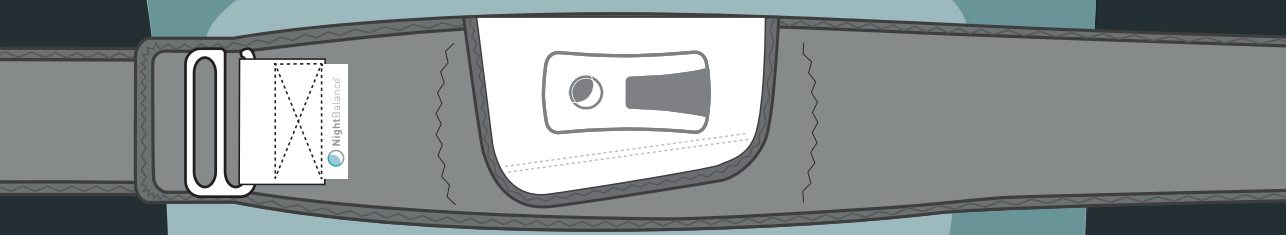
A NEW-GENERATION DEVICE FOR PATIENTS WITH POSITIONAL OBSTRUCTIVE SLEEP APNEA



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A new-generation device for patients with positional obstructive sleep apnea

Linda B.L. Benoist

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A NEW-GENERATION DEVICE FOR PATIENTS WITH POSITIONAL OBSTRUCTIVE SLEEP APNEA

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INTRODUCTION

Evolution

Up to a third of life, humans spend asleep. There is general agreement that good sleep is a prerequisite for good health. In Greek mythology Hypnos was the personification of sleep [1]. He lived in a cave next to his twin brother Thanatos, the daemonic representation of death. The earth in front of the cave was full of sleep-inducing plants. Hypnos used these plants to make Zeus fall asleep and the myth tells that this is the way the Greek won the Trojan War. The word "apnea" also derives from the Greek, which means "without breath".

Obstructive sleep apnea (OSA) is one of the most common chronic respiratory disorders. Sleep apnea was first described as a specific clinical entity in the late 1950s. In a scientific publication of Broadent, a physician from St. Mary's Hospital in London, from 1877 there is already a description which clearly refers to what we call today as obstructive sleep apnea "When a person, especially advanced in years, is lying on his back in heavy sleep and snoring loudly, it very commonly happens that every now and then the inspiration fails to overcome the resistance in the pharynx of which stertor or snoring is the audible sign, and there will be perfect silence through two, three, or four respiratory periods, in which there are ineffectual chest movements; finally, air enters with a loud snort, after which there are several compensatory deep inspirations before the breathing settles down to its usual rhythm" [2]. Gastaut later proved the first comprehensive account of OSA, describing polysomnography (PSG) in obese hypersomnolent patients with frequent nocturnal apneas [3]. During the following decade, the clinical and pathophysiological features of OSA were described [4,5].

American Academy of Sleep medicine (AASM) criteria

OSA is characterized by repetitive episodes of partial reduction (hypopneas) or complete cessation (apneas) in breathing for at least 10 seconds during sleep, occurring more than five times per hour of sleep. This resolves in upper airway collapse leading to decreased oxygen blood levels and arousal from sleep[6].

In the 3rd edition of the International Classification of Sleep Disorders (ICSD-3) four major categories of sleep disordered breathing have been defined [7]:

- obstructive sleep apnea disorders (including OSA);
- central sleep apnea (CSA);
- sleep-related hypoventilation disorders;
- sleep-related hypoxemia disorders.

The first two categories differ in pathophysiology. In patients with OSA upper airway obstruction is often caused by an abnormal craniofacial anatomy and/ or there is difficulty in maintaining the airway patency while having ongoing respiratory effort. In contrast, in CSA patients there is a cessation in air flow without respiratory effort.

According to ICSD-3 diagnosis of OSA (adult) is defined as follows [8];

A. The presence of one or more of the following applies:
i. The patient complains of sleepiness, non restorative sleep, fatigue, or insomnia symptoms. ii. The patient wakes with breath holding, gasping, or choking iii. The bed partner or other observer reports loud snoring, breathing interruptions, or both during the patient's sleep iv. The patient has been diagnosed with hypertension, a mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, or type 2 diabetes mellitus
B. Polysomnography (PSG) or ambulatory polygraphic (PG) recording show the following:
i. Five or more scoreable predominantly obstructive respiratory events (obstructive and mixed apneas, hypopneas, or RERA's, ***table 1***) per hour of sleep during a PSG or per hour of monitoring (PG)
OR **C. Polysomnography (PSG) or ambulatory polygraphic (PG) recording show the following:**
i. Fifteen or more predominantly obstructive respiratory events (apneas, hypopneas, or RERA's) per hour of sleep during a PSG or per hour of monitoring (PG)
The presence of criteria A and B or C satisfies the diagnosis of a clinically significant obstructive sleep apnea syndrome.

The severity of OSA is expressed in the apnea hypopnea index (AHI) (***table 1***), it can be defined as mild (AHI ≥ 5/h), moderate (AHI ≥ 15/h and ≤ 30/h) or severe (AHI > 30/h). AHI thresholds in children are different. This thesis focuses only on adult patients.

Positional Obstructive Sleep Apnea (POSA)

The majority of patients with mild to moderate OSA have more apneic events in the supine sleeping position, as compared to non-supine positions [10-12]. The most common definition that has been used for positional OSA (POSA) is defined as an apnea hypopnea index (AHI) that is at least twice as high in the supine position as compared to non-supine positions [13]. Since its introduction various classifications have been suggesting adding variables such as cut-off values concerning time spent in certain body positions, AHI in supine position and non-supine position. Many studies have looked at position dependency in patients with OSA and potential therapeutic options for this population, and this topic is a particular focus in this thesis [10,11,13,12,14].

Primary snoring

According to the ICDS-3 primary snoring is classified under "isolated symptoms and normal variants" [8]. This type of snoring occurs without episodes of apnea, hypopnea, respiratory effort-related arousals (RERAs) or hypoventilation and therefore subjects with primary snoring do not complain of excessive daytime sleepiness or insomnia. In patients who are at increased risk for OSA (e.g. patients with comorbid cardiovascular disease) PSG is required to rule out OSA.

Table 1 – Definitions according to an update of the 2007 American Academy of Sleep Medicine manual [9]

Apnea	Decrease in the peak signal excursion by ≥ 90% of pre-event baseline using an oronasal thermal sensor with a duration of ≥ 10 seconds.
Hypopnea	Decrease in the peak signal excursions by ≥ 30% of pre-event baseline using nasal cannula, with a duration of ≥ 10 seconds, and ≥ 3% oxygen desaturation from pre-event baseline or the event is associated with an arousal.
RERA	A sequence of breaths lasting at least 10 seconds characterized by increasing respiratory effort leading to arousal from sleep when the sequence of breaths does not meet criteria for an apnea or hypopnea.
AHI	The average number of apneas and hypopneas per hour of sleep as measured by polysomnography (PSG).

Historically, several terms such as primary, simple, benign, habitual or non-apneic have been used in the literature to define snoring. Throughout this thesis primary snoring and non-apneic snoring will be used.

Clinical manifestation

Common symptoms in patients with OSA include loud snoring, excessive daytime sleepiness, insomnia, and morning headaches. When left untreated OSA gradually induces cognitive deficits and impairs performance [15]. It's important to recognize those symptoms however a lot of patients are asymptomatic and therefore OSA is an underrecognized medical condition and about 80-90% remain undiagnosed [7,16]. ***Table 2*** summarizes the cardinal features of OSA in adults.

Table 2 - OSA symptoms in adults

Nocturnal symptoms	• Loud snoring • Witnessed apneas by bed partner • Awaking with choking • Nocturia • Insomnia with frequent awakenings • Restless sleep, with patients often experiencing frequent arousals and tossing or turning during the night
Daytime symptoms	• Non restorative sleep • Morning headaches • Excessive daytime sleepiness • Daytime fatigue/tiredness • Cognitive deficits; memory and intellectual impairment (short-term memory, lack of concentration) • Decreased vigilance • Morning confusion • Personality and mood changes, including depression and anxiety • Sexual dysfunction, including impotence and decreased libido

Prevalence

The overall prevalence of OSA in the general adult population is 9–38% [17-20]. OSA is more common in men and increases with age [17]. Recent data from Switzerland show that OSA is more prevalent than previously reported. The proportion of men and women with an AHI of >5/h on PSG was 84% and 61%, respectively [18]. This high prevalence might also be attributed to a change in scoring criteria according to the AASM recommendations. An AHI of ≥5/h is required for a diagnosis of OSA, with disease severity rated as mild if the AHI is 5–15/h, moderate if the AHI is 15–30/h and severe if the AHI is >30/h[6]. POSA is found in approximately 56% of the OSA patients. Most other patients (30%) also have increased apneic events in supine position, although not twice as much [12]. Mador et al. showed that that the effect of sleep position in patients with OSA is inversely related to the severity of the disease; in other words, the lower a patient's AHI, the more often they were found to be position-dependent (***figure 1***). Result of the study demonstrated that 49.5% of POSA was found in mild OSA (AHI of 5–15/h), 19.4% in moderate OSA (AHI of 15–30/h) and only 6% in severe OSA (AHI >30/h) [21].

Risk factors

OSA is an independent risk factor for hypertension and the development of cardiovascular diseases such as systemic hypertension, coronary artery disease and stroke [22-24]. It also has important consequences for public health with a significant risk of driving accidents and adverse effect on work accidents as a consequence of excessive sleepiness [25-28]. Obesity has been shown to be a significant risk factor for OSA [29,30]. It is estimated that the prevalence of OSA in the obese population is about 40% [30]. A study by Ravesloot et al. reported that approximately 70% of patients undergoing bariatric surgery are diagnosed with OSA [31]. Other risk factors for development of OSA in adult patients include male sex, age, menopause, alcohol, and smoking [32,19,33-42].

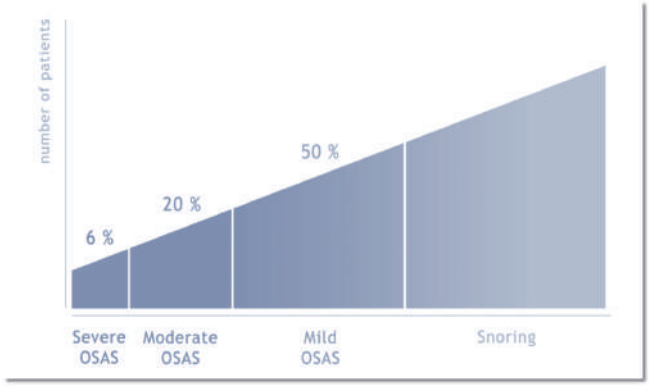

Figure 1. inverse relationship between an increasing AHI and the predominance of position-dependence

POSA seems to correlate with a slightly reduced body mass index (BMI) and age, better sleep efficiency, increased slow-wave sleep, less wake after sleep onset and micro-arousals, and reduced AHI and oxygen desaturations, as well as longer sleep latencies on the multiple sleep latency test (MSLT) [10]. Itasaka et al. studied 257 subjects with OSA and found 90.9% of people with a BMI <24 kg/m2, 74.7% of people with a BMI between 24 and 26.4 kg/m2 and 57.4 % of people with a BMI >24.6 kg/m2 to have POSA [43].

CLINICAL ASSESSMENT

Consultation at the outpatient clinic starts with a thorough history taking including a comprehensive sleep history evaluating daytime and nightly symptoms and sleep hygiene (for example assessing daytime naps, caffeine usage before bedtime, sleep environment and bedtime routines), patient's sleep behavior by spouse or bedpartner (if applicable), medical history (especially cardiac diseases, diabetes mellitus type 2 and psychological disorders), medication use, consumption of alcohol and tobacco and previous therapies for OSA. A number of screening tests have been developed to identify high-risk patients [44,45]. However, many of these screening tests are complicated and lengthy, and their diagnostic accuracy is controversial. A recent study analyzed the following screening tools; Berlin questionnaire (BQ), STOP-BANG questionnaire (SBQ), STOP questionnaire (STOP), and Epworth sleepiness scale (ESS) and assessed diagnostic accuracy by investigating the sensitivity and specificity of the tools [46]. SBQ appeared the most accurate tool for detecting mild, moderate and severe OSA compared with the BQ, STOP and ESS.

Physical examination includes examination of the nose, oral cavity and parameters such as neck circumference and BMI. During oral examination one should look at the dental status and mandibular position, tonsil size, webbing of the soft palate, length of the uvula and tongue size and other factors such as Friedmann palate position and Mallampati score. This latter evaluates the anatomical features of the airway when patients open their mouth and protrude their tongue [47]. This score is frequently used to pre-operatively assess the risk of difficult tracheal intubation, but has also been reported to help in predicting the risk of OSA. Although thorough history taking and carrying out physical examination are important, the predictive value of all these clinical parameters is poor and PSG remains the gold standard diagnostic tool to confirm OSA [48,49,7].

Laboratory testing and home monitoring

Polysomnography is defined as the recording, analysis and interpretation of multiple physiological parameters during sleep and is used to investigate the relationship among impact on sleep and changes in physiology [50,51]. The term 'polysomnography' was firstly introduced by Holland et al. in 1974 [52]. There is a subdivision in types of sleep monitoring systems (***table 3***).

During a full-night PSG different signals are recorded; electroencephalogram (EEG) (FP2-C4/C4-O2), electro-oculogram (EOG), electrocardiogram (ECG) and submental and anterior tibial electromyogram (EMG) readings. A pressure sensor via a nasal cannula is used to measure airflow and finger pulse oximetry to measure arterial oxygen saturation. Straps containing piezoelectric transducers record thoracoabdominal motion. A position sensor (in this thesis we used the Sleepsense, St Charles, IL, USA) attached to the midline of the abdominal wall is used to differentiate between supine, prone, right lateral, left lateral, and upright positions. The system allows continuous monitoring and analysis of snoring throughout the night. Snoring sounds with a minimum duration of 300–3,000 ms were automatically detected based on both the signal of the nasal cannula and a piezoelement sensor taped to the skin over the cricoid. Ambulatory polygraphy (PG), type 3 registration is a simplified recording without measurement of EEG, EOG, ECG and EMG.

Table 3 - Types of sleep monitoring systems

Type	Monitoring system	Parameters measured
1	Standard technician-attended polysomnography in the laboratory setting	Minimum of seven channels, including EEG, EOG, chin EMG, ECG or heart rate, airflow, respiratory effort, and oxygen saturation
2	Comprehensive portable	Minimum of seven channels, including EEG, EOG, chin EMG, ECG or heart rate, airflow, respiratory effort, and oxygen saturation
3	Modified portable	Minimum of four channels, including airflow, respiratory effort, heart rate, and oxygen saturation
4	Continuous single or dual channel	One or two channels, including oxygen saturation and/or airflow

EEG electroencephalography, EOG electro-oculography, EMG electromyography, ECG electrocardiography

Drug-induced sleep endoscopy

Drug-induced sleep endoscopy (DISE) is a rapidly growing method to evaluate airway collapse in patients seeking non-CPAP therapies for sleep disordered breathing (SDB). Clinical and scientific interest in DISE is growing - e.g. in the past two years, the number of scientific publications on DISE is equal to the number of publications from all years prior [53]. Selection criteria for DISE according to the European positional paper on

DISE presented in 2014 are: mild to moderate OSA (i.e. AHI between 5 and 30/h of sleep), or severe OSA and CPAP failure, BMI <32 kg/m2, possible upper airway surgery or oral device candidates, and ASA I or II. Patients with ASA III and severe cardiovascular comorbidity are a relative contraindication for the outpatient endoscopy setting, as these patients still have their DISE performed in the operation room [53]. Selecting patients with a lower BMI is important as it has been shown that surgery and oral devices have lower success rates in patients with a BMI > 32 kg/m2 [54-56]. One of the classification systems applied in the literature as well as in this thesis is the VOTE classification system to classify the upper airway collapse pattern during DISE [57,58]. VOTE stands for the velum (V), oropharynx, including the tonsils (O), tongue (T) and epiglottis (E). During DISE the level(s), degree (partial or complete) and configuration of airway collapse (anteroposterior, concentric of lateral) is assessed. In case an oral device is considered as treatment option, a jaw thrust is performed. Similarly, in positional patients it is of added value to perform DISE in lateral position if positional therapy (PT) is considered [59-62].

TREATMENT

Adequate treatment of OSA is of key importance given the complaints, consequences and health risks. Possible therapeutic interventions include positional therapy (PT), oral appliance therapy (OAT), Continuous Positive Airway Pressure (CPAP) and upper airway surgery (including upper airway stimulation). Every treatment modality has its own indications, and possible complications.

Behavioral modifications

If applicable treatment starts with lifestyle alterations such as weight reduction, cessation of smoking, and avoidance of sedatives and alcohol near bedtime.

Positional therapy

An important risk factor is the supine sleeping position. Several studies show that the severity of OSA in positional patients can be reduced by avoiding the worst sleeping position [63,64,10,12,65-67]. This can be achieved through PT, which has been studied since the 1980s. Studies have been performed comparing variants of PT with other treatment modalities, evaluating efficacy and compliance both short and long-term and, lastly, PT has been included in clinical practice guidelines [64,68,11,10,12,65,69-72,14,63,73-76]. PT can be used as standalone treatment in patients with POSA, but can also be useful as part of combination therapy in patients who have residual POSA whilst treated with a different treatment modality [77,78].

Tennis ball technique

As mentioned various PT modalities have been introduced in the literature. The tennis ball technique (TBT), which uses a bulky mass strapped to the patient's back, is the first technique that was introduced. When patients roll onto their back, they feel the pressure of the mass and instinctively roll back to their side again. Several variants of TBT (vests, tennis or squash balls, shark fins and pillows) have been evaluated [11,79,65,68,74,14,80]. Nevertheless, as with all conservative treatment modalities, effectiveness not only depends on its impact on the airway but also on compliance. Unfortunately, studies have shown that these forms of PT have very low compliance rates [65,68,73,74,14]. When using TBT, short-term compliance ranges between 40-70%, with a quarter of patients still able to avoid the supine sleeping position following treatment cessation and 10% still using TBT after 30 months [14,81,65]. The poor compliance rates and subsequent disappointing long-term results are due to discomfort of the therapy and disruption of sleep architecture caused by the devices.

New-generation devices

New-generation devices, small devices attached to either the neck or chest of the patient, give a subtle vibrational stimulus, alerting the patient to adopt a non-supine sleeping position. Several studies evaluated the efficacy of a neck-worn device [82-84]. Van Maanen et al. evaluated a small vibrating apparatus attached to the skin of the neck with hypoallergenic adhesive tape and Levendowski et al. and Scarlata et al. studied a device, which could be applied with an adjustable nonlatex silicone rubber strap. More studies have been performed evaluating the efficacy of chest-worn devices [85,86,78,87-89]. In 2010 the patent for a new product for PT was filed, the sleep position trainer (SPT). This sleep posture alerting apparatus was invented to comply with the comfort and ergonomic issues such as sensory adaptation which means that patients using TBT tend to gradually adapt to the pressure of a passive object. The SPT (SPT-DEV-PX-11.08) of NightBalanceTM is a small lightweight device (72 x 35 x 10 mm; 25 g) worn across the chest using a neoprene strap (***figure 2***).

The sensor contains a lithium polymer battery cell of 3.7V and 180mAh, a 3.2G vibration motor and a protection circuit integrated in the printed circuit board. A three-dimensional digital accelerometer is used to determine body position. The SPT gives a soft vibration when supine position is detected in order to urge a patient to change body position. Treatment is divided into three phases (***figure 3***).

During the first two nights, the SPT analyzes body position without giving active feedback. During the following seven nights, the SPT trains the patient by vibrating in an increasing percentage of episodes while in the supine sleeping position. If the patient does not change position, the SPT will vibrate again after 2 minutes. At day ten, the full therapy phase begins, in which the SPT will vibrate every time the patient

is in supine sleeping position. The SPT has a USB port to recharge the internal battery and to upload data to an online self-monitoring system that can also be accessed by the patient and physician. The first study evaluating the SPT showed that the device was highly successful and well-tolerated by patients with POSA; it reduced respiratory parameters and subjective sleepiness and improved sleep-related quality of life without negatively affecting sleep efficiency [82]. Over time different studies have been performed evaluating the effect of SPT and all these studies show a beneficial effect of the SPT on efficacy and compliance [86,78,87].

Figure 2. The sleep position trainer

Figure 3. Various phases of the sleep position trainer. The analysis phase contains the first two nights in which no active feedback is given to the user. In the build-up phase, the next seven nights, the SPT starts to vibrate in an increasing amount of episodes of supine position. During the training phase, night ten and onwards, the SPT vibrates every time a supine position is detected. If the subject does not react, the vibrations start again after a pause of 2 min

Continuous positive airway pressure

CPAP, first introduced by Sullivan in 1981, is the current first-line approach for moderate to severe OSA [90]. CPAP is non-invasive and functions as a pneumatic splint to maintain upper airway patency [91]. Possible side effects can be related to the interface (skin abrasion from contact with the mask, claustrophobia, mask leak, irritated eyes), pressure (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 factors [92]. CPAP is the most effective treatment and is regarded as the gold standard treatment, but compliance is poor [93]. When compli-

ance is defined as more than 4 hours of use per night used, 46 to 83% of patients are non-compliant to CPAP [94]. In case of CPAP failure, treatment remains indicated. As seen with all conservative measures, there seems to be a bimodal distribution, patients either tolerate the device well or not at all. Furthermore sufficient counseling is of key importance to comply with adherence issues.

Oral appliance therapy

OAT is an established treatment for patients with mild to moderate OSA, both as a primary therapy and secondary treatment after CPAP failure [95]. OAT works by advancing the mandible and its attached soft tissue structures forward to increase upper airway size. Side effects have been reported with the use of OAT such as excessive salivation or dryness of the mouth, gum irritation, discomfort of the temporomandibular joint, teeth pain and bite change [95]. OAT often decreases the AHI, with clinically relevant improvement [96]. When compared to CPAP, OAT has a non-inferior efficacy based on symptomatic response, although CPAP is more effective in reducing the AHI [97,98]. Although CPAP and OAT have different efficacy and compliance profiles, the overall therapeutic effectiveness is similar in patients with mild and moderate OSA. Oral appliance therapy has better usage rates, while CPAP therapy is more efficacious [93].

Upper airway surgery

Various surgical interventions are available for OSA patients either as single of multiple procedures, tailored to the site and patterns of obstruction. Different parameters play a role in the choice of the surgical modality such as physical examination (including BMI) and assessment of OSA severity. DISE is one of the tools which can help in selecting suitable surgical patients. During DISE the anatomy and the collapsibility of the upper airway is visualized and scored using the VOTE system. Nasal interventions may play a role in improving nasal resistance and subjective snoring, but no improvement is seen in objective respiratory parameters. Nasal surgery could however be performed in patients who deal with CPAP compliance issues due to chronic nasal obstruction [99,100]. For palatal obstruction uvulopalatopharyngoplasty (UPPP) is the most commonly performed procedure to create more space retropalatal by resecting soft tissue. Recently more innovative reconstructive procedures have been developed that not only address the level of palatal obstruction, but also the type of palatal or lateral pharyngeal wall collapse [101]. Different surgical procedures are available for the treatment of hypopharyngeal obstruction ranging from genioglossus advancement (GA), radiofrequent ablation of the tongue base (RFTB) and midline glossectomy, hyoid suspension (HS), and transoral robotic surgery (TORS) in more severe cases [102-105]. In patients with snoring or mild OSA who show an isolated partial or complete anteroposterior (AP) collapse at the tongue base level during DISE RFTB can be the treatment of choice. RFTB

can also be part of the treatment in OSA patients showing a multilevel collapse with a partial AP collapse at the tongue base. In patients with moderate to severe OSA and a complete AP collapse at the tongue base HS can be part of the treatment. After the presurgical evaluation patients are offered either unilevel or multilevel surgery specific for or depending on their site(s) of obstruction. Other more invasive forms of surgical therapy in moderate and severe cases include maxillomandibular advancement (MMA) and tracheostomy, however discussion of these modalities is beyond the scope of this thesis [106,107].

Upper airway stimulation

Neurostimulation of the upper airway aims to open the airway during inspiration by stimulation of the hypoglossal nerve with consequent activation of the genioglossus muscle. The STAR trial was the first prospective cohort study which evaluated the safety and efficacy of an implantable neurostimulator to treat OSA [108]. This cohort enrolled 126 CPAP-intolerant OSA patients with a median baseline AHI of 29.3 events per hour of sleep. At 12 months median AHI decreased with 68% to 9.0 events per hour of sleep ($P<0.001$). The effect remained stable over time and at 36 month follow-up 74% percent achieved 'response' as defined by Sher's criteria of surgical success which are defined as an AHI of less than 20 events/h along with at least 50% decrease from the baseline AHI [109,110]. Results of the STAR trial showed that the device was safe and the effect was durable which eventually led to FDA approval. Recently the therapy has also become available in the Netherlands in selected patients.

OUTLINE OF THESIS

This thesis aims to discuss the following research questions:

1) What is the influence of the sleep position in primary snorers and do subjective outcome measures improve when treating those subjects with positional therapy?
2) What is the effect of weight loss on OSA severity and position dependence in bariatric patients?
3) What is the short-term effectiveness, compliance and the effect on quality of life of positional therapy with the sleep position trainer compared to oral appliances in POSA patients?
4) What is the durability effect of positional therapy compared to oral appliances therapy?
5) Is positional therapy useful in patients in whom OSA surgery was partial effective, resulting in a much better AHI in lateral position as compared to supine position?

Chapter 2 describes the prevalence of position dependency in non-apneic snorers, as defined by the American Academy of Sleep Medicine guidelines, and investigates the influence of various factors such as BMI, neck circumference, age, gender, and sleep efficiency on sleeping position. In this study a cohort of consecutive patients was screened for complaints of excessive snoring or symptoms suspicious for sleep disordered breathing. With an overnight polysomnography position-dependent snoring was assessed using the snore index (total snores/h).

In chapter 3 the prevalence of POSA in patients undergoing bariatric surgery is described and the effect of weight loss brought about by bariatric surgery on POSA is evaluated. Furthermore, predictors for POSA such as BMI, neck circumference, AHI, and age in this specific population are evaluated.

Since the majority of non-apneic snorers are position-dependent, these subjects may potentially benefit from positional therapy. Chapter 4 describes the effect of the SPT in position-dependent non-apneic snorers by evaluating questionnaires which assessed severity of snoring on the patient and the impact of snoring on the bed partner.

Short-term results of a randomized controlled trial comparing positional therapy with the SPT sleep position trainer versus OAT in patients with position-dependent obstructive sleep apnea are described in chapter 5.

Long-term comparative studies of new generation positional therapy devices and oral device therapy were lacking so far. Chapter 6 describes the durability of treatment effects on polysomnographic parameters and quality of life questionnaires of the SPT versus OAT in positional OSA in a 12-month follow-up.

Since the effectiveness of combination treatments, e.g. surgery and positional therapy, still needs to be evaluated, chapter 7 describes the results of a prospective

study in which patients, in whom OSA surgery already has been performed led to partial improvement, receive additional positional therapy with the SPT.

Following chapter 7 a summary, conclusions and future perspectives section is included. Also a summary in Dutch is provided.

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2

Evaluation of position dependency in non-apneic snorers

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ABSTRACT

Purpose

The aims of this study are to determine the prevalence of position dependency in non-apneic snorers, as defined by the American Academy of Sleep Medicine (AASM) guidelines, and to investigate the influence of various factors such as BMI, neck circumference, age, gender, and sleep efficiency on sleeping position.

Methods

A cohort of consecutive patients was screened for complaints of excessive snoring or symptoms suspicious for sleep disordered breathing. Overnight polysomnographic data were collected and non-apneic snorers who met all the inclusion criteria were selected for statistical analysis. To assess position-dependent snoring, the snore index (total snores/h) was used. Supine-dependent patients were defined as having a supine snore index higher than their total non-supine snore index.

Results

76 patients were eligible for statistical analysis. Prevalence of position dependency in non-apneic snorers was 65.8% ($p<0.008$). A stepwise regression showed that only BMI had a significant effect ($p<0.003$) on the supine snore index.

Conclusion

This is the first study that uses the AASM guidelines to accurately define non-apneic snorers (AHI < 5) and provides scientific evidence that the majority of non-apneic snorers are supine-dependent. Furthermore, these results show that non-apneic snorers with a higher BMI snore more frequently in supine position. The use of sleep position therapy therefore, has the potential to play a significant role in improving snoring and its associated physical and psychosocial health outcomes in this population.

INTRODUCTION

Snoring is an acoustic phenomenon that affects approximately 20–40% of the general population [1]. It is caused by vibration of tissue structures in the upper airway during sleep [2,3]. Non-apneic snoring has been shown to be associated with clinical conditions such as depression and excessive daytime sleepiness in adults and may also have clinical implications in the development of hypertension, ischemic heart disease and cerebrovascular diseases [1,4]. Snoring is known to be the most frequently reported symptom in Obstructive Sleep Apnea (OSA) and non- apneic snoring is thought to be a precursor to the development of OSA [5]. Fiz et al. described a 3.2 times higher risk of developing OSA in patients with complaints of non- apneic snoring when compared with non-snorers [6].

Non-apneic snoring has also been shown to have negative impacts on the individual's bed partners, family members and their general quality of life [7]. Armstrong et al. [8] found a statistically significant improvement in marital relations after snoring was treated. In children, there is increasing evidence that neurocognitive impairments are much more frequent in children with non-apneic snoring when compared with non-snorers [9].

Many studies have looked at position dependency in patients with OSA and potential therapeutic options for this population [3,5,10–16]. One study reported that the effect of sleep position in patients with OSA is inversely related to the severity of the disease; in other words, the lower a patient's apnea-hypopnea index (AHI), the more often they were found to be position-dependent [15]. Very few studies, however, have addressed these issues in non-apneic snorers. Furthermore, this is the first study that uses the AASM guidelines to accurately define non-apneic snorers (AHI <5).

The aims of our study are to determine the prevalence of position dependency in non-apneic snorers and to investigate the influence of various factors such as BMI, neck circumference, age, gender, and sleep efficiency on sleeping position.

METHODS

Study design

A retrospective chart review was performed on a cohort of consecutive patients with complaints of excessive snoring or symptoms suspicious for sleep disordered breathing. This was carried out from August to December 2011 at the Department of Otolaryngology.

Inclusion criteria

Hypnograms were screened from subjects aged 18 years or older in whom a polysomnography was performed for suspicion of OSA or excessive snoring. Only the hypnograms from subjects who had no previous bariatric surgery and did not receive any OSA therapy (Mandibular repositioning appliance/continuous positive airway pressure/positional therapy) were reviewed. From these we selected the hypnograms of subjects with an apnea-hypopnea index (AHI) <5, total sleep time >3h and sleep in supine position between 10 and 90% of the total sleep time (TST) [17].

Polysomnography

Polysomnography (PSG) was performed during an overnight visit in the hospital. Recordings were performed using a digital PSG (Embla A10, Broomfield, CO, USA). From this system, electroencephalogram (EEG) (FP2-C4/ C4-O2), electro-oculogram (EOG), electrocardiogram (ECG) and submental and anterior tibial electromyogram (EMG) readings were recorded. A pressure sensor via a nasal cannula was used to measure airflow and finger pulse oximetry to measure arterial oxygen saturation. Straps containing piezoelectric transducers recorded thoracoabdominal motion. A position sensor (Sleepsense, St Charles, IL, USA) attached to the midline of the abdominal wall was used to differentiate between supine, prone, right lateral, left lateral, and upright positions. The system allowed continuous monitoring and analysis of snoring throughout the night. Snoring sounds with a minimum duration of 300–3,000 ms were automatically detected based on both the signal of the nasal cannula and a piezoelement sensor taped to the skin over the cricoid. The amplitudes of the snoring signals were known to be very variable. It was not possible to relate this reliably to the loudness of snoring sounds. Therefore, only the incidence of snoring events was used for further evaluation.

