The role of drug-induced sleep endoscopy and position-dependency in the diagnostic work-up of obstructive sleep apnea

Patty E. Vonk

THE ROLE OF DRUG-INDUCED SLEEP ENDOSCOPY AND POSITION-DEPENDENCY IN THE DIAGNOSTIC WORK-UP OF OBSTRUCTIVE SLEEP APNEA

Patty E. Vonk

ISBN: 978-94-6332-590-5

Cover design: Patty Vonk

Layout: Patty Vonk en GVO drukkers & vormgevers B.V.

Printing: GVO drukkers & vormgevers B.V.

THE ROLE OF DRUG-INDUCED SLEEP ENDOSCOPY AND POSITION-DEPENDENCY IN THE DIAGNOSTIC WORK-UP OF OBSTRUCTIVE SLEEP APNEA

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor

aan de Universiteit van Amsterdam

op gezag van de Rector Magnificus

prof. dr. ir. K.I.J. Maex

ten overstaan van een door het College voor Promoties ingestelde commissie,

in het openbaar te verdedigen in de Aula der Universiteit

op vrijdag 24 januari 2020 te 13.00 uur

door Patty Elisabeth Vonk

geboren te Geldrop

PROMOTIECOMMISSIE

Promotor

Prof. dr. N. de Vries	Universiteit van Amsterdam

Copromotores

Dr. M.J.L. Ravesloot	OLVG
Dr. J. P. van Maanen	OLVG

Overige leden

Prof. dr. J. de Lange	Universiteit van Amsterdam
Prof. dr. F.G. Dikkers	Universiteit van Amsterdam
Prof. dr. F. Lobbezoo	Universiteit van Amsterdam
Prof. dr. B.G. Loos	Universiteit van Amsterdam
Prof. dr. F.R. Rozema	Universiteit van Amsterdam
Prof. dr. O.M. Vanderveken	Universitair Ziekenhuis Antwerpen
Prof. dr. J. Verbraecken	Universitair Ziekenhuis Antwerpen

Faculteit der Tandheelkunde

TABLE OF CONTENTS

General introduction and outline of thesis

1

GENERAL INTRODUCTION

Sleep is one of the most important aspects of our lives. Even though humans spend nearly one third of their lives asleep, the purpose of sleep has long remained elusive. In recent years, however, scientific findings have shed new light on the vital importance of sufficient sleep. Among its many other functions, sleep enhances memory consolidation and brain plasticity, restocking our immune system and ability to learn. [1-3]

Sleep disorders

Research in a Dutch population has estimated the prevalence of too little sleep to be 30.4% and insufficient sleep to be 43.2%. General sleep disturbance (GSD) was reported in 34.8% of females and in 29.1% in males. Female adolescents seem to have the highest prevalence rates of GSD and daytime fatigue. [4]

Due to the gradual increase in public interest in sleep, and also due to increased knowledge of the impact of disturbed sleep on public heath, it is important to rely on an international, standardized system for diagnosing patients with sleep-related problems. The most widely used classification system for sleep disorders is the International Classification of Sleep Disorders (ICSD). The third and latest edition, ICSD-3, comprises seven major categories of sleep disorders:

- Insomnia
- Sleep-related breathing disorders
- Central disorder of hypersomnolence
- Circadian rhythm sleep-wake disorders
- Parasomnias
- Sleep-related movement disorders
- Other sleep disorders [5]

The ICSD-3 refers to and complements the Manual for the Scoring of Sleep and Associated Events published by the American Academy of Sleep Medicine (AASM). [6]

In this thesis we focus on sleep-related breathing disorders, in particular obstructive sleep apnea (OSA) in adults.

Sleep-related breathing disorders

Sleep-disordered breathing is a chronic disorder characterized by recurrent episodes of upper airway (UA) collapse resulting in fragmented sleep, periodic oxygen desaturations and increases in blood pressure due to apneic events. In general, sleep-related breathing disorders (SBD) can be divided into four categories:

- Central sleep apnea (CSA)
- Sleep-related hypoventilation
- Sleep-related hypoxemia disorder
- Obstructive sleep apnea (OSA) [6]

Despite the different ICSD-3 classifications, patients often meet the criteria for more than one sleep disorder. For example, many patients have features of both OSA and CSA, which can change during overnight recording. In some cases, CSA can also occur after effective treatment of obstructive events. In these patients the term treatment-emergent CSA or complex sleep apnea is appropriate.[5, 7] **Table 1** provides an overview of the different forms of SBD.

Table 1. Sleep-Related Breathing Disorders [5]

Disorder
OSA disorders
OSA, adult
OSA, pediatric
Central sleep apnea syndromes
Central sleep apnea with Cheyne-Stokes breathing
Central sleep apnea due to a medical disorder without Cheyne-Stokes breathing
Central sleep apnea due to high altitude periodic breathing
Central sleep apnea due to a medication or substance
Primary central sleep apnea
Primary central sleep apnea of infancy
Primary central sleep apnea of prematurity
Treatment-emergent central sleep apnea
Sleep-related hypoventilation disorders
Obesity hypoventilation syndrome
Congenital central alveolar hypoventilation syndrome
Late-onset central hypoventilation with hypothalamic dysfunction
Idiopathic central alveolar hypoventilation
Sleep-related hypoventilation due to a medication or substance
Sleep-related hypoventilation due to a medical disorder
Sleep-related hypoxemia disorder

Obstructive sleep apnea

Definition and prevalence

OSA is defined according to the criteria of the ICSD and scoring rules of the AASM. Its diagnosis is based on an apnea-hypopnea index (AHI) of ≥ 5 predominantly obstructive events or respiratory effort-related arousals (RERAs) per hour in combination with OSA-associated symptoms, such as fatigue, insomnia, snoring and excessive daytime sleepiness. The criteria for OSA are also met when the AHI is ≥ 15 with primarily obstructive respiratory events per hour, even in the absence of OSA-related symptoms or comorbidities. [5, 8, 9] In the Dutch guideline published in 2018 the distinction has been made between asymptomatic and symptomatic OSA. In patients with elevated AHI levels without any clinical symptoms or comorbidities related to OSA, it has been questioned whether treatment is indicated, even when the AHI is ≥ 15 events/h. [10]

OSA is the most prevalent SBD. In a recent large study in Switzerland, 49.7% of men and 23.4% of women aged 40 years or older, were found to have an AHI of ≥ 15 events/h. 12.5% of men and 5.9% of women had an AHI ≥ 15 events/h and excessive daytime sleepiness. [11] Other symptoms associated with OSA include snoring, diminished intellectual abilities and changes in personality. [12, 13]

Currently, the idea is reinforced that not only an increased AHI, but also OSA-related symptoms and comorbidities must be considered in patient-specific treatment planning. [14] The clinical relevance of elevated AHI levels without any clinical symptoms, or comorbidities related to OSA, has not yet been determined.

Risk factors and consequences of untreated OSA

The most common risk factors for developing OSA are obesity, increased age, male gender and a small or posteriorly positioned lower jaw, also called retrognathia. In obese patients, fatty tissue is often deposited in the neck or tongue, compressing the UA during sleep when the muscle tone is reduced. [15] In women, it has also been shown that pregnancy and menopause can be a risk factor for developing OSA. [16-18] Other predisposing factors are alcohol use, smoking and the use of sedatives. [19] When OSA remains untreated, patients are at a higher risk of developing cardiovascular diseases or being involved in a traffic accident. [20] Studies also suggest that OSA is a risk factor for stroke, and is an independent predictor for functional recovery and mortality in stroke patients. [21-24]

Pathogenesis of OSA

OSA is characterized by recurrent episodes during which airflow decreases during sleep due to a partial or complete obstruction in the collapsible segment of the UA. The pathophysiological mechanism behind this — which also defines its different phenotypes — has attracted great attention in recent years. This is not surprising, since understanding of these mechanisms is of paramount importance when developing effective individual therapies for OSA patients. Historically, treatment modalities such as continuous positive airway pressure (CPAP), mandibular advancement devices (MADs) and different forms of UA surgery were introduced, aiming to reverse anatomical UA obstruction. Nevertheless, these therapies are not always successful and recent studies have shown that not only anatomical, but also non-anatomical traits contribute to the pathophysiology of OSA. [25, 26]

In recent decades, four key contributors to the pathogenesis of OSA have been identified. These include a narrow and/or collapsible airway — anatomical contributors — and non-anatomical contributors, such as a low arousal threshold to narrowing of the upper airway during sleep, an unstable control of breathing (high loop gain) and ineffective UA dilator muscle responsiveness. [25, 26]

Anatomical contributors to OSA

Impaired UA anatomy

The primary cause of OSA is impaired UA anatomy. It is self-evident that a narrow UA is more prone to collapse. In the majority of patients, the main cause of a narrow UA is obesity. This is mainly due to the deposition of adipose tissue in the regions that surround the UA. The most common anatomical structures can be involved in UA collapse: the soft palate (i.e., velum), the oropharynx (e.g., lateral walls or tonsils), the tongue base and the epiglottis. Comparison of OSA patients with healthy non-apneic controls shows that OSA patients tend to have larger pharyngeal walls, a smaller airway at the retropalatal level and narrowing of the airway, predominantly in the lateral dimension. [27] The cross-sectional area of the UA measured by computerized tomography (CT) is also smaller in patients with SDB than in non-apneic controls. [28]

UA collapsibility

The UA contains a collapsible segment that is influenced by the pressure of the surrounding tissue of the airway. If the pressure of the airway exceeds the intraluminal pressure, a negative intraluminal pressure will be created, causing UA collapse and a decrease in airflow. The airway pressure required to collapse the UA is best designated by the pharyngeal critical closing pressure (P_{crit}). P_{crit} is dependent on many variables and is not actually a product of hypopharyngeal pressure, but of the pressure in the UA moving upstream towards the collapsing segment. Thus, the negative pressure generated by the

respiratory pump muscles can reduce airway size, but will generally not collapse the airway. In other words, as long as the intraluminal pressure remains higher than the P_{crit}, inspiratory flow will be maintained. As previous studies have shown, a high P_{crit} is related to increased UA pressure and to OSA. [29-32]

Non-anatomical contributors to OSA

Arousal threshold

For many decades, cortical arousals have been assumed to be an important defensive mechanism for re-establishing UA patency in OSA patients. However, a substantial proportion of respiratory events do not terminate in a cortical arousal; in some OSA patients, these arousals even precede a respiratory event. Whereas arousals may reduce the duration of individual respiratory events, they also interfere with ventilator stability and progression to deeper sleep stages, thereby increasing the frequency of respiratory events. It has also been suggested that a low arousal threshold is associated with OSA. [33, 34]

Loop gain

Another mechanism that contributes to the pathogenesis of OSA is the stability of loop gain (i.e., the respiratory control system). As the respiratory system is influenced by loop gain, it has the potential to become unstable. A high-gain system responds effective and quickly to an event, whereas a low-gain system responds more slowly and weakly. Loop gain can be best described by the following formula:

Response to a disturbance / disturbance itself (apnea or hypopnea)

If loop gain is less than 1, a respiratory disturbance such as an apnea or hypopnea will lead to a response, but the response will be small and sufficient, enabling relatively quick stabilization of the ventilation. If the loop gain is greater than 1, the opposite will happen, causing a waxing and waning pattern of the ventilation. In summary, high gain destabilizes ventilation, and is generally more prevalent during sleep. [32, 35]

Dilator muscle responsiveness

The key process that counteracts the collapsibility of the UA is pharyngeal dilator muscle activation. Activation of the pharyngeal dilator muscles protects UA patency and counteracts the collapsing forces. Although many dilator muscles maintain UA patency, the genioglossus muscle is the best studied. This muscle is an inspiratory phasic muscle, which is controlled by three primary neural inputs. First of all, negative pressure in the UA activates mechanoreceptors that are located mainly in the larynx. Activation of these receptors increases hypoglossal output to the genioglossus muscle. Thus,

when a respiratory event causes negative pressure in the UA, genioglossal activity will increase, thereby countering the event. Secondly, genioglossal activation is influenced by respiratory neurons in the medulla. Thirdly, neurons that modulate arousal – which are active in the waking state and inactive during sleep – have a tonic influence on the activity of the hypoglossal motor neurons, which generally increase muscle activity. Naturally, it is important that, upon the onset of sleep, the control of the muscles in the UA is retained. Unfortunately, due to loss of wakeful neuronal input and a decrease in response to negative pressure in the UA, there is a general fall in muscle activity. [32]

Non-positional OSA and positional OSA

Definition and prevalence

Another phenotypic approach is to categorize OSA patients in non-positional OSA patients (NPP) and positional OSA patients (PP). [36] In approximately 56-75% of patients diagnosed with OSA, the severity of UA collapse is influenced by body position. In these patients obstructive events almost exclusively occur in the supine posture. [12, 36-40] The prevalence of position-dependent OSA (POSA) decreases as the severity of sleep apnea increases and the majority of PP (70-80%) have mild or moderate OSA. [12, 36, 38, 41] PP also have a lower body mass index (BMI), and are younger in comparison with NPP. [12, 36, 38, 42] Furthermore, the prevalence of POSA is thought to be higher in Asian populations. [43-45]

The literature provides many definitions of POSA. In 1984, Cartwright was the first to describe POSA with the arbitrary cut-off point of a difference of 50% or more in apnea index between supine and non-supine positions. [39] Since then, additions to these criteria have been introduced such as a minimum sleeping time spent in supine and non-supine positions and cut-off values for the non-supine AHI. [41, 46-48] In addition, POSA can be divided into supine isolated OSA (non-supine <5 events/h) and supine predominant OSA (non-supine AHI ≥ 5 events/h). [49, 50]

Upper airway collapse patterns

The underlying pathophysiological mechanism explaining different collapse patterns in supine and non-supine sleeping position remains poorly understood. Over the past years, several studies have been published aiming at unraveling the underlying cause of these two different phenotypes.

As described before, there are several levels in the UA that can be involved in UA collapse. Previous studies have shown that especially obstruction at the level of the tongue base and epiglottis, and to a lesser extent the soft palate, are under influence of body position. The prevalence of lateral wall obstruction is in general not affected by change in posture. However, persistent obstruction at the level of the lateral walls of the pharynx in the non-supine position in NPP is more frequent in comparison to PP. [51, 52]

Another interesting phenomenon is the presence of a primary epiglottic collapse, not secondary to tongue base collapse (i.e., floppy epiglottis [FE]). It has been suggested that a FE is mainly present in the supine position and to a lesser extent when the head is rotated to lateral position. [53] This phenomenon is described in more detail in **chapter 5.**

To complicate matters, evidence is also growing that POSA is not only dependent on body position, but also on head position. It has previously been suggested, that OSA severity significantly decreases when the head is rotated from supine to a lateral position, in particular in non-obese patients. [54, 55]

Diagnosis

Clinical assessment

The clinical presentation of patients suspected to have OSA can vary among patients. In all patients a comprehensive sleep and medical history should be taken as well as physical examination. Information concerning intoxications (i.e., smoking, alcohol and drug use), medication use, in particular the use of sedatives, and changes in weight should also be obtained. Symptoms related to OSA are snoring, choking or gasping episodes during sleep, unrefreshing sleep, excessive daytime sleepiness, observed apneas, nocturia, dry mouth, morning headache, memory loss, erectile dysfunction, and a decrease in libido and concentration.

One method to assess daytime sleepiness is the Epworth Sleepiness scale (ESS). This self-administered questionnaire provides eight items where patients answer questions based on how likely they are to doze off or fall asleep during several activities (i.e., 0=would never doze; 1= slight chance of dozing; 2=moderate chance of dozing; 3=high chance of dozing). A total ESS score of more than 10 is considered to correlate with excessive daytime sleepiness. [56, 57] When using self-reporting scales such as the ESS, it is important to keep in mind that the outcome of these scales can be influenced by other external factors as well — and not only OAS severity —Several studies have questioned the strength of the correlation between the ESS and objective measures of sleep. [58-60] In addition, improving the assessment of sleepiness in patients with OSA was recently identified as a key area that future research should prioritize. [61]

Physical examination should include BMI, neck circumference, the size of both palatine and tongue tonsils, position of the soft palate, length of the uvula, mandible position and size, and dental status.

PSG

The gold standard to diagnose OSA is a full-night polysomnography (PSG), during which information regarding the stages of sleep can be determined using an electroencephalogram (Fp1, Fp2, C3, C4, O1, O2), electro-oculogram and electromyogram (EMG) of the submental muscle. To measure the nasal airflow, a nasal cannula with a pressure transducer is inserted in the opening of the nostrils. A finger pulse oximeter is also placed to record arterial blood oxyhemoglobin. To measure thoracoabdominal excursions, respiratory effort belts are placed over the abdomen and rib cage. Furthermore, limb movements are detected by using an anterior tibial EMG with surface electrodes. A position sensor is used to determine body position of the patient, which differentiates between upright, right and left side, prone and supine sleep position.

Data collected should be scored according to the AASM scoring manual [8], preferably by an experienced sleep investigator. An obstructive respiratory event in adults is scored as an apnea if there is a drop in the peak signal excursion by ≥ 90% with a duration of at least ≥ 10 seconds. A hypopnea is defined as a decrease of airflow by ≥ 30% during a period of ≥ 10 seconds combined with an oxygen desaturation of ≥ 3%.

Upper airway assessment

Drug-induced sleep endoscopy (DISE) is a dynamic and unique diagnostic tool that provides additional information regarding the degree, level(s) and configuration of obstruction of the collapsible segment of the UA. DISE should be performed in selected patients in whom additional information concerning the dynamics of the UA is considered to be of added value. Therefore, DISE is especially indicated in OSA patients when UA surgery or UA stimulation is considered, or in case of CPAP or MAD failure. Less well explored, and perhaps more controversial, is the indication for DISE when MAD or combination treatment (e.g., MAD + positional therapy [PT], UA surgery + PT) is considered.

DISE should only be performed in patients with an acceptable overall anesthetic risk profile. Absolute contraindications are American Society of Anesthesiologists (ASA) classification 4, pregnancy and an allergy to DISE sedative agents. Relative contraindications may include morbid obesity, since UA surgery is in general not indicated in morbidly obese patients. [62]

DISE can be performed in any safe clinical setting, such as an operating theatre, endoscopy suite, or a similar clinical room set up with standard anesthetic equipment. A quiet room with dimmed lights is desirable, since one wants to mimic the situation during natural sleep as close as possible. Although several drugs used for DISE are reported in the literature, midazolam and propofol are the two drugs most widely used. [63] In 2018, an update of the European Position Paper on DISE was published,

recommending the use of propofol with target-controlled infusion (TCI), since this provides a more stable and reliable sedation in comparison to manual infusion or bolus technique. [62]

Historically, DISE is performed in the supine position. Although it may be technically easier to perform the procedure only in the supine position, various studies have found significant differences in DISE findings in the supine position in comparison to non-supine body position. [51-53] The role of posture and differences between lateral head rotation and lateral head and trunk position are described in more detail in **chapter 3.**

One of the advantages of DISE is that it allows the physician to perform different passive maneuvers with reassessment of UA patency after each one of them. Besides body posture, two other maneuvers have been described in the literature: chin-lift and jaw thrust, also known as the Esmarch maneuver. A chin-lift is a manual closure of the mouth, whilst a jaw thrust is a gentle advancement of the mandible up to approximately 5mm. [64] By performing either one of these maneuvers, the physician aims to mimic the effect of a MAD. As previously mentioned, the use of DISE before initiation of MAD treatment is controversial and the predictive value of DISE for MAD treatment success varies amongst studies. [65-67]

The main cause for concern is that the passive maneuvers performed mimic, but are not an exact and accurate reproduction of the effect of a MAD. First, the thickness of a MAD is not taken into account, which is relevant since the vertical opening (VO) of the mouth affects UA patency. Second, a MAD is usually set at 60-75% of maximum protrusion. When applying jaw thrust it is difficult to estimate the desired degree of mandible advancement. Subsequently, the use of a simulation bite in a reproducible maximal comfortable protrusion (MCP) during DISE has been suggested. Studies suggest that the latter is a better predictor of MAD response. [68, 69] The value of DISE as a prediction tool for MAD treatment is discussed in more detail in **chapter 4.**

Classification system for DISE

There are several classification systems described in the literature, but the most widely used and accepted one is the VOTE classification system. The VOTE classification system distinguishes between the four different levels and structures that may be involved in UA collapse, namely velum (V), oropharynx (O), tongue base (T) and epiglottis (E). To define the degree of obstruction, three different categories are used: 0) no obstruction (collapse less than 50%); 1) a partial obstruction (a collapse between 50-75% and typically with vibration or 2) a complete obstruction (a collapse of more than 75%). An X is used when no observation can be made due to for example hypersecretion. Depending on the different site(s) involved in UA obstruction, the configuration may be anterior-posterior (A-P),

lateral or concentric. [70] **Table 2** provides an overview of the degree and possible configurations of obstruction at each level according to the VOTE classification system. In **figure 1-6** examples of collapse patterns can be found.

Table 1. The VOTE classification system [70]

Structure	Degree of obstruction[a]	Configuration[c]		
		A-P	Lateral	Concentric
Velum				
Oropharynx[b]				
Tongue Base				
Epiglottis				

A-P Antero-posterior

a. Degree of obstruction: 0 no obstruction; 1 partial obstruction; 2 complete obstruction
b. Oropharynx obstruction can be distinguished as related solely to the tonsils or including the lateral walls
c. Configuration noted for structures with degree of obstruction > 0

Figure 1. Complete antero-posterior collapse at the level of the velum (B)

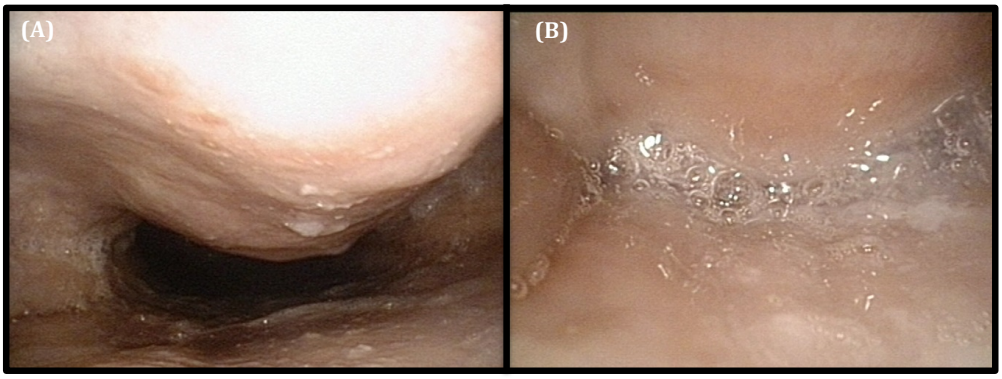


Figure 2. Partial (B) and complete (C) concentric collapse at the level of the velum

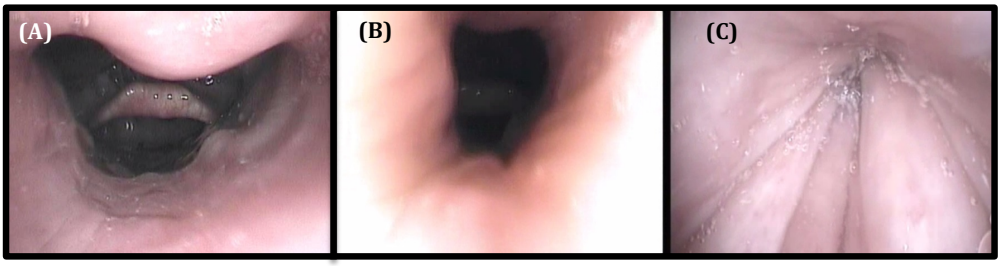


Figure 3. Partial (B) and complete (C) lateral wall collapse at the level of the velum and lateral pharyngeal walls

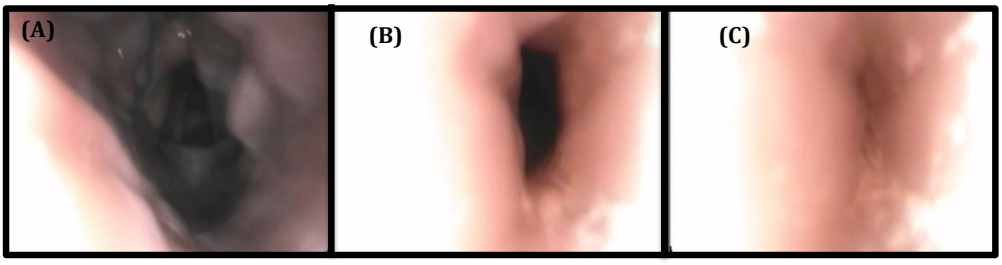


Figure 4. A complete antero-posterior collapse (B) at the level of the epiglottis (i.e., FE, trapdoor phenomenon)

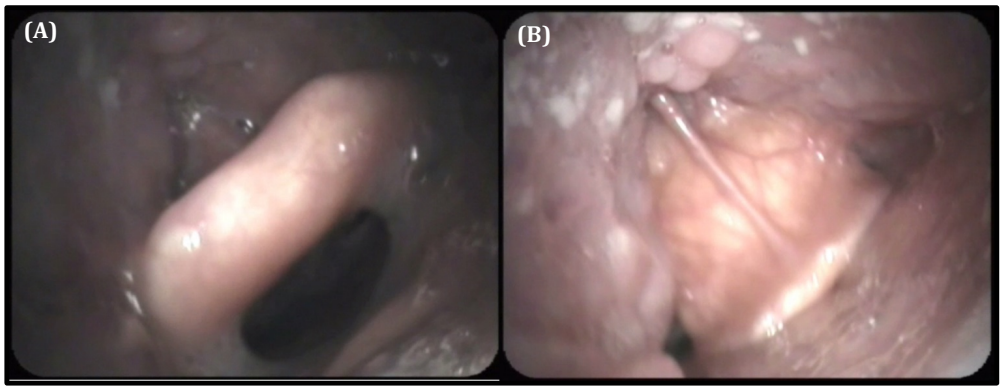


Figure 5. A tongue base collapse due to lingual tonsil hypertrophy (A, B and C)

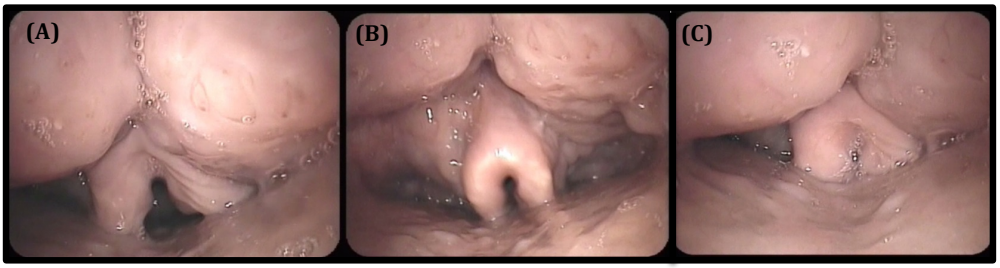
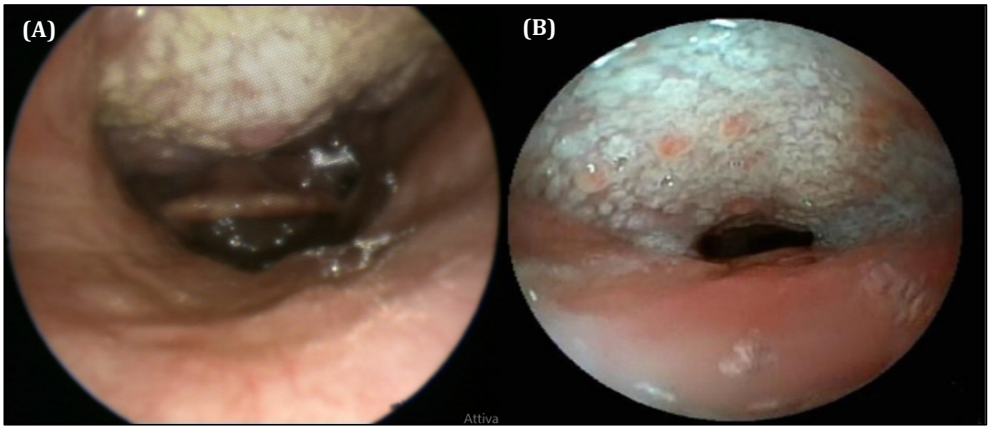


Figure 6. A complete antero-posterior collapse (B) of the level of the tongue base collapse due to muscle relaxation



Conservative treatment

Life style alterations

Standard recommendations in OSA patients include weight loss in overweight patients (BMI > 25kg/m^2), avoidance of sedatives and alcohol, proper sleep hygiene and cessation of smoking. In OSA patients with a BMI of more than 35 kg/m^2, bariatric surgery has proven to be effective as well in reducing OSA severity when other — more conservative — attempts to lose weight have failed. [71]

CPAP

In 1981, CPAP was introduced for the treatment of patients with OSA. [72] Since then, CPAP is considered the gold standard treatment in patients with moderate to severe OSA. CPAP acts as a pneumatic splint, preventing the UA from collapsing. CPAP has proven to be highly effective in reducing AHI and improvement of quality of life, cognitive function and subjective daytime sleepiness. [73]

Despite its effectiveness in reversing OSA, patients are non-adherent in 29-83% when adherence is defined as at least 4 hours of CPAP usage per night. [74] One out of three patients does not tolerate CPAP. [75] Possible side effects contributing to CPAP intolerance or failure are related to the interface (e.g., skin abrasion from contact with the mask, claustrophobia, mask leak, irritated eyes), pressure (e.g., nasal congestion and rhinorrhea with dryness or irritation of the nasal and pharyngeal membranes, sneezing, gastric and bowel distension, recurrent ear and sinus infections) and negative social impact.

PT

In PP, OSA severity depends on the total sleeping time (TST) in the supine position. Avoidance of the supine position is therefore a valuable therapeutic option. PT is aimed at preventing patients from sleeping in the supine position. Various techniques have been described, but the majority of studies on PT use the so-called tennis ball technique (TBT) where a bulky mass is strapped to the patient's back. [37] Even though TBT has proven to be effective in reducing the AHI and the percentage of TST in the supine position, long-term compliance is poor. This is mainly due to backache, discomfort and no improvement, or even deterioration of sleep quality and/or daytime alertness. [37, 76] Compliance rates of TBT reported in the literature range from 40-70% short-term to only 10 % at long-term follow-up.[37, 77-79]

Recent developments have seen the introduction of a new generation of small, lightweight, battery-powered vibro-tactile devices, which are either attached to the neck or chest. [13, 37, 48, 80] When the supine position is identified, these devices provide a vibrating stimulus aiming to turn the patient to a non-supine sleeping position. In a recent meta-analysis, data for studies reporting on the effect of

new-generation devices for PT were combined. The pooled mean reduction in AHI was 11.3 events/h (54%) and the pooled mean reduction in percentage of TST in supine position was 33.6%; a mean difference of 84%. [81] Short-term compliance is high, varying from 76% to 96%, when defined as at least 4 hours of use per night during 7 days a week.[80, 82, 83] Long-term compliance is varying among studies between 64.4 and 75.5%. [84, 85] In another study the proportion of patients using their device more than 4 hours during 5 days a week after 12 months of follow-up was 100%. [86]

MAD

MADs are commonly used in patients with mild to moderate OSA or in case of CPAP failure in moderate and severe disease. In order to prevent UA obstruction, MADs are designed to move the mandible in a forward position. The tongue base, epiglottis and soft palate are protruded and as a consequence, cross-sectional UA dimensions are increased reducing snoring and UA collapse. [87] In addition, MADs may also stimulate the musculature of the palate, tongue and pharynx, resulting in decreased UA resistance. [88] Previous studies have shown that MADs are successful in 84% of patients with mild to moderate OSA and in 69.2% of severe OSA patients. [89] Variety in reported treatment success of MAD is most likely caused by application of different definitions of treatment success.

Combination treatment

During the past few years, combination treatment of non-surgical and surgical interventions has gained more ground. One particular study suggested that in patients with residual supine-dependent OSA under MAD treatment, combination treatment with PT leads to a higher therapeutic efficacy of 50%. [90] Another study also reported effective application of additional PT in patients with residual POSA after UA surgery. [91] PT can also be combined with less invasive forms of UA surgery or can, for example, be applied in patients using CPAP to decrease the pressure needed, potentially improving treatment adherence.

Upper airway surgery

Sleep apnea surgery aims to increase the surface area of the UA, to bypass the pharyngeal airway (e.g., tracheotomy) or to remove specific pathology and can be classified into four types: soft tissue surgery, skeletal surgery, neurostimulatory or airway bypass. After identification of the structures or levels involved in UA obstruction, surgical interventions can address one level or multiple levels in the UA (i.e., multilevel UA surgery). In morbidly obese patients, bariatric surgery is a highly effective treatment for OSA.

Palatal and oropharyngeal procedures

The most commonly performed surgical procedure in OSA patients is still the uvulopalatopharyngoplasty (UPPP) with or without tonsillectomy. UPPP aims to increase the retropalatal lumen and reduce the collapsibility of the pharynx by resection of the free edge of the soft palate and uvula, in combination with a tonsillectomy. The surgical success of the UPPP varies amongst studies and is between 35 and 95.2%. [92] In recent years, new palatal surgical procedures have been described, addressing the lateral pharyngeal wall to enlarge the oropharyngeal lumen, such as the expansion sphincter pharyngoplasty (ESP) and barbed reposition pharyngoplasty (BRP). The latter is a modification of ESP using multiple lateral sustaining loops of barbed suture aiming to create a more stable UA in comparison to the ESP technique, although studies report that BRP is not more effective than ESP. [93-95] Previous studies have shown that both ESP and BRP have better postoperative AHI values and higher surgical success rates than UPPP.

In patients with OSA based on hypertrophic tonsils, a classical tonsillectomy can suffice without additional palatal surgery.

Tongue base surgery

Many surgical procedures to address the area of the tongue base have been described in the literature. These procedures include midline glossectomy [96], radiofrequency thermotherapy of the tongue base [97], genioglossus advancement [98], hyoidthyroidpexia [99], transoral robotic surgery (TORS) [100] and hypoglossal nerve stimulation. [101]

Hypoglossal nerve stimulation

Hypoglossal nerve stimulation, also referred to as selective UA stimulation (UAS), is the most recent, and innovative, development for treatment of moderate to severe OSA patients with CPAP intolerance or failure. By using a unilateral stimulation, selective fibers, which are mainly innervating the tongue protrusors, are stimulated during every breathing cycle. When the cervical spinal nerve (C1) is included, the hyoid bone is also mobilized displaced in an anterosuperior direction. UAS does not only improve UA patency at the level of the tongue base, but also at retropalatal level. It has been suggested that this multilevel effect is caused by palatoglossal coupling. [102] In addition, UAS seems to be successful not only in patients with a primary tongue base collapse, but also in patients with isolated palatal obstruction. [103]

Epiglottis surgery

Several surgical techniques have been developed to resolve epiglottic collapse, including a complete or partial epiglottectomy with a (CO_2) laser. [104-106] Many studies report objective improvement of the AHI, but also several (major) complications — aspiration, bleeding with and without airway compromise, dysphagia and odynophagia — related to epiglottis surgery, which can have serious implications.

Maxillomandibular advancement

Maxillomandibular advancement (MMA) consists of a combination of a Le Fort I osteotomy and bilateral sagittal split osteotomy to enlarge the pharyngeal airway space. Advancement of the maxilla and mandible leads to enlargement of the medial-lateral and anteroposterior dimensions of the UA. [107] This technique is highly effective in treating severe OSA patients with surgical success rates between 80 and 90%. [108-112] Compared to other surgical techniques MMA is considered to be more invasive and in addition associated with considerable morbidity.

OUTLINE OF THIS THESIS

The general aim of this thesis is to assess the role of during DISE and position-dependency in the diagnostic work-up of OSA patients to enable patient-specific treatment planning. In the end, the ultimate goal is to improve treatment outcome of both surgical and non-surgical treatment modalities for OSA.

As previously mentioned, DISE has become an accepted tool in the diagnostic work-up for the evaluation of surgical interventions in OSA patients. More questionable is the use of DISE to predict treatment outcome for non-surgical treatment modalities, such as MAD treatment, PT or a combination of both. **Chapter 2** formed the basis for the studies described in **chapter 3** and **chapter 4.** We introduced a theoretical model to assess the positive effect on UA patency of different maneuvers and compared these outcomes with the effectiveness of MAD treatment, PT and a combination of both published in the literature. Based on the results of the study described in **chapter 2**, we reassessed the similarity between the effect of lateral head rotation and both lateral head and trunk position on UA obstruction in **chapter 3.** In **chapter 4** we focused on the role of DISE for the prediction of MAD treatment outcome focusing on the potential role of a MAD simulation bite used as a screening tool during DISE.

Historically, DISE is performed in the supine position, but with the growing attention for differences in UA collapse and OSA severity between the supine and non-supine position, one could also emphasize the relevance to perform DISE in both positions. The performance of DISE in the lateral position has shed new light on collapse patterns causing UA obstruction. In **chapter 5** the hypothesis was tested that a FE is mainly present in supine position and to a lesser extent when a patient's head is rotated to the lateral position. Currently, OSA caused by a FE is difficult to treat and most treatment options for this type of collapse are mostly lacking. For example, a FE has been linked to CPAP failure, suggesting that the epiglottis is pushed further backwards on application of CPAP. If our hypothesis would be true, PT could be added to the armamentarium for the treatment of OSA caused by a FE. The latter could also underline the relevance of performing DISE for non-surgical interventions since a FE cannot be detected through awake endoscopy.

As previously mentioned, DISE has become an accepted tool in the diagnostic work-up for the evaluation of surgical interventions in OSA patients. Although DISE is performed in most sleep centres before initiating UA surgery, it is not mandatory in the majority of surgical interventions, with exception of UAS. For this type of UA surgery, observations made during DISE are required, since a complete concentric collapse at palatal level has been proven to be a negative predictor for surgical success. In **chapter 6** the short-term effectiveness of UAS in our center was evaluated. In addition, we

analyzed the influence of preoperative DISE findings on surgical success comparing patients with a complete multilevel obstruction and patients with a primarily complete tongue base collapse.

In the second section of this thesis the relevance and role of position-dependency in the diagnostic work-up of OSA patients is outlined. First, in **chapter 7** the hypothesis was tested that PSG apparatus may influence sleeping position causing an overestimation in disease severity, especially in PP. This could potentially lead to unnecessary treatment of patients. Second, when position-dependency could be identified as a predictor for surgical success, this should be taken into consideration when treatment options, including UA surgery, are evaluated. In **chapter 8** a systematic review is presented on the influence of position-dependency on surgical success of different forms of UA surgery. The primary aim of **chapter 9** was to analyze the difference in surgical success in NPP and PP undergoing MMA. Secondly, we evaluated the influence of position-dependency on surgical outcome and the phenomenon of residual POSA in non-responders.

In **chapter 10** the main findings of **chapter 2** through **chapter 9**, general conclusions and suggestions for future research are described.

Chapter 11 provides a summary of this thesis in English and Dutch.

REFERENCES

1. Walker MP. The role of sleep in cognition and emotion. *Ann N Y Acad Sci*. 2009;1156:168-97
2. Walker MP, Stickgold R. Sleep, memory, and plasticity. *Annu Rev Psychol*. 2006;57:139-66
3. Walker MP, Stickgold R, Alsop D, Gaab N, Schlaug G. Sleep-dependent motor memory plasticity in the human brain. *Neuroscience*. 2005;133(4):911-7
4. Kerkhof GA. Epidemiology of sleep and sleep disorders in The Netherlands. *Sleep Med*. 2017;30:229-39
5. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. *Chest*. 2014;146(5):1387-94
6. Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med*. 2017;13(3):479-504
7. Orr JE, Malhotra A, Sands SA. Pathogenesis of central and complex sleep apnoea. *Respirology*. 2017;22(1):43-52
8. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med*. 2012;8(5):597-619
9. Force AAoSMT. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. *Sleep*. 1999;22:667-89
10. Nederlandse Vereniging van Artsen voor Longgeneeskunde en Tuberculose NVvK-heHvhh-hg. Richtlijn diagnostiek en behandeling van obstructief slaapapneu (OSA) bij volwassenen. 2017:1-94
11. Heinzer R, Vat S, Marques-Vidal P, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *The Lancet Respiratory Medicine*. 2015;3(4):310-18
12. Richard W, Kox D, den Herder C, Laman M, van Tinteren H, de Vries N. The role of sleep position in obstructive sleep apnea syndrome. *Eur Arch Otorhinolaryngol*. 2006;263(10):946-50
13. van Maanen JP, Richard W, Van Kesteren ER, et al. Evaluation of a new simple treatment for positional sleep apnoea patients. *J Sleep Res*. 2012;21(3):322-9
14. Heinzer R, Marti-Soler H, Haba-Rubio J. Prevalence of sleep apnoea syndrome in the middle to old age general population. *Lancet Respir Med*. 2016;4(2):e5-6
15. Malhotra A, White DP. Obstructive sleep apnoea. *Lancet*. 2002;360(9328):237-45
16. Pien GW, Fife D, Pack AI, Nkwuo JE, Schwab RJ. Changes in symptoms of sleep-disordered breathing during pregnancy. *Sleep*. 2005;28(10):1299-305

17. Pien GW, Veasey SC. Obstructive sleep apnea and menopause. *Sleep Disorders in Women*. Springer; 2013:325-40

18. Pien GW, Pack AI, Jackson N, Maislin G, Macones GA, Schwab RJ. Risk factors for sleep-disordered breathing in pregnancy. *Thorax*. 2014;69(4):371-7

19. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med*. 2002;165(9):1217-39

20. George CF, Smiley A. Sleep apnea & automobile crashes. *Sleep*. 1999;22(6):790-5

21. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. *New England Journal of Medicine*. 2005;353(19):2034-41

22. Parra O, Arboix A, Montserrat J, Quinto L, Bechich S, Garcia-Eroles L. Sleep-related breathing disorders: impact on mortality of cerebrovascular disease. *European Respiratory Journal*. 2004;24(2):267-72

23. Parra O, Sánchez-Armengol Á, Capote F, et al. Efficacy of continuous positive airway pressure treatment on 5-year survival in patients with ischaemic stroke and obstructive sleep apnea: a randomized controlled trial. *Journal of sleep research*. 2015;24(1):47-53

24. Good DC, Henkle JQ, Gelber D, Welsh J, Verhulst S. Sleep-disordered breathing and poor functional outcome after stroke. *Stroke*. 1996;27(2):252-9

25. Eckert DJ. Phenotypic approaches to obstructive sleep apnoea–new pathways for targeted therapy. *Sleep medicine reviews*. 2018;37:45-59

26. Eckert DJ, White DP, Jordan AS, Malhotra A, Wellman A. Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. *American journal of respiratory and critical care medicine*. 2013;188(8):996-1004

27. Schwab RJ, Gupta KB, Gefter WB, Metzger LJ, Hoffman EA, Pack AI. Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing. Significance of the lateral pharyngeal walls. *Am J Respir Crit Care Med*. 1995;152(5 Pt 1):1673-89

28. Haponik EF, Smith PL, Bohlman ME, Allen RP, Goldman SM, Bleecker ER. Computerized tomography in obstructive sleep apnea. Correlation of airway size with physiology during sleep and wakefulness. *Am Rev Respir Dis*. 1983;127(2):221-6

29. Schwartz AR, Gold AR, Schubert N, Stryzak A. Effect of weight loss on upper airway collapsibility in obstructive sleep apnea1-3. *Am Rev Respir Dis*. 1991;144(3 pt 1):494-98

30. Schwartz AR, Smith PL, Wise RA, Gold AR, Permutt S. Induction of upper airway occlusion in sleeping individuals with subatmospheric nasal pressure. *J Appl Physiol (1985)*. 1988;64(2):535-42

31. Gleadhill IC, Schwartz AR, Schubert N, Wise RA, Permutt S, Smith PL. Upper airway collapsibility in snorers and in patients with obstructive hypopnea and apnea. *Am Rev Respir Dis*. 1991;143(6):1300-3

32. White DP. Pathogenesis of obstructive and central sleep apnea. *Am J Respir Crit Care Med*. 2005;172(11):1363-70

33. Eckert DJ, Younes MK. Arousal from sleep: implications for obstructive sleep apnea pathogenesis and treatment. *J Appl Physiol (1985)*. 2014;116(3):302-13

34. Younes M. Role of arousals in the pathogenesis of obstructive sleep apnea. *Am J Respir Crit Care Med*. 2004;169(5):623-33

35. Eckert DJ, Malhotra A. Pathophysiology of adult obstructive sleep apnea. *Proc Am Thorac Soc*. 2008;5(2):144-53

36. Oksenberg A, Silverberg DS, Arons E, Radwan H. Positional vs nonpositional obstructive sleep apnea patients: anthropomorphic, nocturnal polysomnographic, and multiple sleep latency test data. *Chest*. 1997;112(3):629-39

37. van Maanen JP, Ravesloot MJ, Safiruddin F, de Vries N. The Utility of Sleep Endoscopy in Adults with Obstructive Sleep Apnea: A Review of the Literature. *Current Otorhinolaryngology Reports*. 2013;1(1):1-7

38. Frank MH, Ravesloot MJ, van Maanen JP, Verhagen E, de Lange J, de Vries N. Positional OSA part 1: Towards a clinical classification system for position-dependent obstructive sleep apnoea. *Sleep Breath*. 2015;19(2):473-80

39. Cartwright RD. Effect of sleep position on sleep apnea severity. *Sleep*. 1984;7(2):110-4

40. Heinzer R, Petitpierre NJ, Marti-Soler H, Haba-Rubio J. Prevalence and characteristics of positional sleep apnea in the HypnoLaus population-based cohort. (1878-5506 (Electronic))

41. Mador MJ, Kufel TJ, Magalang UJ, Rajesh SK, Watwe V, Grant BJ. Prevalence of positional sleep apnea in patients undergoing polysomnography. *Chest*. 2005;128(4):2130-7

42. Itasaka Y, Miyazaki S, Ishikawa K, Togawa K. The influence of sleep position and obesity on sleep apnea. *Psychiatry Clin Neurosci*. 2000;54(3):340-1

43. Mo JH, Lee CH, Rhee CS, Yoon IY, Kim JW. Positional dependency in Asian patients with obstructive sleep apnea and its implication for hypertension. *Archives of otolaryngology--head & neck surgery*. 2011;137(8):786-90

44. Teerapraipruk B, Chirakalwasan N, Simon R, et al. Clinical and polysomnographic data of positional sleep apnea and its predictors. *Sleep & breathing = Schlaf & Atmung*. 2012;16(4):1167-72

45. Tanaka F, Nakano H Fau - Sudo N, Sudo N Fau - Kubo C, Kubo C. Relationship between the body position-specific apnea-hypopnea index and subjective sleepiness. (1423-0356 (Electronic))

46. Marklund M, Persson M, Franklin KA. Treatment success with a mandibular advancement device is related to supine-dependent sleep apnea. *Chest*. 1998;114(6):1630-5

47. Permut I, Diaz-Abad M, Chatila W, et al. Comparison of positional therapy to CPAP in patients with positional obstructive sleep apnea. *J Clin Sleep Med*. 2010;6(3):238-43

48. Bignold JJ, Mercer JD, Antic NA, McEvoy RD, Catcheside PG. Accurate position monitoring and improved supine-dependent obstructive sleep apnea with a new position recording and supine avoidance device. *J Clin Sleep Med*. 2011;7(4):376-83

49. Lee SA, Paek JH, Chung YS, Kim WS. Clinical features in patients with positional obstructive sleep apnea according to its subtypes. *Sleep Breath*. 2017;21(1):109-17

50. Kim KT, Cho YW, Kim DE, Hwang SH, Song ML, Motamedi GK. Two subtypes of positional obstructive sleep apnea: Supine-predominant and supine-isolated. *Clin Neurophysiol*. 2016;127(1):565-70

51. Lee CH, Kim DK, Kim SY, Rhee CS, Won TB. Changes in site of obstruction in obstructive sleep apnea patients according to sleep position: a DISE study. *The Laryngoscope*. 2015;125(1):248-54

52. Victores AJ, Hamblin J, Gilbert J, Switzer C, Takashima M. Usefulness of sleep endoscopy in predicting positional obstructive sleep apnea. *Otolaryngol Head Neck Surg*. 2014;150(3):487-93

53. Vonk PE, Ravesloot MJL, Kasius KM, van Maanen JP, de Vries N. Floppy epiglottis during drug-induced sleep endoscopy: an almost complete resolution by adopting the lateral posture. *Sleep Breath*. 2019

54. van Kesteren ER, van Maanen JP, Hilgevoord AA, Laman DM, de Vries N. Quantitative effects of trunk and head position on the apnea hypopnea index in obstructive sleep apnea. *Sleep*. 2011;34(8):1075-81

55. Zhu K, Bradley TD, Patel M, Alshaer H. Influence of head position on obstructive sleep apnea severity. *Sleep Breath*. 2017;21(4):821-28

56. Doneh B. Epworth Sleepiness Scale. *Occup Med (Lond)*. 2015;65(6):508

57. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991;14(6):540-5

58. Lopes C, Esteves AM, Bittencourt LR, Tufik S, Mello MT. Relationship between the quality of life and the severity of obstructive sleep apnea syndrome. *Braz J Med Biol Res*. 2008;41(10):908-13.

