Drug Induced Sleep Endoscopy and its Role as a Selection Tool in Alternative Treatments of Obstructive Sleep Apnea Syndrome

Slaapendoscopie en haar rol als selectiemiddel bij alternatieve behandelingen van obstructief slaapapneu syndroom

Faiza Safiruddin

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“The one who snores will always fall asleep first.”

Fortune Cookie

List of Abbreviations

AASM	American Academy of Sleep Medicine
AHI	apnea-hypopnea index
AP	anteriorposterior
ASA	American Society of Anesthesiologists
BIS	bispectral index monitoring
BMI	body mass index
CCC	complete concentric collapse
CT	computed tomography
CPAP	continuous positive airway pressure
DISE	drug induced sleep endoscopy
EEG	electroencephalography
EMG	electromyography
EOG	electrooculography
ESS	Epworth Sleepiness Scale
MAD	mandibular advancement device
MRI	magnetic resonance imaging
ODI	oxygen desaturation index
OPDA	outpatient department assessment
OSA(S)	obstructive sleep apnea (syndrome)
PSG	polysomnography
REM	rapid eye movement

RFITT	radiofrequency induced thermotherapy
SD	standard deviation
UAS	upper airway stimulation
UPPP	uvulopalatopharyngoplasty
VAS	visual analogue scale

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Chapter 1

General Introduction

General Introduction

Continuous positive airway pressure (CPAP) is the most widely used therapy for obstructive sleep apnea. However, some 30-40% of patients using this therapy cannot tolerate it[1] . These patients still have a serious problem and are in need for alternative therapies. A substantial part of referrals to the otolaryngology department are patients with CPAP failure. One of the most important goals is therefore to research and implement alternative treatments to continuous airway positive pressure.

Currently, two exciting innovative developments are taking place in the field of OSAS treatment. Positional therapy (PT), a behavioral strategy to treat positional sleep apnea and upper airway stimulation (UAS). The severity of OSAS and its consequences can be captured in a spectrum, ranging from mild to moderate and severe based on the patients' Apnea-Hypopnea Index (AHI). While PT is focused as a treatment on the left side of the disease spectrum (mild to moderate OSA); UAS is at the other side of the spectrum, moderate to severe OSA, with CPAP failure. PT is low cost / high volume; UAS is low volume/high cost. Still there are several interesting similarities between the two new modalities. These features are patient-friendliness, being well-tolerated, only active when sleeping, having a start delay, and enabling a degree of self-control so that the patient is in charge of his/her own treatment. For both treatments, short- and long-term effects are now available. Not only are the departments of Otolaryngology and Head and Neck Surgery of Saint Lucas Hospital (now OLVG West) in Amsterdam, The Netherlands, and the University of Antwerp, Belgium, playing a pivotal role in the development and implementation of these two alternative treatments, they are also investigating the role of drug induced sleep endoscopy (DISE). DISE is a method of visualizing the upper airway under sedation using pharmacological agents in these two treatments. To achieve the best possible treatment result, we perform DISE in all patients in whom another treatment than CPAP is considered.

The departments were among the first to research the new positional therapy treatment and have studied most patients with such innovative devices worldwide. In addition to this, the department has played a major role in the Stimulation Therapy for Apnea Reduction (STAR) trial, focusing on the efficacy of a new generation of UAS devices. Twenty-two of the 120 patients were operated on in OLVG hereby making it the biggest contributor to the clinical study. These two

treatments, PT and UAS, and their relation with DISE, will be discussed in further detail in this thesis.

Obstructive Sleep Apnea Syndrome (OSAS)

Obstructive sleep apnea syndrome (OSAS) is a common chronic disorder that often requires lifelong care. It is the most common type of sleep apnea resulting from partial (hypopnea) or total obstruction (apnea) of the upper airway during sleep. [2]

The episodes of airway obstruction are followed by transient awakening (arousal) that leads to the restoration of upper airway permeability. These cycles of apnea/hypopnea are repeated several times every hour, producing fragmented sleep.[3] Recurrent episodes of airway obstructions result in night-time hypoxia and hypercapnia increasing sympathetic neural tone, which in turn causes vasoconstriction and marked increases in blood pressure.[4]

Disease prevalence is estimated in the range of 3% to 7%, with certain subgroups of the population bearing higher risk.[5] Factors that increase vulnerability for the disorder include age, male sex, body mass index (BMI), family history, menopause, craniofacial abnormalities, and certain health behaviors such as cigarette smoking and alcohol use.[3,5,6]

OSAS is an independent risk factor for many diseases, such as hypertension, heart failure, heart attack, cardiovascular events, arrhythmias[3], neurologic, and perioperative morbidities.[2] It has also been associated with a higher number of traffic accidents due to a high degree of diurnal sleepiness which affects the driving capacity.[7] OSAS has therefore many implications when left untreated due to the significant negative impact on the health and behavior of millions of adults.

The pathogenesis of OSAS has been studied for many years. Enlargement of soft tissues in the upper airway, including hypertrophic tonsils, adenoids, and tongue, are important factors predisposing to upper airway collapse, as these can impinge on the pharyngeal lumen and narrow it during sleep.[8,9] OSAS patients also seem to have upper airways that are usually smaller and more collapsible than normal.[10] Impairment of upper airway mechanoreceptor sensitivity and reflexes that maintain pharyngeal patency and respiratory control system instability, have also been identified as possible mechanisms facilitating upper airway instability in patients

with OSAS. This suggests that OSAS may be a heterogeneous disorder, rather than a single disease entity. Therefore, the extent to which various pathogenic factors contribute to the phenomenon of repetitive collapse of the UA during sleep probably varies from patient to patient.[3,8,9]

Definition Obstructive Sleep Apnea Syndrome

The severity of OSAS according to the American Academy of Sleep Medicine (AASM) is defined on basis of the Apnea-Hypopnea Index (AHI)[11]:

- AHI 5-15/h = mild OSAS
- AHI 15-30/h = moderate OSAS
- AHI >30/h = severe OSAS

An **apnea** is scored when all the following criteria are met:

1. There is a drop in the peak thermal sensor excursion by ≥90% of baseline
2. The duration of the event lasts at least 10 seconds
3. At least 90% of the events duration meets the amplitude reduction criteria for apnea

A **hypopnea** is scores if all the following criteria are met[11]:

1. The nasal pressure signal excursions (or those of the alternative hypopnea sensor) drop by ≥30% of baseline
2. The duration of this drop occurs for a period lasting at least 10 seconds
3. There is a ≥4% desaturation from pre-event baseline
4. At least 90% of the event's duration must meet the amplitude reduction of criteria for hypopnea

A **respiratory effort-related arousal (RERA)** is scored[11]:

1. If there is a sequence of breaths lasting at least 10 seconds characterized by increasing respiratory effort or flattening of the nasal pressure waveform leading to an arousal from sleep when the sequence of breaths does not meet criteria for an apnea or hypopnea.

In addition to this, identifying predictors of subjective sleepiness can be helpful in predicting the severity of sleep apnea and this can be achieved by using screening questionnaires such as the Berlin questionnaire, the Wisconsin Sleep questionnaire, STOP–BANG questionnaire and the Epworth Sleepiness Scale.[11,12]

Work Up

Patient History

Snoring

Snoring is caused by the vibration of the structures in the oral cavity, and oropharynx. It is considered one of the most common symptoms for which patients or partners seek medical attention. Habitual snoring is common in the general population; however approximately 70%–80% of patients who snore have OSAS and 95% of patients who have OSAS snore.[13] A study by Boudewyns et al also found a relationship between sleep-related breathing disorders and snoring. In patients with isolated complaint of snoring, 18% had sleep apnea syndrome. This percentage increased significantly to 35% when snoring and excessive daytime sleepiness were both present. The odds ratio for sleep apnea syndrome in patients with snoring and excessive daytime sleepiness was 2.15 (95% CI, 1.48–3.12). The complaints of snoring and/or excessive daytime sleepiness are highly likely to be associated with sleep-related breathing disorders and warrant further diagnostic work-up, including polysomnographic evaluation. It is thus imperative that this question is asked in the history taking when considering OSAS.[14]

Excessive Daytime Sleepiness

Daytime sleepiness has a large differential diagnosis such as medication side effects, bad sleeping habits, screen time, etc. Although poorly correlated with the severity of OSAS, sleepiness is the most common daytime symptom in patients with OSAS. Daytime sleepiness is a screening tool to evaluate response to therapy in patients with OSAS.[15]

Other Symptoms

Other symptoms of OSAS include, but are not restricted to, witnessed apneas, nocturnal choking, unrefreshed sleep, morning headaches, sleep-maintenance insomnia, and fatigue. Although clinical symptoms have a poor correlation with the severity of OSA, several prediction models have been developed to provide an OSA screening tool. Most of those models depend on clinical symptoms, anthropometric

measurements, and an upper airway anatomy evaluation. Despite the high sensitivity, these prediction rules have minimal clinical utility given the low specificity, and also are of limited use in the pediatric population.[13]

Physical Examination

Physical examination such as body mass index (BMI), modified Mallampati classification, hypertrophic tonsils, neck circumference, and pharyngeal anatomical abnormalities are mandatory. Certain findings are to a certain extent related to both presence and severity of obstructive sleep apnea syndrome.

Observation of the patient's facial profile must be performed to recognize developmental disorders of the mandible and maxilla. The patient's dental status must be documented in case of later treatment of OSAS by application of an oral device.

The modified Mallampati classification (figure 1) is examined by asking the patients to open their mouths with the tongue relaxed inside the mouth. The modified Mallampati classification can be graded according to palatal length and tongue size as class I, all the oropharynx including tonsils, pillars, soft palate, and the tip of uvula can be easily visible; class II, tonsils' upper pole and the uvula are visible; class III, part of the uvula and soft palate are visible; and class IV, the hard palate and part of soft palate are barely visible.[16]

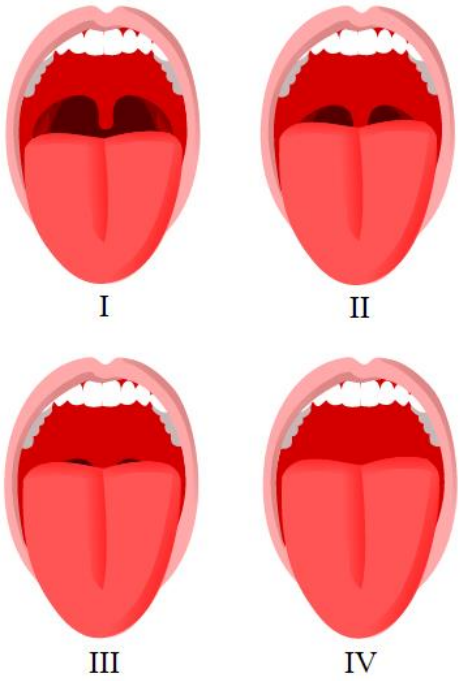

Figure 1: Modified Mallampati classification. Source: Jordi March i Nogué, Wikimedia Commons.

The tongue inspection should include presence of atrophy, movement restriction and/or hypertrophy of the lingual tonsils.

The soft palate should be classified into posteriorly placed, thick, or webbed. When the uvula if elongated or wide, this should also be noted.

Tonsils are classified by the degree of hypertrophy as follows (figure 2): grade 0: surgically removed tonsils, grade I, tonsils inside the tonsillar fossa lateral to posterior pillars; grade II, tonsils occupying 25% of oropharynx; grade III, tonsils occupying 50% of oropharynx; grade IV, tonsils occupying 75% or more of oropharynx, almost meeting in the midline.[16]

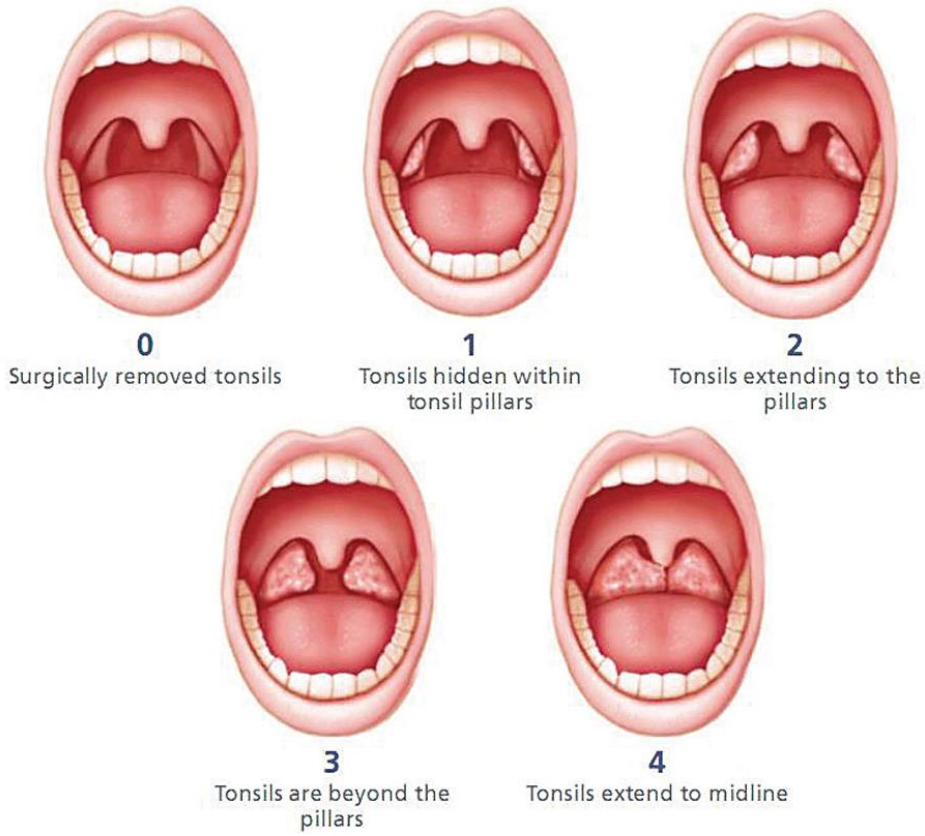

Figure 2: Tonsil grading. Source: Sleep Medicine Board Review.

Nasal examination is performed by anterior rhinoscopy using a speculum with the patient seated while having the head slightly backwards. The inspection is intended to detect septal deviation, turbinate hypertrophy, nasal polyps, other masses, and internal nasal pathway.

Polysomnography (PSG)

A PSG recording is the gold standard for the diagnosis of OSAS through using the following physiologic signals[17]:

- electroencephalogram (EEG)
- electrooculogram (EOG)
- chin electromyogram, airflow
- oxygen saturation
- respiratory effort

- electrocardiogram (ECG) or heart rate
- assessment of body position

Additional recommended parameters include body position and leg EMG derivations. Technical personnel should have appropriate sleep-related training.

The AASM Manual for the Scoring of Sleep and Associated Events[11] should be used as the guidelines for parameters, settings, filters, technical specifications, sleep stage scoring and event scoring. The frequency of obstructive events is reported as an apnea + hypopnea index (AHI) or respiratory disturbance index (RDI). Every sleep study should be reviewed and interpreted by a qualified physician, as defined in the AASM Accreditation Standards (Consensus). Interscorer reliability assessment and other quality assurance measures should be performed on a regular basis. [11,18]

Full-night PSG is recommended for the diagnosis of a sleep-related breathing. In patients where there is a strong suspicion of OSAS, if other causes for symptoms have been excluded, a second diagnostic overnight PSG may be necessary to diagnose the disorder.[11,19]

Home respiratory polygraphies can be used as an alternative to PSG for the diagnosis of OSAS in patients with a high pretest probability of moderate to severe OSAS; e.g. highly obese patients, or in situations where in-laboratory PSG is not possible (immobility, safety, or critical illness). In cases where accurate measurements, namely body position readings, are required a PSG must be performed since polygraphies, at a minimum, only record airflow, respiratory effort, and blood oxygenation. Body position readings are usually not accurately recorded in polygraphies.[20]

Upper airway assessment

Several different techniques can be used to evaluate the upper airway in order to determine the level of obstructive predominance. The aim is not only to reveal potential differences in upper airway anatomy but also to improve patient management and treatment success. These techniques include: lateral cephalography, awake endoscopy, awake endoscopy with the Müller maneuver, endoscopy during sleep, endoscopy with nasal continuous positive airway pressure during sleep, drug induced sleep endoscopy, fluoroscopy, CT scanning, MRI scanning, manometry, and acoustic reflections.[21–24]

Drug Induced Sleep Endoscopy (DISE)

Drug-induced sedation endoscopy (DISE) is an evaluation technique using fiberoptic endoscopy to examine the upper airway that involves assessment of individuals under pharmacologic sedation designed to simulate natural sleep.[25] Sedative agents such as midazolam, propofol or a mix of both are usually used.[26] When considering surgery in sleep apnea patients, it is important to evaluate the site of upper airway obstruction so that the surgeon can tailor the operative procedure to the specific site of collapse. Based on recent data in the literature, DISE is therefore indicated when surgery[27,28] or MRA are considered.[29,30] Several techniques have been described to evaluate the upper airway such as MRI and CT. The downside to these techniques however is the lack of dynamic evaluation.[31]

In 1978, Borowiecki introduced sleep endoscopy during natural physiological sleep in order to better understand the complex mechanism leading to upper airway obstruction during sleep apneas. [32] This method however was cumbersome and so an alternative method was introduced. Croft and Pringle reported on evaluating the upper airway in patients with OSAS under sedation.[33] This allows the patient to tolerate the endoscope and the evaluation to be carried out during the day routine. This method has increased in popularity and has been utilized worldwide.

During DISE the nasal passage, nasopharynx, velum, tongue base epiglottis and larynx are observed.[34] It is possible to perform a chin-lift or jaw thrust during DISE. After this maneuver, the opening of the upper airway could be predictive factor for success of surgical treatment. This will be further researched in this thesis as this information would be important in narrowing the selection of surgical candidates of upper airway surgery increasing the success rate.

Momentarily, there is no general consensus on how to perform the sedation, how to report DISE findings, and in which patients DISE should be performed.[35] A recent paper published by De Vito et al.[26] tackled this very issue. In this paper a proposal of the DISE procedure standardization has been achieved with a general agreement concerning the terminology, indications, contra-indications, required preliminary examinations, setting, technical equipment required, staffing, local anesthesia and nasal decongestion, patient positioning, basis and special diagnostic maneuvers, and the applied sedation drugs and observation windows. This large number of variables involved when performing DISE has possibly prevented the development until now of a universally accepted scoring and classification system.[26]

There are several maneuvers which can be performed during DISE for example: actively opening of the mouth, closing the jaw, head rotation, changing the patient's position etc. All these changes in the physical situation of the patient during the procedure could potentially alter the upper airway patency. It is important to identify whether the maneuvers actually do change the upper airway patency and, if so, which maneuvers do so and to which degree. When identified, the results could help in the standardization of DISE so that research involving DISE world-wide could be more comparative. In addition, this information would give us further insight to the effect of upper airway change in different positions and, hence, using this in the application of different therapy methods. Several of the mentioned maneuvers during DISE will further be investigated in this dissertation.

Currently, little is known about the upper airway anatomy of patients with positional sleep apnea. DISE, due to mainly practical reasons, is usually performed in supine position. The theory behind this is that the level of severity of collapse is usually the highest in supine position. However, after the implementation of new forms of positional therapy in patients with positional OSA, it makes more sense to perform DISE in lateral sleeping position, either as only the position, or in both lateral or supine position. This could give us more insight to a "tailor made" positional therapy treatment for patients.

The possibilities of different maneuvers in various positions during DISE are essentially endless. This is in practice not sustainable, however it may become apparent that various maneuvers have similar effects on the airway, one could conclude that not all maneuvers have to performed and hence simplifying DISE yet receiving maximum information. Different positions during DISE have therefore been investigated in this thesis to answer this question.

The VOTE Classification

There are several scoring and classification systems to record DISE findings. Some of these systems are complex and others group structures together in various combinations making them difficult to use. It is for this reason the VOTE classification was proposed.[36] The VOTE classification is a scoring method for characterizing DISE findings that focus on specific structures that contribute to obstruction. These structures include: velum, oropharyngeal lateral walls (including tonsils), tongue base and epiglottis. The degree of obstruction involves the following categories:

- no obstruction (typically with no vibration of the involved structures)
- partial (typically with vibration) 50-75% narrowing
- or complete (typically with total or near-total obstruction).

The DISE findings can be noted in a table as depicted in figure 3.[36] After a maneuver for example chin-lift or jaw trust, or after upper airway stimulation, mandibular device is used, the findings are recorded again.

The oversimplified scoring systems, including VOTE, do not take position of the patient in consideration or other maneuvers for that matter. Even still, scoring systems such as VOTE are simple, reproducible and a step towards standardizing DISE recordings.

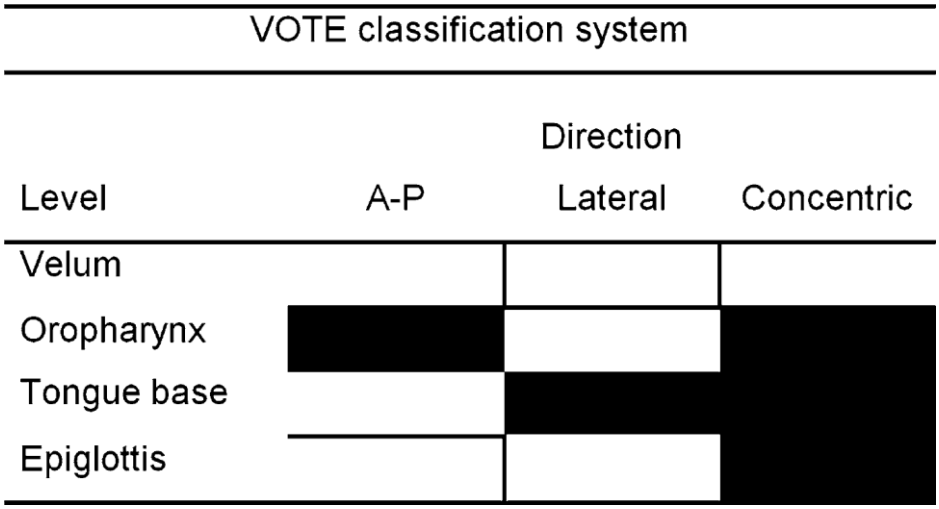

Figure 3: VOTE classification system. Degree of obstruction: 0, no obstruction (no vibration, <50%); 1, partial obstruction (vibration, 50–75%); 2, complete obstruction (collapse, >75%); x, not visualized. A–P anteroposterior

Management

Lifestyle Changes

Avoidance or cessation of smoking, alcohol consumption, and myorelaxant drugs, can be beneficial.[37] It is estimated that 80% of OSAS patients are obese.[38] Significant weight loss, including bariatric surgery in case of morbid obesity, can also have a significant impact on OSAS severity.[39]

Continuous Pressure (CPAP)

First introduced by Sullivan in 1981, continuous positive airway pressure (CPAP) is still considered to be the gold standard treatment in patients with OSAS.[18,40] It has been proposed as the most effective treatment for obstructive sleep apnea and has become the treatment of choice for clinicians. It consists of a nasal or oro-nasal mask held in position with elastic headgear and attached to a flow generator by elephant tubing. The flow generator is set to a specific pressure to produce a force great enough to maintain airway patency and overcome the respiratory disturbance.[41]

However, CPAP is only effective when used appropriately and sufficiently. 30-40% of OSA patients fail to comply with the treatment, often finding it intolerable.[1] Common complaints when using CPAP described by patients are: claustrophobia, redness of skin due to mask, mask leakage, blocked nose, noise from ventilator and negative social aspects. CPAP must be used more than 5 days a week and more than 4 hours per night to be considered "effective".[42] Another definition of compliance is 7 days a week, at least 4 hours per night.[43]

Nasal obstruction

There are many reasons for CPAP failure or non-acceptance. Several studies have reported an association between nasal obstruction and OSAS, but the precise nature of this relationship remains to be clarified.[44] Nasal pathologies should be treated in all patients with OSAS, particularly those undergoing CPAP treatment. However, patients should be counseled that favorable results might not be achieved after nasal surgery.[45]

Nasal congestion due to enlarged inferior nasal turbinates can contribute to the lack of compliance in patients using CPAP. Nasal sprays or heated humidification are usually not effective in this condition.[37] If there was an easy, patient friendly minimal invasive treatment for this condition, while circumventing the problem of nasal packing and general anesthesia, some patients with CPAP failure could still be treated and would be able to continue CPAP therapy. Ideally, such an intervention should have a long-term effect. One of the studies in this thesis therefore is the analysis of the long-term effect of radiofrequency ablation of hypertrophic inferior turbinates, under local anesthesia.