Definitions

Historically, several terms such as primary, simple, benign, habitual or non-apneic have been used in the literature to define snoring. The term non-apneic snorers will be used in this article to define snorers without any apneic events. OSA is defined as a lack of airflow for more than 10 s while there is a continuous or progressive effort to breathe [4]. The apnea-hyponea index (AHI) is defined as the total number of complete cessations (apnea) and partial obstructions (hypopnea) of the upper airway airflow divided by the total sleep time (TST, in hours) [4]. The total snoring index is defined as the number of snore events in any body position (prone, supine, left, right, and upright) per hour of sleep. Non-apneic snorers were defined as patients with a snoring index >1/h and an AHI <5/h [4]. The supine snoring index is the number of snore events <per hour of sleep while lying in supine position. Supine-dependent snoring patients are patients whose

supine snoring index is higher than their total non-supine snoring index (these patients may not necessarily have slept the majority of the night in a supine position).

Statistical analysis

Data were analysed using SPSS statistical package 18.0 (SPSS Inc. Chicago, IL) and Excel 2003 (Microsoft). Demographic variables were expressed as percentages and mean ± standard deviation (SD). Comparison of supine snore index and snore index in other sleeping positions were analyzed using the non-parametric Wilcoxon signed-rank test. A linear regression analysis was performed to analyze the relationship between independent variables. A p value of ≤0.05 was interpreted as statistically significant. The sample size used in this study was based on an estimated power of 90%.

RESULTS

Eighty-one patients were initially enrolled in the study. From this sample, five patients were excluded due to technically insufficient PSG recordings (sensor dislocation or artefacts) (***Figure 1***). Patient demographic data are presented in ***Table 1***. Of the patients, 51% were male and 49% were female. Mean age was 43 ± 13 (range 22–91) and mean BMI was 27.2 ± 5.3 kg/ m^2 (range 18.6–43.9). ***Table 2*** shows the PSG results with a mean supine snore index of 485.51 ± 269.9/h and a mean non-supine snore index of 432.1 ± 275.8/h. Supine-dependent patients comprised 65.8% of our sample group with a statistical significance of 0.008 using the Wilcoxon signed rank test. ***Table 3*** shows no statistical demographic differences between patients who are supine-dependent and those who are not. A logistic regression also confirms this. The influence of factors such as BMI, age, gender, neck circumference, and sleep efficiency on the supine snore index was addressed using a stepwise regression analysis. This analysis demonstrated that only BMI had a significant effect on the supine snore index (p<0.003).

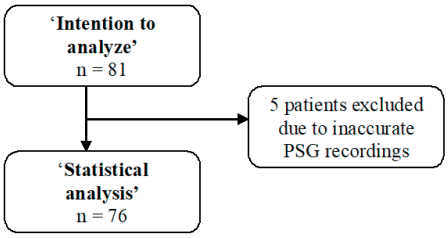

Figure 1. Flowchart of patient selection
PSG - polysomnogram

Table 1 - Patient Demographics

Characteristics	Frequency (%)	Mean ± SD
Gender		
Male	39 (51.3)	
Female	37 (48.7)	
Age		43.0 ± 13.04
BMI		27.18 ± 5.26
Neck circumference (cm)		37.64 ± 3.05
Total	76	

SD standard deviation, *BMI* Body Mass Index

Table 2 - Polysomnographic Results

Characteristics	Mean ± SD	Range
AHI	2.13 ± 1.44	0 – 4.9
Sleep efficiency (%)	87.90 ± 10.01	57 – 99
Total sleep time (min)	440.29 ± 3.79	240 – 602

SD standard deviation, *AHI* apnea-hypopnea index

Table 3 - Comparison of demographics between supine-dependent and non-supine dependent patients

Characteristics	SDS (*n* = 50, 65.8 %) Mean ± SD	NSDS (*n* = 26, 34.2 %) Mean ± SD	Mann-Whitey *p*-value
Male:female	23:27	16:10	0.202
Age	44.26 ± 13.66	40.58 ± 11.64	0.208
BMI	27.26 ± 5.71	27.03 ± 4.36	0.844
Neck circumference (cm)	37.41 ± 3.14	38.08 ± 2.87	0.334
Sleep efficiency (%)	87.43 ± 10.92	88.82 ± 8.27	0.917

SD standard deviation, *SDS* supine-dependent snorers, *NSDS* non-supine dependent snorers

DISCUSSION

The purpose of our study was to evaluate the influence of sleeping position on snoring. Prior studies have addressed the issue of position dependence when looking at patients with OSA. It has been well proven that many patients suffering from OSA have a different rate of apneic events in the lateral position, when compared with the supine position [11]. Position-dependent OSA (POSA) is defined as an AHI which is at least twice as high in supine sleeping position compared to the AHI during sleep in other positions [10,12–14]. Overall, 56% of patients with OSA are diagnosed with POSA [12,14,18]. One study reported that the less severe patients' OSA, the more likely they are to be position-dependent [15]. Mador et al.'s study population consisted of 144

patients. They found that while almost 50% of patients with mild OSA (AHI of 5–15/h) were position-dependent, only 19.4% patients with moderate OSA (AHI of 15–30/h) were position-dependent and even less (6.5%) patients with severe OSA (AHI >30/h) were position-dependent. Our study group has found that in a sample size of 248 patients, 73.3% of the patients were diagnosed with mild POSA, 78.1% with moderate POSA and only 30.0% had severe POSA (unpublished data). Cartwright's definition for POSA was used for the above findings [11]. From these results an inverse relationship was found between an increasing AHI and the predominance of position-dependence. ***Figure 2*** shows the results of these findings in one graph, including a trend line that reflects our hypothesis that position dependency is increased in non- apneic snorers. One possible theory for the development and subsequent worsening of OSA is the transition from having an elevated AHI in the supine position only (mild OSA), to having an elevated AHI in all body positions (severe OSA). This would partly explain why patients with severe OSA are hardly ever position-dependent and also suggests that the prevalence of patients with no OSA who snore may be currently underestimated. Although the criteria for POSA where AHI is used as a parameter, is not comparable with supine-dependent snoring, the results from Mador et al.'s study suggest that the proportion of patients with non-apneic snoring (AHI<5/h), who are position-dependent, may be even higher than 50%.

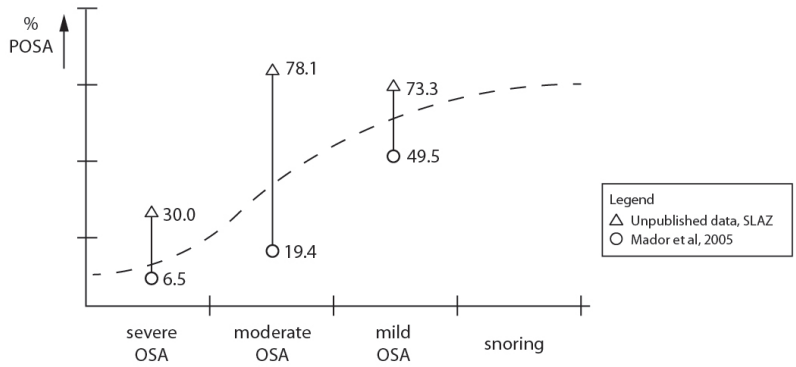

Figure 2. POSA percentages with results from Mador et al. [15] and unpublished data Sint Lucas Andreas Ziekenhuis (SLAZ).

Our aim was to address the issue of position-dependence in patients who have non-apneic snoring, given the prevalence of this condition in the general population, the impact of snoring on an individual's neurocognitive, physical and psychosocial well-being [7,9], and the significant potential for therapeutic intervention. From our study, 65.8% of our non-apneic snorers were supine-dependent. Other studies have tried to look at position dependence and snoring in apneic and non-apneic snorers with dif-

fering results. Braver et al. [3] found that in a combined group of 20 male apneic and non-apneic snorers, snoring was not influenced by changes in sleep position. Nakano et al. [5] reported that while position dependence was seen in patients with non-apneic snoring, variable results were seen in apneic snorers. A more recent study by Koutsourelakis et al. [1], however, found that position dependence was noted in both apneic and non-apneic snorers. The possible reasons for these variable results are a lack of a standardized definition for position-dependent snoring, which will be further discussed in our limitations, and differences in study design and definitions of apnea. In Braver et al.'s study, no attempt was made to separate non-apneic from apneic snorers before assessing position dependence. The latter two studies did attempt to separate apneic snorers from non-apneic snorers but, based on the AASM guidelines [4], the AHI criteria used in these studies to define the non-apneic group, actually included patients with mild OSA [1,5]. Our study objectively measured the influence of position-dependence on non-apneic snorers, adhering to the AASM guidelines for sleep apnea. We also found that the higher patients' BMI, the more likely they were to be position-dependent snorers. This result, however, is within a sample group of non-apneic patients. Other studies looking at the association of BMI with position in apneic patients found that POSA seemed to correlate with a slightly reduced BMI [12,19]. In these studies, however, an increased BMI also correlated with an increased AHI or AI. These findings therefore, corroborate Mador et al.'s [15] findings that patients with less severe OSA, were more likely to be position-dependent.

There were a few limitations to our study. One such limitation is the lack of a quantitative definition for position-dependent snoring. This, however, is seen in the majority of the literature looking at position dependence in non-apneic patients. One study defined position-dependent snoring as a >50% reduction in snoring rate in the lateral position when compared with the supine position [20]. There are, however, no standardized guidelines defining criteria for position-dependent snoring. As such, comparisons made between position-dependent non-apneic and apneic snorers should take this into consideration. Various parameters have been used to measure snoring in the literature. Such methods include snore intensity (decibels), snoring frequency (snores/h), snoring rate (% TST) or duration (seconds or milliseconds) [18]. Our parameter of choice for the measurement of snoring the snore index does not give information regarding the loudness or duration of snoring. While the snore index may not be as comprehensive a research tool when compared with other snoring parameters, it confers the advantage of clinical applicability, as it can be easily obtained from polysomnograms and has also been used in other studies [3]. Also, risk factors such as alcohol consumption, ingestion of tranquilizers/sedatives and smoking, which can influence snoring habits, sleeping quality and body position during sleep, were not included in this study. Lastly, the only position individually analysed for position dependence was the supine position. We have

especially chosen only to analyse this sleeping position, because in the criteria for POSA sleeping mostly in supine position, is also used to define position dependence.

The results of our study potentially have significant implications for the role of positional therapy in non-apneic snorers. Since the 1980s, the effectiveness of positional therapy in patients with POSA has been tested [12–14, 21–23] and compared with other therapeutic approaches [24–27]. Several attempts to decrease the severity of OSA by influencing supine sleeping position have been reported and show that positional therapy can reduce AHI to normal values in patients with POSA [12,14,21–24]. The tennis ball technique (TBT) was the first technique to be implemented, but several other methods have also been used as positional therapy in POSA [28]. While all these techniques may have been successful at reducing the AHI, its limiting factor was a lack of compliance secondary to discomfort and the occurrence of arousals while turning from one lateral position to the other, thereby disturbing the patient's sleep quality and sleep architecture [17]. Long-term (6 months) compliance has been reported to be only 10% [29].

Recently a new product for positional therapy, the sleep position trainer (SPT), has been developed in an attempt to decrease discomfort and improve compliance while maintaining effectiveness. The SPT is a sensor that measures the sleeping position and gives the user feedback with a soft vibration when adopting a supine sleeping posture. The intensity of the vibration increases until the patient reacts to the signal, without awakening and adopts a non-supine position [18]. A recent study showed that positional therapy with the SPT is highly successful and well tolerated in patients with POSA; it reduces subjective daytime sleepiness and improves sleep-related quality of life without negatively affecting sleep efficiency [30]. In this study, 31 patients used the device for 1 month. The median percentage of supine sleeping time decreased significantly from 49.9 to 0.0% and a significant decrease was also seen in the AHI (from 16.4 to 5/h). Sleep efficiency did not change significantly and compliance after 1 month was found to be 92.7%. The sleep position trainer is not only effective at reducing the AHI in patients with POSA but also enables patients to maintain excellent compliance. Such a device has great potential for success in non-apneic snorers.

CONCLUSION

This is the first study that uses the AASM guidelines to accurately define non-apneic snorers (AHI <5/h) and pro- vides scientific evidence that the majority of non-apneic snorers are supine-dependent. Furthermore, our results show that patients within this population who had a higher BMI snored more frequently in the supine position. Given the prevalence of snoring in the general population and its impact on an individual's neurocognitive, physical and psychosocial well-being, there is a tremendous potential

for the use of positional therapy. The sleep position trainer has been able to overcome the major limitations of positional therapy, with its high compliance rates and lack of change in sleep efficiency. Future studies will look at the efficacy of this device in snorers.

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3

The effect of weight loss on OSA severity and position dependence in the bariatric population

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ABSTRACT

Background

The aims of this study were to determine the prevalence of positional obstructive sleep apnea (POSA) in patients undergoing bariatric surgery and to evaluate the effect of weight loss brought about by bariatric surgery on POSA. Furthermore, the authors investigated whether body mass index (BMI), neck circumference, apnea-hypopnea index (AHI), and age are predictors for POSA.

Method

A retrospective cohort study was conducted with data collected from patients who were screened for OSA pre- bariatric surgery and completed a follow-up polysomnography post bariatric surgery from August 2008 to November 2012. Descriptive statistics were used to characterize the prevalence of POSA patients, and the Mann-Whitney and Wilcoxon signed-rank tests were used to examine differences between the POSA and non-POSA groups. A logistic regression model was used to determine predictors for POSA.

Results

Thirty-four percent of patients had POSA, which is significantly lower ($p<0.001$) than in the general population. BMI, neck circumference, and AHI were significantly lower in POSA patients. AHI was the only significant independent predictor for POSA. Of the 91 patients analyzed following bariatric surgery, 35.2% (n=32) no longer had OSA.

Conclusion

The prevalence of POSA in patients undergoing bariatric surgery is significantly lower than the prevalence noted in the general population. A low AHI was shown to be the only significant independent predictor for the presence of POSA.

INTRODUCTION

The prevalence of OSA has been shown in the literature to range from 3–7% in the general population [1], and previous studies have determined that OSA is an independent risk factor for the development of cardiovascular diseases such as systemic hypertension, coronary artery disease, and stroke [1–3].

Obesity has been shown to be a significant risk factor for OSA [4], yet screening for OSA in morbidly obese patients undergoing bariatric surgery is rarely performed. A study by Ravesloot et al. reported that approximately 70% of patients undergoing bariatric surgery are diagnosed with OSA [5].

Studies looking more closely at OSA have reported that a subset of the general population of OSA patients is in fact position-dependent. Cartwright's criteria defined a patient as having positional OSA (POSA) if the apnea-hypopnea index (AHI) in the supine position was at least twice as high as that in a non-supine position [6]. Approximately 53–56% of OSA patients in the general population have POSA [7–9]. Another article looking specifically at the Asian population found the prevalence to be even higher at 67% [10]. Oksenberg et al. found that in the general population, patients who lost weight were more likely to have POSA, while patients who gained weight were more likely to have OSA that was non-positional [11]. Based on these findings, the authors hypothesize that the prevalence of POSA will be lower in obese patients undergoing bariatric surgery when compared with the general population and that a significant increase in POSA would be seen after bariatric surgery once these patients have lost weight.

The primary aim of this study is, therefore, to determine the prevalence of POSA in patients undergoing bariatric surgery. Our second aim is to evaluate the effect of weight loss brought about by bariatric surgery on POSA. Furthermore, we aim to investigate whether BMI, neck circumference, AHI, and age are predictors for POSA.

METHODS

Study

We performed a retrospective study, approved by the institution's ethics committee, with data collected from patients who were screened for OSA pre-bariatric surgery and completed a follow-up polysomnography post bariatric surgery from August 2008 to November 2012.

Patients

Patients were eligible for bariatric surgery if they were able to meet the International Federation for the Surgery of Obesity (IFSO) criteria. These criteria included patients

aged 18–65 years, BMI from 35 kg/m^2 with associated comorbidity, i.e., hypertension, diabetes, OSA, or joint problems [5]. This diagnostic workup consisted of a visit to the Otolaryngology clinic for a medical history intake, physical examination, and investigations, which included measurements of BMI, neck circumference, and a full overnight polysomnography (PSG).

Polysomnography

In accordance with other studies, PSG was performed during an overnight visit in the hospital [5,12]. Recordings were performed using a digital PSG (Embla A10, Broomfield, CO, USA). From this system, electroencephalogram (EEG) (FP2-C4/C4O2), electrooculogram (EOG), electrocardiogram (ECG), and submental and anterior tibial electromyogram (EMG) readings were recorded. Straps containing piezoelectric transducers recorded thoracoabdominal motion. A position sensor (Sleepsense, St Charles, IL, USA) attached to the midline of the abdominal wall was used to differentiate between, supine, right lateral, and left lateral positions. A pressure sensor was used to measure airflow, and finger pulse oximetry was used to measure arterial oxygen saturation. All signals were recorded with digital sampling, digital filtering, digital storage recording technology, permitting a sample efficiency of 90% and a sample rate up to 200Hz. Storage was done on a PCMCIA flash card. The following day, data was downloaded to the computer and analyzed by dedicated sleep software (SomnologicaTM, Broomfield, USA; DOMINO, SOMNOmedics GmbH, Randersacker, Germany). All recordings were manually evaluated and scored by an experienced sleep investigator for apneas and hypopneas.

Definitions

The apnea-hypopnea index (AHI) is defined as the total number of complete cessations (apnea) and partial obstructions (hypopnea) of the upper airway airflow divided by the TST (in hours). According to the American Academy of Sleep Medicine (AASM), OSA can be classified as mild (AHI 5–14/h), moderate (AHI 15–30/h) or severe (AHI >30/h) [13]. We used Cartwright's definition for POSA where the AHI in supine position is at least two times higher than the non-supine AHI [6].

Inclusion and exclusion criteria

Patients were included in the study if the following inclusion criteria were met: PSG was performed in our sleep clinic, a diagnosis of OSA (AHI >5), and supine sleeping position between 10 and 90% of the total sleep time (TST) [8,12]. They were excluded if supine sleeping positions were found to be less than 10% or more than 90% TST and AHI <5.

Statistical analysis

Data were analyzed using SPSS statistical package 18.0 (SPSS Inc. Chicago, Il) and Excel 2003 (Microsoft). Descriptive statistics were used for presentation of demographics. Mann-Whitney and Wilcoxon signed-rank tests were used to examine differences between the groups. To compare the outcomes pre-and post-surgery, the McNemar test was used. A logistic regression model was used to determine predictors for POSA. The accuracy of this model was evaluated using the Hosmer and Lemeshow goodness-of-fit test. A *p* value of ≤0.05 was interpreted as statistically significant. The sample size used in this study was based on an estimated power of 90%.

RESULTS

Prevalence

Of the 370 pre-bariatric surgery patients, 162 patients were analyzed for prevalence of POSA (***Figure 1***). Patient demographics are reported in ***Table 1***. Polysomnographic results are shown in ***Table 2***. Thirty-four percent (*n*=55) had POSA. When comparing positional versus non-positional patients, BMI, neck circumference, and AHI were significantly different among these groups. Positional patients had a significantly lower BMI and neck circumference and the AHI was lower in this group (***Table 3***).

Table 1 - Patient demographics

Characteristics	Patient included for analysis (*n*=162)		All pre-bariatric surgery patients (*n*=370)	
	Mean ± SD	Frequency (%)	Mean ± SD	Frequency (%)
Gender				
Male		43 (26.5)		101 (27.3)
Female		119 (73.5)		269 (72.7)
Age (years)	47.2 ± 9.4		45.8 ± 10.0	
BMI	45.5 ± 7.3		45.0 ± 7.0[a]	
Neck circumference (cm)	43.5 ± 4.8		43.3 ± 4.8[a]	

BMI body mass index, *SD* standard deviation

a No. of missing data variables from excluded patients in BMI group (n=12); neck circumference group (n=72)

Changes following bariatric surgery

Of the 162 patients within this cohort who underwent surgery, 91 patients had their pre- and post surgery PSG results compared (***Figure 1***). There was an average follow-up interval of 7 months (SD±2.0) for PSG recording after surgery. ***Table 4*** summarizes the comparison of both demographic and PSG results before and after surgery of all 91

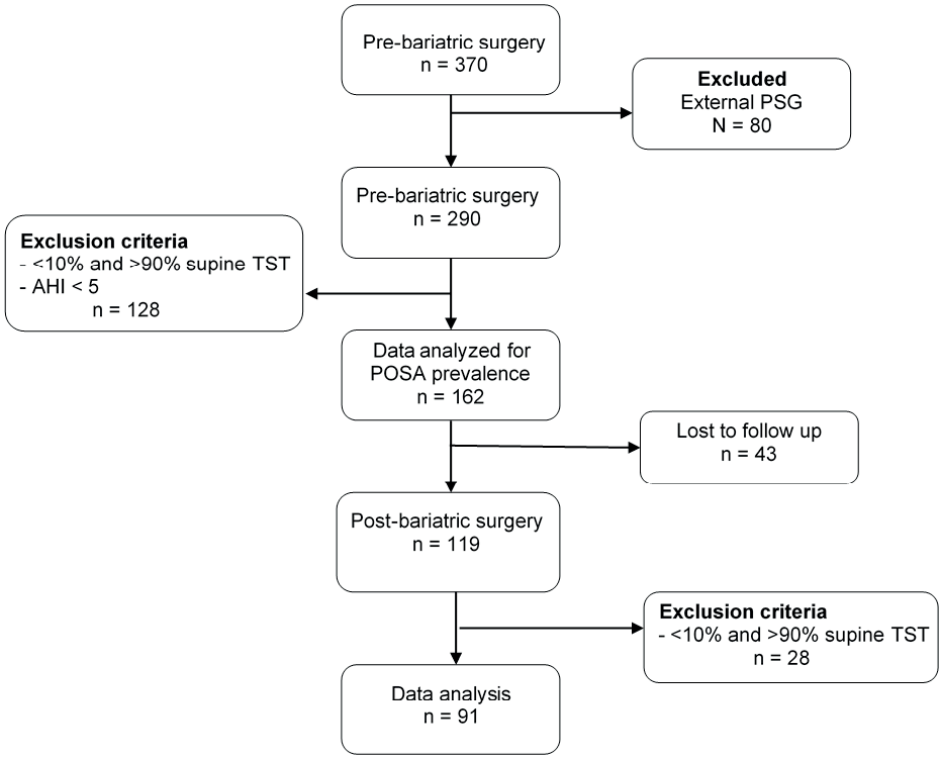

Figure 1. Flowchart of Data Inclusion
PSG – polysomnography
TST – total sleep time
AHI – apnea-hypopnea index
POSA – positional obstructive sleep apnea

patients. A significant decrease in BMI, neck circumference, total AHI, and desaturation index is seen following surgery with an associated increase in sleep efficiency. These parameters were all improved after bariatric surgery. When looking specifically at BMI after surgery, 88 patients had a decrease of at least 1 point in their BMI, 2 patients had no change, and 1 patient had an increase in BMI. Regression analysis showed that only a low AHI (AHI 5.1–11.0) was a significant independent predictor for POSA (p = 0.001). The Hosmer and Lemeshow goodness-of-fit test confirmed the model to be a good fit.

Of the 91 patients included in this cohort, 35.2% (n=32) no longer had OSA after surgery, BMI in this group went from 44.74±5.37 to 35.26±5.68 kg/m^2. The remaining 64.8% (n=59) had either OSA or POSA, BMI in this group went from 45.43±7.29 to 36.37±5.80 kg/m^2. While both groups significantly lost weight after surgery (p<0.001), no significant difference in the magnitude of weight loss were noted between these two groups. ***Table 5*** shows that 44.1% patients who were originally diagnosed with OSA before surgery

developed POSA after surgery. Total prevalence of POSA after bariatric surgery in our patient population was 62.7%. The McNemar test showed a significant development of POSA following surgery (p<0.001).

Table 2 - Polysomnographic results

Characteristics	Median	IQR
Total AHI	21.0	11.6–39.9
Desaturation index	19.5	11.4–44.4
Sleep efficiency (%)	85.7	77.3–92.9
Total sleep time (min)	422.3	380.8–464.0

AHI apnea hypopnea index, *IQR* interquartile range

Table 3 - Comparison of demographics between positional and non-positional OSA patients before bariatric surgery

Characteristics	**Positional OSA** n = 55 (34.0%)		**Non-positional OSA** n = 107 (66.0%)		**Mann-Whitey *p*-value**
	Median	**IQR**	**Median**	**IQR**	
Age (years)	45.00	39.0 – 52.0	48.00	41.0 – 55.0	0.265
BMI	40.80	39.0 – 46.2	45.50	41.1 – 51.4	0.001
Neck circumference (cm)	41.50	39.0 – 44.0	44.00	41.0 – 48.0	0.006
Total AHI	14.90	9.0 – 22.1	25.10	12.8 – 54.4	<0.001

BMI body mass index, *AHI* apnea hypopnea index, *SD* standard deviation, *OSA* obstructive sleep apnea, *IQR* interquartile range

Table 4 - Comparison of pre- and post bariatric surgery results

		Pre BS		**Post BS**		**Wilcoxon Signed Ranks p-value**
Characteristics	**Frequency (%)**	**Median**	**IQR**	**Median**	**IQR**	
Gender						
Male	18 (19.8)					
Female	73 (80.2)					
BMI		44.80	40.0 – 49.6	35.70	31.6 – 40.2	<0.001
Neck circumference (cm)		42.50	40.0 – 46.0	38.75	36.1 – 42.0	<0.001
Total AHI		21.20	11.5 – 34.9	6.30	3.2 – 12.3	<0.001
Desaturation Index		18.60	10.6 – 36.1	6.30	3.3 – 12.2	<0.001
Sleep efficiency (%)		86.30	78.9 – 92.9	93.10	84.8 – 96.5	0.001
Total Sleep Time (min)		412.00	370.5 – 464.0	428.00	385.0 – 476.0	0.052
Total	91					

AHI apnea hypopnea index, *BMI* body mass index, *BS* bariatric surgery, *IQR* interquartile range

Table 5 - Development of POSA following bariatric surgery

		POSA post BS (%)		McNemar test Exact sig. (2-tailed)
		yes	no	
POSA pre BS (%)	**Yes**	11 (18.6)	3 (5.1)	
	No	26 (44.1)	19 (32.2)	<0.001

BS bariatric surgery

DISCUSSION

The prevalence of POSA found in our obese population undergoing bariatric surgery was 34%. This is significantly lower (p<0.001) than the prevalence reported in the general population (53–60%) [8]. These results are comparable to other studies which found that patients with a higher BMI were less likely to be positional [1,6,14,15].

In our study, significant differences were seen in neck circumference, BMI, and AHI when comparing our POSA patients with those who were non-positional. Patients with POSA had smaller neck circumferences, lower BMI, and milder OSA (lower AHI). There were no differences, however, noted in age between both groups. Although varying results are seen when looking at the role of age, BMI, and neck circumference in POSA patients, it has been consistently noted that patients with POSA have a lower AHI than non- positional patients [7–10]. A logistic regression analysis was performed looking at AHI, age, BMI, and neck circumference as potential predictors for POSA. Only AHI was found to be a significant negative predictor for POSA. The lower the AHI, the more likely a patient would have POSA.

A significant number of obese patients undergoing bariatric surgery, who were originally diagnosed with non-positional OSA, had a significant decrease in AHI and became positional once surgery was performed and weight was lost. A retrospective study performed by Oksenberg et al. looked at the relationship between weight change and body posture dominance during sleep in a general population of patients with untreated OSA. Patient data comprised two PSG evaluations that were carried out over a 6.2-year interval. The authors reported that patients who were originally diagnosed with POSA, who then became non-positional over time, had a significant increase in weight and total AHI. Conversely, patients who were originally diagnosed with non-positional OSA that subsequently became positional over time had a decrease in weight and total AHI, but these changes were to a lesser degree when compared with changes seen in patients who had become non-positional. Patients who either remained positional or non-positional over time had minimal changes in weight and AHI [11].

Findings from our study and others support the statement that patients with POSA are more likely to have a lower BMI, neck circumference, and AHI than their non-positional counterparts. The mechanism underlying this, however, is still unclear. Saigusa et al.

reported that positional patients had more backward positioning of the lower jaw with smaller lower facial height and craniofacial volume. They were also noted to have a smaller volume of lateral pharyngeal wall soft tissue [16]. Teerapraipruk et al. also concur that craniofacial structural changes may play an important role in POSA given that in their population of Asian patients, the average BMI noted in both positional and non-positional patients was lower than the average BMI noted in the Western population [10]. It is possible that a subgroup of patients initially develops OSA that is positional, but when left untreated or undiagnosed, increases in weight as a consequence of their disease and further develops an OSA that is more severe and non-positional in nature. Spiegel et al. found that sleep restriction was associated with increased levels of ghrelin, a hunger-stimulating hormone, and decreased levels of the hunger suppressing hormone leptin. As a result, increases in hunger and appetite were noted in this sleep-deprived population [17]. It can be postulated that patients with OSA who suffer from fragmented sleep may experience the metabolic changes described above with an increase in weight and subsequently become obese. Patients may also have decreased energy secondary to sleep deprivation, rendering physical activity more difficult and less desirable, which compounds the issue of weight gain and obesity.

Our findings that a significant improvement is seen in OSA severity in obese patients after bariatric surgery generate a provocative theory that severe non-positional OSA can in fact be reversed to a mild positional OSA or even positional non-apneic snoring with weight loss. Patients may initially have had non-apneic snoring which subsequently progressed to a mild OSA that was positional in nature. When left untreated, metabolic imbalances may have occurred that led to increased weight, obesity, and resulted in a transition from mild to moderate sleep apnea noted only in the supine position (POSA) to a more severe sleep apnea noted in all sleeping positions.

Considerations

Studies looking at the prevalence of and predictors for POSA provide data for early intervention of this disease. Although CPAP is known to be the gold standard for management of patients with OSA, side effects of its use such as mouth leaks, nasal congestion, and dryness and mask irritation on the face result in lower compliance rates [18–20]. Positional therapy has been shown to be effective in reducing AHI [21–23]. A recent meta-analysis conducted by Ha et al. showed that when looking at other outcomes such as arousal index, total sleep time, and sleep efficiency, positional therapy was comparable in effectiveness when compared with CPAP. They also showed that patients with mild OSA may benefit more from positional therapy than patients with severe OSA [24]. This is in keeping with our results that a low AHI was found to be a significant predictor for POSA. Compliance rates for positional therapy have also improved significantly with the development of newer positional therapy devices [12]. Early intervention with

positional therapy not only has significant clinical implications for preventing long-term negative cardiovascular outcomes in these patients, but may also be cost-effective when comparing positional therapy to treatment options such as continuous positive airway pressure (CPAP), oral devices, and surgery for patients with positional OSA.

A major limitation of this study is its retrospective design. In order to further define the relationship between changes in body weight and its effect on positional obstructive sleep apnea, a large, prospective, longitudinal study is needed along with more long-term compliance data and well powered randomized controlled trials to truly assess the efficacy of positional therapy. The authors do acknowledge that this study may have some selection bias due to patients who may have been referred and have not shown up for their appointment, any missing data from the archives, patients who may have been tested elsewhere, or those who may have been on a waiting list for bariatric surgery and were not accounted for in this study. It should also be noted that positional sleep dependency may be multifactorial. Factors such as alcohol consumption and sedative use were not taken into account in this study.