59. Weaver EM, Kapur V, Yueh B. Polysomnography vs self-reported measures in patients with sleep apnea. *Arch Otolaryngol Head Neck Surg*. 2004;130(4):453-8

60. Sforza E, Pichot V, Martin MS, Barthelemy JC, Roche F. Prevalence and determinants of subjective sleepiness in healthy elderly with unrecognized obstructive sleep apnea. *Sleep Med*. 2015;16(8):981-6

61. Randerath W, Bassetti CL, Bonsignore MR, et al. Challenges and perspectives in obstructive sleep apnoea: Report by an ad hoc working group of the Sleep Disordered Breathing Group of the European Respiratory Society and the European Sleep Research Society. *Eur Respir J*. 2018;52(3)

62. De Vito A, Carrasco Llatas M, Ravesloot MJ, et al. European position paper on drug-induced sleep endoscopy: 2017 Update. *Clinical Otolaryngology*. 2018;43(6):1541-52

63. Shteamer JW, Dedhia RC. Sedative choice in drug-induced sleep endoscopy: a neuropharmacology-based review. *The Laryngoscope*. 2017;127(1):273-79

64. Hohenhorst W, Ravesloot M, Kezirian E, De Vries N. Drug-induced sleep endoscopy in adults with sleep-disordered breathing: technique and the VOTE classification system. *Operative Techniques in Otolaryngology-Head and Neck Surgery*. 2012;23(1):11-18

65. Eichler C, Sommer JU, Stuck BA, Hormann K, Maurer JT. Does drug-induced sleep endoscopy change the treatment concept of patients with snoring and obstructive sleep apnea? *Sleep Breath*. 2013;17(1):63-8

66. Johal A, Battagel JM, Kotecha BT. Sleep nasendoscopy: a diagnostic tool for predicting treatment success with mandibular advancement splints in obstructive sleep apnoea. *Eur J Orthod*. 2005;27(6):607-14

67. Johal A, Hector MP, Battagel JM, Kotecha BT. Impact of sleep nasendoscopy on the outcome of mandibular advancement splint therapy in subjects with sleep-related breathing disorders. *J Laryngol Otol*. 2007;121(7):668-75

68. Vroegop AV, Vanderveken OM, Dieltjens M, Wouters K, Saldien V, Braem MJ. Sleep endoscopy with simulation bite for prediction of oral appliance treatment outcome. *Journal of sleep research*. 2013;22(3):348-55

69. Vanderveken OM, Vroegop AV, van de Heyning PH, Braem MJ. Drug-induced sleep endoscopy completed with a simulation bite approach for the prediction of the outcome of treatment of obstructive sleep apnea with mandibular repositioning appliances. *Operative Techniques in Otolaryngology-head and neck surgery*. 2011;22(2):175-82

70. Kezirian EJ, Hohenhorst W, de Vries N. Drug-induced sleep endoscopy: the VOTE classification. *Eur Arch Otorhinolaryngol*. 2011;268(8):1233-36

71. Sarkhosh K, Switzer NJ, El-Hadi M, Birch DW, Shi X, Karmali S. The impact of bariatric surgery on obstructive sleep apnea: a systematic review. *Obes Surg*. 2013;23(3):414-23

72. Sullivan C, Berthon-Jones M, Issa F, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. *The Lancet*. 1981;317(8225):862-65

73. Giles TL, Lasserson TJ, Smith B, White J, Wright JJ, Cates CJ. Continuous positive airways pressure for obstructive sleep apnoea in adults. *Cochrane Database of Systematic Reviews*. 2006(1)

74. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. *Proc Am Thorac Soc*. 2008;5(2):173-8

75. Richard W, Venker J, den Herder C, et al. Acceptance and long-term compliance of nCPAP in obstructive sleep apnea. *Eur Arch Otorhinolaryngol*. 2007;264(9):1081-6

76. Ravesloot MJ, Benoist L, van Maanen P, de Vries N. Novel positional devices for the treatment of positional obstructive sleep apnea, and how this relates to sleep surgery. *Sleep-Related Breathing Disorders*. Karger Publishers; 2017:28-36

77. Bignold JJ, Deans-Costi G, Goldsworthy MR, et al. Poor long-term patient compliance with the tennis ball technique for treating positional obstructive sleep apnea. *J Clin Sleep Med*. 2009;5(5):428-30

78. Oksenberg A, Silverberg D, Offenbach D, Arons E. Positional therapy for obstructive sleep apnea patients: A 6-month follow-up study. *The Laryngoscope*. 2006;116(11):1995-2000

79. Heinzer RC, Pellaton C, Rey V, et al. Positional therapy for obstructive sleep apnea: an objective measurement of patients' usage and efficacy at home. *Sleep medicine*. 2012;13(4):425-8

80. Levendowski DJ, Seagraves S, Popovic D, Westbrook PR. Assessment of a neck-based treatment and monitoring device for positional obstructive sleep apnea. *J Clin Sleep Med*. 2014;10(8):863-71

81. Ravesloot M, White D, Heinzer R, Oksenberg A, Pépin J. Efficacy of the New Generation of Devices for Positional Therapy for Patients with Positional Obstructive Sleep Apnea: A Systematic Review of the Literature and Meta-Analysis. *Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine*. 2017

82. Eijsvogel MM, Ubbink R, Dekker J, et al. Sleep position trainer versus tennis ball technique in positional obstructive sleep apnea syndrome. *J Clin Sleep Med*. 2015;11(2):139-47

83. van Maanen JP, Meester KA, Dun LN, et al. The sleep position trainer: a new treatment for positional obstructive sleep apnoea. *Sleep and Breathing*. 2013;17(2):771-79

84. van Maanen JP, de Vries N. Long-term effectiveness and compliance of positional therapy with the sleep position trainer in the treatment of positional obstructive sleep apnea syndrome. *Sleep*. 2014;37(7):1209-15

85. Laub RR, Tonnesen P, Jennum PJ. A Sleep Position Trainer for positional sleep apnea: a randomized, controlled trial. *J Sleep Res*. 2017

86. de Ruiter MHT, Benoist LBL, de Vries N, de Lange J. Durability of treatment effects of the Sleep Position Trainer versus oral appliance therapy in positional OSA: 12-month follow-up of a randomized controlled trial. *Sleep Breath*. 2017

87. Tsuiki S, Lowe AA, Almeida FR, Kawahata N, Fleetham JA. Effects of mandibular advancement on airway curvature and obstructive sleep apnoea severity. *Eur Respir J*. 2004;23(2):263-8

88. Chan AS, Lee RW, Cistulli PA. Dental appliance treatment for obstructive sleep apnea. *Chest*. 2007;132(2):693-9

89. Hoekema A, Stegenga B, Wijkstra PJ, van der Hoeven JH, Meinesz AF, de Bont LG. Obstructive sleep apnea therapy. *J Dent Res*. 2008;87(9):882-7

90. Dieltjens M, Vroegop AV, Verbruggen AE, et al. A promising concept of combination therapy for positional obstructive sleep apnea. *Sleep Breath*. 2015;19(2):637-44

91. Benoist LB, Verhagen M, Torensma B, van Maanen JP, de Vries N. Positional therapy in patients with residual positional obstructive sleep apnea after upper airway surgery. *Sleep Breath*. 2016

92. Stuck BA, Ravesloot MJ, Eschenhagen T, de Vet H, Sommer JU. Uvulopalatopharyngoplasty with or without tonsillectomy in the treatment of adult obstructive sleep apnea–A systematic review. *Sleep medicine*. 2018;50:152-65

93. Cammaroto G, Montevecchi F, D'Agostino G, et al. Palatal surgery in a transoral robotic setting (TORS): preliminary results of a retrospective comparison between uvulopalatopharyngoplasty (UPPP), expansion sphincter pharyngoplasty (ESP) and barbed repositioning pharyngoplasty (BRP). *Acta otorhinolaryngologica Italica : organo ufficiale della Societa italiana di otorinolaringologia e chirurgia cervico-facciale*. 2017

94. Vicini C, Montevecchi F, Pang K, et al. Combined transoral robotic tongue base surgery and palate surgery in obstructive sleep apnea-hypopnea syndrome: Expansion sphincter pharyngoplasty versus uvulopalatopharyngoplasty. *Head & neck*. 2014;36(1):77-83

95. Montevecchi F, Meccariello G, Firinu E, et al. Prospective multicentre study on barbed reposition pharyngoplasty standing alone or as a part of multilevel surgery for sleep apnoea. *Clinical Otolaryngology*. 2018;43(2):483-88

96. Fujita S, Woodson BT, Clark JL, Wittig R. Laser midline glossectomy as a treatment for obstructive sleep apnea. *The Laryngoscope*. 1991;101(8):805-9

97. Stuck BA, Kopke J, Maurer JT, et al. Lesion formation in radiofrequency surgery of the tongue base. *Laryngoscope*. 2003;113(9):1572-6

98. Riley RW, Powell NB, Guilleminault C. Obstructive sleep apnea syndrome: a surgical protocol for dynamic upper airway reconstruction. *J Oral Maxillofac Surg*. 1993;51(7):742-7; discussion 48-9

99. Riley RW, Powell NB, Guilleminault C. Obstructive sleep apnea and the hyoid: a revised surgical procedure. *Otolaryngol Head Neck Surg*. 1994;111(6):717-21

100. Vicini C, Montevecchi F, Gobbi R, De Vito A, Meccariello G. Transoral robotic surgery for obstructive sleep apnea syndrome: Principles and technique. *World J Otorhinolaryngol Head Neck Surg*. 2017;3(2):97-100

101. Strollo PJ, Jr., Soose RJ, Maurer JT, et al. Upper-airway stimulation for obstructive sleep apnea. *N Engl J Med*. 2014;370(2):139-49

102. Heiser C, Edenharter G, Bas M, Wirth M, Hofauer B. Palatoglossus coupling in selective upper airway stimulation. *The Laryngoscope*. 2017;127(10):E378-E83

103. Mahmoud AF, Thaler ER. Outcomes of Hypoglossal Nerve Upper Airway Stimulation among Patients with Isolated Retropalatal Collapse. *Otolaryngol Head Neck Surg*. 2019:194599819835186

104. Catalfumo FJ, Golz A, Westerman ST, Gilbert LM, Joachims HZ, Goldenberg D. The epiglottis and obstructive sleep apnoea syndrome. *J Laryngol Otol*. 1998;112(10):940-3

105. Golz A, Goldenberg D, Westerman ST, et al. Laser partial epiglottidectomy as a treatment for obstructive sleep apnea and laryngomalacia. *Ann Otol Rhinol Laryngol*. 2000;109(12 Pt 1):1140-5

106. Bourolias C, Hajiioannou J, Sobol E, Velegrakis G, Helidonis E. Epiglottis reshaping using CO2 laser: a minimally invasive technique and its potent applications. *Head Face Med*. 2008;4:15

107. Gokce SM, Gorgulu S, Gokce HS, Bengi AO, Karacayli U, Ors F. Evaluation of pharyngeal airway space changes after bimaxillary orthognathic surgery with a 3-dimensional simulation and modeling program. *Am J Orthod Dentofacial Orthop*. 2014;146(4):477-92

108. Holty JE, Guilleminault C. Maxillomandibular advancement for the treatment of obstructive sleep apnea: a systematic review and meta-analysis. *Sleep Med Rev*. 2010;14(5):287-97

109. Prinsell JR. Maxillomandibular advancement surgery for obstructive sleep apnea syndrome. *J Am Dent Assoc*. 2002;133(11):1489-97; quiz 539-40

110. Prinsell JR. Maxillomandibular advancement surgery in a site-specific treatment approach for obstructive sleep apnea in 50 consecutive patients. *Chest*. 1999;116(6):1519-29

111. Hoekema A, de Lange J, Stegenga B, de Bont LG. Oral appliances and maxillomandibular advancement surgery: an alternative treatment protocol for the obstructive sleep apnea-hypopnea syndrome. *J Oral Maxillofac Surg*. 2006;64(6):886-91

112. Goh YH, Lim KA. Modified maxillomandibular advancement for the treatment of obstructive sleep apnea: a preliminary report. *Laryngoscope*. 2003;113(9):1577-82

Towards a prediction model for drug-induced sleep endoscopy as selection tool for oral appliance treatment and positional therapy in obstructive sleep apnea

2

P.E. Vonk, A.M.E.H. Beelen, N. de Vries

Sleep Breath. 2018 Dec;22(4):901-907

ABSTRACT

Purpose: To evaluate the effect of different passive maneuvers on upper airway patency during drug-induced sleep endoscopy (DISE) compared to recent literature on treatment outcomes of positional therapy (PT), oral appliance therapy (OAT) and combined treatment in obstructive sleep apnea (OSA) patients.

Methods: A retrospective, single-centre cohort study including a consecutive series of 200 OSA patients. All patients underwent DISE with and without manually performed jaw thrust and lateral head rotation by using the VOTE classification. The effect of these maneuvers was analyzed by using the sum VOTE score comparing non-positional (NPP) and positional OSA patients (PP).

Results: 200 Patients were included (80.5% male) with a mean age of 50.1 ± 11.7 years, a BMI of 27.0 ± 3.1 kg/m^2 and a median AHI of 19.2 events per hour. Forty-four per cent of the patients were NPP; of the remaining 56%, 34% was diagnosed with supine isolated and 66% with supine predominant POSA. Manually performed jaw thrust showed a reduction of sum VOTE score of 66.7% in all subgroups. The effect of lateral head rotation was a reduction of 33.3% in NPP and supine predominant PP and 50% in supine isolated PP. Combining these maneuvers a reduction of more than 75% was seen in all patients.

Conclusions: The present model leaves room for improvement. The effect of manually performed jaw thrust is greater and the effect of lateral head rotation alone is less than what was expected compared to recent literature on treatment outcome of OAT, PT and combined treatment.

Key words: Diagnostics, drug-induced sleep endoscopy, obstructive sleep apnea, treatment outcome

INTRODUCTION

Obstructive sleep apnea (OSA) is a sleep related breathing disorder characterized by recurrent episodes of partial or complete collapse of the upper airway, which results in a decrease or cessation in airflow during sleep.[1] This can lead to fragmented sleep accompanied by snoring, excessive daytime sleepiness or restless sleep. The prevalence of OSA is high. 49.7% in men and 23.4% in women have an apnea-hypopnea index (AHI) of more than 15 per hour. When excessive daytime sleepiness is included in the definition with an AHI of 5 or more, the prevalence is 12.5% (men) and 5.9% (women). [2, 3] Continuous positive airway pressure (CPAP) is considered to be the gold-standard therapy in case of moderate to severe OSA. In patients with mild to moderate OSA, other treatment options include oral appliance therapy (OAT), upper airway surgery (UAS), positional therapy (PT) or a combination of different treatments. [4-7] Such other treatments are also indicated in case of CPAP failure, which occurs in approximately 35% of patients. [8]

When alternatives to CPAP are considered, in particular UAS, evaluation of the upper airway is of paramount importance. Drug-Induced Sleep Endoscopy (DISE) is a dynamic and unique diagnostic tool, which is gradually gaining acceptance as a selection tool in OSA patients in whom UAS is considered. [9, 10] DISE provides information regarding the degree, level(s) and configuration of obstruction of the collapsible segment of the upper airway. Less well explored, and perhaps more controversial, is the role of DISE in patients in whom other OSA treatment modalities, such as OAT, PT, combined treatment (e.g., OAT and PT), and PT after UAS, are considered.

Presently, in case OAT is considered, patients are mostly simply prescribed the latter without additional evaluation of the upper airway through DISE. In this pragmatic approach, OAT is effective in 30-81%. [11] The alternative would be to perform a DISE first and mimic the effect of OAT (e.g. by performing a jaw thrust), and only commence with OAT in case the airway opens with jaw thrust. Opinions concerning the performance of jaw thrust during DISE vary among studies and evidence on the positive and negative predictive values of DISE with jaw thrust are however so far limited. [12, 13, 14] Vroegop et al. investigated the use of simulation bites and found significant association between 'positive effect of the simulation bite and treatment response to OAT, but at this point the use of simulation bites is not common practice and mainly used for research purposes. [15]

Similarly, in case PT is considered, it might be useful to compare DISE findings in lateral and supine position. Recent research from the groups from Antwerp and Amsterdam has shown that in mild to

moderately severe positional OSA (POSA) the effect of OAT and PT are comparable, with roughly 50% reduction in AHI, while combined OAT and PT, leads to a further 50% reduction in AHI. [7, 16, 17]
When focusing on the correlation between AHI and observations made during DISE, several studies show similar results. In a study by Vroegop et al. they concluded that higher AHI values are associated with a complete collapse observed during DISE, with in particular a complete concentric collapse (CCC) at palatal level and a complete lateral hypopharyngeal collapse. Lower AHI was associated with a higher probability of a partial concentric collapse at palatal level. [18] Ravesloot et al. found similar results and suggested that a multilevel collapse, a complete collapse and a tongue base collapse are associated with a higher AHI in OSA patients. [19]

Our department serves as a referral centre for patients who seek alternatives to CPAP treatment. In such patients we presently perform DISE in four positions: supine, supine with jaw thrust (to mimic the effect of OAT), lateral head rotation (to mimic the effect of PT), and jaw thrust with head rotation (to mimic combined treatment with OAT and PT). For the present study, we composed a 3 points model, based on the VOTE classification system [9], in which the effects of these maneuvers were retrospectively analyzed. In case of a perfect fit of the model, the effect of jaw thrust and head rotation would be equal, (50% reduction in points) with another 50% reduction in case of combined maneuvers.

We hypothesized that the effect of these maneuvers would correspond with recent literature on treatment outcomes of PT, OAT and combined treatment and as such could serve as a tool in a patient specific treatment planning. [7, 16, 17] When our hypothesis is correct, DISE with these maneuvers could be of additional value to predict treatment outcome of OAT, PT or combined treatment.

METHODS

Patients

We performed a retrospective, single-centre cohort study including a consecutive series of 200 OSA patients, confirmed by polysomnography, who underwent DISE between August 2016 and February 2017. Patients were excluded from analysis when aged < 18 years, medical history of congenital abnormalities of the upper airway, DISE performed with CPAP or OAT and when DISE results were inconclusive due to mucus hypersecretion.

Patients were identified as being non-positional (NPP) or positional (PP) using a modified version of Cartwright's criteria [20], namely a difference of 50% or more in AHI between supine and non-supine positions and a total sleeping time in worse sleeping position of > 10% and < 90%. In PP the

distinction was made between supine isolated (non-supine AHI < 5) and supine predominant (non-supine AHI ≥ 5). [21]

In accordance with the Declaration of Helsinki, the study protocol was approved by the Medical Ethical Committee. Data on study subjects was collected and stored anonymously to protect personal information.

DISE procedure

DISE was performed in patients in whom alternatives to CPAP were considered, with in particular patients eligible for UAS, but also to evaluate the possible effect of other conservative treatments such as OAT or PT or combination of both. In some patients DISE was performed to identify reasons for previous treatment failure (e.g. OAT or CPAP).

DISE was performed in a quiet outpatient endoscopy room with dimmed lights and standard anesthetic equipment. The procedure was executed by two trained ENT residents (PV and AB), with a nurse anesthetist managing sedation. The desired level of propofol concentration was controlled by the nurse anesthetist by using a target-controlled infusion (TCI) pump. Prior to the propofol, 2 cc lidocaine was given intravenously to prevent pain caused by the infusion of propofol. On indication glycopyrrolate was administered before the procedure to avoid excessive secretions, which may interfere with the quality of the DISE video. Propofol concentration was gradually increased until proper sedation was achieved. Proper sedation was reached when the patient began to snore or showed hyporesponsiveness to verbal and tactile stimuli. The upper airway was observed by using a flexible laryngoscopy starting in supine position with and without jaw thrust. Subsequently, lateral head rotation to the right was performed, again with and without jaw thrust.

Classification system

The VOTE system was used to evaluate four different levels and structures that can contribute to upper airway obstruction, namely velum (V), oropharynx (O), tongue base (T) and epiglottis (E). The degree of obstruction was defined by the following categories: no obstruction (collapse less than 50%), partial (collapse between 50-75%, typically with vibration) or complete collapse (>75%) and X if no observation could be made. The configuration of the obstruction may be anterior-posterior, lateral or concentric. **Table 1** shows an overview of the different levels, the degree of obstruction and the possible configurations at each level.

Table 1. The VOTE classification [9]

Structure	Degree of obstruction[a]	Configuration[c]		
		A-P	Lateral	Concentric
Velum				
Oropharynx[b]				
Tongue Base				
Epiglottis				

A-P Antero-posterior

a. Degree of obstruction: 0 no obstruction; 1 partial obstruction; 2 complete obstruction
b. Oropharynx obstruction can be distinguished as related solely to the tonsils or including the lateral walls
c. Configuration noted for structures with degree of obstruction > 0

In the present model, we regarded obstruction at the four levels equally important, but concentric collapse at velum level as more severe than lateral or antero-posterior (A-P) collapse, because literature has shown that a CCC of the palate correspond with a less successful treatment outcome when applying OAT or UAS. [22, 23] Therefore we introduced a 3 point scale: no obstruction: 0 points, partial lateral or A-P obstruction: 1 point, partial concentric obstruction at velum level: 2 points, complete lateral or A-P obstruction: 2 points, complete concentric obstruction at velum level: 4 points.

Statistical analysis

Statistical analysis was performed using SPSS (version 21), SPSS Inc., Chicago, IL). Quantitative data are reported as mean ± SD or as median (Q1, Q3) when not normally distributed.

To analyze the effect of different passive maneuvers on upper airway caliber, the score that describes the degree of obstruction (0, 1 and 2) at the four separate structures (V, O, T and E) was used. For the comparison of overall effect of these maneuvers the total sum VOTE score was calculated by summing the different scores for degree of obstruction at each site. The total sum VOTE score is reported as median (Q1, Q3), since it is a sum of categorical data and therefore must be analyzed as ordinal data.

Comparison of data on total sum VOTE scores in different positions, with and without maneuvers, between the different subgroups was carried out by using the Wilcoxon signed rank test in case of paired data a chi-squared test in case of unpaired data. A p value of <0.05 was considered to indicate statistical significance.

RESULTS

In total 200 patients were included in this study; 80.5% was male. The mean age was 50.1 ± 11.7 years, with a BMI of 27.0 ± 3.1 kg/m^2 and a median AHI of 19.2 events per hour. Forty-four per cent of the patients were NPP; of the remaining 56%, 34% was diagnosed with supine isolated and 66% with supine predominant POSA. As expected, PP had a significant lower AHI in non-supine position and spent more time in supine position. Patients with supine isolated POSA showed a significantly lower total AHI, a lower AHI in supine and non-supine position and spent more time in supine position compared to supine predominant PP. Baseline characteristics are given in **tables 2 and 3**.

Table 2. Baseline characteristics total population and NPP versus PP

	Total	**NPP**	**PP**	**NPP versus PP p value**
Number (%)	200	88 (44)	112 (56)	88 vs 112
Age (years)	50.1 ± 11.7	52.4 ± 10.8	48.2 ± 12.1	0.010*
Male / Female	161/39	68/20	93/19	0.307
BMI (kg/m^2)	27.0 ± 3.1	27.0 ± 3.1	27.1 ± 3.2	0.832
Total AHI (events/hour)	19.2 (11.7, 31.0) °	21.0 (14.0, 38.4) °	18.3 (10.7, 27.3)°	0.073
Supine AHI (events/hour)	34.5 (18.4, 59.0) °	25.7 (15.9, 61.4) °	37.8 (22.6, 57.9) °	0.095
Non supine AHI (events/hour)	10.8 (5.4, 22.8) °	19.4 (9.9, 34.8) °	7.3 (3.4, 14.7) °	0.00*
Supine sleeping time (%)	31.5 (16.6, 50.2) °	21.4 (3.7, 44.4) °	35.4 (22.0, 50.5) °	0.001*

NPP non-positional obstructive sleep apnea patients *PP* positional obstructive sleep apnea patients *BMI* Body Mass index *AHI* apnea-hypopnea index

*° Median (Q1, Q3); *p value < 0.05*

Table 3. Baseline characteristics PP supine isolated versus PP supine predominant

N=112	**Supine isolated**	**Supine predominant**	**Supine isolated versus supine predominant p value**
Number (%)	38 (34)	74 (66)	38 vs 74
Age (years)	46.1 ± 11.0	49.2 ± 12.5	0.196
Male / Female	29/9	64/10	0.175
BMI (kg/m$^{2)}$	26.3 ± 3.2	27.4 ± 3.2	0.087
Total AHI (events/hour)	8.8 (6.2, 16.3) °	23.0 (15.9, 33.3) °	0.00*
Supine AHI (events/hour)	19.1 (11.4, 34.0) °	47.7 (33.6, 63.8) °	0.00*
Non supine AHI (events/hour)	2.5 (1.6, 3.5) °	10.8 (7.4, 19.4) °	0.00*
Supine sleeping time (%)	45.0 (33.6, 64.9) °	30.0 (21.0, 45.5) °	0.002*

PP positional obstructive sleep apnea patients *BMI* Body Mass index *AHI* apnea-hypopnea index

° *Median (Q1, Q3); *p value < 0.05*

In all subgroups the median total sum VOTE score in supine position was 6.0 and respectively 2.0 when jaw thrust was added, a significant reduction of 66.7% (p = 0.00). In NPP and supine predominant PP the median total sum VOTE score of 6.0 in supine position showed a significant reduction of 2 points (33.3%) when lateral head rotation was performed (p = 0.00). This in contrast to patients with supine isolated POSA, where a significant reduction was found (p = 0.00) of 50% (6.0 versus 3.0). When comparing the effect of lateral head rotation in supine isolated and supine predominant PP, a significant difference was found in favour of the supine isolated group (p = 0.03). When both maneuvers were combined (lateral head rotation and jaw thrust) the median total sum VOTE score in all subgroups changed from 6.0 in supine position to 1.0 (p = 0.00), except for the supine isolated PP group, which showed a significant reduction to 0.5 (p = 0.00), but this difference was not significant comparing supine isolated and supine predominant PP (p = 0.682).

An overview of the different total sum VOTE scores in different positions with and without maneuvers is presented in **table 4.**

Table 4. Total sum VOTE score in different positions with and without maneuvers

	Total **N=200**	**NPP** **N=88**	**PP** **N=112**	**PP supine isolated** **N=38**	**PP supine predominant** **N=74**
Supine	6.0 (4.0, 6.0)	6.0 (4.0, 6.0)	6.0 (4.0, 6.0)	6.0 (4.0, 6.0)	6.0 (5.0, 7.0)
Supine + jaw thrust	2.0 (1.0, 3.0)	2.0 (0.0, 2.0)	2.0 (1.0, 3.0)	2.0 (1.0, 2.0)	2.0 (1.0, 3.0)
Lateral head rotation	4.0 (3.0, 6.0)	4.0 (3.0, 6.0)	4.0 (3.0, 6.0)	3.0 (2.0, 5.5)	4.0 (3.0, 6.0)
Lateral head rotation + jaw thrust	1.0 (0.0, 2.0)	1.0 (0.0, 3.0)	1.0 (0.0, 2.0)	0.5 (0.0, 2.0)	1.0 (0.0, 2.0)

Values described as median (Q1, Q3)

NPP non-positional obstructive sleep apnea patients *PP* positional dependent obstructive sleep apnea patients

DISCUSSION

DISE is a diagnostic tool for upper airway evaluation in patients diagnosed with OSA. In many cases DISE findings change patient management and evidence is accumulating that DISE provides valuable information to predict treatment response and surgical success. [24, 25] Different passive maneuvers can be performed during DISE with the intent to predict treatment response of current available treatment modalities. In the present study we evaluate the additional value of DISE including maneuvers for PT, OAT or a combination of both.

A meta-analysis performed by Ravesloot et al. evaluated the effectiveness of PT in improving sleep study variables in positional OSA. The results of six studies were used for analysis and showed that total AHI was significantly reduced when PT was applied from a mean of 21.8 ± 7.2 to 9.9 ± 10.6, a difference of 53.6%. [26]

Several studies have shown that OAT is effective in both reducing AHI and decreasing OSA symptoms. [11, 27] A study by Dieltjens et al. prospectively evaluated the treatment response of a titratable oral appliance (OA). They found a success rate of 55.7%, a decrease of total AHI of more than 50% and a total AHI of less than 10. The effectiveness of combined treatment with OAT + SPT has also prospectively been investigated. Both OAT and SPT were individually effective in reducing AHI with approximately 50%, while the combination of SPT + OAT further reduced total AHI, with another 50% compared to SPT or OAT alone, leading to in total approximately 75% reduction. [17]

In the model we tested in the present study, we regarded obstruction at the four levels (Velum, Oropharynx, Tongue base and Epiglottis) equally important, but a concentric collapse as more severe than lateral or antero-posterior collapse, since it has been shown that a CCC at palatal level corresponds to a worse treatment outcome than A-P or lateral collapse.
Vanderveken et al. found that the overall treatment success with hypoglossal nerve stimulation in patients without a CCC at palatal level was 81%, while treatment success could not be achieved in the presence of a CCC of the palate. [23] In a study by Koutsourelakis et al. similar results were found. They concluded that non-responders to UAS had a higher occurrence of a CCC at palatal level compared to responders. [22]

When interpreting our results, it must be taken into account that the reduction in total sum VOTE score is calculated by summing the median score of the presence of obstruction at the four levels. Therefore, “reduction” actually must be interpreted as a left shift of the median and distribution of the data. If our model would have a perfect fit, the reduction by either performing the jaw thrust and

with head rotation would both give a 50% reduction in points. Jaw thrust however gave a more than 50% reduction. As expected a reduction of a 50% was seen in supine isolated PP when lateral head rotation was performed, but in contrast to what was hypothesized, a reduction of less than 50% was seen in supine predominant PP. The difference in results between supine isolated and supine predominant could might be explained by the greater difference between the supine and non-supine AHI in supine isolated PP. Previous studies also demonstrate an important influence of head position on the AHI, independently of trunk position and sleep stage, but at this point the effect of having supine isolated or supine predominant POSA needs to be further unravelled. [28, 29]
The estimated 75% reduction of the combination of those two maneuvers was almost as predicted, but higher than expected, probably based on the erroneously product of the overestimation of jaw thrust and underestimation of head rotation in some groups.

We performed a manual jaw thrust and tried to protrude the mandible less than 100%, aiming at roughly 50-75% protrusion. We are aware that this is a very unprecise maneuver. The predictive value of manually performed jaw thrust on treatment response to OAT varies between different studies. Johal et al. found a good correlation between the maneuver and treatment success rate. [12, 13] Eichler et al. also concluded that the effect of mandibular advancement can be shown during DISE. [30] In contrast, Vanderveken et al. and Vroegop et al. have been questioning the correlation between the effect of the chin lift maneuver during DISE and treatment success of OAT and suggested the use of a simulation bite during DISE, which tends to better predict response to OAT. [14, 15]

The present study indeed confirms the suspicion that manual jaw thrust leads to an overestimation of an OAT effect, because in this study we found a reduction of 66.7% when jaw thrust was added instead of the expected effect of 50%.

We previously reported two DISE studies on the effect of lateral rotation of the head alone and of both head and trunk. [31, 32] These studies suggested that the effect of head rotation alone, and of head and trunk rotation combined were almost comparable, in terms of level(s) and direction of obstruction. We were less convinced that the quantitative effect was equal, but for practical reasons - head rotation is much easier to carry out than head and trunk rotation combined -, in clinical practice lateral head rotation was subsequently adopted. Still, we remained critical since we are aware that not all patients are capable of a full 90% head rotation.

In this study the range of individual head rotation was not routinely tested before performing DISE. When the maximum of lateral head rotation was limited, an annotation was made, but patients were not excluded in this study. This physical limitation might lead to an underestimation of the effect of

lateral head rotation. The present study confirms the suspicion that head rotation alone might give less improvement than expected.

Overall, NPP tend to have more severe OSA compared to PP and the incidence of POSA increases when the OSA severity decreases. [33-35] Previous study also showed that a multilevel collapse is associated with higher AHI and that a tongue base collapse or epiglottal collapse is associated with POSA. [19] Based on these findings, one would expect a higher sum VOTE score in NPP compared to PP.

In contrast to what was expected, similar results were found in NPP and PP when comparing the sum VOTE score in different positions. We believe, that this could be explained by several reasons.

First of all, patients undergoing DISE are usually diagnosed with mild to moderate OSA, since CPAP is still the gold-standard therapy in case of severe OSA. Therefore, DISE usually is not performed in severe OSA patients, unless they experience CPAP failure/intolerance or when UAS is considered. This selection in patients could influence our results, because as mentioned, the prevalence of POSA decreases as the severity of OSA increases.

Secondly, in our study population no significant difference was found in total and supine AHI. Although a significant difference was found between non-supine AHI in NPP and PP, NPP did show a lower AHI in non-supine position. Previous study showed that head rotation only can influence upper airway collapsibility and can improve AHI compared to supine position, whether patients are diagnosed with POSA or not. [28, 29] On the other hand, it could also be possible that the effect of lateral head rotation only is too minimal to differentiate the effectiveness between NPP and PP.

We are aware of limitations of the model. Several studies have shown a correlation between AHI and observations made during DISE. Vroegop et al. found that higher AHI values were both associated with a complete concentric collapse at palatal level and complete lateral hypopharyngeal collapse, while a lower AHI was associated with a partial concentric collapse at palatal level. [18] Ravesloot et al. confirmed these findings and in addition suggested that a multilevel collapse, a complete collapse and a tongue base collapse are associated with a higher AHI in OSA patients. [19]. Based on the findings of this study, it is however too early to conclude that these relations are completely linear.

CONCLUSIONS AND FUTURE PERSPECTIVES

We conclude that the present model leaves room for improvement. We regard this as work in progress and presently prospectively re-evaluate the effect of head rotation alone and head and trunk rotation. A subsequent study will include the use of a temporary OA that might mimic the

effect of a definitive OA better than manual jaw thrust. We hope this will eventually lead to a good predictive model, which subsequently can be tested in prospective studies.

REFERENCES

1. Cartwright R, Ristanovic R, Diaz F, Caldarelli D, Alder G. A comparative study of treatments for positional sleep apnea. *Sleep*. 1991;14(6):546-52

2. Heinzer R, Marti-Soler H, Haba-Rubio J. Prevalence of sleep apnoea syndrome in the middle to old age general population. *Lancet Respir Med*. 2016;4(2):e5-6

3. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med*. 2012;8(5):597-619

4. Ravesloot M, Van Maanen J, Dun L, De Vries N. The undervalued potential of positional therapy in position-dependent snoring and obstructive sleep apnea—a review of the literature. *Sleep and Breathing*. 2013;17(1):39-49

5. van Maanen JP, Meester KA, Dun LN, et al. The sleep position trainer: a new treatment for positional obstructive sleep apnoea. *Sleep and Breathing*. 2013;17(2):771-79

6. van Maanen JP, de Vries N. Long-term effectiveness and compliance of positional therapy with the sleep position trainer in the treatment of positional obstructive sleep apnea syndrome. *Sleep*. 2014;37(7):1209-15

7. Benoist L, de Ruiter M, de Lange J, de Vries N. A randomized, controlled trial of positional therapy versus oral appliance therapy for position-dependent sleep apnea. *Sleep Med*. 2017;34:109-17

8. Richard W, Venker J, den Herder C, et al. Acceptance and long-term compliance of nCPAP in obstructive sleep apnea. *Eur Arch Otorhinolaryngol*. 2007;264(9):1081-6

9. Kezirian EJ, Hohenhorst W, de Vries N. Drug-induced sleep endoscopy: the VOTE classification. *Eur Arch Otorhinolaryngol*. 2011;268(8):1233-36

10. De Vito A, Llatas MC, Vanni A, et al. European position paper on drug-induced sedation endoscopy (DISE). *Sleep and Breathing*. 2014;18(3):453-65

11. Ferguson KA, Cartwright R, Rogers R, Schmidt-Nowara W. Oral appliances for snoring and obstructive sleep apnea: a review. *Sleep*. 2006;29(2):244-62

12. Johal A, Battagel JM, Kotecha BT. Sleep nasendoscopy: a diagnostic tool for predicting treatment success with mandibular advancement splints in obstructive sleep apnoea. *Eur J Orthod*. 2005;27(6):607-14

13. Johal A, Hector MP, Battagel JM, Kotecha BT. Impact of sleep nasendoscopy on the outcome of mandibular advancement splint therapy in subjects with sleep-related breathing disorders. *J Laryngol Otol*. 2007;121(7):668-75

14. Vanderveken OM, Vroegop AV, van de Heyning PH, Braem MJ. Drug-induced sleep endoscopy completed with a simulation bite approach for the prediction of the outcome of treatment of obstructive sleep apnea with mandibular repositioning appliances. *Operative Techniques in Otolaryngology-head and neck surgery*. 2011;22(2):175-82

15. Vroegop AV, Vanderveken OM, Dieltjens M, Wouters K, Saldien V, Braem MJ. Sleep endoscopy with simulation bite for prediction of oral appliance treatment outcome. *Journal of sleep research*. 2013;22(3):348-55

16. de Ruiter MHT, Benoist LBL, de Vries N, de Lange J. Durability of treatment effects of the Sleep Position Trainer versus oral appliance therapy in positional OSA: 12-month follow-up of a randomized controlled trial. *Sleep Breath*. 2017

17. Dieltjens M, Vroegop AV, Verbruggen AE, et al. A promising concept of combination therapy for positional obstructive sleep apnea. *Sleep Breath*. 2015;19(2):637-44

18. Vroegop AV, Vanderveken OM, Boudewyns AN, et al. Drug-induced sleep endoscopy in sleep-disordered breathing: report on 1,249 cases. *Laryngoscope*. 2014;124(3):797-802

19. Ravesloot MJ, de Vries N. One hundred consecutive patients undergoing drug-induced sleep endoscopy: results and evaluation. *Laryngoscope*. 2011;121(12):2710-6

20. Cartwright RD. Effect of sleep position on sleep apnea severity. *Sleep*. 1984;7(2):110-4

21. Kim KT, Cho YW, Kim DE, Hwang SH, Song ML, Motamedi GK. Two subtypes of positional obstructive sleep apnea: Supine-predominant and supine-isolated. *Clin Neurophysiol*. 2016;127(1):565-70

22. Koutsourelakis I, Safiruddin F, Ravesloot M, Zakynthinos S, de Vries N. Surgery for obstructive sleep apnea: sleep endoscopy determinants of outcome. *The Laryngoscope*. 2012;122(11):2587-91

23. Vanderveken OM, Maurer JT, Hohenhorst W, et al. Evaluation of drug-induced sleep endoscopy as a patient selection tool for implanted upper airway stimulation for obstructive sleep apnea. *J Clin Sleep Med*. 2013;9(5):433-8

24. Huntley C, Chou D, Doghramji K, Boon M. Preoperative Drug Induced Sleep Endoscopy Improves the Surgical Approach to Treatment of Obstructive Sleep Apnea. *Annals of Otology, Rhinology & Laryngology*. 2017;126(6):478-82

25. Certal VF, Pratas R, Guimarães L, et al. Awake examination versus DISE for surgical decision making in patients with OSA: a systematic review. *The Laryngoscope*. 2015

26. Ravesloot M, White D, Heinzer R, Oksenberg A, Pépin J. Efficacy of the New Generation of Devices for Positional Therapy for Patients with Positional Obstructive Sleep Apnea: A Systematic Review of the Literature and Meta-Analysis. *Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine*. 2017

27. Hoekema A, Stegenga B, De Bont LG. Efficacy and co-morbidity of oral appliances in the treatment of obstructive sleep apnea-hypopnea: a systematic review. *Crit Rev Oral Biol Med*. 2004;15(3):137-55

28. van Kesteren ER, van Maanen JP, Hilgevoord AA, Laman DM, de Vries N. Quantitative effects of trunk and head position on the apnea hypopnea index in obstructive sleep apnea. *Sleep*. 2011;34(8):1075-81

29. Zhu K, Bradley TD, Patel M, Alshaer H. Influence of head position on obstructive sleep apnea severity. *Sleep Breath*. 2017;21(4):821-28

30. Eichler C, Sommer JU, Stuck BA, Hormann K, Maurer JT. Does drug-induced sleep endoscopy change the treatment concept of patients with snoring and obstructive sleep apnea? *Sleep Breath*. 2013;17(1):63-8

31. Safiruddin F, Koutsourelakis I, de Vries N. Analysis of the influence of head rotation during drug-induced sleep endoscopy in obstructive sleep apnea. *The Laryngoscope*. 2014;124(9):2195-99

32. Safiruddin F, Koutsourelakis I, de Vries N. Upper airway collapse during drug induced sleep endoscopy: head rotation in supine position compared with lateral head and trunk position. *European Archives of Oto-Rhino-Laryngology*. 2015;272(2):485-88

33. Mador MJ, Kufel TJ, Magalang UJ, Rajesh SK, Watwe V, Grant BJ. Prevalence of positional sleep apnea in patients undergoing polysomnography. *Chest*. 2005;128(4):2130-7

34. Oksenberg A. Positional and non-positional obstructive sleep apnea patients. *Sleep Med*. 2005;6(4):377-8

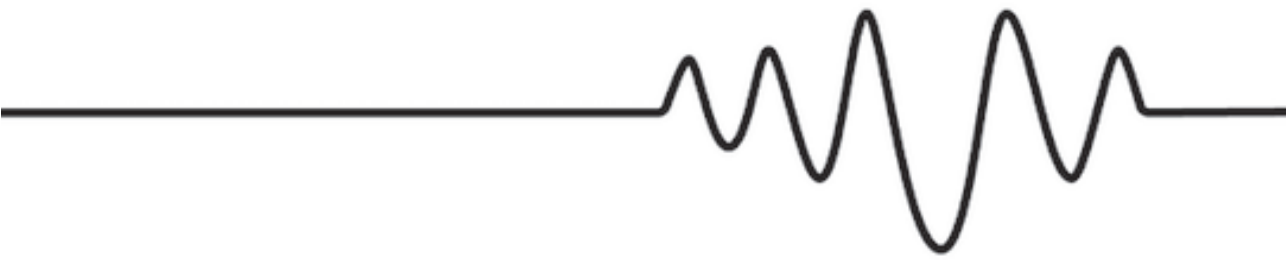
35. Richard W, Kox D, den Herder C, Laman M, van Tinteren H, de Vries N. The role of sleep position in obstructive sleep apnea syndrome. *Eur Arch Otorhinolaryngol*. 2006;263(10):946-50

3

Drug-induced sleep endoscopy (DISE): New insights in lateral head rotation compared to lateral head and trunk rotation in (non) positional obstructive sleep apnea patients

P.E. Vonk, M.J. van de Beek, M.J.L. Ravesloot, N. de Vries

Laryngoscope. 2019 Oct;129(10):2430-2435



ABSTRACT

Objective: To compare the effect of lateral head rotation to lateral head and trunk rotation on upper airway patency during drug-induced sleep endoscopy (DISE) in non-positional obstructive sleep apnea (OSA) patients (NPP) and positional OSA patients (PP).