Radiofrequency turbinate reduction is a minimally invasive surgical option that can reduce tissue volume. This technique uses radiofrequency to create lesions within

the submucosal tissue of the turbinate, reducing tissue volume with minimal impact on surrounding tissues. Radiofrequency turbinate reduction differs fundamentally from traditional methods by using low-power radiofrequency energy to provide a relatively quick and painless procedure for tissue coagulation.[46] The long term effects of this treatment are not clear. This thesis therefore investigates the long-term self-reported treatment effects and experience of radiofrequency-induced thermotherapy of the inferior turbinates performed under local anesthesia. The evaluation of blocked nose in CPAP patients is currently an ongoing trail and this is being evaluated.

Oral devices

Oral appliances (OA) are designed to improve upper airway configuration and prevent collapse through alteration of jaw and tongue position. The most common mechanism of action is to hold the lower jaw in a more anterior position. These appliances are variously termed "mandibular advancement devices (MAD)," "mandibular advancement splints (MAS)," or mandibular repositioning appliances (MRA)." Lateral expansion of the airway space is likely mediated through lateral tissue movement via direct tissue connections between the lateral walls and the ramus of the mandible. Various amounts of anterior tongue movement also occur with mandibular advancement.[47]

Positional Therapy (PT)

Positional obstructive sleep apnea (POSAS), defined as a supine AHI twice or more as compared to the AHI in the other positions.[1] Positional patients make up a substantial component of the OSAS population. Several studies have shown that up to 56% of patients with OSAS qualify as positional.[1,17,48] A recent Swiss study with 1734 patients found even a higher prevalence of POSAS. Position-dependency was found in 74.6% of mild, 70.1% of moderate and 60.4% of severe OSAS patients.[49]

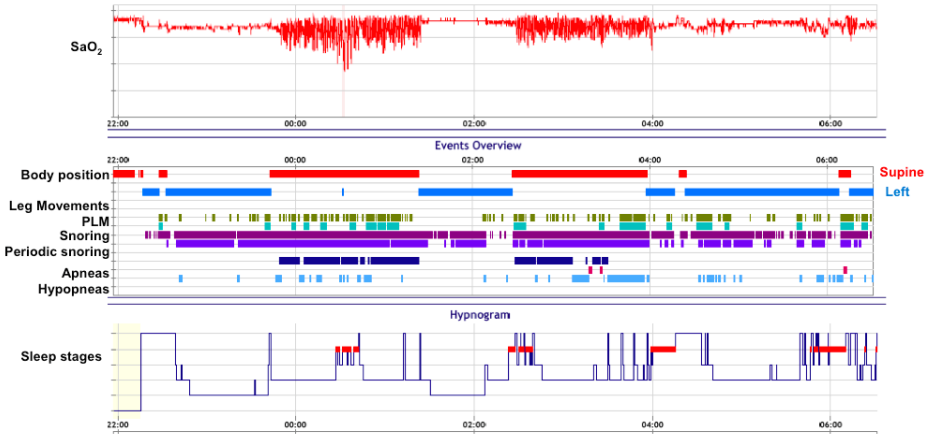

Figure 4: Typical polysomnographic report of a POSAS patient

OSAS.[36] Consequently, preventing POSAS patients from sleeping in supine position would be the most evident form of therapy.

PT can be defined as preventing patients to sleep in the worst sleeping position. The worst sleeping position is in most cases the supine position. Various traditional techniques are described to prevent patients from sleeping in the supine position such as tennis balls, vests, bulky masses or special pillows.[50] Discomfort, backache and lack of sleep quality has been the reason for low compliance rates of such methods. These former techniques resulted in long-term compliance of about 6% after an average of 2.5 years of therapy.[50] Hence, these methods were rarely used in clinical practice. In 2010, the European Respiratory Society called for more innovation and standardization of methods for PT .[51]

Figure 5: Different variations on bulky passive masses: the tennis ball technique

Therefore, newer techniques such as the Sleep Position Trainer (SPT) have been developed and applied and show to be a highly successful and well-tolerated treatment for patients with positional OSA, which diminishes subjective sleepiness and improves sleep-related quality of life without disrupting sleep quality.[52] Further, its application leads to high compliance rates; 68% of patients still use the device on a daily basis for at least four hours after six months of use.[53] The SPT is a small

and ergonomic device that continuously monitors the patient's sleeping position. The device is easy to use and comfortable to wear, using the elasticized waist band that is worn around the chest. It uses a gradual training program to allow patients to get used to not sleeping supine. The sensor reacts with a soft vibration during sleep, if the patient lies in a supine position. The vibro-tactile feedback is provided to the patient during a natural movement arousal. This allows patients to turn to a healthy position without disturbing their natural sleeping pattern and creating extra arousals or awakenings. [52]

Figure 6: The Sleep Position Trainer for avoiding the supine sleeping position

The advantages of the newest techniques for positional therapy are that it is reversible, it is less cumbersome, has higher compliance rates than other alternatives, can be used in combination with other therapies such as MAD and can be still applied when upper airway surgery has failed.[52,54]

As mentioned earlier in this chapter, there is little known about the upper airway anatomy in patients with POSA. Therefore, performing DISE in these patients could give us a greater understanding of the syndrome. Traditional positional therapy devices (bulky masses, so called tennis ball technique) are placed on the back of a patient. New smart devices are placed on the trunk, which still allows freedom of movement and are ergonomically designed. Studies have shown that tilting the head to the side, solely or in combination with the trunk, can to a smaller degree also reduce the AHI in particular patients during sleep studies.[55] While position-

dependency based on the trunk is highly prevalent (52.3%) in OSAS, an additional 6.5% of patients might benefit from changing the head position[55]. Now that positional therapy with its innovative approach is part of the treatment spectrum, it would make more sense to perform DISE in positional patients in other positions than supine only. During DISE, it may be needed to mainly focus on the position of the trunk, but also the position of the head and the combination of head and trunk. Investigation of the extent of interaction between trunk and head position remains to be investigated. Further, little is known about whether DISE should be performed in lateral positions, since sleeping supine can now be avoided. Does DISE lead to different outcomes when comparing the left and right lateral position? Also, to what degree is turning of the head comparable to both turning head and trunk? For this reason analyses of the influence of head rotation during drug-induced sleep endoscopy in obstructive sleep apnea and the influence of difference head positions during DISE in patients with OSA and POSA will be researched in this thesis.

Oropharynx

Tonsils

Tonsillectomy alone may be considered as an effective first line surgical procedure in the treatment of OSA in selected patients. Patients with Friedman grade 3 or 4 tonsils may be considered for tonsillectomy as the initial surgical procedure, reserving other upper airway procedures at a later stage if necessary.[56]

Uvulopalatopharyngoplasty (UPPP)

Uvulopalatopharyngoplasty is, for the most part, both safe and effective as a surgical treatment for obstructive sleep apnea and severe snoring, in well selected patients. The procedure increases the oropharyngeal airspace by removing tissue in the throat, including one or more of the following: the uvula, soft palate, tonsils. Although complications from UPPP have been described in the literature [57] to a large extend these can be avoided with proper surgical technique.

The UPPP technique was originally described by Fujita et al in 1979, and, although many modifications have been published, the basic procedure involves palate shortening with closure of the mucosal incisions, hence encompassing “palatoplasty” component; classical tonsillectomy and pharyngeal closure comprise the “pharyngoplasty” component of the procedure.

Z-palatoplasty (ZPP)

The ZPP is a modified technique of the UPPP, for patients who underwent tonsillectomy earlier. The midline of the soft palate is retracted anterolaterally, which results in a widened retropalatal area. The uvula is split in the midline and sutured laterally along with the adjacent soft palate, thereby creating an effective anterolateral pull on the soft palate and thus widening the retropalatal area.

Other palatal procedures include various palatal stiffening procedures, implants[58], transpalatal advancement pharyngoplasty[59], barbed wire expansion sphincter palatoplasty[60].

Epiglottis

Epiglottis prolapse during inspiration is an unusual cause of airway obstruction and a rare cause of OSA.[61] Treatment of epiglottis collapses as only procedure is rarely performed. Partial epiglottectomy can be performed using CO_2 laser and/or be a part of Trans Oral Robotic Surgery.[61,62]

Tongue

Radiofrequency ablation of the tongue base (RFITT)

Tongue base submucosal radiofrequency ablation (RFA) can be performed in patients with mild to moderate OSAS with a tongue base collapse, in patients with hypertrophy of the lingual tonsils and often as part of multilevel pharyngeal surgical therapy.[34,63]

Upper Airway Stimulation

One of the causes of obstructive sleep apnea is the gradual loss of tone in the genioglossus muscle during sleep, causing the tongue to fall back and block the airway, which is then followed by a surge of genioglossus activity, opening the airway, until the process repeats itself again (figure 7).[64] The genioglossus muscle is known to be the largest upper airway dilator muscle, and may serve as a therapeutic target for treating sleep apnea. Furthermore, these changes in EMG activity in the genioglossus muscle appear to be synchronous with respiratory effort.

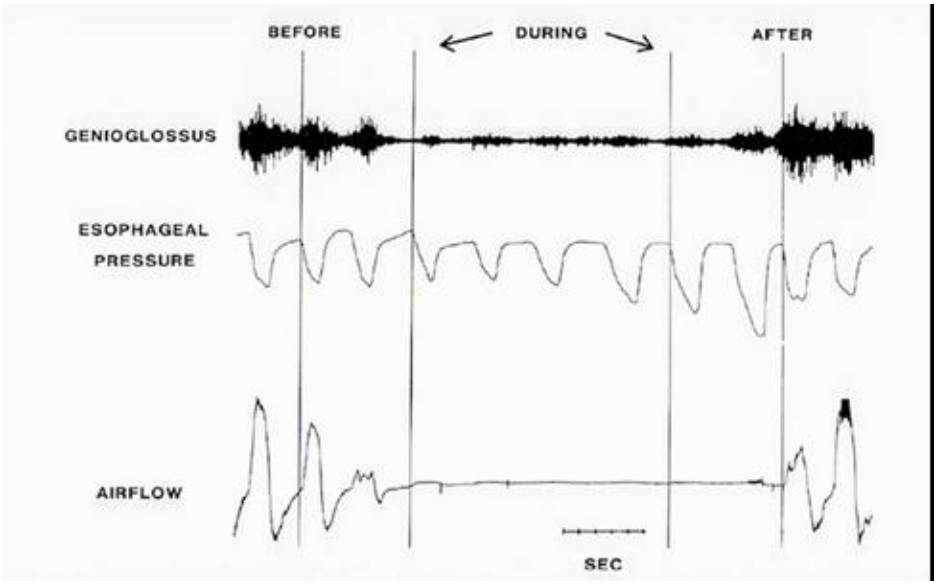

Figure 7: The simultaneous relaxation of the genioglossus muscle and blockage of airflow.[64]

The therapeutic hypothesis is that nocturnal neurostimulation of the hypoglossus nerve, timed with respiration, can be used to open the airway and act as a potential treatment modality for patients with OSAS who are intolerant to CPAP.[65] This therapy differs from current surgical therapy, which focuses on altering or removing the upper airway anatomy, and is typically associated with some period of post-operative pain. The advantages of an implantable hypoglossal nerve stimulator is that it can restore upper airway patency, without the need to remove or alter anatomy, with a lower post-operative pain profile, and the procedure is potentially reversible.

Various groups starting in the late 1990's have attempted to stimulate the genioglossus muscle directly [66,67] as a method to open the airway, or stimulating the genioglossus muscle via hypoglossus nerve with an implanted neurostimulator. [68–70] The results from these early feasibility studies helped to inform the selection of the most appropriate patients who could benefit from stimulation of the hypoglossal nerve, such as BMI, sleep apnea severity, and upper airway shape and collapsibility. Our research team, both at OLVG West and UZA, participated in the STAR trial, which tested the safety and efficacy of an implantable neurostimulator to treat sleep apnea in CPAP intolerant patients.[71] The results of the STAR trial led to the FDA approval of the therapy in April 2014.

Figure 8: Inspire II Upper Airway Stimulation implantable pulse generator

The Inspire Upper Airway Stimulation (UAS) system is an implantable nerve stimulator (IPG, figure 8) used to treat moderate to severe obstructive sleep apnea (AHI of greater or equal to 15 and less than or equal to 65 per hour sleep). The system consists of 3 implantable components, including the implantable pulse generator (IPG), stimulation lead, and respiratory sensing lead, which is typically implanted in a 2-3 hour procedure on the patient's right side. During the surgery, the right-side hypoglossus nerve is identified and intra-operative testing is used to identify branches that contribute to tongue protrusion, and the stimulation electrode is wrapped around the hypoglossus nerve (figure 9), and the remainder of the lead is tunneled to a sub-clavicular subcutaneous pocket that contains the implantable pulse generator, similar to a cardiac pacemaker. Similarly, the respiratory sensing lead is placed in the region of the 4-6 rib, tunneled between the internal and external intercostal muscles, and the remainder is also tunneled to the pocket, and both leads are connected to the IPG (figure 10). Before the closing of all the sutures, the performance of the stimulator is verified through intra-operative testing of the stimulation lead (confirming tongue-protrusion), as well as the sensing lead (confirmed by the display of a respiratory tracing on the tablet programmer for the IPG).[72] Patients are typically discharged on the first or second postoperative day, and may resume light activities, but the therapy remains off for the first month to allow for healing and fixation of the implantable components.

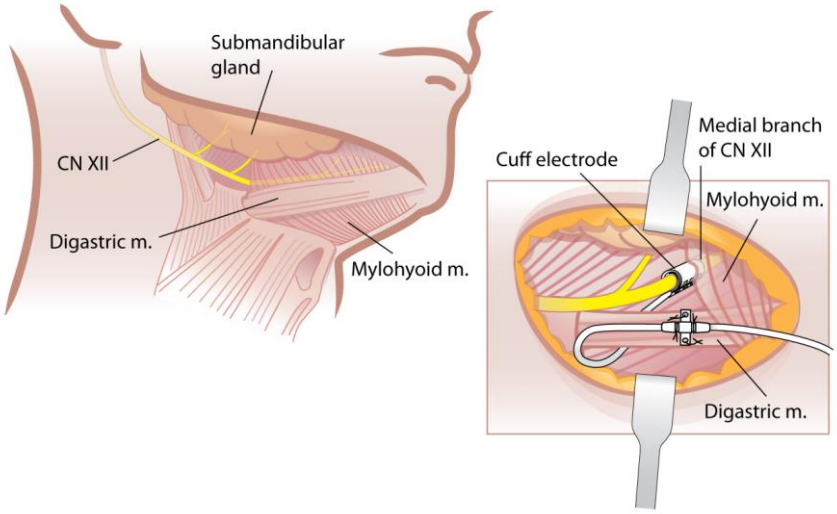

Figure 9: Illustration of the placement of the stimulation lead (source: Maurer, OP Tech Otolaryngol 2012)

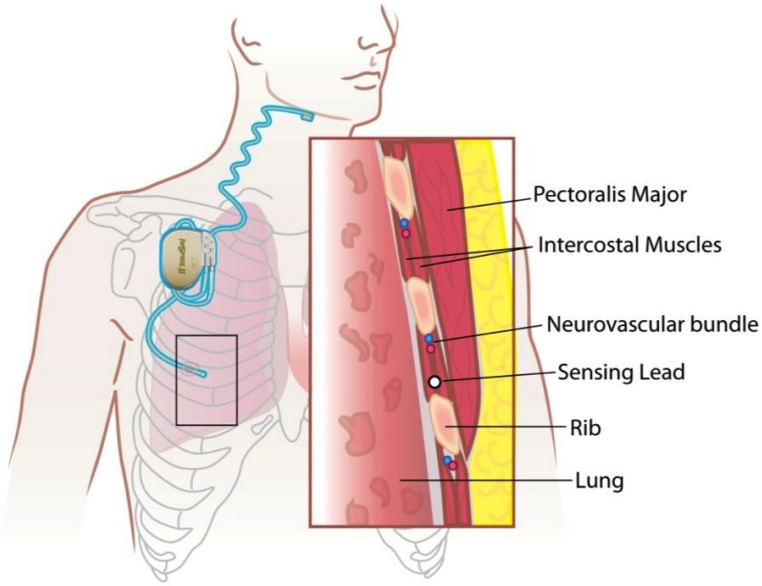

Figure 10: Illustration of the placement of the respiratory sensing lead, as well as the entire implanted system (source: Maurer, OP Tech Otolaryngol 2012)

The external components including the physician programmer and the patient programmer (sleep remote, figure 11) are used in the long-term management of the therapy. The therapy is programmable and titratable, using an external physician tablet programmer which can wirelessly communicate with the IPG.

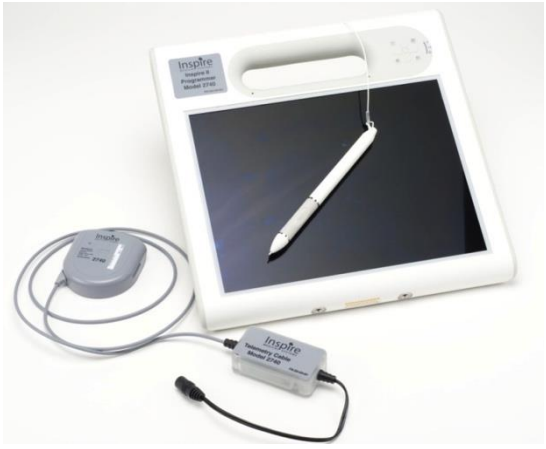

Figure 11: Physician tablet programmer – used to control stimulator settings such as amplitude, start delay, therapy time, and read diagnostic data such as battery status and therapy usage

Figure 12: Patient sleep remote – used to turn the therapy on/off, as well as allow amplitude adjustments within a controlled range

The stimulator is activated at night by the patient using the sleep remote (figure 12), and the IPG detects the patient's breathing pattern and maintains an open airway with mild stimulation of the hypoglossal nerve, which controls tongue movement, during inhaled breathing. The patient sleep remote allows the patient to turn therapy on before he/she goes to sleep and to turn therapy off when waking up.[70]

Typically the patients first receive their sleep remote 1-month after surgery, and are trained to acclimate and self-titrate the therapy amplitude based on symptoms, knowing that 2-month after surgery, the stimulator settings will be adjusted in a sleep lab setting, similar to CPAP titration (figure 13).

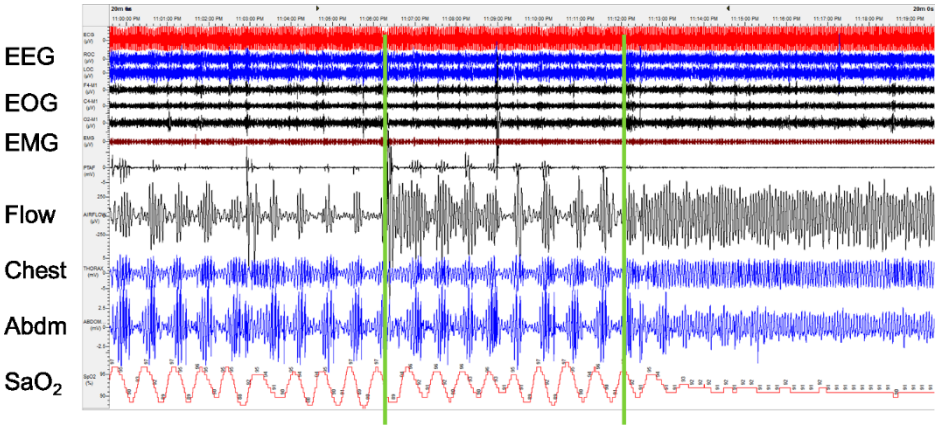

Figure 13: Stimulation strength is titrated in steps during sleep, until breathing is stabilized and obstructive apnea/hypopnea events are no longer seen

During the STAR trial, one hundred twenty-six (126) patients participated in 22 different sites. In these patients, the Inspire UAS therapy provided the majority of patients with significant reductions in the severity of their obstructive sleep apnea and improvements in their quality of life. On overage, the therapy improved the AHI from 29 to 9, and 68% of all patients experienced at least a 50% reduction in AHI and an AHI of less than 20 events per hour at the end of the 12 month study. Qualitative measurements using the Epworth Sleepiness Scale and Functional Outcomes of Sleep Measurement were equally improved.[71]

DISE is performed prior to implantation of the device, to determine the baseline collapse type. Based on previous research, patients with concentric collapse at the velum were less likely to benefit from the therapy, which led to the selection criteria to verify the absence concentric collapse at velum level before surgical implantation of the stimulator.[70] While a majority of patients derived benefit from the therapy, understanding the way stimulation changes airway shape may be useful for understanding therapy mechanisms. We proposed using DISE as diagnostic tool after therapy titration to observe the effect of stimulation on upper airway size and opening in both therapy responders and non-responders. This topic will be further studied in this thesis.

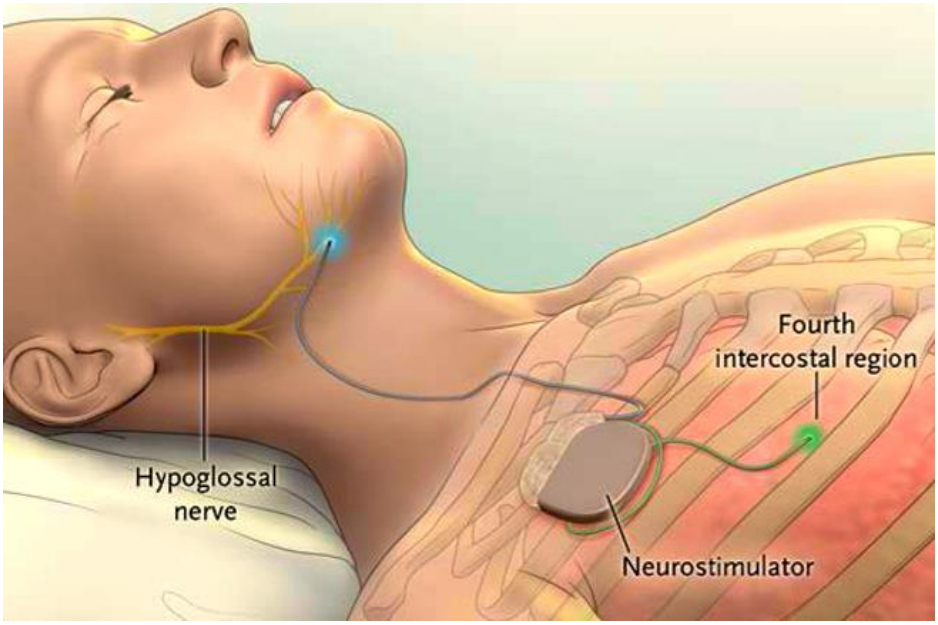

Figure 14: Inspire system

Other alternative treatments

Maxillomandibular Advancement

By moving the upper jaw (maxilla) and lower jaw (mandible) forward, the entire airway can be enlarged. It is also performed in patients with significant jaw deformity that contributes to obstructive sleep apnea. It is an invasive procedure that is mostly performed on patients with moderate to severe obstructive sleep apnea as the only treatment, or when other procedures have failed.[73,74]

Trans Oral Robotic Surgery (TORS)

The application for Transoral robotic surgery (TORS) for resection of base of tongue neoplasms was pioneered by O'Malley et al[75] and since then this technology for treatment of moderate to severe OSAS has been investigated[76,77]. Several articles suggest TORS is well tolerated by patients, with complications related to the specific procedure performed rather than the use of the robot. Potential disadvantages include difficult hemostasis control in some cases, high costs due to the longer hospitalization, surgery time and equipment.[78,79]

Tracheotomy

Until 1981, tracheotomy was the mainstay of treatment for obstructive sleep apnea untill continuous positive airway pressure (CPAP) was introduced. Now it is applied as a last resort solution for severe OSA patients.[40,80]

Outline of this Thesis

This thesis aims to discuss the following research questions:

1. What are the long-term self-reported treatment effects and experience of radiofrequency-induced thermotherapy of the inferior turbinates?

2. Can drug-induced sleep endoscopy variables predict the outcome of upper airway surgery in OSAS patients?

3. Does head rotation during drug-induced sleep endoscopy influence DISE in patients with OSAS and POSA?

4. Are outcomes of DISE performed in supine position with head rotated comparable with DISE performed in lateral position?

5. What is the effect of upper-airway stimulation for obstructive sleep apnea on airway dimensions?

This thesis focuses on the role of DISE as a selection tool for alternative treatments to CPAP. Nasal obstruction due to enlarged nasal turbinates is an important cause of patients who cannot tolerate CPAP treatment. In order to increase the compliance of CPAP one could perform RFITT.

Chapter 2 investigates the long-term self-reported treatment effects and experience of radiofrequency-induced thermotherapy of the inferior turbinates performed under local anesthesia using a retrospective analysis.

Chapter 3 gives a comprehensive review of the literature on the utility of sleep endoscopy in adults with obstructive sleep apnea

Chapter 4 analyses the influence of head rotation during drug-induced sleep endoscopy in obstructive sleep apnea and examined the influence of difference head positions during DISE in patients with OSA and POSA.