Conclusion

The prevalence of POSA in the obese population of patients undergoing bariatric surgery is significantly lower than the prevalence noted in the general population. Although lower BMI, smaller neck circumference, and lower AHI were all found to be significant in the POSA population, a low AHI was the only significant predictor for the presence of POSA. The outcomes of this study can play a very important role in guiding future prospective studies looking at appropriate patient selection criteria for positional therapy.

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4

Subjective effects of the sleep position trainer on snoring outcomes in position-dependent non-apneic snorers

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ABSTRACT

Purpose

To evaluate the effect of a new-generation positional device, the sleep position trainer (SPT), in non-apneic position-dependent snorers.

Methods

Non-apneic position-dependent snorers with an apnea–hypopnea index (AHI) < 5 events/h were included between February 2015 and September 2016. After inclusion, study subjects used the SPT at home for 6 weeks. The Snore Outcome Survey (SOS) was filled out by the subjects at baseline and after 6 weeks, and at the same time, the Spouse/Bed Partner Survey (SBPS) was filled out by their bed partners.

Results

A total of 36 participants were included and 30 completed the study. SOS score improved significantly after 6 weeks from 35.0±13.5 to 55.3±18.6, $p<0.001$. SBPS score also improved significantly after 6 weeks from 24.7±16.0 versus 54.5±25.2, $p<0.001$. The severity of snoring assessed with a numeric visual analogue scale (VAS) by the bed partner decreased significantly from a median of 8.0 with an interquartile range (IQR) of [7.0–8.5] to 7.0 [3.8–8.0] after 6 weeks ($p=0.004$).

Conclusions

Results of this study indicate that positional therapy with the SPT improved several snoring-related outcome measures in non-apneic position-dependent snorers. The results of this non-controlled study demonstrate that this SPT could be considered as an alternative therapeutic option to improve sleep-related health status of snorers and their bed partners.

INTRODUCTION

Snoring is the result of airflow passing through the upper airway, which in turn causes vibrations in the soft tissues. It is indicative of increased resistance in the upper airway and is often associated with obstructive sleep apnea (OSA) [1–4]. The prevalence of snoring in the general population is between 20 and 60%, depending on the definition, measurements, and population variables. Significant gender differences are observed with a higher prevalence in men than in women [1,5–9]. Non-apneic snoring or primary snoring is defined as snoring with less than five apneic and/or hypopneic events per hour of sleep. Primary (self-reported) snoring could, just like OSA, be associated with excessive daytime sleepiness and negative sleep pattern behaviors [6,10,11]. Some research suggests that self-reported non-apneic snoring also has important clinical implications such as increased risk for cardiovascular disease [12,13]. Besides these comorbidities affecting the primary snorer, snoring can also have negative impact on the sleep quality of the bed partner [14–17]. Habitual loud snoring may result in couples choosing to sleep apart or resort to using earplugs to counteract the sound [14]. These aspects can have a negative impact on the psychosocial aspects and the intimacy in a couple's relationship, and even may trigger marital disharmony or result in divorce [1].

Sleeping position can influence the severity of snoring; however, few studies have looked at position dependency in non-apneic snorers. Nakano et al. found that snoring time and snoring intensity were lower in the lateral position than in the supine position in non-apneic snorers [18]. Choi et al. described that in non-apneic snorers, snoring decreased when a subject adopted a non-supine position [19]. A retrospective study performed by Benoist et al. looked at position dependency in non-apneic snorers seeking clinical care and found that 65.8% of this group is position-dependent [20]. These results are in line with studies performed in OSA patients, which show position dependency to be inversely related to disease severity [21,22]. Approximately 56% of patients with mild OSA is position-dependent, defined as having at least twice as many events in supine position compared to the other sleeping positions, while in severe OSA position dependency only occurs in 6% [21,23–25]. Hence, the proportion of position dependency may be highest in non-apneic snorers, followed by mild and moderate OSA, and lowest in severe OSA. Positional therapy (PT) is one of the treatment options for positional OSA (POSA) patients. Van Maanen et al. showed that PT with a new positional device, the Sleep Position Trainer (SPT), effectively reduces disease severity in mild to moderate POSA [26,27]. PT has also been compared to oral appliances, and short- and long-term results show similar efficacy in mild to moderate POSA patients [28,29]. Since the majority of non-apneic snorers are position-dependent, these subjects may potentially benefit from PT. The aim of this study was, therefore, to evaluate the effect of the SPT in position-dependent non-apneic snorers.

METHODS

Study Design

This study was conducted in the OLVG West hospital (Amsterdam, the Netherlands) after approval from the local ethical committee. Non-apneic snorers were recruited for this study. According to the ICSD-3 criteria, patients had no complaints of insomnia, excessive daytime sleepiness, or sleep disruption attributable to snoring; moreover, a diagnostic polysomnography (PSG) to rule out OSA was performed. After informed consent, subjects received the SPT, which they had to use during sleep for a period of 6 weeks. Study subjects and bed partners filled out questionnaires at baseline and after 6 weeks of using the SPT.

Polysomnography

PSG was performed in the Sleep Laboratory of OLVG West using a digital PSG (Embla A10, Broomfield, CO, USA). During an overnight stay, various parameters were measured. To define the apnea–hypopnea index (AHI), airflow was measured using a sensor in the nasal cannula. Snoring was assessed using a nasal cannula and a piezoelement sensor attached to the cricoid. These sensors detected snoring sounds lasting longer than 300–3000ms. This resulted in an index of snoring events per hour, which could be differentiated between the various sleeping positions. Sleeping position was registered using a position sensor (Sleepsense, St Charles, IL, USA). This sensor was placed at the midline of the abdomen to discriminate between the different positions: supine, lateral right, lateral left, prone, and upright position. The recorded data were analyzed using special software (Somnologica™ studio) and manually edited. To exclude OSA patients, an apnea was defined as the cessation of nasal airflow of more than 90% for a period of 10s or longer in the presence of respiratory efforts. In accordance with the prevailing definition from the American Academy of Sleep Medicine (AASM) at that time, a hypopnea was scored whenever there was a greater than 30% reduced oronasal airflow for at least 10s, accompanied by ≥ 4% oxygen desaturation from pre-event baseline. Non-apneic snorers were defined as subjects with a snoring index >1/h and an AHI < 5/h sleep.

Inclusion criteria

Subjects were included after undergoing a full-night PSG under suspicion of OSA in the period between February 2015 and September 2016 at the OLVG West Hospital, Amsterdam, the Netherlands. The inclusion criteria were as follows: adult subjects with a bed partner; AHI <5 events per hour of sleep; supine sleeping position between 10 and 90% of total sleep time (TST); and the snoring was position-dependent according to PSG records. This latter was calculated using the snoring index, which is defined as the frequency of snoring: the number of snore events per hour of sleep. Supine-dependent snoring was defined as a supine snoring index higher than the total non-supine snoring index. The main exclusion criterion was previous therapy with the SPT.

Primary outcomes

To measure the severity of snoring and the impact to patients' quality of life, a validated subjective questionnaire was used: the Snore Outcome Survey (SOS) and the Spouse/Bed Partner Survey (SBPS) (***Figure 1***) [30]. The SOS comprises eight questions on a 5-point Likert scale that evaluated the duration, frequency, severity, and consequences of problems associated with sleep-disordered breathing (SDB), and snoring in particular [Cronbach's α=0.672 (pre), 0.748 (post)]. To evaluate the impact of snoring on the bed partner, the SBPS was used. This questionnaire consists of three items on a 5-point Likert scale and assesses the effect of the snoring on the bed partner [Cronbach's α=0.868 (pre), 0.731 (post)]. The SOS and SBPS scores range from 0 (worst) to 100 (best) [30].

Snore Outcomes Survey (SOS)
1. In the past 4 weeks, when you have been asleep, to the best of your knowledge do you snore? All of the time / Most of the time / Some of the time / A little of the time / None of the time / Don't know 2. In the past 4 weeks, how would you describe your snoring or how has it been described to you? None / Mild / Moderate / Severe / Very severe / Don't know 3. My snoring wakes me from sleep and/or makes me tired the next day. Definitely true / Somewhat true / Don't know / False / Definitely false 4. During the past 4 weeks, how much did your snoring interfere with your normal sleep and your level of energy? Not at all / A little bit / Moderately / Quite a bit / Extremely 5. Does your snoring annoy or bother your spouse/bed partner? Extremely (sleeps in the other room) / Quite a bit / Moderately / A little bit / Not at all / Don't know 6. Compared to one year ago, how would you rate your snoring now? Much less than a year ago / Somewhat less than a year ago / About the same as a year ago / Somewhat more than a year ago / Much more than a year ago 7. How would your spouse/bed partner describe your snoring? Extremely loud / Very loud / Somewhat loud / Soft or quiet / No snoring at all / Don't know 8. Please describe when you snore. I don't snore / Snore very rarely / I snore only in certain positions / I snore most of the time / I snore all of the time
Spouse/Bed Partner Survey (SBPS)
1. How would you describe your spouse/bed partner's snoring? Extremely loud / Very loud / Somewhat loud / Soft or quiet / No snoring at all / Don't know 2. In the past 4 weeks, how would you describe your spouse/bed partner's snoring? None / Mild / Moderate / Severe / Very severe / Don't know 3. In the past 4 weeks, how much has your spouse/bed partner's snoring bothered you? Extremely (sleeps in the other room) / Quite a bit / Moderately / A little bit / Not at all / Don't know

Figure 1. Snore Outcome Survey and Spouse/Bed Partner Survey

Secondary outcomes

Secondary outcomes were the severity of snoring and satisfaction using the SPT. To evaluate the severity of snoring, a numeric visual analogue scale (VAS) containing a score between 1 (no snoring) and 10 (severe snoring) was filled out by the bed partners, at baseline and after 6 week of using the SPT. The study subjects were asked a dichotomous question (containing yes or no) about satisfaction using the SPT for a period of 6 weeks. Furthermore, according to the study by Lee et al. response profiles were determined; VAS ≤ 3 post-treatment was defined as 'major response' and post-treatment VAS ≤ 5 plus SOS ≥ 60 defined as 'fine response' [31].

Intervention: the sleep position trainer

The SPT is a lightweight and small device (72 × 35 × 10 mm, 25 g), which is worn around the chest with a neoprene strap (***Figure 2***). A three-dimensional digital accelerometer is used to determine body position. When lying in supine position, a subtle vibration is provided to give feedback to the user. The self-adaptive device gradually increases the intensity of the vibration until the user turns to a non-supine position. The vibration is adapted to the user in duration, strength, and pattern to maintain a timely response by the subject. Various phases are integrated for subjects to familiarize with the device: an analysis phase, a build-up phase, and a training phase (***Figure 3***).

Figure 2. Sleep position trainer

Statistical Analysis

For the analyses, different descriptive statistics and inferential statistics were used. The SOS questionnaire test survey items use a Likert scaling model scoring system between 0 and 4. The sum score of the eight items, per individual score of the subject, could vary between 0 and 32. Total sum score was rescaled to an overall score between 0 and 100. If one question was left blank, scores were rescaled from 0 to 28 to overall scores between 0 and 100. However, when more than one item was left blank, SOS scores were treated as missing. The SBPS containing a Likert-scale model between 0 and 3 items

Figure 3. Various phases of the sleep position trainer. The analysis phase contains the first two nights in which no active feedback was given to the user. In the build-up phase, the next seven nights, the SPT started to vibrate in an increasing amount of episodes of supine position. During the training phase, night ten and onwards, the SPT vibrated every time a supine position was detected. If the subject did not react, the vibrations start again after a pause of 2 min

that was rescaled to an overall score between 0 and 100 [30]. Categorical variables were expressed as n (%). Continuous normally distributed variables were presented by their mean and standard deviation and non-normally distributed data by their median and interquartile range for skewed distributions. Normally distributed continuous unpaired data were tested with the independent samples Student's *t* test and in case of skewed data, with the independent samples Mann–Whitney *U* test. Normally distributed continuous paired data were tested with the dependent samples Student's *t* test and in case of skewed data, with the Wilcoxon signed-rank test. Per-protocol analyses were completed for all outcome parameters. Significance level was set at *p* value of 0.05. Statistical analysis was performed using IBM SPSS statistical package 24.0.

RESULTS

A total of 36 subjects were included in the study. Six subjects (five males and one female) did not complete the follow-up and were excluded. Baseline characteristics of the 30 subjects who completed the study are shown in ***Table 1***.

SOS and SBPS scores

All individual scores are presented in ***Table 2***. Complete sets of the SOS scores were collected in *n*=19 study subjects. Another six subjects had missing data on one SOS item, for which we corrected. SOS data from a total of 25 subjects were available for analysis. SOS score in these subjects improved significantly from 35.0 ± 13.5 to 55.3 ± 18.6 ($p<0.001$) after 6 weeks of SPT therapy. Total SBPS score (*n*=24/30) also improved significantly from 24.7 ± 16.0 to 54.5 ± 25.2, $p<0.001$.

VAS score and satisfaction

Severity of snoring assessed by the bed partner (*n*=29) decreased significantly from a median VAS score of 8.0 [7.0–8.5] to 7.0 [3.8–8.0] after 6 weeks ($p=0.004$). Furthermore, 81.5% (*n*=22/27) of the subjects reported that they were satisfied with the use of the SPT.

Table 1 - Patient characteristics at baseline inclusion

Characteristics	Baseline N=30 Median [IQR]
Age, years	41.5 [34.0-51.3]
Gender, male no. (%)	15 (50)
BMI, kg/m^2	25.0 [22.5-28.3]
AHI (events/h)	2.5 [1.2-3.4]
% supine sleep of TST	40.3 [24.7-50.4]
Supine snore index	414.8 [252.8-699.5]
Non-supine snore index	205.9 [115.7-503.9]

IQR interquartile range, *BMI* body mass index, *AHI* apnea-hypopnea index, *TST* total sleep time

Response rates

Twenty-four percent of the study subjects (*n*=7/29) reported a VAS ≤ 3 after 6 weeks ('major response'). A VAS ≤ 5 was seen in 34.5% (*n*=10/29) and 36.0% (*n*=9/25) had a SOS score ≥ 60. A combination of VAS ≤ 5 and SOS score ≥ 60 was reported in four subjects 16.7% ('fine response').

DISCUSSION

This is the first prospective study investigating the effect of the SPT on position-dependent non-apneic snorers. After 6 weeks of therapy, we found a socially relevant improvement in the sleep-related health status of snorers and their bed partners, combined with high satisfaction rates assessed by the bed partners. VAS scores evaluating the severity of snoring on 10-point numeric scale did show a reduction as reported by the bed partners. However, since it reduced only by 1 point (8.0–7.0), we did not find a clinically relevant response. Although not all response rates were high, we found considerable improvements in the primary outcomes. Non-apneic snoring is a prevalent problem with clinical and social implications. Since the literature suggests that 68% of snorers are position-dependent, new-generation PT could be very promising. There are several studies that have looked at the effect of PT in apneic snorers using old-generation positional devices: tennis ball techniques and pillows. Chen et al. studied whether a head-positioning pillow could reduce snoring sounds in patients with mild and moderate positional OSA. They found a significant reduction in VAS scale from 5.0 to 4.0 and snoring index from 218.0 events/h to 115.0 events/h [32]. These results are in line with the findings of our study where the VAS score also decreased with one point after therapy (from 8.0 to 7.0). Choi et al. studied the effect of PT using an inflatable vest-type device, in position-dependent snorers, with or without mild OSA [19].

Table 2 - Individual results during baseline and at follow-up

Patient No.	Demographic characteristics			Polysomnographic parameters				Snoring questionnaires					
	Baseline			Baseline				Baseline			At 6 weeks		
	Gender	Age	BMI	AHI	% supine sleep	Supine SI	Non-supine SI	SOS	SBPS	VAS	SOS	SBPS	VAS
1	m	33	25,7	0,1	49,0	389,1	139,3	37,5	/	8	59,4	41,7	7
2	m	37	20,5	2,4	11,3	178,8	136,3	37,5	,00	8	50,0	41,7	9
3	f	51	28,1	1,6	13,0	804,9	561,9	9,4	8,3	10	68,8	75,0	8
4	m	27	28,3	0,8	25,0	923	488,3	34,4	16,7	8	43,8	16,7	8
5	f	46	31,2	2,5	69,0	260,4	112,8	40,6	33,3	7	53,1	66,7	7
6	m	44	28,7	4,4	43,0	732,4	660	18,8	8,3	9	15,6	8,3	9
7	f	37	28,1	1,9	30,0	689,2	628,7	/	33,3	9	46,4	/	2
8	f	50	22,6	3,4	28,2	440,5	179,7	43,8	,00	10	56,3	16,7	9
9	f	53	33,3	4,2	75,3	137,5	6,2	18,8	16,7	8	75,0	75,0	3
10	f	35	19,9	0,9	13,6	550,2	459	28,6	8,3	7	59,4	58,3	2
11	m	66	33,1	4,6	23,6	822,7	575,3	43,8	41,7	8	67,9	75,0	6
12	f	40	24,7	1,9	19,0	683,5	579,6	25,0	33,3	7	50,0	66,7	8
13	f	62	37,8	1,8	37,7	255,5	36	21,9	50,0	4	28,1	/	8
14	f	49	20,3	1,4	44,7	833,3	628,6	37,5	25,0	8	43,8	25,0	8
15	f	48	25,4	0,2	61,0	355,2	126,6	/	25,0	8	60,7	83,3	8
16	f	37	32,7	2,3	50,2	263,3	121,3	65,6	58,3	6	81,3	58,3	6
17	m	34	21,1	3,2	62,0	163,4	10	40,6	25,0	8	68,8	75,0	3
18	f	53	28,3	0,5	29,9	810,3	550,53	/	/	9	39,3	8,3	10
19	m	27	20,3	1	50,8	358,1	218,1	53,1	33,3	7	75,0	50,0	7
20	m	31	25	1,3	77,9	269,5	79	34,4	/	/	37,5	50,0	9
21	f	55	19,4	4,8	25,1	99,8	6,3	50,0	25,0	7	85,7	58,3	7

Table 2 - Individual results during baseline and at follow-up (continued)

Patient No.	Demographic characteristics			Polysomnographic parameters				Snoring questionnaires					
	Baseline			Baseline				Baseline			At 6 weeks		
	Gender	Age	BMI	AHI	% supine sleep	Supine SI	Non-supine SI	SOS	SBPS	VAS	SOS	SBPS	VAS
22	m	31	24,4	3	39,5	306,7	148,7	43,8	33,3	7	43,8	50,0	6
23	m	31	22,5	0,5	17,5	531,4	235,3	/	25,0	6	67,9	83,3	2
24	f	34	22,3	2,7	62,1	244,7	193,7	9,4	,00	9	37,5	25,0	5
25	m	35	25	3,2	45,5	665,4	402,3	/	33,3	7	34,4	100,0	3
26	m	61	27,1	3,6	22,3	698,2	222	25,0	25,0	9	71,9	58,3	4
27	f	52	23,1	3,5	25,3	99,7	34,6	40,6	50,0	6	28,1	50,0	7
28	m	47	25	4,9	41,1	537,7	370,3	35,7	/	8	81,3	66,7	3
29	m	34	23,4	2,6	49,5	150,4	116,7	28,1	16,7	8	40,6	16,7	7
30	m	43	27,7	3	45,0	703,5	264,4	50,0	50,0	5	59,4	75,0	5
Mean±SD								**35.0±13.5**	**26.0±16.2**	**7.6±1.4**	**54.4±17.8**	**52.7±25.1**	**6.2±2.4**

BMI body mass index, *AHI* apnea-hypopnea index, *SI* snoring index, *SOS* snore outcome survey , *SBPS* spouse/bed partner survey, *VAS* visual analogue scale, *f* female, *m* male, / missing value.

A relevant effect was defined as a > 50% reduction of snoring rate in lateral position compared with the snoring rate in supine position. They found a significance decrease in snoring rate from 36.7 to 15.7%. Zuberi et al. also reported a significant reduction in snoring in patients with POSA treated with a triangular pillow [33]. In a study by Wenzel et al., patients with POSA were treated with a vest preventing the supine position [34]. A significance difference was found in snoring time (% of total sleep time) from 15.4 to 9.8%. However, there were other studies that did not find an improvement in snoring in apneic patients using PT [35–37]. We only found one study that evaluated the effect of PT in non-apneic snorers [38]. They used an anti-snoring pillow in primary snorers. Results reported that the snoring index significantly reduced from 269.0 to 162.5 and the mean snoring index was reduced by 39.6%. In the current study, only subjective parameters were evaluated and results showed that both SOS and SBPS scores improved significantly after 6 weeks.

There are not many other treatments available for positional or non-positional non-apneic snoring. Since snoring is regarded a social but non-medical condition, treatment is usually not reimbursed. Upper airway surgery for snoring can theoretically be applied, but often is overaggressive, irreversible, expensive, and not reimbursed [39]. Oral appliance therapy can be considered. However, it is often not reimbursed in non-apneic snoring. The effect of a cheaper option, the “boil and bite” oral device is often suboptimal, and not predictive of the effect of expensive custom-made titratable devices. Oral devices might have side effects such as painful jaws in the morning, dry mouth or hypersalivation, and long-term changes in occlusion. One-third of patients has a contra-indication for oral device therapy [40]. In case of insufficient effect or serious side effects, the considerable amount of money the patient has invested is lost. Continuous positive airway pressure (CPAP) can improve or eliminate snoring. Sériès et al. found that nasal CPAP (NCPAP) improves snoring in non-apneic snorers. In the NCPAP group, the snoring index decreased from 387/h to 320/h after therapy [41]. However, due to its low compliance, the limited acceptance, and high cost, CPAP is almost never used in the treatment of snoring [39]. Hence, PT in position-dependent non-apneic snoring may hold promising potential and results from the current study further highlight this potential. The SPT has been tested before in mild to moderate POSA patients by Van Maanen et al. and showed encouraging short and long-term results [26,27]. These promising results in OSA patients were in line with other studies [28,42]. The advantages of new-generation PT include that, in case it is not effective after a trial period, the device can be returned and side effects are limited.

Major limitations of our study are the uncontrolled design, the small cohort size, subjective outcome measures, and the short follow-up period. We report on short-term (6 weeks) effects, while a long-term effect is not investigated. However, from our experience with the SPT in OSA, we know that the long-term effect of the SPT

remains stable [29]. Accurate measurement of objective snoring is difficult and for this study not possible. Furthermore, both a standardized definition of position-dependent snoring and strict and precise outcome measures to evaluate effect of anti-snoring treatment are lacking. The explanation for this is probably that non-apneic snoring is mostly a social problem, in contrast to OSA, which is a medical condition. This has made the necessity to determine objective snoring outcome measures less urgent and subjective outcomes more appropriate. Still, various parameters have been suggested in the literature to quantify snoring. But by far, the most relevant outcome in snoring is patient and bed partner satisfaction. To further define objective outcome measures and its effect on position-dependent non-apneic snorers, a large, prospective, longitudinal study is needed along with more long-term compliance data to truly assess the efficacy of PT in primary snoring.

CONCLUSIONS

Due to the high prevalence of snoring in the general population and the associated negative mental and physical consequences, new therapeutic options are needed. The results of this study indicate that PT with the SPT improved several outcome measures in non-apneic position-dependent snorers. However, this non-controlled study has a short follow-up, so future studies are needed to review a controlled study design with longer follow-up period. The results of this non-controlled study demonstrate that this SPT could potentially be considered as an alternative therapeutic option in the treatment regime of positional primary snorers.

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A randomized, controlled trial of positional therapy versus oral appliance therapy for position-dependent sleep apnea

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ABSTRACT

Objective

To compare the effectiveness of positional therapy (PT) with the sleep position trainer (SPT) to oral appliance therapy (OAT) in patients with mild to moderate positional obstructive sleep apnea (POSA).

Methods

Multicenter, prospective, randomized, controlled trial. Patients with mild to moderate POSA (apnea-hypopnea index (AHI) ≥5 ≤30/hour sleep) were randomized for PT or OAT. Polysomnography was repeated after 3 months. Efficacy, adherence, mean disease alleviation (MDA), quality of life, dropouts and adverse events were evaluated.

Results

A total of 177 patients were screened for the study; 99 underwent randomization and 81 completed the study. Intention-to-treat (ITT) analysis of median AHI showed a reduction in the PT group from 13.0 [9.7-18.5] to 7.0 [3.8-12.8], $p<0.001$ and in the OAT group from 11.7 [9.0-16.2] to 9.1 [4.9-11.7], $p<0.001$. Mean adherence (≥4 h/night, ≥5 days/week) was 89.3 ± 22.4% for SPT versus 81.3 ± 30.0% in OAT patients, $p=0.208$.

Conclusions

Oral appliance therapy and positional therapy were equally effective in reducing the median AHI in patients with mild to moderate POSA. The results of this study have important implications for future OSA treatment guidelines and daily clinical practice.

INTRODUCTION

OSA has an overall prevalence of 9-38% in the general adult population, which is higher in men and rises with increasing age [1]. Obstructive sleep apnea is associated with daytime sleepiness, snoring, poor sleep quality, increased risk of cardiovascular disease, and motor vehicle accidents [2-5].

Conservative treatment starts with lifestyle alterations, such as weight reduction and avoidance of alcohol near bedtime, if applicable. In the case of position dependency, avoidance of the supine sleeping position is recommended. More aggressive treatment options include continuous positive airway pressure (CPAP) [6], oral appliance therapy (OAT) [7], and surgery, including upper airway stimulation [8]. All treatment modalities have their own specific indications, contraindications and side effects. Oral appliance therapy (OAT) is an established treatment for patients with mild to moderate OSA, both as a primary therapy and secondary treatment after CPAP failure. Oral appliance therapy often decreases the apnea-hypopnea index (AHI), with clinically relevant improvement [9]. When compared to CPAP, OAT has a non-inferior efficacy based on symptomatic response, although CPAP is more effective in reducing the AHI [10,11]. Although CPAP and OAT have different efficacy and compliance profiles, the overall therapeutic effectiveness is similar. Oral appliance therapy has better usage rates, while CPAP therapy is more efficacious [12]. The use of mean disease alleviation (MDA) enables calculation of overall therapeutic effectiveness; MDA is the product of the percentages for sleep time- adjusted adherence and therapeutic efficacy measured by AHI reduction. Since MDA provides data that are a more comprehensive metric of clinical effectiveness, MDA has been preferred above reporting AHI alone for treatment evaluation in recent studies [13,14].

However, OAT might have various downsides. Petit et al. demonstrated that approximately one-third of patients screened for OAT had a contraindication that was mainly associated with insufficient tooth number and periodontopathy coupled with tooth mobility [15]. In addition, OAT may induce dry mouth, jaw discomfort and changes in teeth position and occlusion [9,16]. Self-reported compliance is high (75-100%), although compliance de- creases over time [17]. In one previous study, estimated OAT use was 32% after four years [18]. Non-compliance is due to complications, side effects, or absence of beneficial effects [19].

The majority of patients with mild to moderate OSA have more apneic events in the supine position, as compared to non-supine positions [20-23]. Positional OSA (POSA) is defined as an apnea-hypopnea index (AHI) that is at least twice as high in the supine position as compared to non-supine positions [20]. The prevalence of POSA is 56%, with an additional 30% having more apneic events in the supine position, although not twice as much [24].

Promising results have recently been reported for active positional therapy (PT) with new smart and adaptive devices [14,25-27]. The sleep position trainer (SPT) is a device that is worn around the chest with a strap that gives vibrotactile feedback on supine positions at minimum intensity. The SPT aims to eliminate sleep time in the supine position without disturbing sleep quality [25]. Positional therapy with the SPT has improved sleep-related quality of life outcomes with an objectively measured adherence of 64.4% after six months of treatment [25,28].

It is well known that various patient factors have been associated with therapeutic outcome. For example, OAT has proven to be more effective in POSA patients compared to non-positional OSA patients [7,29,30]. It is believed that active PT has not directly been compared to OAT in the treatment of OSA. This multicenter, prospective, randomized study assessed the effectiveness of PT compared with OAT in mild to moderate POSA patients. The efficacy, adherence, MDA, quality of life and the side effects were evaluated after three months of therapy.

MATERIAL AND METHODS

Patients

Patients were recruited at the departments of Otolaryngology and Clinical Neurophysiology at OLVG West Hospital, Amsterdam. Patients were eligible for inclusion if they met the following criteria: mild to moderate positional OSA, defined as an AHI in supine position at least twice as high as compared with the AHI in non-supine position, with 10-90% of total sleep time (TST) in the supine position, and aged ≥18 years. Exclusion criteria were: inadequate dental status for wearing oral appliances, central sleep apnea, night or rotating shift work, severe chronic heart disease, active psychiatric disease, seizure disorder, medication usage for sleeping disorders, muscular or joint problems in head, neck or back area, previous treatment with OAT or SPT, simultaneous other OSA treatments, reversible morphological upper airway abnormalities (e.g., enlarged tonsils), pregnancy, self-reported severe snoring in the lateral position as a primary complaint, and coexisting non-respiratory sleep disorders (e.g., insomnia, periodic limb movement disorder, narcolepsy) that would influence functional sleep assessment.

Study design

In a multicenter, randomized, controlled trial, randomization was carried out centrally using a specialized computer system maintaining allocation concealment, stratified for BMI and, to a lesser extent, smoking. These two parameters were chosen as both factors could potentially contribute to sleep apnea. It was hypothesized that participants treated with PT would show equivalence in AHI compared with those treated with OAT.

The physician and participant were not blinded to treatment arms. Primary outcome measures were assessed by overnight polysomnography (PSG) and scored manually by scorers blinded to therapy arm. The institutional Medical Ethics Committee of the OLVG West Hospital, Amsterdam and the Academic Medical Center Amsterdam approved the protocol. Written informed consent was obtained before enrollment. Independent monitors performed verification of documentation and source data.

Polysomnography

A digital PSG system (Embla A10, Broomfield, CO, USA) was used and recorded electroencephalogram (EEG) (FP2-C4/C4-O2), electro-oculogram (EOG), electrocardiogram (ECG) and submental and anterior tibial electromyogram (EMG). Nasal airflow was measured by a nasal pressure cannula, and blood oxygen saturation was measured by finger pulse oximetry. Straps containing piezoelectric transducers recorded thoracoabdominal motion, and a position sensor (Sleepsense, St Charles, IL, USA) attached to the midline of the abdominal wall was used to differentiate between supine, prone, right lateral, left lateral, and upright positions. The recorded data were analyzed using special software (Somnologica™ studio, OLVG West Hospital, Amsterdam) and manually edited. Apnea was defined as the cessation of nasal airflow of more than 90% for a period of ≥10 s in the presence of respiratory efforts. In accordance with the prevailing definition from the American Academy of Sleep Medicine (AASM) at that time, a hypopnea was scored whenever there was a >30% reduced oronasal airflow for at least 10 s, accompanied by ≥4% oxygen desaturation from pre- event baseline.

Study treatment

Participants were assigned either to the SPT or OAT after stratified randomization. The SPT (SPT-DEV-PX-11.08) of NightBalance™ (NightBalance B.V., The Hague, The Netherlands) is a small lightweight device (72 x 35 x 10 mm; 25 g) worn across the chest using a neoprene strap (***Figure 1***). The sensor contains a lithium polymer battery cell of 3.7 V and 180 mAh, a 3.2 G vibration motor and a protection circuit integrated in the printed circuit board. A three-dimensional digital accelerometer is used to determine body position. The SPT gives a soft vibration when supine position is detected, in order to urge a patient to change body position. Treatment is divided into three phases. During the first two nights, the SPT analyzes body position without giving active feedback. During the following seven nights, the SPT trains the patient by vibrating in an increasing percentage of episodes while in the supine sleeping position. If the patient does not change position, the SPT will vibrate again after 2 min. At day 10, the full therapy phase begins, in which the SPT will vibrate every time the patient is in the supine sleeping position. The SPT has a USB port to recharge the internal battery and to upload data to an online self-monitoring system that can also be accessed by the patient and physician.