Methods: Prospective cohort study

Results: In total 92 patients were included. Seventy-five patients were male (82%) with a mean age of 47.2 ± 11.3 years, a BMI of 27.0 ± 3.3 kg/m^2 and a median AHI of 16.7/h (8.7, 26,5). Of all patients, 75% were PP. Lateral head rotation and lateral head and trunk rotation findings are similar in NPP at each possible level of obstruction, with exception of the oropharynx, but not in PP. In PP, lateral head rotation and both lateral head and trunk observations were different at every possible obstruction site.

Conclusion: The effect of lateral head rotation and lateral head and trunk rotation on upper airway patency during DISE is significantly different in PP. In NPP, similar results regarding the degree of upper airway obstruction were found at the level of the velum, tongue base and epiglottis.

Keywords: Obstructive sleep apnea, drug-induced sleep endoscopy, lateral head rotation, positional

INTRODUCTION

Obstructive sleep apnea (OSA) is a sleep related condition characterized by recurrent episodes of a decrease in airflow caused by a partial or complete collapse of the upper airway. This results in oxygen desaturation, respiratory arousals and insufficient sleep due to frequent awakenings. In the majority of OSA patients disease severity is influenced by body position, in which the supine position is usually the worst sleeping position (WSP). [1-6] According to Cartwright´s definition, patients are deemed to have position dependent OSA (POSA) when they meet the following criteria: *an apnea-hypopnea index (AHI) greater than 5 and an at least twofold difference between supine and non-supine AHI*. [3] Over time, various modifications have been introduced, including various parameters such as the overall AHI, AHI in supine and non-supine position and time spent in various body positions. [6-10]

Patients with positional OSA (PP) benefit from avoiding the supine position, which can be achieved through positional therapy (PT). Various forms of PT exist varying from the so-called tennis-ball technique to a new generation of PT: vibro-tactile feedback devices. A recent meta-analysis by Ravesloot et al. showed that new generation devices are effective in reducing the AHI during short-term follow up. [11]

Currently, evidence is growing that POSA is not only dependent on body position, but also on head position. Van Kesteren et al. reported that the majority of PP are trunk supine-dependent, of which in 46.2% head position was of considerable influence on the AHI. Furthermore they reported that 6.5% of their study population was head supine dependent alone. [12] These findings were endorsed by Zhu et al. who analyzed the effect of lateral head rotation with the trunk in supine position on OSA severity by using polysomnography (PSG) including visual inspection of the PSG video recording. They concluded that there was a significant decrease in OSA severity when the head was rotated from supine to lateral position, in particular in non-obese patients. [13]

Although increasing evidence shows that head rotation can influence OSA severity, there is actually lack of information on the effect of head rotation on upper airway patency. Drug-induced sleep endoscopy (DISE) is a dynamic endoscopic tool to observe the upper airway during propofol-induced sleep, which can be used to gain more information on upper airway collapse in OSA patients. To the best of our knowledge, only one previous study has evaluated lateral head rotation and the effect on upper airway patency during DISE. This two-part study by Safiruddin et al. first analyzed the influence of different head positons on upper airway collapse in 60 subjects and found a significant improvement on upper airway patency when the head was rotated to lateral position compared to

supine head and trunk position. No differences were found when comparing rotation to the left or right side. In the second part of their study, lateral head rotation alone was compared to lateral head and trunk position. They concluded that these two maneuvers were comparable, when focusing on the level(s) and configuration(s) involved in upper airway obstruction in OSA patients. Therefore it was concluded that these two positions are comparable during DISE, and that there is no need to assess the upper airway in lateral head and trunk position. [14, 15]

In a previous study, we introduced a 3-point scale to retrospectively evaluate the effect of different passive maneuvers during DISE on upper airway patency. One of these maneuvers was lateral head rotation. When comparing the improvement on upper airway patency whilst performing lateral head rotation, the effect was less (<50%) then what was previously expected based on currently available literature on treatment outcome of PT in PP. [16]

Bearing this is mind, the first aim of this study is to compare the effect of lateral head and supine trunk rotation to lateral head and trunk rotation on upper airway patency during DISE distinguishing between non-positional OSA patients (NPP) and PP with particular focus on the severity of collapse at the four levels of obstruction according to the VOTE classification system. We hypothesize that in case of NPP lateral head rotation is similar to lateral head and trunk rotation. In case of PP, we hypothesize that the effect on upper airway patency of lateral head rotation only will be less compared to both lateral head and trunk rotation. We also hypothesize that the more OSA severity is influenced by sleeping position, the less comparable lateral head rotation is to both lateral head and trunk rotation.

MATERIAL AND METHODS

Patients

We performed a prospective, single-centre cohort study, including a consecutive series of patients who underwent DISE in the Department of Otolaryngology, Head and Neck surgery of the OLVG (Amsterdam, the Netherlands) between August 2017 and November 2017. All patients were diagnosed with OSA by PSG. Patients were excluded from this study when they were not willing to sign informed consent or in case of physical disabilities (e.g. back and/or neck problems) and were therefore unable to rotate the head to lateral position or to lie in a non-supine position. When there was no data available of both supine and non-supine AHI or sleeping position, patients were also excluded from this study.

Definitions

When patients met the inclusion criteria, patients were classified as NPP or PP. POSA was defined using a modified version of Cartwright's criteria: a difference of 50% or more in AHI between supine and non-supine positions.[3]

DISE procedure

DISE procedure was performed according to the practice guidelines as recommended in the European position paper on DISE (update 2017).[17]

Indication

The main reason to perform DISE was eligibility for upper airway surgery. Other indications included patients eligible for oral appliance therapy (OAT) or combination therapy (e.g. OAT + PT).

Setting

All patients underwent DISE in daycare in a safe outpatient endoscopy setting with standard anesthetic equipment.

DISE was performed by one experienced ENT resident (PV), with a trained nurse anesthetist managing sedation and monitoring blood pressure, electrocardiogram (ECG) and oxygen levels.

Sedation

The drug of choice for sedation was propofol. The level of sedation was controlled by a target controlled infusion (TCI) pump using the methods described by Schnider et al. to calculate the effective dose. [18, 19] Prior to the intravenous (IV) infusion of propofol, 2cc lidocaine was given IV to prevent pain caused by the infusion of propofol. In some patients Glycopyrrolate (Robinul) was given IV to prevent mucosal hypersecretion, since this could interfere with the quality of the endoscopic assessment. Proper sedation levels were achieved when the patient showed hyporesponsiveness to verbal and tactile stimuli or when the patient began to snore.

Patient positioning

Ideally, the patient should be positioned mimicking sleeping habits during natural, but due to the nature of this study DISE was performed in both supine position and lateral head (and trunk) rotation. Initially, subjects were placed in lateral head and trunk position. When proper level of sedation was achieved, the upper airway was assessed at four different levels (velum, oropharynx,

tongue base and epiglottis) according to the VOTE classification system. Patients were then tilted to the supine position with the head rotated to the right side and finally the upper airway was observed in supine position of both head and trunk. Jaw thrust was performed in all positions, to evaluate the effect on upper airway patency; however it was not the purpose of this study to analyze this maneuver.

Classification system

To report on the anatomical structures causing upper airway collapse, the VOTE classification system was applied. The VOTE classification system distinguishes between four different levels and structures that may be involved in upper airway collapse, namely velum (V), oropharynx (O), tongue base (T) and epiglottis (E). To define the degree of obstruction, three different categories are used, namely no obstruction, with a collapse less than 50%; a partial obstruction with a collapse between 50 and 75% and typically with vibration; or a complete collapse in which a collapse is seen of more than 75%. An X is used when no observation can be made. Depending on the different site(s) involved in upper airway obstruction, the configuration may be anterior-posterior, lateral or concentric. [20] In table 1 an overview is given of the degree and possible configurations of obstruction at each level.

Table 1. The VOTE classification system [20]

Structure	Degree of obstruction[a]	Configuration[c]		
		A-P	Lateral	Concentric
Velum				
Oropharynx[b]				
Tongue Base				
Epiglottis				

A-P Antero-posterior

a. Degree of obstruction: 0 no obstruction; 1 partial obstruction; 2 complete obstruction

b. Oropharynx obstruction can be distinguished as related solely to the tonsils or including the lateral walls

c. Configuration noted for structures with degree of obstruction > 0

In accordance with the Declaration of Helsinki, the study protocol was approved by the local Medical Ethical Committee. Patients signed informed consent previous to the procedure. Data on study subjects was collected and stored anonymously to protect personal information.

Statistical analysis

Statistical analysis was performed using SPSS (version 21), SPSS Inc., Chicago, IL). Quantitative data are reported as mean ± SD or as median (Q1, Q3) when not normally distributed. A p value of <0.05 was considered to indicate statistical significance. To determine whether the effect on upper airway patency during lateral head rotation is similar to lateral head and trunk rotation, the degree of obstruction according to the VOTE classification system was compared by using the Wilcoxon signed rank test in NPP and PP. To analyze the influence of the degree of position dependency, a ratio for position dependency was calculated by dividing non supine AHI by supine AHI; this implicates that a ratio > 0.5 regards non-position dependent OSA. The closer the ratio is to 1, the less OSA severity is influenced by body position.

RESULTS

A total of 109 patients were invited to participate in this study. Five patients declined after receiving additional information. In four patients DISE results could not be analyzed due to physical agitation or mucosal hypersecretion, which rendered DISE outcomes unreliable. In one subject body position during the PSG night could not be determined due to malfunction of the PSG apparatus and in seven patients supine AHI could not be determined due to a TST of zero per cent in supine position. Therefore, only the results of the remaining 92 subjects were analyzed.

Seventy-five patients were male (82%). The mean age was 47.2 ± 11.3 years, with a BMI of 27.0 ± 3.3 kg/m^2 and a median AHI of 16.7/h (8.7, 26,5), a median supine AHI of 31.9/h (16.5, 53.5) and a median non supine AHI of 8.1/h (3.1, 15.2). Patients spent a median percentage of TST in supine position of 34.0% and the median oxygen desaturation index (ODI) was 19.5/h (11.9, 29.2). Twenty-five per cent of all patients were NPP. When comparing baseline characteristics between NPP and PP, PP had as expected a significantly lower non supine AHI. The supine AHI was higher in PP compared to NPP, but not statistically significant. The percentage of male subjects was significantly higher comparing NPP to PP, namely 65.2% versus 87.0%. An overview of baseline characteristics of the total population and subgroups are presented in **table 2.**

Table 2. Baseline characteristics total population and NPP versus PP

	Total	**NPP**	**PP**	**NPP vs PP p value**
Number (%)	92	23 (25)	69 (75)	23 vs 69
Age (years)	47.2 ± 11.3	44.9 ± 13.4	48.0 ± 10.5	0.248
Male / Female	75/17	15/8	60/9	0.019*
BMI (kg/m^2)	27.0 ± 3.3	27.3 ± 3.8	26.9 ± 3.1	0.664
Total AHI (events/hour)	16.7 (8.7, 26.5)°	21.5 (8.7, 33.4)°	15.7 (8.7, 24.1)°	0.262
Supine AHI (events/hour)	31.9 (16.5, 53.5)°	25.2 (9.9, 47.0)°	37.0 (18.4, 54.7)°	0.081
Non supine AHI (events/hour)	8.1 (3.1, 15.2)°	16.3 (9.4, 34.4)°	5.7 (2.4, 11.2)°	<0.001*
Supine sleeping time (%)	34.0 (23.1, 47.5)°	37.0 (30.3, 61.3)°	31.0 (20.7, 46.0)°	0.050
ODI (events/hour)	19.5 (11.9, 29.2)°	19.5 (11.7, 38.2)°	19.5 (11.9, 27.2)°	0.317

NPP non-positional *PP* positional dependent patients *BMI* Body Mass index *AHI* apnea-hypopnea index *ODI* oxygen desaturation index

*° Median (Q1, Q3); *p value < 0.05*

In NPP, lateral head rotation alone was comparable to lateral head and trunk rotation concerning the degree of obstruction at velum, tongue base and epiglottis levels. In PP, lateral head rotation alone significantly differed at all levels observed during DISE compared to lateral head and trunk rotation. An overview is given in **table 3 and table 4**.

Table 3. DISE results comparing lateral head rotation versus lateral head and trunk rotation in NPP

Level	**Configuration (%)**	**Lateral head rotation**			**Lateral head and trunk rotation**			**p value$^{\alpha}$**
		None	Partial	Complete	None	Partial	Complete	
Velum	A-P	10	4	6	11	4	5	0.180
	Concentric		1	2		2	1	
Oropharynx	Lateral	7	5	11	13	1	9	0.011*
Tongue base	A-P	13	5	5	16	5	2	0.655
Epiglottis	A-P	14	5	3	19	3	1	0.058

A-P Antero-posterior

α p values are Wilcoxon signed rank test

Table 4. DISE results comparing lateral head rotation versus lateral head and trunk rotation in PP

Level	**Configuration (%)**	**Lateral head rotation**			**Lateral head and trunk rotation**			**p value$^{\alpha}$**
		None	Partial	Complete	None	Partial	Complete	
Velum	A-P	16	20	11	42	11	1	<0.001*
	Concentric		8	14		11	4	
Oropharynx	Lateral	19	20	30	36	13	20	<0.001*
Tongue base	A-P	38	22	8	50	17	1	0.008*
Epiglottis	A-P	42	15	11	60	4	4	<0.001*

A-P Antero-posterior

α p values are Wilcoxon signed rank test.

Unfortunately, the data extracted to analyze the influence of the degree of position dependency were not reliable due to the small sample size in the different subgroups. Therefore, the statistical power was not high enough.

DISCUSSION

This study describes the effect of lateral head rotation compared to lateral head and trunk rotation on upper airway patency during DISE in NPP and PP. The current results indicate that in NPP the effect on upper airway patency when performing lateral head rotation only is similar to both lateral head and trunk rotation at each possible level of obstruction, with exception of the oropharynx. This does not apply for PP, in which significantly different results were found at all four possible levels of obstruction.

The percentage of PP in our study group was relatively high, namely 75%. This could be explained by the fact that the prevalence of POSA decreases as the severity of OSA increases and that the majority of this study population was diagnosed with mild to moderate OSA. In case of severe OSA, CPAP is the first therapy of choice, which does not require DISE. The percentage of male subjects was significantly higher in PP compared to NPP, a finding which is not described previously in the literature. This difference could not be explained by confounders such as BMI or age.

The underlying pathophysiological mechanism explaining the different patterns of upper airway collapse in supine and non-supine position remains in question. Van Kesteren et al. suggested that with the head in supine position, the tongue and to a lesser extent the soft palate, falls backwards due to gravitational forces and muscle relaxation. This effect would presumably be smaller when the head is rotated to lateral position. [12]

These findings were strengthened by a study of Lee et al. They evaluated the changes in obstruction site according to sleep position to determine which obstructions are responsible for obstruction in lateral body position. They concluded that obstruction due to the tongue base and larynx improved dramatically when moving from supine to lateral body position and that recurrent obstruction in lateral body position was mainly caused by lateral wall collapsibility. They additionally assumed that displacement of the tongue base alters lateral wall tension and causes a secondary collapse of the oropharyngeal walls. [21] The findings of these studies could explain the fact that we found a significant difference at oropharynx level when comparing lateral head rotation alone to both lateral head and trunk rotation, since the oropharyngeal collapse in NPP is enhanced by lateral body position.

The results of this study are in contrast to what was previously described in an earlier study from our group by Safiruddin et al. They concluded that the occurrence of a partial and/or complete collapse

during DISE was similar comparing lateral head rotation to lateral head and trunk rotation, with exception of the palate. Nevertheless, there are some critical comments to be made. First of all, a small study population was used (N=60) of which only 38% of all patients was diagnosed with POSA. This percentage is much lower than the prevalence of POSA found in literature and in the present study. This combined with the fact that no distinction was made between NPP and PP might explain the different results. [15]

Limitations

This study is not without limitations. First of all, we intended to evaluate the effect of position dependency by calculating a ratio dividing non supine AHI by supine AHI. Although we still believe our hypothesis is potentially true, we could not confirm this by statistically analysis of our data. There were a number of problems encountered when analyzing the results. When dividing the total study population into different subgroups to compare the differences in degree of obstruction for each different level, our sample size was too small. Secondly, the degree of obstruction during DISE according to the VOTE classification system consists of only a 3-point system; 0 (< 50% obstruction), 1 (between 50-75% obstruction) or 2 (> 75%). In theory this could mean that although a different degree of obstruction is seen during DISE (e.g. 50% vs 70%), this will both be scored the same.
Thirdly, DISE can also be hampered by interobserver and intraobserver variability. [22, 23] A previous study showed that this variability seems to be less significant in experienced endoscopists. [24] Therefore, to minimize the influence of interobserver and intraobserver variability in this study, DISE was performed by only one experienced ENT resident (PV). Finally, no data on head position during the PSG night was available. Therefore, the effect on upper airway patency of lateral head rotation alone and both lateral head and trunk rotation could not be verified by OSA severity measured with PSG.

Clinical relevance

Currently, the effect of body position, either head or head and trunk, on disease severity is gaining renewed attention. In addition, PT is becoming a more accepted treatment in PP as a standalone treatment or in combination with other treatment modalities. Historically, recommendations were to perform DISE in the WSP, which is usually the supine position. But, especially in PP, in which OSA severity is influenced by body position, lateral assessment of the upper airway is just as important as assessment of the supine position during DISE. For example, when PP tolerate PT, less aggressive forms of upper airway surgery can be applied.

Although it is clear that lateral assessment of the upper airway is of added value in PP, it must be kept in mind that not meeting Cartwright's criteria for position dependency, does not necessarily mean that OSA severity in NPP cannot be influenced by sleeping position. Therefore, it is believed that lateral assessment of the upper airway in NPP can still be of added value.

Impact of these findings on how to perform DISE

Currently, in our centre DISE is performed in supine position followed by assessment of the upper airway with the head rotated to the lateral position with and without jaw thrust. The results of this study suggest that this manoeuvre mimics the effect of non-supine sleeping position on upper airway patency with exception of the level of the oropharynx in NPP. This does not apply for PP. Although lateral head rotation alone is much more practical, lateral head and trunk position in PP seems to be more representative for lateral sleep position.

Therefore, we suggest that in NPP DISE should be performed in supine sleeping position with and without lateral head rotation to mimic non supine sleeping position. This allows the physician to evaluate upper airway patency in both positions. We believe that this maneuver can be of added value in case combination therapy with OAT + PT is considered or to evaluate possibilities to perform less aggressive forms of upper airway surgery when combined with PT.

In PP we recommend to perform DISE in both supine position and lateral head and trunk rotation to gain more sufficient information on upper airway collapse patterns in non-supine sleeping position.

CONCLUSION

In conclusion, the effect of lateral head rotation and lateral head and trunk rotation on upper airway patency during DISE is significantly different in PP. In NPP, similar results were found at the level of the velum, tongue base and epiglottis. In NPP lateral head rotation only seems to be sufficient enough to mimic non supine sleeping position. In PP, we recommend that DISE is performed in both lateral head and trunk position.

REFERENCES

1. Ravesloot M, Van Maanen J, Dun L, De Vries N. The undervalued potential of positional therapy in position-dependent snoring and obstructive sleep apnea—a review of the literature. *Sleep and Breathing*. 2013;17(1):39-49

2. Ravesloot MJ, Frank MH, van Maanen JP, Verhagen EA, de Lange J, de Vries N. Positional OSA part 2: retrospective cohort analysis with a new classification system (APOC). *Sleep Breath*. 2016;20(2):881-8

3. Cartwright RD. Effect of sleep position on sleep apnea severity. *Sleep*. 1984;7(2):110-4

4. Oksenberg A, Silverberg DS, Arons E, Radwan H. Positional vs nonpositional obstructive sleep apnea patients: anthropomorphic, nocturnal polysomnographic, and multiple sleep latency test data. *Chest*. 1997;112(3):629-39

5. Richard W, Kox D, den Herder C, Laman M, van Tinteren H, de Vries N. The role of sleep position in obstructive sleep apnea syndrome. *Eur Arch Otorhinolaryngol*. 2006;263(10):946-50

6. Mador MJ, Kufel TJ, Magalang UJ, Rajesh SK, Watwe V, Grant BJ. Prevalence of positional sleep apnea in patients undergoing polysomnography. *Chest*. 2005;128(4):2130-7

7. Marklund M, Persson M, Franklin KA. Treatment success with a mandibular advancement device is related to supine-dependent sleep apnea. *Chest*. 1998;114(6):1630-5

8. Permut I, Diaz-Abad M, Chatila W, et al. Comparison of positional therapy to CPAP in patients with positional obstructive sleep apnea. *J Clin Sleep Med*. 2010;6(3):238-43

9. Bignold JJ, Mercer JD, Antic NA, McEvoy RD, Catcheside PG. Accurate position monitoring and improved supine-dependent obstructive sleep apnea with a new position recording and supine avoidance device. *J Clin Sleep Med*. 2011;7(4):376-83

10. Kim KT, Cho YW, Kim DE, Hwang SH, Song ML, Motamedi GK. Two subtypes of positional obstructive sleep apnea: Supine-predominant and supine-isolated. *Clin Neurophysiol*. 2016;127(1):565-70

11. Ravesloot M, White D, Heinzer R, Oksenberg A, Pépin J. Efficacy of the New Generation of Devices for Positional Therapy for Patients with Positional Obstructive Sleep Apnea: A Systematic Review of the Literature and Meta-Analysis. *Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine*. 2017

12. van Kesteren ER, van Maanen JP, Hilgevoord AA, Laman DM, de Vries N. Quantitative effects of trunk and head position on the apnea hypopnea index in obstructive sleep apnea. *Sleep*. 2011;34(8):1075-81

13. Zhu K, Bradley TD, Patel M, Alshaer H. Influence of head position on obstructive sleep apnea severity. *Sleep Breath*. 2017;21(4):821-28

14. Safiruddin F, Koutsourelakis I, de Vries N. Analysis of the influence of head rotation during drug-induced sleep endoscopy in obstructive sleep apnea. *The Laryngoscope*. 2014;124(9):2195-99

15. Safiruddin F, Koutsourelakis I, de Vries N. Upper airway collapse during drug induced sleep endoscopy: head rotation in supine position compared with lateral head and trunk position. *European Archives of Oto-Rhino-Laryngology*. 2015;272(2):485-88

16. Vonk PE, Beelen A, de Vries N. Towards a prediction model for drug-induced sleep endoscopy as selection tool for oral appliance treatment and positional therapy in obstructive sleep apnea. *Sleep Breath*. 2018

17. De Vito A, Carrasco Llatas M, Ravensloot M, et al. European position paper on drug-induced sleep endoscopy (DISE): 2017 update. *Clinical Otolaryngology*. 2018

18. Schnider T, Minto C. Pharmacokinetic models of propofol for TCI. *Anaesthesia*. 2008;63(2):206-06

19. Schnider TW, Minto CF, Gambus PL, et al. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology: The Journal of the American Society of Anesthesiologists*. 1998;88(5):1170-82

20. Kezirian EJ, Hohenhorst W, de Vries N. Drug-induced sleep endoscopy: the VOTE classification. *Eur Arch Otorhinolaryngol*. 2011;268(8):1233-36

21. Lee SA, Paek JH, Chung YS, Kim WS. Clinical features in patients with positional obstructive sleep apnea according to its subtypes. *Sleep Breath*. 2017;21(1):109-17

22. Carrasco-Llatas M, Zerpa-Zerpa V, Dalmau-Galofre J. Reliability of drug-induced sedation endoscopy: interobserver agreement. *Sleep Breath*. 2017;21(1):173-79

23. Kezirian EJ, White DP, Malhotra A, Ma W, McCulloch CE, Goldberg AN. Interrater reliability of drug-induced sleep endoscopy. *Arch Otolaryngol Head Neck Surg*. 2010;136(4):393-7

24. Vroegop AV, Vanderveken OM, Wouters K, et al. Observer variation in drug-induced sleep endoscopy: experienced versus nonexperienced ear, nose, and throat surgeons. *Sleep*. 2013;36(6):947-53

Jaw thrust versus the use of a boil-and-bite mandibular advancement device as a screening tool during drug-induced sleep endoscopy

4

P.E. Vonk, J.A.M. Uniken Venema,
M.J.L. Ravesloot, A. Hoekema,
J.A. van de Velde – Muusers, N. de Vries

Submitted

ABSTRACT

Study objectives: 1) to analyse agreement in degree of obstruction and configuration of the upper airway (UA) between jaw thrust and an oral device *in situ* during drug-induced sleep endoscopy (DISE) 2) to evaluate clinical decision making using jaw thrust or a boil-and-bite MAD, the MyTAP.

Methods: single-centre prospective cohort study in obstructive sleep apnea patients who underwent DISE between January - July 2019.

Results: Sixty-three patients were included. Agreement amongst observations in the supine position for degree of obstruction was 60% (N=36, k=0.41) at the level of the velum, 68.3% (N=41, k=0.35) for oropharynx, 58.3% (N=35, k=0.28) for tongue base, 56.7% (N=34, k=0.14) for epiglottis; in the lateral position 81.7% (N=49, k=0.32), 71.7% (N=43, k=0.36), 90.0% (N=54, k=0.23) and 96.7% (N=58, k= could not be determined) respectively. In the supine position agreement for configuration of obstruction at level of the velum was found in 20 of 29 patients (69.0%, k=0.41), in the lateral position 100%. Thirty patients would have been prescribed a MAD using jaw thrust, 34 using the boil-and-bite MAD as a screening instrument. The main reason for being labelled as non-suitable was complete residual retropalatal collapse during jaw thrust. Using the boil-and-bite MAD, this was both due to complete retropalatal or hypopharyngeal collapse.

Conclusion: There is only slight to moderate agreement in degree of obstruction for jaw thrust and a new-generation boil-and-bite MAD during DISE. Greater improvement of UA patency at hypopharyngeal level was observed during jaw thrust, but this manoeuvre was less effective in improving UA obstruction at retropalatal level.

Key words: obstructive sleep apnea, sleep-disordered breathing, jaw thrust, drug-induced sleep endoscopy, mandibular advancement device, treatment outcome

Brief summary

In cases of mild or moderate obstructive sleep apnea (OSA) or if treatment with continuous positive airway pressure fails, treatment with a mandibular advancement device (MAD) can be a viable alternative. Unfortunately, identification of suitable candidates can be challenging. Relevant variables used to predict treatment outcome include body mass index, total apnea-hypopnea index, age, gender and cephalometric outcomes. Another, more controversial, way to predict MAD treatment outcome is the use of jaw thrust during drug-induced sleep endoscopy (DISE). Although alternatives to jaw thrust (e.g., simulation bite) have been proposed, there is still a demand for readily available, quick and easy to use systems that mimic the effect of a MAD during DISE to predict and improve MAD treatment outcome.

INTRODUCTION

Obstructive sleep apnea (OSA) is the most prevalent sleep-related breathing disorder caused by episodes of partial or complete obstruction of the upper airway (UA) during sleep. Currently, continuous positive airway pressure (CPAP) is the standard therapy for moderate to severe OSA, but due to poor tolerance and low acceptance, non-compliance rates are often high. [1] In cases of mild or moderate OSA or if CPAP treatment fails, UA surgery, positional therapy and mandibular advancement devices (MADs) can be viable alternatives.

MADs are designed to advance the mandible, such that the tongue base, epiglottis and soft palate are protruded. This improves UA patency and stability. [2] Previous studies have shown that MADs are successful in 84% of patients with mild to moderate OSA and 69.2% of severe OSA patients. [3] MAD treatment failure might be explained by the fact that it is difficult to identify suitable candidates for this treatment. Relevant variables that are used to predict treatment outcome include body mass index (BMI), total apnea-hypopnea index (AHI), age, gender and cephalometric outcomes. [4]
Another, more controversial, tool that is used to predict MAD treatment outcome is drug-induced sleep endoscopy (DISE). This tool provides additional information on the anatomical sites in the UA related to obstruction. Several studies have shown that MADs are less effective in cases involving a complete concentric collapse at the level of the velum. [5, 6] In addition, DISE has the unique advantage of allowing the physician to perform different passive maneuvers that are considered to serve as predictors for surgical or non-surgical treatment outcomes. [7] One of these maneuvers is the jaw thrust. Through jaw thrust, the physician actively protrudes the mandible. The mandible is protruded up to approximately 5-10mm or 75% of maximal protrusion, thus mimicking the protrusive position of the mandible with MAD treatment. [8]

However, the jaw thrust maneuver during DISE has been criticized, and the positive predictive value of maximal passive protrusion of the mandible during DISE has varied between studies. [9-13] This is probably because this maneuver does not account for the thickness of a MAD, thereby overlooking the fact that the vertical opening (VO) of the mandible is not similar to a MAD. Secondly, a MAD is often set at 60-75% of maximum mandibular protrusion. The degree of advancement of the mandible during jaw thrust is generally less precise than a pre-set degree of protrusion with a MAD. As a result, it is difficult to mimic the real life effect of a MAD during DISE using the jaw thrust maneuver. In addition, there is probably variability in the performance of jaw thrust during DISE among surgeons and in some cases jaw thrust is not performed by the surgeon, but for example a trained nurse anesthetist.

Over recent years, several alternatives to jaw thrust have been proposed. In 2008 *Vanderveken et al.* compared the efficacy of a thermoplastic appliance with a classic custom-made MAD as a screening tool in search of good candidates for a definitive custom-made MAD during 4 months of follow-up. It was concluded that a custom-made MAD was more effective than a thermoplastic monobloc device and that it could not be recommended as a screening method. This was mainly due to the lack of retention and poor comfort of the thermoplastic appliance. [14] In 2013,*Vroegop et al.* evaluated the use of a simulation bite during DISE. They concluded that a positive effect on UA patency with the simulation bite in maximal comfortable protrusion during DISE was significantly associated with a favorable treatment response to MAD. [13]

Although the use of a simulation bite seems to be promising, it is with the exception of a few centres, not part of daily practice. Therefore, readily available, quick and easy to use systems that mimic the effect of a MAD during DISE need to be developed to predict and improve MAD treatment outcome. Since 2008 new thermoplastic MADs have been introduced, which are thinner, have better retention and are easier to use. Due to better retention, these devices may also be used in an in-home setting after using them for UA evaluation during DISE.

The primary aim of the present study was to improve insight in agreement in the degree of obstruction and configuration of the UA between jaw thrust and an oral device *in situ* during DISE with the ultimate goal to improve the predictive value of DISE as a selection tool for MAD treatment in OSA. Secondly, we wanted to evaluate the theoretical implications on clinical decision making using either the jaw thrust or a new generation boil-and-bite MAD as potential screening instruments.

METHODS

Study participants

We performed a single-centre prospective cohort study including patients who underwent DISE at the Department of Otolaryngology, Head and Neck surgery of the OLVG (Amsterdam, the Netherlands) between January 2019 and July 2019. Patients were included when aged 18 years and older, diagnosed with OSA confirmed by polysomnography (PSG, AHI ≥ 5 events per hour) and if they were able to give written informed consent. Patients were excluded in case of poor dental condition (e.g., partial or complete edentulism, extensive periodontal disease or tooth decay) or when patients were diagnosed with central sleep apnea (> 50% of central apneas).

Ethical considerations

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Declaration of Helsinki of 1975. Data on study subjects was collected and stored encoded to protect personal information. All patients gave written informed consent.

Study-related procedures

Polysomnography

The results of a full-night diagnostic PSG (EMBLA® A10/Titanium, Medcare Flaga, Iceland, and SomnoscreenTM, SOMNOmedics GmbH, Randersacker, Germany) were collected in each subject at baseline. To determine the stages of sleep, an electroencephalogram (Fp1, Fp2, C3 C4, O1, O2), electro-oculogram and electromyogram of the submental muscle were obtained. Nasal airflow was measured by a nasal cannula/pressure transducer inserted in the opening of the nostrils. Arterial blood oxyhemoglobin was recorded with the use of a finger pulse oximeter. Thoracoabdominal excursions were measured qualitatively by respiratory effort belts placed over the rib cage and abdomen. Body position was determined by a position sensor, which differentiated between the upright, left side, right side, prone and supine position.

Sleep stages were scored using 30-s epochs according to American Academy of Sleep Medicine (AASM) criteria, with N3 reflecting slow wave sleep. Obstructive respiratory events were analysed according to the AASM criteria 2017 [15] An obstructive respiratory event in adults was scored as an apnea if there was a drop in the peak signal excursion by ≥ 90% with a duration of at least ≥ 10 seconds. A hypopnea was defined as a decrease of airflow by ≥ 30% during a period of ≥ 10 seconds combined with an oxygen desaturation of ≥ 3%. The number of apneic or hypopneic episodes per hour of sleep was referred as the AHI.

Fitting of the MyTAP

The MyTAP (My Thornton Adjustable Positioner, Airway Management Inc., Dallas, TX, USA) is a new-generation thermoplastic boil-and-bite MAD, which consists of two separate trays of polymeric material. The MyTAP fully covers the upper and lower dental arches and can be fixed in a protrusive position by a single screw in the frontal area of the appliance. The appliance was adjusted for each patient according to the manufacturer's recommendations and instructions. First, both trays are heated in boiling water until the material turned transparent. Second, the trays were — one by one — placed covering the upper or lower dental arch whereupon the patient was instructed to bite into habitual occlusion, by actively closing the mouth for three minutes. After fitting both trays, a shim

was placed between the trays resulting in a vertical opening allowing movement of the tongue. In patients with a BMI <30 kg/m^2 a 6mm shim and in patients with BMI >30 kg/m^2 a 9mm shim was used. Subsequently, the mandible was advanced by tightening the screw in the frontal area until the patient indicated an uncomfortable sensation. This was followed by a 1mm retraction of the mandible, described as the maximal comfortable protrusion (MCP).

Drug-induced sleep endoscopy

DISE procedure was performed according to the practice guidelines as recommended in the European position paper on DISE (update 2017). [16] DISE procedure took place in a day care setting in a outpatient endoscopy room with standard anaesthetic equipment. The drug of choice for sedation was propofol. The level of sedation was controlled by a target controlled infusion pump using the methods described by Schnider et al. to calculate the effective dose. [17, 18] Prior to the intravenous (IV) infusion of propofol, 2cc lidocaine was given IV to prevent pain caused by the infusion of propofol. In all patients glycopyrrolate (Robinul) was given IV to prevent mucosal hypersecretion, since this could interfere with the quality of the endoscopic assessment. Proper sedation levels were achieved when the patient showed hyporesponsiveness to verbal and tactile stimuli or when the patient began to snore.

Initially, subjects were placed in the lateral position with the boil-and-bite MAD *in situ*. The boil-and-bite MAD was adjusted to MCP after proper sedation levels were achieved. Adequate and stable sedation levels were retained during the whole procedure. Patients were then tilted to the supine position — both head and trunk — with the boil-and-bite MAD still *in situ*. In both positions the UA was assessed at four different levels (velum, oropharynx, tongue base and epiglottis) according to the VOTE classification system. Subsequently, the boil-and-bite MAD was removed, after which the UA was observed in the lateral and the supine position, with and without a manually performed jaw thrust aiming at 65-75% protrusion of the mandible.

Classification system

To report on the anatomical structures causing UA collapse, the VOTE classification system was applied. [19] The VOTE classification system distinguishes between four different levels and structures that may be involved in UA collapse: velum (V), oropharynx (O), tongue base (T) and epiglottis (E). To define the degree of obstruction, three different categories are used: no obstruction in cases of a collapse less than 50% (scored as 0); a partial obstruction with a collapse between 50-75% and typically with vibration (scored as 1); or a complete collapse with a collapse of more than 75%

(scored as 2). An X is used when no observation can be made. Depending on the different site(s) involved in UA obstruction, the configuration may be anteroposterior (A-P), lateral or concentric.

Definitions

Patients were considered as being suitable candidates for MAD treatment when a decrease in degree of obstruction was observed of at least 1 point at each potential level of obstruction, leading to absence of a complete collapse at V, O, T or E level.

Statistical analysis

Statistical analysis was performed using SPSS (version 22), SPSS Inc., Chicago, IL). Quantitative data were reported as mean and standard deviation (SD) or as median and Q1-Q3 when not normally distributed. A p value of < 0.05 was considered to indicate statistical significance.

Agreement among observations made by using the two different screening instruments —jaw thrust and the boil-and-bite MAD — were calculated by dividing the number of agreements with regard to the degree of obstruction by the number of disagreements between both measurements. To correct for chance agreement and due the use of an ordinal scale, a weighted, Cohen's kappa was determined. Kappa values were interpreted as following: $k < 0$ poor; k 0 to 0.20 slight; 0.21 – 0.4 fair; 0.41 to 0.60 moderate; k 0.61 to 0.8 substantial and $k > 0.81$ almost perfect agreement.

Sample size

The aim of this study was to reject the null hypothesis that the effect on UA patency of manually performed jaw thrust is similar to the effect of the boil-and-bite MAD during DISE. To compare two measure instruments a minimum of 50 subjects had to be included. [20]

RESULTS

A total 63 patients were included in this study. In three patients measurement with the boil-and-bite MAD *in situ* failed due to technical problems with the fitting of the device. Therefore the results of 60 patients were used for analysis.

Of the 60 patients, 50 patients were male (83.3%) and 45 patients were diagnosed with position-dependent OSA (POSA) according to Cartwright's criteria. [21] The mean age of all patients was 46.9 ± 11.8 years, with a BMI of 27.9 ± 2.7 kg/m^2 and a neck circumference of 40.8 ± 3.0 cm. The median AHI was 15.9/h (12.1, 26.0), the median supine AHI 36.4/h (19.4, 65.3) and the median non-supine AHI 7.1/h (2.8, 19.9). Patients spent a median percentage of total sleeping time in the supine position

of 39.3% (12.5, 51.5). The median oxygen desaturation index (ODI) was 21.9/h (15.5, 28.6). The MCP was 84.2 ± 13.2% of the maximal protrusion of the mandible. **Table 1** provides an overview of the baseline characteristics of the total study group.

Table 1. Baseline characteristics

Patient characteristic	**Total** **N=60**
Age (years)	46.9 ± 11.8
Male / Female	50/10
BMI (kg/m^2)	27.9 ± 2.7
Neck circumference (cm)	40.8 ± 3.0
Total AHI (events/hour)	15.9 (12.1, 26.0)°
Supine AHI (events/hour)	36.4 (19.4, 65.3)°
Non-supine AHI (events/hour)	9.9 (3.9, 18.2)°
TST in the supine position (%)	39.3 (12.5, 51.5)°
ODI (events/hour)	21.9 (15.5, 28.6)°
MCP (%)*	84.2 ± 13.8

Data presented as mean ± standard deviation or ° median (Q1, Q3)

BMI body mass index, *AHI* apnea-hypopnea index, *TST* total sleeping time, *ODI* oxygen desaturation index, *MCP* maximal comfortable protrusion

* MCP as a percentage of the maximal protrusion of the mandible during wakefulness

Agreement in degree of obstruction in the supine position comparing jaw thrust and boil-and-bite MAD

Agreement amongst observations in the supine position with regard to degree of obstruction was 60% (N=36, k=0.41) at the level of the velum, 68.3% (N=41, k=0.35) at the level of the oropharynx, 58.3% (N=35, k=0.28) at the level of the tongue base and 56.7% (N=34, k=0.14) at the level of the epiglottis. An overview can be found in **table 2.**

Agreement in degree of obstruction in the lateral position comparing jaw thrust and boil-and-bite MAD

Agreement amongst observations in the lateral position with regard to degree of obstruction was 81.7% (N=49, k=0.32) at the level of the velum, 71.7% (N=43, k=0.36) at the level of the oropharynx, 90.0% (N=54, k=0.23) at the level of the tongue base and in 96.7% (N=58, k= could not be determined) at the level of the epiglottis. **Table 3** provides an overview of the agreement in degree of obstruction comparing jaw thrust and boil-and-bite MAD.

Table 2. Agreement in degree of obstruction in the supine position comparing jaw thrust and MyTAP

Level	Degree of obstruction	Supine position	Jaw thrust (N)	Boil-and-bite MAD (N)	Overall percentage of agreement	Kappa	Interpretation kappa
V	0	7	18	29	60%	0.41	Moderate
	1	9	22	16			
	2	44	20	15			
O	0	30	35	49	68.3%	0.35	Fair
	1	4	13	8			
	2	26	12	3			
T	0	18	43	28	58.3%	0.28	Fair
	1	16	12	23			
	2	26	5	9			
E	0	25	52	32	56.7%	0.14	Slight
	1	12	6	15			
	2	13	2	13			

V velum, *O* oropharynx, *T* tongue base, *E* epiglottis

0 = <50% of obstruction, 1= 50-75% of obstruction, 2= > 75% of obstruction

Table 3. Agreement in degree of obstruction in the lateral position comparing the boil-and-bite MAD and jaw thrust

Level	Degree of obstruction	Lateral position	Jaw thrust (N)	Boil-and-bite MAD (N)	Overall percentage of agreement	Kappa	Interpretation kappa
V	0	27	50	52	81.7%	0.32	Fair
	1	17	4	6			
	2	16	6	2			
O	0	21	44	42	71.7%	0.36	Fair
	1	9	10	10			
	2	30	6	8			
T	0	44	59	53	90%	0.23	Fair
	1	11	1	7			
	2	5	0	0			
E	0	51	60	58	96.7%	CND	N/A
	1	8	0	2			
	2	1	0	0			

MAD mandibular advancement device, *V* velum, *O* oropharynx, *T* tongue base, *E* epiglottis

0 = <50% of obstruction, 1= 50-75% of obstruction, 2= > 75% of obstruction

CND could not be determined, *N/A* not applicable

Agreement of the configuration of collapse in the supine and the lateral position comparing boil-and-bite MAD and jaw thrust

In the supine position agreement with regard to the configuration of obstruction at the level of the velum was found in 20 out of 29 patients (69.0%), with a kappa of 0.41. In seven patients a concentric collapse was found when applying jaw thrust, which was modified to an A-P collapse with the boil-and-bite MAD *in situ*. In two patients a lateral collapse was observed during jaw thrust, which changed to a concentric collapse with the boil-and-bite MAD in place. Agreement on configuration of obstruction in the lateral position was found in all patients (see **table 4 and 5**)

Table 4. Agreement in configuration in the supine position comparing the boil-and-bite MAD and jaw thrust

Level	Configuration	Jaw thrust (N)	Boil-and-bite MAD (N)	Overall percentage of agreement	Kappa	Interpretation kappa
V	A-P	23	24	69.0%	0.41	Moderate
	Lateral	3	1			
	Concentric	16	6			
O	Lateral	25	11	100%	N/A	N/A
T	A-P	17	32	100%	N/A	N/A
E	A-P	8	28	100%	N/A	N/A
	Lateral	0	0			

MAD mandibular advancement device*, V* velum, *O* oropharynx, *T* tongue base, *E* epiglottis, *A-P* Anteroposterior*, N/A* not applicable

Table 5. Agreement in configuration in the lateral position comparing the boil-and-bite MAD and jaw thrust

Level	Configuration	Jaw thrust (N)	Boil-and-bite MAD (N)	Overall percentage of agreement	Kappa	Interpretation kappa
V	A-P	2	3	100%	1.00	Perfect
	Lateral	4	3			
	Concentric	4	2			
O	Lateral	16	17	100%	N/A	N/A
T	A-P	1	7	100%	N/A	N/A
E	A-P	0	2	CND	N/A	N/A
	Lateral	0	0			

MAD mandibular advancement device*, V* velum, *O* oropharynx, *T* tongue base, *E* epiglottis, *A-P* Anteroposterior*, CND* could not be determined, *N/A* not applicable

Theoretical identification of suitable candidates for MAD treatment

Jaw thrust

Assuming that jaw thrust is a valid screening instrument for MAD treatment outcome, 30 patients would have been prescribed a MAD based on the effect of a manually performed jaw thrust. Of the 30 patients that would have been labelled as non-suitable candidates for MAD treatment, this was due to a complete residual retropalatal collapse in 24 patients. In two patients a complete collapse at hypopharyngeal level was observed and in four patients a residual multilevel collapse was present.

Boil-and-bite MAD

When the boil-and-bite MAD would have been used, 34 patients would have been selected for MAD treatment. In that case, 11 patients would have been identified as non-suitable candidates due to a complete residual retropalatal collapse, 11 patients due to a complete residual hypopharyngeal collapse and in three patients a persistent multilevel collapse was found.

A floppy epiglottis was present in only one patient when applying jaw thrust and in five patients with the boil-and-bite MAD *in situ*.

DISCUSSION

Currently, the use of DISE to predict MAD treatment outcome is controversial and there is a lack in consensus on the use of a manually performed jaw thrust mimicking the real life effect of a MAD. To best of our knowledge this is the first study to describe the use and comparison of two potential screening instruments during DISE — jaw thrust and a new-generation thermoplastic boil-and-bite MAD — to predict the effect of MAD treatment. The results of this study indicate that there is only a slight to moderate agreement on the degree of obstruction measured with jaw thrust and the boil-and-bite MAD, especially in the supine position. The latter is not surprising, since the majority of patients was position-dependent with only few UA obstructions in the lateral position. Overall, jaw thrust seems to be more effective in resolving obstructions at hypopharyngeal level — tongue base and epiglottis — than the boil-and-bite MAD during DISE. In contrast, obstructions at retropalatal level — velum and oropharynx — were more often improved with the boil-and-bite MAD *in situ* than when jaw thrust was applied.