In Chapter 5 we compared the outcomes of DISE performed in supine position with head rotated, with the outcomes of DISE performed with head and trunk in lateral position.

Chapter 6 tested the hypothesis that drug-induced sleep endoscopy variables can predict the outcome of upper airway surgery in OSA patients.

In Chapter 7 we evaluated stimulation effects on retropalatal and retrolingual dimensions during drug-induced sedation compared with wakefulness to assess mechanistic relationships in response to UAS.

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Chapter 2

Long-Term Self-Reported Treatment Effects and Experience of Radiofrequency-Induced Thermotherapy of the Inferior Turbinates Performed under Local Anesthesia: A Retrospective Analysis

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Abstract

Nasal obstruction due to inferior turbinate hypertrophy is a common complaint. Radiofrequency-induced thermotherapy of the inferior turbinates (RFITT) under local anesthesia is now a widely used treatment, however reports of assessment of the long-term self-reported benefits and patient satisfaction of the treatment are scarce. This study focuses on the self-reported long-term effects of treatment and experience of RFITT. A questionnaire was sent to 441 patients who underwent RFITT in our clinic to treat symptoms of impaired nasal passage due to enlarged inferior turbinates. All patients had enlarged inferior turbinates on nasal examination. Patients were included if RFITT was done under local anaesthesia, was performed more than a year before the questionnaire was forwarded and on the indication-significant nasal obstruction because of enlarged inferior turbinates. Improvement of nasal breathing (by means of a Visual Analog Scale, VAS), changes in use of nasal spray (VAS), usage of pain medication, patient friendliness of the treatment, complaints reported after treatment, permanent effect of treatment during day and night time and willingness to recommend treatment to others were analyzed. No significant post-operative complications were observed. There was a significant reduction in use of nasal spray and the majority of patients interviewed reported long-term positive effects of RFITT during the daytime. This study shows that RFITT performed under local anesthesia is a valuable, minimally invasive, patient-friendly and well-tolerated treatment in patients with impaired nasal passage due to inferior turbinate hypertrophy.

Keywords: Turbinates, Hypertrophy, Nasal obstruction, Radiofrequency therapy

Introduction

Nasal obstruction due to inferior turbinate hypertrophy is a common complaint in daily otolaryngology. In order to reduce swelling of the inferior turbinates, patients are often initially advised to use nasal corticosteroid sprays. When symptoms of nasal obstruction persist, patients can opt for a surgical intervention. Surgical treatment modalities to reduce turbinate size include, in chronological order of introduction: electrocautery, chemocoagulation, turbinectomy, lateralization, submucosal resection of the turbinate bone, crushing and trimming, turbinoplasty, laser surgery, and high-frequency radiation.[1] Most of these modalities require general anaesthesia with postoperative nasal packing. Literature reviews provide considerable evidence for the efficacy of surgery in adult, symptomatic, inferior turbinate hypertrophy, with a significant increase in use of thermal techniques in the past decade.[2] Submucosal coagulation through radiofrequency-induced thermotherapy of the inferior turbinates (RFITT) can improve nasal passage by means of a minimally invasive procedure causing shrinkage of turbinate volume. Several studies have shown that mucociliary function also remains intact with RFITT.[3-5] In contrast to more invasive surgical turbinate reduction methods, RFITT can be performed in an outpatient setting under local anaesthesia without nasal packing, therefore reducing the burden of nasal packs, side-effects and risks associated with general anaesthesia.[6] Besides the technical feasibility of the treatment, one must also consider patient's tolerance and experience when applying it to the clinical practice. A few studies have already reported on the long-term effects of RFITT.[7,8]

The aim of this study was to analyze the long-term, self-reported effects and experiences of a large group of patients after RFITT.

Patients and Methods

We performed a retrospective, observational study in patients who underwent RFITT in a day care setting between January 2003 and December 2008 in our clinic. Before undergoing RFITT, patients visited the outpatient clinic and patient history was taken with emphasis on nasal symptoms. Routine ENT examination was performed, focusing on nasal pathology. If enlarged inferior turbinates were observed on nasal examination, in most cases a nasal corticosteroid spray was

prescribed for 6 weeks. If the response to the treatment was insufficient, patients were motivated for surgical therapy and RFITT was scheduled under local or general anaesthesia, leaving this choice up to the patient. Other indications for RFITT include: snoring, improving compliancy of continuous positive airway pressure in patient with sleep apnea, sinusitis, night time mouth breathing, rhinorrhoea, and headaches.

Radiofrequency-induced thermotherapy of the inferior turbinates treatment was not performed if patients had a positive medical history for active nasal infection, severe septal deformity producing near total obstruction, septal perforation, previous head and neck cancer, rhinoplasty, facial anomalies, autoimmune disease, connective tissue disorder, uncontrolled asthma, prior radiation therapy to the nose or septal deviation affecting the nasal valve region.

Surgical Procedure

Prior to the procedure the nose was anesthetized with xylocaine spray 100 mg/ml on cotton pads for 15 min, followed by xylocaine spray and local injection of lidocaine 1% and adrenaline 1:200,000 solution for injection in the inferior turbinates. The bipolar coagulation electrode (Celon ProBreath, Celon AG medical instruments, Teltow, Germany) was inserted into the anterior end of the inferior turbinate and then advanced posteriorly beneath the mucous membrane. The radiofrequency generator (Celon LabENT, Celon AG medical instruments, Teltow, Germany) was then activated (power setting: 15 W) until the end-of-procedure signal was audible. The electrode was withdrawn approximately 1 cm and the radiofrequent energy was then reapplied. The withdrawal and energy application were repeated until the entire length of the turbinate was treated. No nasal packing was used. Patients were discharged approximately 1 h after the procedure if there where no signs of bleeding. The patients who underwent the treatment under general anaesthesia were discharged when they were back on the ward.

Self-Reported Outcome Measurements

Patients were interviewed through questionnaires, partially using Visual Analog Scales (VAS). Questions asked included improvement of complaints (VAS), severity of obstruction before treatment (VAS), pain during and after treatment (VAS), usage of pain medication after treatment, complaints after treatment, level of satisfaction (VAS) of treatment, improvement of nasal breathing during daytime and night time (VAS), willingness to recommend treatment to others, willingness to undergo another treatment session, usage of nasal spray before treatment and changes in

use of nasal spray (VAS) after treatment. Patient evaluation data concerning nasal breathing were scored using VAS.

Questionnaires were sent to all the patients' postal address. If there was no response, they were contacted by telephone. Patients were excluded if the questionnaire was filled out within a year of the treatment.

Raw data depicting the VAS scale nasal congestion scores were placed in three categories namely: worse (≤4), no change (5) or improved (≥6).

Statistical Analysis

Statistical analysis was performed using SPSS statistical software (version 18, SPSS Inc, Chicago, USA). The distribution of recorded variables was characterized by calculating the mean and standard deviation. Comparison of pre- and post-operative VAS nasal spray usage values was conducted using McNemar's test. A P value <0.05 was considered significant.

Results

A total of 441 patients were treated in our clinic with RFITT between January 2003 and December 2008. Hundred and seventy-two patients returned filled out questionnaires. We attempted to contact the 269 non-responders by telephone to improve our response rate, thereby obtaining an additional 52 questionnaires. Twenty-six patients were excluded as they received RFITT under general anesthesia and 16 patients were excluded because the questionnaire was filled out within a year of surgery. An additional 40 patients were excluded because RFITT was performed for other complaints (not including nasal congestion). A total of 142 patients could be included in the study. These results are depicted in Fig. 1 to conform the STARD guidelines. The patient characteristics and follow-up of the 142 patients who completed the questionnaire are summarized in Table 1. Table 2 summarizes the number of complaints reported by patients postoperatively.

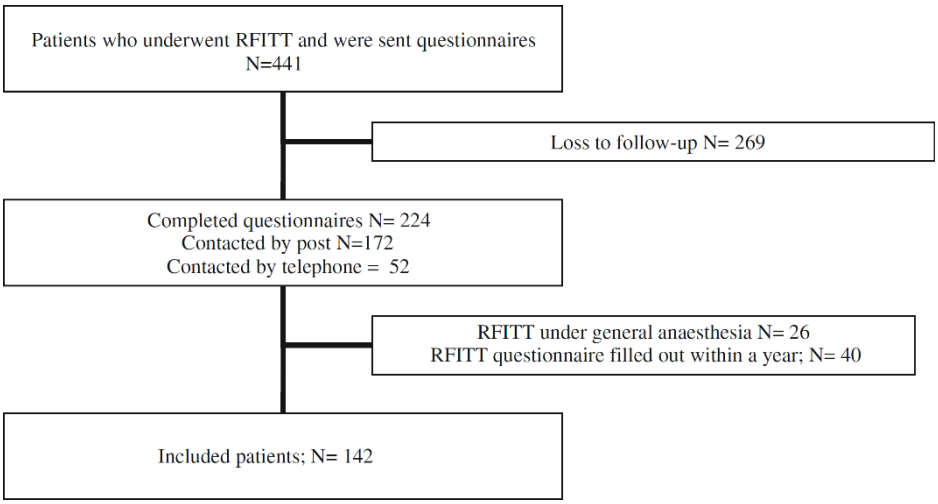

Figure 1: Included and excluded patients

Self-reported nasal congestion after RFITT was categorized into overall congestion, day time and night time congestion. 55.1% (76 patients) reported and improvement of nasal breathing after RFITT. 60.7% of the patients and 52.8% reported improved day and night time nasal congestion, respectively. An overall of 11 patients (8.0%) reported overall worsening of congestion after treatment. Only one patient reported worsening after treatment of RFITT during the day time and four patients (2.8%) during the night. 37% reported no change of overall congestion after treatment. 38.6% reported no change during the day time and 44.4% during the night time. These results are summarized in Table 3.

Of the total included, 96 patients (68.6%) used nasal corticosteroid sprays before treatment. Of these, 18 patients (13.1%) completely stopped using nasal corticosteroid spray after treatment (VAS = 0), which a McNemar's test shows is a significant reduction with $p < 0.000022$. 28 (31.5%) of the patients decreased their nasal spray usage (VAS B 4). 27 patients (30.3%) are using nasal spray in the same frequency as before the RFITT (VAS = 5). 16 patients (18.0%) had increased their usage of nasal spray.

Visual Analog Scale scores for severity of obstruction before treatment, pain during and after treatment are summarized in Table 4. Table 5 summarizes patients willing recommend treatment and undergo another RFITT session.

Table 1: Patient characteristics and follow-up of included patients

	Mean ± SD	Range
Number of included patients	142	
Women	70	
Men	72	
Age (years)	42.6 ± 14.4	(10–80)
Follow-up time (years)	4.5	(1–7)

Table 2: Number of complaints after treatment

0	13 (10.2%)
1	52 (40.6%)
2	29 (22.7%)
3	17 (13.3%)
4	12 (9.4%)
5	5 (3.9%)

Table 3: Self-reported nasal congestion after RFITT

Nasal congestion after RFITT	Overall Congestion	Day time congestion	Night time congestion
Worse *N* (%)	11 (8.0)	1 (0.7)	4 (2.8)
No change *N* (%)	51 (37.0)	54 (38.6)	63 (44.4)
Improvement *N* (%)	76 (55.1)	85 (60.7)	75 (52.8)

Discussion

Radiofrequency-induced thermotherapy of the inferior turbinates is considered as a safe, effective and patient-friendly treatment. Unlike most other surgical treatments of the inferior turbinate, RFITT can be performed in a day care setting under local anaesthesia and does not require nasal packing. The patient friendliness of RFITT is confirmed by the fact that 63.8% of all patients are willing to undergo another treatment session if necessary and the majority of the patients would recommend the treatment to others. These data a consistent with other studies of RFITT. There is a statistically significant decrease in the usage of nasal spray after treatment.

Table 4: Summary VAS scores

	VAS ≤ 4	VAS = 5	VAS > 6
Severity of obstruction before treatment *N* (%)	7 (4.9)	20 (14.1)	115 (81.0)
Pain during treatment *N* (%)	62 (43.7)	17 (12.0)	63 (44.4)
Pain after treatment *N* (%)	84 (59.2)	12 (8.5)	46 (32.4)

Table 5: Summary of patients willing to recommend treatment to others and undergo another RFITT session

	Yes	No
Willingness to recommend treatment to others	81 (63.8)	46 (36.2)
Willingness to undergo another treatment	87 (64.0)	49 (36.0)

Other recent articles confirm our results for long-term effects of radiofrequency tissue volume reduction.[9] Cukurova et al. describe the clinical benefit which persisted 60 months after the procedure. In our paper, we provide additional evidence of a subjective beneficial long-term effect of RFITT with a mean follow-up time of 4.5 years. Subjective data retrieved through patient interviews show a trend of beneficial effect of RFITT on nasal breathing during the day, with 60.7% of all patients reporting long-term improvement after the treatment.

After comparing complication rates of temperature-controlled radiofrequency with those reported in literature, Kezirian et al.[10] showed that the incidence of minor, moderate, and major complications, is low. Our data verify this trend with minimum complications reported post procedure.

Long-term effects of RFITT need to be put in perspective to long-term results of other surgical treatment modalities. Treatment options applied in clinical practice in a day care setting, such as RFITT, should not only have a long-term effect but should be safe and tolerable for patients.

There were a number of limitations in this study due to its retrospective nature. Initially, the data collected were not intended for a specific research, and the questionnaires were of a general nature. However, the response turned out to be unexpectedly positive with a high number of respondents with an indication of potentially interesting results. This study was therefore initiated and was designed

based on the already collected data. Thus, the questions in the data collection stage were not optimally formulated for the proposed research question. Although the data show that there is a significant decrease in nasal corticosteroids post-operatively, it must be mentioned that this is not a comparable study and diagnosis for use (for example allergic, non-allergic rhinitis) had not been researched. As a recommendation, future study designs should include not only subjective measurements but also objective ones such as rhinomanometry, to ensure more accurate results.

Conclusion

In conclusion, RFITT performed under local anesthesia is a well-tolerated surgical treatment for the patients with nasal congestion due to inferior turbinate hypertrophy with an acceptable long-term effect. One should consider opting for RFITT in clinical practice due to the minimal invasive aspect and its patient friendliness. In case of insufficient effect the procedure can be repeated, while more invasive procedures remain in reserve.

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Chapter 3

The Utility of Sleep Endoscopy in Adults with Obstructive Sleep Apnea: A Review of the Literature

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Abstract

Since history and physical examination alone cannot reliably diagnose obstructive sleep apnea (OSA), the gold standard for the diagnosis of OSA is polysomnography. When an oral device or surgery is considered, it is of utmost importance to examine an individual's pattern, degree and site(s) of upper airway obstruction. This article tries to evaluate recent literature published on the use of (drug-induced) sleep endoscopy in evaluating the individually tailored treatment. Different techniques, interrater reliability, test–retest reliability and currently available data on the relationship with treatment outcome are reviewed.

Keywords: Sleep endoscopy, Sleep apnea, Diagnosis, Drug induced sleep endoscopy

Abbreviations:

AHI	Apnea hypopnea index
ASA	American Society of Anesthesiologists
BIS	Bispectral index monitoring
BMI	Body mass index
DISE	Drug-induced sleep endoscopy
OPDA	Outpatient department assessment
OSA	Obstructive sleep apnea
PSG	Polysomnography

Introduction

Obstructive sleep apnea (OSA) is characterized by periods of cessation (apnea) and reduction (hypopnea) of the oronasal airflow during sleep accompanied by desaturations of blood oxygen. This sleep-related breathing disorder is a result of abnormal anatomy (crowding of the upper airway) superimposed on physiological or excessive reduction of muscle tone during sleep. Clinical symptoms are snoring, restless sleep, daytime fatigue, diminished intellectual ability and changes in personality. If OSA remains untreated, patients are at higher risk of developing cardiovascular diseases.[1-6] Furthermore, in the case of an apnea hypopnea index (AHI) >40/h the risk of being involved in a traffic accident increases.[7]

For many years, treatment for OSA has been based on low levels of evidence. A systematic review by Wright et al.[8] drew attention to the need for evidence on the efficacy of its main treatment: continuous positive airway pressure (CPAP). Since then, evidence has been collected on the impact of OSA on quality of life and health as well as the efficacy of various treatment modalities.[9,10] CPAP is regarded as the gold standard in OSA treatment in many countries. However, it is a clinical reality that the use of CPAP is often cumbersome. CPAP patients are considered compliant when CPAP is used ≥4 h per night as an average over all nights observed. We recently analyzed CPAP compliance using the above-mentioned criteria and found this to be true in <60% of a group of 232 CPAP users.[11] Furthermore, it has been proposed that using an AHI value whilst truly using CPAP does not reliably reflect the full overnight situation and it would be better to report mean AHI data in patients using CPAP therapy.[12]

Because of the limited number of high quality (i.e., level one or two) evidence articles on the effects of surgery for OSA some authors deny that there is any role for surgery in the treatment of OSA.[13] A more recent systematic review addressed the limitations of surgical studies of OSA patients and the differences compared to studies concentrating on more conservative treatment options. They identified 12 randomized controlled trials studying palatal implants, radiofrequency surgery, maxillomandibular advancement and uvulopalatoplasty and concluded that high quality trials studying surgical treatment are feasible and can lead to recommendations with high levels of evidence.[14] Other authors concluded in a systematic review that, in a certain percentage of OSA patients who either fail or are unwilling to pursue CPAP therapy, multilevel OSA surgery offers a chance to control their OSA.[15]

In some countries, like The Netherlands, oral devices and surgery are considered as primary treatment options in wellselected patients with snoring or mild to moderate OSA. Obviously, patient selection and assessment of the site(s) of obstruction is paramount to successful treatment with an oral device or surgery. The gold standard for diagnosing OSA is polysomnography (PSG), preferably the attended overnight polysomnogram[16], since history and physical examination alone cannot reliably diagnose OSA.[17,18]

Multiple evaluation techniques have been developed to examine an individual's pattern and site(s) of upper airway obstruction.[19] Ideally, this evaluation technique should be anatomically and physiologically sensible, with findings that correlate with objective indices of OSA like AHI, and should be proven to improve the results of surgery. Good measurement characteristics include accuracy, low test– retest variability and low interrater variability. Sleep endoscopy in the naturally asleep patient was introduced in 1978 by Borowiecki et al.[20] and in the asleep or sedated patient by Croft and Pringle.[21] The evaluation requires pharmacologic induction of sedation and flexible fiberoptic endoscopy to visualize the upper airway obstruction and/or snoring.

The purpose of this article is to systematically review recently published data on sleep endoscopy as part of the diagnostic work-up in adult OSA patients in whom surgery or oral device therapy is being considered.

Materials and Methods

Literature Query and Data Selection

The MEDLINE and EMBASE databases were systematically searched on 22 September 2012 by two researchers (J.v.M. and M.R.) using synonyms for DISE and OSA (see Appendices 1 and 2). The search was limited to articles with adult, human study subjects, written in the English language, accompanied by an abstract, and articles published between January 2007 and September 2012. In addition, the reference lists of included articles were screened for additional relevant citations. Conclusions were evaluated according to the Oxford Centre for Evidence-Based Medicine levels of evidence (Table 1).[54] All abstracts, or full text articles if abstracts provided too little information, were reviewed by two researchers (J.v.M. and M.R.).

Table 1: Oxford Centre for Evidence-Based Medicine levels of evidence[54]

Level	Diagnosis
1a	Systematic review of level 1 diagnostic studies
1b	Validating cohort study with good reference standards
1c	Absolute SpPins and SnNouts[a]
2a	Systematic review of level[2 diagnostic studies
2b	Exploratory cohort study with good reference standards
3a	Systematic review of level[3b studies
3b	Non-consecutive study; or without consistently applied reference standards
4	Case–control study
5	Expert opinion

[a] An absolute SpPin is a diagnostic finding whose specificity is so high that a positive result rules-in the diagnosis. An absolute SnNout is a diagnostic finding whose sensitivity is so high that a negative result rules out the diagnosis.

Results

DISE: Sedation Methods, Contraindications and Complications

The DISE technique has been extensively reported previously.[22••] Different sedation methods have been described, but there does not seem to be a standardized protocol for sedation methods.[22••, 23-27] Drugs most commonly reported for use with DISE are propofol and/or midazolam. Some use propofol only; others use midazolam only. Others start with midazolam and continue with propofol.[28,29] A computerized target-controlled infusion (TCI) system for propofol can be helpful and has been shown to be more accurate, stable and safe than a manual bolus injection.[30] Earlier, Berry et al.[27] demonstrated that TCI using propofol caused 100% of snorers to snore, while 100% of non-snorers did not snore.

Subjects with an AHI below 30/h, or, to be more accurate, patients with a supine AHI below 30/h and with good health (ASA I or II), can undergo midazolam-induced sleep endoscopy in the clinic.[23,31] Patients with a higher ASA score and/or more severe OSA should have DISE performed in the operating room.

Anesthetic depth is of key importance. The target depth of sedation is the transition from consciousness to unconsciousness (loss of response to verbal stimulation).

Because individuals have different susceptibilities to propofol, the required dosage can vary widely. Slow stepwise induction is required to avoid oversedation. Recently, bispectral index monitoring (BIS) during DISE has been introduced to determine the level of sedation required for assessment of snoring and/or obstruction.[28,32] Once the patient has reached a satisfactory level of sedation, a flexible endoscope is introduced into the nasal cavity. The nasal passage, nasopharynx, velum, tongue base, epiglottis and larynx are observed. The levels of snoring and/or obstruction are assessed. During DISE, maneuvers such as a chin lift (a manual closure of the mouth) or a jaw thrust (or Esmarch maneuver) should be performed, with reassessment of the airway after each maneuver.

A recent prospective study by Rabelo et al.[33••] showed no significant differences in AHI and mean oxygen saturation between two diurnal polysomnograms with and without the use of propofol. Since the main respiratory parameters evaluated in OSA treatment did not significantly change between polysomnograms, they concluded that sedation with propofol permits respiratory evaluation. Earlier, Sadaoka et al.[34] had also demonstrated that respiratory and somnological parameters did not significantly change during diazepaminduced sleep endoscopy in comparison with natural sleep, except for a small increase in the apnea index and a minor change in the duration of the longest apnea and REM sleep.

Several studies have shown the discrepancies between awake endoscopy and endoscopy in the (drug-induced) sleeping patient. Campanini et al.[35] showed, in a retrospective analysis of 250 patients, identical sites of obstruction during awake and sleep endoscopy in only 25% of patients, as measured by the Nose Oropharynx Hypopharynx Larynx (NOHL) staging system, introduced by the same authors. Hewitt et al.[36] performed a prospective, blinded, cohort study in 94 consecutive, snoring patients and compared outpatient department assessment (OPDA), consisting of examination of ear, nose, mouth, endoscopy (with and without simulated snoring and in combination with Müller's maneuver), to drug-induced sleep endoscopy (DISE) using midazolam (0.05 mg/kg) and propofol (1.5 mg/kg) titrated individually and maintained with boluses of propofol. During DISE, the jaw was lifted 3–5 mm to simulate the effect of an oral device. Based on the OPDA, a palatal intervention was recommended in 74.4% (n = 70) of patients; based on DISE, only 38 (54%) of these patients were recommended a palatal intervention. In a prospective analysis by Eichler et al.[37••], 97 patients underwent an OPDA, consisting of examination of the ears, nose, mouth, endoscopy and maximum possible protrusion of the mandible, followed by a theoretical treatment plan. A second ENT specialist

conducted a DISE (using midazolam starting with 0.03 mg/kg and adding 1 mg every 5 min until the patient fell asleep deeply enough to snore and show obstructions), also with jaw thrust maneuver, and independently recommended a second therapy without knowing the first one. Based on DISE, 76 (78.4%) patients would have received a different therapy compared to OPDA. Furthermore, they found tongue base surgery and oral device treatment to have the highest rate of change, whereas the indications for tonsil surgery were comparable between DISE and OPDA. Soares et al.[38] retrospectively analyzed 53 patients with OSA and compared OPDA (endoscopy with and without Müller's maneuver) to DISE (with propofol titration of 50/75 mcg/kg/min, the target level of sedation was that of light sleep with arousal to tactile but not vocal stimulation) in diagnosing the presence of severe (>75% collapse) levelspecific upper airway collapse. OPDA and DISE did not differ significantly regarding the presence of severe retropalatal collapse, but did significantly differ in the incidence of severe retrolingual collapse (DISE 84.9%, OPDA 35.8%). In Friedman I and II tongue positions[39] the greatest difference was found (DISE 88.9%, OPDA 16.7%). Gillespie et al.[32] prospectively studied a group of 38 patients and found a change in surgical plan after DISE in 23 (62%) patients compared to awake endoscopy. A high ASA (≥3) score and propofol or midazolam allergies (albeit rare) are considered contraindications. Because of a higher procedure-associated risk and lesser effects on treatment decisions, extremely severe OSA (AHI > 70/h) and severe obesity are relative contraindications. No severe side effects or emergency situations with DISE have been described in the literature. Endotracheal intubation or tracheostomy was never necessary.[22••]

Conclusions

To this point, there has been no gold standard for type(s) of sedative(s) during sleep endoscopy. Target-controlled infusion has proven to be more accurate than a manual bolus injection and seems to be the way to go when it comes to infusion of sedative. Bispectral index monitoring could be an adjunct to the assessment of DISE, although this has not yet been studied thoroughly.