Figure 1. Sleep position trainer (SPT) SPT-DEV-PX-11.08 of NightBalance™ (left panel) and Oral appliance, type SomnoDent flex, SomnoMed, with Orthosmart, TheraMon chip in blue (right panel).

In the present study, OAT was carried out using a custom-made titratable device (SomnoDent flex, SomnoMed™, Sydney, Australia) (***Figure 1***). The device was worn intraorally and had a soft inner liner that supported comfort and maintained retention. The OAT was adjusted individually and advancement was titrated using a standard titration protocol [31]. After adequate assessment of the central relation and maximum protrusion using a construction bite with the George Gauche instrument, the OAT was set at 60% advancement at baseline. At each consecutive visit, the OAT was evaluated and advanced to 75%, or 90% if necessary. On the other hand, if side effects were not acceptable for the participant (e.g., tooth pain or signs of temporomandibular dysfunction) the advancement was adjusted backwards to 75, 60 or 45%. Objective compliance was measured using a temperature-sensitive micro- sensor with on-chip integrated read-out electronics (Theramon®, Handels-und Entwicklungsgeselschaft, Handelsagentur Gschladt, Hargelsberg, Austria). Temperature was recorded by the micro- sensor at a sampling rate of one measurement per 15 min, allowing data acquisition on usage for a consecutive 100-day period. A recorded temperature of ≥30°C indicated that the OAT was worn [32]. This microsensor was embedded in the OAT at the lower right side. Data were extracted at three months (±2 weeks) using a dedicated reading station.

Study end points

The primary outcome measure was AHI. Secondary outcomes were other respiratory indices, including oxygen desaturation index (ODI) (≥4% decrease in oxygen saturation), and percentage of supine sleep time. Other outcome measures were subjective improvement in daytime sleepiness, measured with the Epworth Sleepiness Scale (ESS) (overall score between 0 and 24, a score<10.0 is regarded as normal) [33], and the Functional Outcomes of Sleep Questionnaire (FOSQ) (global score ranging from 5 to 20, the lower the score the more dysfunctional the individual secondary to sleepiness) [34]. Furthermore, adherence and mean disease alleviation (MDA) were addressed. Adherence was defined as the percentage of daily use of ≥4 h per night, during ≥5 days per

week [35]. The MDA (%) was calculated by the product of the percentages for adjusted compliance and therapeutic efficacy, divided by 100. Within this definition, adjusted compliance was defined as the percentage of daily use (≥4 h/night, ≥5 days/week) adjusted for sleep time (recorded by PSG) and limited to 100%. Therapeutic efficacy is defined as the AHI baseline minus AHI with therapy, expressed as a percentage [13].

Adverse events

Adverse events were reported in accordance with the International Conference of Harmonization ICH E2A guidelines (Good Clinical Practices) by the principal investigators and evaluated by clinical data monitors [36].

Statistical analysis

Descriptive statistics and inferential statistics were used. A Kolmogorov-Smirnov test, Q-Q plot and Levene's test first tested all data for normality. Categorical and dichotomous variables were expressed as *n* (%). Normally distributed continuous variables were expressed by their mean and standard deviation (SD) and tested with the independent samples Student's *t*-test. Skewed distributed data were expressed by their median and interquartile range [IQR] and tested with the independent samples Mann-Whitney *U* test or Wilcoxon signed-rank test. Significance level was set at $p<0.05$. Statistical analysis was performed using SPSS Statistical software (version 21.0, SPSS Inc., Chicago, IL). Both intention-to-treat (ITT) (n=99) and per-protocol (PP) (n=81) analyses were executed for the main outcome parameters. For ITT analyses, none of the patients could be excluded, and patients were analyzed according to the original randomization. Therefore, missing data, in case of dropout, were imputed from baseline to the 3-month values.

RESULTS

Characteristics

A total of 177 patients were screened (70.7% men, age 48.3 ± 10.1 years; BMI 27.6 ± 3.8 kg/m^2), of whom 99 underwent randomization (***Figure 2***). Participant characteristics are shown in ***Table 1***. Both groups were similar in the baseline characteristics of age, gender, BMI, AHI, percentage supine time and TST. A total of 81 participants (81.8%) completed the 3-month follow-up. Most dropouts, including withdrawal, were seen in the OAT group (15 versus 3) (***Figure 2***).

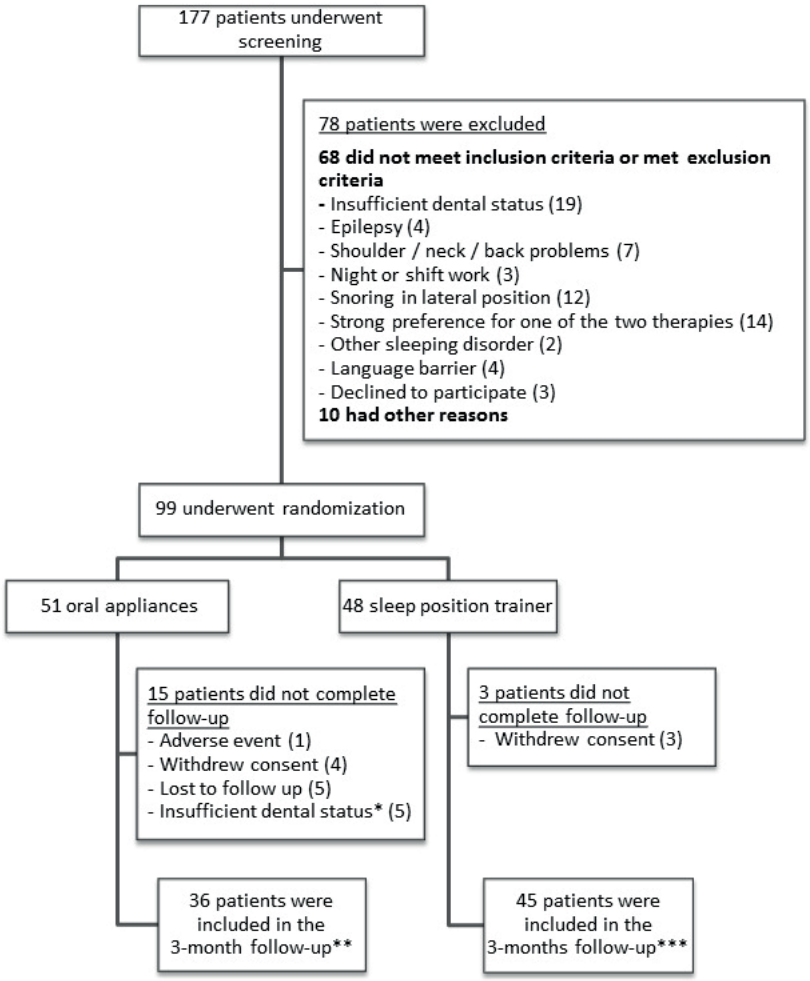

Figure 2. Study enrollment. Overview of screening (enrollment), randomization and 3-month follow-up. *Although insufficient dental status was an exclusion criterion, a dentist checked this through regular physical examination. Some dental problems were only visualized after the orthopantomography was made. **Adherence data for the OAT was retrieved in 32 participants, since there was a technical error with the chip in four participants. ***Adherence data for the SPT was retrieved in 43 participants, since one patient did not show up at his follow-up visit after his 3-month PSG, for exporting the data. The other participant did not use the SPT during the 3-month PSG.

Primary outcome

Intention-to-treat

In an ITT analysis, including dropouts, the median AHI in OAT decreased from 11.7 [9.0-16.2] to 9.1/h [4.9-11.7], $p < 0.001$, and in SPT patients from 13.0 [9.7-18.5] to 7.0/h [3.8-12.8], $p < 0.001$. These results are graphically illustrated in ***Figure 3***. No significant between-group difference was seen at 3 months, $p=0.535$ (***Table 2***).

Table 1 - Characteristics of the study population at baseline (n=99)

	SPT N=48	OAT N=51	P-value[a,b]
Male sex, no. (%)	34 (70.8)	36 (70.6)	0.979
Age, yr.	47.3 ± 10.1	49.2 ± 10.2	0.347
BMI, kg/m^2	27.5 ± 2.9	27.7 ± 4.5	0.797
Neck circumference, cm	38.0 ± 3.6	37.7 ± 3.2	0.624
Smoking, no. (%)	11 (22.9)	12 (23.5)	0.943
Alcohol			
≤2 drinks/day, no. (%)	45 (93.7)	48 (94.1)	0.499
>2 drinks/day, no. (%)	3 (6.3)	3 (5.9)	
Blood pressure, mmHg			
Systolic	135.0 [125.0-150.0]	130.0 [120.0-140.0]	0.032
Diastolic	90.0 [80.0-97.5]	85.0 [80.0-90.0]	0.033
Pulse, bpm	69.0 [64.0-78.0]	72.0 [66.0-80.0]	0.530
AHI, events/h	13.0 [9.7-18.5]	11.7 [9.0-16.2]	0.318
AHI supine, events/h	27.0 [18.7-43.1]	25.8 [17.4-35.0]	0.687
Percentage supine sleep	44.5 [30.0-55.5]	39.0 [26.0-54.0]	0.575

SPT sleep position trainer, *OAT* oral appliance therapy, *BMI* body mass index, *AHI* apnea hypopnea index

Mean ± SD standard deviation, Median [Q1-Q3]

[a] Independent *t*-test

[b] Mann-Whitney *U* test

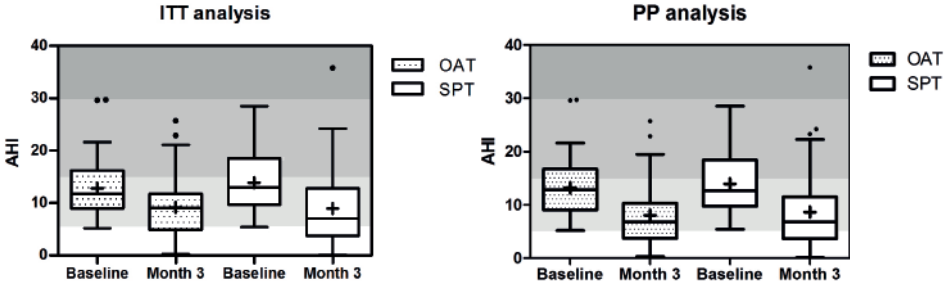

Figure 3. a and b). Intention-to-treat and per-protocol analysis for primary outcome AHI reduction. Overall apnea-hypopnea index (AHI) for OAT and SPT. The different gray scales represent the levels of sleep apnea severity, ranging from normal nocturnal breathing (AHI <5/hour sleep), mild OSA (AHI 5e15/hour), moderate OSA (AHI 15e30/hour), to severe OSA (AHI >30/hour). Box plots are displayed for the two different study nights subdivided for OAT (spotted fill) and SPT (blanc fill). The 25th and 75th percentiles are represented by the upper and lower margins, the mean values by the cross, and the median values by the horizontal line. Whiskers represent the maximum value (top) and the minimum value (bottom) of the dataset. Outliers are represented by a closed dot.

Table 2 - Primary and secondary outcome measures represented as mean ± standard deviation and median with interquartile range.

ITT analysis (n=99)	Sleep position trainer n=48				Oral appliance therapy n=51				
	Baseline	3 months	Change	p Value[a]	Baseline	3 months	Change	*p* Value[a]	*p* Value[b]
Primary outcome									
Total AHI, events/h	13.9 ± 5.9 13.0 [9.7-18.5]	9.0 ± 7.3 7.0 [3.8-12.8]	-5.0 ± 6.3 -5.2 [-9.7 to -1.1]	***<0.001***	12.8 ± 5.6 11.7 [9.0-16.2]	9.2 ± 5.8 9.1 [4.9-11.7]	-3.7 ± 5.4 -2.8 [-7.3 to 0.0]	***<0.001***	0.535
PP analysis (n=81)	**Sleep position trainer n=45**				**Oral appliance therapy n=36**				
	Baseline	**3 months**	**Change**	**p Value[a]**	**Baseline**	**3 months**	**Change**	***p* Value[a]**	***p* Value[b]**
Primary outcome									
Total AHI, events/h	13.9 ± 5.9 12.7 [9.8-18.4]	8.7 ± 7.4 6.8 [3.7-11.5]	-5.3 ± 6.4 -5.4 [-9.8 to -1.5]	<0.001	13.2 ± 6.0 12.9 [9.1-16.7]	8.1 ± 5.9 6.9 [3.7-10.3]	-5.2 ± 5.8 -5.1 [-7.9 to -2.4]	<0.001	0.875
Secondary outcomes									
AHI supine, events/h	31.0 ± 17.2 26.0 [18.8-42.1]	19.6 ± 22.5 12.3 [0.1-32.8]	-11.4 ± 18.2 -14.3 [-23.4 to -2.3]	<0.001	32.3 ± 19.3 27.7 [16.5-42.4]	17.7 ± 13.4 15.0 [6.0-27.0]	-14.5 ± 18.1 -10.6 [-23.7 to -4.4]	<0.001	0.394
AHI *non*-supine, events/h	4.0 ± 3.3 3.4 [1.7-5.6]	6.2 ± 6.0 4.3 [1.9-9.2]	2.2 ± 6.2 1.3 [-1.3 to 4.1]	0.016	3.7 ± 3.0 3.2 [0.9-5.3]	4.0 ± 5.7 1.9 [0.8-4.7]	0.2 ± 5.6 -0.5 [-3.1 to 1.8]	0.402	0.005
ODI, oxygen desaturation Index	11.6 ± 5.8 10.0 [7.0-15.5]	7.5 ± 6.6 5.0 [3.0-10.0]	-4.3 ± 6.0 -3.0 [-7.0 to -1.0]	<0.001	10.4 ± 6.0 10.0 [6.0-13.8]	7.3 ± 5.4 6.5 [4.0-9.0]	-3.1 ± 5.4 -3.0 [-6.0 to -1.0]	0.001	0.689
Percentage supine sleep	42.4 ± 17.4 43.0 [30.0-54.0]	14.4 ± 14.7 11.0 [1.0-22.5]	- 28.0 ± 20.0 -31.0 [-41.0 to -16.0]	<0.001	39.9 ± 20.3 34.0 [25.0-56.3]	38.9 ± 25.7 32.0 [16.8-57.8]	-0.9 ± 19.6 -1.0 [-9.8 to 8.0]	0.922	<0.001
Sleep efficiency	89.6 ± 8.2 92.0 [85.0-95.5]	89.8 ± 7.1 91.0 [86.0-95.0]	0.36 ± 9.2 0.5 [-0.5 to 6.0]	0.617	88.9 ± 7.7 90.5 [86.0-95.0]	87.3 ± 11.0 91.0 [84.0-95.5]	-1.6 ± 9.3 0.0 [-5.0 to 2.0]	0.448	0.526
Epworth Sleepiness Scale score (/24)	8.5 ± 5.3 8.0 [5.0-12.0]	8.1 ± 4.8 7.0 [5.0-10.0]	-0.4 ± 3.9 0.0 [-2.0 to 2.0]	0.836	8.1 ± 5.4 7.0 [4.0-11.0]	6.0 ± 4.6 5.0 [3.0-8.0]	-1.2 ± 3.6 -2.0 [-3.0 to 1.0]	0.112	0.035
FOSQ score	15.2 ± 3.8 16.4 [12.9-18.1]	15.3 ± 4.2 16.2 [13.1-18.6]	0.3 ± 2.9 1.0 [-1.8 to 2.0]	0.590	15.5 ± 3.5 15.8 [12.4-18.3]	15.2 ± 3.7 15.8 [12.5-18.8]	-0.5 ± 2.3 -0.2 [-2.0 to 1.0]	0.332	0.814

Mean ± SD

Median [Q1-Q3]

ITT intention-to-treat, *PP* per-protocol, *AHI* apnea hypopnea index, *ODI* oxygen desaturation index, *FOSQ* Functional Outcomes of Sleep Questionnaire

[a] Wilcoxon signed rank test

[b] Mann-Whitney *U* test comparing the outcome of SPT with OAT at 3 months

Per-protocol analysis

The PP analysis showed that the AHI dropped from 12.4 [9.1-17.2] to 6.8/hour sleep [3.7-10.8], $p<0.001$. No significant between-group differences were seen in AHI reduction, $p=0.875$. The median AHI in the SPT group dropped from 12.7 [9.8-18.4] to 6.8/hour sleep [3.7-11.5] (46.5%, $p<0.001$) and in the OAT group from 12.9 [9.1-16.7] to 6.9/hour sleep [3.7-10.3] (46.5%, $p<0.001$). For the 3-month PSG, 13 participants were titrated at 60% and 23 at 75%. Objective outcome measures for PP analysis, as well as other sleep parameters, are shown in ***Table 2***.

Secondary outcomes

Respiratory indices

The ODI was lower in both groups at three months than at baseline, $p=0.689$, with an equal improvement. Both percentage of supine sleep and the AHI in supine position dropped in the total sample from 41.0 [26.0-54.0] to 19.0% [8.0-35.5] ($p<0.001$) and 26.0 [17.8-40.1] to 13.0/hour sleep

[4.6-27.5] ($p<0.001$), respectively. Sleep efficiency did not change: 92.0 [86.0-95.0] to 91.0% [85.3-95.0], $p=0.928$. Median percentage of supine sleep time, as recorded by PSG, decreased significantly in the SPT group from 43.0 [30.0-54.0] to 11.0% [1.0-22.5], $p<0.001$. For OAT, median percentage supine sleep time remained unchanged from 34.0 [25.0-56.3] to 32.0% [16.8-57.8], $p=0.922$. The median percentage of supine sleep time per night over the three-month period, as recorded by the SPT, is depicted in ***Figure 4***.

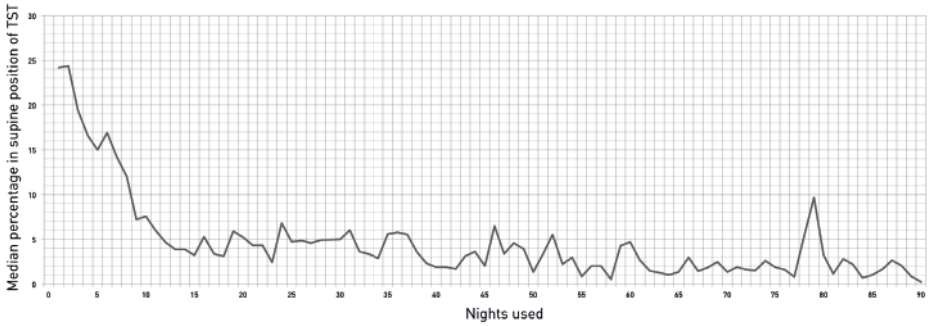

Figure 4. Median percentage of sleep time in the supine position per night. The first 9 days of the SPT therapy are part of the training program in which the SPT gradually decreases the number of times in which patients can sleep on their backs.

Adherence and mean disease alleviation

Mean adherence (≥4 h/night, ≥5 days/week) for PP analysis over three months was similar in both groups, 89.3 ± 22.4% for SPT versus 81.3 ± 30.0% in OAT patients, $p=0.208$ (***Table 3***). Mean adjusted compliance for ITT analysis was 88.4% and 60.5% for SPT and

OAT, respectively, with an efficacy of 36.3% vs 28.0%. Combining these numbers gives a calculated MDA of 33.2% for SPT and 23.6% for OAT, *p*=0.215. For the PP analysis, mean adjusted compliance for SPT was 96.0% and for OAT 88.8%, the efficacy 38.7% (SPT) vs 39.6% (OAT) and, hence, MDA 36.1% for SPT and 34.7% for OAT in the continuing users. This difference in MDA was not significant, *p*=0.879.

Table 3 - Mean disease alleviation (n=81)

	SPT N=45	OAT N=36	P-value[a]
Adherence (≥4hrs/night, ≥5d/week), %	89.3 ± 22.4	81.3 ± 30.0	0.208
Adjusted compliance [b], %	96.0 ± 10.1	88.8 ± 29.5	0.199
Therapeutic efficacy, %	38.7 ± 41.9	39.6 ± 35.9	0.912
Mean disease alleviation, %	36.1 ± 37.7	34.7 ± 35.4	0.879

SPT sleep position trainer, *OAT* oral appliance therapy, *TST* total sleep time
Mean ± SD standard deviation
[a] Independent *t*-test
[b] Used nightly hours as percentage of polysomnography-derived TST

Questionnaires

Questionnaires were collected at baseline and three months. In the OAT group, fully completed questionnaires at three months were collected in 80.6% (*n*=21/36) for the ESS and in 58.3% (*n*=29/

36) for the FOSQ. For SPT these percentages were 88.9 (*n*=40/45) and 64.4 (*n*=29/45) for the ESS and FOSQ, respectively. In both treatment groups, no clinically relevant change in quality of life, as measured with the FOSQ, was found. A minimal increase in mean FOSQ score was seen in the SPT arm (15.2 ± 3.8 to 15.3 ± 4.2). For OAT the mean FOSQ score dropped minimally from 15.5 ± 3.50 to

15.2 ± 3.7. A significant between-group difference was observed in mean ESS score at three months (8.1 ± 4.8 vs 6.0 ± 4.6, *p*=0.035) for SPT and OAT, respectively.

Adverse events

In total, 97 adverse events (AEs) were reported; 40.2% were device-related. In OAT, AEs (e.g., pain/sensitive teeth, dry mouth, occlusion problems) occurred in 26.8% (*n*=26). In the SPT group, 13.4% (*n*=13) reported AEs (e.g., vibro-tactile feedback disturbs sleep quality or wakes up partner, discomfort). Other AEs were: persistent snoring (22.7%; 12 SPT, 10 OAT); persistent tiredness (21.6%; 10 SPT, 11 OAT), other sleeping disorder (5.2%; 3 SPT, 2 OAT), and shoulder/joint complaints (3.1%; 3 SPT).

DISCUSSION

It is believed that this is the first article on three-month results of an effectiveness and efficacy comparison of SPT with OAT in patients with mild to moderate positional OSA. The SPT and OAT were equally effective in reducing the AHI and ODI. In the samples, higher adherence and MDA (efficacy x adherence) values were observed for the ITT analysis in the SPT group compared to OAT.

Earlier studies on short-term results (one month) of the SPT showed a reduction in AHI from 39% to 68% [14,25,27]. The SPT results in the present study were in agreement with this, although the follow-up period in the present study (three months) was longer. OAT has been extensively investigated, being effective in improving respiratory indices [11]. In the current study, the AHI in OAT dropped 46.5%; this is in line with the earlier literature [7]. In reporting treatment outcomes in OSA, there is an essential difference in efficacy and effectiveness [12,37,38]. Efficacy reflects the reduction in apneic events when a device is actually used. Effectiveness also takes adherence into account and is a better reflection of the real success of the treatment. Suboptimal adherence results in less effectiveness. Continuous positive airway pressure, for example, is highly efficacious when used, but the majority of patients have adherence problems that result in poor usage [35,39,40]. In fact, 29-83% of patients using CPAP are non-adherent [2,41-43]. In general, OAT has higher usage rates than CPAP treatment, but is less effective [12,13]. Objective adherence monitoring of OAT is possible by using microsensors thermometers embedded in the OA [7]. In a prospective trial, an objective adherence (≥4 h/night, ≥5 days/week) of 84% was measured in 51 patients with OSA using OAT over a three-month period [13]. These results are in line with the findings in the present study, where the mean adherence (≥4 h/night, ≥5 days/week) was 81.3 ± 30% for OAT participants.

New-generation PT, with chest-worn devices providing vibrotactile feedback if the supine position is adopted, is gaining renewed interest. Short-term [14,25] and long-term [28] objective adherence with SPT have been previously described. Van Maanen et al. reported a median adherence (≥4 h/night, 7 days/week) after one month and six months of 92.7% and 64.4%, respectively. Another study looked at adherence of SPT in comparison with the tennis ball technique and demonstrated that after 1 month, the reduction in AHI was similar, but adherence (≥4 h/night, ≥5 days/ week) was significantly better in the SPT group, 75.9% vs 42.3%, p=0.01 [14]. The present study observed higher mean objective adherence (≥4 h/night, ≥5/week) over the study period of three months in SPT participants as compared with the OAT group (89.3% vs 81.3%, p=0.208).

Objective measurement of therapy adherence is becoming standard clinical practice. A combination of adherence with efficacy results in the calculation of MDA as a measure of effectiveness. An MDA for OAT of 51.1% and 54.9%, respectively, were reported in two studies [13,44]. Another study reported an MDA for the SPT of 70.5% [14]; MDA has also

been reported for OAT and CPAP. Although in general OAT is inferior to CPAP in reducing respiratory indices, adherence on the other hand is higher, resulting in similar overall MDA [10,12]. Recently, Dieltjens et al. identified that a more pronounced decrease in reports of snoring and the presence of dry mouth were the two parameters that were correlated with higher objective compliance during OAT [45]. In the present study, ITT analysis showed higher MDA at three months in the PT group (37.2% for SPT vs 28.9% for OAT), while per-protocol analysis numbers were similar (40.3% for SPT and 42.5% OAT). Both results, however, were not significantly different between the groups.

When comparing SPT with OAT, SPT seems to have several advantages: it is well tolerated and reversible [28], and a daily readout of number of corrections and remaining percentage of supine position is available online for patients. A disadvantage may sometimes be continued snoring in the lateral position. Advantages of OAT are its efficacy and preference. Disadvantages of OAT are more reported side effects [7] and also limited inclusion because of dental status. In the case of insufficient effect, the custom-made OAT cannot be returned and used by someone else. The devices can be combined with each other or with other treatments, if needed.

For POSA patients with a partial response to OAT, combination therapy (adding PT to OAT) has already been shown to further decrease OSA severity in an earlier study; OAT and SPT were equally effective in reducing the AHI. The combination of OAT and PT gave an additional statistically significant AHI reduction [27]. In the present study population, adding PT to the OAT group could have potentially improved the AHI by eliminating the non-supine AHI. For patients using SPT, the AHI will likely decrease in all sleeping positions when OAT is added. Follow-up studies are needed to evaluate the effect of combination therapy. Vanderveken also recently highlighted the importance of combining different treatment options for OSA [46]. Additional effects of PT after partial effective surgery have also been recently reported [47].

The results of this study have important implications for future OSA treatment guidelines and daily clinical practice, where the potential of PT is still undervalued [23]. According to the findings, mild and moderate POSA patients with similar characteristics could benefit from both PT and OAT.

Limitations

Several limitations for this study should be considered. Eighteen of the 99 participants dropped out. Nonetheless, power analysis suggested a minimum sample size of 36 participants per study arm (to reach a power of 80%), which was achieved despite the dropouts. Orthopantomography was not routinely performed before randomization to identify unsuitable patients for OAT. One third of the OAT dropouts were lost to follow-up, perhaps due to the fact that the custom-made titratable device had to be fitted and manufactured at the next visit, and titrated afterwards elsewhere, which might

have caused a delay in patient intake and diminished patient commitment. While the study participants, on average, had mild POSA with limited self-reported sleepiness, it is believed that the results of this study could be generalized to patients with mild to moderate POSA in Western populations. Future studies will need to investigate whether a stepped-care approach is feasible and will result in higher quality of life of patients and increased cost-effectiveness of treatment.

CONCLUSIONS

Results of this first RCT comparing respiratory indices and MDA between OAT and SPT indicate that after three months, OAT and PT are equally effective in reducing the AHI in mild to moderate POSA patients. It is believed that the results of this study have important implications for future OSA treatment guidelines and daily clinical practice. Additionally, long-term results still have to be determined.

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6

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

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ABSTRACT

Purpose

The Sleep Position Trainer (SPT) is a new option for treating patients with positional obstructive sleep apnea (POSA). This study investigated long-term efficacy, adherence, and quality of life during use of the SPT device com- pared with oral appliance therapy (OAT) in patients with POSA.

Methods

This prospective, multicenter trial randomized patients with mild to moderate POSA (apnea-hypopnea index [AHI] 5–30/h) to SPT or OAT. Polysomnography was performed at baseline and after 3 and 12 months' follow-up. The primary endpoint was OSA severity; adherence, quality of life, and adverse events were also assessed.

Results

Ninety-nine patients were randomized and 58 completed the study (29 in each group). Median AHI in the SPT group decreased from 13.2/h at baseline to 7.1/h after 12 months (p<0.001); corresponding values in the OAT group were 13.4/h and 5.0/h (p<0.001), with no significant between-group difference (p=1.000). Improvements throughout the study were maintained at 12 months. Long-term median adherence was also similar in the two treatment groups; the proportion of patients who used their device for ≥ 4 h for 5 days in a week was 100% in the SPT group and 97.0% in the OAT group (p=0.598).

Conclusions

The efficacy of SPT therapy was maintained over 12 months and was comparable to that of OAT in patients with mild to moderate POSA. Adherence was relatively high, and similar in the two groups.

INTRODUCTION

OSA is the most common sleep-related breathing disorder. With an overall prevalence of 9– 38% in the general adult population, OSA is more common in men and increases with age [1]. Recent data from Switzerland showed that OSA was more prevalent than previously reported. The proportion of men and women with an apnea-hypopnea index (AHI) of > 5/h on polysomnography (PSG) was 84 and 61%, respectively [2]. An AHI of ≥ 5/h is required for a diagnosis of OSA, with disease severity rated as mild if the AHI is 5–15/h, moderate if the AHI is 15–30/h, and severe if the AHI is > 30/h [3].

OSA is characterized by recurrent (partial) obstruction of the upper airway, accompanied by oxygen desaturation, sleep disturbance, and sympathetic activation [4]. Consequences of OSA include excessive daytime sleepiness, reduced quality of life, and increased risk of developing cardiovascular disease. More than half of the OSA population (56%), and predominantly those with mild and moderate OSA, have position-dependent OSA (POSA) with more apneic and hypopneic events in supine position. POSA is commonly defined as more than twice as many respiratory events in the supine sleeping position compared to non-supine sleeping position [5–8].

Therapy for OSA generally starts with conservative treatment, consisting of lifestyle changes such as weight reduction and avoidance of alcohol, sedatives, and the supine sleeping position, when applicable. Thereafter, current options include continuous positive airway pressure (CPAP), oral appliance therapy (OAT) and pharyngeal surgery [9–11]. CPAP is the gold standard therapy for moderate to severe OSA, but adherence to CPAP is often suboptimal, necessitating exploration of other options [12]. Oral appliances (OA) are widely used in mild to moderate OSA, and are associated with clinically relevant decreases in the AHI [13], making them an increasingly attractive first-line therapy option in these patients. Vecchierini et al. reported OAT success rates of 40–70 and 78–81% in mild to moderate patients for an AHI to < 5/h and for an AHI reduction of at least 50%, respectively [13]. However, adverse events such as tooth pain, changes in tooth position resulting in a different occlusion and articulation, or temporomandibular dysfunction can limit adherence to this therapy [14,15]. Surgery can be an option for patients who are unresponsive, noncompliant, or desire a permanent treatment for their OSA [16–18].