When comparing the two screening instruments, two major differences can be identified. First, the degree of advancement of the mandible during jaw thrust is less precise than the pre-set degree of protrusion of the boil-and-bite MAD, which is set at the MCP. Second, jaw thrust takes no account for

the thickness of a MAD and therefore does not include VO, which is generated by the boil-and-bite MAD.

The greater improvement of UA patency at hypopharyngeal level with jaw thrust is slightly surprising, since the MCP used for the pre-set degree of protrusion for the boil-and-bite MAD was in general more than 65-75%. The degree of protrusion with jaw thrust was estimated to be 65-75%, while the degree of protrusion with the boil-and-bite MAD was on average 84.2% of the maximal protrusion during wakefulness. One would therefore expect to find greater improvement of UA patency with boil-and-bite MAD *in situ.* On the other, we assume that the estimated 65-75% protrusion of the mandible is probably an underestimation, which could explain the difference in results. Furthermore, we hypothesize that the maximum amount of mandibular protrusion during DISE is more pronounced when compared with the awake state. Firstly because of the neuromuscular boundaries that patients experience when they are not sedated. Secondly, one must keep in mind that the percentage of protrusion during determined during DISE is a subjective and estimated value, which is not objectively determined. These phenomena probably explain why the percentage of protrusion determined during the jaw thrust manoeuvre is an underestimate when compared to the degree of protrusion as determined with the boil-and-bite MAD.

The difference in effect at retropalatal level is a novel finding. We hypothesize that the greater effect of the boil-and-bite MAD on UA patency at this level is probably caused by the VO of the mouth that is created with the oral device in place. By adding VO, stretching forces on the lateral wall of the pharynx increase, leading to a decrease in UA collapsibility and stabilization of the airway. If correct, this would also explain the differences in configuration of obstruction at palatal level. In seven patients a concentric collapse was observed when applying jaw thrust, which was altered to an A-P configuration with the boil-and-bite MAD *in situ* (i.e. opening of the pharynx in the lateral, but not A-P dimension).

Several studies in the literature focus on the effect of VO on MAD effectiveness and UA collapsibility. Unfortunately, the results vary among studies. Pitsis et al. concluded that VO of the mouth induced by a MAD does not significantly influence treatment efficacy [22], while Rose et al. found that MAD treatment was more effective with increased VO. [23] In addition, Ferguson et al. concluded that the effect of VO on the efficacy of MAD remains undecided. [24] The effect of VO on UA patency without a MAD *in situ* was previously studied by Vroegop et al. Their results indicated that increased VO, without advancement of the mandible, had an adverse effect on pharyngeal dimensions in the majority of patients at hypopharyngeal level. [25] Unfortunately, they did not report on outcomes with

regard to obstruction at retropalatal level making adequate comparison with the results of this study difficult.

Limitations

DISE was performed by one experienced endoscopist (PV), but were not reassessed by a second observer. This could potentially have influenced interpretation of DISE. Nevertheless, by using only one observer interobserver variability was avoided. In addition, the majority of patients were diagnosed with mild to moderate position-dependent OSA, which might make the results of this study less applicable to more severe non-positional OSA patients.

Clinical implications and future research

The results of this study emphasize the need for an alternative to jaw thrust as a screening method and prediction tool for MAD treatment outcome used during DISE. Jaw thrust seems to be less effective in improving UA collapse at retropalatal level than the boil and bite MAD, which was used in this study. In several patients, this could have led to an overestimation of assessment of ´not suitable for MAD treatment'. Furthermore, advancement of the mandible using jaw thrust during DISE is probably greater than the MCP during wakefulness in the majority of patients. Therefore the MCP seems to be more representative when is comes to the expected advancement of the mandible that can be achieved when initiating MAD treatment.

CONCLUSIONS AND FUTURE RESEARCH

The results of this study indicate that there is only a slight to moderate agreement in degree of obstruction measured with jaw thrust and a new-generation boil–and-bite MAD — the MyTAP — during DISE. Overall, a greater improvement of UA patency at hypopharyngeal level was observed when applying jaw thrust. In contrast, jaw thrust was less effective in improving UA obstruction at retropalatal level than the MyTAP. There is still a need for an alterative to jaw thrust that can be used as a screening method and prediction tool for MAD treatment outcome during DISE. This is the first part of a two-part study. In the second part of this study the correlation between DISE findings and MAD treatment outcome will be evaluated to further unravel the predictive value on MAD effectiveness.

REFERENCES

1. Rotenberg BW, Vicini C, Pang EB, Pang KP. Reconsidering first-line treatment for obstructive sleep apnea: a systematic review of the literature. *J Otolaryngol Head Neck Surg*. 2016;45:23

2. Chan AS, Lee RW, Cistulli PA. Dental appliance treatment for obstructive sleep apnea. *Chest*. 2007;132(2):693-9

3. Hoekema A, Stegenga B, Wijkstra PJ, van der Hoeven JH, Meinesz AF, de Bont LG. Obstructive sleep apnea therapy. *J Dent Res*. 2008;87(9):882-7

4. Cunha TCA, Guimaraes TM, Schultz TCB, et al. Predictors of success for mandibular repositioning appliance in obstructive sleep apnea syndrome. *Braz Oral Res*. 2017;31:e37

5. Dieltjens M, Wouters K, Verbruggen A, et al. Drug-induced Sedation Endoscopy (DISE) findings correlate with treatment outcome in OSA patients treated with oral appliance therapy in a fixed mandibular protrusion. *Am J Respir Crit Care Med*. 2015;191:A2474

6. Op de Beeck S DM, Verbruggen AE, et al. Op de Beeck S, Dieltjens M, Verbruggen AE, et al. Phenotypic Labeling using Drug-Induced Sleep Endoscopy Improves Patient Selection for Mandibular Advancement Device Outcome. *American journal of respiratory and critical care medicine*. 2018 (submitted)

7. De Vito A, Llatas MC, Vanni A, et al. European position paper on drug-induced sedation endoscopy (DISE). *Sleep and Breathing*. 2014;18(3):453-65

8. Hohenhorst W, Ravesloot M, Kezirian E, De Vries N. Drug-induced sleep endoscopy in adults with sleep-disordered breathing: technique and the VOTE classification system. *Operative Techniques in Otolaryngology-Head and Neck Surgery*. 2012;23(1):11-18

9. Johal A, Battagel JM, Kotecha BT. Sleep nasendoscopy: a diagnostic tool for predicting treatment success with mandibular advancement splints in obstructive sleep apnoea. *Eur J Orthod*. 2005;27(6):607-14

10. Johal A, Hector MP, Battagel JM, Kotecha BT. Impact of sleep nasendoscopy on the outcome of mandibular advancement splint therapy in subjects with sleep-related breathing disorders. *J Laryngol Otol*. 2007;121(7):668-75

11. Eichler C, Sommer JU, Stuck BA, Hormann K, Maurer JT. Does drug-induced sleep endoscopy change the treatment concept of patients with snoring and obstructive sleep apnea? *Sleep Breath*. 2013;17(1):63-8

12. Vanderveken OM, Vroegop AV, van de Heyning PH, Braem MJ. Drug-induced sleep endoscopy completed with a simulation bite approach for the prediction of the outcome of treatment of obstructive sleep apnea with mandibular repositioning appliances. *Operative Techniques in Otolaryngology-head and neck surgery*. 2011;22(2):175-82

13. Vroegop AV, Vanderveken OM, Dieltjens M, Wouters K, Saldien V, Braem MJ. Sleep endoscopy with simulation bite for prediction of oral appliance treatment outcome. *Journal of sleep research*. 2013;22(3):348-55

14. Vanderveken OM, Devolder A, Marklund M, et al. Comparison of a custom-made and a thermoplastic oral appliance for the treatment of mild sleep apnea. *Am J Respir Crit Care Med*. 2008;178(2):197-202

15. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events: deliberations of the sleep apnea definitions task force of the American Academy of Sleep Medicine. *Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine*. 2012;8(5):597

16. De Vito A, Carrasco Llatas M, Ravesloot MJ, et al. European position paper on drug-induced sleep endoscopy: 2017 Update. *Clinical Otolaryngology*. 2018;43(6):1541-52

17. Schnider T, Minto C. Pharmacokinetic models of propofol for TCI. *Anaesthesia*. 2008;63(2):206-06

18. Schnider TW, Minto CF, Gambus PL, et al. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology: The Journal of the American Society of Anesthesiologists*. 1998;88(5):1170-82

19. Kezirian EJ, Hohenhorst W, de Vries N. Drug-induced sleep endoscopy: the VOTE classification. *Eur Arch Otorhinolaryngol*. 2011;268(8):1233-36

20. De Vet HC, Terwee CB, Mokkink LB, Knol DL. *Measurement in medicine: a practical guide*. Cambridge University Press; 2011

21. Cartwright RD. Effect of sleep position on sleep apnea severity. *Sleep*. 1984;7(2):110-4

22. Pitsis AJ, Darendeliler MA, Gotsopoulos H, Petocz P, Cistulli PA. Effect of vertical dimension on efficacy of oral appliance therapy in obstructive sleep apnea. *Am J Respir Crit Care Med*. 2002;166(6):860-4

23. Rose E, Staats R, Virchow C, Jonas IE. A comparative study of two mandibular advancement appliances for the treatment of obstructive sleep apnoea. *Eur J Orthod*. 2002;24(2):191-8

24. Ferguson KA, Cartwright R, Rogers R, Schmidt-Nowara W. Oral appliances for snoring and obstructive sleep apnea: a review. *Sleep*. 2006;29(2):244-62

25. Vroegop AV, Vanderveken OM, Van de Heyning PH, Braem MJ. Effects of vertical opening on pharyngeal dimensions in patients with obstructive sleep apnoea. *Sleep Med*. 2012;13(3):314-6

Floppy epiglottis during drug-induced sleep endoscopy: an almost complete resolution by adopting the lateral posture

5

P.E. Vonk, M.J.L. Ravesloot, K.M. Kasius,
J.P. van Maanen, N. de Vries

Sleep Breath. 2019 Apr 24. doi: 10.1007/s11325-019-01847-x

ABSTRACT

Purpose: To analyze the presence of a floppy epiglottis (FE) during drug-induced sleep endoscopy in non-apneic snoring patients, non-positional obstructive sleep apnea (OSA) patients (NPP) and position-dependent OSA patients (PP) and to evaluate the impact of maneuvers and body position during DISE, including jaw thrust, supine and lateral head (and trunk) position.

Methods: Retrospective cohort study.

Results: In total 324 patients were included. In 60 patients (18.5%) a FE was found in supine position; seven non-apneic snoring patients and 53 OSA patients. When performing lateral head rotation only, a FE was present in four patients (NPP, N=0 ; PP, N=4). When patients were tilted to both lateral head and trunk position a FE was found in only one subject. After applying jaw thrust, a FE was still present in 10 patients. The prevalence of a FE did not differ between NPP and PP. When comparing baseline characteristics between patients with and without a FE in supine position no significant differences were found.

Conclusion: A FE appears almost exclusively in supine position. In patients with a FE, positional therapy can be a promising alternative as a standalone treatment, but also as part of combination therapy with for example mandibular advancement devices or less invasive forms of upper airway surgery.

Keywords: obstructive sleep apnea, epiglottic collapse, floppy epiglottis, drug-induced sleep endoscopy, positional

INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by recurrent episodes of upper airway collapse causing oxygen desaturations and fragmented sleep. In the majority of OSA patients, the severity of upper airway collapse is influenced by body position, in which supine position is usually the worst sleeping position. [1-6]

The underlying pathophysiological mechanism explaining different collapse patterns in supine and non-supine sleeping position remains poorly understood. One of the structures which is known to cause upper airway obstruction and apneas is the epiglottis. It has been suggested that a collapse at this level of the upper airway is enhanced by sleeping position and seems to occur more often in supine compared to non-supine position. [7, 8]

Currently, diagnosis of an epiglottic collapse requires invasive studies, since as a rule it cannot be established by physical examination or awake endoscopy. One of these invasive studies is drug-induced sleep endoscopy (DISE). DISE is an unique and dynamic diagnostic tool used to gain more information on upper airway collapse patterns in order to improve patient selection and treatment planning in OSA patients. In a study by Azarbazin et al. an algorithm has been proposed to identify airflow patterns and its relation to epiglottic collapse as distinct from other sites of collapse leading to less invasive studies. [9] Unfortunately, these algorithms are not externally validated or yet part of daily practice. In literature many definitions have been used to define an epiglottic collapse: 1) secondary to an anterior-posterior collapse of the tongue base pushing the epiglottis backwards; 2) lateral collapse of the epiglottis for example due to underdevelopment of the epiglottis itself; 3) a complete isolated anterior-posterior epiglottic collapse, also called floppy epiglottis (FE) or trap door phenomenon.

Focusing on the latter, treatment remains challenging. Previous studies showed that conventional treatment for this type of collapse is difficult and often not successful. A FE has been linked to CPAP failure, suggesting that the epiglottis is pushed further backwards on application of CPAP. [10-12] Treatment with mandibular advancement devices (MADs), designed to advance the mandible in a forward position and protruding several structures in the upper airway including the epiglottis, regarded as therapy of choice, is not always successful. [13]

Besides conventional OSA treatment, several surgical techniques have been described in literature to resolve epiglottic collapse, including (partial) epiglottectomy with a (CO_2) laser. [14-16] Although many studies report objective improvement of the apnea-hypopnea index (AHI), there are also several (major) complications - aspiration, bleeding whether or not compromising the airway, dysphagia and odynophagia - related to epiglottis surgery, which can have serious implications. In addition, a recent

case report showed that upper airway stimulation also had a beneficial effect on the presence of a FE observed during DISE. [17]

In our center, DISE is performed in different body positions, i.e. in supine position and lateral head (and trunk) position, and when applying jaw thrust. Based on observations made during DISE, we hypothesize that a FE is in particular present in supine position and to a lesser extent when the patient is lying in lateral body position. We were interested to see whether we could confirm our hypothesis by retrospectively analyze if a FE is more common in position-dependent OSA patients (PP) compared to non-positional OSA patients (NPP) during DISE. Furthermore, we were interested in evaluating the impact of maneuvers and body position during DISE on a FE, including jaw thrust, supine and lateral head (and trunk) position.

MATERIAL AND METHODS

Patients

We performed a retrospective study, including a consecutive series of patients who underwent DISE in the Department of Otorhinolaryngology - Head and Neck surgery of the OLVG (Amsterdam, the Netherlands) between the 14th of August 2017 and the 6th of August 2018. Both non-apneic snoring patients and OSA patients were included. Patients were excluded from this study when polysomnography (PSG) data concerning supine and non-supine AHI and sleeping position was missing or when patients slept < 10% or > 90% of the total sleeping time (TST) in supine sleeping position, because subsequently supine or non-supine AHI could not be determined reliably. Patients were also excluded when DISE results were inconclusive (e.g. due to mucosal hypersecretion) and could therefore not be interpreted.

Definitions

Patients were diagnosed with position-dependent OSA (POSA) using Cartwright's criteria: a supine AHI of at least twice as high as non-supine AHI. [3] In this study we were only interested in patients with a complete anterior-posterior epiglottic collapse, not secondary to a collapse of the tongue base, further referred to as a FE.

DISE procedure

DISE was performed according to the practice guidelines as recommended in the European position paper on DISE (update 2017). [18] The procedure was performed in a quiet outpatient endoscopy

setting using propofol. The main reason to perform DISE was to evaluate surgical treatment options. Other indications included patients' eligibility for MAD treatment or combination therapy (e.g. MAD + positional therapy (PT)).

DISE was performed by one experienced ENT resident (PV), with a trained nurse anesthetist managing sedation and monitoring blood pressure, electrocardiogram and oxygen levels. The level of sedation was controlled by a target controlled infusion pump using the methods described by Schnider et al. to calculate the effective dose. [19, 20] Prior to the intravenous (IV) infusion of propofol, 2cc lidocaine was given IV to prevent pain caused by the infusion of propofol. In some patients Glycopyrrolate (Robinul) was given IV to prevent mucosal hypersecretion, since this could interfere with the quality of the endoscopic assessment.

Patient positioning

Initially, DISE evaluation was commenced in supine position. Subsequently, the head was rotated to the lateral position, to mimic the effect of non-supine sleeping position. [21] A jaw thrust was performed to mimic the effect of a MAD by gently protruding the mandible up to 65-75% of maximum protrusion. This maneuver was performed in both positions.

In contrast to what was previously thought, new study findings showed that the effect of lateral head rotation on upper airway patency in PP is not similar to lateral head and trunk position. [22] As a result, our DISE procedure remained unchanged in NPP, but in PP DISE was commenced in lateral head and trunk position. After adequate evaluation patients were maneuvered to supine position. Jaw thrust was performed in both positions. The head was not rotated to lateral position. Subsequently, results in NPP are presented using observations made in supine position and with the head rotated to lateral position. In PP results are described either using lateral head rotation or lateral head and trunk position.

VOTE classification system

To report on the anatomical structures causing upper airway collapse, the VOTE classification system was applied. The VOTE classification system distinguishes between four different levels and structures that may be involved in upper airway collapse, i.e. velum (V), oropharynx (O), tongue base (T) and epiglottis (E). To define the degree of obstruction, three different categories are used: no obstruction, with a collapse of 50% and less; a partial obstruction with a collapse between 50-75% and typically with vibration; or a complete collapse in which a collapse is seen that comprises more

than 75% of the upper airway lumen. An X is used when no observation can be made. Depending on the different site(s) involved in upper airway obstruction, the configuration may be anterior-posterior, lateral or concentric. [23]

Ethical considerations

In accordance with the Declaration of Helsinki, the study protocol was approved by the local Medical Ethical Committee. Informed consent was not required for this type of study. Data on study subjects was collected and stored anonymously to protect personal information.

Statistical analysis

Statistical analysis was performed using SPSS (version 21), SPSS Inc., Chicago, IL). Quantitative data are reported as mean ± SD or as median (Q1, Q3) when not normally distributed. A p value of <0.05 is considered to indicate statistical significance. To compare baseline characteristics between patients with and without a FE the unpaired T test was used in case of normally distributed data and the Mann-Whitney Test when data was not normally distributed. The chi-square test was used to analyze categorical data. A chi-square test was also used to analyze the correlation between the presence of a FE and POSA. To compare DISE findings in different body positions and when applying different maneuvers the Wilcoxon signed rank test was used.

RESULTS

A total of 428 patients were screened for this study. In 87 patients PSG results showed < 10% or > 90% of the TST in worst sleeping position. In 17 patients the degree and configuration of obstruction at the level of the epiglottis could not be observed. Therefore, only the results of 324 patients were used.

Patient characteristics - total population

Of the 324 patients, 269 patients were male (83.0%) and 291 patients (89.8%) were diagnosed with OSA (AHI ≥ 5 events per hour). Of all OSA patients, 211 (72.5%) were PP. The mean age of all patients was 48.4 ± 24.4 years, with a mean BMI of 27.1 ± 3.3 kg/m^2 and a median AHI of 17.7/h (8.3, 31.1) a median supine AHI of 33.5/h (15.3, 56.6) and a median non-supine AHI of 7.1/h (2.8, 19.9) Patients spent a median percentage of the TST in supine position of 38.3% (25.9, 52.2), the median oxygen desaturation index (ODI) was 19.8/h (10.3, 34.2). An overview comparing baseline characteristics in non-apneic snoring patients, NPP and PP can be found in **table 1**.

Patient characteristics - FE versus no FE in supine position

No significant differences were found between baseline characteristics in patients with or without a FE. In PP, 19.4% were diagnosed with a FE compared to 16.8% in NPP, but no significant correlation was found between the presence of a FE and the presence of position dependency (p=0.183). An overview of the baseline characteristics in patients with and without a FE in supine position is given in **table 2**.

Table 1. Baseline characteristics total population, no OSA, NPP and PP

Patient characteristic	**Total** **N=324**	**No OSA** **N=33**	**NPP** **N=80**	**PP** **N=211**	**p value**
Age (years)	48.4 ± 24.4	40.2 ± 10.0	48.3 ± 12.3	49.6 ± 28.8	0.688
Male / Female	269/55	22/11	61/19	186/25	0.002*
BMI (kg/m^2)	27.1 ± 3.3	25.8 ± 3.6	27.2 ± 3.5	27.2 ± 3.5	0.991
Total AHI (events/hour)	17.7 (8.3, 31.1)°	2.8 (1.6, 4.0)°	28.1 (13.1, 48.9)°	17.7 (10.3, 28.9)°	0.001*
Supine AHI (events/hour)	33.3 (15.3, 56.5)°	5.0 (2.0, 8.3)°	30.3 (15.9, 59.9)°	37.5 (22.6, 58.5)°	0.124
Non-supine AHI (events/hour)	7.1 (2.8, 19.8)°	1.1 (0.6, 2.2)°	25.4 (10.4, 41.0)°	6.1 (2.8, 14.0)°	<0.001*
TST in supine position (%)	40.2 ±18.8	42.3 ± 18.0	42.6 ± 18.2	38.9 ± 19.1	0.134
ODI (events/hour)	19.8 (10.3, 34.2)°	3.9 (2.7, 7.0)°	30.2 (15.1, 51.6)°	20.2 (12.3, 32.0)°	<0.001*

Data presented as mean ± standard deviation or ° median (Q1, Q3)

* p value < 0.05 comparing NPP and PP

OSA obstructive sleep apnea, *NPP* non-positional obstructive sleep apnea patients, *PP* positional obstructive sleep apnea patients, *BMI* body mass index, *AHI* apnea-hypopnea index, *TST* total sleeping time, *ODI* oxygen desaturation index

Table 2. Baseline characteristics in patients with and without a FE

Patient characteristic	**FE**	**No FE**	**FE vs no FE p value**
Number (%)	60 (18.5)	264 (81.5)	48 vs 228
Age (years)	47.5 ± 11.9	48.6 ± 26.4	0.756
Male / Female	53/7	216/48	0.914
BMI (kg/m^2)	27.0 ± 3.6	27.1 ± 3.3	0.787
Total AHI (events/hour)	14.4 (8.2, 25.0)°	18.3 (8.3, 32.4)°	0.317
Supine AHI (events/hour)	28.9 (14.3, 56.6)°	35.0 (15.5, 57.0)°	0.260
Non-supine AHI (events/hour)	5.9 (2.7, 16.0)°	8.1 (2.8, 20.1)°	0.173
TST in supine position (%)	41.1 (28.2, 63.1)°	37.6 (25.8, 51.5)°	0.475
ODI (events/hour)	20.0 (10.2, 31.3)°	19.8 (10.3, 34.8)°	0.949

Data presented as mean ± standard deviation or ° median (Q1, Q3)

*p value < 0.05

BMI body mass index; *AHI* apnea-hypopnea index; *TST* total sleeping time; *ODI* oxygen desaturation index

DISE findings

In 60 patients (18.5%) a FE was found in supine position; seven non apneic snoring patients (21.2%) and 53 were OSA patients (18.2%). In 58 patients a FE was part of a multilevel collapse of the upper airway. In only two patients a FE was present as an isolated collapse.

When performing jaw thrust in supine position, a FE was still present in 10 patients; a significant decrease ($p<0.001$). In one patient jaw thrust could not be performed due to temporomandibular joint problems. To mimic non supine sleeping position in NPP lateral head rotation was performed. In one patient this maneuver could not be applied due to preexistent neck injury. In none of the remaining 79 patients a FE was still present after performing this maneuver ($p<0.001$). In PP, lateral head rotation was performed in 89 patients and lateral head and trunk position in 121 patients. When performing lateral head rotation only, a FE was persistent in four patients. When patients were turned to lateral head and trunk position a FE was found to be persistent in only one subject. In lateral head (and trunk) position this improvement was statistically significant ($p<0.001$). An overview of DISE findings can be found in **table 3.**

Table 3. Overview of the presence of a FE in different body positions, with and without maneuvers in patients with no OSA, NPP and PP

Body position (+ maneuver)	**FE (N)**			
	No OSA	NPP	PP	Total
Supine	7	12	41	60*
Supine + jaw thrust	0	2	8	10*
Lateral head rotation	0	0	4	4*
Lateral head and trunk rotation	N/A	N/A	1	1*

FE floppy epiglottis; *OSA* obstructive sleep apnea; *NPP* non-positional OSA patients; *PP* positional OSA patients; *N/A* not applicable

* p value < 0.05

DISCUSSION

This study describes the effect of body position and jaw thrust on the presence of a FE during DISE. To the best of our knowledge, this is the first study that analyzes this phenomenon during DISE in non-apneic snoring patients and OSA patients. The results of this study indicate that a FE appears almost exclusively in supine position and to a lesser extent during lateral head (and trunk) rotation. Despite this phenomenon, the prevalence of a FE did not differ between NPP and PP. When comparing baseline characteristics between patients with and without a FE in supine position no significant differences were found.

The fact that we did not find a correlation between the presence of a FE and POSA might be explained by the finding that in the majority of included patients a multilevel collapse of the upper airway was observed during DISE. In three patients an isolated FE was found. One patient was indeed found to be position-dependent with obstructive events almost exclusively in supine position. The two other patients with an isolated FE were phenotypically different: they were younger, had a low BMI and had a supine AHI twice as high as the non-supine AHI. These characteristics are comparable to those of PP. [2, 5, 24, 25]

The prevalence of a FE in this study was 18.5%. In literature a wide variation of the prevalence of an epiglottic collapse can be found varying from 9.7% to 73.5%. [26] As mentioned before, this variation could be explained by the different definitions used in literature to describe an epiglottic collapse. It must be kept in mind that there is an important difference between a FE and an epiglottic collapse secondary to an anterior-posterior collapse of the tongue base.

In this study, 72.5% of all patients were PP. This is relatively high compared to the prevalence found in literature. This high prevalence could be explained by the fact that the prevalence of POSA decreases when OSA severity increases. [3-6, 27, 28] In case of severe OSA, CPAP is the first treatment of choice and does not require DISE. Therefore, patients undergoing DISE are mainly diagnosed with mild to moderate OSA.

Previous findings

The findings of this study are supported by the results of a study by Marques et al. in which 23 OSA patients underwent upper airway endoscopy during natural sleep. The aim of this study was to evaluate the effect of sleeping position and the correlation with pharyngeal structures involved in upper airway collapse. Additional recordings of airflow and pharyngeal pressure were simultaneously

executed. An epiglottic collapse was found in six subjects who showed substantial improvement in upper airway patency when turned to lateral body position. Objective measurements also showed a decrease in percentage of breaths exhibiting an epiglottic collapse (from 66.5% to 12.3%) and an increase in ventilation by 45% comparing supine to lateral body position. Surprisingly, no effect on upper airway collapse was found in patients with tongue-related obstruction. [7]

In another study by Victores et al. similar results were found with regard to the positive effect of body position on upper airway patency at the level of the epiglottis. [8] Interestingly, Safiruddin et al. found that lateral head rotation only was also associated with a decreased frequency of a partial/complete collapse at epiglottis level compared to supine position. [29]

Physiological aspects

Azarbarzin et al. analyzed flow characteristics correlated with the presence of a FE. They found that a FE was associated with flow features characterized by discontinuity and jaggedness. Unfortunately, changes in body position were not included. [9] When trying to understand the pathophysiological mechanism behind the correlation of body position and the presence of a FE, several hypotheses could be taken into consideration.

First of all, it has been thought that oropharyngeal structures respond to gravitational forces in the upper airway. In a study by Sutthiprapaporn et al. seven subjects were evaluated by cone beam CT while they were in upright or in supine position. They found that gravity enhances movement of oropharyngeal structures, such as the epiglottis and palate when changing from upright to supine position. Surprisingly, the hyoid bone did not move posteriorly but caudally. [30]

One could also argue that altering body position could lead to changes in the negative intrathoracic pressure, which as a result causes an increase in intraluminal pressure. This could hypothetically influence the critical closing pressure of the epiglottis. Unfortunately, no evidence on this topic is yet available in literature.

Limitations

There are several limitations in this study. First, data was retrospectively collected using an inclusion period during which new results were available showing that the effect of lateral head rotation on upper airway patency in PP is not similar to both lateral head and trunk position, in contrast to NPP. [22] Consequently, the results in PP are described either using lateral head rotation or lateral head and trunk position. Nevertheless, no FE was found in NPP during lateral head rotation in contrast to PP, which emphasizes that lateral head rotation in NPP is comparable to lateral head and trunk position and that a FE is a position dependent phenomenon.

Second, DISE was scored according to the VOTE classification system, which is a simplified system with known intra- and interobserver reliability. [31] But in this study, DISE was performed by only one endoscopist, clearly describing an epiglottic collapse caused by a complete anterior-posterior collapse of the tongue base or as an isolated complete anterior-posterior collapse of the epiglottis (e.g. FE), which, to our opinion, enhances intraobserver reliability.

Clinical relevance

Currently, treatment in OSA patients with a FE remains challenging and evidence based treatment options in this population are lacking. In the past, several surgical techniques of the epiglottis have been described, which are not without risks. CPAP might even worsen a FE resulting in low compliance and treatment failure and also MAD treatment is not always successful. It can be concluded that there is a demand for other treatment options in patients with a FE. Based on the results of this study, PT could be a promising alternative in patients with a FE, despite the fact that they might not suffer from POSA. It can be used as a standalone treatment, but due to the fact that a FE is usually part of a multilevel problem it can also be combined with MAD or less invasive forms of upper airway surgery limiting risks and complications. [32-35]

CONCLUSION

The results of this study indicate that a FE is a position dependent phenomenon, which appears almost exclusively in supine position. Despite this phenomenon, the correlation with the underlying pathophysiological mechanism in NPP and PP remains yet unclear.

Treatment planning in OSA patients with a FE remains challenging and evidence based treatment options in this population are lacking. Further studies are needed to show if PT can be a viable alternative as standalone treatment or as part of combination therapy (e.g. MAD or less invasive forms of upper airway surgery).

REFERENCES

1. Ravesloot M, Van Maanen J, Dun L, De Vries N. The undervalued potential of positional therapy in position-dependent snoring and obstructive sleep apnea—a review of the literature. *Sleep and Breathing*. 2013;17(1):39-49

2. Ravesloot MJ, Frank MH, van Maanen JP, Verhagen EA, de Lange J, de Vries N. Positional OSA part 2: retrospective cohort analysis with a new classification system (APOC). *Sleep Breath*. 2016;20(2):881-8

3. Cartwright RD. Effect of sleep position on sleep apnea severity. *Sleep*. 1984;7(2):110-4.

4. Oksenberg A. Positional and non-positional obstructive sleep apnea patients. *Sleep Med*. 2005;6(4):377-8

5. Richard W, Kox D, den Herder C, Laman M, van Tinteren H, de Vries N. The role of sleep position in obstructive sleep apnea syndrome. *Eur Arch Otorhinolaryngol*. 2006;263(10):946-50

6. Mador MJ, Kufel TJ, Magalang UJ, Rajesh SK, Watwe V, Grant BJ. Prevalence of positional sleep apnea in patients undergoing polysomnography. *Chest*. 2005;128(4):2130-7

7. Marques M, Genta PR, Sands SA, et al. Effect of Sleeping Position on Upper Airway Patency in Obstructive Sleep Apnea Is Determined by the Pharyngeal Structure Causing Collapse. *Sleep*. 2017;40(3)

8. Victores AJ, Hamblin J, Gilbert J, Switzer C, Takashima M. Usefulness of sleep endoscopy in predicting positional obstructive sleep apnea. *Otolaryngol Head Neck Surg*. 2014;150(3):487-93

9. Azarbarzin A, Marques M, Sands SA, et al. Predicting epiglottic collapse in patients with obstructive sleep apnoea. *Eur Respir J*. 2017;50(3)

10. Verse T, Pirsig W. Age-related changes in the epiglottis causing failure of nasal continuous positive airway pressure therapy. *J Laryngol Otol*. 1999;113(11):1022-5

11. Dedhia RC, Rosen CA, Soose RJ. What is the role of the larynx in adult obstructive sleep apnea? *Laryngoscope*. 2014;124(4):1029-34

12. Shimohata T, Tomita M, Nakayama H, Aizawa N, Ozawa T, Nishizawa M. Floppy epiglottis as a contraindication of CPAP in patients with multiple system atrophy. *Neurology*. 2011;76(21):1841-2

13. Kent DT, Rogers R, Soose RJ. Drug-Induced Sedation Endoscopy in the Evaluation of OSA Patients with Incomplete Oral Appliance Therapy Response. *Otolaryngol Head Neck Surg*. 2015;153(2):302-7

14. Catalfumo FJ, Golz A, Westerman ST, Gilbert LM, Joachims HZ, Goldenberg D. The epiglottis and obstructive sleep apnoea syndrome. *J Laryngol Otol*. 1998;112(10):940-3

15. Golz A, Goldenberg D, Westerman ST, et al. Laser partial epiglottidectomy as a treatment for obstructive sleep apnea and laryngomalacia. *Ann Otol Rhinol Laryngol*. 2000;109(12 Pt 1):1140-5

16. Bourolias C, Hajiioannou J, Sobol E, Velegrakis G, Helidonis E. Epiglottis reshaping using CO2 laser: a minimally invasive technique and its potent applications. *Head Face Med*. 2008;4:15

17. Heiser C. Advanced titration to treat a floppy epiglottis in selective upper airway stimulation. *Laryngoscope*. 2016;126 Suppl 7:S22-4

18. De Vito A, Carrasco Llatas M, Ravesloot MJ, et al. European position paper on drug-induced sleep endoscopy: 2017 Update. *Clinical Otolaryngology*. 2018;43(6):1541-52

19. Schnider T, Minto C. Pharmacokinetic models of propofol for TCI. *Anaesthesia*. 2008;63(2):206-06

20. Schnider TW, Minto CF, Gambus PL, et al. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology: The Journal of the American Society of Anesthesiologists*. 1998;88(5):1170-82

21. Safiruddin F, Koutsourelakis I, de Vries N. Upper airway collapse during drug induced sleep endoscopy: head rotation in supine position compared with lateral head and trunk position. *European Archives of Oto-Rhino-Laryngology*. 2015;272(2):485-88

22. Vonk PE, van de Beek MJ, Ravesloot MJL, de Vries N. Drug-induced sleep endoscopy (DISE): New insights in lateral head rotation compared to lateral head and trunk rotation in (non) positional obstructive sleep apnea patients. *The Laryngoscope*. 2018

23. Kezirian EJ, Hohenhorst W, de Vries N. Drug-induced sleep endoscopy: the VOTE classification. *Eur Arch Otorhinolaryngol*. 2011;268(8):1233-36

24. Oksenberg A, Silverberg DS, Arons E, Radwan H. Positional vs nonpositional obstructive sleep apnea patients: anthropomorphic, nocturnal polysomnographic, and multiple sleep latency test data. *Chest*. 1997;112(3):629-39

25. Itasaka Y, Miyazaki S, Ishikawa K, Togawa K. The influence of sleep position and obesity on sleep apnea. *Psychiatry Clin Neurosci*. 2000;54(3):340-1

26. Torre C, Camacho M, Liu SY, Huon LK, Capasso R. Epiglottis collapse in adult obstructive sleep apnea: A systematic review. *Laryngoscope*. 2016;126(2):515-23

27. Frank MH, Ravesloot MJ, van Maanen JP, Verhagen E, de Lange J, de Vries N. Positional OSA part 1: Towards a clinical classification system for position-dependent obstructive sleep apnoea. *Sleep Breath*. 2015;19(2):473-80

28. Ravesloot MJ, van Maanen JP, Dun L, de Vries N. The undervalued potential of positional therapy in position-dependent snoring and obstructive sleep apnea-a review of the literature. *Sleep Breath*. 2013;17(1):39-49

29. Safiruddin F, Koutsourelakis I, de Vries N. Analysis of the influence of head rotation during drug-induced sleep endoscopy in obstructive sleep apnea. *The Laryngoscope*. 2014;124(9):2195-99

30. Sutthiprapaporn P, Tanimoto K, Ohtsuka M, Nagasaki T, Iida Y, Katsumata A. Positional changes of oropharyngeal structures due to gravity in the upright and supine positions. *Dentomaxillofacial Radiology*. 2008;37(3):130-35

31. Vroegop AV, Vanderveken OM, Wouters K, et al. Observer variation in drug-induced sleep endoscopy: experienced versus nonexperienced ear, nose, and throat surgeons. *Sleep*. 2013;36(6):947-53

32. Benoist LB, Verhagen M, Torensma B, van Maanen JP, de Vries N. Positional therapy in patients with residual positional obstructive sleep apnea after upper airway surgery. *Sleep Breath*. 2016

33. van Maanen JP, de Vries N. Long-term effectiveness and compliance of positional therapy with the sleep position trainer in the treatment of positional obstructive sleep apnea syndrome. *Sleep*. 2014;37(7):1209-15

34. van Maanen JP, Meester KA, Dun LN, et al. The sleep position trainer: a new treatment for positional obstructive sleep apnoea. *Sleep and Breathing*. 2013;17(2):771-79

35. Ravesloot M, White D, Heinzer R, Oksenberg A, Pépin J. Efficacy of the New Generation of Devices for Positional Therapy for Patients with Positional Obstructive Sleep Apnea: A Systematic Review of the Literature and Meta-Analysis. *Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine*. 2017

Short-term results of upper airway stimulation in obstructive sleep apnea patients: the Amsterdam experience

6

P.E. Vonk, M.J.L. Ravesloot,
J.P. van Maanen, N. de Vries

Submitted

ABSTRACT

Objectives: 1) To retrospectively analyse single-centre results in means of surgical success, respiratory outcomes and adverse events after short-term follow-up in obstructive sleep apnea (OSA) patients treated with upper airway stimulation (UAS). 2) To evaluate the correlation between preoperative drug-induced sleep endoscopy (DISE) findings and surgical success.

Material and methods: retrospective descriptive cohort study, including a consecutive series of OSA patients undergoing UAS implantation.

Results: Forty-four patients were included. The total median AHI and oxygen desaturation index significantly decreased from 37.6 (30.4; 43.4) events/h to 8.3 (5.3; 12.0) events/h ($p < 0.001$) and 37.1 (28.4; 42.6) events/h to 15.9 (11.1; 21.6) events/h. Surgical success was 88.6% and did not significantly differ between patients with or without a complete collapse at retropalatal level ($p=0.784$). The most common therapy-related adverse event reported was (temporary) stimulation-related discomfort.

Conclusions: UAS has proven to be an effective and safe treatment in OSA patients with CPAP intolerance or failure. There was no significant difference in surgical outcome between patients with a tongue base collapse with or without a complete anteroposterior collapse at the level of the palate.

Key words: obstructive sleep apnea, upper airway stimulation, hypoglossal nerve stimulation, drug-induced sleep endoscopy

INTRODUCTION

Obstructive sleep apnea (OSA) is the most prevalent sleep-related breathing disorder caused by episodes of partial or complete obstruction of the upper airway during sleep. Currently, continuous positive airway pressure (CPAP) is the gold-standard therapy for moderate to severe OSA, but its non-compliance rate is often high due to poor tolerance and low acceptance. [1]

Alternative treatments to CPAP include mandibular advancement devices (MAD), positional therapy (PT) or upper airway surgery. The latter aims to improve upper airway patency in order to prevent obstruction during sleep. Conventional surgical approaches to the upper airway for treatment for moderate to severe OSA have mediocre results, are often painful, with potential serious complications and side effects. Therefore, new surgical techniques, which are patient friendly, safe and have a high surgical success, are in high demand, especially in severe OSA patients with CPAP failure.

A recent development is hypoglossal nerve stimulation, also referred to as selective upper airway stimulation (UAS). By using a unilateral stimulation, selective fibres, which are mainly innervating the tongue protrusors, are stimulated during every breathing cycle. Furthermore, by including the cervical spine nerve (C1) the hyoid bone is displaced in an anterosuperior direction during stimulation. Although stimulation activates the tongue protrusors, previous studies have also shown that the effect of UAS is not limited to the level of the tongue base, but also improves upper airway patency at the level of the palate. It has been suggested that this multilevel effect is caused by palatoglossal coupling.[2]

UAS has shown to be effective in reducing objective respiratory parameters, such as the AHI, oxygen desaturation index (ODI) and subjective symptoms related to OSA, such as excessive daytime sleepiness. Adequate patient selection is of paramount importance. Previous studies have shown that UAS is effective in patients with an AHI ≥ 15 events/h and ≤ 65 events/h, a BMI ≤ 32 kg/m^2, a non-supine AHI ≥ 10 events/h, less than 25% central apneas and absence of concentric collapse at palatal level during drug-induced sleep endoscopy (DISE). [3-13] Some studies also show a good response in patients with a BMI ≤ 35 kg/m^2. [4, 7]

The US Food and Drug Administration (FDA) approved this new form of upper airway surgery in April 2014. During the first years after FDA approval, this procedure was only performed in cases of patient-specific reimbursement or in a commercial setting. In addition, since April 2017, UAS for a selective group of OSA patients with an AHI between 30 and 50 events/h and CPAP failure, or

intolerance, has been reimbursed as part of the basic health care system in the Netherlands as well. Currently, this surgical procedure is only performed in two centres in the Netherlands. One of the two centres is OLVG, Amsterdam. The primary aim of this study was to retrospectively analyse single-centre results in means of surgical success, respiratory outcomes and adverse events after short-term follow-up in OSA patients treated with UAS. The second aim was to describe preoperative DISE findings and evaluate whether patients with an isolated tongue base collapse prior to surgery had a higher chance of surgical success in comparison to OSA patients with both a complete collapse of the tongue base and at retropalatal level.

METHODS

Study participants

We performed a retrospective descriptive cohort study including a consecutive series of OSA patients undergoing UAS at the Department of Otorhinolaryngology Head and Neck Surgery, OLVG, Amsterdam, the Netherlands between January 2017 and April 2019. Patients were excluded if preoperative or postoperative polysomnography (PSG) data were not available.

The main criteria for implantation of the UAS system were an AHI ≥ 15 events/h and ≤ 65 events/h, a central apnea index < 25% of the total AHI, a non-supine AHI < 10 events per hour, a BMI < 32kg/m^2, CPAP failure or intolerance, and the absence of a complete concentric collapse (CCC) at the level of the velum observed during DISE.

DISE procedure and classification system

DISE was performed by one experienced ENT (PV) resident in a quiet outpatient endoscopy setting using propofol, to evaluate surgical treatment options. Sedation and monitoring of blood pressure, electrocardiogram and oxygen levels was managed by a trained nurse anaesthesist. The level of sedation was controlled by a target controlled infusion pump using the methods described by Schnider et al. to calculate the effective dose. [14,15] Prior to the intravenous (IV) infusion of propofol, 2cc lidocaine was given IV and in the majority of patients glycopyrrolate (Robinul) was given IV to prevent mucosal hypersecretion.

To report on the anatomical structures causing upper airway collapse, the VOTE classification system was used. The VOTE classification system distinguishes between four different levels and structures that may be involved in upper airway collapse, i.e. velum (V), oropharynx (O), tongue base (T) and epiglottis (E). Three categories were used to define the degree of obstruction: no obstruction, with a collapse of 50% and less; a partial obstruction with a collapse between 50-75% and typically with vibration; or a complete collapse in which a collapse was found that comprises more than 75% of the

upper airway lumen. Depending on the different site(s) involved in upper airway obstruction, the configuration may be anteroposterior, lateral or concentric. [16]

Implantation, activation and titration

Approximately one month after implantation the device was activated during a consultation at the outpatient clinic of the department of Otorhinolaryngology - Head and Neck Surgery. After activation of the device, patients gradually increase the stimulation amplitude to optimize both comfort and subjective effectiveness. Two months postoperatively, a post-titration visit took place consisting of a consultation and an in-lab titration using PSG to optimize therapeutic settings. Although the majority of patients only needed one titration night, a second titration night was indicated when the clinical laboratory technician was not able to titrate the therapy to an effective setting during the first titration night. This could be due to, for example, device-related issues or low sleep efficiency, which made sufficient titration not possible. When a second titration night was needed, data collected during this night was used in our analysis. Since respiratory parameters were collected during a titration PSG, the results used were from the portion of sleep when therapy was under therapeutic settings, also called the *treatment AHI*.

Ethical considerations

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Declaration of Helsinki of 1975. Data on study subjects was collected and stored encoded to protect personal information. For this type of study informed consent was not required.

Definitions

Surgical success is defined according to Sher's criteria: a reduction in preoperative AHI of more than 50% and a postoperative AHI < 20 events/h. [17] Patients who do not meet the criteria for surgical success after (advanced) titration, are further referred to as non-responders.

Obstructive respiratory events are analyzed according to the AASM criteria. An obstructive respiratory event in adults is scored as an apnea if there is a drop in the peak signal excursion by ≥ 90% with a duration of at least ≥ 10 seconds. A hypopnea is defined as a decrease of airflow by ≥ 30% during a period of ≥ 10 seconds combined with an oxygen desaturation of ≥ 3%. [18]

Statistical analysis

Statistical analysis was performed using SPSS (version 22), SPSS Inc., Chicago, IL. Quantitative data were reported as mean and standard deviation (SD) or as median and (Q1, Q3) when not normally distributed. To compare preoperative and postoperative PSG values, a paired T test was performed in case of normally distributed data. A Wilcoxon signed rank test was applied when data was not normally distributed. To identify a possible correlation between surgical success and collapse patterns observed during DISE, patients were divided into two subgroups. The first group consisted of patients with a complete collapse of the tongue base with or without a partial collapse of the palate. In the second subgroup, patients with both a partial or complete collapse of the tongue base, and a complete collapse of the palate were included. To compare the surgical success in both subgroups a chi-squared test was applied. A p value of < 0.05 was considered to indicate statistical significance.

