studies deal with children and evaluate the relationship between allergic rhinitis and OME among them.[30,31] In a recent large American retrospective analysis of cross-sectional national databases, the presence of allergic rhinitis was found to significantly increase the odds of OME, ETD, or tympanic membrane retraction (odds ratio = 4.2) in children age 6 years or older.[31] In a prospective Mexican study, both children and adults with mostly perennial allergic rhinitis had more negative values of tympanometric peak pressure than the controls, indicating a higher risk of ETD.[23] Ohrui et al[5] explored whether there is an association between allergic rhinitis and ear pain experienced in hypobaric chamber training in the Japan Air Self-Defense Force. They hypothesized that the increased incidence of ear pain may be due to the increased incidence of ETD associated with allergic rhinitis. Trainees with allergic rhinitis complained of ear pain significantly more often during the allergy season than trainees without allergic rhinitis.

There are few previous studies that have compared the incidence of ETD between patients with an allergic cause of nasal obstruction and patients with a nonallergic cause of nasal obstruction. In a Danish birth cohort study of 291 children in the sixth year of life, OME was associated with allergic rhinitis (odds ratio = 3.4) but not with nonallergic rhinitis or mucosal swelling.[30] Bakhshaee et al[24] investigated the ET function of patients with nasal obstruction due to nasal polyposis. The ET function in the patients with polyposis was disturbed. However, regression analysis revealed that infection and allergic inflammation associated with polyposis have more important roles in ET function than the obstructive nature of the disease. In the present study, almost half of the patients in the inferior turbinate enlargement group (group 1) had a positive result in allergy testing. However, there was no significant difference in ETD-related symptoms between the participants with allergic sensitization and other participants in the group. This finding supports the idea that nasal obstruction in itself may have a predisposing role in ETD. It is also possible that in some cases of chronic inferior turbinate enlargement, the nasal mucosal edema, which can originally be caused by environmental allergens or nonallergic and nonspecific triggers, can expand to the nasopharyngeal ET orifice, disturbing ET function. However, the degree of mucosal edema in the anterior part of the nose does not seem to correlate directly with the degree of disturbances in the ET, which is supported by the finding that there was no correlation between the ETDQ-7 total score and improvement in V2–5 cm after vasoconstriction.

The consensus statement by Schilder et al[2] shows agreement that to diagnose dilatory ETD, patient-reported symptoms should be combined with evidence of negative pressure in the middle ear as assessed by clinical assessment. Tympanometry was the objective examination method in detecting the possible dilatory ETD in the present study. The finding that there was no significant difference in the amount of abnormal tympanometry results between the groups can partly be explained by the inadequate power of the study. A larger number of participants might have led to significant differences. In any case, that is why we are not able to definitively say that dilatory ETD, and not just ETD-related symptoms, is more common among patients with inferior turbinate enlargement. However, it is sometimes very difficult to detect the signs of negative pressure by clinical methods. In mild or fluctuating cases, patients may have symptoms suggestive of ETD but the clinical tests are within normal limits, whereas in more severe cases, the tympanic membrane findings are usually abnormal. For example, in cases of baro-challenge-induced ETD, tympanometry may be normal.[2] Overall, the added value of tympanometry in this study is low. The weakness of the ETDQ-7, in turn, is that it cannot discriminate between the 3 subtypes of ETD.[16] Therefore, it cannot be used as a sole criterion for the diagnosis of dilatory ETD. In cases of patulous ET, patients often complain of symptoms that are similar to those of patients with dilatory ETD, but there is also otoscopic or tympanometric evidence of excursion of the tympanic membrane with breathing, and patients often report autophony.[2]

Conclusion

Patients with chronic nasal obstruction caused by inferior turbinate enlargement have more symptoms related to ETD than healthy controls. Most patients with ETD had normal tympanometry and normal otoscopy, which indicates a baro-challenge-induced ETD. Whether the patient has allergic sensitization or not does not seem to cause a difference in symptoms related to ETD.

Declaration of Conflicting Interests

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The Effect of Inferior Turbinate Surgery on Ear Symptoms

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Objective: The aim of this placebo-controlled study was to evaluate the effect of various inferior turbinate surgery techniques on Eustachian tube dysfunction-related symptoms.

Study Design: Outcomes were evaluated using the Eustachian Tube Dysfunction Questionnaire (ETDQ-7) and tympanometry results.

Methods: A total of 72 consecutively blinded and randomized adult patients with enlarged inferior turbinates due to persistent year-round rhinitis underwent either a radiofrequency ablation, diode laser, microdebrider-assisted inferior turbinoplasty, or sham surgery procedure. Assessments were conducted prior to surgery and 3 months subsequent to the surgery.

Results: In the evaluation of all patients, radiofrequency ablation, microdebrider-assisted inferior turbinoplasty, and sham surgery procedures decreased the ETDQ-7 total score significantly. In a three-way analysis of covariance, there were no significant differences in the results between sham surgery and any of the active treatment procedures. Allergic sensitization, sex, and age also had no effect on the results. There were no significant changes in the pre- and postoperative amounts of abnormal tympanometry curves or in the pre- and postoperative tympanometric peak pressure values in the actively treated patients or in the sham surgery group.

Conclusion: The improvement of Eustachian tube dysfunction-related symptoms due to surgery of the anterior half of the inferior turbinate was found to be equal to placebo. The findings of this study do not support the use of reduction of the anterior half of the inferior turbinate as a sole procedure intended to treat the ear symptoms assessed by the ETDQ-7 questionnaire.

Key Words: Eustachian tube dysfunction, symptoms, nasal obstruction, inferior turbinate surgery, placebo-controlled, randomized.

Level of Evidence: 1b.

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INTRODUCTION

Inferior turbinate enlargement is one of the main causes of nasal obstruction. Bilateral inferior turbinate swelling is due to allergic or nonallergic rhinitis. Intranasal corticosteroids are the most important medicine group in the treatment of rhinitis. When medical therapy for enlarged inferior turbinates fails, turbinate surgery can be performed.[1,2]

Eustachian tube dysfunction (ETD) is a common condition in otorhinolaryngology practice. Symptoms include fullness or clogging of the ears, pain or discomfort, hearing loss, tinnitus, dizziness, and an inability to rapidly equilibrate middle ear pressure.[3,4] ETD is in most cases caused by mucosal inflammation and edema in the Eustachian tube (ET) lumen.[5] It has been presented that sinonasal diseases, such as nasal viral upper-respiratory tract infections,[6] allergic rhinitis,[7] and chronic rhinosinusitis[8] can cause mucosal inflammation that leads to ETD. However, the relationship between chronic nasal obstruction caused by inferior turbinate enlargement and ETD and the effect of turbinate surgery on ETD have not been evaluated previously in the literature.

Many subjective and objective methods have been reported for measuring ET function, including otoscopic appearance, the Valsalva and Toynbee tests, tympanometry, tubomanometry,[9] and sonotubometry.[10] However, due the complexity of the functional anatomy and physiology of the ET, there still is a lack of a diagnostic gold-standard for obstructive ET dysfunction.[4,11]

McCoul et al. have developed the Eustachian Tube Dysfunction Questionnaire (ETDQ-7), which is a validated, organ-specific tool for the assessment of symptoms in ETD.[4] Its usefulness has been shown in recent studies.[9,12,13] Thus far, it has not been used in the evaluation of the relationship between ETD and functional problems of the nose.

The aim of this placebo-controlled study was to evaluate the effect of various inferior turbinate surgery techniques, such as radiofrequency ablation (RFA), diode laser, and microdebrider-assisted inferior turbinoplasty (MAIT), on ETD-related symptoms using the ETDQ-7 as an assessment method.

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MATERIALS AND METHODS

The study was carried out at Tampere University Hospital, Tampere, Finland, between February 2014 and November 2016. The institutional review board approved the study design (R13144), and all patients provided written, informed consent. A total of 76 consecutive adult patients with enlarged inferior turbinates due to persistent year-round rhinitis were enrolled in this study. The patients presented symptoms of bilateral nasal obstruction related to inferior turbinate congestion that had not responded to a 3-month trial of appropriate treatment with topical corticosteroids. Patients with significant nasal septum deviation affecting the nasal valve region, internal/external valve collapse/stenosis, chronic rhinosinusitis with or without polyposis, previous nasal surgery, sinonasal tumor, Ménière's disease, previous ear surgery, severe systemic disorder, severe obesity, and malignancy were excluded.

Cone-beam computed tomography (Planmeca Max, Planmeca, Helsinki, Finland) was used to exclude patients with chronic rhinosinusitis from the study. Serum-specific IgE level measurements were used to identify the patients with an allergic sensitization. Allergic sensitization was defined as a specific IgE > 0.35 for any common airborne allergen (cat, dog, horse, birch, grass, mugwort, *D. pteronyssinus*, and molds).

The definition of inferior turbinate enlargement was based on persistent bilateral symptoms, a finding of bilateral swelling of the inferior turbinates in nasal endoscopy, and the evident shrinking of both turbinates in a decongestion test. The nasal response to the topical vasoconstrictor 0.5% xylometazoline hydrochloride (Nasolin, Orion, Finland) in both nasal cavities 15 minutes before obtaining the second measurement was evaluated objectively using acoustic rhinometry (Acoustic Rhinometer A1, GM instruments Ltd, Kilwinning, UK). An improvement of less than 30% in anterior nasal cavity volume (V2–5 cm)—the most sensitive measure of change in mucosal swelling during decongestion[14]—in one or both nasal cavities was considered normal, and those patients were excluded from the study. The limit value of 30% was chosen according to previous literature.[15–17]

Patients were consecutively randomized into active treatment groups (RFA, diode laser, MAIT) and a sham surgery group using the Minim program, which is a free MS-DOS program that randomizes patients into treatment groups by the method of minimization.

The surgical treatment was performed in similar circumstances for all groups in the day surgery department of the hospital's ear, nose, and throat clinic. All surgical procedures were performed by the same surgeon (T.H.). The staff of the day surgery section was instructed to avoid any kind of communication—before and during the operation, as well as during the postoperative care—that might reveal the group of the patient. All of the alternative surgical devices were available in the operation room. The procedures were carried out under local anesthesia with patients' eyes covered.

First, the inferior turbinates were topically anesthetized using cotton strips with a mixture of lidocaine 40 mg/mL (Lidocain, Orion, Finland) and two to three drops of epinephrine 0.1% in 5 to 10 mL of lidocaine. The local anesthetic (Lidocain 10 mg/mL c. adrenalin, Orion, Finland) was then applied to the medial portions of the inferior turbinates. All the procedures were performed under the direct vision of a straight, 4 mm-diameter, 0-degree endoscope (Karl Storz, Germany). In all the groups with different techniques, the treatment was given to the medial side of the anterior half of the inferior turbinate. Nasal packing (Ivalon, Fabco, New London, CT, U.S.A) was applied only if active bleeding developed during the surgery.