Drug-induced sleep endoscopy permits respiratory evaluation of the sleeping patient and yields different levels of upper airway collapse and consequently different therapeutic options compared to endoscopy in the awake patient.

Level of evidence 3a.

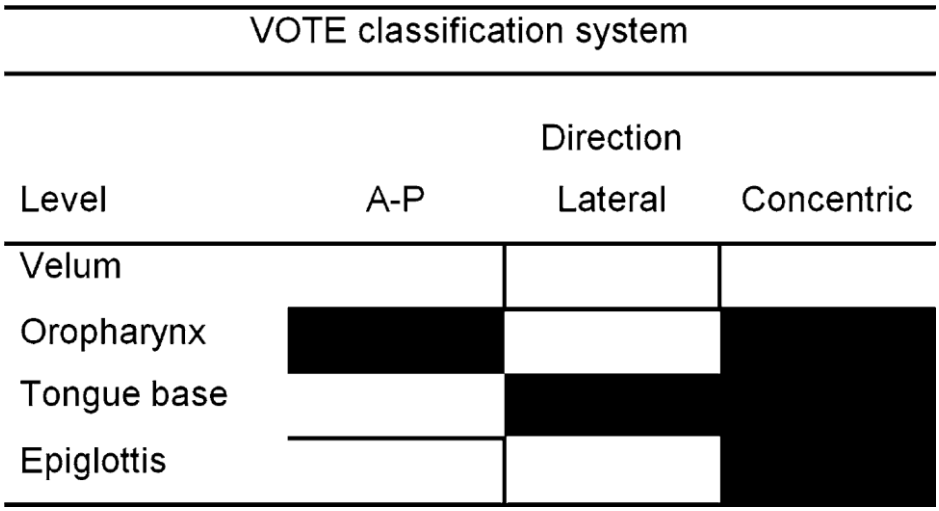

Figure 1: VOTE classification system. Degree of obstruction: 0, no obstruction (no vibration, <50%); 1, partial obstruction (vibration, 50–75%); 2, complete obstruction (collapse, >75%); x, not visualized. *A–P* anteroposterior

DISE: Scoring

Different methods for assessment of level and type of upper airway collapse have been described in the literature. Vicini et al.[40] introduced the nose, oropharynx, hypopharynx and larynx (NOHL) classification and have been using this system since 1996. It is an extensive classification system, grading the degree of obstruction as (1) (0–25% obstruction), (2) (25–50%), (3) (50–75%) or (4) (75–100%) and defining the pattern of collapse as transversal, anterior-posterior or concentric. Additionally, possible laryngeal obstruction can be graded as positive/ negative and supraglottic/glottic. Bachar et al.[41] recently introduced a novel grading system which allows the user to document collapsibility of the upper airway based on five possible anatomical sites: (1) nose and nasopharynx, (2) palatine plane, uvula and tonsils, (3) tongue base, (4) larynx, and (5) hypopharynx. Obstructions can be categorized as being complete (defined as complete blockage of the airway passage for at least 10 s) or partial (defined as narrowing or intermittent collapse). However, the classification system that has been studied the most is the VOTE system (Fig. 1).[29,30,42,43,44••] Velum, oropharynx (including tonsils), tongue base and epiglottis are evaluated. Distinction in configuration is made between anteroposterior, lateral or concentric, depending on the level of obstruction. The degree of airway narrowing is defined as either none (0) (0–50% obstruction), partial (1) (50–75% obstruction) or complete (2) (>75% obstruction). During DISE, a chinlift and a jaw thrust is

performed and the different VOTE levels are assessed once again to evaluate whether an oral device is a viable treatment option.

Conclusions

For upper airway obstruction using DISE, the VOTE system has been studied the most and seems easily applicable.

Level of evidence 3a.

DISE: Interrater and Test–Retest Reliability

Rodriguez-Bruno et al.[45] prospectively studied 32 patients undergoing 2 separate DISE examinations. Both examinations were evaluated by one unblinded surgeon and one blinded surgeon (with only knowledge of whether or not the patient had undergone prior tonsillectomy). These two DISE examinations were reviewed twice by each surgeon (2–6 weeks apart) resulting in 8 evaluations per patient, using a three-tiered method for DISE examination grading: (1) dichotomous (yes or no) assessment of obstruction at palatal and hypopharyngeal levels, (2) degree of palatal and hypopharyngeal obstruction, and (3) specific structures in palatal and hypopharyngeal region contributing to obstruction. They found a good test–retest reliability (range 50–80%), particularly in the evaluation of the hypopharyngeal airway. Using this same three-tiered method for DISE examination grading, Kezirian et al.[46••] prospectively studied 108 patients undergoing DISE. One unblinded surgeon performed all DISE examinations. The video images were later reviewed concurrently but independently by two surgeons (the unblinded surgeon and the blinded surgeon with only knowledge of whether or not the patient had undergone prior tonsillectomy). The interrater reliability for the presence of obstruction at the palate and hypopharynx (κ values, 0.76 and 0.79, respectively) was higher than for the degree of obstruction (weighted κ values, 0.60 and 0.44). The interrater reliability for evaluation of the hypopharyngeal structures was higher than for those of the palate region. Overall, interrater reliability of DISE seemed to be moderate to substantial. Gillespie et al.[29] recently evaluated interrater and test–retest reliability by prospectively evaluating 38 patients using DISE index scores. Test–retest reliability was evaluated by comparing the original intraoperative examination of the DISE index score to the DISE index score assigned on blind review of the DISE recording. Interrater reliability was determined, in a blinded and randomized fashion, by three otolaryngologists trained in DISE examinations. Test–retest reliability was good (κ = 0.61). Interrater reliability also showed good results (κ = 0.65) (κ = 0.62 between observer pairs).

Conclusions

Interrater and test–retest reliability for DISE have shown to be moderate to good. Interrater and test–retest reliability of VOTE need further investigation.

Level of evidence 3a.

DISE: Findings in Relation to Clinical and Sleep Parameters and Therapeutical Outcome

Several studies have evaluated the relation of level(s) of obstruction and AHI. Ravesloot and de Vries[43] prospectively analyzed 100 DISE examinations (mean AHI = 21.3/h) scored using the VOTE system and found multilevel obstruction (which was present in 76 patients) to be statistically significantly related to a higher AHI compared to patients with a unilevel obstruction. They found that the majority of patients had a palatal obstruction (83%), followed by tongue base (56%) and epiglottis obstruction (38%). Patients suffering from a complete concentric collapse of the velum were statistically significantly more likely to have a higher AHI and BMI, whereas an anteroposterior velar collapse was significantly associated with a lower BMI. Furthermore, AHI was found to be statistically significantly higher in patients with a complete anteroposterior collapse of the tongue. Observation of a tongue base or epiglottis obstruction was more common in positional OSA patients; however, this difference was not statistically significant (P = 0.058). As an alternative to the qualitative VOTE system for assessing upper airway collapsibility, Borek et al.[47] recently quantified the collapse seen at multiple levels of the upper airway in 37 OSA patients (mean AHI = 42.9/h). Using cross-sectional areas of captured images during DISE, they also showed that upper airway collapse occurs at multiple levels. Mean reductions in airway cross-sectional area were found to be 84.1% for retropalatal, 39.3% for retroglossal and 44.6% for retroepiglottic region which is in line with the previously mentioned article.[43]

Koutsourelakis et al.[44••] retrospectively analyzed 49 DISE examinations (scored using the VOTE system) of OSA patients (mean AHI = 30.9/h) who had undergone surgery (palatal surgery, and/or radiofrequent ablation of tongue base, and/or hyoid suspension). Multivariate logistic regression analysis revealed the presence of a complete circumferential collapse at the velum or a complete anteroposterior collapse at tongue base to be independent predictors of upper airway surgery failure. Earlier studies have shown that subjects with palatal obstruction alone versus multilevel obstruction on DISE had better outcomes after palate surgery.[48,49]

Johal et al.[36,50,51] showed that the resolution of airway obstruction with manual mandibular advancement under sedation is associated with improved outcomes with treatment using oral devices. More recently, titration of oral device therapy has been investigated by Vanderveken et al.[52], who recently introduced the technique of a simulation bite to be used during DISE and to predict treatment outcome with oral device therapy possibly leading to even more successful treatment of OSA with oral device therapy.

Conclusions

DISE findings (either qualitatively or quantitatively scored) correlate well with AHI and allow for better selection of type of surgery or titration of oral device therapy.

Level of evidence 3a.

DISE: Conclusion and Future Perspectives

DISE is a valid, dynamic, safe and easy-to-perform examination when surgery or oral device treatment is considered. Adequate assessment of the site(s) of obstruction, with use of both DISE and the VOTE classification, targets improvement of OSA treatment success. Furthermore, the shared use of a universally used DISE scoring system can facilitate the scientific evaluation of DISE in individual centers and, just as importantly, the collection of data across multiple centers and comparison of results across studies.

Target-controlled infusion has proven to be more accurate than a manual bolus injection. However, the target depth of sedation is still to be found. BIS monitoring could be of added value.

Increase in the number of DISE examinations is to be expected, not only because of the growing OSA awareness but, perhaps in the near future, also to cut healthcare system costs by means of CPAP titration during DISE instead of during a costly overnight in-hospital polysomnography.[53]

Whilst the gold standard investigation to evaluate level(s) of obstruction is yet to be defined, we believe that DISE provides the clinician with an accurate assessment of the obstruction site(s) as to be able to provide a site(s)-specific treatment.

Disclosure

J.P. van Maanen: none; M.J.L. Ravesloot: none; F. Safiruddin: none; N. de Vries: member of the Medical advisory board of MSD, ReVent Medical and NightBalance, is investigator for Inspire, has had honoraria payments from MSD, is consultant for Philips and has stock options in ReVent Medical.

Appendix 1: Syntax MEDLINE

(sleep[tiab] OR asleep[tiab] OR sedated[tiab] OR ‘‘drug induced’’[tiab]ORdrug-induced[tiab]ORDISE[tiab])AND (‘‘Endoscopy’’[Mesh] OR endoscopy[tiab] OR endoscopies[tiab] OR nasendoscopy[tiab] OR nasendoscopies[tiab] OR telescopy[tiab] OR videoendoscopy[tiab] OR videoendoscopies[tiab]) AND (‘‘Sleep Apnea, Obstructive’’ [Mesh] OR OSA[tiab] OR OSAS[tiab] OR apnoea[tiab] OR apnea[tiab] OR hypopnea[tiab] OR hypopnoea[tiab] OR apneic[tiab] OR ‘‘sleep disordered’’[tiab] OR SDB[tiab] OR sleep-disordered[tiab]) AND (‘‘2007/1/1’’[Date - Publication]: ‘‘3000’’[Date - Publication]).

Appendix 2: Syntax EMBASE

(sleep or asleep or sedated or dise or drug-induced or ‘‘drug-induced’’).ab,ti and (endoscopy or endoscopies or nasendoscopy or nasendoscopies or telescopy or videoendoscopy or videoendoscopies).ab,ti. and (OSA or OSAS or apnoea or apnea or hypopnea or hypopnoea or apneic or ‘‘sleep disordered’’ or SDB or sleep-disordered).ab,ti. limit: yr=’’2007-current’’.

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Chapter 4

Analysis of the Influence of Head Rotation During Drug-Induced Sleep Endoscopy in Obstructive Sleep Apnea

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Abstract

Objectives/Hypothesis: Currently, drug-induced sleep endoscopy (DISE) in obstructive sleep apnea (OSA) is predominantly performed in supine position. When positional therapy (avoidance of supine sleeping position in positional OSA (POSA) is implemented as (part of the) treatment, one should assess levels of obstruction in the other sleeping positions. Therefore, the current study examined the influence of difference head positions during DISE in patients with OSA and POSA.

Study Design: Consecutive prospective study.

Methods: DISE was performed in patients with an apnea hypopnea index at baseline polysomnography greater than 5 events/h. The upper airway was assessed at velum, oropharynx, tongue base, and epiglottis level in supine position. The patient's head was then tilted to the left and the right side and the DISE findings were recorded.

Results: One hundred consecutive patients were included. In positional apneics (n=67), lateral position was associated with decreased frequency of complete anteroposterior collapse at velum ($P<0.01$), tongue base ($P<0.01$), and epiglottis ($P<0.01$) level—and increased frequency of partial anteroposterior collapse at velum ($P<0.01$), tongue base ($P<0.01$), and epiglottis ($P <0.05$) level in comparison with supine position. DISE findings showed no difference between the right and left position, whereas findings after head rotation were significantly different in comparison with the supine position.

Conclusions: Head rotation improves upper airway collapse during DISE in supine position. This improvement of upper airway patency is more predominant in POSA patients.

Key Words: Obstructive sleep apnea, position dependent sleep apnea, drug-induced sleep endoscopy.

Level of Evidence: 4.

Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder caused by repetitive episodes of complete and partial obstructions of the upper airway during sleep.[1] These repetitive periods of collapse cause apnea, hypopnea, increased upper airway resistance, and oxygen desaturation. Patients may experience excessive sleepiness during the day, impaired concentration, social problems, and systemic disorders.[2–4] OSA is an independent risk factor for many diseases such as hypertension, heart failure, heart attack, cardiovascular events, and arrhythmias.[4]

Treatment options for OSA consist of continuous positive airway pressure (the gold standard treatment of OSA,[5], mandibular advancement device, and surgery. It has been well known for several years that supine sleep position plays an important role in the severity of OSA. However, positional therapy (PT)—prevention of the supine position—has never been common practice. PT as a noninvasive treatment modality in patients with positional OSA (POSA) has been tested since the 1980s. POSA was first defined in OSA patients in whom the respiratory disturbance index (RDI) was at least twice as high in the supine position as in the lateral position. The degree of severity of OSA in these patients is mostly related to the sleep time spent or not spent in the supine position.[6] Until recently, PT consisted of variations of the "tennis ball technique," a bulky mass strapped to the back of the patient.[7,8] The discomfort and disruption of sleep architecture have been responsible for a mediocre 40% (short-term) to poor 10% (long-term) compliance and subsequent disappointing results of such intervention.[7–12] For this reason, PT has never gained popularity. In an attempt to decrease discomfort and improve compliance, a new generation of PT devices has been introduced.[13,14] These devices—either a small neck or chest-worn vibrating device—have proven to be effective in correcting patients from adopting a supine position, without significantly reducing total sleep time or disrupting sleep, with high compliance rates.[13,14] Therefore, positional OSA recently has been gaining renewed attention. PT can be applied as a sole treatment for OSA or in combination with mandibular repositioning appliances or surgery as necessary. Studies have shown that more than half of patients with OSA are position-dependant[8,12] which has clinical implications when performing upper airway surgery.[15]

Drug-induced sleep endoscopy (DISE) is widely used to assess the site, direction, and severity of upper airway obstruction in patients with OSA. It has proved to be an important tool in predicting the outcome of upper airway surgery in OSA patients.[3]

The VOTE classification system is a method of characterizing DISE findings in the site, degree of airway narrowing, and configuration of obstruction.[16] The four most common obstruction sites evaluated when using the VOTE are the Velum, Oropharynx (including tonsils), base of Tongue, and Epiglottis. Airway closure can occur with collapse in an anteroposterior, lateral, or concentric configuration. The type of collapse configuration that is possible depends on the level of obstruction. The classification also involves an assessment of the degree of airway narrowing: either none, partial, or complete— depending on the percentage of airway narrowing.[16] Although DISE is indicated in patients when surgery or oral device therapy is considered, the role in patients with positional OSA has not yet been investigated.

DISE is predominantly performed in a supine position. However, when one incorporates PT in combined treatment with surgery, it would make more sense to assess levels of obstruction in other sleeping positions. It is possible that POSA patients have distinct anatomical characteristics whereby the gravitational effects could have a higher effect on the upper airway by displacing anterior pharyngeal structures and the pharynx. DISE performed in different positions could further help to elucidate the pathophysiology of nonpositional and positional apneics.

The aim of this study was to assess the influence of different head positions in patients with positional OSA using the VOTE classification. Our hypotheses were: 1) Rotation of the head to the right or left side will decrease the severity of upper airway obstruction, in particular in POSA. 2) Direction of head rotation (left vs. right) will be irrelevant for the severity of collapse. To test these hypotheses, we evaluated 100 consecutive patients undergoing DISE at our clinic.

Materials and Methods

Study subjects

The population prospectively assessed for this study consisted of OSA patients who underwent propofol-induced sleep endoscopy in the Department of Otolaryngology/Head and Neck Surgery of Saint Lucas Andreas Hospital (Amsterdam, The Netherlands) between May 2012 and August 2012. Further inclusion criteria were: 1) Apnea hypopnea index (AHI) at baseline polysomnography greater than five events/h, 2) age>18 years. Patients were not included if they had

neck injuries or head/neck complaints. This research was approved by the local medical ethics committee.

Protocol

All subjects underwent propofol-induced sleep endoscopy. Subjects were placed in a supine position in a quiet operating room with the lights dimmed. Prior to the DISE, the patient's head was placed in a neutral position using a standard foam pillow.

Propofol was administered by the anesthetist starting with an initial sedation of 20 mg, which allowed passage of the endoscope. The level of concentration was controlled by the anesthesiologist to the desired level of sedation. The rate was adjusted as needed, 50 to 100 lg/kg/min to meet the target level of anaesthesia. When achieved, the upper airway passage at velum, oropharynx, tongue base, and epiglottis levels were observed. The patient's head was then tilted to the left and to the right side. The DISE findings were reported using the VOTE classification.[16] Illustrated examples of these types of collapses have been described in earlier literature.[3] The effects of chin lift, flexion, extension, and bite opening were also evaluated in this patient group; however, it was not the aim of this study and thus has not been included in the results.

The results of the polysomnographies were only reviewed after the DISE was scored, preventing bias.

PSG

All patients underwent a full-night comprehensive sleep study using a digital Embla Recorder (Flaga Medical Devices, Reykjavik, Iceland). Transcutaneous pulse oximetry was used to monitor oxygen saturation and heart rate. The sleep architecture was recorded using electroencephalogram, electrooculogram and submental electromyogram, respiration (thoracic and abdominal measurement), movements of limbs, nasal airflow, and intensity of the snoring (the latter two measured by pressure sensor).

The severity of OSA is expressed in the AHI. Obstructive apneas were defined as cessation of airflow for at least 10 seconds. Hypopneas were defined as periods of reduction of >30% oronasal airflow for at least 10 seconds and a 4% decrease in oxygen saturation. The AHI was calculated as the sum of total events (apneas and hypopneas) per hour of sleep. An AHI of 5 to 15 is mild OSA; an AHI of 15 to 30 is moderate OSA; and an AHI>30 is severe OSA, as assessed by PSG.[17] Patients were

considered to have POSA if the AHI was twice as high in a supine position compared to any other sleep position.

Definitions and Analysis

Sleep stage was scored manually in 30-second epochs, and obstructive respiratory events were scored using standard criteria by an experienced technician.[18] The number of episodes of apneas and hypopneas per hour of sleep is referred to as the AHI-events/hr. OSA was diagnosed if AHI was >5. All measurements were analyzed by a single investigator to ensure consistency; and all polysomnographies were scored by a single, experienced sleep technologist and subsequently reviewed by an investigator who was blinded to the patient's clinical data. SPSS statistical software (version 18, SPSS Inc., Chicago, IL) was used for the data collection and data analysis. Quantitative data are reported as means ± SD. The normality of the data distributions was assessed by the Kolmogorov-Smirnov test. Differences in means of quantitative variables between the right and left position and between positional and nonpositional apneics were assessed by unpaired *t* test, whereas differences in categorical values were assessed by the Yates corrected chi-square or Fisher's exact test, as appropriate. A *P* value of less than 0.05 was considered to indicate statistical significance.

Results

A total of 100 patients were included in the study. The anthropometric and polysomnographic data of these patients are shown in Table 1. Sixty-seven percent of the study patients were positional apneics, and there was no difference between AHI in the right position and AHI in the left position.

DISE findings in the supine position in all patients are presented in Table 2. As can be seen, complete anteroposterior collapse of the velum, tongue base, and epiglottis were the most prevalent types of collapse.

Table 1: Anthropometric Data and Sleep Parameters. Data are presented as n, n (%) or mean SD.

Study participants (n)	100
Age (yrs)	49.3 ± 12.0
Male n (%)	84 (84)
Body mass index kg·m^2	27.9 ± 4.4
Apnea hypopnea index events·h^{-1}	20.9 ± 16.3
Apnea hypopnea index in supine events·h^{-1}	36.2 ± 23.4
Average oxygen saturation %	93.3 ± 12.0
Minimum oxygen saturation %	84.1 ± 8.9
Sleep time in supine posture min	150 ± 107
Neck circumference, cm	40.0 ± 3.1
Positional apneics n (%)	67 (67)

Table 2: Drug-induced Sleep Endoscopy Findings in All Patients (n = 100). Data are presented as n (%).

		Complete Collapse	Partial Collapse
Velum	Anteroposterior (%)	50 (50.0)	10 (10.0)
	Circumferential (%)	35 (35.0)	1 (1.0)
Oro-pharynx	Lateral (%)	17 (17.0)	12 (12.0)
Tongue base	Anteroposterior (%)	62 (62.0)	22 (22.0)
Epiglottis	Anteroposterior (%)	64 (64.0)	16 (16.0)
	Lateral (%)	0 (0)	1 (1.0)

DISE findings had no difference between the right and left position (Table 3), whereas DISE findings in the supine position were significant different in comparison with head rotation (Table 4). Head rotation was associated with a decreased frequency of complete anteroposterior collapse (and partial) at velum ($P<0.05$), tongue base ($P<0.01$) and epiglottis ($P<0.01$) level and an increased frequency of partial anteroposterior collapse at velum ($P<0.05$), tongue base ($P<0.01$), and epiglottis ($P<0.01$) level in comparison with the supine position (Table 4).

Table 3: Drug-induced Sleep Endoscopy Findings in Right and Left Position in All Patients (n = 100). Data are presented as n (%). There was no statistical difference between right and left posture.

		Right Position	
		Complete Collapse	Partial Collapse
Velum	Anteroposterior (%)	32 (32.0)	23 (23.0)
	Circumferential (%)	31 (31.0)	6 (6.0)
Oro-pharynx	Lateral (%)	13 (13.0)	16 (16.0)
Tongue base	Anteroposterior (%)	13 (13.0)	41 (41.0)
Epiglottis	Anteroposterior (%)	21 (21.0)	28 (28.0)
	Lateral (%)	0 (0)	0 (0)
		Left Position	
		Complete Collapse	Partial Collapse
Velum	Anteroposterior (%)	30 (30.0)	21 (21.0)
	Circumferential (%)	32 (35.0)	7 (1.0)
Oro-pharynx	Lateral (%)	15 (15.0)	14 (14.0)
Tongue base	Anteroposterior (%)	14 (14.0)	38 (38.0)
Epiglottis	Anteroposterior (%)	23 (23.0)	29 (29.0)
	Lateral (%)	0 (0)	0 (0)

Table 4: Drug-Induced Sleep Endoscopy Findings in Supine and Lateral Position in Positional Apneics (n = 67). Data are presented as n (%).

		Supine Position	
		Complete Collapse	Partial Collapse
Velum	Anteroposterior (%)	37 (55.2)	7 (10.4)
	Circumferential (%)	21 (31.3)	0 (0.0)
Oro-pharynx	Lateral (%)	7 (10.4)	6 (9.0)
Tongue base	Anteroposterior (%)	47 (70.1)	11 (16.4)
Epiglottis	Anteroposterior (%)	46 (68.7)	10 (14.9)
c	Lateral (%)	0 (0)	1 (1.5)

		Lateral Position	
		Complete Collapse	Partial Collapse
Velum	Anteroposterior (%)	23 (34.3) p=0.04 *	18 (26.9) p=0.02 *
	Circumferential (%)	16 (23.9)	4 (6.0)
Oro-pharynx	Lateral (%)	5 (7.5)	10 (14.9)
Tongue base	Anteroposterior (%)	8 (11.9) p=0.002 †	29 (43.3) p=0.008 †
Epiglottis	Anteroposterior (%)	14 (20.9) p=0.007 †	18 (26.9) p=0.003 *
	Lateral (%)	0 (0)	0 (0)

* P<0.05 versus supine position

† P<0.01 versus supine position

Table 5: Drug-Induced Sleep Endoscopy Findings in Supine and Lateral Position in Nonpositional Apneics (n = 33). Data are presented as n (%).