For POSA, alternatives include the use of specific treatments designed to avoid the supine sleeping position. However, the effectiveness of therapy with first generation devices has been limited. For example, the “tennis ball-technique” is uncomfortable for patients to use and disrupts sleep, leading to poor long-term adherence [19]. Next generation treatment options with active feedback and auto-adapted treatment intensity to decrease discomfort and improve compliance were introduced. These include active positional therapies like supine alarm devices and neck or chest-worn vibrating devices [20,21]. The Sleep Position Trainer (SPT) is such a chest-worn device and it

showed to significantly reduce the average supine sleeping time (from 46 to 5%), the AHI to < 5/h in 48%, and an AHI reduction of at least 50% in 71% of patients with mild or moderate POSA [22]. Effectiveness and adherence were good, with an objective adherence rate (> 4 h of nightly use) of 64.4% after 6 months of treatment and improved sleep-related quality of life [23]. Additionally, short-term results have recently been published on the effectiveness of the SPT versus OAT, showing equal efficacy in reducing the median AHI in patients with mild to moderate POSA [24]. However, there are no data on the use and effect of the SPT beyond 6 months. Therefore, we aimed to study the longer-term efficacy and adherence of the SPT (the intervention) in comparison to OAT (active comparator). Hence, we hypothesized that the SPT would be more efficacious in reducing the AHI compared to OAT in patients with mild to moderate POSA. This paper investigated the durability of the previously reported short-term effects of the SPT with respect to efficacy, adherence, and quality of life, after 12 months of follow-up.

METHODS

Participants

Participants were eligible for enrollment if they had a diagnosis of mild to moderate POSA (AHI of 5–30/h) and spent 10– 90% of their total sleep time in the supine position during baseline PSG. Exclusion criteria included inadequate dentition for wearing an oral appliance, subjective snoring in the lateral position, central sleep apnea, night or rotating shift work, severe chronic heart disease, active psychiatric disease, seizure disorders, medication usage for sleeping disorders, muscular or joint injuries in the head, neck, or back area, previous OAT or SPT usage, simultaneous use of other treatment for OSA, reversible morphological upper airway abnormalities (e.g., enlarged tonsils), pregnancy, and coexisting non-respiratory sleep disorders (e.g., insomnia, periodic limb movement disorder, narcolepsy) that would compromise functional sleep assessment. All participants underwent medical and dental consultations, and a baseline PSG prior to the start of the study.

Study design and oversight

The study was designed as a multicenter, prospective randomized controlled trial. Patients were recruited and followed at the departments of Otolaryngology and Clinical Neurophysiology at OLVG West Hospital, Amsterdam, and at the department of oral and maxillofacial surgery at the Academic Medical Center, Amsterdam. The institutional Medical Ethics Committee of the OLVG West Hospital, Amsterdam, and the Academic Medical Center Amsterdam approved the protocol. The randomization sequence was generated by an independent clinical research unit using ALEA software with a 1:1 al-

location using maximum random block sizes of 6 and stratification for smoking and body mass index (BMI). Independent monitors verified the source data and documentation.

Study treatments

The sleep position trainer (SPT-DEV-PX-11.08; NightBalance) consists of a small lightweight device (72 × 35 × 10 mm; 25 g) worn across the chest using a neoprene strap (***Figure 1***) [22]. The SPT vibrates when a supine position is detected to prompt a change in body position. Data storage on the device allows for objective measurement of adherence to the therapy. Further details on functionality of the SPT are described elsewhere [24]. As active comparator, the OA was a custom-made duo-bloc device (SomnoDent flex; SomnoMed) (**Figure 2**). After adequate assessment of the central relation and maximum protrusion, the OA was set at 60% of maximum protrusion at baseline. The OA was adjusted individually and advancement was titrated using a standard protocol by the dentist, which was described in greater detail elsewhere [24]. Objective adherence was measured using a temperature-sensitive microsensor with on-chip integrated readout electronics (Theramon, Handels- und Entwicklungsgeselschaft, Handelsagentur Gschladt, Hargelsberg, Austria) with a sampling rate of one measurement every 15 min. A recorded temperature of > 30 °C indicated that the OA was worn.

Figure 1. Sleep Position Trainer

Figure 2. Oral appliance therapy, including a blue chip for measuring adherence

Outcome measures

The primary outcome was the change in OSA severity after 12 months compared with baseline. OSA severity was determined based on the AHI and the oxygen desaturation index (ODI; the number of times per hour of sleep that the blood oxygen level drops by ≥ 4% from baseline, according to the prevailing definition at that time). These parameters

were determined from overnight PSG (Embla A10, Broomfield, CO, USA) which records electroencephalogram (EEG) (FP2-C4/ C4-O2), electro-oculogram (EOG), electrocardiogram (ECG), and submental and anterior tibial electromyogram (EMG). Nasal airflow was measured by a nasal pressure cannula and blood oxygen saturation by finger pulse oximetry. Straps containing piezoelectric transducers recorded thoracoabdominal motion, and a position sensor (Sleepsense, St Charles, IL, USA) attached to the midline of the abdominal wall was used to differentiate between supine, prone, right lateral, left lateral, and upright positions. Recordings were manually scored by an independent core laboratory using American Academy of Sleep Medicine (AASM) 2012 scoring criteria [25]. Secondary outcomes included additional polysomnographic variables, percentage of time spent sleeping in the supine position, AHI in the supine and non-supine positions, and sleep efficiency. Self-reported daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS; score range 0–24, score ≥ 10 indicates excessive daytime sleepiness). Disease-specific quality of life was assessed with the Functional Outcomes of Sleep Questionnaire (FOSQ-30; score range 5–20, higher scores indicate better functioning). Adherence was defined as device (SPT or OAT) usage for ≥ 4 h/night at least 5 days per week.

Follow-up

This paper aimed at testing the durability of treatment effect after 12-month follow-up. Throughout the follow-up, patients underwent repeat PSG at 3 and 12 months, while using the SPT or OAT. Patients completed the ESS and FOSQ-30 at baseline and after 3 and 12 months of therapy. Objective adherence and medical evaluation (including heart rate and blood pressure measured twice seated by two independent physicians with an interval of 3 min) were also assessed at 3 and 12 months.

Adverse events

Adverse events were reported in accordance with the International Conference of Harmonization ICH E2A guide- lines (Good Clinical Practice) by the principal investigators and evaluated by independent data monitors [26].

Statistical analysis

Power analysis resulted in a minimum sample size of 36 participants per study arm (to reach a power of 80%). In order to allow for dropout, the recruitment target was inflated to 49 per group. The level for statistical significance was set at $\alpha = 0.05$. The statistical programming and analysis was performed using IBM SPSS statistics version 24 (IBM Corp., Armonk. NY, USA). Due to the proportion of missing data at 12 months, analyses were primarily conducted on a per-protocol (PP) basis. Additionally, illustrative worst-case and best-case intention-to-treat (ITT) analyses were performed through imputing missing data through the Last-Observation-Carried-Forward method.

Variables were summarized using descriptive statistics: mean value with standard deviation for continuous symmetric variables, median and interquartile range for continuous skewed variables, and frequency with percentage for categorical variables. For the primary outcome, repeated measures ANOVA was performed to test for differences over time. Thereafter, within-subject comparisons (patient progression over time; paired) between continuous variables at baseline and follow-up (3 and 12 months) and between the 3- and 12-month follow-ups were made using the paired *t* test (non- skewed data) or the Wilcoxon signed rank test (skewed data). Between-group difference tests (deltas baseline vs. follow-up) were performed using an independent *t* test (non-skewed data) or Mann-Whitney *U* test (skewed data). Both the between- group and within-subject analyses were adjusted for multiple comparisons using the Bonferroni correction.

RESULTS

A total of 177 patients with mild to moderate POSA were screened for eligibility (70.7% male, age 48.3 ± 10.1 years; BMI 27.6 ± 3.8 kg/m^2). Of these, 99 patients met all eligibility criteria and were randomized to OAT (*n*=51) or SPT (*n*=48) (***Figure 3***). Baseline characteristics for these patients are shown in ***Table 1*** with comparison of the characteristics between "completers" and "dropouts". There was only a statistically significant difference in blood pressure between the OAT and SPT groups at baseline (***Table 1***). The total number of patients receiving allocated treatment with OAT and SPT, and completing 3 months' follow-up was 36 and 45, respectively. Over the remaining 9 months of follow-up, an additional seven patients withdrew in the OAT group (one lost to follow-up and six discontinued treatment due to adverse events [*n*=2], lack of efficacy [*n*=3], or both adverse event and efficacy [*n*=1]) (Fig. 3). In the SPT group, 2 patients were lost to follow-up and 14 discontinued treatment (lack of efficacy [*n*=3], persistent snoring [*n*=4], adverse events [*n*=3; 2 not related to SPT], or other non-related reasons [*n*=4]) (***Figure 3***). A total of 58 patients were eligible for per-protocol analysis after 12 months (***Figure 3***).

Primary outcome

PP analysis showed that the AHI and ODI were significantly reduced compared with baseline at both the 3- and 12-month follow-up visits for both treatment groups, with no significant between-group differences (***Table 2***). The absolute reductions in AHI and ODI at 3 months were maintained at 12 months in both groups (***Table 2***). ITT analysis for the primary outcome is provided in ***Table S1***. The AHI reduced for more than 50% in 48.3 and 51.7% of SPT patients after 3 and 12 months, respectively. For the OAT group, this reduction was found in 48.3% patients after 3 months and 55.2% patients after 12

months of follow-up. The outcomes were not statistically different between the two treatment groups (p=1.000 at 3 months and p=0.792 at 12 months). Alternatively, a reduction of the AHI under 5/h for the 3- and 12-month follow-up was found in 34.5 and 41.4% of SPT patients and 41.4 and 51.7% of OAT patients, respectively. These outcomes were also not significantly different between the groups (p=0.5888 at 3 months and p=0.430 at 12 months).

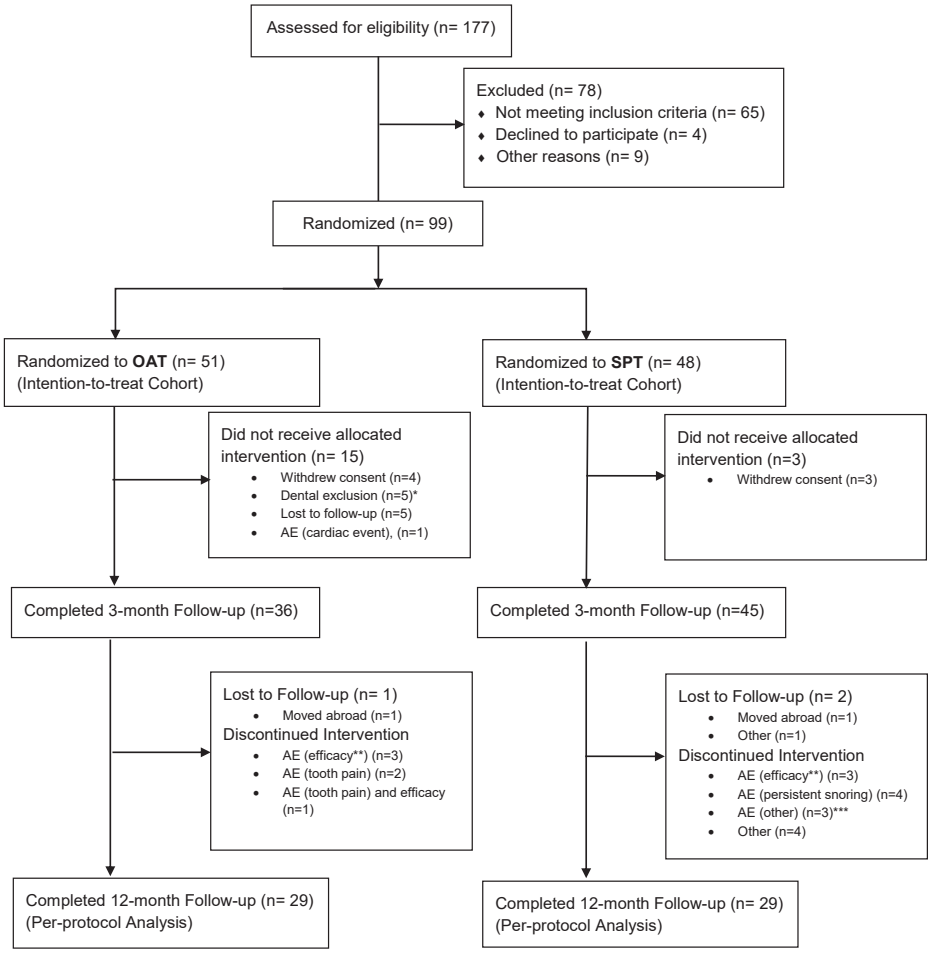

Figure 3. Flow of patients through the study. AE, adverse event; OAT, oral appliance therapy; SPT, Sleep Position Trainer. *Although insufficient dental status was an exclusion criterion, a dentist checked this through regular physical examination. Some dental problems were only visualized after the orthopantomography was made.

** Efficacy: persistent apneas/ AHI. *** Adverse events; one related events (joint problems due to wearing SPT), two non-related events (one patient had nasal problems and was not motivated to continue and one patient had broken ribs due to an accident and did not want to continue)

Durability of the treatment effect of both the SPT and OAT groups was good (***Figure 4***). There was a statistically significant effect of time on the AHI under treatment ($F(2, 56) = 65.97$, $p<0.001$), with no significant between-group difference ($p=0.592$). For the reduction in AHI, stratification by OSA severity at baseline (mild [$n=34$) vs. moderate [$n=24$]) was performed ($F(2, 54) = 102.39$, $p<0.001$). However, no severity-related difference in reduction of AHI was observed between the treatment arms ($p=0.200$).

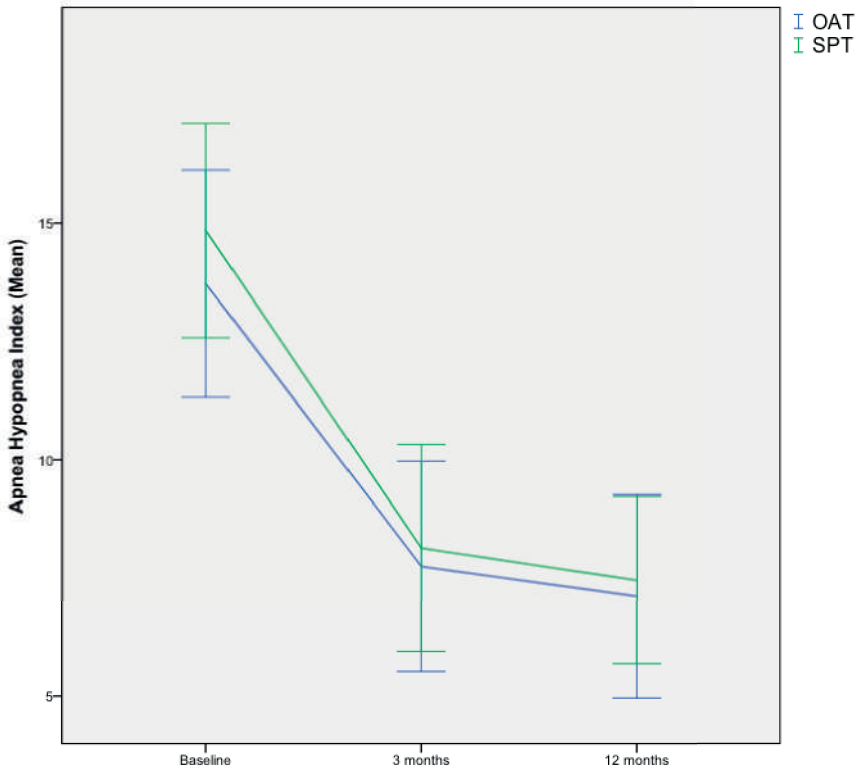

Figure 4. Durability of effects on the apnea-hypopnea index (AHI) over time in the Sleep Position Trainer (SPT) and oral appliance therapy
(OAT) groups (ANOVA repeated measures)

Secondary outcomes

Polysomnographic indices

Treatment with SPT was associated with a significant decrease in supine sleeping time ($p<0.001$ vs. baseline after 3 and 12 months), but supine sleeping time was unchanged from baseline in the OAT group (between-group difference, $p<0.001$) (***Table 2***). Supine AHI decreased to a similar extent in the two groups (***Table 2***). Sleep efficiency remained stable over the 12-month follow-up, and no significant changes in cardiovascular parameters were observed between the two treatment groups (***Table 2***).

Table 1 - Baseline characteristics in all randomized patients (n = 99) and comparison between "completers" and "dropouts"

	SPT		
	Total (*n* = 48)	Completers (*n* = 29)	Dropouts (*n* = 19)
Male, *n* (%)	34 (70.8)	19 (65.5)	18 (62.1)
Age, years	47.3 ± 10.1	49.5 ± 9.4	49.5 ± 8.5
Body mass index, kg/m^2	27.5 ± 2.9	27.7 ± 2.8	28.3 ± 3.6
Height, cm	177.0 ± 10.2	176.7 ± 11.2	172.7 ± 12.1
Weight, kg	86.2 ± 13.2	86.9 ± 14.9	84.2 ± 11.4
Neck circumference, cm	38.0 ± 3.6	37.9 ± 3.8	37.2 ± 3.1
Smokers, *n* (%)	11 (22.9)	5 (17.2)	7 (24.1)
Alcohol intake, *n* (%) ≤ 2 drinks/day	45 (93.7)	26 (89.7)	27 (93.1)
> 2 drinks/day	3 (6.3)	3 (10.3)	2 (6.9)
Blood pressure, mmHg			
Systolic	135.0 (125.0-150.0)	130.0 (125.0-150.0)	130.0 (120.0-141.0)
Diastolic	90.0 (80.0-97.5)	80.0 (90.0-95.0)	85.0 (80.0-90.0)
Heart rate, beats/min	69.0 (64.0-78.0)	68.0 (63.0-78.0)	72.0 (62.0-78.0)
AHI, /h	13.0 (9.7-18.5)	13.2 (10.2-19.0)	13.4 (8.7-16.9)
Supine AHI, /h	27.0 (18.7-43.1)	28.5 (18.9-46.2)	25.8 (15.8-45.1)
Non-supine AHI, /h	3.5 (1.6-5.7)	4.1 (2.4-5.8)	3.8 (0.8-5.7)
Supine sleep time, %	44.5 (30.0-55.5)	41.0 (30.0-54.0)	35.0 (25.0-61.0)
ODI, /h	10.5 (7.0-15.8)	9.0 (7.0-15.5)	10.0 (6.5-14.0)
AI, /h	9.0 (5.0-15.0)	11.0 (5.5-15.5)	8.0 (3.5-12.5)
Sleep efficiency, %	92.0 (84.5-95.0)	92.0 (84.0-95.5)	91.0 (85.5-95.0)
Mean oxygen saturation, %	95.0 (94.0-96.8)	95.0 (94.5-96.0)	95.0 (94.0-96.0)
ESS score	8.1 ± 5.2 (*n* = 42)	8.9 ± 5.7	6.9 ± 4.4
FOSQ score	19.0 (17.3-19.7) (*n* = 33)	18.9 (16.8-19.5)	19.3 (16.9-19.8)

Values are mean ± standard deviation, median (interquartile range), or number of patients (%)
AHI apnea-hypopnea index, *AI* apnea index, *ESS* Epworth Sleepiness Scale score, *FOSQ* Functional Outcomes of Sleep Questionnaire, *OAT* oral appliance therapy, *ODI* oxygen desaturation index, *SPT* Sleep Position Trainer
a Comparing total group scores between SPT and MAD (two groups), b Comparing completers' and dropouts' scores between SPT and MAD (four groups), c Pearson chi-square test, d Independent *T test*, e Mann- whitney test, f One-way ANOVA

Adherence

Device usage and adherence were similar in the SPT and OAT groups throughout the 12-month follow-up (***Table 3 and S2***). The average usage per night was 5.2/h for SPT and 5.0/h for OAT (p=0.743). Median adherence per patient (≥ 4 h for 5 days/week) was 100% in the SPT group and 97.0% in the OAT group (p=0.598).

OAT			*P* value[a]	*P* value[b]
Total (*n* = 51)	Completers (*n* = 29)	Dropouts (*n* = 22)		
36 (70.6)	15 (78.9)	18 (81.8)	0.979[c]	0.340[c]
49.2 ± 10.2	43.8 ± 10.3	48.9 ± 12.3	0.347[d]	0.209[f]
27.7 ± 4.5	27.1 ± 2.9	26.8 ± 5.5	0.797[d]	0.501[f]
174.4 ± 11.9	177.4 ± 8.8	176.5 ± 11.6	0.247[d]	0.422[f]
83.9 ± 14.2	85.1 ± 10.3	83.5 ± 17.4	0.401[d]	0.820[f]
37.7 ± 3.2	38.3 ± 3.4	38.3 ± 3.2	0.624[d]	0.655[f]
12 (23.5)	6 (31.6)	5 (22.7)	0.942[c]	0.719[c]
48 (94.1)	19 (100.0)	21 (95.5)	0.446[c]	0.688[c]
3 (5.9)	0 (0.0)	1 (4.5)		
130.0 (120.0-140.0)	140.0 (122.0-155.0)	129.0 (120.0-136.3)	0.032[e]	0.162[f]
85.0 (80.0-90.0)	90.0 (80.0-100.0)	82.5 (79.5-90.0)	0.033[e]	0.141[f]
72.0 (66.0-80.0)	74.0 (64.0-80.0)	71.0 (67.0-82.3)	0.530[e]	0.292[f]
11.7 (9.0-16.2)	12.1 (7.0-17.2)	10.3 (9.0-13.3)	0.318[e]	0.222[f]
25.8 (17.4-35.0)	26.0 (11.6-36.8)	26.1 (18.8-34.2)	0.687[e]	0.491[f]
3.1 (1.0-5.0)	2.4 (0.9-5.7)	2.6 (1.2-3.7)	0.361[e]	0.057[f]
39.0 (26.0-54.0)	47.0 (25.0-57.0)	42.5 (27.5-47.5)	0.575[e]	0.901[f]
9.0 (6.0-14.0)	13.0 (7.0-16.0)	8.0 (5.5-11.8)	0.137[e]	0.218[f]
8.0 (4.0-12.0)	7.0 (3.0-11.0)	7.0 (3.8-11.3)	0.183[e]	0.310[f]
92.0 (86.0-95.0)	92.0 (89.0-94.0)	93.0 (87.8-96.3)	0.820[e]	0.811[f]
95.0 (94.0-96.0)	95.0 (94.0-97.0)	95.5 (94.0-96.3)	0.451[e]	0.575[f]
8.7 ± 5.6 (*n* = 45)	7.1 ± 4.3	10.7 ± 6.3	0.625[e]	0.073[f]
18.4 (16.2-19.7 (*n* = 40)	19.4 (18.8-19.7)	18.3 (16.2-19.4)	0.646[e]	0.864[f]

Subjective daytime sleepiness and sleep-related quality of life

Complete 12-month data from the ESS questionnaire were available for 21/29 (72%) and 25/29 (86%) patients in the SPT and OAT groups, respectively; corresponding values for completion of the FOSQ were 12/29 (41%) and 13/29 (45%). No significant changes in the ESS score and FOSQ score were identified in either treatment group (***Table 2***).

Adverse events

A total of 114 device-related adverse events (AE) were reported by 48 patients (82.8%) overall, 20 (69.0%) in the SPT group, and 28 (96.6%) in the OAT group (Table 4). Overall, the most common adverse events in both groups were persistent snoring and persistent tiredness. A similar degree of persistent snoring was reported for SPT and OAT; by 14 and 15 patients, respectively. However, for an additional four SPT patients, persistent

Table 2 - Primary and secondary outcome variables (per-protocol analysis)

	SPT (*n* = 29)			OAT (*n* = 29)		
	Baseline	3 months	12 months	Baseline	3 months	12 months
Primary outcome						
Total AHI, /h	13.2 (10.2, 19.0)	*6.8 (4.1, 11.5)*[a]	*7.1 (4.0, 10.0)*[a]	13.4 (8.7, 16.9)	*5.9 (3.8, 9.6)*[a]	*5.0 (3.9, 8.9)*[a]
ODI, /h	9.0 (7.0, 15.5)	*5.0 (4.0, 8.0)*[a]	*6.0 (3.0, 8.0)*[a]	10.0 (6.5, 14.0)	*7.0 (4.0, 9.0)*[b]	7.0 (3.0, 10.5)
Secondary outcomes						
Supine AHI, /h	28.5 (18.9, 46.2)	*12.4 (0.0, 34.3)*[c]	*10.0 (0.0, 20.2)*[a]	25.8 (15.8, 45.1)	*14.3 (5.6, 26.8)*[a]	*10.3 (5.5, 18.3)*[a]
Non-supine AHI, /h	4.1 (2.4, 5.8)	4.3 (2.0, 7.2)	4.5 (2.6, 7.8)	3.8 (0.8, 5.7)	1.6 (0.6, 4.0)	1.8 (0.5, 4.5)
Supine sleep, %	41.6 ± 17.0	*13.3 ± 12.9*[a, d]	*12.7 ± 13.6*[a, d]	42.3 ± 21.4	41.4 ± 26.4	43.9 ± 23.7
AI, /h	11.0 (5.5, 15.5)	*4.0 (1.0, 8.5)*[a]	*3.0 (2.0, 6.0)*[a]	8.0 (3.5, 12.5)	*3.0 (1.0, 6.5)*[a]	*2.0 (1.0, 5.0)*[a]
Sleep efficiency, %	92.0 (84.0, 95.5)	92.0 (89.5, 96.0)	91.0 (84.5, 95.5)	91.0 (85.5, 95.0)	91.0 (84.5, 94.0)	93.0 (86.0, 95.0)
Average SpO_2, %	95.0 (94.5, 96.0)	96.0 (95.0, 97.0)	96.0 (94.5, 97.0)	95.0 (94.0, 96.0)	95.0 (93.5, 96.0)	94.0 (94.0, 96.5)
SBP, mmHg	130.0 (125.0, 150.0)	*125.0 (120.0, 135.0)*[b, e]	130.0 (120.0, 142.5)	130.0 (120.0, 141.0)	125.0 (122.5, 137.5)	125.0 (120.0, 139.0)
DBP, mmHg	90.0 (80.0, 95.0)	*80.0 (75.0, 90.0)*[a, f]	*80.0 (80.0, 90.0)*[b]	85.0 (80.0, 90.0)	85.0 (80.0, 90.0)	80.0 (80.0, 85.0)
Heart rate, bpm	68.0 (63.0, 78.0)	70.0 (66.5, 80.0)	72.0 (69.0, 80.0)	72.0 (62.0, 78.0)	70.0 (63.0, 80.0)	74.0 (67.0, 80.0)
ESS score[g]	9.0 (3.5, 12.8)	7.0 (5.0, 10.0)	7.0 (3.5, 10.0)	6.0 (4.0, 10.8)	4.5 (3.0, 7.0)	4.0 (2.0, 8.0)
FOSQ score[h]	18.9 (16.8, 19.5)	18.9 (17.0, 19.9)	19.0 (18.2, 19.7)	19.3 (16.9, 19.8)	18.5 (16.1, 19.6)	17.7 (16.9, 19.9)

Values are mean ± standard deviation or median (interquartile range). *P* values are adjusted for multiple comparisons by a Bonferroni correction
AHI apnea-hypopnea index, *AI* apnea index, *bpm* beats/min, *DBP* diastolic blood pressure, *ESS* Epworth Sleepiness Scale, *FOSQ* Functional Outcomes of Sleep Questionnaire, *OAT* oral appliance therapy,
ODI oxygen desaturation index, *SBP* systolic blood pressure, *SpO_2* oxygen saturation, *SPT* Sleep Position Trainer
a $P < 0.001$ vs baseline (Wilcoxin signed rank test), b $P < 0.01$ vs. baseline (Wilcoxin signed rank test), c $P < 0.05$ vs. baseline (Wilcoxin signed rank test), d $P < 0.001$ vs. OAT (Mann-Whitney *U* test), e $P < 0.05$ vs. OAT (Mann-Whitney *U* test), f $P < 0.01$ vs. OAT (Mann-Whitney *U* test), g Data available in 24, 27, 21 patients in the SPT group and 24, 24, 25 patients in the OAT group for baseline, 3 months, and 12 months, respectively, h Data available in 19, 19, 12 patients in the SPT group and 20, 18, 18 patients in the OAT group for baseline, 3 months, and 12 months, respectively

snoring was a reason for dropping out of the study (***Figure 3***). The most common SPT-specific adverse events were being woken by the vibration and no reaction to the vibration. In the OAT group, the most common device-specific events were tooth pain, temporomandibular dysfunction, and open bite. In patients treated with the SPT, no events necessitated a temporary discontinuation of device use. For the OAT group,

Table 3 - Objective adherence and device usage (per-protocol analysis)

	SPT (*n* = 29)	OAT (*n* = 28)	*P* value
Total nights	365.0 (362.5–365.0)	356.5 (275.8–373.5)	0.805[a]
Total nights with adherence > 4 h	237.6 ± 96.3	239.9 ± 96.1	0.930[b]
Average hours of use per night	5.2 ± 2.2	5.0 ± 2.0	0.743[b]
Adherence > 4 h on 7 days in a week, % patients	82.0 (47.0–90.5)	79.8 (59.7–97.4)	0.314[a]
Adherence > 4 h on 5 days in a week, % patients	100.0 (65.5–100.0)	97.0 (79.9–100.0)	0.598[a]

Values are mean ± standard deviation or median (interquartile range). One patient missing data in OAT group
OAT oral appliance therapy, *SPT* Sleep Position Trainer
a Mann-Whitney test, b Independent *T* test

Table 4 - Adverse events.

	Total	SPT	OAT
Number of subjects (%)	58 (100)	29 (100)	29 (100)
Reporting at least 1 AE (%)	48 (82.8)	20 (69.0)	28 (96.6)
Frequency of events (%)	114 (100)	37 (100)	77 (100)
Persistent snoring (%)	29 (25.4)	14 (37.8)	15 (19.5)
Persistent tiredness (%)	21 (18.4)	7 (18.9)	14 (18.2)
Persistent apneas (%)	1 (0.9)	1 (2.7)	0 (0.0)
Comfort problems (%)	7 (6.1)	5 (13.5)	2 (2.6)
Other (%)	4 (3.5)	2 (5.4)	2 (2.6)
OAT			
Tooth pain (%)	21 (18.4)		21 (27.3)
TMD (%)	9 (7.9)		9 (11.7)
Open bite (%)	7 (6.1)		7 (9.1)
Dry mouth (%)	4 (3.5)		4 (5.2)
Hypersalivation (%)	1 (0.9)		1 (1.3)
Dental fracture (%)	1 (0.9)		1 (1.3)
Oral lesions (%)	1 (1.3)		1 (1.3)
SPT			
Woken up by vibration (%)	4 (3.5)	4 (10.8)	
No reaction to vibration (%)	4 (3.5)	4 (10.8)	

AE adverse event, OAT oral appliance therapy, SPT sleep position trainer, TMD temporomandibular dysfunction

study treatment was temporarily discontinued as a result of six events in a total of five patients (17.2% of patients). The number of device- specific adverse events (vs. non-specific events) was higher in the OAT group (44 vs. 8 in the SPT group; $p<0.001$). No statistical difference was found in the duration (in days) of adverse events ($p=0.830$) between the groups.

DISCUSSION

The results of this study in patients with POSA showed that the beneficial effects of both the SPT and OAT observed at 3 months' persisted through 12 months of device use. The SPT improved sleep apnea to a similar extent as OAT and was associated with high adherence rates. This is the first long-term, randomized controlled trial comparing positional therapy using the SPT with OAT for the treatment of POSA. These findings are consistent with previous short-term data on the SPT [22,27] and confirm that benefits are maintained over a longer-term follow-up. It is important to assess OSA therapies over longer periods of time because many, including CPAP, show reduced adherence over time. When adherence is defined as device usage for > 4 h/night, 46–83% of CPAP users are nonadherent [12]. Objective data on use of OAT have shown that 83% of patients used the device regularly [28]. Adherence rates for OAT in our study were similar, and SPT device usage was also of a similar magnitude. In this study, SPT had similar long-term efficacy to OAT and was associated with consistently high levels of adherence over 12 months' follow-up, highlighting the potential clinical utility of the SPT in everyday practice.