The RFA treatment was carried out with a radiofrequency generator (Sutter RF generator BM-780 II, Freiburg, Germany). The Binner bipolar needle electrode was inserted into the medial submucosal tissue of the inferior turbinate. The upper and lower parts of the anterior half of the inferior turbinate were treated for 6 seconds at 10-watt (W) output power in three areas.

The diode laser treatment was given with a diode laser (FOX Laser, A.R.C. LASER GmbH, Nuremberg, Germany). The settings were as follows: wavelength of 980 nm, output power of 6 W in continuous-wave mode, and laser delivery by a 600 μm fiber using contact mode. Four parallel stripes were made on the mucosa by drawing the fiber from the posterior to the anterior direction along the medial edge of the inferior turbinate.

TABLE I.
Eustachian Tube Dysfunction Questionnaire-7 (ETDQ-7) Questions.

1. Pressure in the ears?
2. Pain in the ears?
3. A feeling that your ears are clogged?
4. Ear symptoms when you have a cold or sinusitis?
5. Crackling or popping sounds in the ears?
6. Ringing in the ears?
7. A feeling that your hearing is muffled?

In the MAIT treatment, a 2.9 mm-diameter rotatable microdebrider tip (Medtronic Xomed, Jacksonville, FL, U.S.A.) was firmly pushed toward the turbinate bone until it pierced the mucosa of the anterior face of the inferior turbinate. Next, a submucosal pocket was dissected by tunneling the elevator tip in an anterior-to-posterior and superior-to-inferior sweeping motion. Once an adequate pocket had been created, resection of the stromal tissue was carried out by moving the blade back and forth in a sweeping motion, with the system set at 3,000 rpm using suction irrigation.

In the sham surgery procedure, small nasal mucosal biopsies for histological and cilia analysis were first taken from the anterior medial portions of the inferior turbinates, causing minor bleeding. Next, the radiofrequency tissue ablation device was turned on repeatedly near the patient but without the needle electrodes of the device touching the patient; the patient could only hear the acoustic tone of the device. During this sound deception, a suction tube and a nasal endoscope were moved lightly in both sides of the nose for a couple of minutes to convince the patient that they had undergone surgery.

All the patients were evaluated prior to surgery and 3 months subsequent to the surgery. All clinical examinations were performed by the same examiner (T.H.), who also was the operator and not blinded to the patients' groups. The patients filled the ETDQ-7. During the control visits, the patients filled the questionnaire before meeting the examiner. The ETDQ-7 consists of seven questions with a seven-item Likert scale, with a response of 1 indicating no problem and 7 indicating a severe problem. The total score is divided by 7 to give an overall score ranging from 1.0 to 7.0.[4] The questions comprising the ETDQ-7 are shown in Table I. Tympanometry also was performed. The tympanometry curves were classified as follows: type A, normal Eustachian tube function; type B, flat tympanogram, characteristic of the presence of fluid in the middle ear or eardrum perforation; and type C, peak at very negative pressure (< -150 dPa), which may be indicative of eardrum retraction. Tympanometric peak pressure (TPP)—that is, the peak admittance in the tympanogram and an indirect measurement of middle ear pressure—also was documented.

IBM SPSS Statistics 22.0 (IBM Corp., Armonk, NY) was used for the statistical analyses. All the nonparametric data was statistically processed using the Wilcoxon signed rank test. The chi-squared test was used in the evaluation of tympanometry curves. The effects of multiple factors were evaluated using a three-way analysis of covariance (ANCOVA).

RESULTS

Of the 76 patients enrolled in the study, four withdrew from the study before the operation took place.

TABLE II.
Patients' Characteristics.

Age (years), Mean (range)	44 (23–69)
Sex	
Male, No. (%)	42 (58)
Female, No. (%)	30 (42)
Allergic sensitization	
Yes, No. (%)	28 (39)
No, No. (%)	44 (61)
Technique	
RFA, No. (%)	20 (28)
Diode laser, No. (%)	18 (25)
MAIT, No. (%)	23 (32)
Sham surgery, No. (%)	11 (15)
Preoperative ETDQ-7 total score	
1.0–1.9, No. (%)	32 (45)
2.0–2.9, No (%)	24 (33)
3.0 or more, No. (%)	16 (22)

ETDQ-7 Eustachian Tube Dysfunction Questionnaire-7; MAIT = microdebrider-assisted inferior turbinoplasty; RFA = radiofrequency ablation.

A total of 72 patients underwent surgery and finally were included in the study. The patients' characteristics are described in Table II. Some 45% of the patients had a preoperative ETDQ-7 total score of 1.0 to 1.9; 33% had a score of 2.0 to 2.9; and 22% had a score of 3.0 or more (range 3.1–4.4).

In the active treatment groups, there were abnormal tympanometry curves in six (five type B and one type C) ears preoperatively and seven (six type B and one type C) ears postoperatively. The difference was not statistically significant. In the sham surgery group, there was an abnormal tympanometry curve in only one ear (type C) preoperatively, and there were no abnormal findings postoperatively. This difference was not significant either. There were no significant changes in preoperative and postoperative TPP values among either the actively treated patients or the sham surgery patients (Table III).

The results of the ETDQ-7 are shown in Table IV. In the evaluation of all patients, RFA, MAIT, and sham surgery procedures decreased the total score significantly. When only patients with a preoperative score 2.0 or more were evaluated, all the active treatment procedures decreased the total score significantly.

A three-way ANCOVA was run on the sample of 72 patients to examine the effect of sex, allergy status, and procedure group on the ETDQ-7 score change. Age was added to the model as a continuous covariate. In the evaluation of all patients, none of the factors had a significant individual main effect on the change in ETDQ-7 total score. There were no significant differences in the change in ETDQ-7 total score between the procedure groups, nor were there significant differences in the results between the sham surgery and any of the active treatment procedures. Allergic sensitization, sex, and age had no effect on the results either. The analysis was repeated for the patients with a preoperative total score 2.0 or more, and the same results were found.

DISCUSSION

In previous studies, the relationship between ETD and sinonasal factors has been evaluated using various methods, including symptom questions,[7,18] tympanometry,[19,20] and the Toynbee and Valsalva tests.[21] To carry out a placebo-controlled study, it is suitable to use a validated questionnaire, if possible. In the present study, the relationship between nasal obstruction and ETD-related symptoms was evaluated using the ETDQ-7, which is the only patient-reported outcomes tool to have undergone initial outcome studies. It is an organ-specific instrument for the assessment of symptoms, which can provide a more precise estimate of a disease burden and may yield information not readily identified by traditional clinical methods.[4]

The effect of sinonasal procedures and therapies on ET function has been evaluated in a few previous studies. Low and Willatt evaluated the relationship between middle ear pressure and a deviated nasal septum. They found out that middle ear pressure ipsilateral to the obstructed nasal passage was negatively correlated to the degree of asymmetry of the patencies of the two nasal passages. Middle ear pressure improved in both ears after septal surgery. They postulated that postnasal airflow turbulence associated with a deviated nasal septum may lead to Eustachian tube dysfunction.[19] Deron et al. in turn found out that correction of the septal deviation improved the passive opening pressure of the Eustachian tube on the deviated side similarly to the nondeviated side.[22] In a retrospective study by

TABLE III.
Tympanometry Results (N = 144 ears).

	Preoperative	Postoperative
Abnormal tympanometry (B or C)		
Active treatment groups (N = 122), No. (%)	6 (5)	7 (6)*
Sham surgery group (N = 22), No. (%)	1 (5)	0 (0)*
Tympanometric peak pressure (dPa)		
Active treatment groups, median (IQR)	−4.0 (−15.0 to 14.0)	−4.0 (−15.0 to 2.0)†
Sham surgery group, median (IQR)	−8.0 (−16.5 to 16.3)	−5.0 (−16.5 to 14.5)†

*Not significant, chi-squared test.
†Not significant, Wilcoxon signed rank test.
IQR = interquartile range (Q25–Q75)

TABLE IV.
Results of the ETDQ-7.

All Patients				
	Preoperative ETDQ-7, Median (IQR)	Postoperative ETDQ-7, Median (IQR)	ETDQ-7 Change, Mean (95% CI)	*P* Value
Procedure				
All active treatments, n = 61	2.1 (1.4 to 2.9)	1.7 (1.2 to 2.1)	−0.4 (−0.6 to −0.2)	<0.001*
RFA, n = 20	2.5 (1.3 to 3.3)	1.7 (1.5 to 2.3)	−0.4 (−0.8 to −0.02)	0.03*
Diode laser, n = 18	1.6 (1.3 to 2.4)	1.4 (1.1 to 1.9)	−0.3 (−0.6 to 0.01)	0.06
MAIT, n = 23	2.4 (1.6 to 3.3)	1.9 (1.3 to 2.4)	−0.5 (−0.9 to −0.2)	0.006*
Sham surgery, n = 11	2.1 (1.4 to 2.9)	1.4 (1.3 to 2.1)	−0.5 (−0.9 to −0.1)	0.04*
Preoperative ETDQ-7 Total Score 2.0 or More				
Procedure				
All active treatments, n = 34	2.9 (2.4 to 3.4)	2.0 (2.43.4)	-0.8 (−1.0 to −0.5)	<0.001*
RFA, n = 12	2.9 (2.6 to 3.7)	2.1 (1.6 to 3.4)	−0.8 (−1.4 to −0.2)	0.02*
Diode laser, n = 7	2.6 (2.1 to 2.9)	1.9 (1.3 to 2.3)	−0.7 (−1.3 to −0.2)	0.02*
MAIT, n = 15	3.1 (2.4 to 3.3)	2.0 (1.6 to 2.4)	−0.8 (−1.3 to −0.3)	0.01*
Sham surgery, n = 6	2.8 (2.1 to 3.6)	2.1 (1.7 to 2.6)	−0.7 (−1.4 to −0.02)	0.08

*Statistically significant, Wilcoxon signed rank test.
ETDQ-7 = Eustachian Tube Dysfunction Questionnaire-7; IQR = Interquartile range (Q25–Q75); MAIT = microdebrider-assisted inferior turbinoplasty; RFA = radiofrequency ablation.