RESULTS

Baseline characteristics

In total, 47 patients underwent UAS implantation between January 2017 and April 2019. Two patients did not want to undergo a titration night and in one patient a titration night was not yet performed due to a delayed healing process. Therefore, the results of 44 patients were included for analysis. Thirty-eight patients were male (86.4%). The mean age was 58.5 ± 9.6 years old with a mean BMI of 27.2 ± 2.4 kg/m^2. Patients had a preoperative median AHI of 37.6 (30.4; 43.4) events/h, a median supine AHI of 45.8 (34.1; 65.0) events/h and a median non-supine AHI of 26.2 (17.5; 35.9) events/h. The percentage of total sleeping time (TST) in supine position was 26.9% (910.2; 51.2) and the median oxygen desaturation index (ODI, ≥3%) was 37.1 (28.4; 42.6) events/h. An overview of baseline characteristics can be found in **table 1.**

Table 1. Baseline characteristics

	Total **N=44**
Gender (M/F)	38/6
Age (years)	58.5 ± 9.6
BMI (kg/m^2)	27.2 ± 2.4
AHI (events/h)	37.6 (30.4; 43.4)*
ODI (events/h, ≥3%)	37.1 (28.4; 42.6)*

Data presented as mean ± SD or * median (Q1; Q3)

BMI body mass index, *AHI* apnea-hypopnea index, *ODI* oxygen desaturation index

Preoperative and postoperative UAS outcomes

Respiratory parameters

The total median AHI significantly decreased from 37.6 (30.4; 43.4) events/h to 8.3 (5.3; 12.0) events/h, p value < 0.001. Both the supine AHI and the non-supine significantly decreased from 45.8 (34.1; 65.0) events/h to 15.4 (7.2; 27.8) events/h and 26.2 (17.5; 35.9) events/h to 5.2 (2.4; 10.0), respectively. Also a significant reduction in ODI from 37.1 (28.4; 42.6) events/h to 15.9 (11.1; 21.6) events/h, and significant increase in the minimum O_2 was found. An overview of preoperative and postoperative PSG parameters can be found in **table 2. Figure 1 and 2** provide a boxplot of the preoperative AHI vs. the treatment AHI and ODI vs. treatment ODI.

Table 2. Preoperative and postoperative PSG values

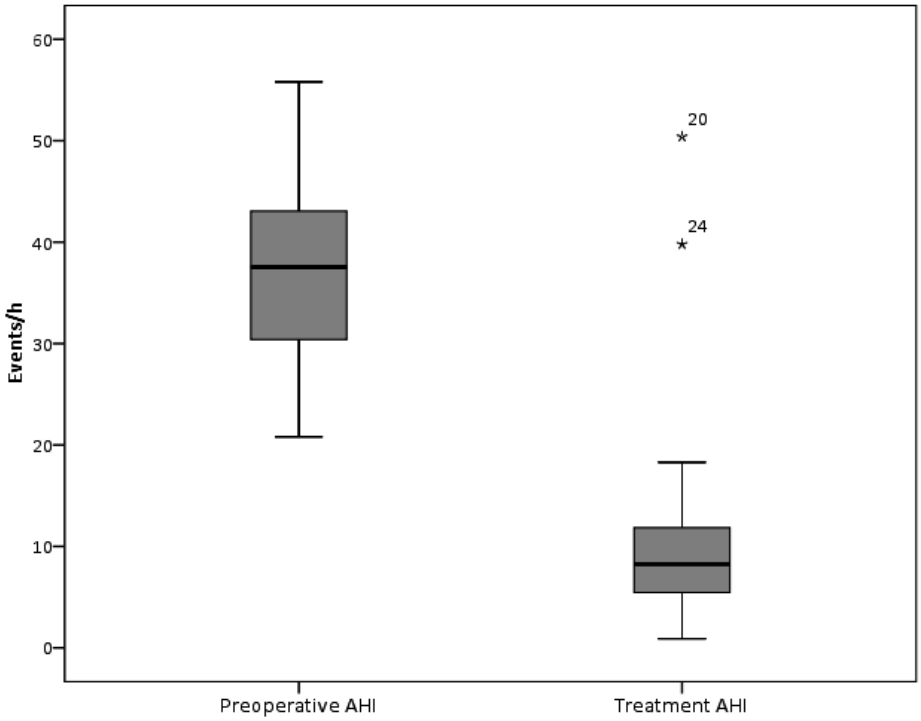
	Preoperative	**Postoperative**	**p value**
	Total N=44	Total N=44	
AHI (events/h)	37.6 (30.4; 43.4)	8.3 (5.3; 12.0)	<0.001*
Obstructive AI (events/h)	11.8 (2.7; 18.9)	0.8 (0.0; 2.2)	<0.001*
Supine AHI (events/h)	45.8 (34.1; 65.0)	15.4 (7.2; 27.8)	<0.001*
Non-supine AHI (events/h)	26.2 (17.5; 35.9)	5.2 (2.4; 10.0)	<0.001*
% TST in supine	26.9 (10.2; 51.2)	11.9 (0.0; 41.3)	0.021*
Minimum O_2 (%)	84.0 (81.0; 87.0)	88.0 (87.0; 90.0)	<0.001*
ODI (events/h, ≥3%)	37.1 (28.4; 42.6)	15.9 (11.3; 21.6)	<0.001*

Data presented as median (Q1; Q3)

* p value < 0.05 (Wilcoxon signed rank test)

PSG polysomnography, *AHI* apnea-hypopnea index, *AI* apnea index, *TST* total sleeping time, *ODI* oxygen desaturation index (≥3%)

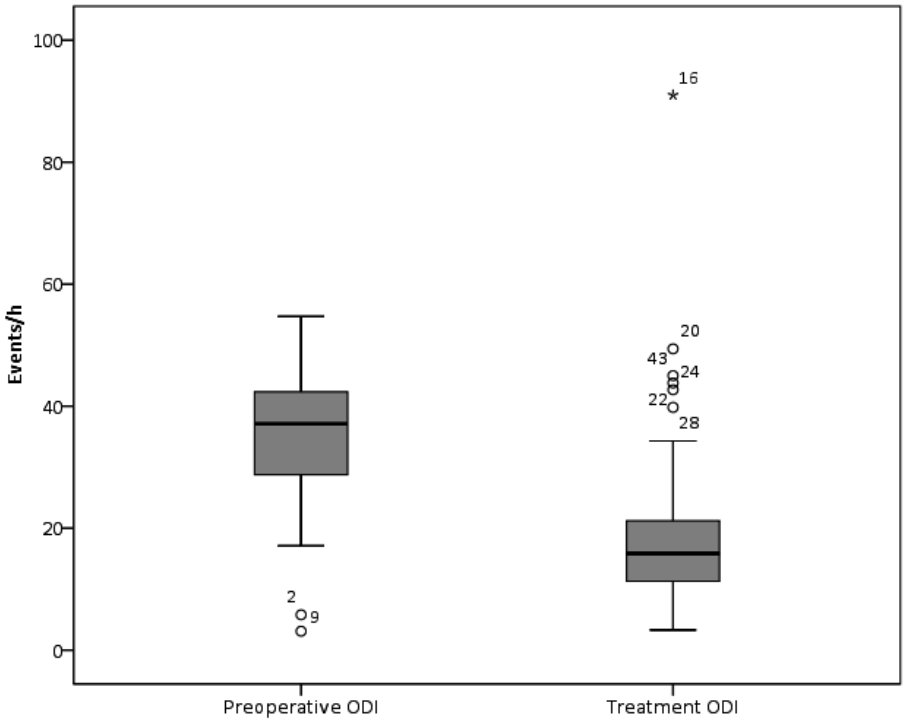
Figure 1. Boxplot of the preoperative and treatment AHI



AHI apnea-hypopnea index

* outlier

Figure 2. Boxplot of preoperative and treatment ODI



ODI oxygen desaturation index (≥3%)

* outlier

Surgical success

The surgical success in our study population was 88.6% (N=39). Reasons for not meeting Sher's criteria for surgical success were an (temporary) increase of mixed and central apneas (N=1) and the inability to perform a sufficient titration due to frequent awakening caused by the strength of the stimulation (N=3). In one patient proper titration of the therapy was not yet possible due to neuropraxia of the hypoglossal nerve after a postoperative bleeding in the area of the neck incision.

Preoperative DISE findings

In all patients a complete anteroposterior collapse of the tongue base was observed during DISE. In 43 patients an additional partial collapse (N=9) or complete collapse (N=33) at the level of the velum was observed. An isolated tongue base collapse was found in only one patient.

In the majority of patients with an epiglottic collapse, this was secondary to a complete collapse of the tongue base. A floppy epiglottis was present in five patients. A partial or complete lateral collapse at the level of the oropharynx was less common. A detailed overview of collapse patterns can be found **in table 3.**

Table 3. Preoperative DISE findings

Level	**Configuration**	**Supine position**		
N=44		No collapse < 50%	Partial collapse 50-75%	Complete collapse > 75%
Velum	A-P	2	9	33
Oropharynx	Lateral	33	10	1
Tongue base	A-P	0	0	44
Epiglottis	A-P	2	4	36
	Lateral	0	1	1

DISE drug-induced sleep endoscopy, *A-P* antero-posterior

As previously mentioned, 33 patients had a complete collapse at multiple levels in the upper airway consisting of a complete anteroposterior collapse of the palate and tongue base. When comparing differences in surgical outcome between patients with a complete multilevel collapse and patients with an anteroposterior tongue base collapse with or without a partial collapse of the palate, no significant difference in surgical success was found (p=0.784).

Adverse events

In total, 26 patients reported therapy-related adverse events. With 45.5%, frequent awakenings or insomnia due to discomfort of the stimulation was the most common therapy-related adverse event reported. Postoperative bleeding and problems with swallowing were both observed in one patient. In five patients a revision of the sensor lead was needed, probably due to damage of the sensor during implantation. Temporary tongue weakness was found in two patients and in eight patients abrasion of the tongue or a dry mouth was seen. **Table 4** provides an overview of patient-reported therapy-related adverse events.

Table 4. Therapy-related adverse events

N=26*	**Events (n)**	**% of total population**
Postoperative bleeding	1	2.3%
Revision interventions of the sensor lead	5	11.4%
Stimulation-related discomfort (including insomnia/arousal)	20	45.5%
Infection	0	0%
Tongue weakness/neuropraxia	2	4.5%
Tongue abrasion, dry mouth	8	18.2%
Problems with swallowing	1	2.3%
Buzzing noise during stimulation	2	4.5%
Total	39	

* In total 26 out of 44 patients reported therapy-related adverse events

DISCUSSION

The aim of this study was to retrospectively analyse postoperative outcomes of UAS treatment in OSA patients (AHI between 15 and 65 events/h) with CPAP failure or intolerance. UAS significantly improved respiratory parameters. At 88.6%, the overall surgical success in our study population was high. There was no significant difference in surgical outcome between patients with a tongue base collapse with or without a complete anteroposterior collapse at the level of the palate.

Our results are in line with those previously published in the literature. During the STAR trial, a 5-year follow-up study, Strollo et al. also found a significant reduction in AHI (29.3 to 9.0 events/h) and ODI (25.4 to 7.4 events/h) in moderate to severe OSA patients 12 months after implantation with a surgical success of 66%. [9] These results were maintained during long-term follow up. [11, 12]
Since FDA approval, several studies on the objective and subjective outcomes of UAS treatment have been published. Heiser et al. reported a decrease in median AHI from 28.6 events/h to 8.3 events/h after six months of follow-up. Boon et al. found similar results. Post-titration patient-outcomes showed a significant decrease in mean AHI from 35.6 ± 15.3 to 10.2 ± 12.9 events/h. The surgical success in this study was 78%. [3] In another small-scale study by Kent et al., post-titration AHI also significantly decreased and found that AHI was reduced within normal range (AHI < 5 events/h) in 70% of all patients. [5]

As stated above, our study found similar results. The higher surgical success in our study compared to the 12-months results of the STAR trial could be due to differences in length of follow-up, and increased knowledge with regard to patient selection and titration since FDA approval. Nevertheless, one could argue that the decrease of the AHI in our study was even greater than that in several previous published studies, since baseline AHI (37.6 events/h) in our study population was higher. The high baseline AHI in this study population can be explained by the fact that, in the Netherlands, treatment with UAS is only reimbursed in patients whose AHI lies between 30 and 50 events/h.
Although it must be taken into account that our sample for this analysis was small, no differences in surgical success were found when comparing patients with a complete collapse of the tongue base with or without a complete anteroposterior collapse at the level of the palate. This finding is supported by two previously published studies. Heiser et al. described the principle of palatoglossal coupling in patients treated with UAS. It was concluded that by selective stimulation of the hypoglossal nerve, more than 80% of all implanted patients had both a significant opening of the upper airway at retropalatal level and the level of the tongue base. [2] In another study the postoperative results of patients with an isolated retropalatal collapse, or multilevel collapse

undergoing UAS, were compared. Postoperative results showed that the reduction in AHI, success and cure rate were comparable between the two groups. [20]

Clinical relevance

OSA is associated with increased risk of developing cardiovascular disease, high morbidity, and mortality. In some studies it has also been suggested that OSA serves as a risk factor for stroke and as an independent predictor for functional recovery and mortality in stroke patients. [21-24] Especially in patients with moderate to severe OSA and CPAP intolerance, or failure, adequate OSA treatment is of paramount importance. Many forms of upper airway surgery have been described in the literature. Many are hampered by low surgical success rates and it is known that a high preoperative AHI is a negative predictor for surgical success. Although patients selected for UAS have often failed both conservative and surgical treatment for their OSA, the surgical success rate of UAS is higher compared to other types of upper airway surgery. [25] Nevertheless, it must be kept in mind that proper patient selection and an adequate and specialized follow-up by a team, trained for this type of surgery, is the key to treatment success.

Limitations

This study is not without limitations. First of all, this study contains data collected during a titration night, whereby in the majority of included patients an adjusted AHI, also referred to as the treatment AHI, was used for analysis. Secondly, interpretation of UAS results is not only dependent on its effect on respiratory events, but also on its compliance. [26] The results of this study show that UAS is an effective treatment in patients with moderate to severe OSA patients, but therapy usage is not taken into account. Hence, the results of this study can be an overestimation of treatment effectiveness when compared to an actual in-home situation. Long-term follow-up of both objective and subjective outcomes including therapy usage are therefore required. Thirdly, subjective outcomes were not included in this study. This was due to lack of data making sufficient analysis of the data not reliable.

CONCLUSION

UAS has proven to be an effective treatment in OSA patients (range AHI 20.8 - 55.8 events/h) with CPAP intolerance or failure, in terms of respiratory outcomes, with a surgical success of 88.6%. There was no significant difference in surgical outcome between patients with a tongue base collapse with or without a complete anteroposterior collapse at the level of the palate. The most common therapy-related adverse event reported was (temporary) stimulation-related discomfort often leading to frequent awakenings or insomnia. Although UAS seems to be a promising alternative for moderate to

severe OSA patients with CPAP intolerance or failure, proper patient selection, adequate implantation of the UAS system and follow-up by trained personnel are the key to treatment success.

Acknowledgements: The authors would like to thank Michella Klitsie – Olie (UAS coordinator, OLVG), Jonate van den Oever (UAS coordinator, OLVG) and Anja van de Velde-Muusers (research coordinator, OLVG) for the extensive work and support with conducting this study.

REFERENCES

1. Rotenberg BW, Vicini C, Pang EB, Pang KP. Reconsidering first-line treatment for obstructive sleep apnea: a systematic review of the literature. *J Otolaryngol Head Neck Surg*. 2016;45:23

2. Heiser C, Edenharter G, Bas M, Wirth M, Hofauer B. Palatoglossus coupling in selective upper airway stimulation. *Laryngoscope*. 2017;127(10):E378-E83

3. Boon M, Huntley C, Steffen A, et al. Upper Airway Stimulation for Obstructive Sleep Apnea: Results from the ADHERE Registry. *Otolaryngol Head Neck Surg*. 2018;159(2):379-85

4. Heiser C, Knopf A, Bas M, Gahleitner C, Hofauer B. Selective upper airway stimulation for obstructive sleep apnea: a single center clinical experience. *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery*. 2017;274(3):1727-34

5. Kent DT, Lee JJ, Strollo PJ, Soose RJ. Upper Airway Stimulation for OSA: Early Adherence and Outcome Results of One Center. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery*. 2016;155(1):188-93

6. Steffen A, Hartmann JT, Konig IR, Ravesloot MJL, Hofauer B, Heiser C. Evaluation of body position in upper airway stimulation for obstructive sleep apnea-is continuous voltage sufficient enough? *Sleep Breath*. 2018;22(4):1207-12

7. Steffen A, Sommer JU, Hofauer B, Maurer JT, Hasselbacher K, Heiser C. Outcome after one year of upper airway stimulation for obstructive sleep apnea in a multicenter German post-market study. *Laryngoscope*. 2018;128(2):509-15

8. Strollo PJ, Gillespie MB, Soose RJ, et al. *Upper Airway Stimulation for Obstructive Sleep Apnea: Durability of the Treatment Effect at 18 Months*. 2015

9. Strollo PJ, Jr., Soose RJ, Maurer JT, et al. Upper-airway stimulation for obstructive sleep apnea. *N Engl J Med*. 2014;370(2):139-49

10. Woodson BT, Gillespie MB, Soose RJ, et al. Randomized controlled withdrawal study of upper airway stimulation on OSA: short-and long-term effect. *Otolaryngology--Head and Neck Surgery*. 2014;151(5):880-87

11. Woodson BT, Soose RJ, Gillespie MB, et al. Three-year outcomes of cranial nerve stimulation for obstructive sleep apnea: the STAR trial. *Otolaryngology--Head and Neck Surgery*. 2016;154(1):181-88

12. Woodson BT, Strohl KP, Soose RJ, et al. Upper Airway Stimulation for Obstructive Sleep Apnea: 5-Year Outcomes. *Otolaryngol Head Neck Surg*. 2018;159(1):194-202

13. Vanderveken OM, Maurer JT, Hohenhorst W, et al. Evaluation of drug-induced sleep endoscopy as a patient selection tool for implanted upper airway stimulation for obstructive sleep apnea. *J Clin Sleep Med*. 2013;9(5):433-8

14. Schnider T, Minto C. Pharmacokinetic models of propofol for TCI. *Anaesthesia*. 2008;63(2):206-06

15. Schnider TW, Minto CF, Gambus PL, et al. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. *Anesthesiology: The Journal of the American Society of Anesthesiologists*. 1998;88(5):1170-82

16. Kezirian EJ, Hohenhorst W, de Vries N. Drug-induced sleep endoscopy: the VOTE classification. *Eur Arch Otorhinolaryngol*. 2011;268(8):1233-36

17. Sher AE, Schechtman KB, Piccirillo JF. The efficacy of surgical modifications of the upper airway in adults with obstructive sleep apnea syndrome. *Sleep*. 1996;19(2):156-77

18. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med*. 2012;8(5):597-619

19. Heiser C, Maurer JT, Hofauer B, Sommer JU, Seitz A, Steffen A. Outcomes of Upper Airway Stimulation for Obstructive Sleep Apnea in a Multicenter German Postmarket Study. *Otolaryngol Head Neck Surg* 156 (2):378-384. doi:10.1177/0194599816683378

20. Mahmoud AF, Thaler ER. Outcomes of Hypoglossal Nerve Upper Airway Stimulation among Patients with Isolated Retropalatal Collapse. *Otolaryngol Head Neck Surg*. 2019:194599819835186.

21. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med*. 2005;353(19):2034-41

22. Good DC, Henkle JQ, Gelber D, Welsh J, Verhulst S. Sleep-disordered breathing and poor functional outcome after stroke. *Stroke*. 1996;27(2):252-9

23. Parra O, Arboix A, Montserrat JM, Quinto L, Bechich S, Garcia-Eroles L. Sleep-related breathing disorders: impact on mortality of cerebrovascular disease. *Eur Respir J*. 2004;24(2):267-72

24. Parra O, Sanchez-Armengol A, Capote F, et al. Efficacy of continuous positive airway pressure treatment on 5-year survival in patients with ischaemic stroke and obstructive sleep apnea: a randomized controlled trial. *J Sleep Res*. 2015;24(1):47-53

25. Kezirian EJ, Goldberg AN. Hypopharyngeal surgery in obstructive sleep apnea: an evidence-based medicine review. *Arch Otolaryngol Head Neck Surg*. 2006;132(2):206-13

26. Ravesloot MJ, de Vries N. Reliable calculation of the efficacy of non-surgical and surgical treatment of obstructive sleep apnea revisited. *Sleep*. 2011;34(1):105

Polysomnography and sleep position, an Heisenberg phenomenon? - a large scale series

7

P.E. Vonk, N. de Vries, M.J.L. Ravesloot

HNO. 2019 Sep;67(9):679-684

ABSTRACT

Background: The severity of position-dependent obstructive sleep apnea (POSA) depends on the non-supine and supine apnea-hypopnea index (AHI) as well as the time spent in supine position. Especially, the latter is susceptible to variation. Several small-scale studies suggest that wearing polysomnography (PSG) apparatus leads to an increase in supine sleeping position.

Objectives: The aim of this study was to evaluate the effect of wearing PSG apparatus on sleeping position and to assess the influence on OSA severity.

Material and methods: A large scale, retrospective study was performed, including a consecutive series of POSA and non-apneic snoring patients who were prescribed positional therapy [Sleep Position Trainer (SPT)]. The effect of wearing PSG apparatus on sleeping position was evaluated by comparing body position during the PSG night and inactive (diagnostic) phase of SPT.

Results: The mean percentage of total recording time (TRT) in supine position was 43.1% during the PSG night compared to 28.6% of TRT during inactive (diagnostic) phase of SPT; a significant decrease of 33.6% ($p < 0.001$). When adjusting the AHI using TRT in different sleeping positions measured with the SPT, median AHI decreased from 13.3/h (9.0, 20.4) to 10.3/h (6.8, 16.2); $p < 0.001$. When using the adjusted AHI, 33% (N=66) of all patients had a change in OSA severity.

Conclusions: The results of this study indicate that wearing PSG apparatus leads to an increase in percentage of supine sleeping position causing an overestimation of OSA severity, especially in patients with POSA. This can have significant impact in both clinical and scientific practice.

Keywords: severity, sleep apnea, obstructive, sleep wake disorders, snoring, supine position

INTRODUCTION AND BACKGROUND

Position-dependent obstructive sleep apnea (POSA) constitutes a considerable proportion of patients diagnosed with obstructive sleep apnea (OSA). In 56-75% OSA severity is influenced by body position, in which the supine position is usually the worst sleeping position (WSP). [1-6]

Currently, a variety of definitions for POSA have been suggested in the literature. The most common classification makes a distinction between two groups; positional patients (PP) and non-positional patients (NPP). [1, 5, 7] In PP, the frequency and duration of hypopneic and apneic events are increased in the supine sleeping position. In some PP, these events occur solely in the supine sleeping position. [8] Cartwright first described the arbitrary cut-off point of a difference of 50% or more in apnea index between supine and non-supine positions. [1]

PP can be treated with positional therapy (PT) as a standalone treatment or in combination with other treatment modalities for OSA (e.g. mandibular advancement devices). [9, 10] PT is used to prevent patients from lying in the supine position. [3] In a recent meta-analysis strong evidence was found that the new generation of vibro-tactile devices for PT is effective in reducing the apnea-hypopnea index (AHI) during short-term follow-up. These small devices, attached to either the trunk or neck, provide a subtle vibrating stimulus that prevents patients from adopting the supine position. Furthermore, these devices are simple to use and reversible. The compliance during short-term follow-up is high, but data on long-term follow-up is limited. [11]

The severity of OSA in PP depends on the AHI in supine and non-supine position as well as the time spent in supine position. Especially, the time spent in supine position is susceptible to variation. A pivotal matter, with considerable impact on both clinical and scientific work on PP. One parameter, which could influence time spent in various body positions, is polysomnography (PSG).

Three small-scale studies have evaluated the effect of PSG apparatus on sleeping position. The results of these studies suggest that through wearing PSG apparatus patients are likely to spend more time in the supine position. [12-14] We were interested to see whether we could confirm these findings in a larger scale study. We hypothesize that PSG apparatus leads to an increase in percentage of total time spent in supine position and subsequently influences OSA severity measured by PSG, especially in PP.

MATERIAL AND METHODS

We performed a retrospective, single-center cohort study including a consecutive series of patients who were prescribed PT between January 2016 and June 2017. Inclusion criteria included the availability of a full-night polysomnography. Patients were eligible for treatment with PT when they met a modified version of Cartwright's criteria for POSA defined as a supine AHI at least two times greater than the non-supine AHI, combined with a non-supine AHI < 10/h. [1] In patients without OSA, AHI < 5/h, patients were prescribed PT in case of the occurrence of snoring merely in supine position based on clinical history. Patients were excluded when data was missing concerning the percentage of TST or TRT in various body positions during the PSG night.

Ethical considerations

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Declaration of Helsinki of 1975. Data on study subjects was collected and stored encoded to protect personal information. For this type of study informed consent was not required.

Sleep Position Trainer (SPT)

PP eligible for PT were prescribed the Sleep Position Trainer (SPT; NightBalance, Delft, the Netherlands), a new generation vibro-tactile device. It weighs 25g and has the following dimensions: 72 X 35 X 10mm, respectively. The device is fastened to the chest with a strap, so that the device is located on the sternum. The SPT is placed in a pocket of the strap, which is closed with a Velcro tab. The device provides a vibrating stimulus if the supine position is identified, which is measured using a 3-dimensional digital accelerometer. [9, 15-17] When no turning movement is detected, the stimulus gradually increases until the patient turns to a non-supine position. If no reaction is monitored, the vibrations are paused and reinitiated after 2 minutes. Initiation of treatment with the SPT is divided into three phases: a diagnostic phase, a training phase and a therapy phase. The first two nights are defined as the diagnostic phase, where the SPT monitors and records sleeping positions. During this phase, no active feedback is given to the patient. The device is inactive. An average is provided of the various body positions measured over the first two nights.

Polysomnography

Each subject underwent a full-night, unattended PSG (type II). To determine the stages of sleep, an electroencephalogram (Fp1, Fp2, C3, C4, O1, O2), electro-oculogram and electromyogram of the submental muscle were obtained. To measure the nasal airflow a nasal cannula with a pressure

transducer was inserted in the opening of the nostrils. A finger pulse oximeter was used to record arterial blood oxyhaemoglobin. Respiratory effort belts were place over the abdomen and rib cage to measure thoracoabdominal excursions. To determine body position, differentiation between upright, right side, left side, prone and supine position, a position sensor was used. Limb movements were detected with an anterior tibial electromyogram with surface electrodes.
For each patient the data were manually scored according to American Academy of Sleep Medicine (AASM) scoring manual by an experienced sleep investigator. [18]

Sleeping position measurements

To evaluate the effect of PSG apparatus on sleeping position, we compared data collected during the PSG night to data collected with the SPT during the first two nights of therapy usage (diagnostic phase). As mentioned before, the SPT is inactive during this phase, but does record sleeping position. Since the SPT is inactive, sleep position is not influenced by a vibrating stimulus of the device. The distribution of different body positions measured by the SPT are described as percentage of total recording time (TRT). The TRT of the SPT is not preset, but is initiated when the SPT is switched on by the patient when going to bed.
It is clear that the SPT cannot distinguish between sleep and awake states. To enable comparison of the distribution of body positions during the PSG night, percentages in different body positions during time in bed (TIB) was used. TIB is the TRT from lights out to lights on and therefore comparable to the TRT of the SPT.

Adjusted AHI

The total AHI depends on several parameters, consisting of the supine AHI, non-supine AHI and the percentage of TST spend in supine and non-supine position. To evaluate the possible influence of PSG apparatus on the percentage of supine body position, and subsequently OSA severity measured with PSG, a separate analysis will be performed using an adjusted AHI. The adjusted AHI will be calculated using the percentage of TRT in supine position as measured with the inactive SPT instead of the percentage of TRT during the PSG night.

Statistical analysis

Statistical analysis was performed using SPSS (version 21), SPSS Inc., Chicago, IL). Quantitative data are reported as mean ± standard deviation (SD) or as median (Q1; Q3) when not normally distributed. Comparison of data collected during the PSG night and inactive (diagnostic) phase of the SPT was carried out using the paired T-test in the case of normally distributed data and the Wilcoxon

signed rank test in case of not normally distributed data. A p value of < 0.05 was considered to indicate statistical significance.

RESULTS

The data of 168 patients were available for analysis. In eight patients (4.8%) the SPT was prescribed because of non-apneic position-dependent snoring. The majority of the study population was male (67.9%). The mean age was 51.7 ± 12.4 years. An overview of baseline characteristics is presented in **table 1**. Patients spent a mean 43.8 ± 22.3% of TST in supine position compared to a mean 43.1 ± 20.8% of the TRT while undergoing PSG, which was not significantly different ($p = 0.132$). During the inactive (diagnostic) phase of SPT patients spent 28.6 ± 15.5% of TRT in supine position; a significant decrease of 33.6% compared to the TRT in supine position during the PSG night; $p < 0.001$. No significant differences were found between male and female patients. **Figure 1** shows the percentage of TRT in supine position during the PSG night and inactive (diagnostic) phase of SPT.

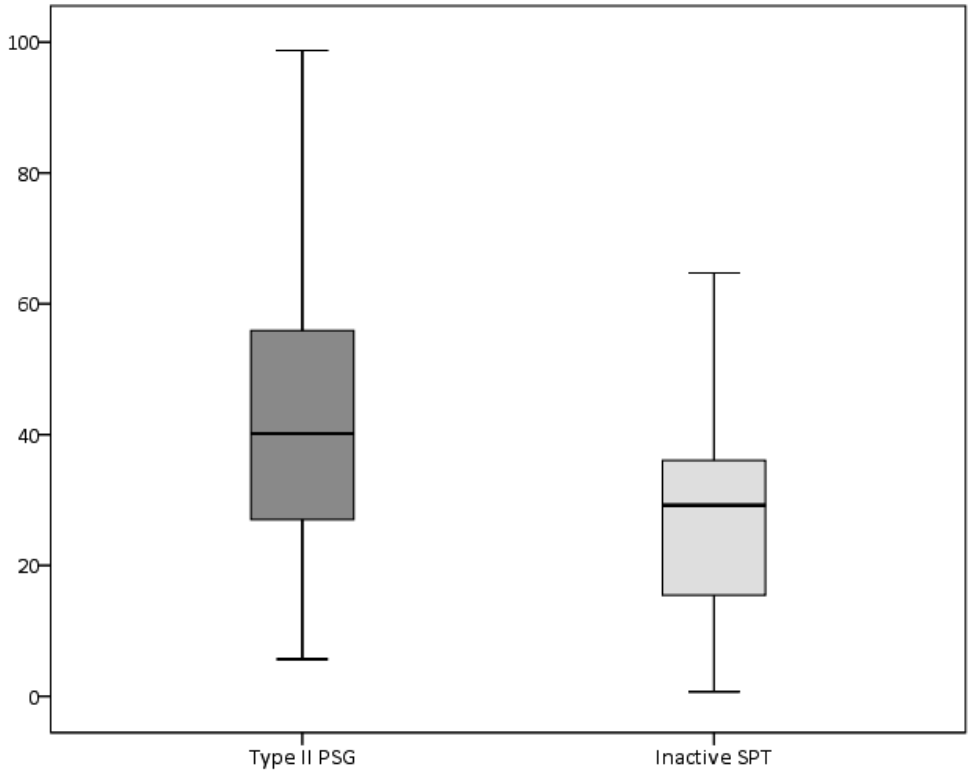
Table 1. Baseline characteristics

Patient characteristic **N=168**	**Mean ± SD**
Age (year)	51.7 ± 12.4
Sex (male/female)	114/54
BMI (kg/m^2)	26.8 ± 4.0
AHI (per hour)	13.2 (9.1, 20.3) †
AHI in supine position (per hour)	28.8 (17.2, 47.2) †
AHI in non-supine position (per hour)	4.0 (2.0, 6.5) †
% TST in supine position	43.8 ± 22.3
% TRT in supine position	43.1 ± 20.8

† median (Q1, Q3)

SD standard deviation *BMI* body mass index *AHI* apnea-hypopnea index *TST* total sleep time *TRT* total recording time

Figure 1. Percentage of TRT in supine position measured with PSG and inactive SPT



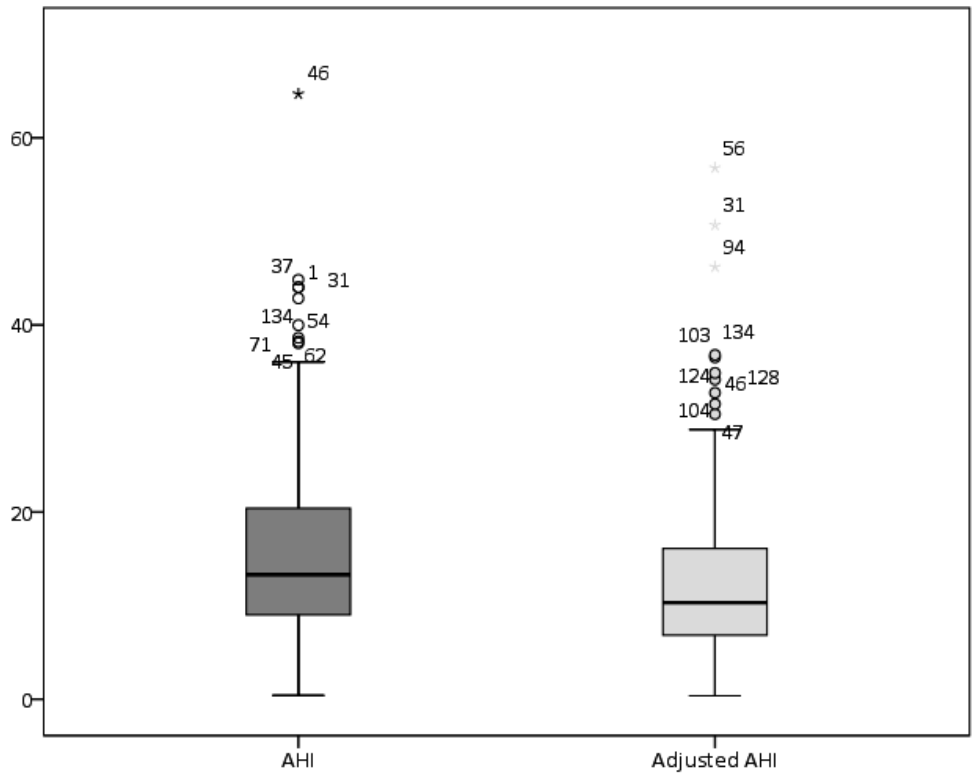
TRT total recording time, *PSG* polysomnography, *SPT* Sleep Position Trainer

OSA severity

Eight patients (4.8%) were diagnosed with non-apneic position-dependent snoring, 87 patients (51.8%) with mild OSA (AHI ≥ 5/h and < 15/h), 53 patients (31.5%) with moderate OSA (AHI ≥ 15/h and < 30/h) and 20 patients (11.9%) with severe OSA (AHI ≥ 30/h).

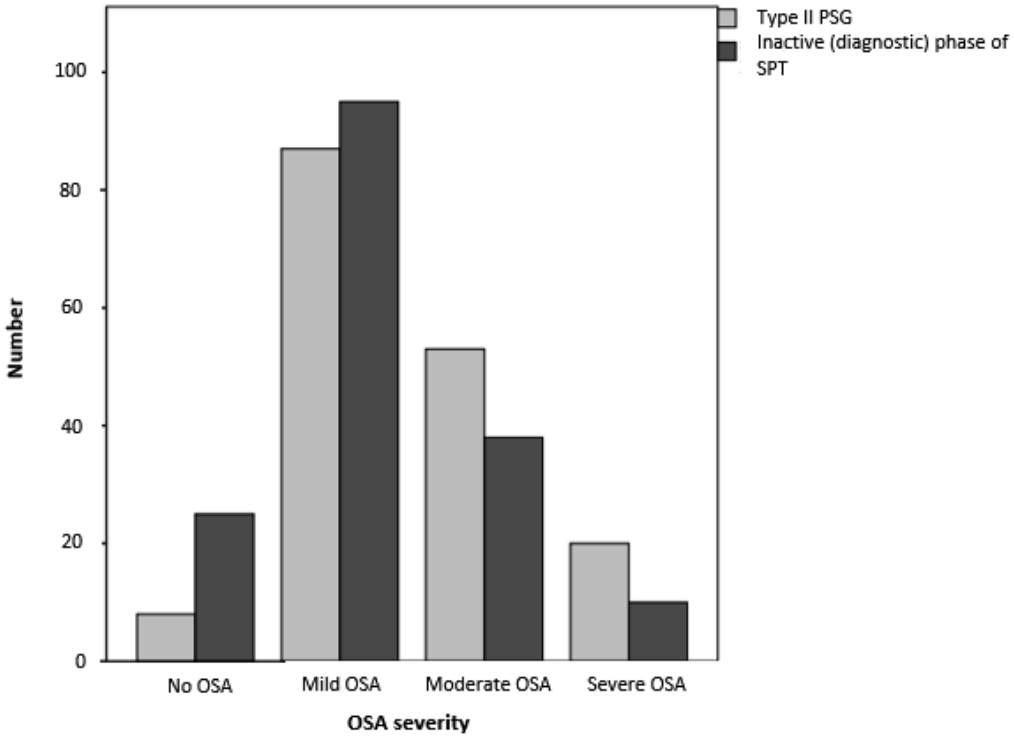
The AHI was corrected for the percentage of TRT in supine position as measured with the inactive SPT – the adjusted AHI. The adjusted median AHI decreased from 13.3/h (9.0, 20.4) to 10.3/h (6.8, 16.2) **(see figure 2)**. Sixty-six patients (39.2%) had a change in severity of OSA when using the adjusted AHI. In theory, 17 patients (10.1%) would not have been diagnosed with OSA when the adjusted AHI is used **(see figure 3)**.

Figure 2. Total AHI measured with type II PSG versus the adjusted AHI



AHI apnea-hypopnea index, *PSG* polysomnography

Figure 3. Distribution of OSA severity measured with type II PSG and during the inactive (diagnostic) phase of SPT



OSA obstructive sleep apnea, *PSG* polysomnography, *SPT* Sleep Position Trainer

DISCUSSION

Heisenberg is credited for the uncertainty principle, the fact that the performance of a test influences its outcome. The results of this study suggest that this phenomenon occurs when PP undergo a PSG. To date this is the largest cohort study objectively evaluating the effect of PSG apparatus on sleeping position. Our results suggest that patients spend significantly more time in the supine position whilst undergoing a PSG, which could result in overestimation of OSA in severity in PP. Supporting this hypothesis, our results are consistent with four similar, small-scale studies. [12-14, 19]

Logan et al. included sixteen patients, who underwent type I PSG followed by at home type II PSG. The sensors were attached to a device situated above the bed, not on the chest. Patients spent significantly less time in the back posture during the second at home PSG compared to in-laboratory PSG. [12] In the study by Metersky et al. twelve PP who underwent an additional PSG during which no PSG leads were attached. Time spent in supine position was 56% greater during the PSG night in comparison to the non-PSG night. [13] Two studies used a similar study design as described in this paper, comparing objective measurement of time spent in various sleeping positions between PSG and a non-active vibro-tactile neck-worn device. [14, 19] In the study by Bignold et al. patients received one week active and one week inactive treatment separated by one week and in randomized order. They found that the supine sleeping time during the in-laboratory sleep study was significantly greater compared to the in-home supine sleeping time measured during inactive treatment. (36.6% ± 5.7% vs. 19.3% ± 4.3%, p = 0.002). [14] Wimaleswaren et al. reported 35.1% ± 25.1% supine sleeping time during PSG vs. 25% ± 21.4% at home, p = 0.007 in 18 patients. [19] Both studies conclude that the in-laboratory bias towards supine sleep might cause overestimation of OSA severity. **Figure 2** clearly illustrates a significant reduction in median AHI, when adjusted, calculated in accordance with the supine sleep time at home with inactive SPT. These results emphasize the vigilance needed when interpreting sleep study results in PP. There is a risk of overestimating OSA severity, resulting in a significant impact in clinical practice, with consequences for treatment recommendations.

Besides the supine trunk body position, the position of the head, and prone sleeping position have impact on OSA severity as well. Van Kesteren et al. reported that in 46.2% of supine position-dependent patients, head position was of considerable influence on the AHI. [20] Bidarion-Moniri et al. studied the effect of prone position in OSA and concluded that upper airway collapse was reduced in prone position with significant improvement of the AHI and oxygen desaturation index compared to both lateral as supine position. These findings indicate that less time spent in prone position, leads to an increase of OSA severity. [21] Disease severity may influence time spent in the supine position. Kaur et al. found an inverse correlation between the supine AHI and the percentage of TST in supine

position. The authors hypothesize a self-correcting effect in PP with more severe disease in supine position. [22]

Limitations

There are some limitations to this study. First of all, the SPT is not a diagnostic modality; therefore the data must be interpreted with care. All patients included in this study were positional. One could argue that this could be of influence, nevertheless studies report no difference in time spent in supine position between NPP and PP. [23] Secondly, it must be taken into account that the SPT cannot distinguish whether a patient is awake or asleep. To enable statistical comparison we recalculated the percentage of total time spend in supine position as part of the TRT during the PSG night. Although the use of comparable equipment is preferred, the difference of supine body position using TRT or TST was not statistically different.

Two very small case series (N = 4 and N = 15) reported that following active verbal instructions to avoid adopting the supine position, patients spent less time in the supine position. [4, 24] Before initiation of SPT, patients had received the results of their PSG and were aware of the fact that they should avoid the supine position. Patients are informed that the SPT has a start delay of 30 minutes and that if they prefer to fall asleep in supine position can do so. Although this might limit the effect of the verbal instruction given to the patient, one must consider that patients may have spent less time in supine position during the inactive (diagnostic) phase of SPT due to the fact that they were aware they should avoid the supine position.

Finally, previous studies report that OSA severity is not only influenced by trunk position, but also by the position of the head during sleep. [20] Head position was not recorded during the PSG. This is not only a limitation of this study but also in clinical practice in general since head position monitoring is as yet not common practice. An advantage of our study is that during the PSG and inactive (diagnostic) phase of SPT the position sensor was attached to the trunk enabling comparison. There is a significant risk of bias when the position sensors are located on different body positions.

Previous mentioned limitations may impact our results, causing an overestimation of the influence of PSG apparatus on body sleeping position. In future, there is a need for less invasive PSG apparatus, with less or no impact on sleeping position.

Clinical relevance

In clinical practice different treatment modalities are considered based on, among other things, OSA severity. While CPAP is the therapy of choice in case of severe OSA, other treatment options, such as PT or mandibular advancement devices or upper airway surgery, can be considered in case of mild or

moderate OSA. The results of this study suggest that body position is influenced by PSG apparatus and as a result may cause a shift in OSA severity in PP. When evaluating our results, 17 patients (N = 9 versus N = 26) would not have been diagnosed with OSA when using the percentage of supine body position measured during the inactive (diagnostic) phase of SPT. This may have consequences for treatment recommendations and in some cases might lead to over treatment.

CONCLUSION

This study shows that wearing PSG apparatus may cause patients to spend more time in the supine sleeping position. This leads to an increase in OSA severity measured by PSG in PP, which could have significant impact on both clinical practice and research. There is a need for less invasive PSG apparatus, with less impact on sleeping position.

REFERENCES

1. Cartwright RD. Effect of sleep position on sleep apnea severity. *Sleep*. 1984;7(2):110-4

2. van Maanen JP, Ravesloot MJ, Safiruddin F, de Vries N. The Utility of Sleep Endoscopy in Adults with Obstructive Sleep Apnea: A Review of the Literature. *Current Otorhinolaryngology Reports*. 2013;1(1):1-7

3. Frank MH, Ravesloot MJ, van Maanen JP, Verhagen E, de Lange J, de Vries N. Positional OSA part 1: Towards a clinical classification system for position-dependent obstructive sleep apnoea. *Sleep Breath*. 2015;19(2):473-80

4. Cartwright R, Ristanovic R, Diaz F, Caldarelli D, Alder G. A comparative study of treatments for positional sleep apnea. *Sleep*. 1991;14(6):546-52

5. Oksenberg A. Positional and non-positional obstructive sleep apnea patients. *Sleep Med*. 2005;6(4):377-8

6. Richard W, Kox D, den Herder C, Laman M, van Tinteren H, de Vries N. The role of sleep position in obstructive sleep apnea syndrome. *Eur Arch Otorhinolaryngol*. 2006;263(10):946-50

7. Marklund M, Persson M, Franklin KA. Treatment success with a mandibular advancement device is related to supine-dependent sleep apnea. *Chest*. 1998;114(6):1630-5

8. Oksenberg A, Gadoth N. Are we missing a simple treatment for most adult sleep apnea patients? The avoidance of the supine sleep position. *J Sleep Res*. 2014;23(2):204-10

9. Dieltjens M, Vroegop AV, Verbruggen AE, et al. A promising concept of combination therapy for positional obstructive sleep apnea. *Sleep Breath*. 2015;19(2):637-44

10. Benoist LB, Verhagen M, Torensma B, van Maanen JP, de Vries N. Positional therapy in patients with residual positional obstructive sleep apnea after upper airway surgery. *Sleep Breath*. 2016

11. Ravesloot MJL, White D, Heinzer R, Oksenberg A, Pepin JL. Efficacy of the New Generation of Devices for Positional Therapy for Patients With Positional Obstructive Sleep Apnea: A Systematic Review of the Literature and Meta-Analysis. *J Clin Sleep Med*. 2017;13(6):813-24

12. Logan MB, Branham GH, Eisenbeis JF, Hartse K. Unattended Home Monitoring in the Evaluation of Sleep Apnea: Is it Equal to Formal Polysomnograph? *Otolaryngology--Head and Neck Surgery*. 1996;115(2):P156-P56

13. Metersky ML, Castriotta RJ. The effect of polysomnography on sleep position: possible implications on the diagnosis of positional obstructive sleep apnea. *Respiration*. 1996;63(5):283-87

14. Bignold JJ, Mercer JD, Antic NA, McEvoy RD, Catcheside PG. Accurate position monitoring and improved supine-dependent obstructive sleep apnea with a new position recording and supine avoidance device. *J Clin Sleep Med*. 2011;7(4):376-83

15. Eijsvogel MM, Ubbink R, Dekker J, et al. Sleep position trainer versus tennis ball technique in positional obstructive sleep apnea syndrome. *J Clin Sleep Med*. 2015;11(2):139-47

16. van Maanen JP, Meester KA, Dun LN, et al. The sleep position trainer: a new treatment for positional obstructive sleep apnoea. *Sleep Breath*. 2013;17(2):771-9

17. van Maanen JP, de Vries N. Long-term effectiveness and compliance of positional therapy with the sleep position trainer in the treatment of positional obstructive sleep apnea syndrome. *Sleep*. 2014;37(7):1209-15

18. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events: deliberations of the sleep apnea definitions task force of the American Academy of Sleep Medicine. *Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine*. 2012;8(5):597

19. Wimaleswaran H, Yo S, Buzacott H, et al. Sleeping position during laboratory polysomnography compared to habitual sleeping position at home In: Editor, ed.^eds. Sleeping position during laboratory polysomnography compared to habitual sleeping position at home. City, 2018

20. van Kesteren ER, van Maanen JP, Hilgevoord AA, Laman DM, de Vries N. Quantitative effects of trunk and head position on the apnea hypopnea index in obstructive sleep apnea. *Sleep*. 2011;34(8):1075-81

21. Bidarian-Moniri A, Nilsson M, Rasmusson L, Attia J, Ejnell H. The effect of the prone sleeping position on obstructive sleep apnoea. *Acta oto-laryngologica*. 2015;135(1):79-84

22. Kaur A, Verma R, Gandhi A, et al. Effect of disease severity on determining body position during sleep in patients with positional obstructive sleep apnea. *Journal of Sleep and Sleep Disorders Research*. 2017;40(suppl_1):A233-A33

23. Joosten SA, O'Driscoll DM, Berger PJ, Hamilton GS. Supine position related obstructive sleep apnea in adults: pathogenesis and treatment. *Sleep medicine reviews*. 2014;18(1):7-17

24. Kavey NB, Blitzer A, Gidro-Frank S, Korstanje K. Sleeping position and sleep apnea syndrome. *American journal of otolaryngology*. 1985;6(5):373-77

Influence of position-dependency on surgical success in sleep apnea surgery - a systematic review

8

P.E. Vonk, P.J. Rotteveel, M.J.L. Ravesloot, C. den Haan, N. de Vries

Sleep Breath. 2019 Oct 17. doi:10.1007/s11325-019-01935-y

ABSTRACT

Purpose: To evaluate the influence of position-dependency on surgical success of upper airway (UA) surgery in obstructive sleep apnea (OSA) patients.