Analysis of patients not allocated to treatment and those withdrawn from the study provides some insight into optimal patient selection and the challenges faced with each therapy. No significant difference between completers and dropouts was found in baseline characteristics (Table 1). Most dropouts in the OAT group were seen before the start of treatment. Dentition played an important role in the initiation to treatment, and prevented device use in 33% of OAT patients who did not start the allocated treatment. It has been reported that dental limitation might preclude the use of OAT in up to 34% of all OSA cases [29]. In our study, the rate of adverse events over the first year of therapy was higher in the OAT group than in the SPT group. However, more subjects discontinued use of the SPT due to AEs between the 3- and 12-month assessments (14 vs. 6 for OAT), although the number of completers was the same in both groups ($n=29$). Within the non-completers, the rate of persistent AHI was similar between groups as reason for dropout. Tooth pain was mentioned in the OAT group, while in the SPT group persistent snoring, joint problems, nasal problems, and broken ribs were reported as reason for dropout. Due to the mechanism of action of the SPT

device, AHI and continuous snoring in the lateral position are not decreased. Just as dentition may play a role in patient selection for OAT, high lateral AHI and/or lateral snoring may be factors that identify patients less suitable for the SPT. Knowledge of the advantages, disadvantages, and adverse effects with each therapy can help guide clinicians to proper individual therapy selection and follow-up regimes that maximize adherence and long-term outcomes.

Study limitations

The main limitation of this study was the slightly higher than expected observed drop-out rate at 3 months. We mitigated this by performing additional ITT analyses on the primary outcome, using the Last-Observation-Carried-Forward method. The relatively low number of patients at 12 months could also be raised as a concern; however, the 20% dropout rate was predicted for the 3-month assessment as the primary outcome, and therefore more dropout would have been expected at 12 months. Regardless, we have included a sensitivity analysis to demonstrate the robustness of our results to the high dropout rate at 3 and 12 months. The best and worst case scenarios demonstrate the maximum and minimum bounds for the treatment effects (respectively) under different missing mechanisms for the treatment and control groups. The best case scenario assumed a 50% decrease in AHI from baseline for patients with missing data in the SPT group compared to a 0% change in AHI from baseline for patients with missing data in the OAT group. The worst case scenario assumed a 0% change in AHI from baseline for patients with missing data in the SPT group compared to a 50% decrease in AHI from baseline for patients with missing data in the OAT group. The results from these analyses demonstrate the extremes that would be expected if the missingness in the SPT and OAT groups occurred for contrasting reasons (***Table S3***).

Conclusion

The results of this study show that the efficacy of SPT was maintained over 12 months of therapy, and was comparable to that of OAT in patients with mild to moderate POSA. Adherence to both treatment modalities was high, and similar in the two groups. Good long-term adherence can make an important contribution to the ongoing effectiveness of treatment in clinical practice.

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Supplementary material

Table S1. Primary and secondary outcome variables (Intention-to-treat analysis)

	SPT (n=48)			OAT (n=51)		
	Baseline	**3 months**	**12 months**	**Baseline**	**3 months**	**12 months**
Primary outcome						
Total AHI, /h	13.0 (9.7,18.5)	**7.0 (3.8,12.8)**[a]	**8.0 (5.1,12.9)**[a]	11.7 (9.0,16.2)	**9.1 (4.9,11.7)**[a]	**8.5 (4.8,11.7)**[a]
ODI, /h	10.5 (7.0,15.8)	**5.5 (3.0,10.0)**[a]	**7.0 (4.0,13.0)**[a]	9.0 (6.0,14.0)	**7.0 (4.0,10.0)**[b]	7.0 (4.0,11.0)
Secondary outcomes						
Supine AHI, /h	27.0 (18.7,43.0)	**12.4 (0.4,32.8)**[a]	**14.1 (1.8,30.0)**[a]	25.8 (17.4,35.0)	**18.9 (9.1,27.0)**[a]	**16.8 (7.6,26.6)**[a]
Non-supine AHI, /h	3.5 (1.6,5.7)	4.4 (1.8,8.5)	3.5 (1.7,6.3)	3.1 (1.0,5.0)	1.9 (0.9,4.1)	2.5 (0.7,4.1)
Supine sleep, %	44.5 (30.0,55.5)	**11.5 (1.3,24.5)**[a,e]	**22.5 (5.0,42.8)**[a,e]	41.5±18.8	40.9±23.0	42.4±20.4
AI, /h	9.0 (5.0,15.0)	**4.0 (1.0,9.3)**[a]	**4.0 (2.0,7.8)**[a]	8.0 (4.0,12.0)	**3.0 (1.0,8.0)**[a]	**4.0 (2.0,8.0)**[a]
Sleep efficiency, %	92.0 (84.5,95.0)	91.0 (86.0,95.0)	91.0 (86.0,95.0)	92.0 (86.0,95.0)	92.0 (85.0,96.0)	93.0 (87.0,96.0)
Average SpO_2, %	95.0 (94.0,96.8)	96.0 (95.0,96.8)	95.5 (94.0,97.0)	95.0 (94.0,96.0)	95.0 (94.0,96.0)	95.0 (94.0,96.0)
SBP, mmHg	133.5 (125.0,150.0)	**130.0 (120.0,140.0)**[b,g]	130.0 (120.0,150.0)	130.0 (120.0,140.0)	125.0 (120.0,135.0)	128.0 (120.0,138.0)
DBP, mmHg	90.0 (80.0,97.5)	**85.0 (75.0,90.0)**[b]	**82.5 (80.0,97.3)**[c]	85.0 (80.0,90.0)	85.0 (80.0,90.0)	80.0 (80.0,86.0)
Heart rate, bpm	69.0 (64.0,78.0)	72.0 (64.3,80.0)	72.0 (65.0,80.0)	72.0 (66.0,80.0)	72.0 (67.0,80.0)	72.0 (67.0,82.0)
ESS score*	7.5 (4.0,12.0)	7.0 (5.0,10.0)	6.0 (3.8,10.0)	8.0 (4.0,13.0)	7.0 (3.0,12.0)	8.0 (3.0,12.5)
FOSQ score**	19.0 (17.3,19.7)	19.3 (16.9,19.8)	19.3 (17.2,19.7)	18.4 (16.2,19.7)	18.3 (16.2,19.5)	18.3 (16.3,19.6)

Values are mean ± standard deviation or median (interquartile range)

AHI apnea-hypopnea index, *AI* apnea index, *bpm* beats/min, *DBP* diastolic blood pressure, *ESS* Epworth Sleepiness Scale, *FOSQ* Functional Outcomes of Sleep Questionnaire, *OAT* oral appliance therapy, *ODI* oxygen desaturation index, *SBP* systolic blood pressure, *SpO_2* oxygen saturation, *SPT* Sleep Position Trainer

Missing data during follow-up coded as no-change.

*Data available in 42 patients in the SPT group and 45 patients in the OAT group

**Data available in 33 patients in the SPT group and 40 patients in the OAT group

P-values are adjusted for multiple comparisons by a Bonferroni correction. [a]p<0.001 vs baseline (Wilcoxin signed rank test); [b]p<0.01 vs baseline (Wilcoxin signed rank test); [c]p<0.05 vs baseline (Wilcoxin signed rank test); [d]p<0.05 for 12-month vs 3-month value; [e]p<0.001 vs OAT (Mann-Whitney U test); [f]p<0.01 vs OAT (Mann-Whitney U test); [g]p<0.05 vs OAT (Mann-Whitney U test)

Table S2. Objective adherence and device usage (Intention-to-treat analysis)

	SPT (n=48)	OAT (n=51)	P-value[a]
Total nights	252.7±139.5	195.5±158.2	0.059
Total nights with adherence >4h	163.5±121.8	143.1±135.9	0.433
Average hours of use per night	3.1±3.1	2.7±2.9	0.522
Adherence >4h on 7 days in a week, % patients	57.4±34.6	47.8±40.9	0.208
Adherence >4h on 5 days in a week, % patients	68.9±37.7	54.5±44.5	0.086

Values are mean ± standard deviation
OAT oral appliance therapy, *SPT* Sleep Position Trainer
[a]Independent T-test

Table S3. Sensitivity Analysis (Intention-to-treat analysis)

	SPT (n=48)				OAT (n=51)			
	Baseline	Δ Baseline to 3 months	Δ Baseline to 12 months	Δ 3 to 12 months	Baseline	Δ Baseline to 3 months	Δ Baseline to 12 months	Δ 3 to 12 months
Best case scenario								
Total AHI, /h	13.0 (9.7,18.5)	**-5.5 (-9.7,-1.5)[a]**	**-6.4 (-10.4,-3.1)[a,e]**	**-3.0 (-6.9,1.7)[b]**	11.7 (9.0,16.2)	**-2.8 (-7.3,0.0)[a]**	**0.0 (-7.9,0.0)[a]**	0.0 (-1.1,0.7)
Worst case scenario								
Total AHI, /h	13.0 (9.7,18.5)	**-5.2 (-9.7,-1.1)[a]**	**-1.0 (-8.8,0.0)[a]**	**0.0 (-0.9,1.7)[e]**	11.7 (9.0,16.2)	**-5.2 (-7.6,-3.2)[a]**	**-5.5 (-9.2,-3.3)[a]**	**-4.3 (-5.9,0.7)[a]**

Values are mean ± standard deviation or median (interquartile range)
Δ change, *AHI* apnea-hypopnea index, *OAT* oral appliance therapy, *SPT* Sleep Position Trainer
P-values are adjusted for multiple comparisons by a Bonferroni correction. [a]p<0.001 vs baseline (Wilcoxin signed rank test); [b]p<0.01 vs baseline (Wilcoxin signed rank test); [c]p<0.05 vs baseline (Wilcoxin signed rank test); [d]p<0.05 for 12-month vs 3-month value; [e]p<0.001 vs OAT (Mann-Whitney U test); [f]p<0.01 vs OAT (Mann-Whitney U test); [g]p<0.05 vs OAT (Mann-Whitney U test)

7

Positional therapy in patients with residual positional obstructive sleep apnea after upper airway surgery

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ABSTRACT

Purpose/background

A considerable portion of patients has residual positional obstructive sleep apnea (POSA) after upper airway surgery. Those patients could benefit from additional treatment with positional therapy (PT). The objective of this prospective study was to assess the additional effect of PT in patients with residual POSA after upper airway surgery for sleep apnea.

Methods

A polysomnography (PSG) was used to diagnose a patient with residual POSA after surgery. After informed consent, patients were treated with PT for 3 months and underwent a follow-up PSG while using the sleep position trainer (SPT). Changes in apnea-hypopnea index (AHI) and sleep position parameters were analyzed. Compliance rates and mean disease alleviation (MDA) were determined.

Results

Thirty-three patients with a median postoperative AHI of 18.3/h sleep were included. With the SPT median AHI dropped to 12.5/h sleep and the Epworth Sleepiness Scale (ESS) improved from 10.0 to 7.0. After 3 months, 37.5% patients were considered responders of whom 31.3% had treatment success. The compliance rate with SPT was 89.0%. MDA was 44.7% for SPT alone. With the combination of both surgery and SPT, MDA was 65.6%.

Conclusions

The results of this study indicate that additional PT in a complex OSA patient population with residual POSA after surgery can increase overall therapeutic effectiveness by improving the median MDA from 39.5% (effect of surgery alone) to 65.6% (effect of combining surgery and PT).

INTRODUCTION

OSA is characterized by recurrent episodes of partial or complete collapse of the upper airway during sleep, leading to decreased oxygen blood levels and microarousals. This results in fragmented sleep accompanied by symptoms such as snoring, observed apneas and excessive daytime sleepiness [1].

The obstruction in the upper airway is caused by muscle relaxation and is aggravated by the influence of gravity. It is hypothesized that in patients who snore but initially do not suffer from OSA, apneas start occurring in the supine position, since gravity can then exert its maximal effect [2]. When left untreated, apneas will eventually develop in all sleeping positions as severity increases. In line with this assumption, it is reported that a considerable number of patients with mild and moderate OSA have a higher apnea-hypopnea index (AHI) in supine sleeping position [3]. Several studies reported a prevalence of position dependency of approximately 56% in patients with mild OSA. Patients with severe OSA often have a high AHI in all sleep positions [4–6]. Positional OSA (POSA) is diagnosed when the AHI is at least twice as high in supine position compared to the non-supine sleeping position [4].

Since various therapeutic options for patients with POSA have been presented over the last years, measurement of sleep posture is one of the key parameters during a sleep registration. Besides conservative measures (e.g., weight reduction, abstinence from alcohol, smoking, and sedatives), promising results of positional therapy (PT) with new devices have recently been shown [7]. The sleep position trainer (SPT) is a chest-worn device that gives a subtle stimulus when supine sleeping position is detected. Studies suggest that the SPT successfully prevents patients from sleeping in supine position without disrupting their sleep and hereby improves sleep- related quality of life parameters with a reported long-term compliance of 64.4% [8].

In patients with moderate and severe OSA, continuous positive airway pressure (CPAP) is still regarded as gold standard treatment, but its compliance is often disappointing [9,10]. Oral appliance therapy (OAT) is an alternative treatment modality for patients with mild or moderate OSA. The therapy is generally well tolerated but one third of the patients experience no therapeutic benefit [11]. Some of the non-responders have a high residual AHI in supine position [12]. Surgery is a treatment option for well-selected patients when noninvasive treatments such as CPAP or OAT have been unsuccessful. A wide variety of interventions is available, both minimally invasive as well as more invasive such as tonsillectomy (TE), uvulopalatopharyngoplasty (UPPP), Z-palatoplasty (ZPP), hyoid suspension (HS), tongue base surgery, and upper airway stimulation [13–19]. In selected patients with severe OSA, maxillomandibular advancement (MMA) can be indicated, both as primary surgery and in case of treatment failure [20–22].

A recent study from Dieltjens et al. showed that 34% of patients treated with OAT still has residual POSA while using oral appliances [12]. In another study, they showed that a combined therapeutic strategy of both OAT and PT with the SPT resulted in a higher therapeutic efficacy than treatment with OAT or PT alone [12].

Similarly to residual POSA under OA therapy, we observed that a number of patients who had undergone upper airway surgery for OSA had residual disease, mainly in supine position, i.e., the AHI in supine sleeping position remained high, whereas the AHI in other sleeping positions had improved considerably. A retrospective analysis by Van Maanen et al. showed that UPPP/ZPP with or without radiofrequency thermotherapy of the tongue base (RFTB) significantly reduced AHI, but the reduction was significantly higher in non-positional OSA than in POSA patients [23].

The effectiveness of combining different treatments for OSA has been little investigated. Since the effect of combining OSA surgery and PT still needs to be determined, the purpose of this prospective study was to assess the efficacy of additional PT with the SPT in patients with residual POSA after upper airway surgery for OSA.

METHODS

Study design

We performed a prospective study, approved by the institution's ethical committee. The first patient was included in January 2014 and the last follow-up polysomnography (PSG) was performed in April 2015. After signing an informed consent form, patients received the SPT (NightBalance B.V., Delft, NL) and filled out the Epworth Sleepiness Scale (ESS) and the Functional Outcomes of Sleep Questionnaire (FOSQ) to assess their daytime sleepiness and quality of life [24,25]. After 3 months of therapy, a follow-up PSG was performed while the patients used their SPT, and the patients filled out the questionnaires again.

Patients

Patients were recruited from the department of Otolaryngology, Head and Neck surgery of the OLVG West Hospital in Amsterdam, The Netherlands. All patients already had undergone (any combination of) surgical treatment for OSA or POSA, i.e., RFTB, TE, UPPP/ZPP, HS, or MMA.

Either after referral from another clinic because of persistent OSA, or as part of regular follow-up, a PSG was performed. Patients were asked to participate in this study when they met the following inclusion criteria: (1) age of 18 years or older, (2) previous upper airway surgery as treatment for POSA/OSA, (3) POSA at baseline PSG after surgery, (4) the percentage of total sleep time in supine position was between 10

and 90%, and (5) ability to use the necessary SPT computer software. Main exclusion criteria were as follows: (1) shoulder or neck complaints, (2) working in changing or night shifts, (3) epilepsy, (4) simultaneous use of other treatment modalities for OSA, (5) other sleep-related disorders (i.e., severe restless leg syndrome).

Polysomnography

A PSG was performed during an overnight stay in the hospital, using a digital PSG system (Embla A10, Broomfield, CO, USA). This system recorded an electroencephalogram (EEG) (FP2-C4/C4-O2), electro-oculogram (EOG), electrocardiogram (ECG), and a submental and anterior tibial electromyogram (EMG). Nasal airflow was measured by a pressure sensor in a nasal cannula and blood oxygen saturation was measured by finger pulse oximetry. Straps containing piezoelectric transducers recorded thoracoabdominal motion and a position sensor (Sleepsense, St Charles, IL, USA) attached to the midline of the abdominal wall was used to differentiate between supine, prone, right lateral, left lateral, and upright positions. The recorded data were analyzed using special software (*Somnologica*™, Broomfield, USA) and manually checked and scored by an employee of the clinical neurophysiology department of the OLVG West hospital Amsterdam.

Definitions

The sleep stages were scored manually in 30-s epochs according to American Academy of Sleep Medicine (AASM) criteria [1]. An apnea was defined as the cessation of nasal airflow of more than 90% for a period of 10 s or longer in the presence of respiratory efforts. In accordance with the prevailing definition at that time, a hypopnea was scored whenever there was a greater than 30% reduced oronasal airflow for at least 10s, accompanied by ≥ 4% oxygen desaturation from pre-event baseline. The AHI is defined as the mean number of apneas and hypopneas per hour during sleep. Oxygen desaturation index (ODI) was defined as the number of times per hour of sleep that the blood oxygen level drops by 4% or more from baseline. POSA was diagnosed when the AHI in supine position was at least twice as high as in the non-supine position, and the percentage of total sleeping time in supine position was between 10 and 90. Similarly to the compliance definition used in CPAP, a patient was declared compliant to the SPT if the mean daily use of the SPT was ≥ 4 h per night, during ≥ 5 days per week [9]. Treatment response to SPT therapy was defined as a reduction in overall AHI of more than 50% from baseline, whereas treatment success was defined as a reduction in overall AHI of more than 50% from baseline combined with an AHI < 5/h [26]. The concept of calculating the mean disease alleviation (MDA) was introduced by Vanderveken et al. It reflects the overall therapeutic effectiveness of OSA therapy by measuring the efficacy of the therapy combined with the compliance. The MDA (%) is calculated by the product of the compliance, adjusted for total sleep time (TST) (i.e., adjusted compliances)

(*X*-axis), combined with therapeutic efficacy (*Y*-axis), divided by 100 [26]. One should be aware of the fact that if the SPT has been switched on but the patient is still awake, the calculation will show that SPT usage will be longer than the TST. This could result in an adjusted compliance >100% in fully compliant users. Average usage of the SPT per patient per night is calculated by the sum of total therapy time with a cutoff point of 9 h maximum per night, to overcome data errors (e.g., patient who forgot to turn/switch off their device) divided by the total nights slept with the SPT.

Sleep position trainer (SPT)

The SPT is a small device (72 × 35 × 10 mm; 25 g) that has to be worn across the chest using a neoprene torso strap and can vibrate in order to urge a patient to change body position (***Figure 1***). The device uses a three-dimensional digital accelerometer to determine the body position. Treatment is divided into three phases. During the first two nights, the SPT analyses body position without giving active feedback to the patient. Then, during the following seven nights, the SPT gradually trains the patient by vibrating in an increasing percentage of episodes of supine sleeping position. Depending on reaction time, the vibration will be adapted automatically in strength, pattern, and duration, until body position will be changed. If the patient does not change position after the stimulus, the SPT will vibrate again after 2 min. At day 10, the so-called therapy phase begins, in which the SPT will vibrate every time the patient is in supine sleeping position, to urge the patient to change his or her sleeping position. The SPT has a USB port to recharge the internal battery and to upload data to an online self-monitoring system, which can also be accessed by the patient's physician.

Figure 1. The Sleep position trainer (SPT)
The SPT is a small, lightweight device (72 x 35 x 10 mm; 25 g) that is worn across the chest using a neoprene torso strap.

Statistical analysis

For analyses we used descriptive statistics and inferential statistics. All data were first tested for normality by a Kolmogorov-Smirnov test, a Q-Q plot, and Levene's test. Categorical variables were expressed as *n* (%).

Continuous normally distributed variables were expressed by their mean and standard deviation (SD), not normally distributed data by their median and interquartile range (IQR) for skewed distributions. To test groups, categorical variables were tested using the Pearson's chi-square test or Fisher's exact test, when appropriate. Normally distributed continuous data were tested with the independent samples Students *t* test and in case of skewed data, with the independent samples Mann-Whitney *U* test. Predictors were evaluated through univariate and multivariable logistic regression analysis. All independent variables counting more than ten events and showing *p* values <0.1 were eligible for multivariable analysis, which was achieved through backward selection. The optimal prediction model was evaluated with -2Log likelihood. Significance level for baseline variables and multivariable regression analysis was set at *p* value <0.05. Statistical analysis was performed using SPSS Statistical software (version 21.0, SPSS Inc., Chicago, IL).

RESULTS

A group of 33 patients (mean age 52.3 ± 9.7 years; mean body mass index (BMI) 27.9 ± 2.8 kg/m2; male to female = 28:5) met the inclusion criteria and were enrolled in this study. One patient withdrew, because he opted for alternative therapy. Patient demographics are shown in ***Table 1***.

Table 1 - Patient characteristics at baseline inclusion and after 3 months of SPT therapy

	Baseline	+ SPT
	N = 33	*N* = 32
Characteristics	Mean ± SD	Mean ± SD
Age, years	52.3 ± 9.7	
Gender, male no. (%)	28 (84.8)	
BMI, kg/m^2	27.9 ± 2.8	27.9 ± 2.6
Neck circumference, cm	39.6 ± 2.7	39.5 ± 2.7
Smoking, no. (%)	8 (24.2)	7 (21.2)
Alcohol, no. (%)		
<2 EH/day	26 (78.8)	26 (78.8)
2 EH/day	3 (12.1)	3 (9.1)
>2 EH/day	4 (9.1)	3 (9.1)

Pre-surgical evaluation

CPAP failure was noted in 76% of the included patients (*n*=25) and 48.5% (*n*=16) of the patients were failures of OAT prior to enrollment in this study. Some patients had upper airway surgery as first choice treatment. In ***Table 2*** an overview is given of the different surgical procedures that have been performed before the patients started with the SPT.

Table 2 - Sleep parameters before upper airway surgery for OSA and an overview of the surgeries performed

N=33	**Median [IQR]**
AHI, /h*	28.5 [18.0-52.8]
AHI supine, /h*	54.9 [29.0-73.0]
AHI *non*-supine, /h**	25.5 [8.9-49.1]
Percentage supine sleep, %**	49.0 [14.1-64.8]
Surgery	**Percentage, % (frequency, n)**
UPPP/ZPP	30.3 (10)
UPPP/ZPP + RFTB	27.3 (9)
UPPP/ZPP + RFTB + HS	18.2 (6)
MMA	21.2 (7)
TE	3.0 (1)

IQR interquartile range, *AHI* apneu-hypopnea index, *UPPP* uvulopalatopharyngoplasty, *ZPP* Z-palatopharyngoplasty, *RFTB* radio- frequency thermotherapy of the tongue base, *HS* hyoid suspension,
MMA maxillomandibular advancement, *TE* tonsillectomy
a missing data *n* = 6,
b missing data *n* = 8

Polysomnographic results

PSG data of the pre-surgical evaluation showed a median AHI of 28.5/h sleep [18.0–52.8]. Six patients were missing in this analysis since the PSG was performed in the center of referral elsewhere and data could not be retrieved. After surgery, median AHI dropped with 35.8% to 18.3/h sleep [13.7–24.0]. Additionally, the median AHI significantly dropped further to 12.5/h sleep [4.5–21.8] after 3 months of treatment with the SPT (*p*=0.034). All PSG parameters are shown in ***Table 3***. AI, AHI, ODI, and percentage supine sleep all decreased significantly. The severity of daytime sleepiness scored with the ESS improved significantly from 10.0 [5.5–15.0] to 7.0 [5.0– 12.0], *p*=0.029. Treatment response was noted in 37.5% of the patients (*n*=12) and 20 patients were considered non- responders. From this last group an increase in AHI with the SPT was seen in seven patients (21.7%). Treatment success was observed in 31.3% (*n*=10). There was no significant difference between the type of surgery performed (uni- or multilevel or MMA) in relation to treatment response. Clinical and polysomnographical characteristics between responders and non-responders are presented in Table 4. In

the responder group, the AHI, AI, ODI, supine AHI, percentage supine sleep, percentage non-supine sleep, the arousal index, and the minimum saturation all significantly improved. In the non-responder group, a significant improvement was seen in percentage supine sleep, AHI non-supine, and the minimum saturation. Comparison of responders and non-responders showed that responders had a significantly lower AHI (p<0.001), AI (p<0.001), supine AHI (p=0.015), non-supine AHI (p=0.001), ODI (p=0.021), arousal index (p=0.009), and ESS score (p=0.043). Time spent in the different sleep stages did not change significantly for both groups.

Table 3 - Comparison of sleep parameters between baseline inclusion and SPT. First and third quartiles (Q1;Q3)

Characteristics	Baseline Median [IQR]	With SPT Median [IQR]	Wilcoxon signed ranks *p* value
	N = 33	*N* = 32	
Total AHI, /h	18.3 [13.7-24.0]	12.5 [4.5-21.8]	*0.034*
Apnea index, /h	13.4 [6.3-18.9]	7.0 [1.6-18.7]	0.051
Obstructive	5.8 [3.0-13.4]	1.9 [0.4-12.6]	*0.030*
Central	0.4 [0.1-1.8]	0.4 [0.0-1.3]	0.204
Mixed	3.2 [0.7-7.2]	1.0 [0.0-2.2]	*0.009*
Total AHI supine, /h	43.0 [24.2-59.6]	32.4 [14.2-66.2]	*0.023*
Total AHI non-supine, /h	4.8 [2.3-8.6]	7.9 [3.3-16.3]	*0.002*
Percentage supine sleep, %	40.1 [32.0-50.0]	7.4 [0.1-17.8]	*<0.001*
Average SaO_2, %	95.0 [94.0-96.0]	95.0 [94.3-96.0]	0.434
Min. SaO_2, %	85.5 [82.3-87.0]	88.0 [86.0-90.0]	*<0.001*
ODI, /h	21.0 [14.7-29.2]	12.9 [5.5-23.3]	*0.011*
Total sleep time, hours	7.2 [6.3-7.8]	6.8 [6.1-8.0]	0.638
Sleep efficiency, %	90.8 [80.8-94.9]	89.5 [85.3-94.0]	0.896
N1 sleep/total sleep time, %	6.9 [3.9-12.4]	6.7 [3.8-12.3]	0.597
N2 sleep/total sleep time, %	50.6 [45.3-58.2]	52.8 [43.3-61.0]	0.556
N3 sleep/total sleep time, %	18.8 [11.0-24.8]	18.7 [13.9-27.4]	0.178
REM sleep/total sleep time, %	20.1 [15.8-24.4]	20.1 [16.0-24.6]	0.525
Positional change index, changes/h	.6 [1.7-3.8]	2.7 [1.6-4.4]	0.530
Questionnaires			
ESS score	10.0 [5.5-15.0]	7.0 [5.0-12.0][a]	*0.029*
FOSQ score	15.8 [10.5-17.0]	16.0 [10.8-18.2][a]	0.616

a *n* = 31

SPT compliance and mean disease alleviation (MDA)

The compliance rate (i.e., ≥4 h per night and ≥5 days of usage per week) with the SPT was 89.0%. Average use per patient per night when the SPT was worn was 6.92 ± 0.75

Table 4 - Comparison of sleep parameters between responders and non-responders of SPT

Characteristics	Responders *N* = 12			Non-responders *N* = 20			
	T = 0	*T* = 3	*p* value*	*T* = 0	*T* = 3	*p* value*	*p* value**
Age, yrs.	52.5 [50.0-60.0]		0.799	51.5 [46.0-57.8]			
Male:female BMI, kg/m^2	9:3 27.6 [24.7-28.6]	27.3 [24.8-29.1]	0.799	18:2 27.7 [26.2-29.1]	28.0 [26.6-30.5]	0.062	0.136
Neck circumference, cm	39.0 [36.3-40.8]	38.0 [37.0-40.8]	0.317	40.0 [39.3-42.0]	41.0 [39.0-42.0]	0.611	0.076
Total AHI, /h	16.8 [11.6-24.0]	3.9 [1.9-7.3]	*0.002*	20.1 [14.9-24.1]	18.8 [12.1-32.7]	0.940	*<0.001*
Apnea index, /h	12.0 [7.1-19.9]	1.7 [0.3-5.3]	*0.002*	14.1 [7.4-18.6]	14.3 [5.4-27.6]	0.779	*<0.001*
Obstructive	6.0 [2.5-11.4]	0.4 [0.1-2.2]	*0.002*	7.1 [3.4-14.4]	8.3 [1.0-17.2]	0.765	*0.001*
Central	0.9 [0.1-2.7]	0.2 [0.0-1.0]	*0.025*	0.3 [0.0-1.3]	0.5 [0.0-1.8]	0.965	0.307
Mixed	3.2 [0.6-8.3]	0.3 [0.0-1.9]	*0.021*	3.5 [1.0-7.2]	1.1 [0.1-5.6]	0.126	0.366
Total AHI supine, /h	30.9 [20.8-42.4]	4.6 [1.5-29.9]	*0.043*	51.4 [29.8-65.9]	48.9 [22.5-68.4]	0.234	*0.015*
Total AHI non-supine, /h	4.1 [1.3-7.5]	3.3 [1.6-7.2]	0.155	6.4 [2.4-9.4]	13.3 [5.6-31.5]	*0.000*	*0.001*
Percentage supine sleep, %	43.4 [38.0-65.0]	0.2 [0.0-14.1]	*0.002*	37.1 [19.6-48.5]	11.3 [2.1-19.7]	*0.000*	0.070
Average SaO_2, %	94.5 [93.0-96.0]	95.0 [94.0-95.8]	0.196	95.0 [94.3-96.0]	95.0 [95.0-96.0]	0.813	0.431
Min. SaO_2, %	86.0 [82.0-88.0]	89.0 [85.0-90.0]	*0.014*	85.0 [82.3-87.0]	87.5 [86.0-89.8]	0.002	0.632
ODI, /h	18.7 [13.7-30.0]	7.1 [4.3-11.7]	*0.041*	22.3 [17.0-29.2]	17.4 [7.9-29.0]	0.113	*0.021*
Total sleep time, minutes	443 [416-484]	471 [410-514]	0.388	424 [370-471]	388 [368-456]	0.227	*0.044*
Sleep efficiency, %	91.2 [88.5-96.3]	89.9 [86.3-92.4]	0.480	89.0 [77.8-93.9]	89.3 [81.4-94.6]	0.538	1.000
N1 sleep/total sleep time, %	7.4 [3.9-13.3]	7.8 [3.4-12.2]	0.784	7.1 [3.9-11.9]	6.7 [3.8-12.7]	0.601	0.954
N2 sleep/total sleep time, %	48.4 [45.2-57.4]	47.4 [42.8-55.9]	0.158	51.8 [44.8-58.4]	55.5 [47.0-62.0]	0.867	0.146
N3 sleep/total sleep time, %	18.6 [12.6-22.9]	23.1 [13.9-27.6]	0.272	19.1 [9.1-25.8]	17.3 [13.9-25.8]	0.332	0.552
REM sleep/total sleep time, %	20.1 [16.4-24.5]	23.9 [17.5-26.8]	0.433	20.0 [14.1-25.0]	19.5 [13.7-22.2]	0.185	0.146
Positional change index, changes/h	2.1 [1.6-3.8]	2.5 [1.5-4.0]	0.814	2.9 [2.0-4.7]	2.7 [1.7-4.7]	0.573	0.366
Arousal index, /h	9.8 [7.7-13.1]	4.2 [3.3-9.3]	*0.008*	7.7 [3.9-13.0]	11.1 [5.8-14.5]	0.179	*0.009*
ESS score	11.0 [3.8-15.0]	5.0 [4.0-7.8]	0.056	10.0 [6.75-14.5]	9.0 [6.0-12.0]	0.213	*0.043*
FOSQ score	15.5 [10.0-16.9]	16.7 [12.4-18.5]	0.374	10.2 [16.1-17.3]	15.8 [9.8-18.2]	0.831	0.509

Median [IQR] *Wilcoxon signed rank; **Mann-Whitney *U* test with/after SPT

h. Median percentage of sleep time in supine position with the SPT was 7.4% [0.1–17.8]. ***Figure 2*** additionally shows the median percentage supine sleep per night from the total group. The median MDA for surgery alone was 39.5% [4.6–55.1], which consists of an adjusted median compliance of 100% (all patients had the operation and were therefore adherent) and a median efficacy of 39.5%.