Stoikes et al., symptoms of ET were found to improve or resolve in the majority of patients undergoing endoscopic sinus surgery.[18] In their randomized, prospective, placebo-controlled trial, Gluth et al. evaluated the efficacy of nasal steroid spray in treating the tympanometric signs and symptoms of ETD. They found no statistically significant difference in the normalization of abnormal tympanometric signs or in the overall poststudy symptom score between the active treatment arm and placebo.[23]

In the present study, the effect of inferior turbinate surgery on ETD-related symptoms was evaluated for the first time. The symptoms were found to improve due to inferior turbinate procedures. However, sham surgery improved the symptom score as effectively as real surgery. Furthermore, in the subgroup with more preoperative ear symptoms, there were no significant differences in the ETDQ-7 total score changes between the active treatments and the sham surgery. In addition, there were no significant changes in the pre- and postoperative amounts of abnormal tympanometry curves or in the pre- and postoperative TPP values among actively treated patients and the sham surgery patients. Possible changes in TPP values may have indicated minor changes in the middle ear pressure as a result of the operation. The lack of improvement in TPP values in the active treatment group suggests that the reduction of the anterior part of the inferior turbinate does not have even a minor effect on ET function. It is likely that in chronic inferior turbinate enlargement, the nasal mucosal edema—which can originally be caused by environmental allergens or nonallergic, nonspecific triggers—can expand to the nasopharyngeal ET orifice, disturbing ET function. Based on the present study, the surgical treatment of the anterior part of the inferior turbinate did not have any real effect on the nasopharyngeal ET orifice and possible ETD.

The internal nasal valve area is the narrowest portion of the upper nasal airway, and the anterior portion of the inferior turbinate is the predominant structure in this part of the nose; therefore, it plays a major role in nasal obstruction.[2,24] Surgical treatment of the anterior part of the inferior turbinate has been found to be effective in decreasing nasal obstruction.[25] The posterior part of the turbinate, which is anatomically located very close to ET orifice, was not operated on in the present study. The idea of this study was also to compare the efficacy of various inferior turbinate surgery techniques in the treatment of the problem. To make the procedures as comparable as possible, we treated the same length of the turbinate with every technique. The easiest way to guarantee that was to limit the operation to the anterior part of the inferior turbinate because in some cases it can be difficult to operate the posterior part of the turbinate under local anesthesia.

In the present study, the patients' main problem was nasal obstruction. Ear symptoms were not their major concern in the first place. The aim of this study was to examine possible ETD-related symptoms among the patients and the effect of inferior turbinate surgery on the symptoms. A recent consensus statement defining ETD agreed that to diagnose dilatory Eustachian tube dysfunction, patient-reported symptoms should go together with evidence of negative pressure in the middle ear.[26] In the present study, more than half of the patients had an ETDQ-7 score of 2.0 or more, and more than one-fifth of the patients had a score of 3.0 or more, which represents the same severity of symptoms as patients found to have ETD in the study by McCoul et al. However, only less than 10% of the patients enrolled had an abnormal tympanogram (type B or C) confirming the diagnosis of ETD. A clear weakness of ETDQ-7, in turn, is that it cannot discriminate between patients with obstructive ET dysfunction and patulous ET. Therefore, it cannot be used as a sole criterion for the diagnosis of ETD. For these reasons, we are not able to generalize the results of this study to ETD. We can only talk about the effect of inferior turbinate procedure on patients' symptoms suggestive of ETD.

All clinical examinations and operations were performed by the same physician, who was not blinded to the patients' groups. Unblinding of the examining physician could introduce unintentional bias by causing misinterpretation of data. However, the examination parameters used in this study were not based on the subjective evaluation of the examining physician. Parameters of tympanometry, unlike otoscopic appearance or Valsalva and Toynbee tests, are not based on the subjective evaluation of the examiner. That is why tympanometry was chosen to be the only objective examination method in this study. However, it sometimes is very challenging to make a confirmed diagnosis of ETD based on both patient-reported symptoms and signs of negative pressure in the middle ear in the form of abnormal tympanometry curves. In mild or fluctuating cases, the patients may have symptoms suggestive of ETD, but their tympanometry curves can be within normal limits.

CONCLUSION

The improvement of ETD-related symptoms due to surgery of the anterior half of the inferior turbinate was found to be equal to placebo. The findings of this study do not support the use of reduction of the anterior half of the inferior turbinate as a sole procedure intended to treat the ear symptoms assessed by the ETDQ-7 questionnaire.

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A Prospective, Randomized, Placebo-Controlled Study of Inferior Turbinate Surgery

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Objectives/Hypothesis: The purpose of this study was to compare radiofrequency ablation, diode laser, and microdebrider-assisted inferior turbinoplasty techniques in the treatment of chronic nasal obstruction caused by inferior turbinate enlargement, and to compare these techniques with a placebo procedure.

Study Design: Prospective, randomized, single-blinded, placebo-controlled study.

Methods: A total of 98 consecutive patients with enlarged inferior turbinates due to persistent year-round rhinitis were randomized into a placebo, radiofrequency ablation, diode laser, and microdebrider-assisted inferior turbinoplasty groups in a ratio of 1:2:2:2. All the procedures were carried out under local anesthesia with the patients' eyes covered. Assessments were conducted prior to surgery and 3 months subsequent to the surgery.

Results: The severity of nasal obstruction measured by visual analog scale score decreased statistically significantly in all the groups, including placebo. Radiofrequency ablation ($P = .03$), diode laser ($P = .02$), and microdebrider-assisted inferior turbinoplasty ($P = .04$) all decreased the symptom score of the severity of nasal obstruction statistically significantly more compared to the placebo procedure.

Conclusions: The placebo effect had a large role in the overall improvement of the severity of nasal obstruction after the inferior turbinate surgery. However, all three techniques provided a statistically significant additional reduction of the severity of nasal obstruction compared to the placebo procedure.

Key Words: Nasal obstruction, inferior turbinate surgery, placebo controlled, randomized.

Level of Evidence: 1b.

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INTRODUCTION

Inferior turbinate enlargement due to persistent year-round allergic or nonallergic rhinitis is one of the main causes of chronic nasal obstruction.[1] Intranasal corticosteroids are the most important medicine group in the treatment of rhinitis and hypertrophied inferior turbinates. When medical therapy for enlarged inferior turbinates fails, turbinate surgery can be considered.[2]

Various surgical techniques have been described for the reduction of hyperplastic inferior turbinates. However, no clear consensus exists in the literature on the exact role of surgery or the most optimal method for surgical treatment.[3] In recent years, surgical procedures have concentrated on the minimal disturbance of the nasal mucosa. The aim of inferior turbinate surgery has been to maximize the volumetric reduction of the turbinate to decrease the nasal obstruction while maintaining nasal function and minimizing complications.[4]

Microdebrider-assisted inferior turbinoplasty (MAIT)—a powered subtype of submucosal resection[5]—and radiofrequency ablation (RFA) are referred to as mucosal sparing techniques; they are widely used and the most commonly studied techniques in the recent literature.[4] The diode laser technique has also gained in popularity due to its ease of use in the office setting.[6]

Thus far, three placebo-controlled trials have been published regarding RFA. These studies have evaluated the influence of the treatment on subjective scores of nasal obstruction, and they found that the placebo effect seems to have a role in the results of turbinate surgery.[7–9]

The purpose of this prospective, randomized, single-blinded, placebo-controlled study was to compare RFA, diode laser, and MAIT techniques in the treatment of chronic nasal obstruction caused by inferior turbinate enlargement, and to compare these techniques with a placebo treatment.

MATERIALS AND METHODS

This prospective randomized study was carried out at Tampere University Hospital, Tampere, Finland, between February 2014 and September 2017. The institutional review board approved the study design (R13144), and all patients provided written, informed consent. A total of 98 consecutive adult patients with enlarged inferior turbinates due to persistent year-round rhinitis were enrolled in this study. The patients presented symptoms of bilateral nasal obstruction related to inferior turbinate congestion that had not responded to a 3-month trial of appropriate treatment with intranasal corticosteroids. Patients with significant nasal septum deviation

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affecting the nasal valve region, internal/external valve collapse/stenosis, chronic rhinosinusitis with or without polyposis, previous nasal surgery, sinonasal tumor, severe systemic disorder, severe obesity, or malignancy were excluded.

Cone beam computed tomography (Planmeca Max; Planmeca, Helsinki, Finland) was used to exclude patients with chronic rhinosinusitis from the study. Serum-specific immunoglobulin E (IgE) level measurements were used to identify the patients with an allergic sensitization. Allergic sensitization was defined as a specific IgE > 0.35 for any common airborne allergen (cat, dog, horse, birch, grass, mugwort, *Dermatophagoides pteronyssinus*, and molds).

The definition of inferior turbinate enlargement was based on persistent bilateral symptoms, a finding of bilateral swelling of the inferior turbinate in nasal endoscopy, and the evident shrinking of both turbinates in a decongestion test, which could not be applied to either bony turbinate enlargement of soft tissue hypertrophy unresponsive to topical decongestant. The nasal response to the topical vasoconstrictor 0.5% xylometazoline hydrochloride (Nasolin; Orion, Espoo, Finland) in both nasal cavities 15 minutes before obtaining the second measurement was evaluated objectively using acoustic rhinometry (Acoustic Rhinometer A1; GM Instruments Ltd., Kilwinning, United Kingdom). An improvement of less than 30% in anterior nasal cavity volume (V2–5 cm) in one or both nasal cavities was considered normal, and those patients were excluded from the study. The limit value of 30% was chosen according to previous literature.[10–12]

Patients were consecutively randomized into placebo, RFA, diode laser, and MAIT groups in a ratio of 1:2:2:2 using Minim, a free MS-DOS program that randomizes patients to treatment groups by the method of minimization. Proportional amounts of patients with allergic sensitization were kept similar for each group. Age and sex distributions were also kept similar for each group.

The surgical treatment was performed in similar circumstances at the day surgery department of the hospital's ear, nose, and throat clinic. All surgical procedures were performed by the same surgeon (T.H). The staff of the day surgery department was instructed to avoid all communication before and during the operation, as well as during the postoperative care, that might reveal the group of the patient. All the alternative surgical devices were available in the operation room. The procedures were carried out under local anesthesia with the patient's eyes covered.