Methods: Systematic review.

Results: Two prospective cohort studies and seven retrospective cohort studies were included in this review. Despite the importance of the subject, it remains unclear whether position-dependency is a predictor for surgical success. No differences were found in surgical success rate between non-positional (NPP) and positional (PP) OSA patients undergoing uvulopalatopharyngoplasty/Z-palatoplasty with or without radiofrequent thermotherapy of the tongue, isolated tongue base or multilevel surgery and hypoglossal nerve stimulation. In one study PP undergoing relocation pharyngoplasty had a greater chance of surgical success. In the majority of the remaining studies surgical success was in favor of NPP. Furthermore, in the vast part of included studies the effect of UA surgery was suggested to be greater in the lateral position than supine position.

Conclusion: Although preoperative characteristics in PP (e.g. lower BMI and AHI) seem to be in favor for higher surgical success compared to NPP, it remains unclear whether position-dependency is a predictor for surgical outcome. It is suggested that the largest differences and expected preoperative and postoperative changes occur in non-supine AHI. In PP the preoperative non-supine AHI is already lower compared to NPP suggesting a lower chance of surgical success in PP.

Keywords: obstructive sleep apnea, position-dependency, upper airway surgery, surgical success

INTRODUCTION

Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder, characterized by repetitive collapse of the upper airway (UA) causing desaturations due to cessation of airflow during sleep. The prevalence of OSA is estimated at 12.5% in men and 5.9% in women.[1] In the majority of OSA patients respiratory obstructive events are more ascribed to supine sleeping position. [2-7] A variety of definitions have been applied in the literature to describe position-dependent OSA (POSA). Cartwright was the first to describe POSA as the arbitrary cut-off point of *a difference of 50% or more in apnea index between supine and non-supine positions.*[4] Overall, positional patients (PP) tend to have a lower total apnea hypopnea index (AHI), a lower body mass index (BMI), fewer symptoms, are younger and have less co-morbidity compared to non-positional patients (NPP).[3, 5, 6, 8, 9] OSA treatment comprises several options such as conservative treatment or surgical interventions of the UA. Non-surgical interventions traditionally include weight loss, treatment with mandibular advancement devices (MAD) or continuous positive airway pressure (CPAP).[10] Recently positional therapy (PT), with new generation devices has been added to the conservative armamentarium.[11-14] When alternatives for conservative treatment are required, different forms of UA surgery can be considered with the aim, among other things, to increase the surface area of the UA by targeting structures related to obstruction.[15]

There are several known factors contributing to lower surgical success, such as a high BMI, high total AHI and a complete concentric collapse at palatal level observed during drug-induced sleep endoscopy (DISE). [16-19] Likewise NPP tend to have more severe disease and a higher BMI in comparison to PP. Based on this information, one could hypothesize that NPP have a lower chance of surgical success. On the other hand, one might argue that since the non-supine AHI in PP is low pre-operatively, NPP have a higher chance of surgical success since an improvement of the AHI in both supine and non-supine position can be achieved, this in contrast to PP. Although various articles have been written on this subject matter, the verdict remains undecided.

Therefore, the aim of this study was to perform a systematic review to evaluate the influence of position-dependency on surgical success of UA surgery in OSA patients. We hypothesize that position-dependency is a predictive factor for surgical success in OSA patients undergoing UA surgery.

METHODS

Search strategy and information sources

A systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[20] Studies were identified by searching PubMed, EMBASE,

Cochrane Database of Systematic Reviews/Wiley, Cochrane Central Register of Controlled Trials/Wiley, CINAHL/Ebsco and Web of Science/Clarivate Analytics up to 24 September 2018 (PR and CdH). A search strategy was used with a combination of Medical Subject Headings (MeSH) and keywords. Full search strategies for all databases are available as supplementary information (**Appendix 1**).

Study selection

Duplicate articles were excluded. The remaining results were screened based on title and abstract by two independent investigators (PV and PR). The full text of potentially relevant articles was retrieved and examined by the same researchers. Disagreement in eligibility was resolved by a third researcher (MR). Reference lists of eligible studies were checked for additional references.

Eligibility criteria

Studies reporting on surgical success of UA surgery in OSA patients (confirmed by polysomnography (PSG)), specifically evaluating the role of position-dependency on surgical success, were included, when (a modified version of) Cartwright's criteria were applied to define position-dependency.[4] Studies reporting on non-surgical interventions only, conference abstracts, editorials, posters, protocols and case reports were excluded. Non-English studies were only included and translated if found to be of high priority (e.g. randomized trials or trials with superior number of patients or follow-up).

Outcome Measures

The primary outcome measure of this review was surgical success in NPP and PP. Secondary outcome measures included preoperative and postoperative total AHI, supine AHI and non-supine AHI.

Data collection

A standardized form was used to extract data from the included studies for assessment of study quality and evidence synthesis. Extracted information included:

- Source: author, publication data;
- Methods: study design, intervention;
- Participants: sample size, gender, mean age, BMI, number of NPP and PP;
- Primary outcome measures: surgical success in NPP and PP;
- Secondary outcome measure: preoperative and postoperative total AHI, supine AHI and non-supine AHI, as measured by PSG in NPP and PP.

Data was extracted independently and discrepancies were identified and resolved through discussion (with a third author if necessary). The flow of citations reviewed in the course of this review was recorded as described by the PRISMA statement see **figure 1**.

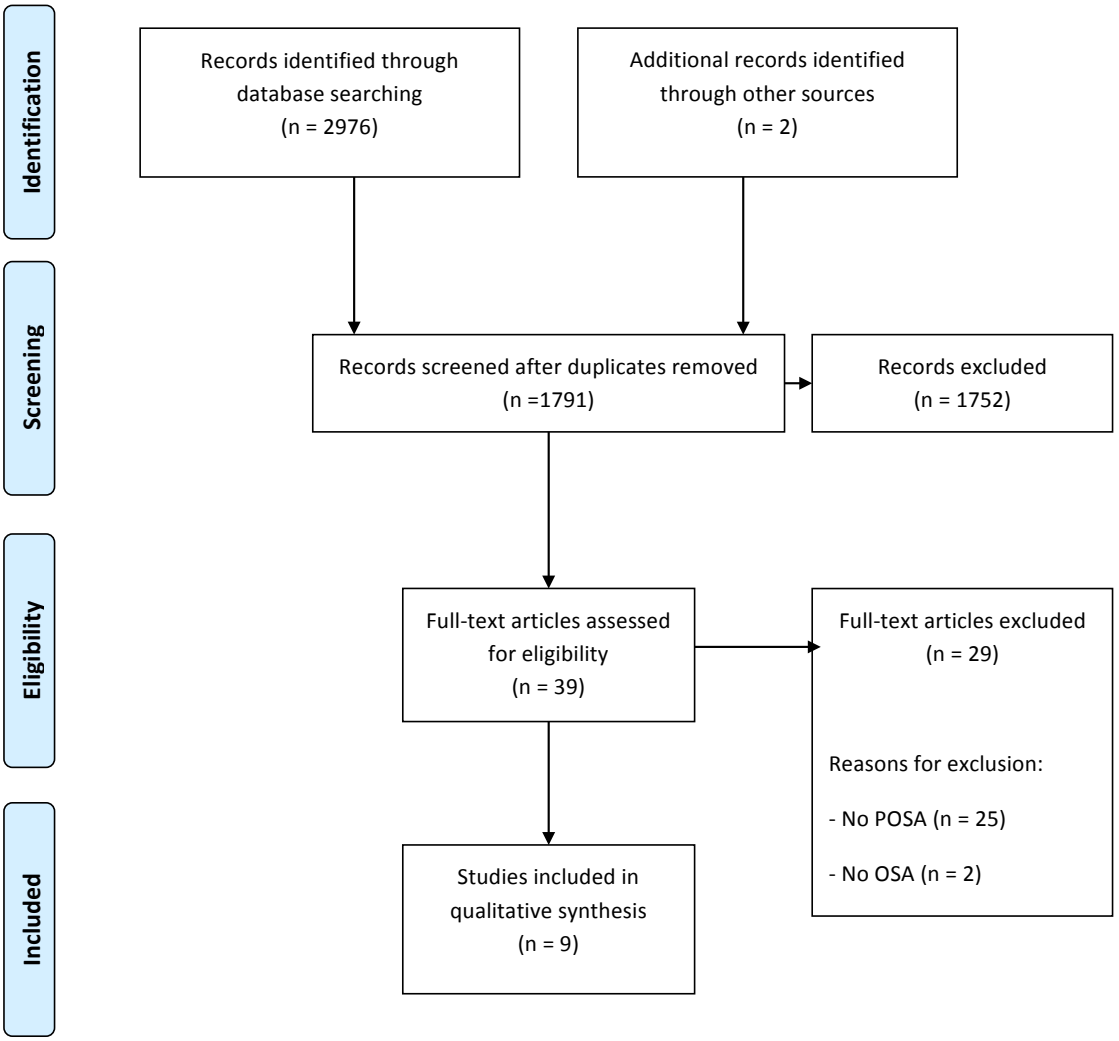
Level of evidence and quality assessment of included studies

Level of evidence was provided for all articles according to the Oxford Centre for Evidence-based Medicine.[21] Quality assessment of the included studies was performed by two independent reviewers (PV and PR) using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.[22]

RESULTS

The results of the search strategy are shown in **figure 1**. A total of 1791 articles were identified after the initial search and removal of duplicates. Two additional articles were identified via reference lists. Based on title and abstract, 39 full text articles were checked for eligibility. Nine articles met the inclusion criteria for this systematic review: two prospective studies and seven retrospective studies. The main reason for exclusion was not reporting surgical success separately in NPP and PP. A summary of the included studies can be found in **table 1**.

Figure 1. Results of literature search



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Table 1. Summary of included studies

Author	Year	Country	Design	Intervention	LOE	Sample size* N (%)			Age (years)	Male N (%)	BMI (m^2/kg)		
						Total	NPP	PP			Total	NPP	PP
Kastoer et al. [23]	2018	Netherlands	Retrospective	Different types of UA surgery	4	63* (100)	24 (38.1)	39 (61.9)	-	-	-	-	-
Steffen et al. [24]	2018	Germany	Prospective	Hypoglossal nerve stimulation	3	44 (100)	13 (29.5)	31 (70.5)	58.2 ± 10.0	44 (100)	28.8 (19.7; 36.6)	28.7 (27.7; 34.1)	28.7 (25.6; 31.0)
Van Maanen et al. [25]	2014	Netherlands	Retrospective	UPPP/ZPP (+/- RFTB)	4	139 (100)	71 (51.1)	68 (48.9)	45.0 [25-69]	127 (91.4)	27.4 [20.4-38.2]	-	-
Li et al. [26]	2013	Taiwan	Retrospective	Relocation pharyngoplasty	4	47 (100)	20 (42.6)	27 (57.4)	38.8 ± 9.0	44 (93.6)	27.3 ± 3.0	27.4 ± 3.4	27.2 ± 2.5
Van Maanen et al. [27]	2012	Netherlands	Retrospective	Hyoid suspension (+/-UPPP/ZPP and RFTB)	4	130 (100)	60 (46.2)	70 (53.8)	49.9 ± 9.7	116 (72.5)	27.3 ± 2.8	-	-
Lee et al. [28]	2011	South Korea	Retrospective	UPPP	4	74 (100)	22 (29.7)	52 (70.3)	47 [21-71]	72 (97.3)	-	26.5	26.0
Kwon et al. [29]	2010	South Korea	Retrospective	Uvula-preserving UPPP	4	20* (100)	3 (15)	17 (85)	40.0 ± 9.4	20 (100.0)	27.2 ± 2.5	-	-
Lee et al. [30]	2009	South Korea	Retrospective	UPPP	4	69 (100)	25 (36.2)	44 (63.8)	45.4 [29-67]	69 (100.0)	-	-	-
Stuck et al. [31]	2005	Germany	Prospective	Isolated hyoid suspension	3	15 (100)	9 (60)	6 (40)	47.3 ± 12.4	-	27.5 ± 3.3	-	-

Data presented as mean ± standard deviation, mean [range] or median (Q25; Q75)

LOE Level of Evidence, *NPP* non-positional obstructive sleep apnea patients, *PP* positional obstructive sleep apnea patients, *BMI* body mass index, *UA* upper airway, *UPPP* uvulopalatopharyngoplasty, *RFTB* radio frequent thermotherapy of the tongue base, *ZPP* Z-palatoplasty, *LTFU* loss to follow-up

* Subgroup consisting of OSA patients undergoing UA surgery with preoperative and postoperative polysomnography

Description of studies

Various types of surgical interventions for OSA of the UA were evaluated in the included studies; the vast majority reported on (a modified version of) uvulopalatopharyngoplasty (UPPP) with or without radiofrequent thermotherapy of the tongue base (RFTB).[23-27] The remaining studies evaluated surgical success rate in OSA patients who underwent hypoglossal nerve stimulation and hyoid suspension with or without UPPP or Z-palatoplasty (ZPP) and RFTB.[28-30] One study did not focus on one type of surgery but reported on a variety of different types of surgical interventions.[31]

In seven studies surgical success was defined according to Sher's criteria: a postoperative decrease of the total AHI of at least 50% and reduction below 20 events/hour in patients whose preoperative AHI was > 20/h.[32] One study reported the respiratory disturbance index (RDI) instead of the AHI.[29] In another study surgical success was defined as a reduction in AHI of more than 50% and/or complete therapeutic response (AHI ≤ 5 events/hour).[31]

In seven studies POSA was defined according to Cartwright's criteria; a difference of 50% or more in AHI between supine and non-supine positions. Two studies used a modified version with additional criteria concerning minimum sleeping time spent in supine position.[29, 31]

Quality assessment individual studies

Overall, studies clearly specified their study population and selection criteria were adequately reported except for one study.[25] The vast part of included studies used a retrospective, but consecutive recruitment of study participants. In two studies a postoperative PSG was performed in only a small number of patients, which makes the results of these studies susceptible to selection bias.[26, 31] In all studies the diagnosis of OSA was confirmed prior to UA surgery using PSG a postoperative PSG after acceptable follow-up. Question 8 was not applicable for all studies, since patients were only included in the studies if they received a form of UA surgery. Measurement instruments used for primary outcome measures were good; all studies used preoperative and postoperative PSG. All studies reported on prognostic factors for surgical success, such as BMI, but only a few studies mentioned changes in BMI or percentage of TST in supine position preoperatively and postoperatively. In only one study, logistic regression analysis was performed to assess the influence of possible confounders.[24] Therefore it is unclear whether the surgical intervention(s) in these studies were independent of other changes and free of bias. **Table 2** shows a detailed overview of the quality assessment of individual studies.

Table 2. Quality assessment individual studies

	Kastoer et al.[23]	Steffen et al. [24]	Van Maanen et al.[25]	Li et al.[26]	Van Maanen et al.[27]	Lee et al.[28]	Kwon et al.[29]	Lee et al.[30]	Stuck et al.[31]
1. Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes*	Yes	Yes	Yes	Yes	Yes	Yes	Yes*
3. Was the participation rate of eligible persons at least 50%?	CD∞	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes
5. Was a sample size justification, power description, or variance and effect estimates provided?	No	No	No	No	No	No	No	No	No
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	NA	NA	NA	NA	NA	NA	NA	NA	NA

9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Was the exposure(s) assessed more than once over time?	No	Yes	No	No	No	No	No	No	No
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Were the outcome assessors blinded to the exposure status of participants?	NA	NA	NA	NA	NA	NA	NA	NA	NA
13. Was loss to follow-up after baseline 20% or less?	NA	Yes	NA	NA	NA	NA	NA	NA	Yes
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	No	No	No	Yes	No	No	No	No	No

(+) = yes, (-) = no, *CD* cannot determine, *NA* not applicable, *NR* not reported

* Study population clearly specified with exception of a given timeframe

∞ Unclear whether a consecutive series of only OSA patients undergoing upper airway surgery was included

Primary outcome measures

Prospective studies

Two prospective studies were identified. Steffen et al. reported treatment outcome in OSA patients undergoing hypoglossal nerve stimulation. Surgical success rate was comparable in NPP and PP, namely 83.3% versus 90.3%; p=0.608. An AHI < 5 events/hour was seen more often in PP (N=14) compared to NPP (N=1), which was significantly higher (p=0.033).[30] In a second prospective study Stuck et al. found surgical success of isolated hyoid suspension in favor of NPP, namely 35.7% compared to 16.7% in PP.[29]

Retrospective studies

Seven retrospective studies were identified. No significant difference was found in surgical success rate between NPP and PP undergoing hyoid suspension with or without additional UPPP or ZPP and RFTB (40.0% versus 35.7%, p=0.615) [28] or UPPP/ZPP (with or without RFTB) (43.7% versus 35.3%; p=0.313). [23] In addition, two other studies analysing the results of (a modified version) of UPPP also found comparable results in surgical success, but did not test our hypothesis with statistical testing.[25, 26] Li et al. found that severe PP undergoing relocation pharyngoplasty had a greater chance of surgical success compared to NPP (67% vs. 25%; p = 0.008).[24] Other studies were in favor of NPP. Kastoer et al. reported a lower efficacy of UA surgery in PP as compared to NPP (33.3% vs 62.5%).[31] Lee et al. reported that patients who failed UPPP were predominantly PP. Surgical success rate in NPP and PP was 40% and 22.7%, respectively.[27] An overview of primary outcome measures can be found in **table 3.**

Because of the heterogeneity amongst the studies (i.e. medians vs. means, differences in scoring criteria, surgical interventions and outcomes reported), a meta-analysis was not performed.

Table 3. Primary outcome measure: comparison of surgical success between NPP and PP

Author	Year	Intervention	Surgical success			p value	Surgical success comparing NPP and PP
			Total	NPP	PP		
Kastoer et al. [23]	2018	Different types of UA surgery	44.4%	62.5%	33.3%	-	In favor of NPP
Steffen et al. [24]	2018	Hypoglossal nerve stimulation	88.4%	83.3%	90.3%	0.608	No significant difference
Van Maanen et al. [25]	2014	UPPP/ZPP (+/- RFTB)	39.6%	43.7%	35.3%	0.313	No significant difference
Li et al. [26]	2013	Relocation pharyngoplasty	49%	25%	67%	0.008*	In favor of PP
Van Maanen et al. [27]	2012	Hyoid suspension (+/-UPPP/ZPP and RFTB)	37.7%	40.0%	35.7%	0.615	No significant difference
Lee et al. [28]	2011	UPPP	33.8%	31.8%	34.6%	-	Suggestive to be similar
Kwon et al. [29]	2010	Uvula-preserving UPPP	40%	33.3%	41.1%	-	Suggestive to be similar
Lee et al. [30]	2009	UPPP	29%	40.0%	22.7%	-	In favor of NPP
Stuck et al. [31]	2005	Isolated hyoid suspension	42.8%	35.7%	16.7%	-	In favor of NPP

NPP non-positional obstructive sleep apnea patients, *PP* positional obstructive sleep apnea patients, *UA* upper airway, *UPPP* uvulopalatopharyngoplasty, *RFTB* radio frequent thermotherapy of the tongue base, *ZPP* Z-palatoplasty,

Secondary outcome measures

Five out of nine included studies reported on all secondary outcome measures stratifying between NPP and PP. Two studies only reported on total AHI.

Six studies[23-25, 27, 28, 33] reported a reduction in total AHI in both NPP and PP, whilst one study only in NPP.[31] In NPP, the supine AHI significantly decreased in two studies.[34, 35] Four studies reported a significant decrease in supine AHI in PP postoperatively.[23-25, 28] In one study, supine AHI only slightly reduced from 49.8 ±19.9 to 44.2 ±31.2 events/hour.[27] In NPP, a decrease in the non-supine AHI was found in five studies.[24, 25, 27, 28, 35] In PP, a significant decrease of the non-supine AHI was reported in only one study.[24] An overview of available secondary outcome measures can be found in **table 4.**

Table 4. Secondary outcome measures: preoperative and postoperative *PSG parameters* of study population as stratified between NPP and PP

Author	Year	**Preoperative PSG parameters**									**Postoperative PSG parameters**								
		Total AHI			Supine AHI			Non-supine AHI			Total AHI			Supine AHI			Non-supine AHI		
		Total	NPP	PP	Total	NPP	PP	Total	NPP	PP	Total	NPP	PP	Total	NPP	PP	Total	NPP	PP
Kastoer et al. [23]	2018	-	38.5 (25.6, 52.5)	19.0 (14.3, 27.4)	-	-	-	-	-	-	-	17.8* (5.3, 25.2)	13.1 (7.2, 28.5)	-	-	-	-	-	-
Steffen et al. [24]	2018	27.5 (18.4,42.3)	26.5 (17.5, 37.0)	30.0 (19.5, 54.5)	38.3 (21.6, 55.3)	-	-	-	-	-	9.0* (4.0, 17.5)	11.3 (5.0, 18.5)	8.5 (3.0, 14.0)	12.5* (5.0, 24.1)	-	-	-	-	-
Van Maanen et al. [25]	2014	18.0 (5.1, 69.6)	23.0 (14.3, 31.0)	15.5 (10.9, 21.7)	30.2 (19.1, 49.5)	27.2 (15.0, 49.5)	33.9 (22.2, 50.6)	12.5	29.2	5.6	11.2* (5.6, 20.2)	11.0* (6.1, 20.1)	11.5* (5.0, 21.2)	20.5* (8.3, 39.9)	20.5* (7.8, 42.2)	20.9* (8.4, 38.3)	5.7*	9.1*	3.6
Li et al. [26]	2013	59.5 ±18.2	68.9** ±17.4	52.5** ±15.7	63.4 ±22.5	65.4 ±28.6	61.9 ±17.1	33.7 ±27.7	61.4** ±14.8	13.3** ±13.1	22.6* ±19.6	31.0* ±19.6	16.4* ±12.8	27.6* ±21.5	40.6* ±24.4	17.9* ±12.4	10.7* ±16.7	15.8* ±20.3	6.9* ±12.6
Van Maanen et al. [27]	2012	36.7 ±14.4	41.3	32.7	51.2 ±24.8	43.5	57.9	25.9	38.8	14.9	25.1*	26.6*	23.7*	39.3*	35.6	42.2*	16.8*	20.8*	13.3
Lee et al. [28]	2011	-	50.0** ±19.2	30.9** ±13.7	-	53.0 ±20.9	51.1 ±21.6	-	46.3** ±21.8	9.7** ±8.4	-	35.4* ±23.7	22.9* ±18.1	-	46.1 ±30.1	35.3* ±26.2	-	18.5* ±22.9	8.2 ±10.8
Kwon et al. [29]	2010	34.7 ±20.0	-	-	51.2	-	-	18.4	-	-	24.2* ±17.2	-	-	31.5	-	-	10.5	-	-
Lee et al. [30]	2009	-	48.8** ±18.3	35.6** ±16.9	-	49.8 ±19.9	53.0 ±20.9	-	45.1** ±19.2	8.2** ±8.5	-	33.3 ±25.1	27.4 ±19.5	-	44.2 ±31.2	38.7 ±26.4	-	15.6 ±21.6	10.0 ±12.4
Stuck et al. [31]	2005	35.2° ±19.1	-	-	-	-	-	-	-	-	27.4°* ±26.2	-	-	-	-	-	-	-	-

Data presented as mean ± standard deviation or median (Q1, Q3), ° respiratory disturbance index (RDI)

AHI apnea-hypopnea index, *NPP* non-positional obstructive sleep apnea patients, *PP* positional obstructive sleep apnea patients

* p value < 0.05 comparing preoperative and postoperative PSG parameters in separate groups (total, NPP and PP)

** p value < 0.05 comparing differences in PSG parameters between NPP and PP

DISCUSSION

The aim of this systematic review was to evaluate the influence of position-dependency on surgical success of UA surgery in OSA patients. We hypothesized that there is a difference in surgical success in NPP and PP undergoing UA surgery. Despite the importance of the subject, it remains unclear whether position-dependency is a predictor for surgical success. Various small-scale studies, evaluating different surgical modalities report on this matter. The majority of studies reported on the surgical outcomes of different forms of palatal surgery, in particular UPPP. UPPP aims to increase the retropalatal lumen and reduce the collapsibility of the pharynx by resection of the free edge of the soft palate and uvula, in combination with a tonsillectomy. In some studies palatal surgery was combined with RFTB — a temperature-controlled reduction of the tissue of the tongue base — or hyoid suspension, consisting of a dissection of the hyoid bone at both sides of the midline, after which sutures are placed through the thyroid cartilage and around the hyoid bone.[29] The latter aims at creating a greater airway dimension at the level of the tongue base and epiglottis. In one study the results of hypoglossal nerve stimulation were discussed, which is a novel development for treatment of moderate to severe OSA patients with CPAP intolerance or failure. By using a unilateral stimulation, selective fibres, which are mainly innervating the tongue protrusors, are stimulated causing opening of the UA during every breathing cycle.

When evaluating the influence of position-dependency on the surgical success of these different forms of UA surgery, no differences were found in surgical success rate between NPP and PP undergoing UPPP/ZPP (+/- RFTB)[23], isolated tongue base or multilevel surgery[28] and hypoglossal nerve stimulation.[30] One study found that PP undergoing relocation pharyngoplasty had a greater chance of surgical success.[24] In the majority of the remaining studies surgical success was in favor of NPP.[27, 29, 31] Furthermore, in the vast part of included studies the effect of UA surgery was suggested to be greater in the lateral position than supine position. In studies reporting on preoperative and postoperative PSG parameters in NPP and PP a significant reduction of the non-supine AHI was found in NPP, but not in PP.

There is a significant clinical diversity in these studies, complicating interpretation of the results, such as different forms of UA surgery and different definitions of surgical success and in some studies a modified versions of Cartwright's criteria for POSA was applied. Level of evidence is low; studies are generally small-scale and retrospective. Another important consideration is that the inverse relationship with BMI and AHI, is not only related to PP, but also to surgical success. Considering these confounders is of utmost importance. Last but not least, studies did not correct for

postoperative changes in the time spent in supine position. Especially in PP, OSA severity is strongly dependent on this factor and subsequently may also have influenced surgical success.
Although the results of this study are inconclusive, there are several findings that are of importance when evaluating the possibility of UA surgery in OSA patients. As previously mentioned, the decrease in non-supine AHI is significantly greater in NPP compared to PP.[23, 25, 27, 28] This is not surprising, since in PP, the non-supine AHI is usually low and therefore one does not expect a significant decrease, this in contrast to NPP. These findings are strengthened by a study by Bababemez et al. including only PP. They found a significant decrease in supine AHI, but no significant changes were observed in non-supine AHI postoperatively. The surgical cure rate of supine and non-supine AHI in this study was 87.5% compared to 56.3%, respectively.[36]

Furthermore, another interesting finding is that NPP often improve to less severe PP after UA surgery; the drop in AHI is more pronounced in non-supine as compared to supine position. Lee et al. reported that 64% of NPP undergoing UPPP changed to less severe PP.[25] In a second study evaluating OSA patients, 42% of all NPP changed to less severe PP.[31] In a third study similar results were found; 66.7% of all NPP changed to PP after multilevel surgery. In the PP group only 9.1% shifted to NPP.[37]

Clinical relevance

Recent developments have seen the introduction of a new, effective treatment modality for PP, assisting patients in avoiding the supine position.[38, 39] PP effectively treated with PT, with persistent milder OSA, may need less aggressive secondary treatment.[40] Furthermore, previous studies have shown beneficial effects in patients with postoperative persistent POSA. In a study by Benoist et al. patients were included with partial effective UA surgery, total AHI decreased from 28.5 (18.0-52.8) events/hour before surgery to 18.3 (13.7-24.0) events/hour after surgery. After additional treatment with PT a further decrease to 12.5 (4.5 – 21.8) events/hour was found.[41] Similar results were found in a study by the same group in patients with residual POSA after maxillomandibular advancement.[42] These results are strengthened by a study using a theoretical approach of concomitant PT in PP after UPPP/ZPP (+/- RFTB). Mathematical calculations suggested that in such patients with additional PT, median AHI would decrease from 18.0 events/hour to 4.5 events/hour ($p<0.001$).[23]

Future perspectives

Current high quality data is lacking evaluating the impact of position-dependency on surgical success. There is a demand for high-quality evidence from larger prospective studies evaluating differences in surgical success between NPP and PP, especially since the majority of OSA patient are PP.[4, 6, 11, 43]

There should be a focus on confounders influencing surgical success, such as the BMI and total AHI. Evaluating surgical success in NPP and PP is also hindered by the fact that different types of UA surgery have been applied and no general consensus has been reached on the usage of POSA criteria and surgical success. To enable accurate comparison of surgical success in NPP and PP universal definitions should be used and sub analysis must be performed focusing on the different types of UA surgery in OSA patients.

CONCLUSION

This systematic review evaluates the influence of position-dependency on surgical success of UA surgery in OSA patients. Although patient characteristics in PP seem to be in favor for higher surgical success compared to NPP, it remains unclear whether position-dependency is a predictor for surgical outcome. Previous studies suggest that the largest differences and expected preoperative and postoperative changes occur in the non-supine AHI. In PP the preoperative non-supine AHI is already lower compared to NPP suggesting a lower chance of surgical success in PP. Furthermore, in patients with partial effective surgery (improvement, but not cured), a transition of NPP to less severe PP is often seen. In these patients additional treatment with PT can be offered as additional therapy.

Appendix 1. Supplementary information – full search strategies

PubMed, 24-9-2018

Search	Query	Results
#9	#1 AND #2 AND #8	644
#8	#3 OR #4 OR #5 OR #6 OR #7	189576
#7	((velopharyn*[tiab] OR palat*[tiab] OR "Palate"[Mesh] OR "Tongue"[Mesh] OR tongue*[tiab] OR gloss*[tiab] OR "Oropharynx"[Mesh] OR oropharyn*[tiab] OR laryngopharyn*[tiab] OR tonsil*[tiab] OR "Hypopharynx"[Mesh] OR hypopharyn*[tiab] OR "Maxilla"[Mesh] OR maxill*[tiab] OR bimaxill*[tiab] OR mandib*[tiab] OR "Mandible"[Mesh] OR "Nose"[Mesh] OR nose[tiab] OR nasal[tiab] OR upper airway[tiab]) AND ("Surgical Procedures, Operative"[Mesh] OR "surgery" [Subheading] OR surge*[tiab] OR surgical*[tiab] OR operati*[tiab] OR operate*[tiab] OR procedure*[tiab]))	184062
#6	((Genioglossus[tiab] OR genioglossal) AND (advancement*[tiab])) OR (("Mandibular Advancement"[Mesh] OR "Surgical Procedures, Operative"[Mesh] OR "surgery" [Subheading] OR surge*[tiab] OR surgical*[tiab] OR operati*[tiab] OR operate*[tiab] OR procedure*[tiab] OR advancement*[tiab] OR osteotom*[tiab] OR "Osteotomy"[Mesh]) AND ("Maxilla"[Mesh] OR maxill*[tiab] OR bimaxill*[tiab] OR mandib*[tiab] OR "Mandible"[Mesh])) OR (("Osteogenesis, Distraction"[Mesh] OR distraction osteogenes*[tiab]) AND ("Maxilla"[Mesh] OR maxill*[tiab] OR bimaxill*[tiab] OR mandib*[tiab] OR "Mandible"[Mesh]))	85296
#5	Hyoid suspension*[tiab] OR Hyoidthyroidpexi*[tiab] OR glossectom*[tiab] OR (("Hyoid Bone"[Mesh] OR hyoid*[tiab] OR "Hypopharynx"[Mesh] OR hypopharyn*[tiab] OR laryngopharyn*[tiab] OR Lower pharyngeal airway*[tiab] OR "Tongue"[Mesh] OR tongue*[tiab]) AND ("Surgical Procedures, Operative"[Mesh] OR "surgery" [Subheading] OR surge*[tiab] OR surgical*[tiab] OR operati*[tiab] OR operate*[tiab] OR procedure*[tiab] OR resect*[tiab])) OR tongue suspension*[tiab] OR tongue base suspension*[tiab] OR Transoral robotic surg*[tiab] OR trans-oral robotic surg*[tiab] OR TORS[tiab]	20942
#4	"Tonsillectomy"[Mesh] OR adenotonsillectom*[tiab] OR tonsillectom*[tiab] OR Tonsillotom*[tiab] OR palatopharyngoplast* [tiab] OR palatoplast* [tiab] OR palate plast*[tiab] OR pharyngoplast* [tiab] OR uvulopalatopharyngoplast* [tiab] OR uvulopharyngoplast* [tiab] OR pharyngouvulopalatoplast*[tiab] OR velopharyngoplast* [tiab] OR UPP [tiab] OR UPPP [tiab] OR UVPP* [tiab] OR UP3[tiab]	14784
#3	LAUP[tiab] OR laser assisted uvulop*[tiab] OR laser uvulop*[tiab] OR (("Pulsed Radiofrequency Treatment"[Mesh] OR radiofrequency[tiab]) AND ("Palate"[Mesh] OR palat*[tiab] OR "Tongue"[Mesh] OR tongue*[tiab])) OR Palatal stiffening [tiab] OR injection snoreplast*[tiab]	494
#2	"Posture"[Mesh] OR position*[tiab] OR postur*[tiab] OR supine*[tiab]	625134
#1	"Sleep Apnea, Obstructive"[Mesh] OR OSA[tiab] OR OSAS[tiab] OR OSAHS[tiab] OR apnoea[tiab] OR apnea[tiab] OR hypopnea[tiab] OR hypopnoea[tiab] OR apneic*[tiab] OR apnoeic*[tiab] OR sdb[tiab] OR sleep disordered[tiab] OR obesity hypoventilat*[tiab] OR pickwickian[tiab] OR upper airway resistance syndrom*[tiab]	51649

Embase.com, 24-9-2018

Search	**Query**	**Results**
#16	#1 AND #2 AND #15	1064
#15	#3 OR #4 OR #8 OR #13 OR #14	219060
#14	('palate'/exp OR 'tongue'/exp OR 'oropharynx'/exp OR 'velopharynx'/exp OR 'hypopharynx'/exp OR 'maxilla'/exp OR 'mandible'/exp OR 'nose'/exp OR velopharyn*:ab,ti OR palat*:ab,ti OR tongue*:ab,ti OR gloss*:ab,ti OR oropharyn*:ab,ti OR laryngopharyn*:ab,ti OR tonsil*:ab,ti OR hypopharyn*:ab,ti OR maxill*:ab,ti OR bimaxill*:ab,ti OR mandib*:ab,ti OR nose:ab,ti OR nasal:ab,ti OR 'upper airway':ab,ti) AND ('surgery'/exp OR 'surgery'/lnk OR surge*:ab,ti OR surgical*:ab,ti OR operati*:ab,ti OR operate*:ab,ti OR procedure*:ab,ti)	209245

#13	#9 OR #10 OR #11 OR #12	93845
#12	('distraction osteogenesis'/exp OR (distraction:ab,ti AND osteogenes*:ab,ti)) AND ('maxilla'/exp OR 'mandible'/exp OR maxill*:ab,ti OR bimaxill*:ab,ti OR mandib*:ab,ti)	2896
#11	('surgery'/exp OR 'surgery'/lnk OR surge*:ab,ti OR surgical*:ab,ti OR operati*:ab,ti OR operate*:ab,ti OR procedure*:ab,ti OR advancement*:ab,ti OR osteotom*:ab,ti) AND ('maxilla'/exp OR 'mandible'/exp OR maxill*:ab,ti OR bimaxill*:ab,ti OR mandib*:ab,ti)	92919
#10	'mandibular advancement'/exp OR 'mandible osteotomy'/exp OR 'maxilla osteotomy'/exp	4935
#9	'genioglossus advancement'/exp OR (((genioglossus OR genioglossal) NEAR/9 advancement*):ab,ti)	157
#8	#5 OR #6 OR #7	28400
#7	'tongue surgery'/exp OR 'transoral robotic surgery'/exp OR 'tongue suspension*':ab,ti OR 'tongue base suspension*':ab,ti OR 'transoral robotic surg*':ab,ti OR 'trans oral robotic surg*':ab,ti OR tors:ab,ti	1419
#6	('hyoid bone'/exp OR 'hypopharynx'/exp OR 'tongue'/exp OR hyoid*:ab,ti OR hypopharyn*:ab,ti OR laryngopharyn*:ab,ti OR 'lower pharyngeal airway*':ab,ti OR tongue*:ab,ti) AND ('surgery'/exp OR 'surgery'/lnk OR surge*:ab,ti OR surgical*:ab,ti OR operati*:ab,ti OR operate*:ab,ti OR procedure*:ab,ti OR resect*:ab,ti)	26666
#5	'hyoid suspension'/exp OR 'glossectomy'/exp OR hyoidthyroidpexi*:ab,ti OR glossectom*:ab,ti	2113
#4	'tonsillectomy'/exp OR 'palatopharyngoplasty'/exp OR 'palatoplasty'/exp OR 'uvulopalatal flap'/exp OR 'uvulopalatopharyngoplasty'/exp OR 'pharynx reconstruction'/exp OR adenotonsillectom*:ab,ti OR tonsillectom*:ab,ti OR tonsillotom*:ab,ti OR palatopharyngoplast*:ab,ti OR palatoplast*:ab,ti OR 'palate plast*':ab,ti OR pharyngoplast*:ab,ti OR uvulopalatopharyngoplast*:ab,ti OR uvulopharyngoplast*:ab,ti OR pharyngouvulopalatoplast*:ab,ti OR velopharyngoplast*:ab,ti OR upp:ab,ti OR uppp:ab,ti OR uvpp*:ab,ti OR up3:ab,ti	22065
#3	(laup:ab,ti OR 'laser assisted uvulop*':ab,ti OR 'laser uvulop*':ab,ti OR 'palatal stiffening':ab,ti OR 'injection snoreplast*':ab,ti OR 'pulsed radiofrequency treatment'/exp OR radiofrequency:ab,ti) AND ('palate'/exp OR 'tongue'/exp OR palat*:ab,ti OR tongue*:ab,ti)	506
#2	'position'/exp OR position*:ab,ti OR postur*:ab,ti OR supine*:ab,ti	764917
#1	'sleep disordered breathing'/exp OR osa:ab,ti OR osas:ab,ti OR osahs:ab,ti OR apnoea:ab,ti OR apnea:ab,ti OR hypopnea:ab,ti OR hypopnoea:ab,ti OR apneic*:ab,ti OR apnoeic*:ab,ti OR sdb:ab,ti OR 'sleep disordered':ab,ti OR ((obesity NEXT/1 hypoventilat*):ab,ti) OR pickwickian:ab,ti OR (('upper airway resistance' NEXT/1 syndrom*):ab,ti) OR 'upper airway resistance syndrome'/exp	90375

Cochrane Library, 24-9-2018
Only CENTRAL had results

Search	Query	Results
#1	(osa OR osas OR osahs OR apnoea OR apnea OR hypopnea OR hypopnoea OR apneic* OR apnoeic* OR sdb OR "sleep disordered" OR (obesity NEXT hypoventilat*) OR pickwickian OR ("upper airway resistance" NEXT syndrom*)):ti,ab,kw	7677
#2	(LAUP OR ("laser assisted" NEXT uvulop*) OR (laser NEXT uvulop*) OR "Palatal stiffening" OR (injection NEXT snoreplast*) OR (radiofrequency AND (palat* OR tongue*))):ti,ab,kw	91
#3	(adenotonsillectom* OR tonsillectom* OR Tonsillotom* OR palatopharyngoplast* OR palatoplast* OR (palate NEXT plast*) OR pharyngoplast* OR uvulopalatopharyngoplast* OR uvulopharyngoplast* OR pharyngouvulopalatoplast* OR velopharyngoplast* OR UPP OR UPPP OR UVPP* OR UP3):ti,ab,kw	2534
#4	(Hyoidthyroidpexi* OR glossectom* OR (tongue NEXT suspension*) OR ("tongue base"	1016

	NEXT suspension*) OR (“Transoral robotic” NEXT surg*) OR (“trans oral robotic” NEXT surg*) OR TORS OR ((hyoid* OR hypopharyn* OR laryngopharyn* OR (“lower pharyngeal” NEXT airway*) OR tongue*) AND (surge* OR surgical* OR operati* OR operate* OR procedure* OR resect*))):ti,ab,kw	
#5	((Genioglossus NEXT advancement*) OR (genioglossal NEXT advancement*) OR ((surge* OR surgical* OR operati* OR operate* OR procedure* OR advancement* OR osteotom*) AND (maxill* OR bimaxill* OR mandib*)) OR ((distraction NEXT osteogenes*) AND (maxill* OR bimaxill* OR mandib*))):ti,ab,kw	5050
#6	((velopharyn* OR palat* OR tongue* OR gloss* OR oropharyn* OR laryngopharyn* OR tonsil* OR hypopharyn* OR maxill* OR bimaxill* OR mandib* OR nose OR nasal OR “upper airway”) AND (surge* OR surgical* OR operati* OR operate* OR procedure*)):ti,ab,kw	13853
#7	#2 OR #3 OR #4 OR #5 OR #6	15220
#8	(position* OR postur* OR supine*):ti,ab,kw	28653
#9	#1 AND #7 AND #8	114

CINAHL via Ebscohost, 24-9-2018

Search	Query	Results
S5	S3 AND S4	402
S4	(MH "Body Positions+") OR (TI (position* OR postur* OR supine*)) OR (AB (position* OR postur* OR supine*))	70,431
S3	(TI (OSA OR OSAS OR OSAHS OR apnoea OR apnea OR hypopnea OR hypopnoea OR apneic* OR apnoeic* OR sdb OR “sleep disordered” OR “obesity hypoventilat*” OR pickwickian OR “upper airway resistance syndrom*”) OR AB (OSA OR OSAS OR OSAHS OR apnoea OR apnea OR hypopnea OR hypopnoea OR apneic* OR apnoeic* OR sdb OR “sleep disordered” OR “obesity hypoventilat*” OR pickwickian OR “upper airway resistance syndrom*”)) OR (S1 OR S2)	8,867
S2	(MH "Pickwickian Syndrome")	94
S1	(MH "Sleep Apnea, Obstructive")	3,575