The adjusted median compliance after 3 months of SPT therapy was 107.5% [95.9–116.8] (with a maximum of 9 h usage). Median therapeutic efficacy was 31.0% [7.0–65.9], which led to an objective MDA with the SPT therapy of 41.3% [10.4–70.9]. Combining the effectiveness of surgery with the SPT results led to an overall MDA (from pre-surgical evaluation until *T*=3 months) of 65.6% [28.2–87.6], as depicted in ***Figure 3***.

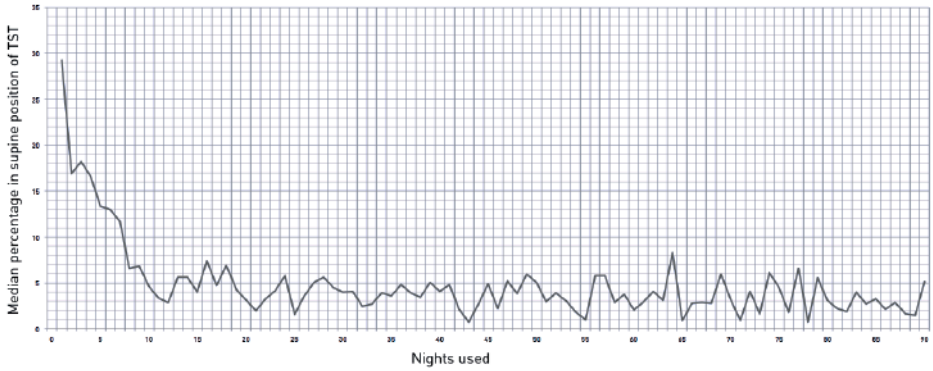

Figure 2. Median percentage of sleep time in the supine position per night
The first 9 days of the SPT therapy are part of the training program in which the SPT gradually decreases the number of times in which patients can sleep on their backs

DISCUSSION

The present study is the first to our knowledge to report on additional treatment with positional therapy in patients with residual POSA after partial effective upper airway surgery. Patients with good response to upper airway surgery were obviously not eligible for this study. The results demonstrate a positive effect of additional treatment with the SPT in about one third of the patients within this cohort. The overall treatment response was 37.5% and the compliance rate with PT was 89.0%. Effectiveness of the SPT has been previously evaluated by Van Maanen et al. [7]. They showed a significant reduction in median AHI (from 16.4 to 5.2/h sleep) after 1 month of therapy, with a compliance rate (>4h per day during 7 days per week) of 92.9%. The same authors reported on the long-term efficacy and compliance in a multicenter study, in which patients used the SPT for 6 months. Compliance (>4h per day during 7 days per week) was 64.4% [8]. Combination therapy of SPT and OAT was reported by Dieltjens et al.

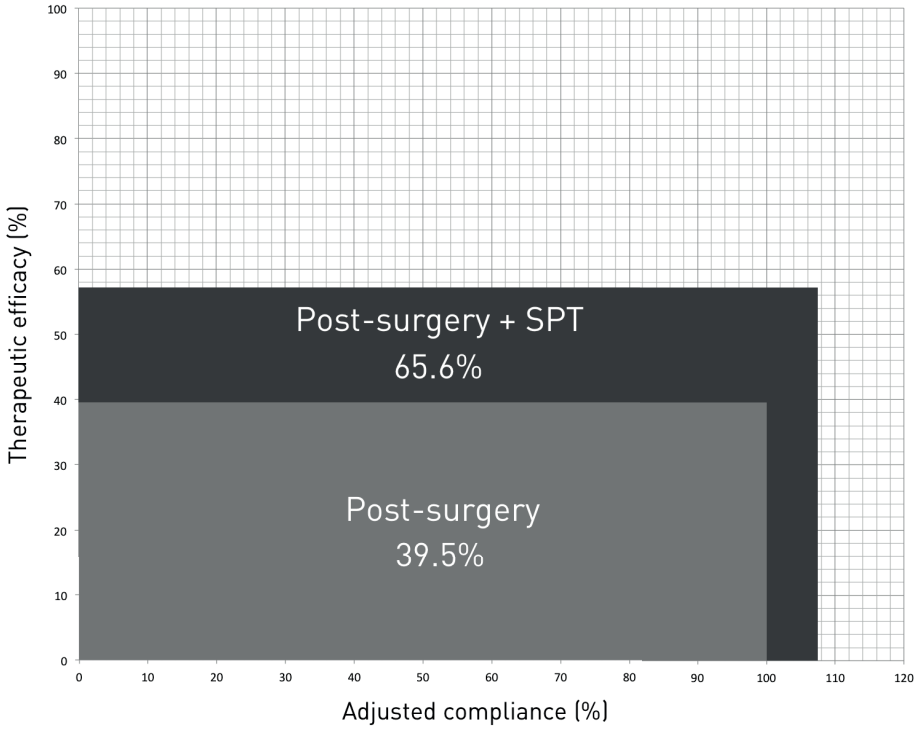

Figure 3. The mean disease alleviation (MDA)
MDA is calculated by the adjusted compliance (objective use/TST) in % + therapeutic efficacy (AHI baseline-AHI with therapy) in % / 100

[12] They demonstrated that both therapies individually reduced the overall AHI, but with the combination of both the AHI was significantly lower than with monotherapy of each modality.

Despite the high compliance rate during this study period, the number of responders was lower than we had expected beforehand. We can conclude that more research is required to identify predictors of non-responsiveness to therapy, especially since our patient population involved complex cases and the design was a non-controlled selected cohort. Most patients were already failures of other OSA therapy. CPAP was already tried in 76% of the patients, 48.5% underwent OAT, and all patients had some type of upper airway surgery (mono- or multilevel) before they were included in this study. It is well-known that the prevalence of multilevel collapse increases with increasing severity of OSA, postoperative drug-induced sleep endoscopy (DISE) could have been performed to gain more detailed information on site(s), configuration, and severity of the upper airway collapse [27]. Another reason for the limited response might be due to involvement of head position, since percentage of supine TST significantly decreased in

both groups, but the AHI remained high in non-responders. This suggests that the trunk position might be lateral (due to an effective response on the SPT) but the head possibly remained in supine position.

Sleep position and surgical outcome

The AHI in mild and moderate OSA patients is usually higher in the supine sleeping position when compared to other sleeping positions, due to the effect of gravity. In some cases, surgery will only have a partial treatment effect and it appears that those patients can have residual apneic events in only the supine sleep position. In addition, some studies found that surgical success was inversely related to the AHI: the higher the AHI preoperatively, the lower the success rate [17,28–32]. The influence of gravity (i.e., sleep position) has, therefore, impact on the surgical outcome. Within our cohort, the median AHI was reduced with surgery from 28.5 [18.0–52.8] to 18.3 [13.7–24.0], which means that moderate and severe OSA reversed into mild and moderate POSA patients before they were included in the study.

In general, there is a wide dispersion in success rates of surgery, depending not only on the applied surgical technique but also on variables such as baseline AHI and BMI; level, severity, and configuration of obstruction assessed during DISE; and on the definition of success used [16,17,28,32]. Besides the aforementioned parameters, we believe that sleep position is equally important in the evaluation of success rates, and indeed, some studies have evaluated the influence of sleep position after upper airway surgery for OSA. Katsantonis et al. found a significant improvement of the AHI in lateral sleep position following UPPP and suggested that additional PT could significantly improve response to treatment with UPPP [33].

A retrospective analysis by Lee et al. also evaluated the effect of sleep position on surgical outcome and found that patients with treatment failure were more often POSA patients compared to the other groups and that fluctuation of sleep position in each polysomnography might confound the surgical outcome [34]. A second paper from the same group indicated that UPPP is a successful treatment for obstructive events occurring in the lateral sleep position, especially in patients without positional dependency [35].

Van Maanen et al. showed that in patients who previously underwent UPPP/ZPP +/− RFTB, the reduction in AHI was significantly higher in non-positional OSA patients compared to POSA patients [23]. They suggest to apply PT after surgery or even to start with PT as a monotherapy prior to surgery. Furthermore, they concluded that the effect of UPPP is most successful in decreasing the AHI in the lateral sleep position. Additional PT postoperatively could potentially improve treatment outcome.

Li et al. analyzed a series of patients treated with relocation pharyngoplasty. They showed that the AHI significantly decreased in both positional and non-positional pa-

tients. They also noted that non-positional patients frequently became positional following the operation and suggested the latter could additionally benefit from positional therapy which is in line with the results of our study [10,36].

Compliance and MDA

Even the most efficient therapy is only effective when it is used appropriately, and therefore, objective compliance and efficacy need to be taken into account when evaluating therapeutic effectiveness [37]. Previous studies have reported on the compliance of OAT and CPAP therapy. It is well-known that CPAP therapy is highly effective but compliance is often poor, in contrast with OAT therapy which has higher adherence rates but is less effective in reducing the AHI [10]. Dieltjens et al. showed that the objective MDA for OAT after a 1-year follow-up was 54.9 % [38]. In the study of Ravesloot et al., a comparison has been made between CPAP therapy (high efficacy, low adherence) and surgical treatment (100% compliance, sub-therapeutic). They concluded that both treatment modalities may achieve the same mean AHI due to differences in efficacy and usage per night [36]. In a prospective randomized study by Eijsvogel et al., the short-term results of SPT versus tennis ball technique (TBT) were evaluated. Both therapies effectively reduced respiratory indices and supine sleeping; however, compliance improved significantly more in the SPT group resulting in a MDA of 70.5% versus 48.6% for TBT. The combination of surgery with PT resulted in a MDA of 65.6% in our study.

Limitations

This study has various limitations, mainly because of its design with selected cases and a small sample size which limits the strength of our conclusions. We could not run extensive tests on predictors for responsiveness since the power of our model would not be sufficient. Given the fact that we had 32 participants, a maximum of three possible variables could be tested. Since none of these variables were significant in our cohort, we were unable to perform advanced statistical analysis. Due to the small number of patients included, our cohort mainly consisted of male patients. Disparity in treatment response between the genders could therefore not be tested. Third, in the present study, different surgical techniques were applied and compared with each other. Although we combined surgical data for the present study, no significant differences were found in treatment response between the surgical subgroups. Further research is needed to reveal not only the factors predicting therapeutic response and success of PT but also to gain objective results with the implementation of a more qualitative and comparative study design with larger cohort sizes.

CONCLUSIONS

This study demonstrates that additional PT in a complex patient population with residual POSA after partial effective upper airway surgery can increase overall therapeutic effectiveness. Previous studies have reported on combining different OSA therapies to increase therapeutic response; however, this is still an under-evaluated and under-investigated matter. More research is required to identify the predictors of non-responders of PT in residual post-operative OSA/or in patients who have OSA treatment failure.

Although the results of this study demonstrate that the number of non-responders is high, PT could still be considered a valuable treatment option in positional patients with previous therapy failure since it has proven to be very successful in the responders group, in terms of both AHI decrease and compliance. Further research, however, is required to assess the factors for predicting therapeutic responsiveness.

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8 Summary, conclusions and future perspectives

SUMMARY, CONCLUSIONS AND FUTURE PERSPECTIVES

This thesis reports research discussing the following questions;

1) What is the influence of the sleep position in primary snorers and do subjective outcome measures improve when treating those subjects with positional therapy?
2) What is the effect of weight loss on OSA severity and position dependence in bariatric patients?
3) What is the short-term effectiveness, compliance and the effect on quality of life of positional therapy with the sleep position trainer compared to oral appliances in POSA patients?
4) What is the durability effect of positional therapy compared to oral appliances therapy?
5) Is positional therapy effective in patients in whom OSA surgery already has been performed?

In this chapter results have been summarized and conclusions are made upon these outcomes. Furthermore, concerning future perspectives much remains to be studied. Some new values of PT will be discussed to fulfil the potential need of individualized medicine.

SUMMARY AND CONCLUSIONS

Positional OSA

Over the last two decades there has been a dramatic increase in OSA prevalence, which has serious health implications [1,2]. Therefore management of this chronic condition is mandatory to improve symptoms and prevent long-term health risks. It has been well proven that many patients suffering from OSA have a different rate of apneic events in the lateral position, when compared with the supine position [3]. Several studies support the statement that patients with POSA are more likely to have a lower BMI, neck circumference, and AHI than their non-positional counterparts [3,4]. In subjects with primary snoring it is already seen that a majority is position dependent with most snoring events in the supine position (**chapter 2**). This chapter was the first article that used the AASM guidelines to accurately define non-apneic snorers [5]. We screened 81 patients for complaints of excessive snoring or symptoms suspicious for sleep disordered breathing. To assess position-dependent snoring overnight polysomnographic data were collected. Prevalence of position dependency in non-apneic snorers was found to be 65.8 % and the results also showed that non-apneic snorers with a higher BMI snored more frequently in supine position. With the transition of non-apneic snoring to OSA

it is seen that POSA is frequently present in patients with mild to moderate disease. When OSA is left untreated, metabolic and neuronal imbalances may occur that lead to increased weight and subsequent obesity which eventually progresses into a more severe sleep apnea, noted in all sleeping positions. On the contrary, in patients with severe non-positional OSA who respond to therapy (e.g., maxillomandibular advancement, bariatric surgery, upper airway surgery or upper airway stimulation) the OSA can be reversed to a less severe POSA [6].

In **chapter 3** prevalence of POSA was determined in patients undergoing bariatric surgery. Also the effect of weight loss brought about by bariatric surgery on POSA was evaluated. Thirty-four percent of patients had POSA, which was significantly lower than prevalence noted in the general population. BMI, neck circumference, and AHI were significantly lower in POSA patients, but AHI was shown to be the only significant independent predictor for the presence of POSA. Following bariatric surgery, 35.2 % no longer had OSA. These findings generate a provocative theory that severe non-positional OSA can in fact be reversed to a mild positional OSA or even positional non- apneic snoring with weight loss. In order to further define the relationship between changes in body weight and its effect on POSA, large, prospective, longitudinal studies are needed along with more long term compliance data and well powered randomized controlled trials.

Benefits of new generation devices

The therapeutic arsenal for patients with POSA has changed from the tennis ball technique (TBT) into newer smart positional devices. The first historical mention of positional therapy (PT) originates from the American War of Independence (1775-1783) where soldiers were advised to wear bulky backpacks during the night to avoid lying in supine position to avert raising caution to their enemy about their location due to the occurrence of snoring sounds [6]. The first patent for PT was filed by Sullivan in 1872 (“apparatus for preventing a person while asleep from turning on his back”) [7]. This apparatus consisted of a bulky mass strapped on the user’s back preventing the patient from turning into supine position. In the following decades a variety of alternatives on the TBT have been developed and patented. More than 100 years later, in 1986, a patent for an alarm device was registered by Lloyd (“sleep posture monitor and alarm system”) which comprises of a position sensor measuring the sleep posture and an alarm warning the patient by giving a stimulus to adapt the sleep position. In 2010 a patent for a sleep posture alerting apparatus was filed (“method and device for sleep posture correction”) by NightBalance. This device consisted of a body posture detecting sensor and an alarming device connected to the control unit and was named the sleep position trainer (SPT). The SPT (SPT-DEV-PX-11.08; NightBalance) consists of a small lightweight device worn across the chest using a neoprene strap. The SPT vibrates when a supine position is detected to prompt a change in body position. Data storage on the device

allows for objective measurement of adherence to the therapy. The first two studies evaluating the effect of the SPT showed that the device was effective in reducing in the AHI and percentage of supine sleep and the compliance was high after 6 months of therapy [8,9]. Following studies compared the effect of the SPT with other existing therapies; e.g., the tennis ball technique and oral appliances [10,11]. CPAP and PT have been compared but the value of adding PT to CPAP remains to be studied [12].

In **chapter 4** we reported on the subjective effects of the SPT in non-apneic position-dependent snorers. The severity of snoring and the impact to patients' quality of life were measured using a validated subjective questionnaire: the Snore Outcome Survey (SOS) and the Spouse/Bed Partner Survey (SBPS). The SOS evaluates the frequency, severity and consequences of snoring, whereas the SBPS evaluates the impact of snoring on the bed partner. A total of 36 participants were included and 30 completed the study. All participants were treated with the SPT for a period of 6 weeks. Results of this study indicated that PT with the SPT improved several snoring-related outcome measures and could therefore be considered as a therapeutic option to improve sleep-related health status of snorers and their bed partners.

Lastly, to be accepted for reimbursement the SPT needed to be compared to existing forms of therapy for a specified group of patients. In case of mild and moderate OSA standard treatment is oral appliance therapy (OAT). In a multicenter prospective randomized trial the efficacy of the SPT was compared with OAT over a period of 12 months. A total of 177 patients with mild to moderate POSA (AHI ≥5 ≤30/hour sleep) were screened for the study; 99 underwent randomization and 81 completed the study. In **chapter 5** results after 3 months of therapy have been evaluated and in **chapter 6** the long-term data (after 12 months) were discussed. Overall results showed that both therapies were equally effective in reducing the AHI, also compliance was comparable and side effects were minimal. With the publication of this study the SPT is now reimbursed by the Dutch healthcare system [13].

Combination therapy

Patients with severe sleep apnea may not be able to achieve complete response with one treatment modality. In case of CPAP for example, the device can be effective but dissuades the patients use because of compliance issues [14,15]. OAT, which is the first-line non-surgical therapy in mild and moderate OSA patients, is a portable device which is personalized for each patient and easy in usage. Adverse events such as tooth pain or temporomandibular dysfunction can limit adherence to this therapy [14,15]. Unfortunately, in severe cases the effect of OAT is often not sufficient in reducing the AHI [16]. This is where combination therapy comes in. A big advantage of the SPT is that it can be used as single therapy but can also be effective when combining it with other treatments such as oral appliance or as a supplementary after surgery (**chapter**

7). In this chapter we studied a complex patient population who had undergone surgical treatment for OSA and were left with residual POSA. Thirty-three patients with POSA and a median postoperative AHI of 18.3/h sleep were included. These patients received additional treatment with the SPT for 3 months. The median AHI dropped to 12.5/h and the Epworth Sleepiness Scale (ESS) improved from 10.0 to 7.0. The results of this study indicate that additional position therapy in a complex OSA patient population with residual POSA after surgery can increase overall therapeutic effectiveness.

The best sequence of the treatments, when considering combining positional therapy with other treatment, remains to be examined. Some patients only benefit when using both therapies simultaneously, others will be offered SPT after surgical failure due to residual apneas in supine position. In some patients position dependency is already visible prior to surgery. In these cases it would be more logical to try PT first since it is reversible, non-invasive, cheap, and without major side effects.

Prevalence of position dependency in non-apneic snorers is more than 65% and this group can potentially be treated with the SPT. Our study has showed that the SPT is effective in reducing the severity of snoring and improving the impact to patients' quality of life. In a randomized controlled trial we evaluated respiratory indices between OAT and SPT after 3 and 12 months. We demonstrated that both therapies are equally effective in reducing the AHI in mild to moderate POSA and that the efficacy was maintained over 12 months of therapy. Adherence to both treatment modalities was high, and similar in the two groups. Lastly, we showed that the SPT also has the potential of being combined with other therapies.

FUTURE PERSPECTIVES

OSA is a highly heterogeneous disorder and the prevalence is still rising. Clinical presentation, risk factors, and pathophysiology differs among patients. OSA has important impact on physical and psychological health outcome, safety and economic issues. Pathophysiology of OSA is multifactorial and therefore the causes and consequences can vary substantially on an individual level between patients [17]. For example some patients with severe OSA are not objectively or subjectively sleepy, while others with only mild OSA can experience excessive sleepiness.

In the last years, important contributors to OSA have been characterized which play a key role in the pathogenesis [17-19]. It is now known that OSA is not only caused by an impaired upper airway anatomy which predisposes to airway collapse, but also several non-anatomical factors play a role, such as a low respiratory arousal threshold to airway narrowing during sleep, and a hypersensitive or unstable ventilatory control

system (high loop gain) [18]. These non-anatomical traits could in part explain the non-responders from the studies in this thesis.

When considering the anatomical abnormalities of OSA patients, patients with mild OSA tend to have a less collapsible upper airway compared with severe OSA patients. Also, different site(s) of obstruction has been noted in mild OSA (mainly retropalatal), while in severe OSA patients multilevel collapse occurs more often [20]. In POSA patients evidence suggests that both the site(s) and degree of upper airway collapse are the most important anatomical causes of the positional component [20]. When looking at abnormalities in non-anatomical traits, POSA patients had a greater improvement in muscle responsiveness and high loop gain and low arousal thresholds have been seen more often in patients with mild OSA [21]. But it has to be stated that the contribution of non-anatomical factors may differ strongly among the variations seen in upper airway anatomy and degree of upper airway collapse.

Since clear individual differences exist in efficacy, treatment of OSA may become more effective when tailored to each patient's need and the relative contributions of the various anatomical and non-anatomical causative components. When developing a personalized approach one should consider different domains such as; the variation in clinical presentation, different clinical consequences and response to therapy [22]. P4 medicine, introduced by Dr. Leroy Hood, describes an approach to personalized medicine which is applicable in many fields [23]. Different studies show that P4 medicine is also applicable to OSA, taking the various clinical subtypes into account [22,24,25].

The main goal of P4 medicine is to identify individuals that are susceptible for developing certain diseases, reverse progression before it affects someone, and making participation in wellness of individual's part of health outcomes. The four P's comprises of the following; prediction, prevention, personalization and participation. Predict who will develop disease and co-morbidities; prevent rather than react to disease with the goal being to maintain health; personalize diagnosis and treatment; and have patients participate in their own care [24,22]. When translating P4 medicine to OSA, it is clear that each patient has a different pathway in developing the disease and also consequences differ [19]. The influence of anatomical and non-anatomical traits clearly diverges as mentioned earlier. Also different molecular profiles have been identified affecting each OSA patient in a different way, establishing a potential for prevention [26,27]. Once an individual is diagnosed with OSA, treatment is tailored to maximize outcome. It is well known that treatment response to, for example, OAT, SPT and upper airway stimulation varies. Measuring compliance and efficacy is one of the key determinants of current therapy in CPAP and SPT to evaluate response and improve usage or change therapy (or combine therapy) in an early stage to prevent further progression of the disease. Additionally, current modern technology allows patients these days to participate in their own wellness by for example providing screening tools to diagnose

(snoring and sleep apps), monitor response to therapy (e.g., the capability of the SPT to follow progress online, but also measure blood pressure, heart rate and oxygen saturation are other possibilities) and discuss disease related issues with other individuals through social media to improve health care.

With P4 medicine we're moving away from a traditional diagnosis with only AHI, and the therapeutic concept "one size fits all" (left panel of ***figure 1***) to personalized medicine where diagnosis is more focused on the individual including risk factors and comorbidity [25]. Therapies will be more tailored taking patient's preference and compliance into account (right panel of ***figure 1***).

From current studies it is clear that P4 medicine in OSA is an interesting and valuable approach to advance health care. Although there are still some important key determinants that have to be examined, it seems that recent studies have provided new pathways for targeted therapies. Future research has to focus also on the potential of

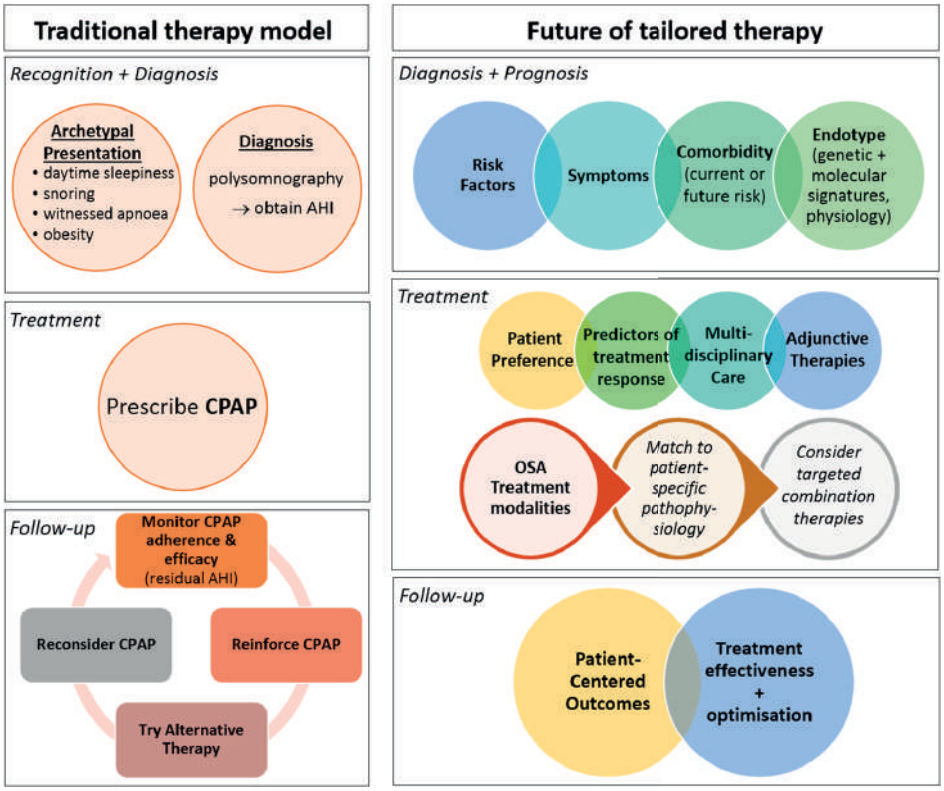

Figure 1. An overview of the traditional model versus the future of tailored therapy from K. Sutherland et al. From CPAP to tailored therapy for obstructive sleep apnea. Multidiscip Respir Med. 2018; 13: 44.[25] This figure is part of the article that is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

biomarkers in the screening for OSA and the correlation with clinical outcome measures [28]. Also the contribution of non-anatomical traits (i.e., physiological risk factors such as the muscle responsiveness or overall loop gain) in diagnosis has to be evaluated and how those factors can be altered as part of OSA therapy. The personalized medicine approach can form the basis for future OSA research efforts given its complex pathophysiology and variable clinical presentation. However, more research is needed to evaluate and understand the specific clinical application.

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9 Samenvatting

SAMENVATTING

In dit proefschrift is onderzoek gedaan naar drie soorten patiëntengroepen; primair snurkers, patiënten met obstructief slaapapneu (OSA) en patiënten met positieafhankelijke obstructief slaapapneu (POSA). Primaire snurkers zijn mensen die een sociaal snurkprobleem hebben. Zij hebben geen last van apneus (ofwel ademstops, een periode van niet ademen tijdens de slaap) of hypopneus (verminderde ademhaling). Patiënten met OSA hebben wel last van apneus gedurende de slaap. Dit zijn episodes waarbij herhaaldelijk een gedeeltelijke (hypopneu) of volledige (apneu) vernauwing optreedt van de hogere luchtwegen. Door deze vernauwing treedt tevens een verlaging op van de zuurstofsaturatie (het zuurstofgehalte) in het bloed. De ernst van het probleem wordt weergegeven in het aantal apneus en hypopneus per uur/slaap, ook wel apneu-hypopneu index (AHI). Bij een AHI <5/uur heeft iemand geen OSA, bij een AHI van 5-15/uur heeft iemand licht OSA, 15-30/uur een matige OSA en >30/u ernstig OSA. Wanneer bij een patiënt met OSA de hypopneus en apneus voornamelijk aanwezig zijn in rugligging spreekt men van positieafhankelijke OSA (POSA). Hoe vaak OSA voorkomt in Nederland (ook wel prevalentie genoemd) is niet bekend. Er wordt geschat dat er tussen de 315.000 en 500.000 patiënten zijn, wat overeenkomt met 2-3% van de Nederlandse bevolking.

In dit proefschrift wordt antwoord gegeven op verschillende onderzoeksvragen. In **hoofdstuk 2** is onderzocht in welke slaaphouding primaire snurkers het meest snurken. In **hoofdstuk 3** worden twee onderzoeksvragen beantwoord. Enerzijds wordt gekeken naar het effect van gewichtsverlies op de ernst van OSA bij patiënten die een chirurgische maagverkleining hebben ondergaan (ook wel bariatrische chirurgie genoemd). Anderzijds wordt beoordeeld of de OSA bij deze patiënten na gewichtsafname verandert in POSA. In **hoofdstuk 4** wordt beschreven of subjectieve uitkomstmaten (o.a. de ernst van het snurken en de impact van het snurken op de kwaliteit van leven) verbeteren wanneer primaire snurkers worden behandeld met positietherapie. In **hoofdstuk 5** wordt het korte termijneffect van positietherapie met de slaappositietrainer (zie pagina 78 voor een afbeelding) vergeleken met dat van een antisnurkbeugel (zie pagina 78 voor een afbeelding). Er wordt specifiek gekeken naar de therapietrouw (dragen mensen het apparaat), de effectiviteit (slaat de behandeling goed aan) en de kwaliteit van leven bij patiënten met POSA. In **hoofdstuk 6** worden vervolgens de langetermijnresultaten (na 1 jaar therapie) van de slaappositietrainer en de antisnurkbeugel geanalyseerd. **Hoofdstuk 7** focust op een groep patiënten die al eerder was behandeld met een operatie aan de bovenste luchtweg voor hun OSA en nadien nog steeds POSA bleken te hebben. De resultaten van deze complexe groep patiënten die werd behandeld met positietherapie na gedeeltelijk effectieve chirurgie van de bovenste luchtweg wordt geanalyseerd.

In dit hoofdstuk zal een samenvatting en conclusie worden gegeven over de uitkomsten van bovengenoemde onderzoeksvragen.

Positieafhankelijke obstructieve slaapapneu (POSA)

De laatste decennia wordt een toename gezien in het aantal patiënten met OSA in onze populatie. De toename in OSA heeft serieuze gevolgen voor de individuele patiënt, de maatschappij en de gezondheidszorg. Een toegenomen slaperigheid overdag en vermindering van cognitieve functies (zoals aandacht en concentratie) kan leiden tot problemen thuis, tot problemen bij het uitoefenen van het beroep, tot een vermindering in kwaliteit van leven en tot een grotere kans op ongevallen. Daarom is behandeling van deze chronische aandoening van groot belang. Het behandelen van patiënten met OSA is niet alleen bedoeld om de kwaliteit van leven van de patiënt te verbeteren maar ook om risico's voor de gezondheid op lange termijn te voorkomen. Langetermijnrisico's voor patiënten met OSA kunnen onder andere zijn een hogere kans op hypertensie (een verhoogde bloeddruk) of andere cardiovasculaire morbiditeit (hart- en vaatziekten).