First, the inferior turbinate was topically anesthetized using cotton strips with a mixture of lidocaine 40 mg/mL (Lidocain; Orion) and 2 to 3 drops of epinephrine 0.1% in 5 to 10 mL of lidocaine. Next, 1.5 mL of local anesthetic (Lidocain 10 mg/mL c. Adrenalin 10 μg/mL; Orion) was then applied to the medial portions of both inferior turbinates. All the procedures were performed under the direct vision of a straight, 4-mm-diameter, 0° endoscope (Karl Storz, Tuttlingen, Germany). In all the groups with every technique, the treatment was given to the medial side of the anterior half of the inferior turbinate. Short-term (until the next morning) nasal packing with a nonabsorbable packing material (Ivalon; Fabco, New London, CT) was applied only if active bleeding developed during the surgery.

The RFA treatment was carried out with a radiofrequency generator (Sutter RF generator BM-780 II; Sutter, Freiburg, Germany). A Binner bipolar needle electrode was inserted into the medial submucosal tissue of the inferior turbinate. The upper and lower parts of the anterior half of the inferior turbinate were treated for 6 seconds at 10 W output power in three areas.

The diode laser treatment was given with a FOX Laser (A.R.C. Laser GmbH, Nuremberg, Germany). The settings were as follows: wavelength of 980 nm, output power of 6 W in continuous-wave mode, and laser delivery by a 600-μm fiber using contact mode. Four parallel stripes were made on the mucosa by drawing the fiber from the posterior to the anterior direction along the medial edge of the anterior half of the inferior turbinate.

In the MAIT treatment, a 2.9-mm-diameter rotatable microdebrider tip (Medtronic Xomed, Jacksonville, Florida) was firmly pushed toward the turbinate bone until it pierced the mucosa of the anterior face of the inferior turbinate. Next, a submucosal pocket was dissected by tunneling the elevator tip in an anterior-to-posterior and superior-to-inferior sweeping motion. Once an adequate pocket had been created, resection of the stromal tissue was carried out by moving the blade back and forth in a sweeping motion, with the system set at 3,000 rpm using suction irrigation.

In the placebo procedure, small (2–3 mm in diameter) nasal mucosal biopsies were first taken from the anterior medial portions of the inferior turbinates, causing minor bleeding. Next, a radiofrequency tissue ablation device was turned on repeatedly near the patient, but without the needle electrodes of the device touching the patient; the patient could only hear the acoustic tone of the device. During this sound deception, a suction tube and a nasal endoscope were moved lightly in both sides of the nose for a couple of minutes to convince the patients that they had undergone surgery.

After the operation, none of the patients were given medical treatment, including analgesics, nasal steroids, and nasal decongestants. The patients were given a 100-mm visual analogue scale (VAS) questionnaire, which had been filled for the first time during the preoperative visit. They were asked to mark on the line the point that they feel represents their perception of their current state regarding postoperative nasal symptoms, including severity of nasal obstruction (not obstructed–very obstructed), discharge (no discharge–much discharge), crusting (no crust–much crust), and pain (no pain–much pain). The questionnaire was to be filled daily for the first week, and then after 2, 3, and 4 weeks postoperatively. They were instructed to return the questionnaire by mail 1 month after the operation.

All of the patients were evaluated prior to surgery and 3 months following the surgery. All clinical examinations were performed by the same examiner (T.H), who was also the operator and not blinded to the patients' group. The patients filled the VAS questionnaire regarding nasal symptoms during both visits. They were asked to mark on the line the point that they feel represents their perception of their current state. Acoustic rhinometry was also performed both before the surgery and during the control visit at 3 months. During the control visit, the patients filled the questionnaire before meeting the examiner.

IBM SPSS Statistics 22.0 (IBM, Armonk, NY) was used for the statistical analyses. All nonparametric data were statistically processed using the Wilcoxon signed rank test, Mann-Whitney *U* test, and Kruskal-Wallis test. In the cases with parametric data, the comparison between the groups was carried out by one-way analysis of variance.

RESULTS

The patients' characteristics are described in Table I and the data of the operations in Table II. The operation time for the MAIT procedure was statistically significantly longer compared to the other procedures.

TABLE I. Patients' Characteristics (N = 98).	
Characteristic	Value
Age, yr, median (range)	46 (19–69)
Sex, no.	
Male	56
Female	42
Group	
Placebo, no.	14
Allergic sensitization, no. (%)	
Yes	6 (43)
No	8 (57)
RFA, no.	28
Allergic sensitization, no. (%)	
Yes	12 (43)
No	16 (57)
Diode laser, no.	28
Allergic sensitization, no. (%)	
Yes	12 (43)
No	16 (57)
MAIT, no.	28
Allergic sensitization, no. (%)	
Yes	13 (46)
No	15 (54)

MAIT = microdebrider-assisted inferior turbinoplasty; RFA = radiofrequency ablation.

The operation time for the diode laser, in turn, was statistically significantly longer than the time for the RFA. The VAS score for pain during the operation was highest in the MAIT group, but there were no statistically significant differences between the groups. Five patients in the MAIT group and one patient in the diode laser group had moderate bleeding that required short-term (until next morning) nasal packing. Four patients in the MAIT group complained of notable bleeding during the first postoperative day, and three of them had to be treated at the outpatient clinic with short-term (until next morning) nasal packing.

The changes in nasal symptoms reported by the patients after the operation are described in Figure 1. The severity of nasal obstruction started to decrease immediately after MAIT and continued up to 4 weeks. In the diode laser and RFA groups, the response appeared slightly slower. In the placebo group, the response also started immediately and reached its final level after 2 weeks.

At the control visit at 3 months, minor crusting was seen in the nasal cavities of a single patient in the placebo group, in 12 patients in the RFA group, in six patients in the diode laser group, and in two patients in the MAIT group. One patient in the MAIT group had a small synechia. Atrophy was not found in any of the cases.

The changes in the VAS scores for nasal symptoms at 3 months are described in Table III. The severity of nasal obstruction decreased statistically significantly in all the groups. All the techniques used were compared separately with placebo using the Mann-Whitney *U* test. RFA ($P = .02$), diode laser ($P = .03$), and MAIT ($P = .04$) all decreased the symptom score for the severity of nasal obstruction statistically significantly more compared to the placebo procedure. In all the groups, nasal discharge and crusting decreased statistically significantly, but there were no statistically significant differences between the groups, including the placebo group (Table III). The change in V2–5 cm acoustic rhinometry values is described in Table IV. All three techniques improved the V2–5 cm values significantly, but there were no statistically significant differences between the groups, including placebo.

DISCUSSION

There are studies reporting notable intraoperative bleeding[13] or postoperative bleeding in the early days after MAIT,[14] and this was also the case in the present study. During the operation, the mean VAS score for pain was the highest in the MAIT group, but there was no statistical difference between the groups. Postoperatively, there was an increase in the VAS score for pain in the MAIT group, which lasted up to 1 week. This can possibly be explained by the direct surgical tissue trauma caused by the operation. Short-term nasal packing, which was most common in the MAIT group, may also partly explain the increase of pain during the first days of the follow-up. Increased pain was also reported during the first 2 days after diode laser treatment. This can possibly be explained by the higher temperature and therefore the more severe tissue damage caused by the laser compared to RFA. In the present study, a temporary increase in the symptom of nasal discharge and a

TABLE II.
Comparison of Operation Time, Pain During the Operation, and Bleeding of the Groups.

Group	Time, sec (95% CI)	Pain, VAS (95% CI)	Nasal Packing Needed, No.	Postoperative Bleeding, No.	Postoperative Bleeding Requiring Treatment, No.
Placebo	186 (167-205)	1.4 (0.6-2.1)	0	0	0
RFA	217 (194-240)	2.4 (1.6-3.1)	0	1	0
Diode laser	374 (329-420)	2.3 (1.6-3.1)	1	0	0
MAIT	545 (508-583)	2.9 (2.1-3.6)	5	4	3

CI = confidence interval; MAIT = microdebrider-assisted inferior turbinoplasty; RFA = radiofrequency ablation; VAS = visual analog scale.

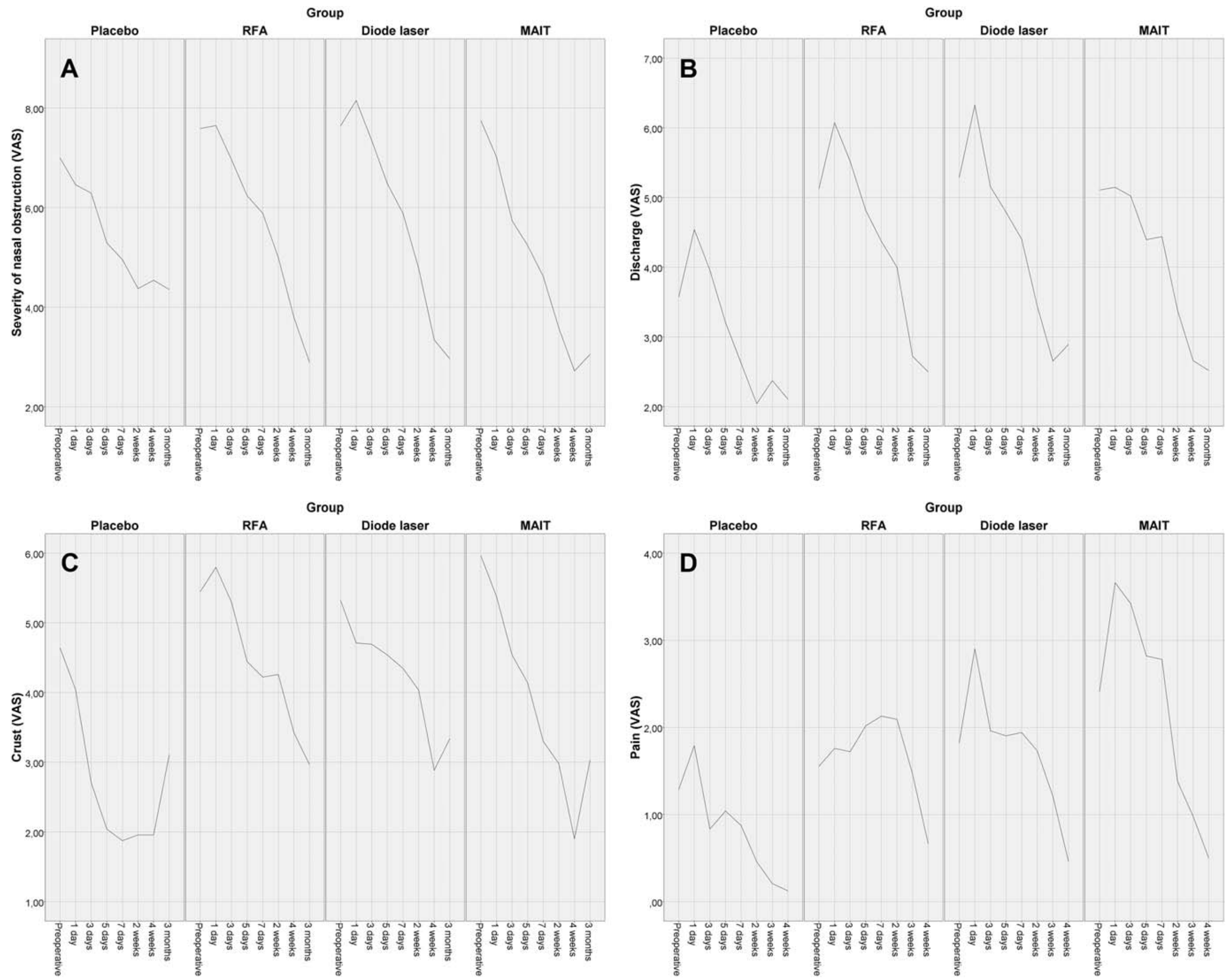

Fig. 1. Mean changes in the severity of nasal obstruction (A), discharge (B), crust (C), and pain (D) after the surgery. MAIT = microdebrider-assisted inferior turbinoplasty; RFA = radiofrequency ablation; VAS = visual analog scale.