Web of Science, 24-9-2018

Search	Query	Results
# 9	#8 AND #2 AND #1 *Indexes=SCI-EXPANDED, SSCI, ESCI Timespan=All years*	752
# 8	#7 OR #6 OR #5 OR #4 OR #3 *Indexes=SCI-EXPANDED, SSCI, ESCI Timespan=All years*	115,558
# 7	TOPIC: (((velopharyn* OR palat* OR tongue* OR gloss* OR oropharyn* OR laryngopharyn* OR tonsil* OR hypopharyn* OR maxill* OR bimaxill* OR mandib* OR nose OR nasal OR "upper airway") AND (surge* OR surgical* OR operati* OR operate* OR procedure*))) *Indexes=SCI-EXPANDED, SSCI, ESCI Timespan=All years*	93,966
# 6	TOPIC: (((Genioglossus OR genioglossal) NEAR/5 advancement*) OR ((surge* OR surgical* OR operati* OR operate* OR procedure* OR advancement* OR osteotom*) AND (maxill* OR bimaxill* OR mandib*)) OR ("distraction osteogenes*" AND (maxill* OR bimaxill* OR mandib*))) *Indexes=SCI-EXPANDED, SSCI, ESCI Timespan=All years*	48,130
# 5	TOPIC: (Hyoidthyroidpexi* OR glossectom* OR "tongue suspension*" OR "tongue base suspension*" OR "Transoral robotic surg*" OR "trans oral robotic surg*" OR TORS OR ((hyoid* OR hypopharyn* OR laryngopharyn* OR "lower pharyngeal airway*" OR tongue*) AND (surge* OR surgical* OR operati* OR operate* OR procedure* OR resect*))) *Indexes=SCI-EXPANDED, SSCI, ESCI Timespan=All years*	22,918
# 4	TOPIC: (adenotonsillectom* OR tonsillectom* OR Tonsillotom* OR palatopharyngoplast* OR palatoplast* OR "palate plast*" OR pharyngoplast* OR uvulopalatopharyngoplast* OR uvulopharyngoplast* OR pharyngouvulopalatoplast* OR velopharyngoplast* OR UPP OR UPPP OR UVPP* OR UP3) *Indexes=SCI-EXPANDED, SSCI, ESCI Timespan=All years*	12,164
# 3	TOPIC: (LAUP OR "laser assisted uvulop*" OR "laser uvulop*" OR "Palatal stiffening" OR "injection snoreplast*"OR (radiofrequency AND (palat* OR tongue*))) *Indexes=SCI-EXPANDED, SSCI, ESCI Timespan=All years*	554
# 2	TOPIC: (position* OR postur* OR supine*) *Indexes=SCI-EXPANDED, SSCI, ESCI Timespan=All years*	1,007,448
# 1	TOPIC: (osa OR osas OR osahs OR apnoea OR apnea OR hypopnea OR hypopnoea OR apneic* OR apnoeic* OR sdb OR "sleep disordered" OR "obesity hypoventilat*" OR pickwickian OR "upper airway resistance syndrom*") *Indexes=SCI-EXPANDED, SSCI, ESCI Timespan=All years*	67,157

REFERENCES

1. Heinzer R, Marti-Soler H, Haba-Rubio J. Prevalence of sleep apnoea syndrome in the middle to old age general population. *Lancet Respir Med*. 2016;4(2):e5-6

2. van Maanen JP, Ravesloot MJ, Safiruddin F, de Vries N. The Utility of Sleep Endoscopy in Adults with Obstructive Sleep Apnea: A Review of the Literature. *Current Otorhinolaryngology Reports*. 2013;1(1):1-7

3. Frank MH, Ravesloot MJ, van Maanen JP, Verhagen E, de Lange J, de Vries N. Positional OSA part 1: Towards a clinical classification system for position-dependent obstructive sleep apnoea. *Sleep Breath*. 2015;19(2):473-80

4. Cartwright RD. Effect of sleep position on sleep apnea severity. *Sleep*. 1984;7(2):110-4

5. Oksenberg A, Silverberg DS, Arons E, Radwan H. Positional vs nonpositional obstructive sleep apnea patients: anthropomorphic, nocturnal polysomnographic, and multiple sleep latency test data. *Chest*. 1997;112(3):629-39

6. Richard W, Kox D, den Herder C, Laman M, van Tinteren H, de Vries N. The role of sleep position in obstructive sleep apnea syndrome. *Eur Arch Otorhinolaryngol*. 2006;263(10):946-50

7. Heinzer R, Petitpierre NJ, Marti-Soler H, Haba-Rubio J. Prevalence and characteristics of positional sleep apnea in the HypnoLaus population-based cohort. (1878-5506 (Electronic))

8. Mador MJ, Kufel TJ, Magalang UJ, Rajesh SK, Watwe V, Grant BJ. Prevalence of positional sleep apnea in patients undergoing polysomnography. *Chest*. 2005;128(4):2130-7

9. Itasaka Y, Miyazaki S, Ishikawa K, Togawa K. The influence of sleep position and obesity on sleep apnea. *Psychiatry Clin Neurosci*. 2000;54(3):340-1

10. Epstein LJ, Kristo D, Strollo PJ, Jr., et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med*. 2009;5(3):263-76

11. Ravesloot MJ, van Maanen JP, Dun L, de Vries N. The undervalued potential of positional therapy in position-dependent snoring and obstructive sleep apnea-a review of the literature. *Sleep Breath*. 2013;17(1):39-49

12. van Maanen JP, de Vries N. Long-term effectiveness and compliance of positional therapy with the sleep position trainer in the treatment of positional obstructive sleep apnea syndrome. *Sleep*. 2014;37(7):1209-15

13. van Maanen JP, Meester KA, Dun LN, et al. The sleep position trainer: a new treatment for positional obstructive sleep apnoea. *Sleep and Breathing*. 2013;17(2):771-79

14. Ravesloot M, White D, Heinzer R, Oksenberg A, Pépin J. Efficacy of the New Generation of Devices for Positional Therapy for Patients with Positional Obstructive Sleep Apnea: A Systematic

Review of the Literature and Meta-Analysis. *Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine*. 2017

15. Sundaram S, Bridgman SA, Lim J, Lasserson TJ. Surgery for obstructive sleep apnoea. *Cochrane Database Syst Rev*. 2005(4):CD001004

16. Shie DY, Tsou YA, Tai CJ, Tsai MH. Impact of obesity on uvulopalatopharyngoplasty success in patients with severe obstructive sleep apnea: a retrospective single-center study in Taiwan. *Acta Otolaryngol*. 2013;133(3):261-9

17. Liu SA, Li HY, Tsai WC, Chang KM. Associated factors to predict outcomes of uvulopharyngopalatoplasty plus genioglossal advancement for obstructive sleep apnea. *Laryngoscope*. 2005;115(11):2046-50

18. Vanderveken OM, Maurer JT, Hohenhorst W, et al. Evaluation of drug-induced sleep endoscopy as a patient selection tool for implanted upper airway stimulation for obstructive sleep apnea. *J Clin Sleep Med*. 2013;9(5):433-8

19. Koutsourelakis I, Safiruddin F, Ravesloot M, Zakynthinos S, de Vries N. Surgery for obstructive sleep apnea: sleep endoscopy determinants of outcome. *The Laryngoscope*. 2012;122(11):2587-91

20. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535

21. OCEBM Levels of Evidence Working Group. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

22. Quality assessment tool for observational cohort and cross-sectional studies – NHLBI N. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

23. van Maanen J, Witte B, de Vries N. Theoretical approach towards increasing effectiveness of palatal surgery in obstructive sleep apnea: role for concomitant positional therapy? *Sleep and Breathing*. 2014;18(2):341-49

24. Li HY, Cheng WN, Chuang LP, et al. Positional dependency and surgical success of relocation pharyngoplasty among patients with severe obstructive sleep apnea. *Otolaryngol Head Neck Surg*. 2013;149(3):506-12

25. Lee CH, Kim SW, Han K, et al. Effect of uvulopalatopharyngoplasty on positional dependency in obstructive sleep apnea. *Arch Otolaryngol Head Neck Surg*. 2011;137(7):675-9

26. Kwon M, Jang YJ, Lee BJ, Chung YS. The effect of uvula-preserving palatopharyngoplasty in obstructive sleep apnea on globus sense and positional dependency. *Clin Exp Otorhinolaryngol*. 2010;3(3):141-6

27. Lee CH, Shin HW, Han DH, et al. The implication of sleep position in the evaluation of surgical outcomes in obstructive sleep apnea. *Otolaryngol Head Neck Surg*. 2009;140(4):531-5

28. van Maanen JP, Ravesloot MJ, Witte BI, Grijseels M, de Vries N. Exploration of the relationship between sleep position and isolated tongue base or multilevel surgery in obstructive sleep apnea. *Eur Arch Otorhinolaryngol*. 2012;269(9):2129-36

29. Stuck BA, Neff W, Hormann K, et al. Anatomic changes after hyoid suspension for obstructive sleep apnea: an MRI study. *Otolaryngol Head Neck Surg*. 2005;133(3):397-402

30. Steffen A, Hartmann JT, Konig IR, Ravesloot MJL, Hofauer B, Heiser C. Evaluation of body position in upper airway stimulation for obstructive sleep apnea-is continuous voltage sufficient enough? *Sleep Breath*. 2018;22(4):1207-12

31. Kastoer C, Benoist LBL, Dieltjens M, et al. Comparison of upper airway collapse patterns and its clinical significance: drug-induced sleep endoscopy in patients without obstructive sleep apnea, positional and non-positional obstructive sleep apnea. *Sleep Breath*. 2018;22(4):939-48

32. Sher AE, Schechtman KB, Piccirillo JF. The efficacy of surgical modifications of the upper airway in adults with obstructive sleep apnea syndrome. *Sleep*. 1996;19(2):156-77

33. Steffen A, Hartmann JT, König IR, Ravesloot MJ, Hofauer B, Heiser C. Evaluation of body position in upper airway stimulation for obstructive sleep apnea—is continuous voltage sufficient enough? *Sleep and Breathing*. 2018;22(4):1207-12

34. Baker AB, Xiao CC, O'Connell BP, Cline JM, Gillespie MB. Uvulopalatopharyngoplasty: Does Multilevel Surgery Increase Risk? *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery*. 2016;155(6):1053-58

35. van Maanen JP, Witte BI, de Vries N. Theoretical approach towards increasing effectiveness of palatal surgery in obstructive sleep apnea: role for concomitant positional therapy? *Sleep Breath*. 2014;18(2):341-9

36. Babademez MA, Ciftci B, Acar B, et al. Low-temperature bipolar radiofrequency ablation (coblation) of the tongue base for supine-position-associated obstructive sleep apnea. *ORL J Otorhinolaryngol Relat Spec*. 2010;72(1):51-5

37. Lee YC, Eun YG, Shin SY, Kim SW. Change in position dependency in non-responders after multilevel surgery for obstructive sleep apnea: analysis of polysomnographic parameters. *Eur Arch Otorhinolaryngol*. 2014;271(5):1081-5

38. Ravesloot MJL, White D, Heinzer R, Oksenberg A, Pepin JL. Efficacy of the New Generation of Devices for Positional Therapy for Patients With Positional Obstructive Sleep Apnea: A Systematic Review of the Literature and Meta-Analysis. *J Clin Sleep Med*. 2017;13(6):813-24

39. Vonk P, Ravesloot M. Positional obstructive sleep apnea. *Somnologie*. 2018:1-6

40. Ravesloot MJ, Frank MH, van Maanen JP, Verhagen EA, de Lange J, de Vries N. Positional OSA part 2: retrospective cohort analysis with a new classification system (APOC). *Sleep Breath*. 2016;20(2):881-8

41. Benoist LB, Verhagen M, Torensma B, van Maanen JP, de Vries N. Positional therapy in patients with residual positional obstructive sleep apnea after upper airway surgery. *Sleep Breath*. 2016

42. Benoist LBLdR, M.H.T.; de Lange, J.; de Vries, N. Residual POSA After Maxillomandibular Advancement in Patients with Severe OSA. In: de Vries NR, M.; van Maanen, J., ed. *Positional Therapy in Obstructive Sleep Apnea*. Springer, Cham; 2015:321-29

43. Oksenberg A. Positional and non-positional obstructive sleep apnea patients. *Sleep Med*. 2005;6(4):377-8

The influence of position-dependency on surgical success in obstructive sleep apnea patients undergoing maxillomandibular advancement

9

P.E. Vonk, P.J. Rotteveel, M.J.L. Ravesloot, J.P.T.F. Ho, J. de Lange, N. de Vries

J Clin Sleep Med. 2019 Nov 27. pii: jc-19-00306

ABSTRACT

Study objectives: 1) to evaluate surgical success in obstructive sleep apnea (OSA) patients undergoing maxillomandibular advancement (MMA) stratifying for the reduction of both the total apnea-hypopnea index (AHI) and the AHI in supine and non-supine position 2) to evaluate the influence of position-dependency on surgical outcome 3) to analyze the prevalence of residual position-dependent OSA in non-responders after MMA.

Methods: a single-centre retrospective study including a consecutive series of OSA patients undergoing MMA between August 2011 and February 2019.

Results: In total, 57 patients were included. The overall surgical success was 52.6%. No significant difference in surgical success between non-positional (NPP) and positional (PP) OSA patients was found. Surgical success of the supine AHI was not significantly different between NPP and PP, but surgical success of the non-supine AHI was significantly greater in NPP than in PP. Of the 17 preoperative NPP, 13 patients shifted to less severe PP postoperatively. In total, 21 out of 27 (77.8%) non-responders were PP postoperatively.

Conclusion: No significant difference in surgical success between NPP and PP undergoing MMA was found. However, the improvement of total and non-supine AHI in NPP was significantly greater compared to PP. In non-responders, a postoperative shift from severe NPP to less severe PP was found, caused by a greater reduction of the non-supine AHI than the supine AHI postoperatively. In patients with residual OSA in the supine position after MMA, additional treatment with positional therapy can be indicated.

Keywords: obstructive sleep apnea, sleep-disordered breathing, maxillomandibular advancement, surgical success, positional, position-dependency

Brief summary

Preoperative evaluation of possible predictors for surgical success is of paramount importance before initiating upper airway surgery. Currently, the influence of position-dependency on surgical success in obstructive sleep apnea (OSA) patients undergoing MMA is unknown. We found that surgical success was similar in non-positional (NPP) and positional OSA patients (PP), but that the decrease in non-supine AHI was significantly greater in NPP than in PP, often resulting in a postoperative shift from severe NPP to less severe PP. Additional treatment with positional therapy can be of added value in non-responders with residual OSA in the supine position.

INTRODUCTION

In patients with moderate to severe obstructive sleep apnea (OSA), Continuous Positive Airway Pressure (CPAP) is considered the "gold-standard" therapy, but this therapy is often hampered by poor tolerance and low acceptance. [1-3] In patients with severe OSA (apnea-hypopnea index (AHI) > 30 events/h) and failure of CPAP treatment, several surgical therapies are available aiming to target structures related to upper airway (UA) collapse in order to reduce obstructions during sleep. One of these surgical techniques is maxillomandibular advancement (MMA). MMA consists of a combination of a Le Fort I osteotomy and a bilateral sagittal split osteotomy to enlarge the pharyngeal airway space. By advancement of the maxilla and mandible the medial-lateral and anteroposterior dimensions of the UA are enlarged. [4] This technique is highly effective in treating severe OSA patients with surgical success rates varying from 80 to 90%. [5-9] Compared to other surgical techniques, MMA is considered to be more invasive and in addition it has considerable morbidity. Therefore, patients are usually referred in cases of severe to extreme OSA, and when the chance of surgical success of less invasive forms of UA surgery is considered to be low.

There are several known negative predictors for the surgical success of MMA. Older patients and those with an increased neck circumference are at a greater risk of surgical failure. [10] Another potential predictor is position-dependency. In a small-scale study, results showed that in partially effective MMA (response but not cured), a shift was often seen from severe non-positional OSA to less severe positional OSA. In such cases, there is a successful decrease of the AHI in the non-supine position, but insufficient reduction of the AHI in the supine position. [11] Although this finding suggests a correlation between position-dependency and surgical success, further evidence is needed.

Therefore, the aim of this study was to evaluate surgical success in OSA patients undergoing MMA stratifying for the reduction of both the total AHI and the AHI in supine and non-supine position. Secondly, we wanted to evaluate the influence of position-dependency on surgical outcome. Thirdly, we wanted to analyze the prevalence of residual position-dependent OSA (POSA) in non-responders after MMA. Our hypothesis is that there is a difference in surgical success in non-positional OSA patients (NPP) and positional OSA patients (PP). Secondly, we hypothesize that surgical failure is caused by insufficient reduction of the AHI in the supine position rather than non-supine AHI.

METHODS

Study participants

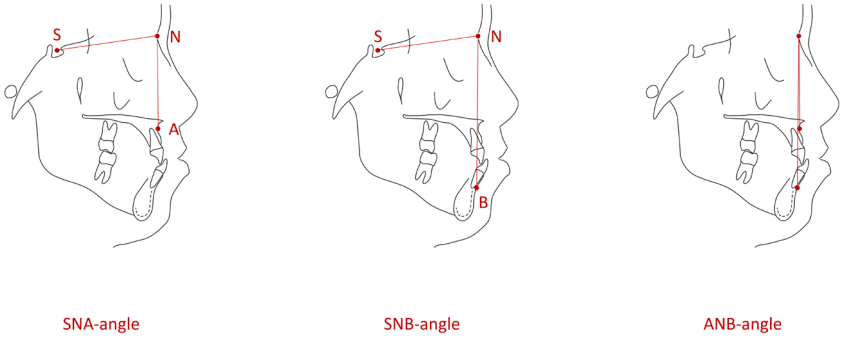
We performed a single-centre retrospective study including a consecutive series of OSA patients undergoing MMA between August 2011 and February 2019. Patients were only included if

preoperative and postoperative polysomnography (PSG) data after 3 to 6 months of follow-up were available. When patients slept 0% of the total sleeping time (TST) in the supine or non-supine position, position-dependency could not be adequately determined. In that case, patients were excluded from further analysis.

Cephalometric work-up and MMA procedure

Preoperative and postoperative cephalometric data was collected including the following skeletal landmarks: center of sella turnica (S), nasion (N), subspinal (A-point) and supramentale (B-point). Sella-nasion–A-point angle (SNA-angle) indicates whether or not the maxilla is normal, prognatic, or retrognatic. Sella–nasion–B-point angle (SNB-angle) assesses the mandible in a similar way and the A-point to B-Point angle (ANB-angle) describes the sagittal discrepancy between the maxilla and the mandible (**figure 1**). [12]

Figure 1. Skeletal landmarks



S center of sella turnica, *N* nasion, *A* A-point (subspinal), *B* B-point (supramentale)

All MMA procedures were performed by two dedicated maxillofacial surgeons and consisted of a Le Fort I osteotomy and a BSSO to advance the maxillary and mandibular facial skeleton. The maxilla was advanced to the preoperatively planned position (~8-10mm anteriorly) and an acrylic intermediate splint was used to guarantee correct alignment and fixation of the maxilla in the intended planned position.

Definitions

Surgical success was defined according to Sher's criteria, which means that MMA was considered to be successful when a postoperative reduction of more than 50% of the preoperative AHI was achieved combined with a postoperative AHI below 20 events/h. [13] To determine surgical success stratified to supine and non-supine position a modified versions of Sher's criteria was applied using supine and non-supine AHI instead of total AHI.

Patients not meeting Sher's criteria for surgical success were referred to as non-responders. Surgical success for total AHI, supine AHI and non-supine AHI was determined in the total study population, NPP, PP, responders, and in non-responders.

Patients were identified as being position-dependent using Cartwright's criteria, a supine AHI of at least twice as high as non-supine AHI. [14]

Ethical considerations

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Declaration of Helsinki of 1975. Data on study subjects was collected and stored encoded to protect personal information. For this type of study informed consent was not required.

Statistical analysis

Statistical analysis was performed using SPSS (version 22), SPSS Inc., Chicago, IL. Quantitative data were reported as mean and standard deviation (SD) or as median and (Q1, Q3) when not normally distributed. To determine whether continuous variables were normally distributed, the Shapiro-Wilk Test was used. A p value of < 0.05 was considered to indicate statistical significance. To compare baseline characteristics between NPP and PP the unpaired t test was used in case of normally distributed data and the Mann-Whitney U test when data was not normally distributed. A Pearson's chi-squared test was used to determine whether there was a correlation between position-dependency and surgical success. To compare preoperative and postoperative values in total population, NPP and PP a paired t test was used when data was normally distributed. In case of not

normally distributed data a Wilcoxon signed rank test was applied. When comparing differences in surgical outcome between groups an unpaired T test or the Mann-Whitney U test was used in case of normally or not normally distributed data respectively. To correct for possible confounders a multivariate logistic regression analyses was performed. Descriptive statistics were used to analyze the occurrence of a shift in position-dependency after MMA.

RESULTS

In total 68 patients underwent MMA for OSA. Eight patients were excluded because (partial) preoperative or postoperative PSG data was missing. In three patients position-dependency could not be determined due to a TST of 0% in the supine position. Therefore, 57 patients were included for analysis. Forty-eight patients were male (84.2%). The mean age was 51.3 ± 8.6 years with a body mass index (BMI) of 28.6 ± 4.0 kg/m^2. Twenty-four patients were daily smokers (42.1%) and 23 patients (40.4%) were previously diagnosed with cardiovascular problems (myocardial infarction N=9, hypertension N=9, atrial fibrillation N=2, other N=2). Fifty-five patients (96.5%) had CPAP intolerance or failure and 23 patients (40.4%) received another form of UA surgery prior to MMA (e.g. uvulopalatopharyngoplasty (UPPP), thermotherapy of the tongue base or hyoidthyroidpexia).

Patients had a total mean AHI of 51.4 ± 22.2 events/h, a mean supine AHI of 68.1 ± 20.7 events/h and a non-supine AHI of 44.4 ± 24.5 events/h. The mean oxygen desaturation index (ODI ≥ 3%) was 46.9 ± 22.3 events/h and the median average was SpO_2 93.0 % (92.0; 95.0). Of all patients, 38 were NPP preoperatively (66.7%). A detailed overview of baseline characteristics can be found in **table 1**.

Table 1. Baseline characteristics of the total population, NPP and PP

	Total	**NPP**	**PP**	**p value**
Number of patients (N)	57	38	19	-
Male : female	48:9	32:6	16:3	1.000
Age (years)	51.3 ± 8.6	51.2 ± 9.1	51.6 ± 7.8	0.872
BMI (kg/m^2)	28.6 ± 4.0	29.0 ± 3.9	27.8 ± 4.2	0.302
Total AHI (events/h)	51.4 ± 22.2	61.9 ± 17.5	30.4 ± 14.5	<0.001*
Obstructive AI (events/h)	21.7 [10.4, 44.3]	33.5 [19.5, 54.8]	11.0 [3.8, 18.2]	<0.001*
Mixed AI (events/h)	3.9 [0.3, 15.3]	4.4 [1.5, 21.9]	1.3 [0.3, 10.3]	0.257
Central AI (events/h)	0.8 [0.2, 3.0]	0.8 [0.2, 2.5]	0.9 [0.1, 3.3]	0.739
Supine AHI (events/h)	68.1 ± 20.7	70.7 ± 17.6	63.0 ± 25.6	0.188
Non-supine AHI (events/h)	44.4 ± 24.5	57.0 ± 19.1	19.3 ± 10.9	<0.001*
% of TST in the supine position	35.2 ± 19.6	39.2 ± 18.2	27.4 ± 20.5	0.031*
ODI (events/h)	46.9 ± 22.3	56.4 ± 19.1	28.5 ± 15.9	<0.001*
Median average SpO_2 (%)	93.0 [92.0, 95.0]	95.0 [91.0, 94.5]	94.0 [93.0, 95.3]	0.079

Data presented as mean ± standard deviation or median [Q1, Q3]

* p value <0.05 comparing NPP and PP

NPP non-positional obstructive sleep apnea patients, *PP* positional obstructive sleep apnea patients, *BMI* body mass index, *AHI* apnea-hypopnea index, *AI* apnea index, *TST* total sleeping time, *ODI* oxygen desaturation index, *SpO_2* saturation of peripheral oxygen

Baseline characteristics NPP versus PP

When comparing baseline characteristics between NPP and PP, mean age, the distribution of gender, mean BMI and supine AHI did not significantly differ. Total AHI (p<0.001), obstructive apnea index (AI; p<0.001), non-supine AHI (p<0.001), percentage of TST in the supine position (p=0.036) and ODI (p<0.001) were significantly higher in NPP. The median average SpO_2 did not significantly differ in NPP from that in PP (p=0.079) **(table 2).**

Table 2. Results before and after MMA in total population

	Total population (N=57)		
	Preoperative	Postoperative	p value
BMI (kg/m^2)	28.6 ± 4.0	28.1 ± 3.8	0.125
Total AHI (events/h)	51.4 ± 22.2	19.9 ± 15.3	<0.001*
Obstructive AI (events/h)	21.7 [10.4, 44.3]	5.0 [1.4, 10.1]	<0.001*
Mixed AI (events/h)	3.9 [0.3, 15.3]	0.6 [0.1, 4.1]	0.004*
Central AI (events/h)	0.8 [0.2, 3.0]	0.3 [0.1, 1.1]	0.021*
Supine AHI (events/h)	68.1 ± 20.7	35.2 ± 25.9	<0.001*
Non-supine AHI (events/h)	44.4 ± 24.5	11.2 ± 11.8	<0.001*
% of TST in supine sleeping position	35.2 ± 19.6	38.3 ± 21.8	0.236
ODI (events/h)	46.9 ± 22.3	25.1 ± 15.8	<0.001*
Median average SpO_2(%)	93.0 [92.0, 95.0]	95.0 [93.0, 96.0]	<0.001*

Data presented as mean ± standard deviation or median [Q1, Q3], * p value <0.05

MMA maxillomandibular advancement, *NPP* non-positional obstructive sleep apnea patients, *PP* positional obstructive sleep apnea patients, *BMI* body mass index, *AHI* apnea-hypopnea index, *AI* apnea index, *TST* total sleeping time, *ODI* oxygen desaturation index, *SpO_2* saturation of peripheral oxygen

Preoperative and postoperative MMA results

The median advancement of the maxillomandibular complex was 10mm (range 8-12mm). The preoperative and postoperative skeletal relationship based on the SNA, SNB and ANB are shown in **table 3.**

Table 3. Cephalometric analysis

	SNA	**SNB**	**ANB**
Preoperative	81.0 (79.5-85.2)	77.4 (73.1-81.8)	5.0 (2.7-7.7)
Postoperative	87.0 (84.2-91.7)	80.2 (76.7-85.6)	6.8 (5.1-11.1)

Data presented as median (*IQR* interquartile range)

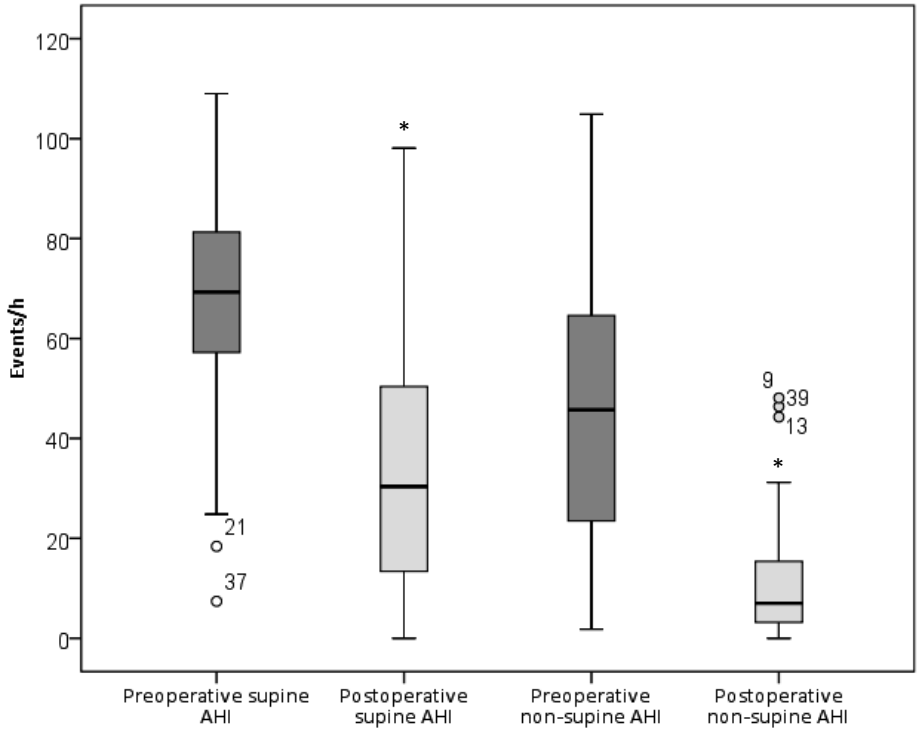
SNA S-N line and A-point, SNB S-N line and B-point

The total mean AHI was significantly reduced from 51.4 ± 22.2 to 19.9 ± 15.3 events/h ($p<0.001$). In NPP, the total mean AHI decreased from 61.9 ± 17.5 to 21.9 ± 16.8 events/h compared to a decrease from 30.4 ± 14.5 to 16.1 ± 11.0 events/h in PP.

In the total population, supine AHI was significantly reduced from 68.1 ± 20.7 to 35.2 ± 25.9 events/h ($p<0.001$). In NPP, supine AHI was reduced from 70.6 ± 17.6 to 38.2 ± 28.9 events/h compared to 63.0 ± 25.6 to 29.2 ± 17.6 events/h in PP.

The non-supine AHI in all patients significantly decreased from 44.4 ± 24.5 to 11.2 ± 11.8 events/h ($p<0.001$). A reduction in non-supine AHI from 57.0 ± 19.1 to 12.0 ± 13.0 events/h and 19.3 ± 10.9 to 9.7 ± 9.3 events/h was found in NPP and PP respectively (see **figure 2**). An overview of preoperative and postoperative PSG parameters in the total population, and in both NPP and PP can be found in **table 2 and table 4**.

Figure 2. Boxplot of the preoperative and postoperative MMA supine and non-supine AHI in total population



* p value <0.05 comparing the preoperative and postoperative supine and non-supine AHI

MMA maxillomandibular advancement, *AHI* apnea-hypopnea index

Table 4. Preoperative and postoperative PSG values comparing NPP and PP

	NPP (N=38)				**PP (N=19)**				**NPP vs PP**
	Preoperative	Postoperative	p value	Δ	Preoperative	Postoperative	p value	Δ	p value
BMI (kg/m^2)	29.0 ± 3.9	28.6 ± 3.7	0.401	0.3 ± 2.4	27.8 ± 4.2	27.1 ± 3.9	0.082	0.7 ± 1.6	0.577
Total AHI (events/h)	61.9 ± 17.5	21.9 ± 16.8	<0.001*	40.0 ± 20.3	30.4 ± 14.5	16.1 ± 11.0	0.002*	14.3 ± 17.7	<0.001**
Obstructive AI (events/h)	33.5 [19.5, 54.8]	6.3 [2.1, 10.7]	<0.001*	23.1 [11.3, 45.2]	11.0 [3.8, 18.2]	3.3 [0.3, 7.5]	0.017*	7.0 [-1.0, 14.0]	0.001*
Mixed AI (events/h)	4.4 [1.5, 21.9]	0.8 [0.0, 7.0]	0.017*	2.0 [-1.5, 18.2]	1.3 [0.3, 10.3]	0.6 [0.1, 1.8]	0.044*	0.6 [-0.2, 9.7]	0.865
Central AI (events/h)	0.8 [0.2, 2.5]	0.3 [0.0, 1.0]	0.033*	0.3 [-0.3, 2.4]	0.9 [0.1, 3.3]	0.4 [0.1, 1.3]	0.434	0.1 [-0.3, 2.3]	0.182
Supine AHI (events/h)	70.6 ± 17.6	38.2 ± 28.9	<0.001*	32.5 ± 30.9	63.0 ± 25.6	29.2 ± 17.6	<0.001*	33.8 ± 32.2	0.884
Non-supine AHI (events/h)	57.0 ± 19.1	12.0 ± 13.0	<0.001*	44.9 ± 20.6	19.3 ± 10.9	9.7 ± 9.3	0.020*	9.6 ± 16.4	<0.001**
% of TST in the supine position	39.2 ± 18.2	41.0 ± 22.6	<0.001*	1.8 ± 21.5	27.4 ± 20.5	32.9 ± 19.6	0.104	5.4 ± 14.3	0.509
ODI (events/h)	56.4 ± 19.1	27.4 ± 17.4	0.608	28.9 ± 20.0	28.5 ± 15.9	20.5 ± 11.1	0.073	7.9 ± 18.2	<0.001**
Median average SpO_2 (%)	93.0 [91.0, 94.5]	95.0 [93.0, 96.0]	<0.001*	1.0 0.0, 2.0]	94.0 [93.0, 95.3]	95.0 [94.0, 96.0]	0.018*	0.5 [0.0, 2.0]	0.119

Data presented as mean ± standard deviation or median [Q1, Q3]

* p value <0.05 comparing preoperative and postoperative PSG values

** p value <0.05 comparing Δ (preoperative and postoperative change) in NPP and PP

PSG polysomnography, *NPP* non-positional obstructive sleep apnea patients, *PP* positional obstructive sleep apnea patients, *BMI* body mass index, *AHI* apnea-hypopnea index, *AI* apnea index, *TST* total sleeping time, *ODI* oxygen desaturation index, *SpO_2* saturation of peripheral oxygen

Surgical success of the total AHI, supine AHI and non-supine AHI

Surgical success was achieved in 30 out of 57 patients (52.6%); 55.3% (N=21) in NPP and 47.4% (N=9) in PP. This difference was not statistically significant (p=0.574). Multivariate logistic regression analysis showed no significant correlation between surgical success and age (OR 0.96 CI 95% 0.90-1.02; p=0.198), preoperative BMI (OR 1.0 CI 95% 0.90-1.20; p=0.561) or preoperative total AHI (OR 0.99 CI 95% 0.97-1.01); p=0.630).

Surgical success in the supine position was achieved in 19 patients (33.3%) of the total population, in 13 NPP (34.2%) and in 6 PP (31.6%). No significant difference was found between the surgical success in the supine position comparing preoperative NPP and PP (p=0.843).

In the non-supine position surgical success was achieved in 41 patients (71.9%) of the total population, in 31 NPP (81.6%) and in 10 PP (52.6%). Surgical success in the non-supine positions was significantly greater in NPP than in PP (p=0.022). **Table 5** provides an overview of surgical success percentages stratified for the total AHI, the supine AHI and the non-supine AHI in the total population and comparing NPP with PP**.**

Table 5. Surgical success of AHI, supine AHI and non-supine AHI in total population, NPP and PP

Surgical success	**Total population (N=57)**	**NPP (N=38)**	**PP (N=19)**	**p value**
Total AHI	52.6%	55.3%	47.4%	0.574
Supine AHI	50.9%	34.2%	31.6%	0.843
Non-supine AHI	75.4%	81.6%	52.6%	0.022*

* p value <0.05 comparing NPP and PP

AHI apnea-hypopnea index, *NPP* non-positional obstructive sleep apnea patients, *PP* positional obstructive sleep apnea patients

Postoperative shift in position-dependency

Of all patients, 38 patients (66.7%) were NPP preoperatively. Twenty-five NPP shifted to PP postoperatively (65.8%). Nineteen patients (33.3%) were PP preoperatively. After MMA 14 patients remained PP, 5 shifted to NPP (26.3%), see **figure 3.** In total, 39 out of 57 patients were PP postoperatively (68.4%).

Responders versus non-responders

In the non-responder group, 10 out of 27 patients (37.0%) were PP preoperatively. Eight preoperative PP remained position-dependent. Of the 17 preoperative NPP, 13 patients shifted to less severe PP postoperatively. In total, 21 out of 27 (77.8%) non-responders were PP postoperatively. The surgical success of the supine AHI was 83.3% in responders versus 14.8% in non-responders ($p<0.001$). When comparing the surgical success of the non-supine AHI we found a surgical success of 93.3% compared to 55.6% in responders and non-responders respectively ($p<0.001$). **Table 6** provides an overview of surgical success percentages of the total, supine and non-supine AHI comparing responders with non-responders.

Table 6. Surgical success in total AHI, supine AHI and non-supine AHI comparing responders and non-responders

Surgical success	**Responders (N=30)**	**Non-responders (N=27)**	**p value**
Total AHI	100%	N/A	-
Supine AHI	83.3%	14.8%	<0.001*
Non-supine AHI	93.3%	55.6%	<0.001*

*p value <0.05 comparing surgical success of the supine and non-supine AHI in responders and non-responders

AHI apnea-hypopnea index

DISCUSSION

Most studies on MMA show success rates of approximately 85%. [15] This is the first series that focusses on non-responders to MMA. In contrast to what was expected, our results did not show a significant difference in surgical success between NPP and PP, suggesting the absence of a correlation between position-dependency and surgical outcome in patients undergoing MMA. When stratifying for surgical success of the supine and non-supine AHI no significant difference was found in the surgical success of the supine AHI, but surgical success of the non-supine AHI was significantly greater in NPP than in PP. In the majority of non-responders, a shift from severe NPP to less severe PP was seen caused by a more pronounced reduction of the non-supine AHI than the supine AHI.

When interpreting the results, there are several factors that must be taken into consideration. Our overall success rate is lower than reported in the literature. [15] This is probably due to the fact that MMA in our institute is strictly reserved for severe to extreme OSA (mean AHI of 51.5 events/h), while many other series also include moderate and even mild pathology. Forty percent of our MMA patients underwent previous, unsuccessful UA surgery, or were considered poor candidates for standard UA surgery or upper airway stimulation for a variety of reasons (e.g., unfavorable findings during drug-induced sleep endoscopy, such as complete concentric palatal collapse or multilevel total collapse), which might have interfered with a positive surgical outcome. Lastly, the average age in this study was higher than in other studies reporting on the surgical outcome of MMA. It is known that a higher age has a negative impact on the surgical success of UA surgery and MMA. [10]

Nevertheless, we did not find a significant correlation between age and surgical success in our study population. When evaluating the possible relation of REM–related OSA and the increase of the percentage of REM sleep postoperatively, we did not find a significant correlation between the presence of REM-related OSA and surgical success (p=0.136) Furthermore, the high percentage of NPP is not surprising, due to the fact that the prevalence of positional OSA decreases when OSA severity increases. [16-20]

A significant decrease of the total AHI, supine AHI and non-supine AHI was found in both NPP and PP after MMA. ODI and average SpO_2 also significantly improved in NPP, but not in PP. Although total and non-supine AHI significantly decreased in both NPP and PP, the decrease was significantly greater in NPP than in PP. No significant difference was found in the decrease of the supine AHI. This finding might be explained by the fact that the preoperative total AHI and non-supine AHI in NPP were significantly higher. As a result, a greater reduction in non-supine AHI was possible.

The finding of a postoperative shift from severe NPP to less severe PP is not new. In previously published studies, similar results were found in patients undergoing uvulopalatopharyngoplasty or Z-palatoplasty with or without radiofrequency thermotherapy of the tongue base and multilevel

surgery.[21-24] This phenomenon also occurs in the case of extensive weight loss after bariatric surgery in OSA patients [25], while unpublished data suggests that treatment with mandibular advancement devices can also lead to more reduction of the lateral AHI than the supine AHI.

Clinical relevance

Since MMA is often positioned as a last resort and taking into account its considerable morbidity, surgical failure is a very disappointing outcome. It is often seen that the AHI in non-supine positions is successfully reduced, this in contrast to the supine AHI. As a result, apneic events may still occur in the supine position, which can have a negative effect on the outcome of MMA. However, additional positional therapy (PT) using either the so-called tennis ball technique – in which a bulky mass is attached to the back –, or with new-generation vibro-tactile devices attached to the chest or trunk aiming to prevent patients from lying in the supine position. In that case, PT can be of added value in non-responders with residual OSA in the supine position. [23, 26, 27] Furthermore, hypoglossal nerve stimulation has been added to the treatment armamentarium of OSA. Several patients treated with MMA could in theory also have benefitted from this form of UA surgery, which may explain the decrease in number of MMA procedures over the past few years. Nevertheless, hypoglossal nerve stimulation is currently only performed in patients with an AHI between 15 and 65 events/h, therefore almost half of our study population would not have been selected for this therapeutic option.

Limitations

This study is not without limitations. First, a retrospective study design was used, where a prospective study would have been preferred. Second, when comparing NPP and PP one must take several confounders into consideration. PP tend to have lower total AHI, lower BMI and are usually younger as compared to NPP. These factors are also related to surgical outcome. [15, 28, 29] Nevertheless, after correcting for confounders such as age, preoperative total AHI and BMI, no significant difference in surgical success between NPP and PP was found. Third, especially in PP, total AHI is influenced by the time spent in the supine position. Although this could have influenced differences in surgical success when comparing NPP and PP, we did not find a significant difference in percentage of TST in the supine position. Therefore, in our opinion the effect of this limitation was negligible.

CONCLUSION

No significant difference in surgical success between NPP and PP undergoing MMA was found. However, the improvement of total and non-supine AHI in NPP was significantly greater compared to PP. In non-responders, a postoperative shift from severe NPP to less severe PP was seen, caused by a greater reduction of the non-supine AHI than the supine AHI. In patients with residual OSA in the supine position after MMA, additional treatment with PT can be indicated.

REFERENCES

1. Haniffa M, Lasserson TJ, Smith I. Interventions to improve compliance with continuous positive airway pressure for obstructive sleep apnoea. *Cochrane Database Syst Rev*. 2004(4):CD003531

2. Richard W, Venker J, den Herder C, et al. Acceptance and long-term compliance of nCPAP in obstructive sleep apnea. *Eur Arch Otorhinolaryngol*. 2007;264(9):1081-6

3. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. *Proc Am Thorac Soc*. 2008;5(2):173-8

4. Gokce SM, Gorgulu S, Gokce HS, Bengi AO, Karacayli U, Ors F. Evaluation of pharyngeal airway space changes after bimaxillary orthognathic surgery with a 3-dimensional simulation and modeling program. *Am J Orthod Dentofacial Orthop*. 2014;146(4):477-92

5. Holty JE, Guilleminault C. Maxillomandibular advancement for the treatment of obstructive sleep apnea: a systematic review and meta-analysis. *Sleep Med Rev*. 2010;14(5):287-97

6. Prinsell JR. Maxillomandibular advancement surgery for obstructive sleep apnea syndrome. *J Am Dent Assoc*. 2002;133(11):1489-97; quiz 539-40

7. Prinsell JR. Maxillomandibular advancement surgery in a site-specific treatment approach for obstructive sleep apnea in 50 consecutive patients. *Chest*. 1999;116(6):1519-29

8. Hoekema A, de Lange J, Stegenga B, de Bont LG. Oral appliances and maxillomandibular advancement surgery: an alternative treatment protocol for the obstructive sleep apnea-hypopnea syndrome. *J Oral Maxillofac Surg*. 2006;64(6):886-91

9. Goh YH, Lim KA. Modified maxillomandibular advancement for the treatment of obstructive sleep apnea: a preliminary report. *Laryngoscope*. 2003;113(9):1577-82

10. de Ruiter MHT, Apperloo RC, Milstein DMJ, de Lange J. Assessment of obstructive sleep apnoea treatment success or failure after maxillomandibular advancement. *Int J Oral Maxillofac Surg*. 2017;46(11):1357-62

11. Benoist LBLdR, M.H.T.; de Lange, J.; de Vries, N. Residual POSA After Maxillomandibular Advancement in Patients with Severe OSA. In: de Vries NR, M.; van Maanen, J., ed. *Positional Therapy in Obstructive Sleep Apnea*. Springer, Cham; 2015:321-29

12. Paoli JR, Lauwers F, Lacassagne L, Tiberge M, Dodart L, Boutault F. Craniofacial differences according to the body mass index of patients with obstructive sleep apnoea syndrome: cephalometric study in 85 patients. *Br J Oral Maxillofac Surg*. 2001;39(1):40-5

13. Sher AE, Schechtman KB, Piccirillo JF. The efficacy of surgical modifications of the upper airway in adults with obstructive sleep apnea syndrome. *Sleep*. 1996;19(2):156-77

14. Cartwright RD, Diaz F, Lloyd S. The effects of sleep posture and sleep stage on apnea frequency. *Sleep*. 1991;14(4):351-3

15. Zaghi S, Holty JE, Certal V, et al. Maxillomandibular Advancement for Treatment of Obstructive Sleep Apnea: A Meta-analysis. *JAMA Otolaryngol Head Neck Surg*. 2016;142(1):58-66

16. Frank MH, Ravesloot MJ, van Maanen JP, Verhagen E, de Lange J, de Vries N. Positional OSA part 1: Towards a clinical classification system for position-dependent obstructive sleep apnoea. *Sleep Breath*. 2015;19(2):473-80

17. Oksenberg A, Silverberg DS, Arons E, Radwan H. Positional vs nonpositional obstructive sleep apnea patients: anthropomorphic, nocturnal polysomnographic, and multiple sleep latency test data. *Chest*. 1997;112(3):629-39

18. Richard W, Kox D, den Herder C, Laman M, van Tinteren H, de Vries N. The role of sleep position in obstructive sleep apnea syndrome. *Eur Arch Otorhinolaryngol*. 2006;263(10):946-50

19. Mador MJ, Kufel TJ, Magalang UJ, Rajesh SK, Watwe V, Grant BJ. Prevalence of positional sleep apnea in patients undergoing polysomnography. *Chest*. 2005;128(4):2130-7

20. Itasaka Y, Miyazaki S, Ishikawa K, Togawa K. The influence of sleep position and obesity on sleep apnea. *Psychiatry Clin Neurosci*. 2000;54(3):340-1

21. Lee CH, Shin HW, Han DH, et al. The implication of sleep position in the evaluation of surgical outcomes in obstructive sleep apnea. *Otolaryngol Head Neck Surg*. 2009;140(4):531-5

22. Kastoer C, Benoist LBL, Dieltjens M, et al. Comparison of upper airway collapse patterns and its clinical significance: drug-induced sleep endoscopy in patients without obstructive sleep apnea, positional and non-positional obstructive sleep apnea. *Sleep Breath*. 2018;22(4):939-48

23. van Maanen J, Witte B, de Vries N. Theoretical approach towards increasing effectiveness of palatal surgery in obstructive sleep apnea: role for concomitant positional therapy? *Sleep and Breathing*. 2014;18(2):341-49

24. van Maanen JP, Ravesloot MJ, Witte BI, Grijseels M, de Vries N. Exploration of the relationship between sleep position and isolated tongue base or multilevel surgery in obstructive sleep apnea. *Eur Arch Otorhinolaryngol*. 2012;269(9):2129-36

25. de Raaff CAL, Gorter-Stam MAW, de Vries N, et al. Perioperative management of obstructive sleep apnea in bariatric surgery: a consensus guideline. *Surg Obes Relat Dis*. 2017;13(7):1095-109

26. Benoist LB, Verhagen M, Torensma B, van Maanen JP, de Vries N. Positional therapy in patients with residual positional obstructive sleep apnea after upper airway surgery. *Sleep Breath*. 2016

27. Ravesloot MJL, White D, Heinzer R, Oksenberg A, Pepin JL. Efficacy of the New Generation of Devices for Positional Therapy for Patients With Positional Obstructive Sleep Apnea: A Systematic Review of the Literature and Meta-Analysis. *J Clin Sleep Med*. 2017;13(6):813-24

28. Shie DY, Tsou YA, Tai CJ, Tsai MH. Impact of obesity on uvulopalatopharyngoplasty success in patients with severe obstructive sleep apnea: a retrospective single-center study in Taiwan. *Acta Otolaryngol*. 2013;133(3):261-9

29. Liu SA, Li HY, Tsai WC, Chang KM. Associated factors to predict outcomes of uvulopharyngopalatoplasty plus genioglossal advancement for obstructive sleep apnea. *Laryngoscope*. 2005;115(11):2046-50

Discussion and future perspectives

10

DISCUSSION AND FUTURE PERSEPECTIVES

The general aim of this thesis is to assess the role of drug-induced sleep endoscopy (DISE) and position-dependency in the diagnostic work-up in obstructive sleep apnea (OSA) patients to enable patient-specific treatment planning.