		Supine Position	
		Complete Collapse	Partial Collapse
Velum	Anteroposterior (%)	14 (42.4)	2 (6.1)
	Circumferential (%)	14 (42.4)	2 (6.1)
Oro-pharynx	Lateral (%)	9 (27.3)	7 (21.2)
Tongue base	Anteroposterior (%)	16 (48.5)	8 (24.2)
Epiglottis	Anteroposterior (%)	18 (54.5)	5 (15.2)
	Lateral (%)	0 (0)	1 (1.5)
		Lateral Position	
		Complete Collapse	Partial Collapse
Velum	Anteroposterior (%)	9 (27.3)	5 (15.2) p=0.03 *
	Circumferential (%)	15 (45.5)	2 (6.1)
Oro-pharynx	Lateral (%)	8 (24.2)	6 (18.2)
Tongue base	Anteroposterior (%)	5 (15.2) p=0.001 †	12 (36.4)
Epiglottis	Anteroposterior (%)	7 (21.2) p=0.008 †	10 (30.3) p=0.025 *
	Lateral (%)	0 (0)	0 (0)

* P<0.05 versus supine position

† P<0.01 versus supine position

Discussion

The results from this study confirm this article's hypothesis that the severity of upper airway collapse in patients with sleep apnea decreases significantly when the head is rotated to the lateral side. However, there is no significant difference between the rotation of the head to the right or left side. The airway improves significantly more in patients with POSA. Patients with POSA have significantly more complete anteriorposterior collapse at the palate and tongue-base level than OSA patients. To the best of our knowledge, this is the first study in which DISE is performed in different head positions and scored using the VOTE criteria.

Previous studies have already shown that difference head positions can influence collapsibility of the passive pharynx in patients with sleep disordered breathing.[19,20] Van Kesteren et al.[21] have provided additional evidence that head position, separately from trunk position, is an additional important factor in the occurrence of apnea/ hypopnea in a subpopulation of OSA patients. Intuitively, these head positions could influence the outcome of DISE. And, when one incorporates PT in the treatment of OSA, assessment of the level(s) of obstruction in a lateral position appears more important than in a supine position, the sleep position that is eliminated after PT.

Our method of utilizing DISE is validated because we obtain comparable results to Isono et al. through this study.[22] Another research shows that the head posture has a marked effect on the collapsibility and site of collapse of the passive upper airway (measured by electromyography); thus, manipulating head posture during propofol sedation may assist with identification of pharyngeal regions vulnerable to collapse during sleep and may be useful for guiding surgical intervention.[19] Although this study was not performed in OSA patients, it is a guide that head position is an important factor in assessing upper airway patency and could be important during DISE.

These findings are of clinical importance because it may not be necessary for patients to rotate to the lateral side during DISE; the head rotation is enough to improve the AHI. In addition, patients who cannot tolerate PT due to back complaints could potentially benefit from head rotation only. Currently, PT devices are placed on the trunk of the body. The device could also be placed at the back of the neck or on the head in order to independently rotate the patients head. Further studies are

ongoing to investigate whether this will be an effective way of treating POSA patients.

Based on the results of this current study, we recommend that DISE procedures should be standardized to minimize variability in DISE outcomes. In POSA patients, when incorporation of PT in the treatment plan is considered, the assessment of the level(s) of obstruction in lateral position can be more valuable than in the supine position.

This study is not without limitations. First, there is an ongoing discussion whether propofol-induced sleep is a reliable method of assessing the upper airway. Ideally, endoscopies should be performed under natural sleep; however, this is hardly applied due to the practicality issues. This prospective study was performed on consecutive OSA patients in whom DISE was performed; therefore, the distribution of patients' characteristics varies. This could have possible implications when comparing groups. Although all DISE procedures were performed by one endoscopist, due to the dynamic airway there is the possibility of intra-rated variability when scoring using the VOTE system, making this study difficult to reproduce. Also, the endoscopist was not blinded to the patient's position when interpreting the DISE.

The mechanism responsible for the worsening of sleep disordered breathing in the supine posture is not clear, but most likely relates to the effect of gravity on upper airway size or shape.[23] During head rotation, it is clear that the tongue and palate are displaced. POSA patients have a remarkable improvement in DISE in lateral position, so this could explain why these groups of patients have a lower AHI in the lateral sleep positions. Therefore, DISE could be an indicator for potential success in PT.

Once positional therapy is implemented in patients, it would make more sense to perform DISE in the lateral position instead of in the supine position in order to treat the residual collapse. In our study, DISE was not performed in a "full" lateral position; only the head was rotated. An ongoing study has been designed to compare DISE with patients on their side compared to patients rotating their heads.

Conclusion

In summary, the present study indicates that head rotation during DISE improves upper airway collapse. This improvement is predominantly seen in POSA patients. In addition, there was no difference in upper airway collapse between the right and left head rotation.

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Chapter 5

Upper Airway Collapse During Drug Induced Sleep Endoscopy: Head Rotation in Supine Position Compared with Lateral Head and Trunk Position

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Abstract

Drug induced sedated sleep endoscopy (DISE) is often employed to determine the site, severity and pattern of obstruction in patients with sleep apnea. DISE is usually performed in supine position. We recently showed that the obstruction pattern is different when DISE is performed in lateral position. In this study, we compared the outcomes of DISE performed in supine position with head rotated, with the outcomes of DISE performed with head and trunk in lateral position. The Prospective study design was used in the present study. Sixty patients with OSA (44 male; mean apnea hypopnea index (AHI) 20.8 ± 17.5 events/h) underwent DISE under propofol sedation. Patients were placed in lateral position, and the upper airway collapse was evaluated. The patients were then placed in supine position with the head rotated to the right side. DISE outcomes were scored using the VOTE classification system. During head rotation and trunk in supine position, nine patients (15.0%) had a complete antero-posterior (A-P) collapse at the level of the velum, nine had a partial A-P collapse. In lateral position, at the level of the velum, four patients (6.7%) had a complete A-P collapse, while two patients (3.3%) had a partial A-P collapse. The patterns of collapse were not significantly different between head rotation and lateral position. During DISE, rotation of the head in supine position, and lateral head and trunk position present similar sites, severity and patterns of upper airway collapse.

Keywords: Drug induced sedated endoscopy, Sleep apnea, Head rotation, Positional sleep apnea, Obstructive sleep apnea, Positional therapy

Introduction

Obstructive sleep apnea (OSA) is a prevalent disorder caused by partial or complete relaxation of muscle tone in the upper airway during sleep, resulting in oxygen desaturation, apneas, arousals and frequent awakenings.[1,2] Common complaints experienced by patients include excessive sleepiness during the day, impaired concentration, social problems, and systemic disorders.[2-4]

Continuous positive airway pressure is still considered the gold standard treatment for OSA.[5] However, due to a high intolerance rate in chronic usage[6], surgery and other non-invasive alternative therapies—such as oral devices or positional therapy (PT)[7]—should be considered in selected patients as well. New forms of PT can be successfully applied in positional OSA (POSA). POSA is defined as an AHI that is twice as high in the worst sleeping position compared to other sleeping positions. Several recent articles have shown short- and long-term effectiveness and tolerance of these new forms of PT.[7,8] PT devices can be placed on the head, neck[8] or the trunk[7] of the patient with the aim to rotate at least their head (left/ right) or change both head and trunk to a complete lateral position during sleep, respectively.

Drug induced sleep endoscopy (DISE) is a method that assesses upper airway obstruction under conditions that mimic sleep.[9] The VOTE classification system is a method of characterizing DISE findings with regards to the site, degree of airway narrowing, and configuration of obstruction. The four obstruction sites of the VOTE system are the Velum, Oropharynx (including tonsils), base of Tongue, and Epiglottis. Total or partial airway collapse can occur in an antero-posterior, lateral, or concentric configuration.[9,10]

Traditionally, DISE has always been performed in the 'worst' sleeping position, namely the supine position. However, with the implementation of new forms of PT in patients with POSA, it would be more logical to perform DISE in the lateral position. We recently showed that change of body position (rotation from supine to lateral) during DISE leads to improvement of upper airway collapse in patients with POSA.[11] This improvement was regardless of the direction (left or right) of head rotation. This previous study did not investigate possible differences of upper airway collapse in DISE with head rotation compared to lateral head and trunk position. The aim of this study was to evaluate if head rotation has the same sites, severity and pattern of collapse compared to lateral head and trunk position during DISE, using the VOTE system. To answer this question we performed a prospective study.

First, it would give insight if during DISE only head rotation maneuvre would suffice, or that the more elaborate total change of body position is needed. Second, if head rotation is as effective as change of both head and trunk in positional OSA, this could provide opportunities for forms of PT that focus on head rotation only.

Materials and Methods

Study Subjects

The population prospectively assessed for this study consisted of OSA patients who underwent propofol-induced DISE at the Department of Otolaryngology/Head and Neck Surgery of Sint Lucas Andreas Hospital (Amsterdam, The Netherlands) between November 2012 and March 2013. Further inclusion criteria were: (1) AHI at baseline polysomnography greater than 5 events/h, (2) age >18 years. Patients were not included if they had neck injuries or head/neck complaints. This research was approved by the local medical ethics committee.

Protocol

All subjects underwent propofol-induced DISE. Subjects were placed in lateral position in a quite operating room with the lights dimmed using a standard foam pillow.

Propofol was administered by the anesthetist starting with an initial sedation of 20 mg which allowed passage of the endoscope. The level of concentration was controlled by the anesthesiologist to the desired level of sedation i.e. when the patient began to snore or did not respond to external stimuli. The rate was adjusted as needed 50–100 lg/kg/min to meet the target level of anesthesia. This target was variable per patient depending on the patient's weight, age, severity of OSA etc. When achieved, the upper airway passage at velum, oropharynx, tongue base and epiglottis levels was observed. The patients were then tilted to the supine position followed by rotation of the head to the right side. The DISE findings were reported using the VOTE classification.[9] The effect of chin lift in supine position was also evaluated in this patient group but was not the aim of this study and therefore has not been included in the results.

The results of the polysomnography (PSG) were only reviewed after the DISE was scored, preventing bias.

Polysomnography

All patients underwent a full-night comprehensive sleep study using a digital Embla recorder (Flaga medical devices, Reykjavik, Iceland). Transcutaneous pulse oximetry was used to monitor oxygen saturation and heart rate. The sleep architecture was recorded using electroencephalogram, electro-oculogram, and submental electromyogram, respiration (thoracic and abdominal measurement), movements of limbs, nasal airflow, and the intensity of the snoring (the latter two measured by pressure sensor). A positional sensor was placed on the trunk of the body to indicate different sleeping positions during sleep time.

The severity of OSA is expressed in the apnea hypopnea index (AHI). Obstructive apneas were defined as cessation of airflow for at least 10 s. Hypopneas were defined as periods of reduction of >30% oronasal airflow for at least 10 s and a ≥4% decrease in oxygen saturation. The AHI was calculated as the sum of total events (apneas and hypopneas) per hour of sleep. An AHI of 5–15 is mild OSA, an AHI of 15–30 is moderate, and an AHI >30 is severe OSA, as assessed by PSG. Patients were considered to have POSA if the AHI was twice as high in supine position compared to any other sleep position.[12]

Definitions and Analysis

Sleep stage was scored manually in 30 s epochs and obstructive respiratory events were scored using standard criteria by an experienced technician.[13] The number of episodes of apneas and hypopneas per hour of sleep is referred to as the apnea hypopnea index (AHI—events/h). OSA was diagnosed if the AHI was >5. All measurements were analysed by a single investigator to ensure consistency, and all polysomnographies were scored by a single experienced sleep technologist and subsequently reviewed by an investigator, who was blinded to the patient's clinical data.

SPSS statistical software (version 18, SPSS Inc., Chicago, USA) was used for the data collection and data analysis. Quantitative data are reported as mean ± SD. The normality of the data distributions was assessed by the Kolmogorov–Smirnov test. Differences in categorical values between lateral position and head rotation were assessed by McNemar's test. A p value of less than 0.05 was considered to indicate statistical significance.

Results

Sixty-eight patients met the initial inclusion criteria. Of these patients, 8 had head/neck injuries and were excluded from further analysis. A total of sixty patients were included. The anthropometric and polysomnographic data of the remaining 60 patients are shown in Table 1. Twenty-three of the total patients had POSA.

Table 1: Anthropometric data and sleep parameters. Data are presented as *n*, *n* (%) or mean ± SD.

Study participants n	60
Age, years	48.5 ± 14.5
Male n (%)	44 (73)
Body mass index, kg/m^2	26.9 ± 4.0
Neck circumference, cm	39.8 ± 3.9
Apnea-hypopnea index, events/h	20.8 ± 17.5
Apnea-hypopnea index in supine, events/h	36.0 ± 28.0
Average oxygen saturation, %	95.0 ± 1.5
REM, % of total sleep time	20.3 ± 6.5
Sleep time in supine position, % of total sleep time	31.1 ± 20.9

Table 2 presents the differences in DISE variables between head rotation and lateral position in all patients. There was no significant difference in number of collapses in any of the categories of collapse.

Table 2: Differences in DISE variables between lateral position and head rotation in all patients (n = 60)

	Lateral Position	
	Complete Collapse	**Partial Collapse**
Velum		
Anteroposterior (%)	4 (6.7)	2 (3.3)
Circumferential (%)	20 (33.3)	6 (10.0)
Oro-pharynx		
Lateral (%)	12 (20.0)	4 (6.7)
Tongue base		
Anteroposterior (%)	7 (11.7)	2 (3.3)
Epiglottis		
Anteroposterior (%)	7 (11.7)	1 (1.7)
Lateral (%)	0 (0.0)	0 (0.0)
	Head Rotation	
	Complete Collapse	**Partial Collapse**
Velum		
Anteroposterior (%)	9 (15.0)	9(15.0)
Circumferential (%)	21 (35.0)	5 (8.3)
Oro-pharynx		
Lateral (%)	14 (23.3)	3 (5.0)
Tongue base		
Anteroposterior (%)	7 (11.7)	3 (5.0)
Epiglottis		
Anteroposterior (%)	7 (11.7)	1 (1.7)
Lateral (%)	0 (0.0)	0 (0.0)

Discussion

We compared DISE findings using the VOTE classification in lateral head and trunk position to head rotation only in patients with OSA. To the best of our knowledge this is the first paper that looks at DISE in lateral position and head rotation using the VOTE classification.

The main finding is that during DISE, rotation of the head and lateral head and trunk position have similar sites, degree and pattern of upper airway collapse. The severity of A-P collapse is more severe during head rotation than in lateral head and trunk position, but statistical testing did not prove this to be a significant difference.

Despite the fact that DISE has been around for several decades[9] there is still no standardized protocol for performing or analyzing DISE. Due to the lack of consensus on a system, it has proven to be difficult to compare data and interpreting DISE outcomes.[14] A common language is mandatory, and attempts to come a generally accepted system are under way. The lack of standardization is a cause of inconsistency in DISE related data reported in the literature. The VOTE system has been a step forward in noting DISE findings in an effective, clear and concise manner.[9,10] The logic and simplicity of the VOTE system is a deliberate feature to maximize interrater agreement in favor of comprehensiveness.

Even so, many variations of the procedure are possible. DISE can be performed in a standard setting only, or combined with passive maneuvers such as chin lift, jaw trust, and mouth closure. All variations can be performed in five positions: left, right, supine, and supine with the head rotated to left and right. It is obvious that routine DISE assessment of all possible combinations would be unworkable. This paper is a follow-up of a previous research study, where we showed that DISE findings in left and right position are comparable.[11] It was concluded that assessment in only one lateral (either left or right) position would suffice. It would be easiest to start DISE in lateral position and turn patients subsequently to their back. The present study shows that an even easier way is to perform DISE in supine position and to turn the head to (only one) lateral position. In this way the five possible DISE positions (left lateral, supine with head tilt to left, supine, supine with head tilt to the right, right lateral) are reduced to only two, simple, positions: supine and supine with head tilted to one side.

The second potential implication has to do with positional therapy (PT) in patients with positional OSA (POSA). We have recently performed several studies with new forms of positional therapy in patients with POSA.[7,8] A first study was with a buzzing device attached at the neck and later generations had a positional belt around the chest. Some patients with back complaints or similar physical conditions may have a problem with other sleeping positions than supine position. In such POSA patients only rotating the head might be effective PT as well. Research with such forms of PT is ongoing.

This study is not without limitations. First, a larger sample size would have been preferable to increase the reliability of our outcomes. We included both OSA and POSA patients. In future, larger studies will focus on POSA patients only.

In conclusion, in patients with OSA performing DISE with head rotation only, instead of placing the patient in full lateral position, appears to be a valuable, less cumbersome alternative. Second, further research is needed to prove if in positional OSA patients head rotation is as effective as full head and trunk rotation, which can then open new avenues for forms of PT that focus on head rotation only.

Conflict of Interest

None of the authors has any financial support or conflict of interest to disclose.

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Chapter 6

Surgery for Obstructive Sleep Apnea: Sleep Endoscopy Determinants of Outcome

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Abstract

Objectives/Hypothesis: Although drug-induced sleep endoscopy is often employed to determine the site of obstruction in patients with obstructive sleep apnea (OSA) who will undergo upper airway surgery, it remains unknown whether its findings are associated with surgical outcome. This study tested the hypothesis that drug-induced sleep endoscopy variables can predict the outcome of upper airway surgery in OSA patients.

Study Design: Case series retrospective analysis.

Methods: Forty-nine OSA patients (41 male; mean apnea-hypopnea index [AHI] 30.9 6 18.5 events/hour) underwent propofol-induced sleep endoscopy followed by upper airway surgery (palatal surgery, and/or radiofrequency ablation of the tongue base, and/or hyoid suspension) and subsequently a follow-up polysomnography to assess surgical outcome.

Results: Twenty-three patients (47%) were responders, and twenty-nine were nonresponders (53%). Nonresponders had a higher occurrence of complete or partial circumferential collapse at velum and complete antero-posterior collapse at tongue base or epiglottis in comparison with responders. Multivariate logistic regression analysis revealed that among baseline clinical and polysomnographic characteristics (e.g., AHI, body mass index) and sleep endoscopy findings, the presence of complete circumferential collapse at velum, and of complete antero-posterior collapse at tongue base were the only independent predictors of upper airway surgery failure.

Conclusions: Drug-induced sleep endoscopy can be used to predict higher likelihood of response to upper airway surgery in OSA.

Key Words: Obstructive sleep apnea, sleep endoscopy, upper airway surgery.

Level of Evidence: 4

Introduction

Obstructive sleep apnea (OSA) is a prevalent disorder[1] that is associated with excessive daytime sleepiness[2] and with an increased risk for hypertension,[3] cardiovascular[4] and cerebrovascular incidents,[5] and type II diabetes.[6] Continuous positive airway pressure (CPAP) is often employed as the first-line treatment for OSA.[7] However, long-term compliance to CPAP treatment is considered suboptimal,[8] prompting a substantial proportion of patients with OSA to seek alternative treatment, including upper airway surgery.[9]

Yet, the role of such procedures in the management of OSA remains controversial, with inconsistent outcomes found in the surgical literature.[10] Indeed, palatal surgery, the most commonly used surgical procedure for OSA, is associated with contradicting results ranging from a significant reduction to a considerable increase of apnea-hypopnea index (AHI), with nonobese and mild/ moderate OSA patients having the most chances of benefitting.[11,12] Thus, it is not surprising that the recommendations of the American Academy of Sleep Medicine underline the lack of rigorous data evaluating upper airway surgery and emphasize the need to preoperatively determine which populations are most likely to respond to a particular procedure.[10]

Drug-induced sleep endoscopy (DISE) has been used the last two decades to determine the exact site of upper airway collapse in OSA patients.[13] It is intuitively obvious that by directing surgical procedures toward obstruction-specific structures, surgical outcomes will improve.[14] However, data associating DISE results with the outcome of surgical procedures are sparse and inconclusive because they have fail to determine any independent predictive value of DISE features for surgical results.[15–17] A further evaluation of DISE findings in the context of a bigger sample of patients undergoing upper airway surgery for OSA might be an important step in preoperatively distinguishing responders from nonresponders, thus assisting sleep physicians in deciding the optimum treatment option.

Therefore, the aim of this study was to investigate whether DISE findings could eventually predict the outcome of upper airway surgery in OSA patients. Our hypothesis was that the level (velum, oropharynx, tongue base, epiglottis), type (circumferential, anteroposterior, lateral) and severity of collapse (partial, complete) could predict the outcome of upper airway surgery. Along with endoscopic findings,

we also investigated the predictive value of known polysomnographic and clinical variables (e.g., AHI, body mass index [BMI]).

Materials and Methods

Study Subjects

The population retrospectively assessed for this study consisted of OSA patients who underwent propofol-induced sleep endoscopy and upper airway surgery in the Department of Otolaryngology/ Head and Neck Surgery of Saint Lucas Andreas Hospital (Amsterdam, the Netherlands) during 1 year (June 2010–June 2011). Further inclusion criteria were: 1) AHI at baseline polysomnography >10 events/hour, 2) follow-up polysomnography at least 3 months after upper airway surgery, 3) no treatment of OSA with CPAP during the course of the followup, and 4) no upper airway surgery for OSA in the patients' history. Patients with a history of tonsillectomy for an indication other than OSA were included. The protocol was approved by the hospital human ethics committee.

Polysomnography

All patients underwent a full-night diagnostic standard polysomnography before and at least 3 months postoperatively (EMBLA Titanium; Medcare Flaga, Reykjavik, Iceland). To determine the stages of sleep an electroencephalogram (C4-A1, C3-A2, O2-A1, O1-A2), electro-oculogram, and electromyogram of the submentalis muscle were obtained. Arterial blood oxyhemoglobin was recorded with the use of a finger pulse oximeter. Thoracoabdominal excursions were measured qualitatively by respiratory movement sensors placed over the rib cage and abdomen. Snoring was detected with a vibration snore sensor and body posture with a body position sensor. Airflow was monitored using an oral thermistor placed in front of the mouth and a nasal cannula/pressure transducer inserted in the opening of the nostrils. All variables were recorded with a digital acquisition system (Somnologica 3.3; Medcare Flaga). Sleep stage was scored manually in 30-second epochs, and obstructive respiratory events were scored using standard criteria.[18]

DISE

All patients underwent DISE in supine position in the operation theatre. A topical vasoconstrictor/anesthetic combination (oxymetazoline/lidocaine) was applied to both nostrils. Propofol was administered by the anesthetist as the sole agent to achieve a target level of anesthesia of arousal to loud verbal stimulation, as per the

authors' usual protocol.[19] In brief, initial infusion rate of propofol was 50 to 75 lg/kg/min, and the rate was adjusted to meet the target level of anesthesia. When achieved, a flexible endoscope was introduced into the nasal cavity. The nasal passage, nasopharynx, velum, oropharynx, tongue base, epiglottis, and larynx were observed, and the level of obstruction during inspiration was assessed.

VOTE Classification

DISE findings were illustrated using the VOTE classification system, reported previously.[19] Accordingly, three parameters were reported: 1) site of obstruction (velum, oropharynx, tongue base, and/or epiglottis), 2) degree of obstruction (0% to 50% of narrowing corresponds to none/mild obstruction, 50% to 75% of narrowing corresponds to partial obstruction, 75% to 100% of narrowing corresponds to complete obstruction), and 3) configuration of obstruction (anteroposterior, circumferential, or lateral).

Upper Airway Surgery and Success Definition

All patients underwent upper airway surgery for OSA, which included one or a combination of the following procedures: uvulopalatopharyngoplasty, Z-palatopharyngoplasty, radiofrequency ablation of the tongue base, and hyoid suspension.[20] Multilevel surgery was considered the combination of palatal surgery with radiofrequency ablation of the tongue base and hyoid suspension.[20]

Upper airway surgery success was defined as a postoperative AHI of <10 events/hour along with at least 50% decrease from the baseline AHI (responders); treatment failure was defined as a postoperative AHI of >10 events/hour and/or a decrease of AHI from baseline less than 50% (nonresponders).[21] The postoperative difference of AHI was defined as the postoperative AHI minus the baseline AHI.

Statistical Analysis

Quantitative data are reported as mean ± SD. The normality of the data distributions was assessed by the Kolmogorov-Smirnov test. Differences in means of quantitative variables between responders and nonresponders to surgical treatment were assessed by unpaired *t* test, whereas differences in categorical values were assessed by the Yates corrected χ^2 or Fisher exact test when appropriate. Multivariate logistic regression analysis followed to identify the variables that were independently associated with the response to upper airway surgery. The stepwise procedure was used to select the best logistic regression model, and the goodness of fit of this model was assessed using the Hosmer–Lemeshow test. The

independent variables included in the model were those that showed significant difference in the univariate comparison between responders and nonresponders to upper airway surgery; age, gender, BMI, and AHI were also included in the model despite lack of significance because of their potential importance.[11,12] A P value of <.05 was considered to indicate statistical significance.