minor increase in the symptom of crusting during the first postoperative days after RFA was noted. A similar finding has been reported in the previous studies.[15,16] Some patients treated with RFA complained of crust formation for as long as 3 months. In a study by Janda et al., patients showed moderate-to-severe nasal obstruction, crusting, and nasal secretion in the first 4 weeks following diode laser treatment.[6] In the present study, however, patients in the diode laser group on average reported a decrease in crusting immediately after the operation and an increase in nasal discharge only during the first 2 days. In some cases, however, crust formation continued up to 3 months.

In recent years, studies have been published comparing RFA and MAIT in the treatment of nasal obstruction. There are studies where the results of MAIT have been better in the short follow-up[14] and also in the longer follow-up.[17] There are also studies where the techniques have been found equal in efficacy.[18] A systematic review and meta-analysis by Acevedo et al. compared RFA and MAIT. They concluded that inferior turbinate reduction produces a significant subjective and objective improvement in nasal airflow in the short term, which is not related to the technique used.[19] There are also studies comparing RFA and the diode laser[20,21] and MAIT and the diode laser,[13] and no significant differences between the techniques have been found in any of these studies. No previous studies have compared all three techniques together.

In the present study, the decrease in the VAS score for severity of nasal obstruction started faster after MAIT. In MAIT, the submucosa of the turbinate is emptied immediately during the operation, whereas in the RFA and diode laser procedures, the heat caused by the device creates a submucosal lesion, inducing scarring and tissue volume reduction during the following weeks.[1,22] Postoperative nasal packing, which was most common in the MAIT group, squeezes the mucosa of the emptied turbinate against the bone and may so contribute to the faster response. Based on this conclusion and the higher rate of postoperative bleeding in the MAIT group, nasal packing can be recommended in the MAIT

TABLE III.
Change in the VAS Scores for Nasal Symptoms at Three Months.

	Placebo	RFA	Diode Laser	MAIT	*P* Value*
Severity of obstruction					
Preoperative, median (IQR)	7.0 (5.8 to 8.0)	8.0 (6.3 to 8.9)	8.0 (7.0 to 8.0)	8.0 (7.0 to 9.0)	NS
Postoperative, median (IQR)	4.0 (2.0 to 6.3)	2.0 (1.0 to 3.8)	3.0 (1.6 to 4.0)	3.0 (1.6 to 4.0)	
Change, median (IQR)	−2.5 (−5.0 to −0.8)	−5.0 (−7.0 to −3.3)	−5.0 (−6.0 to −3.0)	−5.5 (−6.4 to −3.0)	.04†
Change, mean [95% CI]	−2.6 [−4.0 to −1.3]	−4.7 [−5.6 to −3.8]	−4.7 [−5.4 to −4.0]	−4.7 [−5.7 to −3.7]	
P value‡	.004†	<.001†	<.001†	<.001†	
Change compared to placebo, mean [95% CI]		−2.1 [−4.0 to −0.1]	−2.1 [−4.0 to 0.1]	−2.1 [−4.1 to −0.1]	
P value§		.03†	.02†	.04†	
Discharge, median (IQR)					
Preoperative	3.5 (1.8 to 5.3)	6.0 (2.3 to 7.8)	5.5 (3.3 to 7.0)	5.0 (3.3 to 7.0)	NS
Postoperative	2.0 (0.9 to 3.0)	2.0 (0.0 to 4.8)	2.0 (1.0 to 4.1)	2.0 (1.0–4.5)	
Change	−1.5 (-4.0 to −0.3)	−2.0 (−5.0 to −0.6)	−2.5 (−4.0 to −1.0)	−2.0 (−4.8 to −0.4)	NS
P value‡	.06	<.001†	<.001†	.001†	
Crust, median (IQR)					
Preoperative	4.6 (3.0 to 6.3)	5.4 (4.6 to 6.3)	5.3 (4.6 to 6.0)	6.0 (5.1 to 6.8)	NS
Postoperative	3.1 (1.6 to 4.6)	3.0 (2.1 to 3.8)	3.3 (2.4 to 4.3)	3.0 (2.1 to 4.0)	
Change	−2.0 (−3.3 to −0.4)	−2.0 (−5.0 to −1.0)	−2.0 (−3.8 to 0.0)	−3.0 (−4.0 to −1.3)	NS
P value‡	.08	<.001†	<.001†	<.001†	

The distribution of the data is nonparametric; therefore, medians and interquartile ranges (IQR: Q25 to Q75) are used in the statistical testing.
*Kruskal-Wallis test.
†Statistically significant.
‡Wilcoxon signed rank test.
§Mann-Whitney *U* test with Bonferroni correction.
CI = confidence interval; IQR = interquartile range; MAIT = microdebrider-assisted inferior turbinoplasty; NS = not significant; RFA = radiofrequency ablation.

procedures. At the end of the 3-month follow-up, all three techniques decreased the VAS score for the severity of nasal obstruction and V2–5 cm values statistically significantly compared to the preoperative values, and they were equal in efficacy regarding both parameters.

So far, there have been only three placebo-controlled trials evaluating the influence of the treatment on the subjective scores of nasal obstruction. In a double-blinded, placebo-controlled trial by Powell et al., 22 patients were randomly assigned to either an RFA (n = 17) or placebo (n = 5) group. The beneficial effect of treatment on nasal obstruction with RFA was demonstrated, but it did not reach statistical significance, probably due to the small sample size.[7] A single-blinded, placebo-controlled trial with a crossover option by Nease et al. included 32 patients who were randomized to

TABLE IV.
Change in V2–5 cm Acoustic Rhinometry Values (One Side of the Nasal Cavity).

	Placebo	RFA	Diode Laser	MAIT	*P* Value*
V2–5 cm, cm^3					
Preoperative					
Median (IQR)	3.60 (2.82 to 4.94)	4.39 (3.02 to 5.65)	3.47 (2.71 to 4.36)	3.57 (2.52 to 4.58)	NS
Postoperative					
Median (IQR)	3.94 (2.82 to 5.33)	5.39 (4.29 to 6.48)	4.37 (3.56 to 5.60)	4.27 (3.37 to 5.41)	
Change					
Median (IQR)	0.39 (−0.21 to 0.96)	1.12 (−0.38 to 2.39)	0.84 (−0.41 to 1.66)	0.64 (−0.27 to 1.56)	NS
Mean [95% CI]	0.13 [−0.51 to 0.77]	1.14 [0.51 to 1.78]	0.85 [0.43 to 1.26]	0.86 [0.30 to 1.41]	
P value†	NS	<.001‡	.001‡	.003‡	

The distribution of the data is nonparametric; therefore, medians and interquartile ranges (IQR: Q25–Q75) are used in the statistical testing.
*Kruskal-Wallis test.
†Wilcoxon signed rank test.
‡Statistically significant.
CI = confidence interval; IQR = interquartile range; MAIT = microdebrider-assisted inferior turbinoplasty; NS = not significant; RFA = radiofrequency ablation.

either an RFA (n = 16) or placebo (n = 16) group. Improvement was shown in the frequency of nasal obstruction, severity of nasal obstruction, and overall ability to breathe for both the placebo and RFA treatment arms at 8 weeks. However, the effects of RFA were significantly better than those of placebo in the severity of nasal obstruction and overall ability to breathe.[8] In a single-blinded, placebo-controlled, crossover trial by Bran et al. with 22 patients, the first group received RFA first followed by a placebo treatment 6 to 8 weeks later. In the second group, the order was reversed. Nasal obstruction decreased significantly only after RFA in both groups. There was a tendency of improvement after placebo in both treatment arms. However, the observed trends of a placebo effect were not statistically significant.[9]

Our study is the first placebo-controlled study involving three different techniques, and also the first study where the diode laser and MAIT have been compared with placebo treatment. The follow-up time of 3 months with the placebo group is also the longest so far. RFA, diode laser, and MAIT all improved the VAS score for the severity of nasal obstruction statistically significantly better than placebo. The finding is in line with the study by Nease et al. regarding RFA.[8] The true treatment effect is the difference in improvement between the intervention group and the control group (placebo effect).[7] In the present study, the mean true treatment effect in the VAS score change was found to be −2.1 for all three techniques. The placebo effect accounted for a large part of the total improvement seen in the intervention groups. Without a placebo control, we would have falsely found a greater improvement and significance due to treatment.

In the present study, all the techniques decreased the symptom scores of nasal discharge and crusting statistically significantly compared to the preoperative values at the end of the 3-month follow-up, but none of them statistically significantly compared to the placebo. In addition, minor crusting was still found in some noses at 3 months, especially in the RFA and diode laser groups. Therefore, the major part of the improvement of these symptoms can be explained by the placebo effect.