DISE is an accepted tool in the diagnostic work-up for surgical candidates to identify the structures involved in upper airway (UA) obstruction. More controversial is the application of DISE in the work-up for non-surgical interventions, such as a mandibular advancement device (MAD), positional therapy (PT) or combination treatment (i.e., MAD and PT or PT and UA surgery). Based on the results of **chapter 4** and **chapter 5,** we advocate that DISE can be of added value prior to these non-surgical interventions since this procedure in combination with the maneuvers described can provide valuable information.

The foundation for the studies leading to these conclusions was presented in **chapter 2**. By using a theoretical model we concluded that the effect of jaw thrust on UA patency is probably greater than the effect of MAD treatment. Secondly, we suggested that lateral head rotation is not similar to lateral head and trunk position, especially not in patients with position-dependent OSA (PP). We are aware of the fact that the present model leaves room for improvement and we still regard this as work in progress. But, the outcomes of this study generated the aims and hypotheses evaluated in the subsequent chapters.

The use of jaw thrust during DISE to predict MAD treatment outcome

Ideally, by mimicking the effect of MAD through passive maneuvers during DISE one could reliably predict its actual effect resulting in greater cost-effectiveness. The predictive value of passive maneuvers remains under discussion. In recent years, several alternatives to the jaw thrust have been proposed varying from thermoplastic appliances — a mono-bloc splint — to the use of a simulation bite — consisting of a registration fork in maximal comfortable protrusion (MCP) — during DISE. Although the latter seems to be promising, it is time-consuming and in almost all centres not part of daily practice. In **chapter 4** the effect on UA patency of two potential screening methods was compared. Unfortunately, the agreement in degree of obstruction measured with jaw thrust and a new-generation thermoplastic boil-and-bite MAD — the MyTAP —was only slight to moderate. Overall, a greater improvement of UA patency at hypopharyngeal level was observed when applying jaw thrust. In contrast, jaw thrust was less effective in improving UA obstruction at retropalatal level than the MyTAP during DISE. The results of this study emphasize the need for an alternative to jaw thrust as a screening method and prediction tool for MAD treatment that can be used during DISE. **Chapter 4** describes the first part of a two-part study. In the future, it will be essential to assess the

correlation between the screening methods previously described and actual MAD treatment outcome. This will be necessary to further unravel the predictive value on MAD effectiveness using DISE as screening tool.

Body position and DISE

Historically, DISE is performed in the worst sleeping position, which is usually the supine position. With the growing attention for the effect of body position — either lateral head rotation or lateral head and trunk position — on OSA severity, one could argue that assessment of the UA in lateral position is at least as important as observations made in the supine position. The results described in **chapter 3** indicate that in non-positional OSA patients (NPP) the effect of lateral head rotation only on UA patency is comparable to lateral head and trunk position at each possible level of obstruction, with exception of the oropharynx. The latter is probably caused by displacement of the tongue base, which alters lateral oropharyngeal wall tension causing a secondary collapse of the lateral oropharyngeal walls. This collapsibility is presumably higher in NPP, since NPP tend to have a higher body mass index (BMI) in combination with a greater neck circumference. In PP, the degree of obstruction during lateral head rotation was significantly different from the observations made when patients were lying in lateral position, at every possible obstruction site. Therefore, in NPP DISE should be performed in supine position with and without lateral head rotation, which suffices to imitate lateral sleeping position. In PP, it is recommended to perform DISE in supine and lateral position to gain more information on UA collapse patterns. This can provide a broader perspective on possible treatment options, especially since PT is becoming a more accepted treatment in PP as a standalone treatment, or in combination with other treatment modalities (e.g., MAD or UA surgery or UA stimulation).

Another finding that underlines the relevance of performing DISE — also when non-surgical interventions are considered — is the phenomenon of a floppy epiglottis (FE). The diagnosis of an epiglottic collapse still requires invasive studies, since as a rule it cannot be established by physical examination or awake indirect or flexible laryngoscopy. Although algorithms have been proposed to identify airflow patterns and its relation to epiglottic collapse, these studies are not externally validated or yet part of daily practice. Nevertheless it is important to evaluate whether a FE is involved in the underlying pathology of OSA, since it has been linked to CPAP failure. In addition, treatment with MADs — which is often recommended as therapy of choice — is also not always successful. In **chapter 5** we tested the hypothesis that the presence of a FE is influenced by body

position and jaw thrust. The results of this study indicated that a FE appears almost exclusively in the supine position. A FE was still present in the minority of patients when jaw thrust was applied.

As previously stated, treatment of a FE remains challenging and evidence based treatment options are lacking. In the past, several surgical techniques of the epiglottis have been described, which are unfortunately not without any risks. Based on the results described in **chapter 5**, PT could be a promising alternative in patients with a FE, despite the fact that they might not suffer from position-dependent OSA (POSA). It can be used as a standalone treatment, but since a FE is usually part of a multilevel problem, it can also be combined with a MAD or less invasive forms of UA surgery limiting risks and complications.

Polysomnography and sleep position

In **chapter 8** the influence of wearing type II polysomnography (PSG) apparatus on sleeping position was analyzed. The results suggested that patients spend significantly more time in the supine position whilst undergoing a PSG. This leads to an increase in OSA severity measured by PSG, especially in PP, which could have significant impact on both clinical practice and research. As a matter of fact, several patients would not even have been diagnosed with OSA when using the percentage of supine body position measured during the inactive (diagnostic) phase of the Sleep Position Trainer (SPT). We are aware of the fact that the presented study leaves room for improvement. First we only included PP who were aware of the fact that they were position-dependent and that they should avoid the supine position. Nevertheless, similar results were found in a few previously published small-scale studies. In clinical practice, therapeutic options are evaluated based on, among other things, OSA severity. While CPAP is the therapy of choice in case of severe OSA, other treatment options, such as PT, MADs or UA surgery can be considered in case of mild or moderate OSA. If wearing PSG apparatus truly causing an overestimation OSA severity, this has an important impact on diagnosis and treatment, since many recommendations in guidelines are based on the total AHI. In the future, there is a demand for less invasive PSG apparatus, with less impact on sleeping position.

Position-dependency and sleep apnea surgery

There are several known factors contributing to lower surgical success rates, such as a high BMI, high total AHI and a complete concentric collapse at palatal level observed during DISE. Likewise NPP tend to have more severe disease and a higher BMI in comparison to PP. Based on this information, one could hypothesize that NPP have a lower chance of surgical success. On the other hand, one might argue that since the non-supine AHI in PP is low pre-operatively, NPP have a higher chance of surgical

success since an improvement of the AHI in both supine and non-supine position can be achieved, this in contrast to PP.

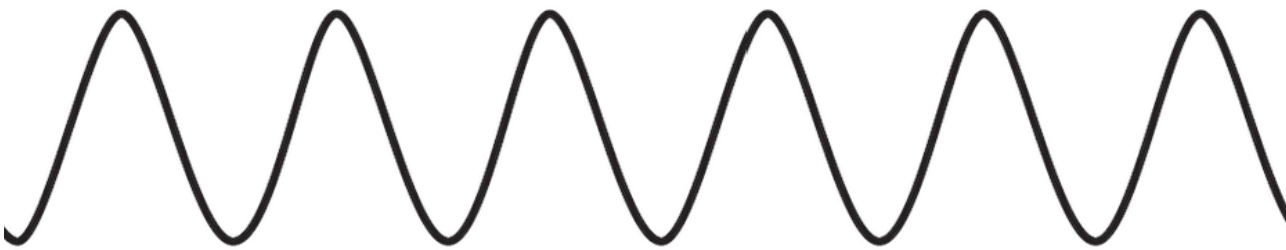
To evaluate whether position-dependency is a predictor for surgical success of sleep apnea surgery, a systematic review was performed including nine studies; two prospective and seven retrospective cohort studies (**chapter 9**). Despite the importance of the subject, the results of this study were inconclusive. The significant clinical diversity among studies (e.g., different forms of UA surgery and variations in the definition of surgical success) complicated the interpretation of the results. Furthermore, none of the included studies corrected for postoperative changes in the time spend in supine position. As previously mentioned, OSA severity is strongly dependent on this factor — especially in PP — and subsequently this may also have influenced surgical success. These factors could have contributed to the fact that we did not find a difference in surgical success between NPP and PP. We did find that in the vast part of included studies the effect of UA surgery was suggested to be greater in the lateral position than the supine position. In studies reporting on preoperative and postoperative PSG parameters in NPP and PP, a significant reduction of the non-supine AHI was found in NPP, but not in PP. Another interesting finding was that NPP often improve to less severe PP after UA surgery; the drop in AHI is more pronounced in non-supine as compared to supine position.

When evaluating the surgical success of maxillomandibular advancement (MMA) in more detail, no difference in surgical success was found comparing NPP and PP (**chapter 10).** When stratifying for surgical success of the supine and non-supine AHI no significant difference was found in the surgical success of the supine AHI, but surgical success of the non-supine AHI was significantly greater in NPP than in PP. In the majority of non-responders, a shift from severe NPP to less severe PP was seen caused by a more pronounced reduction of the non-supine AHI than the supine AHI.

In summary, it remains undecided whether position-dependency is a predictor for surgical success. But, since the majority of OSA patients are PP, there is a demand for high-quality evidence from larger prospective studies evaluating differences in surgical success between NPP and PP. To enable accurate comparison of surgical success in NPP and PP universal definitions for position-dependency and surgical success should be used. Furthermore, we believe that it is recommended to use a standardized framework to report on the role of body position in the management of OSA patients.

Summary/Samenvatting

11



SUMMARY

Studies enclosed in this thesis focused on the role of posture and different passive maneuvers during drug-induced sleep endoscopy (DISE) and its relevance with regard to obstructive sleep apnea (OSA) treatment outcome and patient-specific treatment planning. **Chapter 1** provides a general introduction to OSA.

In **chapter** 2 a retrospective, single-center cohort study including a consecutive series of OSA patients who underwent DISE was presented. We composed a 3-points model, based on the VOTE (**V**elum, **O**ropharynx, **T**ongue base, **E**piglottis) classification system, evaluating the effect of different passive maneuvers — manually performed jaw thrust, lateral head rotation, and a combination of both — on upper airway (UA) patency. The effect of these maneuvers was analyzed by using the sum VOTE score comparing non-positional OSA patients (NPP) and positional OSA patients (PP) and compared to the expected effect based on treatment outcome of a mandibular advancement device (MAD), positional therapy (PT), and combined treatment as reported in the literature. It was concluded that the effect of manually performed jaw thrust was greater and the effect of lateral head rotation alone during DISE less than what was expected.

Based on the findings described in **chapter 2,** we prospectively compared the effect of lateral head rotation only and both lateral head and trunk position on UA obstruction in **chapter 3.** In total, 92 patients underwent DISE in trunk and head supine, trunk and head lateral and when only the head was rotated to lateral position but trunk remained in the supine position. The effect of lateral head rotation and lateral head and trunk rotation on UA patency during DISE was significantly different in PP. In NPP, similar results regarding the degree of UA obstruction were found at the level of the velum, tongue base and epiglottis.

In the study described in **chapter 2** we also found that jaw thrust had a greater effect on UA patency than expected based on data published in the literature on MAD treatment outcome. In **chapter 4** the agreement between jaw thrust and an oral device *in situ* during DISE — in means of opening of the collapsible segment of the UA — was assessed. Secondly, the theoretical implications on clinical decision-making using either jaw thrust or a new generation boil-and-bite MAD (MyTAP, Airway Management Inc.) as potential screening instruments were evaluated. The results of this study indicated that there was only a slight to moderate agreement in degree of obstruction measured with jaw thrust and the MyTAP *in situ* during DISE. Overall, a greater improvement of UA patency at hypopharyngeal level was observed when applying jaw thrust. In contrast, jaw thrust was less

effective in improving UA obstruction at retropalatal level than the MyTAP. It was concluded that there is still a need for an alternative to jaw thrust that can be used as a screening method and serve as a better prediction tool for the effect of MAD treatment outcome during DISE.

In **chapter 5** the presence of a floppy epiglottis (FE) during DISE in non-apneic snoring patients, NPP and PP was assessed and the impact of maneuvers and posture was evaluated. In this retrospective study 324 patients were included. In 60 patients (18.5%) a FE was found in supine position. When performing lateral head rotation only, a FE was present in four patients, while in lateral position a FE was found in only one subject. After applying jaw thrust, a FE was still present in 10 patients. The prevalence of a FE did not significantly differ between NPP and PP. In patients with a FE, PT can be a promising alternative as a standalone treatment, but also as part of combination therapy with for example MADs or less invasive forms of UA surgery.

Chapter 6 presents the objective outcomes and safety of upper airway stimulation (UAS), and the influence of preoperative DISE findings on surgical success. A consecutive series of 44 moderate to severe OSA patients with continuous positive airway pressure (CPAP) intolerance or failure were included. The total median apnea-hypopnea index (AHI) significantly decreased from 37.6 (30.4; 43.4) events/h to 8.3 (5.3; 12.0) events/h ($p < 0.001$), the oxygen desaturation index was significantly reduced from 37.1 (28.4; 42.6) events/h to 15.9 (11.1; 21.6) events/h. With 88.6%, surgical success was high. UAS has proven to be an effective and safe treatment in OSA patients with CPAP intolerance or failure, in which proper patient selection, adequate implantation of the UAS system and follow-up by trained personnel are key to treatment success. There was no significant difference in surgical outcome between patients with a tongue base collapse with or without a complete anteroposterior collapse at the level of the palate.

Past years not only the number of studies on DISE has rapidly increased, also the influence of body posture on OSA severity has gained growing attention. Especially in PP, OSA severity depends on the supine and non-supine AHI, as well as the time spent in supine position. Especially, the latter is susceptible to variation. In **chapter 7**, the effect of wearing polysomnography (PSG) apparatus on sleeping position and the influence on OSA severity was evaluated. One hundred and sixty-eight position-dependent OSA (POSA) and non-apneic snoring patients who were prescribed PT (Sleep Position Trainer [SPT]) were retrospectively included. The effect of wearing PSG apparatus on sleeping position was analyzed by comparing body position during the PSG night and inactive (diagnostic) phase of the SPT. The results of this study indicated that wearing PSG apparatus lead to an increase in supine sleep of 33.6% causing an overestimation of OSA severity, especially in PP.

Chapter 8 described a systematic review on the influence of position-dependency on surgical success of different forms of UA surgery. In total, nine studies were included. Although preoperative characteristics in PP (e.g., lower body mass index and AHI) seem to be in favor for higher surgical success compared to NPP, it remains unclear whether or not position-dependency is a predictor for surgical outcome. It is suggested that the largest differences and expected preoperative and postoperative changes occur in non-supine AHI. In PP, the preoperative non-supine AHI is already lower compared to NPP suggesting a lower chance of surgical success in PP.

Chapter 9 focuses on the differences in surgical success in NPP and PP undergoing maxillomandibular advancement (MMA). Furthermore, the influence of position-dependency on surgical outcome and the phenomenon of residual POSA in non-responders to MMA were evaluated. A consecutive series of 57 patients undergoing MMA were retrospectively included. The overall surgical success was 52.6%. No significant difference in surgical success between NPP and PP undergoing MMA was found. However, the improvement of total and non-supine AHI in NPP was significantly greater compared to PP. In non-responders, a postoperative shift from severe NPP to less severe PP was found, caused by a greater reduction of the non-supine AHI than the supine AHI postoperatively.

SAMENVATTING

De studies in dit proefschrift zijn gericht op de rol van lichaamshouding en verschillende passieve manoeuvres toegepast tijdens een medicamenteus-geïnduceerde slaapendoscopie (*drug-induced sleep endoscopy*, DISE) bij patiënten met obstructieve slaapapneu (OSA). Hierbij ging het in het bijzonder om de relevantie ervan met betrekking tot behandeluitkomsten en patiëntselectie voor diverse vormen van therapie. In hoofdstuk 1 werd een algemene introductie gegeven.

Hoofdstuk 2 gaf de uitkomsten van een retrospectieve cohort studie weer, waarbij OSA-patiënten werden geïncludeerd die een DISE hebben ondergaan. Er werd een 3-punten systeem ontwikkeld, gebaseerd op het VOTE (**V**elum, **O**rofarynx, **T**ongbasis, **E**piglottis) classificatie systeem. Door middel van dit systeem werd het effect op de opening van de bovenste luchtweg van verschillende passieve manoeuvres, te weten *jaw thrust*, laterale hoofdrotatie en een combinatie van beide, geanalyseerd. Hiervoor werd de totale som berekend van de score die gegeven werd voor de mate van bovenste luchtwegobstructie in zowel niet-positionele (NPP) als positionele OSA patiënten (PP). Er werd geconcludeerd dat het effect van *jaw thrust* op bovenste luchtwegobstructie groter was dan wat verwacht werd op basis van het behandeleffect van een mandibulair repositie apparaat (MRA) beschreven in de literatuur. Dit in tegenstelling tot het effect van laterale hoofdrotatie: dit effect was minder dan verwacht in vergelijking met het behandeleffect van positietherapie (PT) gerapporteerd in de literatuur.

De resultaten beschreven in **hoofdstuk 2** hebben de basis gevormd voor de studies weergegeven in **hoofdstuk 3** en **hoofdstuk 4**. **Hoofdstuk 3** behandelde een prospectieve studie waarbij het effect op bovenste luchtwegobstructie van laterale hoofdrotatie werd vergeleken met het effect van volledige zijligging (romp en hoofd). In totaal werden 92 patiënten geïncludeerd. Deze patiënten ondergingen een DISE in rugligging, zijligging en met het hoofd geroteerd naar lateraal. Het effect van laterale hoofdrotatie op bovenste luchtwegobstructie verschilde significant van het effect van volledige zijligging bij PP. Bij NPP was het effect vergelijkbaar op het niveau van het velum, tongbasis en epiglottis, maar niet op orofarynx niveau.

In **hoofdstuk 4** werd de overeenstemming tussen bovenste luchtwegobstructie tijdens *jaw thrust* en een *boil and bite* MRA (MyTAP) in situ tijdens DISE beoordeeld. Daarnaast werden de theoretische gevolgen met betrekking tot klinische besluitvorming geanalyseerd bij het gebruikt van de *jaw thrust* of de MyTAP als potentieel screeninginstrument. De resultaten van deze studie toonden slechts een lichte tot matige overeenstemming in de mate van obstructie gemeten met *jaw thrust* en de MyTAP

in situ tijdens DISE. Over het algemeen werd een aanzienlijke verbetering van bovenste luchtwegobstructie op hypofarynxaal niveau gezien tijdens *jaw thrust*. *Jaw thrust* was minder effectief als het ging om het opheffen van bovenste luchtwegobstructie op retropalataal niveau in vergelijking met de MyTAP. De resultaten bevestigen de noodzaak voor een alternatief voor de *jaw thrust*, dat kan worden gebruikt als screeningmethode tijdens DISE om het effect van behandeling met een MRA te voorspellen.

In **hoofdstuk 5** werd de aanwezigheid van een floppy epiglottis (FE) tijdens DISE bij snurkers, NPP en PP beoordeeld en werd de impact van verschillende manoeuvres en lichaamshouding geëvalueerd. In deze retrospectieve studie werden 324 patiënten geïncludeerd. Bij 60 patiënten (18,5%) werd een FE in rugligging gevonden. Bij het uitvoeren van alleen laterale hoofdrotatie was een FE aanwezig bij vier patiënten, terwijl in zijligging slechts bij één patiënt een FE werd gevonden. Na het toepassen van *jaw thrust* was een FE aanwezig bij 10 patiënten. De prevalentie van een FE bij NPP en PP was niet significant verschillend. Bij patiënten met een FE kan PT een veelbelovend alternatief zijn als monotherapie, maar ook als onderdeel van combinatietherapie met bijvoorbeeld een MAD of minder invasieve vormen van bovenste luchtwegchirurgie.

In **hoofdstuk 6** werden de objectieve resultaten en veiligheid van nervus hypoglossus stimulatie (NHS) en de invloed van preoperatieve DISE-bevindingen op chirurgisch succes gepresenteerd. Een opeenvolgende reeks van 44 matige tot ernstige OSA-patiënten met continue positieve luchtwegdruk (CPAP) intolerantie of –falen werd geïncludeerd. De apneu-hypopneu-index (AHI) daalde aanzienlijk van 37,6 (30,4; 43,4) events/u naar 8,3 (5,3; 12,0) events/u ($p < 0,001$), de zuurstofverzadigingsindex daalde van 37,1 (28,4; 42.6) events/u naar 15.9 (11.1; 21.6) events/u. Het chirurgische succes van de behandeling was hoog, namelijk 88,6%. NHS is een bewezen effectieve en veilige behandeling bij OSA-patiënten met CPAP-intolerantie of –falen. Hierbij is goede patiëntselectie, adequate implantatie van het NHS-systeem en follow-up door hiertoe opgeleid personeel cruciaal voor het slagen van de behandeling. Er werd geen verschil gevonden in chirurgisch succes tussen patiënten met enkel een tongbasiscollaps of een volledige collaps op zowel tongbasis- als velumniveau.

De afgelopen jaren is niet alleen het aantal publicaties over DISE snel toegenomen, ook de invloed van lichaamshouding op de ernst van OSA heeft steeds meer aandacht gekregen. Vooral in PP is de ernst van OSA sterk afhankelijk van de AHI in rugligging en AHI in niet-rugligging, evenals de tijd die in rugligging wordt doorgebracht. Vooral de tijd in rugligging is onderhevig aan variatie. In **hoofdstuk 7** werd het effect van het dragen van polysomnografie (PSG)-apparatuur op de slaaphouding en hiermee de invloed op de ernst van de OSA geëvalueerd. Honderdachtenzestig PP en snurkers aan

wie PT [Sleep Position Trainer (SPT)] werd voorgeschreven, werden retrospectief geïncludeerd in deze studie. Het effect van het dragen van PSG-apparatuur op de slaaphouding werd geanalyseerd door de lichaamspositie tijdens de PSG-nacht en tijdens de inactieve (diagnostische) fase van SPT te vergelijken. De resultaten van deze studie lieten zien dat het dragen van PSG-apparatuur leidde tot een toename van de rugligging met 33,6%. Met name in PP kan dit leiden tot een overschatting van de ernst van OSA.

In **hoofdstuk 9** werden de resultaten van een systematische review van de literatuur met betrekking tot de invloed van positie-afhankelijkheid op het chirurgische succes van verschillende vormen van bovenste luchtwegchirurgie beschreven. In totaal werden negen studies geïncludeerd. Hoewel de preoperatieve kenmerken van PP (bijv. lagere body mass index en AHI) geassocieerd lijken te zijn met hogere kans op chirurgisch succes in vergelijking met NPP, blijft het onduidelijk of positie-afhankelijkheid een positieve of negatieve voorspeller is voor chirurgisch succes. Het grootste verschil tussen pre- en postoperatieve waardes lijkt op te treden bij de AHI in niet-rugligging. Aangezien in PP de preoperatieve AHI in niet-rugligging bij voorbaat al laag is, lijkt het desalniettemin aannemelijk dat het te behalen chirurgisch succes in NPP hoger ligt dan in PP.

Hoofdstuk 10 richtte zich op de verschillen in chirurgisch succes tussen NPP en PP die m*axillomandibular advancement* (MMA) hebben ondergaan. Daarnaast werden de invloed van positie-afhankelijkheid op chirurgische succes en het fenomeen van residueel POSA bij *non-responders* geëvalueerd. Er werden retrospectief 57 patiënten geïncludeerd. Het chirurgische succes bij hen was 52,6%. Er werd geen significant verschil in chirurgisch succes gevonden tussen NPP en PP. De verbetering van totale AHI en AHI in niet-rugligging in NPP was echter aanzienlijk groter in vergelijking met PP. Bij *non-responders* werd een postoperatieve verschuiving van ernstige NPP naar minder ernstige PP gevonden. Dit werd waarschijnlijk veroorzaakt door een grotere daling van de postoperatieve AHI in niet-rugligging in vergelijking met de daling van de AHI in rugligging.

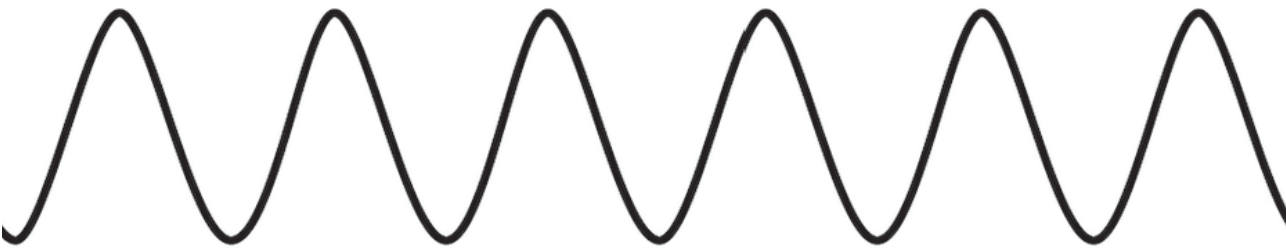
APPENDICES

LIST OF PUBLICATIONS AND PRESENTATIONS

PHD PORTFOLIO

CURRICULUM VITAE

DANKWOORD



PEER-REVIEWED PUBLICATIONS

P.E. Vonk, M.J.L. Ravesloot. Positional obstructive sleep apnea: an underestimated phenomenon? Somnologie, June 2018, Volume 22, Issue 2, pp 79–84

P.E. Vonk, A.M.E.H. Beelen, N. de Vries. Towards a prediction model for Drug-Induced Sleep Endoscopy as selection tool for Oral Appliance Treatment and Positional Therapy in Obstructive Sleep Apnea. Sleep Breath. 2018 Mar 9. 11325-018-1649

C. Kastoer, L.B.L. Benoist, M. Dieltjens, B. Torensma, L.H. de Vries, **P.E. Vonk**, M.J.L. Ravesloot, N. de Vries. Comparison of upper airway collapse patterns and its clinical significance: drug-induced sleep endoscopy in patients without obstructive sleep apnea, positional and non-positional obstructive sleep apnea. Sleep Breath. 2018 Dec;22(4):939-948. doi: 10.1007/s11325-018-1702-y

A. de Vito, M. Carrasco Llatas, M.J. Ravesloot, B. Kotecha B, N de Vries, E. Hamans, J. Maurer, M. Bosi, M. Blumen, C. Heiser, M. Herzog, F. Montevecchi, R.M. Corso, A. Braghiroli, R. Gobbi, A. Vroegop, **P.E. Vonk**, W. Hohenhorst, O. Piccin, G. Sorrenti, O.M. Vanderveken, C. Vicini. European Position Paper On Drug-Induced Sleep Endoscopy (DISE): 2017 Update. Clin Otolaryngol. 2018 Dec;43(6):1541-1552. doi: 10.1111/coa.13213

A.M.E.H. Beelen, **P.E. Vonk**, N. de Vries. Drug-Induced Sleep Endoscopy: The effect of different passive maneuvers on the distribution of collapse patterns of the upper airway in obstructive sleep apnea patients. Sleep Breath. 2018 Dec;22(4):909-917. doi: 10.1007/s11325-018-1732-5

P.E. Vonk, M.J. van de Beek, M.J.L. Ravesloot, N. de Vries. Drug-induced sleep endoscopy (DISE): New insights in the influence of lateral head position compared to lateral head and trunk rotation in non-positional and positional obstructive sleep apnea patients. Laryngoscope. 2018 Dec 24. doi: 10.1002/lary.27703

P.E. Vonk, N. de Vries, M.J.L. Ravesloot. Polysomnography and sleep position, a Heisenberg phenomenon? - A large-scale series. HNO. 2019 Jun 4. doi: 10.1007/s00106-019-0678-7

P.E. Vonk, L.B.L. Benoist, J.P. van Maanen, M.J.L. Ravesloot, H.J. Reesink,

K. Kasius, N. de Vries. Stimulatie van tongzenuw bij obstructieve slaapapneu. Techniek, indicatie en toekomst. Ned Tijdschr Geneeskd. 2019 May 3;163.: D3286

P.E. Vonk, M.J.L. Ravesloot, K.M. Kasius, J.P. van Maanen, N. de Vries. Floppy epiglottis during drug-induced sleep endoscopy: an almost complete resolution by adopting the lateral posture. Sleep Breath. 2019 Apr 24. doi: 10.1007/s11325-019-01847-x

M.J.L. Ravesloot, C.A.L. de Raaff, M. van de Beek, L.B.L. Benoist, J. Beyers, R. M. Corso, G. Edenharter, C. den Haan, J. Hedari-Azad1, J.T.F. Ho, B. Hofauer, E.J. Kezirian, J.P. van Maanen, S. Maes, J.P. Mulier, W. Randerath, O.M. Vanderveken, J. Verbraecken, **P.E. Vonk**, E.M. Weaver, N. de Vries. Perioperative Care of Patients With Obstructive Sleep Apnea Undergoing Upper Airway Surgery: A Review and Consensus Recommendations. JAMA Otolaryngol Head Neck Surg, 2019 Jun 27. doi: 10.1001/jamaoto.2019.1448

L.B.L. Benoist, **P.E. Vonk**, N. de Vries, H.C.J.P. Janssen, J. Verbraecken. New-generation positional therapy in patients with positional central sleep apnea. Eur Arch Otorhinolaryngol. 2019 Jul 13. doi: 10.1007/s00405-019-05545-y

M.J. van de Beek, **P.E. Vonk**, J.P. van Maanen, M.J.L. Ravesloot, N. de Vries. Tongzenuwstimulatie voor obstructief slaapapneu en benodigde capaciteit in Nederland. Nederlands Tijdschrift voor Keel-Neus-Oorheelkunde, jaargang 25, nummer 4, november 2019

P.E. Vonk, P.J. Rotteveel, M.J.L. Ravesloot, C. den Haan, N. de Vries. The influence of position-dependency on surgical success in sleep apnea surgery - a systematic review. Sleep Breath. 2019 Oct 17. doi: 10.1007/s11325-019-01935-y

P.E. Vonk, P.J. Rotteveel, M.J.L. Ravesloot, J.P.T.F. Ho, J. de Lange, N. de Vries, The influence of position-dependency on surgical success in OSA patients undergoing maxillomandibular advancement. J Clin Sleep Med. 2019 Nov 27. pii: jc-19-00306

P.E. Vonk, M.J.L. Ravesloot, J.P. van Maanen, N. de Vries. Short-term results of upper airway stimulation in obstructive sleep apnea patients: the Amsterdam experience. *Submitted*

P.E. Vonk, M.J.L. Ravesloot, J.P. van Maanen, N. de Vries. Kortetermijnresultaten van stimulatie van de bovenste luchtweg bij obstructieve slaapapneupatiënten: de Amsterdamse ervaring. *Submitted*

OTHER NON-PEER REVIEWED PUBLICATIONS

P.E. Vonk, M.J.L. Ravesloot, N. de Vries. Positional therapy for positional obstructive sleep apnea: what's new? Current Sleep Medicine Reports, September 2017, Volume 3, Issue 3, pp 113–121

P.E. Vonk, M.J.L. Ravesloot, N. de Vries. Advances in the role of drug induced sleep endoscopy in Investigating sleep apnea. Current Otorhinolaryngology Reports, September 2017, Volume 5, Issue 3, pp 187–190

CONTRIBUTIONS TO TEXTBOOKS

Sleep and Sleep disorders. A practical handbook.

Editors: Johan Verbraecken, Bertien Buyse, Hans Hamburgen, Viviane van Kasteel, Reindert van Steenwijk

Hoofdstuk 21.9.2.2: **Patty Vonk**, Nico de Vries, Nina Michiels, Marc Willemen, Johan Verbraecken. Behandeling van OSA: positietherapie

Drug-induced Sleep Endoscopy: Diagnostic and Therapeutic Applications: A Guide for Clinical Practices.

Editors: De Vries, Piccin, Vanderveken & Vicini

Chapter 14: **P.E. Vonk**, A.M.E.H. Beelen, N. de Vries. Work in progress: a prediction model for DISE as selection tool for MAD and positional therapy

Chapter 18: **P.E. Vonk**, M.J.L. Ravesloot, N. de Vries, Epiglottic collapse

Chapter 21: M.J.L. Ravesloot, **P.E. Vonk**, N. de Vries, DISE and Position-Dependent OSA

Chapter 22: **P.E. Vonk**, M.J.L. Ravesloot, O.M. Vanderveken, A.V.M.T. Vroegop, N. de Vries, DISE and Oral Appliance Treatment in Obstructive Sleep Apnea

PHD PORTFOLIO

PhD period: January 2017 – January 2020

PhD supervisors: Prof. dr. N. de Vries, dr. M.J.L. Ravesloot, dr. J.P. van Maanen

	Year	ECTS
General courses		
Good Clinical Practice	2018	1
Introduction in statistics and methodology	2018	3
Advanced biostatistics		1.5
Scientific Writing and English presenting	2019	4
Scientific Integrity	2019	2
Seminars, workshops and master classes		
Refereeravonden en intercollegiale overleggen (>15x)	2017-2020	2
Organisatie Refereermiddag "OSA en innovaties in diagnostiek en behandeling"	2017	1
Organisatie en deelname Mini-OSAS cursus	2017	1
Oral presentations		
Refereermiddag OLVG, Amsterdam, the Netherlands	2017	1
231e KNO-ledenvergadering, Nieuwegein, the Netherlands Mini-OSAS cursus (2x)	2017 2017	1 1
9th International Surgical Sleep Society Meeting, Munich, Germany (3x)	2018	3
Sleepless 2019, Amersfoort, the	2019	1

Netherlands		
iBEDSMA 2019, Knokke, Belgium	2019	1
SLAAP 2019, Ermelo, the Netherlands	2019	1
Poster presentations		
Wetenschapsdag OLVG 2018, Amsterdam, the Netherlands	2018	0.5
Wetenschapsdag OLVG 2019, Amsterdam, the Netherlands	2019	0.5
10th International Surgical Sleep Society Meeting, New York, USA	2019	0.5
Conferences		
IFOS ENT world congress	2017	1
231ste KNO-ledenvergadering, Nieuwegein, the Netherlands	2017	1
Wetenschapsdag OLVG	2018	1
9th International Surgical Sleep Society Meeting	2018	1
233ste KNO-ledenvergadering, Nieuwegein, the Netherlands	2019	1
European Sleep Research Society (ESRS) congress	2018	1
10th International Surgical Sleep Society Meeting	2019	1
Wetenschapsdag OLVG	2019	1
iBEDSMA	2019	1
SLAAP 2019	2019	1
Teaching		
Lectures for medical students – Diagnostics and treatment in obstructive sleep apnea patients	2017-2019	2
Supervising medical students (3x)	2017-2019	4
Guidance and supervision by the	2017-20120	6

supervisor		
Other		
Completion C-SSRS Training	2017	0.5
Titratietraining Inspire	2017	2
Kadaverlab training Inspire	2018	1
Researcher and attendee consensus meeting "Perioperative care in OSA patient undergoing upper airway surgery"	2018	3
Author of five book chapters	2018-2019	-
Total ECTS		**51**

CURRICULUM VITAE

Patty Vonk werd geboren op 20 januari 1991 in Geldrop. Vanaf 2009 studeerde zij Geneeskunde aan de Universiteit van Maastricht. Na het behalen van haar artsenexamen in augustus 2016 begon zij, onder begeleiding van Prof. dr. N. de Vries, dr. M.J.L. Ravesloot en dr. J.P. van Maanen, met het onderzoek dat geleid heeft tot dit proefschrift. Daarnaast was zij tijdens deze periode werkzaam als arts-assistent op de afdeling Keel-, Neus- en Oorheelkunde van het OLVG, Amsterdam. Zij was medeverantwoordelijk voor het opzetten en implementeren van het zorgtraject rondom OSA-patiënten die behandeld worden door middel van nervus hypoglossus stimulatie. In augustus 2019 is zij begonnen met de opleiding tot KNO-arts in het Amsterdam UMC, locatie AMC (Prof. dr. F.G. Dikkers).

DANKWOORD

De totstandkoming van dit proefschrift was me nooit alleen gelukt. In dit dankwoord wil ik graag mijn dank uitspreken naar alle collegae, vrienden, familie en de patiënten die hieraan hebben bijgedragen. Er zijn een aantal mensen die ik in het bijzonder wil bedanken.

Mijn promotor, Prof. dr. N. De Vries.
Lieve Nico, ik weet nog goed dat ik 3.5 jaar geleden na een open sollicitatie bij jou op gesprek mocht komen. Werk en een plek voor me had je zeker, geld daarentegen was nog een puntje van aandacht. Gelukkig kwam dat, zoals je overigens al die tijd geroepen hebt, goed en konden we samen dit traject aangaan. Wat ik altijd in jou bewonderd heb, is de manier waarop jij mensen weet te stimuleren en mee weet te nemen in jouw enthousiasme. We hebben vaak lopen sparren als een van ons weer een hersenspinsel had wat in onze ogen weer een mooi project zou kunnen opleveren (ook al liepen er al 20). De trots waarmee jij mensen om je heen naar voren duwt en in de schijnwerpers weet te zetten, waardeer ik enorm. Dank voor alle kansen die je me hebt gegeven en de manier waarop je me onder je hoede hebt genomen.

Mijn co-promotores, dr. M.J.L. Ravesloot en dr. J.P. van Maanen.
Lieve Madeline, waar was ik zonder jou geweest in deze onderzoekswereld en het mannenteam, zoals jij zou zeggen. Naast het feit dat je me onwijs geholpen hebt om de inhoud en kwaliteit van dit proefschrift naar een hoger niveau te tillen, zijn we de afgelopen jaren naast goede collega's ook vriendinnen geworden. Ik bewonder je als persoon met in het bijzonder je gedrevenheid en zorg die je draagt voor de mensen om je heen. En laten we eerlijk zijn: ik ken niemand die zo attent is als jij. Dankjewel.

Lieve Peter, mijn steun en toeverlaat als het gaat om relativering. En dat was af en toe zeker nodig. De nuchtere manier waarop jij in het leven staat, daar zou ik nog wat van kunnen leren. De afgelopen jaren heb ik veel van je geleerd als dokter en heb ik met plezier met je samengewerkt. Gelukkig zijn we naast collega's ook vrienden geworden, dus ik hoop dat we na het afronden van dit proefschrift contact blijven houden.

De leden van de leescommissie en oppositie.
Prof. dr. O.M. Vanderveken, beste Olivier, dank voor de steun die u op afstand de afgelopen jaren heeft geboden en het prettige contact op de vele congressen waar wij elkaar hebben getroffen. Ook ben ik dankbaar voor de bezoeken aan het UZA waar Nico en ik keer op keer weer hartelijk werden ontvangen.

Prof. dr. F.G. Dikkers, beste Freek, dank voor je deelname in mijn leescommissie en de kans die je me hebt geboden om mijn droom KNO-arts te worden, te verwezenlijken.

Prof. dr. J. de Lange, prof. dr. F. Lobbezoo, prof. dr. B.G. Loos, prof. dr. F.R. Rozema en prof. dr. J. Verbraecken, dank voor het accepteren van de uitnodiging om zitting te nemen in mijn leescommissie en de zorgvuldige en kritische beoordeling van mijn proefschrift.

Daarnaast wil ik de dames van de poli KNO, Marije en David bedanken voor al hun steun en zorg die ze mij hebben geboden in de soms roerige tijd waarin we met z'n allen zaten, met name op het einde. Wat had ik toch zonder jullie gemoeten. Het is niet de eerste keer dat dit gezegd wordt, maar wat ben ik dankbaar dat ik ben opgenomen in de KNO-familie van het OLVG West.

Dr. P.M. van Rijn, lieve Peter. Ook al had je helemaal niks met de OSA-onderzoeken en had je soms geen idee waar ik mee bezig was, je hebt altijd voor me klaar gestaan en je om mij bekommerd. Jouw enthousiasme om me dingen te leren en jouw vertrouwen hebben me absoluut doen groeien als dokter. De loyaliteit die jij hebt tegenover je collega's en onuitputbare inzet hebben mij keer op keer weer doen verbazen. Dankjewel voor de fijne en leerzame tijd.

Dr. M.A.J. van Looij, lieve Marjolein, wat vond ik het leuk dat jij het laatste jaar van mijn promotie in het OLVG kwam werken. Dank voor je luisterend oor en fijne tijd samen!

Ook wil ik graag de collega's van de KNF, Longgeneeskunde en MKA-chirurgie bedanken. De vele overlegmomenten, nauwe samenwerking en het vaste MDO Slaap laten zien dat slaap-gerelateerde ademhalingsstoornissen, met in het bijzonder obstructieve en centrale slaapapneu, multidisciplinaire ziektebeelden zijn, waarbij samenwerking centraal moet staan. Dank voor de vele inzichten en verdieping gedurende mijn tijd in het OLVG West.

Lieve Linda, het was geen makkelijke taak om in jouw voetsporen te treden. Gelukkig was je ten allen tijde bereid om me te helpen waar nodig en heb je me meerdere malen een luisterend oor geboden. Ik ben blij dat we elkaar beter hebben leren kennen en elkaar op het einde hebben kunnen aanvullen en helpen met alle zaken die geregeld moesten worden rondom het hele promotietraject. Behalve "het stappenplan" hadden we namelijk niet heel veel om op te varen. Inmiddels ben jij ook gepromoveerd en is het ons allemaal gelukt. Ik ben trots op je.

Lieve Pien, ik had me geen betere opvolger kunnen wensen. Dank voor de hulp die je me hebt geboden bij het afronden van alle projecten. Hopelijk gaan er nog een aantal gezamenlijke projecten en borrels volgen, ik kijk er naar uit.

Mijn liefste vriendinnetjes, ik mag van geluk spreken dat ik de afgelopen jaren zo'n fijne groep mensen om me heen heb weten te verzamelen. Dank voor de afleiding, steun en dosis positiviteit die jullie mij hebben geboden. Ik hoop dat er nog veel hoogtepunten gaan komen, met om te beginnen het feest van vanavond. Laat die danspasjes en hitjes maar komen!

Lieve Marleen, ik hoor je nóg zeggen "je moet me niet vragen, omdat ik jou gevraagd heb". En ik maar denken, die is gek.. Ik denk dat er maar weinig mensen zijn die me écht zo goed kennen als jij. Er is dan ook geen moment geweest dat ik er aan heb getwijfeld om jou als mijn paranimf te vragen. Dank voor al je hulp en fijne gesprekken. Onze vriendschap is heel belangrijk voor mij!

Lieve Fen, mijn maatje. YOLO is ons motto en dat heb ik de afgelopen tijd bijzonder goed kunnen gebruiken. Inmiddels kennen we elkaar al bijna een *decade* en ik kan me niet voorstellen dat onze vriendschap nog stuk kan. Vanzelfsprekend en trots ben ik dat jij mijn paranimf bent!

Lieve pap en mam, wat zou ik zonder jullie moeten. Waar ik zelf soms het vertrouwen was verloren, hebben jullie nooit aan mij getwijfeld. Jullie onvoorwaardelijke steun en vrijheid die jullie mij altijd hebben gegeven, hebben me gemaakt tot de persoon die ik nu ben. Ik weet niet hoe ik jullie daarvoor kan bedanken, woorden schieten tekort. Dank voor alles.

Lieve Xan en Deb, mijn zusjes, de afgelopen jaren zijn we steeds hechter geworden, iets wat mij heel veel goed heeft gedaan. Jullie zijn me heel dierbaar en ook al zijn we alle drie verschillend, de goede band die we hebben opgebouwd, neemt niemand ons meer af. Lieve Gijs en Don, wat ben ik blij dat jullie deel zijn gaan uitmaken van onze familie, iedereen is nu compleet. Lieve Mia Luna, mijn lieve nichtje, wat ben je toch een dropje. Ik ben knettergek op je en trots dat ik mijzelf jouw tante mag noemen!

Allerliefste Mark, leukerd, jij bent mijn steun en toeverlaat. Dank voor je eindeloze geduld, relativeringsvermogen en afleiding wanneer ik het nodig had. Jij was en bent er altijd voor mij. Jij houdt me met beide benen op de grond en steunt me in alles wat ik doe. Wat ben ik blij dat ik dit avontuur samen met jou heb mogen beleven. Zonder jou was het me niet gelukt.

SPONSOREN

Deze uitgave werk mede mogelijk gemaakt door:

Airway Management

Aurora Medical Support Belgium (AMSB)

Apneu Vereniging

Inspire Medical Systems

Nederlandse Vereniging voor Slaap- en Waakonderzoek (NSWO)

Nyxoah

Vivisol

OLVG

Slaapgeneeskunde Vereniging Nederland

apneu vereniging

Inspire
Sleep Apnea Innovation

NSWO

AM™
AIRWAY
MANAGEMENT

VIVISOL
SOLGROUP

Nyxoah™
The path to restful nights

olvg
een santeon ziekenhuis

SVNL