Results

Among 80 patients who underwent upper airway surgery for sleep-disordered breathing between June 2010 and June 2011, 31 did not meet the inclusion criteria (10 had AHI ≤10 events/hour, six patients had undergone DISE with midazolam as the sedating agent, six patients had undergone previous sleep surgery, seven patients did not have a follow-up polysomnography, and two patients used CPAP during the course of follow-up). Of the 49 patients who met the inclusion criteria and were finally included in the analysis, eight patients underwent palatal surgery, 17 patients underwent palatal surgery with radiofrequency ablation of the tongue base, 21 underwent multilevel surgery, and three patients underwent hyoid suspension with radiofrequency ablation of the tongue base. The type of operation was decided on the basis of the level of obstruction, so that whenever palatal and/or oropharyngeal obstruction were found, palatal surgery was employed (Z-palatopharyngoplasties or uvulopalatopharyngoplasties, if tonsils have been removed or not, respectively), and whenever tongue base and/or epiglottis obstruction were found, radiofrequency ablation of the tongue base and/or hyoid suspension were employed. Patients were stratified in responders (23 patients, 47%) and nonresponders (26 patients, 53%) according to follow- up polysomnography, which took place 4.1 ± 0.7 months after upper airway surgery. The postoperative difference of AHI was 26.0 ± 19.4 events/hour and -1.8 ± 14.8 events/hour in responders and nonresponders, respectively. The baseline clinical and polysomnographic characteristics and the types of surgical procedures performed in these two groups of patients are summarized in Tables 1 and 2, respectively. No difference in any parameter was detected between the two groups.

Table 1: Anthropometric Data and Baseline Clinical and Polysomnographic Variables in Responders and Nonresponders

	Responders (n = 23)	Nonresponders (n = 26)
Age, yr	48.6 ± 10.5	46.0 ± 10.7
Male sex, %	78	88
Body mass index, kg/m^2	28.3 ± 3.4	28.7 ± 3.3
Apnea-hypopnea index, events/hr	31.9 ± 21.1	30.0 ± 16.1
Epworth Sleepiness Scale score	8.5 ± 4.8	7.6 ± 5.8
Neck circumference, cm	41.0 ± 3.4	40.9 ± 3.3
Minimum oxygen desaturation, %	81.3 ± 7.9	82.6 ± 3.9
Friedman soft palate position score	1.85 ± 0.97	1.58 ± 1.00
Tonsils size	1.25 ± 1.02	1.50 ± 0.88
History of tonsillectomy, %	23.2 ± 7.8	16.4 ± 11.2

Continuous data are presented as number or mean 6 SD. There was no statistical difference between the variables of responders and nonresponders.

Table 2: Surgical Procedures Performed in Responders and Nonresponders

Surgical Procedure	Responders (n = 23)	Nonresponders (n = 26)
Palatal surgery, n (%)	22 (95.7)	24 (92.3)
Radiofrequency ablation of the tongue base, n (%)	18 (78.3)	23 (88.5)
Hyoid suspension, n (%)	18 (78.3)	13 (50)

There was no statistical difference between surgical procedures performed in responders and nonresponders.

Table 3: Drug-Induced Sleep Endoscopy Findings in Responders and Nonresponders

		Responders (n = 23)		
		Complete Collapse	Partial Collapse	No/Mild Collapse
Velum	Anteroposterior (%), n (%) Lateral	16 (69.6)	6 (26.1)	0 (0)
	Circumferential, n (%)	1 (4.3)	0 (0)	
Oro-pharynx	Lateral, n (%)	3 (13.0)	3 (13.0)	17 (74.0)
Tongue base	Antero-posterior, n (%)	7 (30.4)	12 (52.2)	4 (17.4)
Epiglottis	Antero-posterior (%), n (%) Lateral	10 (43.4)	6 (26.1)	
	Lateral (%)	0 (0)	1 (4.3)	
		Nonresponders (n = 26)		
		Complete Collapse	Partial Collapse	No/Mild Collapse
Velum	Anteroposterior (%), n (%) Lateral	5 (19.2) p=0.008 *	0 (0) p=0.001 †	1 (3.9)
	Circumferential (%)	11 (42.3) p=0.001 *	9 (34.6) p=0.001 †	
Oro-pharynx	Lateral (%)	6 (23.1)	3 (11.5)	17 (65.4)
Tongue base	Antero-posterior (%)	20 (76.9) p=0.02 *	4 (15.4) p=0.007 †	2 (7.7) ‡
Epiglottis	Antero-posterior (%), n (%) Lateral	17 (65.4) p=0.04 *	1 (3.8) p=0.003 †	7 (26.9)
	Lateral (%)	0 (0)	1 (3.8)	

* P <.05 versus complete collapse of responders
† P <.05 versus partial collapse of responders
‡ P <.05 versus no/mild collapse of responders

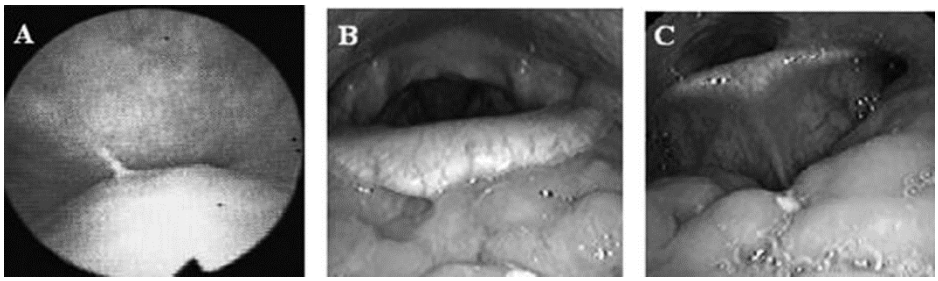

Figure 1: Patterns of collapse on drug-induced sleep endoscopy during inspiration associated with response to upper airway surgery. (A) Complete antero-posterior collapse at velum. (B) Partial antero-posterior collapse at tongue base. (C) Partial antero-posterior collapse at epiglottis.

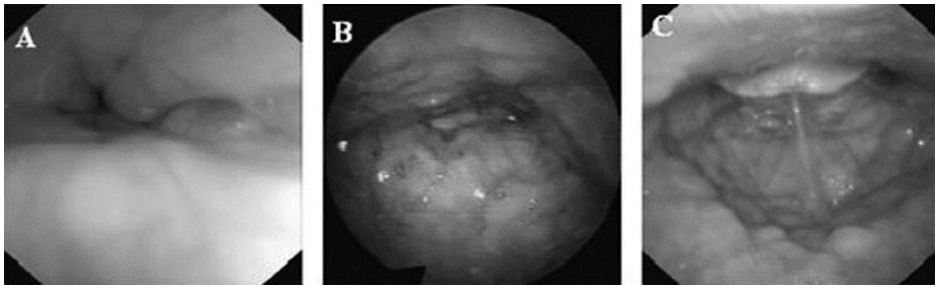

Figure 2: Patterns of collapse on drug-induced sleep endoscopy during inspiration associated with nonresponse to upper airway surgery. (A) Complete circumferential collapse at velum. (B) Complete antero-posterior collapse at tongue base. (C) Complete antero-posterior collapse at epiglottis.

DISE findings of responders and nonresponders are presented in Table 3. As shown, responders had a higher occurrence of complete or partial antero-posterior collapse at velum and of partial antero-posterior collapse at tongue base and epiglottis compared to nonresponders. In contrast, nonresponders had and a higher occurrence of complete or partial circumferential collapse at velum and complete antero-posterior collapse at tongue base or epiglottis in comparison with responders. Patterns of collapse on DISE during inspiration associated with response and nonresponse to upper airway surgery are shown in Figures 1 and 2, respectively.

Multivariate logistic regression analysis was performed to identify the independent predictors of the response to upper airway surgery. The parameters that showed significant difference in the univariate comparison between responders and nonresponders (Table 3) were entered into a forward stepwise model. Additionally, age, gender, BMI, and AHI were included in the model. This analysis revealed that

the independent predictors of failure to upper airway surgery were the presence of complete circumferential collapse at velum (odds ratio [OR], 5.27; 95% confidence interval [CI], 2.20–16.71; P < .001), and of complete antero-posterior collapse at tongue base (OR, 2.44; 95% CI, 1.31–5.87; P = .004). The Hosmer-Lemeshow test indicated that the fit of the model was good (P = .63). Backward procedure gave identical results.

Discussion

The main finding of this study were: 1) responders to upper airway surgery for OSA had a higher occurrence of complete or partial antero-posterior collapse at velum and of partial antero-posterior collapse at tongue base and epiglottis compared to nonresponders; in contrast, nonresponders had and a higher occurrence of complete or partial circumferential collapse at velum and of complete antero-posterior collapse at tongue base or epiglottis in comparison with responders; and 2) among baseline clinical and polysomnographic variables (e.g., AHI, BMI) and DISE findings, only the presence of complete circumferential collapse at velum and of complete antero-posterior collapse at tongue base were independently associated with failure of upper airway surgery in OSA patients.

In OSA patients, especially mild and moderate cases, multiple treatment modalities besides CPAP might be considered. One of them is upper airway surgery, but given its inconsistent effect, it is of paramount importance to establish preoperative criteria, which could potentially distinguish responders from nonresponders.[10] To this end, DISE was initially employed to determine the site of obstruction and accordingly the corresponding surgical procedure.[13] However, data associating DISE results with the outcome of surgical procedures are sparse and inconclusive.[15–17] Two studies[15,16] that included only patients undergoing uvulopalatopharyngoplasties, and very recently Soares et al.,[17] have all failed to determine any independent predictive value of DISE features for surgical results. In particular, the latter authors[17] (their work was published while the current manuscript was in the process of being written) compared a group of 15 nonresponders with a group of 19 responders to upper airway surgery, and found that lateral oropharyngeal wall and supraglottic airway collapse was more prevalent in nonresponders.[17] The data of the current study make the findings of previous trials more conclusive in the same direction by providing evidence that

propofolinduced sleep endoscopy variables can predict the outcome of upper airway surgery, corroborating in that way the importance of using DISE in clinical practice.

The presence of circumferential collapse at velum was found to predict the occurrence of failure to upper airway surgery. This result is consonant with previous reports, which documented that concentric velar collapse is associated with an increased BMI[15] and that increased BMI, in turn, is associated with surgical failure.[22] Accordingly, Iwanaga et al.[15] found a lower improvement rate for patients with circumferential velar collapse (53.3%) in comparison with patients with other types of obstruction (76.2%). It is reasonable, then, to make the assumption that current palatal surgery might be ineffective in resolving a circumferential type of collapse.

Additionally, complete tongue base collapse proved to be a significant determinant of failure of upper airway surgery. This finding is consistent with previous studies, which report a positive association between the degree of tongue base collapsibility and OSA severity,[23] and in conjunction with that, a positive association between OSA severity and surgical failure.[12,24] Thus, it appears that surgical procedures addressing tongue base obstruction such as radiofrequency ablation (thermal damage to the tongue base creating lesions that diminish the bulk and flaccidity of the tongue base through fibrosis) and hyoid suspension (improvement of the retroglossal space by placing traction on the hyoid directly and advancing hyoid complex) have limited efficacy.[9,20] Interestingly, Kezirian[25] performed DISE in nonresponders to these procedures and found a high occurrence of residual tongue base collapse. In consequence, it is plausible to suggest that tongue base collapse, especially in higher degrees, might be refractory to treat with the procedures currently applied, and novel treatment modalities such as hypoglossal nerve stimulation are herein greatly anticipated.[26]

Some possible weaknesses of the current study must be acknowledged and deserve consideration. As with any retrospective analysis, a limitation of our study was the inability to control the data.[27] Furthermore, the patients undergoing upper airway surgery for OSA in our institution in most cases have BMI <32 kg/m2 and AHI <40 events/hour.[11,12] Consequently, our results cannot be safely extrapolated in the general population of OSA patients. Last, the precise relationship between natural and propofol-induced sleep remains elusive.[28] It would be ideal if sleep endoscopy could be performed under natural sleep, but this challenging procedure is seldom applied.[29] However, Rabelo et al.[30] have recently reported that although propofol

reduced rapid eye movement sleep, it did not influence the respiratory pattern or significantly influence the occurrence of obstructive events.

Conclusion

This study highlights the significance of DISE by providing evidence that the presence of circumferential collapse at velum and of complete collapse at tongue base are independently associated with failure of upper airway surgery in OSA patients. Further larger-scale studies are needed to confirm prospectively the performance of the aforementioned variables in predicting surgical outcome.

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Chapter 7

Effect of Upper-Airway Stimulation for Obstructive Sleep Apnea on Airway Dimensions

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Abstract

Upper-airway stimulation (UAS) using a unilateral implantable neurostimulator for the hypoglossal nerve is an effective therapy for obstructive sleep apnea patients with continuous positive airway pressure intolerance. This study evaluated stimulation effects on retropalatal and retrolingual dimensions during drug-induced sedation compared with wakefulness to assess mechanistic relationships in response to UAS.

Patients with an implanted stimulator underwent nasal video endoscopy while awake and/or during drug-induced sedation in the supine position. The cross-sectional area, anterior–posterior and lateral dimensions of the retropalatal and retrolingual regions were measured during baseline and stimulation.

15 patients underwent endoscopy while awake and 12 underwent drug-induced sedation endoscopy. Increased levels of stimulation were associated with increased area of both the retropalatal and retrolingual regions. During wakefulness, a therapeutic level of stimulation increased the retropalatal area by 56.4% (p=0.002) and retrolingual area by 184.1% (p=0.006). During stimulation, the retropalatal area enlarged in the anterior–posterior dimension while retrolingual area enlarged in both anterior–posterior and lateral dimensions. During drug-induced sedation endoscopy, the same stimulation increased the retropalatal area by 180.0% (p=0.002) and retrolingual area by 130.1% (p=0.008). Therapy responders had larger retropalatal enlargement with stimulation than nonresponders.

UAS increases both the retropalatal and retrolingual areas. This multilevel enlargement may explain reductions of the apnea–hypopnea index in selected patients receiving this therapy.

Introduction

Obstructive sleep apnea (OSA) is caused by repetitive episodes of complete or partial obstructions of the upper airway during sleep.[1] These repetitive periods of upper airway collapse produce nocturnal hypoxaemia and sleep fragmentation, contributing to a number of OSA-related comorbidities.[1] Continuous positive airway pressure (CPAP) is the first-line treatment for OSA. Despite its efficacy, treatment effectiveness is limited by patient nonadherence, to the point where many with moderate-to-severe disease remain untreated.[2] A number of non-CPAP therapies for moderate-to-severe OSA, such as oral appliance therapy or upper-airway surgery, can be considered as alternatives, but also have their challenges.[3-5]

Therapeutic applications using neuromuscular electrical stimulation of the hypoglossal nerve and genioglossus muscle have been designed and evaluated as a potential alternative to positive airway pressure therapy and upper-airway surgical procedures.[6-13] The therapy consists of an implanted, programmable neurostimulation system, with a stimulation electrode around the protrusor branches of the right hypoglossal nerve and a respiration sensor placed in the right intercostal space to detect respiration.[10,14,15] More specifically, upper-airway stimulation (UAS) therapy through unilateral stimulation of the hypoglossal nerve timed with ventilation using an implantable neurostimulator is an effective treatment for selected patients with moderate-to-severe OSA who have failed or are intolerant to CPAP.[15]

The mechanism by which UAS prevents collapse deserves further investigation. UAS might be suspected to be of use in patients only with retrolingual collapse; however, empirically, it appears that stimulation may alleviate apneas that also have a component of retropalatal collapse.[16,17] While the effect of UAS on retrolingual area can be directly attributed to tongue-base advancement through activation of the genioglossus muscle, the effect of stimulation on retropalatal area is less intuitive. During acute hypoglossal nerve stimulation, other groups have demonstrated increased retrolingual and retropalatal lucency in sagittal neck fluoroscopic images during periods of acute stimulation during surgery, indicating an increase of airway size in the anterior–posterior dimension[16]; however, this two-dimensional approach using a single stimulation setting may not fully capture quantitative and dynamic upper-airway dimensions. Observations during graded stimulation would better describe the action and help develop an understanding of UAS effects.

We used awake nasopharyngoscopic evaluation[18] and drug-induced sedation endoscopy (DISE). The latter technique is a widely used method to determine the degree, configuration and site of upper-airway obstruction when selecting patients for non-CPAP treatments for OSA.[19] DISE offers a method to visually quantify upper-airway changes during sedation, which has been shown to simulate upper-airway collapse during sleep.[20,21] Such a controlled setting permits evaluation of differing stimulation levels.

In this study, we measured the effects of graded stimulation on multilevel airway dimensions during wakefulness and DISE in OSA patients with chronically implanted UAS systems. The hypotheses were that stimulation would simultaneously enlarge retropalatal and retrolingual airway dimensions compared with no stimulation, and that increasing stimulation amplitude would produce larger upper-airway dimensions compared with periods of no stimulation.

Methods

Patient Selection

A subset of patients was enrolled from three European centres participating in a multicentre, prospective trial for the safety and efficacy of an implantable UAS system (Inspire Medical Systems, Minneapolis, MN, USA) for the treatment of moderate-to-severe OSA in patients intolerant to CPAP.[15] Per protocol, all patients underwent DISE screening prior to implant, and patients with retropalatal complete concentric collapse were excluded from implantation. Other pre-surgical selection criteria have been described separately.[15] All patients had provided written informed consent for the study, and the protocol was approved by the local medical ethics committees.

2 and 6 months after implantation, patients had overnight titration polysomnography (PSG) to identify the therapeutic stimulation amplitude needed to abolish respiratory events during sleep, and 12 months after implant, a PSG was performed at the identified therapeutic amplitude. At least 2 months after implantation, patients from three European centres in this study were invited to participate in an awake endoscopy and/or DISE.

Awake Endoscopy

Awake nasal endoscopy was performed with the patient in the supine position, during nasal breathing. The endoscope was inserted through the nasal cavity until the retropalatal region was visualised. Stimulation was applied at four increasing amplitudes, representing first sensation, bulk tongue movement, therapeutic level determined from a titration sleep study and sub-discomfort, while ensuring the endoscope position remained unchanged during periods with and without stimulation. This same technique was performed after distal positioning to observe the retrolingual level.

Drug-Induced Sedation Endoscopy

After awake endoscopy, with the patient still in the supine position, propofol and/or midazolam were administered as sedatives.[19] DISE was performed in the same manner as the pre-implant screening, following the study's DISE protocol. The targeted sedation depth was a loss of response to verbal stimulation and the presence of snoring and/or obstructed airway events.[19] When the sedation target was achieved, the endoscope was inserted distally to visualise the nasopharyngeal, retropalatal, oropharyngeal, retrolingual and retroepiglottic regions, and assess the baseline direction and degree of upper-airway collapse over several respiratory cycles during inspiration using a standardised protocol.[15] Stimulation was applied at the same amplitudes during DISE as during wakefulness, and endoscopic images of the retropalatal and retrolingual regions were captured in the same manner.

Image Analysis

Images were captured prior to stimulation and during stimulation in both the retropalatal and retrolingual region. Images where the retropalatal or retrolingual region could not be visualised due to saliva, air bubbles, lens fogging or other visual artefacts were excluded from the analysis. Images of the retropalatal and retrolingual regions from the periods just prior to and during UAS were digitally measured by a single observer (F. Safiruddin) using ImageJ (US National Institutes of Health, Bethesda, MD, USA).

Quantitative measurement of upper-airway dimensions was performed similarly to the method as described by BOREK et al.[20] During baseline and stimulation, the anterior–posterior and lateral dimensions of the airway were measured at the centre of the airway lumen. Cross-sectional area and dimensions were calculated as a percentage of the total scope image to normalise for the varying digital image resolution of endoscopy machines among investigational centres.

Comparison of Upper-Airway Area with the 12-Month Apnea–Hypopnea Index Response Criterion

Analysis of the endoscopic images was combined with the apnea–hypopnea index (AHI) from the 12-month visit to understand the association between changes in upper-airway area during stimulation and the change in AHI between responders and nonresponders. Therapy response was prospectively defined as a 50% reduction of the AHI from baseline to <20 events·h^{-1}.[22,23]

Statistical Analysis

Descriptive statistics were calculated for demographic variables and upper-airway area measurements. Wilcoxon signed rank tests were used to compare measurements between periods before and during stimulation, and the Mann–Whitney–Wilcoxon two-sample test was used for comparisons between responders and nonresponders. A p-value <0.05 was considered statistically significant.

Results

Patient Demographics

15 patients underwent awake nasal endoscopy; 12 patients underwent DISE. One patient was excluded from awake endoscopy due to gag reflex caused by the endoscope, thus leaving 11 patients with both measurements. Demographic and baseline information are presented in table 1.

Table 1: Description of the cohort undergoing endoscopic evaluation. Data are presented as n or mean ± SD, unless otherwise stated.

	Awake endoscopy	Drug-induced sedation endoscopy
Subjects	15	12
Age years	50.4 ± 10.2	51.2 ± 9.0
Males %	100	100
Body mass index kg·m^{-2}	27.9 ± 1.9	28.2 ± 1.5
Baseline apnoea–hypopnoea index events·h^{-1}	29.3 ± 7.5	28.8 ± 7.8
Responders/nonresponders at 12 months	8/7	6/6

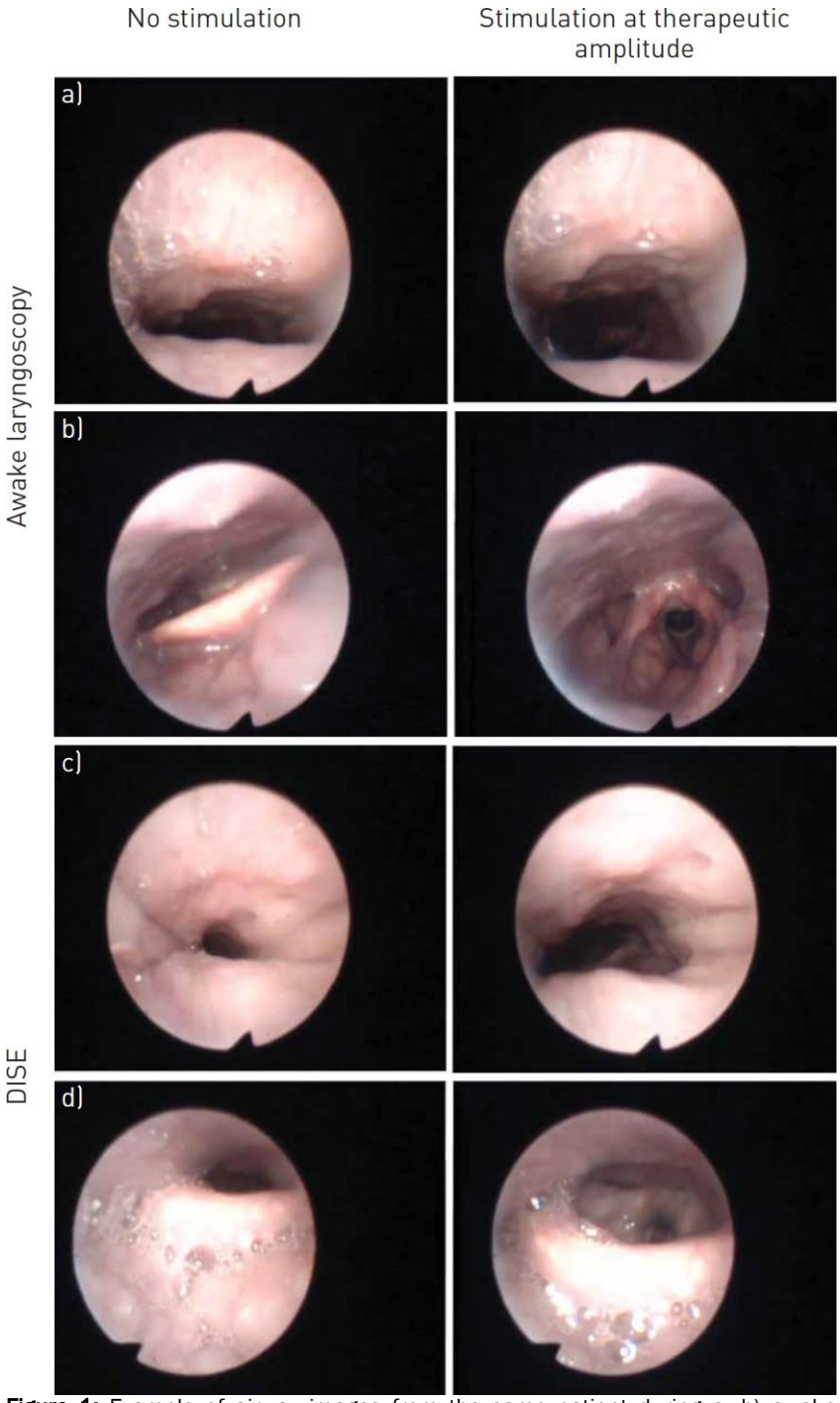

Figure 1: Example of airway images from the same patient during a, b) awake endoscopy and c, d) drug-induced sedation endoscopy (DISE). a, c) At the top of the images is the posterior pharyngeal wall and at the bottom is the soft palate. b, d) At the top of the images is the posterior wall and at the bottom is the tongue base.