Anterior nasal cavity volume (V2–5 cm) in acoustic rhinometry was used as a parameter for objective examination. It represents well the operated anterior half of the inferior turbinate. Acoustic rhinometry will give a valid result in most instances, at least for the first 5 to 6 cm of the nasal cavity.[23] Measurement of V2–5 cm is the most sensitive measurement for change in mucosal swelling during decongestion,[24] and that is why the parameter also had an important role in the preoperative decongestion test in defining inferior turbinate enlargement. In the 3-month follow-up, RFA, diode laser, and MAIT techniques all improved the V2–5 cm values statistically significantly compared to the preoperative values. Due to lack of a real surgical procedure, there was understandably no statistically significant change in the V2-5 cm values in the placebo group. This supports the conclusion that the improvement in the VAS score for severity of nasal obstruction in the placebo group was due to a placebo effect. However, none of the techniques improved the volume statistically significantly compared to placebo. This finding can be partly explained by the relatively small number of patients in the placebo group. A larger number might have led to a statistical significance. In addition, environmental conditions and technical difficulties in measurement may have an influence in the volume values.[25] Furthermore, the symptom of nasal obstruction and objective parameters do not always correlate very well.[26] On the other hand, it is wise to remember that the increase in the nasal cavity volume should be optimal instead of too large to avoid making the nose too wide, which might lead to problems such as nasal dryness, crusting, atrophy, worsening of the symptom of nasal obstruction, and empty nose syndrome.[1,27]

CONCLUSION

After 3 months follow-up, there were no statistically significant differences between the examined techniques in their efficacy in treating nasal obstruction. Possible differences in their efficacy may emerge in the long term. Therefore, more studies comparing these techniques with longer follow-ups are needed. RFA, diode laser, and MAIT were all genuinely effective in treating chronic nasal obstruction caused by inferior turbinate enlargement. The placebo effect had a large role in the overall reduction of the severity of nasal obstruction after the inferior turbinate surgery, but all three techniques provided a statistically significant additional reduction in the severity of nasal obstruction compared to the placebo procedure.

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The Effect of Inferior Turbinate Surgery on Ciliated Epithelium: A Randomized, Blinded Study

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Objectives/Hypothesis: The aim of this study was to evaluate statistically the effects of radiofrequency ablation, diode laser, and microdebrider-assisted inferior turbinoplasty techniques on ciliated epithelium and mucociliary function.

Study Design: Prospective randomized study.

Methods: A total of 66 consecutively randomized adult patients with enlarged inferior turbinates underwent either a radiofrequency ablation, diode laser, or microdebrider-assisted inferior turbinoplasty procedure. Assessments were conducted prior to surgery and 3 months subsequent to the surgery. The effect on ciliated epithelium was evaluated using a score based on the blinded grading of the preoperative and postoperative scanning electron microscopy images of mucosal samples. The effect on mucociliary function, in turn, was evaluated using saccharin transit time measurement.

Results: The score of the number of cilia increased statistically significantly in the radiofrequency ablation ($P = .03$) and microdebrider-assisted inferior turbinoplasty ($P = .04$) groups, but not in the diode laser group. The score of the squamous metaplasia increased statistically significantly in the diode laser group ($P = .002$), but not in the other two groups. There were no significant changes found between the preoperative and postoperative saccharin transit time values in any of the treatment groups.

Conclusions: Radiofrequency ablation and microdebrider-assisted inferior turbinoplasty are more mucosal preserving techniques than the diode laser, which was found to increase the amount of squamous metaplasia at the 3-month follow-up. The number of cilia seemed to even increase after radiofrequency ablation and microdebrider-assisted inferior turbinoplasty procedures, but not after diode laser. Nevertheless, the mucociliary transport was equally preserved in all three groups.

Key Words: Inferior turbinate, radiofrequency ablation, diode laser, microdebrider-assisted inferior turbinoplasty, cilia, mucociliary function, scanning electron microscopy.

Level of Evidence: 1b

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INTRODUCTION

Cilia are complex structures of the respiratory mucosa that play an important role in airway defense. Each respiratory epithelial cell is lined with between 50 and 200 cilia,[1] which are about 5 μm to 6 μm long and about 0.2 μm wide.[2,3] The beating cilia are the driving force of mucociliary clearance, which is a process by which the mucus blanket overlying respiratory mucosa is transported to the gastrointestinal track for ingestion. Furthermore, mucociliary clearance is the primary mechanism by which the airway clears pathogens, allergens, debris, and toxins.[1]

Various factors can affect cilia and mucociliary function. Mucociliary disorders can be primary, caused by an inherited defect resulting in abnormal cilia structure, or more commonly, secondary, caused by environmental, infectious, or inflammatory factors, such as chronic rhinosinusitis,[1,4] allergic and nonallergic rhinitis,[5,6] septum deviation,[7] bacterial[1] and viral[8] infections, and smoking.[9]

Inferior turbinate enlargement is one of the main causes of chronic nasal obstruction. Various surgical techniques have been described for the reduction of hypertrophied inferior turbinates. Microdebrider-assisted inferior turbinoplasty (MAIT) and radiofrequency ablation (RFA) are widely used and the most commonly studied techniques in the recent literature.[10] The diode laser has also gained popularity during recent years.[11]

There have been previous studies that have evaluated the effect of inferior turbinate surgery on ciliated epithelium. Most of them, however, have only been descriptive and lacked statistical analysis with relatively small numbers of specimens examined. The aim of this study was to evaluate statistically the effects of the RFA, diode laser, and MAIT techniques on ciliated epithelium and mucociliary function.

MATERIALS AND METHODS

This prospective randomized study was carried out at Tampere University Hospital, Tampere, Finland, between

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February 2014 and September 2017. The institutional review board approved the study design (R13144), and all patients provided written informed consent. A total of 66 consecutive adult patients presenting with enlarged inferior turbinates due to persistent year-round rhinitis were enrolled in this study. The patients presented symptoms of bilateral nasal obstruction related to inferior turbinate congestion that had not responded to a 3-month trial of appropriate treatment with intranasal corticosteroids. Patients with significant nasal septum deviation affecting the nasal valve region, internal/external valve collapse/stenosis, chronic rhinosinusitis with or without polyposis, previous nasal surgery, sinonasal tumor, severe systemic disorder, severe obesity, or malignancy were excluded from the study.

Cone beam computed tomography (Planmeca Max; Planmeca, Helsinki, Finland) was used to exclude patients with chronic rhinosinusitis from the study. Serum-specific immunoglobulin (Ig)E level measurements were used to identify those patients with allergic sensitization. Allergic sensitization was defined as a specific IgE > 0.35 for any common airborne allergen (cat, dog, horse, birch, grass, mugwort, *Dermatophagoides pteronyssinus*, and molds).

The definition of inferior turbinate enlargement was based on persistent bilateral symptoms, a finding of bilateral swelling of the inferior turbinate in nasal endoscopy, and the evident shrinking of both turbinates in a decongestion test. The nasal response to the topical vasoconstrictor 0.5% xylometazoline hydrochloride (Nasolin; Orion, Espoo Finland) in both nasal cavities 15 minutes before obtaining the second measurement was evaluated objectively using acoustic rhinometry (Acoustic rhinometer A1; GM Instruments Ltd, Kilwinning, United Kingdom). An improvement of less than 30% in anterior nasal cavity volume (V2–5 cm) in one or both nasal cavities was considered normal, and those patients were excluded from the study. The limit value of 30% was chosen according to the previous literature.[12–14]

Patients were consecutively randomized into RFA, diode laser, and MAIT groups. The surgical treatment was performed under local anesthesia at the day surgery department of the hospital's ear, nose, and throat clinic. All the procedures were performed under the direct vision of a straight, 4-mm-diameter, 0 ° endoscope (Karl Storz, Tuttlingen, Germany). First, the inferior turbinates were topically anesthetized using cotton strips with a mixture of lidocaine (Orion) 40 mg/mL and two to three drops of epinephrine 0.1% in 5 mL to 10 mL of lidocaine. The local anesthetic (lidocain 10 mg/mL cum adrenalin) was then applied to the medial portions of the inferior turbinates. Before the treatment, preoperative samples for scanning electron microcopy (SEM) were taken from each patient in the form of small (2–3 mm in diameter) nasal mucosal biopsies from the anterior medial portion of the left inferior turbinate. In all of the groups with every technique, the treatment was given to the medial side of the anterior half of the inferior turbinates.

The RFA treatment was carried out with a radiofrequency generator (Sutter RF generator BM-780 II; Sutter, Freiburg, Germany). A Binner bipolar needle electrode was inserted into the medial submucosal tissue of the inferior turbinate. The upper and lower parts of the anterior half of the inferior turbinate were treated for 6 seconds at 10 W output power in three areas.

The diode laser treatment was given with a FOX Laser (A.R.C. Laser GmbH, Nuremberg, Germany). The settings were as follows: wavelength of 980 nm, output power of 6 W in continuous-wave mode, and laser delivery by a 600 μm fiber using contact mode. Four parallel stripes were made on the mucosa by drawing the fiber from the posterior to the anterior direction along the medial edge of the inferior turbinate.

In the MAIT treatment, a 2.9-mm-diameter rotatable microdebrider tip (Medtronic Xomed, Jacksonville, FL) was firmly pushed toward the turbinate bone until it pierced the mucosa of the anterior face of the inferior turbinate. Next, a submucosal pocket was dissected by tunneling the elevator tip in an anterior-to-posterior and superior-to-inferior sweeping motion. Once an adequate pocket had been created, resection of the stromal tissue was carried out by moving the blade back and forth in a sweeping motion, with the system set at 3,000 rpm using suction irrigation.

All the patients were evaluated prior to surgery and 3 months subsequent to the surgery. During both visits, nasal mucociliary transport was evaluated with saccharin transit time (STT) by placing a saccharine particle on the anterior portion of the left inferior turbinate, and the time until the patient tasted sweetness was measured. Postoperative samples for SEM were taken under local anesthesia from the anterior medial portion of the left inferior turbinate of every patient at the control visit. The SEM samples were first immersed in 1% glutaraldehyde for fixation. Then, the samples were dehydrated in a graded alcohol series. Finally, the samples were immersed in hexamethyldisilazane for 15 minutes at room temperature and air dried overnight. The samples were glued on the SEM specimen stubs with carbon glue. To avoid sample charging during the SEM studies, the specimens were coated for 3 minutes with gold using Edwards S150 sputter coater in an argon atmosphere. Then, four to eight randomly selected fields were viewed and imaged with a Philips XL30 SEM at primary magnification of 2,000×.

After SEM, the quality of both the preoperative and postoperative SEM image series of 44 patients out of 66 was of a technically acceptable quality to be further evaluated. The main reasons for sample rejection were fibrin or other impurity covering the surface, glue covering the surface, broken sample, and sample wrong side up. The preoperative and postoperative image series of each patient were put into separate folders. Then, the folders were coded and evaluated by five examiners (T.H., I.K., M.H., M.V., M.R.), who did not know which technique had been used or whether the images were preoperative or postoperative, and were therefore blinded. The evaluated parameters were the number or amount of cilia, nonciliated pseudostratified columnar cells, squamous metaplasia, microvilli, goblet cells, and disorientation of the cilia. The parameters were graded as follows: 0 = no, 1 = a little, 2 moderately, 3 = a lot. The mean of the grades given to an image series by the five examiners was used as a score of one image series.