Uit eerder onderzoek is gebleken dat veel patiënten met OSA een verschil hebben in het aantal hypopneus/apneus als zij op hun zij liggen in vergelijking met rugligging. Als het aantal apneus/hypopneus in rugligging twee keer zo hoog is in vergelijking met de zijligging wordt gesproken van positieafhankelijke obstructieve slaapapneu (POSA). Uit verschillende studies blijkt dat patiënten met POSA een lagere *body mass index* (BMI), een smallere nekomtrek en een lagere AHI (minder apneus/hypopneus per uur) hebben in vergelijking met niet-positieafhankelijke OSA patiënten. Ook bij patiënten die enkel last hebben van primair snurken (dus zonder apneus/hypopneus) wordt gezien dat het merendeel positieafhankelijk is en voornamelijk in rugligging snurkt. In **hoofdstuk 2** wordt voor het eerst volgens de officiële richtlijnen van de Amerikaanse Slaap Academie gekeken naar hoe vaak het voorkomt dat primaire snurkers last hebben van positieafhankelijkheid. Bij 81 patiënten werd gedurende een nacht de slaap geregistreerd vanwege de verdenking op snurken en slaapapneu. De grafische weergave van een dergelijke nachtelijke registratie wordt een hypnogram genoemd. Hierbij wordt in een grafiek weergegeven wat de verschillende slaapstadia zijn, hoeveel iemand snurkt en of er ook apneus zijn. Bij deze studie hebben we enkel patiënten zonder slaapapneu geanalyseerd (dus met een AHI <5/uur). Uiteindelijk bleek 65,8% van deze groep snurkers voornamelijk te snurken in rugligging.

Positieafhankelijkheid (dus het vaker voorkomen van apneus/hypopneus in rugligging) komt vaker voor bij een lichte en matige vorm van OSA en nauwelijks bij ernstig OSA. Wanneer de OSA onbehandeld blijft kunnen er uiteindelijk veranderingen in de stofwisseling en in de zenuwcellen optreden wat kan lijden tot een toename in gewicht, die zich uiteindelijk uit in obesitas. Bij de groep patiënten met obesitas wordt vaak een toename gezien in de ernst van de OSA met daarbij apneus/hypopneus in alle

slaappositions. Daarentegen wanneer patiënten met ernstige OSA goed reageren op een behandeling (bijvoorbeeld een maagverkleining of bovenste luchtwegoperatie) kan de OSA veranderen in een minder ernstige vorm en kan deze tevens veranderen in POSA (dus waarbij de apneus/hypopneus voornamelijk in rugligging voorkomen).

In **hoofdstuk 3** wordt de prevalentie van POSA bepaald in een groep patiënten die bariatrische chirurgie (maagverkleining) ondergaat. Daarnaast wordt bekeken wat het effect van het gewichtsverlies, na deze operatie, is op de positieafhankelijkheid (of het relatieve aantal apneus/hypopneus in rugligging toeneemt door deze ingreep). Er werd gevonden dat POSA voorkomt bij 34% van de patiënten die bariatrische chirurgie ondergaat. De BMI, nekomtrek en AHI waren alle significant lager bij POSA-patiënten dan bij patiënten die geen positieafhankelijke OSA hadden. Na de bariatrische ingreep had iets meer dan een derde van de patiënten (35,2%) geen OSA meer. Deze resultaten wijzen in de richting van een omstreden theorie die luidt dat ernstige OSA door gewichtsverlies kan verbeteren naar een minder ernstige POSA of zelfs positiefhankelijk primair snurken. Deze theorie is omstreden omdat wetenschappelijk bewijs nog ontbreekt. Om deze theorie te bekrachtigen zal de precieze relatie tussen verandering in gewicht en het effect op OSA in grotere studies uitgezocht moeten worden waarbij patiënten over de tijd gevolgd moeten worden (dit wordt een prospectieve studie genoemd).

Nieuwe generatie apparaten

Behandelmogelijkheden voor patiënten met POSA zijn in de loop van de tijd veranderd. Waar eerder bijvoorbeeld de tennisbal-techniek (TBT) gebruikt werd zijn tegenwoordig modernere apparaten beschikbaar. Positietherapie werd voor het eerst beschreven tijdens de Amerikaanse Onafhankelijkheidsoorlog (1775-1783). Soldaten werd geadviseerd om hun zware rugtas om te hebben gedurende de nacht zodat ze niet naar hun rug konden draaien, wat hun positie aan de vijand zou verraden vanwege het gesnurk in deze slaappositie.

Het eerste patent voor positietherapie dateert uit 1872 van Sullivan. Dit apparaat bestond uit een bolvormige massa die op de rug van de patiënt werd gedragen, zodat hij/zij niet in rugligging kon slapen. In de decennia daaropvolgend zijn er verschillende variaties van deze zogeheten tennisbal-techniek ontwikkeld en gepatenteerd. Meer dan 100 jaar later, in 1986, kwam er een patent op de markt, geregistreerd door Lloyd, voor een alarm-aangestuurd apparaat (“slaappositie monitor en alarmsysteem”). Dit systeem bestond uit een positiesensor die de slaappositie kon meten en daarnaast zat er een alarm in het systeem wat de patiënt een stimulus kon geven en zo zou waarschuwen een andere slaaphouding aan te nemen. In 2010 kwam het patent van NightBalance op de markt (“methode en apparaat om de slaaphouding aan te passen”). Dit apparaat, de slaappositietrainer (SPT), bestaat uit een sensor die de lichaamshouding kan meten die gekoppeld is aan een ingebouwd vibratiesysteem. De SPT (SPT-DEV-PX-11.08; Night-

Balance) is een klein lichtgewicht apparaat dat met een elastische band om iemands middel wordt gedragen. De SPT geeft een vibratie wanneer rugligging wordt gedetecteerd zodat een andere slaappositie kan worden aangenomen. Per nacht worden de geregistreerde gegevens opgeslagen die vervolgens via een computer bekeken kunnen worden. Hierdoor wordt de therapietrouw (de tijd dat het apparaat daadwerkelijk wordt gedragen) in kaart gebracht. De eerste twee onderzoeken die de effectiviteit hebben gemeten van de SPT, toonden aan dat het apparaat effectief was in het verlagen van de AHI en het percentage rugligging. Op basis van 6 maanden behandeling bleek ook de therapietrouw hoog. Nadien zijn nog verschillende publicaties verschenen die onder andere het effect van de SPT, bij patiënten met POSA, met bestaande behandelingen als de tennisbaltechniek en de antisnurkbeugel (ook wel het mandibulair repositie apparaat, MRA, genoemd) hebben onderzocht. Positietherapie is ook al eens vergeleken met continue positieve luchtwegdruk (CPAP). CPAP is een apparaat dat via een masker lucht onder een verhoogde druk de bovenste luchtweg binnen blaast waardoor de luchtweg open blijft. Het aanvullende effect van positietherapie op deze behandeling moet nog verder worden onderzocht.

In **hoofdstuk 4** worden de resultaten besproken van een studie waarbij is gekeken naar subjectieve uitkomsten van de SPT bij positieafhankelijke primaire snurkers. Het gaat hierbij om zowel de ernst van het snurken als de impact van het snurken op de kwaliteit van leven. Deze uitkomsten werden gemeten aan de hand van onder andere twee gevalideerde vragenlijsten; de “Snore Outcome Survey” (SOS) en de “Spouse/ Bed Partner Survey” (SBPS). Met behulp van de SOS wordt onder andere gemeten hoe vaak de patiënt snurkt, hoe ernstig dit snurken is en wat de gevolgen van het snurken voor de patiënt zijn. Met de SBPS wordt bepaald wat de impact van het snurken is op de bedpartner. In deze studie werden 36 patiënten geëvalueerd die last hadden van primair snurken. Zij werden gedurende zes weken behandeld met de SPT. De resultaten van deze studie toonden aan dat patiënten met de SPT minder vaak snurkten en dat de ernst van het snurken afnam. Er was ook een duidelijke verbetering te zien in de impact van het snurken op de bedpartner. De SPT kan voor primaire snurkers daarom worden toegevoegd aan het therapeutisch arsenaal om zo de gezondheidsstatus, met betrekking tot de slaap, te verbeteren van snurkers en hun bedpartners.

In **hoofdstuk 5 en 6** wordt de SPT vergeleken met een al bestaande behandeling voor patiënten met OSA. De standaard niet chirurgische therapie in het geval van lichte tot matige OSA (een AHI van 5 tot 30/uur) is behandeling met een antisnurkbeugel, de MRA. In een studie waarbij patiënten van meerdere ziekenhuizen meededen die elk willekeurig werden ingedeeld in de experiment- en de controlegroep (dit wordt een multicenter gerandomiseerd gecontroleerde studie genoemd) werd de SPT vergeleken met een MRA gedurende een periode van 12 maanden. Voor deelname aan deze studie werden 177 patiënten gescreend. Uiteindelijk waren 99 kandidaten geschikt, die wil-

lekeurig (*at random*) werden verdeeld over de twee groepen. In de SPT groep zaten 48 patiënten en in de MRA groep 51. In **hoofdstuk 5** worden de kortetermijnresultaten getoond, dat wil zeggen de uitkomsten na 3 maanden therapie. **Hoofdstuk 6** geeft de resultaten weer van de behandeling na 12 maanden. Uit deze studie bleek dat beide behandelingen, de SPT en MRA, even effectief zijn in het verlagen van de AHI. Daarnaast hebben beide behandeling een vergelijkbare therapietrouw ('compliance'). Compliance is het verdragen van de behandeling over een bepaalde periode uitgedrukt in een percentage. De bijwerkingen van de SPT en MRA waren minimaal. De resultaten van dit wetenschappelijke onderzoek hebben uiteindelijk geleid tot opname van de SPT als verzekerde zorg in het basispakket.

Combinatietherapie

Patiënten met ernstige slaapapneu kunnen soms niet volledig worden genezen met maar één behandeling. Bij CPAP (continue positieve luchtwegdruk) bijvoorbeeld, kan de behandeling wel aanslaan maar veel patiënten ervaren bijwerkingen, zoals een droge mond of neus, irritatie van de huid door het dragen van het masker en luchtlekkage. Hierdoor kunnen zij op korte of langere termijn stoppen met deze therapie. De eerstekeustherapie in het geval van lichte en matige OSA is de antisnurkbeugel, de MRA. Ook bij de behandeling met een MRA worden bijwerkingen gezien. Hierbij kunnen patiënten last krijgen van comfortproblemen zoals pijn aan de tanden of het kaakgewricht. Soms wordt na het falen van behandeling met CPAP een MRA geprobeerd bij patiënten met ernstige OSA. Echter blijkt uit onderzoek dat bij patiënten met ernstig OSA de AHI vaak onvoldoende daalt met alleen een MRA. In dit geval zou combinatietherapie een oplossing kunnen zijn. Het doel van combinatietherapie is om meerdere behandelingen te combineren zodat de effectiviteit groter wordt met zo min mogelijk bijwerkingen. Combinatietherapie kan worden geprobeerd bij matige en ernstige (P)OSA. Een groot voordeel van de SPT is dat de behandeling eenvoudig valt te combineren, bijvoorbeeld met een MRA of na eerdere bovensteluchtwegchirurgie voor OSA. Het is nog niet duidelijk wat de beste volgorde van behandeling is wanneer combinatietherapie wordt overwogen. Sommige patiënten krijgen de SPT aangeboden in geval van onvoldoende effect van eerdere behandeling, bij andere patiënten werkt het beter wanneer de behandelingen tegelijk worden toegepast.

In **hoofdstuk 7** beschrijven we een complexe groep patiënten die al een operatie heeft ondergaan van de bovenste luchtweg voor behandeling van hun slaapapneu en nadien nog last heeft van apneus/hypopneus in rugligging. Er werden 33 patiënten geïncludeerd voor deze studie met een gemiddelde AHI van 18.3/uur waarbij de AHI in rugligging tweemaal zo hoog was als in niet-rugligging (dus matige POSA). Al deze patiënten kregen de SPT als aanvullende behandeling. Aangetoond werd dat combinatietherapie bij deze patiënten zorgde voor verdere afname van de AHI. Hierdoor

werd de effectiviteit van de behandeling groter. Er werd ook duidelijk dat een deel van de patiënten niet goed reageerde op de behandeling (*non-responders*). Toekomstig onderzoek zal moeten uitwijzen wat de voorspellende factoren zijn die bepalen welke patiënten wel en welke niet goed reageren op behandeling met de SPT.

Positieafhankelijkheid komt voor in meer dan 65% bij primaire snurkers. De SPT is een nieuwe behandeling voor positiefafhankelijke primaire snurkers. We hebben aangetoond dat de SPT bij hen een effectieve behandeling kan zijn. Daarnaast hebben we laten zien dat de SPT bijdraagt aan verbetering van de kwaliteit van leven van zowel patiënten met primair snurken als patiënten met POSA. De SPT geeft bij lichte en matige POSA gelijkwaardige resultaten als een MRA. Daarnaast blijkt de SPT ook geschikt als onderdeel van combinatietherapie om patiënten met ernstigere vorm van OSA te behandelen waarbij één behandeling niet effectief genoeg blijkt te zijn. In dit proefschrift wordt duidelijk dat er een nieuwe mogelijkheid is om mensen met sociaal hinderlijk snurken of patiënten met POSA te behandelen.

List of abbreviations and acronyms

AASM	American academy of sleep medicine
AE	adverse event
AHI	apnea hypopnea index
AI	apnea index
AP	anteroposterior
ASA	American society of anesthesiologists
BQ	berlin questionnaire
BMI	body mass index
CPAP	continuous positive airway pressure
CSA	central sleep apnea
ODI	oxygen desaturation index
DISE	drug-induced sleep endoscopy
ECG	electrocardiogram
EEG	electroencephalogram
EMG	electromyogram
EOG	electro-oculogram
ESS	Epworth sleepiness scale
FDA	food and drug administration
FOSQ	functional outcomes of sleep questionnaire
GA	genioglossal advancement
HS	hyoidsuspension
ICH	international conference of harmonization
ICSD	international classification of sleep disorders
ITT	intention-to-treat
IQR	interquartile range
MDA	Mean disease alleviation
MMA	maxillomandibular advancement
MSLT	multiple sleep latency test
NCPAP	nasal continuous positive airway pressure
OA	oral appliances
OAT	oral appliance therapy
OSA	obstructive sleep apnea
POSA	positional obstructive sleep apnea
PG	polygraphy
PP	per-protocol
PSG	polysomnography
PT	positional therapy
RCT	randomized clinical trial
RDI	respiratory disturbance index

REM	rapid eye movement
RERA	respiratory effort-related arousal
RFTB	radiofrequent ablation of the base of tongue
SBQ	STOP-BANG questionnaire
SD	standard deviation
SDB	sleep disordered breathing
SBPS	spouse/bed partner survey
SOS	snore outcome survey
SPT	Sleep Position Trainer
STOP	STOP questionnaire
TBT	tennis ball technique
TE	tonsillectomy
TORS	transoral robotic surgery
TST	total sleep time
UPPP	uvulopalatopharyngoplasty
VAS	visual analogue scale
VOTE	velum, oropharynx, tongue, epiglottis
ZPP	Z-palatoplasty

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Onderzoek

International Expert Meeting 04-04-2018, München Duitsland
Perioperative care of patients with OSA undergoing upper airway surgery
Onderzoeker, publicatie zie lijst

ZonMw DoelmatigheidsOnderzoek ronde 2015, Type 1 Onderzoek
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Presentaties

Philips Sleep and Respiratory Care Symposium 11 oktober 2019, Eindhoven
Presentator: "Positietherapie bij positieafhankelijke obstructieve slaapapneu"

Wetenschapsdag OLVG 30-05-2018, presentatie Dr. Keeman prijs, beste publicatie 2017
Presentator: "Positietherapie versus MRA; resultaten van een multicenter RCT"

9th International Surgical Sleep Society Meeting 2018, 07-04-2018 München
Presentator: "Combination therapy – PT combined with, or compared to other treatments"

Wetenschappelijke 231e KNO-vergadering 17-11-2017 Nieuwegein, OSAS bijeenkomst
Presentator: "Positietherapie versus MRA; resultaten van een multicenter RCT"

25. Jahrestagung der Deutschen Gesellschaft für Schlafforschung und Schlafmedizin vom 9.-11. November 2017 in Münster
Presentator: “Positional therapy versus oral appliance therapy for position-dependent sleep apnea”

Wetenschapsdag Maasstadziekenhuis 31-10-2017
Presentator: “Positional therapy versus oral appliance therapy for position-dependent sleep apnea”

Refereeravond AMC 31-05-2016, OLVG West Amsterdam
Presentator: “Organisatie en logistiek van DISE in een opleidingskliniek”
Presentator: “Positietherapie vs MRA studie”

NVTS Pre-conference course MRA en Positietherapie, 6-04-2017 St. Antonius ziekenhuis
Presentator: “Onderzoeksresultaten van de SPT en patiënt selectie”

SORG course Current Developments in OSA Treatment, Haarlem 19-01-2017
Presentator: “Positional therapy versus oral appliance therapy for position-dependent sleep apnea”

Nederlandse Slaapcongres, SLAAP 2016, Ermelo 3-11/ 4-11-2016
Presentator sessie: Slaapgebonden ademhalingsstoornissen. **“**MRA en positietherapie”

EUROSAS surgery up to date 2016, Rimini 16-09-2016
Presentator session: “Short- and long-term results of new generation positional therapy, alone or combined with MRA and surgery”

Symposium OSAS: time to wake up. Rotterdam Erasmus MC 20-06-2016
Presentator: “Diagnostiek en behandeling van OSAS”

Symposium OSA Revisited. Implementation of innovations in diagnosis and treatment ACTA Amsterdam 20-05-2016
Presentator: “Research projects in OLVG West”

8e NVTS Congres Nieuwegein 15-04-2016
Presentator: “Positietherapie versus MRA; resultaten van een multicenter RCT”

De 4e Mini-OSAS cursus, SLAZ 16-10-2015
Presentator: “Slaapendoscopie volgens VOTE classificatie”
Presentator: “Beoordeling van slaapendoscopieën, interactieve sessie”

Nascholing voor verpleegkundige 26-8-2015
Presentator: “Chirurgische behandeling binnen de KNO-heelkunde en de postoperatieve zorg”

Posterpresentatie, wetenschapsdag SLAZ/OLVG 10-6-2015
Presentator: “Positional therapy in patients with residual positional obstructive sleep apnea after upper airway surgery”

De 3e Mini-OSAS cursus, SLAZ 14-11-2014
Presentator: “Beoordeling van slaapendoscopieën, interactieve sessie”

Carrouselspreker, wetenschapsdag Sint Lucas Andreas Ziekenhuis (SLAZ)/ Onze Lieve Vrouwe Gasthuis (OLVG) 4-6-2014
Presentator: “Promotieonderzoek: Positietherapie voor de behandeling van slaapapneu”

Posterpresentatie, wetenschapsdag SLAZ/OLVG 4-6-2014
Presentator: “Upper-airway Stimulation for Obstructive Sleep Apnea”

De 2e Mini-OSAS cursus, SLAZ 09-05-2014
Presentator: “Beoordeling van slaapendoscopieën, interactieve sessie”

223e Wetenschappelijke KNO-vergadering 15-11-2013 Maastricht, OSAS bijeenkomst
Presentator: “The effect of weight loss on OSA severity and position dependence in bariatric patients”

223e Wetenschappelijke KNO-vergadering 15-11-2013 Maastricht, OSAS bijeenkomst Presentator: “Upper airway stimulation in OSA patients resolves multi-level airway collapse in a dose-response manner”

221e Wetenschappelijke KNO-vergadering 8-11-2012 Nieuwegein, OSAS bijeenkomst
Presentator: “Evaluation of position dependency in non-apneic snorers”

Subsidie / Prijzen

2e prijs dr. Keeman Wetenschapsprijs beste publicatie 2017, OLVG Amsterdam
Presentatie: “Positietherapie versus MRA; resultaten van een multicenter RCT”

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“Positional therapy versus oral appliance therapy for position-dependent sleep apnea”

Piet Visser Posterprijs. Nederlands Slaapcongres, SLAAP 2016
“Positional therapy as a treatment for Central Sleep Apnea syndrome”

Project: “Economic evaluation of treatment modalities for position-dependent obstructive sleep apnea patients”
Toegekende subsidie ZonMw; € 250.000,- 26-6-2014
Toegekende subsidie Stichting Medisch Wetenschappelijk Onderzoek SLZ; € 8.460,- 21-8-2015

Poster Publiekprijs wetenschapsdag SLAZ/OLVG 4-6-2014
“Upper-airway Stimulation for Obstructive Sleep Apnea”

Cursus / congres

11.2019	13e cursus KNO-Radiologie, Dunnebier
10.2019	Sleep and Respiratory Care Symposium, Eindhoven
06.2019	Chirurgische anatomie van het hoofd-halsgebied 2019
05.2019	AIOS ENTERdag, Amsterdam
03.2019	Antistolling bij ingrepen & bloedingen: veel nieuws onder de zon 2019
01.2019	Mini oren cursus, Nijmegen
01.2019	Teach the Teacher II, Rotterdam
09.2018	DOO cursus Gezondheidsrecht ErasmusMC Rotterdam
05.2018	AIOS ENTERdag, Amsterdam
04.2018	Stemsymposium, OLVG-West
04.2018	9th International Surgical Sleep Society Meeting 2018, München
03.2018	Cursus Medische Integriteit, ACTA
11.2017	Mini FESS cursus, Leiden
05.2017	Mini Endoscopie- en luchtwegcursus KNO voor AIOS, Groningen.
01.2017	SORG course Current Developments in OSA Treatment, Haarlem 19-01-2017
11.2016	Nederlandse Slaapcongres, SLAAP 2016, Ermelo 3-11-2016/4-11-2016
09.2016	EUROSAS surgery up to date 2016, Rimini 15-09-2016/17-09-2016
05.2016	Symposium OSA Revisited. Implementation of innovations in diagnosis and treatment ACTA Amsterdam

04.2016	8e Nederlandse Vereniging voor Tandheelkundige slaapgeneeskunde (NVTS) Congres Nieuwegein
10.2015	Mini-OSAS cursus, Sint Lucas Andreas Ziekenhuis
06.2015	OSAS Up to date congres, Arnhem. “Nieuwe behandelingen 2015”.
12.2014	Deelname internationaal symposium Antwerpen “Update & Novelties in OSA therapy”
11.2014	Mini-OSAS cursus, Sint Lucas Andreas Ziekenhuis
06.2014	Deelname 25ste European Rhinologic Society Congress (ERS), Amsterdam
06.2014	Kadaverlab Inspire, Leiden
02.2014	Cursus Mondpathologie. “Een nascholingscursus voor KNO-artsen en dermatologen”
01.2014	Avondsymposium slaapapneu. “Innovatie in de behandeling van obstructief slaapapneu”, Universitair Ziekenhuis Antwerpen
11.2013	Mini-OSAS cursus, Sint Lucas Andreas Ziekenhuis
11.2013	Cursus Good Clinical Practice (GCP). Examen behaald 27-11-2013
10.2013	Workshop “Hoe schrijf ik een succesvolle ZonMw aanvraag?”
01.2013	Cursus Scientific Writing, Sint Lucas Andreas Ziekenhuis
11.2012	Cursus Statistiek en SPSS, OLVG
05.2012	Basiscursus SPSS, Sint Lucas Andreas Ziekenhuis
2008	Basiscursus Brandwonden voor medisch studenten, Beverwijk

List of publications

“New-generation positional therapy in patients with positional central sleep apnea”
L.B.L. Benoist, P.E. Vonk, N. de Vries, H.C.J.P. Janssen, J. Verbraecken
Eur Arch Otorhinolaryngol. 2019 Sep;276(9):2611-2619

“Perioperative Care of Patients with Obstructive Sleep Apnea undergoing Upper Airway Surgery: A Consensus Guideline”
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-Azad, 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
JAMA Otolaryngol Head Neck Surg. 2019 Jun 27

Case report “A jackass and a fish: a case of life-threatening intentional ingestion of a live pet catfish (Corydoras aeneus)”
L.B.L. Benoist, B. van der Hoven, A.C de Vries, B. Pullens, E.J.O. Kompanje, C.W. Moeliker
Acta Oto-Laryngologica Case Reports (ICRO), Volume 4, 2019 - Issue 1

“Tongzenuwstimulatie voor obstructief slaapapneu. Techniek, indicatie, toekomst”
P.E. Vonk, **L.B.L. Benoist**, K. Kasius, J.P. van Maanen, M.J.L. Ravesloot, H.J. Reesink, N. de Vries.
Ned Tijdschr Geneeskd. 2019;163:D3286

“Subjective effects of the Sleep Position Trainer on snoring outcomes in position-dependent non-apneic snorers”
L.B.L. Benoist, A.M.E.H. Beelen, B. Torensma, N. de Vries
Eur Arch Otorhinolaryngol. 2018 Aug;275(8):2169-2176

“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”
C. Kastoer, **L.B.L. Benoist**, M. Dieltjens, B. Torensma, L.H. de Vries, P.E. Vonk, M.J.L Ravesloot, N. de Vries
Sleep Breath. 2018 Dec;22(4):939-948

“Advances in the Diagnosis of Obstructive Sleep Apnea: Drug-Induced Sleep Endoscopy”
Ravesloot MJL, **Benoist L,** van Maanen P, Kezirian EJ, de Vries N.
Adv Otorhinolaryngol. 2017;80:22-27

“Novel Positional Devices for the Treatment of Positional Obstructive Sleep Apnea, and How This Relates to Sleep Surgery”
Ravesloot MJL, **Benoist L**, van Maanen P, de Vries N.
Adv Otorhinolaryngol. 2017;80:28-36

“Durability of treatment effect of the sleep position trainer compared to oral appliance therapy in positional OSA: a randomized controlled trial over 12 months”
M.H.T. de Ruiter*, **L.B.L. Benoist***, N. de Vries, J. de Lange.
***equally contributed**
Sleep Breath. 2018 May;22(2):441-450

“A randomized controlled trial of positional therapy versus oral appliance therapy for position-dependent sleep apnea”
L.B.L. Benoist, M.H.T. de Ruiter, J. de Lange, N. de Vries.
Sleep Med. 2017 Jun;34:109-117

“Positional therapy in patients with residual positional obstructive sleep apnea after upper-airway surgery”
L.B.L. Benoist, M. Verhagen, J.P. van Maanen, N. de Vries
Sleep Breath. 2017 May;21(2):279-288

Een ‘andere’ toepassing van de valsalva manoeuvre; de oplossing van een gedetineerde
L.B.L. Benoist, R.H. de Roest, T.P. Tan, T.H.M. Tan
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“Hyoid suspension: hyo-thyroid and hyo-mandibular options”
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L.B.L. Benoist, N. de Vries
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“CPAP wash-out prior to reevaluation polysomnography: A sleep surgeon’s perspective”
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Sleep and Breathing, 2015 May 19(2):433-9

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Case report: "The great imitator: een man met keelpijn"
L.B.L. Benoist, C. Kastoer, C.G. Scheepstra, T.H.M. Tan
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"How I do it: OSAS, diagnostisch traject en behandelopties"
A.V.M.T. Vroegop, **L.B.L. Benoist**, N. de Vries
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"The Effect of Weight Loss on OSA Severity and Position Dependence in Bariatric patients"
S. Morong, **L.B.L. Benoist**, M.J.L. Ravesloot, D.M. Laman, N. de Vries
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"Upper-airway Stimulation for Obstructive Sleep Apnea"
Strollo PJ Jr, Soose RJ, Maurer JT, de Vries N, et al.
New England Journal Medicine, 2014 Jan 370(2):139-49
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"Evaluation of Position Dependency in Non-Apneic Snorers"
L.B.L. Benoist, S. Morong, J.P. van Maanen, A.A.J. Hilgevoord, N. de Vries
European Archives of Oto-Rhino-Laryngology, 2014 Jan 271(1):189-94.

"Melanoma of the Oral Cavity"
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Book chapters

"Current concepts of sleep apnea surgery", redactie: T. Verse, N. de Vries 2019 Thieme publishers

- Chapter 3.4.1 *"Awake Nasopharyngoscopy"* and 3.4.2 *"Drug-induced Sleep Endoscopy"* N. de vries, P. van Maanen, **L.B.L Benoist**
- Chapter 4 *"Nonsurgical treatment: lifestyle, weight loss, positional therapy, mandibular advancement devices, continuous positive airway pressure, multimodality treatment"* N. de Vries, P. van Maanen, **L.B.L Benoist,** A. Hoekema

- Chapter 5.1.1 *"Continuous positive airway pressure washout"* A. Vroegop, J. Smithuis, **L.B.L. Benoist**, O.M. Vanderveken, N. de Vries

"TransOral Robotic Surgery for Obstructive Sleep Apnea A Practical Guide to Surgical Approach and Patient Management", redactie: C. Vicini, Sep 2016 Springer

- Chapter 19: *"Failures Management"* Claudio Vicini, Claudia Zanotti, **Linda Benoist**, Nico de Vries.

"Positional Therapy in Obstructive Sleep Apnea", redactie: N. de Vries, Nov 2014 Springer

- *"Influence of sleep position on the transition of mild to moderate and severe OSA"* **L.B.L. Benoist**, S. Morong. Part II p.81
- *"Correlation between calculated/predicted and actual AHI after positional therapy"* **L.B.L. Benoist**, A.V.M.T Vroegop. Part IV p.137
- *"Influence of sleep position on snoring"* **L.B.L. Benoist**, S. Morong. Part V p.143
- *"Positional OSA in the morbidly obese and the effect of weight loss on OSA severity"* S. Morong, **L.B.L. Benoist**. Part V p.185
- *"Residual POSA after maxillomandibular advancement in patients with severe OSA"* **L.B.L. Benoist**, M.H.T. de Ruiter. Part VI p.321

Curriculum vitae

Linda Benoist was born in Harderwijk, the Netherlands on February 21, 1987. She graduated from the Christelijk Collega Nassau Velume in Harderwijk in 2005. All her childhood she wanted to become a veterinarian, but (un)fortunate luck with the numerus fixus system in the Netherlands made her decide to exchange her fascination for animals into human beings. She was accepted to the study of medicine in 2006 at the VU University in Amsterdam. During her studies, she travelled abroad to Ghana, Africa for voluntary work in a medical clinic. Besides all the impressive and educational experiences there, she especially learned to appreciate our health system compared to almost "nothing". After her first short rotation in otorhinolaryngology (ENT hereafter), she knew she wanted to become an ENT specialist. She did two more rotations in ENT at Tergooi hospital, Blaricum and OLVG West, Amsterdam. The latter resulted in her first job in 2013 as a resident (ANIOS) at OLVG West in Amsterdam. Under the supervision of prof. dr. N. de Vries she started a scientific career next to her clinical work, ultimately resulting in this thesis. In 2016 Linda was accepted for the specialization in ENT at Erasmus Medical Center, Rotterdam (Prof. dr. R. Baatenburg de Jong). During her residency she did internships in Maasstad hospital, Rotterdam and Amphia hospital, Breda with great joy. She aims to finish her residency program in January 2021 after which she would like to improve her skills in endoscopic sinus- and skull base surgery.

Linda lives with her husband Arjan and their son Sven in Amsterdam.

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