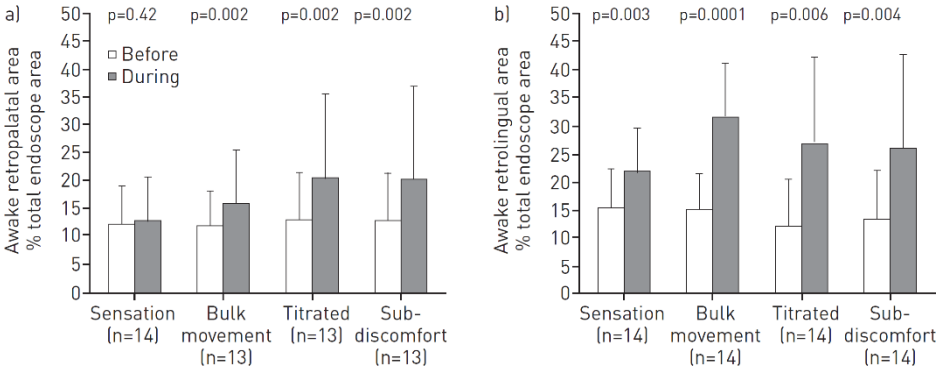

Figure 2: a) Retropalatal and b) retrolingual area before and during stimulation at the four functional stimulation amplitudes while awake. Bars represent the mean and whiskers the standard deviation.

Awake Airway Dimensions During Stimulation

Both retropalatal and retrolingual regions were open without stimulation, when patients were breathing normally through the nose. With stimulation, mild tongue protrusion was visible. From an endoscopic view of the upper airway, there was an immediate increase in retropalatal and retrolingual area. Airway area returned to baseline after stimulation and the tongue returned to its resting position (fig. 1). Increasing stimulation amplitudes were associated with progressively larger area (fig. 2).

During awake stimulation at the therapeutic amplitude, retropalatal area increased by 56.4% and retrolingual area increased by 184.1%, as compared with the area without stimulation (p=0.002 and p=0.006, respectively). The retrolingual area appeared the most sensitive to stimulation, as the lowest stimulation amplitude (sensation) was sufficient to increase retrolingual area compared with no stimulation ($p<0.005$) but a higher stimulation amplitude (bulk movement) was required to significantly increase retropalatal area versus no stimulation (p=0.002).

In regard to shape, stimulation increased the retropalatal anterior–posterior dimension from baseline without changes in the laterolateral dimension, while stimulation increased retrolingual in both anterior– posterior and laterolateral dimensions as compared to baseline (table 2).

Table 2: Effect of stimulation on retropalatal and retrolingual area, and dimensions during awake endoscopy and drug-induced sedation endoscopy, reported as a percentage of the endoscope image size. Data are presented as mean ± SD, unless otherwise stated. AP: anterior–posterior; LL: laterolateral.

Dimension	Awake endoscopy		
	No stimulation	Therapeutic stimulation	p-value
Retropalatal			
AP	15 ± 7	26 ± 14	0.0002
LL	64 ± 19	65 ± 20	0.4143
Retrolingual			
AP	24 ± 7	45 ± 20	0.0004
LL	54 ± 16	60 ± 15	0.0245
	Drug-induced sedation endoscopy		
	No stimulation	Therapeutic stimulation	p-value
Retropalatal			
AP	6 ± 4	16 ± 9	0.0078
LL	49 ± 22	56 ± 19	0.3223
Retrolingual			
AP	26 ± 13	42 ± 18	0.0039
LL	44 ± 19	63 ± 23	0.06

Sedated Airway Dimensions During Stimulation

Sedation decreased cross-sectional area at both the retropalatal and retrolingual levels, compared with awake endoscopy. At baseline without stimulation, the majority of patients had retropalatal and retrolingual airway collapse (n=9), while three patients had only retrolingual collapse. Anterior–posterior collapse was the most common collapse direction in the retropalatal region. At the retropalatal level, four patients had complete anterior–posterior collapse, three patients had partial anterior–posterior collapse and five patients had no palatal collapse. At the retrolingual level, nine patients had complete anterior– posterior collapse, two patients had partial anterior–posterior collapse and one patient had complete concentric collapse.

Similar to awake endoscopy, stimulation at the bulk-movement amplitude and higher amplitudes led to significantly increased retropalatal and retrolingual area compared with no stimulation (fig. 3). During stimulation at the therapeutic amplitude, retropalatal area increased by 180.0% (p=0.002) and retrolingual area increased by 130.1% (p=0.008). There was a progressive increase in retropalatal and retrolingual area with higher stimulation levels compared with no stimulation, although increases in retrolingual area appeared to plateau beyond the bulk movement threshold (fig. 4).

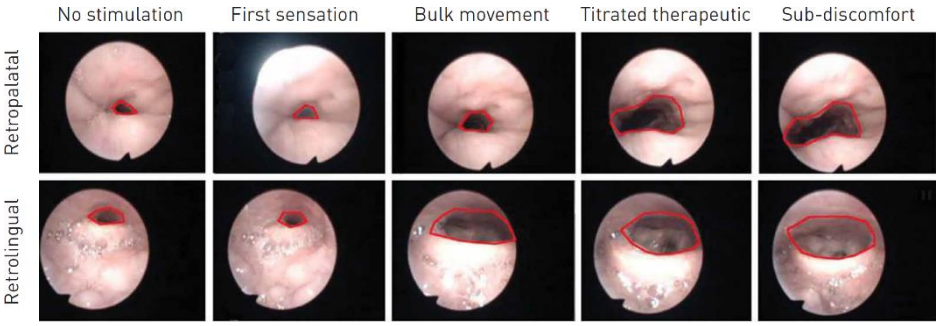

Figure 3: Increases in retropalatal and retrolingual area comparing no stimulation with progressively higher levels of stimulation during drug-induced sedation endoscopy. The outline indicates the measured retropalatal and retrolingual area; this area was recorded as a percentage of the total endoscope image area. Retropalatal images (top) are orientated with the posterior pharyngeal wall at the top of the image and the soft palate/uvula at the bottom of the image. Retrolingual images (bottom) are similarly orientated, with the posterior tongue base and epiglottis at the bottom of the image.

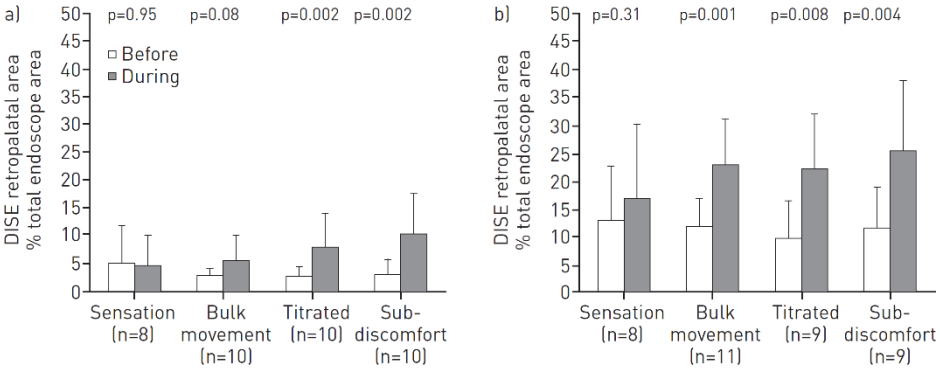

Figure 4: a) Retropalatal and b) retrolingual airway area before and during stimulation, while undergoing drug-induced sedation endoscopy (DISE). Bars represent the mean and whiskers the standard deviation.

The increase in airway area with stimulation at the therapeutic amplitude during DISE was due to statistically significant anterior–posterior enlargement at the retropalatal region without any change in laterolateral length. There was anterior–posterior and laterolateral enlargement at the retrolingual region, although the change in laterolateral dimension was slightly short of meeting statistical significance (table 2).

Comparing Relative Changes in Upper-Airway Area between Awake Endoscopy and DISE

The percentage change in area between periods without and with stimulation was used to compare the effect of stimulation amplitudes on open-airway area between awake endoscopy and DISE. The percentage change was measured instead of an absolute difference to control for any variation in endoscope positional depth between awake endoscopy and DISE.

Stimulation during awake endoscopy had a similar percentage increase in retrolingual and retropalatal area. During DISE, however, stimulation had a larger percentage increase in retropalatal than retrolingual area. This was due to the greater baseline collapse in retropalatal area during DISE when compared with the retrolingual level. Proportionately, changes in retropalatal area were nearly three times more expansive to stimulation during DISE than awake, whereas the retrolingual region was 1.3 times more expansive to stimulation during DISE than awake endoscopy (fig. 5).

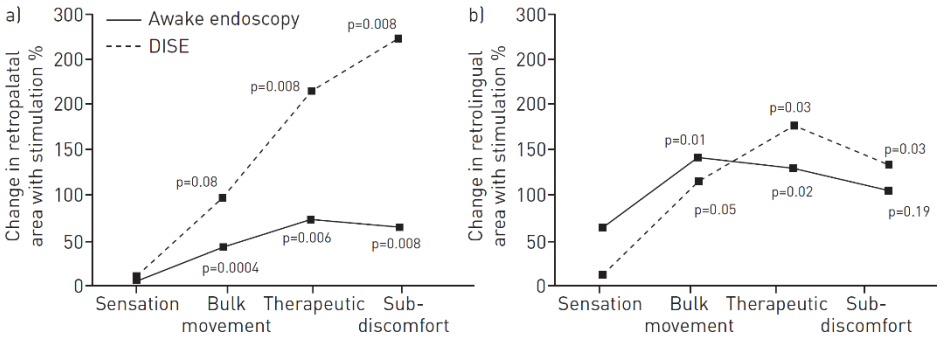

Figure 5: Comparing the effect of stimulation on a) retropalatal and b) retrolingual airway area between awake endoscopy and drug-induced sedation endoscopy (DISE). p-values are for comparisons with the area at the sensation amplitude.

Comparison of Stimulation Effects on Airway Area in Responders and Nonresponders

Stimulation reduced the AHI in responders from 29±3 events·h^{-1} at baseline to 8±3 events·h^{-1} at 12 months (p=0.02), while nonresponders had no change in AHI (31±10 events·h^{-1} to 43±23 events·h^{-1}, p = 0.30). Using the awake endoscopy data, both responders and nonresponders had a statistically significant increase in retrolingual area during stimulation at the therapeutic amplitude, compared with no stimulation. However, responders had a statistically significant increase in retropalatal area during stimulation, while in contrast, nonresponders had a smaller increase in retropalatal area during stimulation, which was not statistically significant. There was no difference in the degree of retrolingual area change during stimulation between responders and nonresponders (p=0.71); however, responders had a greater degree of retropalatal enlargement during stimulation than nonresponders (p=0.047) (table 3).

Table 3: Comparing the effect of stimulation on retropalatal and retrolingual area in responders and nonresponders, reported as a percentage of the endoscope image size. Data are presented as mean ± SD, unless otherwise stated.

	Subjects n	Retropalatal area		
		No stimulation	Therapeutic stimulation	p-value
Responders	7	11 ± 10	22 ± 21	0.031
Nonresponders	7	15 ± 6	19 ± 10	0.109
		Retrolingual area		
		No stimulation	Therapeutic stimulation	p-value
Responders	7	10 ± 5	26 ± 20	0.016
Nonresponders	7	14 ± 6	28 ± 14	0.047

Discussion

The key findings in this study confirm the hypotheses that unilateral stimulation of the hypoglossal nerve using an implantable UAS system, timed with ventilation, increases airway area at multiple levels and that the degree of upper-airway opening corresponds to higher amplitudes of stimulation. These findings of multilevel

opening at the different collapsible levels of the upper airway with stimulation probably explain the effectiveness of UAS therapy in reducing AHI severity in a recent multicentre, prospective trial evaluating this UAS therapy, as well as explain the return to baseline AHI in patients who were randomised to therapy withdrawal.[15]

The findings of improvement in upper-airway cross-sectional area at the retropalatal level during unilateral hypoglossal nerve stimulation are in line with the results from groups visualising retropalatal area during direct genioglossus muscle stimulation under anaesthesia[6,8], as well as others visualising palatal anterior displacement and thinning from fluoroscopic images during intraoperative testing of an implantable hypoglossal neurostimulator.[16] The present study found this result in patients undergoing a therapeutic clinical trial.

The effect of stimulation on anterior–posterior and lateral dimensions of the airway is relevant, particularly regarding the role of airway shape for OSA therapies. In general, a retropalatal shape change from circular to elliptical, specifically a lateral elliptical shape, is believed to be a therapy mechanism of CPAP[24] and oral appliances.[18] In this study, the dominant effect of stimulation was the enlargement of the retropalatal and retrolingual airway in the anterior–posterior dimension, which may be due to patient selection, the therapy mechanism, or both. First, patients were pre-selected with retropalatal anterior–posterior collapse, and patients with retropalatal concentric collapse were excluded because of data indicating they would benefit less from the therapy.[17] The stimulation lead was placed to recruit the genioglossus muscle, resulting in an anterior–posterior enlargement of at least the retro-lingual airway area during stimulation. Activation of the genioglossus may address a particular phenotype of OSA with blunted genioglossus activity.[25] In addition to the increased anterior–posterior dimension, there was also an additive retrolingual lateral effect, albeit a smaller one. The finding of an increased anterior– posterior retropalatal dimension, and an increased anterior–posterior and lateral retrolingual dimension from stimulation may suggest an additive therapy mechanism that differs from that of oral appliances, which were associated with increases in lateral retropalatal dimension and anterior–posterior retrolingual dimension.[18]

Resolving multilevel collapse occurring at the palate and tongue base is probably crucial in order to achieve treatment success. While a majority of patients with an established diagnosis of moderate-to-severe OSA have multilevel collapse, as also seen in this cohort, the soft palate is the most collapsible region of the upper

airway.[26] In this study, the palate demonstrated the largest improvement in terms of increase in cross-sectional area at that specific upper-airway level during stimulation, in part due to reduced baseline area before stimulation during DISE. When comparing responders with nonresponders, the degree of retropalatal enlargement in response to stimulation was statistically significant only in the responders.

The mechanisms by which hypoglossal stimulation increases retropalatal area deserve consideration. Retrolingual opening is expected from stimulation of the genioglossus, but the that of the retropalatal region is not. One concept is that the retropalatal effect seen during stimulation is due to a mechanical linkage between the soft palate and the tongue base.[27,28] Anatomically, the soft palate is linked to the tongue base through the anterior palatal pillar. The anterior pillar also contains the palatoglossus muscle, which courses through the soft palate and the uvula, and inserts into the sides of the tongue.[29] This structure can have a passive and active effect of pulling the soft palate inferiorly and anteriorly. The palatoglossus muscle exhibits phasic respiratory electromyographic activity and has a reflex activation to negative pressure in OSA patients[29], which suggests it could play a role in restoring airway patency. When stimulation moves the tongue base forward, it might result in palatal advancement through anterior displacement of the anterior palatal pillar and the palatoglossus muscle, moving the soft palate anteriorly, and causing an increase in the retropalatal cross-sectional area and dimensions.

A passive effect of tongue-base manipulation causing retropalatal opening can be inferred from other studies. In an animal model, forward motion of the hyoid apparatus caused nasopharynx opening.[28] Furthermore, mandibular advancement devices, which also have the effect of moving the tongue base due to its attachment to the mandible, have demonstrated an increase in retropalatal area to varying degrees.[30,31] Furthermore, computed tomographic imaging of the airway while wearing a mandibular device demonstrated increases in retropalatal and retrolingual airway area.[32]

Variation in the retropalatal area response to stimulation among patients was observed. Responders and nonresponders had similar degrees of retrolingual opening to stimulation; however, responders had a greater increase in retropalatal area. One potential explanation for these differences is that the linkages between retropalatal and retrolingual regions may vary among individuals. This

interconnection between hypoglossal activation and upper-airway structural movement deserves further investigation.

This study is consistent with previous work that increasing stimulation amplitudes increases airflow, until reaching a plateau at higher amplitudes.[13] The previously reported plateau effect in flow is probably explained by the plateau of airway size at the retrolingual area, as seen in this study. There may be two reasons for this ceiling effect. First, the passive distension of the pharynx is limited by surrounding tissue boundaries such as the hard palate or the spine. Second, if all fibres of the genioglossus muscle are activated, there is a diminishing effect of higher amplitudes, as further increase in stimulation is less likely to further stabilise the upper airway. The relationship of amplitude with increases of airway area and airflow is relevant to the clinical management of OSA patients with UAS. It suggests that the stimulation amplitude can be titrated to a level sufficient to abolish OSA events, similar to CPAP, yet below a level that would arouse the patient from sleep. In our study, a significant increase in airway area was obtained at stimulation amplitudes less than the amplitude that would be uncomfortable while awake. Thus, UAS can be effectively titrated during natural sleep in the clinical setting without arousing the patient.

Limitations

The patients in this analysis were a subset of the patients reported in a separate investigation evaluating the efficacy of stimulation on the AHI on a larger cohort. It should be noted that the baseline age, body mass index and AHI of the patients in this subanalysis were similar to the entire cohort in the larger trial.[15] Nevertheless, as this investigation was a subgroup analysis of patients in a larger clinical trial, the conclusions of this paper may not be generalisable to the larger cohort. Furthermore, the comparison of airway responses to stimulation between responders and nonresponders was possible by combining the endoscopic results of this investigation, which preceded the polysomnographic data from the 12-month post-implant visit. Our findings regarding the upper-airway responses to stimulation in responders and nonresponders are preliminary and in a limited number; however, this suggests the differential response to stimulation at the retropalatal airway deserve further investigation.

Due to protocol design, patients were pre-selected for implantation to be without retropalatal complete concentric collapse, and had various degrees of retropalatal anterior–posterior collapse.[15] Thus, our findings are limited to this study population.

We made the decision to use stimulation amplitude according to functional action rather than fixed numeric amplitudes. Due to individual differences in electrical conductance, nerve–electrode impedances and individualised stimulation parameters among patients, we chose to compare functional stimulation amplitudes instead of absolute stimulation amplitudes. Furthermore, the individual stimulation amplitudes at sensation threshold, bulk tongue movement, therapeutic amplitude for sleep and sub-discomfort level describe comparable functional responses to stimulation across subjects. Therefore, we believe the choice of amplitude setting in this manner is reasonable.

Regarding the reliability of DISE compared to natural sleep, a study of respiratory events in non-OSA controls and OSA patients undergoing PSG during propofol sedation and diurnal sleep did not find significant differences in apnea severity[33]; thus, to some extent, DISE may be an approximation of upper-airway function with sedation. Variability during DISE assessment may occur due to differences in sedation depth during the procedure or between patients, which may influence collapsibility. In our study, the DISE procedure was set by protocol, with a sedation depth target of loss of verbal response to stimuli, and the presence of snoring and/or sleep apnea events.[19] While our approach was based on visual symptoms of airway obstruction, quantitative methods for measuring DISE sedation depth via electroencephalography have also been suggested.[34] Other DISE limitations include a time-dependent effect of sedation on upper-airway collapse and/or shape, after the initiation of a stable moderate sedation plane. Confounding by subtle changes in sedation state could be avoided in the future by applying the stimulation amplitudes in random order.

The use of nasopharyngoscopic endoscopy is dependent on image quality and visibility of the upper-airway structures. The multicentre nature of this study led to use of different endoscopy systems with different imaging resolutions, making it difficult to compare images among centres directly. Furthermore, the exact position of the endoscope camera tip in the airway was not standardised between awake endoscopy and DISE, making it difficult to compare images among patients, and between awake and sedation endoscopy in the same patient. To address this issue, we normalised our measurements to the total endoscope image, which was unchanged between periods with and without stimulation. Future studies would use an endoscope with calibrated distance markers to determine precise scope depth.[20] Another limitation is the lack of information on airway stiffness during stimulation, as changes in airway stiffness, particularly along the longitudinal dimension of the

airway, may not be visible when measuring changes in area or dimensions during DISE or awake laryngoscopy. Concerning DISE, the impact of interand intra-observer variations has been evaluated in different studies that indicate that variability is moderate to substantial.[21,35]

Conclusion

UAS of the hypoglossal nerve increases retropalatal and retrolingual area, primarily in the anteroposterior direction. The mechanism of retropalatal opening with stimulation is reasoned to be due to a linkage to the tongue-base effects, while retrolingual opening happens due to unilateral hypoglossal stimulation. The reductions of AHI in patients with UAS are probably due to a multilevel effect on upper-airway opening during hypoglossal nerve stimulation timed with ventilation.

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Chapter 8

Summary, Discussion and Future Perspectives

Summary, Discussion and Future Perspectives

CPAP is the current therapy of choice in patients with moderate to severe OSAS. CPAP is regarded as being non-invasive and if used correctly CPAP can significantly improve quality of life and decrease cardiovascular morbidity and mortality.[1–3] However, the device is cumbersome and compliance rates are only moderately satisfactory.[4,5] Patients who cannot tolerate CPAP for a variety of reasons still suffer from a serious condition and are in need of a non-CPAP treatment. Currently, many exciting new developments are taking place in both the diagnosis as well as the treatment of OSAS. For diagnosis, the role of drug induced sedated endoscopy (DISE) is gaining momentum; and alternatives to CPAP treatment such as surgery, positional therapy, oral device therapy, and combined "multimodality treatment" are becoming increasingly popular. This thesis focusses on various aspects of alternative treatments for OSAS, in part based on findings with DISE. New developments such as DISE, positional therapy and upper airway stimulation are brought together. Gradually, treatment of OSAS is drifting way from one size fits all CPAP therapy, to an individually tailored treatment or "treatment diversification".

One reason for CPAP non acceptance or refusal is nasal congestion. Nasal congestion, rhinorrhea, and sneezing are among the most frequent side effects of nasal CPAP therapy for OSAS directly affecting patient adherence to treatment.[6] Therefore, interventions to improve these side effects could potentially lead to improved compliance and furthermore to a better quality of life. Heated humidification and topical nasal steroid sprays are frequently prescribed to treat nasal complaints. Surgery for reduction of the nasal turbinates is also an option. In general, most surgeries for the inferior turbinates are performed under general anesthesia and usually nasal packs are indicated for several days.[7] The combination of general anesthesia and nasal packs is one that preferably is avoided in OSAS patients. A minimally invasive, outclinic procedure, in which no packs are necessary, with long term beneficial effects, would be more favorable. In **Chapter 2** of this thesis, radiofrequency-induced thermotherapy (RFITT) performed under local anesthesia is shown to be a valuable, minimally invasive, patient-friendly and well-tolerated treatment in patients with impaired nasal passage due to inferior turbinate hypertrophy. The results presented in Chapter 2 are reporting on patients that received the treatment and their self-reported long-term effects of the treatment. Patients' experience of RFITT were assessed using a questionnaire. The results indicate that was a significant reduction in use of nasal spray and the majority of patients reported long-term positive effects of RFITT during the daytime.[8]

Another alternative non-invasive treatment is Positional Therapy. Due to innovative new devices, positional therapy has gained more popularity in the last few years. In one study, positional therapy has been shown to be equivalent to CPAP at normalizing the AHI in patients with positional OSA (POSA), with similar effects on sleep quality and nocturnal oxygenation and, as a results, to be as effective as CPAP in mild to moderate patients with POSA.[9] Recent studies have shown that long-term effectiveness and compliance of positional therapy with the sleep position trainer (SPT) are promising. The study also showed that the compliance and regular use rate were relatively good.[10] Due to these positive results, this therapy has gained momentum and the number of patients using positional therapy has increased. In case positional therapy is consider as (part of) treatment of OSA, it makes more sense to perform DISE, which is predominantly performed in supine position in other sleeping positions as well. A literature review on DISE has been outlined in **Chapter 3**. In **Chapter 4**, we examined the influence of different head positions during DISE in patients with OSA and POSA. Using a consecutive prospective study, the results showed that there was no difference in upper airway collapse between right and left rotation of the head. The findings of head rotation were significantly different in comparison with the supine position and head rotation improves upper airway collapse during DISE in supine position.[11] This improvement of upper airway patency is more predominant in POSA patients. The idea that head rotation would be sufficient versus lateral body position was further explored in **Chapter 5**. The outcomes of DISE performed in supine position with head rotated were compared with the outcomes of DISE performed with head and trunk in lateral position. The results showed that rotation of the head in supine position, and lateral head and trunk position present similar sites, severity and patterns of upper airway collapse, with the exception of collapse at the level of the velum. Here the severity of A-P collapse is less severe during head rotation than in lateral head and trunk position.[12]

The outcome of these studies has important consequences on how to perform DISE. As a rule, DISE is performed in supine position. The traditional assumptions were that in this position the obstruction is often worse, making it the best position for assessment. DISE is performed and on indication repeated with a maneuver that brings the mandible forward, because such maneuvers are to a certain extend a predictor for the effect of an oral device. So DISE is usually performed twice: first spontaneous and then repeated with a maneuver such as the “chin lift”, “jaw trust”, mouth closure or simulation bite.[13] In case positional therapy is considered as part of treatment one would have to add DISE in left, and right lateral position and with

the head turned to left and right; five positions in which the passive maneuvers should also be performed. The results presented in this thesis open up possibilities for a more focused way to perform DISE, only one lateral position is sufficient and turning of the head only is almost equal to turning the body from the supine to the lateral position.