IBM SPSS statistics 22.0 (IBM, Armonk, NY) was used for the statistical analyses. All nonparametric data were statistically processed using the Wilcoxon signed rank test. In cases with parametric data, the analysis was carried out by paired samples t test and one-way analysis of variance. A χ^2 test was used in the evaluation of the total loss of cilia and the detected metaplasia. Correlations were evaluated using Spearman's ρ.

TABLE I.
Characteristics of the Patients Whose Samples Were Evaluated

	All Patients, N = 44	RFA, N = 17	Diode Laser, N = 13	MAIT, N = 14
Age, yr, mean (range)	43 (19–69)	43 (24–68)	41 (25–65)	45 (19–69)
Sex, no. (%)				
Male	27 (61)	11 (65)	7 (54)	9 (64)
Female	17 (39)	6 (35)	6 (46)	5 (36)
Allergic sensitization, no. (%)				
Yes	16 (36)	6 (35)	3 (23)	7 (50)
No	28 (64)	11 (65)	10 (77)	7 (50)

MAIT = microdebrider-assisted inferior turbinoplasty; RFA = radiofrequency ablation.

TABLE II.
Findings of Total Loss of Cilia and Squamous Metaplasia

	Preoperative	Postoperative	*P* Value*
Total loss of cilia, no. (%)			
All patients	23 (52)	7 (16)	.001†
RFA	10 (59)	2 (12)	.01†
Diode laser	4 (31)	2 (15)	NS
MAIT	9 (64)	3 (21)	.05
Squamous metaplasia detected, no. (%)			
All patients	27 (61)	38 (86)	.01†
RFA	12 (71)	13 (77)	NS
Diode laser	4 (31)	12 (92)	.004†
MAIT	11 (79)	13 (93)	NS

*χ^2 test.
†Statistically significant.
MAIT = microdebrider-assisted inferior turbinoplasty; NS = not significant; RFA = radiofrequency ablation.

RESULTS

The characteristics of the patients whose samples were evaluated are described in Table I. The total loss of cilia (no cilia found by any of the examiners) was detected in 52% and squamous metaplasia in 61% of the preoperative samples (Table II). The median preoperative scores of the number of cilia and amount of squamous metaplasia of all the patients were 0.0 (interquartile range [IQR]: 0.0 to 1.0) and 0.2 (IQR: 0.0 to 0.8), respectively (Table III). There were no significant differences in the preoperative scores of the number of cilia and amount of squamous metaplasia between the patients with and without allergic sensitization. The preoperative scores of the number of cilia and amount of squamous metaplasia did not have significant correlations with age either.

In the RFA group, the preoperative and postoperative number of cases with total loss of cilia was 10 and 2, respectively. The difference was statistically significant ($P = .01$). In the MAIT group, a decrease in the number of cases was also detected. The result was, however, on the borderline regarding statistical significance ($P = .05$). In the diode laser group, there was no significant difference between the preoperative and postoperative number of total loss of cilia cases. In the diode laser group, the preoperative and postoperative number of the cases where squamous metaplasia was detected were 4 and 12, respectively. The difference was statistically significant ($P = .004$). There were no significant differences between the preoperative and postoperative number of squamous metaplasia cases in the RFA and MAIT groups (Table II).

The score of the number of cilia increased statistically significantly in the RFA ($P = .03$) and MAIT ($P = .04$) groups, but not in the diode laser group. The score of the squamous metaplasia increased statistically significantly in the diode laser group ($P = .002$). No significant changes in the score were found in the RFA and MAIT groups. The score of the microvilli increased statistically significantly in all three groups (Table III) (Figures 1–3).

The preoperative mean score of the nonciliated pseudostratified columnar cells was 1.6 (95% confidence interval: 1.3-1.9), and the median score of the goblet cells was 0.4 (IQR: 0.1 to 0.6). Regarding these parameters, there were no significant differences found between the preoperative and postoperative values in any of the treatment groups.

The median preoperative score of ciliary disorientation was 2.6 (IQR: 2.1 to 3.0). There was a statistically significant negative correlation found between the

TABLE III.
Scores of the Number and Amount of Cilia, Squamous Metaplasia, and Microvilli

	All Patients	RFA	Diode Laser	MAIT
No. of cilia				
Preoperative	0.0 (0.0 to 1.0)	0.0 (0.0 to 1.0)	0.6 (0.0 to 1.8)	0.0 (0.0 to 0.5)
Postoperative	1.0 (0.2 to 1.6)	0.8 (0.2 to 2.1)	1.0 (0.3 to 1.5)	0.8 (0.2 to 1.9)
Change	0.2 (−1.0 to 1.2)	0.2 (−0.1 to 1.9)	0.6 (−1.3 to 1.2)	0.2 (0.0 to 1.2)
P value*	.01†	.03†	NS	.04†
Squamous metaplasia				
Preoperative	0.2 (0.0 to 0.8)	0.2 (0.0 to 0.8)	0.0 (0.0 to 0.3)	0.6 (0.3 to 1.0)
Postoperative	1.0 (0.5 to 1.4)	1.0 (0.5 to 1.4)	1.0 (0.6 to 1.4)	0.9 (0.6 to 1.3)
Change, mean (95% CI)	0.5 (0.2 to 0.8)	0.5 (−0.2 to 1.1)	0.9 (0.5 to 1.3)	0.2 (−0.3 to 0.7)
P value*	.002†	NS	.002†	NS
Microvilli				
Preoperative	0.8 (0.4 to 1.8)	0.6 (0.4 to 1.5)	0.8 (0.3 to 1.8)	0.8 (0.4 to 2.1)
Postoperative	2.1 (1.2 to 2.6)	2.0 (1.3 to 2.5)	2.2 (1.5 to 2.8)	2.0 (0.9 to 2.5)
Change, mean (95% CI)	0.8 (0.5 to 1.1)	0.9 (0.3 to 1.5)	0.9 (0.1 to 1.7)	0.6 (0.1 to 1.1)
P value*	< .001†	.008†	.04†	.04†

Medians and interquartile ranges (Q25 to Q75) are used due to nonparametric data unless otherwise indicated.
*Wilcoxon signed rank test.
†Statistically significant.
CI = confidence interval; MAIT = microdebrider-assisted inferior turbinoplasty; NS = not significant; RFA = radiofrequency ablation.

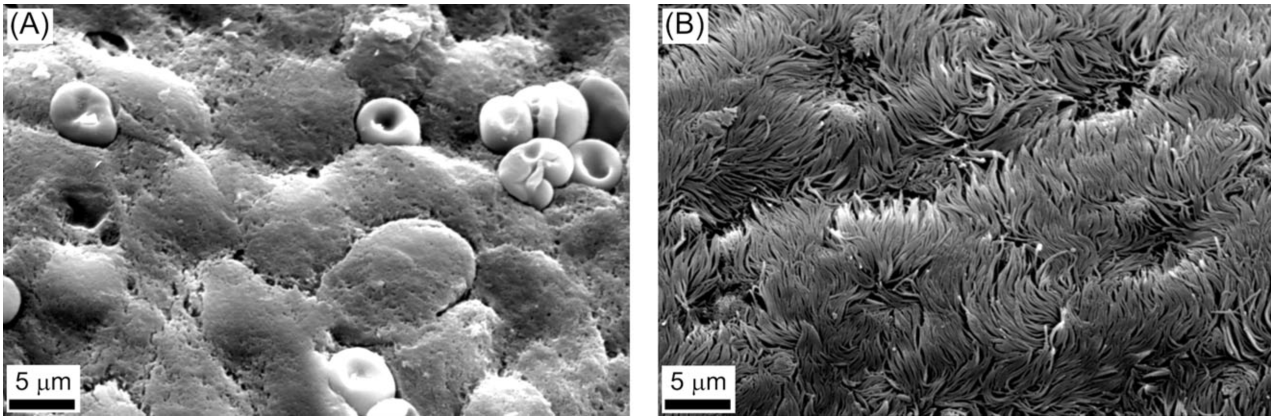

Fig. 1. (A) Preoperative scanning electron microcopy image from a patient in the radiofrequency ablation group showing squamous metaplasia. (B) Postoperative image from the same patient showing oriented ciliated epithelium.

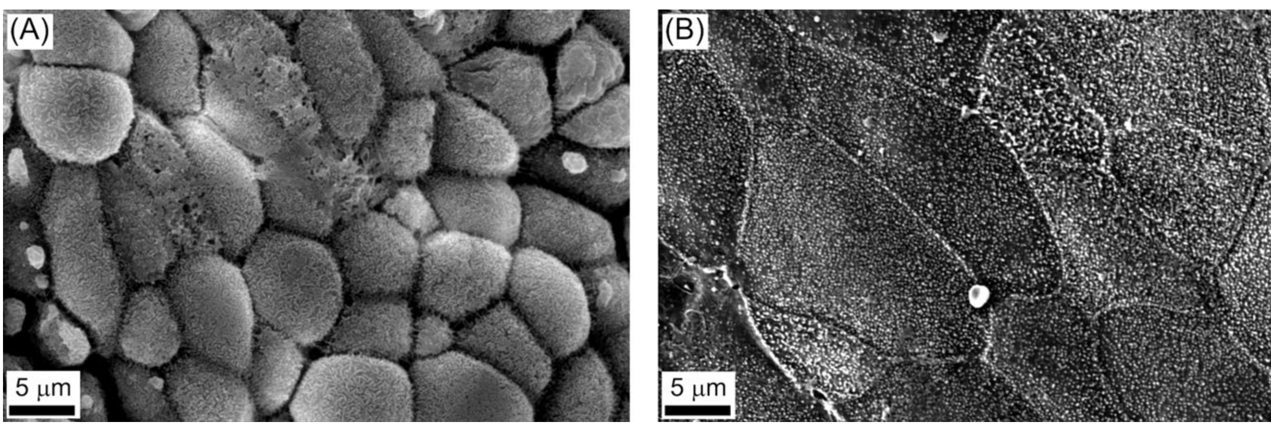

Fig. 2. (A) Preoperative scanning electron microcopy image from a patient in the diode laser group showing non-ciliated columnar epithelium with microvilli. (B) Postoperative image from the same patient showing squamous metaplasia with microvilli.

preoperative scores of the ciliary disorientation and the number of cilia (Spearman's $\rho = -0.6$; $P = .007$). There was no statistically significant correlation found between the postoperative values. Cilia were found in both the preoperative and postoperative samples of 16 patients. These samples were used in the paired comparison of the ciliary disorientation. There were no significant differences found in ciliary disorientation between the preoperative and postoperative values in any of the treatment groups.

STT results are described in Table IV. There were no significant changes found between the preoperative and postoperative STT values in any of the treatment groups.

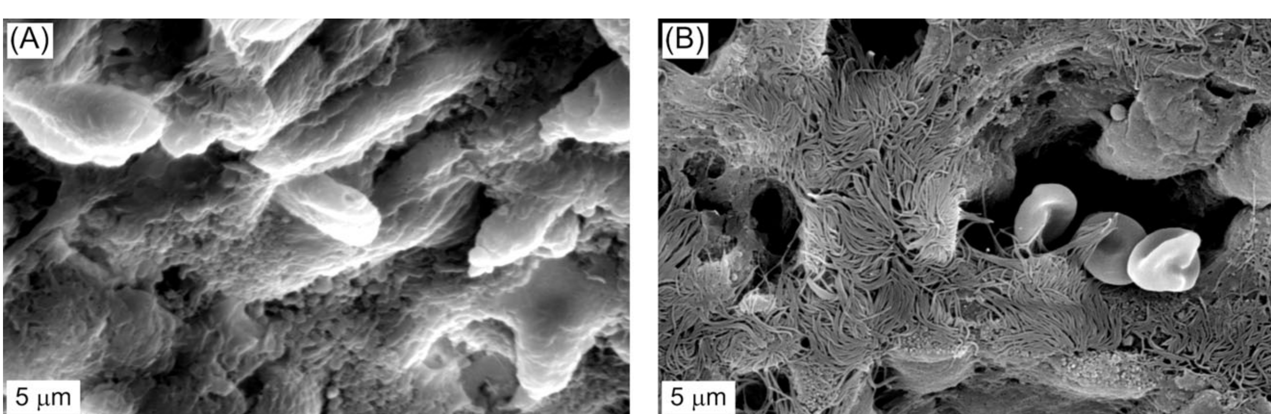

Fig. 3. (A) Preoperative scanning electron microcopy image from a patient in the microdebrider-assisted inferior turbinoplasty group showing non-ciliated columnar epithelium. (B) Postoperative image from the same patient showing that cilia have emerged on the epithelium.

TABLE IV.
Saccharin Transit Time Results (n = 66)

	Preoperative, sec (95% CI)	Postoperative, sec (95% CI)	Change, sec (95% CI)
RFA, n = 23	588 (471 to 704)	602 (482 to 721)	14 (−148 to 176) NS
Diode laser, n = 20	609 (487 to 732)	547 (464 to 630)	−62 (−205 to 81) NS
MAIT, n = 23	608 (485 to 731)	583 (478 to 689)	−24 (−162 to 113) NS

CI = confidence interval; MAIT = microdebrider-assisted inferior turbinoplasty; NS = not significant (paired samples *t* test); RFA = radiofrequency ablation.

There were no significant differences in the change in STT values between the treatment groups either.

DISCUSSION

In the present study, the five examiners who evaluated the SEM images did not know which technique had been used or whether the images were preoperative or postoperative. Blinding of the evaluators was extremely important to prevent possible expectations and attitudes of the examiners toward the treatments from affecting their evaluations.

In previous light and electron microcopy studies of inferior turbinate surgery, the preoperative findings regarding cilia have been controversial. There have been studies that have reported preoperative findings of epithelial metaplasia and loss of ciliated cells.[6,15,16] On the other hand, there are studies that have shown a normal appearance of the epithelium with a preserved number of cilia.[17,18] In the present study, squamous metaplasia and total loss of ciliated cells were found in the majority of the preoperative samples. This may partly be explained by the chronic rhinitis associated with inferior turbinate enlargement. Furthermore, previous studies have shown that a loss of cilia is more common in both allergic and nonallergic rhinitis compared with healthy controls.[5,6]

In the present study, however, the most likely explanation for the high incidence of squamous metaplasia and total loss of ciliated cells in the preoperative samples is that the biopsies were taken from the anterior portion of the inferior turbinate, approximately 1 cm behind the anterior edge. Halama et al. examined 214 biopsies taken from various parts of the nose and paranasal sinuses postmortem. They found that the density of ciliated cells was increased in the nasal cavity in the anteroposterior direction. Cilia start occurring just behind the front edge of the inferior turbinate. More posteriorly, the density of ciliated cells ranges from 50% in the one-third middle to 100% in the posterior part of the inferior turbinate. The distribution pattern of ciliated cells corresponds well with a map of nasal airflow, indicating that the density of ciliated cells is inversely proportional to the linear velocity of inspiratory air in the nasal cavity. Furthermore, it is also assumed that other physical properties of the nasal airflow, such as low temperature, low humidity, and contamination contribute to the reduced number of ciliated cells.[19] In the study by Augusto et al., ciliated epithelium with goblet cells (normal respiratory epithelium) was found in only half of the samples taken from the anterior portions of the inferior turbinates of normal noses, and various degrees of epithelial metaplasia was found in half of the samples taken from the same sites. The anterior part of the inferior turbinate is more exposed to external elements, such as strong air flow, and is therefore prone to metaplastic transformation.[20]

There have been some previous light and electron microscopy studies that have evaluated the effect of inferior turbinate surgery on ciliated epithelium. Based on the findings of previous studies, RFA[6,17,18,21] and submucosal electrocautery[6,22,23] do not have a significant effect on ciliated epithelium. After endoscopic turbinoplasty, some improvement has been described.[24] The findings have, however, been controversial regarding lasers.[15,24,25] Ultrasound reduction, in turn, may also have an improving effect on ciliated epithelium.[6] A worsening has previously been described regarding partial inferior turbinectomy.[18] In a recent study by Neri et al. with 18 patients, however, a complete reepithelization of nasal mucosa with well differentiated columnar ciliated epithelium was detected 4 months after the total removal of the mucosa of the medial and inferior portions of the inferior turbinate with the microdebrider.[16]

In our study, the effect of various inferior turbinate surgery techniques on ciliated epithelium has for the first time been evaluated with a statistical analysis using a score based on the mean of the grades given to the image series by the blinded examiners. Based on our score, the number of cilia increased significantly after RFA and MAIT treatments. The number of cases with total loss of cilia was also found to have decreased after these treatments. No similar changes were found after diode laser treatment. On the other hand, the score of metaplasia seemed to increase significantly after diode laser treatment as well as the overall number of cases where metaplasia was detected. No similar findings were found after RFA or MAIT. Regarding the diode laser, the findings can be explained by the damage the laser causes to the mucosal surface during the treatment of submucosa. RFA and MAIT are more clearly submucosal techniques that do not notably harm the mucosal surface. Inferior turbinate surgery creates more airspace at the level of the anterior part of the inferior turbinate, which decreases nasal airway resistance, causes changes in the airflow patterns, and likely decreases the shear stress on the mucosa of the anterior part of the inferior turbinate. This could be a possible explanation for the increase in the number of cilia after RFA and MAIT treatments.

In human nasal epithelial cells, the number of microvilli has been found to increase before the ciliogenesis starts.[26] In chronic rhinosinusitis, an increased number of microvilli and short cilia are thought to indicate the regeneration of epithelium and ciliated cells.[27] In the present study, the number of microvilli increased significantly in all three groups, which can be interpreted to be related to a regeneration of the mucosal epithelium.

The degree of ciliary disorientation was relatively high both preoperatively and postoperatively in all three groups, and there were no significant differences in disorientation between the preoperative and postoperative samples. The disorientation can be explained mainly by the inflammation caused by chronic rhinitis[28] and the shear stress caused by the airflow.[20] Preoperatively, there was also a negative correlation found between the scores of the ciliary disorientation and the number of cilia, indicating that the lower the number of cilia is the more disorientated they are. This finding is in line with a previous study by Rautiainen, where a few cilia or small groups of cilia that differed dramatically from the main orientation were found in most fields.[29]

The effect of various inferior turbinate surgery techniques on mucociliary function has been examined in several studies using STT. Based on the findings of previous studies, diode laser may worsen mucociliary transport during the first 3 months after operation, but in longer follow-up it returns to normal.[30,31] In most of the studies regarding RFA, the STT has either been preserved[32–34] or improved[21,31] after the operation in 1- to 3-month follow-ups. However, there are also studies where STT has been prolonged at 2[35] and 6[18] months after the operation. Regarding MAIT, there have been studies where STT has been preserved after three months[36] or decreased in a longer, up to 3 years, follow-up.[37] There are some comparative studies that have compared RFA with MAIT or diode laser. For example, Kizilkaya et al. compared RFA and MAIT. In their study, STT showed no significant post-treatment variation between the groups three and six months postoperatively.[38] Liu et al. compared MAIT and RFA over a 3-year follow-up period. Compared to preoperative values, the STT for the MAIT group significantly decreased and returned to normal at 6 months to 3 years after surgery. In the RFA group, the STT significantly improved from 6 months to 1 year postoperatively compared with preoperative levels. However, no improvement in the STT from 2 to 3 years was noted.[37] Veit et al. compared standard septoplasty in combination with anterior turbinoplasty, RFA, and diode laser. After 3 months, mucociliary transport time was slightly decreased in the anterior turbinoplasty and RFA groups and slightly increased in the diode laser group. After 1 year, a slight decrease in all groups was noticed.[31]

In the present study, there were no significant changes found between the preoperative and postoperative STT values in any of the treatment groups. There were also no significant differences in the change of STT values between the treatment groups. These findings are in line with previous studies regarding RFA and MAIT. Although the amount of squamous metaplasia was found to increase in the diode laser group, the STT was not found to increase. One possible explanation for this could be the contact technique used, where parallel stripes were made on the mucosa along the turbinate leaving lanes of mucosal surface with preserved mucociliary function between them.

The results of the present study provide information on the short-term effects of the examined techniques on ciliated epithelium and mucociliary function. A longer follow-up period is required if we are trying to better understand the possible permanent effects of the techniques. In addition, the degree of the scores was based on the subjective evaluation by the examiners. Although the examiners were blinded, other methods of quantitative analysis might still be needed to justify the results and conclusions of the study.

CONCLUSION

RFA and MAIT are more mucosal-preserving techniques than diode laser, which was found to increase the amount of squamous metaplasia at a 3-month follow-up. The number of cilia seemed to even increase after RFA and MAIT procedures, but not after diode laser. Nevertheless, the mucociliary transport was equally preserved in all three groups.

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