Further innovative options in positional sleep apnea treatment can be researched in the future as well. For example, an alternative option would be to place the device on the patient's head as opposed to the back. During sleep the device would have to vibrate subtlety in order for the patient to turn his or her head thereby re-opening the airway. The study also showed that the airway opening is comparable whether the head is turned left or to the right making it less complex. Once the head is turned the device would switch off. The best way to demonstrate if this effect would decrease AHI during sleep would be to place position sensors on the patient's head during PSG. Van Kesteren at al.[14] have performed such a study where patients underwent overnight polysomnography with 2 position sensors: one on the trunk, and one in the mid-forehead. Of the 300 subjects, 241 were diagnosed with OSA, based on an AHI > 5 per hour sleep. Of these patients, 199 could be analyzed for position-dependent OSA based on head and trunk position sensors (AHI in supine position twice as high as AHI in non-supine positions[15]): 41.2% of the cases were not position dependent, 52.3% were supine position dependent based on the trunk sensor, 6.5% were supine position dependent based on the head sensor alone. In 46.2% of the trunk supine position-dependent group, head position was of considerable influence on the AHI. The results of this study confirm our hypothesis that the occurrence of OSA may also be dependent on the position of the head. Therefore in patients with a suspicion of position-dependent OSA, sleep recording with dual position sensors placed on both trunk and head should be considered.[14]

Although positional therapy has a promising future with many possibilities, not all patients are eligible for this treatment because most patients with severe OSAS are not positional; their AHI is high in all sleep positions.[16] A possible solution currently gaining more popularity is the combining of multiple non-surgical therapies.[17] A recent study has shown that the combination of positional therapy with the use of oral appliances leads to a higher therapeutic efficacy in patients with supine-dependent obstructive sleep apnea under oral appliance therapy when compared to one of the treatment modalities alone.[18]

Despite these recent developments, in a significant group of patients with severe OSAS such treatments are not sufficiently effective. In this group surgery is unavoidable. Unfortunately, the results reported in the literature for upper airway surgery in OSAS are often inconsistent.[19,20] Which tools can we use to better predict the surgical outcome? In **Chapter 6** we investigated if DISE can be used to predict higher likelihood of response to upper airway surgery.[8] The main findings of this study were that responders to upper airway surgery for OSA had a higher occurrence of complete or partial antero-posterior collapse at velum and of partial antero-posterior collapse at tongue base and epiglottis compared to nonresponders; in contrast, nonresponders of upper airway surgery had a higher occurrence of complete or partial circumferential collapse at the level of the velum and of complete antero-posterior collapse at tongue base or epiglottis in comparison with responders. In addition to this, among baseline clinical and polysomnographic variables and DISE findings, only a complete circumferential collapse at the level of the velum and a complete antero-posterior collapse at the level of the tongue base were independently associated with failure of upper airway surgery in OSA patients. These results do confirm that an assessment of the upper airway prior to upper airway surgery using DISE is mandatory in OSAS patients that seek an alternative for CPAP or oral appliance therapy.

For OSAS patients that are intolerant to CPAP, hypoglossal nerve stimulation technology is yet another alternative treatment option. As opposed to most other surgical techniques that address the upper airway in OSAS patients, upper airway stimulation comes without removal, stiffening or transpositionig of tissue. A recent multicenter cohort study with 126 participants showed that upper-airway stimulation led to significant improvements in objective and subjective measurements of the severity of obstructive sleep apnea in selected patients.[21] In addition, within this multicenter project, arandomized controlled therapy withdrawal study was performed to assess the short- and long-term effect of upper airway stimulation including objective and subjective clinical outcome measures. The study showed that withdrawal of therapeutic upper airway stimulation results in worsening of both objective and subjective measures of sleep and breathing. When the upper airway stimulation waswhen resumed, this resulted in a sustained effect at 18 and 24 months. The results of this RCT indicated that the reduction of obstructive sleep apnea severity and improvement of quality of life were attributed directly to the effects of the electrical stimulation of the hypoglossal nerve.[22] Although this therapy only targets the hypoglossal nerve, **Chapter 7** evaluated stimulation effects on retropalatal and retrolingual dimensions during DISE. Patients with an implanted

stimulator underwent nasal video endoscopy while awake and/or during drug-induced sedation in the supine position. The cross-sectional area, anterior-posterior and lateral dimensions of the retropalatal and retrolingual regions were measured during baseline and stimulation. This novel way of measuring the cross-sectional area at different collapsible levels of the upper airway during DISE is a more objective method as compared to some other methods currently in use. Further studies need to be performed to assess whether this particular methodology of DISE analysis is reproducible.

The results of this study indicate that UAS increases both the retropalatal and retrolingual areas. This multilevel enlargement may explain reductions of the apnea-hypopnea index in selected patients receiving this therapy.

This thesis illustrates the role of DISE in the selection of the proper patients for the alternative treatments in OSAS. DISE has clearly increased the knowledge on the pathophysiology, diagnosis, objective measurements and predictability of outcome of treatment in alternative OSA treatments. Additionally, DISE has hinted at the high potential of hypoglossal nerve stimulation as a future treatment option in well-selected OSAS patients. Due to the multilevel issues, it is possible that many OSAS patients will be using a combination of the treatments mentioned above.[23–26]

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Appendix A

Samenvatting, discussie en toekomstperspectieven

Samenvatting, discussie en toekomstperspectieven

Continuous positive airway pressure (CPAP) is de eerste keus bij de huidige behandeling van patiënten met matige tot ernstige obstructieve slaap apneu syndroom (OSAS). Het is niet invasief en kan, indien correct toegepast, de kwaliteit van leven significant verbeteren en cardiovasculaire morbiditeit en mortaliteit verminderen.[1,2,3] Het apparaat is echter onhandig en therapietrouw is slechts matig.[4,5] Patiënten die CPAP om verscheidene redenen niet kunnen verdragen lijden nog steeds aan een ernstige aandoening en behandeling is nog steeds noodzakelijk. Een van de aantrekkelijke kanten van het werken als onderzoeker op het gebied van OSA is dat er op dit moment zoveel nieuwe ontwikkelingen gaande zijn binnen zowel de diagnostiek als de behandeling van OSAS. Binnen de diagnostiek neemt de rol van drug induced sedated endoscopy (DISE) een vlucht; bij behandeling worden alternatieven voor CPAP zoals chirurgie, positional therapy, oral device therapy en gecombineerde "multimodality" behandeling steeds belangrijker. Deze thesis richt zich op verscheidene aspecten van alternatieve therapieën voor OSAS, deels gebaseerd op bevindingen van DISE. Nieuwe ontwikkelingen zoals DISE, positional therapy en upper airway stimulation (UAS) worden samengebracht. De behandeling van OSAS drijft langzaam weg van gelijke CPAP therapie voor iedereen richting persoonlijk aangepaste behandeling: "treatment diversification".

Een reden voor het stoppen of weigeren van CPAP door patiënten is nasale verstopping. Nasale verstopping, rhinorrhea en niezen zijn sommige van de meest voorkomende bijwerkingen van nasale CPAP therapie voor OSAS die direct invloed hebben op therapietrouw.[6] Daarom zouden interventies die deze bijwerkingen verminderen kunnen leiden tot verbeterde therapietrouw en daarmee tot een betere kwaliteit van leven. Verwarmde bevochtiging en plaatselijke nasale steroïdensprays worden veelvuldig voorgeschreven om nasale klachten te behandelen. Chirurgische reductie van de neusschelpen is ook een optie. Over het algemeen worden de meeste operaties aan de onderste neusschelpen onder narcose verricht en meestal worden nasale tampons voor enkele dagen voorgeschreven. De combinatie van narcose en nasale tampons dient bij voorkeur te worden vermeden bij patiënten met OSAS. Een minimum invasieve, poliklinische ingreep waarbij geen tampons nodig zijn en met effecten op de lange termijn zou de voorkeur hebben. In **Hoofdstuk 2** van deze thesis wordt aangetoond dat radio frequency induced thermotherapy

(RFITT) onder lokale anesthesie een waardevolle, minimum invasieve, patiëntvriendelijke en goed verdragen behandeling is bij patiënten met verkleinde nasale doorgang ten gevolge van hypertrofie van de onderste neusschelpen. De resultaten die in dit hoofdstuk worden gepresenteerd zijn van patiënten die de behandeling hebben ondergaan en zelf-gerapporteerde effecten van de behandeling op de lange termijn en de ervaring van RFITT werden getoetst door middel van een vragenlijst. Er was sprake van een significante afname van het gebruik van nasale spray en de meerderheid van de ondervraagde patiënten rapporteerden positieve effecten van de RFITT overdag op de lange termijn. RFITT zou dus een alternatieve behandeloptie kunnen zijn voor patiënten die CPAP niet kunnen verdragen ten gevolge van vergrote onderste neusschelpen. Op het moment van schrijven loopt er een studie in het Sint Lucas Andreas Ziekenhuis in Amsterdam en de Universiteit van Antwerpen om te onderzoeken of RFITT inderdaad therapietrouw zou kunnen verhogen bij patiënten die CPAP niet verdragen.

Een andere alternatieve niet-invasieve behandeling is positional therapy. Dankzij innovatieve nieuwe apparaten heeft positional therapy de afgelopen jaren aan populariteit gewonnen. Een studie heeft aangetoond dat positional therapy even effectief is als CPAP om de AHI van patiënten met milde tot matige positional OSA te normaliseren, met vergelijkbare effecten op de slaapkwaliteit en nachtelijke oxygenatie.[7] Recent onderzoek heeft aangetoond dat de effecten bij positional therapy met de sleep position trainer op de lange termijn positief zijn. Bovendien heeft de studie aangetoond dat de therapietrouw en mate van regelmatig gebruik relatief goed waren.[8] Ten gevolge van deze positieve resultaten is deze therapie aan een opmars begonnen en is het aantal patiënten dat positional therapy gebruikt toegenomen. Wanneer positional therapy wordt overwogen als (deel van) een behandeling van OSA, ligt het voor de hand DISE (welke voornamelijk in rugligging wordt toegepast) ook in de andere slaaphoudingen toe te passen. In **Hoofdstuk 3** wordt een literatuurstudie naar DISE omschreven. In **Hoofdstuk 4** onderzoeken we de invloed van verschillende posities van het hoofd tijdens DISE bij patiënten met OSA en POSA. Na een consecutive prospective studie toonden de resultaten dat er geen verschil was tussen de collaps van de bovenste luchtweg bij rotatie van het hoofd naar links of rechts. Rotatie van het hoofd levert een significante verbetering op van collaps van de bovenste luchtweg tijdens DISE in rugligging. Deze verbetering van de doorgankelijkheid van de bovenste luchtweg is uitgesprokener bij patiënten met POSA. Het idee dat rotatie van het hoofd voldoende zou zijn in tegenstelling tot zijligging wordt verder verkend in **Hoofdstuk 5**. De uitkomsten van DISE in rugligging met rotatie met het hoofd werden vergeleken met de uitkomsten van DISE

uitgevoerd met het hoofd en de romp in zijligging. De resultaten toonden aan dat rotatie van het hoofd in rugligging en het hoofd en de romp in zijligging vergelijkbare locaties, ernst en patronen van collaps van de bovenste luchtweg in beeld brengen, met als uitzondering collaps op het niveau van het velum. Daar is de ernst van anterio-posterieure collaps minder ernstig bij rotatie van het hoofd dan bij het hoofd en de romp in zijligging.

De uitkomst van deze studies hebben belangrijke gevolgen voor de uitvoering van DISE. In het algemeen wordt DISE uitgevoerd in rugligging. De gebruikelijke aanname was dat de obstructie in deze positie vaak ernstiger is en dat daarmee deze positie het meest geschikt is voor evaluatie. DISE wordt uitgevoerd en bij indicatie herhaald met een handeling waarbij de onderkaak naar voren wordt gebracht, omdat deze beweging tot op zekere hoogte het effect van een oral device voorspelt. DISE wordt dus vaak tweemaal uitgevoerd: eerst spontaan en daarna herhaald met een handeling als de “chin lift”, “jaw thrust”, “mouth closure” or “simulation bite”.[9] Wanneer positional therapy wordt overwogen als deel van de behandeling zou men DISE in linker en rechter zijligging en met het hoofd naar links en naar rechts gedraaid moeten toevoegen; vijf posities waarin de passieve handelingen ook zouden moeten worden uitgevoerd. De resultaten die in deze thesis worden gepresenteerd scheppen mogelijkheden om DISE op een specifiekere manier uit te voeren. Slechts één zijligging is voldoende en enkel het draaien van het hoofd is bijna gelijk aan het draaien van zowel hoofd als romp.

Verdere innovatieve opties in de behandeling van positional sleep apneu kunnen in de toekomst worden onderzocht. Een alternatieve optie zou bijvoorbeeld plaatsing van het apparaat op het hoofd van de patiënt zijn in tegenstelling tot op de rug. Terwijl de patiënt slaapt zou het apparaat subtiel kunnen trillen om de patiënt zijn of haar hoofd te laten draaien, waarbij de luchtweg zich opent. De studie toonde ook aan dat het openen van de luchtweg vergelijkbaar is bij het draaien van het hoofd naar links of naar rechts, wat het vereenvoudigt. Zodra het hoofd is gedraaid zou het apparaat uitschakelen. De beste manier om te demonstreren of dit effect de AHI tijdens slaap zou verminderen zou zijn om positiesensoren op het hoofd van de patiënt te plaatsen tijdens een PSG. Van Kesteren et al. heeft een dergelijke studie uitgevoerd waarbij patiënten nachtelijke polysomnografie ondergingen met twee positiesensoren: één op de romp en één midden op het voorhoofd. Van de 300 proefpersonen werden er 241 gediagnostiseerd met OSA, gebaseerd op een AHI > 5. Van deze patiënten konden 199 worden geanalyseerd als hebbende positieafhankelijke OSA op basis van hoofd en romp positiesensoren (de AHI in

rugligging was tweemaal zo hoog als de AHI in een andere positie): 41.2% van de casus waren niet positieafhankelijk, 52.3% waren op basis van de sensor op de romp afhankelijk van rugligging, 6.5% waren enkel op basis van de sensor op het hoofd afhankelijk van rugligging. Bij 46.2% van de groep met afhankelijkheid van de rugligging op basis van de romp had de positie van het hoofd aanzienlijke invloed op de AHI (AHI was > 5 meer wanneer het hoofd ook in rugligging was vergeleken met wanneer het hoofd naar de zijkant was gedraaid). De resultaten van deze studie bevestigen onze hypothese dat het voorkomen van OSA mogelijk ook afhankelijk is van de positie van het hoofd. Daarom zouden bij patiënten met een verdenking op positieafhankelijke OSA slaapopnames met dubbele positiesensoren op zowel de romp als het hoofd moeten worden overwogen.[10]

Hoewel positional therapy een veelbelovende toekomst heeft met veel mogelijkheden, komen niet alle patiënten in aanmerking voor deze behandeling. De meeste patiënten met POSA hebben milde tot matige OSAS, terwijl de meeste patiënten met ernstige OSA niet positioneel zijn; hun AHI is in alle slaaphoudingen hoog. Patiënten met milde, matige of ernstige OSA die CPAP niet kunnen verdragen hebben ook behandeling nodig. De meeste van dergelijke patiënten met ernstige OSAS kunnen niet behandeld worden met een oral device. Circa 33% van de patiënten hebben sowieso een contraindicatie voor behandeling met een oral device. Een toenemend aantal patiënten kiest voor ingrepen aan de bovenste luchtweg.

Standaard chirurgische technieken kunnen vele nadelen hebben, met vaak hoogstens matige resultaten en verscheidene onvoorspelbare resultaten, onsuccesvolle ingrepen, morbiditeit en bijwerkingen. Ondanks verbeteringen in de selectie van patiënten en nieuwere persoonlijk aangepaste chirurgische technieken zijn deze problemen nog steeds aanwezig. De resultaten van operaties aan de bovenste luchtweg bij OSAS die in de wetenschappelijke literatuur gerapporteerd worden zijn om die reden niet consistent.[11,12] Het is daarom lastig als arts advies te geven aan individuele patiënten over de kans op succes van chirurgische uitkomsten. In **Hoofdstuk 6** onderzoeken we of DISE gebruikt kan worden om een hogere kans op effect van operaties aan de bovenste luchtweg te voorspellen. De belangrijkste bevinding van deze studie was dat volledige of gedeeltelijke, antero-posterieure collaps bij het velum en van partiële, antero-posterieure collaps bij de tongbasis en epiglottis meer voorkwamen bij patiënten die goed reageerden op chirurgische ingrepen aan de bovenste luchtweg voor OSA dan bij patiënten die niet goed reageerden; volledige of gedeeltelijke, cirkelvormige collaps bij het velum en

volledige, antero-posterieure collaps bij de tongbasis of epiglottis kwamen daarentegen meer voor bij patiënten die niet goed reageerden op chirurgische ingrepen aan de bovenste luchtweg dan bij patiënten die wel goed reageerden. Daarnaast waren van de baseline klinische en polysomnografische variabelen en bevindingen bij DISE alleen de aanwezigheid van volledige, cirkelvormige collaps bij het velum en van volledige, anterio-posterieure collaps bij de tongbasis onafhankelijk geassocieerd met onsuccesvolle chirurgische ingrepen aan de bovenste luchtweg bij patiënten met OSA. Men kan concluderen dat bij patiënten die op zoek zijn naar chirurgie als alternatieve behandeling het belangrijk is de bovenste luchtweg van tevoren te evalueren door gebruik te maken van DISE om te zien of de patiënt een geschikte kandidaat is en de kans op succes te vergroten.

Voor patiënten die CPAP niet verdragen en niet goed reageren op chirurgische ingrepen aan de bovenste luchtweg is stimulatie van de nervus hypoglossus nog een alternatief. Het nadeel van chirurgische ingrepen aan de bovenste luchtweg is dat ze meestal pijnlijk en irreversibel zijn en niet kunnen worden bijgesteld, wat mogelijk de reden is dat er weinig effect is op de lange termijn. “Upper airway nerve stimulation” lost deze problemen op. In tegenstelling tot andere chirurgische technieken wordt er bij upper airway nerve stimulation geen weefsel verwijderd, versterkt of verplaatst. De techniek werkt samen met de fysiologie van de patiënt. Een recente uncontrolled multicenter cohort studie met 126 participanten toonde aan dat UAS tot significante verbeteringen in objectieve en subjectieve maten van de ernst van obstructieve slaap apneu leidde bij geselecteerde patiënten.[13] Bovendien is er recente een andere randomized controlled therapy withdrawal studie uitgevoerd om de effecten van UAS op de korte en lange termijn te bestuderen, inclusief objectieve en subjectieve klinische uitkomstmaten. De studie toonde aan dat het staken van therapeutische UAS resulteert in een verergering van zowel objectieve als subjectieve maten van slapen en ademen, terwijl opnieuw starten duurzaam effect oplevert bij 18 en 24 maanden. Afname van de ernst van obstructieve slaap apneu en verbetering van de kwaliteit van leven werden direct toegeschreven aan de effecten van de elektrische stimulatie van de nervus hypoglossus.[14] Hoewel deze therapie zich slechts op de nervus hypoglossus richt, evalueert **Hoofdstuk 7** de effecten van stimulatie op retropalataire en retrolinguale afmetingen tijdens DISE. Patiënten met een geïmplanteerde stimulator ondergingen nasale video-endoscopie terwijl ze wakker waren en/of gedurende DISE in rugligging. De oppervlakte bij doorsnede, anterio-posterieure en laterale afmetingen van de retropalataire en retrolinguale gebieden werden bij baseline en stimulatie gemeten. Deze vernieuwende wijze van meten tijdens DISE is een objectievere

methode dan sommige andere methodes die momenteel in gebruik zijn. Verder onderzoek is nodig om te zien of deze manier om DISE te scoren reproduceerbaar is. UAS vergroot zowel het retropalataire en retrolinguale gebied. Deze vergroting op meerdere niveaus verklaart mogelijk de afname van de apneu-hypopnea index bij geselecteerde patiënten die deze therapie ontvangen. Het onderzoek rondom deze nieuwe therapie wordt vervolgd met verschillende amplitudes bij stimulatie van de nervus hypoglossus en verschillende inclusiecriteria (bijvoorbeeld het opereren van patiënten met hogere AHIs). De verwachting is dat verzekeraars de kosten van deze therapie binnenkort zullen vergoeden bij zorgvuldig geselecteerde patiënten.

Deze thesis illustreert de rol en belangrijke toepassingen van DISE bij alternatieve therapieën voor OSAS. Het heeft de kennis op de gebieden van de pathofysiologie, diagnostiek, objectieve maten en voorspelbaarheid van de uitkomst van behandeling bij alternatieve behandelingen voor OSA vergroot. Bovendien heeft het een tipje van de sluier opgelicht over het enorme potentieel van stimulatie van de nervus hypoglossus als toekomstige behandeloptie. Ten gevolge van de problemen op vele niveaus is het mogelijk dat veel patiënten met OSAS een combinatie van de bovengenoemde behandelingen zullen benutten.

Appendix B

Dankwoord

Dankwoord

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Appendix C

Curriculum Vitae

Curriculum Vitae

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Opleiding

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Academisch Medisch Centrum (AMC), Nederland
Diploma behaald.

2001 - 2003 **International Baccalaureate** (IB)
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Diploma behaald.

1999 - 2001 **International and General Certificate of Secondary Education** (IGCSE)
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Relevante werkervaring

2011 - 2013 **Arts-assistent KNO**
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2011 - 2013 **Research co-ordinator en Co-investigator; Stimulation Therapy for Apnea Reduction (STAR) trial**
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2013- heden **Arts-assistent in opleiding tot oogarts**
Academische ziekenhuis Maastricht

Cursussen

2011 **American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNSF)**
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2011 **Upper airway Simulation Inspire Surgical training and cadaver lab**
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Wetenschappelijke ervaring

2012 **Surgery for obstructive sleep apnea: sleep endoscopy determinants of outcome**
Y.Koutsourelakis, F Safiruddin MD, MJL Ravesloot MD, N de Vries MD PhD

2012 **Long-term self-reported effects of Radiofrequency Induced Thermotherapy (RFITT) of the turbinates: A retrospective analysis.**
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27 apr 2012 **Screening van patiënten met slaap apneu voor een nieuwe behandeling: de ervaring van een onderzoekscentrum**
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Nieuwegein, Nederland

28 mrt 2012 **Screening outcome for Upper Airway Stimulation Trials: Sint Lucas Andreas Hospital**
International Surgical Sleep Society (ISSS)
Venetië, Italië

07 juni 2011 **Nervus Hypoglossus stimulatie voor OSAS**
Refereeravond van de afdeling Keel-Neus-Oorheelkunde: Wat is nieuw sinds de introductie van de OSAS-richtlijn?
Leids Universitair Medisch Centrum (LUMC), Nederland

11 feb 2011 **Who is the perfect surgical candidate for upper airway stimulation?**
Inspire Surgical Summit
Mannheim, Duitsland

Appendix D

Over de auteur

Over de auteur

Faiza Safiruddin werd geboren op 21 februari 1985 in Karachi, Pakistan. In 2001 behaalde ze haar International and General Certificate of Secondary Education (IGCSE) in Braeburn International School, Nairobi, Kenia. Na haar verhuizing naar Nederland behaalde ze haar International Baccalaureate diploma op het Rijnlands Lyceum Oegstgeest International School in 2003. Ze startte daarna haar studie geneeskunde aan de Universiteit van Amsterdam. In haar laatste jaar deed ze haar oudste co-schappen in het Sint Lucas Andreas Ziekenhuis op de afdeling Keel-, Neus- en Oorheelkunde en bleef daar aansluitend werken als ANIOS en onderzoeker. Op 28 januari 2011 behaalde ze haar artsexamen.

Op 1 mei 2013 is ze begonnen aan haar opleiding tot oogarts in het Maastricht Universitair Medisch Centrum.